

a series of articles
written by medical
professionals about
the management
and treatment of
hepatitis C

Hepatitis B Virus in the Setting of HIV Infection *A Clinical Challenge*

**Richard K. Sterling, M.D.,
F.A.C.P., F.A.C.G.**

Division of Gastroenterology,
Hepatology, and Nutrition
Virginia Commonwealth
University Health System
Richmond, Virginia

Introduction

Due to shared routes of transmission, the majority of patients infected with human immunodeficiency virus (HIV) have markers of past exposure to hepatitis B virus (HBV). Until recently, the morbidity (illness) and mortality (death) from HIV overshadowed coexisting conditions, such as hepatitis B virus (HBV). Consequently, clinicians taking care of coinfecting patients put HBV on the back burner. As anti-HIV therapy has become more effective, associated with marked improvements in life expectancy, comorbid conditions, like HBV and hepatitis C virus (HCV), have become the focus of attention (1;2). This article will briefly review HBV in the setting of HIV.

Epidemiology

Approximately 400 million persons worldwide have chronic HBV infection and up to 1 million die annually from HBV related liver disease. In the United States, up to 1.25 million are infected. The most common risk factors for acquiring HBV, similar to HIV, are illicit drug use and sex, including both heterosexual and homosexual activity. Although the prevalence of past exposure is high (90-95%), active infection with HBV is much less common and occurs in 10-15% with HIV infection (2-7). Because of the

high rate of transmission (90%) from mother to child (vertical transmission), all pregnant mothers are tested and all infants born to infected mothers are given both HBV immune globulin (passive immunization) and HBV vaccine (active immunization) which reduces the incidence of vertical transmission to 5%. Also, because HBV can be transmitted to household contacts (horizontal transmission), all persons living with an infected patient should be tested and vaccinated if no markers of exposure are present.

HBV Virology and Testing

Understanding HBV testing is paramount when evaluating HBV. HBV is a DNA virus composed of 4 genes: surface, core, polymerase, and X genes. Routine laboratory testing can measure both the products of 2 of these genes (surface antigen [S Ag] made by the surface gene and E antigen [E Ag] made by the core gene) as well as the antibodies to S Ag (surface antibody, S Ab), to core antigen (both acute [core IgM] and chronic [core IgG] core antibodies), to E antigen (E antibody [E Ab]), and to HBV DNA itself (see table). Acute HBV is determined by the presence of HBV core IgM. Chronic infection with HBV is defined as persistent HBV S Ag for more than 6 months. Chronic active infection

requires active HBV viral replication with presence of HBV DNA. The majority of these patients also are positive for HBV E Ag and negative for E Ab. A chronic carrier state is defined as presence of HBV S Ag without detectable HBV DNA or HBV E Ag. These patients usually have HBV E Ab and normal liver chemistries. There are however several caveats to HBV testing. Patients with a pre-core mutation are positive for HBV DNA without detectable E Ag. Also, patients with antibodies to HBV core protein without HBV S Ag can have HBV DNA (8), and occult HBV infection has been recently recognized in patients with chronic HCV (9-12). The recent identification of these patients is in part related to the increased sensitivity of polymerase chain reaction (PCR) HBV DNA assays that are finding low levels of HBV DNA in patients who were previously negative for HBV DNA by older assays. Lastly, all patients with chronic HBV should be screened for the presence of antibodies to HIV, HCV as well as hepatitis D virus (HDV) which can only occur in the presence of chronic HBV.

Natural History

Once exposed, the risk of developing chronic infection, defined as the presence of HBV surface antigen (S Ag) for greater than 6 months duration, depends on the

age of the individual and is highest in neonates (90%) compared to adolescents (50%) and adults (<10%). However, the rate of spontaneous clearance in immunosuppressed adults, as in those with HIV, is felt to be much lower **(1)**. The majority of patients with chronic HBV are asymptomatic. Many, however, will complain of fatigue associated with fluctuating liver chemistries. The annual rate of spontaneous E Ag loss and development of E Ab (seroconversion) is 5-15% while spontaneous loss of S Ag and development of S Ab occurs less frequently (1%/year). Chronic HBV can result in cirrhosis and liver decompensation associated with jaundice (yellow eyes and skin), ascites (fluid in the abdomen), hepatic encephalopathy (confusion), and variceal bleeding. The risk of progression is dependent on several factors including the presence of active viral replication, concomitant alcohol use, and coinfection with HCV, HDV, and HIV. Another major complication of chronic HBV is hepatocellular carcinoma (HCC). It is important to note that HCC can develop with or without cirrhosis in chronic HBV and should be screened for periodically with serum alpha-fetoprotein and liver ultrasound. Lastly, because superinfection with hepatitis A virus may not be well tolerated in those with chronic HBV, HAV vaccine is recommended.

Impact of HIV on HBV

Early studies before effective HIV therapy suggested that HBV may be more mild in those coinfecting with HIV **(13;14)**. These conclusions however, were based on lower serum aminotransferase levels and not on liver histology. Several more recent studies have shown more significant histology in those coinfecting with HBV **(15)**. Furthermore, several recent reports have shown higher HBV DNA levels **(15;16)** in those coinfecting with HIV. Also, the rate of spontaneous E Ag seroconversion to E Ab is

HBV TESTING							
PHASE	TEST						
	S Ag	S Ab	Core Ig M	Core Ig G	E Ag	E Ab	HBV DNA
Acute	pos	neg	pos	neg	pos	neg	pos
Window	neg	neg	pos	pos/neg	neg	pos	neg
Resolved	neg	pos	neg	pos	neg	pos	neg
Chronic Active	pos	neg	neg	pos	pos	neg	pos
Chronic Carrier	pos	neg	neg	pos	neg	pos	neg
Chronic mutant*	pos	neg	neg	pos	neg	neg	pos
Vaccinated	neg	pos	neg	neg	neg	neg	neg

S = surface, Ag = antigen, Ab = antibody, Ig = immune globulin, pos = positive, neg = negative
*Pre-core mutation.

lower in those coinfecting with HIV. Finally, the annual risk of developing cirrhosis in HBV appears to be much higher in those coinfecting with HIV. This may especially be true in those with low CD4 counts.

Impact of HBV on HIV

In contrast to the negative effect of HIV on HBV disease, the impact of HBV on HIV disease is less clear **(4;5)**. However, coinfection with HBV or HCV has been associated with increased hepatotoxicity to highly active antiretroviral therapy (HAART) **(17;18)**. Consequently, its recognition and treatment has received increasing attention.

Treatment of HBV in the Setting of HIV

The management of acute HBV is supportive. In those who develop chronic infection, optimum treatment remains controversial. All patients with active replication (HBV DNA >100,000 copies/ml) should be considered for therapy. In those with low titer HBV DNA (< 50,000 copies/ml) and negative for HBV E antigen (occult HBV infection), treatment may be of little value and these patients can be observed. The primary goal of therapy in HBV is viral suppression which in turn may prevent liver disease progression and development of HCC. Several approved treatment options are

now available for HBV and include alpha interferon, lamivudine (Epivir, GlaxoSmithKline), and most recently adefovir (Hepsera, Gilead Sciences) **(19)**. Use of interferon for HBV in HIV has been disappointing **(20)** and a recent trial utilizing 5 MU of interferon alpha-2b three times a week for 24 weeks in chronic active HBV showed lower loss of HBV DNA (27% vs 56%), less HBV E antigen seroconversion (15% vs 52%), and higher reactivation rates following therapy (35% vs 9%) in HIV coinfecting patients compared to HIV uninfected HBV controls **(21)**. Although short term use of lamivudine can lead to HBV DNA clearance in the majority of treated patients **(22)**, continued use results in a high rate (20%/year) of HBV resistance associated with the emergence of YMDD mutations **(23)**. This is especially true in those on lamivudine to help control HIV infection. Therefore, other agents for HBV are needed. Newer medications such as adefovir **(24-29)** are effective against HBV and are associated with low rates of HBV viral resistance **(30)**. However, their use in HIV coinfecting patients has not been well studied. Although there are limited data on the use of tenofovir (Viread, Gilead Sciences) to treat HBV in HIV coinfection **(31-33)**, results from ongoing trials are anxiously awaited, and only experience with these drugs

either alone or in combination will determine the emergence of viral resistance.

Conclusions

Markers of HBV exposure are present in the majority of HIV infected individuals and 10-15% have chronic HBV. In those with presence of HBV surface antigen, it is important to establish the activity of HBV to differentiate those with active viral replication (HBV DNA positive with or without HBV E antigen) from chronic carriers (HBV DNA negative, HBV E antibody positive). Furthermore, with highly sensitive PCR based HBV DNA assays, an increasing number of occult HBV infections are now being recognized. Because liver transaminases are not predictive of the severity of liver disease, liver biopsy is required to determine the extent of histologic damage. In addition, all HBV surface antigen positive patients should be screened for HCV, HDV and HCC as appropriate. Although data is limited for HBV in the setting of HIV coinfection, treatment should include at least 2 agents to prevent the emergence of HBV escape mutants. In those already on lamivudine for HIV, options include adding either adefovir or tenofovir to their anti-retroviral regimen. Until new agents emerge that are effective against both HIV and HBV, treating coinfecting patients will remain challenging.

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