

# Extrahepatic Complications of Hepatitis C Virus Infection in HIV and the Impact of Successful Antiviral Treatment

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Chronic hepatitis C virus (HCV) infection exerts its main effects on the liver, promoting hepatic inflammation and fibrosis and increasing the risk of cirrhosis, hepatic decompensation, and hepatocellular carcinoma [1]. However, chronic HCV infection also affects organ systems outside of the liver and can contribute to the development of a variety of extrahepatic diseases, most notably atherosclerosis, metabolic alterations (eg, insulin resistance, diabetes mellitus, hepatic steatosis), renal disease (eg, proteinuria, membranoproliferative glomerulonephritis), bone disease (eg, arthralgias, osteoporosis, fractures), neuropsychiatric manifestations (eg, fatigue, cognitive impairment), B-cell non-Hodgkin's lymphoma, cutaneous disorders (eg, lichen planus, porphyria cutanea tarda), and autoimmune and immune-mediated conditions (eg, mixed cryoglobulinemia, thyroid disease, sicca syndrome) [2, 3]. Some studies have suggested that the incidence of these diseases might be higher for human immunodeficiency virus (HIV)/HCV-coinfected individuals

than for those with HCV alone [4, 5]. Regardless of HIV status, HCV-related extrahepatic conditions contribute to morbidity and could increase the risk of nonliver-related mortality [6–9].

The mechanisms for the extrahepatic comorbidities associated with chronic HCV infection are incompletely understood but are likely multifactorial. HCV replication in extrahepatic cells, interactions between HCV proteins and intracellular signaling pathways, HCV-induced stimulation of B-lymphocytes, and immune activation leading to chronic inflammation have all been hypothesized to play a role in the development of these conditions [2, 3]. Lifestyle factors, such as drug and alcohol abuse, smoking, and poor nutrition, may also be important contributors to the development of HCV-related extrahepatic diseases.

There is evidence that successful eradication of chronic HCV infection with interferon-based therapy can ameliorate some extrahepatic complications. Achieving cure of chronic HCV has been associated with improvements in insulin resistance [10–12], reduced risk of diabetes [13], decreased incidence of stroke [14] and lymphoma [15], improvement in neurocognitive function [16], reduction in fatigue [17], and resolution of mixed cryoglobulinemia [18]. These studies were primarily conducted among HIV-uninfected patients, and it remains unclear if HIV differentially affects the impact of cured HCV on specific extrahepatic conditions. Successful treatment

of chronic HCV also has been shown to reduce non-liver-related mortality. One cohort study of 530 chronic HCV-infected patients with advanced hepatic fibrosis or cirrhosis found that eradication of chronic HCV with interferon-based treatment significantly reduced rates of all-cause mortality [7], but this study excluded individuals with HIV coinfection. However, a separate cohort study of 1599 HIV/HCV-coinfected patients found that cure of chronic HCV with interferon plus ribavirin was associated with reductions in non-liver-related deaths as well as decreased HIV progression [8].

All-oral direct-acting antiviral (DAA) agents for the treatment of chronic HCV are now available and result in high (≥94%) rates of cure, regardless of HIV status, with minimal adverse effects [19–22]. Because of their high costs, access to these drugs has been limited in many settings, often only restricted to patients with advanced liver fibrosis or cirrhosis [23–26]. However, if successful treatment of chronic HCV with DAA regimens is shown to improve HCV-related extrahepatic diseases and can reduce nonhepatic morbidity and mortality, including among HIV/HCV-coinfected individuals, then extrahepatic manifestations of chronic HCV may become a major indication for antiviral treatment, even in the absence of advanced liver fibrosis.

There has been a paucity of data related to the risk of HCV-related extrahepatic diseases according to the presence of

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HCV viremia and successful antiviral treatment in the setting of HIV infection. In this issue of *Clinical Infectious Diseases* [27], investigators from the Swiss HIV Cohort Study, a nationwide community-based HIV cohort study, comprehensively examined the effects of HCV seropositivity, detectable HCV viremia, and successful HCV treatment with predominantly interferon-based therapy (10% were treated with DAAs) on a variety of important extrahepatic outcomes, including diabetes mellitus, chronic kidney disease, non-AIDS-defining malignancies, osteoporosis/fractures, and cardiovascular events. Data collection was prospective over a mean of 8.2 years, and stringent validation methods were used to minimize the likelihood of misclassification of extrahepatic events. The risk of each extrahepatic outcome was evaluated among 4 categories of HIV/HCV-coinfected patients—untreated HCV antibody-positive who spontaneously cleared their infection, untreated HCV antibody-positive with viremia, antiviral treated and cured, and antiviral treated but not cured—compared to HIV-monoinfected patients. These comparisons are valuable in helping to differentiate the potential contributions of HCV viremia-related mechanisms from lifestyle factors on the development of extrahepatic diseases and provide important insights on the effects of cured HCV on these conditions.

The study found that rates of chronic kidney disease and osteoporosis/fractures were significantly higher for HCV antibody-positive patients but not for those with HCV viremia compared to HIV-monoinfected individuals. Rates of diabetes, cardiovascular disease, and non-AIDS malignancies were not increased among either HCV-seropositive or HCV viremic persons compared to those with HIV alone. These findings suggest that behavioral factors associated with HCV infection might be more important contributors to the development of renal and bone disease among coinfecting patients than HCV viremia-related mechanisms.

This observation is consistent with that from a large Danish study that showed that HCV-exposed patients had a higher risk of all fracture types compared to uninfected persons and that fracture risk did not differ between patients with HCV viremia vs those who spontaneously cleared their HCV infection (ie, HCV antibody-positive but RNA-negative), though this study was largely comprised of HIV-uninfected individuals [28]. However, there are some data that suggest that HCV viremia and viremia-related inflammation might contribute, to some degree, to the development of chronic kidney and bone disease. A recent large cohort study from the North American AIDS Cohort Collaboration on Research and Design found that both HCV viremic and HCV antibody-positive but aviremic individuals were at increased risk for moderate and advanced chronic kidney disease compared to HIV-monoinfected persons [29]. Differences in the definitions of chronic kidney disease between the studies may account for the disparate results. Moreover, a recent cross-sectional study using tibia peripheral quantitative computed tomography found that HIV/HCV viremic women had decreased tibial trabecular volumetric bone mineral density, diminished cortical dimensions, and significant endocortical bone loss—a pattern observed in chronic inflammatory diseases (eg, rheumatoid arthritis, inflammatory bowel disease)—compared to uninfected persons [30]. Trabecular volumetric bone mineral density was lower and median tumor necrosis- $\alpha$  levels were higher in coinfecting women compared to either HCV- or HIV-monoinfected women, suggesting that HIV- and HCV viremia-associated chronic inflammation might contribute to structural bone deficits among HIV/HCV patients. Additional studies are needed to understand the contributions of HCV viremia, lifestyle factors, and alternative mechanisms on the development of these and other extrahepatic diseases in the setting of HIV coinfection. Future analyses should also consider

whether the stage of liver fibrosis or presence of hepatic decompensation modifies the risk of extrahepatic outcomes.

In analyses evaluating the effects of HCV eradication with interferon-based therapy on nonhepatic outcomes, patients who did not achieve cure of HCV had higher rates of diabetes, but not other extrahepatic events, compared to successfully cured persons. This finding persisted after adjustment for baseline stage of hepatic fibrosis. Of note, rates of liver complications and liver-related deaths remained higher for treated patients who did not achieve cure, which were valuable additional analyses that provide face validity to the findings. These results demonstrate the beneficial effect of antiviral therapy on at least 1 extrahepatic outcome but must be interpreted in the context of several limitations, particularly the small sample of antiviral-treated patients (626 patient overall; 345 with cured HCV), the limited number who received a DAA (10%), and the relatively few events for some of the extrahepatic outcomes.

The comprehensive approach taken by Kovari and colleagues [27] in evaluating a number of clinically important extrahepatic complications according to both HCV viremia and viral cure status provides a model for studies on this topic. However, more work in this area is needed. Specific cohorts, or preferably cohort collaborations, that include large samples of DAA-treated patients with long-term follow-up are needed to determine the impact of successful treatment with these new regimens on extrahepatic diseases among HIV/HCV patients. These data will help inform whether reductions in rates of extrahepatic outcomes can help to justify DAA-based HCV treatment and if extrahepatic diseases should be included as a major indication for DAA therapy, even in the absence of significant liver fibrosis.

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