HHS Public Access

Author manuscript

Curr Opin HIV AIDS. Author manuscript; available in PMC 2018 September 28.

Published in final edited form as:

Curr Opin HIV AIDS. 2016 May ; 11(3): 285–293. doi:10.1097/COH.0000000000000259.

Hepatitis C Virus Coinfection as a Risk Factor for Osteoporosis and Fracture

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Abstract

Purpose of Review—With increased survival of HIV-infected patients, osteoporotic fractures have developed as a major cause of morbidity in these patients, and chronic hepatitis C virus (HCV) co-infection has emerged as a significant contributor to this increased fracture risk. This article reviews the epidemiologic and clinical evidence for osteoporosis and increased fracture risk among HIV/HCV co-infected patients, as well as potential mechanisms for these outcomes with HCV co-infection.

Recent Findings—Epidemiologic studies suggest that HIV/HCV co-infected patients exhibit a 3-fold increased fracture incidence compared to uninfected controls, and 1.2–2.4-fold increased fracture risk compared to HIV mono-infected patients. Recent reports suggest that chronic HCV co-infection is independently associated with reduced bone mineral density in HIV, but that it is not associated with significantly increased bone turnover. The deleterious impact of chronic HCV on BMD and fracture risk occurs even in the absence of advanced liver fibrosis or cirrhosis. New tools to assess bone quality, including the trabecular bone score, high resolution peripheral quantitative computed tomography, and in vivo microindentation, may help improve understanding

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Conflicts of interest:

Dr. Bedimo is currently receiving a grant (AI424-552) from Bristol Myers Squibb and has served on ad-hoc scientific advisory boards for BMS, Merck & Co, Theratechnologies and Gilead Sciences. The remaining authors have no conflicts of interest.

of the mechanisms of HCV-associated skeletal fragility. The impact of approved anti-osteoporosis medications and direct-acting antivirals for the treatment of chronic HCV infection on patients' bone health remain to be studied.

Summary—Chronic HCV infection is an independent risk factor for osteoporosis and fractures among HIV-infected patients, even prior to the development of cirrhosis. The underlying mechanisms are being unraveled, but major questions persist regarding the optimal evaluation and management of bone health in HIV/HCV co-infected patients.

Keywords

HIV; Hepatitis C; Osteoporosis; Osteoporotic Fractures

Introduction

With increased survival of HIV-infected patients, there has been a significant shift in the causes of morbidity and mortality from AIDS-defining (infections and AIDS-related malignancies) to non-AIDS-defining conditions, principally cardiovascular diseases, liver-related complications, and non-AIDS malignancies. Osteoporosis and increased fracture risk is also a major cause of morbidity in these patients [1–3].

Like many non-AIDS complications, the pathogenesis of increased fracture risk among HIV-infected patient is incompletely understood. It likely involves patient factors (over-representation of "traditional" risk factors); direct effects of HIV infection, HIV-associated inflammation and immune activation; and effects of antiretroviral therapy [4]. Chronic hepatitis C virus (HCV) co-infection (present in up to a third of HIV-infected patients [5]) likely contributes to the increased fracture risk, since recent observational studies have demonstrated HIV/HCV co-infected patients have an increased fracture incidence compared to HCV mono-infected, HIV mono-infected, and uninfected persons [6].

In this article, we will review the epidemiologic and clinical evidence for increased fracture risk among HIV/HCV co-infected patients and discuss potential mechanisms of osteoporosis and increased fracture risk associated with HCV co-infection.

I. Fracture Incidence in HIV/HCV Co-Infection

In several large cohort studies from North America, Europe, Australia and Asia, an estimated 15 to 30% of HIV-infected patients are co-infected with chronic HCV because of shared risk factors [6–10]. The incidences of liver- and non-liver-related complications of chronic HCV infection are higher among HIV/HCV co-infected patients than HCV mono-infected patients [11,12]. In addition to its ability to induce liver fibrosis, chronic HCV infection is also associated with extra-hepatic complications, particularly abnormalities in bone metabolism and increased fracture risk, that may contribute to morbidity among HIV/HCV co-infected patients as this group ages [2,6,13,14].

HIV and HCV infections have been associated with an increased risk of osteoporotic fracture compared to uninfected persons [6,15,16]. Osteoporotic fractures were more common in HIV/HCV co-infected compared with HIV mono-infected patients in several

reports [2,8,16–18] (Table 1). Rates of hip fractures are also significantly higher in HIV/HCV-coinfected compared to HIV-monoinfected, HCV-monoinfected, and uninfected persons (hazard ratios ranging from 1.2 to 2.4) [6] (Table 1). While cirrhosis and advanced liver disease are known risk factors for osteoporosis [19], the deleterious impact of HCV on BMD [20] and fracture risk [2] appears to occur prior to the development of severe liver fibrosis or cirrhosis, although the exact mechanism(s) remain to be elucidated.

II. Mechanisms of Increased Bone Fragility in HIV/HCV Co-Infection

Low bone mineral density (BMD) is a recognized metabolic complication of HIV [1,21] and chronic hepatitis C virus (HCV) infection [19,22]. Among HIV-infected patients, BMD further decreases 2–6% over the first two years of antiretroviral therapy (ART) initiation [23–25]. HCV coinfection has been associated with further reductions in BMD among HIV-infected patients in some [26–30], but not all studies [30–33]. These findings raise the possibility that the higher fracture risk observed in patients with chronic HCV infection might not be due to low BMD alone, but could involve other mechanism(s).

A number of factors related to HIV and chronic HCV have been hypothesized to contribute to skeletal fragility. HIV-related inflammation, ART-related toxicity, increased prevalence of tobacco/alcohol use, and traditional osteoporosis risk factors exacerbated by HIV contribute to low BMD and increased fracture risk in HIV [4]. Chronic HCV-associated inflammatory cytokines, particularly tumor necrosis factor-alpha, might inhibit bone formation and increase bone resorption [34,35]. The development of HCV-related hepatic decompensation might further contribute to a decrease in BMD by impairing production of factors (e.g., 25-hydroxyvitamin D, insulin-like growth factor-1) that promote bone formation and mineralization [19,22]. Each of the potential mechanisms that have been explored will be discussed below (Figure 1).

a. Over-representation of “traditional” fracture risk factors—Observations of an increased fracture risk in HIV/HCV co-infected patients led to speculations that the risk is likely due to either behavioral factors (such as substance abuse and intoxication leading to traumas) or an overrepresentation of “traditional” fracture risk factors in these populations [8]. This was reinforced by the observation that, unlike HIV-mono-infected patients, HIV/HCV co-infected patients had a higher incidence of “high-energy” fractures (not deemed to be osteoporotic in nature) [8]. These findings suggest that HCV-infected patients might be more likely to engage in activities leading to traumatic fractures, or that fracture risk factors such as tobacco use, alcohol consumption, and corticosteroid use, are more prevalent among chronic HCV-infected patients [36,37].

b. Role of severity of liver disease—While advanced liver disease is associated with hepatic osteodystrophy, several studies have shown that the incidence of osteoporosis and increased fracture risk are not associated with severity of liver disease in chronic HCV-infected patients. In a large cohort of HIV-infected US Veterans, HCV co-infection remained a strong independent osteoporotic fracture predictor, even after controlling for the severity of liver diseases (assessed by aspartate aminotransferase-to-platelet ratio index [APRI]) and presence of cirrhosis (adjusted hazard ratio, 1.31; 95% confidence interval [CI], 1.12–1.52)

[2]. Similarly, El-Maouche et al [38] showed that severity of liver disease was not associated with risk of osteoporosis in an HIV/HCV co-infected cohort. Taken together, these findings suggest that the severity of liver fibrosis is, at best, a weak determinant of increased fracture risk among HIV/HCV co-infected patients.

c. Increased Inflammation and Immune Activation—While increased inflammation in HIV and HCV has been associated with increased rates of non-AIDS complications [39] and extra-hepatic complications [40], it remains unclear if chronic inflammation contributes to increased bone turnover and fragility. In one recent cross-sectional study using tibia peripheral quantitative computed tomography (pQCT) to evaluate skeletal parameters in ART-treated HIV/HCV co-infected, HCV mono-infected, and ART-treated HIV mono-infected women, co-infected participants had substantially lower tibial trabecular volumetric BMD and diminished cortical dimensions with significant endocortical bone deficits compared to healthy reference participants. These findings support the hypothesis that HIV- and HCV-mediated chronic inflammation might contribute to the structural bone deficits observed in this group. Moreover, studies of patients with other chronic inflammatory conditions, particularly inflammatory bowel disease [41,42] and rheumatoid arthritis [43], have demonstrated a similar pattern of trabecular bone loss and endocortical thinning. In addition, median tumor necrosis factor-alpha levels in this study were found to be higher among coinfected than either HCV mono-infected or HIV mono-infected women, further suggesting the contribution of chronic inflammation. Tumor necrosis factor-alpha can reduce trabecular and cortical bone formation by inhibiting osteoblast differentiation, inhibiting osteoblast collagen secretion, and inducing osteoblast apoptosis [34,35]. This cytokine can also promote accelerated trabecular and cortical bone resorption by inducing expression of receptor activator of nuclear factor kappa B ligand (RANKL), which stimulates osteoclast activation and inhibits osteoblast apoptosis [44,45]. Additional studies are needed to evaluate the potential contribution of chronic inflammation to bone deficits as well as associated metabolic and body composition abnormalities among HIV/HCV co-infected patients.

d. Vitamin D Deficiency—Observational studies also suggest that HIV/HCV co-infected patients are more likely to have low serum 25-hydroxyvitamin D levels [46], and vitamin D deficiency has been shown to be associated with liver disease severity in HIV/HCV co-infected patients [47,48]. However, it remains unclear whether lower vitamin D levels are associated with either decreased bone mineral density or increased fracture risk in the setting of HIV/HCV co-infection [49].

e. Bone Turnover in HIV and HCV—In order to assess the impact of HIV and HCV on skeletal health, a recent cross-sectional study compared BMD, bone turnover markers, inflammatory markers, and sex hormones between HIV/HCV co-infected, HIV mono-infected, HCV mono-infected, and uninfected men of similar age, race, and body mass index distribution [29]. HIV infection was associated with increased bone turnover, with significant elevations in serologic markers of bone formation (osteocalcin) and resorption (collagen type 1 cross-linked C-telopeptide) [29]. Conversely, chronic HCV was not associated with increased bone resorption (Figure 2), and its effect on BMD reduction was

largely independent of bone turnover markers. These results are corroborated by another study of 40- to 60-year-old chronic HCV-infected patients without cirrhosis that demonstrated high rates of osteoporosis, but BMD was not associated with systemic inflammatory markers or markers of bone resorption (i.e., collagen type 1 cross-linked C-telopeptide) [50].

These findings could have significant implications in the prevention and management of osteoporosis in chronic HCV-infected patients. Since bone turnover is not increased among HCV mono-infected patients, use of pharmacological agents to decrease bone resorption may be neither safe nor effective among chronic HCV patients.

f. Regulation of Bone Metabolism in HIV and HCV: Role of IGF-1 and Sex Hormones—Insulin-like growth factor-1 (IGF-1) [51–53] and the sex steroids testosterone and estradiol play key roles in osteogenesis and bone resorption [54], but their contribution to bone health in relation to HIV and HCV infections remain unclear.

IGF-1 contributes to osteogenesis from mesenchymal stem cells, promoting osteoblast survival and differentiation [51,52]. It is produced primarily by the liver, and its production can be impaired in decompensated cirrhosis [55], potentially resulting in reduced bone formation. In one study, IGF-1 was lower in chronic HCV-infected than uninfected patients and median levels decreased as APRI scores increased [29]. However, IGF-1 was not associated with bone resorption or BMD [29]. It is therefore not likely an important mechanism by which chronic HCV infection contributes to low BMD.

Significant differences have been observed in the effects of estradiol and testosterone on osteogenesis using human-bone-marrow-derived mesenchymal stem cells from men and women [54,56]. It is unclear whether HIV or HCV modulate these effects. Chronic HCV-infected patients have higher levels of total estradiol and testosterone, likely because of increased levels of steroid hormone binding globulin [29]. Bioavailable testosterone and estradiol were associated with higher markers of bone formation, but neither were associated with low BMD [29].

III. Managing Fracture Risk in HIV/HCV Co-Infected Patients

a. Assessment of Fracture Risk in HIV/HCV: Can We Do Better?—As mentioned above, although not associated with significantly lower BMD than HIV or HCV mono-infection in most studies [27,31,32,57,58], HIV/HCV co-infection has been consistently shown to predict much greater fracture risk than HIV mono-infection (hazard ratios ranging from 1.2 to 2.4) [2,6,8]. This suggests that BMD might be inadequately assessing fracture risk in this population. Novel techniques to assess bone strength are being evaluated to predict fracture risk for a variety of conditions. These methods should be explored in the context of HIV/HCV co-infection and HCV mono-infection

i. Trabecular Bone Score: Trabecular bone score (TBS) is a novel measurement of bone microarchitecture from dual-energy X-ray absorptiometry (DXA) images. In TBS, numbers and amplitudes of pixel-to-pixel gray-level variations of a projection of a BMD image is used to infer the 3-dimensional density of trabecular structure using mathematical

"experimental variograms" [59]. While not a direct measurement of bone microarchitecture, TBS is a close approximation of 3-dimensional bone characteristics and has recently been shown to be a practical, non-invasive, surrogate technique for the assessment of cancellous bone microarchitecture in pre-menopausal women and in men with osteoporosis [60]. There is growing recognition that TBS can predict risk of fracture in conditions such as glucocorticoid therapy [61], subclinical hypercortisolism [62], and diabetes mellitus [63,64], which are associated with increased fracture risk but not decreased BMD. These conditions might cause a deleterious effect on bone structure that is not captured by BMD alone, but may be detected by TBS. Similarly, TBS might improve fracture risk prediction in other conditions associated with secondary osteoporosis, such as HCV or HIV.

In a recent study by Martinez et al [65], compared to antiretroviral naïve patients, those receiving a boosted protease inhibitor (PI) with or without tenofovir (TDF) had significantly lower BMD ($p<.03$), but much lower TBS ($p<.0001$). Furthermore, only those receiving boosted PI with or without TDF had lower BMD than antiretroviral-naïve patients while all regimens were associated with lower TBS. These results suggest that TBS might improve fracture risk prediction among HIV-infected and HIV/HCV co-infected patients and highlight bone effects of ART not detected by BMD alone.

ii. High Resolution Peripheral Quantitative CT: Other direct or indirect measurements of cortical or trabecular properties are now being used to assess bone strength and predict fracture risk in post-menopausal women and conditions of increased bone fragility. Assessment of bone quality has also been performed in conditions with increased bone fragility using high-resolution peripheral quantitative computed tomography (HRpQCT). HRpQCT allows for 3-dimensional assessment of bone macro- and microarchitecture (e.g., cortical porosity and trabecular connectivity) of the distal radius and tibia. This technology has showed increased cortical porosity in post-menopausal women [66], patients with type 2 diabetes mellitus [67], and with HIV-1 infection [68].

Using tibial HRpQCT, Lo Re et al [33] conducted a cross-sectional analysis of 50 HIV/HCV-coinfected, 51 HCV-monoinfected, and 50 HIV-monoinfected women. The study found that compared with 263 healthy reference patients, HIV/HCV co-infected women had decreased tibial trabecular volumetric BMD, diminished cortical dimensions, and significant endocortical bone loss. Also, trabecular volumetric BMD was lower in coinfected than in HCV- or HIV-monoinfected participants. More analyses of HRpQCT in HIV/HCV patients will help to further elucidate the mechanisms of the structural defects leading to increased bone fragility in these patients.

iii. In Vivo Microindentation: Recently, a new device has been developed that can perform in vivo measurement of bone material properties (bone material strength index) using a "microindentation" technique [69]. This technique has been used to assess bone quality in post-menopausal women and in those with type 2 diabetes mellitus [70]. Future studies should evaluate its use among HIV/HCV co-infected patients.

b. Management of Fracture Risk in HIV/HCV—If corroborated by other studies, the lack of association of elevated bone turnover with decreased BMD in chronic HCV infection

could have important implications in the prevention and management of osteoporosis in these patients. The most commonly used anti-osteoporosis agents, bisphosphonates, are anti-resorptive agents. Since bone turnover is not increased in HCV mono-infected patients, it is unclear whether pharmacologic means of decreasing bone resorption would be safe and effective in chronic HCV-infected patients. 'Data in post-menopausal women show that the anti-fracture efficacy of bisphosphonates is significantly lower among both osteoporotic and non-osteoporotic women with lower baseline levels of bone turnover markers.[71]. It also remains unclear if achieving viral cure of chronic HCV infection (i.e., sustained virologic response) will significantly improve bone health, and this should be a focus of future observational studies.

Primary prevention: The National Osteoporosis Foundation (NOF) recommends DXA scans for postmenopausal women aged ≥65 years and men aged ≥70 years [72], as well as for younger individuals with conditions that predispose to bone loss and increased fracture risk. HIV infection is now listed among these conditions. Guidelines for the management of fracture risk in HIV-infected patients have also been published [4,73]. The indications for treatment are not different from those of the general population, except that the threshold for DXA evaluation is lower for patients with HIV infection (50 years) [4,73]. At present, there are no specific recommendations for osteoporosis screening or management for HIV/HCV co-infected patients.

The main interventions aimed at treating osteoporosis and reducing the risk of fragility fractures include dietary and supplemental calcium and vitamin D, weight-bearing exercises, and pharmacological agents (mostly bisphosphonates and the biological agent denosumab). The adherence to and effectiveness of recommended measures for preventing fractures among HIV- and HCV-infected populations have not been evaluated.

Secondary prevention: The National Osteoporosis Foundation 2014 Clinicians' Guide recommends pharmacologic therapy for post-menopausal women and men age ≥50 with a previous hip or vertebral fracture, osteoporosis, or osteopenia with a high FRAX® score (i.e., 10-year probability of a hip fracture ≥3% or 10-year probability of a major osteoporosis-related fracture ≥20%). TBS is a proven osteoporotic fracture predictor, even after adjustment for BMD, and is now included as an independent risk factor in the FRAX® algorithm for fracture risk prediction [74].

Impact of Antiviral Therapy for Chronic HCV Infection: For HIV/HCV patients, limited data suggest that treatment of HCV could have significant benefits in decreasing fracture risk. Successful HCV clearance in response to interferon (IFN) therapy was associated with a two-thirds reduction in the risk of bone fracture in postmenopausal women with osteoporosis and chronic HCV-induced liver disease [75]. In another cohort of HCV mono-infected patients, antiviral therapy with PEG-IFN led to significant on-treatment increases in lumbar spine and hip BMD and reduction in serologic markers of bone resorption irrespective of subsequent treatment response [76].

The impact of anti-HCV therapy with pegylated interferon and ribavirin on bone turnover among HIV/HCV co-infected patients was recently investigated to explore the relative effect

of HCV virologic control and the use of pegylated interferon on bone health. Combination pegylated interferon and ribavirin treatment resulted in approximately 40% decline in the marker of bone resorption, determined by collagen type 1 cross-linked C-telopeptide, by week 12, with a greater decline observed among patients achieving HCV RNA suppression [77]. In another small prospective study of 36 non-cirrhotic HCV patients, treatment with pegylated interferon was associated with decreased levels of the bone turnover marker urine deoxypyridinoline and subsequent increased BMD [78].

These data suggest that successful treatment of chronic HCV could result in improvements in HCV-associated bone fragility. However, it remains unclear whether these declines in BTM are pegylated interferon-related or will be observed with current interferon-free direct-acting antiviral regimens. It is also unknown if these changes post-treatment are durable and if they will lead to improvements in BMD or TBS. Given the significantly increased fracture risk associated with chronic HCV, improvement of bone health could be a significant added advantage of antiviral therapy for chronic HCV infection.

Conclusions

HIV/HCV co-infection is associated with significantly increased fracture risk, even in the absence of advanced hepatitis fibrosis or cirrhosis. However, the mechanisms for the low BMD and increased risk in this setting have not been fully elucidated. New tools to assess bone quality, such as the trabecular bone score, pQCT, and in vivo microindentation, may help improve understanding of the mechanisms of HCV-associated skeletal fragility in HIV-infected persons. Additional studies are needed to determine the effects of anti-osteoporosis medications and direct-acting antivirals for the treatment of chronic HCV infection on HIV/HCV co-infected patients' bone health.

Acknowledgments

We would like to thank Drs. Irfan Farukhi and Geri Brown from the VA North Texas Department of Nuclear Medicine and Division of Gastro-enterology and Hepatology, respectively, for their assistance with the studies described.

Financial support and sponsorship:

This work was funded by VA MERIT grant I01 CX000418-01A1 and by Award Number U01AI068636 from the National Institute of Allergy and Infectious Diseases and supported by National Institute of Mental Health (NIMH), National Institute of Dental and Craniofacial Research (NIDCR). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Veterans Health Administration, the National Institute of Allergy and Infectious Diseases or the National Institutes of Health.

References

1. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. Aids. 2006; 20:2165–2174. [PubMed: 17086056]
2. Maalouf NM, Zhang S, Drechsler H, Brown GR, Tebas P, Bedimo R. Hepatitis C co-infection and severity of liver disease as risk factors for osteoporotic fractures among HIV-infected patients. J Bone Miner Res. 2013; 28:2577–2583. [PubMed: 23677838]
3. Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. J Clin Endocrinol Metab. 2008; 93:3499–3504. [PubMed: 18593764]

4. McComsey GA, Tebas P, Shane E, Yin MT, Overton ET, Huang JS, Aldrovandi GM, Cardoso SW, Santana JL, Brown TT. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. Clin Infect Dis. 2010; 51:937–946. [PubMed: 20839968]

5. Sherman KE, Rouster SD, Chung RT, Rajicic N. Hepatitis C Virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. Clin Infect Dis. 2002; 34:831–837. [PubMed: 11833007]

6. Lo Re V 3rd, Volk J, Newcomb CW, Yang YX, Freeman CP, Hennessy S, Kostman JR, Tebas P, Leonard MB, Localio AR. Risk of hip fracture associated with hepatitis C virus infection and hepatitis C/human immunodeficiency virus coinfection. Hepatology. 2012; 56:1688–1698. [PubMed: 22619086]

7. Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS. 2012; 26:825–831. [PubMed: 22301411]

8. Hansen AB, Gerstoft J, Kronborg G, Larsen CS, Pedersen C, Pedersen G, Obel N. Incidence of low and high-energy fractures in persons with and without HIV infection: a Danish population-based cohort study. AIDS. 2012; 26:285–293. [PubMed: 22095195]

9. Staples CT Jr, Rimland D, Dudas D. Hepatitis C in the HIV (human immunodeficiency virus) Atlanta V.A (Veterans Affairs Medical Center) Cohort Study (HAVACS): the effect of coinfection on survival. Clin Infect Dis. 1999; 29:150–154. [PubMed: 10433578]

10. Solomon SS, Srikrishnan AK, Mehta SH, Vasudevan CK, Murugavel KG, Thamburaj E, Anand S, Kumar MS, Latkin C, Solomon S, et al. High prevalence of HIV, HIV/hepatitis C virus coinfection, and risk behaviors among injection drug users in Chennai, India: a cause for concern. J Acquir Immune Defic Syndr. 2008; 49:327–332. [PubMed: 18845962]

11. Lo Re V 3rd, Kallan MJ, Tate JP, Localio AR, Lim JK, Goetz MB, Klein MB, Rimland D, Rodriguez-Barradas MC, Butt AA, et al. Hepatic decompensation in antiretroviral-treated patients co-infected with HIV and hepatitis C virus compared with hepatitis C virus-monoinfected patients: a cohort study. Ann Intern Med. 2014; 160:369–379. [PubMed: 24723077]

12. Chen TY, Ding EL, Seage GR Iii, Kim AY. Meta-analysis: increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression. Clin Infect Dis. 2009; 49:1605–1615. [PubMed: 19842982]

*13. Dong HV, Cortes YI, Shiau S, Yin MT. Osteoporosis and fractures in HIV/hepatitis C virus coinfection: a systematic review and meta-analysis. AIDS. 2014; 28:2119–2131. Meta-analysis of studies reporting BMD and fracture risk in HIV/HCV co-infected patients vs controls. [PubMed: 24977441]

*14. O'Neill TJ, Rivera L, Struchkov V, Zaheen A, Thein HH. The effect of HIV-hepatitis C co-infection on bone mineral density and fracture: a meta-analysis. PLoS One. 2014; 9:e101493. Meta-analysis of studies reporting BMD and fracture risk in HIV/HCV co-infected patients vs controls. [PubMed: 25033046]

15. Womack JA, Goulet JL, Gibert C, Brandt C, Chang CC, Gulanski B, Fraenkel L, Mattocks K, Rimland D, Rodriguez-Barradas MC, et al. Increased risk of fragility fractures among HIV infected compared to uninfected male veterans. PLoS One. 2011; 6:e17217. [PubMed: 21359191]

16. Young B, Dao CN, Buchacz K, Baker R, Brooks JT. Investigators HIVOS. Increased rates of bone fracture among HIV-infected persons in the HIV Outpatient Study (HOPS) compared with the US general population, 2000–2006. Clin Infect Dis. 2011; 52:1061–1068. [PubMed: 21398272]

17. Yin MT, Kendall MA, Wu X, Tassiopoulos K, Hochberg M, Huang JS, Glesby MJ, Bolivar H, McComsey GA. Fractures after antiretroviral initiation. AIDS. 2012; 26:2175–2184. [PubMed: 22951635]

18. Yin MT, Shi Q, Hoover DR, Anastos K, Sharma A, Young M, Levine A, Cohen MH, Shane E, Golub ET, et al. Fracture incidence in HIV-infected women: results from the Women's Interagency HIV Study. Aids. 2010; 24:2679–2686. [PubMed: 20859192]

19. Leslie WD, Bernstein CN, Leboff MS. AGA technical review on osteoporosis in hepatic disorders. Gastroenterology. 2003; 125:941–966. [PubMed: 12949738]

20. Schiefke I, Fach A, Wiedmann M, Aretin AV, Schenker E, Borte G, Wiese M, Moessner J. Reduced bone mineral density and altered bone turnover markers in patients with non-cirrhotic

chronic hepatitis B or C infection. World J Gastroenterol. 2005; 11:1843–1847. [PubMed: 15793878]

21. Brown TT, Chen Y, Currier JS, Ribaudo HJ, Rothenberg J, Dube MP, Murphy R, Stein JH, McComsey GA. Body composition, soluble markers of inflammation, and bone mineral density in antiretroviral therapy-naive HIV-1-infected individuals. J Acquir Immune Defic Syndr. 2013; 63:323–330. [PubMed: 23591634]
22. Rouillard S, Lane NE. Hepatic osteodystrophy. Hepatology. 2001; 33:301–307. [PubMed: 11124849]
23. van Vonderen MG, Lips P, van Agtmael MA, Hassink EA, Brinkman K, Geerlings SE, Sutinen J, Ristola M, Danner SA, Reiss P. First line zidovudine/lamivudine/lopinavir/ritonavir leads to greater bone loss compared to nevirapine/lopinavir/ritonavir. AIDS. 2009; 23:1367–1376. [PubMed: 19424051]
24. Stellbrink HJ, Orkin C, Arribas JR, Compston J, Gerstoft J, Van Wijngaerden E, Lazzarin A, Rizzardini G, Sprenger HG, Lambert J, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. Clin Infect Dis. 2010; 51:963–972. [PubMed: 20828304]
25. McComsey GA, Kitch D, Daar ES, Tierney C, Jahed NC, Tebas P, Myers L, Melbourne K, Ha B, Sax PE. Bone Mineral Density and Fractures in Antiretroviral-Naive Persons Randomized to Receive Abacavir-Lamivudine or Tenofovir Disoproxil Fumarate-Emtricitabine Along With Efavirenz or Atazanavir-Ritonavir: AIDS Clinical Trials Group A5224s, a Substudy of ACTG A5202. J Infect Dis. 2011; 203:1791–1801. [PubMed: 21606537]
26. Anastos K, Lu D, Shi O, Mulligan K, Tien PC, Freeman R, Cohen MH, Justman J, Hessol NA. The association of bone mineral density with HIV infection and antiretroviral treatment in women. Antivir Ther. 2007; 12:1049–1058. [PubMed: 18018763]
27. Yin MT, McMahon DJ, Ferris DC, Zhang CA, Shu A, Staron R, Colon I, Laurence J, Dobkin JF, Hammer SM, et al. Low bone mass and high bone turnover in postmenopausal human immunodeficiency virus-infected women. J Clin Endocrinol Metab. 2010; 95:620–629. [PubMed: 19965927]
28. Lawson-Ayayi S, Cazanave C, Kpozehouen A, Barthe N, Mehsen N, Hessamfar M, Dupon M, Dabis F, Neau D. Chronic viral hepatitis is associated with low bone mineral density in HIV-infected patients, ANRS CO 3 Aquitaine Cohort. J Acquir Immune Defic Syndr. 2013; 62:430–435. [PubMed: 23296138]
*29. Bedimo R, Cutrell J, Zhang S, Drechsler H, Gao A, Brown G, Farukhi I, Castanon R, Tebas P, Maalouf NN. Mechanisms of bone disease in HIV and hepatitis C virus: impact of bone turnover, tenofovir exposure, sex steroids and severity of liver disease. AIDS. 2015 Cohort study comparing bone mineral density, bone turnover markers, sex steroids and IGF-1 in men who were HCV/HIV co-infected vs. HCV mono-infected, HIV mono-infected and uninfected controls.
30. Lo Re V 3rd, Guaraldi G, Leonard MB, Localio AR, Lin J, Orlando G, Zirilli L, Rochira V, Kostman JR, Tebas P. Viral hepatitis is associated with reduced bone mineral density in HIV-infected women but not men. AIDS. 2009; 23:2191–2198. [PubMed: 19779322]
31. Sharma A, Flom PL, Weedon J, Klein RS. Prospective study of bone mineral density changes in aging men with or at risk for HIV infection. AIDS. 2010; 24:2337–2345. [PubMed: 20683316]
32. Sharma A, Cohen HW, Freeman R, Santoro N, Schoenbaum EE. Prospective evaluation of bone mineral density among middle-aged HIV-infected and uninfected women: Association between methadone use and bone loss. Maturitas. 2011; 70:295–301. [PubMed: 21944566]
*33. Lo Re V 3rd, Lynn K, Stumm ER, Long J, Nezamzadeh MS, Baker JF, Hoofnagle AN, Kapalko AJ, Mounzer K, Zemel BS, et al. Structural Bone Deficits in HIV/HCV-Coinfected, HCV-Monoinfected, and HIV-Monoinfected Women. J Infect Dis. 2015; 212:924–933. Cross-sectional study evaluating skeletal parameters using tibia peripheral quantitative computed tomography in ART-treated HIV/HCV co-infected, HCV mono-infected, and ART-treated HIV mono-infected women. [PubMed: 25754980]
34. Gilbert L, He X, Farmer P, Rubin J, Drissi H, van Wijnen AJ, Lian JB, Stein GS, Nanes MS. Expression of the osteoblast differentiation factor RUNX2 (Cbfa1/AML3/Pebp2alpha A) is inhibited by tumor necrosis factor-alpha. J Biol Chem. 2002; 277:2695–2701. [PubMed: 11723115]

35. Radeff JM, Nagy Z, Stern PH. Involvement of PKC-beta in PTH, TNF-alpha, and IL-1 beta effects on IL-6 promoter in osteoblastic cells and on PTH-stimulated bone resorption. Exp Cell Res. 2001; 268:179–188. [PubMed: 11478844]

36. Hansen AB, Gerstoft J, Kronborg G, Pedersen C, Sorensen HT, Obel N. Mortality in siblings of patients coinfected with HIV and hepatitis C virus. J Infect Dis. 2007; 195:230–235. [PubMed: 17191168]

37. Hansen AB, Lohse N, Gerstoft J, Kronborg G, Laursen A, Pedersen C, Sorensen HT, Obel N. Cause-specific excess mortality in siblings of patients co-infected with HIV and hepatitis C virus. PLoS One. 2007; 2:e738. [PubMed: 17710138]

38. El-Maouche D, Mehta SH, Sutcliffe C, Higgins Y, Torbenson MS, Moore RD, Thomas DL, Sulkowski MS, Brown TT. Controlled HIV viral replication, not liver disease severity associated with low bone mineral density in HIV/HCV co-infection. J Hepatol. 2011; 55:770–776. [PubMed: 21338640]

39. Tenorio AR, Zheng Y, Bosch RJ, Krishnan S, Rodriguez B, Hunt PW, Plants J, Seth A, Wilson CC, Deeks SG, et al. Soluble markers of inflammation and coagulation but not T-cell activation predict non-AIDS-defining morbid events during suppressive antiretroviral treatment. J Infect Dis. 2014; 210:1248–1259. [PubMed: 24795473]

40. Zampino R, Marrone A, Restivo L, Guerrera B, Sellitto A, Rinaldi L, Romano C, Adinolfi LE. Chronic HCV infection and inflammation: Clinical impact on hepatic and extra-hepatic manifestations. World J Hepatol. 2013; 5:528–540. [PubMed: 24179612]

41. Dubner SE, Shults J, Baldassano RN, Zemel BS, Thayu M, Burnham JM, Herskovitz RM, Howard KM, Leonard MB. Longitudinal assessment of bone density and structure in an incident cohort of children with Crohn's disease. Gastroenterology. 2009; 136:123–130. [PubMed: 19026647]

42. Tsampalieros A, Lam CK, Spencer JC, Thayu M, Shults J, Zemel BS, Herskovitz RM, Baldassano RN, Leonard MB. Long-term inflammation and glucocorticoid therapy impair skeletal modeling during growth in childhood Crohn disease. J Clin Endocrinol Metab. 2013; 98:3438–3445. [PubMed: 23690309]

43. Aeberli D, Eser P, Bonel H, Widmer J, Caliezi G, Varisco PA, Moller B, Villiger PM. Reduced trabecular bone mineral density and cortical thickness accompanied by increased outer bone circumference in metacarpal bone of rheumatoid arthritis patients: a cross-sectional study. Arthritis Res Ther. 2010; 12:R119. [PubMed: 20565921]

44. Gilbert L, He X, Farmer P, Boden S, Kozlowski M, Rubin J, Nanes MS. Inhibition of osteoblast differentiation by tumor necrosis factor-alpha. Endocrinology. 2000; 141:3956–3964. [PubMed: 11089525]

45. Lee SE, Chung WJ, Kwak HB, Chung CH, Kwack KB, Lee ZH, Kim HH. Tumor necrosis factor-alpha supports the survival of osteoclasts through the activation of Akt and ERK. J Biol Chem. 2001; 276:49343–49349. [PubMed: 11675379]

46. Villar LM, Del Campo JA, Ranchal I, Lampe E, Romero-Gomez M. Association between vitamin D and hepatitis C virus infection: a meta-analysis. World J Gastroenterol. 2013; 19:5917–5924. [PubMed: 24124339]

*47. Guzman-Fulgencio M, Garcia-Alvarez M, Berenguer J, Jimenez-Sousa MA, Cosin J, Pineda-Tenor D, Carrero A, Aldamiz T, Alvarez E, Lopez JC, et al. Vitamin D deficiency is associated with severity of liver disease in HIV/HCV coinfected patients. J Infect. 2014; 68:176–184. In this cross-sectional study in 174 HIV/HCV co-infected patients, vitamin D deficiency was prevalent and associated with severity of liver disease. [PubMed: 24184809]

48. Terrier B, Carrat F, Geri G, Pol S, Piroth L, Halfon P, Poynard T, Souberbielle JC, Cacoub P. Low 25-OH vitamin D serum levels correlate with severe fibrosis in HIV-HCV co-infected patients with chronic hepatitis. J Hepatol. 2011; 55:756–761. [PubMed: 21334402]

49. Di Carlo P, Siracusa L, Mazzola G, Colletti P, Soresi M, Giannitrapani L, Li Vecchi V, Montalto G. Vitamin D and Osteoporosis in HIV/HCV Coinfected Patients: A Literature Review. Int J Endocrinol. 2015; 2015:969040. [PubMed: 26273302]

*50. Lai JC, Shoback DM, Zipperstein J, Lizaola B, Tseng S, Terrault NA. Bone Mineral Density, Bone Turnover, and Systemic Inflammation in Non-cirrhotics with Chronic Hepatitis C. Dig Dis Sci. 2015; 60:1813–1819. Among middle aged HCV-infected patients without cirrhosis, low

BMD was prevalent and associated with elevated P1NP levels but not with inflammatory markers. [PubMed: 25563723]

51. Hock JM, Centrella M, Canalis E. Insulin-like growth factor I has independent effects on bone matrix formation and cell replication. Endocrinology. 1988; 122:254–260. [PubMed: 3335207]
52. Zhao G, Monier-Faugere MC, Langub MC, Geng Z, Nakayama T, Pike JW, Chernausek SD, Rosen CJ, Donahue LR, Malluche HH, et al. Targeted overexpression of insulin-like growth factor I to osteoblasts of transgenic mice: increased trabecular bone volume without increased osteoblast proliferation. Endocrinology. 2000; 141:2674–2682. [PubMed: 10875273]
53. Crane JL, Cao X. Function of matrix IGF-1 in coupling bone resorption and formation. J Mol Med (Berl). 2014; 92:107–115. [PubMed: 24068256]
54. Leder BZ, LeBlanc KM, Schoenfeld DA, Eastell R, Finkelstein JS. Differential effects of androgens and estrogens on bone turnover in normal men. J Clin Endocrinol Metab. 2003; 88:204–210. [PubMed: 12519853]
55. Moller S, Juul A, Becker U, Flyvbjerg A, Skakkebaek NE, Henriksen JH. Concentrations, release, and disposal of insulin-like growth factor (IGF)-binding proteins (IGFBP), IGF-I, and growth hormone in different vascular beds in patients with cirrhosis. J Clin Endocrinol Metab. 1995; 80:1148–1157. [PubMed: 7536200]
56. Leskela HV, Olkku A, Lehtonen S, Mahonen A, Koivunen J, Turpeinen M, Uusitalo J, Pelkonen O, Kangas L, Selander K, et al. Estrogen receptor alpha genotype confers interindividual variability of response to estrogen and testosterone in mesenchymal-stem-cell-derived osteoblasts. Bone. 2006; 39:1026–1034. [PubMed: 16782420]
57. Cutrell J, Maalouf NM, Zhang S, Drechsler H, Gao A, Tebas P, Bedimo R. Mechanism of Bone Disease in HIV and HCV: Impact of Tenofovir Exposure and Severity of Liver Disease. Conference on Retroviruses and Opportunistic Infections; Boston, Massachusetts. 2014. Abstract 1430
58. Lo Re V 3rd, Lynn K, Stumm ER, Long J, Nezamzadeh MS, Baker JF, Hoofnagle AN, Kapalko AJ, Mounzer K, Zemel BS, et al. Structural Bone Deficits in HIV/HCV-Coinfected, HCV-Monoinfected, and HIV-Monoinfected Women. J Infect Dis. 2015; 212:924–933. [PubMed: 25754980]
*59. Silva BC, Leslie WD, Resch H, Lamy O, Lesnyak O, Binkley N, McCloskey EV, Kanis JA, Bilezikian JP. Trabecular bone score: a noninvasive analytical method based upon the DXA image. J Bone Miner Res. 2014; 29:518–530. Recent review on trabecular bone score as an emerging technology for fracture risk assessment. [PubMed: 24443324]
60. Muschitz C, Kocijan R, Haschka J, Pahr D, Kaider A, Pietschmann P, Hans D, Muschitz GK, Fahrleitner-Pammer A, Resch H. TBS reflects trabecular microarchitecture in premenopausal women and men with idiopathic osteoporosis and low-traumatic fractures. Bone. 2015; 79:259–266. [PubMed: 26092650]
61. Leslie WD, Krieg MA, Hans D. Manitoba Bone Density P. Clinical factors associated with trabecular bone score. J Clin Densitom. 2013; 16:374–379. [PubMed: 23452869]
62. Eller-Vainicher C, Morelli V, Ulivieri FM, Palmieri S, Zhukouskaya VV, Cairoli E, Pino R, Naccarato A, Scillitani A, Beck-Peccoz P, et al. Bone quality, as measured by trabecular bone score in patients with adrenal incidentalomas with and without subclinical hypercortisolism. J Bone Miner Res. 2012; 27:2223–2230. [PubMed: 22549969]
63. Dhaliwal R, Cibula D, Ghosh C, Weinstock RS, Moses AM. Bone quality assessment in type 2 diabetes mellitus. Osteoporos Int. 2014; 25:1969–1973. [PubMed: 24718377]
64. Kim JH, Choi HJ, Ku EJ, Kim KM, Kim SW, Cho NH, Shin CS. Trabecular bone score as an indicator for skeletal deterioration in diabetes. J Clin Endocrinol Metab. 2015; 100:475–482. [PubMed: 25368976]
65. Martinez E. Role of antiretroviral therapy on bone mass and bone texture. 17th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV; Barcelona, Spain. 2015.
66. Vilayphiou N, Boutroy S, Sornay-Rendu E, Van Rietbergen B, Chapurlat R. Age-related changes in bone strength from HR-pQCT derived microarchitectural parameters with an emphasis on the role of cortical porosity. Bone. 2015

67. Burghardt AJ, Issever AS, Schwartz AV, Davis KA, Masharani U, Majumdar S, Link TM. High-resolution peripheral quantitative computed tomographic imaging of cortical and trabecular bone microarchitecture in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2010; 95:5045–5055. [PubMed: 20719835]

*68. Yin MT, Shu A, Zhang CA, Boutroy S, McMahon DJ, Ferris DC, Colon I, Shane E. Trabecular and cortical microarchitecture in postmenopausal HIV-infected women. Calcif Tissue Int. 2013; 92:557–565. This report identifies lower cortical thickness and area at the tibia by high resolution peripheral quantitative CT to significantly differ between HIV-infected vs uninfected postmenopausal women. [PubMed: 23460340]

69. Randall C, Bridges D, Guerri R, Nogues X, Puig L, Torres E, Mellibovsky L, Hoffseth K, Stalbaum T, Srikanth A, et al. Applications of a New Handheld Reference Point Indentation Instrument Measuring Bone Material Strength. J Med Device. 2013; 7:410051–410056. [PubMed: 24115973]

70. Farr JN, Drake MT, Amin S, Melton LJ 3rd, McCready LK, Khosla S. In vivo assessment of bone quality in postmenopausal women with type 2 diabetes. J Bone Miner Res. 2014; 29:787–795. [PubMed: 24123088]

71. Bauer DC, Garnero P, Hochberg MC, Santora A, Delmas P, Ewing SK, Black DM. Fracture Intervention Research G. Pretreatment levels of bone turnover and the antifracture efficacy of alendronate: the fracture intervention trial. J Bone Miner Res. 2006; 21:292–299. [PubMed: 16418785]

72. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R. National Osteoporosis F. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. 2014; 25:2359–2381. [PubMed: 25182228]

*73. Brown TT, Hoy J, Borderi M, Guaraldi G, Renjifo B, Vescini F, Yin MT, Powderly WG. Recommendations for evaluation and management of bone disease in HIV. Clin Infect Dis. 2015; 60:1242–1251. Updated recommendations for osteoporosis evaluation and treatment in HIV. [PubMed: 25609682]

74. McCloskey EV, Oden A, Harvey NC, Leslie WD, Hans D, Johansson H, Barkmann R, Boutroy S, Brown J, Chapurlat R, et al. A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. J Bone Miner Res. 2015

75. Arase Y, Suzuki F, Suzuki Y, Akuta N, Kobayashi M, Sezaki H, Hosaka T, Kawamura Y, Yatsuji H, Hirakawa M, et al. Virus clearance reduces bone fracture in postmenopausal women with osteoporosis and chronic liver disease caused by hepatitis C virus. J Med Virol. 2010; 82:390–395. [PubMed: 20087925]

76. Hofmann WP, Kronenberger B, Bojunga J, Stamm B, Herrmann E, Bucker A, Mihm U, von Wagner M, Zeuzem S, Sarrazin C. Prospective study of bone mineral density and metabolism in patients with chronic hepatitis C during pegylated interferon alpha and ribavirin therapy. J Viral Hepat. 2008; 15:790–796. [PubMed: 18673425]

*77. Bedimo R, Kang M, Tebas P, Overton ET, Hollabaugh K, McComsey G, Bhattacharya D, Evans C, Brown TT, Taiwo B. Effects of Pegylated Interferon/Ribavirin on Bone Turnover Markers in HIV/Hepatitis C Virus-Coinfected Patients. AIDS Res Hum Retroviruses. 2015 In this study of HIV/HCV-coinfected patients, pegylated interferon-α and ribavirin treatment of HCV markedly reduced bone turnover.

*78. Redondo-Cerezo E, Casado-Caballero F, Martin-Rodriguez JL, Hernandez-Quero J, Escobar-Jimenez F, Gonzalez-Calvin JL. Bone mineral density and bone turnover in non-cirrhotic patients with chronic hepatitis C and sustained virological response to antiviral therapy with peginterferon-alfa and ribavirin. Osteoporos Int. 2014; 25:1709–1715. Another study showing that treatment of HCV led to improvement in bone mass and normalization in bone turnover. [PubMed: 24676843]

Key Points

1. HCV coinfection is associated with a significant increased fracture risk among HIV-infected patients. The deleterious impact of chronic HCV on BMD and fracture risk occurs even in the absence of advanced liver fibrosis or cirrhosis.
2. The mechanisms(s) underlying HCV-associated increased risk are incompletely understood. Unlike HIV, HCV doesn't seem to be associated with increased bone turnover.
3. New tools to assess bone quality, including the trabecular bone score, high resolution peripheral quantitative computed tomography, and in vivo microindentation, may help improve understanding of the mechanisms of HCV-associated skeletal fragility.
4. Treatment of HCV might result in improvements in bone health, but data on the effect of newer regimens with direct-acting antivirals is lacking.

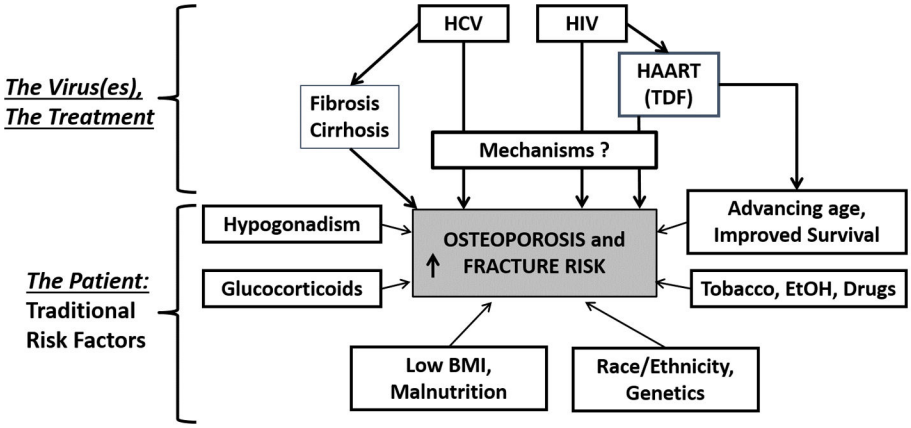

Figure 1. Fracture Risk in HIV and HCV

Risk factors attributable to the viruses (HIV and HCV), the treatment (antiretroviral therapy) and the patient ("traditional" fracture risk factors).

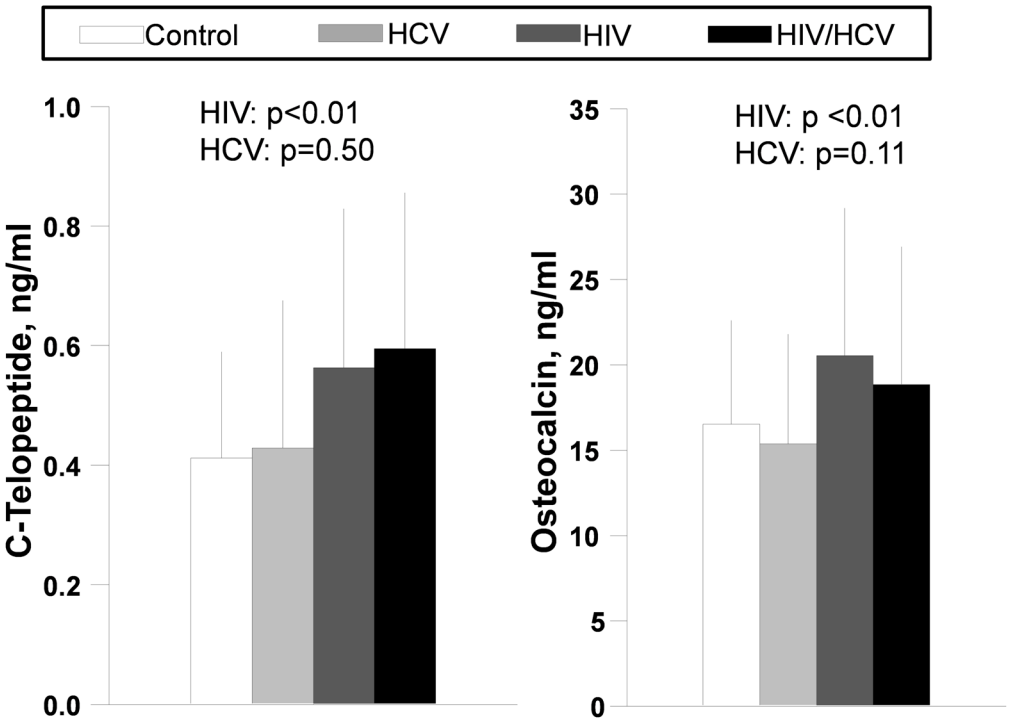

Figure 2. Evaluation of bone turnover markers, by HIV/chronic hepatitis C virus infection status
C-telopeptide (marker of bone resorption) and Osteocalcin (marker of bone formation).

Table 1

Studies evaluating the risk of fracture among HIV/chronic hepatitis C virus co-infected patients.

Study	Study Population	Fracture Type/Site	No. of Patients, by HIV/HCV Status	Incidence Rate of Fracture	Risk of Fracture (Hazard Ratio [95% CI])
Lo Re (2012) [3]	Men, women	Hip	HCV/HIV (N=36,950) HCV (N=276,901) HIV (N=95,827) Uninfected (N=3,110,904)	3.06/1000 patient-years 2.69/1000 patient-years 1.95/1000 patient-years 1.29/1000 patient-years	HCV/HIV vs HCV: 1.38 (1.25–1.53) HCV/HIV vs HIV: Female: 1.76 (1.44–2.16) Male: 1.36 (1.20–1.55) HCV/HIV vs Uninfected: Female: 2.65 (2.21–3.17) Male: 2.20 (1.97–2.47).
Maalouf (2013) [12]	Men	Hip, wrist, vertebra	HIV/HCV (N=17,762) HIV (N=38,898)	2.57/1000 patient-years 2.07/1000 patient-years	HCV/HIV vs HIV: 1.24
Hansen (2012)[5]	General population	Low-energy fractures	HIV/HCV (N=851) HIV (N=4,455) Uninfected (N=26,530)	17.7/1000 patient-years 7.4/1000 patient-years 4.8/1000 patient-years	HCV/HIV vs. uninfected: 3.8 (3.0–4.9)
Yin (2010) [16]	Post-menopausal Women	Self-reported fragility and non-fragility fractures	HIV/HCV (N=438) HIV(N=1,290) Uninfected (N=567)	NR	HCV/HIV vs. HIV: 2.0 (1.49–2.70)
Young (2011) [14]	Men, women	All fractures	HIV/HCV (NR) * HIV (NR) *	NR	HCV/HIV vs. HIV: 2.18 (1.12–4.26)
Yin (2012) [15]	Peri-menopausal women	Self-reported fragility and non-fragility fractures	HIV/HCV (N=434) HIV(N=4,206)	NR	HCV/HIV vs. HIV: 2.2 (1.2–4.1)
Yin (2010) [16]	Post-menopausal Women	Self-reported fragility and non-fragility fractures	HIV/HCV (N=438) HIV(N=1,290) Uninfected (N=567)	NR	HCV/HIV vs. HIV: 2.0 (1.49–2.70)

Abbreviations: CI=confidence interval; HCV=hepatitis C virus; NR=not reported.

* Total study population was 5,826 HIV-infected patients. Number of HCV-co-infected not provided in this report.