



Published in final edited form as:

Clin Gastroenterol Hepatol. 2010 December ; 8(12): 1002–1012. doi:10.1016/j.cgh.2010.08.024.

Liver Disease in the HIV-Infected Individual

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Abstract

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]. Prior to 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

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Disclosures: The authors do not have any potential conflicts to disclose.

Writing Assistance: Both authors, JCP and CLT, were involved in writing this manuscript. No other individuals provided writing assistance.

sarcoma^[8, 9]. Since the ART-era, however, the spectrum of liver disease among HIV-infected individuals has shifted to concomitant infection with chronic hepatitis C virus (HCV), chronic hepatitis B virus (HBV), medication-related hepatotoxicity, alcohol abuse, and nonalcoholic fatty liver disease (NAFLD)^[7, 10, 11](see 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^[12]. Due to 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 coinfecting 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 coinfecting subjects had a two-fold increased risk of histologic cirrhosis and five-fold increased risk of decompensated liver disease compared to 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 coinfecting individuals treated for HCV, patients who achieved SVR had lower rates of HIV progression and non-liver mortality after adjusting for fibrosis, CDC 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 disease progression, all HIV-infected patients should be tested for chronic HCV infection using 3rd generation enzyme immunoassays followed by quantitative HCV RNA testing, if positive. Although 3rd 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]. Over the past decade, outbreaks of sexually-transmitted HCV among non-injection-drug-using men who have sex with men (MSM) have been reported in Europe, the United States, and Australia; MSM 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 coinfecting patients.

Due to the limitations and invasiveness of liver biopsy, non-invasive 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 coinfecting population suggested that they may be useful in excluding cirrhosis if used at their most sensitive thresholds; however, their diagnostic odds ratios were suboptimal^[23]. Transient elastography (TE) employs ultrasound technology to estimate liver stiffness by measuring elastic shear wave velocity through the

liver. In a study of 169 HIV-HCV coinfecting 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, as the benefits must be weighed against safety and efficacy concerns. HCV treatment should be prioritized in coinfecting patients without decompensated cirrhosis who have a liver biopsy revealing portal fibrosis or more advanced disease^[25]. Women of child-bearing age may desire treatment prior to becoming pregnant, as pregnancy must be avoided during and six months after anti-HCV therapy due to ribavirin teratogenicity. Because they usually have favorable treatment responses, patients with HCV genotypes 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 may 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 FDA-approved treatment for HCV in the setting of HIV-infection is pegylated interferon alfa and ribavirin, which is the standard of care based on four 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 is contraindicated and zidovudine is not recommended, as 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 due to competition with ribavirin as 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 coinfecting population. In addition, ART may have beneficial effects on the progression of liver disease in HIV-HCV coinfection, as improvement in CD4 count may decrease fibrosis progression, though 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: three associated ART with less severe fibrosis, six failed to show a link, one associated protease inhibitors (PI's) with decompensated liver disease, and one 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 (AASLD) recommends screening these patients every six to twelve months with alpha-fetoprotein measurement and imaging^[42]. Though separate recommendations for HIV-HCV coinfection do not exist, screening remains important in this population as HCC incidence has been increasing among HIV-infected individuals^[43]. Finally, HIV-HCV coinfecting patients without immunity to hepatitis A virus (HAV) should receive vaccination, as HAV can cause a fulminant hepatitis in patients with underlying liver disease.

Hepatitis B Virus

Though 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 to 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 hepatitis B surface antigen (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/mm³^[50]. Patients should therefore also be counseled to avoid risk factors for HBV transmission. Individuals with persistent HBsAg over six 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, though 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. Though serum alanine aminotransferase levels are lower in coinfecting patients, this correlates poorly with liver disease^[48]. Non-invasive 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, as many anti-viral 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 $\geq 2,000$ 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 due to 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 may 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 AASLD 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

ART-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 four 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 due to rapid immune restoration in the setting of successful HIV RNA suppression. The syndrome generally manifests within the first two 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 a clinical hepatitis due to 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 pre-existing advanced fibrosis, pre-treatment 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].

While all antiretroviral drugs have some risk of hepatotoxicity, some are more implicated than others, and classes of drugs have characteristic patterns of injury (*see* Table 2). The nonnucleoside reverse transcriptase inhibitors (NNRTI's) typically cause either hypersensitivity reactions or direct drug toxicity and therefore have two peaks of onset: within days to weeks or several months after initiation^[60]. Nevirapine (NVP) is the NNRTI most associated with hepatotoxicity, though hypersensitivity 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 PI's 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 PI's 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 (NRTI's) are associated with mitochondrial toxicity due to their ability to inhibit mitochondrial polymerase γ . Clinically this presents

with hepatic steatosis and lactic acidosis from weeks to months after initiation. Stavudine, didanosine (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]. Though less associated with mitochondrial toxicity, abacavir may 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 due to 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 (*see* Table 3).

Non-ART-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 (*see* Table 4).

Alcoholic Liver Disease

Although alcoholic liver disease is responsible for nearly half of all deaths due to chronic liver disease in the US, 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 US, 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 of HIV-HCV coinfecting 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

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 US 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 NRTI's^[61]. Most of the prevalence data come from studies in HIV-HCV coinfecting individuals, with rates of steatosis in this population 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 lipatrophy and visceral adiposity^[76]. NRTI's can also lead to hepatic steatosis via inhibition of mitochondrial DNA replication, resulting in triglyceride accumulation in the liver^[77]. Hypertriglyceridemia, low HDL, and low total cholesterol have also been independently associated with HIV infection and may 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 may 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]. Though 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.

AIDS-related Liver Disease

AIDS Cholangiopathy

AIDS cholangiopathy occurs when infection-related strictures in the biliary tract lead to biliary obstruction. It typically presents with right upper quadrant pain (RUQ) and a markedly increased alkaline phosphatase with a less elevated bilirubin and normal or slightly increased transaminases. Patients may also have fever, nausea, vomiting, and diarrhea; jaundice is uncommon^[84]. 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 ARTera. 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. *Microsporidium*, *Cyclosporacayetanensis*, *Mycobacterium avium* intracellulare, and *Histoplasma capsulatum* have all been reported with AIDS cholangiopathy as well^[84]. Ultrasound or magnetic resonance cholangiopancreatography may 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 may help identify the infectious cause. Sphincterotomy improves the abdominal pain but does not extend survival,

and the alkaline phosphatase often remains elevated^[85, 86]. The most important aspect to treatment of AIDS cholangiopathy is ART administration, as 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.

AIDS-related Neoplasms

The AIDS-defining malignancies non-Hodgkin lymphoma (NHL) and Kaposi's sarcoma (KS), involve the liver in 33% and 9% of cases respectively^[89, 90]. Hepatic involvement of NHL may present with asymptomatic liver function test abnormalities, although patients may develop abdominal pain or jaundice. Hepatic involvement of KS rarely causes symptoms or mortality^[90].

Opportunistic Infections

Several opportunistic infections have been associated with hepatic involvement in advanced AIDS (see Table 5). Of these, *Mycobacterium avium* complex (MAC) 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 a clinical hepatitis^[90, 92]. When CMV presents as hepatitis, patients usually have a 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. Though LFT's are often abnormal, the liver involvement is usually asymptomatic^[94, 95]. Extrapulmonary *Pneumocystis jirovecii* involving the liver has been described and may be seen in the setting of inhaled pentamidine for prophylaxis of *Pneumocystis jirovecii* 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 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].

Conclusion

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.

Acknowledgments

Grant Support: This publication was made possible by Grant Numbers 1KL2RR025006-01 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research (JCP), NIH R01 AI071820 (CLT) and NIH R01 AI060449 (CLT). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Information on NCRR is available at <http://www.ncrr.nih.gov/>.

Abbreviations

AIDS	(acquired immunodeficiency syndrome)
anti-HBc	(hepatitis B core antibody)
anti-HBs	(hepatitis B surface antibody)
ART	(antiretroviral therapy)
CMV	(cytomegalovirus)
ddI	(didanosine)
HBsAg	(hepatitis B surface antigen)
HBV	(hepatitis B virus)
HCC	(hepatocellular carcinoma)
HCV	(hepatitis C virus)
HIV	(human immunodeficiency virus-1)
IRIS	(immune reconstitution inflammatory syndrome)
KS	(Kaposi's sarcoma)
MAC	(Mycobacterium avium complex)
AFLD	(nonalcoholic fatty liver disease)
NASH	(nonalcoholic steatohepatitis)
NHL	(non-Hodgkin lymphoma)
NNRTI	(nonnucleoside 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
<i>Infection</i>
Viral Hepatitis: HCV, HBV, HDV, HAV, HEV, CMV, EBV, HSV, VZV, HHV6
<i>Mycobacterium avium</i> complex
<i>Cryptococcus neoformans</i>
<i>Microsporidium</i>
<i>Pneumocystis jirovecii</i>
Bacillary peliosis hepatis
<i>Histoplasma capsulatum</i>
<i>Nonalcoholic fatty liver disease</i>
<i>Medication toxicity</i>
<i>Alcoholic liver disease</i>
<i>Recreational Drugs</i>
Cocaine
MDMA (Ecstasy)
<i>Neoplasm</i>
Lymphoma
Kaposi's sarcoma
Hepatocellular carcinoma
<i>Nodular regenerative hyperplasia</i>
<i>Autoimmune hepatitis</i>
<i>Hemochromatosis</i>
<i>Wilson's disease</i>
<i>Alpha-1 antitrypsin deficiency</i>
BILIARY DISEASE
<i>AIDS Cholangiopathy</i>
<i>Cryptosporidium</i>
CMV
<i>Microsporidium</i>
<i>Cyclospora cayetanensis</i>
<i>Mycobacterium avium intracellulare</i>
<i>Histoplasma capsulatum</i>
<i>Acalculous cholecystitis</i>
<i>Cryptosporidium</i>
CMV
<i>Isospora</i>
<i>Microsporidium</i>
<i>Neoplasm</i>
Lymphoma
Kaposi's sarcoma

HEPATIC PARENCHYMAL DISEASE

Primary sclerosing cholangitis

Primary biliary cirrhosis

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	Not defined, caution advised	Hypersensitivity reaction, direct drug toxicity/drug

MEDICATION	TYPICAL DOSE	DOSE ADJUSTMENT FOR HEPATIC INSUFFICIENCY	MECHANISM OF LIVER INJURY
	regimen		metabolism

Table 3

Features associated with presentation, prevention, and management of ART-related liver injury.

HYPERSENSITIVITY REACTION		DIRECT DRUG TOXICITY/METABOLISM	
<p>Associated Drugs: NVP, ETR, RTV, T20, MVC</p> <p>Onset: Greatest risk in first 6 weeks</p> <p>Can present through 18 weeks</p> <p>Clinical Manifestations: Abrupt onset flu-like symptoms, abdominal pain, jaundice, fever, with or without skin rash</p>	<p>Management</p> <ul style="list-style-type: none"> Discontinue all ART and all other potentially hepatotoxic medications Rule out other causes of symptoms Management is supportive Unknown whether other NRTI's can be used safely after NVP-associated hepatotoxicity After ABC-associated hepatotoxicity, switch to another NRTI. ABC contraindicated in future use 	<p>Associated Drugs: All NNRTI's, all PI's, most NRTI's, MVC</p> <p>Onset: Weeks to months</p> <p>Clinical Manifestations: May present with asymptomatic transaminase elevation Clinical hepatitis may present with anorexia, weight loss, fatigue, jaundice, abdominal pain, nausea, vomiting</p> <p>Prevention/Monitoring Monitor LFT's in NVP as above For other agents, monitor LFT's 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)</p>	<p>Management</p> <ul style="list-style-type: none"> Rule out other causes of hepatotoxicity, including viral hepatitis or HBV reactivation Symptomatic patients: <ul style="list-style-type: none"> Discontinue ART and other potentially offending medications Once symptoms and LFT abnormalities resolve, resume ART without offending agent(s) Asymptomatic patients: <ul style="list-style-type: none"> Mild elevations usually resolve without drug discontinuation If ALT >5-10x ULN and elevated direct bilirubin, discontinue ART If ALT >10x ULN, discontinue ART Once LFT abnormalities resolve, resume ART without offending agent(s)
MITOCHONDRIAL TOXICITY		IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME	
<p>Associated Drugs: NRTI's: ddI > D4T > AZT/ZDV > 3TC=FTC=ABV=TDF</p> <p>Onset: Weeks to months</p> <p>Clinical Manifestations: Anorexia, abdominal pain, nausea, vomiting, weight loss, fatigue May 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</p>	<p>Prevention/Monitoring: Check lactate in symptomatic patients or in patients with elevated anion gap or low bicarbonate</p> <p>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 may include hemodialysis or hemofiltration, mechanical ventilation •IV thiamine and/or riboflavin</p>	<p>Associated Drugs: Any ART</p> <p>Onset: First 2 months</p> <p>Clinical Manifestations: Nonspecific symptoms (fever, night sweats, fatigue, jaundice, nausea) May 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</p> <p>Prevention/Monitoring: Screen for HCV and HBV prior to 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 LFT's at least every month x first 3 months of ART initiation</p>	<p>Management: Symptomatic patients: •Discontinue ART Asymptomatic patients: AST/ALT > 10 x ULN •Closely monitor patients with less severe increases in AST/ALT Symptomatic patients: •Discontinue ART Asymptomatic patients: •Discontinue ART if AST/ALT > 10 x ULN •Closely monitor patients with less severe increases in AST/ALT</p>
HEPATITIS B REACTIVATION		HEPATITIS B REACTIVATION	
<p>Associated Drugs: 3TC, FTC, TDF</p> <p>Onset: After withdrawal of medication with anti-HBV activity or development of HBV resistance (usually months to years of therapy)</p> <p>Clinical Manifestations: Ranges from asymptomatic increase in LFT's to severe fulminant hepatitis Median onset 12-16 weeks after withdrawal agent(s)</p>	<p>Associated Drugs: 3TC, FTC, TDF</p> <p>Onset: After withdrawal of medication with anti-HBV activity or development of HBV resistance (usually months to years of therapy)</p> <p>Clinical Manifestations: Ranges from asymptomatic increase in LFT's to severe fulminant hepatitis Median onset 12-16 weeks after withdrawal agent(s)</p>	<p>Management: In setting HBV, ART regimen should include TDF and FTC (Truvada) or TDF and 3TC If 3TC is withdrawn due to HIV resistance, replace it with an agent with anti-HBV activity Management: •Resume anti-HBV therapy with appropriate agent based on resistance profile</p>	<p>Prevention/Monitoring: In setting HBV, ART regimen should include TDF and FTC (Truvada) or TDF and 3TC If 3TC is withdrawn due to HIV resistance, replace it with an agent with anti-HBV activity Management: •Resume anti-HBV therapy with appropriate agent based on resistance profile</p>

Table 4

Partial list of potentially hepatotoxic non-ART medications prescribed to HIV-infected individuals

MEDICATION	PATTERN OF LIVER INJURY
<i>Antifungals</i>	
Ketoconazole, Fluconazole, Amphotericin B	Hepatocellular injury
<i>Antibiotics</i>	
Ciprofloxacin	Hepatocellular injury
Azithromycin, Dapsone	Cholestatic injury
Trimethoprim-sulfamethoxazole	Mixed hepatocellular-cholestatic injury
<i>Tuberculosis treatment</i>	
Isoniazid, Rifampin, Pyrazinamide	Hepatocellular injury
Ethambutol	Cholestatic injury
<i>Anti-virals</i>	
Ganciclovir, Acyclovir	Hepatocellular injury
<i>Anabolic/Androgenic steroids</i>	
Testosterone, Nandrolone, Oxandrolone	Cholestatic injury, liver tumors, peliosis hepatis

Table 5

Key points regarding infections affecting the liver in HIV-infected individuals

Pathogen	Key Points
Hepatitis C Virus	<ul style="list-style-type: none"> •Screen all HIV-infected patients with HCV antibody •Test HCV RNA in patients with positive HCV antibody. If Ab negative, also consider if suspected acute HCV, or significant risk factors and advanced immunosuppression •If chronic HCV, immunize against HBV and HAV if not immune
Hepatitis B Virus	<ul style="list-style-type: none"> •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
Hepatitis D Virus	<ul style="list-style-type: none"> •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
Hepatitis A Virus	<ul style="list-style-type: none"> •Can cause fulminant hepatitis especially in presence of underlying liver disease
Hepatitis E Virus	<ul style="list-style-type: none"> •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
Cytomegalovirus	<ul style="list-style-type: none"> •Rarely symptomatic; may present with fever, malaise, weight loss, hepatomegaly •Usually mild transaminitis and mild cholestasis •May present as mass and mimic neoplasm on CT •Liver biopsy with large intranuclear and small cytoplasmic inclusions +/- granulomas
<i>Mycobacterium avium complex</i>	<ul style="list-style-type: none"> •Presents with fever, night sweats, weight loss, abdominal pain, nausea, diarrhea, HSM •Marked elevation of AP (>10-20x ULN) is hallmark •U/S shows diffusely hyperechoic liver +/- focal lesions •Liver biopsy with poorly formed non-caseating granulomas, foamy histiocytes, acid-fast bacilli
<i>Cryptococcus neoformans</i>	<ul style="list-style-type: none"> •May be asymptomatic or present with fever, RUQ pain, hepatomegaly •Labs usually show cholestasis with increased AP, variable bilirubin •May cause liver abscess •Liver biopsy may demonstrate ill-defined cystic areas or granulomas
<i>Mycobacterium tuberculosis</i>	<ul style="list-style-type: none"> •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
<i>Microsporidium</i>	<ul style="list-style-type: none"> •May cause increased bilirubin, transaminases, and especially AP
<i>Pneumocystis jirovecii</i>	<ul style="list-style-type: none"> •More common in patients receiving inhaled pentamidine for PCP prophylaxis •Usually moderate increases in aminotransferases and AP, but high elevations have been reported •CT may show hepatic calcifications •Liver biopsy with foamy nodules with <i>pneumocystis</i> cysts on methamine silver staining
<i>Bartonella henselae</i>	<ul style="list-style-type: none"> •Consider in patients with a history of cat contact

Pathogen	Key Points
	<ul style="list-style-type: none">•May present with HSM, liver failure, portal hypertension, fever, anemia, LAD, and skin lesions•AP elevated; may develop coagulopathy•U/S may show irregular hypoechoic regions•CT may reveal multiple hypoattenuating lesions of varying size•Liver biopsy with multiple blood-filled cavities of varying size
<i>Histoplasma capsulatum</i>	<ul style="list-style-type: none">•May 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

Abbreviations: HSM (hepatosplenomegaly), AP (alkaline phosphatase), RUQ (right upper quadrant) LAD (lymphadenopathy), U/S (ultrasound)