Hepatitis C in the HIV-Infected Person

Mark S. Sulkowski, MD, and David L. Thomas, MD

Because of shared routes of transmission, hepatitis C virus (HCV) infection is common in HIV-infected persons, who have been experiencing increasing HCV-related morbidity and mortality since the advent of effective antiretroviral therapy. Infection with HIV appears to adversely affect the outcome of hepatitis C, leading to increased viral persistence after acute infection, higher levels of viremia, and accelerated progression of HCV-related liver disease. In addition, hepatitis C may affect the course and management of HIV infection. The medical management of hepatitis C in HIV-infected persons is complicated by immune suppression, potential drug interactions and toxicities, and other forms of liver disease. In addition, there is little published experience with the safety and efficacy of the best available anti-HCV medications in HIV-infected persons. Thus, current efforts must be directed at preventing HCV and HIV infections and applying the principles learned in treating persons with either infection to manage those with both. Future efforts should include studies of the pathogenesis of HCV infection in HIV-infected persons and large, prospective studies that demonstrate the optimal management of persons co-infected with HIV and HCV. Such efforts will help to eliminate HCV-related liver disease as an emerging threat to HIV-infected persons.

Ann Intern Med. 2003;138:197-207. www.annals.org

For author affiliations, see end of text.

In the United States, 150 000 to 300 000 persons are infected with both HIV-1 and hepatitis C virus (HCV), representing 15% to 30% of all HIV-infected persons and 5% to 10% of all HCV-infected persons (1, 2). Whereas HCV-related liver disease was once a relatively minor medical problem in persons co-infected with HIV and HCV, highly active antiretroviral therapy (HAART) has led to a marked decline in most opportunistic illnesses, and HCV infection has emerged as an important cause of morbidity and death (3–5). Medical management of HCV infection has improved in recent years (6–9). However, the management of hepatitis C in the HIV-infected person is complicated not only by differing epidemiologic characteristics and natural history but also by other issues, such as reduced HCV antibody production, drug interactions, and other causes of liver disease. The objective of this review is to discuss the management of hepatitis C in the HIV-infected person by using the available literature to provide recommendations and, when necessary, highlight areas of controversy.

Methods

Computerized, English-language literature searches were performed through the MEDLINE database (January 1966 to December 2002) for published studies in humans that examined HIV and hepatitis C. For the search, the terms *HIV*, *AIDS*, *human immunodeficiency virus*, or *acquired immunodeficiency syndrome* and *HCV* or *hepatitis C* or *non-A, non-B hepatitis* had to be present in keywords, titles, or abstracts. The bibliographies of selected articles were also searched for pertinent studies. One or both of the authors reviewed study titles or abstracts to select published studies that examined hepatitis C and HIV co-infection for inclusion.

Epidemiology

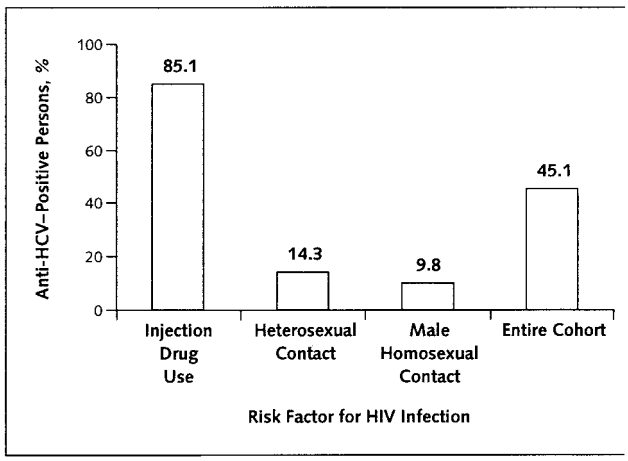
Both HIV and HCV can be transmitted by percutaneous exposure to blood, through sexual intercourse, and from a mother to her infant. However, the relative efficiency of transmission by these routes varies. Hepatitis C virus is approximately 10 times more infectious than HIV through percutaneous blood exposures; it is transmitted by 15 to 30 of every 1000 accidental needlestick exposures, compared with 3 per 1000 for HIV (before the use of postexposure prophylaxis) (10). In addition, the incidence of HCV infection is substantially higher than that of HIV among injection drug users (11, 12).

Transfusion of contaminated blood and blood products was once an important route of HIV and HCV transmission and explains high rates of HIV–HCV co-infection among persons with hemophilia (13, 14). However, transmission of HIV and HCV through blood products was reduced markedly in the United States by the establishment of a volunteer donor system, screening donations for antibodies to HIV (in 1985) and HCV (in 1990), use of viral inactivation procedures of clotting factors (in 1987) and immune globulin (in 1994), and most recently screening for HIV and HCV RNA (in 1999) (15).

Between heterosexual partners, HIV is more transmissible than HCV (16–19). In one study, HIV infection was detected in 13% and HCV in only 3% of 162 female sexual partners of persons with hemophilia who were co-infected with HIV and HCV (18). In other studies of monogamous heterosexual partners of persons with HCV infection alone, an even lower percentage of HCV-infected persons was found (20, 21). Thus, heterosexual transmission of HCV is uncommon but may be more likely in persons with partners who are co-infected with HIV and HCV. Likewise, existing data suggest that sexual contact is a relatively inefficient mode of HCV transmission between men. In most studies (but not all), the prevalence of HCV infection is not substantially higher among men who have sex with men (17, 22, 23). Although prospective studies of HCV-discordant male homosexual couples are needed to clarify the risk, the existing data indicate that intercourse is a more efficient mode of transmitting HIV than HCV.

Without antiretroviral treatment, HIV infection oc-

Figure 1. **Prevalence of anti–hepatitis C virus (*HCV*) in HIV-infected persons receiving medical care in the Johns Hopkins HIV clinic (*n* = 1955) according to self-reported HIV exposure risk category.**



curs in 20% to 30% of infants born to HIV-infected mothers; HCV infection occurs in approximately 2% to 5% of infants born to HCV-positive mothers (24–26). In most studies, the incidence of HCV transmission from mother to infant increases if the mother is co-infected with HIV (25, 27). A higher HCV RNA level has been correlated in some studies with greater perinatal HCV transmission (26). However, it is not known whether the association of HIV infection with higher HCV RNA levels is the reason for more frequent perinatal (and possibly sexual) HCV transmission (28, 29). In one study, the risk for perinatal HIV transmission was 1.8-fold higher for infants born to mothers who were co-infected with HIV and HCV; this association was even greater among HIV- and HCV-positive women with the highest HCV RNA levels (30).

Because of shared routes of transmission, HIV–HCV co-infection is common. In the United States and Europe, 15% to 30% of HIV-infected persons are also infected with HCV (1). However, the prevalence of HIV–HCV co-infection varies markedly depending on the route of HIV infection (**Figure 1**).

NATURAL HISTORY

Effect of HIV Infection on Hepatitis C

Infection with HCV can be self-limited (viral clearance), can persist without causing clinical disease, or can lead to cirrhosis or hepatocellular carcinoma (31–33). Infection with HIV appears to adversely affect each outcome. Although approximately 20% of persons clear HCV RNA from their blood after acute infection, HCV clearance occurs in only 5% to 10% of HIV-infected persons, less frequently in those with lower $CD4^+$ cell counts (31, 34, 35). In one study, persons with ongoing injection drug use (and thus probably continual exposure to HCV) were able to maintain HCV clearance status for years until they acquired HIV, whereupon persistent HCV infection was detected (36).

In persons with persistent HCV infection, the probability of cirrhosis after 20 years of infection is estimated to be 5% to 25% (32, 37, 38). After cirrhosis has developed, the annual rates of progression to liver failure and hepatocellular carcinoma are estimated to be approximately 2% to 4% and 1% to 7%, respectively (39).

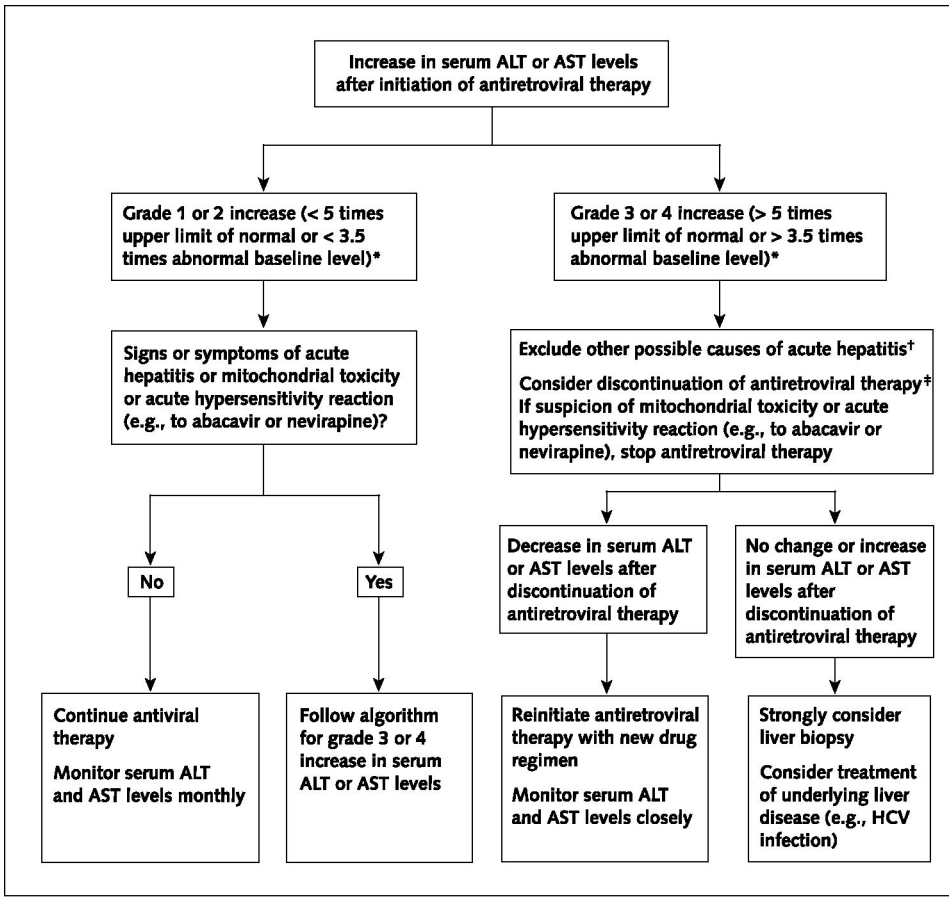
Infection with HIV has been associated with higher HCV RNA viral load and, in most studies, more rapid progression of cirrhosis, liver failure, and hepatocellular carcinoma (5, 14, 28, 29, 40–51). Eyster and colleagues (29, 41) reported that HCV RNA levels were higher in persons with hemophilia who became infected with HIV than in those who did not and that liver failure occurred exclusively in those co-infected with HIV and HCV. Similarly, Darby and coworkers (14) studied death from liver disease and hepatocellular carcinoma among 4865 men with hemophilia who were exposed to HCV-contaminated blood products. At all ages, the cumulative risk for liver-related death after the presumed HCV exposure was 1.4% (range, 0.7% to 3.0%) for men who were not infected with HIV and 6.5% (range, 4.5% to 9.5%) for men who were (14). In contrast, Thomas and colleagues (35) did not detect more end-stage liver disease in HIV-infected members of a study of 1667 HCV-infected current and former injection drug users. However, there were competing causes of death in the HIV-positive group.

As survival of HIV-infected persons increases because of potent antiretroviral therapies and the prophylaxis of traditional opportunistic pathogens, hepatitis C–related morbidity and mortality should also increase (3). In some settings, HCV-related liver disease has already been reported to be a major cause of hospital admissions and death among HIV-infected persons (4, 52, 53).

Effect of Hepatitis C on HIV Progression

There are conflicting reports on the effect of HCV infection on the natural history of HIV disease (54–58). In a prospective study of 416 HIV seroconverters in Italy, those who were co-infected with HCV (51%) and those who were not progressed to AIDS at similar rates (54). However, the reported follow-up may have been too short (an average of <3 years) to detect an effect. Among 1955 persons in a Baltimore, Maryland, HIV clinic, no difference was detected in the progression to AIDS or death after adjustment for exposure to HAART and HIV suppression (57). Conversely, among 3111 persons receiving HAART, Greub and colleagues (56) reported that HCV-infected persons had a modestly increased risk for progression to a new AIDS-defining event or death, even among the subgroup with continuous suppression of HIV replication. Of interest, Greub and colleagues also found that the CD4 cell increase after effective anti-HIV therapy was significantly

Figure 2. **Clinical management of antiretroviral-associated hepatotoxicity in the person co-infected with hepatitis C virus (*HCV*) and HIV.**



Clinical management of antiretroviral-associated hepatotoxicity must be individualized. In addition, serious hepatotoxicity has been associated with the use of all available antiretroviral medications; the optimal use of these medications in persons with underlying liver disease has not been established. The long-term impact of mild to moderate elevations in liver enzyme levels on progression of HCV-related fibrosis is unknown, and the effectiveness of anti-HCV therapy for the suppression of drug-related liver toxicity has not been evaluated. *Based on reference 61. †Consider acute hepatitis A and hepatitis B virus infection, other infectious causes of hepatitis (for example, cytomegalovirus, Epstein–Barr virus, *Mycobacterium avium* complex), acute cholecystitis, ethanol and other illicit drugs, other hepatotoxic medications (for example, fluconazole and trimethoprim–sulfamethoxazole), and nucleoside analogue reverse transcriptase inhibitor–related lactic acidosis syndrome due to mitochondrial toxicity. ‡ Patients with grade 3 or 4 hepatotoxicity and no symptoms of acute hepatitis who do not discontinue antiretroviral therapy should be monitored closely. ALT = alanine aminotransferase; AST = aspartate aminotransferase.

smaller in persons with HCV infection than in those without, suggesting that HCV co-infection may blunt immune recovery (56). However, two subsequent studies evaluating the immunologic response to HAART in co-infected persons failed to confirm this observation (57, 59).

All studies of the natural history of persons co-infected with HIV and HCV are limited in the extent to which findings can be attributed to co-infection per se, since co-infected persons may differ in important respects from those with only one of these infections. For example, persons who acquired HIV and HCV from contaminated blood products tend to have more severe hemophilia (14, 41), and persons infected with HIV and HCV in other settings are more likely to acknowledge injection drug use (56, 60). These differences may bias observational studies and may explain the contradictory findings. Understanding how HCV infection modifies the outcome of HIV infection is also complicated by the dominant effect of HAART on HIV natural history and the various ways that HCV infection and drug use might affect the receipt of HAART.

HCV Co-Infection and HAART-Associated Hepatotoxicity

Antiretroviral drug use has been associated with hepatotoxicity that can interrupt HIV therapy and cause significant morbidity and mortality (61–63). In some cases, HAART-associated hepatotoxicity has been linked to liver failure and death (64). Some but not all studies suggest that drug-induced hepatotoxicity may be more common among persons with HIV–HCV co-infection, particularly those taking HIV-1 protease inhibitors (62, 63, 65). However, it is difficult to attribute risk to HCV co-infection in individual case reports, since HAART-associated liver failure also occurs in persons not infected with HCV (66). In fact, 88% of a large cohort of HCV co-infected persons did

not experience substantial hepatotoxicity after HAART, and no irreversible outcomes were observed among persons experiencing toxicity (62). Thus, while the available evidence indicates that antiretroviral therapies can be safely administered to most persons with HIV–HCV co-infection, those receiving HAART should be closely monitored (60, 67).

There are currently no established guidelines for the management of antiretroviral-associated hepatotoxicity. Some studies have suggested that it is not necessary to discontinue antiretroviral therapy unless persons are symptomatic or develop significant elevations in liver enzyme levels (for example, more than five times the upper limit of the reference range) (62) (**Figure 2**). The mechanisms of enhanced drug-induced hepatotoxicity among patients with HIV–HCV co-infection are unknown but may include decreased drug metabolism, HCV-specific immune reconstitution, or increased susceptibility to mitochondrial dysfunction (68–70).

Pathogenesis

There are similarities and important differences in the pathogenesis of HIV and HCV. Both are RNA viruses whose genomes are transcribed frequently (greater than 10^{10} virions produced per day) by polymerases that lack the capability to proofread errors, a process that results in the accumulation of a swarm of the "fittest" variants (71, 72). The HIV genome is reverse transcribed and the complementary DNA integrated into the DNA of latent T cells, contributing to persistence and precluding HIV clearance (73). In contrast, HCV infection is sustained by ongoing replication. Thus, when HCV RNA cannot be detected in the blood years after initial infection or treatment, HCV infection has resolved, an outcome that has not been described with HIV (2, 74).

Replication of HCV has been reported in monocytes and lymphocytes (75, 76). However, the major site of replication is the liver, and there are clearly differences in the cells that these two viruses preferentially infect (77). The immunologic effects of HIV infection are extensive, and the precise biological effects of HIV infection on hepatitis C are unknown. Even less is known about how HCV might alter HIV progression. It is plausible that immune activation from any source would enhance HIV progression by increasing the number of activated $CD4^+$ lymphocytes (78). Cirrhosis itself, regardless of its cause, increases the incidence and severity of other infectious diseases (for example, *Vibrio vulnificus* infection), and effects on HIV infection would not be surprising. Direct viral interactions have also been proposed but are more difficult to defend given differences in the principle sites of replication. Thus, the mechanisms through which these viruses interact remain an important research topic.

Diagnosis

All HIV-infected persons should be screened for HCV infection at entry into health care (67). Screening for HCV should be done with enzyme immunoassays licensed for the detection of antibody to HCV in blood (79). Persons with positive HCV antibody results should have further testing using supplemental antibody testing (RIBA Ortho Diagnostics, Raritan, New Jersey) or preferably a test for HCV RNA, such as a reverse transcription polymerase chain reaction assay (80). The detection of HCV RNA in a person with positive results on tests for HCV antibody indicates current infection. However, since some persons with chronic HCV infection experience intermittent viremia, a single undetectable HCV RNA result must be interpreted cautiously (31). We suggest that clinicians should perform at least two HCV RNA tests 6 or more months apart before concluding that a person has cleared HCV infection.

Antibody titers to HCV may decrease below the level of detection in persons co-infected with HIV and HCV, especially those with advanced immunodeficiency (CD4 cell count $< 0.1 \times 10^9$ cells/L) (81–83). The HCV antibody level may also be undetectable for weeks in persons with acute HCV infection (31). Therefore, blood should be assessed for the presence of HCV RNA when HCV infection is suspected in persons with negative anti-HCV results (for example, elevated liver enzyme levels).

The clinical significance of quantitative HCV RNA testing (that is, virus load) in HIV-infected persons is not known and should not be interpreted on the basis of the well-described relationship of the magnitude of HIV viremia and the rate of HIV disease progression (84). Nonetheless, since some practitioners use HCV RNA levels to predict and monitor treatment responses, quantitative HCV RNA testing can be an expedient means of confirming a positive HCV antibody test result. In addition, HCV genotype assessment provides the best predictor of HCV response to interferon-based treatment (6, 7).

Management

Persons who are co-infected with HIV and HCV should be counseled to prevent liver damage and HCV transmission, evaluated for chronic liver disease, and considered for anti-HCV treatment. Because alcohol ingestion, particularly in quantities greater than 50 g (approximately 3 drinks) per day, accelerates the progression of liver disease, all co-infected persons should be advised to abstain from alcohol (80, 85).

Co-infected persons should be evaluated for the presence of chronic liver disease. Assessments of disease severity should include a history and physical examination for signs and symptoms of chronic liver disease; measurement of blood albumin levels, prothrombin time–international normalized ratio, direct bilirubin level, and platelet count (although specificity of these tests for liver disease in co-

infected persons may be poor); and, in many persons, evaluation of liver histologic characteristics by biopsy. Measurements of serum alanine aminotransferase and HCV RNA levels are important to establish that the infection is ongoing but provide limited information about severity of HCV disease (85).

Histologic evaluation by liver biopsy provides the best information about HCV-related disease activity and fibrosis stage and can be performed as safely in HIV-infected persons as in those without HIV infection (86, 87). Histologic characteristics of the liver can be used to guide HCV treatment decisions; to estimate prognosis; and to reveal other potential causes of liver disease, such as medication- or alcohol-related liver injury (87). For these reasons, we typically perform liver biopsy on persons co-infected with HIV and HCV, including those who have serum alanine aminotransferase levels within the normal reference range. In addition, among persons who defer HCV treatment, liver disease progression should be monitored by follow-up liver biopsy at an interval of 2 to 5 years. However, liver biopsy is a relatively expensive, invasive procedure that is generally not needed to confirm the diagnosis of chronic hepatitis C. In addition, the natural history of HCV may be sufficiently accelerated in HIV-infected persons to justify more widespread provision of HCV treatment. Thus, routinely offering HCV treatment in lieu of liver biopsy to persons co-infected with HIV and HCV is sure to become more common as treatment success improves.

Persons who are co-infected with HIV and HCV should be tested for previous or concurrent hepatitis B virus infection. Testing for hepatitis B virus core antibody can be done first, and persons with positive results can receive additional tests for hepatitis B surface antigen and DNA (88). Despite evidence of decreased response in immunosuppressed persons, those without previous hepatitis B virus infection should be vaccinated (89). Likewise, persons co-infected with HIV and HCV should be vaccinated against hepatitis A virus, unless tests for total antibodies (IgG and IgM) show evidence of previous infection (90). This recommendation is based on the apparent increased risk for fulminant hepatitis in persons with chronic HCV infection and the fact that many HIV-infected persons are at increased risk for hepatitis A virus infection (91).

Treatment

Because there are relatively few published data about treating persons with both HIV and HCV infection, current practice is dictated largely by principles established for the treatment of persons infected with HCV alone (**Tables 1** and **2**). Treatment is currently recommended for persons with chronic hepatitis C who are at the greatest risk for progression to cirrhosis, as characterized by detectable HCV RNA and histologic findings of portal or bridging fibrosis or at least moderate degrees of inflammation or necrosis (104, 105). Because HIV-infected persons more frequently progress to liver disease and, in the era of effective HIV therapy, have substantially prolonged survival, the impetus to treat HCV infection should be at least as strong as in adults without HIV infection. Accordingly, the 2002 National Institutes of Health Consensus Development Conference Panel on the management of hepatitis C recommended that HIV–HCV co-infected persons be considered for HCV treatment (105).

Two distinct benefits have been attributed to HCV treatment. First, treatment can lead to viral eradication (that is, cure or a sustained virologic response), defined as undetectable HCV RNA at the end of treatment and 6 months later. After 3 to 13 years of follow-up, several studies have shown that viral clearance (and improvements in liver histologic characteristics) will be durable in persons achieving a sustained viral response (74, 106). Similarly, Soriano and coworkers (94, 107) have reported that viral eradication can be achieved in persons with HIV–HCV co-infection.

A second potential benefit of HCV treatment is a reduction in the risk for liver failure and liver cancer (108, 109). Although relatively few data link HCV treatment to long-term clinical outcomes, it is important to note that this benefit may not be restricted to persons with sustained virologic response. These preliminary data form the basis for treating persons at the greatest risk for end-stage liver disease (that is, those with advanced hepatic fibrosis) to prevent hepatic decompensation and hepatocellular carcinoma, without regard to virologic response. If substantiated, this approach could be especially pertinent to co-infected persons, who generally have more liver disease, lower sustained virologic response, and limited access to orthotopic liver transplantation compared with persons infected with HCV alone.

Although no therapies have been approved by the U.S. Food and Drug Administration for the treatment of chronic hepatitis C in HIV-infected persons, the following therapies have been approved for use in persons with HCV infection: monotherapy with interferon-α2b, interferon-α2a, interferon alfacon-1, pegylated interferon-α2b, and pegylated interferon-α2a and combination therapy with interferon-α2b, pegylated interferon-α2b, or pegylated interferon-α2a plus ribavirin.

Interferon-α Monotherapy

To date, few well-designed studies have examined the use of interferon-α for treatment of chronic HCV infection in HIV-infected persons (92–96). In the largest published study to date, Soriano and colleagues treated 90 co-infected persons (CD4 cell count $> 0.2 \times 10^9$ cells/L) with interferon-α for 12 months. In an intention-to-treat analysis, 18 of 90 HIV-infected persons (20%) achieved a sustained virologic response, which was associated with a pretreatment CD4 cell count greater than 0.5×10^9 cells/L (94, 107).

Table 1. **Selected Clinical Trials of Interferon-α and Interferon-α plus Ribavirin for the Treatment of Chronic Hepatitis C Infection in HIV-Infected Persons***

Study (Reference)	Year of Publication	Patients, *n*	Treatment Regimen	Response, %	Comments
Boyer et al. (92)	1992	12	IFN-α2b, 1, 2, or 3 MIU/d, × 4–6 mo	33	Response reported as normalization of ALT levels
Marriott et al. (93)	1993	14	IFN-α2a, 9 MIU/d, then tapered × 12 mo	21	Response reported normalization of ALT levels
Soriano et al. (94)	1996	90	IFN-α2b, 5 MIU, three times/wk × 3 months, then 3 MIU × 9 mo	20	Sustained viral response (data shown as intention to treat)
Mauss et al. (95)	1998	17	IFN-α, 5 MIU three times/wk	29	Sustained viral response associated with higher CD4 cell count
Causse et al. (96)	2000	64	IFN-α2a, 3 MIU three times/wk × 6 mo	12.5	Retrospective cohort; response reported as normalization of ALT levels
Zylberberg et al. (97)	2000	21	IFN-α, 3 MIU three times/wk, + RBV, 1000–1200 mg/d	14.3	Retrospective cohort; all patients had previously failed to respond to IFN-α monotherapy
Nasti et al. (98)	2001	17	IFN-α2b, 3 MIU three times/wk, + RBV, 1000–1200 mg/d	19	69% end-of-treatment viral response (7 patients had viral relapse)
Landau et al. (99)	2001	51	IFN-α2b, 3 MIU three times/wk + RBV, 1000–1200 mg/d	21	29% discontinued therapy early because of adverse events
Sauleda et al. (100)	2001	20	IFN-α2b, 3 MIU three times/wk, + RBV, 800 mg/d	40	Sustained viral response in patients with HCV genotype 1 (26%)
Kostman et al. (101)	In progress	110	IFN-α2b, 3 MIU three times/wk, + RBV, 800 mg/d	23	Multicenter, randomized, double-blind, controlled trial; data shown are viral response after 12 weeks of treatment
			IFN-α2b, 3 MIU three times/wk, + placebo	5	
Chung et al. (102)	In progress	134	IFN-α2a, 6/3 MIU three times/wk, + RBV, 600–1000 mg/d	44	Multicenter, randomized, controlled trial; data shown are viral response after 24 weeks of treatment
			Pegylated IFN-α2a, 180 μg weekly, + RBV, 600–1000 mg/d	15	
Perronne et al. (103)	In progress	416	IFN-α2b, 3 MIU three times/wk, + RBV, 800 mg/d	27	Multicenter, randomized, controlled trial; data shown are viral response at end of treatment (week 48)
			Pegylated IFN-α2b, 1.5 μg/kg weekly, + RBV, 800 mg/d	44	

* ALT = alanine aminotransferase; HCV = hepatitis C virus; IFN = interferon; RBV = ribavirin.

More recently, the addition of polyethylene glycol to the interferon-α molecule allows once-weekly subcutaneous injection that provides continuous exposure to interferon-α. In persons without HIV infection, randomized clinical trials have demonstrated that both pegylated interferon-α2a (branched, 40-kilodalton polyethylene glycol) and pegylated interferon-α2b (linear, 12-kilodalton polyethylene glycol) are more effective than standard interferon-α monotherapy and have a similar adverse effect profile (110, 111).

Interferon-α and Ribavirin Combination Therapy

Among HCV-infected patients without HIV infection, randomized, placebo-controlled clinical trials have clearly demonstrated that combination therapy with interferon-α plus ribavirin is as safe as and more effective than interferon monotherapy (6, 7). Although studies are under way, few published data are available on the safety and efficacy of interferon-α and ribavirin therapy in HIV-infected persons (97–101). In the largest study presented to date, Kostman and coworkers (101) treated 110 persons infected with both HIV and HCV with interferon-α2b plus ribavirin or plus placebo. After 12 weeks of therapy, HCV RNA was undetectable in 23% of persons receiving combination therapy compared with 5% of those receiving monotherapy. Although data on sustained virologic response are not yet available, the safety profile was similar in both treatment groups (101). Similarly, several published retrospective series have suggested that interferon-α2b plus ribavirin is reasonably well tolerated and may eradicate HCV infection among some HIV-infected persons (97–100).

Among persons not infected with HIV, two large randomized, controlled clinical trials have demonstrated that combination therapy with pegylated interferon-α2a or interferon-α2b plus ribavirin is superior to standard interferon-α2b and ribavirin therapy and has a similar frequency of adverse events (8, 9). Because of its ease of administration (once-weekly injection) and its superior efficacy, it is anticipated that combination therapy with pegylated interferon-α plus ribavirin will largely replace the use of standard interferon-α plus ribavirin for the treatment of chronic HCV infection (105). Among HIV-infected persons, Chung and colleagues recently reported preliminary viral response and safety data from an ongoing AIDS Clinical Trials Group study that randomly assigned 134 adults to receive standard or pegylated interferon-α2a plus ribavirin (102). After 24 weeks of HCV therapy, HCV RNA was undetectable in 15% and 44% of persons receiving standard and pegylated interferon-α2a, respectively ($P = 0.001$). In addition, improvements in liver histologic activity were observed in 35% of persons who did not achieve a viral response. Severe (grade 4) adverse events were more common among recipients of pegylated interferon ($n = 17$) than standard interferon ($n = 4$), but no difference was observed in early treatment discontinuation.

Similarly, no adverse effect on control of HIV replication was observed. While these preliminary data suggest that pegylated interferon plus ribavirin is currently the optimal therapy for most persons co-infected with HIV and HCV, crucial data on the safety and effectiveness of this regimen in HIV-infected persons have not yet been published.

Adverse Effects

Interferon-α is associated with many adverse effects (112). Most persons experience influenza-like symptoms with the first several doses, and fatigue, malaise, anorexia, weight loss, skin rash, and reversible alopecia can occur months into therapy. Neuropsychiatric side effects (for example, irritability, insomnia, and mood and cognitive changes) are observed in as many as 60% of persons. Depression can be severe, and suicides have been reported (112). Interferon-associated thyroid dysfunction occurs in approximately 4% of persons. Interferon may cause dose-related leukopenia and thrombocytopenia. Lymphopenia may be associated with a decrease in absolute CD4 cell count; however, in such cases, the CD4 cell percentage is typically unchanged or increased and no additional risk for infection has been observed (113).

Ribavirin-related hemolysis and interferon-related suppression of hematopoiesis cause anemia in most persons n during the initial weeks of therapy (6, 114). Anemia may be a greater problem in persons co-infected with HIV because of the high prevalence of anemia and limited myeloid reserves that may exist as a result of comorbid diseases or concurrent drug toxicity (115). Ribavirin causes birth defects and must not be administered to pregnant women. All persons, both men and women, must use effective contraception during therapy and for 6 months after therapy with the drug is discontinued (116).

An additional concern is the potential for drug–drug interactions between ribavirin, a guanosine nucleoside analogue, and nucleoside analogue reverse transcriptase inhibitors. In vitro, ribavirin antagonizes the anti-HIV activity of pyrimidine 2′, 3′-dideoxynucleosides, including zidovudine, zalcitabine, and stavudine, through the inhibition of their intracellular phosphorylation (117–119). Conversely, ribavirin inhibits inosine-5′-monophosphate dehydrogenase, which facilitates the intracellular conversion of didanosine to its active metabolite. This leads to enhanced anti-HIV activity in vitro but may also increase in vivo toxicity, including mitochondrial effects (119, 120). Moreover, symptomatic, even fatal, hyperlactataemia has been reported in some co-infected persons receiving ribavirin and didanosine. Accordingly, ribavirin should not be administered to persons taking didanosine (121). Although in vivo studies to evaluate the potential drug–drug interactions among ribavirin and other nucleoside analogue reverse transcriptase inhibitors (for example, zidovudine and stavudine) are under way, several small case series pub-

Table 2. **Algorithm for HCV Treatment in HIV-Infected Patients***

- Before starting therapy
  - Review HIV disease status
    - CD4 cell count (current and nadir), HIV RNA level
    - Antiretroviral therapy
    - Active opportunistic diseases
  - Examine comorbid conditions
    - Psychiatric disease
    - Drug and alcohol use
    - Cardiopulmonary disease
    - Kidney disease
  - Measure complete blood count, serum creatinine concentration, and alanine and aspartate aminotransferase levels
  - Measure serum HCV RNA level by PCR to document that viremia is present (quantitative)
  - Test for HCV genotype to help determine the probability of virologic response
  - Consider a liver biopsy
    - Assess the grade and stage of liver disease
    - Exclude other diagnoses
    - If biopsy is contraindicated or not available or patient declines, therapy can be given without liver biopsy
  - Counsel the patient about the relative risks and benefits of interferon-α plus ribavirin treatment
    - Side effects should be thoroughly discussed
- During therapy
  - Pegylated interferon-α plus ribavirin combination therapy unless specific contraindications to the use of ribavirin (e.g., uncontrolled cardiopulmonary disease or renal insufficiency)
  - Reinforce the need to practice strict birth control during therapy and for 6 months thereafter
  - Measure complete blood count and alanine and aspartate aminotransferase levels at weeks 2 and 4 and at 4- to 8-week intervals thereafter
  - Adjust dose of interferon downward if significant neutropenia occurs (absolute neutrophil count $< 0.75 \times 10^9$ cells/L)
  - Stop interferon if severe neutropenia occurs (absolute neutrophil count $< 0.5 \times 10^9$ cells/L)
  - Consider the concurrent administration of filgrastim in the management of interferon-associated neutropenia
  - Adjust the dose of ribavirin downward (by 200 mg at a time) if significant anemia occurs (hemoglobin level $<$ 10 g/dL or hematocrit $<$ 0.3)
  - Stop ribavirin if severe anemia occurs (hemoglobin level $<$ 8.5 g/dL or hematocrit $<$ 0.26)
  - Consider the concurrent administration of epoetin-α (40 000 IU by subcutaneous injection weekly) in the management of treatment-related anemia
  - Measure HIV RNA, absolute CD4 cell count, and CD4 percentage at 12-week intervals
  - Evaluate for neuropsychiatric complications monthly (e.g., depression screen)
    - Consider use of antidepressants (e.g., SSRIs) and/or consultation with a mental health provider
  - Measure thyroid-stimulating hormone levels every 3 to 6 months during therapy
  - Measure HCV RNA by PCR at 24 weeks
  - If HCV RNA is still present, stop therapy or, if indicated, consider maintenance interferon-α monotherapy (maintenance interferon therapy has not been evaluated in co-infected patients).
  - If results of tests for HCV RNA are negative, continue therapy for at least an additional 24 weeks (some clinicians favor stopping therapy in persons with HCV genotype 2 or 3 infection; this approach has not been evaluated in co-infected patients)
  - At the end of therapy, test HCV RNA by PCR to assess whether there is an end-of-treatment response
- After therapy
  - Six months after stopping therapy, test for HCV RNA by PCR
    - If results of tests for HCV RNA are still negative, the chance for a long-term virologic response is very high; relapses have rarely been reported after this point

* Adapted from reference 104. HCV = hepatitis C virus; PCR = polymerase chain reaction; SSRI = selective serotonin reuptake inhibitor.

lished to date have failed to detect clinically significant antagonism (97, 122).

Advanced Liver Disease

Management of persons who have HIV and HCV co-infection and compensated cirrhosis is complex. In conjunction with hepatologists, cirrhotic persons should be evaluated for evidence of hepatic dysfunction, portal hypertension, encephalopathy, ascites, and hepatocellular carcinoma. Persons with hepatic decompensation are infrequently candidates for interferon-based therapy. Although several medical centers in the United States are investigating the feasibility of liver transplantation in co-infected persons with end-stage liver disease, it is important to treat co-infected persons before severe liver disease occurs (123).

PREVENTION

Persons with HIV infection who are not infected with HCV should be counseled to stop using injection drugs, and those who continue to inject drugs should be counseled to use safer injection practices (80). Use of barrier precautions and other methods to prevent sexual transmission of HIV should be more than adequate to prevent sexual HCV transmission. The U.S. Public Health Service and American Academy of Pediatrics call for HIV screening for all pregnant women but HCV screening only for those with known HCV risk factors (80, 124). Although antiretroviral therapy is safe and effective in reducing perinatal HIV transmission, interferon-α and ribavirin are contraindicated in pregnancy (80, 116, 125). Mothers who have HIV infection are generally advised not to breast feed or provide their milk to infants (124). However, discontinuation of breast feeding is not recommended for HCV-infected women (124). Elective cesarean section has been associated with reduced transmission of both HIV and HCV but is not currently recommended for women with either infection (in HIV, because maternal antiretroviral therapy markedly reduces transmission risk) (27, 126). Vaccines are not available to prevent HIV or HCV infection. Although antiretroviral therapy can prevent HIV infection after an exposure, postexposure antiviral prophylaxis is not recommended to prevent HCV transmission (10, 80, 124).

SUMMARY

Infection with HCV is common in HIV-infected persons and represents an increasingly important public health problem. The medical management of hepatitis C in HIV-infected persons is complicated by immune suppression, potential drug interactions and toxicities, other forms of liver disease, and the relative paucity of published data on the safety and outcomes of the best available medications. Thus, while existing efforts should be directed at preventing HCV and HIV infections and applying the principles learned in treating hepatitis C in persons without HIV, future efforts should be focused on conducting large, prospective studies that demonstrate the natural history and optimal management of co-infected persons, including the feasibility of liver transplantation. The pathogenesis of hepatitis C in HIV-infected persons should also be investigated, and findings should be translated into novel approaches to eliminate the emerging threat of liver disease.

From Johns Hopkins University School of Medicine, Baltimore, Maryland.

Grant Support: In part by the National Institute on Injection Drug Abuse (DA-011602, DA-16078, and DA-13806).

Requests for Single Reprints: David L. Thomas, MD, MPH, Division of Infectious Diseases, Johns Hopkins University School of Medicine, 424 Bond Street, Baltimore, MD 21231; e-mail, dthomas@jhmi.edu.

Current author addresses are available at www.annals.org.

References

1. **Sherman KE, Rouster SD, Chung RT, Rajicic N.** Hepatitis C virus prevalence among patients coinfected with human immunodeficiency virus: a cross-sectional analysis of the U.S. Adult AIDS Clinical Trials Group. Clin Infect Dis. 2002;34:831-7. [PMID: 11833007]

2. **Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, et al.** The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med. 1999;341:556-62. [PMID: 10451460]

3. **Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al.** Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med. 1998;338:853-60. [PMID: 9516219]

4. **Bica I, McGovern B, Dhar R, Stone D, McGowan K, Scheib R, et al.** Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. Clin Infect Dis. 2001;32:492-7. [PMID: 11170959]

5. **Monga HK, Rodriguez-Barradas MC, Breaux K, Khattak K, Troisi CL, Velez M, et al.** Hepatitis C virus infection-related morbidity and mortality among patients with human immunodeficiency virus infection. Clin Infect Dis. 2001;33:240-7. [PMID: 11418885]

6. **McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, et al.** Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med. 1998;339:1485-92. [PMID: 9819446]

7. **Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, et al.** Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet. 1998;352:1426-32. [PMID: 9807989]

8. **Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al.** Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001;358:958-65. [PMID: 11583749]

9. **Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, et al.** Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002;347:975-82. [PMID: 12324553]

10. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. MMWR Morb Mortal Wkly Rep. 2001;50:1-52. [PMID: 11442229]

11. **Garfein RS, Doherty MC, Monterroso ER, Thomas DL, Nelson KE, Vlahov D.** Prevalence and incidence of hepatitis C virus infection among young adult injection drug users. J Acquir Immune Defic Syndr Hum Retrovirol. 1998;18 Suppl 1:S11-9. [PMID: 9663618]

12. **Villano SA, Vlahov D, Nelson KE, Lyles CM, Cohn S, Thomas DL.** Incidence and risk factors for hepatitis C among injection drug users in Baltimore, Maryland. J Clin Microbiol. 1997;35:3274-7. [PMID: 9399533]

13. **Bove JR.** Transfusion-associated hepatitis and AIDS. What is the risk? N Engl J Med. 1987;317:242-5. [PMID: 3110619]

14. **Darby SC, Ewart DW, Giangrande PL, Spooner RJ, Rizza CR, Dusheiko GM, et al.** Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. UK Haemophilia Centre Directors' Organisation. Lancet. 1997;350:1425-31. [PMID: 9371165]

15. **Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ.** The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. N Engl J Med. 1996;334:1685-90. [PMID: 8637512]

16. **Kingsley LA, Detels R, Kaslow R, Polk BF, Rinaldo CR Jr, Chmiel J, et al.** Risk factors for seroconversion to human immunodeficiency virus among male homosexuals. Results from the Multicenter AIDS Cohort Study. Lancet. 1987; 1:345-9. [PMID: 2880160]

17. **Thomas DL, Zenilman JM, Alter HJ, Shih JW, Galai N, Carella AV, et al.** Sexual transmission of hepatitis C virus among patients attending sexually transmitted diseases clinics in Baltimore—an analysis of 309 sex partnerships. J Infect Dis. 1995;171:768-75. [PMID: 7535827]

18. **Eyster ME, Alter HJ, Aledort LM, Quan S, Hatzakis A, Goedert JJ.** Heterosexual co-transmission of hepatitis C virus (HCV) and human immunodeficiency virus (HIV). Ann Intern Med. 1991;115:764-8. [PMID: 1656825]

19. **Gray RH, Wawer MJ, Brookmeyer R, Sewankambo NK, Serwadda D, Wabwire-Mangen F, et al.** Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. Lancet. 2001;357:1149-53. [PMID: 11323041]

20. **Conry-Cantilena C, VanRaden M, Gibble J, Melpolder J, Shakil AO, Viladomiu L, et al.** Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. N Engl J Med. 1996;334:1691-6. [PMID: 8637513]

21. **Everhart JE, Di Bisceglie AM, Murray LM, Alter HJ, Melpolder JJ, Kuo G, et al.** Risk for non-A, non-B (type C) hepatitis through sexual or household contact with chronic carriers. Ann Intern Med. 1990;112:544-5. [PMID: 1690526]

22. **Buchbinder SP, Katz MH, Hessol NA, Liu J, O'Malley PM, Alter MJ.** Hepatitis C virus infection in sexually active homosexual men. J Infect. 1994;29: 263-9. [PMID: 7884219]

23. **Donahue JG, Nelson KE, Muñoz A, Vlahov D, Rennie LL, Taylor EL, et al.** Antibody to hepatitis C virus among cardiac surgery patients, homosexual men, and intravenous drug users in Baltimore, Maryland. Am J Epidemiol. 1991; 134:1206-11. [PMID: 1720924]

24. **Landesman SH, Kalish LA, Burns DN, Minkoff H, Fox HE, Zorrilla C, et al.** Obstetrical factors and the transmission of human immunodeficiency virus type 1 from mother to child. The Women and Infants Transmission Study. N Engl J Med. 1996;334:1617-23. [PMID: 8628356]

25. **Zanetti AR, Tanzi E, Paccagnini S, Principi N, Pizzocolo G, Caccamo ML, et al.** Mother-to-infant transmission of hepatitis C virus. Lombardy Study Group on Vertical HCV Transmission. Lancet. 1995;345:289-91. [PMID: 7530793]

26. **Thomas DL, Villano SA, Riester KA, Hershow R, Mofenson LM, Landesman SH, et al.** Perinatal transmission of hepatitis C virus from human immunodeficiency virus type 1-infected mothers. Women and Infants Transmission Study. J Infect Dis. 1998;177:1480-8. [PMID: 9607823]

27. **Gibb DM, Goodall RL, Dunn DT, Healy M, Neave P, Cafferkey M, et al.** Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. Lancet. 2000;356:904-7. [PMID: 11036896]

28. **Thomas DL, Shih JW, Alter HJ, Vlahov D, Cohn S, Hoover DR, et al.** Effect of human immunodeficiency virus on hepatitis C virus infection among injecting drug users. J Infect Dis. 1996;174:690-5. [PMID: 8843204]

29. **Eyster ME, Fried MW, Di Bisceglie AM, Goedert JJ.** Increasing hepatitis C virus RNA levels in hemophiliacs: relationship to human immunodeficiency virus infection and liver disease. Multicenter Hemophilia Cohort Study. Blood. 1994; 84:1020-3. [PMID: 8049420]

30. **Hershow RC, Riester KA, Lew J, Quinn TC, Mofenson LM, Davenny K, et al.** Increased vertical transmission of human immunodeficiency virus from hepatitis C virus-coinfected mothers. Women and Infants Transmission Study. J Infect Dis. 1997;176:414-20. [PMID: 9237706]

31. **Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL.** Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. Hepatology. 1999;29:908-14. [PMID: 10051497]

32. **Tong MJ, el-Farra NS, Reikes AR, Co RL.** Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med. 1995;332:1463-6. [PMID: 7739682]

33. **Kiyosawa K, Sodeyama T, Tanaka E, Gibo Y, Yoshizawa K, Nakano Y, et al.** Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma: analysis by detection of antibody to hepatitis C virus. Hepatology. 1990;12:671-5. [PMID: 2170265]

34. **Alter MJ, Margolis HS, Krawczynski K, Judson FN, Mares A, Alexander WJ, et al.** The natural history of community-acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team. N Engl J Med. 1992;327:1899-905. [PMID: 1280771]

35. **Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, et al.** The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA. 2000;284:450-6. [PMID: 10904508]

36. **Mehta SH, Cox A, Hoover DR, Wang XH, Mao Q, Ray S, et al.** Protection against persistence of hepatitis C. Lancet. 2002;359:1478-83. [PMID: 11988247]

37. **Seeff LB, Buskell-Bales Z, Wright EC, Durako SJ, Alter HJ, Iber FL, et al.** Long-term mortality after transfusion-associated non-A, non-B hepatitis. The National Heart, Lung, and Blood Institute Study Group. N Engl J Med. 1992; 327:1906-11. [PMID: 1454085]

38. **Kenny-Walsh E.** Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. N Engl J Med. 1999;340:1228-33. [PMID: 10210705]

39. **Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al.** Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology. 1997;112:463-72. [PMID: 9024300]

40. **Thomas DL, Astemborski J, Vlahov D, Strathdee SA, Ray SC, Nelson KE, et al.** Determinants of the quantity of hepatitis C virus RNA. J Infect Dis. 2000;181:844-51. [PMID: 10720503]

41. **Eyster ME, Diamondstone LS, Lien JM, Ehmann WC, Quan S, Goedert JJ.** Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with human immunodeficiency virus. The Multicenter Hemophilia Cohort Study. J Acquir Immune Defic Syndr. 1993;6:602-10. [PMID: 8098752]

42. **Lesens O, Deschênes M, Steben M, Bélanger G, Tsoukas CM.** Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus-positive hemophiliacs and should be treated as an opportunistic infection. J Infect Dis. 1999;179:1254-8. [PMID: 10191232]

43. **Pol S, Lamorthe B, Thi NT, Thiers V, Carnot F, Zylberberg H, et al.** Retrospective analysis of the impact of HIV infection and alcohol use on chronic hepatitis C in a large cohort of drug users. J Hepatol. 1998;28:945-50. [PMID: 9672168]

44. **Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al.** Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis. 2001;33:562-9. [PMID: 11462196]

45. **Ragni MV, Belle SH.** Impact of human immunodeficiency virus infection on progression to end-stage liver disease in individuals with hemophilia and hepatitis C virus infection. J Infect Dis. 2001;183:1112-5. [PMID: 11237838]

46. **Soto B, Sánchez-Quijano A, Rodrigo L, del Olmo JA, García-Bengoechea M, Hernández-Quero J, et al.** Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol. 1997;26:1-5. [PMID: 9147999]

47. **García-Samaniego J, Rodríguez M, Berenguer J, Rodríguez-Rosado R, Carbó J, Asensi V, et al.** Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. Am J Gastroenterol. 2001;96:179-83. [PMID: 11197250]

48. **Kim WR, Gross JB Jr, Poterucha JJ, Locke GR 3rd, Dickson ER.** Outcome of hospital care of liver disease associated with hepatitis C in the United States. Hepatology. 2001;33:201-6. [PMID: 11124837]

49. **Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al.** Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. Hepatology. 1999;30:1054-8. [PMID: 10498659]

50. **Di Martino V, Rufat P, Boyer N, Renard P, Degos F, Martinot-Peignoux**

M, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. Hepatology. 2001;34:1193-9. [PMID: 11732009]

51. **Serfaty L, Costagliola D, Wendum D, Picard O, Meyohas MC, Girard PM, et al.** Impact of early-untreated HIV infection on chronic hepatitis C in intravenous drug users: a case-control study. AIDS. 2001;15:2011-6. [PMID: 11600830]

52. **Martín-Carbonero L, Soriano V, Valencia E, García-Samaniego J, López M, González-Lahoz J.** Increasing Impact of Chronic Viral Hepatitis on Hospital Admissions and Mortality among HIV-Infected Patients. AIDS Res Hum Retroviruses. 2001;17:1467-71. [PMID: 11709090]

53. **Cacoub P, Geffray L, Rosenthal E, Perronne C, Veyssier P, Raguin G, et al.** Mortality among human immunodeficiency virus-infected patients with cirrhosis or hepatocellular carcinoma due to hepatitis C virus in French Departments of Internal Medicine/Infectious Diseases, in 1995 and 1997. Clin Infect Dis. 2001; 32:1207-14. [PMID: 11283811]

54. **Dorrucci M, Pezzotti P, Phillips AN, Lepri AC, Rezza G.** Coinfection of hepatitis C virus with human immunodeficiency virus and progression to AIDS. Italian Seroconversion Study. J Infect Dis. 1995;172:1503-8. [PMID: 7594709]

55. **Piroth L, Duong M, Quantin C, Abrahamowicz M, Michardiere R, Aho LS, et al.** Does hepatitis C virus co-infection accelerate clinical and immunological evolution of HIV-infected patients? AIDS. 1998;12:381-8. [PMID: 9520167]

56. **Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H, et al.** Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. Lancet. 2000;356:1800-5. [PMID: 11117912]

57. **Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL.** Hepatitis C and progression of HIV disease. JAMA. 2002;288:199-206. [PMID: 12095384]

58. **Staples CT Jr, Rimland D, Dudas D.** Hepatitis C in the HIV (human immunodeficiency virus) Atlanta V.A. (Veterans Affairs Medical Center) Cohort Study (HAVACS): the effect of coinfection on survival. Clin Infect Dis. 1999; 29:150-4. [PMID: 10433578]

59. **Chung RT, Evans SR, Yang Y, Theodore D, Valdez H, Clark R, et al.** Immune recovery is associated with persistent rise in hepatitis C virus RNA, infrequent liver test flares, and is not impaired by hepatitis C virus in co-infected subjects. AIDS. 2002;16:1915-23. [PMID: 12351951]

60. **Sulkowski MS, Mast EE, Seeff LB, Thomas DL.** Hepatitis C virus infection as an opportunistic disease in persons infected with human immunodeficiency virus. Clin Infect Dis. 2000;30 Suppl 1:S77-84. [PMID: 10770916]

61. **Martínez E, Blanco JL, Arnaiz JA, Pérez-Cuevas JB, Mocroft A, Cruceta A, et al.** Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. AIDS. 2001;15:1261-8. [PMID: 11426070]

62. **Sulkowski MS, Thomas DL, Chaisson RE, Moore RD.** Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. JAMA. 2000;283: 74-80. [PMID: 10632283]

63. **den Brinker M, Wit FW, Wertheim-van Dillen PM, Jurriaans S, Weel J, van Leeuwen R, et al.** Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. AIDS. 2000;14:2895-902. [PMID: 11153671]

64. **Cattelan AM, Erne E, Salatino A, Trevenzoli M, Carretta G, Meneghetti F, et al.** Severe hepatic failure related to nevirapine treatment. Clin Infect Dis. 1999;29:455-6. [PMID: 10476768]

65. **Núñez M, Lana R, Mendoza JL, Martín-Carbonero L, Soriano V.** Risk factors for severe hepatic injury after introduction of highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2001;27:426-31. [PMID: 11511818]

66. **Sha BE, Proia LA, Kessler HA.** Adverse effects associated with use of nevirapine in HIV postexposure prophylaxis for 2 health care workers. [Letter] JAMA. 2000;284:2723. [PMID: 11105176]

67. **Kaplan JE, Masur H, Holmes KK.** Guidelines for preventing opportunistic infections among HIV-infected persons—2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. MMWR Recomm Rep. 2002;51:1-52. [PMID: 12081007]

68. **Veronese L, Rautaureau J, Sadler BM, Gillotin C, Petite JP, Pillegand B, et al.** Single-dose pharmacokinetics of amprenavir, a human immunodeficiency virus type 1 protease inhibitor, in subjects with normal or impaired hepatic function. Antimicrob Agents Chemother. 2000;44:821-6. [PMID: 10722476]

69. **John M, Flexman J, French MA.** Hepatitis C virus-associated hepatitis following treatment of HIV-infected patients with HIV protease inhibitors: an immune restoration disease? AIDS. 1998;12:2289-93. [PMID: 9863871]

70. **Barbaro G, Di Lorenzo G, Asti A, Ribersani M, Belloni G, Grisorio B, et al.** Hepatocellular mitochondrial alterations in patients with chronic hepatitis C: ultrastructural and biochemical findings. Am J Gastroenterol. 1999;94:2198-205. [PMID: 10445550]

71. **Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD.** HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. Science. 1996;271:1582-6. [PMID: 8599114]

72. **Neumann AU, Lam NP, Dahari H, Gretch DR, Wiley TE, Layden TJ, et al.** Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. Science. 1998;282:103-7. [PMID: 9756471]

73. **Bukrinsky MI, Stanwick TL, Dempsey MP, Stevenson M.** Quiescent T lymphocytes as an inducible virus reservoir in HIV-1 infection. Science. 1991; 254:423-7. [PMID: 1925601]

74. **Marcellin P, Boyer N, Gervais A, Martinot M, Pouteau M, Castelnau C, et al.** Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. Ann Intern Med. 1997;127:875-81. [PMID: 9382365]

75. **Laskus T, Radkowski M, Piasek A, Nowicki M, Horban A, Cianciara J, et al.** Hepatitis C virus in lymphoid cells of patients coinfected with human immunodeficiency virus type 1: evidence of active replication in monocytes/macrophages and lymphocytes. J Infect Dis. 2000;181:442-8. [PMID: 10669324]

76. **Lerat H, Rumin S, Habersetzer F, Berby F, Trabaud MA, Trépo C, et al.** In vivo tropism of hepatitis C virus genomic sequences in hematopoietic cells: influence of viral load, viral genotype, and cell phenotype. Blood. 1998;91:3841-9. [PMID: 9573022]

77. **Shimizu YK, Feinstone SM, Kohara M, Purcell RH, Yoshikura H.** Hepatitis C virus: detection of intracellular virus particles by electron microscopy. Hepatology. 1996;23:205-9. [PMID: 8591842]

78. **Goletti D, Weissman D, Jackson RW, Graham NM, Vlahov D, Klein RS, et al.** Effect of *Mycobacterium tuberculosis* on HIV replication. Role of immune activation. J Immunol. 1996;157:1271-8. [PMID: 8757635]

79. **Thio CL, Nolt KR, Astemborski J, Vlahov D, Nelson KE, Thomas DL.** Screening for hepatitis C virus in human immunodeficiency virus-infected individuals. J Clin Microbiol. 2000;38:575-7. [PMID: 10655348]

80. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep. 1998;47:1-39. [PMID: 9790221]

81. **Ragni MV, Ndimbie OK, Rice EO, Bontempo FA, Nedjar S.** The presence of hepatitis C virus (HCV) antibody in human immunodeficiency virus-positive hemophilic men undergoing HCV "seroreversion", Blood. 1993;82:1010-5. [PMID: 7687887]

82. **Marcellin P, Martinot-Peignoux M, Elias A, Branger M, Courtois F, Level R, et al.** Hepatitis C virus (HCV) viremia in human immunodeficiency virus-seronegative and -seropositive patients with indeterminate HCV recombinant immunoblot assay. J Infect Dis. 1994;170:433-5. [PMID: 7518489]

83. **Chamot E, Hirschel B, Wintsch J, Robert CF, Gabriel V, Déglon JJ, et al.** Loss of antibodies against hepatitis C virus in HIV-seropositive intravenous drug users. AIDS. 1990;4:1275-7. [PMID: 1965126]

84. **Mellors JW, Rinaldo CR Jr, Gupta P, White RM, Todd JA, Kingsley LA.** Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. Science. 1996;272:1167-70. [PMID: 8638160]

85. **Poynard T, Bedossa P, Opolon P.** Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet. 1997;349:825-32. [PMID: 9121257]

86. **Poles MA, Dieterich DT, Schwarz ED, Weinshel EH, Lew EA, Lew R, et al.** Liver biopsy findings in 501 patients infected with human immunodeficiency virus (HIV). J Acquir Immune Defic Syndr Hum Retrovirol. 1996;11:170-7. [PMID: 8556399]

87. **Saadeh S, Cammell G, Carey WD, Younossi Z, Barnes D, Easley K.** The role of liver biopsy in chronic hepatitis C. Hepatology. 2001;33:196-200. [PMID: 11124836]

88. Hepatitis B virus: a comprehensive strategy for eliminating transmission in

the United States through universal childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR Morb Mortal Wkly Rep. 1991;40:1-25. [PMID: 1835756]

89. **Lemon SM, Thomas DL.** Vaccines to prevent viral hepatitis. N Engl J Med. 1997;336:196-204. [PMID: 8988900]

90. Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 1999;48:1-37. [PMID: 10543657]

91. **Vento S, Garofano T, Renzini C, Cainelli F, Casali F, Ghironzi G, et al.** Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. N Engl J Med. 1998;338:286-90. [PMID: 9445408]

92. **Boyer N, Marcellin P, Degott C, Degos F, Saimot AG, Erlinger S, et al.** Recombinant interferon-alpha for chronic hepatitis C in patients positive for antibody to human immunodeficiency virus. Comité des Anti-Viraux. J Infect Dis. 1992;165:723-6. [PMID: 1348079]

93. **Marriott E, Navas S, del Romero J, García S, Castillo I, Quiroga JA, et al.** Treatment with recombinant alpha-interferon of chronic hepatitis C in anti-HIV-positive patients. J Med Virol. 1993;40:107-11. [PMID: 8395552]

94. **Soriano V, García-Samaniego J, Bravo R, González J, Castro A, Castilla J, et al.** Interferon alpha for the treatment of chronic hepatitis C in patients infected with human immunodeficiency virus. Hepatitis-HIV Spanish Study Group. Clin Infect Dis. 1996;23:585-91. [PMID: 8879784]

95. **Mauss S, Klinker H, Ulmer A, Willers R, Weissbrich B, Albrecht H, et al.** Response to treatment of chronic hepatitis C with interferon alpha in patients infected with HIV-1 is associated with higher CD4 + cell count. Infection. 1998;26:16-9. [PMID: 9505174]

96. **Causse X, Payen JL, Izopet J, Babany G, Girardin MF.** Does HIV-infection influence the response of chronic hepatitis C to interferon treatment? A French multicenter prospective study. French Multicenter Study Group. J Hepatol. 2000;32:1003-10. [PMID: 10898321]

97. **Zylberberg H, Benhamou Y, Lagneaux JL, Landau A, Chaix ML, Fontaine H, et al.** Safety and efficacy of interferon-ribavirin combination therapy in HCV-HIV coinfected subjects: an early report. Gut. 2000;47:694-7. [PMID: 11034587]

98. **Nasti G, Di Gennaro G, Tavio M, Cadorin L, Tedeschi RM, Talamini R, et al.** Chronic hepatitis C in HIV infection: feasibility and sustained efficacy of therapy with interferon alfa-2b and tribavirin. AIDS. 2001;15:1783-7. [PMID: 11579239]

99. **Landau A, Batisse D, Piketty C, Duong Van Huyen JP, Bloch F, Belec L, et al.** Long-term efficacy of combination therapy with interferon-alpha2b and ribavirin for severe chronic hepatitis C in HIV-infected patients. AIDS. 2001;15: 2149-55. [PMID: 11684934]

100. **Sauleda S, Juárez A, Esteban JI, Altisent C, Ruiz I, Puig L, et al.** Interferon and ribavirin combination therapy for chronic hepatitis C in human immunodeficiency virus-infected patients with congenital coagulation disorders. Hepatology. 2001;34:1035-40. [PMID: 11679976]

101. **Kostman JR, Smith J, Giffen C, Frost KR.** Interferon alfa-2b/ribavirin combination therapy in HCV/HIV co-infected persons: results of a multi-center, randomized, double-blind, placebo-controlled trial [Abstract]. The amFAR DCR1 010 Study Group. Hepatology. 2001;34:330A. Abstract no. 634.

102. **Chung RT, Anderson J, Alston B, Vallee M, Robbins G, Nevin T, et al.** A randomized, controlled trial of pegylated interferon alpha-2s with ribavirin versus interferon alpha-2a with ribavirin for the treatment of chronic HCV in HIV co-infection: ACTG 5071 [Abstract]. Seattle, Washington: Ninth Conference on Retrovirology and Opportunistic Infections 2002. Abstract LB15.

103. **Perrone C, Carrat F, Banisadr F, Morand P, Lunel F, Rosenthal E, Pol S.** ANRS HC02-RIBAVIC: A randomized controlled trial of pegylated inteferon alfa-2b plus ribavirin versus interferon alfa-2b plus ribavirin as primary treatment of chronic hepatitis C in HIV coinfected patients [Abstract]. Hepatology. 2002; 36:283A.

104. Chronic hepatitis C: current disease management. National Institute of Diabetes and Digestive and Kidney Diseases. Accessed at www.niddk.nih.gov on 6 December 2002.

105. National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C: 2002—June 10-12, 2002. Hepatology. 2002; 36(5 Suppl 1):S3-20. [PMID: 12407572].

106. **Shiratori Y, Imazeki F, Moriyama M, Yano M, Arakawa Y, Yokosuka O, et al.** Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. Ann Intern Med. 2000;132:517-24. [PMID: 10744587]

107. **Soriano V, Bravo R, García-Samaniego J, Castilla J, González J, Castro A, et al.** Relapses of chronic hepatitis C in HIV-infected patients who responded to interferon therapy. Hepatitis/HIV Spanish Study Group. [Letter] AIDS. 1997; 11:400-1. [PMID: 9147443]

108. Effect of interferon-alpha on progression of cirrhosis to hepatocellular carcinoma: a retrospective cohort study. International Interferon-alpha Hepatocellular Carcinoma Study Group. Lancet. 1998;351:1535-9. [PMID: 10326535]

109. **Nishiguchi S, Kuroki T, Nakatani S, Morimoto H, Takeda T, Nakajima S, et al.** Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. Lancet. 1995;346: 1051-5. [PMID: 7564784]

110. **Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, et al.** Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med. 2000; 343:1666-72. [PMID: 11106715]

111. **Lindsay KL, Trepo C, Heintges T, Shiffman ML, Gordon SC, Hoefs JC, et al.** A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. Hepatology. 2001; 34:395-403. [PMID: 11481625]

112. **Fattovich G, Giustina G, Favarato S, Ruol A.** A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alfa interferon. J Hepatol. 1996;24:38-47. [PMID: 8834023]

113. **Lane HC, Davey V, Kovacs JA, Feinberg J, Metcalf JA, Herpin B, et al.** Interferon-alpha in patients with asymptomatic human immunodeficiency virus (HIV) infection. A randomized, placebo-controlled trial. Ann Intern Med. 1990; 112:805-11. [PMID: 1971503]

114. **De Franceschi L, Fattovich G, Turrini F, Ayi K, Brugnara C, Manzato F, et al.** Hemolytic anemia induced by ribavirin therapy in patients with chronic hepatitis C virus infection: role of membrane oxidative damage. Hepatology. 2000;31:997-1004. [PMID: 10733558]

115. **Moore RD.** Human immunodeficiency virus infection, anemia, and survival. Clin Infect Dis. 1999;29:44-9. [PMID: 10433563]

116. Rebetron [package insert]. Kenilworth, NJ: Schering-Plough; 2000.

117. **Vogt MW, Hartshorn KL, Furman PA, Chou TC, Fyfe JA, Coleman LA, et al.** Ribavirin antagonizes the effect of azidothymidine on HIV replication. Science. 1987;235:1376-9. [PMID: 2435003]

118. **Hoggard PG, Kewn S, Barry MG, Khoo SH, Back DJ.** Effects of drugs on 2′,3′-dideoxy-2′,3′-didehydrothymidine phosphorylation in vitro. Antimicrob Agents Chemother. 1997;41:1231-6. [PMID: 9174176]

119. **Baba M, Pauwels R, Balzarini J, Herdewijn P, De Clercq E, Desmyter J.** Ribavirin antagonizes inhibitory effects of pyrimidine 2′,3′-dideoxynucleosides but enhances inhibitory effects of purine 2′,3′-dideoxynucleosides on replication of human immunodeficiency virus in vitro. Antimicrob Agents Chemother. 1987;31:1613-7. [PMID: 3435108]

120. **Lafeuillade A, Hittinger G, Chadapaud S.** Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection [Letter]. Lancet. 2001;357:280-1. [PMID: 11214134]

121. Videx [package insert]. Princeton, NJ: Bristol-Myers-Squibb; September 2002.

122. **Landau A, Batisse D, Piketty C, Jian R, Kazatchkine MD.** Lack of interference between ribavirin and nucleosidic analogues in HIV/HCV co-infected individuals undergoing concomitant antiretroviral and anti-HCV combination therapy. AIDS. 2000;14:1857-8. [PMID: 10985327]

123. **Gow PJ, Pillay D, Mutimer D.** Solid organ transplantation in patients with HIV infection. Transplantation. 2001;72:177-81. [PMID: 11477334]

124. American Academy of Pediatrics. Committee on Infectious Diseases. Red Book. 25th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2000.

125. **Lallemant M, Jourdain G, Le Coeur S, Kim S, Koetsawang S, Comeau AM, et al.** A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. N Engl J Med. 2000;343:982-91. [PMID: 11018164]

126. **Peckham C, Gibb D.** Mother-to-child transmission of the human immunodeficiency virus. N Engl J Med. 1995;333:298-302. [PMID: 7596375]

Current Author Addresses: Dr. Sulkowski: Division of Infections Diseases, Johns Hopkins University School of Medicine, 1830 East Monument Street, Room 448, Baltimore, MD 21287-0003.
Dr. Thomas: Division of Infectious Diseases, Johns Hopkins University School of Medicine, 424 Bond Street, Baltimore, MD 21231.