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PROVIDING HIV/AIDS CARE IN A CHANGING ENVIRONMENT SEPTEMBER 2003

Hepatitis C and HIV Co-Infection: An Update

Over the past two decades, AIDS advocates and service providers have become self-trained experts on retrovirology and immunology. Now many of them are finding that they also need to learn about a new group of microorganisms—the hepatitis family of viruses. Hepatitis—meaning any inflammation of the liver—is increasingly common among people with AIDS and thus presents a new challenge for the health care and social service providers who assist them.

Although alcohol, drugs, autoimmune disease, and metabolic disease all can cause hepatitis, viruses result in more cases than any other etiology (see box, p. 2).[1] Hepatitis B is the most common viral hepatitis infection in people with HIV, but hepatitis C is more likely than any other form of hepatitis to result in chronic or long-term disease, liver failure, or death.[2]

More than 3 percent of the world's population, about 2 percent of the U.S. population (4 million people), and up to 10 percent of U.S. health care workers are currently infected with the hepatitis C virus (HCV).[3,4] In the United States, the disease is more prevalent among people of color than among Caucasians, and it infects more men than women. In total, about 30,000 new cases of HCV infection occur every year. The disease results in approximately 10,000 deaths per year.

Like HIV, HCV is transmitted by blood products and other body fluids. Until 1986, when routine testing of donated blood began, blood transfusions were responsible for the greatest number of HCV cases.[5] Now, the virus is rarely transmitted through that route: Injection drug use—specifically, sharing contaminated needles and other paraphernalia—is the new leading cause, accounting for 60 percent of HCV cases. The virus also can be transmitted in other ways: perinatally, by kidney dialysis, and by organ transplantation. HCV is less frequently transmitted by sexual intercourse, although people with other sexually transmitted infections, including HIV, appear to be at increased risk of contracting the disease in this way.[6]

Various studies have reached different conclusions about the rate of HIV and HCV co-infection in the United States. Between 200,000 and 300,000 people have both diseases. About 25 percent of Americans with HIV also have HCV; the proportion may be as high as 90 percent among certain groups of people living with HIV disease.[7] About 10 percent of people with HCV also have HIV.[8]

Course of the Disease

HCV infection has both an acute and a chronic phase. In the acute phase—the initial period after infection—most people are asymptomatic, although about 25 percent to 35 percent may experience loss of appetite, jaundice, fatigue, nausea, an enlarged liver, or abdominal pain.[9] HCV is so widespread because up to 85 percent of people infected with the virus are unable to clear it from their body and subsequently develop chronic or long-term disease. Chronic HCV infection is defined as hepatitis C virus remaining in the body for more than 6 months.

Although chronic HCV also may be asymptomatic for a time, it is generally much more serious than the acute form of the disease. It results in a continued risk for liver scarring (cirrhosis), liver failure, liver cancer, and death, usually occurring from one to four decades after initial infection.

Types of Hepatitis

- Hepatitis A is in the picornavirus family. Transmission is through fecal-oral contact. The greatest risk is in countries in the developing world with poor sanitation. Acute illness usually is symptomatic, and chronic illness is rare. A vaccine is available.

- Hepatitis B is a member of the hepadnaviridae family. The virus is transmitted through sexual contact, blood products, and body fluids and from mother to infant during delivery. Hepatitis B has both acute and chronic stages. A vaccine is available.

- Hepatitis C, formerly called non-A/non-B hepatitis, is a member of the flavivirus family. A more complete discussion of hepatitis C is found in the body of this article.

- Hepatitis D is a single-stranded RNA virus. It uses part of the hepatitis B virus as its envelope protein. As a result, it can infect only people who also are infected with hepatitis B. Clinical disease from infection with both viruses simultaneously is identical to infection with hepatitis B alone. However, infection with hepatitis D in someone already infected with hepatitis B may result in a significant exacerbation of the hepatitis.

- Hepatitis E is a calicivirus. Like hepatitis A, it is transmitted through a fecal-oral route. It has an acute phase but rarely causes chronic infection.

- Hepatitis G is structurally similar to hepatitis C and also is transmitted through blood products. It is not clear whether it causes disease in humans.

Source: Wolf DC. Viral hepatitis. May 10, 2002. Available at: http://www.emedicine.com/med/topic3180.htm

Acute HCV infection is rarely detected and is generally not treated. Chronic disease, however, is treated aggressively. The most effective treatment is a combination of interferon alfa and ribavirin. Neither drug was designed to treat HCV, but both appear to boost the immune system and increase its activity against the virus, although the exact way in which they work is not understood.[12] The drugs are unsuccessful in many patients: Only 56 percent of the participants in a recent large-scale clinical trial achieved sustained viral suppression.[13] In addition, interferon and ribavirin can cause significant side effects and toxicities, including anemia and other blood disorders, heart disease, birth defects, depression, anxiety, insomnia, headache, fatigue, nausea, and muscle and joint aches.

HIV–HCV Co-Infection

In people who also have HIV, chronic HCV may be especially destructive. Some studies have reported that people with co-infection have higher levels of hepatitis virus in their blood, more rapid progression of liver damage, and a greater rate of death due to hepatitis than people with only HCV infection.[10] Other recent research found no correlation between HCV progression and HIV status.[11] Clearly, much is yet to be learned about the nature of HIV/HCV co-infection.

Because HCV also infects infants and children, generally through perinatal transmission or blood transfusion, co-infection is an issue in pediatric HIV. Children's National Medical Center in Washington, DC, cares for about 180 children younger than age 12 who have

HIV, one of the largest groups of such children in the United States. Still, according to Andrew Bonwit, M.D., an attending pediatrician at the hospital, only three or four of his patients have HIV–HCV co-infection; none have developed chronic hepatitis and have thus not needed hepatitis treatment. "We are fortunate not to have to add this therapy, because these children already have enough to do in adhering to their highly active antiretroviral therapy," he commented. Children with HIV–HCV co-infection are followed by a liver specialist (i.e., a hepatologist), who monitors their liver function and the status of their hepatitis.

Kenneth E. Sherman, M.D., Ph.D., professor of medicine in the Division of Digestive Diseases at the University of Cincinnati College of Medicine, has been studying hepatitis and other liver diseases for more than two decades. He believes that HIV–HCV co-infection may complicate treatment of each disease individually, in part because so much remains to be learned about the interactions among the two diseases and their treatments. For example, because many HIV medications may be toxic to the liver, drugs of choice should be those that minimize liver damage while treating HIV aggressively. However, "data are not tight enough that we are able to say 'this is a liver-friendly [HIV] regimen and this is not,'" according to Sherman.

A recent journal article noted that with co-infection, the effects of HCV and HIV medications may put a patient's liver at high risk: "The combination of rare nucleoside analogue-related hepatitis with the more common protease inhibitor-related hepatitis and some non-nucleoside hepatitis is complex, but this volatile mix is made even worse by the addition of viral hepatitis."[14]

Not enough is known about the interactions among drugs used for treating HIV and those used in HCV treatment to be sure which can be used together safely and effectively. The most solid evidence in this area indicates that people on ribavirin should not be treated with Videx (ddI) and probably should not be treated with Zerit (d4T), Sherman explained. However, most doctors who treat co-infected patients must base their drug selection decisions on anecdotal information because reliable data are not available.

Little is known about the optimal treatment for HCV in people who also have

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HIV and HCV: Comparisons and Contrasts

	HIV	HCV
Virus discovery	1983	1969
Number of infected persons	40 million	170 million
Genetic material	RNA	RNA
Virion half-life	< 3 hours	2.7 hours
Main cell target	CD4+ T-lymphocyte	Hepatocyte
Main transmission route	Sexual	Parenteral
Rate of chronicity	100%	76%
Rate of cure with therapy	0%	40%
Asymptomatic period	10 years	30 years
Main outcome predictors	CD4 count; viral load	Fibrosis; stage; co-factors
Main pathogenic mechanism	Direct cell killing	Immune-mediated
Treatment	Antivirals	Immunomodulators
Treatment predictors	Viral load; CD4 count; compliance; resistance	HCV genotype; HCV load; compliance; cirrhosis

Source: Soriano V. *HIV and hepatitis C coinfection: from biology to treatment strategies.* International AIDS Society-USA.

RYAN WHITE AGENCIES SHOW LEADERSHIP IN TREATING HIV/HCV CO-INFECTION

Programs for people co-infected with HIV and hepatitis C (HCV) range from comprehensive co-infection clinics to limited offerings of specific services, such as education and support. To learn what services Ryan White CARE Act agencies provide for people who are co-infected, subscribers to the Title III grantee email list were surveyed about their offerings. Representatives of several clinics responded with descriptions of their programs. Although their answers may not represent the full range of Ryan White services for people co-infected with HIV and HCV, they provide important information about many grantees' state-of-the-art responses to a growing medical concern. The HIV/AIDS Bureau at HRSA is grateful to the agencies that have shared information about their work so that other service providers and their patients may benefit.

The **PATH Center of the Brooklyn Hospital Center** (Brooklyn, NY) has a well respected co-infection clinic, which was presented as a model of care at a March 2003 congressional briefing. PATH screens all of its HIV-positive clients for hepatitis A, B, and C; patients who are not already immune are vaccinated against hepatitis A and hepatitis B (there is no hepatitis C vaccine). Approximately 30 percent of the center's HIV-positive clients have hepatitis C; the center provides them with comprehensive primary care. The center offers a multidisciplinary team consisting of medical providers, case managers, social workers, a dental hygienist, a psychiatrist, a nutritionist, counselors, an outreach coordinator, and treatment adherence specialists as well as linkages with more than 50 community-based agencies. The center also offers a peer education program led by educators who are co-infected themselves. Contact: Dan Sendzik, (718) 940-5934.

HIV ACCESS, a Title III project serving Oakland, CA, and surrounding Alameda County, has a comprehensive HIV/HCV program. One component consists of a full-time nurse devoted to case management, support groups, and individual support for people receiving treatment. A gastroenterologist performs liver biopsies on site, as needed. "Mini-residencies" for HIV providers are offered through the AIDS Education and Training Center (AETC). ACCESS also offers patient education and hepatitis A and hepatitis B vaccination. Contact: Kathleen Clanon, MD, (510) 271-4513.

Sixty percent of the **Jordan Hospital ACCESS Program's** (Plymouth, MA) clients are co-infected, and most have a history of drug use. ACCESS offers clients health education and counseling on co-infection management and disease progression and provides community-based educational programs for consumers and providers. The program offers clinical case conferences and linkages to substance abuse and mental health programs, and the agency is planning to offer an HCV support group. Contact: H. Dawn Fukuda, MSPH, (508) 830-2330, ext 2.

Co-infected clients at **AIDS Resources of Rural Texas** (Weatherford, TX) have access to specialized case management, support groups, a food pantry, and counseling services. The agency is working to provide housing assistance through the State of Texas. It is also preparing a notebook for co-infected patients that will contain information on HCV, treatment protocols, and general information about the liver. Contact: Sandie Wright, MSN, FNP, (800) 700-2037.

The **Florida Title II Area 8 Program** encourages primary care providers to treat co-infected patients in the course of their primary care services. Because many Title II physicians in this program are part-time and thus treat relatively few co-infected patients, the development of protocols and training takes on special importance. The program has drafted a clinical protocol for the evaluation, care, and treatment of co-infection, with assistance from the Florida/Caribbean AETC. Once the protocol becomes final, in-service training and "mini-residencies" for clinical providers will be scheduled. Contact: Jeffrey Beal, MD, Jeff_Beal@ doh.state.fl.us.

The **Alaska Native Tribal Health Consortium** (Anchorage, AK) has its own hepatology department. HIV-positive patients are tested for HCV using the polymerase chain reaction (PCR) test, rather than through antibody testing, reflecting that PCR may be more sensitive in people with HIV. Contact: Beth Schenck, MD, (907) 729-2908.

A feature of co-infection activities at **District Four Health Services** (La Grange,

GA), is integration of co-infection adherence into its general adherence program. An adherence nurse follows up with all clients on medications as often as needed, whether daily, weekly, or bi-monthly. When side effects or other difficulties with medication regimens occur, the entire care team addresses the problem. Contact: Kathy Brawner, RN, BSN, ACRN, (706) 845-4035.

At the **Christiana Care HIV Program** (Wilmington, DE) all patients are screened for HCV. Those who are positive receive counseling on managing the disease, including information on the risks of alcohol consumption. HCV viral loads are measured, and on-site treatment for HCV is initiated if it is indicated. Contact: Arlene Bincsik, abincsik@christianacare.org, (302) 255-1300.

The **HUG Me Program** (Orlando, FL) offers an interdisciplinary team approach to co-infection that includes peer educators, primary care and infectious disease physicians, substance abuse counselors, medical social workers, dieticians, pharmacists, and mental health providers. Contact: Suellen T. Cirelli, MSN, ARNP, ACRN, (510) 271-4513.

Bornemann Internal Medicine (Reading, PA) treats co-infection in its clinic. Patients in the most advanced stages of liver failure are referred to a specialist, as needed. In addition to clinical care, the clinic offers counseling and case management. Contact: Sandy Lloyd, (717) 782-2363.

Online Resources on Hepatitis C and HIV/HCV Co-Infection

AIDS Education and Training Center National Resource Center
http://www.aidsetc.org/aidsetc?page=et-30-15

American Liver Foundation
http://www.liverfoundation.org/

The Body
http://www.thebody.com/Forums/AIDS/Hepatitis/

Centers for Disease Control and Prevention
http://www.cdc.gov/ncidod/diseases/hepatitis/

Gay and Lesbian Medical Association
http://www.glma.org/hepatitis/

Hepatitis C Association
http://http://www.hepcassoc.org/index.html

Hepatitis Foundation International
http://www.hepfi.org/

HIVandHepatitis.com
http://www.hivandhepatitis.com/

Mountain Plains AIDS Education and Training Center HIV/HCV Co-infection Center of Excellence
http://www.uchsc.edu/sm/aids/coe.htm

National Hepatitis C Coalition
http://www.nationalhepatitis-c.org/

National Institutes of Health National Institute of Allergy and Infectious Diseases
http://www.niaid.nih.gov/dmid/hepatitis/

National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases
http://www.niddk.nih.gov/health/digest/pubs/hep/hepa-e/hepa-e.htm

World Health Organization
http://www.who.int/health-topics/hepatitis.htm

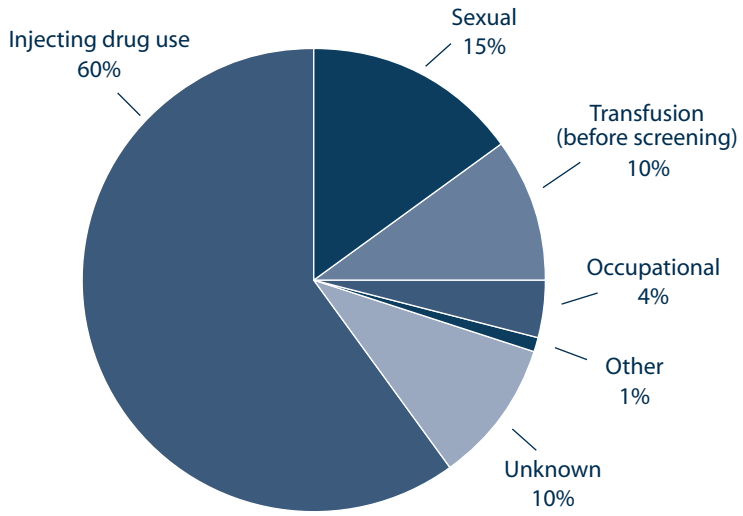
HIV. In people whose immune systems have been compromised to the point that their CD4+ lymphocyte cell count is below 500, HCV appears to respond poorly to treatment. Consequently, efforts to keep the CD4+ count above 500 in people with co-infection might be important. In people with HIV monoinfection, this goal might not be as critical. Again, more study is needed.

No clinical trials on HCV treatment in people who also have HIV are complete, but Sherman is familiar with some of the preliminary data from three trials that are ongoing. On the basis of that information, he said, the response rate to hepatitis medications is likely to be "significantly lower, maybe 40 percent lower [in people with co-infection] than in other populations." It may be that people who are co-infected require higher medication doses or a longer course of treatment. Improved adherence also may be critical for this population, he said. Considerable research remains to be done before clinical guidelines can be developed on the safest and most effective ways to treat both diseases in people who are co-infected.

Role of Case Managers and Other AIDS Service Providers

It is important for social workers, case managers, and others who work with people with HIV and AIDS to recognize the risk factors for hepatitis and to ensure that their clients are screened for the disease (see box). In fact, the widely used *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and*

Sources of Infection for Persons With Hepatitis C



Source: Centers for Disease Control and Prevention. Adapted from *Viral Hepatitis C.* Available at: http://www.cdc.gov/ncidod/diseases/hepatitis/c/plan/HCV_infection.htm

Risk Factors for Hepatitis C

- Intravenous drug use
- Birth to a mother who is positive for hepatitis C
- Employment as a health care worker
- Hemophilia
- Blood transfusion or organ transplant before 1986
- Sexual activity with someone who is positive for hepatitis C, especially for people who have another sexually transmitted disease
- Kidney failure treated with hemodialysis
- Sharing personal items such as a razor, toothbrush, or tattoo needle with someone who is positive for hepatitis C

Tips for Maintaining a Healthy Liver for People With HIV

People with HIV infection should take the following steps to protect against co-infection with hepatitis:

1. Get vaccinated against hepatitis A and hepatitis B.
2. Avoid alcohol. Studies show that alcohol can cause liver damage, especially in people with viral hepatitis.
3. Be cautious about using prescription drugs, over-the-counter medications, street drugs, and herbal remedies. Be especially careful when combining different drugs. Tell health care providers about all drugs and herbs being used.
4. Avoid exposure to environmental toxins, such as solvents, paint thinners, and pesticides. If it is necessary to use such chemicals, work in a well-ventilated area and wear gloves and a protective face mask.
5. Get regular health checkups, including monitoring of liver enzymes and blood cell counts.

Source: Adapted from Highleyman L. Keeping your liver healthy [article online]. *The Body.* 2002;11(3). Available at: http://www.thebody.com/cria/summer02/ liver _health.html.

Adolescents recommends that all people with HIV be tested for HCV and, in certain circumstances, for hepatitis B as well.[15] According to Sherman, it also is important for mental health providers and other providers of support to people with HIV to address the emotions that can arise when someone with HIV is diagnosed with HCV infection—a second serious, life-threatening disease.

Gabriel Lamazares is a treatment educator and counselor for the Alliance of AIDS Services–Carolina, an agency that offers a variety of services for people with AIDS and provides prevention activities for populations at risk for infection in the Raleigh-Durham-Chapel Hill area of North Carolina. Lamazares observes that staff at the agency are aware of several clients infected with HCV and a smaller number infected with hepatitis B. The major medical facilities that serve their clients screen HIV patients for hepatitis. "One of the salient needs of the co-infected population is understanding their complex situation," he said, especially given the challenge simply of coming to terms with HIV itself. Lamazares also noted that it has been a challenge for him, as an educator, "to get up to speed on hepatitis." Although he feels well informed with regard to HIV, "my knowledge of hepatitis is much sketchier," he said.

Future Directions

Many new candidate agents for HCV treatment are under investigation, but most are in the preliminary stages of study. Hepatitis researchers have learned much from the approach to HIV treatment developed over the past two decades and are trying to find new drugs that are safer and more effective than existing treatments.[16] Unlike current treatments, many drug candidates are designed to work by interfering with one of the stages of the hepatitis viral life cycle. The new drugs being studied would block the enzymes needed for the hepatitis C virus to reproduce, just as HIV drugs target enzymes that HIV needs to replicate itself, such as protease or reverse transcriptase.

Several pharmaceutical companies have developed potential drugs that are designed to inhibit the HCV-specific

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protease or polymerase enzyme. A few such drugs are being tested in clinical trials. However, said Sherman, some scientists are concerned that the drugs' use would lead to viral resistance. As a result, he expects that multiple drugs will be used simultaneously to treat hepatitis in order to avoid resistance—again, much like HIV combination therapy.

The next few years are likely to see advances in treatments both for HCV and for those who have HIV–HCV co-infection. However, it remains critical for people with HIV and/or hepatitis, as well as those at risk for either disease, to take steps to protect the health of their liver (see box, p. 7). In addition, providers need to be ready to identify clients who are at risk for co-infection and to ensure that their clients receive state-of-the-art treatment as knowledge about managing both of these complex diseases grows.

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