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a series of articles
written by medical
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the management
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Hepatitis C Virus in HIV-Infected Persons: A Brief Review

Relationships between HIV and HCV

The presence of both human immunodeficiency virus (HIV) and hepatitis C virus (HCV) in an individual is called coinfection. Due to shared routes of transmission, coinfection is common. Overall, approximately 30% of HIV-infected persons in the United States are coinfecting. In HIV-seropositive populations where drug injection is the greatest risk factor for HIV acquisition, prevalence of HCV is as high as 90%.¹ In total, there are between 150,000 and 300,000 coinfecting persons in the United States.^{2,3}

HCV can be an especially challenging illness for those who are coinfecting. As treatment for HIV has advanced due to highly active antiretroviral therapy (HAART) and prophylaxis (prevention with use of medications) against traditional opportunistic infections (OIs), coinfecting individuals are more and more at risk for illness and death due to HCV. This is because HIV accelerates HCV progression, leading to an increased incidence of cirrhosis (scarring), liver failure and hepatocellular carcinoma (liver cancer).^{4,5} The increased prevalence and severity of HCV in HIV-infected persons has led to HCV being considered an OI.⁶

There is conflicting data about whether HCV has an impact

on the course of HIV disease, although it appears likely that HCV does negatively affect HIV progression. For example, coinfection has been shown to hasten time to AIDS and death.⁷ Among coinfecting persons, CD4 counts do not rise in response to HAART to the same degree as in HIV-infected persons without HCV.⁷ Furthermore, HCV can complicate the treatment of HIV by increasing the hepatotoxicity (harm to the liver) of HAART.

Although perinatal transmission (passage from a pregnant woman to fetus) of HCV is relatively rare among HCV-monoinfecting (having HCV but not HIV) women, coinfection with HIV increases the rate of perinatal HCV transmission.⁸ Coinfection may also increase perinatal transmission of HIV.⁹ Liver transplant is not available for the vast majority of HIV-seropositive persons. For all of these reasons, HCV can be a damaging disease for certain coinfecting individuals.

HCV Testing and Diagnosis

All persons with HIV infection should be tested for HCV.⁶ The enzyme-linked immunosorbent assay (ELISA), a screening test used to detect HCV antibody, designates past or present HCV infection. An additional test for HCV RNA, which detects the presence of the HCV virus, should be

performed to diagnose chronic infection. This is the case in approximately 90-95% of HIV-seropositive persons exposed to HCV. The remainder clear the virus spontaneously (are cured of HCV without medications), with a lower rate of viral clearance than is seen in HCV-monoinfecting individuals.^{11,12} Because "false negative" ELISAs can occur, persons with a negative ELISA who are at risk for HCV should have a test for HCV RNA performed.

HCV RNA is sometimes called the viral load, or plasma viral load (pvl, a measure of the amount of virus in the blood). There are important differences between HIV and HCV viral loads. Unlike HIV pvls, which correlate with HIV disease severity, HCV pvls do not indicate the degree of liver damage; a person can have a high or low HCV viral load and have cirrhosis or a healthy liver. The *qualitative* test indicates *whether* HCV virus is in the blood—just yes or no—signifying active infection. This is the test that should be used to diagnose chronic HCV infection. The *quantitative* viral load determines *the amount* of virus in the blood. This test is helpful for guiding treatment decisions. Persons with higher quantitative viral loads are less responsive to HCV treatment than those with lower counts. A reduction in quantitative viral load indicates that treatment is working.

For people living with HIV who do not have HCV, disease prevention is essential. For example, individuals with the health problem of drug dependence should receive treatment so that they can stop injecting illicit drugs. Those who are unable to stop need to be educated about safe injection practices to avoid acquiring HCV and other blood-borne infections.

HCV Treatment in Coinfected Individuals

All coinfected individuals should be vaccinated against hepatitis A and B, if they have not had these illnesses before, and educated about how to prevent the spread of HCV and HIV. They should avoid alcohol, have their liver enzymes monitored after

include delaying clinical and histological progression (slowing down how long it takes for a person to feel ill, and slowing down damage to liver cells), limiting HAART hepatotoxicity and preventing hepatocellular carcinoma.

The decision to treat a coinfected person can be complicated. Considerations include the disease stage of HIV and HCV, other health problems, and possible outcomes of treatment. A physician or group of physicians with knowledge of both HIV and HCV should direct the evaluation. A liver biopsy is the best way to determine the severity of liver damage from HCV, exclude other causes of liver disease, and guide treatment decisions. However, a liver biopsy is not mandatory before initiating therapy, especially

before starting HAART. For example, this eliminates the potential for interactions between HCV and HIV medications, and may lessen future HAART-associated hepatotoxicity. Treating HCV may reduce the risk of illness from this disease, and may improve response to HAART once it is started. However, delaying HIV treatment in order to treat HCV can be dangerous, as HIV can progress rapidly.

Because HCV treatment for coinfected persons has only recently become a concern, many people will already be on HAART when being assessed for HCV treatment. Treating HIV first has the benefit of raising HIV CD4 counts, lowering HIV pvl, and decreasing the risk of OIs. Improving the status of the immune system

oxygen), which can be more severe in HIV-seropositive persons. This can be managed with ribavirin dose-reduction, or erythropoietin (a red blood cell growth factor). Interferon may transiently decrease CD4 count, although the percentage of CD4 cells should remain stable.

Ribavirin interactions with certain medications used to treat HIV may increase risk for mitochondrial toxicity and lactic acidosis (damage to parts inside cells and the build-up of harmful substances). Didanosine (ddI, Videx) is the nucleoside analogue which appears to pose the greatest threat, with lactic acidosis leading to death having occurred in persons taking didanosine with ribavirin. Stavudine (d4T, Zerit), zidovudine (AZT, Retrovir) or other nucleoside analogues may also interact with ribavirin. The HIV-HCV International Panel recommends that doctors be aware of these possibilities, try to avoid prescribing ribavirin with didanosine or zidovudine, and monitor patients on these combinations. The makers of didanosine recommend that this medication not be taken with ribavirin.¹³

Challenges to HCV treatment for coinfected persons

Perhaps more limiting than these potential side effects are the often co-occurring conditions of drug dependence and/or psychiatric illness. Coinfected individuals are frequently considered ineligible for HCV treatment due to these health issues.¹⁴

Because injection drug use is the most common route of HCV transmission in the United States, history of drug injection is prevalent among coinfected populations. Addiction is a chronic illness; therefore waiting until addiction is 'cured' before initiating HCV treatment is unrealistic and places coinfected patients at risk for HCV disease progression.

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about HCV treatment and appears to be the optimal treatment for coinfected persons. ■

HAART initiation, and be assessed for liver disease and the need for treatment.⁶

Combination therapy with pegylated interferon and ribavirin has increased optimism about HCV treatment and appears to be the optimal treatment for coinfected persons. However, there is limited data available about HCV treatment in coinfected patients. Current practices are based upon what is known about treatment in HCV mono-infected persons. The U.S. Food and Drug Administration has not approved any medications for HCV treatment in coinfected populations. Nevertheless, response to HCV medications in coinfected persons appears to be similar to that of non-HIV infected individuals, making it increasingly important that coinfected patients be offered treatment for HCV. The primary goal of HCV treatment is to cure HCV infection. Secondary goals

for persons with genotypes 2 or 3 who are more likely to respond to treatment. Persons with chronic HCV at risk for progression to cirrhosis, based on the degree of fibrosis (scarring), should be considered for treatment.

Coinfected persons with higher CD4 counts, especially with those greater than 500 cells/mm³, are more likely to achieve a sustained virological response (SVR, absence of HCV in the blood six months after treatment, considered a cure). However, this must be balanced against the concern that lower CD4 counts are associated with progression to cirrhosis. Treating individuals with lower CD4 counts can help achieve the secondary goals outlined above; and therefore, HIV should be treated concurrently with HAART to raise CD4 counts.

Another factor is whether to treat HIV or HCV first. There are reasons to consider treating HCV

may itself slow down HCV progression. Alternatively, delaying HCV treatment may mean that HCV is treated at a later stage of HIV, when HCV treatment is less effective.

There are many reasons why a person should not be treated. These include having decompensated cirrhosis (fluid in the belly, bleeding from swollen veins or other signs that the scarred liver is causing damage to other parts of the body) or contraindications to interferon and/or ribavirin (health issues that make these medications unsafe, such as pregnancy).

Side Effects Specific to Coinfected Persons

There are side effects of therapy that may be more common and/or severe in coinfected individuals. For example, ribavirin can cause anemia (a drop in red blood cells, the cells that carry

Emerging data indicate that HCV treatment is safe and effective in persons with drug dependence.^{15,16} The National Institutes of Health endorses evaluating people who inject drugs on a case-by-case basis.¹⁷

Neuropsychiatric symptoms, including depression, anxiety and irritability, may be induced or exacerbated by interferon.¹⁸ Though there is evidence that interferon-induced depression can be effectively treated,^{19,20} this adverse effect can be limiting for persons who already suffer from depression or other forms of mental illness. Psychiatric history and symptoms can also be assessed and treated on a case-by-case basis.

Strategies to extend HCV treatment to coinfecting individuals with substance disorders and/or psychiatric disease must be developed. This will entail evaluating, treating, and stabilizing co-existing drug dependence and/or psychiatric illness prior to, during and after HCV treatment to optimize safety; maximize adherence for treatment efficacy; and prevent post-treatment reinfection. For example, the Coinfection Clinic at The Miriam Hospital in Rhode Island provides a program including coinfection education; weekly nursing assessments and administration of pegylated interferon injections; psychiatric care as needed; counseling and home-based case management for issues of substance abuse as needed; a support group; and medical care provided by HIV specialists and a gastroenterologist.

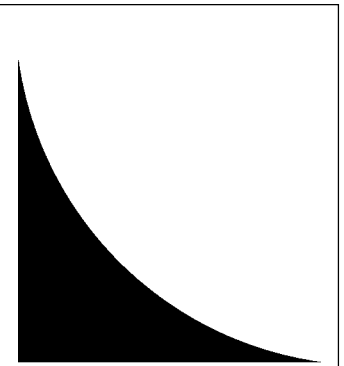
Future Directions

Despite progress in HCV treatment for HIV-seropositive individuals, many questions remain. Studies are underway to determine when during the course of HIV infection to treat HCV. Additional research is needed to determine the most advantageous use of growth factors to maintain blood counts, length of treatment,

and role of maintenance therapy (continued HCV medications beyond a year) for those without SVR. The efficacy and safety of current HCV treatment in coinfecting persons warrants further study, and novel medications are under investigation.

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