Hepatitis C virus and human immunodeficiency virus co-infection in women

ROBERT ORENSTEIN, DO
NICKOLAOS TSOGAS, MD

Women account for almost one of four newly diagnosed cases of the human immunodeficiency virus (HIV) infection in the United States. It is believed that up to 20% of them are co-infected with hepatitis C virus (HCV). AIDS is now the third leading cause of death in women aged 25 to 44 years in the United States. The ability to better control the HIV infection and improve survival among the co-infected population will make managing chronic liver disease due to hepatitis C the next clinical challenge for these women. This article reviews the available data and summarizes the primary care approach to the female patient with HCV-HIV co-infection.

(Key words: hepatitis C virus, human immunodeficiency virus, HIV, co-infection, women)

The converging epidemics of the human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections have significant impact on women. Both of these are chronic viral infections, which are clinically silent until late in their course. However, for each, earlier recognition may be associated with improved access to care, decreased transmission, and perhaps better treatment responses. As women become increasingly affected by both of these chronic diseases, physicians need to be aware that counseling, screening, and referral are important parts of the management of co-infection. Both illnesses carry a significant social, public health, and financial impact and disproportionately affect women in our inner cities.

The significant advances in HIV management and survival have led to the recognition of chronic hepatitis as the preeminent comorbid illness that now accounts for the majority of non-AIDS-related deaths in this population. About 300,000 persons in the United States are co-infected.1 A recent study2 reported that end-stage liver disease (ESLD) had become the leading cause of death in HIV-positive patients. As the proportion of women affected by HIV continues to rise, many of these women will struggle with HCV co-infection. Currently, there are little gender-specific data on the impact of co-infection and its management in women. This review focuses on data extrapolated from infection with each virus individually to provide background for the diagnosis and management of this increasingly common condition.

Epidemiology

Women now represent approximately 25% of newly reported AIDS cases in the United States compared with 8% in the mid-1980s.3 The care of these women is complicated by poverty and competing issues such as substance abuse, mental health disorders, children, homelessness, and immigration. The majority of HIV-infected women in the United States are unemployed; 83% live in households with incomes of less than $10,000; and only 14% are married. African American women account for 57% of cases; Latinas, 20%; and white women, 23%.4 Many suffer from low self-esteem and fear governmental intervention in their lives. Acquisition of HIV from injection drug use (IDU) among women has stabilized, and most new HIV cases are acquired heterosexually. Of the almost 40% of women who acquired HIV via the heterosexual route, almost one third report having sex with an injection drug user. In our large urban clinic of more than 1400 patients with HIV, 20% of the 364 co-infected patients are women (Orenstein R, unpublished data).

Since 1999, hepatitis C has been classified as an opportunistic infection in persons with HIV.5 Furthermore, the identification and management of hepatitis C infection has become an important consideration in management of people with HIV, especially since the advent of modes of highly active antiretroviral therapy (HAART). These potent antiviral modalities have extended the life of people living with HIV and facilitated the development of other chronic illnesses. Women, however, appear to have benefited less from the revolution in anti-HIV therapy and continue to have problems with access to care. They also have more side effects from antiretroviral therapy (especially gastrointestinal symptoms from protease inhibitors).6

Hepatitis C virus infection is the most important cause of chronic liver disease in the United States. It is estimated that more than 30,000 new infections occur annually and that almost 4 million persons are infected.7 Like HIV, HCV infection is concentrated in specific risk groups (Figure 1). Injection drug use is the major risk factor for HCV infection. Approximately 60% to 90% of injecting drug users become infected within 12 months of first shared-needle use.8 Approximately 80% to 90% of long-term users are HCV-infected, and 15% to 20% are HIV-infected. Injecting drug users account for 60% of the new HCV cases. In one large cohort of injecting drug users, 22% of those infected were women, predominantly African Americans, who were co-infected with HIV.9 Reports of sexual transmission are rare but may be associated with high-risk sex practices and multiple partners.10 Co-infection with HIV may also increase sexual transmission of HCV.

Overall, it is estimated that around 300,000 Americans are co-infected with HCV and HIV.1 This high frequency is related to similar modes of transmission.
Hepatitis C virus virology
The hepatitis C virus is an RNA virus of the Flaviviridae family, which has an error-prone replication cycle leading to frequent mutations and multiple genotypes. There are six major genotypes, eight subtypes, and numerous quasi species. In the United States, two thirds of HCV-infected persons have genotype 1; 10%, genotype 2; and 6%, genotype 3. These genotypes are important because they are predictive of treatment responsiveness to interferon-based modes of therapy, with genotype 1 being the least responsive.

Natural history
Hepatitis C infection alone may lead to the development of chronic liver disease in 70% of those infected and cirrhosis in 10% to 20% over several decades. It is the leading cause for liver transplantation in the United States. Because of shared routes of transmission, co-infection with HCV and HIV is common, affecting 60% to 95% of those infected via a parenteral route. In the HCV-HIV co-infected patient, there appears to be an increased rate of HCV progression to fibrosis, cirrhosis, and death. In 92% of those infected with HCV and HIV, chronic liver disease eventually develops. Additionally, alcohol advances the progression of fibrosis. Drinking more than 50 g of alcohol daily and having a CD4 count of less than 200 cells/mm³ markedly increase rates of progression to cirrhosis. The impact of antiretroviral therapy on HCV-related fibrosis is unknown. It has been postulated that protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) might potentiate hepatotoxicity and lead to advanced fibrosis. However, Benhamou and associates found four independent predictors of progression to cirrhosis in co-infection: absence of protease inhibitor therapy (relative risk [RR] 4.74), heavy (>50 g/d) alcohol consumption (RR 4.71), low CD4 count (<200 cells/mm³) (RR 2.74), and age at HCV acquisition younger than 20 years (RR 2.37).

They did not find that gender affected rate of progression. Additionally, co-infection with HCV-HIV appears to increase the risk of development of type 2 diabetes, nephropathy, and B-cell lymphomas in persons with HIV. As such, HCV behaves like an opportunistic pathogen in persons with HIV. Co-infection also is associated with increased mortality despite well-controlled HIV disease: Bica and colleagues found that 55% of those that died of ESLD had a CD4 count greater than 200 cells/mm³ and an undetectable HIV viral load. Although we do not have all the answers yet, we know that HIV infection has many different effects on HCV-infected patients. Many recent studies have clearly revealed an increased transmission (both sexual and perinatal) of HCV in the co-infected patient. Co-infection with HIV and HCV has also been associated with higher titers of HCV (viral load) as well as an increased risk for HCV-related fibrosis and cirrhosis of the liver. Furthermore, there is an increased genotypic variability of the HCV among the co-infected and a higher percentage of hepatotoxicity after the initiation of HAART.

Gender-specific issues in hepatitis C virus
Knowledge of the natural history of HIV and HCV infections is based primarily on data from studies in men, most of which showed relatively little impact of gender. Several issues are specific to women who are infected with either HCV or HIV or both: the rate of infection, the rate of perinatal transmission, role of age, the rate of HCV progression, the response to treatment regimens, the toxicity of HAART, and the toxicity of anti-HCV treatment. Many of the social barriers that inhibit HIV-infected women from entering care affect the identification and management of HCV infection.

Rate of infection
The prevalence of HCV in pregnant women varies from 0.8% to 2.4% depending on the population studied. Women with IDU have the highest rates (70.1% to 95.4%). The factors that determine this risk include maternal HCV viral load greater than 100,000 copies/mL, HIV co-infection, and IDU (Figure 2). Breast-feeding, C-section versus vaginal delivery, and genotype do not appear to affect transmission. The rate of perinatal transmission of HCV is 15% to 36% or at least threefold greater for infants born to mothers infected with both HIV and HCV when compared with those born to mothers who are HCV-positive alone. This risk, similar to HIV perinatal transmission, appears to be linked to HCV viral load. The risk of transmission was low in women with HCV viral load of less than 100,000 copies/mL. Similarly, the risk of HIV vertical transmission is increased among co-infected women (26% vs 16%) not given antiviral agents during labor.

Viremia and transaminases with HCV may vary throughout pregnancy. In a cohort of Italian women with only HCV infection, 56% had elevated levels of serum alanine transaminase (ALT) in the first trimester, 7% in the last trimester, and 55% after delivery with no change in the proportion of those with detectable HCV viremia. In another study, findings were similar but there was also an
increase in HCV-RNA in the second and third trimester as compared with that before pregnancy.\textsuperscript{21} One study showed an increased risk of HCV transmission in infants born via forceps compared with those delivered by cesarean section (odds ratio [OR] 3.24).\textsuperscript{22}

**Role of age**

Age and menopausal state may also have an impact on HCV disease in women. Several studies have suggested a slower rate of progression in HCV-infected women compared with that in men.\textsuperscript{9,23,24} Biopsies show lower histologic scores in menstruating women than in age-matched men. Additionally, iron-deficient women (transferrin saturation <2%) showed significantly less histologic progression than women with normal iron stores, thus suggesting that iron deposition may be an important factor for the development of ESLD.\textsuperscript{23,25}

**Rate of progression of hepatitis C virus infection**

Data from the Johns Hopkins cohort indicate that women have increased clearance of HCV compared with that in men (OR 1.38), and a decreased risk of ESLD (OR 0.28).\textsuperscript{26} The same observation regarding more frequent elimination of HCV from serum in women was reported from a Japanese study.\textsuperscript{27}

**Responses to treatment**

Few treatment data exist as few women participated in clinical trials of HCV infection alone, and even fewer in studies of co-infection. Most of the large studies of HCV infection enrolled a significantly greater percentage of male patients (65% to 75%), which reached 90% in the four large retrospective cohorts of hemophiliacs. A study from Japan of 112 women with HCV infection alone treated with interferon (IFN) monotherapy showed comparable sustained virologic responses (24% vs 27%) to men, but improved responses (75% vs 16%) for the women who were younger than 39 years.\textsuperscript{24}

**Toxicity issues**

Anemic women and pregnant women should not receive ribavirin (Rebetron; RBV) because of the risks of hemolysis and teratogenicity, respectively. Sexually active women and their partners should use at least two forms of contraception if either is receiving RBV. Additionally, weight-adjusted dosing of both RBV and IFN is preferable to avoid toxicity and improve effectiveness. A final issue is drug-related hepatotoxicity in the co-infected patient. Women with HIV infection are at increased risk for both mitochondrial toxicity of nucleoside analogs (didanosine, stavudine, zalcitabine, zidovudine), and nevirapine (Viramune) hepatotoxicity. Approximately 16% of patients treated with nevirapine and 4% of patients treated with efavirenz (Sustiva) have hepatotoxicity, which is increased twofold to threefold in patients co-infected with HCV.\textsuperscript{28,29}

**Evaluation of HCV-HIV co-infection**

The evaluation of women co-infected with HCV and HIV should include a comprehensive history and physical examination with specific laboratory studies to assess the risk of disease progression, the impact of co-infection on the quality of life, and the women’s candidacy for therapy (Figure 3). Important concerns are the stage of HIV and HCV infection, potential interactions of the diseases or their treatment modalities, and an assessment of which disease, if either, should be treated and in what order.

**History**

- **Human immunodeficiency virus infection**—Women should be evaluated for risk factors and duration of HIV disease. Important information includes current CD4 count and nadir (lowest ever) CD4 count, history of opportunistic infections, and use of antiretroviral agent. Social factors such as children, housing, access to care, and psychosexual history are critical to the overall assessment and management.

Comorbid illnesses such as psychiatric illness, depression, cardiac or pulmonary disease, and adherence to antiretroviral modalities of therapy need to be evaluated.

- **Hepatitis C virus infection**—In addition to the foregoing assessments, the evaluation of co-infected women should include: risk for HCV infection; duration of infection based on first IDU; symptoms of hepatitis, including hepatitis A, B; current and past alcohol use (CAGE questionnaire [JAMA 1984;252:1903-1907]); medication hepatotoxicity; and family history of liver diseases.

**Physical examination**

In addition to doing a good general examination, clinicians should search for manifestations of chronic liver disease such as spider angiomas, jaundice, ascites, or easy bruising. These conditions may suggest advanced liver disease that may preclude or complicate treatment.

**Laboratory evaluation**

Before ordering the initial laboratory evaluation, clinicians should offer counseling regarding the meaning of a positive HIV or HCV antibody test and assure patients that they will be provided with posttest counseling and follow-up care. The initial serologic test for HCV should be the HCV antibody (second- or third-generation enzyme immunoassay). In late-stage HIV disease, up to 5% of patients may lose their antibodies to HCV but remain viremic. In these patients, an HCV viral load should be quantitated by bDNA or reverse transcription polymerase chain reaction assays. The HCV RNA assay differs from HIV RNA in that it is neither predictive of disease progression nor indicative of severity. An HCV genotype should also be performed as part of the initial evaluation as specific genotypes are associated with a better or worse response to IFN-based therapy. Specifically, patients with genotypes 2 and 3 have better responses than those patients who have genotype 1a, 1b.

Liver function should be assessed by measurement of serum albumin and bilirubin levels and prothrombin time (PT). Hepatic transaminase levels should be monitored, though normal levels may be seen even with cirrhosis. A complete blood cell count, renal tests, pregnancy screen, and screening for other causes of hepatic disease (especially autoimmune ones, which tend to worsen with IFN therapy) should be done. Antibodies should be checked for hepatitis A virus–total (IgG and IgM) and hepatitis B virus, and patients who are not immune should be vaccinated. The responsiveness to these vaccines clearly wanes with CD4 counts of less than 200/mm\(^3\) in persons with HIV infection. The serum TSH level should be checked if the patient has a history of thyroid problems or if treatment with IFN is considered.

**Imaging studies**

Liver imaging is not mandatory, but an ultrasound examination of the liver should be considered for patients with suspected cirrhosis and for portal flow evaluation. Additionally, ultrasound guidance may be helpful in reducing complications from liver biopsy.
Liver biopsy

Liver biopsy is the gold standard for assessing hepatic injury due to hepatitis C, and it should be strongly recommended as elevations of HCV-viral load and transaminase levels fail to reflect the degree of liver damage. A biopsy is contraindicated if the PT is greater than 3 seconds prolonged or platelet count is less than 60,000/mm.

The fibrosis score allows prognostication regarding progression of liver disease and therapy. Several scoring methods are used, with the Ishak score being most accepted. Histologic appearances are classified as mild, moderate, or severe based on the degree of inflammation and fibrosis.

Management of HCV infection in HIV co-infection

A variety of health maintenance issues are important in the management of co-infection. Vaccinations should be offered to prevent pneumococcal disease, hepatitis A virus and hepatitis B virus in the nonimmune patient. Patients need counseling regarding risk of transmission (sexual, parenteral, maternal-fetal), and they may need referral to be treated for alcohol or substance abuse. It is important to emphasize a healthy diet and to discuss the pros and cons of using herbal supplements. Depending on the patient’s comorbidities, extent of HIV and HCV disease, and motivation, the next step is to institute...
specific therapy for HCV infection. Current modes of therapy involve the use of IFNs, usually in combination with RBV.

**Interferon-based modes of therapy**

The optimal outcome of treatment of patients with hepatitis C is the inability to detect HCV viral load 6 months after completing the course of therapy (sustained virologic response [SVR]). Several studies have demonstrated that the combination of IFN-RBV is significantly more effective than IFN monotherapy with SVR 40% versus 17%, respectively.31,32 in the group infected only with HCV. Predictors of response are non-1 genotype, HCV viral load less than 3.5 million copies/mL, age younger than 40 years, female gender (possibly related to increased RBV per kilogram of body weight), and minimal or no portal fibrosis. Most of the responders could be identified by week 24. Recent studies have now shown even better responses using the combination of pegylated interferons (PEG-IFNs) with RBV in this group. The use of PEG-alfa 2b (Peginteron) plus RBV was associated with a 54% SVR (33% with genotype 1) versus 47% for standard IFN-RBV versus 42% PEG-alfa-2b alone.33-34

Relatively few studies exist in the co-infected population, and much is extrapolated from the population infected only with HCV. Treatment approaches are rapidly evolving, and several large studies in patients with co-infection are ongoing. Several smaller studies in HIV-HCV co-infected patients with preserved immune function suggest that these patients respond similarly to combination therapy as the mono-infected patients.35-37 Interferon alfa-2b (Intron A), IFN alfa-2a (Roferon A), IFN alfacon-1 (Infergen), IFN alfa-2a/RBV (Rebetron), and PEG-IFN alfa-2b (Peginteron) are all Food and Drug Administration–approved formulations. It is anticipated that PEG-IFN alfa-2a (Pegasys) is to be approved later this year. These compounds appear to be safe and relatively well tolerated. Their efficacy is greatest with preserved CD4 counts. Pegylated IFNs are long-acting IFNs, given subcutaneously once weekly; these agents offer improved efficacy and convenience. Their response rates are better than those to IFN monotherapy, but they are considered less effective than combination treatment modalities using either IFN and RBV or PEG-IFN and RBV (Figure 4).

Common side effects associated with IFN include fatigue, flu-like syndrome, bone marrow suppression (especially thrombocytopenia with PEG), depression, insomnia, irritability, anorexia, and thyroid dysfunction. Ribavirin-related side effects include hemolytic anemia (average 2-g to 3-g drop in hemoglobin level), nausea, respiratory symptoms (dyspnea, nasal congestion, cough), and teratogenicity.

**Who should be treated?**

All patients infected with HCV and HIV who should be offered to patients with well-controlled HIV disease (CD4 count >200 cells/mm³ and HIV viral load <10,000 copies/mL), a detectable serum HCV RNA, evidence of portal fibrosis or moderate inflammation seen on liver biopsy, compensated liver disease, and no contraindications to treatment with IFN or RBV. Patients with lesser degrees of hepatic inflammation or fibrosis should be assessed on an individual basis. Currently, cirrhotic patients should be treated only in the context of clinical trials.

**Comments**

The significant advancement in clinical knowledge as well as pharmacotherapy during the past 10 years has effected marked changes in the way we currently treat HCV-infected patients. As HAART and prophylaxis of opportunistic infections have transformed HIV into a chronic disease, HCV-related liver disease has become a significant cause of morbidity and mortality among co-infected patients. Many large clinical trials are under way in an effort to address important issues on how to manage co-infection. For the female co-infected patient, substantial questions still need to be answered regarding such issues as: the role of female hormones, menstrual cycles, and menopause on the natural history of HCV; the ability to prevent the vertical transmission from co-infected mothers to infants; the sequence, effectiveness, and safety of treatment, and the differences between women and men in the progression of HCV infection and response to treatment.

**References**


