

Medical Writers' Circle

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a series of articles
written by medical
professionals about
the management
and treatment of
hepatitis C

HCV in the Setting of HIV Co-Infection

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Since 1995, with the advent of protease inhibitors, there has been declining morbidity and mortality in patients with HIV. This has been most striking between 1995 and 1996 when up to 80% of patients were placed on protease inhibitor therapy. Simultaneous with this change, the number of deaths fell from 30 per 100 person years to an average of less than 10 per 100 person years.¹ The probability of survival after an AIDS defining opportunistic infection has hence improved dramatically from the 1980s and early 1990s from approximately 10-30% up to 80% in 1997.² Contained within the 2001 U.S. Public Health Service Infectious Disease Draft Guidelines for the Prevention of Opportunistic Infections are recommendations specific for hepatitis C infection occurring in HIV individuals.

These include the following:

1. Screening all HIV infected persons for HCV by EIA.
2. Advising patients to abstain from alcohol use.
3. Screening for HAV and HBB antibodies; if negative, vaccinate.
4. Monitoring liver enzymes after initiation of HAART therapy.

5. Evaluating for liver disease and consideration of HCV treatment.³

An overview of HCV and HIV shows the similarities and differences of these two RNA viruses. HCV is a flavivirus while HIV is a retrovirus. Both are positive single-stranded RNA viruses and are spread worldwide. HCV has 6 genotypes and numerous sub-genotypes. HIV has 11 clades. Both result in subclinical chronic infection. HCV results in a viral load of trillions of virus per day. HIV in billions of virus per day. Roughly one-third of the 800,000 HIV positive patients identified in the U.S. are HIV-HCV co-infected.⁴ Prevalence of HCV-HIV co-infection among high risk groups ranges from a low of 4-8% in HIV positive men having sex with other men, to a high of roughly 60-90% in hemophilia patients receiving clotting factor prior to 1987 and injection drug users.⁵

Diagnosis

HCV antibody testing in HIV positive patients is highly sensitive and specific. However, if HCV antibody is negative and there is still significant suspicion for HCV, an HCV-RNA PCR assay should be used.⁶ HCV replication is enhanced by HIV

infection. Therefore, patients with co-infection with both viruses have an increase in HCV viremia. This increase seems to be directly related to HIV induced immunosuppression and therefore is inversely correlated with CD4 counts. This may result in increased facilitation of HCV transmission via sexual or perinatal routes. Thomas et al. have shown a direct relationship of HCV-RNA with HIV-RNA measurements, indicating that HCV-RNA levels are generally in a range of 6 logs in patients with HIV-RNA counts less than 2,760 copies/ml. However, if the CD4 count is below 200, then HCV-RNA levels are generally higher (closer to 7 logs) regardless of the HIV-RNA measurement.⁷ An increased effect of co-infection on sexual transmission of HCV has been shown in the partners of co-infected men with hemophilia, indicating that they have a higher rate of HCV positivity (3%) than partners of patients who are HCV positive without HIV infection (0%).⁸ Likewise, there's an increased risk of maternal-infant HCV transmission for HCV positive women who are co-infected with HIV (15.1% vs. 3.7%, $p < 0.01$).⁹

Liver Disease Progression

The natural history of hepatic fibrosis in HCV infected persons with and without co-infection may differ significantly. HIV co-infection has been shown to accelerate progression of fibrosis and is an independent predictor of fibrosis progression in two prior studies.^{10,11} Benhamou et al. have shown an increase in fibrosis grades with duration of HCV infection in co-infected individuals over matched controls

deaths in 1991, up to 50% of deaths in 1998.^{14,15}

HIV Disease Progression

The effect of HCV infection on HIV disease is controversial. HCV may increase the rate of progression to AIDS and AIDS related death, may impair immune reconstitution, and may increase the risk of hepatotoxicity from HAART therapy. Greub et al. have shown that the proportion of patients alive and

Vento et al. have shown the mean Knodell score to increase significantly from 8 to 13, nine months after starting HAART therapy in HIV co-infected individuals.¹⁷ Likewise, Sulkowski et al. have shown HCV infection increases the risk of hepatotoxicity in patients treated with HAART therapy by 3.7-fold increase.¹⁸ However, 88% of these patients did not develop severe toxicity. Most developed toxicity that was mild to moderate, and not requiring

depending upon the severity of HIV disease. For those with stable HIV disease, the goal is HCV eradication. For those with advanced liver fibrosis, the goal is to delay the clinical and histologic progression of liver disease. In those with recurrent antiretroviral associated hepatotoxicity, the goal is to permit aggressive treatment and to postpone or avoid liver transplantation. In general, if patients have severe liver disease, they should be treated with combination interferon/ribavirin therapy first, unless they have a very low CD4 count. One should wait 2-3 months to allow for adjustment of HCV therapy before starting HAART therapy.²⁰ Both therapies should not be started simultaneously. Patients with co-infection who have contraindications to HCV therapy include those with hemoglobinopathies, active opportunistic infections, decompensated liver disease, and the other usual contraindications to treatment. Very little data is available on the safety and efficacy of HCV treatment in HIV co-infected population, although a number of studies are currently in progress. Therefore, treaters should be advised to monitor patients very carefully and to defer therapy in those where contraindications are questionable. Presumably, further guidelines will be available as soon as the ongoing trials are completed.

A large multicenter trial using PEG-interferon alfa-2a (Peginterferon alfa-2a) in combination with ribavirin in co-infected individuals is currently underway. At week 12, an interim analysis of this trial showed that roughly 40% of patients had either a 2 log decrease or undetectable HCV-

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with HCV alone. Fibrosis grade worsened with age, alcohol use and CD4 counts below 200/mm³.¹¹ Meta-analysis of numerous studies in co-infected individuals show that the relative risk of development of cirrhosis increased by over 2-fold and the relative risk of development of decompensated liver disease increased by over 6-fold, over non co-infected individuals.¹² A separate study by Darby et al. has shown that HCV infection in HIV-positive individuals increased liver related mortality by 16.7-fold over individuals who are not co-infected. The risk of liver cancer in this population was 5.6-fold greater than that of non-HIV infected individuals.¹³ This has resulted in the striking increase seen in mortality from end-stage liver disease in patients with HIV, from approximately 11% of

without clinical progression is lower in those who are HCV co-infected than those who are not.¹⁶ They also showed that HCV-HIV co-infected individuals have an increase in CD4 count after starting HAART therapy, although the overall level of CD4 count remained lower than in those who were not co-infected. It is unclear if this is clinically meaningful information.

The impact of HAART therapy on HCV and hepatotoxicity is also currently being debated. The risk of drug-induced hepatotoxicity appears to be 3- or 4-fold higher in HCV co-infected persons than in those who are not. This may be directly related to the severity of underlying liver disease (i.e., decreased drug metabolism), or related to the effect of HAART induced immune recovery (immune reconstitution syndrome).

dose reduction or cessation of HAART therapy. The development of severe hepatotoxicity appears to be more common in patients treated with Ritonavir than in those treated with other protease inhibitors such as Indinavir, Nelfinavir, and Saquinavir. The rate of discontinuation of HAART therapy due to hepatotoxicity appears to be approximately 16% in patients treated for approximately two years, as opposed to 2-4% of controls treated for the same period.¹⁹ Discontinuation of HAART therapy is recommended whenever there is severe elevation greater than 3-fold of immunotransferase levels or symptomatic elevation of liver tests.

Goals of Therapy

The goals of therapy in HCV co-infected individuals vary

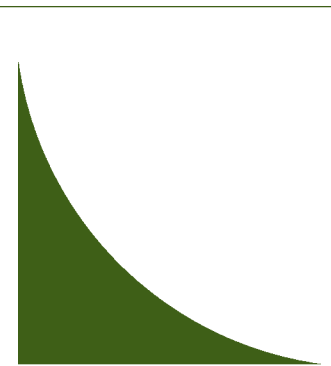
RNA, and this increased at week 24 to roughly 60% of patients. This suggests that the standard 12-week guidelines will not likely hold in co-infected individuals.²¹ Serious adverse events in this population seem to be similar to those in nonco-infected individuals, although there were SOME cases of lactic acidosis and severe anemia, which are not seen in mono-infected individuals. This suggests that patients should be treated with this combination with great care and strict monitoring.

In summary, many HIV/HCV co-infected individuals are suffering from increased morbidity and mortality from their HCV infection, as HCV fibrosis appears to be more progressive in the presence of HIV. Therefore, stable HIV co-infected patients should be evaluated for liver disease and HCV therapy. Anti-HCV therapy may permit the addition of anti-HIV therapeutic regimens. Further data on anti-HCV therapy, safety and efficacy is pending current trials.



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