REVIEW

Liver Disease in the HIV–Infected Individual

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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).[1–3] 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.[3,4] In some series, nearly half of deaths among hospitalized HIV-infected patients in the ART era have been attributed to liver disease.[5,6]

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.[7] Before ART, the most common causes of liver dysfunction in HIV-infected patients were opportunistic infections, including cytomegalovirus (CMV) and mycobacterium infections, and AIDS-related neoplasms such as lymphoma and Kaposi's sarcoma (KS).[8,9] 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).[7,10,11] 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.[12] 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.[13] Overall, approximately 30% of HIV-infected individuals in the United States and Europe are coinfected with HCV.[14]

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.[15] 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.[16–18] 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.[19] 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.[20]

Given both the high prevalence of HCV among the HIV-infected population and the impact of HIV on HCV-related liver

Abbreviations used in this paper: AIDS, acquired immunodeficiency syndrome; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; ART, antiretroviral therapy; CMV, cytomegalovirus; ddI, didanosine; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus-1; IRIS, immune reconstitution inflammatory syndrome; KS, Kaposi's sarcoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NHL, non-Hodgkin lymphoma; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRH, nodular regenerative hyperplasia; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RTV, ritonavir; RUQ, right upper quadrant; TE, transient elastography; VBDS, vanishing bile duct syndrome.

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Table 1. Differential Diagnosis of Liver Disease in HIV Infection in the ART Era

Hepatic parenchymal disease
Infection
Viral hepatitis: HCV, HBV, HDV, HAV, HEV, CMV, EBV, HSV, VZV, HHV-6
Mycobacterium avium complex
Cryptococcus neoformans
Microsporidia
Pneumocystis jiroveci
Bacillary peliosis hepatis
Histoplasma capsulatum
NAFLD
Medication toxicity
Alcoholic liver disease
Recreational drugs
Cocaine
Methylenedioxymethamphetamine (Ecstasy)
Neoplasm
Lymphoma
KS
HCC
NRH
Autoimmune hepatitis
Hemochromatosis
Wilson's disease
Alpha-1 antitrypsin deficiency
Biliary disease
AIDS cholangiopathy
Cryptosporidium
CMV
Microsporidia
Cyclospora cayetanensis
Mycobacterium avium intracellulare
Histoplasma capsulatum
Acalculous cholecystitis
Cryptosporidium
CMV
Isospora
Microsporidia
Neoplasm
Lymphoma
KS
Primary sclerosing cholangitis
Primary biliary cirrhosis

EBV, Epstein–Barr virus; HHV–6, human herpesvirus 6; HSV, herpes simplex virus; VSV, varicella-zoster virus.

disease progression, all HIV-infected patients should be tested for chronic HCV infection by using third-generation enzyme immunoassays, followed by quantitative HCV RNA testing if positive. Although third-generation immunoassays are highly sensitive, even in the setting of HIV infection (>99%), HCV RNA should be checked in patients with significant risk factors for HCV and advanced immunosuppression or in whom acute infection is suspected.[21] During the past decade, outbreaks of sexually transmitted HCV among noninjection-drug–using men who have sex with men have been reported in Europe, the United States, and Australia; men who have sex with men should therefore be considered at risk for acquiring HCV.[22] Because there is no available vaccine to prevent HCV infection, HIV-infected individuals who test negative for HCV should be counseled to avoid risk factors for HCV infection. For individuals who test positive for HCV, the extent of liver disease should be determined. Aminotransferase levels are not sensitive for fibrosis in the setting of HIV infection; therefore, liver biopsy remains the preferred modality for staging disease among coinfected patients.

Because of the limitations and invasiveness of liver biopsy, 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.[23] 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.[24]

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.[25] 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 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.[26] Early treatment of acute HCV infection has also been associated with improved response rates in HIV-infected individuals.[27] 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.[28–31] 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.[28] 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.[32] Stavudine should also be avoided in patients receiving HCV treatment because of the risk of steatosis.[33] Abacavir has been associated with decreased SVR, possibly as a result of competition with ribavirin because both are guanosine analogues.[34–36] However, this competitive interaction appears to be insignificant when weight-based ribavirin dosing is used.[37,38]

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

profound; therefore, ART should not be withheld in the coinfected population. In addition, ART might have beneficial effects on the progression of liver disease in HIV-HCV coinfection, because improvement in CD4 count might decrease fibrosis progression, although studies investigating this have 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.[39] In other studies, HIV viral suppression has been linked to slower fibrosis progression, and ART has been associated with decreased liver-related mortality.[40,41]

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 alpha-fetoprotein measurement and imaging.[42] 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.[43] 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.[44] 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.[45,46] 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.[47] Coinfected individuals also experience an increased progression to cirrhosis and higher liver-related mortality compared with HBV monoinfected individuals.[48,49] 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-HBc). Individuals without immunity to HBV should be vaccinated; however, response to vaccination is poor, especially in patients whose CD4 cell count is $<$200 cells/mm.[3,50] 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-HBc is more common in HIV infection than in the general population; in one study, 42% of HIV-infected patients were only positive for anti-HBc.[51] 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.[52] The clinical implications of isolated anti-HBc 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.[53]

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.[48] 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.[54] 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 $\geq$2000 IU/mL and more than mild liver disease on biopsy.[54]

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.[55] 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.[47] 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.[56] 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.[42] 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.[57] The clinical presentation can range from mild asymptomatic increases in serum transaminases to overt liver failure.[58] 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.[59,60]

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.[60,61] IRIS is characterized by the paradoxical worsening of preexisting infectious diseases as a result of rapid immune restoration

Table 2. Most Common ART Agents Associated With Liver Injury in HIV-Infected Patients

Medication	Typical dose	Dose adjustment for hepatic insufficiency	Mechanism of liver injury
NNRTI			
Nevirapine (NVP)	200 mg po bid	Child–Pugh class B or C: contraindicated	Hypersensitivity reaction, direct drug toxicity/drug metabolism
Etravirine (ETR)	200 mg po bid	Child–Pugh class A or B: no adjustment; Child–Pugh class C: not defined	Hypersensitivity reaction
PI			
Ritonavir (RTV) full-dose	No longer used		Direct drug toxicity/drug metabolism
Tipranavir (TPV) + RTV low-dose	(TPV 500 mg + RTV 200 mg) po bid	Child–Pugh class A: use with caution; Child–Pugh class B or C: contraindicated	Direct drug toxicity/drug metabolism
Atazanavir (ATV)	400 mg po once daily	Child–Pugh class B: 300 mg po once daily; Child–Pugh class C: contraindicated	Indirect hyperbilirubinemia: does not cause liver injury
Indinavir (IDV)	800 mg po q8h	Mild to moderate hepatic insufficiency: 600 mg po q8h	Indirect hyperbilirubinemia: does not cause liver injury
NRTI			
Stavudine (D4T)	≥60 kg: 40 mg po bid <60 kg: 30 mg po bid	Not defined	Mitochondrial toxicity
Zidovudine (AZT, ZDV)	300 mg po bid	Not defined	Mitochondrial toxicity
Didanosine (ddI)	Enteric coated: ≥60 kg: 400 mg po once daily <60 kg: 250 mg po once daily Oral solution: ≥60 kg: 200 mg po bid or 400 mg po once daily <60 kg: 150 mg po bid or 250 mg po once daily	No adjustment	Mitochondrial toxicity, cryptogenic liver disease, noncirrhotic portal hypertension
Abacavir (ABC)	300 mg po bid	Child–Pugh class A: 200 mg po bid (use oral solution); Child–Pugh class B or C: contraindicated	Hypersensitivity reaction, especially in HLA-B*5701 positive patients
Lamivudine (3TC)	300 mg po once daily or 150 mg po bid	No adjustment	HBV reactivation due to medication withdrawal or resistance
Emtricitabine (FTC)	Oral capsule: 200 mg po once daily Oral solution: 240 mg po once daily	Not defined	HBV reactivation due to medication withdrawal or resistance
Tenofovir (TDF)	300 mg po once daily	No adjustment	HBV reactivation due to medication withdrawal or resistance
Other			
Enfuvirtide (T20)	90 mg subcutaneous bid	Not defined	Hypersensitivity reaction
Maraviroc (MVC)	Recommended dose depends on other drugs in regimen	Not defined, caution advised	Hypersensitivity reaction, direct drug toxicity/drug metabolism

bid, twice daily; po, by mouth; q8h, every 8 hours.

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 nonnucleoside 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.[55] 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.[65] However, clinical hepatitis and liver failure have been reported with the newer PI tipranavir in combination with RTV boosting.[55,60] Atazanavir and indinavir both commonly cause an indirect hyperbilirubinemia, which is not associated with liver injury and does not require treatment discontinuation.[66]

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.[67,68] 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.[55] 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.[69]

Active alcohol intake is known to be associated with faster liver disease progression in HCV monoinfection.[70] In one study

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

- Hypersensitivity reaction
  - Associated drugs
    - NVP, ETR, RTV, T20, MVC
  - Onset
    - Greatest risk in first 6 weeks
    - Can present through 18 weeks
  - Clinical manifestations
    - Abrupt onset flu-like symptoms, abdominal pain, jaundice, fever, with or without skin rash
  - Prevention/monitoring
    - Educate patients on signs/symptoms
    - Check ALT/AST if rash develops
    - NVP
      - Avoid in women with CD4 >250 cells/mm^3, men with CD4 >400 cells/mm^3
      - Two-week dose escalation might decrease incidence
      - Check ALT/AST every 2 weeks × first month, then monthly × 2 months, then every 3 months
    - ABC
      - Screen for HLA-B*5701 before initiation; do not start ABC if positive
  - Management
    - Discontinue all ART and all other potentially hepatotoxic medications
    - Rule out other causes of symptoms
    - Management is supportive
    - Unknown whether other NNRTIs can be used safely after NVP-associated hepatotoxicity
    - After ABC-associated hepatotoxicity, switch to another NRTI. ABC contraindicated in future use
- 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/ZDV > 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 symptomatic 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 HCV 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 × 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
  - Prevention/monitoring
    - In setting HBV, ART regimen should include TDF and FTC (Truvada) or TDF and 3TC
    - If 3TC is withdrawn because of HIV resistance, replace it with an agent with anti-HBV activity
  - Management
    - Resume anti-HBV therapy with appropriate agent on basis of resistance profile

3TC, lamivudine; ABC, abacavir; AZT/ZDV, zidovudine; D4T, stavudine; ETR, etravirine; FTC, emtricitabine; HAART, highly active antiviral 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.[71] 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.[72] 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.[73] 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.[61] 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

Medication	Pattern of liver injury
Antifungals	
Ketoconazole, fluconazole, amphotericin B	Hepatocellular injury
Antibiotics	
Ciprofloxacin	Hepatocellular injury
Azithromycin, dapsone	Cholestatic injury
Trimethoprim-sulfamethoxazole	Mixed hepatocellular-cholestatic injury
Tuberculosis treatment	
Isoniazid, rifampin, pyrazinamide	Hepatocellular injury
Ethambutol	Cholestatic injury
Antivirals	
Ganciclovir, acyclovir	Hepatocellular injury
Anabolic/androgenic steroids	
Testosterone, nandrolone, oxandrolone	Cholestatic injury, liver tumors, peliosis hepatis

ranging from 40%–69%.[33,74] 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.[75]

Metabolic abnormalities are extremely common in HIV-infected persons on ART, especially NRTI-PI combinations. These include insulin resistance, dyslipidemia, hypertriglyceridemia, and lipodystrophy, a disorder of peripheral fat distribution resulting in lipotrophy and visceral adiposity.[76] NRTIs can also lead to hepatic steatosis via inhibition of mitochondrial DNA replication, resulting in triglyceride accumulation in the liver.[77] Hypertriglyceridemia, 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.[78] These metabolic abnormalities have been associated with the development of NASH in HIV-infected patients.[79]

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.[80] 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.[81] Similarly, in cohorts of HIV-HCV coinfection, hepatic steatosis has been associated with more advanced liver fibrosis.[33,74] 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 with cryptogenic liver disease.[82] Although the etiology is unclear, both ddI use and thrombophilia have been associated with the disease.[82,83] 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.[84] It is usually seen in low CD4 counts ($<100/mm^3$). 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.[85]

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.[84] 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.[85,86] The most important aspect to treatment of AIDS cholangiopathy is ART administration, because survival after diagnosis is poor without ART.[85]

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.[87,88] 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.[88] 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.[89,90] 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.[90]

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.[90,91] Patients often present with nausea, diarrhea, and abdominal pain. Alkaline phosphatase is usually disproportionately increased.[92] Hepatic involvement of *Mycobacterium tuberculosis*, including liver abscesses, has been reported in approximately 8% of patients with extrapulmonary tuberculosis and HIV infection.[91,93] 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.[90,92] When CMV presents as hepatitis, patients usually have mild transaminitis, fever, malaise, weight loss, and hepatomegaly.

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.[94,95] 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.[96] Bacillary peliosis hepatis 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.[97] Other reported opportunistic infections involving

Table 5. Key Points Regarding Infections Affecting the Liver in HIV-Infected Individuals

Pathogen	Key points
HCV	• Screen all HIV-infected patients with HCV antibody • Test HCV RNA in patients with positive HCV antibody. If antibody is negative, also consider HCV RNA testing if suspected acute HCV, or significant risk factors and advanced immunosuppression • If chronic HCV, immunize against HBV and HAV if not immune
HBV	• All HIV-infected patients should be screened with HBsAg, anti-HBs, and anti-HBc • Vaccinate patients without HBV immunity • When initiating or adjusting ART, regimen must include adequate anti-HBV coverage • Vaccinate against HAV, if not immune
HDV	• Requires concomitant HBV infection for replication • Acquired during simultaneous infection with HBV or as superinfection in setting of chronic HBV • HDV superinfection is associated with fulminant acute hepatitis and severe chronic progressive hepatitis
HAV	• Can cause fulminant hepatitis especially in presence of underlying liver disease
HEV	• Consider in patients with travel to endemic areas; autochthonous cases have also been reported in United Kingdom, France, Germany, and the United States • Chronic infection has been reported in HIV-infected patients
CMV	• Rarely symptomatic; might present with fever, malaise, weight loss, hepatomegaly • Usually mild transaminitis and mild cholestasis • Might present as mass and mimic neoplasm on CT • Liver biopsy with large intranuclear and small cytoplasmic inclusions ± granulomas
Mycobacterium avium complex	• Presents with fever, night sweats, weight loss, abdominal pain, nausea, diarrhea, HSM • Marked elevation of AP (>10–20 × ULN) is hallmark • U/S shows diffusely hyperechoic liver ± focal lesions • Liver biopsy with poorly formed non-caseating granulomas, foamy histiocytes, acid-fast bacilli
Cryptococcus neoformans	• Might be asymptomatic or present with fever, RUQ pain, hepatomegaly • Labs usually show cholestasis with increased AP, variable bilirubin • Might cause liver abscess • Liver biopsy might demonstrate ill-defined cystic areas or granulomas
Mycobacterium tuberculosis	• Presents with fever, night sweats, weight loss, LAD, and hepatomegaly • AP usually elevated with mildly elevated aminotransferases and bilirubin • U/S shows diffusely hyperechoic liver ± focal lesions; abscesses have also been described • Liver biopsy with well-formed granulomas
Microsporidia	• Might cause increased bilirubin, transaminases, and especially AP
Pneumocystis jiroveci	• More common in patients receiving inhaled pentamidine for PCP prophylaxis • Usually moderate increases in aminotransferases and AP, but high elevations have been reported • CT might show hepatic calcifications • Liver biopsy with foamy nodules with pneumocystis cysts on methenamine silver staining
Bartonella henselae	• Consider in patients with history of cat contact • Might present with HSM, liver failure, portal hypertension, fever, anemia, LAD, and skin lesions • AP elevated; might develop coagulopathy • U/S might show irregular hypoechoic regions • CT might reveal multiple hypoattenuating lesions of varying size • Liver biopsy with multiple blood-filled cavities of varying size
Histoplasma capsulatum	• Might be asymptomatic or present with constitutional symptoms, LAD and HSM, multisystem organ failure in fulminant cases • Labs usually show cholestasis with increased AP, variable bilirubin • Liver biopsy with poorly formed granulomas, rounded yeast with budding on silver staining

AP, alkaline phosphatise; CT, computed tomography; HSM, hepatosplenomegaly; lymphadenopathy; U/S, ultrasound.

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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Conflicts of interest

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