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Virologic and Immunologic Aspects of HIV-HCV Coinfection

Kara W. CHEW, MD, MS and Debika BHATTACHARYA, MD, MS

David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Keywords

HIV; Hepatitis C; Co-Infection

Introduction

Globally, there are 115 million infected with HCV and 37 million infected with HIV, approximately 2 million are infected with HIV/HCV [1]. HCV coinfection is common in the US and Europe in HIV and mortality and liver-related deaths are a leading cause of death in HIV infection, primarily attributed to HCV infection. This review will focus on the clinical outcomes in HIV/HCV coinfection and the virologic and immunologic interplay between the viruses that contribute to accelerated disease progression.

Epidemiology and Transmission

Hepatitis C (HCV) coinfection in HIV infection is common, affecting up to 25% of those in the US and Europe [2, 3] and 45–90% prevalence in some injection drug using cohorts. The viruses share routes of transmission, including parenteral (injection drug use, blood transfusion), perinatal, and sexual (primarily in HIV-infected men who have sex with men (MSM)).

Impact of HIV on HCV transmission

Injection drug use is the most common route of transmission of HCV in the US. There are no studies to suggest that HIV infection facilitates HCV acquisition in injection drug users, but HIV infected individuals, independent of risk cohort, are more likely to develop chronic HCV infection. Although not considered a significant route of transmission in heterosexual couples, there have been several reports of epidemics of sexually transmitted HCV infection in Europe, the US, Australia, and Asia in HIV infected MSM [4–10]. In one cohort, the

Corresponding Author: Debika Bhattacharya, M.D., M.S., Associate Clinical Professor of Medicine, Division of Infectious Diseases, Center for Clinical AIDS Research and Education (CARE), David Geffen School of Medicine at the University of California, Los Angeles, 11075 Santa Monica Blvd, Suite 100, Los Angeles, CA 90025, Phone: (310) 825-0137, Fax: (310) 825-3632, debikab@mednet.ucla.edu. **Alternate Author:** Kara Chew, M.D., M.S., Assistant Clinical Professor of Medicine, Division of Infectious Diseases, Center for Clinical AIDS Research and Education (CARE), David Geffen School of Medicine at the University of California, Los Angeles, 11075 Santa Monica Blvd, Suite 100, Los Angeles, CA 90025, Office: (310) 825-0796, Fax: (310) 477-7657, kchew@mednet.ucla.edu.

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yearly incidence of HCV infection was increased by 18-fold from 1998–2011[11]. There have to date been no similar epidemics in HIV-uninfected men who have sex with men, although there have been a few reported sexual transmission cases in the setting of pre-exposure prophylaxis for HIV[12]. Risk factors in HIV/HCV coinfection include unprotected receptive anal intercourse, sharing sex toys, sex while high on methamphetamines, rectal bleeding, frequent or unprotected receptive fisting, snorting cocaine or amphetamines, group sex participation, sharing straws when snorting drugs, lower CD4 cell count, recent diagnosis of sexually transmitted infection, younger age, HBsAg infection, and ETOH abuse [13–18]. It is not clear why HIV-infected men are at higher risk of infection, but etiologies are likely multifactorial including potentially higher HCV seminal viral loads in HIV infection when compared to HCV mono-infection [19] (although this was not supported in another study [20]) more porous rectal mucosa, immune dysregulation, blood based transmission and fomite transmission [21]. HIV infection also impacts perinatal HCV transmission. Infants born to HIV/HCV coinfecting women were 3.2-fold more likely to acquire HCV infection, compared to infants born to HIV-1 uninfected women [22] and two meta-analyses demonstrated risk estimates (OR=1.9, 95% CI: 1.36–2.67 [23] and 2.82, 95% CI: 1.78–4.45 [24]) of HCV acquisition. Maternal antiretroviral therapy was associated with a reduction in the risk of HCV transmission in one but not another study [25]. Notably, several studies have suggested that perinatal HIV transmission is increased in HIV/HCV coinfection, compared to HIV infection alone with one study reporting a nearly doubled rate of HIV transmission (odds ratio [OR] 1.82, $p=0.001$). However, maternal drug use was suspected as a confounding factor.

Impact of HCV on HIV disease

Whereas the impact of HIV co-infection on HCV disease progression is well established as described below, whether or not HCV infection significantly impacts the natural history of HIV progression is unclear. The data in this area, most published over a decade ago and in both the pre- and post-combination antiretroviral therapy (cART) eras, are mixed in their findings. Largely using composite endpoints of AIDS-defining events or death, some have found accelerated clinical progression in HCV co-infected persons [26–29]. Rates of immunologic progression, measured by CD4 cell count decline, have also been examined. In one study in the pre-cART era, where risk of clinical progression (defined as one or more of: a 30% decrease in Karnofsky index, 20% loss of body weight, AIDS-defining illness, or death) was increased in co-infected persons over a median of 3 years of follow-up, no difference was seen in immunologic progression, defined as a 50% decrease in CD4 cell count, between co-infected and HIV mono-infected persons, except in stratified analyses of subjects with CD4 cell count $>600 \times 10^6/\text{mL}$, where HCV was associated with CD4 decline [27]. This might suggest a greater impact of HCV on HIV disease progression in early HIV infection. Other studies have found no impact of HCV on clinical or immunological progression, although analytical approaches differed with regard to immunological endpoints [30–33].

Multiple studies have also examined CD4 cell recovery following ART initiation, with again varied findings. Whereas virologic response to ART does not appear to be affected by HCV status, some have found impaired initial CD4 recovery in HCV-infected compared with

HCV-uninfected persons (either without impact on clinical outcomes or without evaluation of impact on clinical outcomes) [26, 28, 34], and others no difference in immune recovery [35]. In a meta-analysis of 8 trials (all studies published 2002–2003) that examined this question, mean CD4 recovery in co-infected patients was 33.4 cells/mm³ less than in HIV mono-infected patients after 48 weeks of ART [36]. Postulated mechanisms of impaired CD4 cell recovery include chronic immune activation driven by HCV infection leading to CD4 T cell apoptosis [37, 38], and suppression of CD4 cell proliferation, as well as Fas-mediated apoptosis, due to HCV replication in peripheral blood mononuclear cells (replication demonstrated in CD4 T cells and CD34+ progenitor cells) and lymphoid tissue [39–41].

Impact of HIV on HCV disease

HIV influences the progression of HCV disease through several mechanisms, including through increased HCV replication, a decreased rate of HCV clearance during acute infection, and accelerated fibrogenesis which leads to increased rates of hepatic decompensation, liver-related mortality, and hepatocellular carcinoma. In the interferon-era, HCV treatment efficacy was diminished in HIV coinfection but studies with all-oral direct-acting antiviral agents (DAA) have demonstrated similar efficacy rates.

Higher HCV viral loads in HIV

It has repeatedly been demonstrated that HIV co-infection is associated with higher levels of HCV viremia compared with HCV mono-infection [42–46]. In one longitudinal hemophiliac cohort of initially HCV-monoinfected patients, some of whom went on to have HIV seroconversion, HCV RNA levels pre-HIV seroconversion were similar to levels in those who remained HIV negative, but following HIV seroconversion, increased 58-fold over the study period, compared with an approximately threefold increase in patients who remained HIV negative [47]. Multiple studies have also demonstrated an association between higher HCV viral load and lower CD4 T cell count in co-infected patients [44, 48–51], suggesting cellular immune responses play a significant role in control of HCV viral replication during chronic HCV infection. Indeed, they are likely critical in clearing acute HCV and preventing the establishment of chronic HCV infection, as will be discussed subsequently. Interestingly, a few prospective studies have also reported increases in HCV viral loads in some patients following ART initiation (with subsequent return to baseline levels), with one study finding greater viral load increases in patients with lower CD4 cell count (< 350 cells/mm³) [35, 52]. Sherman et al explored immunologic mechanisms for the increase in HCV viral load further and found a weak positive correlation between HCV viral load and HCV-specific peripheral T- cell responses measured by IFN- γ ELISPOT assays ($r^2=0.21$, $p=0.0018$) [52]. They also found significant downregulation of interferon-stimulated genes (ISGs), suggesting initial increases in HCV viral load following initiation of ART may be due to reduced interferon-mediated inhibition of HCV replication.

Spontaneous clearance of HCV infection in HIV-infected persons

A majority, approximately 75–85%, of those acutely infected with HCV will go on to develop chronic infection. HIV infection is a risk factor for failing to spontaneously clear

HCV after acute infection [45, 53–55], likely in greatest part due to the impact of HIV infection on effective HCV-specific T-cell responses. Consistent with this, lack of spontaneous clearance has been associated with low CD4 T cell count [45]. In a longitudinal study of patients with chronic HIV and acute HCV infection, HCV-specific T cell responses were measured by T-cell proliferation, ELISpot, intracellular cytokine staining and pentamer assays. HCV-specific proliferative responses were associated with lower HCV viral load and spontaneous clearance, as well as HIV-p-24-specific responses, independent of degree of immunodeficiency, but overall, while present in the majority of patients, interferon-gamma-producing T cells specific for HCV were present only at low intensity [54]. Weak HCV-specific memory CD4 T cells in HIV likely contribute to lower rates of HCV clearance. Other studies have also demonstrated a decrease in HCV-specific IFN-gamma secreting CD4 responses in HIV/HCV-coinfected patients, independent of CD4 cell count [56, 57]. HCV-specific CD8 responses also appear to play a role in HCV clearance. Barrett et al demonstrated reduced breadth and frequency of HCV-specific CD8 T cell responses in co-infected compared with mono-infected subjects, independent of CD4 cell count, although when present, CD8 responses were actually stronger in the co-infected subjects. This has been postulated as a mechanism for accelerated hepatic fibrosis progression [57].

HIV infection may also lead to impaired innate immune responses that may impact HCV clearance, through impaired CD4 stimulation of B-cell responses and antibody production. Studies have explored the relationship between B-cell function and CD4 cell count in a cohort of hemophiliacs with established HCV infection who subsequently seroconverted, finding reduced HCV-specific antibody responses. Netski et al found CD4 cell count of <500 cells/mm³ as well as longer duration of HIV infection to be associated with lower HCV antibody titers [58]. Bailey et al found lower HCV envelope-specific binding antibody and neutralizing antibody (nAb) titers in subjects with CD4 cell counts <350 /mm³, without significant change in antibody levels in those with CD4 >350 cells/mm³ [59]. Further immunodeficiency with CD4 cell count <200 cells/mm³ was associated with additional reduction breadth of nAb titers.

As in HCV monoinfection, host IL28B genotype similarly strongly influences spontaneous clearance of acute HCV in HIV, with the CC genotype being protective [55, 60]. A number of studies have also demonstrated that effective antiretroviral therapy may restore immune responses to HCV. In support of that, there have been reports of spontaneous clearance of HCV after initiation of ART, particularly in individuals carrying the IL28B-CC alleles [61, 62]. HCV-specific T-cell responses may improve with virologic suppression. In one study comparing HIV virologically suppressed co-infected persons and HCV mono-infected persons, HCV-specific CD4 and CD8 T-cell responses were measured IFN- γ and TNF- α production following HCV peptide stimulation, by flow cytometry, and found comparable responses between co-infected and mono-infected subjects [63].

Accelerated Fibrogenesis

HIV/HCV coinfecting patients are at an increased risk of developing cirrhosis and develop cirrhosis more quickly than their HCV monoinfected counterparts. In a 2001 meta-analysis of 8 studies, investigators found that HIV/HCV coinfecting patients had an overall RR of 2.1

(95% CI: 1.15–3.97, $P=0.024$) for developing cirrhosis [64] while a 2008 meta-analysis of 7500 patients in 26 studies demonstrated an increased RR of cirrhosis of 2.1 (95% CI: 1.5–3.0), 2.5 (95% CI: 1.8–3.4), and 1.7 (95% CI: 1.1–2.8) in HIV/HCV coinfecting patients overall, without HAART, and with HAART, respectively, suggesting that potent antiretroviral therapy does not completely attenuate fibrosis progression ($n=26$ studies; $P=0.25$) [65] (see below). Indeed, two studies have demonstrated that histologic progression occurs in 16–24% of HIV/HCV coinfecting individuals over 3 years [66, 67].

Mechanisms of Liver Fibrosis

Liver fibrosis occurs when extracellular matrix protein (ECM) deposition exceeds the rate of ECM clearance, resulting in a net increase of ECM proteins. ECM proteins in turn stimulate fibrosis, initiating the cascade of nodule development and cirrhosis [68]. Hepatic stellate cells (HSCs) are the primary cellular instigators of fibrogenesis, quiescent until activated by hepatocytes or Kupffer cells. HSCs then become myofibroblast-like cells, producing ECM and tissue inhibitors of metalloproteinases (TIMPs). The mechanisms of accelerated fibrogenesis are interdependent but can be broadly grouped into immune dysregulation, infection and interaction of HIV with cells in the liver, and microbial translocation [69].

Immune dysregulation

Systemically, HCV-specific IFN- γ responses are correlated to CD4 cell counts and in, acute HCV infection, these responses are impaired when compared to acute HCV infection without HIV infection [70]. Similarly, in chronic HCV infection, although coinfecting patients with higher CD4 cell have more robust HCV specific lymphoproliferative responses than those with lower CD4 cell counts, there is an overall impairment in HCV-specific lymphoproliferative responses in HIV infection.

There are several important chemokines and cytokines that have intrahepatic effects that are affected by HIV and HCV coinfection. Interferon gamma-induced protein 10 (IP-10) is a chemokine that, in HCV infection, directs CD4 lymphocytes to the liver. Plasma IP-10 levels correlate with intrahepatic IP-10 levels [71]. Higher baseline IP-10 levels are associated with higher ALT levels and more hepatic inflammation in HCV infection [72–75]. When compared to HCV mono-infection, HIV/HCV coinfecting individuals have higher IP-10 levels [73]. It is postulated that CD4 cell depletion in HIV may, in attempts to increase CD4 recruitment, be causing upregulation of IP-10 expression, causing liver damage through an innocent bystander mechanism [76]. IL-8, a neutrophil chemokine that contributes to liver inflammation, is also increased, and synergistically so in HIV/HCV coinfection. The HCV envelope protein E2 produces IL-8 as does the HIV gp120 protein and the combination of HCV envelope protein E2 and gp120 further increases IL-8 production. This combined exposure may also aggravate liver inflammation [77]. Finally, increased intrahepatic mRNA levels of regulated upon activation, normal T-cell expressed and secreted (RANTES) and macrophage inflammatory protein 1 alpha (MIP-1 α), which have also been associated with subset-specific leukocyte activation and chemoattraction, have been found in HIV/HCV coinfection. Moreover, these changes in mRNA levels were less pronounced in HIV infected patients receiving antiretroviral therapy [78]. Cytokines, which induce broad-spectrum antiviral activity and inhibit viral replication, can also lead to accelerated fibrosis

progression. HIV/HCV coinfecting patients have increased intrahepatic IFN- γ and TNF- α levels with higher IFN- γ mRNA levels correlating with higher degrees of fibrosis [79]. Receipt of antiretroviral therapy was again associated with comparatively decreased pro-inflammatory cytokines.

HIV effect on the liver

The role of HIV and its interaction with cells in the liver, hepatocytes, hepatic stellate cells (HSC), and Kupffer cells, is critical to the enhanced fibrogenesis in HIV/HCV coinfection. Although there is no definitive evidence that HIV infects hepatocytes, circulating viral HIV proteins can exert effects on hepatocytes by increasing hepatocyte HCV replication, inducing apoptosis and being profibrotic. HCV replication in hepatocytes is increased up to 3 fold after in vitro exposure HIV gp120, inducing TGF- β 1 production. HIV gp120 induces hepatocyte apoptosis through CXCR4 G-protein-mediated signaling [80]. Similarly, combined exposure to gp120 and the HCV E2 protein also induces apoptosis through STAT1 phosphorylation and Fas ligand upregulation [81, 82]. Apoptosis itself can lead to fibrogenic HSC activity [83, 84], demonstrated in HIV/HBV and HIV/HCV coinfection. When Kupffer cells uptake apoptotic cells, they produce death ligands including TRAIL, FasL, and TNF- α , which can all further induce apoptosis. Hepatocyte exposure to HIV also leads to increased production ROS, collagen, and tissue inhibitor of metalloproteinase 1 (TIMP1), all of which are pro-fibrogenic, an effect that is magnified by HCV exposure [85].

Hepatic stellate cells (HSC), the primary cells involved in liver fibrogenesis, are also a target of HIV, both by direct infection by HIV and by HIV exposure. HIV can infect HSCs and HIV-infected HSCs produce increased collagen and monocyte chemoattractants (MCP-1) [86]. Similarly, exposure to HSCs by HIV results in ROS, collagen, and TIMP1 production, an effect that is increased in the presence of HCV [85]. HSC fibrogenesis is mediated by Kupffer cells, macrophage cells that reside in the liver, and HSCs can also be infected by both HIV [87, 88] and HCV. HCV infection of Kupffer cells produces ROS and inflammatory and fibrogenic mediators and it is thought that an HIV-mediated shift to a Th2 cytokine response in Kupffer cells may lead to activation of HSCs [89]. Hepatic sinusoidal endothelial cells can also be infected in vitro with HIV [90] although its effect is unclear. There are other proteins that may be important. Tat, an HIV protein secreted by HIV, has been associated with hepatocellular cancer in transgenic [91, 92] mice where the transgene was comprised of the HIV LTR-regulatory region directing expression of the HIV *tat* gene.

Microbial Translocation

The systemic CD4 T cell depletion that occurs in HIV also occurs in gut-associated lymphoid tissue [93]. This leads to disrupted gut epithelial cell integrity and an increased permeability to bacterial products, including lipopolysaccharide (LPS), a pro-inflammatory component of gram-negative cell wall bacteria [94]. In HIV infection, LPS levels have been associated with immune activation, T cell depletion, and disease progression [94]. Elevated LPS levels have also been associated with fibrosis progression in NAFLD, NASH [95–97], HCV monoinfection [98], and HIV/HCV coinfection [99]. Kupffer cells are the main liver cells targeted by LPS. Binding of LPS to Toll-like receptor 4 (TLR-4) increases profibrotic and proinflammatory TGF- β 1, TIMP1, type I collagen [100], tumor necrosis factor- α (TNF-

a), interleukin-6 (IL-6), IL-12 and IL-18 [101]. Kupffer cells are normally physiologically tolerant to repeated LPS exposure, however, HCV infection induces a loss of this tolerance in peripheral monocytes (and perhaps in Kupffer cells), due to the combination of HCV core protein, endotoxin, and gamma interferon [98]. HSCs are also activated by LPS, with studies demonstrating increased CCL-2 production in vivo [102] and increased CXCL9, 10, and 11 in vitro [103], causing T-cell and monocyte migration to the liver. These phenomena may, in part, explain the increased fibrosis progression in HIV/HCV coinfection.

Hepatic decompensation and increased mortality

Accelerated fibrogenesis leads to hepatic decompensation and increased mortality. Several studies have demonstrated an association between HIV/HCV coinfection and higher rates of hepatic decompensation and mortality. In a 2001 meta-analysis (mentioned above), the adjusted relative risk (RR) for decompensated cirrhosis was 6.14 [64]. Similar but smaller increases in relative risk were seen in a recent VA study where the incidence of decompensated cirrhosis was 7.4% vs. 4.8% at 10 years $p < 0.001$ in HIV/HCV compared to HCV monoinfected veterans. Indeed, decompensation rates were higher in co-infection even when HIV RNA levels were less than 1000 copies/mL [104]. Risk factors for decompensation in this study were baseline advanced hepatic fibrosis, baseline lower hemoglobin, diabetes, and non-black race. Similarly, there is a concurrent increased in the risk of liver-related and all-cause mortality. The D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) [105] demonstrated that liver disease represented 14.5% of all deaths in this HIV-infected cohort, second only to AIDS-related mortality. When compared to HCV mono-infection, mortality rates were higher in HIV/HCV coinfecting patients with 1-, 2-, and 5- year survival estimates of 54%, 40%, and 25%, respectively in HIV/HCV coinfection compared to 74%, 61%, and 44%, respectively in HCV mono-infection [106]. Risk factors for liver-related death include lower baseline CD4 count, absence of antiretroviral and HCV therapy, baseline fibrosis stage and CPT class [107–110]. Curative therapy for HCV, however, is associated with reductions in liver- and all- cause mortality. In one study of 1599 patients with a follow-up of 5 years, adjusted hazard ratios (HR) for non-liver-related deaths, and non-liver-related, non-AIDS-related deaths for HCV nonresponders compared with responders were 1.90 (95% CI, .89–4.10; $P = .095$), 3.19 (1.21–8.40; $P = .019$), and 2.85 (1.07–7.60; $P = .036$), respectively, suggesting that non-liver related mortality was also improved after successful HCV therapy [109]. This finding was corroborated in another study of 638 co-infected patients where there were no events of ESLD, HCC, or death in the 51 patients with sustained virologic response and HCV relapse [110].

Hepatocellular Carcinoma (HCC)

The prevalence of HCC is rising in HIV/HCV coinfection and is increased in HIV/HCV coinfection, compared to HCV mono-infection [111–113]. One study demonstrated an increasing risk of HCC over 3 decades and a current 4-fold higher risk of HCC, when compared to the general population [114]. This increased incidence was attributed to HCV, as HCC risk was 2-fold higher in those who were at high risk for HCV, compared to those where not. Similarly, HCC is estimated to occur earlier in HIV coinfection, after an average of 17.8 years, compared to 28.1 years in HCV mono-infection. Risk factors include lower CD4 counts [115].

Attenuation of liver fibrosis by antiretroviral therapy

The accelerated hepatic fibrosis progression in HIV/HCV co-infection may be mitigated in part, although likely not fully, by HIV antiretroviral therapy. Thein et al conducted a systematic review and meta-analysis of natural history studies published from 1990–2007 to examine rates of untreated HCV fibrosis progression and risk of cirrhosis in the highly active antiretroviral therapy (HAART) era [65]. In the analysis of fibrosis progression, all studies were cross-sectional/retrospective in design and the majority of patients reported IDU as the risk factor for HCV acquisition, with mean age (range) of 40 years (34–50) and estimated duration of HCV infection of 17 years (10–24). CD4 cell counts at the time of liver fibrosis assessment were included. Data on HIV viral loads were not available in 9 studies. Fibrosis progression rates were estimated using both Markov maximum likelihood estimation to derive the annual probabilities of stage-specific transitions (e.g. F0→F1, ... F3→F4) and a stage-constant method assuming constant rates of fibrosis progression, whereby the fibrosis progression rate was calculated by dividing fibrosis stage on liver biopsy with estimated duration of HCV infection. These approaches, the latter used by multiple studies, have clear limitations given the challenge of precisely determining duration of infection in many patients. In this analysis, adjusting for sex, age, duration of HCV infection, excess alcohol use, genotype 1 HCV, injecting drug use, and blood transfusion history, use of HAART and CD4 cell count were not associated with fibrosis progression. In the analysis of risk of cirrhosis, 27 reports of 7666 individuals, 4970 with HCV mono-infection and 2646 with co-infection. CD4 T cell count at liver disease assessment was available in 17 of the studies, with mean CD4 cell count of 429 cells/mm³, with HAART use reported in 13 studies. The majority of participants had received HAART for at least 1 year at time of liver disease assessment. The authors found that, compared to the HCV monoinfected group, the relative risk of cirrhosis for the non-HAART group was 2.49 (95% CI, 1.81–3.42) and 1.72 (95% CI, 1.06–2.80) for the HAART group, suggesting a protective but incomplete effect of ART on HCV-associated liver disease. Sterling et al examined fibrosis progression in a study of 66 co-infected subjects without cirrhosis and with well-characterized HIV characteristics (79% [IQR 67–88] on HAART, median CD4 500 [IQR 290–700], HIV viral load <400 in 51% [IQR 36–66]), and 59 HCV viremic monoinfected subjects matched on age and baseline Knodell fibrosis score, using paired liver biopsies [116]. Subjects were seen in care between 1998–2009. Mean interval between biopsies was 4.7 +/- 2.3 years in coinfecting subjects and 5.8 +/-1.7 years in monoinfected subjects. Restricting the analysis to 59 HCV viremic coinfecting subjects and 59 age and stage-matched monoinfected subjects, there was no difference in fibrosis progression rate between coinfecting and monoinfected groups. Comparison of difference in CD4 cell count, change in CD4 cell count, HAART use, or HIV viral load between progressors and non-progressors was limited to univariate analysis, with no difference found. Despite this, the similar progression on liver histology between coinfecting and monoinfected patients where the majority of HIV patients were on effective ART, suggests the benefits of ART on the progression of HCV-associated liver disease. Konerman et al, in a separate cohort of 282 non-cirrhotic co-infected individuals with paired liver biopsies collected between 1993 and 2008, also examined risk factors for fibrosis progression in coinfection. Median CD4 cell count was 386 (267–550) in the cohort, 69.2% were on ART, and HIV VL was <400 in 55.9% and median interval between biopsies was 2.5 years. In this analysis, ART, HIV virologic suppression, and CD4 cell count were not

associated with fibrosis progression, but metabolic factors (greater BMI, diabetes, and hepatic steatosis at baseline) were associated with progression. Altogether, the evidence to date suggests ART may have benefits for fibrosis progression in HIV/HCV coinfecting persons, but that other comorbid factors contribute to ongoing high risk for progression.

The mechanisms by which HIV treatment may attenuate fibrosis progression have not been thoroughly examined. It could be considered that all the pathways by which HIV is thought to increase fibrogenesis, such as increased transforming growth factor- β 1 (TGF- β 1) expression in hepatocytes and hepatocyte apoptosis [117, 118], may be attenuated by HIV virologic suppression. Virologic suppression with ART is associated with reductions in CD8 T cell activation, particularly with early ART [119]. Reduced CD8 T cell activation may lead to reduced HSC activation and fibrogenesis.

Conclusions

There is a dynamic interplay between HIV and HCV viruses during HIV/HCV coinfection with an impact on transmission, the natural history of disease, and attenuation of liver disease with HIV and HCV treatment. Mechanisms of fibrosis are being elucidated but include immune dysregulation, infection and interaction of HIV with cells in the liver, and microbial translocation. With the advent of all-oral direct-acting antiviral agents (DAA), more research will be needed to characterize and understand the impact of HCV cure on both liver and HIV disease.

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