Perspective

Hepatitis C and B Viruses: The New Opportunists in HIV Infection

Coinfection with HIV accelerates disease progression in both hepatitis C virus (HCV) and hepatitis B virus (HBV) infection. Management of coinfected patients is complicated by a number of factors, including disease characteristics, drug-drug interactions, and augmented toxicity. Results of HCV and HBV treatment trials in HIV-coinfected patients and strategies for patient management are discussed herein. This article summarizes a presentation by Raymond T. Chung, MD, at the International AIDS Society–USA course in New York in March 2006.

Hepatitis C Virus and HIV Coinfection

Coinfection with HIV and hepatitis C virus (HCV) is associated with loss of immunologic control of HCV and more rapid progression of HCV disease. HIV seroconversion is associated with a dramatic increase in HCV RNA levels and HCV-specific CD8+ T-cell activity is reduced with progressive lowering of CD4+ cell counts in HIV infection (Figure 1; Kim et al, *Blood*, 2005). More rapid progression of liver fibrosis has been demonstrated with coinfection (Figure 2; Benhamou et al, *Hepatology*, 1999). Among patients with progressive HCV disease, HIV coinfection appears to markedly accelerate progression compared with HCV monoinfection; eg, reducing time to progression to cirrhosis from approximately 20 years to 10 years and time to progression to hepatocellular carcinoma, transplant, or death from approximately 25 years to 15 years. A retrospective analysis of death from end-stage liver disease among all HIV-infected patients showed an increase from rates of 10% in 1991 and 15% in 1996 to 50% in 1998 (Bica et al, *Clin Infect Dis*, 2001). Of those patients dying from end-stage liver disease in 1998, 55% had a plasma HIV RNA level below the limits of detection or a CD4+ cell

count greater than 200/µL and all of the 91% of patients tested for HCV were HCV-seropositive.

The potential benefits of anti-HCV therapy are shared in HIV-coinfected and HCV-monoinfected patients; ie, the possibility of viral eradication, delay of progression of fibrosis, and prevention of such clinical complications as decompensation, hepatocellular carcinoma, and death. In coinfected patients, improved liver function might also improve tolerability of antiretroviral agents with hepatic adverse effects. However, anti-HCV treatment with interferon (IFN) alfa and ribavirin in HIV-coinfected patients is associated with adverse effects that can differ in type, frequen-

cy, or severity from those seen in patients without HIV infection. In HIV-coinfected patients, IFN alfa is associated with a dose-related myelosuppression (lymphocytes), flu-like symptoms, and depression. Ribavirin is associated with a dose-dependent hemolytic anemia (especially in the presence of zidovudine), teratogenicity, the potential for antagonism of zidovudine and stavudine phosphorylation, a potential increase in didanosine metabolites, and an increased risk for lactic acidosis.

Three recent trials compared pegylated IFN (peg-IFN) alfa with standard IFN alfa combined with ribavirin in patients with HIV/HCV coinfection. In the US AIDS Clinical Trials Group (ACTG) A5071 trial, biopsied patients received either peg-IFN alfa-2a 180 µg weekly plus ribavirin 600 mg/day (escalated up to 1 g/d; n=66) or IFN alfa-2a 6 mIU thrice weekly for 12 weeks and 3 mIU thrice weekly thereafter plus ribavirin at the same dose for a total of 48 weeks. Patients without virologic response were biopsied again at 24 weeks. Those with histologic
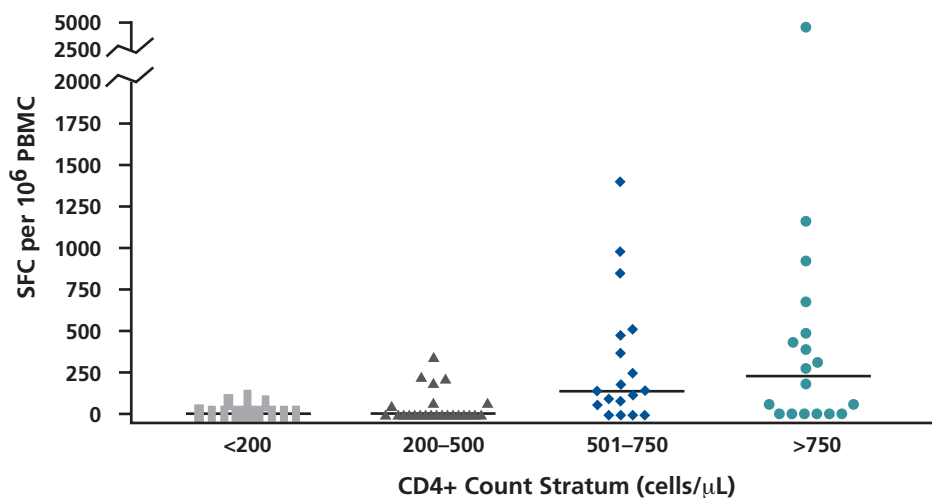

Figure **1**. Hepatitis C virus (HCV)-specific CD8+ T-cell response according to CD4+ cell count in HCV and HIV-coinfected patients. PBMC indicates peripheral blood mononuclear cell; SFC indicates spot forming cells, Adapted from Kim et al, *Blood,* 2005.

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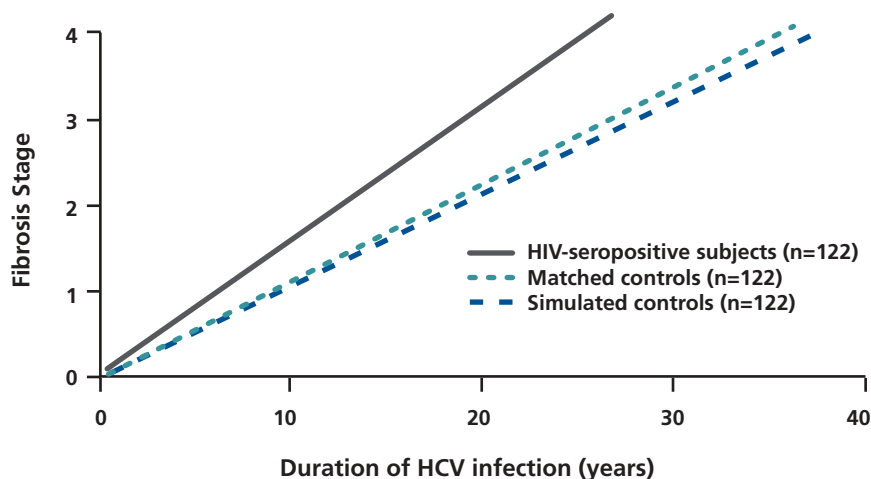
Figure **2**. Effect of HIV coinfection on hepatitis C virus (HCV) fibrosis progression. Adapted from Benhamou et al, *Hepatology,* 1999.

response continued in the trial and those without response discontinued treatment. In the international APRICOT trial, patients received: (1) peg-IFN alfa-2a 180 µg weekly plus ribavirin 800 mg daily (n = 289); (2) peg-IFN alfa-2a 180 µg weekly alone (n = 286); or, (3) IFN –alfa-2a 3 mIU thrice weekly plus ribavirin 800 mg daily (n = 285) for 48 weeks. In the French RIBAVIC trial, patients received peg-IFN alfa-2b 1.5 µg/kg/week plus ribavirin 800 mg/day (n = 205) or IFN alfa-2b 3 mIU thrice weekly plus ribavirin 800 mg/day (n = 207) for 48 weeks. All 3 trials assessed rates of sustained virologic response (SVR) at 72 weeks. The characteristics of the patients are listed in Table 1. Important differences include the fact that ACTG A5071 had a high proportion of African American patients; response rates in African American patients typically are markedly reduced compared with those in white patients, particularly among those with HCV genotype-1 infection. Genotype-1 infection, which is more resistant to treatment than other genotypes, was also more common in this trial. Both ACTG A5071 and the RIBAVIC trials included higher proportions of patients with bridging fibrosis or cirrhosis, factors associated with lower rates of SVR.

In ACTG A5071, SVR occurred in a significantly greater proportion of patients in the peg-IFN alfa plus rib-

avirin arm than in the IFN alfa plus ribavirin arm, 27% versus 12% (P = .03). SVR occurred in 14% versus 6% with genotype-1 infection and in 73% versus 33% (P < .001) with nongenotype-1 infection (Chung, *N Engl J Med*, 2004). Among virologic nonresponders, 45 of 57 in the IFN alfa plus ribavirin arm had a biopsy at 24 weeks and 16 (36%) showed histologic response. The median changes in HCV RNA were -0.61 $\log_{10}$ IU/mL in histologic responders and -0.58 $\log_{10}$ IU/mL in histologic nonresponders. Of 37 virologic nonresponders in the peg-IFN alfa group, 26 had a biopsy and 9 (35%) had a histologic response The median changes in HCV RNA were —1.01 $\log_{10}$ IU/mL in histologic responders and -0.71 $\log_{10}$ IU/mL in histologic

nonresponders. These latter findings suggest that clinical benefit is obtained with treatment despite the absence of SVR in a sizeable proportion of patients. Among 106 patients assessed at week 12, 43 (41%) had early virologic response (a 2-$\log_{10}$ IU/mL or greater decrease in HCV RNA or conversion to HCV-seronegative status). Of these, 21 (49%) did not have SVR at 72 weeks, indicating that early response was not predictive of SVR. Of the 63 patients (59%) without early virologic response at week 12, none had SVR, indicating that absence of early response was highly predictive of absence of SVR.

In the APRICOT trial, SVR occurred in 40% of subjects in the peg-IFN alfa plus ribavirin arm, 20% of the peg-IFN alfa alone arm, and 12% of the IFN alfa plus ribavirin arm (P < .05 for each peg-IFN alfa arm vs IFN alfa arm; Torriani et al, *N Engl J Med*, 2004); SVR rates were 29% (P < .05 vs IFN alfa), 14%, and 7%, respectively, among those with genotype-1 infections, and 62% (P < .05 vs IFN alfa), 36%, and 20%, respectively, in those with nongenotype-1 infections. Figure 3 shows SVR rates by treatment and genotype. A noteworthy finding was that among patients with genotype-1 infection, those with lower HCV RNA level (≤800,000 IU/mL) had markedly greater rates of SVR than those with higher viral load (>800,000 IU/mL). In the peg-IFN alfa plus ribavirin group, SVR was observed in 61% of patients with lower HCV viral load. These find-

Table **1**. Baseline characteristics in hepatitis C virus (HCV)/HIV-coinfected patients in 3 HCV treatment studies.

	ACTG A5071	APRICOT	RIBAVIC
White/African American (%)	48/33	79/10	Not reported
Genotype 1 or 4/2 or 3 (%)	78/22	68/32	58/42
$\log_{10}$ IU/mL HCV RNA	6.2	6.7	5.9
Bridging fibrosis or cirrhosis (%)	44	16	39
CD4+ count (cells/µL)	444–492	520–542	514
Antiretroviral therapy (%)	86	84	82

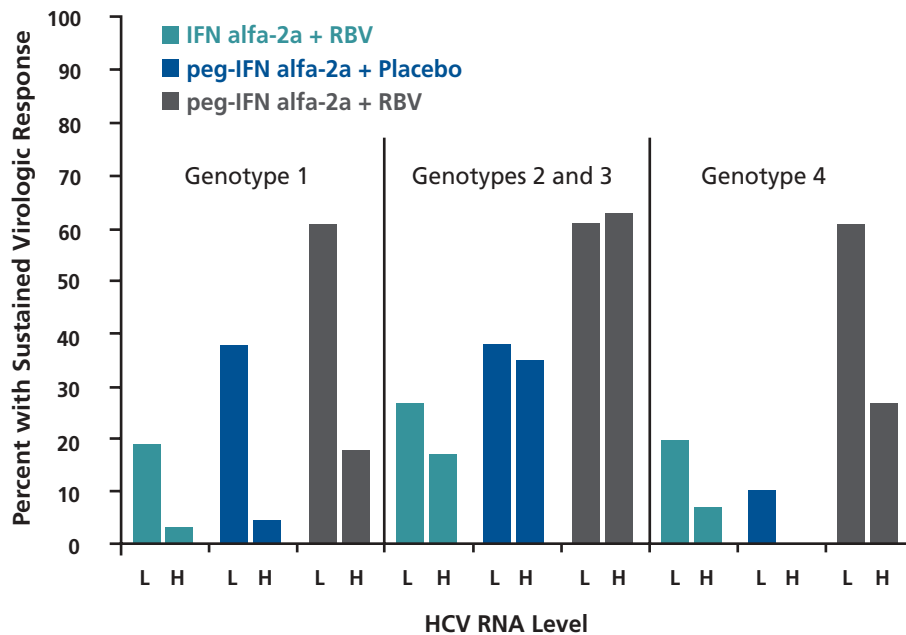ACTG indicates AIDS Clinical Trials Group.

Figure 3. Sustained virologic response (SVR) rates by treatment, hepatitis C virus (HCV) genotype, and low (L) HCV RNA level (≤800,000 IU/mL) or high (H) HCV RNA level (>800,000 IU/mL) in the APRICOT trial. IFN indicates interferon; peg-IFN, peginterferon; RBV, ribavirin. Adapted from Torriani et al, *N Engl J Med*, 2004.

ings suggest that HCV viral load bears prognostic information for treatment response in patients with genotype-1 infection.

In the RIBAVIC trial, SVR occurred in 27% of subjects in the peg-IFN alfa plus ribavirin arm versus 19% in the IFN alfa plus ribavirin arm (P < .05), including rates of 15% versus 5% (P < .05) in genotype-1 infections and 43% versus 41% in nongenotype-1 infections (Carrat et al, *JAMA*, 2004).

In all of the studies, peg-IFN alfa with ribavirin was significantly superior to standard IFN alfa with ribavirin in achieving SVR, and all studies showed that absence of early virologic response was highly predictive of absence of SVR. One potential difference among studies was the somewhat lower relapse rate among peg-IFN alfa patients in the APRICOT trial. In APRICOT, the-end-of treatment (48-week) virologic response rate was 47% and the SVR rate was 40%, compared with the rates of 41% and 27%, respectively, in the ACTG trial and 37% and 27%, respectively, in the RIBAVIC trial. Differences in virologic outcomes in the trials could be related to the use of

the dose-escalation ribavirin in the ACTG trial versus the flat doses of ribavirin 800 mg used in the other trials. It is possible that patients in the ACTG trial were receiving too little ribavirin at the beginning of treatment, which may be a period crucial to virologic response. In addition, the greater proportion of African American patients in the ACTG trial likely had an impact on response rates in genotype-1 infections. It is also likely that the greater proportions of patients with bridging fibrosis or cirrhosis in the ACTG and RIBAVIC trials were associated with reduced response rates compared with response rates in the APRICOT trial. With regard to safety and tolerability, premature discontinuation rates were 12% in ACTG A5071 and 15% to 16% in the APRICOT trial, rates comparable to those observed in treatment trials in patients without HIV infection. The discontinuation rate of 31% in the RIBAVIC trial was at least partly due to psychiatric adverse effects, particularly depression, and hyperlactatemia, with the relative risk of the latter being extremely high in patients receiving didanosine. In all of the studies, abso-

lute CD4+ cell count decreased, but CD4+ percentage increased. No loss of HIV virologic control or clinical progression of HIV disease was observed. Among patients with detectable HIV RNA at entry in the APRICOT trial, a reduction in plasma HIV RNA level (0.9 $\log_{10}$ copies/mL) was observed in those receiving peg-IFN alfa but not in those receiving standard IFN alfa. In a pharmacokinetics substudy in this trial, ribavirin did not alter intracellular concentrations of the active triphosphate forms of zidovudine or stavudine. Other data reported since completion of these trials indicate that anemia associated with either zidovudine or ribavirin is worsened when the 2 are given together.

Recommendations for treating HIV/HCV coinfection are shown in Figure 4. Among patients without clinically advanced liver disease who do not yet require antiretroviral therapy or in whom HIV infection is controlled with antiretroviral therapy, the goal is to eradicate HCV using a full 48 weeks of peg-IFN alfa/ribavirin treatment. In patients with genotype-1 infection and higher HCV viral load, early discontinuation of treatment may be considered if there is no early virologic response. In patients with bridging fibrosis or cirrhosis, the goal of treatment is to delay progression. Treatment with 24 weeks of peg-IFN alfa/ribavirin or maintenance treatment should be considered. In patients with poorly controlled HIV infection and those with low CD4+ cell counts not yet receiving antiretroviral therapy, control of HIV infection is the primary objective, and anti-HCV treatment can be initiated when HIV infection is stabilized. In patients receiving antiretroviral therapy, didanosine-containing regimens should be avoided or switched, and consideration should be given to avoiding or switching zidovudine-containing regimens. Erythropoietic treatment may be considered to avoid anemia and permit optimizing of ribavirin dosing.

A mental health liaison should be in place before peg-IFN alfa treatment is initiated to assess risk for depression, and very early use of antidepressant treatment with selective serotonin
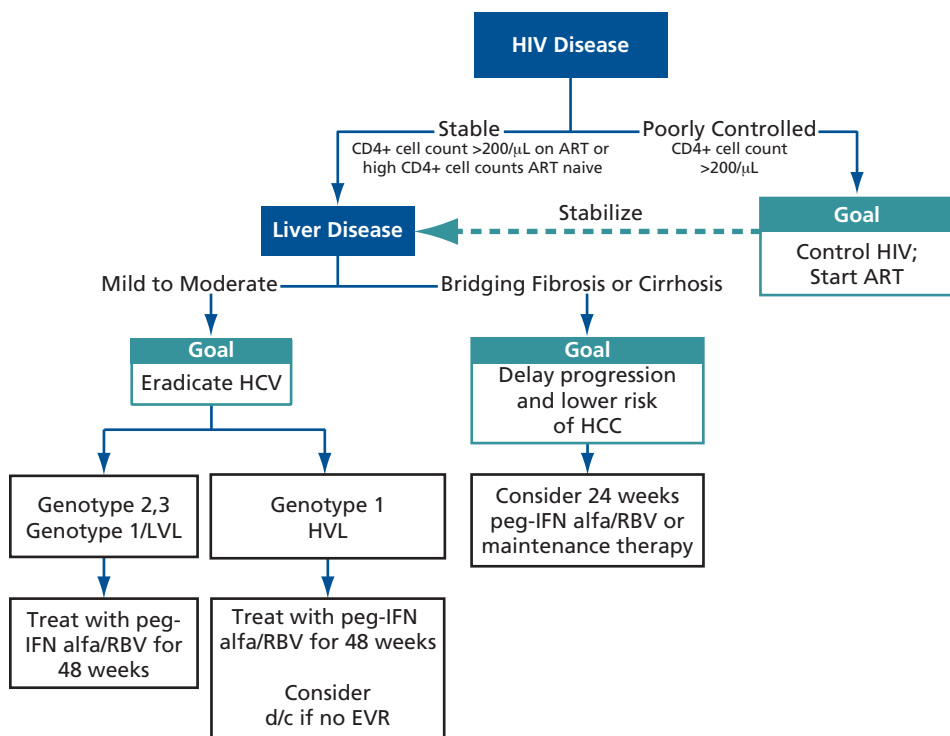
ly of virologic suppression, rather than clearance. All clinical improvements in the form of improved liver biochemistry, delay of cirrhosis and hepatocellular carcinoma, and reversal of histopathology, have been achieved with viral suppression alone in trials in HBV-monoinfected patients. Viral clearance in the form of conversion to HBV surface antigen-negative (HBsAg-) status, is a rare event in coinfected patients; conversion to HBV envelope antigen-negative (HBeAg-) status is rare even in HBV-monoinfected patients. Anti-HBV therapy can also be used to prevent HBV disease flares in patients with immune reconstitution syndrome after initiating antiretroviral therapy for HIV. In addition to the original standard of lamivudine monotherapy (100 mg/d po), approved therapies for HBV monoinfection include IFN alfa-2b (5 mIU sq qd or 10 mIU tiw for 16 weeks), peg-IFN alfa-2a (180 μg/week for 48 weeks), and the newer agents adefovir dipivoxil (10 mg/d po) and entecavir (0.5-1.0 mg/d po). Factors complicating HBV therapy in coinfected patients include the fact that lamivudine experience is nearly universal in this population, resulting in a very high rate of lamivudine resistance in HBV (approximately 90 % by 4 years) accompanied by increases in HBV viral load. The high resistance rates also raise concerns about cross-resistance with other nucleoside analogue reverse transcriptase inhibitors (nRTIs) in this population. Durable beneficial outcomes of lamivudine monotherapy treatment are rarely observed in the coinfected population, in whom treatment of lamivudine for HIV duration is often indefinite. IFN alfa is generally poorly tolerated in the coinfected population and has limited efficacy in this setting.

The nucleotide analogues adefovir and tenofovir and the nucleoside analogue entecavir exhibit activity against both wild-type HBV and the YMDD variants resistant to lamivudine. In a study in 35 lamivudine-experienced coinfected patients, adefovir 10 mg resulted in reductions of HBV DNA of $4.68 \log_{10}$ IU/mL at week 48, $5.24 \log_{10}$ IU/mL at week 96, and $5.90 \log_{10}$ IU/mL at week 144. HBeAg serocon-

Figure **4**. Management of hepatitis C virus (HCV) and HIV coinfection. ART indicates antiretroviral therapy; d/c, discontinuing therapy; EVR, early virologic response; HCC, hepatocellular carcinoma; HVL, high viral load; LVL, low viral load; peg-IFN, peginterferon; RBV, ribavirin.

reuptake inhibitors can be effective in stabilizing patients with symptoms of depression. Improvement of insulin resistance may improve response to anti-HCV therapy, since there are some data indicating that insulin resistance impairs sustained response to IFN alfa. Maintenance therapies are currently being evaluated in the ACTG 5178 trial. The ACTG 5184 trial is examining the effects of antiretroviral therapy on CD4+ and CD8+ T-cell response to HCV and assessing whether improvements in this regard result in improved SVR rates with peg-IFN alfa/ribavirin treatment. Patients include those with high CD4+ cell counts for whom initiation of antiretroviral therapy is not yet required according to current guidelines. Extended duration of treatment is being evaluated among patients in whom there is a failure to achieve early virologic responses.

Investigation of new agents for treating HCV continues, with promising early results being achieved with HCV protease inhibitors. One such agent, an inhibitor of the HCV NS3

serine protease, has been found to decrease HCV RNA by up to 4 $\log_{10}$ IU/mL in HCV-monoinfected patients.

Hepatitis B Virus and HIV Coinfection

The course of hepatitis B virus (HBV)-associated liver disease is also accelerated by coinfection with HIV. For example, comparison of outcomes among HIV-monoinfected, HBV-monoinfected, and HBV/HIV-coinfected patients in the Multicenter AIDS Cohort Study (MACS) reported in 2002 showed that liver-attributable mortality rates per 1000 –person-years of observation were 1.7 in HIV-seropositive patients, 0.8 in HBV surface antigen-positive (HBsAg+) patients, and 14.2 ($P < .0001$) in coinfected patients (Thio et al, *Lancet*, 2002). The relationship between coinfection and risk was strongest in the setting of low CD4+ cell count and with treatment in the post-antiretroviral therapy treatment era.

Goals of anti-HBV treatment in both mono- and coinfection consist primari-

version occurred in 6% of patients. Histologic improvement was observed in all 14 patients undergoing biopsy. The study dose was well tolerated; discontinuation occurred in 1 patient, due to increased serum creatinine level, with the increase resolving off treatment. A low frequency of major adefovir resistance in HBV was observed at 144 weeks; in addition, no HIV reverse transcriptase mutations were observed, a concern given the anti-HIV activity of adefovir at higher doses. These latter findings provide some hope that long-term use with this agent may be possible without prohibitive resistance (Benhamou, *J Hepatol*, 2006; Delaugerre et al, *Antimicrob Agents Chemother*, 2002). However, recent data from HBV monoinfected patients indicate that primary adefovir resistance rates increase to 18% at year 4 and to 28% at year 5 (Hadziyannis et al, AASLD 2005).

An analysis of outcome in 10 HBV/HIV-coinfected patients showed that tenofovir 300 mg/day added to pre-existing antiretroviral therapy for HIV resulted in a 4.9 $\log_{10}$ IU/mL decrease in HBV DNA at week 24. Another analysis in 11 antiretroviral-naive coinfected patients showed that the addition of tenofovir 300 mg to the backbone of lamivudine/efavirenz produced a 4.7-$\log_{10}$ IU/mL decrease in HBV DNA at 48 weeks in 5 patients, compared with a 3.0-$\log_{10}$ IU/mL decrease and development of YMDD mutants in 4 of 6 patients in whom stavudine was combined with lamivudine/efavirenz. The ACTG 5127 trial showed that tenofovir was noninferior to adefovir in the treatment of lamivudine-resistant HBV in coinfected patients, with HBV DNA being reduced by 4.4 $\log_{10}$ IU/mL in the tenofovir group and 3.2 $\log_{10}$ IU/mL in the adefovir group. In a study in France in a coinfected population, 80% of whom had received lamivudine, tenofovir reduced HBV DNA by 4.56 $\log_{10}$ IU/mL in 52 HBeAg+ patients, with 30% having undetectable levels (<200 IU/mL), and by 2.53 $\log_{10}$ IU/mL in 13 HBeAg-patients, with 82% having undetectable levels (Dore et al, *J Infect Dis*,

2004; Peters et al, CROI 2005; Benhamou et al, *Hepatology,* 2006).

Entecavir is approved for treatment of HBeAg+, HBeAg-, and lamivudine-resistant HBV infection, and has no activity against HIV reverse transcriptase. In a study in patients with HBV monoinfection, entecavir 0.5 mg reduced HBV DNA by 6.98 $\log_{10}$ IU/mL at 48 weeks, compared with a 5.48-$\log_{10}$ IU/mL reduction with lamivudine 100 mg. In a randomized trial in lamivudine-experienced coinfected patients, the addition of entecavir 1.0 mg to lamivudine produced a 3.66 $\log_{10}$ IU/mL decrease in HBV DNA at week 24 compared with no change in patients with placebo added to lamivudine. There is a lower threshold for entecavir resistance in patients with pre-existing lamivudine resistance; in the current study, mutations associated with entecavir resistance were found in 2 (4%) of 48 patients but no phenotypic evidence of resistance was observed at 48 weeks (Pessoa et al, CROI, 2005; Colonno et al, CROI, 2006. See also Chang et al, *N Engl J Med*, 2006 and Lai et al, *N Engl J Med*, 2006).

Management of HBV/HIV coinfection should include assessment of HBV status in all patients prior to the initiation of antiretroviral therapy for HIV. For patients on antiretroviral therapy for HIV that includes lamivudine, a reasonable approach is the addition of an anti-HBV agent with robust activity, such as tenofovir 300 mg. In patients who have not started antiretroviral therapy for HIV and who have replicative HBV, institution of antiretroviral therapy containing tenofovir plus lamivudine or emtricitabine is a recommended approach to provide coverage for both HBV and HIV. For those in whom antiretroviral therapy for HIV can be deferred, use of agents without crossover anti-HIV activity or that pose less risk for the emergence of HIV resistance is preferable, with adefovir 10 mg and entecavir 1 mg being reasonable choices. Development of effective combination therapies will be necessary to minimize development of resistance during longer-term therapy.

Suggested Reading

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