Mechanisms of Non-AIDS Complications of HIV: Role of Hepatitis C Co-Infection

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Dr. Bedimo is the Chief of the Infectious Diseases Section at the VA North Texas Health Care System. His clinical practice includes HIV care and in-patient and outpatient general infectious diseases consultations. His research interests included the epidemiology and determinants of chronic complications of HIV disease and antiretroviral therapy, with special interest on the role of hepatitis C co-infection on HIV-associated morbidity.

Purpose and Overview

The widespread availability and efficacy of antiretroviral therapy has led to a dramatic drop in the mortality rate of HIV-infected patients. With increased survival of these patients, there has been a significant shift in the causes of morbidity and mortality from AIDS-defining (infections and AIDS malignancies) to non-AIDS-defining conditions, principally cardiovascular diseases, liver-related complications, and non-AIDS malignancies. Osteoporosis and increased fracture risk is a largely unrecognized cause of morbidity in these patients.

The pathogenesis of these non-AIDS complications is incompletely understood. It likely involves patient factors (over-representation of "traditional" risk factors, direct and direct effects of HIV infection and HIV-associated inflammation and immune activation, and effects of antiretroviral therapy. HCV co-infection (present in up to a third of HIV patients) likely contributes to the causality of many of these complications.

We will discuss the potential contribution of the traditional risk factors, HIV disease itself and antiretroviral therapy, as well as HCV co-infection in the mechanism of the non-AIDS complications. Further emphasis will be put on cardiovascular disease and osteoporosis to illustrate these non-AIDS complications in the aging HIV population.

Any significant improvement in the morbidity and mortality of HIV-infected patients on HAART will require better understanding of the pathogenesis of non-AIDS complications, their assessment and management.

Learning Objectives

- To delineate the trends in morbidity and mortality in HIV Disease and the role of chronic complications
- To discuss the proposed pathophysiologic mechanisms for chronic complications of HIV
- To evaluate the role of hepatitis C co-infection in chronic complications of HIV

I. Trends in Morbidity and Mortality: The Changing Face of HIV Disease

a. Increased survival and aging of HIV-infected patients

The survival of HIV-infected patients has significantly improved following the discovery and widespread use of protease inhibitors (PI) in the context of combination antiretroviral therapy, known as HAART [1, 2]. During the second half of the 1990's decade, mortality of HIV-infected patients in the U.S. and Europe dropped to less than 1/3 of the rate of the previous half-decade [1-3], and continued declines observed in the 2000's [4].
Furthermore the HIV population is significantly aging. It is expected that by 2015, more than one-half of all HIV-infected individuals in the United States will be aged >50 years [5] with expected increase in age-related morbidities such as cardiovascular diseases, cancers and accelerated bone loss [6]. By 2007, the largest number of new HIV/AIDS diagnoses was for persons aged 40–44 years, who accounted for 15% of all HIV/AIDS cases diagnosed during that year [7].

b. Trends in causes of death among persons with HIV/AIDS in the HAART era

The increase in overall survival of HIV-infected patients has been associated with a shift in underlying cause of death among these patients, with lesser representation of "AIDS-related causes" (opportunistic infections and AIDS-defining cancers) and greater representation of "non-AIDS-related" deaths. Between 1999 and 2004, the proportion of deaths due to non–AIDS-related causes increased by 33% in HIV-infected patients in New York [8]. A French cohort observed similar trends between 2000 and 2005. In that study, the proportion of underlying causes of death due to AIDS decreased (36% in 2005 vs. 47% in 2000). The non-AIDS causes of death increasing in proportion included non-AIDS cancers (17% vs. 11%), chronic liver disease (15% vs. 13%), and cardiovascular disease (CVD: 8% vs. 7%) [4]. Others include HIV-associated neurocognitive disorders, chronic kidney disease and osteoporosis. The causes of the persistence of these chronic complications despite optimal antiretroviral therapy are subject of intensive investigation, and some controversy.

This greater representation of non-AIDS complications – and the still lower survival of HIV patients compared to the general population – suggest that further reductions in morbidity and mortality of HIV-infected patients will require a greater understanding of the mechanisms and factors associated with these non-AIDS complications and a shift to a more comprehensive health care approach including enhanced screening for malignancy and heart disease as well as preventive measures for substance abuse, liver disease, bone disease, and other metabolic complications.

II. Potential Mechanisms of Non-AIDS Complications: The Patient, The Virus (or Viruses) and the Treatment

The pathogenic mechanism(s) of the increased incidence of these non-AIDS (mostly "age-related") complications in HIV-infected patients on stable antiretroviral therapy are incompletely understood. A useful framework to use in elucidating these is to consider the

potentially overlapping contributions of three different factors: 1) **The patient factors**: possible overrepresentations of known ("traditional") risk factors for these non-AIDS complications among HIV-infected patients, such as smoking and other behavioral factors; 2) **The Virus(es):** possible direct or indirect effects of HIV itself, HIV-associated immune dysfunctions, or viral co-infections such as Hepatitis C Virus (HCV); and 3) **The treatment:** possible short- or long-term toxicity of HAART.

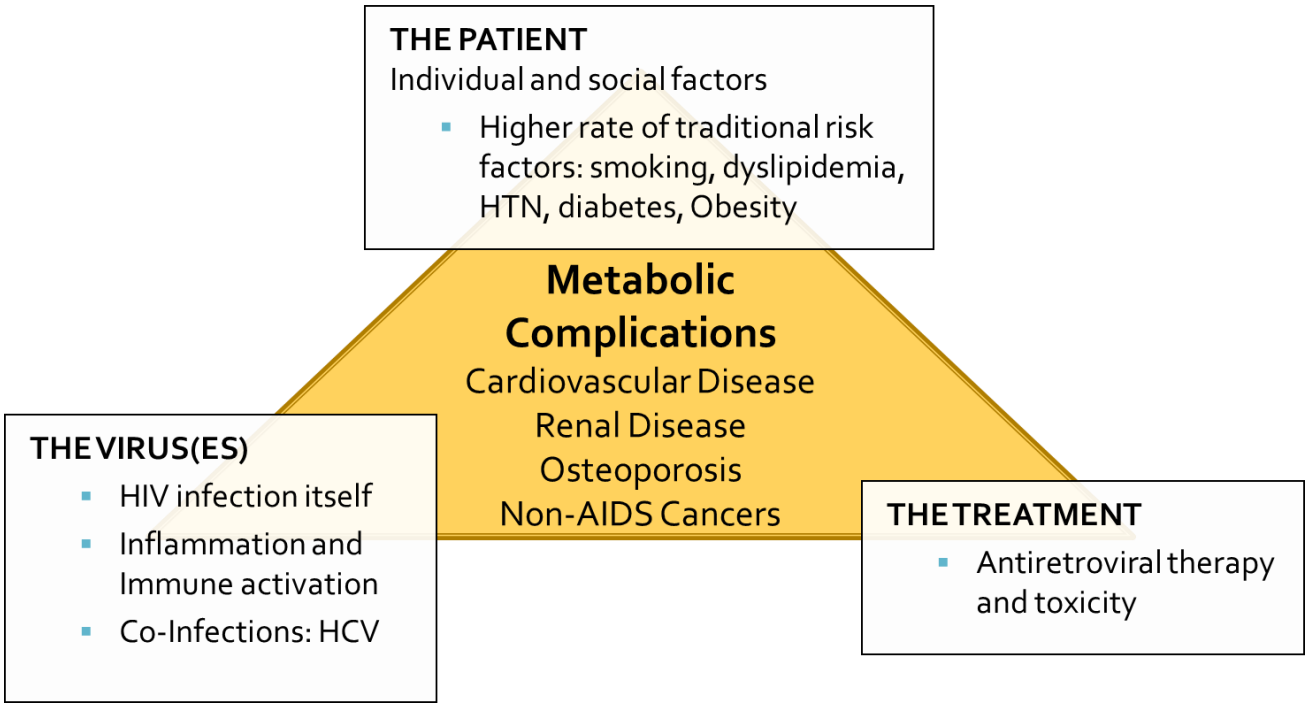


Figure 1: Mechanisms of Non-AIDS Complications of HIV Disease

a. The Patient: Prevalence of "Traditional" Risk Factors in HIV

It has been long recognized that HIV-infected patients have an increased rate of behavioral and lifestyle risk factors (such as smoking or drug use) that predispose them to non-AIDS morbidities. Multiple non-AIDS complications will therefore likely cluster among the same patients. Consistent with this hypothesis, associations exist between decreased bone mineral density (BMD), dyslipidemia and lipodystrophy [9-11], lactic acidosis [12], coronary artery calcification [13], and increased cardiovascular risk [14] among HIV-infected persons.

Furthermore, the effect of these conditions appears to be worse among HIV-infected patients. For instance, smoking has been shown to be associated with higher mortality in the setting of HIV disease than in the general population. In a recent cohort, loss of life-years associated with smoking was twice as high as that associated with HIV; 60% of deaths in HIV patients could be attributable to smoking (compared to 34% in the general population) [15]; and almost 3 of 4 myocardial infarctions among HIV-infected individuals are associated with ever smoking compared to only 1 of 4 MIs among population controls [16].

b. The Virus (or Viruses)

i. HIV: Increased Inflammation and Immune Activation

Immune activation and chronic inflammation are recognized as major component of HIV disease even in patients with optimal virologic suppression. Significant increases in several inflammatory markers have been observed among HIV-infected than uninfected patients. Most of these improve during HAART, but remain significantly higher than in HIV sero-negative subjects [17, 18]. Persistent inflammation and immune activation in patients on long-term suppressive HAART has been associated with increased risk of non-AIDS complications and mortality [19-21].

It remains unclear whether interventions aimed at reducing the level of inflammation would reduce morbidity and mortality from non-AIDS complications among HIV-infected patients on HAART. For instance, cohort studies suggest that 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) significantly decrease the incidence of malignancies [22, 23] and mortality among HIV-infected patients on HAART [24]. A large prospective study (the REPRIEVE trial) is underway to confirm these observations.

ii. Hepatitis C Co-Infection

Fifteen to 30% of all HIV-infected persons in the U.S. are co-infected with HCV. HCV co-infection is also associated with significantly higher levels of markers of inflammation and endothelial dysfunction [25-27]. These might be improved by successful HCV therapy, but are exacerbated by HIV treatment interruption [27]. On the other hand, HIV infection of both hepatocytes and hepatic stellate cells leads to accelerated HCV replication and worsening of HCV-induced hepatic inflammation and fibrosis [28]. Likely as a result of these interactions, HIV infection is associated with accelerated fibrosis progression rate and increased risk of cirrhosis, liver decompensation [29] and hepatocellular carcinoma [30] in HCV patients. HCV co-infection has been associated with the development of chronic kidney disease among HIV-positive patients [31]. However, observational studies have yielded discordant findings regarding HCV's association with increased cardiovascular disease in HIV, with most studies suggesting an increased risk [32-34]. In our VA cohort, we've found an association of HCV infection with increased risk of several non-AIDS complications, including CVD [35, 36], and osteoporotic fractures [37]. These studies will be presented in detail in the next chapters.

iii. Accelerated Aging?

Since many of the changes in innate and adaptive immunity observed in HIV-infected patients are similar to those associated with the ageing process (including increased inflammation and immune activation), HIV infection has been thought to induce a process akin to accelerated aging [38-40]. This appeared to be substantiated by the above-referenced increased risk of the non-AIDS complications among relatively younger HIV-infected patients. However, it remains unclear whether "immune-senescence" – if proven to be present in HIV – is causing an early onset of non-AIDS complications in this population. Analysis of the Veterans Aging Cohort Study (VACS) data found no significant differences in age at incidence of several non-AIDS complications between HIV-infected and non-HIV population [41]. It is possible that

important confounders had not been adjusted for in prior studies that had observed larger age differences [42, 43].

c. The Drugs: Role of HAART on the Risk of Non-AIDS Complications

Given the aging of the HIV population and the over-representation of the non-AIDS complications of HIV disease in older patients, the DHHS guidelines have recently been amended to recommend initiation of antiretroviral therapy in all patients 50 years or older. The theoretical benefit is double: 1) the magnitude of immune recovery on HAART is smaller in older patients [44], so it's better to initiate therapy earlier; 2) antiretroviral therapy decreases HIV-associated inflammation and immune activation, which are thought to be major drivers of these non-AIDS complications. Indeed, in a randomized controlled trial, deferring antiretroviral therapy was associated with an increased risk of mortality from non-AIDS complications [45].

On the other hand, exposure to antiretroviral therapy has been linked to increased risk of cardiovascular disease [46], even if the mechanisms of such increased risk are still incompletely understood. Also, some antiretroviral drugs such as tenofovir have also been associated with increased fracture risk [47] and chronic kidney disease. There are currently few studies that have explored the long-term safety of antiretrovirals in older HIV patients.
In the following sections, we will examine in greater detail the mechanisms of increased cardiovascular risk and bone mineral loss in HIV-infected patients.

III. Cardiovascular Disease in HIV

a. Incidence and Trends

Several database analyses and observational cohort studies have reported a higher incidence of cardiovascular events among HIV-infected patients than HIV-negative controls [48-52]. CVDs now account for 8% to 22% of deaths among HIV-infected patients and this percentage appears to be increasing [2, 4, 53, 54].

However, while the studies mentioned above show a relative increase over time in the proportion of HIV deaths caused by CVD [2, 4], there is to date no documented absolute increase in cardiovascular morbidity or mortality [48]. In fact rates of, and mortality from acute myocardial infarctions (AMI) among HIV patients appear to have either stabilized or to have decreased in the recent years in a number of cohort analyses [4, 49, 55].

b. The Patients: "Traditional" CVD Risk Factors in HIV-Infected Patients

It has already been shown that HIV-infected patients are more likely to smoke than age- and gender-matched controls [56]. Indeed, tobacco smoking appears to not only independently predict HIV infection, but also progression to AIDS [56]. A population-based cohort study in France [57], evaluated the distribution of risk factors for cardiovascular disease in HIV patients. The predicted CAD risk was greater among HIV-infected compared with the HIV-uninfected cohort. However, the estimated attributable risks due to smoking were 65% and 29% for HIV-infected men and women, respectively. Smoking was also the most prevalent

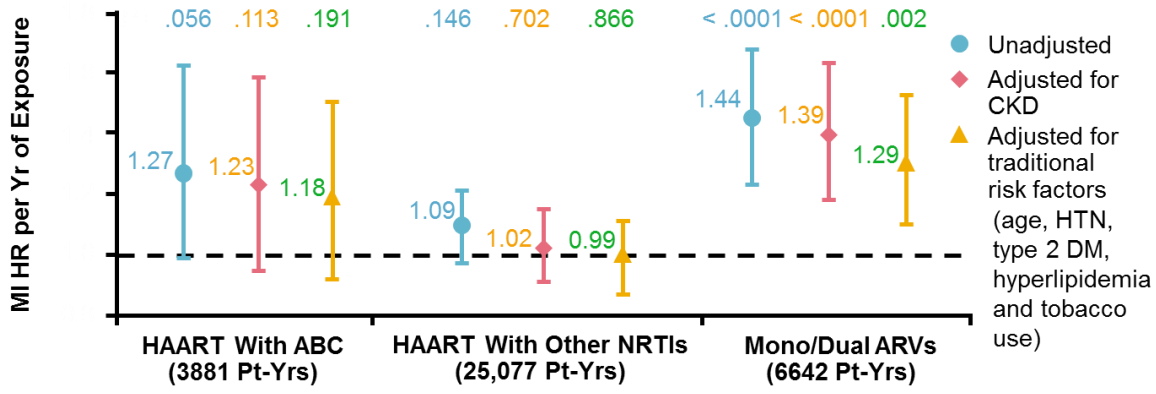
cardiovascular risk factor among HIV-infected patients in the Swiss Cohort [58]. Smoking and other potential lifestyle differences can therefore account for at least part of the excess cardiovascular morbidity, but is not adequately accounted for in the many referenced cohort analyses of the impact of HAART on cardiovascular risk in HIV patients [59, 60].

c. The Treatment: Impact of Antiretroviral Therapy

In a relatively recent meta-analysis by Islam et al, the risk of CVD in HIV-infected patients receiving antiretroviral therapy was found to be 2 times greater than the risk of antiretroviral treatment-naïve HIV-infected patients [46]. Antiretroviral drugs such as protease inhibitors could promote atherogenesis through induction of dyslipidemia, or by increasing CD36-dependent cholesteryl ester accumulation in macrophages [61]. The role of specific antiretroviral drugs has however been significantly controversial. In a European cohort (the D:A:D cohort), abacavir has been associated with a significantly increased risk CVD [62]. The association of abacavir with increased CVD risk has not been consistently observed in other cohorts or clinical trials [48-52, 63]. Whether cumulative exposure to antiretrovirals increases the risk of CVD is further made improbable by the overall decline in CVDs in the HIV population in recent years, despite increased exposure to antiretrovirals [4, 49]. The discrepancy was hypothesized to be due to either better cardiovascular risk management among HIV patients or safer metabolic side-effect profiles of newer antiretroviral drugs [55].

To explore the association of antiretroviral therapy containing ABC with cardiovascular and cerebrovascular events, we utilized Veterans Affairs' Clinical Case Registry (CCR). Rates of myocardial infarctions remained relatively constant from 1996 to 2004. We found a small (not statistically significant) increased risk of CVD associated with abacavir exposure, which was further attenuated by chronic kidney disease (CKD) and other "traditional" CVD risk factors.

- 19,424 HIV patients contributed 76,376 patient-years of follow-up '96 to '04.
- Events during period of observation
  - 278 MIs; rate: 3.69 per 1000 pt-yrs (95% CI: 3.28-4.15)
  - 868 CVAs; rate: 11.68 per 1000 pt-yrs (95% CI: 10.93-12.48)



Bedimo R, et al. Clin Infect Dis. 2011 Jul 1;53(1):84-91.

Figure 2: VA cohort: Cumulative Exposure to Abacavir Not Associated with Increase AMI Risk

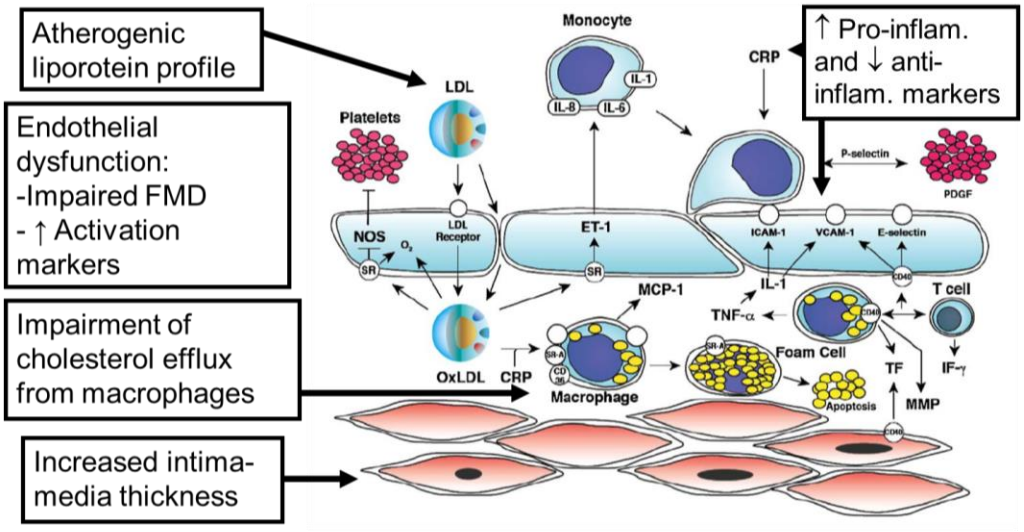
Furthermore, we've shown that both CKD and co-infection with hepatitis C were associated with significantly higher risk of CVD, and these factors were not controlled for in most previous cohorts, including the D:A:D. Finally, there was a significant channeling of HIV patients with CKD to abacavir vs. tenofovir (the other main nucleoside reverse transcriptase inhibitor) because of the increased renal toxicity associated with tenofovir.

d. The viruses

i. HIV Infection, Inflammation and Immune Activation.

As mentioned above, HIV infection is associated with increased inflammation and immune activation that do not completely resolve even with complete virologic suppression on HAART. These are known to be key drivers of atherosclerosis [64]. In the early stages of atherogenesis, chemo-attractants such as MCP-1 help recruit monocytes into the sub-endothelial space where they mature into macrophages. They then uptake oxidized LDL, transforming into foam cells and driving atheroma plaque formation. As the plaque grows, proximate events leading to acute myocardial infarction include plaque destabilization and rupture leading to thrombosis.

In HIV-infected patients (especially with exposure to antiretroviral drugs), over-representation of "traditional" cardiovascular risk factors (diabetes, smoking, dyslipidemia) as well as "non-traditional" risk factors likely promote all those phases of atherogenesis. Beside the above-mentioned increased inflammation, HIV has been shown to be associated with 1) an atherogenic lipoprotein profile; 2) Increased arterial inflammation leading to high-risk coronary plaque morphology [65]. 3) Impairment of "cholesterol efflux" from these foamy macrophages [66], which is an independent risk cardiovascular risk factor in the general population [67].



Sudano et al., AHJ. 2006 Jun;151(6):1147; Seminari, Atherosclerosis 2002;162:433 -8.
Mujawar et al., PLoS Biol. 2006;4; Blanco et al., JAC. 2006 Jul;58(1):133-9

Figure 3: Potential Atherogenic Effects of HIV Infection and HAART

ii. Hepatitis C Co-Infection

Despite being associated with decreased lipid levels, HCV has been associated with increased endothelial dysfunction [25]. Also, HCV co-infection among HIV patients on antiretroviral therapy is associated with higher values for some biomarkers of early atherosclerosis, suggesting that co-infection in treated patients raises patients' risk for cardiovascular disease [26], perhaps through increased systemic inflammation. However, observational studies have yielded discordant findings regarding its association with cardiovascular disease, with most studies suggesting an increased risk [32-34].

HCV therapy might be associated with a reversal of HCV-associated lower lipids, but also a decrease in carotid intimal thickness [68]. HCV therapy with Pegylated interferon and ribavirin was shown to improve some (but not all) markers of inflammation and monocyte activation and increased CVD risk [69], a change likely restricted to patients achieving SVR [70]. Much less is known about the effects of direct-acting antiviral agents on cardiovascular risk markers.

e. Assessment and Management of Cardiovascular Risk in HIV

While the increased risk of CVD among HIV-infected patients is fully recognized, there are no specific guidelines to assess and manage this risk. It has long been shown that the Framingham Risk Score underestimates the risk of CVD among HIV patients, likely because of unmeasured variables specific to HIV disease and/or its therapy. The 2013 AHA/ACC cholesterol guidelines have widened the focus from coronary heart disease to cerebrovascular AND cardiovascular disease risk. The recommended risk calculation tool is now the pooled cohort equations (PCE) that, in contrast to Framingham, also incorporates African American race and diabetes. The focus is no longer the LDL target to be achieved but whether a high or moderate intensity statin therapy is indicated.

In retrospective analyses of the national VA HIV cohort, we recently showed that application of the 2013 AHA/ACC guidelines improved the identification of HIV-infected patients with AMI and CVD events, and significantly increased the proportion of patients with statin indication: 50% would qualify for high-intensity statin indication [71].

IV. Bone Mineral Loss in HIV

a. Prevalence of Osteoporosis and Osteoporotic Fractures

It has long been observed that bone mineral density (BMD) is lower among HIV-infected patients than age-matched uninfected subjects, and patients on antiretroviral therapy have even lower BMD than anti-retroviral naïve patients [72, 73]. The clinical significance of these findings was made apparent by the observation of a higher incidence of fractures among HIV-infected patients than age-matched uninfected subjects [74].

Hepatitis C virus (HCV) infection, either as mono-infection or as co-infection in HIV-positive individuals, has also been associated with an increased risk of fracture in several studies [37,

75, 76] The deleterious impact of HCV on BMD [76] and fracture risk [37] appears to occur prior to the development of severe liver fibrosis or cirrhosis, although the exact mechanism(s) remain to be elucidated. In order to assess the impact of HIV and HCV on skeletal health, we compared bone mineral density (BMD) and bone turnover markers (BTMs) between HIV/HCV, HIV, HCV and uninfected men of similar age, race and BMI distribution [77]. We found that HIV and HCV independently lowered BMD, likely through different mechanisms.

b. The Patient: "Traditional" Fracture Risk Factors in HIV Patients.

One possible cause of the high prevalence of osteopenia among HIV-infected patients is an enrichment of the "traditional" risk factors among HIV-infected patients [78]. These include low body mass index, steroid use, IV drug use, smoking, vitamin D deficiency, other nutritional deficiencies, low levels of calcium intake, immobilization, hypogonadism renal insufficiency and derangements of the parathyroid-calcium-vitamin D and the pituitary-gonadal axes (Figure 4) [78, 79]. Opiate use has also been associated with altered bone metabolism and reduced trabecular bone mass, attributable, at least in part, to gonadal deficiency [80, 81].

Beyond these attributable causes, chronic HIV infection itself, HAART, and HCV co-infection could also be associated with an increased risk of low BMD:

c. The Viruses: Effects of HIV and HCV Co-Infection on Fracture Risk

i. Direct Effect of HIV on Bone Metabolism and Fracture Risk

HIV infection itself may increase the risk of bone loss through enhanced osteoclastic activity due to chronic T cell activation and production of pro-inflammatory cytokines such TNF-alpha and IL-6 [82, 83]. Although it has been tempting to assume that chronic inflammation associated with untreated HIV infection was also a significant contributor, this is probably not the case. Untreated HIV infection, like other infections is a pro-inflammatory state, however low bone mineral density was not a very significant problem before the potent antiretroviral therapy era [84].

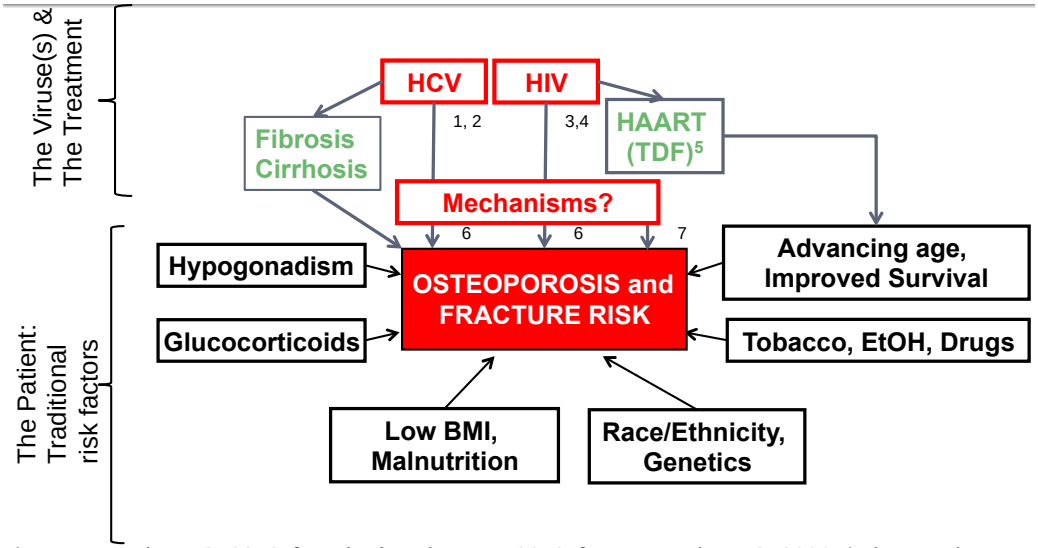
Nonetheless, our data has shown that HIV infection is associated with significant increases in serologic markers of bone turnover, and these are predictive of decreased bone mineral density [77]. The drivers of this increase in bone turnover are still unclear.

ii. Effect of HCV Co-Infection

The importance of osteoporosis as a complication of cirrhosis or advanced liver disease is well known [85]. However, decreases in BMD also appear to occur in earlier stages of chronic hepatitis C infection, without cirrhosis [76, 86]. Indeed, in our analyses, compared to age-matched uninfected patients, HCV-infected patients without cirrhosis had significantly lower bone mineral density [77] and, similarly to El-Maouche et al, [87] severity of liver disease was not associated with risk of osteoporosis in the HCV group. The pathophysiologic mechanisms underlying the effects of non-cirrhotic hepatitis C on bone health are not clearly understood. Like for HIV, one possible explanation for the association of HCV infection with bone disease is

an imbalance in pro- and anti-inflammatory mediators, favoring the former [25]. HCV infection is also associated with higher levels of inflammation (TNF-α, IL-8) in the general population [88], and among HIV infected patients [26]. These inflammatory cytokines could in turn enhance osteoclastogenesis leading to excessive bone resorption and osteoporosis [89, 90]. However, unlike HIV, our analyses suggest that HCV is not associated with increased bone turnover [77]. Also, our data and most other studies showed no clinically relevant abnormalities in calciotropic or gonadal hormones, among HCV-infected patients [76, 91, 92].

In a large cohort of HIV-infected US Veterans, we have shown that HCV co-infection remained a strong independent predictor of osteoporotic fractures after controlling for the severity of liver disease: AST-to-platelet ratio (APRI) or the presence of cirrhosis [37]. Our findings are consistent with those of Hansen et al [93] who showed that the incidence of fractures among HIV/HCV co-infected patients was three times that of the general population.



[1]Hansen et al. AIDS. 2012; [2]Maalouf et al. JBMR 2013; [3]Brown et al. AIDS. 2006; [4]Triant et al. JCEM 2008; [5]Bedimo et al., AIDS 2012; [6]Cutrell et al. CROI 2014; [7]Stellbrink et al. CID 2010

Figure 4: Mechanisms of Osteoporosis in HIV and HCV

d. The Drugs: Antiretroviral Drugs and HCV Therapy Effects

i. Impact of Antiretroviral Therapy on Fracture Risk

While HIV infection itself has adverse skeletal effects, HAART may also contribute to accelerated bone loss [72, 73, 94, 95]. After initiation of antiretroviral therapy, all inflammatory markers improve, and unexpectedly, almost universally, all patients lose between 2 and 4% of their total bone mass [96], a loss similar in magnitude to the transition to menopause or following the initiation of steroid treatment. When patients with HIV infection discontinue their antiretroviral treatment, inflammation increases, but bone mineral density improves [97]. These lines of evidence suggest that antiretroviral therapy whether directly (by toxicity) or indirectly contribute significantly to the problem of bone demineralization in this population.

The acute bone loss associated with the initiation of anti HIV treatment occurs quickly, within six months of initiation of antiretroviral therapy and then it tends to stabilize [96, 98]. This bone loss is universal with all antiretroviral regimens, but significantly worse with one of the most popular antiretroviral drugs: tenofovir [96, 98].

In an open-label randomized 48-week study in antiretroviral-naive subjects with HIV [99] we found the nucleoside-sparing regimen raltegravir + darunavir/ritonavir (RAL + DRV/RTV) to be virologically inferior to the traditional regimen tenofovir/emtricitabine + darunavir/ritonavir (TDF/FTC + DRV/RTV). Both regimens led to similar changes in inflammatory markers (TNF) over time but had distinctly different effects on bone turnover markers and bone mineral density. TDF/FTC + DRV/RTV use led to an early increase in bone turnover markers, which was associated with a decline in BMD, whereas RAL + DRV/RTV use did not significantly impact bone health. This suggests that a nucleoside-free regimen with equivalent virologic efficacy will likely lead to better long-term bone tolerance.

Finally, in our national VA HIV cohort, we explored the association of the cumulative exposure to different antiretroviral drugs on incident osteoporotic fractures [47]. Cumulative exposure to tenofovir and, among protease inhibitors, lopinavir/ritonavir was independently predictive of increased risk of osteoporotic fracture in the HAART era.

ii. Impact of HCV Therapy on Bone Health

Limited data suggest that HCV therapy with interferon-based regimens reduces the risk of bone fracture in postmenopausal HCV-mono-infected women with osteoporosis and chronic HCV-induced liver disease [100]. It is unclear whether this a result of HCV virologic suppression, or suppression of HCV-induced chronic inflammation [25] or a direct effect of interferon on bone metabolism [101, 102]. Should the latter be the case, this effect will not persist at the end of IFN therapy, and might not be observed in current interferon-free regimens.

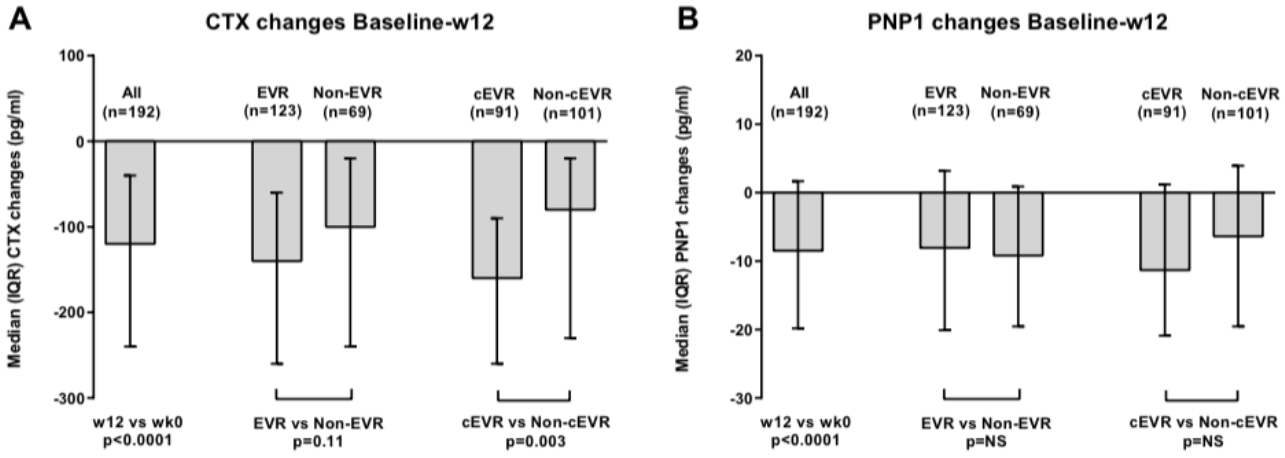


Figure 5: CTX Changes from Baseline in Bone Resorption (CTX) and Bone Formation (P1NP) Markers in During PegIFN/RBV Therapy amon HIV/HCV Patients ([103]).

We have recently shown that treatment of HIV/HCV co-infected patients with PegIFN + RBV resulted in approximately 40% decline in the marker of bone resorption CTX by week 12, and that decline was sustained with continued IFN [103]. Furthermore, patients who achieved complete early virologic response (cEVR) had a greater CTX decline. Bone formation marker P1NP also declined but to a lesser extent, and did not correlate with cEVR status. Post treatment samples were not available to assess whether they were sustained following the end of therapy or correlated with sustained virologic response.

In conclusion, our findings suggest that IFN-based HCV therapy has a net beneficial effect on BTMs in HIV/HCV patients. If these findings are confirmed with IFN-free regimens, improvements in bone health may be a secondary goal of HCV therapy.

V. Conclusions

The widespread availability and efficacy of antiretroviral therapy has led to a dramatic drop in the mortality rate of HIV-infected patients. With increased survival of these patients, there has been a significant shift in the causes of morbidity and mortality from AIDS-defining (infections and AIDS malignancies) to non-AIDS-defining conditions, principally cardiovascular diseases, liver-related complications, and non-AIDS malignancies. Osteoporosis and increased fracture risk is a largely unrecognized cause of morbidity in these patients.

The pathogenesis of these non-AIDS complications is incompletely understood. It likely involves patient factors (over-representation of “traditional” risk factors, direct and direct effects of HIV infection and HIV-associated inflammation and immune activation, and effects of antiretroviral therapy. HCV co-infection (present in up to a third of HIV patients) likely contributes to the causality of many of these complications.

Understanding the mechanisms of these non-AIDS complications and mitigating their risk will be needed to achieve significant improvements in the morbidity and mortality of HIV-infected patients on HAART.

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