HIV and Hepatitis COINFECTION

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Coinfection with HIV and the hepatitis C virus (HCV) or hepatitis B virus (HBV, see sidebar on page 36) is a growing public health concern. Because the diseases are spread in similar ways—notably through shared use of needles to inject drugs and sexual activity—many people are coinfected with HIV and HCV, HIV and HBV, or even all three viruses.

Hepatitis C and hepatitis B are viral infections of the liver; over time they can lead to serious consequences including liver cirrhosis and liver cancer. Most studies show that HIV infection leads to more aggressive hepatitis C or hepatitis B and a higher risk of liver damage. Studies of how HCV and HBV affect HIV disease are less clear. Most research shows that HCV does not accelerate HIV disease progression, but HIV/HCV coinfection may impair immune system recovery after starting antiretroviral therapy.

Coinfection can complicate treatment. People with liver damage due to chronic hepatitis are more likely to experience hepatotoxicity (liver toxicity) related to anti-HIV drugs. In addition, drugs used to treat HIV and hepatitis can interact and side effects may be exacerbated. Most experts recommend that HIV should be controlled first before a person begins HCV treatment. With careful management, most people with HIV/HCV or HIV/HBV coinfection can be successfully treated for both diseases. In fact, several recent studies suggest that HIV/HCV-coinfected people with well-controlled HIV disease and relatively high CD4 cell counts may do as well as those with HCV alone.

HIV/HCV: A Growing Public Health Problem

Coinfection refers to infection with two or more different disease-causing organisms. Hepatitis C is a common coinfection in people with HIV. An estimated 200,000–300,000 people in the U.S. have both HIV and HCV. Experts believe that about 25% of Americans with HIV also have HCV; conversely some 10% of people with HCV are thought to also have HIV. In an analysis published in the March 15, 2002 issue of *Clinical Infectious Diseases,* Kenneth Sherman, MD, of the University of Cincinnati, Ohio, and colleagues found an overall HCV prevalence rate of 16% in a cohort of people with HIV; in different subpopulations coinfection rates ranged from 3% to 73%.

HIV/HCV coinfection is increasingly recognized as a growing public health problem. Early in the HIV/AIDS epidemic most people with HIV were expected to die from AIDS, and less attention was devoted to other long-term conditions. Because chronic hepatitis C progresses so slowly, many HIV positive people who were infected with HCV in the 1970s or 1980s are only now beginning to develop advanced liver disease. At several recent conferences a number of presentations were devoted to HIV/HCV coinfection. David Thomas, MD, from Johns Hopkins University in Baltimore, Maryland, reviewed the current state of knowledge about HIV/HCV coinfection at a June 2002 meeting convened by the National Institutes of Health (NIH) to generate a new consensus statement about HCV treatment, care, prevention, and future research.

As improved HIV treatment has reduced mortality due to opportunistic illnesses (OIs), liver failure—often related to chronic viral hepatitis—has become a major cause of hospitalization and death in people with HIV/AIDS. In some recent studies liver failure due to HCV was the leading cause of death.

Several studies at the 9th Conference on Retroviruses and Opportunistic Infections (CROI) held in February 2002 looked at illness and death in HIV/HCV-coinfected people. Ronald Reisler, MD, MPH, of the NIH and colleagues reported that the rates of severe (grade 4) adverse events and death were higher in HIV positive people coinfected with HCV or HBV than in those with HIV alone. David Rimland, MD, of the Atlanta Veterans' Administration Medical Center and colleagues showed that coinfected people had shorter survival times after an HIV or AIDS diagnosis than those with HIV alone. Kelly Gebo, MD, of Johns Hopkins and colleagues found that HIV/HCV coinfection substantially increased the likelihood of hospitalization compared with those who had only HIV. On the other hand, Ellen Tedaldi, MD, of Temple University in Philadelphia and colleagues reported that after controlling for CD4 cell count, survival rates were comparable in HIV/HCV-coinfected people and those with HIV alone, suggesting that effective HIV treatment can minimize the detrimental effects of HCV coinfection.

Because the presence of HIV accelerates the progression of hepatitis C, HCV is thought of as an OI in people with HIV; however, it is not considered an AIDS-defining illness.

The "Twin Epidemics"

HCV and HIV share many characteristics. Both are blood-born RNA viruses that replicate rapidly. The two viruses also share similar transmission routes. Direct blood-to-blood transmission—for example through needle sharing—is the most efficient means of transmitting both viruses. Among some populations of injection drug users, the HIV/HCV coinfection rate may be as high as 90%. Coinfection is also common among hemophiliacs and others who received repeated blood product transfusions before such products were heat-treated to inactivate pathogens. Some people contracted HCV through blood transfusions before the early 1990s. A reliable HCV blood test became widely available in 1992. The rate of HIV/HCV coinfection is also high among prisoners.

Along with these similarities, there are also several differences between the two viruses. HCV, unlike HIV, does not integrate into human cells and is thus easier to eradicate. HCV is less likely than HIV to be transmitted sexually or from mother to child during pregnancy, birth, or breast-feeding. According to the Centers for Disease Control and Prevention (CDC), people who contracted HIV through sexual activity have HCV infection rates similar to those of the adult population as a whole (estimated at under 3% for people in monogamous heterosexual relationships, but somewhat higher among gay men and people with multiple sex partners).

However, studies show that the risk of sexual or perinatal transmission of HCV is greater if a person also has HIV—possibly due to the fact that HIV/HCV-coinfected people tend to have higher HCV viral loads. Recent data reported by researchers from Chelsea and Westminster Hospital in London suggest that sexual transmission is responsible for an increasing proportion of HCV infections among people with HIV. And while 5% or less of HCV-infected mothers without HIV transmit HCV to their infants, among HIV/HCV-coinfected mothers the transmission rate may be three times as high.

Because many people are coinfected with HCV and HIV, the U.S. Public Health Service and the Infectious Disease Society of America recommend that all people with HIV should be screened for HCV. Detecting HCV in people whose immune systems are severely compromised can be difficult because they may not produce enough antibodies to show up on a test. In HIV positive people with a CD4 cell count over 200 cells/mm^3, a standard HCV antibody test is usually sufficient; if the CD4 cell count is below 200 cells/mm^3, an HCV RNA viral load test may be necessary to diagnose hepatitis C.

Hepatitis C Basics

Hepatitis C is a slowly progressing disease of the liver. Because this organ carries out some 500 bodily functions, damage to the liver can lead to a variety of symptoms and associated

conditions. HCV was identified only in 1989; before that it was known as non-A/non-B hepatitis. In some people infected with HCV the immune system can completely eradicate the virus, but in an estimated 80% of infected people hepatitis C becomes chronic (lasting more than six months). HCV is most often spread through contaminated needles used to inject drugs. Tattoo needles and shared personal items such as razors and toothbrushes may also spread the virus. As discussed above, HCV transmission through sexual contact or from mother to infant are uncommon, but do occur.

Most people with acute or chronic HCV have no symptoms. Those that do may experience fatigue, nausea, loss of appetite, abdominal pain, and a flu-like feeling. An estimated 10–25% of people with chronic HCV develop severe liver disease—usually after 10–40 years—which may include liver inflammation, fibrosis (the development of tough, stringy tissue in the liver), cirrhosis (scarring), hepatocellular carcinoma (liver cancer), and liver failure. A minority may develop jaundice (yellowing of the skin and whites of the eyes). When people develop decompensated cirrhosis, scar tissue blocks the flow of blood through the liver and the organ is no longer able to function properly. This can lead to serious conditions such as bleeding veins (varices) in the esophagus or stomach, abdominal swelling (ascites), and brain dysfunction (hepatic encephalopathy). Liver failure due to HCV is the leading reason for liver transplants in the U.S.

Antibody tests (ELISA and RIBA) are used to detect whether a person has been infected with HCV. Genotype tests are used to determine what strain of HCV a person has. There are six known HCV genotypes; 1a and 1b, which are most common in the U.S., are more difficult to treat. Liver enzymes, in particular alanine transaminase (ALT) and aspartate transaminase (AST), are measured as an indication of liver inflammation. Many—but not all—people with chronic hepatitis have elevated liver enzyme levels. Viral load tests (PCR, bDNA, and TMA) measure the amount of HCV genetic material (RNA) in the blood, and can help indicate whether treatment is working. In contrast with HIV, HCV viral load is not correlated with disease severity.

Liver biopsy, in which a small sample of tissue is withdrawn using a needle and examined under a microscope, is considered the "gold standard" for gauging the extent of liver damage. Biopsies are used to help make decisions about whether treatment is needed. Liver tissue damage is graded on a scale of 0–4. Although several tests are under study, there currently is no reliable noninvasive means of detecting liver fibrosis.

Not everyone with HCV needs to be treated. Many different factors—such as a person's age, how long he or she has been infected, HCV genotype, and extent of existing liver damage—should be taken into account when deciding whether to treat. The usual treatment for HCV is a combination of interferon-alpha (Intron-A or Roferon-A) plus ribavirin (Rebetol, Copegus). Pegylated interferon (Peg-Intron or Pegasys) is a new, chemically altered form of interferon that lasts longer in the body and appears to work better than standard interferon.

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Recent studies show that combination therapy with pegylated interferon plus ribavirin can clear HCV in about 50% of HIV negative people with genotype 1 and about 80% of those with genotypes 2 or 3. As discussed below, treatment response rates tend to be lower in people coinfected with HIV. Traditionally, HCV therapy is administered for a specified period of time (usually 6–24 months) and discontinued if HCV viral load does not decrease. However, experts increasingly believe that treatment may reduce liver damage even if HCV viral load does not become undetectable. A trial called HALT-C is now underway to study the possible benefits of long-term HCV maintenance therapy.

Side effects of interferon are common, and may include fever, fatigue, headaches, flu-like symptoms, muscle aches, low blood cell counts, and irritability or depression. Ribavirin may cause hemolytic anemia (destruction of red blood cells) and birth defects.

How HIV and HCV Interact

The Impact of HIV on HCV

HIV/HCV coinfection is still poorly understood, but recent research has shed light on how the two viruses interact. In the February 2002 issue of *Current Gastroenterology Reports,* Andrew Talal, MD, MPH, from Cornell University's Weill College of Medicine in New York City and colleagues reviewed the pathophysiology of HIV/HCV coinfection. According to the authors, a strong cell-mediated immune response involving both CD4 and CD8 cells is required to keep HCV under control. A strong immune response also appears necessary to enable successful HCV treatment with interferon. In people with HIV, the immune response may be compromised, making it less likely that an infected person will clear HCV and allowing HCV to replicate more rapidly.

Much of the liver damage related to hepatitis C is caused not by the virus itself, but rather by the immune system's response to HCV. Thus, it might be expected that people with compromised immune systems would mount a weaker immune response that causes less liver tissue damage. However, research indicates that the opposite seems to be the case.

Most studies show that HCV disease progression is more rapid in HIV/HCV-coinfected people and is more likely to lead to severe liver damage. Many studies show higher rates of cirrhosis in coinfected individuals. For example, at the November 2001 meeting of the American Association for the Study of Liver Disease, Vincent di Martino, MD, and colleagues with the French MULTIVIRC study team reported that coinfected people died earlier than those with only HCV because they progressed to cirrhosis sooner. At the XIV International AIDS Conference held in Barcelona this past July, A.H. Mohsen from St. Thomas School of Medicine in London and colleagues estimated that the average time between HCV infection and the development of cirrhosis is 22 years in coinfected people compared with 33 years in those with HCV alone—a 1.5-fold increase in the rate of liver disease progression.

At the June NIH consensus meeting Dr. Thomas cited a meta-analysis showing that HIV/HCV-coinfected people had a two-fold greater risk of progression to cirrhosis and a six-fold greater chance of developing end-stage liver disease. Javier Garcia-Samaniego from Madrid, Spain, and colleagues reported in the January 2001 issue of the *American Journal of Gastroenterology* that HIV/HCV-coinfected individuals had a higher rate of hepatocellular carcinoma than people with HCV alone. In addition, most research indicates that HIV/HCV-coinfected people typically have higher HCV viral loads than those with only HCV.

Importantly, the longer-term studies of HIV/HCV coinfection were initiated prior to the widespread use of highly active antiretroviral therapy (HAART), and many of the participants had low CD4 cell counts. More recent research suggests that the differences in HCV disease progression between coinfected people and those with HCV alone may not hold for people who have well-controlled HIV and whose immune systems remain relatively intact with high CD4 cell counts. For example, Yves Benhamou, MD, and colleagues, also with the MULTIVIRC team, reported in the October 1999 issue of *Hepatology* that HIV/HCV coinfection, having a CD4 cell count below 200 cells/mm^3, and heavy alcohol consumption were all associated with a greater likelihood of HCV disease progression. But HIV/HCV-coinfected participants with over 200 cells/mm^3 had hepatitis C progression rates similar to those of people with HCV alone.

Massimo Puoti, MD, and colleagues with the HIV-HCV Coinfection Study Group reported in the January 1, 2001 issue of the *Journal of Infectious Diseases* that the presence of fibrosis was associated with CD4 cell counts below 500 cells/mm^3, whether or not a person had HIV. And at the Barcelona AIDS conference C. Arizcorreta and colleagues from Cadiz, Spain, presented research showing that both lower CD4 cell counts and higher HIV viral loads were associated with worse liver damage in coinfected individuals.

In a study published in the August 2001 issue of *Hepatology,* Dr. Benhamou's team reported that people receiving antiretroviral regimens that included a protease inhibitor (PI) had lower fibrosis scores and lower rates of progression to cirrhosis than those who had not taken PIs (2% vs 5% progression rate at five years, 5% vs 18% at 15 years, and 9% vs 27% at 25 years). This and other research suggests that by keeping their HIV under control, HIV/HCV-coinfected people may do nearly as well as people with HCV alone.

The Impact of HCV on HIV

The impact of HCV on HIV disease is less clear, and study results are conflicting. However, a majority of research indicates that HCV does not increase HIV viral load or directly accelerate HIV disease progression. For example, Mark Sulkowski, MD, of Johns Hopkins and colleagues reported at the Barcelona AIDS conference and in the July 10, 2002 issue of the *Journal of the American Medical Association (JAMA)* that among their cohort of nearly 900 HIV/HCV-coinfected people, those with both viruses were not more likely to experience accelerated HIV disease progression, develop an AIDS-defining illness, or die from AIDS. HCV coinfection did not appear to reduce the effectiveness of HAART, and the researchers concluded that HCV should not be seen as a barrier to HIV treatment. Notably, in this cohort coinfected people were less likely than those with HIV alone to be taking HAART, and most deaths occurred in the untreated subjects.

Similarly, Dr. Rimland's team reported in the July 1999 issue of *Clinical Infectious Diseases* that HIV/HCV coinfection appeared to have no effect on the progression of HIV disease or survival in 100 coinfected people treated between January 1992 and May 1997. Dr. Rimland concluded that there was "absolutely no difference" in HIV disease progression and survival—as assessed by time from HIV

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What About HEPATITIS B?

Hepatitis B (formerly known as serum hepatitis) is caused by a blood-borne virus called HBV. Most people with healthy immune systems are able to clear HBV. Only about 5% of adults infected with HBV develop chronic hepatitis B; this figure is far higher—up to 90%—in those infected as infants. An estimated 1.5 million Americans are chronic HBV carriers and some 150,000 are newly infected each year. Unlike hepatitis C, hepatitis B can be prevented with a vaccine.

Like HIV and HCV, HBV can be transmitted through sharing contaminated needles, through sexual contact, and from mother to infant. The CDC estimates that 30–60% of new HBV infections may be sexually transmitted. Studies indicate that the likelihood of sexual or perinatal (mother-to-infant) transmission of HBV is higher if a person is coinfected with HIV or HCV.

HIV/HBV coinfection can lead to complications and affect treatment for both diseases, but to date it has not received as much attention as HIV/HCV coinfection. People with HIV are 3–6 times more likely to develop chronic hepatitis B than those with HBV infection alone. In addition, HBV genetic material remains in human cells, and the virus may be reactivated as immune function deteriorates. About 25% of people with chronic hepatitis B develop liver damage including cirrhosis or liver cancer, usually after years or decades. The rate of liver damage is higher and hepatitis B disease progression is more rapid in HIV/HBV-coinfected people.

Conversely, most research indicates that HBV infection does not appear to adversely affect HIV disease progression. Dr. Andrea De Luca and colleagues reported in the October 14, 2002 issue of the

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diagnosis to AIDS diagnosis, from HIV diagnosis to death, or from AIDS diagnosis to death—in HIV/HCV-coinfected people compared with those who had HIV alone.

However, not all research confirms that HCV has no effect on HIV progression. Some studies suggest that infection with certain HCV genotypes may be associated with more rapid progression to AIDS or death. Dr. Sherman's team found that HCV genotype 1 is more common in people with HIV/HCV coinfection (about 83%) than in people with HCV alone (about 70%), which may contribute to more aggressive hepatitis C. In the October 14, 2002 issue of the *Archives of Internal Medicine,* Andrea de Luca, MD, and colleagues with the Italian Cohort Naive Antiretrovirals Study Group reported that coinfection with HCV (but not HBV) was associated with increased risk of progression to AIDS-defining illness and death. In addition, coinfected people in this study experienced "consistently reduced recovery" of CD4 cells when treated with HAART compared with those who had HIV alone.

Several other studies confirm that immune recovery after starting HAART may be impaired in HIV/HCV-coinfected people. For example, in the November 25, 2000 issue of *The Lancet* Gilbert Greub, MD, and colleagues with the Swiss HIV Cohort Study reported on response to HIV treatment in 3,111 HIV positive participants, 1,157 of whom also had HCV. Both the coinfected participants and those with HIV alone were equally likely to achieve HIV viral loads below 400 copies/mL after starting HIV treatment. But the coinfected people were less likely than those with HIV alone to experience a CD4 cell count increase of at least 50 cells/mm^3 (75% vs 84%). By the end of follow-up, about 8% of the coinfected participants had developed an OI compared with about 5% of those with HIV alone, and the death rate due to all causes was more than twice as high among the coinfected participants.

More recent studies offer similar results related to immune recovery. At the 8th Retrovirus conference in February 2001, J. Martin and colleagues from Madrid reported that among 902 study participants with HIV—72% of whom were coinfected with HCV—responses to HAART differed dramatically. Participants with HIV alone experienced an average HIV viral load decrease of over 5,700 copies/mL and an average CD4 cell count increase of 111 cells/mm^3. In contrast, the HIV/HCV-coinfected participants experienced an HIV viral load decrease of only 606 copies/mL and a CD4 cell count increase of just 53 cells/mm^3. At the Barcelona AIDS conference Juan Antonio Pineda and colleagues from Seville, Spain, presented evidence showing that CD4 cell recovery after starting HAART is slower in HIV/HCV-coinfected people compared with those who have HIV alone. Likewise, Maria Dorrucci, MD, and colleagues from Rome also reported at the same conference that coinfected people had a poorer response to HAART.

The question of how HCV affects HIV disease remains unsettled. As HIV/HCV-coinfected people live longer, more data will become available that should shed light on how HCV infection influences the long-term natural history of HIV disease.

SUMMARY

Hepatitis C progresses more rapidly and is more likely to lead to serious liver damage in people coinfected with HIV.

The effect of HCV on HIV disease is less clear, but most studies show that HCV does not increase HIV viral load or directly accelerate HIV disease progression.

Coinfection with HCV does appear to impair immune recovery after starting HAART.

HCV Treatment in People with HIV

Treatment Considerations

Treatment of HIV/HCV-coinfected people is not well understood, largely because most of the studies that led to the approval of HCV treatments excluded difficult-to-treat populations such as people with HIV. With the improvements in health and longevity brought about by HAART, however, views about hepatitis C treatment for people with HIV/HCV coinfection have changed. At the June NIH consensus conference Dr. Thomas reported that HIV/HCV-coinfected people can achieve good responses to HCV treatment and that the rate of side effects appears similar in people with and without HIV. The final NIH consensus guidelines released in August 2002 recommend that HCV treatment should be considered for all people at greatest risk for hepatitis C progression. Unlike the previous 1997 consensus statement, the new guidelines no longer recommend against treatment for HIV/HCV-coinfected people or those with alcohol or drug use issues.

People with HIV who are diagnosed with hepatitis C should be evaluated and considered for HCV treatment. Many people with chronic hepatitis C—coinfected or not—do not experience symptoms for decades and may never develop serious liver disease. Most experts recommend against treatment for people who are asymptomatic, have normal liver enzyme levels, and have minimal existing liver fibrosis; many believe that for such people, watchful waiting with regular monitoring is a better option. For people with moderate to severe liver fibrosis, most physicians recommend that hepatitis C should be treated.

Treatment is most successful in people who have low HCV viral loads, are under age 40, are female, have HCV genotypes other than 1, and have not yet sustained extensive liver damage. Interferon is usually not recommended for people with decompensated cirrhosis, although some may be treated in clinical trials. Treatment decisions should be guided by biopsy results, not liver enzyme levels alone, since some people maintain persistently normal ALT levels despite progressive liver damage. HCV viral load is likewise not a good marker of disease progression. However, reductions in ALT and HCV viral load can be useful indications that treatment is working.

In general, guidelines for deciding whether to treat hepatitis C apply to coinfected people. However, some experts believe that it is best to treat HCV early in people with HIV, while their immune systems are still functioning well and their CD4 cell counts are still high. Studies have shown that coinfected people with higher CD4 cell counts respond better to HCV treatment. This may be because interferon works in part by boosting immune activity, and the immune systems of people with advanced HIV disease may be too damaged to respond. In addition, interferon can sometimes cause a decrease in CD4 cell count (although the CD4 percentage may remain the same). Thus, it may be appropriate to treat some asymptomatic HIV/HCV-coinfected people who might otherwise not be considered candidates for treatment if they had HCV alone.

Hepatitis C treatment generally is not recommended for people with advanced HIV disease and severe immunosuppression. Those with CD4 cell counts below 200 cells/mm^3 or a concurrent OI are usually not considered good candidates for HCV treatment. Therefore, OIs should be treated and antiretroviral therapy should be used to control HIV and raise the CD4 cell count before starting HCV treatment.

However, while experts generally recommend that HIV be treated first before beginning HCV therapy, there are some cases in which the opposite

HEPATITIS B

Archives of Internal Medicine that coinfection with HCV—but not HBV—increased the risk of AIDS-defining illnesses and death. One study presented at the September 2002 ICAAC even suggested that HBV coinfection was associated with reduced HIV replication.

As with HIV/HCV coinfection, much remains unknown about coinfection with HIV and HBV, and studies to date are conflicting. For example, some researchers have shown that the risk of death due to liver complications is increased in HIV/HBV-coinfected people compared with those who have either HIV or HBV alone, but others have not found this to be the case.

Many people with chronic hepatitis B do not need treatment. Most doctors recommend against treatment for people who have low HBV viral loads, normal ALT levels, and minimal liver damage as determined by liver biopsy. Three drugs are currently approved to treat hepatitis B: interferon-alpha-2b (Intron-A), 3TC (lamivudine, Epivir), and adefovir (Hepsera, approved this past September). Pegylated interferon is under study for HBV, as are several other drugs including emtricitabine (FTC, Coviracil), entecavir, famciclovir, and tenofovir DF (TDF, Viread).

Unlike HCV drugs, certain medications used to treat HBV—notably the NRTIs 3TC and emtricitabine, and the nucleotide reverse transcriptase inhibitors (NtRTIs) adefovir and tenofovir—are also active against HIV. Coinfected people who take 3TC as part of their HIV regimen typically have lower HBV viral loads. Use of 3TC almost always leads to the development of 3TC-resistant "YMDD" HBV mutations, and coinfected people who use 3TC to treat HBV without any other anti-HIV drugs are likely to

develop 3TC-resistant HIV as well. Adefovir was originally developed as an HIV treatment (under the brand name Preveon), but was never approved because it caused kidney toxicity; Hepsera is used in lower doses (about one-tenth as much) to treat hepatitis B and is therefore safer. Tenofovir was approved for use in HIV therapy in October 2001.

Much of the liver damage associated with hepatitis B is due to the immune system's response to the virus, and in some cases initiation of HAART leads to potentially life-threatening liver enzyme "flares" in people with HBV as the anti-HIV drugs promote immune recovery. Flares may also occur when people with HBV stop taking 3TC. For this reason, many experts recommend that people who develop 3TC-resistant HBV should keep taking 3TC and add a new anti-HBV drug.

Several studies presented at recent conferences have shown that adefovir and tenofovir are promising treatments for people with HIV/HBV coinfection. The drugs appear to be effective against both wild-type (nonmutated) and 3TC-resistant HBV. For example, at the Barcelona AIDS conference Dr. Yves Benhamou and colleagues presented results from a study of 35 HIV/HBV-coinfected people with evidence of 3TC-resistant HBV. After adefovir was added to their existing antiretroviral regimens for 72 weeks, participants experienced a median HBV DNA decrease of almost 5 logs; nine achieved undetectable HBV viral loads and three became negative for HBe antigen. ALT levels also decreased, and among the 14 who had repeated liver biopsies over one-half showed a decrease in liver tissue damage.

At this year's ICAAC, Mark Nelson, MD, from Chelsea and Westminster Hospital in London and colleagues reported that 55% of the approach may be preferable. In people who are newly infected with HIV and have minimal immune system damage and high CD4 cell counts, but advanced hepatitis C, HCV treatment might be started first to control liver damage and improve the chances of tolerating anti-HIV drugs in the future. Treatment decisions should be made on an individual basis. Once treatment is underway, regular monitoring should be done to assess liver disease progression. Dr. Thomas suggests that liver biopsies be repeated perhaps every three years in coinfected people who are not receiving HCV therapy.

Much remains to be learned about how HCV treatment impacts HIV disease and vice versa. Some researchers have reported that interferon therapy leads to decreased CD4 cell counts, while others have found no such effect. HCV treatment does not appear to directly affect HIV viral load. Similarly, anti-HIV drugs do not appear to have a direct effect on HCV. While a majority of researchers have reported that HAART does not affect HCV viral load, others have seen HCV RNA increases in people starting antiretroviral therapy for HIV. In some cases HAART can produce an increase in liver inflammation (a "flare") as anti-HIV drugs improve immune system function. Clearly, more research is needed in this area.

HCV Regimens

Until 1998 the only treatment approved by the Food and Drug Administration (FDA) for chronic hepatitis C was interferon-alpha monotherapy. Interferons are natural immune proteins that appear to work by enhancing immune system activity, inhibiting HCV replication, and protecting cells from infection. Genetically engineered brands of interferon-alpha include Intron-A (interferon-alpha-2b, manufactured by Schering-Plough) and Roferon-A (interferon-alpha-2a, produced by Roche Laboratories). Standard interferon is typically injected three times per week.

Studies have shown that combination therapy with interferon-alpha plus the antiviral drug ribavirin is more effective than interferon monotherapy. Ribavirin is a nucleoside reverse transcriptase inhibitor (NRTI) like many anti-HIV medications. (In fact, ribavirin was studied as an HIV treatment but did not show much promise and was never approved for this indication.) As is the case with therapy for HIV, using multiple drugs that work by different mechanisms appears to be the most effective approach to treating hepatitis C.

As mentioned above, pegylated interferon is a recently developed long-acting formulation of interferon that can be injected less often, typically once per week. Pegylation is a process in which polyethylene glycol is attached to a protein to extend its activity in the body. Schering-Plough's Peg-Intron brand of pegylated interferon-alpha-2b was approved in 2001; Roche's Pegasys brand of pegylated interferon-alpha-2a was approved this past October. Most studies show that treatment response rates for combination therapy with pegylated interferon plus ribavirin are higher than those for standard interferon plus ribavirin.

To date, no treatments have been specifically approved for use by individuals with HIV/HCV coinfection, but most physicians use the same regimens for coinfected people as they do for those with HCV alone. In general, research has shown that treatment response rates for all types of HCV therapy are somewhat lower for HIV/HCV-coinfected people than for those with HCV alone. However, some studies suggest that people with well-controlled HIV disease and high CD4 cell counts may respond nearly as well to HCV treatment as those without HIV. Whether a person is coinfected or not, the relative effectiveness of the various regimens appears to be the same: pegylated interferon plus ribavirin is generally superior to standard interferon plus ribavirin, which in turn is more effective than interferon monotherapy. Likewise, treatment response rates are consistently higher for people with HCV genotypes 2 or 3 compared with those who have genotypes 1 or 4, whether or not they are coinfected with HIV.

Numerous studies have looked at the safety and efficacy of standard interferon with or without ribavirin in HIV/HCV-coinfected people. But the most recent results presented at conferences concern pegylated interferon, which is increasingly considered the standard of care for chronic hepatitis C.

The most promising results to date are from AIDS Clinical Trials Group (ACTG) study 5071. In a late-breaker presentation at the February 2002 Retrovirus conference, Raymond Chung, MD, from Massachusetts General Hospital in Boston reported on an analysis of 133 coinfected participants treated with ribavirin plus either Pegasys or standard interferon. After 24 weeks, 44% of those in the Pegasys arm achieved an undetectable HCV viral load compared with 15% of those in the standard interferon arm using an intent-to-treat (ITT) analysis (in which all participants were analyzed whether or not they completed therapy).

Among those with HCV genotype 1, the response rates were 33% for Pegasys and 7% for standard interferon; among those with genotypes 2 or 3, the respective response rates were 80% and 40%. These response rates—especially for genotype 1—are somewhat lower than those seen in studies of people with HCV alone. At the time of this presentation, sustained virological response rates (undetectable HCV viral load six months after the end of treatment) were not yet available and the study is continuing. Severe adverse side effects were more common in the pegylated interferon group (17 events) than in the standard interferon group (5 events), but dropout rates were similar in both groups (15% and 12%, respectively).

At the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) this past September, Margaret Hoffman-Terry, MD, of Lehigh Valley Hospital in Allentown, Pennsylvania, and colleagues reported results from 119 coinfected people (most with HCV genotype 1) treated with Pegasys with or without ribavirin. After 24 weeks, 39% experienced at least a 2 log decrease in HCV viral load.

Results from other studies do not look so good, however. A trial by Christian Perronne, MD, and colleagues from Paris (the RIBAVIC study)—also reported at the September ICAAC—compared Peg-Intron plus ribavirin against standard interferon plus ribavirin in 416 HCV-treatment-naive coinfected individuals, most of whom were taking HAART. After 48 weeks, 38% in the Peg-Intron group and 24% in the standard interferon group achieved an undetectable HCV viral load using an ITT analysis. Using a less rigorous as-treated analysis (in which only those who completed therapy were analyzed), the respective response rates were 51% and 31%. By genotype, about 40% of those with genotypes 2 or 3 and about 25% of those with genotypes 1 or 4 achieved an undetectable viral load in the Peg-Intron group. The response rate in the Peg-Intron group (25%) was better than that seen in the standard interferon group (10%) for those with genotype 1 or 4, but the difference was not significant for those with genotypes 2 or 3.

In both treatment groups, participants with CD4 cell counts above 500 cells/mm^3 had better response rates. The incidence of serious side effects was high (about 25% in the Peg-Intron group and 21% in the standard interferon group), and about one-third of participants discontinued treatment. The lower response rates in this study compared with ACTG 5071 may reflect a difference between Peg-Intron and Pegasys; the two brands of pegylated interferon have not yet been compared in head-to-head trials.

Pegylated interferon also offers promise for HIV/HCV-coinfected people who have not responded to previous HCV therapy. Also at ICAAC, Maribel Rodrigues-Torres, MD, of the University of Puerto Rico in Rio Piedras and colleagues reported results of a study in which 75 coinfected people who had not responded to prior treatment with standard interferon monotherapy were given either Pegasys or Pegasys plus ribavirin. After 24 weeks, 27% of participants in both groups experienced at least a 2 log decrease in HCV RNA

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HEPATITIS B

18 HIV/HBV-coinfected people in their study achieved undetectable HBV viral loads when tenofovir was added to their anti-HIV regimens. Both adefovir and tenofovir appear to be well tolerated, with few trial participants discontinuing treatment due to side effects.

Dr. Raymond Chung offered several recommendations regarding HIV/HBV coinfection in a September 2002 *Medscape* review article. He advised that people with HIV should be screened for HBV as well as HCV. HIV/HBV-coinfected individuals with active, replicating HBV should be considered for treatment. Given the promising results of new drug trials, Dr. Raymond predicted that treatment-naive HIV/HBV-coinfected people would soon start using combination therapy rather than adding drugs in a serial manner. Use of 3TC plus adefovir or tenofovir as part of a HAART regimen should lead to less drug-resistant HBV and better hepatitis B treatment outcomes.

Hepatitis Resources

American Liver Foundation:
800-223-0179
www.liverfoundation.org

Hepatitis B Foundation:
215-489-4900
www.hepb.org

Hepatitis C Support Project:
www.hcvadvocate.org

Hepatitis Information Network:
www.hepnet.com

Hepatitis Foundation International:
800-891-0707
www.hepfi.org

Hepatitis A and B
VACCINATION

It is strongly recommended that people with HCV be vaccinated against the hepatitis A and hepatitis B viruses if they are not already immune. (Hepatitis A is an acute, inflammatory viral disease of the liver transmitted by ingesting contaminated food or water and by fecal-oral contact.) HAV and HBV disease can be much worse in people with hepatitis C. In addition, the HBV vaccine is recommended for sexually active gay men (regardless of HIV status), health-care workers, and others at risk for infection; it is also now routinely administered to infants and adolescents. In HIV/HCV-coinfected people, vaccination should be done early—while CD4 cell counts are still high—to ensure an adequate antibody response. The HAV vaccine consists of two doses within a six-month period; the HBV vaccine requires three doses within a six-month period. A combination HAV/HBV vaccine is also available. Both vaccines are considered safe for people with HIV.

and 30% achieved an undetectable HCV viral load. These response rates are higher than those seen in other studies of previous nonresponders.

While some early research suggested that response to HCV therapy tended to be slower in coinfected people, recent studies using pegylated interferon plus ribavirin suggest that coinfected people are as likely as those with only HCV to achieve an early treatment response (although response is slower in people with HCV genotypes 1 or 4 compared with those who have genotypes 2 or 3, regardless of HIV status). In terms of treatment length, researchers from the European Benelux Study presented evidence at the May 2001 Digestive Disease Week conference showing that 18 months of HCV treatment—rather than the typical 12 months—may be more effective for coinfected people.

Most studies of HCV treatment have looked at virological response rates. But a few have focused on histological response (improved liver health, including decreased inflammation and fibrosis). In a study published in the February 15, 2002 issue of *AIDS,* Dr. di Martino and colleagues reported that while sustained virological response rates in coinfected people receiving standard interferon plus ribavirin were lower than those in people with HCV alone, histological response rates were similar in the two groups.

These results and others suggest that HCV treatment may improve liver health even if undetectable HCV viral loads are not achieved. According to Douglas Dieterich, MD, of New York University School of Medicine, "even in so-called 'failures' interferon therapy decreases fibrosis, increases T-cell responsiveness to hepatitis C antigens, and decreases the rate of fatal hepatomas [liver cancer].... Lowering the [HCV] viral load can only help the ultimate outcome of the liver disease, and may permit [coinfected people] to take protease inhibitors that will certainly prolong life."

Side effects of HCV treatment are common in people with or without HIV coinfection. While many studies show that coinfected people are less able to tolerate HCV treatment and have higher discontinuation rates, others have found similar side effect and dropout rates. More research is needed in this area. Another issue requiring further study is whether pegylated interferon is associated with more or less frequent and severe adverse effects than standard interferon; here again, study results are conflicting. HIV/HCV-infected people should report all new or changed symptoms to their physicians. Health-care providers, support groups, and HCV advocacy organizations can offer help in learning to manage and live with HCV treatment side effects.

SUMMARY

HCV can be successfully treated in most HIV/HCV-coinfected people.

Most experts recommend that HIV disease and OIs should be controlled first before starting HCV treatment.

In people with little immune system impairment but advanced hepatitis C, starting HCV treatment first may help them tolerate anti-HIV drugs later.

HCV treatment response rates tend to be lower in coinfected people than in those with HCV alone.

Pegylated interferon plus ribavirin is currently the most effective HCV treatment option.

HIV Treatment in People with HCV

HIV/HCV coinfection can complicate HIV treatment due to adverse drug effects. These complications are of two types:

1. ***Hepatotoxicity***—liver-specific side effects of antiretroviral drugs, which may be worse in people with existing liver damage due to chronic hepatitis.
2. ***Drug interactions***—in which anti-HIV and HCV drugs that have similar side effects produce intensified (additive or synergistic) adverse events when the drugs are used together.

Hepatotoxicity

Many anti-HIV drugs are metabolized by the liver. When drugs are taken in high doses—and especially when different drugs are combined—they can cause liver injury. This is especially likely in people who have existing liver damage due to chronic viral hepatitis or other factors such as heavy alcohol consumption. For example, Dr. Sulkowski and colleagues reported in the January 2002 issue of *Hepatology* that 69% of the cases of severe liver toxicity seen in their study of HIV positive people taking nevirapine (Viramune) or efavirenz (Sustiva) occurred in people coinfected with HCV or HBV. Research also suggests that women are more likely to experience drug-related hepatotoxicity, perhaps due to their lower average body weight.

Drug-related liver injury is often signaled by increased levels of liver enzymes, in particular ALT and AST. In fact, when combination antiretroviral therapy was first used many physicians noticed dramatic increases in their patients' liver enzyme levels and began testing them for hepatitis C—thus revealing that HIV/HCV coinfection was more common than previously suspected. Mild-to-moderate hepatotoxicity is usually asymptomatic, but some people may experience nausea, fatigue, itching, or elevated bilirubin (bile pigment) levels leading to jaundice. Elevated liver enzyme levels are most common soon after starting a new drug and typically stabilize over time, but in some cases hepatotoxicity develops after a longer period on therapy.

Different studies have shown that antiretroviral regimens on the whole are associated with a two-fold to five-fold increased risk of hepatotoxicity. All classes of anti-HIV drugs have been linked with liver toxicity. Most studies show that the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine and the PI ritonavir (Norvir) at full dosage are the worst offenders; the small amounts of ritonavir sometimes added to regimens to "boost" blood levels of other PIs are

HEALTHY *Liver Tips*

- Get vaccinated against hepatitis A and hepatitis B.
- Avoid alcohol. Many studies show that alcohol contributes to liver damage, especially in people with chronic viral hepatitis.
- 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.
- 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.
- Eat a healthy, well-balanced diet.
- Get regular, moderate exercise.
- Sleep enough at night and rest during the day as needed to help manage fatigue.
- Get regular health check-ups, including monitoring of liver enzymes and blood cell counts.

less likely to be problematic. Other anti-HIV drugs associated with liver toxicity include the NRTIs AZT (zidovudine, Retrovir), ddI (didanosine, Videx), ddC (zalcitabine, Hivid), d4T (stavudine, Zerit), and abacavir (Ziagen); the NNRTIs delavirdine (Rescriptor) and efavirenz; and the PIs indinavir (Crixivan) and saquinavir (Fortovase). 3TC (lamivudine, Epivir) causes minimal liver toxicity. Studies have shown that severe hepatotoxicity related to the PIs nelfinavir (Viracept) and lopinavir/ritonavir (Kaletra) is uncommon, and recent research suggests that the new PI atazanavir (Zrivada) may have a similar low liver toxicity rate.

Elevated liver enzyme levels are most common soon after starting a new drug and typically stabilize over time, but in some cases hepatotoxicity develops after a longer period on therapy.

As with many aspects of HIV/HCV coinfection, researchers do not all agree that antiretroviral drugs lead to higher rates of liver toxicity in people with viral hepatitis. Some studies have shown low rates of hepatotoxicity even for drugs that have proven most problematic in other trials. For example, Dr. Dieterich and colleagues reported in the April 1, 2002 issue of the *Journal of AIDS* that they saw severe (grade 3 or 4) ALT or AST elevations in just 1.1% of their cohort of HIV positive men taking efavirenz, nevirapine, or delavirdine; none of these severe events occurred among the subset of 40 men coinfected with HCV. And in the May 1, 2002 issue of *Clinical Infectious Diseases,* Curtis Cooper, MD, from the University of Ottawa and colleagues reported similar rates of liver toxicity in people taking ritonavir and those on ritonavir-sparing regimens.

Even mild liver enzyme elevations should be taken seriously, especially in people with chronic hepatitis. At the Barcelona AIDS conference Amy Justice, MD, from the University of Pittsburgh and colleagues reported that in their population of 5,700 participants from two observational studies, elevations of ALT or AST were associated with a higher risk of death. Those with mild-to-moderate liver enzyme elevations had a 1.7-fold increased risk of death, while those with liver enzyme levels two or more times normal had a five-fold increased mortality rate. According to Dr. Justice, "Our study shows that even patients whose elevations are mild to moderate have a death rate that is nearly twice that of patients with mid-range normal levels. This association with increased mortality suggests that any elevation in ALT and AST should be addressed." [For Dr. Justice's perspective on liver health concerns specific to women, see page 30.]

In related research, Corinne Rancinan, MD, and colleagues with the French Aquitaine study group reported in the July 5, 2002 issue of *AIDS* that HCV coinfection itself was not associated with a greater risk of death in people with HIV unless they had elevated liver enzyme levels.

Drug Interactions

Anti-HIV drugs are associated with a number of non-liver-specific side effects, several of which are common to drugs used for HCV treatment. When these drugs are used together, additive or synergistic adverse events may occur.

NRTI drugs are known to cause bone marrow suppression leading to low blood cell counts, and HIV treatment regimens almost always include at least one of these drugs. Likewise, interferon—especially pegylated interferon—often causes neutropenia (low white blood cell count). Ribavirin causes hemolytic anemia in 20% or more of patients. Using certain anti-HIV drugs (in particular, AZT) and HCV therapies together can potentially lead to dose-limiting blood cell deficiencies.

Mitochondrial toxicity refers to drug-induced damage to small organelles within cells that are involved in energy production. It is associated with elevated levels of lactic acid in the blood (hyperlactatemia or lactic acidosis). Symptoms may include fatigue and muscle weakness. Mitochondrial toxicity is a known side effect of NRTI drugs, especially ddI and d4T. It is also a possible side effect of ribavirin, and the risk is compounded when people take ribavirin and ddI and/or d4T together. In the RIBAVIC study, for example, Dr. Perronne and colleagues detected evidence of mitochondrial toxicity in 22% of those taking ribavirin, ddI, and d4T; in 7% of those taking ribavirin and ddI but not d4T; in 1% of those taking ribavirin and d4T but not ddI; and in 1% of those taking ribavirin with neither ddI nor d4T.

This past September the FDA announced that the ddI label had been revised to include a warning about use of the drug with ribavirin. The warning states that ddI blood levels may increase when taken with ribavirin, and recommends that people taking both drugs should be monitored carefully and that ddI should be discontinued if signs of pancreatitis (inflammation of the pancreas), symptomatic hyperlactatemia, or lactic acidosis develop.

Interestingly, high blood fat levels—one of the most worrisome side effects associated with anti-HIV drugs—appear less likely to occur in HIV/HCV-coinfected individuals. For example, Jack Stapleton, MD, and colleagues from the Veterans Administration Medical Center in Iowa City, Iowa, and colleagues presented data at

the Barcelona AIDS conference showing that HIV/HCV-coinfected people taking HAART were significantly less likely to have high cholesterol levels—both total cholesterol and low-density lipoprotein (LDL) "bad" cholesterol—than those with HIV alone. The researchers suggested that the difference may be related to the way HCV binds to lipoproteins or due to altered liver metabolism of fats and glucose.

These results are not isolated. Julio Collazos, MD, and colleagues from Vizcaya, Spain, presented data at the September 2002 ICAAC showing that HIV/HCV-coinfected people taking HAART had hyperlipidemia (high blood fat) rates similar to those of people not receiving HIV therapy. However, L. Casado and colleagues from Ovideo, Spain, reported at the same conference that they saw similar cholesterol and triglyceride levels in HAART-treated coinfected individuals and those with HIV alone; moreover, in their study lipodystrophy (body fat irregularities) was more common in those with both HCV and HIV.

High blood fat levels—one of the most worrisome side effects associated with anti-HIV drugs—appear less likely to occur in HIV/HCV-coinfected individuals.

Monitoring and Managing Side Effects

As liver failure becomes a more common cause of illness and death in people with HIV/AIDS, it is increasingly important to manage hepatotoxicity related to antiretroviral drugs—and this is especially true for people with existing liver damage due to chronic hepatitis.

To some extent, careful drug selection and dose modification can help prevent or reduce hepatotoxicity and intensified side effects. Since there are many more anti-HIV drugs than medications for HCV, there is more leeway for adjustment of HIV regimens.

Among the NRTIs, AZT is most often associated with low blood cell counts, and ddI and d4T are most often linked to mitochondrial toxicity. Many experts recommend that people being treated for HCV use NRTIs other than AZT, ddI, or d4T.

Among the PIs, ritonavir and saquinavir are most often associated with severe liver toxicity. Nelfinavir and the new PI atazanavir may be the best options for coinfected people.

Among the NNRTIs, nevirapine has often been linked to hepatotoxicity, so one of the other NNRTI drugs—or a regimen that does not include an NNRTI—may be better choices.

Despite these suggestions, it is important to construct an anti-HIV regimen that has adequate potency. If drugs associated with greater toxicity must be used, frequent and careful monitoring is essential.

While hepatotoxicity and other side effects should be minimized if possible, studies show that a majority of people with HIV/HCV coinfection do not experience serious adverse events, regardless of what drugs they use. Discussing his July 2002 *JAMA* article, Dr. Sulkowski stated that HAART was safe for people with HCV and that HIV/HCV-coinfected people do "just as well" on antiretroviral therapy as those with HIV alone.

Although some physicians are daunted by the many possible drug side effects and interactions—and thus may be hesitant to treat coinfected people for either HCV or HIV—such reluctance does not seem warranted. Again, many people with HIV and HCV can be successfully treated for both diseases. Effective control of HIV can slow HCV disease progression and lessen the risk of severe liver damage. And treatment for HCV can be beneficial even in the absence of a sustained virological response.

A variety of therapies can be used to help manage the side effects of anti-HIV and HCV drugs. For example, erythropoietin (Epogen or Procrit) may be used to stimulate red blood cell production and granulocyte colony-stimulating factor (Neupogen) can promote white blood cell proliferation. Antidepressants are often used to manage the psychological side effects of interferon therapy. In addition, there are many practical, supportive, and self-help measures that can help people cope with adverse effects, such as injecting interferon at bedtime to sleep through the worst symptoms and avoiding spicy or greasy foods to lessen nausea.

The key to successful therapy for people with HIV/HCV coinfection is careful monitoring. ALT, AST, and bilirubin levels should be measured regularly for signs of hepatotoxicity. Blood cell counts should be monitored for indications of neutropenia or anemia. Most side effects are worse when a new drug is first started and often improve over time. Therefore, monitoring is especially important when beginning a new medication. However, some side effects—including hepatotoxicity and mitochondrial toxicity—may develop over time. Monitoring should not stop just because a person is currently doing well.

Since management of HIV/HCV coinfection can be complex, the care of coinfected people ideally should be managed by physicians who have experience with both diseases or by teams that include both a hepatologist (liver disease specialist) and an infectious disease expert.

SUMMARY

HIV can be successfully treated in most coinfected people.

Hepatotoxicity and drug interactions can complicate HIV treatment in coinfected individuals.

Medication regimens often can be adjusted to minimize adverse events; do not adjust doses or change drugs without medical advice. Report all new or worsening symptoms to a health-care provider.

Future Directions

Therapies for both HIV disease and hepatitis C have improved dramatically in the past five years. In fact, several lessons learned from treating HIV have been fruitfully applied to the development of therapies for HCV. It is increasingly apparent that for HCV, as for HIV, regimens of multiple drugs that work by different mechanisms are more effective than monotherapy. In contrast to anti-HIV drugs that target specific viral enzymes, current treatments for hepatitis C are nonspecific. However, new drugs that target the HCV protease and helicase enzymes are under development and may provide better future treatment options. Unlike HIV, HCV does not integrate itself into human cells, and therefore may be more easily eradicated. The latest treatment regimen, pegylated interferon plus ribavirin, produces sustained viral clearance in one-half or more of people with HCV alone. Researchers are exploring the use of long-term maintenance therapy, as is done for HIV, in an effort to reduce hepatitis C disease progression and prevent liver damage.

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CORRECTION NOTICE

The telephone number listed for the T-20 (enfuvirtide, Fuzeon) expanded access program in the Summer/Autumn 2002 issue of *BETA* was incorrect. Instead, visit www.T20EAP.com for more information.

Trial results presented by Giorgio Barbarini, MD, and colleagues at the XIV International AIDS Conference and mentioned in the Summer/Autumn 2002 issue ("Cardiovascular Disease in People with HIV") have been withdrawn by the study authors following a request to verify the originality of their data. The study had appeared to show an association between protease inhibitors and cardiovascular disease.

Note should have been made in the Summer/Autumn 2002 issue that Lisa Garbus, MPP, author of the "HIV/AIDS in Asia and the Pacific" article, is no longer an editor at HIV InSite. Since March 2002 she has been director of the Country AIDS Policy Analysis Project at the AIDS Policy Research Center at the University of California at San Francisco. The article reprinted in *BETA* was last updated in December 2001 and did not reflect new data released since then, including revised national adult HIV prevalence figures issued by UNAIDS in July 2002.