HIV and the liver

Gary Brook

Abstract

There are different ways that HIV-related liver disease can be categorized. Clinically, it can be split into: disease that relates to the immunocompromised state; disease that involves co-infection with hepatitis viruses; and drug-related adverse events. In the immunocompromised patient with a low $CD4^+$ lymphocyte count, biliary tract disease caused by cytomegalovirus and cryptosporidia, granulomatous hepatitis with infections such as tuberculosis and leishmaniasis, and malignant hepatic infiltration including lymphoma, Kaposi's sarcoma and hepatoma have to be considered. HIV patients are more likely to develop chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection in which the prognosis is worse and treatment less effective than in HIV-uninfected individuals. Drug-related liver dysfunction is also common in HIV infection and includes hepatocellular dysfunction with antiretrovirals such as nevirapine, hyperbilirubinaemia due to atazanavir, portal hypertension due to didanosine and hepatic steatosis due to stavudine. These conditions can be treated and combination antiretroviral therapy (cART) has made HIV-related liver disease of all types more amenable to therapy. Chronic HBV infection responds to a range of drugs including pegylated interferon, adefovir, telbivudine and the antiretrovirals tenofovir, lamivudine and emtricitabine. Acute and chronic hepatitis C will respond to pegylated interferon and ribavirin. More recently, the direct-acting antivirals for hepatitis C (boceprevir and telaprevir) have greatly increased treatment response rates in HIV co-infected patients to levels similar to those seen in HCV mono-infected patients. Liver transplantation can be also offered when appropriate.

Keywords antiretrovirals; cholangitis; chronic liver disease; drug-related hepatitis; hepatitis B; hepatitis C; liver transplantation

Introduction

Liver disease in HIV-positive patients can be categorized in several ways. One way is to look at patterns of liver enzyme abnormality (Table 1). An alternative and clinically useful categorization is to divide the causes into three types:

- diseases seen in immunocompromised patients
- viral hepatitis co-infection
- drug-related hepatic dysfunction

In order to understand the differential diagnosis of liver dysfunction, the history should include the CD4+ lymphocyte count, any history of potential exposure to pathogens or blood-borne viruses, treatment history, including antiretrovirals and other potentially hepatotoxic drugs (e.g. tuberculosis (TB) therapy), and the duration of symptoms.

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What's new?

- Portal hypertension and nodular regenerative hyperplasia of the liver is being increasingly recognized in HIV-positive patients previously treated with the antiretroviral didanosine
- Syphilis is common, especially amongst men who have sex with men, and should be considered as a cause of abnormal liver function tests and granulomatous hepatitis
- All patients with HIV and hepatitis B co-infection should be considered for therapy and this would often be with triple antiretroviral therapy that includes tenofovir plus lamivudine or emtricitabine
- All patients with chronic hepatitis C should be considered for therapy with pegylated interferon, ribavirin and boceprevir or telaprevir and a treatment response rate of >50% is likely
- Newer, direct-acting antivirals for hepatitis C are likely to be licensed soon, further increasing response rates and possibly leading to non-interferon regimens

Liver disease in immunocompromised HIV-positive patients

Cholestatic liver disease[1]

Causes: chronic cholangitis simulating sclerosing cholangitis is seen mostly when the $CD4^+$ lymphocyte count is less than 200 cells/μl. The two pathogens most commonly associated with this are *Cryptosporidium parvum* and cytomegalovirus (CMV). In a proportion of patients, a pathogen cannot be identified (HIV-related cholangiopathy).

Presentation: right hypochondrial pain or painless jaundice with low-grade fever. *C. parvum* will also cause watery diarrhoea and CMV can present with systemic illness and retinitis.

Diagnosis: typically serum alkaline phosphatase (ALP) and total bilirubin are raised with normal alanine aminotransferase (ALT). Imaging techniques such as magnetic resonance imaging (MRI) or endoscopic retrograde cholangiopancreatography (ERCP) will reveal changes suggestive of cholangitis. *C. parvum* can be seen in the stool (auramine staining) and CMV is detected in blood by polymerase chain reaction (PCR). Both pathogens may be identified from biliary samples taken at ERCP. Idiopathic HIV-related cholangiopathy is a diagnosis of exclusion.

Management: it may be necessary to improve biliary drainage using a stent or sphincterotomy. Management focuses on combination antiretroviral therapy (cART); improved host immunity facilitates recovery. CMV will respond to ganciclovir, foscarnet or cidofovir. Cryptosporidiosis is less amenable to therapy, although paromomycin, nitazoxanide or atovaquone may have some benefit.

Infiltrative and mass lesions of the liver[2]

Causes: some infections and malignancies affecting the liver present as infiltrative or mass lesions. The most common cause of diffuse granulomatous hepatitis is mycobacterial infection (TB or atypical), but less commonly other infections such as syphilis

Patterns of liver enzyme abnormality seen in HIV-related pathology

Liver enzyme abnormality	Mechanisms	Examples
Raised bilirubin, normal ALT/ALP/GGT	Inhibition of bilirubin conjugation Haemolysis	Antiretrovirals such as atazanavir (common) Dapsone for PCP prophylaxis in G6PD deficiency
Raised ALP and GGT, normal bilirubin/ALT	Space-occupying lesions in the liver parenchyma	• Granulomatous infiltration (e.g. TB, syphilis, visceral leishmaniasis) • Malignancy (e.g. lymphoma)
Raised ALT alone	Chronic hepatocellular damage	• Chronic hepatitis B or C • Drug-related hepatitis (e.g. nevirapine, anti-TB drugs)
Acutely raised ALT, bilirubin and ALP	Acute hepatocellular damage	• Acute viral hepatitis (A, B, C, etc.) • Drug toxicity (e.g. nevirapine or anti-TB drugs) • Hepatic steatosis
Raised bilirubin/ALP with normal or modestly raised ALT	Biliary dysfunction Cholangitis	HIV-related idiopathic cholangiopathy Cryptosporidiosis, CMV infection
Normal LFT or modest rise in ALT or ALP in the presence of portal hypertension	Atrophy of the portal venules, sometimes with hepatic nodular regenerative hyperplasia	Past or current didanosine treatment, possibly with other co-factors

ALP, alkaline phosphatase; ALT, alanine aminotransferase; CMV, cytomegalovirus; G6PD, glucose-6-phosphate dehydrogenase; GGT, gamma glutamyl transferase; HIV, human immunodeficiency virus; LFT, liver function test; PCP, *Pneumocystis carinii (jirovecii)* pneumonitis; TB, tuberculosis.

Table 1

(secondary or tertiary), disseminated fungal infections (e.g. histoplasmosis) or visceral leishmaniasis (VL) will present similarly. Lymphomas (typically non-Hodgkin's type) and solid malignancies, such as hepatocellular carcinoma or Kaposi's sarcoma, can also present in this way.

Presentation: right hypochondrial discomfort and/or hepatomegaly and fever.

Diagnosis: ALP and γ-glutamyl transferase (GGT) will be raised with little or no abnormality of the ALT or bilirubin. Ultrasound, CT or MRI scanning of the liver will reveal infiltrative or mass lesions. TB or lymphoma may be suspected from other systemic features such as lymphadenopathy or lung disease. Ultrasound-guided liver biopsy usually provides the diagnosis.

Management: therapy is directed at the underlying cause. Antiretroviral therapy also improves the prognosis.

Acute viral hepatitis[3]

Causes: viral hepatitis types A, B, C, D and E. Consider CMV, Epstein–Barr virus and drug-related hepatitis. Acute relapse of chronic viral hepatitis due to falling immunity may also present in this way.

Presentation: the symptoms of acute viral hepatitis are as seen in the immunocompetent host. The rate of progression to chronic infection in hepatitis B is much higher in HIV-seropositive patients and is in the order of 20%. All patients known to be HIV-positive with no immunity to hepatitis B or C should be vaccinated accordingly.

Diagnosis: the virological diagnosis and liver function test (LFT) abnormalities are as seen in the immunocompetent host. In HIV-seropositive patients with a very low CD4 count (<50 cells/μl), relapse of chronic hepatitis B or C may not be associated with positive serological markers other than HBV DNA or HCV RNA, respectively.

Management: patients with acute hepatitis C should be considered for treatment with weekly pegylated interferon α injections and ribavirin for 3–6 months. Otherwise treat symptomatically.

Chronic viral hepatitis[3–8]

Causes: viral hepatitis types B (±D) or C. Drug-related hepatitis or hepatic steatosis can present in a similar way.

Presentation: most patients are asymptomatic, apart from some lethargy, unless cirrhosis and hepatic decompensation ensue. Progression to cirrhosis and liver cancer is two to five times higher in HIV-seropositive patients compared to those who are hepatitis mono-infected.

Diagnosis: chronic viral hepatitis should be considered if serum ALT is raised with normal ALP and bilirubin. ALT is frequently normal; so all HIV-seropositive patients should be screened for hepatitis B and C annually and more often if the patient is at particular risk. Screening should involve testing for anti-HBc or HBsAg for hepatitis B and anti-HCV antibodies for hepatitis C. A small number (1–2%) will be negative on serological testing, but will have detectable serum HBV DNA or HCV RNA. Therefore, patients with raised ALT of unknown cause should be tested for HBV DNA or HCV RNA. A liver scan is mandatory. Liver biopsy or hepatic elastography should be considered for any patient with suspected cirrhosis. It will also help the decision as to when to treat chronic hepatitis C (Table 2).