Chronic Liver Disease in the Human Immunodeficiency Virus Patient

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Disclosure: None.
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KEYWORDS

- Highly active antiretroviral therapy
- Hepatitis
- Fatty liver
- Nonalcoholic fatty liver disease
- Nonalcoholic steatohepatitis
- Metabolic syndrome
- Drug-induced liver injury
- Opportunistic infections

KEY POINTS

- Liver disease in HIV is an emerging etiology of morbidity in HIV. It is the second most common cause of mortality after HIV itself and hence merits vigilance and meticulous work-up.
- Hepatitis C virus is the most common viral hepatitis in HIV. It is hoped that newer all-oral drug regimens soon will allow for improved efficacy and increased compliance in all patients; they are already effective in some.
- Fatty liver in HIV is a multifactorial, potentially reversible etiology for chronic liver disease. No definitive treatment is available yet.
- Drug-induced liver injury is a common etiology of elevated liver functions in HIV, but close monitoring and identification of the culprit drug prevent morbidity.
- Opportunistic infections are on the decline in the age of highly active antiretroviral therapy but should still be considered as clinical situations dictate.

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INTRODUCTION

Since the discovery of the human immunodeficiency virus (HIV) 3 decades ago to the initiation of combination highly active antiretroviral therapy (HAART), the epidemiology of HIV and AIDS in the United States has fluctuated. Currently, there are 1.1 million HIV-positive individuals living in the United States, with nearly 16% of them being unaware of their infection.

With HIV-infected patients now living longer, liver disease has emerged as a significant cause of morbidity and mortality,\(^1\),\(^2\) and liver enzyme elevations are frequently noted in patients with HIV.\(^3\) Due to well-controlled HIV, opportunistic infections (OIs) involving the liver are now rarely seen. Although HIV-infected patients are not protected from having any specific liver disease, most liver diseases now seen in patients with HIV include drug-induced liver injury (DILI), viral hepatitis, and both alcohol and nonalcohol-related steatohepatitis (fatty liver).

This article discusses the common etiologies of increased liver enzymes or otherwise abnormal liver panel and hepatitis in HIV (Fig. 1), keeping in mind the pathogenesis for various etiologies. It shall briefly discuss diagnostics and treatment strategies for each condition, with the overall goal of providing the reader a basic framework for the management of liver disease in HIV. In general, the severity of liver enzyme elevations should be assessed using the National Institutes of Health (NIH)-NIAI (National Institute for Allergy and Immunology) guidelines (Table 1). In addition, liver synthetic function should be assessed with total and direct bilirubin and prothrombin time (PT) and international normalized ratio (INR). Those with evidence of hepatic decompensation (ascites, jaundice, hepatic encephalopathy), regardless of the etiology, should be considered for referral to a specialized liver center.

HEPATITIS C VIRUS/HUMAN IMMUNODEFICIENCY VIRUS COINFECTION

Globally there are 40 million HIV-infected individuals. The prevalence of hepatitis C virus (HCV) infection by itself was estimated at 4 million in the United States,\(^4\) and HCV has recently overtaken HIV as a cause of mortality.\(^5\) Because of shared routes of transmission, coinfection with hepatitis C and HIV, is common and the incidence of HCV/HIV coinfection ranges from 10% in those who acquired HIV sexually, to over 80% in those who acquired HIV by intravenous drug use.\(^4\) With the mortality of AIDS on the decline because of effective treatment strategies, liver disease caused by hepatitis C coinfection has become the leading cause of mortality in this group.\(^6\)

![Fig. 1. The potential etiologies of abnormal LFTs in HIV.](https://clinicalkey.com/assets/images/fig.png)
The presence of HIV skews the natural history of HCV infection, leading to increased viral load and increased rates of persistence, with an increase in liver-related mortality and morbidity. The risk of progression to chronicity in the presence of HIV increases to 95%, and death from hepatocellular cancer is as high as 13%.7,8

Although the risk of progression of liver disease to cirrhosis and end-stage liver disease (ESLD) in HCV/HIV coinfection is double and amplified sixfold, respectively,8 the presence of HCV does not influence disease progression of HIV to AIDS, even with HAART.9 This translates to cirrhosis being diagnosed within 12 years10 and hepatic decompensation by 15 years. Interestingly, HCV foretells a threefold likelihood of hepatotoxicity from older regimens of HAART,11–13 and close monitoring of liver function is required.

Pathogenesis

The mechanisms by which HCV promotes rapid progression of fibrosis and ESLD are under study and better understood. Apart from HIV causing dysregulation of T cells and increased replication of HCV, there are many other important mechanisms through which HIV accelerates the natural course of HCV (Fig. 2).

HIV is associated with intestinal villous effacement and CD4 cell depletion, and this in turn is associated with an increase in intestinal microbial product translocation into the bloodstream.

### Table 1

<table>
<thead>
<tr>
<th>Grade</th>
<th>With Normal Baseline AST/ALT</th>
<th>With Elevated Baseline AST/ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;1.25 × ULN</td>
<td>&lt;1.25 × BL</td>
</tr>
<tr>
<td>1</td>
<td>1.25–2.5 × ULN</td>
<td>1.25–2.5 × BL</td>
</tr>
<tr>
<td>2</td>
<td>2.6–5.0 × ULN</td>
<td>2.6–3.5 × BL</td>
</tr>
<tr>
<td>3</td>
<td>5.1–10 × ULN</td>
<td>3.6–5 × BL</td>
</tr>
<tr>
<td>4</td>
<td>&gt;10 × ULN</td>
<td>&gt;5 × BL</td>
</tr>
</tbody>
</table>

**Abbreviations:** BL, below limit; ULN, upper limit of normal.

The presence of HIV skews the natural history of HCV infection, leading to increased viral load and increased rates of persistence, with an increase in liver-related mortality and morbidity. The risk of progression to chronicity in the presence of HIV increases to 95%, and death from hepatocellular cancer is as high as 13%.7,8

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### Pathogenesis

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HIV is associated with intestinal villous effacement and CD4 cell depletion, and this in turn is associated with an increase in intestinal microbial product translocation into the bloodstream.
the portal venous system. The liver filters the portal venous blood and is exposed to lipopolysaccharide (LPS). Free LPS binds to Kupffer cells via interactions with circulating LPS-binding protein, cell surface CD14 (sCD14), and toll-like receptor 4 (TLR-4), leading to up-regulation of proinflammatory and profibrogenic cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-12.14,15

HCV induced TGF-β1 release from hepatocytes is enhanced by HIV.16 TGF-β1 is a profibrogenic cytokine that is instrumental in the immunopathogenesis of coinfection through various stimulatory pathways.

There is accelerated hepatocyte apoptosis in coinfection, leading to more inflammation and fibrosis.17,18 There is also an increase in steatohepatitis, which in turn up-regulates inflammation in the liver and is pro-fibrogenic.19,20 Finally, there is also evidence that HIV directly infects the stellate cells, and this promotes inflammation and secretion of fibrogenic stroma.21

**Diagnosis**

All HIV patients should be screened for HCV by enzyme-linked immunosorbent assay (ELISA). However, false-negative antibody tests can occur in those with CD4 counts less than 100. In those with a negative antibody, repeat testing is recommended yearly as long as patients have ongoing risks of transmission (high-risk sexual activity, illicit drug use). In addition, the presence of elevated liver enzymes should trigger diagnostic testing for HCV, although moderate elevations in liver enzymes from other etiologies can also be observed.3 Patients who test negative for HCV Ab should be counseled on risk factors for HCV.

In subjects with a positive HCV antibody, HCV infection must be confirmed by HCV RNA testing (Fig. 3). In those with a positive RNA, HCV genotype is required if treatment is contemplated. All HCV RNA-positive patients require assessment of disease severity, and although liver biopsy remains the gold standard for disease staging, it can be associated with complications. As such, noninvasive strategies for assessment of hepatic fibrosis have been developed. These can be divided into biochemical tests (simple and proprietary) and elastography (which measures liver stiffness). Two commonly used noninvasive fibrosis scores are APRI

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**Fig. 3.** Evaluation of HCV.

- **HCV Ab +**
- **HCV RNA and Genotype**
- **Liver Enzymes**
  - complete blood cell count with Plt
  - HBV sAg/sAb/cAb
- **HAV IgG**
- **HIV**
- **ANA**
  - Assess severity of disease (liver biopsy or non invasive test)
  - Assess for treatment (May require referral)
- **Avoid alcohol**
- **Counsel on household and sex**
- **Vaccinate for HAV and HBV**
- **Avoid raw shell fish**
- ** Repeat HCV RNA**
- **Resolved HCV**

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(aspartate aminotransferase to platelet ratio index) and the FIB-4 indices (patient age, aspartate aminotransferase, alanine aminotransferase, and platelets). Each has shown clinical utility in HIV-HCV.\textsuperscript{22–24} Noninvasive imaging studies such as transient elastography\textsuperscript{25,26} and magnetic resonance elastography are other means for staging but need referral to specialized centers. Those with suspected or proven cirrhosis require screening for esophageal varices and hepatocellular carcinoma (Fig. 4).

**Management**

Treatment of HCV/HIV coinfection is based on similar principles as treatment of HCV without HIV. Given the increased mortality with HCV in HIV, most patients should be considered for treatment. Given the improved response rates and lower adverse effect profiles of interferon-free treatment strategies, the most important determining factor to initiate treatment is the current stage of HCV (mild vs significant fibrosis), presence or absence of comorbidities, the control of HIV, and compliance. In certain individuals, treatment could be deferred if there is no fibrosis and/or if there are contraindications to treatment.

Until recently, the standard US Food and Drug Administration (FDA)-approved therapy for HCV has been pegylated interferon alfa (Peg-IFN) and ribavirin (RBV).\textsuperscript{27} The field of HCV treatment is moving fast, and it is anticipated that several interferon-free, all-oral regimens will be available for those with chronic HCV genotype 1, regardless of HIV coinfection, by 2015. All-oral regimens are currently available for HCV genotypes 2 and 3. Overall, sustained virologic response (SVR) rates exceeding 90% for genotypes 1, 2, and 4 are expected. Genotype 3 patients remain a challenge, particularly if patients have cirrhosis and have previously failed Peg-IFN and RBV. While choosing the appropriate drugs, consideration should also be given to the class due to strong drug–drug interactions between HAART and certain classes of HCV direct-acting antiviral agents. For those who develop ESLD and decompensation, liver transplant can be considered. Although overall post-transplant survival is suboptimal, if patients are carefully selected, outcomes approach HCV mono-infected patients.\textsuperscript{28} Hopefully, with more effective pre and post-transplant HCV therapy, this will become even less of an issue.

![Fig. 4. Diagnosis of significant fibrosis in HCV/HIV coinfection.](image-url)
HEPATITIS B VIRUS/HUMAN IMMUNODEFICIENCY VIRUS COINFECTION

Similar to HCV/HIV coinfection, HBV coinfection among HIV-positive persons is common because of shared route of transmission. Worldwide, an estimated 2 to 4 million people are currently living with HBV/HIV coinfection. In the United States, the prevalence is around 8%, which is approximately 20 times higher than the general US population. Up to two-thirds of HIV-infected individuals have markers of past exposure to HBV, and about 10% of these patients have chronic HBV coinfection. HIV coinfection adversely affects the natural history of HBV at every stage, and is associated with increased HBV replication and increased levels of HBV DNA. Coinfected individuals consequently are up to 6 times more likely to progress to chronicity. The progression of fibrosis is accelerated; the risk of cirrhosis and hepatocellular carcinoma is subsequently higher, and these patients are more likely to die from liver-related causes than HBV mono-infected individuals. Chronic HBV infection, however, does not appear to have a significant impact on the natural history or treatment outcome of HIV disease.

Pathogenesis

The exact mechanisms by which the disease course in HBV/HIV coinfection is altered have yet to be studied in detail. In general, the immunopathogenesis is similar to HCV/HIV coinfection (see Fig. 2), although only increased intrahepatic apoptosis has been documented in HBV/HIV coinfection. Furthermore, antiretroviral therapy (ART) can lead to hepatocellular injury by immune reconstitution and/or direct hepatotoxicity, accentuating liver dysfunction in coinfected patients.

Diagnosis

Similar to HIV-negative individuals, the diagnosis of HBV coinfection should be suspected when there is presence of elevated serum aminotransferases and the detection of hepatitis B surface antigen (HBsAg) and/or HBV DNA in the serum. Initial screening serology should include HBsAg, hepatitis B surface antibody (HBsAb), and anti-HBc (total or immunoglobulin g [IgG]) as detailed in Fig. 5. The hepatitis B e antigen (HBeAg) may or may not be detectable and is not essential for diagnosis.

Fig. 5. Clinical phases of chronic hepatitis B infection and diagnosis.

<table>
<thead>
<tr>
<th>Immune tolerant</th>
<th>Immune active</th>
<th>Chronic inactive carrier</th>
<th>Reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistently normal</td>
<td>Persistently high</td>
<td>Normal to minimal elevation</td>
<td>Elevated</td>
</tr>
<tr>
<td>HBsAg + HBsAb - HBeAg + Anti-HBe -</td>
<td>HBsAg + HBsAb - HBeAg +/- Anti-HBe +/-</td>
<td>Low to undetectable</td>
<td>Elevated</td>
</tr>
<tr>
<td>High</td>
<td>Moderate to high</td>
<td>Low to undetectable</td>
<td>Elevated</td>
</tr>
<tr>
<td>Asymptomatic Usually young individuals</td>
<td>Symptomatic Clinically diagnosed as chronic hepatitis B</td>
<td>Asymptomatic inactive histology but can have significant fibrosis</td>
<td>Symptomatic May behave like acute infection</td>
</tr>
</tbody>
</table>

a Normal ALT is < 30 IU/mL for males and < 20 IU/mL for females
b High HBV DNA is > 20,000 IU/mL and low HBV DNA is < 2000 IU/mL
HBV DNA should be tested as a marker of viral replication, and should also be obtained in all patients with positive isolated core antibody (presence of anti-HBc in the absence of HBsAg or HBsAb) to rule out occult HBV infection. Because spontaneous seroreversion (disappearance of HBsAb and reappearance of HBsAg) is possible among HIV-infected patients, especially those with very low CD4 counts (<200 cells/µL), HBV serologic tests should be repeated in the event of unexplained liver enzyme abnormalities to rule out reemergence of HBV infection. Noninvasive studies for diagnosis of fibrosis have been validated in HIV coinfected patients and have been discussed in the HCV/HIV co-infection section. The role of liver biopsy is more defined during follow-up after therapy initiation, but can also be used to aid in decision-making for patients not clearly meeting criteria for treatment.

Management

Management should be initiated in specialized centers with a multidisciplinary approach. The primary goal of anti-HBV therapy among HBV/HIV coinfected patients is to prevent liver-related complications by sustained suppression of HBV replication to the lowest achievable level. Because HBV DNA integrates into the host nuclear material, long-term treatment is usually needed. In most cases, dual therapy for HBV and HIV is started concomitantly; however anti-HBV therapy should be considered for all HBV coinfected individuals irrespective of the need for ART because of the overwhelming liver-related mortality.

Three anti-HBV agents, tenofovir (TDF), emtricitabine (FTC), and lamivudine (3TC), have potent antiretroviral activity and are also approved for HIV treatment. Entecavir appears to have weak antiretroviral activity and is also approved for HIV treatment. The preferred regimen is TDF in combination with either FTC or 3TC (which will also act as the nucleoside reverse transcriptase inhibitor backbone of ART) along with a third agent, such as efavirenz (EFV) or raltegravir (aidsinfo.nih.gov, WHO 2013 AIDS guideline). In the event of prior 3TC exposure or resistance, TDF plus FTC should be used. In case TDF cannot be used, (eg, because of bone or renal toxicity) entecavir can be used as a substitute, but only in the context of fully suppressive ART. When there is no indication for ART, then agents without antiretroviral activity such as peginterferon, adefovir, and telbivudine should be used. Agents with antiretroviral activity (TDF, FTC, 3TC, and entecavir) should be avoided in this setting as they can lead to selection of resistant HIV strains. Liver transplant for ESLD could be considered for the appropriate candidate, as long as the patient is maintained on HAART, and HIV is well controlled.

HUMAN IMMUNODEFICIENCY VIRUS—FATTY LIVER

Abnormal liver enzymes are common and occur in 40% to 60% of HIV-infected patients on ART, even in the absence of viral hepatitis. Given its prevalence in the general population, the majority of these subjects may have nonalcoholic fatty liver disease (NAFLD). NAFLD affects one-third of the US population and is the most common cause of elevated aminotransferases in the general population. The prevalence of NASH in estimated to be approximately 3% to 5%, and NASH-associated cirrhosis is projected to be the most common etiology for liver transplantation in the future. Few studies have looked at the prevalence of NAFLD and NASH in HIV-infected persons, and most of the data on prevalence of steatosis come from studies of HCV/HIV coinfected patients. Not surprisingly, the prevalence of NAFLD in HCV/HIV coinfected patients is significant, between 40% and 75%, while the prevalence of NAFLD in the HIV population without comorbidities such as viral hepatitis is slightly lower, at 31%. NASH is prevalent, at 26%. Similar to
HIV-negative patients, those with NAFLD, and in particular NASH, have increased cardiovascular disease and increased all-cause and cardiovascular mortality as well. With a significantly higher burden of NASH in the coinfected population, it is important to recognize that this population is also at heightened risk for cardiovascular incidents and for the development of progressive liver disease and eventually cirrhosis.

**Pathogenesis**

NAFLD in the general population is said to be the hepatic manifestation of the metabolic syndrome. The risk factors of obesity, hypertension, insulin resistance, dyslipidemia, and diabetes mellitus are prevalent, even for HIV patients. However, HIV patients also have additional complicating risk factors to make them more prone to NAFLD. In HIV, NAFLD could be caused by HIV itself, secondary to hepatitis viruses (HCV genotype 3), or due to certain HAART medication toxicity acting directly on the liver or via lipodystrophy (Box 1). Enumerated are some of the pathogenic mechanisms and risk factors related to NAFLD in HIV:

- Presence of ART is an independent risk factor for developing NAFLD in HIV.  
  Presence of HCV genotype 3 may be directly responsible for NAFLD.

Increased intestinal permeability through villous effacement and depletion of CD4 cells increases the amount of bacterial lipopolysaccharide reaching the liver and upregulates inflammation, accelerating NAFLD/NASH. Elevated soluble CD14 (sCD14, a marker of monocyte activation via LPS engagement of TLR-4) and soluble tumor necrosis factor (TNF) receptor II (sTNFRII) have been associated with severity of fibrosis in HCV/HIV coinfection, and have also been noted to be elevated in non-HIV NAFLD subjects.

**Diagnosis**

As with most chronic liver diseases, liver biopsy is the benchmark for diagnosis, but clinicians are implementing other noninvasive means to aid in diagnosis and assessment of hepatic fibrosis. Liver ultrasound or abdominal computed tomography (CT) scan is sensitive in detecting NAFLD, but results are not consistent in patients with less than 30% steatosis. A noninvasive test with 84% sensitivity for NAFLD is the fatty liver index (FLI). It incorporates body mass index (BMI), waist circumference, triglycerides, and gamma glutamyl transpeptidase (GGT), but has not been independently tested on HIV patients. Other noninvasive means of diagnosis of NAFLD are the

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**Box 1**  
**Pathogenesis of NAFLD in HIV**

- Insulin resistance and lipodystrophy related to the use of nucleoside inhibitors and other HAART drugs. Presence of ART is an independent risk factor for developing NAFLD in HIV.  
- HIV is associated with impaired glucose tolerance/insulin resistance. HIV is a direct suppressor of peroxisome proliferator-activated receptor and indirectly alters the signal pathway affecting modulation of TNF.
- Presence of HCV genotype 3 may be directly responsible for NAFLD.
- Intestinal permeability through villous effacement and depletion of CD4 cells increases the amount of bacterial lipopolysaccharide reaching the liver and upregulates inflammation, accelerating NAFLD/NASH.
liver fat score (LFS) and lipid accumulation product (LAP), which have been assessed in HIV patients.72

Management

HIV patients have comorbidities including DM (diabetes mellitus) and obesity, and similar to the rest of the US population, they are increasing in prevalence.73,74 At present, there are no therapeutic interventions to treat NASH that have been studied in the HIV-infected patient. Once a diagnosis of NAFLD unrelated to HCV/HIV coinfection has been established, a management strategy of conservative measures to control these modifiable risk factors would be beneficial. No studies have been performed, however, in HIV patients to confirm benefit. Although therapy with vitamin E or pioglitazone has been shown to reduce fibrosis in NAFLD,75 further studies to validate this effect in HIV patients are needed. Once decompensation occurs in the setting of cirrhosis, if there are no contraindications, liver transplantation should be considered. It should be noted that no studies have been performed regarding transplantation for NAFLD in an HIV population.

MISCELLANEOUS

Drug-Induced Liver Injury

Elevated liver enzymes related to drug toxicity (see Table 1) have been well documented1,13,51 and occur frequently, in 40% to 60% of patients on HAART, especially on older regimens. DILI has significant consequences on the health care of HIV individuals. First, it is associated with medication substitution or discontinuation of HAART, which leads to increase in OIs and a direct effect on mortality. Second, it has also been shown to increase the burden on the health care system in terms of office visits and health care costs. The spectrum of DILI in HIV-infected patients ranges from asymptomatic elevations of aminotransferases to hepatic failure and death.76

Classically, the NRTIs (nucleoside reverse transcriptase inhibitor) were most studied for association with hepatotoxicity. Compared with protease inhibitors (PIs), NRTIs have shown a greater rise in lactic acid and hepatotoxicity.77 The incidence of grade 3 or 4 hepatotoxicity in NRTIs is low, approximately 1%, although the presence of symptomatic lactic acidosis is high.78–80 NRTIs are also known to be associated with a syndrome of hepatic steatosis.81,82 Comparing NRTIs to NNRTIs (non-nucleoside reverse transcriptase inhibitor), NRTIs are more hepatotoxic. In clinical studies, nevirapine has been shown to have more hepatotoxicity than efavirenz.64 Overall, however, NNRTIs have a low rate of clinically significant hepatotoxicity.84,85 Among PIs, ritonavir and ritonavir-boosted HAART regimens have been most studied and identified as independent risk factors for the development of hepatotoxicity. Wit and colleagues86 documented ritonavir (full-dose therapy) as an independent risk factor, with a 5.8-fold increased risk of developing grade 4 liver enzyme elevations. Importantly, although full-dose ritonavir was identified as an independent risk factor for hepatotoxicity,83,87 Wit and colleagues also showed that low-dose ritonavir (defined as ≤200 mg twice daily) was not independently associated with an increased risk of liver injury.

The presence of chronic infection with HBV and/or HCV is a major risk factor for DILI, as several studies in HIV-infected patients have demonstrated.12,63,87 In fact, the presence of HCV coinfection increases the risk of severe hepatotoxicity by twofold after adjusting for the type of medication received and baseline liver enzyme levels.

Pathogenesis

Drugs, in particular NRTIs, have been proposed to cause hepatotoxicity primarily by a direct toxic effect on the hepatocyte mitochondria and resultant break in the
generation of adenosine triphosphate (ATP) and accumulation of lactic acid. When greater inhibition of mitochondrial DNA polymerase occurs, a higher degree of hepatotoxicity is observed. No exact mechanism for NNRTI and PI (protease inhibitors)-related hepatotoxicity has been clearly identified yet. The various drug categories and their toxic effects are summarized in Tables 2 and 3.

Management
The diagnosis of DILI is one of exclusion. In general, the diagnosis should have the key elements of time of onset with relation to initiation of a drug, clinical features, and course and recovery after discontinuation of the drug. Liver panel abnormalities reflect an elevation of ALT greater than aspartate aminotransferase (AST) and elevated alkaline phosphatase, but certain PIs like indinavir and atazanavir are associated with unconjugated hyperbilirubinemia resembling Gilbert syndrome. The dilemma of DILI is whether to discontinue the drug, as this impacts the clinical outcome of HIV. A general principle that one should be mindful of in the setting of DILI is that symptomatic hepatitis is more concerning than asymptomatic hepatitis. Symptomatic hepatitis should prompt discontinuation of HAART, as continuation of the offending drug is associated with worse outcomes. There is expert consensus that drugs that elevate ALT or AST levels greater than 10 times the upper limit of normal should be discontinued even if the patient is asymptomatic. When dealing with drug hypersensitivity reactions like fevers and rash, the offending drug should be discontinued immediately, as readministration could be fatal. Any symptoms of mitochondrial toxicity should also prompt discontinuation pending work-up of possible lactic acidosis. Drugs associated with hepatitis and significant direct hyperbilirubinemia are associated with a higher mortality rate and should be discontinued.

Human Immunodeficiency Virus-Associated Noncirrhotic Portal Hypertension or Nodular Regenerative Hyperplasia
Noncirrhotic portal hypertension (NCPH) is now recognized as an uncommon, but serious cause of hepatitis in HIV-infected patients without hepatitis coinfection. The most widely cited studies regarding NCPH have reported prevalence ranging from 1% to 8%. Diagnosis of NCPH is one of exclusion, and it is aided with a finding of an abnormal liver panel and portal hypertension in the absence of viral hepatitis, NAFLD, or other causes of portal hypertension. There is no standard diagnostic feature on liver biopsy, but nodular regenerative hyperplasia has been recognized. Liver biopsies have also revealed the absence of cirrhosis with paucity of and fibrous obliteration of small portal veins. Although researchers have not found a single etiology, several studies have noticed an association with older nucleoside inhibitors like didanosine (ddl) and stavudine. Studies have shown that cumulative ddl exposure may lead to NCPH, and this led the FDA to issue a warning linking ddl with this serious hepatopathy in 2010. Management is primarily supportive, and studies have shown that substituting ddl prior to development of portal hypertension was associated with slowing of NCPH, and could also result in a decline in mean ALT levels with clinical improvement.

Opportunistic Infections
The common systemic OIs that also affect the liver are Mycobacteria, fungi, pneumocystis, Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), Kaposi sarcoma and bacillary angiomatosis. OIs affecting AIDS patients with effective HAART are becoming less common in western countries. Management should be directed in conjunction with an infectious disease specialist.
| Idiosyncratic Reaction or Intrinsic Toxicity | Hypersensitivity Reaction Mitochondrial Toxicity Immune Reconstitution Steatosis |
|------------------------------------------|---------------------------------|--------------------------------|---------------------------------|--------------------------------|
| Drug example | NVP | NVP > ABV | ddI > d4T > AZT > ABV = TDF = LAM = FTC | Any NRTIs, PIs |
| Characteristic | Dose-dependent for intrinsic | Often associated with rash | Lactic acidosis | Low CD4 and chronic HBV |
| Time of onset | Can vary by agent | Usually within 8 wk | Tends to occur after prolonged exposure | Usually within the first few months |
| Abbreviations: ABV, abacavir; AZT, zidovudine; FTC, emtricitabine; GT, genotype; HBV, hepatitis B virus; LAM, lamivudine; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; TDF, tenofovir. | Increased with certain polymorphisms. |
AIDS cholangiopathy

AIDS cholangiopathy is a nonfatal cause for hepatitis in HIV patients.\textsuperscript{105–107} It has been reported to affect 24% of HIV patients, but this was prior to the advent of HAART.\textsuperscript{108} Its incidence now is said to be on the decline.\textsuperscript{109} The exact pathogenesis is still being studied, but there has been a clear association seen with opportunistic infections such as \textit{Cryptosporidium}, CMV, \textit{Microsporidium}, \textit{Giardia}, \textit{Mycobacterium avium} [MAC], \textit{Cyclospora cayetanensis}, and even \textit{isospora}.\textsuperscript{106,109–114} suggesting that HIV cholangiopathy is an infectious sclerosing cholangitis. It is typically observed in patients with CD4 counts of less than 100/mm\textsuperscript{3}.\textsuperscript{105} Patients generally present with biliary pain (ie, right upper quadrant [RUQ]) and/or midepigastric abdominal pain, but can also present with nausea, diarrhea,\textsuperscript{114–118} weight loss, and jaundice.\textsuperscript{105} Blood chemistry studies reveal mild-to-moderate elevation in alkaline phosphatase and gamma-glutamyl transferase levels.\textsuperscript{106} Diagnosis is best confirmed by ERCP, which is the most specific diagnostic tool. It has an added advantage of therapeutic intervention with sphincterotomy. Similar to ERCP for diagnosis, but a cheaper initial screening test is a simple biliary ultrasound. Based on a positive or negative screen, further confirmatory diagnostic tests like MRCP or ERCP can be obtained.

Treatment consists of endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy. This procedure has been shown to alleviate symptoms, but has no bearing on mortality\textsuperscript{105,116,117,119} or improvement in liver enzymes. The only definitive therapy is initiation of HAART, which has the most important effect on survival.\textsuperscript{119,120}

\textbf{Mycobacterial infections}

Prior to HAART, mycobacterial infections (tuberculosis and MAC) were the most commonly diagnosed infections on liver biopsy in patients with HIV. In a retrospective study by Lanjewar and colleagues\textsuperscript{121} examining liver specimens from 171 patients, the most prevalent infection found was tuberculosis (41%). In another large study in North America, MAC was identified in 17.4% of liver biopsies in HIV-positive patients.\textsuperscript{122} Symptoms are systemic and nonspecific, including fever, weight loss, and diarrhea. On biochemical testing, abnormal liver enzyme elevations with jaundice can occur,

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
\textbf{Drug} & \textbf{Hepatotoxicity} & \textbf{Example} \\
\hline
Anti-PJP agents & Increased AST, ALT, and ALP possible & Trimethoprim-sulfamethoxazole \\
\hline
Antiherpes and CMV agents & Rare elevations in AST and ALT, bilirubin & Acyclovir \\
\hline
Antifungal agents & Increased AST and ALT inhibits cytochrome P450 and may increase PI levels & Ketoconazole \\
\hline
Macrolide antibiotic & Increased ALP inhibits cytochrome P450 and may increase PI levels & Erythromycin \\
\hline
Antituberculosis agents & Increased AST and ALT & Isoniazid, rifampicin, pyrazinamide \\
\hline
Lipid-lowering agents & Increased AST and ALT & Statins \\
\hline
Anabolic steroids & Increased ALP, bilirubin & Nandrolone \\
\hline
\end{tabular}
\caption{Nonhuman immunodeficiency virus drugs associated with drug induced liver injury}
\end{table}

\textit{Abbreviations:} ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; PI, protease inhibitor; PJP, \textit{Pneumocystis jiroveci}. 

\section*{AIDS cholangiopathy}

AIDS cholangiopathy is a nonfatal cause for hepatitis in HIV patients.\textsuperscript{105–107} It has been reported to affect 24% of HIV patients, but this was prior to the advent of HAART.\textsuperscript{108} Its incidence now is said to be on the decline.\textsuperscript{109} The exact pathogenesis is still being studied, but there has been a clear association seen with opportunistic infections such as \textit{Cryptosporidium}, CMV, \textit{Microsporidium}, \textit{Giardia}, \textit{Mycobacterium avium} [MAC], \textit{Cyclospora cayetanensis}, and even \textit{isospora}.\textsuperscript{106,109–114} suggesting that HIV cholangiopathy is an infectious sclerosing cholangitis. It is typically observed in patients with CD4 counts of less than 100/mm\textsuperscript{3}.\textsuperscript{105} Patients generally present with biliary pain (ie, right upper quadrant [RUQ]) and/or midepigastric abdominal pain, but can also present with nausea, diarrhea,\textsuperscript{114–118} weight loss, and jaundice.\textsuperscript{105} Blood chemistry studies reveal mild-to-moderate elevation in alkaline phosphatase and gamma-glutamyl transferase levels.\textsuperscript{106} Diagnosis is best confirmed by ERCP, which is the most specific diagnostic tool. It has an added advantage of therapeutic intervention with sphincterotomy. Similar to ERCP for diagnosis, but a cheaper initial screening test is a simple biliary ultrasound. Based on a positive or negative screen, further confirmatory diagnostic tests like MRCP or ERCP can be obtained.

Treatment consists of endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy. This procedure has been shown to alleviate symptoms, but has no bearing on mortality\textsuperscript{105,116,117,119} or improvement in liver enzymes. The only definitive therapy is initiation of HAART, which has the most important effect on survival.\textsuperscript{119,120}
which can be due to extrahepatic obstruction from porta hepatitis and peripancreatic lymphadenopathy. Diagnostic work-up is initiated with an abdominal ultrasound, which in the case of tuberculosis would reveal focal lesions, and in the case of MAC would show hepatosplenomegaly. Confirmation of tuberculosis of the liver is by liver biopsy that reveals granulomas. For MAC, liver biopsy shows microscopic obstruction of small biliary ducts, similar to AIDS cholangiopathy. Treatment of HIV with HAART is of the utmost importance. For tuberculosis, adjunctive treatment with RIPE (Rifampin, Isoniazid, Pyrazinamide, Ethambutol) therapy is necessary. For MAC, adjunctive therapy with macrolide antibiotics is indicated, until there is a CD4 cell response to the HAART.

**Fungal infections**

The common fungal infections that affect the liver are Cryptococcus, Histoplasma, Coccidiomycosis, and Candida. Incidence of opportunistic fungal disease in general, localized or widespread in form has been reported to be 58% to 81%. Fungal involvement of the liver is usually in the context of disseminated disease with a low CD4 count. In 2001, Shibuya and colleagues retrospectively found liver involvement with generalized cryptococcosis in 66.7% of 162 patients with evident fungal infection. Lamps and colleagues found that of 36 patients retrospectively analyzed with histoplasma involving the liver, 47% had enlarged liver, but only 17% had discrete grossly apparent hepatic lesions on pathology. Apart from HAART, rapid initiation of specific antifungals helps reduce mortality.

**Pneumocystis jiroveci infection**

The liver is a common extrapulmonary site of Pneumocystis jiroveci (PJP) involvement in the setting of disseminated disease. PJP has also been reported to be associated with aerosolized pentamidine prophylaxis. The clinical picture resembles hepatitis. Diagnosing PJP of the liver starts with imaging; ultrasound reveals hypoechoic or echogenic foci representing calcifications. CT of the abdomen shows hypodense lesions or calcifications that suggest PJP. Specific treatment is with systemic antibiotics such as sulfamethoxazole/trimethoprim, pentamidine, or dapsone.

**Epstein-Barr virus**

Hepatic involvement with infectious mononucleosis is estimated in 30% of cases in the elderly and 10% of cases in young adults. It presents with mild elevations of serum aminotransferases and elevated bilirubin in the majority of patients. Fulminant hepatic failure may occur in immunocompetent patients, in those with HIV coinfection, and in patients with complement deficiency, in whom it may be fatal. The pathogenesis is likely not direct hepatocyte infection or cytotoxicity, but is more likely related to immune responses to viral antigens expressed on hepatocytes. Diagnosis is primarily by serology with positive antibodies and serum polymerase chain reaction (PCR). EBV has a self-limited course, and initial treatment should be supportive, although several case reports have shown success with ganciclovir in immunocompromised post-liver transplant patients for EBV fulminant hepatitis and immunocompetent patients with severe EBV hepatitis.

**Cytomegalovirus**

CMV is a common OI in HIV, especially in the setting of severe immunosuppression. Liver involvement has been reported in as many as 44% of patients at autopsy in certain studies. Most clinically significant infection occurs by reactivation of a previously latent infection. Although liver involvement is generally clinically silent, severe disease can occur in the setting of disseminated/systemic involvement. Serology
and culture are the mainstays of diagnosis. Imaging studies with ultrasound show echogenic liver lesions, and abdominal CT demonstrates multiple low-attenuated lesions. Ganciclovir and related antiviral agents are the mainstays of treatment in setting of the immunocompromised patient, especially with diffuse disease.

**Kaposi sarcoma**

Once a common presentation of AIDS, the incidence of KS is now on the decline in the HAART era.\(^{135}\) Previously, prevalence rates of up to 22% were reported in autopsy series. Herpesvirus 8 has classically been associated with Kaposi sarcoma. Liver involvement presents with hepatomegaly and related abdominal pain and is observed in the setting of other manifestations of Kaposi sarcoma. Ultrasound shows multiple hyperechoic periportal bands and nodules, and CT of the abdomen shows periportal involvement. Liver biopsy is confirmatory for diagnosis. Treatment of Kaposi sarcoma is with HAART, in particular ritonavir-boosted therapy, which has antiangiogenic effects and will resolve tumor burden.\(^{136}\)

**Bacillary angiomatosis**

Bacillary angiomatosis commonly manifests as a mucocutaneous disease irrespective of HIV status. In HIV, it is considered to be a late-stage infection, and although seroprevalence can be high,\(^{137}\) clinical prevalence rates have been reported to be low at 1.2 cases per 1000 patients.\(^{138}\) Bacillary angiomatosis presents with lymphadenopathy and abdominal pain, and manifests as disseminated lesions on the skin, and in the liver and other solid organs.\(^{139–141}\) In the liver, cystic spaces filled with blood (peliosis hepatitis) are seen. Diagnosis is by radiography, with findings of hepatomegaly and cystic lesions.\(^{142,143}\) Diagnosis is confirmed by biopsy of cutaneous lesions, which reveal *Bartonella henselae* and *Bartonella quintana* on Warthin-Starry staining. Management is with HAART and antibiotics for 4 to 6 months. The disease is fatal if not treated early.

**SUMMARY**

Chronic liver disease in the HIV-infected individual is common and poses a challenge to clinicians and scientists. It is an entity that requires management in specialized centers. The more common etiologies that clinicians are now encountering are viral hepatitis coinfection, fatty liver, and DILI. Despite extensive research, much has yet to be elucidated about the underlying pathophysiology. For HCV/HIV coinfection, newer drug therapies that offer better SVR, compliance, and fewer systemic adverse effects are forthcoming. The future era in HIV and chronic liver disease should be a promising one.

**REFERENCES**


