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HCV and HIV Co-infection: Mechanisms and Management

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Abstract

HCV and HIV co-infection is associated with accelerated hepatic fibrosis progression and higher rates of liver decompensation and death compared to HCV monoinfection, and liver disease is a leading cause of non-AIDS related mortality among HIV-infected patients. New insights have revealed multiple mechanisms by which HCV and HIV lead to accelerated disease progression, specifically that HIV infection increases HCV replication, augments HCV-induced hepatic inflammation, increases hepatocyte apoptosis, increases microbial translocation from the gut, and leads to an impairment of HCV-specific immune responses. Treatment of HIV with antiretroviral therapy and treatment of HCV have independently been shown to delay the progression of fibrosis and reduce complications from end-stage liver disease among co-infected patients. However, rates of sustained virologic response with PEG-IFN and ribavirin have been significantly inferior among co-infected patients compared to HCV monoinfected patients, and treatment uptake has remained low given the limited efficacy and tolerability of current HCV regimens. With multiple direct acting antivirals in development to treat HCV, a unique opportunity exists to redefine the treatment paradigm for co-infected patients, which incorporates data on fibrosis stage as well as potential drug interactions with antiretroviral therapy.

Introduction

More than 150 million people are infected with HCV, and ∼35 million people are infected with HIV [cotte1]. Because of their overlapping modes of acquisition, recognition is increasing of the burden of HIV and HCV co-infection, which is estimated to affect 5–7 million people worldwide. [2, 3] In the USA, up to 25% of the ∼1.2 million HIV-infected population is estimated to be co-infected with HCV. [4] Moreover, the accelerated nature of fibrosis progression in people co-infected with HIV and HCV has contributed to the emergence of HCV-related liver disease as a major cause of mortality in the era of highly active antiretroviral therapy (HAART). [5] Although substantial achievements have been made in the treatment of both HIV and HCV infection, those patients with co-infection have not reaped these benefits for a myriad of reasons, including the limited efficacy and even

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more limited tolerability of current HCV regimens. However, with the development of novel direct-acting antiviral therapeutics for the management of HCV, it is an exciting time to redefine treatment paradigms for the management of co-infection. In this Review, we address the epidemiology, natural history, pathogenesis, and management of HIV and HCV co-infection.

Epidemiology

Transmission of HIV and HCV can occur through percutaneous exposure to blood, sexual intercourse, and from a mother to her infant, but the efficiency of transmission varies for each virus. HCV is ∼10 times more infectious than HIV through percutaneous blood exposures[6], and HIV-infected persons who inject drugs represent the majority of HCV/HIV co-infection. More specifically, HCV co-infection rates among HIV-infected individuals who use injection drugs often exceed 90%, as demonstrated in studies in Europe and Asia. [7-9]

Studies have revealed that transmission of HIV through sexual intercourse and from a mother to her infant is more efficient than for HCV transmission, although the efficiency of HCV transmission in these settings might increase in the presence of co-infection. [10-12] For example, in the Women and Infants Transmission Study, the risk of HCV infection was 3.2-fold greater in HIV-1-infected infants compared with HIV-1-uninfected infants (17.1% versus 5.4%),[11] and two meta-analyses reported similar findings. [13, 14] The impact of HIV suppression on perinatal HCV transmission is less clear: a European multicentre study reported that among those with co-infection, maternal HAART use was associated with a reduction in the risk of HCV transmission (adjusted odds ratio 0.26, 95% CI 0.07–1.01)[15], but a French study did not observe an association between HIV viral load, $CD4^+$ T cell count, and risk of HCV perinatal transmission. [16]

Owing to their shared routes of transmission, HCV–HIV co-infection is common, with differences in prevalence according to the route of HIV infection. In a cohort of 1,955 HIV-infected persons receiving care in the Johns Hopkins HIV clinic, the majority of co-infected patients reported injection drug use as their HIV risk exposure (65%), in contrast to heterosexual contact (15%) and male homosexual contact (8%). [17]

Although men who have sex with men (MSM) remain a minority of those with co-infection, several epidemics of HCV infection among HIV-infected MSM have been described, particularly in urban centres in Europe, Australia and the USA. [18-22] Moreover, an analysis of the Swiss HIV Cohort between 1998 and 2011 revealed that the yearly incidence rate of HCV infection increased 18-fold in MSM, and inconsistent condom use and history of previous syphilis infection were significantly associated with HCV seroconversion in MSM. [23] These data highlight the importance of yearly HCV screening among HIV-infected MSM who engage in high-risk sexual behaviour, in conjunction with intensified prevention and counselling efforts. [24-26] Furthermore, the true burden of co-infection might be further elucidated with increased screening interventions for HCV and HIV. It has been reported that >50% of HCV and >20% of HIV cases remain undiagnosed [27].

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Natural History

The effects of HCV infection on the natural history of HIV infection remain unclear. HCV infection is not associated with an increased rate of AIDS-defining events or deaths, but co-infected patients might have lower $CD4^+$ T cell counts compared to HIV-monoinfected patients. [28, 29]

By contrast, HIV infection has several adverse effects on the natural history of HCV infection, including the following: enhanced HCV replication; decreased rate of HCV clearance after an acute infection; accelerated fibrogenesis; increased frequency of liver decompensation and death; and diminished response to antiviral therapy for HCV. In a study comparing HCV RNA levels before and after HIV seroconversion among HCV-infected patients with haemophilia, Eyster *et al*.[30] revealed that the rate of increase in HCV RNA levels was eightfold faster for HIV-infected patients compared to those who remained HIV-uninfected. In addition, HCV RNA levels correlated inversely with $CD4^+$ T cell count. [30] In contrast to the 20% clearance rate of HCV RNA after an acute infection, it has been estimated that only 5–10% of HIV-infected patients successfully clear the virus. [31, 32]

Several retrospective studies have demonstrated a more rapid progression of liver disease in patients co-infected with HIV and HCV, an effect that might be attenuated by HIV suppression. For example, in a case–control study by Benhamou et al.33 of 122 co-infected patients and 122 HCV-monoinfected patients, the rate of fibrosis progression was significantly increased among coinfected patients, and HIV status and CD4+ T cell count were independent risk factors for progression.[33] In a study of 174 co-infected patients who underwent at least two liver biopsies over a median period of 2.9 years, 24% progressed more than two histological stages [34] (by contrast, studies among HCV-monoinfected patients have reported that 8–12% progressed two or more stages over a period of 30–44 months).[35, 36] Similarly, Macias et al.[37] observed that 28% of patients with co-infection progressed one fibrosis stage and 16% progressed at least two stages over a period of 3 years, and effective antiretroviral therapy (ART) was associated with slower fibrosis progression. Additional studies have observed an attenuation of fibrosis progression with ART, [38, 39] suggesting an important role of HIV suppression; however, other studies did not report an association between HIV viral load, CD4+ T cell count, and risk of fibrosis progression.[36, 40] A meta-analysis of 27 studies involving 3,567 patients with co-infection was subsequently performed by Thein *et al*.,[39] and reported a slightly lower risk of cirrhosis in the HAART era compared with the pre-HAART era reported by Graham *et al*.[40] (RR: 2.11, 95% CI, 1.51–2.96 versus 2.92, 95% CI 1.70–5.01). [41, 42] However, Thein *et al*. found that the estimated risk of cirrhosis was twofold higher in co-infected patients than those with HCV monoinfection, and there was no association between receipt of HAART, the mean CD4 cell count, and fibrosis progression. [39] The authors concluded that HAART did not fully reverse the adverse effect of HIV infection on HCV prognosis.

Moreover, HIV/HCV co-infection is associated with higher rates of liver failure and death compared to HCV monoinfection. In a retrospective cohort study by Pineda *et al*.,[43] co-infected patients in the setting of decompensated cirrhosis experienced a higher rate of mortality compared to HCV monoinfected patients: the 1-year, 2-year, and 5-year survival

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estimates were 54%, 40%, and 25%, respectively, among co-infected patients and 74%, 61%, and 44%, respectively, among individuals without HIV monoinfection. Of note, 43% of co-infected patients received HAART and 15% had a documented HIV RNA load <200 copies/ml. Studies have also reported baseline $CD4^+$ T cell count ≤300/mm^3 and absence of HAART as risk factors for liver-related death among co-infected patients, in addition to Child–Pugh–Turcotte (CPT) class and lack of HCV therapy [44, 45]. Co-infected patients also develop hepatocellular carcinoma at a younger age and are more symptomatic at presentation than monoinfected patients. [46]

As reviewed by Verma, specific conclusions regarding the natural history of HIV/HCV co-infection are difficult to draw from these studies, given their retrospective design, heterogeneity of study populations, missing data on $CD4^+$ T cell count and HIV viral load, and inherent selection bias (patients unwilling to undergo liver biopsies were excluded). [47] Additional prospective studies are needed to better define the risks of fibrosis progression and liver-related morbidity and mortality, particularly with the introduction of novel HCV therapeutic agents.

Mechanisms of Accelerated Fibrosis

Although HIV infection significantly impairs cellular immunity by $CD4^+$ T cell depletion, it has become clear that the increased liver inflammation and fibrosis seen in HIV/HCV co-infection is due to a combination of impaired cellular immunity with direct effects on the gastrointestinal tract and the liver (Figure 1).

Hepatic effects of HIV

In vitro exposure to HIV (or its envelope protein gp120) increases HCV replication in hepatocytes 2-3 fold, along with increased TGF-β1 production and enhanced TGF-β1 gene expression. Furthermore, this effect can be blocked by TGF-β1 antibodies, suggesting that the effect of HIV exposure on HCV replication in infected hepatocytes occurs in a positive feedback loop through TGF-β1 (Figure 2) [48]. This increased replication can be blocked by antibodies to the HIV co-receptors CCR5 and CXCR4, suggesting that although HIV does not directly infect hepatocytes, it mediates its effects indirectly through these co-receptors. [48] In addition, exposure of HCV-infected hepatocytes to HIV leads to increased apoptosis and expression of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and the TRAIL death receptors DR4 and DR5. [49, 50] Finally, infecting hepatocytes with HCV leads to induction of ROS and activation of p38 MAPK, JNK, ERK1/2 and NFκB pathways, which leads to increased TGF-β1.[51] In a similar manner, exposing hepatocytes to HIV directly leads to increased production of ROS, collagen, and tissue inhibitor of metalloproteinase 1 (TIMP1), an effect that is magnified by concurrent HCV exposure and can be blocked by ROS inhibition or siRNA to NFκB. [52]

Similar to hepatocytes, exposure of hepatic stellate cells (HSCs) to HIV *in vitro* leads to increased production of ROS, and expression of and production of collagen and TIMP1 (Figure 2). These effects are increased by addition of HCV, and are abrogated by ROS inhibitors and siRNA to NFkB. [52] HIV can directly infect HSCs, leading to increased collagen and monocyte chemoattractant (MCP-1) production, although the mechanism by

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which HIV gains entry to these cells is unclear as this effect is not blocked by antibodies to CD4, CXCR4 or CCR5. [53] These data show that HIV infection has direct effects on two major cell types within the liver leading to increased HCV replication, increased production of profibrogenic cytokines and extracellular matrix components, and increased cell death.

Microbial translocation

HIV infection leads to an early and marked decline in mucosal lymphoid tissue in the gastrointestinal tract. [54] Evidence also exists of increased circulating lipopolysaccharide (LPS) in HIV infection, which seems to be of gastrointestinal origin and correlates with chronic immune activation (as measured by levels of plasma interferon alpha and circulating activated T cells). [55] It has been shown that LPS can bind to Toll-like receptor 4 (TLR4) on Kupffer cells and increase the release of TGF-β1, TIMP1 and type I collagen. [56] In patients co-infected with HIV and HCV, levels of LPS are strongly associated with the development of cirrhosis. [57]

Immune dysfunction

Although HIV infection causes chronic immune activation as outlined above, the immune response to specific pathogens, including HCV, is dysfunctional, presumably related to depletion of $CD4^+$ T cells. For example, in acute HCV infection in patients infected with HIV, there is an impairment in HCV-specific IFN-γ responses (which correlates with lower $CD4^+$ T cell counts), compared to acute infection in HIV-negative patients. [58] In chronic HCV infection, co-infected patients have reduced HCV-specific lymphoproliferative responses, and those with higher nadir $CD4^+$ T cell counts tend to have more robust responses. [59] Natural killer (NK) cells are stimulated by $CD4^+$ T-cells in an IL-2 dependent fashion and can modulate liver fibrosis by killing activated HSCs. [60] Supernatants from $CD4^+$ T cells from individuals co-infected with HIV and HCV (as compared to HCV monoinfected or healthy controls) have been shown to have a reduced ability to stimulate NK cells to induce an apoptotic response in HSCs *in vitro*. [61] These findings suggest that both quantitative and qualitative immune dysfunction contributes to accelerated fibrosis in HIV/HCV co-infection.

Taken together, these data indicate that HIV infection directly increases HCV replication, augments HCV-induced hepatic inflammation and the release of profibrogenic cytokines, increases hepatocyte apoptosis, increases microbial translocation from the gut, and leads to an impairment of HCV-specific immune responses. These combined effects might explain much of the increased liver inflammation and fibrosis seen in HIV/HCV co-infection. Additional factors that might promote fibrosis among co-infected patients include metabolic abnormalities induced by chronic HIV infection, including glutathione deficiency (which might predispose T cells to undergo apoptosis), as well as those induced by HIV therapy. Steatosis and insulin resistance are potential adverse effects of antiretroviral therapy, and might also promote accelerated disease progression by increasing oxidant stress.

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Management of HIV and HCV Co-infection

Prevention

No vaccines are currently available to prevent HCV or HIV infection, and trials to date have been disappointing. An integral part of public health strategy is therefore case detection, surveillance, and increasing awareness of risk behaviours in those at risk of HIV and HCV infection. Among injection drug users, needle exchange programs help prevent HIV infection, but might not be as effective at preventing HCV, given the higher infectivity of HCV and persistence of borrowing of needles even with availability of exchange programs [62-64]. Outbreaks of acute HCV infection (and reinfection) in HIV-infected MSM highlight the need for continued education about risk and potential preventive measures.[65] Finally the benefit of antiviral treatment in preventing viral transmission is increasingly being realized in both HIV and HCV.[66, 67]

Treatment of HIV

In patients co-infected with HIV and HCV, treatment of HIV with antiretroviral therapy (ART) has been shown to delay the progression of cirrhosis [68], and those with undetectable HIV RNA tend to progress more slowly to cirrhosis than those with detectable viraemia. [37] In addition, treatment of HIV is associated with reduced complications from end-stage liver disease, including hepatocellular carcinoma and death. [69]. Therefore, consideration of ART initiation is recommended for all co-infected patients, regardless of CD4+ T cell count, with some differences between European and US guidelines. [70, 71]However, co-infected patients receiving concurrent HIV and HCV treatment face a higher pill burden as well as an increased risk of drug–drug interactions and drug-induced liver injury, particularly among those with advanced liver disease. [72] Therefore, in a select group of clinically well, treatment-naïve HIV–HCV co-infected patients with CD4+ T cell counts >500 cells/μL, it may be warranted to treat HCV first, delaying HIV treatment to reduce the potential for drug toxicity and interactions. [70] In those starting ART who are likely to be treated for HCV in the near future, treatment regimens should be selected with a view towards potential drug–drug interactions with planned HCV therapy. For example, HIV integrase inhibitors such as raltegravir and dolutegravir have relatively few drug–drug interactions, while use of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors might preclude the use of some HCV direct acting antivirals, particularly those targeting the HCV protease.

Treatment of HCV

Given the multitude of direct-acting antivirals in varying phases of development, the optimal treatment regimen for HCV infection (and HCV/HIV co-infection) is a moving target (Figure 3). Several new HCV direct-acting antivirals are close to obtaining FDA approval, which will soon lead to the availability of interferon-free regimens with high sustained viral response rates, even among patients with cirrhosis and prior treatment failure. Historically, patients co-infected with HIV and HCV have had lower SVR rates compared to HCV-monoinfected patients using PEG-IFN and ribavirin-based regimens, but this disparity seems to be dissipating with the addition of direct-acting antivirals (Table 1).

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Acute HCV—As in HCV monoinfection, several studies have demonstrated a significant benefit of treating acute HCV infection among HIV-infected patients when compared to treatment of chronic infection [73, 74] For instance, in a retrospective study of MSM diagnosed with and treated for acute HCV over a period of 10 years, the SVR rates after 48 weeks of therapy with IFN and ribavirin was 92%, though many subsequent studies reported rates of 60–75%.[74-76] Direct-acting antivirals seem to improve this outcome and enable a shorter treatment course; for example, in a small study of HIV-infected men treated for acute HCV genotype 1 infection with a 12-week course of telaprevir, PEG-IFN and ribavirin, the SVR rate was 84%. [77] Although additional randomized studies are needed to determine the optimal duration of IFN-based therapy as well as efficacy of IFN-free regimens, it would seem that all acute HCV infections, even in HIV-infected persons, should be treated. Comprehensive guidelines for the treatment of acute HCV infection among HIV-infected patients are summarized by the NEAT (European Aids Treatment Network) consensus conference. [26]

Chronic HCV—Multiple studies have shown significant benefits associated with the successful treatment of chronic HCV infection, including halting progression of fibrosis and reducing rates of hepatic decompensation. These benefits have been observed in persons with HCV monoinfection as well as those co-infected with HIV and HCV. [78-84]. These findings are particularly important in view of the observations that co-infected patients with advanced fibrosis progress rapidly to decompensated liver disease. [85, 86] It is therefore important to adopt a comprehensive approach that integrates prognostic information with recognition of the changing landscape of antiviral therapy and to identify co-infected patients for whom deferral of therapy is not an option. Until all-oral direct-acting antiviral regimens become widely available, we recommend assessing the stage of fibrosis and strongly considering treatment for those with advanced fibrosis.

The previous standard therapy of PEG-IFN and ribavirin for HCV infection is associated with significantly inferior SVR rates among co-infected patients, particularly in genotype 1 infection, with SVR rates of <30% in several studies. [87-93] compared with typical SVR rates in HCV-monoinfected patients of ∼40%. [94] A study conducted in a public health setting in Brazil observed a similarly low SVR rate (27%) as those observed in clinical trials. [95] The use of weight-based ribavirin (compared to fixed low-doses of ribavirin) and extended duration of therapy has resulted in increased SVR rates, as demonstrated in the PRESCO trial in co-infected patients (SVR 50%) [96] In addition, avoidance of antiretroviral drugs such as zidovudine, didanosine, and stavudine in combination with ribavirin is recommended, given the risks of severe anaemia, pancreatitis, and lactic acidosis. [97-101]

The addition of first generation HCV NS3/4A protease inhibitors, such as telaprevir or boceprevir, in conjunction with PEG-IFN and ribavirin for a total treatment course of 48 weeks, led to significantly greater responses, with SVR rates of 74% and 63%, respectively in two phase II studies. [102, 103] In a single-arm, open-label phase III trial of genotype 1 HCV treatment-naïve and treatment-experienced patients co-infected with HIV, 72% achieved undetectable HCV RNA at week 12 after response-guided therapy with telaprevir, PEG-IFN, and ribavirin, comparable to SVR rates observed in HCV monoinfection trials.

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[104, 105] In addition, interim data from two ANRS (French National Agency for AIDS Research) studies of co-infected patients with prior virologic failure on PEG-IFN and ribavirin therapy revealed unexpectedly high efficacy results of triple HCV therapy: at week 48, the SVR rate for telaprevir, PEG-IFN and ribavirin was 83%, while the SVR rate for boceprevir, PEG-IFN, and ribavirin was 56%. [106, 107] Of note, the studies included a considerable portion of patients with advanced fibrosis and there was no difference in response according to fibrosis at baseline. However, these protease inhibitors need to be taken three times a day and are associated with multiple adverse reactions, including rash and anaemia. In addition, several ART regimens are excluded owing to drug–drug interactions.

'Second generation' HCV protease inhibitors with more favourable tolerability and dosing intervals have been increasingly studied in the co-infected population. Simeprevir is a once-daily HCV protease inhibitor; when given for 12 weeks in combination with PEG-IFN and ribavirin (which were continued for a further 12–36 weeks in a response-guided therapy paradigm) among co-infected individuals with HCV genotype 1, the overall SVR12 was 74%, which included an impressive SVR of 57% in prior null responders. [108] Simeprevir does interact with HIV protease inhibitors and efavirenz, and thus most study patients were placed on raltegravir-based ART. Faldaprevir, another second generation protease inhibitor taken once daily, was studied with PEG-IFN and ribavirin in patients with HIV and HCV genotype 1 co-infection (including both HCV treatment-naïve and prior relapsers), and the overall SVR rate at 4 weeks was 74%. In this study (STARTVerso4), response-guided therapy was utilized and patients were permitted to use the ritonavir-boosted HIV protease inhibitors atazanavir, darunavir and the non-nucleoside reverse transcriptase inhibitor efavirenz. [109]

Other direct-acting antiviral classes are of interest because of their efficacy and reduced propensity to cause drug–drug interactions. Sofosbuvir, a direct-acting NS5B nucleotide polymerase inhibitor approved by the FDA in December 2013, has potent antiviral activity against all HCV genotypes, and has been associated with high SVR rates, a high barrier to resistance, and better tolerability compared to IFN-based regimens in several phase II trials among patients with chronic HCV infection. [110-112]. In addition, because it is a nucleotide analogue that does not rely on cytochrome P450 for its metabolism, it averts significant drug interactions with ART. In the PHOTON-1 study, co-infected patients who were HCV treatment-naïve received an IFN-free regimen of once-daily sofosbuvir and ribavirin for either 24 weeks (genotype 1) or 12 weeks (genotype 2 and 3), and SVR rates at 12 weeks were 76%, 88% and 67% in genotypes 1,2, and 3, respectively [113]– rates similar to sofosbuvir and ribavirin use in HCV monoinfection. [114]

Combination regimens containing two or more direct-acting antivirals seem to have the potential for very high cure rates in HCV monoinfection; for example in the LONESTAR study the combination of sofosbuvir and the NS5A inhibitor ledipasvir once daily with or without ribavirin for 12 weeks led to SVR rates of 95% in genotype 1 infection. [115] In the COSMOS study, 12–24 weeks of sofosbuvir and simeprevir with or without ribavirin led to SVR rates as high as 96% in genotype 1 noncirrhotic prior nonresponders. [116] In both the LONESTAR and COSMOS studies, SVR rates without ribavirin were similar to those with

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ribavirin. Studies of these (and other) direct-acting antiviral combinations in HIV-infected patients are eagerly awaited. [117, 118]

Furthermore, additional data are needed to better elucidate the contribution of factors such as IL28B genotype in predicting virologic response to all-oral direct-acting antiviral agents. Genome-wide association studies have identified an association between the single nucleotide polymorphism (SNP) rs12979860 and achievement of SVR among HCV-monoinfected patients,[119, 120] and this association has been similarly observed among patients co-infected with HIV and HCV.[121] Patients with the favourable genotype (CC) experience improved viral kinetics, particularly during the initial weeks of therapy. [122] Interestingly, studies among co-infected patients have reported that the association between IL28B genotype and SVR varies according to HCV subtype: for example, in a Spanish study of HCV-treatment-naive co-infected patients receiving PEG-IFN and ribavirin, the positive effect of the favourable CC genotype on HCV viral clearance was observed among those with HCV 1b genotype but not those with HCV 1a. [123] Whether the association between IL28B genotype and achievement of SVR will persist with interferon-free regimens remains unclear and is an active area of research among HCV-monoinfected and co-infected patients. For example, the LONESTAR study examined the interferon-free regimen of sofosbuvir and ledipasvir with or without ribavirin in 100 genotype 1 HCV-monoinfected patients. In this study, 97 patients achieved SVR at 12 weeks, even though only 15 patients had a favourable IL28B CC genotype.[115]

Suggested management algorithm

With the approval of simeprevir and sofosbuvir (in November 2013 and December 2013, respectively), adding to the armamentarium of available antiviral therapies, patients co-infected with HCV and HIV and their physicians will have complex conversations surrounding when to treat HCV and with what agents. For many patients, it is clear that there is a benefit to waiting **the approval of new direct-acting antiviral agents and the availability of interferon-free treatment regimens (particularly for patients with genotype 1 infection**), while monitoring fibrosis and cirrhosis, with an expectation of initiating treatment in the next 1–2 years in view of the more accelerated natural history of liver disease in these patients. However, for co-infected patients with advanced fibrosis or cirrhosis, HCV therapy should be strongly considered immediately, particularly in recognition of the increased risk of decompensation as well as potential unforeseen delays in the approval of all-oral direct-acting antivirals.

On the basis of available data among co-infected patients as well as data from HCV-monoinfected patients, we recommend the following management algorithm for patients co-infected with HIV and HCV who are naïve to HCV therapy (Table 2) First, every patient co-infected with HCV and HIV should be considered for ART. Second, every patient should have an assessment of fibrosis (Figure 4). Multiple noninvasive scoring systems have been tested among HCV monoinfected patients, including APRI (aspartate aminotransferase/ platelet ratio index), FIB-4, and the Forns index and are accurate for diagnosis of cirrhosis but not for stages F2–F4. [124] Several of these scoring systems have been studied among co-infected patients and found to perform similarly, despite the reduced platelet counts more

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commonly observed among patients infected with HIV. [125, 126]. Transient elastography is another noninvasive modality with high accuracy for diagnosis of F3+ and cirrhosis. Several studies have suggested the predictive value of hepatic fibrosis stage (with either liver biopsy or hepatic stiffness) for the development of liver-related complications [127], and reduction in liver stiffness after HCV therapy has been observed [128, 129]. A liver biopsy might still be required if an indeterminate stage of fibrosis is found using serum testing and/or transient elastography.

For those with minimal-to-moderate disease (F0–F2), deferring HCV therapy might be considered among patients infected with HCV genotype 1 and 4 until even more effective all-oral regimens are available by 2015. For patients with genotype 2 and minimal to moderate disease, therapy with sofosbuvir (400 mg daily) and weight-based ribavirin for 12 weeks should be considered. For those with genotype 3, therapy with sofosbuvir (400 mg daily) and weight-based ribavirin for 24 weeks is recommended.

For patients infected with HCV genotype 1 with significant fibrosis or compensated cirrhosis (F3–F4) who are eligible for PEG-IFN, HCV therapy with sofosbuvir (400 mg daily) plus PEG-IFN α2a (180 mcg subcutaneous once weekly) and weight-based ribavirin for 12 weeks should be initiated. For interferon-intolerant or ineligible patients, treatment with sofosbuvir plus ribavirin for 24 weeks could be considered, although this regimen has limited efficacy in patients with cirrhosis. Another possibility in interferon-intolerant or ineligible patients would be sofosbuvir plus simeprevir for 12 weeks, although permitted antiretroviral regimens with simeprevir are currently limited to raltegravir, rilpivirine, maraviroc, tenofovir, emtricitabine, lamivudine, and abacavir. For patients infected with HCV genotype 2, we suggest sofosbuvir (400 mg daily) and weight-based ribavirin for 12 weeks. For genotype 3 patients, sofosbuvir (400 mg daily) and weight-based ribavirin for 24 weeks is recommended.

For genotype 4 patients who are IFN eligible, we suggest initiating HCV therapy with sofosbuvir (400 mg daily) plus PEG-IFN alpha 2a (180 mcg SC every week) and weight-based ribavirin for 12 weeks. For IFN-intolerant or ineligible patients, sofosbuvir plus ribavirin for 24 weeks could be used, although this regimen has limited efficacy in cirrhosis.

Even with successful SVR, continued screening for hepatocellular carcinoma and esophageal varices should be performed, given that complications of advanced fibrosis and cirrhosis, although substantially reduced, are not eliminated. For patients who obtain an SVR with therapy but remain at risk for reinfection (for example, MSM who engage in any risk behaviour or injection drug users), HCV RNA should be measured annually to assess for reinfection. It should be noted that once more tolerable and safer regimens are available, it will be likely that *all* HIV-HCV co-infected patients will be offered HCV treatment regardless of their fibrosis stage; indeed those with a lower fibrosis stage will have a higher likelihood of achieving SVR.

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Conclusion

The past 20 years have marked a period of significant achievement in HIV and HCV research. With the introduction of ART, a significant reduction in HIV-related morbidity and mortality has been observed. Similarly, improved understanding of the HCV life cycle and virus–host interactions has led to the development of potent antiviral agents associated with increased rates of cure among HCV-monoinfected patients as well as those with HIV and HCV co-infection. Furthermore, new insight have been made into the multiple mechanisms of HCV and HIV pathogenesis that lead to accelerated disease progression. However, despite these advances, patients co-infected with HCV and HIV remain at highest risk of accelerated liver disease and mortality.

There exist unique challenges ahead in translating these achievements to increased rates of cure in a historically difficult-to-treat population. These challenges include: improving the detection rate of co-infection; increasing the rates of treatment uptake; developing individualized approaches to treatment that incorporate information regarding fibrosis stage, efficacy and tolerability according to genotype; and minimizing potential drug interactions between HCV and HIV therapeutic regimens. It is expected that the revolution in direct-acting antivirals will greatly enhance the number of persons with co-infection capable of being successfully treated.

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Box 1

Overview of Fibrosis

Hepatic fibrosis is the accumulation of extracellular matrix including collagens, fibronectin and proteoglycans into the space of Disse, the area between the hepatocytes and the hepatic sinusoids, and occurs in response to liver injury.130 Marked progress has been made in the understanding of hepatic fibrogenesis, including the key role of the hepatic stellate cell. Originally described by Kupffer in the 19th century, the hepatic stellate cell is now recognized for its versatility: in the quiescent state, it serves as the main reservoir for vitamin A in the liver; however, upon activation, the structure of stellate cells changes significantly and they evolve into myofibroblast-like cells. They migrate and accumulate at the sites of tissue repair, secreting large amounts of extracellular matrix. Moreover, they secrete a multitude of growth factors and cytokines that stimulate inflammation, fibrosis, contraction and mitosis.[130] Transforming growth factor beta 1 (TGF-β1) is one of the best-characterized cytokines expressed following liver injury, and upregulation occurs through several mechanisms. For example, reactive oxygen species (ROS) are oxygen-containing free radicals that cause injury through DNA mutations and lipid peroxidation, and arise with dysregulation of the electron transport chain in hepatic mitochondria.[131] With production of ROS, activation of several pathways occurs, including extracellular signal-related kinase (ERK), c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (p38 MAPK), and each pathway leads to the upregulation of nuclear factor κB (NFκB) and the induction of expression of TGF-β1.51 Additional cytokines released during fibrogenesis include angiotensin II, endothelin-1, platelet-derived growth factor and platelet activating factor. Another potent trigger of hepatic fibrogenesis is hepatocyte apoptosis, which occurs via two signalling pathways; the extrinsic pathway in response to extracellular stimuli, or the intrinsic (or mitochondrial) pathway, instigated in response to intracellular stimuli such as ROS production or DNA damage. [132] Engagement of these pathways leads to the formation of apoptotic bodies, which activate stellate cells.[133] These activated stellate cells phagocytose the apoptotic bodies and produce TGF-β1 [134] and tissue inhibitor of metalloproteinase 1 (TIMP1), promoters of hepatic fibrosis. [135]

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Key Points

- Patients co-infected with HCV and HIV are at increased risk of accelerated disease progression, resulting in higher rates of liver decompensation and death
- HIV accelerates HCV-related fibrosis progression through multiple mechanisms
- HIV suppression seems to reduce fibrosis progression and decrease rates of hepatic decompensation among co-infected patients
- Successful HCV therapy is associated with a halting of fibrosis progression and decreased complications from end-stage liver disease, but historical rates of sustained virologic response have been significantly lower among co-infected patients than those for chronic HCV monoinfection
- There are promising data for all oral DAAs suggesting improved efficacy and tolerability, which supports their use in co-infection

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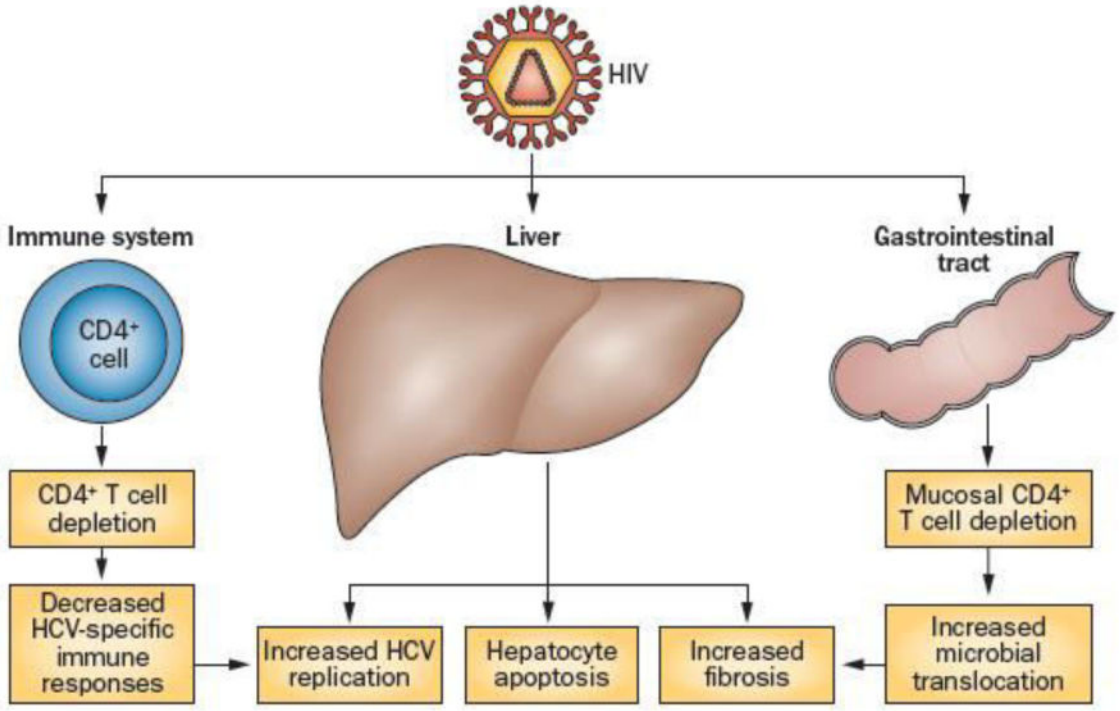

Figure 1. Driving factors underlying liver disease pathogenesis in HCV/HIV co-infection

Driving factors underlying liver disease pathogenesis in HCV–HIV co-infection. HIV infection leads to an impaired immune response against HCV, increased HCV replication, hepatic inflammation and apoptosis, increased microbial translocation from the gastrointestinal tract and increased fibrosis.

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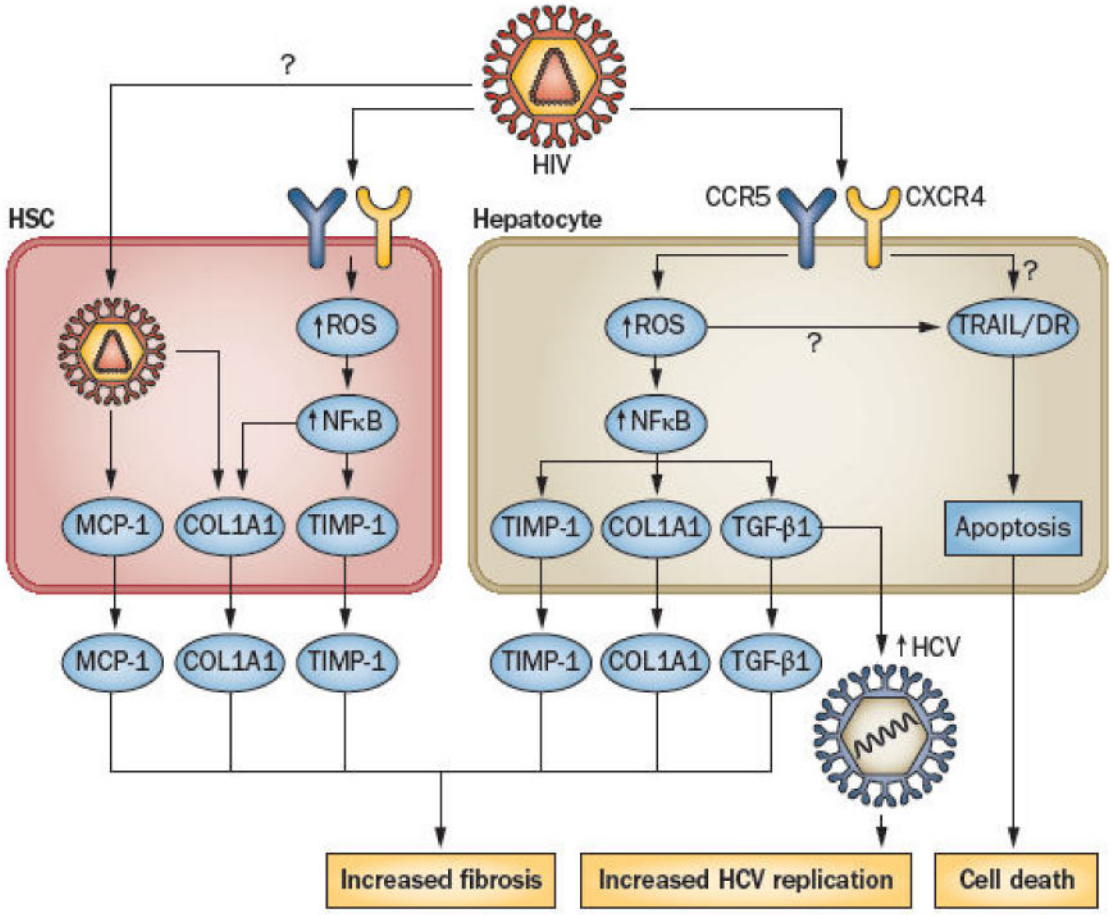

Figure 2. Interactions between HCV and HIV in hepatocytes and hepatic stellate cells that contribute to hepatic fibrogenesis

In the liver, HIV has indirect effects on HSCs and hepatocytes. HIV might be able to infect HSCs, but can indirectly lead to increased production of ROS. This increased level of ROS, in turn, leads to increased production of MCP and TIMP-1, two highly profibrotic proteins, along with COL1A1, a component of the extracellular matrix. In hepatocytes, exposure to HIV also increases ROS, TIMP-1 and COL1A1 production, but also increases TGF-β1 production, which drives fibrosis and increases HCV replication. In both HSCs and hepatocytes these effects can be abrogated by inhibition of the transcription factor NFκB. Finally, hepatic apoptosis is induced by HIV exposure through upregulation of TRAIL binding to DRs, leading to cell death. Abbreviations: CCR5, C-C chemokine receptor type 5; COL1A1, type 1 collagen; CXCR4, C-X-C chemokine receptor type 4; DR, death receptor; HSC, hepatic stellate cell; MCP-1, monocyte chemoattractant protein 1; ROS, reactive oxygen species; TGF-β1, transforming growth factor beta-1; TIMP-1, tissue inhibitor of metalloproteinases; TRAIL, TNF-related apoptosis-inducing ligand.

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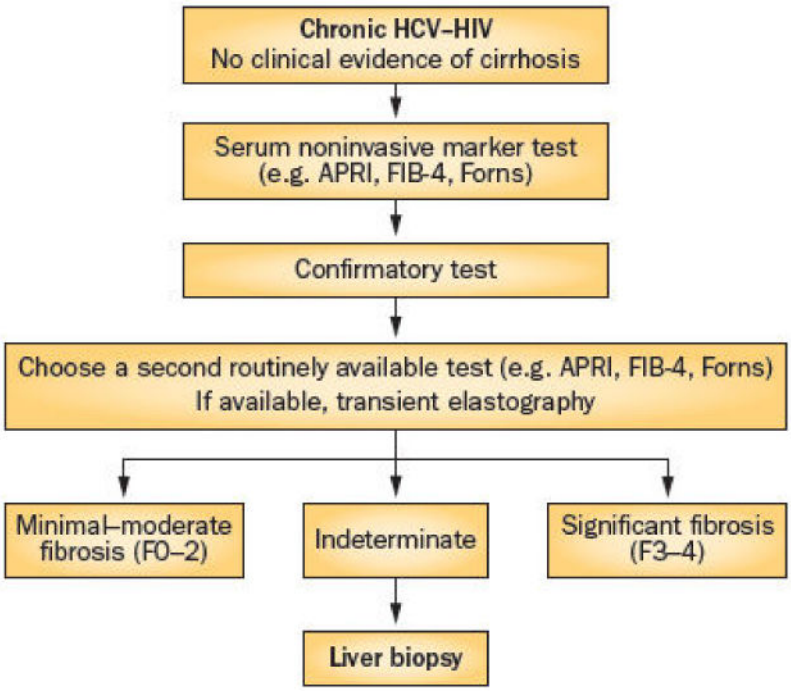

Figure 3. Algorithm to assess fibrosis in patients co-infected with HCV and HIV

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Table 1
Summary of HCV Treatment Outcomes Among HIV-HCV Coinfected Patients

Study	Treatment	SVR	Comments
Zylberberg *et al*. (2000) [93]	IFNα + RBV(*n* = 21) (genotype 1 = 10, genotype 2 = 2, genotype 3 = 7, genotype 4 = 2)	14%	Treated for a mean period of 8.5 months All patients on ART
Chung *et al*. (2004)[89]	PEG-IFNα + RBV (*n* = 66) versus IFN + RBV (*n* = 67) for 48 weeks	27% versus 12%	∼80% were infected with genotype 1 ∼85% patients in each arm on ART
Carrat *et al*. (2004)[90]	PEG-IFNα + RBV (*n* = 205) versus IFNα + RBV (*n* = 207) for 48 weeks	27% versus 20%	∼50% were infected with genotype 1 ∼80% patients in each arm on ART
Sulkowski *et al*. (2013) [103]	PEG-IFNα + RBV + boceprevir (*n* = 64) or PEG-IFNα + RBV + placebo (*n* = 34) for 48 weeks total	63% versus 29%	All patients were genotype 1 All patients on ART Similar SVR to HCV-monoinfected patients
Sulkowski *et al*. (2013) [102]	PEG-IFNα + RBV + telaprevir (*n* = 38) or PEG-IFNα + RBV + placebo (*n* = 22) for 48 weeks total	74% versus 45%	All patients were genotype 1 82% in telaprevir arm and 73% in placebo arm on ART Similar SVR to HCV-monoinfected patients
Sulkowski *et al*. (2013) [113]	Sofosbuvir + RBV in genotype 1 (*n* = 114, 24 weeks) and genotype 2 or 3(*n* = 68, 12 weeks)	Genotype 1: 76% Genotype 2: 88% Genotype 3: 67%	85–98% on ART Similar SVR to HCV-monoinfected patients

Abbreviations: ART, antiretroviral therapy; RBV, ribavirin; SVR, sustained virologic response.

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Table 2
Treatment recommendations for HCV treatment-naive co=infection patients

Genotype	Limited or no fibrosis (F0–F2)	Advanced fibrosis or cirrhosis (F3–F4)
Genotype 1	Consider deferral of therapy or SOF + PEG-IFN + RBV for 12 weeks PEG-IFN-ineligibte: SOF + RBV for 24 weeks SMV + SOF for 12 weeks on selected ART*	SOF + PEG-IFN + RBV for 12 weeks PEG-IFN-ineligible: SOF + RBV for 24 weeks SMV + SOF for 12 weeks on selected ART*
Genotype 2	SOF + RBV for 12 weeks	SOF + RBV for 12 weeks
Genotype 3	SOF + RBV for 24 weeks	SOF + RBV for 24 weeks
Genotype 4	Consider deferral of therapy or SOF + PEG-IFN + RBV for 12 weeks PEG-IFN-ineligible: SOF + RBV for 24 weeks	SOF + PEG-IFN + RBV for 12 weeks PEG-IFN-ineligible: SOF + RBV for 24 weeks

* Permitted ART with simeprevir: raltegravir, rilpivirine, maraviroc, tenofovir, emtricitabine, lamivudine and abacavir. Abbreviations: ART, antiretroviral therapy; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.