

HEPATITIS B VIRUS

II. HEPATITIS B VIRUS

Hepatitis B virus (HBV) is a major cause of acute and chronic hepatitis worldwide. In the United States, approximately 250,000 to 300,000 new HBV infections occur 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. HBV infection will resolve in 90% to 95% of immunocompetent adults with resultant immunity and no long-term consequences. However, the infection fails to clear in 5% to 10% of patients, and they become chronic hepatitis B carriers with persistence of hepatitis B surface antigen (HBsAg) for >6 months. There are approximately one million chronic carriers of HBV in the United States, and 4000 to 5000 persons die annually from cirrhosis or liver cancer, which are the major complications of chronic HBV carriage. Approximately 25% to 40% of chronically HBV-infected patients will develop one or more serious complications.

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, >50% of the population is 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 approximately 25% to 40% of persons who are first infected with HIV and subsequently become infected with HBV will become chronically HBV infected; this represents a 3- to 5-fold higher likelihood of chronic hepatitis B infection in this population than in non-HIV-infected populations. Approximately 10% of HIV-infected patients are co-infected with HBV.

HBV is similar to HIV in that it is spread mostly by sexual activity and injection drug use. HBV is generally found in high concentrations in serum (10⁸–10¹⁰ virions/mL), and HBV levels have been shown to be even higher in HIV-infected individuals compared with non-HIV-infected individuals. HBV is more easily transmitted via the sexual and percutaneous routes than HIV.

B. Clinical Syndromes

RECOMMENDATIONS:

Clinicians should obtain baseline hepatic function tests as well as HBV serologies for all HIV-infected patients to determine their HBV infection status; these include HBsAg, anti-HBs (HBsAb), and IgG anti-HBc (HBcAb).

Clinicians should strongly encourage all HIV-infected patients who do not have serologic evidence of prior HBV infection or who have not previously received the complete series of HBV vaccination to receive the hepatitis B vaccination series. Serologic testing for anti-HBs 1 to 2 months after the third dose should be performed. If the patient did not respond to the vaccine series, the clinician should administer a second series when the patient's CD4 count is ≥ 200 cells/mm³.

In the setting of unexplained elevations in serum liver enzymes, clinicians should consider obtaining an HBV DNA viral load, 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, right upper quadrant pain, anorexia, aversion to tobacco, headache, and

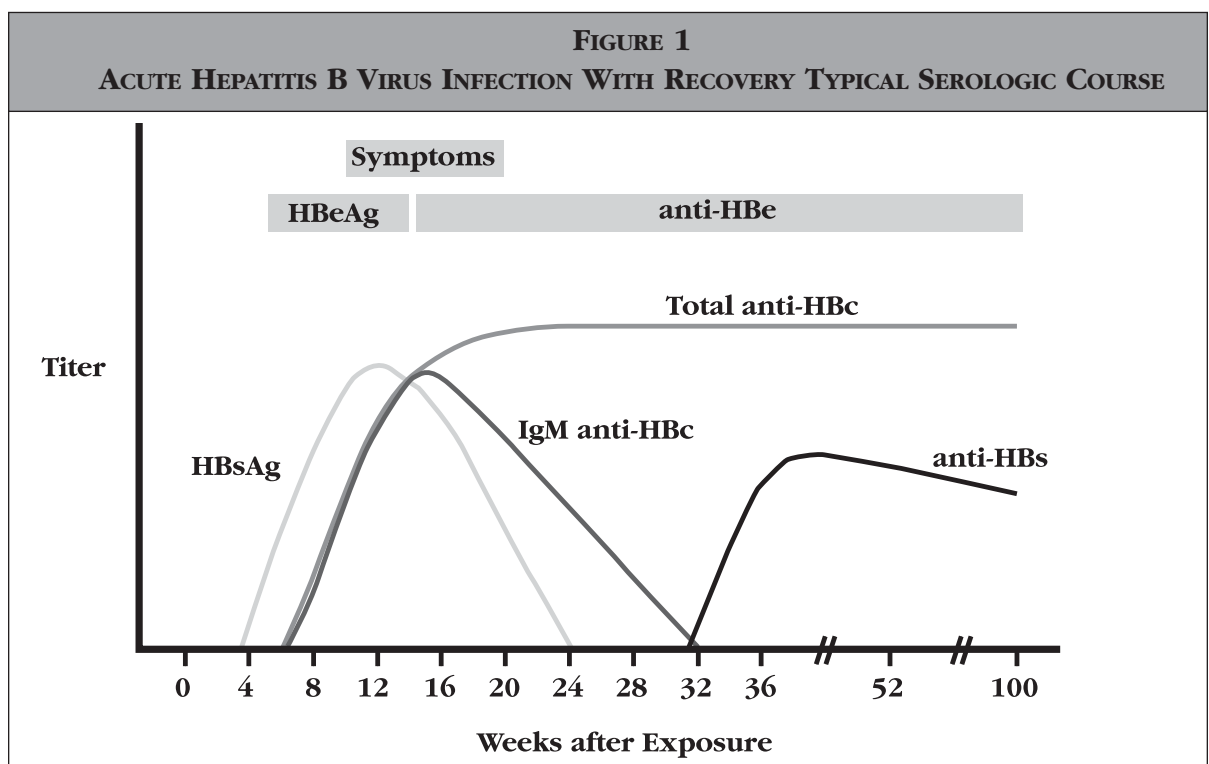
malaise may appear 1 to 2 weeks prior to the onset of jaundice. In as many as 20% of patients with acute HBV infection, a characteristic serum sickness-like syndrome with arthralgias or frank arthritis is seen. Recovery from clinical symptoms occurs over 4 to 6 weeks. There is no evidence that HBV has any effect on the clinical course of previously acquired HIV infection. Conversely, the clinical presentation of acute HBV infection is similar in both the HIV-infected and non-infected 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. Although IgM anti-HBc is rapidly followed by IgG anti-HBc, IgM may persist for months to years and may even reappear during flares of chronic HBV. In self-limited infection, 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

TABLE 2 SEROLOGIC RESPONSES TO HBV INFECTION						
Stage of Infection	HBsAg	HBsAb	HBcAb IgG	HBcAb IgM	HBeAg	HBeAb
Incubation	+	-	-	-	+ or -	-
Acute hepatitis B	+	-	+	+	+	-
HbsAG-negative acute hepatitis B	-	-	+	+	-	-
Healthy HbsAg carrier	+	-	+++	+ or -	+	-
Chronic hepatitis B	+	-	+++	+ or -	-	+
Convalescent HBV infection	-	++	++	+ or -	-	+
HBV vaccination	-	++	-	-	-	-

Ab, antibody; Ag, antigen.

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



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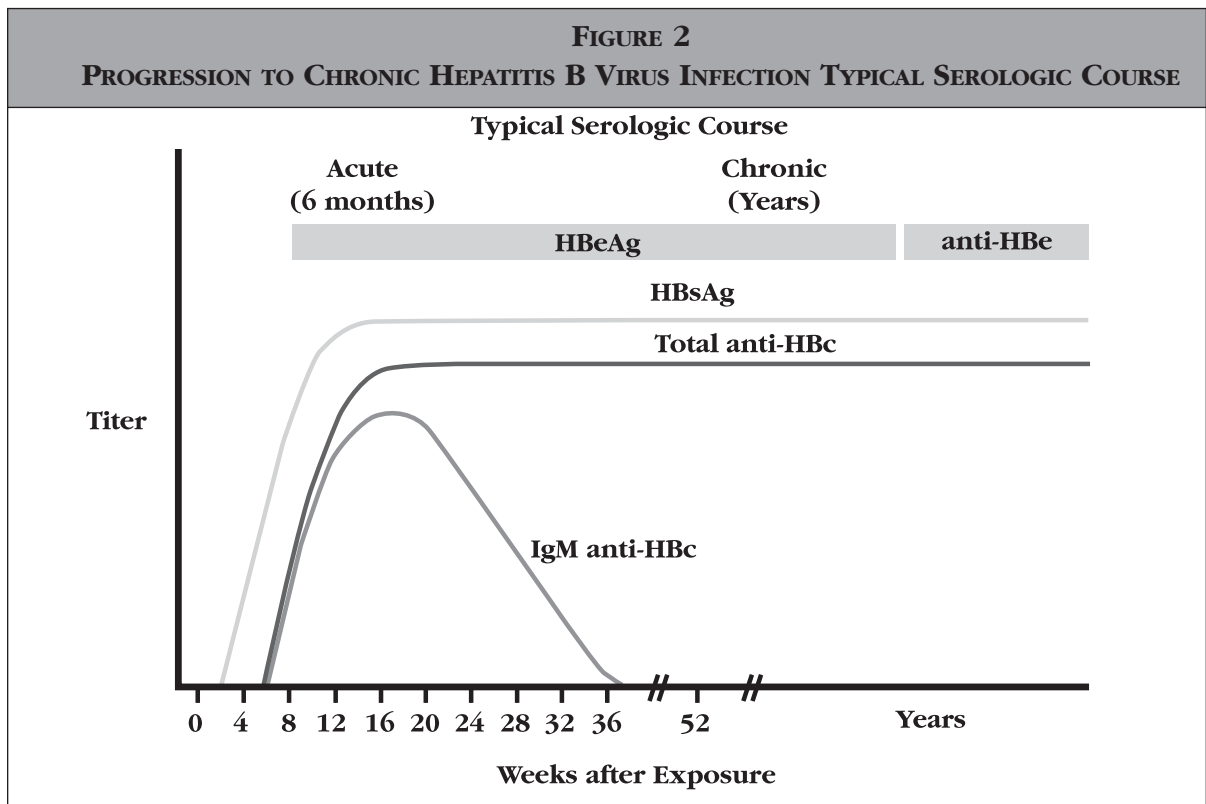
serum HBsAg, HBe antigen (HBeAg) and HBV DNA are markers of active viral replication in hepatocytes. Although these markers are present early in the course of acute infection, they may also persist in the chronically infected individual. When detected, HBsAg, HBeAg, and HBV DNA are not specific for acute infection. Table 2 and Figure 1 provide a schematic representation of the serologic responses to self-limited HBV infection.

2. Chronic Hepatitis B Infection

Chronic hepatitis B infection is responsible for 4000 to 5000 deaths annually in the United States. These deaths are related to cirrhosis or hepatocellular carcinoma (HCC). Cirrhosis is almost always present prior to developing HCC in the setting of hepatitis C; however, this is not true for hepatitis B, in which 30% of HCC cases occur in the absence of cirrhosis. Most hepatologists recommend screening for HCC in patients with cirrhosis by measuring α -fetoprotein and performing ultrasound every 6 months.

Chronic hepatitis B is serologically defined as a positive HBsAg for >6 months. Chronic HBV infection is characterized by hepatic inflammation with concomitant reparative changes and fibrosis. This may then progress to bridging necrosis and destruction of hepatic architecture by cirrhosis. The Ishak or Metavir scoring system should be used to grade liver biopsy results. These scales are based on visual assessment of cellular inflammation of hepatocytes and fibrosis.

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(+), HbcAb IgG(+), and HBsAb(-) (see Table 3). HBsAg will clear in approximately 2% of chronic carriers per year. HBeAg may also be spontaneously cleared, independent of HBsAg, at rates that approach 45% over 7 years of observation. Clearance of HBeAg, even with persistence



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of HBsAg, is associated with resolution of the inflammatory process, 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. Figure 2 provides a schematic representation of the serologic responses to chronic HBV infection.

Compared with non-HIV-infected patients, those with chronic HIV/HBV co-infection have a lower aminotransferase level, higher HBV viral loads, and lower rates of HBeAg loss over time. Generally, abnormal histopathology in a liver biopsy tends to be reduced in HIV-infected patients, although some studies show no difference between HIV-infected and non-infected populations. One large recent study found no difference in necroinflammatory lesions between groups but did find a higher incidence of cirrhosis in the HIV-infected 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.

Patients may have an isolated antibody to HBV core (HBcAb IgG, see Table 3). Repeat testing for HBcAb, HBsAb, and HBsAg should be performed. If the patient is still positive only to anti-HBc, then HBcAb IgM should be performed to exclude recent infection. If chronic liver disease is present, as evidenced by persistently elevated transaminases or abnormal histology on liver biopsy, HBV DNA PCR (HBV viral load) should be performed to exclude chronic infection.

Occasionally, HBV DNA may be present when the HBeAg is absent. This may represent either the original virus (“wild-type”) or it may signify the presence of virus “pre-core” or “core promoter” mutations. These mutations increase with time and are present in approximately 10% of patients in the United States. Patients with these viral isolates are HBsAg(+),

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 negative or positive positive	immune
HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive positive negative	acutely infected
HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive negative negative	chronically infected
HBsAg anti-HBc anti-HBs	negative positive negative	four interpretations possible*

Ab, antibody; Ag, antigen.

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

HBeAg(-), and HBeAb(+) (anti-HBeAg(+)). They are distinct from the “inactive” carrier by the presence of ALT (>2× normal), (+) HBV DNA in serum, and chronic hepatitis on liver biopsy. Other causes of hepatitis should be excluded. It is important to recognize carriers of these mutant strains because therapy may differ from that for non-mutant strains (see Section D: *Treatment of Chronic HBV Infection*).

3. Hepatitis Delta Virus

Hepatitis delta virus (HDV) can only infect HBV-infected individuals. Although in the general population HBV/HDV co-infection is associated with more severe disease than 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 HBsAb, if present) and 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 chronic HBV infection, defined as conversion from HBeAg(-) to HBeAg(+), seems to be more common in HIV-infected persons. In one study of persons with chronic HBV infection, reactivation occurred in 5 of 11 HIV-infected patients compared with 1 of 21 non-HIV-infected patients over an observational period of 3 to 6 years.

C. Prevention

RECOMMENDATIONS:

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

Due to the limited efficacy of HBV vaccine in the HIV-infected population, all patients should be given counseling concerning behavior modifications to decrease the risk of acquiring HBV infection 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 prior to exposure to HBV (pre-exposure prophylaxis) or after exposure (post-exposure prophylaxis) over a 6-month time period. After exposure to a known chronic HBV carrier, 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 patients should include HBsAg, HBsAb, and HbcAb IgG.

The clinician should ideally administer the hepatitis vaccination in HIV-infected patients early in the course of HIV disease, before severe immune suppression has occurred.

The clinician should test for HBsAb 1 to 2 months after completion of the third vaccine dose.

HBsAg, HBsAb, and HbcAb IgG should be included in pre-vaccination screening for HIV-infected persons. This panel identifies patients with prior HBV infection as well as responders to prior hepatitis B vaccination. People who are negative for all three tests are eligible to receive the hepatitis B vaccine. Of note, some data suggest that inadvertent initiation of hepatitis B vaccination during acute HBV infection in HIV-infected persons may actually increase the risk of chronic HBV infection.

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

Several factors reduce the vaccine's immunogenicity. These include age >40 years, tobacco use, and HIV infection, especially when CD4 counts are low. Ideally, the HBV vaccine series should be administered early in the course of HIV disease, before severe immune suppression has occurred. However, advanced immune suppression is not a contraindication to vaccination, and vaccination of susceptible persons should not be deferred or delayed because of advanced immune suppression or in anticipation of expected immune recovery due to the effect of HAART.

Generally, in HIV-infected patients who do not respond to the vaccine series, a rapid loss of induced antibody occurs. These patients are, therefore, at risk for HBV infection following exposure. The clinician should test for HBsAb 1 to 2 months after completion of the third vaccine dose. If no antibody is detected, a repeat vaccination series may be initiated, although its success is not likely. If a second vaccination series is being considered, HBV seroconversion may be enhanced by immune reconstitution (>200 cells/mm³) prior to re-vaccination.

A combined hepatitis A and B vaccine is available and may be used in persons susceptible to both hepatitis A and B. It is given in three total doses at 0, 1, and 6 months.

2. Post-Exposure HBV Prophylaxis

RECOMMENDATIONS:

Administration of prophylactic hepatitis B immune globulin (HBIG) and the initiation of the hepatitis B vaccine series (at different sites) are recommended when the non-HBV-immune patient sustains a blood or body fluid exposure to a source with acute or chronic HBV (see Table 4).

Following an HBV exposure, determination of the source patient's HBV serologic status should be sought.

The risk for transmission of HBV from a non-occupational or occupational exposure is significantly greater than the risk for transmission of HIV. The risk for HBV infection ranges from 6% to 30% depending on the presence of hepatitis e antigen. Initiation of the HBV vaccine series within 12 to 24 hours of an exposure has been demonstrated to be 70% to 90% effective in preventing HBV infection. The combination of vaccine and HBIG achieves a similar level of efficacy. Among known non-responders to vaccination, one dose of HBIG is 70% to 90% effective in preventing HBV when administered within 7 days of percutaneous HBV exposure, and multiple doses have been shown to be 75% to 95% effective. Pregnant women can safely receive both the HBV vaccination and HBIG. When considering PEP for HBV exposures, both the source HBsAg status and the exposed person's vaccination status and antibody response should be considered (see Table 4). Both HBIG and the hepatitis B vaccine should be ideally administered within 24 hours of exposure. Hepatitis B antibodies should be drawn 1 to 2 months after completion of the third dose of the vaccine, but it is unreliable if the exposed person received HBIG within the past 3 to 4 months.

TABLE 4
RECOMMENDED POST-EXPOSURE PROPHYLAXIS FOR
BLOOD OR BODY FLUID EXPOSURE TO HEPATITIS B VIRUS

Vaccination and/or antibody response status of exposed person*	Treatment when source is:		
	HBsAg positive	HBsAg negative	Source unknown or not available for testing
Unvaccinated/non-immune	HBIG† ×1; initiate HB vaccine series	Initiate HB vaccine series	Initiate HB vaccine series
Previously vaccinated, known responder‡	No treatment	No treatment	No treatment
Previously vaccinated, known non-responder‡	HBIG† ×2 or HBIG† ×1 and initiate revaccination§	No treatment	If known high-risk source, treat as if source were HBsAg positive
Previously vaccinated, anti-body response unknown	Test exposed person for anti-HBs: - If adequate‡, no treatment - If inadequate‡, HBIG* ×1 and vaccine booster	No treatment	Test exposed person for anti-HBs - If adequate‡, no treatment - If inadequate‡, initiate revaccination

Reprinted from the Updated US Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Post-Exposure Prophylaxis. *MMWR Morb Mortal Wkly Rep* 2001;50(RR-11):1-52. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5011a1.htm>.

HBsAg, hepatitis B surface antigen; HBIG, hepatitis B immune globulin; anti-HBs, antibody to hepatitis B surface antigen.

* Persons who have previously been infected with HBV are immune to re-infection and do not require PEP.

† Dose 0.06 mL/kg intramuscularly.

‡ Responder is defined as person with adequate levels of serum antibody to HBsAg (serum anti-HBs >10mIU/mL); non-responder is a person with inadequate response to vaccination (serum anti-HBs <10mIU/mL).

§ The option of giving one dose HBIG and re-initiating the vaccine series is preferred for non-responders who have not completed a second 3-dose vaccine series. For persons who previously completed a second vaccine series but failed to respond, two doses of HBIG are preferred.

3. Prophylaxis for Perinatal HBV Transmission

RECOMMENDATION:

Administration of prophylactic HBIG and the initiation of the hepatitis B vaccine series (at different sites) are recommended within 12 hours of birth.

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 is combined with vaccination beginning within 12 hours of birth.

D. Treatment of Chronic HBV Infection

RECOMMENDATIONS:

HIV-infected patients with active hepatitis B disease should be considered for therapy.

The clinician should consult with a specialist with experience in treating hepatitis B in patients with HIV infection to determine whether HBV therapy should be initiated, which therapy should be given, and how the patient should be monitored clinically once treated.

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

In HIV/HBV co-infected patients receiving HAART (with or without lamivudine) or interferon, clinicians should periodically measure hepatic transaminases during the course of treatment because of the potential for a flare of hepatitis. Clinicians should closely monitor hepatic function in HIV/HBV co-infected patients who discontinue lamivudine, emtricitabine, and tenofovir.

Although many questions still remain, the understanding and treatment of hepatitis B infection have dramatically improved. Patients with active hepatitis B disease [HBsAg(+), HBV DNA(+)] with or without (+)HBeAg and an ALT >2× normal should be considered for therapy. Patients with ALT ≤2× normal have a poor response to interferon or lamivudine. The goal of therapy is to normalize the ALT, convert the HBeAg to HBeAb(+) (if initially HBeAg(+)), and eradicate HBV DNA (by hybridization assay). 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. The PCR assay for HBV DNA may be preferable when following the response of HBeAg(-) isolates because the HBV DNA serum antibody may be low initially.

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

1. Interferon alfa-2b

Interferon alfa-2b and 2a at a dose of either 5 million units daily or 10 million units thrice weekly subcutaneously for 4 months was the first approved therapy for HBV. Responses to therapy (defined as a loss of HBeAg, decrease or loss of HBV DNA, and normalization of ALT within 6 months after therapy is completed) in patients not infected with HIV occurs in 35% to 40% of patients versus 12% in placebo controls. The relapse rate is 10% to 15%, and HBsAg may not disappear for years in responders. Preliminary data suggest that pegylated interferon alfa-2a may be superior to the short-acting interferon. Patients are most likely to respond if the initial ALT level is >200 IU/L, HBV DNA is <100 pg/mL, the infection is of short duration, necroinflammatory activity is present on liver biopsy, and no underlying immunosuppressive disease is present. Although some success has been reported in HIV-infected patients with near-normal CD4 counts, the overall response rate in HBV/HIV co-infection is low. In HBeAg(-) patients, the response to interferon alfa does not appear to be durable, and 12 months of therapy is recommended for these isolates. Interferon-alfa should not be used in patients with decompensated cirrhosis. Interferon alfa is associated with many toxicities (some life-threatening) and should only be used by clinicians who are experienced with its use. Because of its toxicity and limited efficacy, other therapies are considered preferable.

2. Lamivudine

RECOMMENDATIONS:

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 or 300 mg once daily.

If lamivudine is discontinued as part of a change in the HAART regimen in patients being treated for HBV, a significant flare of ALT may result; therefore, continuing lamivudine should be considered even when HIV resistance to it has developed.

In 1998, lamivudine monotherapy at a dose of 100 mg daily was approved for the treatment of chronic HBV infection. Following 1 year of therapy, HBV DNA was suppressed in most patients. ALT levels normalized in 40% to 50%, HBeAg decreased in 17% to 33%, HBeAb developed in 20%, and improvement in liver histology occurred in 50% to 60%. Predictors of response are similar to those for interferon alfa-2b. A recent retrospective review of HIV/HBV co-infected patients with CD4 cell counts of 25 to 250 cells/mm³ showed the lamivudine-containing arm to have HBV DNA and HBeAg decreases of 40% and 20%, respectively, after 1 year of therapy. After 1 year of therapy, viremia may reappear, although continued response is predicted by the development of HBeAb and decrease in HBV DNA. In contrast to interferon, lamivudine may be used in advanced (decompensated) cirrhosis with resultant improvement in the Childs-Pugh score. As with interferon, the relapse rate is high in initially HBeAg(-) patients, and, thus, long-term therapy beyond 1 year seems to be necessary.

Unfortunately, HBV resistance to lamivudine occurred in up to 20% to 40% of isolates and seemed more likely to occur in persistently HBeAg(+) patients after 1 year of therapy and in as many as 65% of isolates after 4 years. 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.

Four 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 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 the drug. However, clinical benefit has not been demonstrated in long-term clinical trials.
- The seroconversion from HBeAg to HBeAb may be associated with acute hepatitis that will resolve within a few months.

3. Adefovir

In September 2002, adefovir was approved for the treatment of HBV. The dose is 10 mg once daily and is taken without regard to meals; this dose has no anti-HIV activity. In both HBeAg(+) and HBeAg(-) patients, adefovir results in significant histologic and fibrosis improvement, normalization of ALT, and HBeAg seroconversion (in the HBeAg group) compared with placebo. In two studies, the mean decreases in HBV DNA while receiving adefovir were 3.57 and 3.65 log₁₀ copies/mL versus a decrease of 0.98 and 1.32 log₁₀ copies/mL for placebo in the HBeAg(+) and HBeAg(-) groups, respectively. In a study of HIV/HBV co-infected patients, treatment for 1 to 2 years was associated with a 4 to 5 log₁₀ copies/mL decrease in HBV DNA. Adefovir is effective against lamivudine-resistant isolates and HBeAg(-) isolates. As with lamivudine, severe exacerbations of hepatitis may occur when adefovir is discontinued. Of note, no resistance mutations have been detected in patients receiving adefovir monotherapy after 2 years of therapy.

4. Other Drugs With Activity Against HBV

Famciclovir has moderate activity against HBV. Resistance may arise during therapy and may be associated with a rise in HBV DNA and ALT. A small pilot trial of famciclovir at 500 mg three times daily plus interferon alfa at 5 million units daily suggest that the combination may be additive in suppressing HBV. The combination of lamivudine and famciclovir are synergistic or additive *in vitro*, and one small study demonstrated that famciclovir/lamivudine resulted in a further decrease in HBV DNA compared with lamivudine alone. In the interim, famciclovir may have a role in combination with a HAART regimen containing lamivudine when tenofovir or adefovir cannot be used.

Tenofovir was approved for treatment of HIV infection (not HBV) in 2001. Although tenofovir is active against HBV, the safety and efficacy of tenofovir have not been established in patients co-infected with HIV and HBV. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV and have discontinued tenofovir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue tenofovir and are co-infected with HIV and HBV.

Of the other approved antiretroviral drugs, *abacavir* and *didanosine* have some limited activity against HBV. No clinical data are available concerning their use to treat HBV.

There are other promising anti-HBV drugs being studied. Emtricitabine has activity against both HIV and HBV with impressive HBeAg conversion rates (50%) by 1 year. L-dT (telbivudine) has resulted in a mean decrease of 3.6 log₁₀ copies/mL. Studies of entecavir and val-LdC are also in progress.

E. Choosing Therapy for Patients With HBV/HIV Co-Infection

RECOMMENDATION:

Before initiating therapy for HIV or HBV in co-infected persons, the clinician should consider possible consequences a specific regimen will have on future treatment options for both HIV and HBV.

Some therapies for HIV or HBV may have possible repercussions on future treatment options for both HIV and HBV. For example, if an HIV/HBV co-infected person is not receiving ARV therapy, and a decision is made to treat HBV, the use of lamivudine is discouraged because resistance of HIV to lamivudine will inevitably develop. When lamivudine is used as part of HAART for persons with HIV/HBV co-infection, the dosage is 150 mg twice daily or 300 mg once daily (both are standard dosages for the treatment of HIV infection in adults with normal renal function). Few data are available concerning the effect of low-dose adefovir (10 mg) on HIV resistance (to tenofovir and/or nucleoside reverse transcriptase inhibitors) when used with either no therapy or incompletely suppressive therapy for HIV. One small study (13 patients) using adefovir in HIV/HBV co-infected persons in the presence of poorly controlled HIV infection found no adefovir-specific resistance mutations after 3 to 12 months. However, more data are needed to address this important question.

It is becoming increasingly likely that combination therapy will be preferable for the treatment of HBV infection. In lamivudine-naïve patients, a combination of lamivudine/adevovir or lamivudine/tenofovir as part of a HAART regimen seems reasonable (adevovir at 10 mg/day has no anti-HIV activity). However, few data prove that the combination is superior to monotherapy, and results of combination therapy trials are awaited before this can be considered the standard of care. Consultation with a provider with expertise in this field is advisable to determine whether therapy should be undertaken.

F. Conclusion

Previous HBV infection as well as chronic HBV co-infection is common in HIV-infected patients. Assessing baseline serologic status is necessary to determine whether vaccination is needed and whether immunity or chronic infection is present. Many unanswered questions remain regarding

therapy for chronic HBV in HIV-infected persons. More information is needed about HBV natural history in the HIV-infected patient. Because optimal therapy and therapy duration are still unknown, answers are needed as to whether a HAART regimen for the HBV/HIV co-infected patient should include lamivudine and tenofovir. Targeting extra-hepatic HBV reservoirs and the integrated HBV form in the human genome are issues with therapeutic implications that are unclear. Patients with HIV/HBV/HCV tri-infection present with further complications and uncertainties. Finally, immune restoration secondary to ARV therapy may modify the course of HBV. These recently recognized issues suggest the need to periodically monitor hepatic function after initiating HAART in chronic HBV carriers.

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