HEPATITIS B

Hepatitis B virus (HBV) is a major cause of acute and chronic hepatitis worldwide. In the United States, there are approximately 250,000 to 300,000 new HBV infections annually. The risk factors for these infections are sexual activity (30%-60%), and injection drug use (15%). No recognizable risk factors can be found for up to 30% of cases. Following infection, 90% to 95% of immunocompetent adults will resolve their infection with resultant immunity and no long-term consequences. However, 5% to 10% of persons fail to clear the infection and become chronic hepatitis B carriers with persistence of hepatitis B surface antigen (HbsAg) for more than 6 months. There are approximately one million chronic carriers of HBV in the United States, and 4,000 to 5,000 persons die annually from cirrhosis or liver cancer, the major complication of chronic HBV carriage.

A. Epidemiology

HBV is a major cause of morbidity and mortality around the world. There is significant geographic variation in infection rates, but it is estimated that 300 to 350 million people worldwide have chronic HBV infection. In Southeast Asia, Africa and China, more than 50% of the population are infected, and 8% to 15% become chronically infected. Neonatal HBV infection nearly always results in chronic HBV infection. Pre-existing immunosuppression also increases the risk of chronic infection. Studies suggest that about 25% to 40% of persons who are first infected with human immunodeficiency virus (HIV) and subsequently become HBV infected, will then become chronically HBV infected. This represents a 3- to 5-fold higher likelihood of chronic hepatitis B infection than in HIV-negative populations.

HBV is similar to HIV in that it is spread mostly by sexual activity and injection drug use. HBV is generally found in very high concentrations in serum (108 – 1010 virions/ml), and HBV levels have been shown to be even higher in HIV-infected patients compared with those who are HIV-negative. Transmission of HBV is more efficient via the sexual and percutaneous routes than HIV.

B. Clinical Syndromes

RECOMMENDATIONS:

All HIV-infected patients should have baseline HBV serologies obtained to determine their HBV infection status; these include HbsAg, anti-HBs (HbsAb), and IgG anti-HBc (HbcAb).

All HIV-infected patients without serologic evidence of prior HBV infection or history of prior HBV vaccination (complete series) should be strongly encouraged to receive the hepatitis B vaccination series. Serologic testing for anti-HBs 1 to 2 months after the third dose should be performed.

In some situations, such as unexplained elevations in liver enzymes, consideration may be given to HBV DNA testing even in the absence of serologic evidence of active hepatitis B virus replication (reactive HBsAg or HBeAg).

1. Acute hepatitis B infection

Acute HBV infection has a mean incubation period of 90 days (range 30-180 days). Hepatitis B cannot easily be clinically differentiated from other infectious and non-infectious causes of hepatic injury. The clinical course may be mild and anicteric or severe and associated with jaundice. In almost all cases, significant elevations of the serum transaminases (ALT, AST) occur. Fever, RUQ pain, anorexia and aversion to tobacco, headache and malaise may appear 1 to 2 weeks prior to the onset of jaundice. In up to 20% of patients with acute HBV infection, a characteristic serum sickness-like syndrome with arthralgias or frank arthritis is seen. Recovery from clinical symptoms occurs over 4 to 6 weeks. There is no evidence that HBV has any effect on the clinical course of previously acquired HIV infection. Conversely, acute HBV infection is similar in both the HIV-positive and negative populations. There is no evidence that treating acute HBV has an effect on chronicity.

The diagnosis of acute HBV infection is most reliably made by the presence of IgM antibody to HBV core antigen (IgM anti-HBc) which appears a few weeks following HBV surface antigenemia (HbsAg). Although IgM anti-HBc is rapidly superceded by IgG anti-HBc, IgM may persist for months to years and may even reappear during flares of chronic HBV. In self-limited infection in the immunocompetent host, the appearance of antibody to the hepatitis B surface antigen (anti-HBs) identifies recovery from infection. This generally appears weeks to months following disappearance of serum HbsAG. HBe antigen, HBeAg, and HBV DNA are markers of active viral replication in hepatocytes. While these markers are present early in the course of acute infection, they may also persist in the chronically infected individual. When detected, neither HBsAg, HbeAg nor HBV-DNA are specific for acute infection. Table 1 provides a schematic representation of the serologic responses to self-limited HBV infection.

TABLE 1
SEROLOGIC RESPONSES TO HBV INFECTION

Stage of Infection	HbsAG	Anti-HBs	IgG-anti-HBc anti-HBc	IgM-	HbeAg	Anti-HBe
Incubation	+	-	-	-	+ or -	-
Acute HepB	+	-	+	+	+	-
HbsAG-negative acute HepB	-	-	+	-	-	-
Healthy HbsAg carrier	+	-	+++	+ or -	-	+
Chronic HepB	+	-	+++	+ or -	+	-
Convalescent HBV infection	-	++	++	+ or -	-	+
HBV vaccination	-	++	-	-	-	-

Adapted from Mandel GL, Bennett JE, Dolin R, eds. Mandell, Douglas, amd Bennett's Principles and Practice of Infectious Diseases. Philadelphia, PA: Churchill Livingstone; 2000:1671.

2. Chronic hepatitis B Infection

Chronic hepatitis B is serologically defined as a positive HbsAg for greater than six months. Two forms of chronic HBV infection are chronic persistent hepatitis (CPH) and chronic active hepatitis (CAH). Both forms are characterized by hepatic inflammation with concomitant reparative changes and fibrosis. In CAH, bridging necrosis and destruction of hepatic architecture by cirrhosis is seen. It should be noted that new systems for describing liver pathology in chronic hepatitis are replacing "old" nomenclature such as CAH and CPH. A frequently used system is the Knodell Scoring System (or Histologic Activity Index) which quantifies the stage of fibrosis and grade of inflammation (see Table 2). Cirrhosis is associated with hepatocellular carcinoma.

TABLE 2
HISTOLOGY ACTIVITY INDEX (HAI - KNODELL SCORE)

Periportal ± Bridging Necrosis	Score	Intralobular Degeneration and Focal Necrosis	Score	Portal Inflammation	Score	Fibrosis	Score
None	0	None	0	No portal inflammation	0	No fibrosis	0
Mild piecemeal necrosis	1	Mild (acidophilic bodies, ballooning degeneration and/or scattered foci of hepatocellular necrosis in 1/3 of lobules or nodules)	1	Mild (sprinkling of inflammatory cells in <1/3 of portal tracts)	1	Fibrous portal expansion	1
Moderate piecemeal necrosis	3	Moderate (involvement of 1/3-2/3 of lobules or nodules)	3	Moderate (increased inflammatory cells in 1/3-2/3 of portal tracts)	3	Bridging Fibrosis (portal-portal or portal-central linkage)	3
Marked piecemeal necrosis	4	Marked (involvement of >2/3 of lobules or nodules)	4	Marked (dense packing of inflammatory cells in >2/3 of portal tracts)	4	Cirrhosis	4
Moderate piecemeal necrosis *plus* bridging necrosis	5	**Total HAI (Knodell Score) = __/22**					
Marked piecemeal necrosis *plus* bridging necrosis	6						
Multilobular necrosis	10						

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Chronic infection is frequently asymptomatic. Occasionally, hepatomegaly, splenomegaly, transient episodes of jaundice and persistent elevations of transaminases are seen. Serologically, chronic HBV infection is characterized by HbsAg(+), HbeAg(+), HBV-DNA (+), anti-HBc (+), and anti-HBs (-) (see Table 3). Approximately 2% per year of chronic carriers will spontaneously clear their HbsAg. HbeAg may also be spontaneously cleared, independent of HbsAg, at rates that approach 45% over seven years of observation. Clearance of HbeAg, even with persistence of HbsAg, is associated with resolution of the inflammatory process and recovery and decreased infectivity HbsAg detection in these cases represents integration of the surface antigen gene into the genome of the host hepatocyte, expression of which is not injurious to the cell.

TABLE 3 INTERPRETATION OF THE HEPATITIS B PANEL		
Tests	**Results**	**Interpretation**
HBsAg anti-HBc anti-HBs	negative negative negative	susceptible
HBsAg anti-HBc anti-HBs	negative neg or pos positive	immune
HBsAg anti-HBc IgM anti-HBc antiHBs	positive positive positive negative	acutely infected
HBsAg anti-HBc IgM anti-HBc antiHBs	positive positive negative negative	chronically infected
HBsAg anti-HBc anti-HBs	negative positive negative	four interpretations possible*

* 1. May be recovering from acute HBV infection.
2. May be distantly immune and test not sensitive enough to detect very low level of anti-HBs in serum.
3. May be susceptible with a false positive anti-HBc.
4. May be undetectable level of HBsAg present in the serum and the person is actually a carrier.

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Compared with HIV-negative patients, those with chronic HBV/HIV co-infection have a lower aminotransferase level, higher HBV viral loads, and lower HbeAg rate of loss over time. Generally, abnormal histopathology in a liver biopsy tends to be reduced in HIV-positive patients although some studies show no difference between HIV-positive and negative populations. One large recent study found no difference in necroinflammatory lesions between groups but did find a higher incidence of cirrhosis in the HIV-positive group. The implication of the latter is unclear; however, given the prolonged survival of dually infected patients following the introduction of highly active antiretroviral therapy (HAART), chronic HBV infection and associated complications may emerge as a significant clinical problem.

3. Hepatitis delta virus

Hepatitis delta virus (HDV) can only infect HBV-infected individuals. In the general population, although HBV/HDV co-infection is associated with more severe disease than for HBV alone, it is not clear whether the natural history is altered in HIV-infected patients. Preventing or eradicating HBV infection will prevent HDV infection.

4. Reactivation of previously resolved HBV infection

Reactivation of previously resolved HBV infection as indicated by the reappearance of HbeAg, HbsAg, and HBV-DNA (with loss of anti-HBs if present) as well as an increase of biochemical markers of hepatitis (ALT, AST) is a well described, albeit uncommon, event in immunosuppressed patients. Such reactivation may be associated with a severe clinical illness. Reactivation of HBV should be in the differential diagnosis of acute hepatitis in an individual who previously had serologic evidence of resolved HBV infection and immunity. Reactivation of the chronic HBV infection, defined as conversion from HbeAg(-) to

HbeAg(+), appears to be more common in HIV-infected persons. In one study of persons with chronic HBV infection, reactivation occurred in 5/11 HIV-positive patients compared with 1/21 HIV-negative persons over an observational period of 3 to 6 years.

C. Prevention

RECOMMENDATION:

Clinicians should counsel HBV/HIV co-infected patients regarding transmission.

Due to the limited efficacy of HBV vaccine in the HIV-infected population, all patients should be given counseling about behavior modifications to decrease the risk of HBV transmission through sexual activity and injection drug use.

Active immunization and passive immunization are two types of prophylaxis for hepatitis B. Active immunization involves the administration of the hepatitis B vaccine series given prior to exposure to HBV (pre-exposure prophylaxis) or after exposure (post-exposure prophylaxis) over a six-month time period. In the latter instance, the hepatitis B vaccine is usually given along with passive immunization, using hepatitis B immunoglobulin (HBIG).

1. Pre-exposure HBV prophylaxis

RECOMMENDATIONS:

Pre-vaccination screening for HIV-infected persons should include HbsAG, anti-HBs, and IgG anti-HBc.

Hepatitis vaccination in the HIV-infected patient ideally should be performed early in the course of HIV disease, before severe immune suppression has occurred.

HbsAG, anti-HBs, and IgG anti-HBc should be included in pre-vaccination screening for HIV-infected persons. This panel captures patients with prior HBV infection as well as responders to prior hepatitis B vaccination. Persons who are negative for all three serologic assays are eligible to receive the hepatitis B vaccine.

In over 90% of adult immunocompetent patients, three doses of the hepatitis B vaccine is highly efficacious and induces protective antibody. The two commercially available vaccines Recombivax-HB™ and Energix-B™ are equally immunogenic. Three vaccine doses are given at 0, 1 to 2 months, and 6 months. The doses of vaccine vary by patient's age.

Several factors reduce the vaccine's immunogenicity. These include age over 40 years, tobacco use, and HIV-infection, especially when the CD4 counts have been severely depressed. Generally, HIV-infected patients who do not respond have a rapid loss of induced antibody and are subsequently at risk of HBV infection following exposure. One to two months after completion of the third vaccine dose, it is advisable to test anti-HBs antibody. If no antibody is detected, a repeat vaccination series can be initiated although its success is not likely. If a second vaccination series is being considered, HBV seroconversion may be enhanced by immune reconstitution prior to re-vaccination. Given the above, it is preferable, when at all possible, to initiate the HBV vaccine series early in the course of HIV disease.

Some data suggest that HIV-infected persons beginning hepatitis B vaccination inadvertently during acute HBV infection may actually increase the risk of chronic HBV infection. Prior to the initiation of vaccination, testing to exclude a recent HBV infection would be advisable.

2. Post-exposure prophylaxis

RECOMMENDATION:

Post-exposure prophylaxis should be offered following a mucosal (including sexual) or percutaneous exposure to an HBV-infected source patient.

Percutaneous exposure of HbsAg(+) blood for a non-immune person carries a transmission risk ranging from 5% to 10% in HBeAg(-) samples and 25 to 30% in HBeAg(+) samples.

Following a percutaneous or mucous membrane exposure, both active and passive immunization may be indicated. Management of a sexual exposure to an HBsAg source patient should be similar. Perinatal HBV transmission occurs in 70% to 90% of neonates born to women who are both HBsAg(+) and HBeAg(+); without treatment, 85% to 95% of these infants become chronic carriers. For neonates born to women who are HBsAg(+) and HBeAg(-), the transmission risk is 10% to 20%. The transmission rate decreases by 85% to 95% when a single dose of HBIG is given within 24 hours of birth and combined with vaccination beginning within 12 hours of birth.

3. Sexual Exposure

RECOMMENDATION:

As soon as possible after sexual exposure to HBV, a person should receive HBIG.

HBIG given within 14 days of exposure reduces the infection risk by about 75%. At the same time that passive immunization is given an HBV serologic panel should be drawn. HBV vaccine should be strongly recommended to susceptible persons.

D. Treatment of Chronic HBV Infection

RECOMMENDATIONS:

Consultation with an expert provider in the field of hepatitis B treatment is advised to determine whether HBV therapy should be undertaken, which therapy should be given, and how the patient should be monitored clinically once treated.

The drug regimen of choice is currently unknown since no randomized trials have been conducted in this patient population. Options include interferon-alfa-2b or lamivudine alone; there are insufficient data to recommend combinations of drugs at this time.

Patients should, if possible, be on a HAART regimen initiated early in the course of HIV infection.

If lamivudine is given for treatment of hepatitis B, it should never be used alone. Rather, it should be used in combination with other HIV-active antiretroviral agents as a component of HAART. The recommended dose is 150 mg twice daily.

Because of the potential for a flare of hepatitis, periodic measurement of hepatic transaminases is recommended during the course of treatment with HAART (with or without lamivudine) or interferon.

If 3TC is discontinued as part of change of HAART regimen in patients being treated for HBV, a significant flare of ALT may result. Therefore, continuing 3TC should be considered even if it is not an integral part of the HIV regimen.

Treatment is aimed at reducing continued inflammation either through elimination of chronic HBV carriage or reduced expression of HBV antigens on the surfaces of infected hepatocytes via suppression of viral replication. Candidates for treatment are patients who are chronically HBeAg(+) and HBV DNA+, have repeatedly elevated transaminase levels, and demonstrate liver biopsy findings consistent with chronic HBV infection (although some experts feel treatment may be given in the absence of a liver biopsy).

Several case reports have described a flare of hepatitis following initiation of HAART with subsequent clearance of HbsAg, postulated to reflect improved immune function. The frequency of this phenomenon is unknown, and it should be noted that there are rare cases of fulminant hepatic failure and death following initiation of HAART. HAART is probably an important management strategy for the co-infected patient; however, it should not be relied upon to clear chronic HbsAg carriage. Thus, the clinician must be aware of the potential for significant hepatitis either due to immune reconstitution, to direct hepatic drug toxicity, or to 3TC withdrawal.

1. Interferon alfa-2b

Interferon alfa-2b (Intron-A™) at a dose of either 5 million units daily or 10 million units three times per week subcutaneously for four month results in HbeAg loss, an HBV-DNA decrease of loss, and ALT normalization (within six months after therapy completion) in 35% to 40% of HIV-negative patients, compared with 12% in placebo controls. The relapse rate is 10% to 15% and in responders HbsAg may not disappear for years. Patients most likely to respond have an initial ALT level > 200 IU/L, HBV DNA < 100 copies/mL, if the infection is of short duration, if the necroinflammatory activity is present on liver biopsy, and if no underlying immunosuppressive disease or treatment is present. The overall response rate in HBV/HIV co-infection is low although some success has been reported in HIV-infected patients with near normal CD-4 counts. INF-alfa-2b is associated with many toxicities (some life-threatening) and should be used only by those who are thoroughly familiar with it. Due to toxicity and limited efficacy, the role of monotherapy with INF-alfa-2b in HBV/HIV co-infected patients is limited. The trend in practice is now expanding to use HBV DNA by PCR as a measure of viral activity to monitor the response to therapy.

2. Lamivudine

In 1998, based upon studies in non-immunocompromised patients, lamivudine monotherapy (3TC, Epivir-HBV™) as a dose of 100 mgs daily was approved for the treatment of chronic HBV infection. Following one year of therapy, HBV-DNA was suppressed in almost all patients; ALT levels normalized in 40% to 50%; HbeAg was lost in 17% to 33%; HbeAb developed in 20%; and improvement in the liver histology occurred in 50% to 60%. Predictors of response were similar to those for INF-alfa-2b. A retrospective analysis of HBV/HIV co-infected patients with CD-4 cell counts of 25 to 50 cells/mm^3 who had received lamivudine as a component of HAART showed HBV-DNA and HbeAg reductions of 40% and 20% after one year of therapy respectively. Following discontinuation of therapy, viremia may reappear although continued response is predicted by the development of anti-HbeAb and loss of HBV DNA.

Unfortunately, HBV resistance to lamivudine occurred in up to 20% to 40% of isolates and appeared more likely to occur in persistently HbeAg(+) patients after one year of therapy. Despite persistent HbeAg in these patients, histologic improvement may be seen as well as reductions in HBV DNA and transaminase levels. Lamivudine may, therefore, be of therapeutic benefit despite the limited efficacy in eliminating HbeAg.

Three important observations should be anticipated when lamivudine is used for HBV infection.

- The ALT levels will frequently rise within 1 to 2 months when lamivudine is used for the HBV infection. This rise is transient and should not prompt discontinuation of therapy if the patient is otherwise well.
- Post-treatment ALT elevations (“flares”) may occur within 4 months of drug discontinuation. With rare exceptions, these “flares” do not seem to be clinically severe.
- Based on evidence that lamivudine-resistant HBV strains may be less pathogenic, some experts recommend the indefinite continuation of lamivudine in persons with chronic HBV infection despite evidence of HIV or HBV resistance to this agent. However, clinical benefit has not been demonstrated in long-term clinical trials.
- The seroconversion from HbeAg to anti-HbeAb may be associated with acute hepatitis that will resolve within a few months.

3. HBV Treatments in Development

Famciclovir (Famvir™) has good activity against HBV. Resistance can arise during therapy and may be associated with a rise in HBV DNA and ALT. A small pilot trial of famciclovir at 500 mgs three times daily plus INF- alfa-2b at 5 million units daily suggests that the combination may be additive in suppressing HBV. The combination of lamivudine and famciclovir are synergistic or additive in vitro and could be an attractive regimen for further clinical trials.

Abacavir (Ziagen™), didanosine (DDI., Videx™), and genciclovir which are approved for the treatment of HIV infection, have some activity against HBV. No clinical data are yet available on their use to treat HBV infection. Investigational drugs such as adefovir and entcavir have very good in vitro activity against HBV. The clinical development of lobucavir has been discontinued. Adefovir, at 30 mgs daily, is actively being studied against HBV and exhibits activity against 3TC-resistant HBV even though the trials for HIV therapy using this agent at higher doses have been terminated because of renal toxicity. Importantly, adefovir appears to retain activity against lamivudine-resistant HBV strains.

E. Conclusion

There are many unanswered questions with regard to therapy for chronic HBV in HIV-infected persons. More information is needed about HBV natural history in the HIV-infected patient. Since optimal therapy and therapy duration are still unknown, answers must be found to such issues as whether a HAART regimen for the HBV/HBV co-infected patient should include lamuvidine with didanosine or abacavir. Targeting extra-hepatic HBV reservoirs and the integrated HBV form in the human genome are issues whose therapeutic implications are unclear. The HBV/HCV/HIV co-infection patients present further complications and uncertainties.

Finally, immune restoration secondary to antiretroviral therapy may modify the course of HBV. These recently recognized cases suggest the need to periodically monitor hepatic function after starting HAART in chronic HBV carriers.