Growing Importance of Liver Disease in HIV-Infected Persons

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Liver disease is a growing problem in HIV-infected persons. In those who are able to take antiretroviral therapy, the forms of liver disease have changed and their relative importance has increased. This review focuses on liver disease in HIV-infected persons, caused by hepatitis C virus, hepatitis B virus, or treatment of HIV infection. (Hepatology 2006;43: S221-S229.)

Types of Liver Disease and Public Health Importance

Although human immunodeficiency virus-1 (HIV)-infected individuals contract the same forms of liver disease as persons without HIV, there are important differences in the prevalence and severity of some types (Table 1). For example, because of shared transmission routes, in HIV-infected persons a high prevalence of chronic hepatitis caused by hepatitis C virus (HCV) or hepatitis B virus (HBV) is seen.1,2 Some so-called opportunistic hepatic infections, such as cryptosporidial cholangitis, occur almost exclusively in persons with severe HIV-related immunosuppression.3 In addition, some drugs used only to treat HIV infection can affect the liver. These differences are important to remember when evaluating liver disease in an HIV-infected person.

The relative importance of liver disease has been significantly affected by the availability of potent antiretroviral therapies. In economically developed countries, effective antiretroviral therapies were first available for widespread use in the mid 1990s, and their use dramatically reduced HIV-related mortality (Fig. 1).4,5 The proportion of mortality attributed to liver disease increased sharply, chiefly because of the reduced overall mortality rate.5 By examining death certificate databases, the U.S. Centers for Disease Control and Prevention estimates that liver disease now accounts for 10% to 15% of deaths in HIV-infected persons in the United States.5 However, this proportion is probably an underestimate attributable to limitations of these forms of data, and substantially higher estimates have been reported from individual centers.6

The types of liver disease also have changed in HIV-infected persons receiving effective antiretroviral therapy. Before effective antiretroviral use, the liver was one of many organs in which opportunistic infections and neoplasms were detected. In one series of 501 HIV-infected persons who had liver biopsies performed in New York between 1984 and 1992, granulomatous hepatitis (mostly due to mycobacteria) was the most common finding (37.2%), followed by nonspecific results (35.7%) and chronic viral hepatitis/cirrhosis (18.2%).7 One characteristic syndrome is HIV-related cholangitis, which refers to a syndrome of right upper quadrant pain associated with an elevated alkaline phosphatase that typically occurs in persons with a CD4+ lymphocyte count < 200/mm3.3 Intrahepatic and extrahepatic bile ducts are dilated. The infectious causes include Cryptosporidium parvum, cytomegalovirus, microsporidia, and Mycobacterium avium complex. Fortunately, antiretroviral treatment has both reduced the incidence of cholangitis and improved the prognosis.8 Now, most liver disease in HIV-infected persons is caused by chronic viral hepatitis.

Chronic Hepatitis C

Epidemiology and Natural History. Many HIV-infected persons have chronic hepatitis C. In the United States, Europe, and Australia, approximately one fourth of HIV-infected persons also has chronic hepatitis C.2 However, the likelihood of HIV/HCV coinfection varies substantially according to the route of HIV infection (Fig. 2). More than 60% of persons who acquired HIV infection from injection drug use also have HCV infection, which typically was acquired years earlier.9 In contrast, the prevalence of HCV infection is typically less than 5%
in men who have acquired HIV by having intercourse with other men.\textsuperscript{10}

HIV infection adversely affects all stages in the natural history of hepatitis C. HIV infection reduces the likelihood of spontaneous recovery from HCV infection.\textsuperscript{11} In one study of injection drug users in Baltimore, spontaneous clearance of HCV infection occurred 5.15 times more often in persons without HIV-infection than among those who were HIV-infected, a risk that was inversely correlated with the CD4/H11001 lymphocyte count.\textsuperscript{11} HIV infection also increases the serum HCV RNA level and the risk of cirrhosis.\textsuperscript{12,13} The greatest risk of liver disease attributed to HIV infection has been reported in cohorts of persons with hemophilia.\textsuperscript{13} In one large hemophilia cohort, the 16-year cumulative risk of liver failure was 14.0\% in HIV/HCV-coinfected persons compared with 2.6\% in those with just HCV infection.\textsuperscript{13} In a meta-analysis, the average risk of cirrhosis was estimated to be twofold higher in HIV-infected persons, compared with HCV-infected persons without HIV.\textsuperscript{14}

Pathogenesis. Exactly how HIV infection affects the natural history of hepatitis C is unknown (and probably multi-factorial). Although HCV replication in monocytes and lymphocytes has been inferred, robust replication in more than a minority of cells is unlikely. That coupled with the fact that HIV only infects approximately 1\% of CD4/H11001 lymphocytes makes direct viral interactions unlikely. HIV preferentially infects activated CD4/H11001 T cells and affects the function and number of uninfected CD4/H11001 T cells that orchestrate adaptive immune responses and are clearly necessary for spontaneous clearance of HCV infection.\textsuperscript{15} Thus, it is not surprising that HIV infection reduces the likelihood of spontaneous HCV clearance. HIV infection also directs the immune response toward a Th2 bias, which has been associated with accelerated hepatic fibrosis.\textsuperscript{16} Nonetheless, animal and in vitro model systems of HIV/HCV coinfection do not exist, making it difficult to dissect the actual biological mechanisms.

Treatment. The accelerated course of liver disease associated with HIV infection underscores the importance of HCV treatment. Although acute HCV infection is uncommonly detected in HIV-infected persons, interferon alfa treatment appears to be more effective at this early stage, as in persons without HIV.\textsuperscript{17} Also similar to persons without HIV infection, the best available treatment of chronic hepatitis C in HIV-infected persons is the combination of peginterferon and ribavirin (RBV), and peginterferon alfa 2a and RBV has been approved for use in HIV/HCV-coinfected persons in Europe and the United States (Table 2).\textsuperscript{18,19} That peginterferon and RBV is the best available treatment was shown in 2004 by 4 “pivotal” studies in which HIV/HCV-coinfected patients
were randomized to receive 48 weeks of peginterferon and RBV or standard interferon and RBV.\textsuperscript{20–23} Persons enrolling in these studies had to have well-controlled HIV infection; only the AIDS Pegasys Ribavirin International Coinfection Trial (APRICOT) study enrolled subjects with CD4+ lymphocyte counts below 200/mm\textsuperscript{3}, and they represented just 6% of the peginterferon/RBV arm (and all had HIV RNA levels < 5,000 copies/mL).\textsuperscript{21}

Important differences also exist in the patients enrolled in these studies. The severity of baseline liver disease was higher in patients enrolled in the French Agence Nationale de Recherches HCO\textsubscript{2} study (RIBAVIC): 40% had bridging fibrosis or cirrhosis compared with only 16% in APRICOT and 10% in the AIDS Clinical Trials Group study (ACTG 5071). HCV infections were genotype 1 in 77% of those randomized to peginterferon/RBV in ACTG 5071, 61% in APRICOT, and only 55% in the Barcelona study. These and other more nuanced differences are important to consider when comparing studies.

Virological response to peginterferon and ribavirin varied substantially between the studies, and within studies, according to well-known response predictors. Overall sustained virological response (SVR) rates varied from 44% to 29%.\textsuperscript{20–23} Genotype 1 SVR rates ranged from 29% (APRICOT) to 14% (ACTG 5071), whereas the Barcelona study reported a 38% SVR rate for those with either genotype 1 or 4. As in studies of persons without HIV infection, SVR rates for HCV genotypes other than 1 were generally higher: 62% (APRICOT), 73% (ACTG 5071), 44% (RIBAVIC), and 53% (Barcelona study).

SVR rates generally were lower in persons with higher pretreatment HCV RNA levels. In the APRICOT study, SVR rates were more than 60% in genotype 1–infected persons who were randomized to peginterferon alfa and ribavirin for 48 weeks and had a HCV RNA level $\leq$800,000 IU/mL compared with 18% for genotype 1–infected persons with higher HCV RNA levels and the same treatment.\textsuperscript{21} Interestingly, the SVR rate in APRICOT for HIV/HCV-coinfected persons with genotype 1 infection and HCV RNA level $\leq$800,000 IU/mL (61%) is similar to that reported in another study of HIV-uninfected persons with the same genotype, HCV RNA level threshold, and therapy (55%).\textsuperscript{21,24}

As in persons without HIV infection, there is a high negative predictive value of failing to suppress HCV RNA on treatment. Fewer than 2% of persons in these 4 pivotal studies whose HCV RNA was still detectable 12 weeks after starting treatment and was not reduced by at least 2 logs went on to SVR.\textsuperscript{20–23}

Limited data are available regarding histological responses in HIV/HCV-coinfected persons, and almost no studies examine at long-term clinical outcomes. In ACTG 5071, 24 weeks into therapy, liver biopsies were requested for 94 persons whose HCV RNA was still detectable, and 71 agreed.\textsuperscript{22} A histological response, defined as a ≥2- or greater point reduction in histological activity, was observed in 35% of these virological non-responders. Interestingly, the magnitude of the virological decline was not greater in those with histological improvements compared with those with less or no improvement. In the same study, liver biopsies were obtained on 24 of the 39 persons with viral responses at week 24, and 52% had histological improvement. In the RIBAVIC study, a second posttreatment liver biopsy assessment was available for 205 (50%) of those studied.\textsuperscript{22} A significant difference in the overall improvement in liver activity was seen in the peginterferon/RBV group compared with the standard interferon/RBV group, but the improvement in liver histology was only seen in persons who achieved SVR.

Higher SVR rates possibly can be achieved in HIV-infected persons by longer therapy or by higher doses of peginterferon or RBV. In most of the published literature on HIV/HCV-coinfected patients, the RBV dose was 800 mg. This dosing was meant to avoid anemia, which is a

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### Table 2. Four Pivotal Studies of Treatment of Chronic Hepatitis C in HIV-Infected Persons Published in 2004

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>APRICOT</th>
<th>ACTG 5071</th>
<th>RIBAVIC</th>
<th>Barcelona</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number enrolled</td>
<td>868</td>
<td>133</td>
<td>412</td>
<td>95</td>
</tr>
<tr>
<td>Peginterferon</td>
<td>2a</td>
<td>2a</td>
<td>2b</td>
<td>2b</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>800 mg</td>
<td>600 up to 1g</td>
<td>800 mg</td>
<td>0.8 g, 1 g, 1.2 g³</td>
</tr>
<tr>
<td>HIV and CD4+ status</td>
<td>$&gt;200$/mm\textsuperscript{3} or 100-200$/mm\textsuperscript{3} and HIV RNA $&lt;5,000$ c/mL</td>
<td>$&gt;100$/mm\textsuperscript{3} and HIV RNA $&lt;10,000$ c/mL</td>
<td>$&gt;200$/mm\textsuperscript{3}</td>
<td>$&gt;250$/mm\textsuperscript{3} and HIV RNA $&lt;10,000$ c/mL</td>
</tr>
<tr>
<td>ALT</td>
<td>*Elevated’ 2 times</td>
<td>NA</td>
<td>NA</td>
<td>1.5 ULN</td>
</tr>
<tr>
<td>% Genotype 1†</td>
<td>60</td>
<td>77</td>
<td>48</td>
<td>55</td>
</tr>
<tr>
<td>% bridging fibrosis or cirrhosis‡</td>
<td>12</td>
<td>11 (cirrhosis)</td>
<td>39</td>
<td>29</td>
</tr>
<tr>
<td>Genotype 1 peg-RBV SVR rate$^\dagger$</td>
<td>29%</td>
<td>14%</td>
<td>17% (1 &amp; 4)</td>
<td>38% (1 &amp; 4)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALT, alanine aminotransferase; ULN, upper limit of normal; c/mL, copies/mL; NA, not applicable.

*Based on body weight <65, 65–75, >75 kg.

†Taken from peginterferon and ribavirin arm; cirrhosis defined as F4–6 MHAI or F3–4 metavir and Scheurer.

‡Refers to the sustained virological response (SVR) rate for HIV-infected persons taking peginterferon and ribavirin. Rates are for patients with genotype 1 HCV infection except for the RIBAVIC and Barcelona studies, which grouped genotypes 1 and 4.
greater problem in HIV-infected persons, especially those taking AZT. Higher RBV doses appeared to be well tolerated in the Barcelona study in which RBV was given by body weight as follows (per day): 800 mg for <60 kg; 1 g for 60 to 75 kg; and 1.2 g for >75 kg. Because in HIV-negative persons with genotype 1 HCV infection higher SVR rates are achieved with 1.0/1.2 g RBV (≤75 kg/>75 kg) compared with 800 mg, many authorities recommend 1.0/1.2 g RBV dosing for HIV/HCV-coinfected persons as well.

In HIV-negative persons, SVR rates are the same for genotypes 2 and 3 HCV infections if they are treated for 24 weeks instead of 48. However, analogous studies have not been reported for HIV-infected persons, and delayed virological responses have been attributed to HIV infection. Thus, studies emphasizing alternative dosing intervals are also needed for genotype 2 and 3 HCV infection before shorter regimens can be recommended in HIV-infected persons.

In addition to the adverse effects of peginterferon alfa and RBV that occur in persons without HIV, there are additional safety concerns in treatment of HIV/HCV-coinfected persons. Ribavirin-associated anemia may be a greater problem in persons coinfected with HIV than in those with mono-infection, a problem that is compounded by concomitant zidovudine (AZT) use. Ribavirin inhibits inosine-5-monophosphate dehydrogenase and consequently raises ddI anti-HIV activity and toxic-ity. Because symptomatic, even fatal, hyperlactatemia has been reported in some coinfected persons receiving ribavirin and ddI, if equivalent therapeutic options are available, changing ddI to another drug before starting ribavirin is advisable. Although *in vitro* ribavirin may antagonize 2’, 3’-dideoxynucleotides, such as zidovudine and stavudine, significant clinical interactions have not been shown. Although interferon alfa therapy is associated with a dose-related reduction in white blood cell count and absolute CD4 count, the percentage of CD4 cells remains essentially unchanged, and its use is not associated with the development of opportunistic infections. Liver failure has also occurred in HIV/HCV-coinfected persons on peginterferon alfa and ribavirin therapy, especially when treatment is started in persons who already have Child’s B cirrhosis.

Liver transplantation is the only treatment available for HIV/HCV-coinfected persons with decompensated cirrhosis (that is, Child’s B or C cirrhosis). (See recent review by Neff et al.) Early success with liver transplants of HIV/HCV-coinfected persons has been reported in selected centers. However, the availability of liver transplants for HIV/HCV-coinfected persons in most areas is low, and questions remain about the long-term success.

**Prevention.** The chief means of reducing the impact of HIV infection on chronic hepatitis C is to prevent HCV infection by reducing HCV and HIV transmission. Published guidelines for reducing transmission by perinatal, sexual, occupational, and injection drug use exposures are available. Unfortunately, vaccines are not available for prevention of either HIV or HCV infection.

**Chronic Hepatitis B**

**Epidemiology and Natural History.** Worldwide, more than 300 million persons have chronic hepatitis B, and more than 40 million have HIV infection. In the United States and Europe, approximately 8% of HIV-infected persons have chronic hepatitis B. Substantially more HIV-infected persons (50%-90%) have antibody to HBV core protein (anti-HBc) without hepatitis B surface antigen, and HBV DNA has been detected in 10% to 50% of these (so-called occult hepatitis B). The prevalence of chronic HBV is higher in HIV-infected persons in some areas in sub-Saharan Africa and Asia. No reliable estimates are available of the number of persons dually infected with HBV and HIV worldwide.

HIV infection adversely affects the natural history of HBV. HIV infection is associated with a greater prevalence of chronic HBV, probably a result of both reducing spontaneous hepatitis B surface antigen clearance as well as causing recrudescence of previously controlled infection. In some studies, HIV-infected persons with chronic hepatitis B have had less necroinflammatory activity than those without HIV. However, several large studies indicate that HIV infection accelerates progression of chronic hepatitis B. In the Multicenter AIDS Cohort Study, the incidence of liver-related mortality was 17-fold higher in persons with chronic HBV and HIV infection compared with HIV-uninfected persons with chronic hepatitis B. In the HIV-infected EuroSIDA cohort, the incidences of all-cause and liver-related mortalities were greater in HIV-infected persons with chronic HBV compared with hepatitis B surface antigen negative controls.

Worldwide, most HIV-infected persons still die rapidly of wasting, tuberculosis, and other opportunistic infections. As widespread efforts to treat HIV and tuberculosis are implemented worldwide, HBV-related mortality likely will increase sharply, as has occurred with HIV/HCV-coinfected persons in the West. However, this outcome does not need to occur, because some antiretroviral medications are also effective chronic HBV therapies.

**Pathogenesis.** As with HCV infection, little is known about how HIV affects the pathogenesis of chronic hep-
atitis B. Because HBV establishes latent infection that in many adults is suppressed by ongoing T cell responses, HIV-related immunosuppression may even play a greater role in the pathogenesis than for HCV, for which latency has not been shown.39 In one study of persons taking anti-HBV therapy, CD4+ (but not CD8+) T cell responses were reduced in HIV-infected persons compared with those without HIV.40 In another small study, HBV-specific T cell responses were restored in some persons by antiretroviral therapy.41 Antiretroviral-related restoration of T cell responses to HBV may explain some cases of hepatitis that occur after initiation of antiretroviral therapy (immune reconstitution syndrome).42

**Treatment.** Although general guidelines have been published, the optimal treatment of chronic hepatitis B in HIV-infected persons has not been established.19,32 Compared with persons without HIV infection, treatment of chronic hepatitis B in someone dually infected is complicated by the fact that both viruses are inhibited by some compounds including lamivudine (3TC or Epivir, Glaxo SmithKline, Research Triangle Park, NC), emtricitabine (FTC or Emtriva, Gilead, Foster City, CA), and tenofovir disoproxil fumerate (tenofovir DF or Viread, Gilead) (Table 3). One implication of dual activity is that when these antiretroviral therapies are stopped in HIV/HBV-coinfected persons, there can be clinically significant flares of hepatitis unless effective alternative anti-HBV therapies are substituted. Accordingly, HBV-related concerns have been added to the regulatory warnings for antiretroviral drugs active against both HIV and HBV. Another implication of dual activity of some compounds is cross-resistance. For example, in persons in whom lamivudine was used for treatment of HIV, the incidence of resistance is approximately 25% per year.43 Consequently, in many clinic populations where lamivudine was the only HBV-active antiretroviral compound used for years, most HBV is resistant to lamivudine (and the chemically related compound, emtricitabine). Likewise, drugs that are active against both viruses cannot be used alone to treat chronic hepatitis B, because they will select for resistant HIV.

**Treating Just Chronic Hepatitis B.** Currently, several options are available for treatment of chronic hepatitis B in HIV-infected persons, and the overall strategy chiefly depends on whether treatment of HIV infection is also anticipated.19,32 When there is no intention to treat HIV infection, then medications with dual activity cannot be used, leaving interferon alfa, adefovir dipivoxil (Hepsera, Gilead), and entecavir (Baraclude, Bristol-Myers Squibb, New York, NY) as options. Interferon alfa has not been well-studied in HIV/HBV-coinfected persons, but its efficacy appears low.44 We are aware of a cumulative total published experience of 98 HIV/HBV-coinfected persons (all before effective antiretroviral therapy) treated with interferon alfa with an overall hepatitis B e

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**Table 3. Approach to Treatment of Chronic Hepatitis B in HIV-Infected Persons**

<table>
<thead>
<tr>
<th>Treatment of HBV and HIV</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Truvada</td>
<td>Probably optimal because of potency of tenofovir DF for both HBV and HIV and added activity of FTC</td>
</tr>
<tr>
<td>Tenofovir DF</td>
<td>Well tolerated and potent against both HIV and HBV; active against lamivudine-resistant HBV</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Very well tolerated but reasonably potent against HBV but low HBV resistance barrier; incidence ~25/year.</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>Similar to lamivudine in potency, tolerability, and propensity to select for resistant HBV</td>
</tr>
<tr>
<td>Peginterferon alfa</td>
<td>Probably has some activity versus HIV; likelihood of durable HBV response in HIV-infected person low, but limited data</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment of HBV, not HIV</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entecavir</td>
<td>No activity against HIV (thus, no selection of resistant HIV mutations); potent suppressor of HBV; reduced potency in lamivudine-resistant HBV requires 1.0-mg dose.</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>Approved for treatment of chronic hepatitis B in persons without HIV; long-term data on 35 patients with HIV indicates efficacy. Cross-resistance with tenofovir a theoretical concern.</td>
</tr>
<tr>
<td>Peginterferon alfa</td>
<td>In persons without HIV infection, better than standard interferon alfa or lamivudine. Ability to effect durable response in HIV-infected persons remains unproven.</td>
</tr>
</tbody>
</table>

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Fig. 3. Liver mortality rate (MR) per 1,000 person-years (PY) according to HIV and hepatitis B surface antigen status among members of the Multicenter AIDS Cohort Study.1
antigen response rate of 14.3%.\textsuperscript{45,46} The pegylated form of interferon alfa (Peg-Intron, Kenilworth, NJ; or Pegasis, Hoffman-LaRoche, Nutley, NJ) appears to be more effective than standard interferon alfa for treatment of chronic hepatitis B in HIV-uninfected persons\textsuperscript{47}; however, no published data are available on peginterferon in persons coinfected with HBV and HIV.

Adefovir dipivoxil is active against lamivudine-resistant HBV and has suppressed HBV DNA in 35 HBV/HIV-coinfected persons treated for 192 weeks.\textsuperscript{48} This study and the experience with HIV-uninfected persons indicate that the incidence of clinically evident HBV resistance to adefovir dipivoxil is substantially lower than for lamivudine.\textsuperscript{49} Although use of adefovir dipivoxil in coinfected persons poses a theoretical risk of HIV developing cross-resistance to tenofovir DF (since adefovir dipivoxil is active against HIV at higher doses), cross-resistance has not been detected in the 35-person long-term study.

Entecavir is the only drug specifically licensed in the United States for the treatment of chronic hepatitis B in both HIV-infected and -uninfected persons and does not have activity against the HIV reverse transcriptase. In a randomized controlled trial of 68 HIV/HBV-coinfected persons on lamivudine, 24 weeks of entecavir resulted in a 3.65 log copies/mL decrease in HBV DNA, which is similar to that reported for HIV-uninfected persons (package insert and Pelleos et al.\textsuperscript{50}). In clinical trials, entecavir resistance mutations were detected after 48 weeks in 7% of HIV-uninfected persons with lamivudine-resistant HBV; however, entecavir resistance occurs rarely in nucleoside-naïve patients. Nonetheless, given the high rate of lamivudine-resistant HBV in HIV-coinfected persons, one must use the higher 1.0-mg dose unless prior lamivudine use can be confidently excluded.

\textbf{Treating Both HIV and HBV.} When treatment of both HIV and HBV is planned, it is possible to exploit the dual activity of certain compounds. The leading candidate is tenofovir DF, which is approved by the FDA for treatment of HIV. \textit{In vitro}, tenofovir DF has at least equivalent activity to adefovir dipivoxil with a similar median inhibitory concentration (IC\textsubscript{50}).\textsuperscript{51} However, at the doses typically given (300 mg tenofovir DF versus 10 mg adefovir dipivoxil), tenofovir DF is more potent and is active against lamivudine-resistant HBV.\textsuperscript{52,53} In an AIDS Clinical Trial Group study in which 27 and 25 persons received tenofovir DF and adefovir dipivoxil, respectively, there was a trend toward superiority of tenofovir DF, with larger declines in HBV DNA compared with adefovir dipivoxil (5.74 log copies/mL vs. 4.03 log copies/mL)\textsuperscript{52}. In one study of persons with lamivudine-resistant HBV infection, tenofovir DF was given to 35 and adefovir dipivoxil to 18.\textsuperscript{53} The tenofovir-treated group had a more rapid decline in HBV DNA and greater hepatitis B e antigen loss. In addition, multiple retrospective studies have been presented at meetings with the largest following 107 HIV/HBV-coinfected persons who received tenofovir DF for a median of 10 months (range 2-24 months).\textsuperscript{54} Significant side effects are uncommonly reported in tenofovir DF trials, but there are concerns about the long-term nephrotoxicity of tenofovir DF that will need to be monitored.

Although both lamivudine and emtricitabine select for resistant HBV at rates that diminish their utility as the sole agent for treatment of chronic hepatitis B, they are attractive adjuncts to tenofovir DF. Recently, emtricitabine in combination with tenofovir DF (Truvada, Gilead) was approved for the treatment of HIV infection, and this formulation pairs 2 agents with potent anti-HBV activity.
Based on available data, this compound is probably the optimal choice for treatment of chronic HBV and HIV.19

Prevention. The most important way to reduce the impact of HIV on chronic hepatitis B is to prevent HBV infection by vaccination. According to published guidelines, all HIV-infected persons should be screened for HBV infection, and those who are susceptible should be vaccinated.32 Although the recombinant HBV vaccine is safe in HIV-infected persons, its immunogenicity is reduced, especially in persons with low CD4+ lymphocyte counts. This consideration underscores the importance of providing the vaccination as soon as possible. In addition, in persons with very low CD4+ lymphocyte counts (e.g., <100/mm³), it is reasonable to vaccinate after immune responses are optimized by effective antiretroviral therapy.

Antiretroviral-Associated Liver Disease

Epidemiology. Approximately one of every eight persons taking a new antiretroviral regimen develops hepatotoxicity.55 Although antiretroviral-associated hepatotoxicity can cause liver failure and death, it usually refers to asymptomatic >5-fold elevations in aminotransferases.56 This type of antiretroviral hepatotoxicity occurs more frequently among patients with chronic viral hepatitis (HCV or HBV coinfection) (Fig. 4).55,57 Nonetheless, most HIV/HCV- or HIV/HBV-coinfected patients tolerate antiretroviral therapy. In one large cohort, 88% of HCV-coinfected patients did not experience significant hepatotoxicity with new antiretroviral therapies, and no irreversible outcomes were observed.55

In addition to the >5-fold asymptomatic elevations in aminotransferases associated with antiretroviral therapy, several clinically distinct syndromes should be appreciated (Table 4). One common condition is hyperbilirubinemia associated with particular medications, especially atazanavir and indinavir. In fact, 49% of persons taking atazanavir had a ≥2.6-fold increase in total bilirubin, chiefly indirect bilirubin, and jaundice is noted in approximately 10%. The mechanism is believed to be disruption in bilirubin transport that is clinically insignificant. Although there is no need to stop therapy, one must be aware of the syndrome and reassure the patient accordingly.

Another important antiretroviral-related syndrome is the hypersensitivity reaction. Most characteristic of the compound abacavir, this syndrome includes systemic symptoms (fever, fatigue, malaise), rash, and elevated liver enzymes. Recognition of this syndrome is important because it can be fatal, especially if there is re-exposure. Nevirapine also can cause a systemic reaction with rash, fever, and severe hepatitis that can be fatal.58 This syndrome occurs more often in women with high CD4 lymphocyte counts.

Antiretroviral agents can also cause mitochondrial toxicity that can manifest with steatosis, and in some instances, symptomatic lactic acidosis syndrome.59,60 Although the syndrome has been reported with several nucleoside reverse transcriptase inhibitors, stavudine (d4T) use is strongly associated.61 Typically, little apparent hepatocellular damage occurs. In symptomatic cases, discontinuation of the medications is essential. Although antiretroviral drugs also probably contribute to asymptomatic chronic steatosis, whether long-term complications of asymptomatic steatosis occur is unknown, especially when it is mild/moderate (e.g., <30% of field).62

Pathogenesis. The mechanisms of enhanced drug-induced hepatotoxicity among HIV/HCV-coinfected patients are unknown and probably vary according to the clinical syndrome. Liver enzyme elevations have been attributed to HCV-specific immune reconstitution or increased susceptibility to mitochondrial dysfunction.53,64 Similar mechanisms are possible for HIV/HBV-coinfected persons, in whom one must also consider loss of suppression of HBV if the new regimen does not include at least one HBV-active drug (and this type of switch should be avoided).65 In persons without symptoms, continuation of antiretroviral therapy in persons with antiretroviral-associated hepatotoxicity is well tolerated.57

At the population (or clinic) level, the net effect of antiretroviral therapy on the liver is controversial. Antiretroviral therapy can cause long-term elevations of liver enzymes (and probably steatosis), and the incidence of this type of hepatotoxicity is increased in persons with chronic viral hepatitis in whom there is already an increased risk of cirrhosis, compared with HIV-infected persons without chronic viral hepatitis. Conversely, antiretroviral therapy can markedly reduce HIV replication, restore immune responses, and eliminate the risk of opportunistic infections. Thus, antiretroviral therapy may
attenuate the increased risk of liver disease associated with HIV infection, especially in those coinfected with HCV or HBV. Interestingly, evidence to support this hypothesis has been found in two recent studies.66,67 If confirmed by prospective research, the presence of chronic viral hepatitis may be another indication for the use of antiretroviral agents in HIV-infected persons.

References


