

## **HIV and Liver Diseases**

Prof. Suresh Makvana<sup>1</sup>, Ankit Patel<sup>2</sup>

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Coinfection with hepatitis B virus (HBV) and HIV is common, with 70-90% of HIV-infected individuals in the United States having evidence of past or active infection with HBV. Factors affecting the prevalence of chronic HBV include age at time of infection and mode of acquisition, which vary geographically. In the United States and Western Europe, HBV often is acquired in adolescence or adulthood via sexual contact or injection drug use. Although spontaneous clearance of HBV acquired in adulthood occurs in >90% of immunocompetent individuals, HIV-infected persons are half as likely as HIV-uninfected persons to spontaneously clear HBV. Therefore, chronic HBV infection occurs in 5-10% of HIV-infected individuals who are exposed to HBV, a rate 10 times higher than that for the general population. In the United States, HIV/HBV coinfection rates are highest among men who have sex with men (MSM) and injection drug users. In contrast, in Asia and sub-Saharan Africa, where vertical and early childhood exposure are the most common modes of transmission, respectively, and overall HBV prevalence is higher, the prevalence of HBV among HIV-infected individuals also is higher, at an estimated 20-30%.

HBV is a DNA virus that forms stable circular covalently closed (ccc) DNA that can persist in the liver indefinitely. Individuals with evidence of past infection (core antibody positivity) are at risk of HBV reactivation, particularly in the setting of severe immunocompromise, prolonged steroid use, or chemotherapy. There are 8 genotypes of HBV. Genotype G may be predictive of more severe fibrosis in HIV-coinfected patients, and genotypes C and D may be more responsive to interferon. However, in general, knowledge of the HBV genotype is not consistently associated with a response to nucleoside therapy and therefore is not particularly useful in clinical care of HIV/HBV coinfection, as nucleosides are the mainstays of HBV treatment.

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<sup>1</sup>(PhD) Professor, Dept. of Psychology, Sardar Patel University, Vallbh Vidyanagar

<sup>2</sup> Clinical Psychology, Dept. of Psychology, Sardar Patel University, Vallbh Vidyanagar

### **ACUTE AND CHRONIC HEPATITIS B**

When a person is first infected with the hepatitis B virus, this is called an acute infection. A person may not have any symptoms or s/he could become seriously ill. Most adults will recover and get rid of the virus without any problems. If the virus remains in the blood for more than six months, then a person is diagnosed as having a *chronic infection*.

Unfortunately, this is not true for infants and young children *90% of infants and up to 50% of young children infected with hepatitis B will not get rid of the virus and will develop a chronic infection*. A smaller number of infected adults (5-10%) will also become chronically infected with hepatitis B.

### **Epidemiology**

The leading cause of chronic liver disease and is transmitted through sexual contact and IV drug use. HIV infection is associated with an increased risk developing hepatitis B. Patients with chronic hepatitis B infection are at increased risk of hepatocellular carcinoma.

### **Clinical features**

Acute infection may present with fatigue, right upper quadrant abdominal pain, nausea, vomiting, fever, arthralgia and jaundice. The disease may remain asymptomatic until the onset of end-stage liver disease (ESLD) which is heralded by ascites, coagulopathy, palmar erythema, jaundice, hepatosplenomegaly, variceal bleeding or encephalopathy. There may also be polyarteritis nodosa, glomerulonephritis and vasculitis.

### **Diagnosis**

Test for hepatitis B surface antigen (HBsAg) antibody to hepatitis B core antigen (anti-HBc) and antibody to hepatitis B surface antigen (anti-HBs) will identify the majority of patients. It will also determine which individuals require vaccination. A chronic stage is said to occur when HBsAg is present for more than six months. Once detected, the severity of the liver disease must be followed with assessment of alanine transaminase (ALT) serum albumin, prothrombin time, platelet count, and completed blood count and bilirubin levels. Patients should also be monitored every six months with alpha-fetoprotein levels and ultrasound of the liver, especially if they are older than 45 years, alcoholic, have cirrhosis or have a family history of chronic liver disease. Liver biopsy should be done to assess the grade and stage of liver disease. Transient elevation of enzymes can occur as a result of the hepatotoxicity of various drugs used in HAART. It may also occur as a result of concomitant infection with hepatitis A, hepatitis C or hepatitis delta virus.

### **Treatment**

Patient should avoid alcohol. All their contacts-sexual, household and needle sharing need to be immunized. If the person also develops hepatitis A, it is likely to be fulminant and therefore active immunization with two doses of hepatitis A vaccine should be administered before the CD4 count falls to  $<200$  cells/mm<sup>3</sup>.

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Antiviral treatment is advised if there is actively replicating virus in the blood, indicated by a positive hepatitis B core antigen (HBcAg) or HBV DNA levels  $>10^5$  copies/ml and a raised ALT level that is twice the normal. Pegylated interferon (PEN IFN) alpha 2,5-10 MU can be given thrice a week subcutaneously (SC) for 16-24 weeks. If the patient is HAART-naïve, lamivudine is the preferred drug along with other ARV drugs. Adefovir dipivoxil 10 mg OD can be used in patients who do not require HAART. Tenofovir 300 mg OD can also be used. Emtricitabine 200 mg OD is also active against replication of the hepatitis B virus. If the patient is infected with HBV, HBC, and HIV-1, starting HAART should be the first priority. If HAART is not required then treatment for HBV should be considered first.

If ESLD develops I managed is the same way as in HIV negative individuals. IFN is contraindicated in ESLD. Liver transplantation can be done.

## ACUTE AND CHRONIC HEPATITIS C

### Epidemiology

Chronic Hepatitis C infection is caused by the single long-stranded RNA Hepatitis C virus. There are 6 genotypes and 50 subtypes. It is transmitted sexually, through infected blood products, needle-sharing and from mother to child. Cirrhosis sets in approximately 20 years after infection. The incidence of cirrhosis is higher in males, those  $>45$  years and which concomitant alcoholism. Co-infection with HIV increases the rapidity of progression to ESLD.

### Clinical Features

Patients may be asymptomatic or only mildly systemic so that acute infection is not recognized. There may be low-grade fever, fatigue, anorexia, right upper quadrant pain, nausea, vomiting, dark-coloured urine and frank jaundice. ALT and aspartate aminotransferase (AST) may be elevated. Serum cryoglobulins are present in 60% but may not cause symptoms. As liver disease progress, signs of portal hypertension may appear. There may be leukocytoclastic vasculitis and porphyria cutanea tarda. Fibrosing cholestatic Hepatitis might occur.

### Diagnosis

Qualitative HCV RNA assay in the blood shows  $>50$  copies/ml. A recombinant immunoblot assay (RIBA) can be performed if the HCV RNA is negative but the immunoassay for anti-HCV is positive. HCV viral load does not correlate with the degree of histological injury. Co-infected persons should be checked for other co-morbid liver conditions such as hepatocellular carcinoma by serum alfafetoprotein level and ultrasound examinations of the liver. ALT is the simplest and least expensive test to evaluate the activity of liver disease.

### Treatment

All patients should be counseled to stop alcohol consumption. Fulminant hepatic failure occurs if there is co-infection with Hepatitis A. Hence, all patients should receive two doses of Hepatitis A

vaccine before the CD4 count falls to  $<200$  cell/mm<sup>3</sup>. In addition, they should also receive Hepatitis B vaccine.

Treatment should be offered to patients at increased risk of developing cirrhosis, patients with detectable plasma HCV RNA levels, and in those in whom liver biopsy shows inflammation, necrosis, portal or bridging fibrosis and elevated ALT levels. IFN alfa-2b 180 µg weekly by subcutaneous injection plus ribavirin 600-1400 daily might eradicate HCV infection. Patients with unstable cardiopulmonary disease, anaemia unresponsive to erythropoietin or haemoglobinopathy can not be given ribavirin. The exact duration of treatment is not known but it is usually continued for 48 weeks. The critical CD4 level is 500 cells/mm<sup>3</sup>. Before it falls below this level, treatment for HCV should be started. If the CD4 count is already below this level, HAART should be started first. Liver transplantation is a primary treatment option.

Quantitative HCV RNA levels are the best estimate for treatment. A sustained virological response means an absence of detectable HCV RNA ( $<50$  IU/ml) after antiviral treatment for 2 weeks. Relapse is defined as the presence of detectable HCV RNA at the end of treatment.

## HBV MEDICATIONS

### Interferon

IFN is most effective for HBV treatment in patients with low levels of viremia and elevated transaminases, and it therefore may be less useful in patients with HIV/HBV coinfection than in those with HBV alone. In coinfecting patients, IFN has been associated with lower rates of HBV treatment success and increased toxicity. It cannot be used for patients with decompensated cirrhosis and is not feasible as a long-term treatment, owing to adverse events and tolerability issues. There are no data for use of pegylated IFN in HIV/HBV coinfection.

### Lamivudine and emtricitabine

These nucleoside analogues have similar activity against both HIV and HBV and they are commonly used components for HIV/HBV cotreatment. However, HIV-infected individuals should not receive 3TC or FTC monotherapy for HBV infection because resistance to those drugs develops in up to 90% of patients within 4 years of single-drug treatment. Resistance to 3TC and FTC is characterized by the development of mutations at HBV rtM204 (also known as YMDD mutations). Once 3TC resistance has developed, HBV medications such as telbivudine will no longer have activity against HBV, and agents such as entecavir may be less efficacious and more prone to development of HBV resistance. As with other agents that have activity against HIV, 3TC and FTC should be used only for patients on fully suppressive ART.

### Entecavir

Entecavir is a guanosine analogue that appears to be more potent than either 3TC or adefovir. Entecavir resistance requires the development of several resistance mutations, including the rtM204 mutation that confers resistance to 3TC. In the presence of 3TC resistance, entecavir

usually is active but may be more vulnerable to the development of further resistance (see above). Although entecavir initially was thought to have no anti-HIV activity, it has been demonstrated to select for the M184V mutation and should not be used in the absence of combination ART with full suppression of HIV viremia.

### **Telbivudine**

Telbivudine is a thymidine analogue that also selects for the HBV rtM204 mutation, which leads to 3TC cross-resistance, and should not be used after 3TC or FTC failure. Telbivudine also may have anti-HIV activity and is not recommended for use without fully suppressive ART.

### **Adefovir**

Adefovir initially was formulated as an anti-HIV agent but was not developed for that purpose, owing to an association with renal toxicity. At lower dosages, adefovir suppresses HBV replication but is less potent than telbivudine or tenofovir. Adefovir appears to be active against 3TC-resistant HBV. The use of adefovir largely has been supplanted in favor of treatment with tenofovir, a related but more potent agent and one that is active against HIV. At the dosage used to treat HBV, adefovir does not appear to be active against HIV and has not been associated convincingly with the development of HIV resistance mutations such as K65R. Adefovir is an option for HBV treatment in HIV-infected patients who decline or cannot take ART, but it should be used with caution.

### **Tenofovir**

TDF is related to adefovir but it has more potent HBV activity and also can be used for HIV treatment. As with other agents that have activity against HIV, TDF should be used only for patients who are on fully suppressive ART. It usually is used in combination with 3TC or FTC as first-line therapy. HBV that is resistant to 3TC or adefovir can be treated effectively with TDF therapy.

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