Therapeutic Interventions for HIV Infection and Chronic Viral Hepatitis

Curtis L. Cooper
Department of Medicine, University of Ottawa, Division of Infectious Diseases, The Ottawa Hospital–General Campus, Ottawa, Ontario, Canada

Combination antiretroviral therapy reduces overall and liver-specific morbidity and mortality in coinfection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) and represents the most beneficial pharmaceutical treatment intervention for most coinfected patients. Antiviral therapy for HCV infection is potentially organ- and life-saving but, in general, should be reserved for patients who achieve suppression of HIV RNA and immune restoration from combination antiretroviral therapy or for patients with nadir CD4+ T lymphocyte levels of ≥350 cells/μL. Safe and virologically active treatment of coinfection with HIV and hepatitis B virus can be concurrently achieved by the use of combination antiretroviral therapy regimens containing lamivudine and/or tenofovir.

Coinfection with HIV and hepatitis C virus (HCV) is common [1, 2]. Among injection drug users infected with HIV, the prevalence of HCV infection approaches 90% [2, 3]. The prevalence of hepatitis B virus (HBV) coinfection is ~5%. It is likely that chronic viral hepatitis will have a great effect on the morbidity and mortality in and therapeutic decisions made for HIV-seropositive persons for the foreseeable future. Relevant treatment issues for HIV-HCV and HIV-HBV coinfection are considered here. Concerns specific to the treatment of patients with concurrent excess alcohol use are discussed.

ANTIRETROVIRAL THERAPY AND THE LIVER

HCV infection is modified by antiretroviral therapy. An initial increase in levels of HCV RNA and liver enzymes (i.e., alanine aminotransferase and aspartate aminotransferase) after initiation of therapy is often observed [4, 5]. In patients who achieve prolonged suppression of HIV RNA, plasma [4] and intrahepatic [6, 7] HCV RNA levels often decrease to below baseline. This is dependent on pretreatment CD4+ T lymphocyte count [8] and alcohol consumption [4]. With long-term adherence to virologically potent HAART, liver enzyme levels generally remain similar to baseline levels [4] and may decrease to below baseline in subjects who had high pretreatment levels [9, 10]. Scores of liver inflammation activity are lower, and rates of fibrosis are reduced in subjects coinfected with HIV and HCV who are receiving protease inhibitor–based HAART regimens [11, 12]. These positive changes in virological, enzymatic, and histological measures may reflect restoration of HCV-specific cell-mediated immunity. Despite rare flare-ups of HCV disease during HAART [13], the weight of evidence demonstrates that combination antiretroviral therapy has a beneficial influence on HCV disease in coinfection with HIV and HCV.

There is ongoing debate as to whether specific antiretroviral drugs and/or entire classes of HIV medications should be used preferentially to treat patients with HIV-HBV and HIV-HCV coinfection, to avoid elevations in liver enzyme levels and clinically apparent hepatotoxicity. Irrespective of the antiretrovirals used, careful clinical and laboratory monitoring is advised for all persons coinfected with HIV and HCV. Rare cases of hepatic steatosis and fulminant hepatitis have been reported with nucleoside reverse-transcriptase inhibitor treatment [14–17]. Subclinical nucleoside-induced he-
patent steatosis may have long-term clinical consequences, but this remains to be proven. The frequency of pancreatitis and lactic acidosis is increased with combination treatment with didanosine and ribavirin and, therefore, should be avoided [15, 16].

The relative incidence of elevations in liver enzyme levels with the 2 nonnucleoside reverse transcriptase inhibitors currently in use is controversial. Prospective evaluation of efavirenz- and nevirapine-containing HAART in treatment-naive patients demonstrated a 2%–4% incidence of transaminitis [18]. An early nevirapine hypersensitivity syndrome, consisting of fever, rash, and transaminitis, is well described [19, 20] and is more common in women and in patients with higher levels of CD4+ T lymphocytes.

Protease inhibitors are often cited as being particularly injurious to the liver in patients with chronic viral hepatitis [20, 21]. In most cases, elevation of liver enzymes levels occurring early after the initiation of protease inhibitor–containing antiretroviral therapy is asymptomatic and is generally self-limited. Full-dose ritonavir (600 mg b.i.d.) may produce more episodes of asymptomatic elevations in levels of liver enzymes [20]. The incidence of elevations in liver enzyme levels (i.e., >3 times the upper limit of normal) occurring with low-dose ritonavir–boosted HAART regimens (100–200 mg b.i.d.) is between 5% and 10% [22–25] and is similar to that observed with other protease inhibitor–based HAART regimens [5]. Although careful observation is advised, the majority of patients coinfected with HIV plus HCV or HBV who initiate treatment with protease inhibitor–containing regimens achieve desirable virological suppression and immunologic restoration [12] without treatment-limiting liver toxicity [5, 26].

Hepatotoxicity with the HIV fusion inhibitor enfuvirtide is infrequent [27, 28]. Additional research will determine whether this class of antiretrovirals will become a primary consideration for treatment of coinfected patients.

ANTIVIRAL THERAPY FOR HBV AND HCV

There are several treatment options for HIV-HBV coinfection. The rates of normalization in levels of liver enzymes, elimination of HBV viremia, loss of hepatitis B e antigen, and development of antibodies to hepatitis B e antigen are similar between patients treated with IFN, lamivudine, and tenofovir [29–33]. Drug resistance in HBV evolves more slowly with tenofovir than with lamivudine, and tenofovir is effective in treating patients with lamivudine-resistant HBV infection [33, 34]. Monotherapy for HBV with lamivudine or tenofovir is not advised in HIV-HBV coinfection. Infection with both viruses can be treated simultaneously by inclusion of lamivudine and/or tenofovir in combination antiretroviral regimens.

Sustained virological response (SVR) is achieved in no more than 40% of patients coinfected with HIV and HCV who receive treatment for 48 weeks with pegylated IFN plus ribavirin [12, 35–38]. The reported SVR with pegylated IFN-α2a plus ribavirin was 29% for HCV genotype 1–infected subjects receiving optimal clinical care in a hospital-based, research clinic setting [38–40]. Lower SVRs (15%) were reported in genotype 1–infected patients without the same degree of clinical support [39]. SVRs for patients infected with HCV genotype 2 or 3 range between 40% and 60% [38–41]. These reduced SVR results occur even in patients treated with virologically potent HAART who have CD4+ T lymphocyte counts well above 200 cells/μL [12].

Drug therapy for HCV infection is often contraindicated because of the heavy burden of comorbid illness in the HIV-infected population. These include psychiatric illness, cytopenias, and uncontrolled substance abuse. The physical and psychological side effects of drug therapy for HIV and HCV are frequent but, in general, are no more plentiful or severe in patients with coinfection with HIV and HCV [42]. Although the additive toxicity of combined drug therapy for HIV and HCV is often discussed, severe adverse interactions are rare and can usually be avoided by careful laboratory monitoring and avoidance of certain combinations of medications. Combination of didanosine and ribavirin is contraindicated [15, 16]. Both zidovudine and ribavirin produce anemia; therefore, careful attention to this measure is warranted if the drugs are coadministered. Erythropoietin is a valuable supportive adjuvant to current drug therapies for HCV and helps to avoid reduction in ribavirin dosage [42]. Because IFN possesses antiviral activity against HIV, drug therapy for HCV infection may actually increase the potency of combination antiretroviral therapy [43]. Absolute CD4+ T lymphocyte counts decrease in half of HIV-seropositive persons treated with IFN but rapidly return to pretreatment levels after completion of HCV therapy, and these decreases are not associated with an increased occurrence of opportunistic infection. The CD4+ cell percentage and ratio of CD4+ to CD8+ cells are unchanged with HCV therapy.

IFN may slow or reverse hepatic fibrosis resulting from both HBV and HCV infection. The use of long-term, low-dose IFN for this purpose is under investigation [44–46].

MERITS OF HAART VERSUS DRUG THERAPY FOR HCV IN COINFECTION

The best strategy for treatment of coinfection with HIV and HCV is controversial. Because HAART benefits both HIV directly and HCV indirectly, it usually represents the most beneficial initial pharmaceutical treatment intervention for patients coinfected with HIV and HCV who have CD4+ T lymphocyte counts of <350 cells/μL. HAART often suppresses HIV viremia, is generally associated with fewer adverse effects than are IFN-based regimens for HCV, slows progression of HCV disease, infrequently causes clinically apparent liver toxicity, and creates an immunologic milieu that may optimize the efficacy of drug therapy for HCV. For patients with nadir CD4+ T lymphocyte
counts of >350 cells/μL, the strategy of first treating HCV and then HIV is reasonable. This approach will avoid the combined toxicities of medications for HIV and HCV.

ALCOHOL

Alcohol accelerates the rate of hepatic fibrosis in HIV-HBV and HIV-HCV coinfection [11, 47]. The efficacy of IFN-based therapy for HCV infection is diminished as well [48, 49]. Our work suggests that levels of HCV RNA increase and remain elevated after initiation of antiretroviral therapy in persons consuming >50 g of alcohol per day, even with full HIV suppression [4]. This may be clinically relevant, because baseline HCV RNA level predicts the likelihood of SVR. Alcohol blunts HAART-induced restoration of HCV-specific immunity and may explain these findings [50].

CONCLUSIONS

In my opinion, combination antiretroviral therapy provides the greatest benefit to persons coinfected with HIV and HCV. HAART often controls HIV disease, is generally associated with fewer adverse effects than is IFN-based therapy for HCV, slows HCV progression, infrequently causes clinically apparent liver toxicity, and creates an immunologic milieu that may optimize the effectiveness of drug therapy for HCV. Antiviral therapy for HCV, in most cases, should be reserved for patients who abstain from alcohol and who achieve suppression of HIV RNA and immune restoration from HAART or for patients whose nadir CD4+ T lymphocyte counts are >350 cells/μL. Alcohol cessation should be emphasized for all persons coinfected with HIV and either HCV or HBV. Liver injury will be reduced, HCV RNA levels will decrease, and efficacy of HAART and drug therapies for HCV will be increased. This intervention requires sustained commitment to alcohol cessation programs and patience.

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