



Pharmacy

Advances in the pharmaceutical care of hepatitis C/HIV co-infection

Tina Ogbuokiri, PharmD, FASCP

An estimated 170 million people worldwide (approximately 3% of the world's population, including approximately four million in the United States) are infected with the hepatitis C virus (HCV). Co-infection with HIV and hepatitis C has occurred in approximately 300,000 persons here in the United States. Both HIV and HCV are blood-borne. Due to shared risk factors for transmission including IVDU, high-risk sexual activity and perinatal transmission, co-infection with both viruses, which is quite common, continues to be on the increase. It is estimated that by the year 2020, the rates of liver transplantation due to HCV-associated liver diseases will have tripled. Since several key studies have documented effective treatment of HIV/HCV co-infected patients with antiretroviral therapy (with 88% of patients in key studies not experiencing severe hepatotoxicity from antiretroviral therapy), today's HIV providers can benefit from a brief review of the pharmaceutical care issues involved in optimizing therapy for co-infected patients.

Highlights of the comparative virology and pathogenesis of HCV and HIV

Both HIV and HCV are single-stranded RNA flavoviruses that are widely distributed worldwide. Whereas HCV is known to have six major genotypes, there are 11 subtypes of HIV. HIV-1 and HIV-2 can be further categorized into genetic subtypes or clades. The system currently used to classify HIV-1 and HIV-2 into subtypes is based primarily on genetic sequences coding the envelope (Env) and structural (Gag proteins) and methods to infer phylogenetic relationships between them. HIV-1 has at least 11 subtypes that are designated A through K in the order that they were identified, while HIV-2 has 5 genetic subtypes designated A through E.

Certain key differences exist with regard to the virology and pathogenesis of hepatitis C virus and the HIV virus. Hepatitis C virus does not integrate into the host genome and plasma HCV RNA levels do not correlate as well with disease progression as does HIV RNA. The means by which HCV causes liver injury is not completely understood and a cure

of hepatitis C infection, unlike HIV infection, is possible and achievable. Iron, fat and alcohol are critical co-factors that lead to progressive fibrosis and there is no association between viral serotype and the degree of hepatic inflammation or fibrosis.

Differences in transmission between hepatitis C and the HIV virus

Hepatitis C is ten times more likely to be transmitted parenterally and five times less likely to be transmitted sexually than HIV; it is rarely transmitted sexually in monogamous long-term relationships. Perinatal transmission of hepatitis C increases more than two-fold (14-16%) if the mother is also HIV-infected.

Goals of HCV therapy in HIV-infected patients

Several key goals drive the need to treat co-infected patients. These include eradication of HCV in patients with adequate immune response, delay of disease progression in patients with advanced fibrosis assessed by liver biopsy, and suppression of HCV disease activity in order to prevent HAART-associated hepatotoxicity. Treatment of hepatitis C/HIV co-infection is best accomplished using a multidisciplinary approach with close interaction between a hepatologist, an HIV care provider, and a psychiatrist.

Treatment issues of relevance for hepatitis C/HIV co-infection

General aspects of treatment

As a general rule, treatment of hepatitis C appears to be just as effective in patients with HIV as in HIV sero-negative persons. HIV infection, except in cases of late stage disease, does not prevent successful treatment of HCV. Interferon treatment of hepatitis C in patients with AIDS may reduce fibrosis even without sustained virologic response. Abstinence from alcohol is critical and as a general rule, therapy with ribavirin and interferon should not be started simultaneously with antiretroviral therapy. The standard procedure is to treat the hepatitis C first, if possible obtain a cure, and by so doing rejuvenate a liver that can then become the body's workhorse to metabolize HAART and other medications in the life-long therapy needed in HIV disease.

Contraindications to HCV therapy include patients with severe psychiatric disorders, on-going substance abuse, uncontrolled thyroid disorders, autoimmune disorders, decompensated cirrhosis and pregnancy.

Recommended treatment for hepatitis C/HIV co-infections

Initially, treatment of HCV/HIV co-infection was carried out with interferon monotherapy (Infergen, Intron-A, Roferon-A, Peg-Intron and Pegasys). However, this led to unsatisfactory rates of just 10-20%. The first real clinical improvement was seen when combination treatment with standard interferon and ribavirin increased the response rates to 20-25%. Side effects, which included influenza-like symptoms, depression, asthenia caused by the interferon, as well as hemolytic anemia caused by ribavirin, were problematic and led to discontinuation in approximately 30% of patients.

The standard treatment of choice currently recommended for HIV/HCV co-infection includes use of pegylated interferons rather than standard interferons, along with weight-based ribavirin. The introduction of pegylated interferons represented further significant progress. By binding standard interferons onto polyethylene glycol, PEG, the interferon-a protein, is shielded from enzymatic degradation and so considerably increases the half-life of the interferons, thereby making it possible to give weekly instead of thrice weekly injections. Other advantages of pegylation include a slower absorption of the pegylated form, thereby producing less peak concentrations, which in turn are associated with less side effects along with a consistently high plasma level, which guarantees less trough levels during which efficacy could be jeopardized.

The APRICOT Trials

The largest study to be performed in HIV/HCV co-infected patients to date (AIDS Pegasys Ribavirin International Co-infection Trial) supported previous results from several trials using the combination of pegylated interferon with ribavirin in co-infected patients (2001-2003). In most of these studies, the response rates were increased to 40% in HIV/HCV co-infection; however discontinuation rates remained high, sometimes up to 30%.



The APRICOT Trial compared three arms: pegylated interferon with ribavirin, pegylated interferon with placebo, and standard interferon-2a plus ribavirin. The sustained treatment responses in this trial were 40%, 20%, and 12% respectively.

It is particularly noteworthy that genotype 1, which is usually associated with a poor clinical response, showed better responses to this treatment compared to standard interferon/ribavirin therapy (nonetheless still less than 30%). Genotypes 2 and 3, which often respond better to treatment, showed response rates of about 60%. Relapses tended to occur more in patients with HIV/HCV co-infection than in mono-infected patients.

Concerns about effect of interferons on HIV infection

Concerns about negative effects of interferons on HIV infection have not been confirmed in any study. In fact some studies have reported additional suppression of HIV viremia due to the antiviral activity of interferons. Though absolute T-lymphocyte counts may decrease due to drug-induced leukopenia, percentage values usually increase. So far, no studies have shown a deterioration of HIV infection when interferons are used in HCV/HIV co-infection.

New studies in African-American patients showing better outcomes using weight-based ribavirin for patients with genotype 1 HCV infection

In a recent study reported November 4, 2004, by Dr. Ira Jacobson, weight-based ribavirin dosing was found to be clearly superior to the current fixed dose of 800mg by a significant degree when applied to a group of 387 African-American patients with chronic HCV genotype 1 infection. Patients who received weight-based ribavirin doses (up to 1400 mg daily for the heaviest patients) had twice the sustained virologic response (SVR) rates of those who received the standard fixed dose of 800mg daily. In addition, the relapse rate for patients treated with weight-based ribavirin was 22% compared with 31% for those who received the fixed dose. We await reports of larger studies to confirm this finding.

Adverse events associated with treatment of HCV infections

Interferon treatment is associated with major side effects such as neuropsychiatric symptoms, influenza-like symptoms that may include fatigue,

fever, muscle aches and weakness, headache, chills and bone pain (patients often describe these as "feeling sick as a dog"), hematologic abnormalities (especially anemia and neutropenia) and depression which may occur in up to 30% of patients. Loss of appetite, nausea and diarrhea occur in about 50% of patients taking this drug, while vomiting and abdominal pain occur less frequently. The most commonly reported CNS side effect of interferon is dizziness, while other less commonly reported side effects include hair loss, coughing, difficulty breathing and chest pain. Alfa interferon may increase the bone marrow toxicity due to AZT, flucytosine, ganciclovir, pentamidine, pyrimethamine and anti-cancer drugs.

Since medication tolerability is so critical for success, both caregivers and

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patients should be educated regarding the potential side effects of therapy prior to and during the treatment process. Regular follow-up visits are essential for close monitoring of patients regarding adherence to therapy, as well as for detection and management of adverse events.

Adverse events prompting dose reduction in phase III clinic trials

In major clinical trials, dose reduction occurred in 32% to 42% of patients and treatment discontinuation in 10% to 14%. Hematopoietic growth factors (epoetin alfa) were used to improve tolerability and to prevent dose reduction in patients. The costs of these growth factors can be prohibitive.

Patient education as a major component of adherence to therapy and successful outcomes

In order to increase patient adherence and to improve virologic and clinical outcomes, patient education is an important component of care. Patient educa-

tion should begin prior to therapy and be continued and repeated at follow-up encounters and visits as needed. Apart from physicians, all support staff including nurse practitioners, clinical pharmacists, physician assistants, nurses and others can provide valuable assistance in educating patients.

Key elements to be shared with the patient prior to initiation of and during the course of treatment include:

- Potential consequences of untreated hepatitis C infection
- Strategies for prevention of transmission
- The need to avoid ingestion of alcohol and IDU
- Potential benefits of combination interferon and ribavirin (cure, reduction in liver damage)
- Dietary recommendations: 2500 to 3000 calories/day. Hydration: 3000-3500 ml/day
- Dosing and administration of drugs including proper injection techniques (individualize instructions with return demonstration and printed instructions)
- Duration of treatment
- Importance of adherence to therapy
- Teratogenicity of ribavirin and the need for two methods of contraception and monthly pregnancy testing during and for six months following treatment
- Expected side effects and how to manage these
- Significance of HCV RNA results and genotypes
- Schedule for office visits, laboratory tests and immunizations
- Resources for patient support while in treatment

Role of pharmacists when trained in HIV/HCV care

As the healthcare provider who is often the most easily accessible to all patients, pharmacists can play a major role in assisting patients with hepatitis C and HIV infection to understand and manage their side effects when this knowledge is offered to pharmacists in ambulatory care clinics and community drug stores in areas of high prevalence of both HIV and HCV co-infections. As the rates of both infections continue to rise, pharmacists in HIV care may need to embrace the new challenges offered in this exciting area and by so doing assist in improving both clinical and virologic outcomes for patients with both diseases.

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A multidisciplinary approach works best with co-infection

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Hepatotoxicity of antiretroviral agents and drug-drug interactions with antiviral therapies for HCV infection

In the treatment of HIV infection, all three classes of antiretroviral agents have been associated with hepatotoxicity, which may lead to interruption of HIV therapy and can cause significant morbidity and mortality. Severe hepatotoxicity occurs in approximately 6 to 12% of patients on HAART therapy. Factors contributing to hepatotoxicity include use of alcohol, concomitant use of other hepatotoxic medications commonly used in the treatment of opportunistic infections such as fluconazole, trimethoprim/sulfamethoxazole, use of medications metabolized by the cytochrome P450 enzymes which are inhibited by some antiretroviral agents such as ritonavir and the presence of other infections such as hepatitis C and hepatitis B.

The risk of hepatotoxicity has been shown to be increased in patients with hepatitis C co-infection. In addition, the use of ribavirin in the treatment of hepatitis C virus infection may increase the risk of adverse events due to some theoretical pharmacokinetic interactions with some antiretroviral agents. While more data is being awaited, currently available evidence suggests that HCV and HIV infections may be treated together successfully with close clinical monitoring for hepatotoxicity as well as an increase in adverse events.

See adjacent Table 1 for a listing of the drugs that are currently approved and for investigational use in the treatment of hepatitis infection.

See Table 2 on facing page for a breakdown of the key aspects of hepatotoxicity associated with HAART therapy that may impact treatment. ❖

References are available upon request.

Tina Ogbuokiri is Associate Professor of Clinical Pharmacy, Xavier University College of Pharmacy; Consultant Clinical Pharmacist, HIV Outpatient Program, New Orleans; and Delta Region AETC faculty.

Table 1.

FDA-approved Investigational Drugs

Drugs currently approved for investigational use in the treatment of hepatitis infection.

Adenovirus dipivoxil (Hepsera)	HBV
Interferon alfa-2b (Roferon-A)	Abacavir (Ziagen)*
Interferon-alfa 2b (Intron A)	BAM-205
Interferon alfa-n3 (Alferon)	Clavudine(L-FMAU)
Interferon alfacon (Infergen)	Elvucitabine (ACH-126, 443, Beta-L-Fd4C)
Lamivudine (EpiVir-HBV)	Emtricitabine (Emtriva, FTC)
Peginterferon alfa-2* (Pegasys)	Entecavir (BMS 200, 475)
Peginterferon alfa 2-b (Peg-Intron)	Hepex-B
Ribavirin (Rebetol, Virazole)	Telbivudine (LdT)
Ribavirin & interferon alfa-2b (Rebetron)	Tenofovir disoproxil fumarate (Viread)*
FDA-approved Vaccines and Sera	HCV
Hepatitis A vaccine (Havrix, Vaqta)	Amanatadine*
Hepatitis A vaccine and Hepatitis B vaccine (Twinrix)	BILN-2061
Hepatitis B immune globulin (BayHep B, Nabi-HB)	FK788
Hepatitis B vaccine (Engerix-B, Recombivax HB)	Hepex-C
Hepatitis B vaccine and Haemophilus influenzae type b polysaccharide conjugate vaccine (Comvax)	Histamine dihydrochloride (Ceplene)
	Interferon gamma -1b
	ISIS 14803
	Levovirin
	Merimempodib (VX-497)
	Mycophenolate mofetil (Cellcept)
	Thymosin alpha 1 (Zadaxin, Thymalfasin)
	Viramidine
	*FDA-approved for other indications

For information about HIV treatment guidelines, HIV drugs, and HIV clinical trials, visit aidsinfo.nih.gov



Table 2

Breakdown of the key aspects of hepatotoxicity associated with HAART therapy that may impact treatment

Drug Class	Key features of associated hepatotoxicity
Protease inhibitors (PIs) (especially ritonavir)	Hepatitis including hepatic failure and death. Risk may be increased in patients with significant alcohol abuse, pre-existing liver disease or underlying HBV or HCV infection.
Nucleoside reverse transcriptase inhibitors (NRTIs) especially stavudine and didanosine	Mitochondrial toxicity, fatal in a few cases. Classic syndrome consists of hepatomegaly, nausea, ascites, edema, dyspnea, increased ALT/AST and lactate, (incidence < 1%). With long-term use, possible liver failure in absence of cirrhosis.
Non-nucleoside reverse transcriptase inhibitors (Norris) especially nevirapine	Severe life-threatening and possibly fatal hepatotoxicity including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure +/- early acute hypersensitivity syndrome. More than 50% may occur beyond 12 weeks of therapy. Risk may be increased in patients with high T cell count (250 and above in females, 400 and above in males) and/or in patients with HCV coinfection.

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Case Consultation for HIV Clinicians

**Delta Region health care providers can consult with
HIV experts at university medical centers:**

- Louisiana 504-903-0788
- Mississippi 601-984-5542
- Arkansas 870-535-3062 x104

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