Liver Disease in the HIV–Infected Individual

JENNIFER C. PRICE* and CHLOE L. THIO†

*Division of Gastroenterology and Hepatology and †Division of Infectious Diseases, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland

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Since the advent of effective antiretroviral therapy (ART) for human immunodeficiency virus-1 (HIV), there has been a substantial decrease in deaths related to acquired immunodeficiency syndrome (AIDS). However, in the ART era, liver disease is now the most common non-AIDS–related cause of death among HIV-infected patients, accounting for 14%–18% of all deaths in this population and almost half of deaths among hospitalized HIV-infected patients. Just as the burden of non-AIDS morbidity and mortality has changed in the ART era, the types of liver disease the clinician is likely to encounter among these patients have changed as well. This review will discuss the causes of liver disease in the HIV-infected population in the ART era, including chronic hepatitis C virus, chronic hepatitis B virus, medication-related hepatotoxicity, alcohol abuse, nonalcoholic fatty liver disease, and AIDS-related liver diseases.

Keywords: Human Immunodeficiency Virus; Liver Disease; Hepatitis C Virus; Hepatitis B Virus.

Managing liver disease is an increasingly important component to the care of individuals infected with human immunodeficiency virus-1 (HIV). Since the advent of effective antiretroviral therapy (ART) for HIV, there has been a substantial decrease in deaths related to acquired immunodeficiency syndrome (AIDS). However, liver disease has emerged as the most common non-AIDS–related cause of death among HIV-infected patients, accounting for 14%–18% of all deaths. In some series, nearly half of deaths among hospitalized HIV-infected patients in the ART era have been attributed to liver disease.

Just as the burden of non-AIDS morbidity and mortality has changed in the ART era, the types of liver disease the clinician is likely to encounter among these patients have also changed. Before ART, the most common causes of liver dysfunction in HIV-infected patients were opportunistic infections, including cytomegalovirus (CMV) and mycobacterial infections, and AIDS-related neoplasms such as lymphoma and Kaposi’s sarcoma (KS). Since the ART era, however, the spectrum of liver disease among HIV-infected individuals has shifted to concomitant infection with chronic HCV, chronic HBV, medication-related hepatotoxicity, alcohol abuse, and nonalcoholic fatty liver disease (NAFLD) (Table 1). This review will focus on the major causes of liver disease in the HIV-infected population in the ART era and will briefly review liver disease in persons with AIDS.

Viral Hepatitis

Hepatitis C Virus

Most liver disease among HIV-infected individuals is secondary to coinfection with HCV and/or HBV. Because of shared risk factors, coinfection with HCV and HIV is common. Reported prevalence rates of HIV-HCV coinfection vary depending on the route of HIV transmission, from 10% among those with high-risk sexual behavior to 90% with injection drug use. Overall, approximately 30% of HIV-infected individuals in the United States and Europe are coinfected with HCV.

HIV infection alters the natural history of HCV in several ways. HIV-infected patients who are acutely infected with HCV are half as likely as HIV-uninfected individuals to clear HCV viremia. Coinfected individuals also have higher HCV RNA levels, accelerated progression to hepatic fibrosis, an increased risk of developing cirrhosis, and a higher risk of decompensated liver disease once cirrhotic. In a meta-analysis of 8 studies, HIV-HCV coinfected subjects had a 2-fold increased risk of histologic cirrhosis and 5-fold increased risk of decompensated liver disease compared with HCV-monoinfected individuals. Studies of the role of HCV on the natural history of HIV have been conflicting. However, in a recent analysis of 1428 HIV-HCV coinfected individuals treated for HCV, patients who achieved sustained virologic response had lower rates of HIV progression and nonliver mortality after adjusting for fibrosis, Centers for Disease Control and Prevention clinical category, and nadir CD4 count.

Given both the high prevalence of HCV among the HIV-infected population and the impact of HIV on HCV-related liver disease, understanding the pathogenesis and clinical implications of this dual viral infection is crucial.
should therefore be considered at risk for acquiring HCV. Because there is no available vaccine to prevent HCV infection, noninvasive methods to determine liver disease are being actively investigated and are becoming a viable alternative to liver biopsy. A variety of laboratory markers have been studied as potential surrogates for hepatic fibrosis; most were derived from studies in individuals without HIV infection. A meta-analysis of studies of the markers in the HIV-HCV coinfected population suggested that they might be useful in excluding cirrhosis if used at their most sensitive thresholds; however, their diagnostic odds ratios were suboptimal. Transient elastography (TE) uses ultrasound technology to estimate liver stiffness by measuring elastic shear wave velocity through the liver. In a study of 169 HIV-HCV coinfected patients, TE accurately detected significant fibrosis and cirrhosis but was less accurate in discriminating mild from significant fibrosis.

The decision to treat HCV in the HIV-infected patient should be made on an individual basis, because the benefits must be weighed against safety and efficacy concerns. HCV treatment should be prioritized in coinfected patients without decompensated cirrhosis who have a liver biopsy revealing portal fibrosis or more advanced disease. Women of child-bearing age might desire treatment before becoming pregnant, because pregnancy must be avoided during and 6 months after anti-HCV therapy because of the risk of ribavirin teratogenicity. Because they usually have favorable treatment responses, patients with HCV genotype 2 or 3 who are motivated and can tolerate treatment should be offered it regardless of liver disease stage. Certain IL28B genotypes respond well to treatment and so might also become an indication to treat without liver disease staging. Early treatment of acute HCV infection has also been associated with improved response rates in HIV-infected individuals. Patients with decompensated cirrhosis should be referred to a liver transplant center with experience in transplantation with HIV infection.

The current Food and Drug Administration–approved treatment for HCV in the setting of HIV infection is pegylated interferon alfa and ribavirin, which is the standard of care based on 4 large randomized trials. This regimen is less effective in HIV-infected patients, with sustained virologic response rates ranging from 14%–38% among those with HCV genotype 1 infection and 44%–73% among genotype 2 and 3 infections. Similar to HCV-monoinfected individuals, genotype, baseline HCV RNA, and early response to therapy are predictors of treatment response. In patients receiving HCV treatment, didanosine (ddI) is contraindicated and zidovudine is not recommended, because ribavirin potentiates the risk of mitochondrial toxicity and anemia, respectively. stavudine should also be avoided in patients receiving HCV treatment because of the risk of steatosis. Abacavir has been associated with decreased SVR, possibly as a result of competition with ribavirin because both are guanosine analogues. However, this competitive interaction appears to be insignificant when weight-based ribavirin dosing is used.

Although HCV-infected patients have a higher incidence of ART-related liver toxicity, this infrequently leads to ART discontinuation, and the benefits of ART for HIV treatment are
estimates range widely. The clinical implications of isolated HBV DNA in the setting of negative HBsAg, has also been described in HIV-infected subjects, although prevalence has been inconsistent. A recent systematic review of 11 studies examined the impact of ART on liver disease in HIV-HCV coinfection; 3 associated ART with less severe fibrosis, 6 failed to show a link, 1 associated protease inhibitors (PIs) with decompensated liver disease, and 1 showed varied effects depending on drug class. In other studies, HIV viral suppression has been linked to slower fibrosis progression, and ART has been associated with decreased liver-related mortality.

Individuals with HCV infection and cirrhosis have an increased risk of developing hepatocellular carcinoma (HCC). The American Association for the Study of Liver Disease recommends screening these patients every 6–12 months with alphafetoprotein measurement and imaging. Although separate recommendations for HIV-HCV coinfection do not exist, screening remains important in this population because HCC incidence has been increasing among HIV-infected individuals. Finally, HIV-HCV coinfected patients without immunity to HAV should receive vaccination, because HAV can cause fulminant hepatitis in patients with underlying liver disease.

**Hepatitis B Virus**

Although the prevalence of HIV-HBV coinfection varies by geographic location, approximately 10% of HIV-infected individuals worldwide are also chronically infected with HBV. Like HIV-HCV coinfection, HIV alters the natural history of HBV. Individuals with HIV infection are 3–6 times more likely to develop chronic HBV after an acute exposure than individuals without HIV infection, and hepatitis B surface antibody (anti-HBs) development is improved with higher CD4 cell counts. In addition, HIV-infected patients have a lower rate of spontaneous clearance of HBeAg, increased HBV replication, and a higher rate of loss of anti-HBs and reactivation of HBV. Coinfected individuals also experience an increased progression to cirrhosis and higher liver-related mortality compared with HBV monoinfected individuals. The impact of HBV infection on the natural history of HIV is less clear.

All HIV-infected patients should be screened for HBV with HBsAg, anti-HBs, and hepatitis B core antibody (anti-HBe). Individuals without immunity to HBV should be vaccinated; however, response to vaccination is poor, especially in patients whose CD4 cell count is <200 cells/mm³. Patients should therefore also be counseled to avoid risk factors for HBV transmission. Individuals with persistent HBsAg for a period of 6 months have chronic HBV and should be evaluated for treatment. Isolated anti-HBe is more common in HIV infection than in the general population; in one study, 42% of HIV-infected patients were only positive for anti-HBe. Occult HBV, defined as positive HBV DNA in the setting of negative HBsAg, has also been described in HIV-infected subjects, although prevalence estimates range widely. The clinical implications of isolated anti-HBe positivity and occult HBV are still unclear, but reactivation of inactive or occult HBV and reverse seroconversion (reappearance of HBsAg and HBV DNA in a patient with evidence of previously resolved infection) have been reported in HIV-infected individuals.

Once HIV-HBV coinfection is diagnosed, staging of liver disease is important but challenging. Although serum alanine aminotransferase levels are lower in coinfected patients, this correlates poorly with liver disease. Noninvasive measures of hepatic fibrosis have not been well-studied in HIV-HBV coinfection; therefore, liver biopsy remains the gold standard for disease staging.

The decision to initiate HBV treatment depends on whether the patient meets indications to treat either the HIV or HBV. Treatment regimens for either virus must consider both infections, because many antiviral agents have dual activity, including tenofovir, lamivudine, emtricitabine, entecavir, and adefovir at doses >10 mg. Treatment for HBV is indicated in any patient with cirrhosis and detectable HBV DNA. Although a specific HBV DNA threshold for treatment in the absence of cirrhosis has not been determined, treatment should be considered in patients with HBV DNA ≥2000 IU/mL and more than mild liver disease on biopsy.

If there is no indication to treat either infection, the patient should be monitored closely. If treatment is indicated for either HIV or HBV, ART should be initiated and should include the combination of tenofovir and emtricitabine (Truvada) or tenofovir and lamivudine. If tenofovir is contraindicated, entecavir can be used with the ART regimen, but then lamivudine or emtricitabine should be avoided because of overlapping resistance patterns. For patients requiring treatment for HBV but in whom ART is not feasible, options are limited by the need to avoid agents with anti-HIV activity to prevent development of drug-resistant HIV. In these patients, pegylated interferon alfa and adefovir 10 mg can be considered. Telbivudine is also a consideration, but some in vivo studies show declines in HIV RNA without emergence of drug-resistant HIV. Elevated ALT and AST during the course of ART might be due to a variety of potential causes including medications, drug-resistant HBV, HBV reactivation in the setting of medication withdrawal (especially with lamivudine withdrawal due to HIV resistance via the M184V mutation), loss of HBeAg, or the immune reconstitution inflammatory syndrome (IRIS).

Screening for HCC among individuals with HIV-HBV coinfection should follow American Association for the Study of Liver Disease guidelines recommending screening for all cirrhotic HBV carriers and for certain groups of noncirrhotic carriers. The hepatitis A vaccine should also be provided to individuals without hepatitis A immunity.

**Medication Toxicity**

**Antiretroviral Therapy–Related Medication Toxicity**

Liver toxicity is one of the most common serious adverse events associated with ART. The clinical presentation can range from mild asymptomatic increases in serum transaminases to overt liver failure. In retrospective studies, the incidence of ART-related severe hepatotoxicity is approximately 10%, and life-threatening events occur at a rate of 2.6 per 100 person-years. There are 4 primary mechanisms by which ART can lead to liver damage: direct drug toxicity and/or drug metabolism, hypersensitivity reactions, mitochondrial toxicity, and IRIS. IRIS is characterized by the paradoxical worsening of preexisting infectious diseases as a result of rapid immune restoration.
in the setting of successful HIV RNA suppression. The syndrome generally manifests within the first 2 months of ART initiation and is accompanied by a precipitous decline in HIV RNA and rise in CD4 count. In patients with viral hepatitis, immune restoration can lead to clinical hepatitis as a result of the immune response to the virus. There have been case reports of clinical flares of HBV in the setting of ART initiation, even with regimens including anti-HBV activity, and of rapidly progressive HCV-related cirrhosis associated with ART-related immune restoration.62,63

Coinfection with HBV or HCV has consistently been associated with increased risk of ART-related hepatotoxicity.57,60 Other risk factors associated with ART-related liver injury include preexisting advanced fibrosis, pretreatment elevated ALT or AST, alcohol abuse, older age, female gender, first exposure to ART, significant increase in CD4 cell count after ART initiation, concomitant tuberculosis medications, and cocaine use.60,61,64

Although all antiretroviral drugs have some risk of hepatotoxicity, some are implicated more than others, and classes of drugs have characteristic patterns of injury (Table 2). The non-nucleoside reverse transcriptase inhibitors (NNRTIs) typically cause either hypersensitivity reactions or direct drug toxicity and therefore have 2 peaks of onset, within days to weeks or several months after initiation.60 Nevirapine (NVP) is the NNRTI most associated with hepatotoxicity, although hyper-
sensitivity reactions resulting in liver failure have been reported with the newer NNRTI etravirine. Efavirenz can also cause hepatotoxicity but does so less frequently than NVP or etravirine.

Hepatotoxicity associated with PIs generally occurs weeks to months after drug initiation. Full-dose ritonavir (RTV) was strongly associated with hepatotoxicity but is no longer used. The low-dose RTV used to boost levels of other PIs does not appear to increase the risk of hepatotoxicity. However, clinical hepatitis and liver failure have been reported with the newer PI tipranavir in combination with RTV boosting. Atazanavir and indinavir both commonly cause an indirect hyperbilirubinemia, which is not associated with liver injury and does not require treatment discontinuation.

The nucleoside reverse transcriptase inhibitors (NRTIs) are associated with mitochondrial toxicity as a result of their ability to inhibit mitochondrial polymerase γ. Clinically this presents with hepatic steatosis and lactic acidosis from weeks to months after initiation. Stavudine, ddI, and zidovudine are the most frequently implicated. Prolonged ddI use has also been associated with cryptogenic liver disease and recently has been linked to noncirrhotic portal hypertension and esophageal varices. Although less associated with mitochondrial toxicity, abacavir might cause hypersensitivity reactions especially in HLA-B*5701 positive patients. Finally, lamivudine, emtricitabine, and tenofovir can lead to HBV reactivation and severe acute hepatitis if withdrawn in an HBV-infected patient or if resistance develops.

The fusion inhibitor enfuvirtide has been rarely associated with hypersensitivity reactions, and the newer drug maraviroc, a CCR5 inhibitor, carries a black box warning for hepatotoxicity as a result of hypersensitivity.

Given the relatively high incidence of ART-related hepatotoxicity, all patients should have baseline ALT and AST checked, followed by regular monitoring every 3 months. Patients should be educated regarding symptoms of hepatitis and hypersensitivity reactions. If an adverse liver event occurs, ART should be discontinued in patients with symptoms, jaundice and elevated direct hyperbilirubinemia, grade 4 hepatotoxicity (ALT/AST >10 times upper limit of normal), or severe lactic acidosis. Mild asymptomatic ALT or AST elevations usually spontaneously resolve without drug discontinuation (Table 3).

Non–Antiretroviral Therapy–Related Medication Toxicity

HIV-infected patients are often prescribed a number of non-ART medications that can have adverse liver effects either alone or in combination (Table 4).

Alcoholic Liver Disease

Although alcoholic liver disease is responsible for nearly half of all deaths due to chronic liver disease in the United States, the role of alcohol abuse on liver disease in HIV-infected populations has not been well-defined. In one study of 2864 HIV-infected adults in the United States, 8% of the entire cohort and 15% of current alcohol drinkers were classified as heavy drinkers, which is almost twice as prevalent as in the general population.

Active alcohol intake is known to be associated with faster liver disease progression in HCV monoinfection. In one study...

Table 3. Features Associated With Presentation, Prevention, and Management of ART-Related Liver Injury

<table>
<thead>
<tr>
<th>Hypersensitivity reaction</th>
<th>Associated drugs</th>
<th>Onset</th>
<th>Clinical manifestations</th>
<th>Prevention/monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td>NVP, ETR, RTV, T20, MVC</td>
<td>Greatest risk in first 6 weeks</td>
<td>Can present through 18 weeks</td>
<td>Educate patients on signs/symptoms</td>
</tr>
<tr>
<td>ABC</td>
<td>NVP</td>
<td>Avoid in women with CD4 &gt;250 cells/mm³, men with CD4 &gt;400 cells/mm³</td>
<td>Two-week dose escalation might decrease incidence</td>
<td>Check ALT/AST every 2 weeks × first month, then monthly × 2 months, then every 3 months</td>
</tr>
<tr>
<td>ABC</td>
<td>ABC</td>
<td>Screen for HLA-B*5701 before initiation; do not start ABC if positive</td>
<td>Management</td>
<td></td>
</tr>
<tr>
<td>ABC</td>
<td>ABC</td>
<td>Discontinue all ART and all other potentially hepatotoxic medications</td>
<td>Rule out other causes of symptoms</td>
<td>Unknown whether other NNRTIs can be used safely after NVP-associated hepatotoxicity</td>
</tr>
<tr>
<td>ABC</td>
<td>ABC</td>
<td>ABC contraindicated in future use</td>
<td>After ABC-associated hepatotoxicity, switch to another NRTI.</td>
<td></td>
</tr>
</tbody>
</table>

Direct drug toxicity/metabolism

Associated drugs

All NNRTIs, all PIs, most NRTIs, MVC

Onset

Weeks to months

Clinical manifestations

Might present with asymptomatic transaminase elevation
Clinical hepatitis might present with anorexia, weight loss, fatigue, jaundice, abdominal pain, nausea, vomiting

Prevention/monitoring

Monitor LFTs in NVP as above
For other agents, monitor LFTs every 3 months, more frequently in at-risk patients (HBV or HCV coinfection, elevated transaminases at baseline, underlying liver disease, alcohol abuse, cocaine use, use of other potentially hepatotoxic drugs, first exposure to ART)

Management

Rule out other causes of hepatotoxicity, including viral hepatitis or HBV reactivation

Symptomatic patients

Discontinue ART and other potentially offending medications
Once symptoms and LFT abnormalities resolve, resume ART without offending agent(s)

Asymptomatic patients

Mild elevations usually resolve without drug discontinuation
If ALT >5–10 × ULN and elevated direct bilirubin, discontinue ART
If ALT >10 × ULN, discontinue ART
Once LFT abnormalities resolve, resume ART without offending agent(s)
Table 3. Continued

Mitochondrial toxicity

Associated drugs
NRTIs: ddI > D4T > AZT/3TC = FTC = ABC = TDF

Onset
Weeks to months

Clinical manifestations
Anorexia, abdominal pain, nausea, vomiting, weight loss, fatigue
Might progress to tachycardia, tachypnea, jaundice, muscle weakness, altered mental status, multi-organ failure
Lab abnormalities include increased lactate, low arterial pH, low bicarbonate, increased anion gap

Prevention/monitoring
Check lactate in asymptomatic patients or in patients with elevated anion gap or low bicarbonate

Management
Mild symptoms
- Change ART regimen to NRTI with lower risk of mitochondrial toxicity or to NRTI-sparing regimen
- Closely monitor lactate after resuming NRTI

Severe symptoms
- Discontinue ART
- Supportive care, which might include hemodialysis or hemofiltration, mechanical ventilation
- Intravenous thiamine and/or riboflavin

IRIS

Associated drugs
Any ART

Onset
First 2 months

Clinical manifestations
Nonspecific symptoms (fever, night sweats, fatigue, jaundice, nausea)
Might be difficult to distinguish from hepatitis due to drug toxicity without liver biopsy
If performed, liver biopsy shows hepatic necrosis with CD8+ T-cell infiltration

Prevention/monitoring
Screen for HBV and HBV before ART initiation (should be done in all HIV-positive patients regardless of ART)
In HIV-HBV, treat HBV when initiating HAART
Consider diagnosis in patients with HBV or HCV coinfection and robust response to ART

In patients with HBV or HCV, monitor LFTs at least every month for first 3 months of ART initiation

Management
Symptomatic patients
- Discontinue ART

Asymptomatic patients
- Discontinue ART if AST/ALT >10 × ULN
- Closely monitor patients with less severe increases in AST/ALT

Hepatitis B reactivation

Associated drugs
3TC, FTC, TDF

Onset
After withdrawal of medication with anti-HBV activity or development of HBV resistance (usually months to years of therapy)

Clinical manifestations
Ranges from asymptomatic increase in LFTs to severe fulminant hepatitis
Median onset 12–16 weeks after withdrawal

Hepatitis B reactivation

Management
Resume anti-HBV therapy with appropriate agent on basis of resistance profile

3TC, lamivudine; ABC, abacavir; AZT/3TC, zidovudine; D4T, stavudine; ETR, etravirine; FTC, emtricitabine; HAART, highly active antiretroviral therapy; LFT, liver function test; MVC, maraviroc; T20, enfuvirtide; TDF, tenofovir; ULN, upper limits of normal.

of HIV-HCV coinfected patients, excessive alcohol use was associated with elevated HCV RNA levels. In another study of 1358 HIV-infected individuals at an urban center, 10% reported hazardous drinking, which was independently associated with an elevated surrogate for hepatic fibrosis. These results suggest that alcohol abuse is prevalent among HIV-infected individuals and can independently contribute to liver disease progression. As a modifiable risk factor for liver disease, it is important that physicians provide counseling regarding alcohol consumption in this population.

Nonalcoholic Fatty Liver Disease

NAFLD refers to fat deposition in hepatocytes, or steatosis, in individuals with little or no alcohol use. When accompanied by inflammation and fibrosis, it is referred to as nonalcoholic steatohepatitis (NASH). The prevalence of NAFLD in the U.S. population ranges from 17%–33%, and risk factors include obesity, hyperglycemia, diabetes mellitus, and hypertriglyceridemia. Recently, mounting evidence suggests that the prevalence of hepatic steatosis in HIV-infected patients is high, especially in patients with chronic HCV or on NRTIs. Most of the prevalence data come from studies in HIV-HCV coinfected individuals, with rates of steatosis in this population.

Table 4. Partial List of Potentially Hepatotoxic Non-ART Medications Prescribed to HIV-Infected Individuals

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pattern of liver injury</th>
</tr>
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<tbody>
<tr>
<td>Antifungals</td>
<td></td>
</tr>
<tr>
<td>Ketokonazole, fluconazole, amphotericin B</td>
<td>Hepatocellular injury</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Hepatocellular injury</td>
</tr>
<tr>
<td>Azithromycin, dapsone</td>
<td>Cholestatic injury</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Mixed hepatocellular-cholestatic injury</td>
</tr>
<tr>
<td>Tuberculosis treatment</td>
<td></td>
</tr>
<tr>
<td>Isoniazid, rifampin, pyrazinamide</td>
<td>Hepatocellular injury</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Cholestatic injury</td>
</tr>
<tr>
<td>Antivirals</td>
<td></td>
</tr>
<tr>
<td>Ganciclovir, acyclovir</td>
<td>Hepatocellular injury</td>
</tr>
<tr>
<td>Anabolic/androgenic steroids</td>
<td>Cholestatic injury, liver tumors, peliosis hepatis</td>
</tr>
</tbody>
</table>
ranging from 40%–69%. However, in a recent study of 216 HIV-infected patients without viral hepatitis coinfection, 31% had NAFLD diagnosed, although most were diagnosed with ultrasound rather than the gold standard of liver biopsy.

Metabolic abnormalities are extremely common in HIV-infected persons on ART, especially NRTI-PI combinations. These include insulin resistance, dyslipidemia, hypertriglycerideremia, and lipodystrophy, a disorder of peripheral fat distribution resulting in lipotrophy and visceral adiposity. NRTIs can also lead to hepatic steatosis via inhibition of mitochondrial DNA replication, resulting in triglyceride accumulation in the liver. Hypertriglycerideremia, low high-density lipoprotein, and low total cholesterol have also been independently associated with HIV infection and might be mediated by cytokines like interferon alfa. These metabolic abnormalities have been associated with the development of NASH in HIV-infected patients.

The natural history of NAFLD in HIV infection is unknown. In the general population, approximately 10%–15% of patients with simple steatosis progress to NASH, and 15%–20% of these patients progress to cirrhosis. In general, steatosis alone is not concerning for liver damage, but it might exacerbate underlying chronic liver disease. In HCV-monoinfected patients, steatosis is associated with faster progression of fibrosis and decreased response to treatment. Similarly, in cohorts of HIV-HCV coinfection, hepatic steatosis has been associated with more advanced liver fibrosis.

With continued investigation and research into NAFLD, its impact on liver disease progression in HIV-infected individuals will likely be further elucidated.

### Nodular Regenerative Hyperplasia

Nodular regenerative hyperplasia (NRH) is a rare condition characterized by multiple small regenerative nodules in the liver parenchyma. NRH has recently become increasingly recognized in HIV-infected patients withcryptogenic liver disease. Although the etiology is unclear, both ddi use and thrombophilia have been associated with the disease. NRH should be considered in HIV-infected patients with portal hypertension of unclear etiology, especially those on ddi.

### Acquired Immunodeficiency Syndrome–Related Liver Disease

#### Acquired Immunodeficiency Syndrome Cholangiopathy

AIDS cholangiopathy occurs when infection-related strictures in the biliary tract lead to biliary obstruction. It typically presents with right upper quadrant (RUQ) pain and a markedly increased alkaline phosphatase level, with less elevated bilirubin and normal or slightly increased transaminase levels. Patients might also have fever, nausea, vomiting, and diarrhea; jaundice is uncommon. It is usually seen in low CD4 counts (<100/mm³). Consequently, although previously relatively common among HIV-infected patients, it is much less common in the ART era. Indeed, in a recent retrospective study of 94 patients diagnosed with AIDS cholangiopathy at an urban hospital between 1983 and 2001, only 13 were diagnosed after 1996.

The most common infection associated with AIDS cholangiopathy is Cryptosporidium parvum, followed by CMV. Microsporidia, Cyclospora cayetanensis, Mycobacterium avium-intracellulare, and Histoplasma capsulatum have all been reported with AIDS cholangiopathy as well. Ultrasound or magnetic resonance cholangiopancreatography might reveal intrahepatic and common bile duct dilation with terminal stenosis. However, endoscopic retrograde cholangiopancreatography remains the gold standard for diagnosis. Biopsies of the papilla and bile duct as well as bile duct brushings might help identify the infectious cause. Sphincterotomy improves the abdominal pain but does not extend survival, and the alkaline phosphatase level often remains elevated. The most important aspect to treatment of AIDS cholangiopathy is ART administration, because survival after diagnosis is poor without ART.

#### Acalculous Cholecystitis

Acalculous cholecystitis has been well-documented in HIV infection and is usually associated with CMV or Cryptosporidium, although other infections, including Isospora and microsporidia have been implicated. Patients typically present with RUQ abdominal pain and fever with cholestasis; leukocytosis is often not present. Imaging reveals a thickened, distended, acalculous gallbladder, and HIDA scan often shows a nonfunctioning gallbladder. Cholecystectomy is the treatment of choice.

#### Acquired Immunodeficiency Syndrome–Related Neoplasms

The AIDS-defining malignancies non-Hodgkin lymphoma (NHL) and KS involve the liver in 33% and 9% of cases, respectively. Hepatic involvement of NHL might present with asymptomatic liver function test abnormalities, although patients might develop abdominal pain or jaundice. Hepatic involvement of KS rarely causes symptoms or death.

#### Opportunistic Infections

Several opportunistic infections have been associated with hepatic involvement in advanced AIDS (Table 5). Of these, Mycobacterium avium complex is the most common. It is usually characterized histologically by acid-fast bacilli-containing poorly formed granulomas, although mass lesions have been described. Patients often present with RUQ abdominal pain, diarrhea, and abdominal pain. Alkaline phosphatase is usually disproportionately increased. Hepatic involvement of Mycobacterium tuberculosis, including liver abscesses, has been reported in approximately 8% of patients with extrapulmonary tuberculosis and HIV infection. CMV is one of the most common opportunistic infections involving the liver detected on autopsy of patients with advanced AIDS but rarely results in clinical hepatitis.

Hepatic involvement of fungal infections, including Cryptococcus neoformans, Histoplasma capsulatum, and Coccidioides immitis, can be seen in patients with AIDS and is usually detected on liver biopsy or autopsy. Although liver function test results are often abnormal, the liver involvement is usually asymptomatic. Extrapulmonary Pneumocystis jiroveci involving the liver has been described and might be seen in the setting of inhaled pentamidine for prophylaxis of Pneumocystis jiroveci pneumonia. Bacillary peliosis hepatitis is a rare disease characterized by multiple blood-filled cavities in the liver parenchyma; it has been reported in patients with AIDS and Bartonella henselae infection. Other reported opportunistic infections involving...
the liver of patients with AIDS include disseminated herpes simplex virus, human herpesvirus 6, varicella-zoster virus, Epstein–Barr virus, adenovirus, Candida albicans, Aspergillus fumigatus, Toxoplasma gondii, and Strongyloides stercoralis.90–92

### Vanishing Bile Duct Syndrome

The vanishing bile duct syndrome (VBDS) is an acquired disease resulting in loss of small and medium-sized...
intrahepatic bile ducts. Multiple causes have been identified, and there have been case reports of VBDS associated with advanced AIDS, with cases attributed to CMV viremia and medication toxicity.98,99 The presentation is variable and often related to cholestasis. Diagnosis is based on histology, although the work-up should include imaging to rule out extrahepatic biliary obstruction. The outcome of reported AIDS-associated VBDS cases is very poor, with progression to liver failure and death.98,99

**Conclusions**

Liver disease among HIV-infected individuals is a common and important cause of non-AIDS-related morbidity and mortality. In the ART era, the spectrum of liver disease among patients with HIV infection has changed dramatically, shifting from opportunistic infections to sequelae of chronic infections, medication toxicities, alcohol use, and fatty liver. Management of HIV-infected patients requires recognition of these conditions and targeted diagnosis and treatment.

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Reprint requests
Address requests for reprints to: Dr Jennifer C. Price, MD, Division of Gastroenterology and Hepatology, Johns Hopkins School of Medicine, 600 N Wolfe Street, Blalock 415, Baltimore, Maryland 21287. e-mail: jcohen@jhmi.edu; fax: (410) 502-7010.

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