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Evaluating Liver Disease in HIV-Infected Patients for the Primary Care Physician

by Gaurav Singhvi, George Tan

Patients with HIV are living longer given the improvement in antiretroviral medications, and consequently liver disease has emerged as one of the leading causes of morbidity and mortality in this cohort. As this patient population becomes more complex, primary care providers and specialists will need to work together in order to deliver optimal care. This article explores the major etiologies of liver disease in HIV patients, which include both infectious and non-infectious entities. Infectious causes include HBV, HCV, and HIV itself, whereas non-infectious contributors include highly active antiretroviral therapy (HAART), non-alcoholic fatty liver disease (NAFLD), and hepatotoxins such as alcohol. Many of these etiologies overlap with one another and synergistically produce hepatic injury. Internists need to be aware of these mechanisms so that they may better counsel, educate, and co-manage this patient population.

INTRODUCTION

HIV continues to be a major worldwide epidemic. Globally, there are approximately 40 million people living with HIV,¹ and in the United States there are more than 1.1 million Americans infected with HIV with an incidence of nearly 60,000 new cases per year.² In the past, many HIV patients died from pathogens that were able to invade an immunocompromised host, but more recently there has been a dramatic decline in the incidence of these fatal opportunistic infections.

This significant decrease in mortality is a direct result of the development of HAART in the mid 1990's.^{2,3} Though HAART has successfully prolonged longevity, HIV patients are now more likely to suffer significant morbidity and mortality from other disorders such as liver disease and its associated complications.^{4,5} In fact, liver disease has emerged as one of the leading causes of death in the HIV positive population. For example, in a retrospective chart review in a 280 bed hospital in Jamaica Plain, MA, HIV deaths due to liver disease increased from 11.5% in 1991, to 13.9% in 1996, to 50% in 1998-1999 ($P = 0.003$), while the rate of opportunistic infections and bacterial pneumonia declined accordingly.⁶ Additionally, a French mortality

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study described increasing proportions of liver death over a five-year interval (13.4% in 2000 to 15.4% in 2005), with a simultaneous rise in hepatocellular carcinoma deaths from 15% to 25% (P=0.03).⁷

Indeed, the long-term consequences of chronic liver disease is significant since it leads to a variety of grave sequelae and a decreased quality of life.⁵ Early effects of liver disease manifest in a variety of ways, from asymptomatic to generalized symptoms such as fatigue, nausea, loss of appetite, or abdominal pain. HIV related liver injuries may spontaneously resolve, although some patients may decompensate and develop jaundice, fibrosis, or cirrhosis, which in turn may lead to serious conditions such as gastric or esophageal varices, ascites, hepatocellular carcinoma, hepatic encephalopathy, and ultimately death. In addition to the impact on personal health, liver disease in HIV infected patients significantly increases health care costs, largely due to protracted hospital admissions.⁸ Before the widespread use of HAART, hepatologists rarely had a direct role in the management of HIV patients. Now, however, several studies are highlighting the need to focus on liver disease in HIV-infected patients.² Undoubtedly, primary care physicians too will have to play an important role in the co-management of non-AIDS related HIV conditions. The aim of this article is to discuss several major etiologies (infectious versus non-infectious) and recommendations for generalists to consider when evaluating liver disease in the HIV-infected patient (see Table 1).

Infectious

Hepatitis C

Of the approximately 40 million people living with HIV worldwide, roughly five million are also co-infected with the Hepatitis C virus (HCV).¹ Of the 1.1 million HIV patients in the United States, 25-30% are also infected with HCV.^{9,10} HIV and HCV co-infection is common given the similar routes of transmission.^{9,11} In fact, over 60% of patients who acquired HIV infection via intravenous drug use are also infected with Hepatitis C.¹⁰ Liver disease has become a major cause of mortality in HIV patients primarily co-infected with HCV. For instance, in the North American AIDS Cohort Collaboration on Research and Design, HCV co-infected patients had an 85% increased risk of death.¹² Furthermore, other cohort studies have shown that HCV related liver disease has emerged as one of the leading

Table 1. Major Etiologies of Liver Disease in HIV Patients

Infectious	Non-Infectious
HCV Co-infection	HAART
HBV Co-infection	NAFLD
HIV itself	Alcohol and other Hepatotoxins

Abbreviations:

HCV, hepatitis C virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; NAFLD, nonalcoholic fatty liver disease.

causes of morbidity and mortality in co-infected persons partly due to a more rapid progression of liver disease in those with concurrent HIV infection.¹³ Patients with co-infection have an increased rate of progression to cirrhosis, decompensated liver disease, hepatocellular carcinoma, and death.^{14,15} It should be noted that although newly approved direct-acting antivirals (DAA) have the potential to cure patients infected with Hepatitis C, this may be more challenging in the HCV/HIV co-infected patient due to several barriers including high cost and adverse drug interactions between HAART and DAA.¹⁶

Hepatitis B

Similar to HCV, Hepatitis B virus (HBV) infection is also common among patients with HIV due to similar transmission routes.¹¹ Of the 40 million people living with HIV globally, almost four million are chronically infected with Hepatitis B.¹ In the United States, nearly 10% of the 1.1 million HIV patients also have HBV co-infection, with the rates of liver related morbidity and mortality higher in this group compared to patients infected with either virus alone.¹⁷ A retrospective study from an Iranian infectious disease center, which examined 124 HIV infected patients found HIV/HBV co-infected patients to have significantly higher serum AST and ALT concentrations, as well as higher rates of morbidity and mortality.¹⁸ Furthermore, it has been clearly established that HIV alters the natural history

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of both HBV and HCV by increasing viremia levels.⁹ Additionally, the histological course of HBV and HCV is exacerbated by HIV since it enhances the severity of liver fibrosis and hastens the risk of cirrhosis.¹⁹ Also worth mentioning is the fact that managing Hepatitis B in HIV co-infected patients is much more complicated due to the dual activity of several nucleoside analogues, the decreased response to interferons, and the more rapid development of lamivudine-resistant HBV.²⁰

HIV

In addition to HCV and HBV, HIV itself may play a major role in liver injury. For instance, Brau et al. found that a higher HIV RNA level was linked to a more rapid progression of liver fibrosis.²¹ while Mehta et al. reported that detectable HIV RNA levels (>400 copies/mL) were connected to a 3.8 fold higher risk of necroinflammation of the liver.²² Furthermore, the Swiss HIV Cohort Study showed that HIV RNA levels > 100,000 copies/mL was associated with an elevated ALT, independent of HAART.²³ This independent association between greater plasma HIV-RNA levels and faster liver fibrosis progression has also been observed by others.¹⁹ Additionally, there is now growing evidence that HIV can harm the liver through both direct and indirect mechanisms. Directly, hepatic Kupffer cells and endothelial cells may be infected with HIV, and hepatic stellate cell receptors such as CXCR4 may be activated by HIV, which induces fibrogenesis.²⁴ Moreover, abnormalities in liver function tests may be produced exclusively by direct inflammation of hepatocytes caused by HIV itself. The main mechanism theorized involves apoptosis and mitochondrial dysfunction coupled with HIV proteins, which stimulate hepatic inflammation.²⁵ Indirectly, HIV can also damage a patient's intestinal mucosa and alter the gut wall permeability, resulting in microbial translocation of bacterial endotoxins such as lipopolysaccharide (LPS), which has been shown to contribute to liver disease injury and progression.²⁶

Non-infectious

HAART

While HIV itself may cause liver injury, its treatment may as well. Even though HAART has saved millions of lives and is one of the most successful breakthroughs in modern medicine,² all antiretroviral medications

carry the risk of hepatotoxicity. This hepatotoxicity may be associated with a single antiretroviral drug or with a cocktail of HIV medications, which are given in combination. These medication related injuries can range in severity from mild, transient elevations in liver function tests, to sudden and severe hepatic failure. Severe hepatic failure due to HAART was observed in approximately 10% of HIV patients in retrospective studies, with life threatening events appearing at a rate of 2.6 per 100 person years.⁸ The four primary pathways of HAART associated liver damage include mitochondrial toxicity, direct hepatocellular toxicity, hypersensitivity reactions, and immune reconstitution in the presence of HCV or HBV.¹

NAFLD

Nonalcoholic fatty liver disease (NAFLD), associated with the metabolic syndrome, is a term which comprises a spectrum of liver conditions that range from simple steatosis (fat alone) to steatohepatitis (NASH). These disorders are becoming increasingly common in HIV positive patients with and without chronic viral hepatitis. NASH is associated with advanced liver fibrosis and cirrhosis.^{27,28} Over the past decade it has been shown to be an early marker of cardiovascular disease as well, which is another emergent issue itself.²⁹ The prevalence of NAFLD ranges between 14-31% in the general population,³⁰ with approximately 6% affected by NASH.³¹ Unlike most other liver diseases, NAFLD remains a clinicopathologic diagnosis since there is no reliable biochemical, serologic, radiologic, or genetic marker of disease presence or severity. It is characterized by the presence of excessive fat in the hepatocytes of non-alcoholics.³¹ Non-invasive sonography, CT, and MRI may be effective at detecting steatosis, but only if greater than 33% of fat is present in the liver.³⁴ The gold standard for diagnosis is liver biopsy,²⁷ although this may be limited in many clinical care settings due to the lack of availability, the risk of complications (including pain, bleeding, and death), and the relatively high cost of the procedure.^{32,33} Nevertheless, NAFLD has become the most common etiology of chronic liver disease in HIV patients who do not have viral co-infection,³⁵ as MRI and CT studies report a 37-42% rate of steatosis among HIV patients alone, and this percentage increases to 67% among those with HBV or HCV co-infection.³⁶ Linking of steatosis to NAFLD involves an association with the

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metabolic syndrome, which involves visceral obesity, insulin resistance and diabetes mellitus, hyperlipidemia (especially hypertriglyceridemia), and hypertension.^{37,38} These metabolic abnormalities may accelerate liver fibrosis,³⁸ and the rates of NAFLD in HIV patients will continue to rise as the degree of obesity and metabolic syndrome become more prevalent in the community.³¹

Overlapping Etiologies

While many individual etiologies of hepatic injury in HIV patients have been discussed so far, the underlying mechanism is most likely a more complicated, interactive, and multifactorial process, which is best summed up pictorially (Figure 1). As mentioned earlier, HIV itself or its treatment may cause liver damage. Therefore, since HIV RNA and HAART are opposing mechanisms of liver damage, HAART induced damage could be more noticeable in patients with well-suppressed viral loads, while HIV RNA generated hepatic injury might be more readily seen in patients with poorly controlled HIV viral loads.²⁴ In addition, HAART related hepatotoxicity may be more likely to develop in patients with underlying HCV or HBV. For instance, studies indicate that HIV/HCV co-infected patients have higher degrees of liver fibrosis and an accelerated progression of liver disease,^{39,40} while HIV/HBV co-infected patients on HAART are susceptible to clinically significant hepatotoxicity.¹⁷ Antiretroviral medications may also lead to the development of metabolic syndrome,³¹ with one mechanism seen in the protease inhibitor associated development of insulin

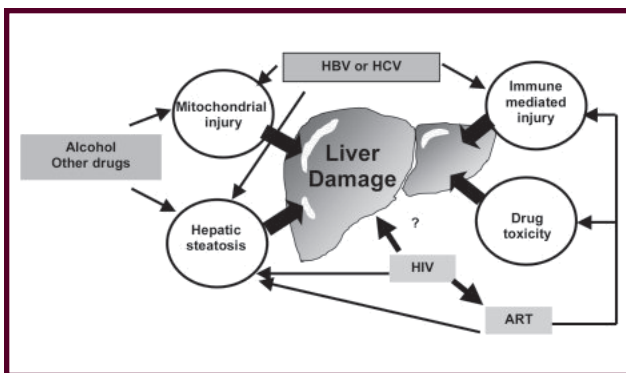


Figure 1. Diagram showing factors associated with hepatic injury in HIV-infected patients.¹

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Table 2. Recommendations for the Primary Care Provider

Get baseline liver function tests and monitor periodically
Screen for co-infection (HAV/HBV/HCV) and vaccinate when appropriate
Counsel on safe sex and to not share needles
Advise against alcohol and other hepatotoxins
Encourage healthy diet and exercise
Reinforce medication adherence

Abbreviations:

HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

resistance and dyslipidemia, both of which are risk factors for steatosis.⁴¹ Steatosis itself may cause liver damage, but it may also sensitize the liver making it more susceptible to inflammatory and immune mediated injuries.²⁴ Both HAART and HBV/HCV co-infection may also affect the liver via immune mediated injury as well.¹ Furthermore, alcohol and other hepatotoxins may exacerbate liver toxicity, and like HBV/HCV co-infection, this may directly cause mitochondrial injury in the liver and promote hepatic steatosis.^{1,6,30}

Recommendations for the Primary Care Provider (See Table 2)

Based on experience from managing other chronic medical conditions, primary care providers should be highly capable of overseeing and coordinating a multidisciplinary approach to HIV care. In fact, a study involving 5,247 patients linked to 177 physicians (102 generalists and 75 infectious disease specialists) showed that PCPs with experience in HIV management were able to provide high-quality care to complex HIV patients.⁴² Indeed, when working together with a team

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of specialists, there are several things that internists may do to help co-manage liver disease in HIV patients. First, the PCP should obtain baseline liver function tests and periodically monitor for hepatotoxicity. While evaluation of the risk versus benefit for many medications continues to be a dilemma for regulatory agencies, the US Food and Drug Administration (FDA) defines hepatotoxicity as aminotransferase levels exceeding three times the upper limit of normal and/or when bilirubin levels are more than twice normal.¹ Next, all HIV patients should be screened for viral Hepatitis A, B and C, and if non-immune, these patients should be vaccinated against both HAV and HBV since the increased severity of hepatitis in patients with preexisting liver disease is significant.^{8,11} While there is currently no vaccine for the Hepatitis C virus, HIV patients should be educated on transmission patterns and counseled on safe sex and the risk of needle sharing.¹¹ Along similar lines, excessive alcohol intake has been observed in one-third of HIV-infected individuals³⁰ and clinicians should advise these patients to avoid consumption and limit the exposure of other hepatotoxins such as acetaminophen.¹¹ In addition, primary care providers should always encourage a healthy diet and exercise, since lifestyle may play a significant role in the development of liver disease among HIV patients. Studies have not only shown a link between BMI, high cholesterol levels, and diabetes in liver disease progression,²⁶ but they have also highlighted the fact that optimum nutrition can improve the quality of life for persons living with HIV/AIDS, slow the progression of HIV to AIDS, and improve the tolerance to antiretroviral therapy.⁴² Lastly, health care providers must reinforce medication adherence, as there is a huge potential for adverse outcomes given the possibility of drug resistance, treatment failure, and progression of disease if medications are utilized inappropriately.⁴³

CONCLUSION

As patients with HIV are living longer and experiencing increasing morbidity and mortality from liver disease, primary care providers will have to be aware of the major etiologies of hepatic injury in this special patient population. This article presented a broad overview of many major infectious and non-infectious factors that every clinician should keep in mind when managing these complex patients. Internists will continue to

play an important role in disease management of these patients in the future, and since primary care providers often develop a long lasting relationship and rapport with their patients, this provides an ideal setting for generalists to screen HIV patients for co-infections, vaccinate the non-immune, encourage healthy lifestyles and emphasize medication adherence at every visit. This reinforcement at both the primary care and specialty levels will ensure that patients do not receive fragmented care or conflicting information, but rather obtain coordinated care from health care providers working together to provide the best care for their patients. ■

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