2 Epidemiology of Liver Disease in Human Immunodeficiency Virus-Infected Persons

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Introduction

In the era of combination antiretroviral therapy (CART) and improved survival [1], liver disease has become a leading cause of morbidity and mortality among HIV-infected persons [2–4]. The term "liver disease" encompasses a wide spectrum, ranging from asymptomatic mild elevations of liver enzymes (aspartate aminotransferase, AST; alanine aminotransferase, ALT; alkaline phosphatase, ALP) to cirrhosis and end stage liver disease with all its complications (e.g., ascites, esophageal varices, hepatic encephalopathy). Liver disease in HIV-infected persons may be due to the virus itself, combination antiretroviral therapy (CART) used to treat HIV, infectious and noninfectious complications of HIV, or a combination of the above. Since several potential factors may be at play in any given HIV-infected person with liver disease, at times it is very difficult to clearly ascribe etiology. In addition to opportunistic infections and cancers, several conditions that are common in the general population may be seen with increasing frequency in HIV-infected persons. In this chapter, we discuss the epidemiology of liver disease in HIV-infected patients by etiology. Pathogenesis, natural history, and treatment for these conditions are discussed separately in other chapters.

While the majority of liver related morbidity and mortality is due to coinfection with hepatitis C virus (HCV) and excess alcohol use [5–7], the list of causes is extensive. Liver disease is implicated as the cause of death in 15–17% of the deaths in HIV-infected persons of which two thirds to three quarter are attributed to HCV coinfection [7, 8]. The proportion of liver related deaths among HIV-infected persons increased from <2% in 1995 to 17% in 2005 [8]. Excessive alcohol was reported in 48% of those patients, and 62% had undetectable HIV RNA levels [8]. The prevalence of liver enzyme elevation in HIV-infected persons in the absence of HCV or HBV coinfection is approximately 16%, with an incidence of 3.9 per 100 person years [9, 10]. Such elevations are associated with higher HIV RNA levels higher body mass index, and excess alcohol use. However, mild to moderate elevations do not seem to have a significant effect upon disease progression or mortality [9, 11]. Liver cirrhosis is a more serious consequence in HIV-infected persons, with an estimate overall prevalence of 8.3% (95% CI 7.2–9.5). The presence of liver cirrhosis in HIV-infected persons in the absence of viral hepatitis or alcohol use is 1.1% (95% CI 0.5–1.8) [12].

Combination Antiretroviral Therapy

Therapy with combination antiretroviral therapy is associated with liver enzyme elevation in 6–30% of patients [13]. Severe CART-related hepatotoxicity is reported in approximately 10% of patients, and life-threatening events are reported at a rate of 2.6 per 100 person years [14]. Most antiretroviral drugs used to treat HIV infection can lead to liver injury, but is particularly true for nonnucleoside reverse transcriptase inhibitors and protease inhibitors. Even within a class, there may be differences in the degree of liver injury potential. In a prospective study of 568 subjects, nevirapine-containing regimen was associated with twice as many grade 3 or 4 liver enzyme elevations compared with efavirenz-containing regimens [13]. Concomitant alcohol use and HCV coinfection may increase risk of liver injury in these people. However, the overall risk is small and is usually reversible when recognized in time. In one study, 88% of HIV–HCV coinfected persons on combination antiretroviral therapy remained free of any liver toxicity [15]. Risk of liver toxicity

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K.E. Sherman (ed.), HIV and Liver Disease,
DOI 10.1007/978-1-4419-1712-6_2, © Springer Science+Business Media, LLC 2012

was higher among those who were on a ritonavir-based regimen. The risk of liver enzyme abnormalities in most studies was substantially higher in patients with HCV or HBV coinfection.

While most protease inhibitor-based regimen may cause liver enzyme elevation, other effects may be seen and differ by drug. For example, the typical pattern of liver abnormality associated with the protease inhibitors indinavir and atazanavir is an asymptomatic elevation of unconjugated bilirubin in the absence of AST/ALT elevation, seen in 6–40% of patients treated with these agents [16]. Progression to overt clinical jaundice is uncommon (7–8%), and the usual course of action is to observe such patients unless clinical jaundice or other liver abnormalities are found.

HIV and HCV–HBV Coinfection

Due to shared routes of transmission and similarities in behavioral patterns, there is a high risk of HCV and HBV coinfection among HIV-infected persons. In large national cohorts, the prevalence of HCV coinfection among HIV-infected persons is 18% [17–19]. In comparison, the prevalence of HCV infection in the general population in the USA is 1.6% [20].

HIV–HCV coinfected persons are more likely to have advanced liver disease and an accelerated progression of liver disease [21, 22]. But the effect of liver disease upon HIV progression is less well established. Some studies have demonstrated that HIV–HCV coinfected persons have more AIDS at baseline, more rapid progression to AIDS and decreased rate of CD4+ lymphocyte recovery [23, 24], while others have not found any such association [25, 26].

The prevalence of chronic HBV coinfection among HIV-infected persons is reported to be 7–11% [27, 28]. HIV-infected persons with negative serologic markers still have a substantial risk of occult chronic HBV infection defined as the presence of HBV DNA. In a study by Lo Re et al., 10% of HIV-infected subjects with negative HBsAg/anti-HBc had detectable HBV DNA [29].

Approximately 25–30% of HCV monoinfected persons have persistently normal liver enzymes. Some studies have found no significant difference in liver enzyme abnormalities between HCV monoinfected and HIV–HCV coinfected persons, while other have reported higher levels in the coinfected persons. Nearly 30% of HIV–HCV coinfected persons with persistently normal liver enzymes have stage F2 fibrosis on liver biopsy [30]. A recent clinical trial in HIV–HCV coinfected persons failed to show a significant benefit of long term pegylated interferon maintenance therapy in slowing progression of liver fibrosis. The trial was halted due to very slow rates of liver fibrosis progression in patients on CART [31].

Other Infectious Diseases

Viruses from the herpesviridae family (HSV, CMV), parasites (*Toxoplasma gondii*), mycobacteria (*M. tuberculosis, M. avium* complex), and fungi (*Cryptococcus, Histoplasma*) can all affect liver and manifest mostly as elevated liver enzymes. Many of these infections are classified as "opportunistic infections" and most are more common in HIV-infected persons compared to HIV-uninfected controls. In HIV-infected patients with elevated liver enzymes and appropriate clinical setting and epidemiologic exposure, these should be considered in the differential diagnosis.

Noninfectious Comorbidities

Alcohol Use

The prevalence of alcohol abuse or dependence is much higher in HIV-infected persons compared to the general population [32]. In an urban cohort of HIV-infected persons in the USA, 10.4% of the patients reported hazardous alcohol drinking. The overall prevalence of liver fibrosis as determined by an AST to platelet ratio (APRI) of >1.5 was 11.6% [33]. Among those without HCV coinfection, 5.3% had APRI >1.5 with hazardous alcohol drinking associated with an adjusted relative risk ratio of 3.72. Among the HCV coinfected persons, 18.3% had APRI >1.5, and in this population hazardous alcohol use was not independently associated with APRI.

Nonalcoholic Fatty Liver Disease (NAFLD)

NAFLD is defined as accumulation of fat in the hepatocytes exceeding 5% of the liver weight [34, 35]. NAFLD is not a static disease and may progress over a period of time. At one end of the spectrum is the relatively benign mild fatty infiltration of the liver, while the more severe forms, or nonalcoholic steatohepatitis (NASH) are characterized by significant steatosis with increasing degree of lobular and/or portal inflammation as the disease progresses [34].

NAFLD is a common liver condition. It is estimated that 20–30% of the US adults have some degree of hepatic steatosis or NAFLD, with 2–3% having the more severe form, NASH [34–37]. NAFLD is a common cause of elevations in serum alanine aminotransferase (ALT) levels accounting for 60–90% of ALT elevations in afflicted patients [38–40]. NAFLD is associated with accelerated liver fibrosis progression [41], as well as increased all-cause and liver-related mortality [41, 42].

There are scant data about the prevalence of NAFLD in patients with HIV alone. Using magnetic resonance spectroscopy, Hadigan and colleagues identified hepatic steatosis in 42% of HIV-infected subjects [43]. Another recent study

Table 2.1 Studies showing the relationship between antiretroviral use and steatosis

Author	Year	*N*	% With steatosis	None (minimal)	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	F3/F4 fibrosis
Castera et al. [47]	2007	137	67	33	35	20	12	32
Neau et al. [48]	2007	148	67	33	36	19	12	32
McGovern et al. [49]	2006	183	69	31	27	18	1	NR
Gaslightwala and Bini [50]	2006	154	72	NR	24	37	11	43
Bani-Sadr et al. [53]	2006	241	61	NR	38	16	7	NR
Marks et al. [51]	2005	106	56	44	47	7	2	25
Monto et al. [54]	2005	92	NR	52	45	2	0	21

NR not reported

using liver–spleen attenuation of CT scan found steatosis in 37% of HIV-infected persons [44]. In this study, factors associated with NAFLD included a higher serum ALT–AST ratio, male sex, greater waist circumference, and longer NRTI use [44]. HIV-infected subjects with NAFLD have a lower BMI and a lower percentage of fat mass when compared with HIV-uninfected subjects with NAFLD [45]. Hepatic steatosis can progress rapidly to cirrhosis in HIV-infected persons, even in the absence of HCV coinfection, and despite effective control of HIV replication [46].

Hepatic steatosis/NAFLD is even more common among HCV–HIV coinfected patients, being reported in 67–69% of patients [47–49]. While HCV genotype 3 and BMI are associated with NAFLD/steatosis in this population, this association persists even after adjusting for BMI and HCV genotype [47, 48]. Hepatic steatosis in HCV–HIV coinfected subjects has been associated with more advanced fibrosis in multiple studies [49–52], and fibrosis progression correlates with the degree of steatosis [50]. The relationship between antiretroviral use and steatosis is less clear, with some studies reporting an increased risk [49, 52], while others did not find such an association (Table 2.1) [53, 54]. There was no association between steatosis and HIV RNA or CD4 counts [47, 48, 53, 54].

Hepatocellular Carcinoma

Globally, HCV, HBV, and alcoholic cirrhosis are the leading causes of hepatocellular carcinoma (HCC) [55]. An association between HIV and HCC has been reported by some recent studies. Since HCV, HBV, and excessive alcohol use are all more prevalent in HIV-infected persons, careful study of the role of each of these factors is important. In an analysis of HIV-infected veterans in the USA, McGinnis et al. found that while HIV-infected veterans were at a greater risk for HCC compared to uninfected veterans, this was largely explained by the higher prevalence of HCV and alcohol abuse or dependence [56]. However, among HIV-infected population with liver related death, HCC accounts for an increasing proportion of deaths, increasing from 15% in 2000 to 25% in 2005 [57]. Screening for HCC is important among HIV-infected persons, especially those with HCV or HBV coinfection or excessive alcohol use.

Other Conditions

A newer entity called "nodular regenerative hyperplasia" has been recently reported [58]. The prevalence of nodular regenerative hyperplasia in the general population has been estimated between 0.7 and 2.6% based on autopsy series, but may be as high as 8% in the HIV-infected persons [58, 59]. While some studies have suggested an association with CART, the number of reported patients in literature is too small to make any definitive conclusions.

Summary

Liver injury and liver disease are common among HIV-infected persons, and liver disease is now a leading cause of morbidity and mortality in this group. While nearly all antiretrovirals have been associated with liver injury, the overall risk from such therapy is relatively small and reversible. NAFLD is another common condition that needs to be considered. Excessive alcohol use is more prevalent among HIV-infected persons and has significant consequences, both in terms of liver disease as well as nonadherence to HIV medication and progression of HIV disease. Opportunistic infections are another important cause of liver injury. Finally, the incidence of HCC is on the rise among HIV-infected persons. For almost all conditions listed above, coinfection with HCV substantially increases the risk.

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http://www.springer.com/978-1-4419-1711-9

HIV and Liver Disease
Sherman, K.E. (Ed.)
2012, XV, 209 p., Hardcover
ISBN: 978-1-4419-1711-9