Double whammy

Update on HCV and HIV co-infection research

by Glen Hillson

Liver illness is a common problem for people living with HIV/AIDS. Evidence of impaired liver function comes in various forms, including elevated enzymes (ALT and AST), which may only be noticed during routine blood monitoring; clinical symptoms such as loss of appetite, nausea, bloating, and jaundice; or by more sophisticated diagnostic procedures such as ultrasound or liver biopsy. Liver illness is always potentially very serious and even life threatening.

One of the most difficult challenges for HIV-positive people with liver problems is to determine the underlying reason(s). HIV itself affects many body systems, including organs such as the liver. Combination drug therapies can also affect liver function because the body relies heavily on the liver to process most drugs. Different drugs can adversely affect the liver through different biological processes that are generally not well-defined medically. For example, nucleoside drugs can cause serious liver failure by interfering with the function of cell mitochondria throughout the body and cause a condition called lactic acidosis, leading to terminal liver failure. Non-nucleosides and protease inhibitors can also add to liver stress, either through rapid adverse reactions or by adding to other compound stresses. Viral illnesses such as hepatitis A, B, and C are well-known causes of liver disease and damage.

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Shortfalls in the HCV screening process

Hepatitis C virus (HCV) was only discovered in 1989, and scientists still need to learn a great deal about it. Because HCV is transmitted through blood, medical practice has generally viewed blood transfusion recipients and injection drug users as the only populations at risk of becoming infected. Consequently, they are frequently the only people to receive the test normally used to identify HCV.

This medical approach to screening for and diagnosing hepatitis C has proven unreliable for many, especially gay men and people with HIV/AIDS, for several reasons. People with diminished immune capacity may be HCV-infected but may not have antibodies to the virus because they may have developed them and then lost them; therefore, they may have false negative test results. Recent research suggests people with HIV disease may be biologically more vulnerable to HCV through sexual transmission. Although experts generally report that the risk of sexual transmission is low, they also acknowledge that risk is greater for individuals with multiple sex partners. Finally, Canadian research suggests that men who have sex with men and those who practice rimming and fisting may be at greater risk.

Last year, the BC Centre for Excellence in HIV/AIDS advised HIV-treating physicians not to rely solely on antibody testing for HCV identification in people with HIV who have unexplained liver illness. They suggest qualitative polymerase chain reaction (PCR) testing, which is designed to identify HCV itself rather than antibodies. (This method of identification is similar to HIV viral load testing, which genetically identifies and measures HIV.)

Many other theoretical risk factors for HCV transmission need to be tested through research. Timely detection of HCV is

just one of many issues for people who are co-infected. Many people who have HCV never find out how they were infected. In addition to the routes of transmission previously discussed, many other possibilities exist that are not well understood, such as toothbrushes, razors, and body piercing.

Optimal strategies for the concurrent medical management of HIV and hepatitis C are highly experimental, as are many of the combinations of drugs that are used to treat each disease separately.

Progression rates in co-infected people

HCV disease progression is relatively slow. Many people who are HCV mono-infected will remain free of symptoms. One in five will eventually develop cirrhosis of the liver, and one in twenty patients will experience liver failure or liver cancer.

Most research studies of people who are also infected with HIV show faster rates of progression than in mono-infected HCV patients. The reason for this difference in rate of progression has never been explained, and in most cases, it is attributed to the fact that people with HIV have a weaker immune response to HCV.

A recent report in the journal Gastroenterology suggests that it is possible to have advanced chronic hepatitis C even while ALT levels remain at normal levels. This finding is important since access to expensive HCV therapy is based solely or primarily on ALT levels in some jurisdictions.

One report characterized some of the most frequently occurring differences between HCV and HCV/HIV patients. In co-infected patients

- HCV viral load was higher
- Liver fibrosis was more pronounced
- Response to interferon treatment was poorer
- Higher HCV viral loads were associated with low CD4 counts
- Progression to cirrhosis was accelerated.

Other factors shown to increase the rate of HCV disease progression include being overweight, old age at time of infection, and alcohol consumption.

Treatment of HCV

Standard therapy for HCV is treatment with a combination of interferon alfa-2b and the nucleoside ribavirin. Newer "pegylated" forms of interferon alpha-2b have also been developed. Treatment response seems to be improved with the pegylated versions and injection dosing is weekly, compared to three times per week or daily. Both these advantages are the effect of pegylated interferon's longer serum half-life. This means it stays in the body longer and maintains target drug levels more consistently—sort of like a time-released version.

Because HCV disease progression is slow and a majority of patients never require treatment, people normally don't receive treatment until their disease is at least somewhat advanced. Others factors that support this approach are the high cost and poor safety profile of HCV medication. However, in a German study of recently infected patients published in the New England Journal of Medicine, 43 of 44 subjects were able to clear their HCV completely. Further research is necessary to identify which patients are more likely to benefit from early treatment.

Long-term follow-up of patients from three large international studies looked at 395 patients who responded to therapy (no detectable HCV) and had sustained response for at least 24 weeks after discontinuing treatment. Only 10 of the patients who remained undetectable 24 weeks after stopping treatment relapsed and all of those relapses occurred within the first 2.5 years. Although factors such as viral load and HCV genotype are known predictors of initial response to treatment, they did not appear to be related to relapse.

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Other research studies seem to provide further confirmation that even in patients categorized as "non-responders" to treatment because they don't eliminate HCV altogether, treatment can provide clinical benefits. Even among non-responders, the progression of fibrosis was often slowed or reversed. The risk of liver cancer may be diminished and reversal of cirrhosis may be possible. All of these factors are likely to extend life.

For patients starting with standard treatment, one study suggests that starting patients on higher doses of interferon, then later reducing dosage in two stages according to the rate of viral load decline, might provide a better response. Frequent viral load monitoring is not likely available in most clinical settings, but this research could improve treatment methods in the future.

Liver transplantation is a topic of increasing interest for people with HCV. The success rate for the procedure has improved and is now increasingly available to people with viral hepatitis. In patients with consistently detectable viral load, a transplanted liver will also become infected soon often surgery. Nonetheless, liver transplant does offer extended survival to patients with severe liver disease. Larry Kramer's recent highly publicized transplant may increase availability of transplants to people who are co-infected. ⊕