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HIV/HCV Coinfection Natural History and Disease Progression, A Review of The Most Recent Literature

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Abstract

Purpose of Review—Up to one third of HIV-infected patients are infected with HCV. It is now widely accepted that HIV accelerates the course of HCV-related chronic liver disease. The improved survival of HIV patients after successful ART has led to a significant decline in HIV-related morbidity, and liver disease caused by HCV infection has emerged as a major threat to the survival of HIV patients. HIV/HCV coinfected patients have a more rapid progression to cirrhosis and its complications than HCV monoinfected patients. Even though the effect of HCV on HIV infection and disease progression is less clear, most advocate early anti-HCV treatment to reduce the risk of chronic liver disease.

Recent findings—Recent studies support current recommendations to begin ART early in the course of HIV infection in order to limit progression of liver disease in co-infected patients. HIV co-infection has a negative impact on HCV pathogenesis, and despite increased risk of drug-related hepatotoxicity, successful response to ART might lessen progression of chronic liver disease and improve response to anti-HCV therapy.

Summary—HIV infection affects rate of liver disease progression in those with HCV coinfection. Treatment of HIV may result in slower rates of progression and liver mortality.

Keywords

HIV; HCV; Coinfection; Natural history; progression

Introduction

There are 33.3 million people globally living with HIV infection. It is estimated that approximately 20–30% of HIV patients are also infected with hepatitis C (HCV). The main source of HCV transmission is the blood-borne route; this fact explains the high rates of HIV/HCV co- infection among IV drug users (IVDU) with prevalence rates reported as high as 90%. Coinfection is also common among hemophiliacs who received contaminated blood or blood products prior to the implementation of routine serologic screening of donated blood for HCV (1, 2). The risk of transmission of HCV via percutaneous route is 10-fold higher than the risk of transmission of HIV, therefore, a much higher prevalence of HCV than HIV-1 is seen among injection drug users, and while co-transmission of both viruses can occur, coinfected individuals with percutaneous exposure were usually infected first with HCV (2,3).

Transmission of HCV via sexual intercourse occurs less frequently; the reported prevalence of HCV infection among long term sexual partners of HCV positive individuals is between

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2–8%. However, the risk of infection is higher among people reporting high risk sexual practices (anal intercourse, multiple sexual partners). Vertical transmission of HCV is uncommon; the reported risk of transmission of hepatitis C from a HCV positive mother to her child ranges between 2–5%, and the risk is threefold higher if the mother is also HIV positive (3,4).

Following acute HCV infection 90% of HIV patients will develop chronic disease. This is significantly higher than the risk of chronicity among those with HCV monoinfection where more than 30% of infected individuals will spontaneously clear the virus (5,6).

HIV and Its Effect on Chronic HCV

The negative impact of HIV infection on hepatitis C is well described. HIV infection has been associated with persistent HCV viremia, higher HCV viral load, and with reduced response to interferon-based HCV therapy. The increased risk of chronic HCV infection and the higher HCV RNA levels seen among HIV infected patients are believed to be in part related to a decline in CD4 and CD8 T-cell response to HCV infection. It has been hypothesized that virus specific T-cell responses play a role in the control of virus during chronic HCV, and the quantitative loss of memory lymphocytes that occurs in HIV infection could potentially be responsible for the elevated HCV RNA levels observed in co-infected patients (7, 8, 9). However, it is possible that HIV proteins (tat, gp120) or HIV itself directly mediates the hepatic cytokine mileau through binding (and possibly entry) into hepatocytes, stellate cells, and immune cell population resident in the liver (10). This hypothesis is supported by the observation that HIV is associated with a decline in HCV-specific interferon (IFN)-gamma responses, related to the CD4 count in the periphery with IFN-gamma known to exert an inhibitory effect on the replication of HCV in vitro. These responses are preserved in people who avoid significant HIV-related progression, either by use of antiretroviral drugs or due to spontaneous control of HIV. In addition to quantitative changes of T-cells, HIV may induce qualitative defects in immune responses through alteration of cytokine secretion profiles, and/or dendritic cell function. Innate effectors such as natural killer (NK) cells and natural killer T (NKT) cells also mediate antiviral defenses. Disruption of NK cell function such as increased activation or decreased cytokine secretion induced by HIV-1 could also be responsible for the development of chronic HCV (11,12).

Additionally, during acute HCV infection, a HCV specific CD4+ response is seen first followed by the rapid release of HCV specific CD8+ cells. Some of the mechanisms proposed to explain the uncontrolled proliferation of HCV among HIV patients are the escape of the HCV virus from the immune response through sequence evolution or T-cell dysfunction.

With the critical role of the adaptive immune system in resolving HCV and the detrimental effect of HIV-1 infection on T-cells, it was perhaps predictable that HCV persistence would be more common in HIV/HCV coinfection, especially if HIV precedes HCV and has already induced impairment of CD4 function. In this scenario, the primary HCV response may be insufficient to control HCV. To support this assumption, there is evidence that use of HAART partially restores T-cell responses to core HCV peptides. Successful response to ART among HIV/HCV patients is associated with increased cellular immune responses to HCV infection, long-term reduction in HCV RNA levels and with HCV clearance (9, 11, 12).

Intrinsic genetic factors have also been implicated in the pathogenesis of chronic liver disease among HIV/HCV patients. A study conducted on HIV/HCV co-infected patients known to be natural viral suppressors (NVS; HIV-1 patients with the ability to suppress HIV viral loads to less than 400 copies) demonstrated higher rates of spontaneous HCV clearance

when they were compared to historic mono-infected and co-infected controls. NVS patients showed a 23.3% rate of spontaneous HCV clearance compared to 9.1% for HCV mono-infected patients, and 6.5% for HIV/HCV co-infected patients. This finding suggested a common genetic factor accounting for either adaptive or innate immune response to viral infection. Of importance, NVS patients with chronic HCV infection had statistically significant reduction of CD4 cells and CD4 %, suggesting a possible detrimental effect of HCV on HIV infection (13,14).

The SWISS cohort study group recently showed that after successful ART, HIV/HCV coinfected patients had an increased response to HCV core peptides and had a slight decrease in HCV RNA levels compared to pre-ART viral levels (14). These findings support recent recommendations to start ART early in the course of HIV infection to limit the progression of liver disease among co-infected patients.

It is clear that HIV co-infection has a negative impact on HCV pathogenesis, and despite the increased risk of drug-related hepatotoxicity, it is strongly suggested that successful response to HAART restores cellular immune response to HCV antigens and might lessen the progression of chronic liver disease and improve the response to anti-HCV therapy which supports the early initiation of ART (15).

HIV/HCV Co-infection and Accelerated Hepatic Fibrosis Progression Rates

Co-infection with the human immunodeficiency virus (HIV) and manifest by low CD4 count, along with alcohol use are the most common factors associated with rapid fibrosis progression to cirrhosis. The mechanisms associated with accelerated fibrosis progression rates among HIV/HCV co-infected patients are not well understood, but multiple hypotheses have been proposed. These include a direct viral effect on the hepatocytes and/or stellate cells, and many immunologic alterations such as diminished HCV specific T-cell responses, immune activation, increased hepatocyte apoptosis and immunologic dysregulation that promotes hepatic fibrosis (10,11).

Once chronic HCV infection is established faster fibrosis progression rates (FPR) are seen among HIV patients. A meta-analysis of eight separate studies investigating the role of HIV on liver disease in HCV-infected patients found that HIV/HCV co-infected patients had approximately two times the risk of cirrhosis diagnosed on liver biopsy and approximately six times the risk of decompensated liver disease (severe liver disease accompanied by clinical conditions including ascites, varices, or encephalopathy) when compared to HCV-monoinfected patients (9, 10). Moreover, a study conducted in 1996, showed that a decline in CD4 counts among HIV and HCV co-infected patients was independently associated with death in a cohort of hemophiliac patients (16).

Multiple hypothesis have been proposed to explain the faster FPR seen among HIV/HCV co-infected patients; it has been proposed for example, that HIV present in the liver can promote fibrosis by exerting an indirect effect on hepatocytes via CCR5 and CXCR4 co-receptors for HIV-1 that are expressed in hepatocytes and other liver cells.

It has also been postulated that among HIV patients alteration in the balance between CD4 and CD8 T cell activities with a predominant CD8 cell response is mediated by cytokines such as IL-4, IL-5 and TGF-α which promote collagen deposition by fibroblasts and accelerate FPR among HIV/HCV co-infected patients. It has been observed that accelerated fibrosis is most pronounced when peripheral blood CD4 T-cell counts are decreased (11,12).

The hypothesis that relates HIV infection with an overactivated and deranged immune system causing depletion of CD4+ T-cells and accelerated FPR among HIV/HCV patients

has been tested multiple times with conflicting results. Some studies have shown that HIV/HCV patients are at increased risk for faster fibrosis progression and development of portal hypertension when CD4 cell nadirs are low, some others have found CD4 T cell counts to be an independent predictor of fibrosis, especially when the CD4 counts drop below 200/mL (17,18).

A large study found that CD4 cell gains lower than 100/mL was associated with mortality due to liver failure. In opposition, a recent study reported that a decline in CD4 cell count to be an independent determinant of death because of liver failure in hemophiliacs (18).

The mechanism by which reduced CD4 cell counts promote hepatic fibrosis has been explained by a reduction in IFN-gamma (an antifibrotic cytokine) secretion by CD-8 T cells as CD4 counts decline. A direct role of HIV in promoting fibrosis in the liver has also been postulated. HIV-1 causes direct activation by single-stranded HIV RNA of TLR, which then activate lymphocyte or dendritic cell subsets that ultimately results in polyclonal B-cell activation and increased expression of multiple activation markers in CD4 and CD8 T cells and promotes CD4 T cell depletion (19).

Another pathway that could mediate the negative effects of HIV-1/HCV coinfection on liver fibrosis is the tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), also called Apo-2L, which induces apoptosis in transformed cells (19, 20,21). TRAIL can induce apoptosis in normal human hepatocytes, but its effects are more pronounced in inflammatory conditions, such as during HCV infection; TRAIL is up-regulated by TGF-α. CD4 T cells are more susceptible to TRAIL-induced cell death, possibly induced by IFN-γ in HIV-1–infected individuals, which is in turn associated with increased levels of circulating TRAIL. Overall the continuous cycle of cell death and regeneration among lymphocytes and hepatocytes is likely to promote fibrogenesis (19, 20, 21).

A direct effect of the HIV virus on hepatocytes has also been explored as a potential source for the accelerated FPR among HIV/HCV patients, and although HCV viral titers are particularly high in the presence of HIV-1, and there is increasing evidence that HIV replicates in hepatocytes and hepatic stellate cells (HSC), a direct correlation of fibrosis with viral titers has not been confirmed. Brau et al. found that HIV/HCV coinfected patients with undetectable HIV RNA through HAART had a slower FPR than those with any HIV RNA level and an FPR similar to HCV-monoinfected patients. This study suggested that suppression of HIV infection through HAART was associated with a slower HCV-induced liver fibrosis progression rate and that HIV viremia and not CD4 cell count independently predicted FPR. These data imply that in coinfected individuals, treatment of HIV before significant T cell depletion could help preserve HCV-specific immunity and prevent fibrosis progression (22).

Finally, it is important to recognize that there are several additional factors that could lead to more severe liver disease in HIV/HCV coinfected patients; those include drug related hepatotoxicity, concurrent use of drugs and alcohol, and steatosis related to metabolic syndrome.

Effect of HCV infection on HIV progression

There are conflicting reports on the effect of HCV infection on the natural history of HIV disease. Multiple studies have addressed this issue. The Swiss HIV cohort study for example found that in the first year of HAART, HCV seropositive patients had smaller increases in CD4 lymphocytes than HCV seronegative patients, but this difference disappeared during the 4 years the study patients were followed. The EUROSIDA study in the other hand, did

not find an effect of HCV serostatus on HIV disease progression but there was an increased risk of liver related deaths among HCV co-infected patients (23, 24).

Another study performed at a Baltimore HIV clinic found no difference in the progression to AIDS or death among HCV co-infected patients after adjustment for exposure to HAART and HIV suppression. Conversely, Greub and colleagues found that after effective ART, HIV/HCV patients had a modest increased risk of progression to a new AIDS defined illness or death. HCV coinfection has been reported to have a modest negative effect on the magnitude of CD4 T cell reconstitution following antiretroviral therapy in some cohorts (25).

A review of 8 cohort studies showed that the CD4 cell count response for patients with HIV/HCV coinfection after they started receiving HAART was less than that for patients with HIV infection alone by an average 33.4 cells/mL. The findings suggested that HIV-infected patients were more likely to have a better immunological response to antiretroviral therapy if they are not coinfected with hepatitis C (26). In contrast, Al-Harti et al, showed that among a cohort of HIV/HCV co-infected women, HCV was associated with an increase in CD4+ and CD8+ primed/memory T cells, but did not alter the immune response to HAART (27). More recently, the structure of the women and infants transmission study (WITS) found that after controlling for pregnancy, CD4+ cell percentages and HIV RNA levels, there was no evidence that HCV coinfection accelerated the progression of HIV disease (28).

The mechanisms by which chronic HCV replication could have a deleterious effect on CD4 cell count reconstitution include ongoing T cell activation related to HCV infection that could limit the immunologic responses of patients with sustained viral suppression on ART. Other implicated mechanisms include direct infection of CD4 T cells by HCV that has been shown to be lymphotropic in the setting of HIV coinfection. Negative strand RNA has been detected in both CD4 and CD8 T cells as well as in monocytes which may lead to direct interactions between these viral pathogens that could influence CD4 cell recovery (28, 29, 30).

Conclusion

Despite the adverse clinical consequences of HIV/HCV co-infection, the mechanisms by which these two viruses interact at the cellular level remain largely unexplored. At present, the overall literature suggests that the major contribution of HCV to mortality of coinfected individuals is attributable to accelerated liver disease and not increased AIDS-related complications (31, 32). A better understanding of the interactions between these two viruses is vital to the development of novel treatment strategies to control HIV/HCV co-infection.

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Key Points

- Liver disease progression is accelerated in patients with HIV/HCV coinfection compared to those with HCV alone
- Early treatment of HIV may slow liver disease progression
- Liver disease progression is multifactoral and may be associated with immune activation, the interaction of HIV and HIV protein products with stellate cells, hepatocytes, and immune cells dwelling in the liver