# Hepatitis B: Diagnosis and Treatment

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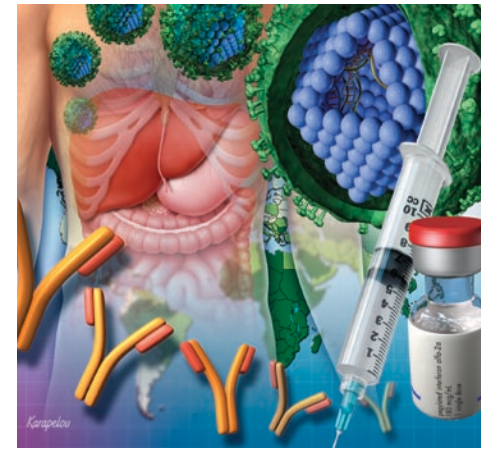
**Although an estimated 1 million persons in the United States are chronically infected with hepatitis B virus, the prevalence of hepatitis B has declined since the implementation of a national vaccination program. Hepatitis B virus is transmitted in blood and secretions. Acute infection may cause nonspecific symptoms, such as fatigue, poor appetite, nausea, vomiting, abdominal pain, low-grade fever, jaundice, and dark urine; and clinical signs, such as hepatomegaly and splenomegaly. Fewer than 5 percent of adults acutely infected with hepatitis B virus progress to chronic infection. The diagnosis of hepatitis B virus infection requires the evaluation of the patient's blood for hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody. The goals of treatment for chronic hepatitis B virus infection are to reduce inflammation of the liver and to prevent complications by suppressing viral replication. Treatment options include pegylated interferon alfa-2a administered subcutaneously or oral antiviral agents (nucleotide reverse transcriptase inhibitors). Persons with chronic hepatitis B virus infection should be monitored for disease activity with liver enzyme tests and hepatitis B virus DNA levels; considered for liver biopsy; and entered into a surveillance program for hepatocellular carcinoma. (*Am Fam Physician.* 2010;81(8):965-972. Copyright © 2010 American Academy of Family Physicians.)**

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▶ **Patient information:** A handout on hepatitis B is available at http://familydoctor.org/032.xml.

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Globally, an estimated 350 million persons are chronically infected with hepatitis B virus (HBV), resulting in 600,000 deaths annually from cirrhosis, liver failure, and hepatocellular carcinoma.[1,2] Approximately 88 percent of the world's population live in regions where the prevalence of chronic HBV infection among adults is more than 2 percent.[3] The prevalence of HBV infection in the United States is 0.4 percent, with an estimated 0.8 to 1.4 million persons chronically infected.[3,4] With the implementation of vaccination programs in 1991, the incidence of new infections in the United States has declined from 11.5 cases per 100,000 persons in 1985 to 1.6 cases per 100,000 persons in 2006.[3,4]

## Virus Description

HBV is a small (diameter of 42 nm), incompletely double-stranded DNA hepadnavirus. Substantial genetic variations occur within distinct regions, globally facilitating classification of eight distinguishable genotypes (A through H), which have treatment implications.[5] All genotypes are present in the United States, with genotypes A and C comprising 35 and 31 percent of viruses, respectively.[6] The HBV genome produces a nucleocapsid that contains the hepatitis B core antigen (HBcAg). This nucleocapsid is encompassed with an outer envelope referred to as the hepatitis B surface antigen (HBsAg). One segment of HBcAg results in the production of the hepatitis B e antigen (HBeAg), which is associated with viral replication and high infectivity. The DNA polymerase reverse transcriptase is a target for antiviral therapy.[7] HBV is transmitted in blood and secretions (e.g., semen, saliva) and is infectious outside the body for seven or more days.[3]

## Screening and Prevention

High-risk populations should be screened for HBV infection[6] *(Table 1[3])*. The Centers for Disease Control and Prevention recommends routine HBV screening in populations in which HBsAg prevalence is at least 2 percent, including immigrants from these regions.[1]

**SORT: KEY RECOMMENDATIONS FOR PRACTICE**

| *Clinical recommendation* | *Evidence rating* | *References* |
|---|---|---|
| High-risk populations should be screened for HBV infection. | C | 6 |
| Health care professionals should receive hepatitis B vaccination. | A | 12 |
| Hepatitis B vaccination and hepatitis B immune globulin are effective at preventing HBV infection in newborns of mothers infected with HBV. | A | 15 |
| All persons who meet criteria for chronic HBV infection should be evaluated for treatment. | C | 6 |
| Persons with chronic HBV infection who are not immune to hepatitis A should receive two doses of hepatitis A vaccine at least six months apart. | C | 6 |
| Patients in the active phase of chronic HBV infection should receive treatment. | C | 6 |
| Patients in the inactive or immune tolerant phases of chronic HBV infection should be monitored on a regular basis (every six to 12 months) for reactivation of their infection. | C | 6 |

*HBV = hepatitis B virus.*

*A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.*

**Table 1. Populations Recommended for HBV Screening**

| |
|---|
| Donors of blood, plasma, organs, tissue, or semen* |
| Health care professionals |
| Household contacts of persons with HBV infection |
| Infants born to mothers identified as HBsAg positive |
| Injection drug users* |
| Men who have sex with men* |
| Persons born in countries with HBsAg prevalence of ≥ 2 percent |
| Persons born in the United States who were not vaccinated as infants and whose parents were born in regions with HBsAg prevalence of ≥ 8 percent |
| Persons infected with human immunodeficiency virus |
| Persons needing immunosuppressive therapy (chemotherapy and immunosuppression for rheumatologic or gastrointestinal diseases)* |
| Persons undergoing hemodialysis* |
| Persons with persistently elevated aspartate and alanine transaminase levels |
| Pregnant women |
| Sex partners of persons with HBV infection |
| Survivors of sexual assault |

*HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.*

**—New recommendations from the Centers for Disease Control and Prevention.*

*Information from reference 3.*

Hepatitis B vaccine is part of routine immunizations in the United States, and as a result, the incidence of HBV has declined.[8] *Table 2* lists hepatitis B vaccines and recommended dosing schedules.[9-11] A Cochrane review confirmed that hepatitis B vaccination decreased HBV infection in health care professionals (relative risk = 0.51; 95% confidence interval, 0.35 to 0.73).[12] Because there is a high risk of acquiring HBV from a needlestick injury,[13] health care professionals exposed to HBsAg-positive blood should be given hepatitis B immune globulin after the exposure and started on the hepatitis B vaccine series if not previously vaccinated.[14] Hepatitis B vaccination and hepatitis B immune globulin are also effective in preventing HBV infection in newborns of mothers infected with HBV.[15] Populations to consider for hepatitis B vaccination are listed in *Table 3*.[3]

## Diagnosis

The diagnosis of HBV infection requires the evaluation of the patient's blood for HBsAg, hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb). Although the presence of HBsAg indicates that the person is infectious, the presence of HBsAb indicates recovery and immunity from HBV infection or successful immunization against HBV. HBcAb appears at the onset of acute HBV infection, but may also indicate chronic HBV infection. Interpretation of HBV immunologic markers is shown in *Table 4*.[11] HBV DNA sometimes may be the only marker present in early infections.

### ACUTE INFECTION

Symptoms of acute HBV infection are nonspecific and include fatigue, poor appetite, nausea, vomiting, abdominal pain, low-grade fever, jaundice, and dark urine. Clinical signs include liver tenderness, hepatomegaly, and splenomegaly. Acute HBV infection typically lasts two to four months. Approximately 30 to 50 percent of children five years and older and most adults are symptomatic; infants, children younger than five years, and immunosuppressed adults are more likely to be asymptomatic.[14] In adults

**Table 2. Hepatitis B Vaccines and Recommended Dosing Schedules**

| | Dosing | | | |
|---|---|---|---|---|
| *Vaccine* | *Children* | *Schedule* | *Adult* | *Schedule* |
| Engerix-B | 10 mcg (0.5-mL vial) | Birth; one to two months, and six to 18 months of age | 20 mcg (1-mL vial) | Time of first injection and then at one to two, and four to six months |
| Recombivax HB | 5 mcg (0.5-mL vial) | | 10 mcg (1-mL vial) | |
| Comvax (hepatitis B and *Haemophilus influenzae* type b)* | 5 mcg (0.5-mL vial) | Two, four, and 12 to 15 months of age | — | — |
| Pediarix (hepatitis B; diphtheria and tetanus toxoids and acellular pertussis; and inactivated polio)*† | 10 mcg (0.5-mL vial) | Two, four, and six months of age | — | — |
| Twinrix (hepatitis A and B) | — | — | 20 mcg (1-mL vial) | Time of first injection and then at one, and six to 12 months |

NOTE: *Other vaccination regimens can be found at http://cdc.gov/vaccines/recs/schedules/child-schedule.htm and http://cdc.gov/vaccines/recs/schedules/adult-schedule.htm.*

**—Should not be given to infants younger than six weeks.*
*†—Should not be given to persons older than seven years.*

*Information from references 9 through 11.*

with healthy immune systems, approximately 95 percent of acute infections are self-limited, with patients recovering and developing immunity.[6] Fewer than 5 percent of adults acutely infected with HBV progress to chronic infection. A small number (1 percent) develop acute hepatic failure and may die or require emergent liver transplantation.[16]

#### CHRONIC INFECTION

HBV infection is considered chronic when it persists longer than six months. Risk of chronic HBV infection is inversely related to age, with chronic infection developing in about 90 percent of infected infants, 30 percent of children younger than five years, and less than 5 percent in all other persons.[6] Occult HBV infection may be reactivated by chemotherapy or other immunosuppressants. Coinfection with human immunodeficiency virus (HIV) or hepatitis C virus can occur. All persons who meet criteria for chronic HBV infection should be evaluated for treatment.[6] Persons with chronic HBV infection who are not immune to hepatitis A should receive two doses of hepatitis A vaccine at least six months apart.[6]

## Goals of Therapy

The goals for treatment of chronic HBV infection are to reduce inflammation of the liver; prevent liver failure and cirrhosis; and reduce the risk of hepatocellular carcinoma by suppressing HBV replication.

**Table 3. Populations to Consider for Hepatitis B Vaccination**

- Children and adolescents younger than 19 years who have not been vaccinated previously
- Health care and public safety workers at risk of exposure to blood or blood-contaminated body fluids
- Infants, beginning at birth
- Injection drug users
- Men who have sex with men
- Persons seeking evaluation or treatment for a sexually transmitted infection
- Persons seeking protection from HBV infection (acknowledgment of a specific risk factor is not a requirement for vaccination)
- Persons with chronic liver disease; end-stage renal disease (including predialysis, peritoneal dialysis, hemodialysis, and home dialysis); or human immunodeficiency virus infection
- Residents and staff of facilities for persons who are developmentally disabled
- Sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than one sex partner during the past six months)
- Susceptible household contacts or sex partners of persons identified as HBsAg positive
- Travelers to regions with intermediate or high rates of endemic HBV infection

*HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.*

*Information from reference 3.*

**Table 4. Interpretation of HBV Immunologic Markers**

| Markers | | | |
|---|---|---|---|
| *HBsAg** | *HBcAb†* | *HBsAb‡* | *Interpretation* |
| – | – | – | Susceptible to HBV infection (should be vaccinated) |
| – | – | + | Immune because of vaccination |
| – | + | + | Immune because of natural HBV infection |
| + | + | – | Acute or chronic HBV infection |
| – | + | – | Interpretation unclear; four possibilities:<br>1. Resolved HBV infection (most common)<br>2. False-positive HBcAb, thus susceptible<br>3. "Low-level" chronic HBV infection<br>4. Resolving acute HBV infection |

*HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; + = positive test result; – = negative test result.*

**—The presence of HBsAg indicates that the person is infectious.*
*†— HBcAb appears at the onset of acute HBV infection. Presence may also indicate chronic HBV infection or a false-positive test.*
*‡—The presence of HBsAb indicates recovery and immunity from HBV infection or successful immunization against HBV.*

*Adapted from Mast EE, Margolis HS, Fiore AE, et al., for the Advisory Committee on Immunization Practices (ACIP). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents [published corrections appear in* MMWR Morb Mortal Wkly Rep. *2006;55(6):158-159, and* MMWR Morb Mortal Wkly Rep. *2007;56(48):1267].* MMWR Recomm Rep. *2005;54(RR-16):4.*

Normalization of alanine transaminase (ALT), loss of HBeAg (seroconversion), decrease in serum HBV DNA level, and improvement in liver histology indicate treatment effectiveness.[1,6,17,18] A recent systematic review found insufficient evidence to assess treatment effectiveness on patient-oriented outcomes, such as decreased mortality and improved quality of life.[19] A disease-oriented outcome, suppression of HBV DNA levels, is often used as an end point of treatment.[20]

It is important to distinguish between patients who are HBeAg positive and those who are HBeAg negative because of a viral mutation. Seroconversion (i.e., conversion from HBeAg positive to HBeAg negative, followed by conversion from hepatitis B e antibody [HBeAb] negative to HBeAb positive) predicts long-term reduction in viral replication and is used as a response marker to therapy. Genotypes affect response and guide treatment choices. For example, genotype A is highly responsive to pegylated interferon alfa-2a (Pegasys) therapy.[21] Certain populations (e.g., persons with renal insufficiency or decompensated liver disease, liver transplant recipients) require additional monitoring and expertise.

## Treatment Indications and Phases of Chronic HBV Infection

Over time, chronic HBV infection can go through four phases that can affect therapeutic considerations *(Table 5)*.[22]

### ACTIVE PHASE

During the active phase of chronic HBV infection, ALT levels are elevated and HBV DNA levels exceed 20,000 IU per mL ($10^5$ copies per mL).[18,22] Patients in the active phase of chronic HBV infection should be offered treatment.[6] Liver biopsy may not be necessary.

### INACTIVE PHASE

During the inactive phase of chronic HBV infection, ALT levels are normal and HBV DNA levels are low (less than 20,000 IU per mL).[18,22] Treatment and liver biopsy are

**Table 5. Phases of Chronic HBV Infection**

| | *Tests* | | | | *Histology* | | |
|---|---|---|---|---|---|---|---|
| *Phase* | *Alanine transaminase level* | *Hepatitis B e antigen* | *Hepatitis B e antibody* | *HBV DNA (IU per mL)* | *Inflammation* | *Fibrosis* | *Treatment* |
| Active | Elevated | +/– | +/– | > 20,000 | Active | Variable | Indicated |
| Inactive | Normal | – | + | < 20,000 | None | Minimal | Not indicated |
| Gray zone | Elevated or normal | +/– | +/– | Variable | Variable | Variable | May or may not be indicated |
| Immune tolerant | Normal | + | – | > 20,000 | Minimal | Minimal | Not indicated |

*HBV = hepatitis B virus; + = detectable; – = undetectable; +/– = may or may not be detectable.*

*Information from reference 22.*

not indicated in patients with inactive HBV infection. Patients should be monitored every six to 12 months for reactivation of their infection.[6]

#### GRAY ZONE PHASE

During the gray zone phase of chronic HBV infection, a discordance of ALT and HBV DNA levels is present.[18,22] A liver biopsy may be helpful to determine the presence of other underlying concomitant liver pathology, and to determine if treatment should be initiated.

#### IMMUNE TOLERANT PHASE

During the immune tolerant phase of chronic HBV infection, HBeAg is positive, HBV DNA levels are high (greater than 20,000 IU per mL), and ALT levels are normal.[18,22] In this phase, there is minimal inflammation or fibrosis, and treatment is not indicated. Because there is a direct relationship between HBV DNA levels and the risk of hepatocellular carcinoma, patients in this phase should be monitored every six months with ultrasonography and serum α-fetoprotein levels.[2,23] Patients should also be monitored every six to 12 months for reactivation.[6] Patients who convert to the active phase should be treated.

## Treatment Options

Several medications are approved in the United States for the treatment of HBV infection *(Table 6)*.[1] Although interferon is approved for treatment, pegylated interferon alfa-2a has higher effectiveness, with a similar adverse effect profile, and is preferred over interferon.

#### PEGYLATED INTERFERON ALFA-2A

Pegylated interferon alfa-2a is administered subcutaneously in well-compensated patients once weekly for six to 12 months. More than 50 percent of patients with HBeAg-positive genotype A infections will achieve seroconversion, whereas only 30 percent of those with non-A genotypes will seroconvert.[1] Seroconversion may not occur for up to six months after therapy has ended. Aspartate transaminase and ALT levels should be monitored often during treatment, and a complete blood count should be performed regularly. An increase in ALT levels often occurs during interferon therapy and typically precedes seroconversion. Serum HBV DNA level, HBeAg, and HBeAb should be measured at the end of treatment, and at three and six months after treatment.[18,24,25] Pegylated interferon alfa-2a should not be used in patients with advanced liver disease or in those coinfected with HIV. The advantage of a long-term response to the drug must be weighed against its potential adverse effects.

#### ORAL ANTIVIRAL AGENTS

Five oral nucleotide reverse transcriptase inhibitors are approved for the treatment of HBV infection *(Table 7)*.[1] These medications require renal function monitoring. If HBV DNA levels do not become undetectable within six to 12 months, a second antiviral agent should be used. The incidence of seroconversion increases in a stepwise fashion with ongoing treatment and with the duration of undetectable HBV DNA levels. After three years of therapy with oral antiviral agents, the incidence of seroconversion approaches that of 12 months of therapy with pegylated interferon alfa-2a. Oral therapy should be continued for at least an additional six months once seroconversion is achieved.[22] If seroconversion does not occur, treatment should be continued.[6] Regardless of patient seroconversion status, HBV DNA and liver enzyme levels should be monitored, and therapy should be reinitiated if needed.[6]

#### RESISTANCE

The primary limitation of all oral antiviral agents is development of viral resistance because of mutations in the viral DNA during replication.[18,22] Lamivudine (Epivir) and telbivudine (Tyzeka) are most likely to fail because of resistance. If resistance develops to one agent, the effectiveness of a second agent with the same site of action is reduced. The risk of resistance increases whenever patients have persistent detectable HBV DNA levels.[18,22] The addition of a second agent with a different site of action is vital in patients with detectable serum HBV DNA levels after six to 12 months of therapy.[18,22] Adding a second agent may be preferable to switching agents.

## Complications

Chronic HBV infection can lead to cirrhosis and its complications, including ascites, portal hypertension, hemorrhage, and hepatocellular carcinoma. Hepatocellular carcinoma surveillance in patients with chronic HBV infection is often performed every six to 12 months using α-fetoprotein levels and abdominal ultrasonography[18,26]; however, a Cochrane review found insufficient evidence to demonstrate that hepatocellular carcinoma surveillance improves survival.[27] A randomized trial of 18,816 persons with chronic HBV infection found a mortality reduction of 37 percent at one year in those screened versus those not screened.[28] A recent meta-analysis of six studies including 2,984 patients found a

## Table 6. Antiviral Therapies for Patients with Treatment-Naïve HBeAg-Positive Chronic HBV Infection

| *Drug* | *Adult dosage** | *Duration (weeks)* | *Undetectable HBV DNA at one year (%)* | *HBeAg seroconversion at one year (%)* | *Durability of seroconversion at one year (%)†* | *Histologic improvement in one year (%)* | *Estimated cost of one year of treatment‡* |
|---|---|---|---|---|---|---|---|
| **Injectable** | | | | | | | |
| Pegylated interferon alfa-2a (Pegasys) | 180 mcg per week | 48 | 25 | 27 | 82 | 38 | $32,590 |
| **Oral** | | | | | | | |
| Adefovir (Hepsera) | 10 mg per day | ≥ 48 | 13 to 21 | 12 | 91 | 53 to 68 | $11,135 |
| Entecavir (Baraclude) | 0.5 mg per day | ≥ 48 | 67 | 21 | 82 | 72 | $9,195 |
| Lamivudine (Epivir) | 100 mg per day | 48 to ≥ 52 | 36 to 44 | 16 to 21 | 70 to 80 | 49 to 62 | $4,290 |
| Telbivudine (Tyzeka) | 600 mg per day | ≥ 52 | 60 | 22 | 80 | 65 | $8,180 |
| Tenofovir (Viread) | 300 mg per day | ≥ 52 | 80 | 21 | NA | 74 | $8,320 |

*HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; HIV = human immunodeficiency virus; NA = not available.*

**—Based on patients with normal renal function.*

*†— Durability of response is defined as the percentage of patients who achieved seroconversion and maintained their HBeAg-negative status at one year after the termination of treatment.*

*‡—Estimated retail price of treatment based on information obtained at http://www.drugstore.com (accessed January 19, 2010).*

*Adapted with permission from Dienstag JL. Hepatitis B virus infection.* N Engl J Med. *2008;359(14):1490.*

## Table 7. Antiviral Therapies for Patients with Treatment-Naïve HBeAg-Negative Chronic HBV Infection

| *Drug* | *Adult dosage** | *Undetectable HBV DNA at one year (%)* | *Histologic improvement in one year (%)* | *Durability of response at one year (%)†* |
|---|---|---|---|---|
| **Injectable** | | | | |
| Pegylated interferon alfa-2a (Pegasys) | 180 mcg per week | 63 | 48 | 18 |
| **Oral** | | | | |
| Adefovir (Hepsera) | 10 mg per day | 51 to 64 | 64 | < 10 |
| Entecavir (Baraclude) | 0.5 mg per day | 90 | 70 | NA |
| Lamivudine (Epivir) | 100 mg per day | 60 to 73 | 61 to 66 | < 10 |
| Telbivudine (Tyzeka) | 600 mg per day | 88 | 67 | NA |
| Tenofovir (Viread) | 300 mg per day | 95 | 72 | NA |

*HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; NA = not available.*

**—Based on patients with normal renal function.*

*†—Durability of response is defined as the percentage of patients who achieved undetectable serum HBV DNA levels and maintained this status at one year after the termination of treatment.*

*Adapted with permission from Dienstag JL. Hepatitis B virus infection.* N Engl J Med. *2008;359(14):1491.*

| *Strengths* | *Weaknesses* |
|---|---|
| No resistance; highest seroconversion rate at one year; finite treatment time | Not well tolerated; expensive; subcutaneous injections; cannot use in persons with decompensated liver disease or HIV infection |
| Oral; well tolerated | Mild effectiveness; moderate probability of resistance development; need to monitor renal function |
| Oral; well tolerated; moderate effectiveness; low probability of resistance development | Not recommended in persons coinfected with HIV because of possible development of HIV resistance; need to monitor renal function |
| Oral; well tolerated | Mild effectiveness; high probability of resistance development; need to monitor renal function |
| Oral; well tolerated; moderate effectiveness | High resistance; need to monitor renal function |
| Oral; well tolerated; moderate effectiveness; low probability of resistance development | Need to monitor renal function |

pooled sensitivity of 94 percent and a pooled specificity of 94 percent for screening ultrasonography, with screening every six months superior to screening every 12 months ($P = .001$).[29] Hepatocellular carcinoma is relatively uncommon in the United States (2.8 cases per 100,000 white men and 6.1 cases per 100,000 black men), but the incidence has increased 71.4 percent over the past 30 years.[30] Risk factors are shown in *Table 8*.[26,30] Treatment algorithms for hepatocellular carcinoma, which include liver transplantation, should prompt referral to a subspecialist. Coinfection with hepatitis D (delta) virus may occur in patients with chronic HBV infection; this increases the risk of cirrhosis and fulminant hepatitis.

## Pregnancy

Every pregnant woman should be tested for HBsAg at her first prenatal visit.[3] The risk of an infant acquiring HBV from an HBsAg- or HBeAg-positive mother is 80 to 90 percent if the infant is not given an intramuscular injection of 0.5 mg of hepatitis B immune globulin within 12 hours of birth, followed by three timed doses of hepatitis B vaccine.[11,18] Because the risk of transmission is directly related to the mother's serum HBV DNA level at the time of birth, it is reasonable to treat women with high serum HBV DNA levels (greater than 20,000 IU per mL) with oral agents during the final trimester of pregnancy. Lamivudine, entecavir (Baraclude), and telbivudine are U.S. Food and Drug Administration pregnancy category C.[18] Breastfeeding is safe in women who are HBsAg positive[3]; however, women should not breastfeed while undergoing treatment for HBV infection.

**Table 8. Risk Factors for Developing Hepatocellular Carcinoma with Chronic HBV Infection**

| | |
|---|---|
| Alcohol abuse | HBV DNA viral load > 10,000 IU per mL |
| Asian or African race | HBV genotype C |
| Cirrhosis | Longer duration of infection |
| Coinfection with hepatitis C and D virus | Male sex |
| Exposure to aflatoxin | Older age |
| Family history of hepatocellular carcinoma | Presence of hepatitis B e antigen |
| | Smoking |

*HBV = hepatitis B virus.*

*Information from references 26 and 30.*


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Author disclosure: Nothing to disclose.


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