Hepatitis C in the HIV-Infected Person

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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.

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-
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**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.**

![Prevalence of anti–hepatitis C virus (HCV) in HIV-infected persons](image)

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...
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 develop HAART-associated liver failure (67).
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 (83).

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 × 10⁹ 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 × 10⁹ cells/L (94, 107).
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 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.

### 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

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

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

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

<table>
<thead>
<tr>
<th>Before starting therapy</th>
<th>After therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review HIV disease status</td>
<td>Six months after stopping therapy</td>
</tr>
<tr>
<td>CD4 cell count (current and nadir), HIV RNA level</td>
<td>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</td>
</tr>
<tr>
<td>Antiretroviral therapy</td>
<td>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</td>
</tr>
<tr>
<td>Active opportunistic diseases</td>
<td>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</td>
</tr>
<tr>
<td>Examine comorbid conditions</td>
<td>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</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>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</td>
</tr>
<tr>
<td>Drug and alcohol use</td>
<td>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</td>
</tr>
<tr>
<td>Cardiopulmonary disease</td>
<td>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</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>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</td>
</tr>
<tr>
<td>Measure complete blood count, serum creatinine concentration, and alanine and aspartate aminotransferase levels</td>
<td>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</td>
</tr>
<tr>
<td>Measure serum HCV RNA level by PCR to document that viremia is present (quantitative)</td>
<td>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</td>
</tr>
<tr>
<td>Test for HCV genotype to help determine the probability of virologic response</td>
<td>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</td>
</tr>
<tr>
<td>Consider a liver biopsy</td>
<td>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</td>
</tr>
<tr>
<td>Assess the grade and stage of liver disease</td>
<td>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</td>
</tr>
<tr>
<td>Exclude other diagnoses</td>
<td>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</td>
</tr>
<tr>
<td>If biopsy is contraindicated or not available or patient declines, therapy can be given without liver biopsy</td>
<td>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</td>
</tr>
<tr>
<td>Counsel the patient about the relative risks and benefits of interferon-α plus ribavirin treatment</td>
<td>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</td>
</tr>
<tr>
<td>Side effects should be thoroughly discussed</td>
<td>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</td>
</tr>
</tbody>
</table>

*Adapted from reference 184. HCV = hepatitis C virus; PCR = polymerase chain reaction; SSRI = selective serotonin reuptake inhibitor.
Hepatitis C in the HIV-Infected Person

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Learned in treating hepatitis C in persons without HIV, and applying the principles of treatment 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). Effective 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.

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References


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