

HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE

HUMAN IMMUNODEFICIENCY VIRUS AND HEPATITIS C VIRUS CO-INFECTION

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ABSTRACT : Hepatitis C virus (HCV) infection is a major cause of liver disease and hepatocellular carcinoma worldwide, as well as the leading cause of liver transplantations in the United States. As a result of similar modes of transmission, approximately 30% of HIV-infected individuals are co-infected with HCV. Among intravenous drug users, almost 90% of people infected with HIV are also infected with HCV. Because of treatment with highly active anti-retroviral therapy, HIV-infected individuals have improved survival and are no longer suffering from opportunistic infections and malignancy as in years past. As a result, co-infection with HCV has now become a frequent cause of morbidity and mortality in HIV-infected individuals. Furthermore, liver disease secondary to HCV infection is now the leading cause of hospital deaths in HIV-infected people in the US. HIV infection accelerates the course of HCV-related liver disease and viremia. It is less clear whether HCV infection affects the clinical course of HIV ; however, HCV-related liver disease can limit many individuals from receiving anti-HIV therapy. HIV/HCV co-infection is common, and serious. Physicians caring for HIV-infected patients worldwide must now address hepatitis C virus co-infection.

PREVALENCE

HIV/HCV co-infection is common ; and occurs in approximately 15-30% of HIV-infected people in the US and Europe, with the rate varying according to the mode of transmission [1]. In urban areas, where intravenous drug use (IDU) is more common, almost 50% of all HIV-infected people are HCV co-infected. Although both HIV and HCV can be transmitted by percutaneous exposure to blood, HCV is approximately 10 times more infectious than HIV. The rate of transmission after a needle stick injury is estimated to be 3‰ for HIV but 15 to 30‰ for HCV. The transmission of percutaneous HIV and HCV has decreased since the screening of blood

products for HIV in 1985, and HCV in 1990. The HCV epidemic in the US and Europe predated the HIV epidemic, so many people were infected with HCV before contracting HIV percutaneously. There are a number of risk factors for percutaneous HIV and HCV infection, in addition to IDU. Sharing straws for intranasal cocaine, tattooing, and body piercing can transmit blood borne viruses but are also much more likely to transmit HCV than HIV.

Both HIV and HCV can be transmitted sexually, but in contrast to percutaneous exposure, HIV is far more transmissible than HCV. Female sex partners of HIV/HCV co-infected men have a rate of 13% HIV infection, but only 3% HCV infection [2]. A number of studies suggest that HCV is transmitted heterosexually more often from co-infected than mono HCV-infected individuals. Some data suggests that HCV is transmitted at a slightly higher rate in men who have sex with men than heterosexually. In a cohort of men who have sex with men, subjects had an 8% higher incidence of HCV infection than age matched heterosexual controls, with no other risk factors for HCV infection [3]. Other studies however, have found no difference in the prevalence of HCV in men who have sex with men than heterosexual controls [4].

HIV and HCV can be transmitted perinatally ; however, the transmission rate of HIV remains higher than HCV. With highly active antiretroviral therapy (HAART), the rate of transmission from an HIV-infected mother to her newborn child has decreased from 20-30% to approximately 1%. HCV mono-infected mothers, transmit HCV to their newborn children about 2 to 3% of the time. Transmission is more likely from co-infected mothers [5]. Some studies have correlated HCV viral load to the rate of transmission of HCV from pregnant mother to child, with the highest rates of transmission seen in the women with the highest HCV viral loads, whether they are HIV co-infected or mono-infected with HCV.

THE EFFECT OF HIV ON THE NATURAL HISTORY OF HCV

HIV co-infection worsens the natural history of HCV infection. Death associated with HCV mono-infection results from the development of liver fibrosis and subsequent cirrhosis, liver failure and hepatocellular carcinoma. People who are co-infected with HIV are less likely to clear the HCV virus when exposed to HCV than those who are not HIV-infected. Herring et al. have recently

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reported that almost 40% of young immunocompetent intravenous drug users exposed to HCV can clear the HCV virus and not become chronically infected [6]. However, in HIV-infected individuals exposed to the HCV virus, clearance occurs in only 5-10% of people, and even less in those with low CD4⁺ lymphocyte counts [7-8].

About 6% of immunocompetent HCV-infected individuals will eventually develop liver cirrhosis and end stage liver disease over a 20-year period. HCV liver disease has an accelerated course in HIV co-infected patients. There are several theories that explain the accelerated natural history of HCV during HIV co-infection. One potential explanation is that liver disease results from the higher HCV viral loads during HIV infection, as a result of the immunodeficient state. A number of studies demonstrate that HCV viral loads are higher in HIV co-infected subjects than HCV mono-infected subjects infected for equal lengths of time. Furthermore, the CD4⁺ lymphocyte level also correlates with the HCV viral load. Subjects with more advanced HIV and lower CD4⁺ lymphocyte counts have higher HCV viral loads than the HIV-infected subjects with higher CD4⁺ lymphocyte counts. Interestingly, during HCV mono-infection, the HCV viral load has little prognostic value. The most reliable factor to predict outcome during HCV infection is the fibrotic stage of the liver.

Individuals co-infected with HIV and HCV have worse fibrosis on liver biopsy than HCV mono-infected controls and an increased rate of progression of fibrosis when compared to HCV mono-infected patients [1-9]. Also, subjects with high grade fibrosis or cirrhosis are also more likely to develop hepatocellular carcinoma if they are co-infected with HIV [10]. Martinez-Sierra et al. evaluated 41 patients with HIV/HCV co-infection and reported that they had a higher HCV viral load, more advanced liver fibrosis, and a higher liver fibrosis progression rate than did non-HIV-infected HCV patients. A high HCV load and a low CD4⁺ lymphocyte count were associated with the higher fibrosis progression rates [11]. Interestingly, in this study HAART did not influence the progression of fibrosis in the liver [12]. These results may be difficult to interpret, however, because individuals with the most severe liver disease may not be taking HAART, which requires hepatic metabolism. This demonstrates that larger prospective studies are needed to determine if lowering the HIV viral load with HAART will improve the liver fibrotic grade and slow the progression to end stage liver disease.

THE EFFECT OF HCV ON THE NATURAL HISTORY OF HIV

The effect hepatitis C has on the natural history of HIV infection is controversial. A number of studies have demonstrated that HCV infection has no impact on the HIV viral load, CD4⁺ lymphocyte count, the response to HAART or mortality [13-15]. Whereas, other investiga-

tions have shown blunted immune responses to HIV treatment and increased mortality rates, in HIV/HCV co-infected individuals compared to those infected with HIV alone [16-18]. A recent meta-analysis reported that people with HIV/HCV co-infection had poorer immune reconstitution, as determined by CD4⁺ lymphocyte count, after 48 weeks of HAART [19]. However there is little evidence to suggest that this corresponds to any physiologically relevant virologic or clinical outcome.

HCV infection is associated with a number of extra hepatic manifestations such as glomerulonephritis, insulin resistance, and cryoglobulinemia [20]. These disease states can cause renal and cardiovascular disease and possibly effect morbidity and mortality in HIV/HCV co-infected individuals. A number of reports, however, did not show greater morbidity or mortality in co-infected versus HIV mono-infected people [21-22]. Tedladi et al. examined mortality rates and presence of disease in an observational cohort of 823 HIV-infected patients with and without HCV co-infection over five years. They found no difference in renal or cardiovascular disease between the two groups, but did find more cirrhosis and transaminasemia in the HCV co-infected population. Age, CD4⁺ lymphocyte count and duration of HAART were significantly associated with survival, but HCV infection was not [21].

One way that HCV infection can affect HIV disease is by causing liver disease, which in turn limits a patient's ability to tolerate hepatically metabolized anti-HIV therapy [23-24]. There have been reports that drug related hepatotoxicity is more common in HIV/HCV co-infected patients [25-26]. However, in a large cohort of co-infected patients, 88% of people did not experience significant hepatotoxicity with HAART and no irreversible disease occurred in the patients who did experience toxicity [23]. Therefore, HCV is rarely a reason to withhold potentially helpful treatment for the HIV infection.

The demographic differences between the HIV/HCV and the HIV populations may explain some of the contradictory findings as to whether HCV affects the natural history of HIV. HIV/HCV co-infected hemophiliacs tend to have more severe hemophilia than HIV-infected alone [9]. Also, HIV/HCV co-infected people are more likely to acknowledge intravenous drug use [16]. These factors may alter the disease course intrinsically or through access to medical care.

DIAGNOSIS OF HCV IN HIV-INFECTED PATIENTS

All individuals infected with HIV should be screened for HCV infection with an enzyme immunoassay licensed to detect antibody to HCV in the blood. Patients who have a positive HCV antibody test should have further testing for HCV RNA. Although some centers use supplemental antibody testing (RIBA Ortho Diagnostics, Raritan, NJ) to confirm a positive enzyme immunoassay result, people with HIV have a higher frequency of indeterminate RIBA results. Therefore, an HCV RNA test serves to

confirm the diagnosis, evaluate the state of infection with the HCV viral load, and provide a baseline value for future reference. However, it may take weeks to develop an anti-HCV antibody during acute HCV infection, and not all people with HCV viremia develop an antibody response to the hepatitis C virus. In fact, different studies have reported between 6-20% of HIV-infected people had HCV RNA in their blood but had negative HCV antibody tests [27-28]. Therefore, anyone with HIV infection that is suspected of having acute HCV infection, or has unexplained liver disease should have an HCV RNA screen despite normal HCV antibody tests.

People who have positive HCV antibody tests but negative HCV RNA have either cleared the virus and are no longer HCV infected, or have very low HCV RNA levels below the limit of detection. If a repeat HCV RNA is negative 3-6 months later, it is reasonable to assume the patient is not HCV infected.

MANAGEMENT OF HIV/HCV CO-INFECTION

People co-infected with HIV and HCV should be screened for other causes of liver disease, counseled to avoid activities that may increase the risk of further liver damage, and assessed for anti-HCV treatment. A history and physical exam should be performed to screen for signs and symptoms of chronic liver disease. In addition, serum albumin, prothrombin time, direct bilirubin, platelet count, alanine amino-transferase and a liver ultrasound should be performed to further define the state of liver disease. This clinical evaluation should aim to exclude hemochromatosis, autoimmune hepatitis, Wilson's

disease, and cholangiopathy. If the patient is not already immune to hepatitis A or B, they should be immunized. Because alcohol ingestion and smoking are associated with accelerated progression of liver disease, HIV/HCV co-infected patients should be advised to abstain from alcohol and the use of tobacco products. Lastly, an HCV genotype should be determined. Although HCV RNA levels have little prognostic value, the HCV genotype is the best predictor for response to interferon (IFN)-based treatment [29].

Patients with HIV/HCV co-infection also should have a liver biopsy to evaluate the stage of HCV infection. The liver histology is useful to determine the fibrotic stage, which reflects the prognosis of the disease, and to rule out liver diseases such as alcohol or medication related injury, non-alcoholic steatohepatitis (NASH), or even autoimmune hepatitis. Patients who do not qualify for, or choose not to pursue anti-HCV therapy, should have a repeat liver biopsy every three years to follow the fibrotic stage of the liver. If cirrhosis develops, the patient should be screened for hepatocellular carcinoma every six months with liver imaging (such as ultrasound) and a serum alpha feta protein (AFP).

TREATMENT OF HCV DURING HIV/HCV CO-INFECTION

The recommended treatment for HCV infection is pegylated interferon plus ribavirin in patients at risk for developing cirrhosis. This would include those with a measurable serum HCV RNA and a liver biopsy showing portal or bridging fibrosis [30]. The goals of anti-HCV therapy are to suppress the virus and obtain a sustained virologic response (SVR), which represents undetectable HCV RNA after six months, and to slow the progression of liver disease. Patients with HIV/HCV co-infection have slightly lower response rates to interferon-based therapy compared to patients with HCV mono-infection.

The sustained virologic response rates of HIV/HCV co-infected patients who completed anti-HCV therapy with an HCV genotype 1 ranged from 14% to 29%. Co-infected patients with genotypes 2 or 3 had sustained virologic response rates between 44%-73% [13, 31-32]. HCV genotype 4 (found most commonly in the north of Africa and the Middle East) has response rates similar to HCV genotype 1 and HCV genotype 5 (found most commonly in Asia) has response rates similar to HCV genotypes 2 and 3. Recent trials in HIV/HCV co-infected individuals confirmed that pegylated interferon plus ribavirin is superior for achieving a sustained virologic response than standard interferon or pegylated interferon alone (Figure 1) [31].

Interferon based treatment for HCV does not increase HIV viral loads. During standard anti-HCV treatment in co-infected individuals, the CD4⁺ lymphocyte count decreased temporarily but returned to baseline after interferon therapy was complete [32-33].

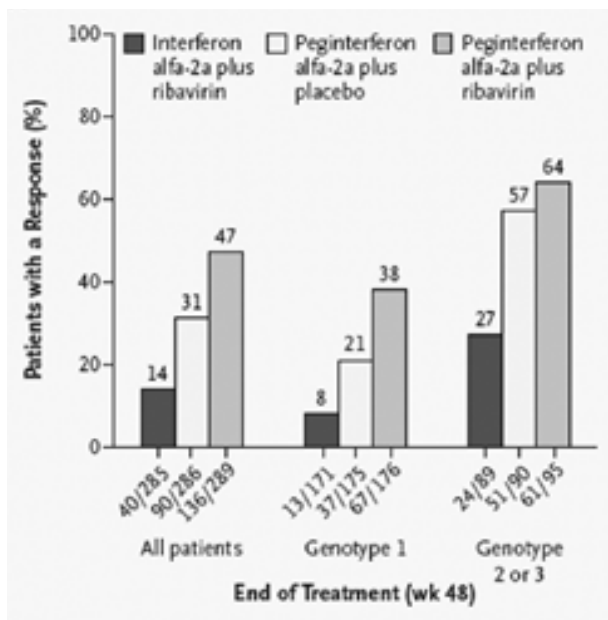


FIGURE 1

The HCV virologic response rates in HIV/HCV co-infected patients after 48 weeks of therapy, as reported by Torriani et al. in 2004 [31].

Interferon therapy is associated with many adverse effects. Interferon frequently causes a “flu-like” syndrome for the first several weeks of use, resulting in fevers, chills, muscle aches and fatigue. In addition, interferon can cause neuropsychiatric effects, such as irritability, mood swings, insomnia, and cognitive changes, in up to 60% of patients [34]. Although rare, suicides have also been reported as a result of interferon therapy. The adverse effects of HCV therapy has led to high rates of discontinuing HCV treatment in the HIV/HCV co-infected population. In fact, one study reports that 55 of 107 (51%) HIV/HCV co-infected patients discontinued HCV therapy prematurely because of adverse effects or patient decision to stop secondary to intolerance [33].

Anemia is another common problem in HIV/HCV co-infected people. Both infections result in limited myeloid reserves and treatment for each infection is associated with drug toxicities that can cause anemia. Of greater concern is the potential for drug-drug interactions between ribavirin and nucleoside analog reverse transcriptase inhibitors such as zidovudine, zalcitabine, and stavudine, which are used as part of HAART regimens to treat HIV. Ribavirin antagonizes these reverse transcriptase inhibitors by preventing their intracellular phosphorylation, thereby reversing their anti-HIV activity [35-36]. Moreover, patients on HAART are more susceptible to the hemolytic effects of ribavirin [37-38] which, in some cases, has resulted in fatal lactic acidosis.

SUMMARY

Co-infection with HCV has become a prominent clinical entity in HIV-infected patients. The natural history of HCV is worsened by HIV infection, resulting in higher HCV viral loads, more rapid progression of liver disease, and higher incidence of hepatocellular carcinomas. The effect of HCV on HIV remains controversial; however, HCV-related liver disease can often limit a patient's ability to tolerate anti-HIV medications. All co-infected patients should be considered for anti-HCV therapy although response rates are lower and the adverse effects of therapy often limit treatment in the co-infected population. Future studies and therapeutic options are needed to improve our understanding of how the HIV and HCV interact and improve host immune responses to both viruses.

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