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HIV and its effects on bone: A primer for rheumatologists

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Abstract

Purpose of review—As patients with HIV are living longer because of effective treatments, rates of comorbid chronic diseases such as bone complications are increasing. There is growing body of literature showing increased rates of osteopenia and osteoporosis in the HIV population. Less is known about the risk of fracture, as well as other bone complications, such as avascular necrosis (AVN).

Recent findings—Increased rates of osteopenia and osteoporosis are seen in the HIV population, likely secondary to an interaction of traditional osteoporotic and HIV-specific risk factors, and possibly the effect of antiretroviral therapy (ART). There is conflicting recent data as to whether the decrease in bone mineral density seen in the HIV population, specifically with particular ART regimens, translates into an increased risk of fracture. Conflicting evidence emerges from recent studies exploring whether supplementation of vitamin D and calcium can prevent the bone loss seen with specific ART regimens.

Summary—Bone disease is common in the HIV population, and will likely be a medical problem increasingly seen by rheumatologists. The role of ART regimens on bone complications such as fracture and AVN is unclear, and further research in this area as well as possible prevention strategies are needed.

Keywords

HIV; bone disease; osteoporosis; fracture; avascular necrosis

Introduction

While infection with the Human Immunodeficiency Virus (HIV) remains a significant health problem throughout the world, the introduction of effective antiretroviral therapy (ART) regimens has radically shifted the public health implications of the disease. As patients with HIV on treatment are living longer, an increasing number of chronic health problems are

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Conflict of interest

D.H.S receives research support for unrelated projects from Amgen and Lilly who both make products for osteoporosis.

occurring in an already vulnerable population; bone complications, such as osteoporosis and avascular necrosis, are one such area that rheumatologists may begin to see. This paper aims to review the current literature on the association of HIV with higher rates of osteoporosis, fracture, and avascular necrosis, as well as the possible mechanisms by which the virus can begin to affect bone composition.

Osteoporosis and HIV

Research published in the last decade suggests that patients infected with HIV have a higher rate of osteoporosis than the general population. Several cross-sectional studies examining this are summarized in a meta-analysis published in 2006, which reports that the probability of developing osteoporosis is over three times higher in HIV patients as compared to HIV-negative controls [1]. There is animal data suggesting that HIV infection itself can induce bone resorption [2]. However in humans the association may be complicated by the findings that HIV patients have higher rates of other known osteoporotic risk factors, including low body mass index (BMI), and lifestyle factors such as tobacco use [3, 4, 5].

The increase in osteoporosis found in HIV-infected individuals may be in part due to the widespread use of combination antiretroviral therapy (ART). While time on ART has been cited as a risk factor for decreasing bone mineral density (BMD) [6], other studies suggest most of the decrease in BMD occurs during the first year of therapy [7, 8]. Tenofovir, a nucleotide analogue reverse transcriptase inhibitor (NRTI), and protease inhibitors are the specific medications that are particularly associated with decrease in BMD. Data from randomized controlled trials show that an ART regimen including tenofovir is associated with significantly decreased BMD at one and even two years as compared to another NRTI, abacavir [8, 9]. In addition, HIV-negative men participating in a trial examining the effects of tenofovir for pre-exposure prophylaxis experienced a small but significant drop in BMD in men taking the medication [10]. Similarly, protease inhibitors are implicated in decreasing BMD and increased rates of osteoporosis [1, 11, 12]. Analyses of randomized trial data suggest that this bone loss is present as early as one year after start of treatment [13].

However, studies with longer follow-up time find that this initial decrease in BMD is attenuated with length of time on ART treatment. For example, a study examining BMD measurements in a small cohort of HIV-positive men on established ART compared to HIV-negative controls finds no significant difference in BMD between the HIV-positive and –negative men at six years, except at the lumbar spine where a greater increase is seen in the HIV-positive men [14]. A recent meta-analysis reviewing several longitudinal studies of HIV cohorts demonstrates a decrease in BMD, especially in the first year of treatment, in patients who are untreated at baseline. However, in those patients on established ART at baseline have stable BMD throughout follow-up [15].

HIV and fracture

While there is substantial evidence that low BMD is more prevalent in HIV-positive individuals as compared to those who are HIV-negative, the question remains whether this finding translates to an increased risk of fracture (see Table 1). One of the first papers

examining this outcome is a large hospital-based cross-sectional study which finds increased rates of fractures in HIV-positive patients when compared to HIV-negative patients [16]. While certainly suggestive, this study is unable to address many possible risk factors that could confound this relationship. Subsequent studies in both predominantly male as well as female populations demonstrate that it is an increased burden of traditional osteoporotic risk factors, such as decreased BMI, that may explain this finding of increased risk of fracture in the HIV-positive population rather than the virus itself [17•, 18]. Other studies show that in addition to classic osteoporotic risk factors, HIV-specific risk factors such as history of AIDS-defining illness, low CD4 counts, or co-infection with hepatitis C are associated with increased rates of fracture [18, 19] (see Table 2).

The data suggesting ARTs decrease BMD led to an interest in examining the role of ARTs on fracture risk. To date, there are conflicting data as to whether HIV-positive patients taking ARTs are at higher risk for fracture as compared to HIV-positive patients not taking ARTs [18, 19•, 20•, 21••, 22••, 23•] (see Table 3). These observational studies are difficult to perform in observational studies because of the inherent difference in the types of patients taking ARTs compared to those who take no ARTs. They also require controlling for numerous classic osteoporotic as well as HIV-specific risk factors.

Information about changes in BMD has increased focus on the possibility that given agents, such as tenofovir and protease inhibitors may increase fracture risk (see Table 3). Cumulative exposure to tenofovir increases osteoporotic fracture risk in a recent cohort study of US Veterans [21••]. This same study also suggests increasing risk of fracture with exposure to a certain combination of protease inhibitors, lopinavir/ritonavir. However, a recent claims-based case-control study did not support these findings, and in fact suggests decreasing risk of fracture with longer tenofovir exposure [20•]. In light of this conflicting data, further research examining the effect of ART on fracture risk is needed in order to selection of ART regimens, especially in those who carry other osteoporotic risk factors.

Measures to prevent bone loss in HIV-positive patients

There is growing interest in finding potential modifiable factors that could prevent the increase in bone loss seen in the HIV-positive population, such as the correction of vitamin D deficiency. Vitamin D deficiency is common in the HIV-positive population, with studies citing 29–73% prevalence, although it is not clear that the rate of deficiency is different than matched HIV-negative controls [24••]. In the HIV population, vitamin D deficiency is associated with well-known risk factors such as race, as well as HIV-specific factors like CD4 count [25, 26]. Particular ART medications may also play a role in vitamin D deficiency; low vitamin D levels are associated with the non-nucleoside reverse transcriptase inhibitor efavirenz [25, 27], and tenofovir is associated with elevated parathyroid hormone levels [28, 29•].

There is no clear evidence that vitamin D repletion improves BMD in the HIV-positive population [24••], particularly for those patients on ART regimens that potentially affect vitamin D homeostasis. There is suggestion of benefit in a recent trial randomizing young HIV-positive adults to vitamin D supplementation versus placebo over a three month period

[30•]. This study shows that supplementation of vitamin D significantly decreases PTH and bone resorption markers, especially in the tenofovir-based regimen arm. However another trial randomizing HIV-positive children and teens to receive either vitamin D repletion and calcium supplementation or double placebo for two years did not find a significant difference in BMD between the two groups [31•]. There are currently no published randomized controlled trials supporting vitamin D and calcium supplementation use to prevent BMD loss seen on particular ART regimens in older adult HIV-positive patients, where a larger impact may be seen.

Studies show that bisphosphonates improve low BMD in the HIV-positive population, and can be administered safely. Two randomized controlled trials on HIV-positive populations with low BMD found that weekly alendronate in addition to calcium and vitamin D supplementation was not only safe but improved BMD at 48 weeks[32, 33]. Studies examining the use of zoledronic acid in patients with HIV and low BMD found similar safety and efficacy [34, 35]. However, it remains unknown if there is a utility in prescribing bisphosphonates in HIV-positive patients as preventive therapy, in order to avert the decrease in BMD seen during initiation of ART, and potentially decrease fractures.

HIV and avascular necrosis

The effect of HIV on bone is not limited to low BMD and fracture; in the last decade studies show an association between HIV infection and risk of development of avascular necrosis (AVN) (see Table 4). Incidence of symptomatic AVN in the HIV-positive population is reported as high as 0.3–3.4/1,000 person years [36–38], as compared to the general population where reports of AVN are 0.03–0.04/1,000 person years [39, 40]. A small study examining bilateral hip MRI on asymptomatic patients with HIV found the prevalence of AVN to be 4.4% (15/339) as compared to 0% (0/118) in HIV-negative controls matched on age and sex [41].

However, unlike the osteoporosis and HIV literature, there is a paucity of data linking AVN with risk factors specific to HIV and its treatment. Initial case reports link AVN to initiation of protease inhibitors [42, 43]. However this association is not supported in subsequent case-control studies, and instead associations are found with known risk factors of AVN, for example steroid use and hyperlipidemia [44, 45]. One large French case-control study suggests an association of AVN with HIV-specific factors, such as a history of AIDS-defining illness, as well as with use of a combination of three or more ART medications. In this study, the relative risk of AVN attributable to taking combination ART for less than 12 months compared to no ART is 2.6 (95% CI 1.2–5.9), but rises to 5.1 (95% CI 2.1–12.6) in those being treated for over 60 months[36]. Further research is needed to validate these findings in another cohort, as well as determine whether a particular ART regimen, such as one including protease inhibitors, is associated with development of AVN as this may help guide therapeutic choices for patients with other classic risk factors for AVN.

Osteoimmunology and relation with HIV

In recent years, research is illuminating the relationship between a chronic inflammatory state and changes in bone metabolism. Chronic inflammation and persistently elevated

cytokines, for example TNF or interleukins, appear to activate proteins like RANKL, which in turn activates osteoclasts that resorb bone. The effect of these inflammatory molecules on bone degradation begins to explain the mechanism by which medications such as TNF-inhibitors not only decrease inflammation in patients with diseases like rheumatoid arthritis, but decrease formation of erosions as well [46]. While we often consider these changes in the setting of inflammatory arthritis, studies suggest the effect of inflammation on bone occurs in the general population as well—for example, high-sensitivity C-reactive protein (CRP) is associated with increased rate of fracture [47].

A persistent inflammatory state secondary to infection with HIV may also detrimentally effect bone composition. Elevation in inflammatory proteins such as CRP and TNF- α is associated with HIV infection, but there is conflicting data in regards to whether inflammatory markers decrease with treatment for HIV [48, 49]. Research continues to elucidate how inflammatory markers are activated in the face of B and T cell dysfunction due to HIV, in addition to the effect HIV infection has directly on bone. A recent review by Ofotokun and others describes research suggesting that HIV infection increases expression of certain pro-osteoclast proteins such as RANKL, and decreases expression of other proteins that regulate the activation of osteoclasts, such as osteoprotegerin, which is an inactivator of RANKL[50••]. These complex associations may begin to explain the effects of HIV infection on bone metabolism, and perhaps why patients with HIV may be at an increased risk of osteoporosis.

Conclusion

Rheumatologists are well-versed in seeing patients with systemic inflammation. While not a rheumatologic illness per se, HIV is becoming a chronic disease that is also associated with systemic inflammation. This inflammation may play a role in bone complications such as osteoporosis and fracture. HIV presents a difficult clinical situation; in addition to the systemic inflammation and HIV infection itself there are increased rates of several risk factors of bone complications, such as increased comorbidities, higher rates of co-infection with hepatitis C, and the potential effects of ART on bone. As research on the association of bone disease and HIV continues to grow, we will likely learn more about the complicated interplay of potential risk factors seen in the HIV-positive population, but also may gain knowledge regarding the effect a systemic chronic illness has on bone which could be extrapolated to the general population.

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Abbreviations

HIV	Human Immunodeficiency Virus
ART	antiretroviral therapy
BMI	body mass index
BMD	bone mineral density
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
AVN	avascular necrosis

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Key points

- Recent studies suggest that the HIV-positive population is at an increased risk of development of osteoporosis (low BMD), which is likely due to many factors.
- Antiretroviral therapy has been associated with decreasing BMD particularly in the first year of therapy, but it is unclear if this early bone loss translates into increased risk of fracture.
- There is a need for further trials examining the effects of vitamin D and calcium supplementation in prevention of bone loss in the HIV population, especially in those on specific ART regimens.
- While there is an increased risk of AVN in the HIV-positive population, further studies are needed to determine the role of specific HIV-related risk factors, such as particular ART regimens.

Table 1

Selected epidemiologic studies reporting unadjusted incidence rate of fracture in HIV-positive as compared to HIV-negative population.

Study, year of publication, country	Study design	Study population, years of study	Mean/median age, in years	Percent male	Mean/median follow-up, years	Type of fracture and data source	Number of fractures	Unadjusted incidence rate, per 1000 person-years, and risk ratio (95% C.I.)
Hansen et al, 2011, Denmark	Cohort, matched for sex, age and index date	5,406 HIV+ and 26,530 HIV- patients in a national hospital register	HIV+ 37 HIV- 37	76	HIV+ 6.5 HIV- 9.6	All fractures EMR	HIV+ 806 HIV- 3312	HIV+ 21.0 (19.8–22.2) HIV- 13.5 (13.1–13.9)
Womack et al, 2011, USA	Cohort, matched for age, race, gender, site	40,115 HIV+ and 79,203 HIV- in a cohort of veterans	HIV+ 54 HIV- 53	100	HIV+ 6.0 HIV- 6.9	Hip, vertebral, upper arm fractures	HIV+ and HIV- 1615	HIV+ 2.5 ^a HIV- 1.9
Yin et al, 2010, USA	Cohort	1,728 HIV+ and 663 HIV- women at risk for HIV	HIV+ 40 HIV- 36	0	HIV+ 5.4 HIV- 5.4	EMR	HIV+ 148 HIV- 47	HR 1.32 (1.20–1.47) ^b
Triant et al, 2008, USA	Cross-sectional	8,525 HIV+ and 2,208,792 HIV- patients at one tertiary hospital system	NA	HIV+ 65 HIV- 44	NA	Vertebral/hip/wrist fractures EMR	HIV+ 245 HIV- 39073	NA ^d
Arnstien et al, 2007, USA	Cohort	317 HIV+ and 209 HIV- men at risk for HIV	HIV+ 55 HIV- 56	100	NA (686 PY for HIV+, 453 for HIV-)	All fractures Self-report	HIV+ 21 HIV- 12	HIV+ 31 (20–46) HIV- 26 (15–45)

C.I., confidence intervals; NA, not available; EMR, electronic medical record; IRR, incidence rate ratio; HR, hazard ratio.

^a Confidence intervals not provided and unable to be calculated from data given.

^b Statistically significant unadjusted, but lost significance when controlled for age, white race, alcohol abuse, liver disease, steroids, PPI, BMI.

^cNot a significant difference, $p = 0.13$
^dIn this cross-sectional study, incidence rates could not be calculated. However prevalence is given for HIV+ population as 28.7 per 1000 patients, and for HIV- population is 17.7 per 1000 patients

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Table 2

Selected studies in support of indicated risk factors of fracture among HIV-positive populations.

Potential Risk Factor	Study, year, country
<i>Traditional osteoporotic risk factors</i>	
Low BMI	Bedimo et al, 2011, USA Womack et al, 2011, USA Mundy et al, 2012, USA ^a
Older age	Bedimo et al, 2011, USA Yin et al, 2010, USA Hansen et al, 2011, Denmark Womack et al, 2011, USA
Race	Bedimo et al, 2011, USA Yin et al, 2010, USA Hansen et al, 2011, Denmark Womack et al, 2011, USA Arsten et al, 2007, USA
Alcohol consumption	Collin et al, 2009, France ^a Mundy et al, 2012, USA ^a
Tobacco use	Bedimo et al, 2011, USA Yin et al, 2010, USA Hansen et al, 2011, Denmark
Low physical activity	Mundy et al, 2012, USA ^a
Prior fractures	Mundy et al, 2012, USA ^a
Liver disease	Womack et al, 2011, USA
Corticosteroid use	Yong et al, 2011, Australia Womack et al, 2011, USA
Proton-pump inhibitor use	Womack et al, 2011, USA
Anti-epileptic medications	Yong et al, 2011, Australia
Higher Charlson comorbidity score	Hansen et al, 2011, Denmark
<i>HIV-associated risk factors</i>	
Co-infection with hepatitis C	Collin et al, 2009, France ^a Bedimo et al, 2011, USA Young et al, 2011, USA Hansen et al, 2011, Denmark Mundy et al, 2012, USA ^a
History of AIDS-defining illness	Yin et al, 2010, USA
CD4 count	Yong et al, 2011, Australia Young et al, 2011, USA

AIDS, acquired immune deficiency syndrome.

^aUnivariate analysis only.

Table 3

Selected epidemiologic studies exploring relationship of antiretroviral therapy (ART) and fracture among HIV-positive populations.

Study, year, country	Study design	Study population, years of study	Mean/median follow-up (years)	Number of fractures	Any ART-use associated with fracture (as compared to no ART use)	Specific class of ART associated with fracture (as compared to no use of given class of ART)	Specific ART medications associated with fracture (as compared to non-users of the specific medication)
Mundy et al. 2012, USA	Nested case-control Matched on age/gender/year of birth	59,594 patients with HIV from an administrative claims database 1997–2008	NA	2411	Decrease risk	Decrease risk with all ART classes: PI, NRTI, NNRTI	Increased risk with darunavir, saquinavir
Bedimo et al. 2012, USA	Cohort	56,660 patients with HIV from a veterans registry 1988–2009	5.9	951	No association	Increased risk with boosted ^{a,b} PI	Increased risk with tenofovir ^b
Hansen et al. 2011, Denmark	Cohort Matched on sex/age/index date	5,306 patients with HIV in a nation hospital registry 1995–present	7.3	806	Increased risk	NA	No association ^c found with tenofovir, abacavir, efavirenz
Yong et al. 2011, Australia	Case-control Matched on gender/age/duration of known HIV	2,424 HIV patients at one institution 1998–2009	7.3	73	No association (univariate analysis)	No association with PI, NNRTI (univariate analysis)	No association found with tenofovir (univariate analysis)
Young et al. 2011, USA	Cohort	5,826 patients with HIV from a cohort from ten subspecialty clinics 2000–2008	3.8	233	No association (univariate analysis)	NA	NA
Womack et al. 2011, USA	Cohort Matched for age/race/gender/site	40,115 patients with HIV from a cohort of veterans 1997–2009	6	NA	NA	Increased risk with PI	No association found with tenofovir

Study, year, country	Study design	Study population, years of study	Mean/median follow-up (years)	Number of fractures	Any ART-use associated with fracture (as compared to no ART use)	Specific class of ART associated with fracture (as compared to no use of ART)	Specific ART medications associated with fracture (as compared to non-users of the specific medication)
Yin et al, 2010, USA	Cohort	1,728 HIV patients in Women's Interagency Study 2002–2008	5.4	148	No association (univariate analysis)	Decreased risk with cumulative NNRTI use No association with PI, NRTI (univariate analysis)	No association found with tenofovir (univariate analysis)

NA, not available; PI, protease inhibitors; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitor.

Multivariate analysis results reported unless otherwise noted, using $p < 0.05$ as measure of significance.

^a A boosted regimen includes two protease inhibitors, one being ritonavir. This finding lost significance when adjusted for other ART in a second multivariate analysis.

^b This data is from a subset of cohort collected from 1996–2009, when combination antiretrovirals were available and used in increased frequency.

^c Unknown if this is univariate or multivariate analysis.

Table 4
Summary of selected case-control and cohort studies examining avascular necrosis (AVN) among HIV-positive populations.

Study	Study design	Population	Determination of AVN	Risk factors associated with AVN	Number of cases of AVN (%)	Estimated unadjusted incidence of AVN, per 1000 person-years (95% C.I.)
Mazzotta et al, 2011, Italy	Case-control Matched for age/sex/CD4 counts at time of diagnosis	HIV+ patients seen in 23 outpatient clinics (total number NA) 2000–2009	Survey of practitioners AND Radiologic confirmation by scintigram, CT, MRI	Corticosteroid use Exposure to 1 medications in addition to ART Loss of working ability Increased cholesterol and triglycerides Serum level of IgE > 100 (<i>no multivariate analysis</i>)	15 (NA)	NA
Morse et al, 2007, USA	Cohort	239 asymptomatic HIV+ patients with previous negative MRI for AVN enrolled in clinical studies at one research center 2001–2003	Radiographic confirmation by MRI ^a	<i>No association with:</i> Sex Age Duration of HIV ART history (<i>no multivariate analysis</i>)	3 (1.3%)	6.5 (1.3–18.9) <i>asymptomatic AVN</i>
Ho et al, 2007, Taiwan	Cohort	968 HIV+ patients seen at one hospital referral center 1994–2003	Medical record review AND Radiologic confirmation by x-ray or MRI	Lipodystrophy (<i>no multivariate analysis</i>)	11 (1.1%)	3.4 (3.2–3.6)
Mary-Krause et al, 2006, France	Cohort	56,393 HIV+ patients belonging to multicenter HIV cohort 1996–2002	Medical record review AND Radiographic or surgical diagnosis, or clinical findings	Nadir CD4 count Prior AIDS-defining illness Time on combination ART	104 (0.18%)	0.45 (0.37–0.54)
Martin et al, 2004, France	Cohort	2,700 HIV+ patients belonging to a hospital-based cohort 1999–2002	Practitioner report AND Radiographic diagnosis	NA	8 (0.3%)	0.3 (0.14–0.62)
Glesby et al, 2001 USA	Case-control Matched for date of clinic visit and CD4 count	Approximately 1,600 HIV+ patients seen at two outpatient clinics 1992–2000	Medical record review and survey of practitioners AND Radiographic diagnosis	Corticosteroid use <i>No association with ART and protease inhibitor use</i>	17 (NA)	NA
Scribner et al, 2000, USA	Case-control Matched for day and location of case diagnosis	HIV+ patients seen at one teaching hospital (total number NA) 1984–1998	Medical record review and survey of practitioners AND Radiographic confirmation or pathologic diagnosis	Concurrent diagnosis of a classic AVN risk factor (e.g. hyperlipidemia) Saqueinivir current use	25 (NA)	NA

C.I., confidence intervals; NA, not available; ART, antiretroviral therapy.

^aExamined for hip AVN only.