2013

Physician's Guide *to* Hepatitis B

a silent killer

Developed by the Asian Liver Center at Stanford University

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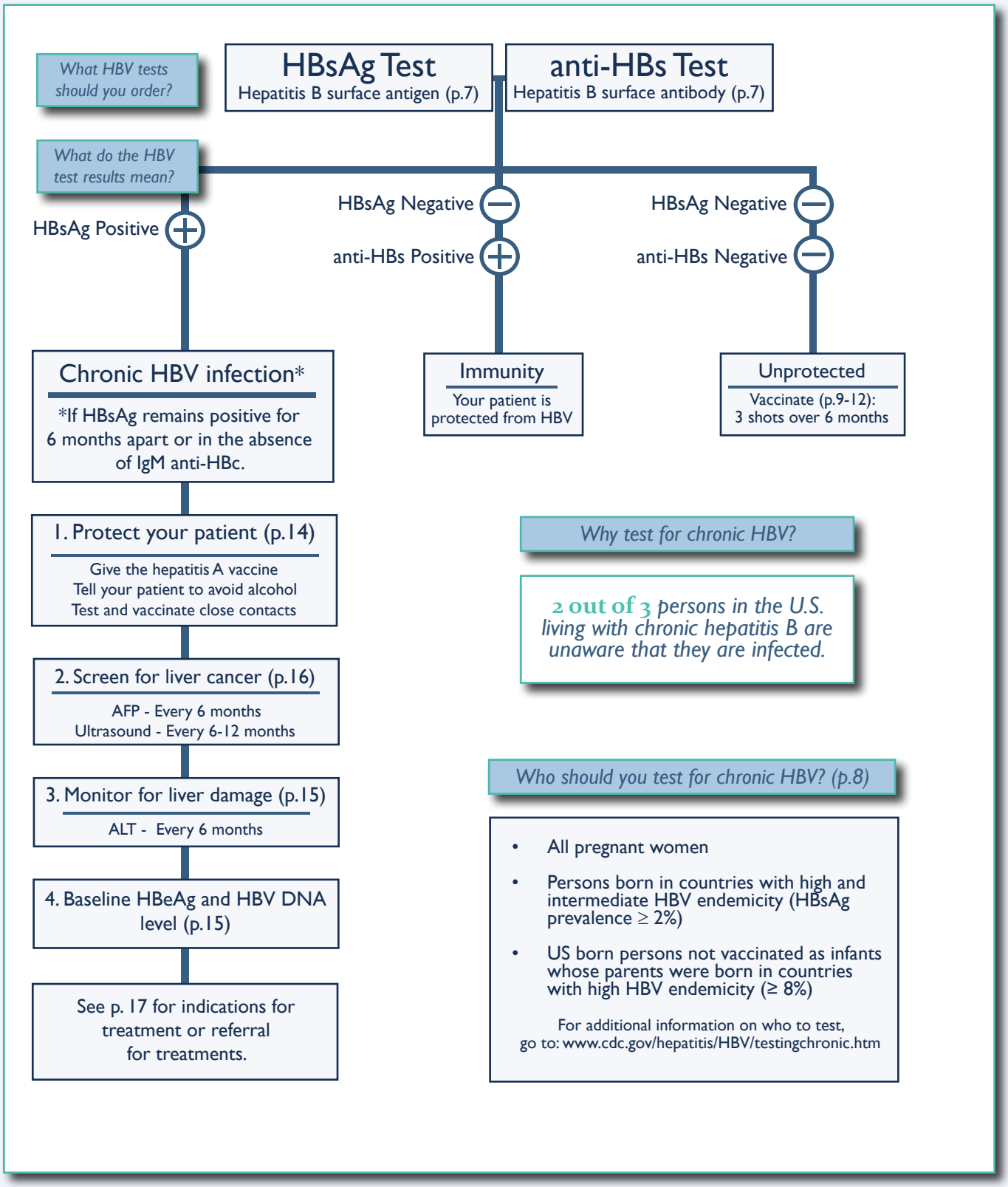
> "Providers should build screening, testing, and vaccination strategies into their routine practices. Without concerted action, thousands more Americans will die each year from liver cancer or liver failure related to [hepatitis B and C]."

- Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C
2010 Institute of Medicine Report

Recommended Tests to Screen for Chronic Hepatitis B



Recommendations are abridged from the Morbidity and Mortality Weekly Report (MMWR), published by the U.S. Centers for Disease Control and Prevention (CDC),[1] and the 2009 practice guidelines released by the American Association for the Study of Liver Diseases.[2]

HBV and Liver Cancer Facts

Hepatitis B is a serious infection of the liver caused by the hepatitis B virus (HBV) and can lead to premature death from cirrhosis (scarring of the liver), liver failure, or liver cancer.

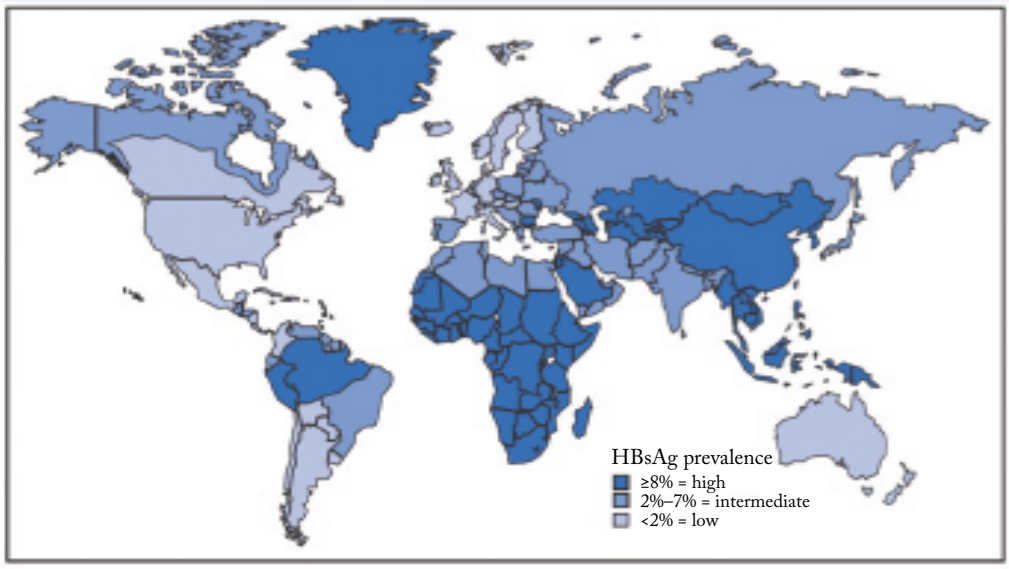
HBV is a global epidemic

- Although a safe and effective recombinant hepatitis B vaccine has been available since 1982, HBV still kills 600,000 people every year worldwide.[3,4]
- About 1 in 20 people in the world (350 million individuals) is living with chronic HBV infection.[4]
- The burden of disease is greatest in Asia. China alone has an estimated 93 million people chronically infected.[5,6]
- Without appropriate medical management, 1 in 4 of those chronically infected will die from liver cancer or liver failure.[4]
- Every 50 seconds, one person dies from the complications of this vaccine-preventable disease.[4]

Worldwide, there are **10 times** more people living with chronic HBV infection than with HIV/AIDS.[4,6]

Without appropriate medical management, **1 in 4** will die from liver cancer or liver failure.[4]

Geographic Distribution of Chronic Hepatitis B Virus Infection – Worldwide, 2006[1]



U.S. Centers for Disease Control and Prevention. Available at http://www.cdc.gov/mmwr/PDF/rr/rr5708.pdf

In the U.S., there are nearly as many people living with chronic HBV infection as **HIV/AIDS**.[10]

But **two-thirds** are not aware they are infected because they have not been tested.[11]

Burden of chronic HBV infection in the U.S.

- CDC estimates 800,000 - 1.4 million people in the U.S. are chronically infected with HBV compared to about 1.1 million infected with HIV.[1]
- A major risk factor in the U.S. for chronic HBV infection is having been born in an endemic country where many are infected at birth or during early childhood.[1]
- Although Asian Americans make up only 5% of the U.S. population, they account for more than half of the burden of chronic HBV infection.[7]
- An estimated 1 in 12 Asian Americans is living with chronic HBV infection, compared to 1 in 1,000 in the non-Hispanic white population.[8]
- Liver cancer frequently caused by chronic HBV infection is the second leading cause of cancer death for Asian men living in the U.S.[11]
- Liver cancer incidence is up to 8 times higher in Asian American men than in non-Hispanic white men.[9]

1 in 12 Asian Americans is chronically infected with HBV.[1,3]

HBV and liver cancer are the greatest health disparities between Asian and white Americans.[8]

HBV is a silent killer

- Chronic HBV infection is dangerous because there are often no symptoms (even blood tests for liver enzymes may be normal).[1,3]
- As many as 2 out of 3 chronically infected persons are not aware that they are infected.[11]
- By the time symptoms such as abdominal pain and/or abdominal distension appear, it is often too late for treatment to be effective.
- The World Health Organization (WHO) estimates that about 90% of HBV-related deaths are associated with chronic HBV infection (70% from hepatocellular carcinoma with or without cirrhosis and 20% from cirrhosis) while less than 10% are associated with acute infection.[5]

Regular screening for liver cancer in persons with chronic HBV infection can save lives.

HBV causes 60-80% of liver cancer cases worldwide[12]

- HBV is a carcinogen that is third only to smoking tobacco and *Helicobacter pylori* infection in causing the most cancer deaths worldwide.[4]
- Chronic HBV infection is the leading cause of hepatocellular carcinoma (HCC), the most common type of primary liver cancer.[13]
- People chronically infected with HBV are 100 times more likely to develop liver cancer than those who are not infected.[13]

Early detection of liver cancer is key

- Liver cancer is a silent killer because patients typically show no symptoms until the end stages of disease.[14]
- Asians who are chronically infected with HBV at birth or during childhood may develop liver cancer as early as adolescence.
- If diagnosed late, liver cancer is one of the most difficult cancers to treat. Even today, the 5-year survival rate is only around 10% for all liver cancers.[15]
- Currently, there is no effective systemic chemotherapy for advanced liver cancer.
- However, early detection by regular screening can lead to successful surgical or non-surgical treatments and improved long-term survival (p. 16).[2,14]

Liver cancer can develop even in the absence of cirrhosis in persons with chronic HBV infection.

Hepatitis B is preventable with a vaccine

The 3-shot hepatitis B vaccine series can provide lifelong protection against HBV, thus eliminating the most common cause of liver cancer (p. 9–12).

- The hepatitis B vaccine is so effective at preventing HBV and liver cancer that the World Health Organization has declared it the world's **first "anti-cancer vaccine."**
- With awareness and proactive health practices, hepatitis B and liver cancer can be eliminated as a worldwide health problem.

How HBV is Transmitted

HBV is transmitted via infected blood or semen. The modes of transmission are similar to HIV and can be easily remembered using the mnemonic "BBS": Birth, Blood, Sex.

Birth: Mother-to-child infection

HBV can be transmitted from a chronically infected mother to her child during the birthing process. This is one of the most common modes of transmission for Asians.[18] Many pregnant mothers with chronic hepatitis B are unaware of their infection and end up silently passing the virus to the next generation.

Bloodborne infection

HBV can be transmitted through direct contact with infected blood. This includes:

- Wound-to-wound contact
- Reusing or sharing needles for tattoos, piercings, acupuncture, or injection drugs
- Sharing razors or toothbrushes contaminated by blood
- Reusing syringes or medical devices including lapses in infection control practices related to blood glucose monitoring in diabetes care
- Unsafe blood transfusion

Sexually transmitted infection

HBV can be transmitted through unprotected sex with a person infected with HBV. The use of condoms can reduce, but not eliminate, the risk of infection. Vaccination remains the most effective way to protect against HBV (p. 9–12).

HBV is NOT transmitted through food or water

There are many myths about how HBV is transmitted. A common misconception is that HBV can be spread through contaminated food or water, like the hepatitis A virus. This is not true.

HBV is *NOT* spread through:

- Sharing food or water
- Sharing eating utensils or drinking glasses
- Tears, sweat, urine, or stool
- Coughing or sneezing
- Hugging or kissing
- Breastfeeding
- Mosquitoes

HBV can survive outside the body for 7 days, whereas HIV can survive for only a few hours outside the body.[4]

HBV is 50–100 times more infectious than HIV.[4]

Dispel discrimination against people with HBV

Misconceptions and fears about transmission fuel discrimination against people with HBV.[16] Explain to your patients that there is no reason to distance themselves from people with chronic HBV infection, who should not be excluded from work, school, or other daily activities. In the U.S., several state laws, as well as the Americans with Disabilities Act (1991), protect against discrimination related to chronic hepatitis B.

Acute vs. Chronic Infection

3 possible outcomes after initial HBV infection

1. Acute hepatitis B resulting in fulminant liver failure

Infection with HBV causes extensive liver cell death resulting in liver failure and sometimes death. Fortunately, this most severe form of acute hepatitis is uncommon, occurring in only 1% of hepatitis B cases.[17]

2. Acute hepatitis B with full recovery and development of immunity

HBV is spontaneously cleared from the body within a few months, and immunity against future infection develops. There is currently no FDA-approved drug treatment for acute infection, and the main form of therapy is supportive care.

3. Chronic hepatitis B

Failure to clear the initial HBV infection will result in a chronic (lifelong) infection. There are seven FDA-approved drugs to treat chronic HBV infection, but regular screening for liver damage and cancer is needed to determine if drug therapy is necessary. Without appropriate medical management, 1 in 4 chronically infected persons will die from cirrhosis, liver failure, or liver cancer.[4]

Symptoms of **acute** HBV infection include:

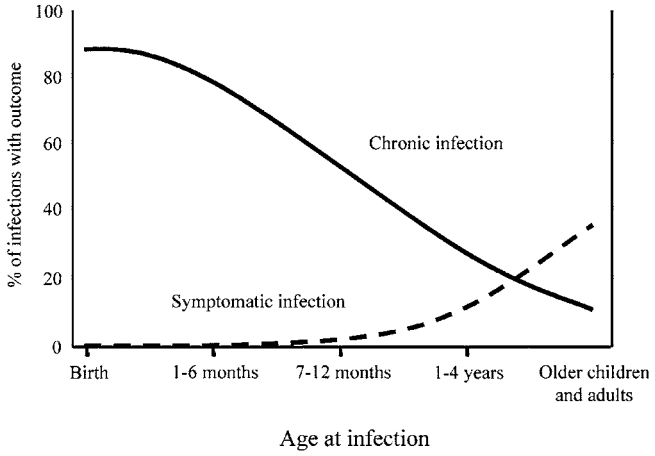
- Jaundice
- Fatigue
- Nausea
- Abdominal pain
- Loss of appetite

People with **chronic** HBV infection usually **exhibit NO SYMPTOMS** until they have developed cirrhosis or advanced liver cancer.

Newborns are most vulnerable to chronic infection

Anyone who is not protected against HBV can become infected. However, newborns and young children who become infected with HBV have the greatest risk of developing a lifelong infection. Without appropriate prophylaxis, as many as 90% of infected newborns develop chronic hepatitis B. This is why it is important for all newborns to be vaccinated against HBV at birth (p. 9). **When infants and children are infected, they usually exhibit few or no symptoms.** When *adults* are infected, 30–50% are likely to become ill with symptoms of acute infection (e.g., fatigue, loss of appetite, or jaundice), and 6-10% of infected adults will develop chronic hepatitis B infection.[18]

Outcome of hepatitis B virus infection by age at infection[5]



World Health Organization. Western Pacific Regional Plan for hepatitis B control through immunization; December 2007. Manila, Philippines.

As many as 90% of infected newborns develop chronic hepatitis B.

Unvaccinated young children who became infected through unsafe injections in the healthcare setting or wound-to-wound contact also have high risk of developing chronic infection.

Screening At-Risk Populations for Chro

Since up to 10% of foreign-born Asian Americans have chronic HBV infection acquired in early childhood, it is important to test for HBsAg and anti-HBs before vaccination.

HBV screening is important!

Many chronically infected persons show no outward signs of HBV infection; therefore, screening for hepatitis B is necessary to:

- Identify individuals who have chronic HBV infection so they can receive appropriate medical management.
- Identify those who are unprotected so they can be vaccinated.
- Avoid unnecessary vaccination (to help reduce costs). Vaccination is *not* beneficial for persons already chronically infected with HBV, and is unnecessary for persons already immune (either through prior vaccination or a previous resolved acute infection).

HBV screening is a simple blood test for the following markers:

HBsAg+
Chronic HBV Infection

HBsAg- / anti-HBs-
Needs vaccination

HBsAg- / anti-HBs+
Immune to HBV

1. Hepatitis B surface antigen (HBsAg)

The HBsAg test is the ONLY way to definitively diagnose chronic HBV infection. By definition, if a patient remains HBsAg-positive for more than 6 months, then he/she has developed chronic (lifelong) infection. Since most Asians become infected at birth or during early childhood, most Asian patients who test positive for HBsAg will have chronic HBV infection. HBsAg-positive patients require counseling and medical management for chronic HBV infection to reduce their risk for chronic liver disease (p. 14–18).

2. Hepatitis B surface antibody (anti-HBs)

The anti-HBs test will tell if your patient is protected against HBV. Anti-HBs can be produced in response to vaccination or recovery from an acute hepatitis B infection.

Quick Test Results

Result	Interpretation
HBsAg (+) anti-HBs (-)	Chronic HBV infection*
HBsAg (-) anti-HBs (+)	Immune to HBV
HBsAg (-) anti-HBs (-)	Unprotected; needs vaccination
HBsAg (+) anti-HBs (+) (rare)	Chronic HBV infection*

*If HBsAg remains positive for 6 months or in the absence of IgM anti-HBc

nic HBV Infection

Who should get screened for HBV?

Foreign-born persons from endemic countries account for over 50% of persons living with chronic HBV in the U.S. Updated 2008 guidelines from the U.S. Centers for Disease Control and Prevention (CDC) call for routine HBV screening of all foreign-born persons from both high and intermediate endemic areas (HBsAg prevalence ≥2%).[1]

All pregnant women should be screened for hepatitis B infection. Refer to p.9 for guidelines for screening expectant mothers. Other groups recommended for HBV screening include:

- U.S. born persons not vaccinated as infants whose parents were born in countries with high HBV endemicity (≥ 8%)
- Household, needle-sharing, or sexual contacts of persons known to be HBsAg-positive
- Infants born to HBsAg-positive mothers
- Injection drug users
- Men who have sex with men
- Persons with elevated ALT/AST of unknown etiology
- Persons with HIV
- Persons who require immunosuppresive or cancer chemotherapy
- Blood and organ donors

What can physicians do to increase screening?

If you are seeing the patient for the first time, ask whether they are foreign-born or have a foreign-born parent from an endemic country. If so, screen for HBsAg and anti-HBs. If they are not infected and not protected, start the hepatitis B vaccination series (p. 10). In addition, you can help raise awareness about hepatitis B by having educational brochures in the waiting area and around the office (p. 22).

What about other hepatitis B blood tests?

- **Total hepatitis B core antibody (total anti-HBc) test:**
  Tells if your patient has been previously infected with HBV, which is useful for screening potential blood donors (the U.S. does not allow people with past HBV infections to donate blood – even if they have recovered). The test by itself does not indicate whether your patient is chronically infected with or protected against HBV infection.
- **Hepatitis B core IgM antibody (IgM anti-HBc) test**:
  Tells if an unprotected patient has recently been infected with HBV.

Blood Test	Result	Interpretation
Total anti-HBc	Positive (+)	Was infected with HBV (the test alone does not tell if immunity or chronic infection has developed)
	Negative (-)	Never been infected with HBV; candidate for donating blood
IgM anti-HBc	Positive (+)	Recently acquired acute HBV infection

Only order the IgM anti-HBc test if you suspect your patient recently became infected with HBV (e.g., through a needlestick injury or sexual contact with an HBV-infected person). If your patient has acute HBV infection, his/her infection may or may not become lifelong.

CDC recommends routine screening of **FOREIGN-BORN PERSONS** from endemic countries *regardless of vaccination history.*

ALL PREGNANT WOMEN should be screened to prevent perinatal transmission.

Regions of high and intermediate HBsAg endemicity* include:

- *Africa*
- *Asia and Pacific Islands*
- *Eastern Europe (except Hungary)*
- *Middle East (except Cyprus and Israel)*
- *Mexico and Central America (Belize, Guatemala, Honduras, and Panama)*
- *Alaska, Northern Canada, and Greenland (indigenous populations)*
- *Caribbean*
- *South America*

* HBsAg prevalence of ≥2%.

For a complete list refer to the CDC. *http://www.cdc.gov/mmwr/PDF/rr/rr5516.pdf*

Screening Pregnant Women

All pregnant women should be screened

Federal guidelines recommend that all pregnant women be tested for HBsAg at an early prenatal visit (i.e., in the first trimester) during each pregnancy, even if they have been previously tested or vaccinated. The CDC Advisory Committee on Immunization Practices also recommends the following measures:[19]

If your pregnant patient is HBsAg-negative and anti-HBs-negative:

- Send copy of lab report documenting woman's HBsAg status to birth hospital.
- Inform your patient that she is not protected from hepatitis B, and encourage her to get vaccinated in the future. The vaccine is safe even when given during pregnancy.[19]

If your pregnant patient is HBsAg-positive:

- Send a copy of the lab report documenting the woman's positive HBsAg status to the birth hospital. A hospital notice or alert should also be included in the woman's medical record to remind the delivery hospital/nursery that the infant needs the HBV vaccine and HBIG.
- Send another copy of the lab report to the local health department for case management and indicate the positive test result is from a pregnant woman (reporting all HBsAg-positive cases is required by law in most states).
- Emphasize to the expecting mother the importance of having her newborn receive HBIG and the birth dose of hepatitis B vaccine within 12 hours and complete the vaccine series and post-vaccination testing to prevent perinatal hepatitis B transmission. Infants who become infected should be referred for care, and infants who remain susceptible can receive additional vaccine doses.
- Refer the expecting mother to a physician experienced in the long-term medical management of chronic hepatitis B.
- Advise family, household members, and sex partners to be screened for chronic HBV infection and get vaccinated if they are not protected.[19]

All newborns should be vaccinated at birth

Federal guidelines recommend that all newborns be vaccinated against HBV at birth, regardless of the mother's HBV status. It is important that even infants born to HBsAg-negative mothers receive the first dose at birth or before hospital discharge (or by 1 month of age), and complete the hepatitis B vaccination series to receive long-term protection against HBV.[19] See page 12 for the vaccine schedule.

Infants born to women with chronic HBV must also receive the HBIG shot at birth

Without immunoprophylaxis, infants born to HBsAg-positive mothers are at the highest risk of developing chronic HBV infection. Therefore, they must:

- Receive the first dose of hepatitis B vaccine ***and*** the hepatitis B immune globulin (HBIG) shot within 12 hours of birth.
- Complete the vaccine series.
- Be tested at 9–18 months of age for HBsAg and anti-HBs to confirm protection against HBV.

FAQs for Moms-to-Be

Is breastfeeding safe?
HBV is not transmitted through breast milk. Breastfeeding is safe for all newborns, regardless of the mother's HBV status.[20]

Can C-sections prevent HBV?
Cesarean sections cannot prevent HBV transmission from mother to child. Hepatitis B vaccination plus the HBIG shot is the best way to protect newborns against HBV.[21]

Can women with chronic HBV infection be treated during pregnancy?
Antiviral treatment is not currently approved for use during pregnancy.[21] Antiviral treatment for selected women with high HBV DNA levels to further reduce the risk of perinatal transmission is currently being investigated for safety and effectiveness.[22]

Vaccinating Against Hepatitis B

3-for-Life

The hepatitis B vaccine is safe and >95% effective at preventing HBV infection.[3] Vaccination involves a series of 3 shots given over 6 months, and can provide lifelong immunity against HBV. The hepatitis B vaccine is so effective at preventing HBV infection and liver cancer that it is known as the world's **first "anti-cancer vaccine."** No routine booster shots are recommended by the CDC. The vaccination series can be started at any age. For people who have fallen behind schedule, the series may be continued without starting over. The usual schedule is as follows:

1st shot → (**1 month**) → **2nd shot** → (**5 months**) → **3rd shot**

Who should get vaccinated against HBV?

The CDC recommends universal vaccination of all newborns and previously un-vaccinated children and adolescents. Adult immunization is recommended for:[17]

- Anyone seeking protection from HBV infection
- Household, sex, and needle-sharing contacts of HBsAg-positive persons
- Healthcare and public safety workers
- Intravenous drug users
- Those with more than one sex partner
- Men who have sex with men
- Those infected with HIV and/or other sexually transmitted diseases
- Those with end-stage renal disease or chronic liver disease
- Unvaccinated adults with diabetes mellitus who are aged 19 through 59 years
- Travelers to regions with high or intermediate HBsAg prevalence

ALL newborns should be vaccinated.

Anyone who has not already been vaccinated or infected should be offered hepatitis B vaccination.

Who should get tested after vaccination?

After completing the vaccination series, most people do not need to be tested for anti-HBs to confirm protection against HBV. However, the following high-risk groups should receive post-vaccination testing:

- **Infants born to HBsAg-positive mothers:** Test for both HBsAg and anti-HBs at 9–18 months of age.[19]
- **Healthcare and public safety workers; immunocompromised persons (e.g. HIV/AIDS, hemodialysis patients); sexual partners of HBsAg-positive people:** Test for anti-HBs 1–2 months after completing the vaccination series.[17]

If your patient is NOT immune after vaccination

Although uncommon, about 5% of those who complete the hepatitis B vaccination series may not acquire immunity (anti-HBs levels <10 mIU/mL). In these cases, take these steps:

1. Administer another 3-shot series at the normal schedule (p. 12).
2. Test again for anti-HBs 1–2 months after completion of the series to confirm protection. 44 – 100% of these patients will successfully develop immunity.

The rare group of people not protected after six doses should take care to avoid HBV transmission (e.g., cover wounds, use condoms). Nonresponders exposed to HBV-infected bodily fluids should get the HBIG shot to prevent chronic infection (p. 13).[17]

Vaccinating Against Hepatitis B

FDA-Approved hepatitis B vaccines

Monovalent vaccines:

Engerix-B and Recombivax HB

For any age: These single-antigen hepatitis B vaccines are typically given as a 3-shot series. For adolescents 11–15 years old, an alternative 2-dose Recombivax HB regimen may be used. Engerix-B and Recombivax HB can be used interchangeably and administered concurrently with hepatitis B immune globulin (HBIG) or other vaccines.[23]

Combination vaccines

Pediarix: HBV+diphtheria+tetanus+pertussis+polio

For children (6 weeks–7 years of age): All newborns, regardless of their mother's HBsAg status, should receive a birth dose of the hepatitis B vaccine with either Engerix-B or Recombivax HB. After the initial birth dose, a 3-dose Pediarix regimen can be used to complete the series.[23]

Comvax: HBV + Haemophilus influenza type B

For children (6 weeks–6 years of age): All newborns, regardless of their mother's HBsAg status, should receive a birth dose of the hepatitis B vaccine with either Engerix-B or Recombivax HB. After the initial birth dose, a 3-dose Comvax regimen can be used to complete the series.[23]

Twinrix: HBV + hepatitis A

For adults (18 years of age and older): Suitable for anyone seeking protection from HBV and/or hepatitis A virus (HAV), and high risk groups (p. 10). Whereas hepatitis B vaccine is usually given in three shots and hepatitis A vaccine is given in two shots, Twinrix is given as a 3-shot series.[23]

Free vaccines for children

Hepatitis B vaccine is free for children 0–18 years of age who are on Medicaid or whose vaccinations are not covered by insurance. These vaccines can be obtained through the federal Vaccines for Children program. For more information, visit http://www.cdc.gov/vaccines/programs/vfc/index.html.

Vaccine administration and storage

Follow these simple precautions to protect your patients:

- **Shake the vaccine before use.** Hepatitis B vaccine normally looks cloudy, but if the vaccine stands for a long time, it may separate from the liquid and look like fine sand at the bottom of the vial. Shake until mixed.

- **Do NOT freeze or expose to freezing temperatures.** Store hepatitis B vaccine at 2–8°C (36–46°F). The "shake test" will determine if the vaccine has been damaged by freezing. If the vaccine fails the shake test (the vaccine and liquid do not mix) you must discard it since it may no longer be effective.

- **Administer the hepatitis B vaccine intramuscularly** (i.e., in the arm for children and adults, and in the thigh for infants). It is ineffective if given subcutaneously in fatty tissue (i.e., in the buttocks). Use a longer 1.5 inch instead of a 1 inch needle for obese adolescents or adults.

Adult Vaccine Schedules			
	Hepatitis B Vaccines		HBV + HAV vaccine
	Engerix-B	**Recombivax HB**	**Twinrix**[i,ii]
Adults (≥20 yrs)	0 mo: 1st dose 1 mo: 2nd dose 6 mo: 3rd dose	0 mo: 1st dose 1 mo: 2nd dose 6 mo: 3rd dose	0 mo: 1st dose 1 mo: 2nd dose 6 mo: 3rd dose
Immunocompromised[iii] **Adults (≥20 yrs)**	0 mo: 1st dose 1 mo: 2nd dose 2 mo: 3rd dose 6 mo: 4th dose 7-8 mo: Test for anti-HBs	0 mo: 1st dose 1 mo: 2nd dose 6 mo: 3rd dose 7-8 mo: Test for anti-HBs	--

[i] Twinrix may be given to adults ≥18 years old.
[ii] An alternative schedule can also be used at 0, 7, 21-30 days, and a booster at 12 months.
[iii] E.g., patients undergoing hemodialysis or chemotherapy, or HIV-infected persons. Higher doses are recommended for predialysis and hemodialysis patients, and can be used to revaccinate non-responders (Engerix-B: 40µg/2.0mL, Recombivax HB: 40µg/1.0mL).

Pediatric Vaccine Schedules			
	Hepatitis B Vaccines	Combination Vaccines	
	Engerix-B or Recombivax HB	**Pediarix**	**Comvax**
Infants (0-1yr) with HBsAg(–) mother	Birth[iv]: 1st dose 1-2 mo: 2nd dose 6 mo: 3rd dose	Birth[iv]: Eng/Rec[v] 2 mo: Pediarix 4 mo: Pediarix 6 mo: Pediarix	Birth[iv]: Eng/Rec[v] 2 mo: Comvax 4 mo: Comvax 12-15 mo: Comvax
Infants (0-1yr) with HBsAg(+) mother	Birth[iv]: 1st dose + HBIG[vi] 1-2 mo: 2nd dose 6 mo: 3rd dose 9-18 mo: Test for HBsAg, antiHBs	Birth[iv]: Eng/Rec[v] + HBIG[vi] 2 mo: Pediarix 4 mo: Pediarix 6 mo: Pediarix 9-18 mo: Test for HBsAg, anti-HBs	Birth[iv]: Eng/Rec[v] + HBIG[vi] 2 mo: Comvax 4 mo: Comvax 12-15 mo: Comvax 18 mo: Test for HBsAg, anti-HBs
Children and Adolescents[vii] **(1-19 yrs)**	0 mo: 1st dose 1 mo: 2nd dose 6 mo: 3rd dose	--	--

[iv] **Within 12 hours of birth.**
[v] Either Engerix-B (Eng) or Recombivax HB (Rec) should be used for the birth dose or any second dose given before 6 weeks of age.
[vi] Hepatitis B immune globulin (0.5mL) administered intramuscularly in a separate site from vaccine.
[vii] For adolescents (11–15 yrs), an alternative 2-dose Recombivax HB regimen may be given at 0 and 4–6 months.

Notes regarding infants weighing less than 2000 grams:

- For infants < 2000 grams born to HBsAg-positive mothers: Give the HBIG shot and HBV vaccine within 12 hours of birth, and then restart the vaccine series beginning at age 1–2 months (do not count birth dose as part of the vaccine series).
- For infants < 2000 grams born to HBsAg-negative mothers: Delay administration of the vaccine series until age 1 month or hospital discharge (whichever comes first), and then resume the series according to the schedule.

Modified from Centers for Disease Control and Prevention. A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States.[23,24]

Preventing HBV Transmission in Healthcare Settings

Avoiding needlestick injuries

How to protect yourself:

- Practice universal precautions to prevent transmission of HBV and other bloodborne pathogens, including safe needle handling and the use of gloves.
- Vaccinate all health care workers against HBV, then test for anti-HBs 1–2 months after completion of the vaccination series to confirm protection (anti-HBs level ≥ 10mIU/mL).

Preventing patient-to-patient transmission

- **Do NOT reuse needles and syringes.** Always use sterile syringes, preferably with auto-disable features to prevent reuse.[24]
- **Immediately dispose used needles into puncture-resistant safety containers.**
- **Avoid use of multi-dose vials.** Use of single-dose vials greatly reduces the risk of patient-to-patient transmission.
- **Adhere to Standard Precaution and aseptic technique principles.** Relatively safe procedures such as dialysis, glucose monitoring, and endoscopy can become sources of hepatitis B outbreak when infection control practices are not followed. Ensure that shared equipment is properly sterilized between patients and that disposable parts are used when available.[24]

Preventing physician-to-patient transmission

CDC recommendations currently restrict HBeAg-positive healthcare providers from performing exposure-prone procedures.[25] However, because high viral loads can be found in some HBeAg-negative individuals, HBV DNA levels may be used as a more accurate measure of infectivity.[26,27] Prolonged antiviral treatment has been demonstrated as a possible safe solution to work restrictions.[27]

Post-exposure prophylaxis

HBIG (Hepatitis B Immune Globulin)

For any age:[28] HBIG should be administered to unprotected persons as soon as possible after exposure to blood or bodily fluids infected with HBV (e.g., when infants are born to HBsAg-positive women, after needlestick injuries, and after sexual contact with an infected person). Administration of HBIG more than 7 days after percutaneous or perinatal exposure and after 14 days after sexual exposure is unlikely to be effective.

When you are exposed to a needlestick from a HBsAg positive person:[28]

1. Perform baseline testing for anti-HBs, HBsAg, and ALT.
2. If you are unvaccinated, uncertain of hepatitis B vaccination history, or anti-HBs titer < 10 mIU/mL, get the HBIG shot (0.06 mL/kg or 5 mL for adults) preferably within 24 hours of exposure, and initiate the 3-shot hepatitis B vaccine series.
3. If you are a known nonresponder (anti-HBs < 10 mIU/mL after hepatitis B vaccination), give HBIG and repeat a second HBIG dose a month later.
4. If you are a known responder or baseline testing anti-HBs level ≥ 10 mIU/mL, no treatment is recommended.
5. Perform follow up testing for anti-HBs, HBsAg, and ALT after 6 months.

Checklist for Managing Chronic HBV Infection

7 Steps to care for your chronic HBV patients

1. Help your patients understand their hepatitis B status

Make sure test results are clear, and give your patient HBV informational brochures that are culturally and linguistically appropriate.

See page 22

2. Screen patients regularly for liver damage and cancer

People with chronic HBV infection can live completely normal lives as long as they are screened regularly for liver damage and cancer. Early detection and treatment will increase your patient's chance of long-term survival.[2,14]

See pages 15–16

3. Give the hepatitis A vaccine

Hepatitis A is an infection of the liver caused by a different virus known as HAV (transmitted by contaminated food or water). Hepatitis A vaccination is recommended for patients with chronic liver disease including chronic viral hepatitis to reduce the risk of further liver damage.[1]

4. Tell your patients to avoid regular alcohol consumption

Alcohol is toxic to the liver and may accelerate the progression of liver damage to cirrhosis and liver failure. Drugs, herbal supplements, and other substances with known liver toxicity should also be avoided.[1]

5. Test and vaccinate your patients' close contacts

Your patient's family members and sexual partner(s) should be tested for HBsAg and anti-HBs. This will help determine if they are 1) also chronically infected with HBV and need medical management, 2) vulnerable and need vaccination, or 3) already protected.[1]

See page 7

6. Educate your patients about how to minimize the risk of infecting others

Cover wounds, use condoms, and do not share toothbrushes or razors. If diabetic, do not share blood glucose monitoring equipment that could be contaminated by blood. Advise your patients not to donate blood, organs, tissue, or semen.[1]

See page 5

7. Give HBV treatment if indicated

Not everyone with HBV needs drug treatment, but medication may be appropriate for patients with high levels of both ALT and HBV DNA, patients with cirrhosis, or patients receiving cancer chemotherapy.[1,2]

See pages 17–18

Monitoring for Liver Damage

Every 6 months, order the ALT and AFP tests.

Every year, perform a liver ultrasound. For patients with cirrhosis or a family history of liver cancer, increase ultrasound screening to every 6 months.

Monitor for liver damage regularly

Many chronically infected persons show no symptoms and feel perfectly healthy, even though they may already have cirrhosis or be in the early stages of liver cancer. Therefore, it is important for physicians who see patients with chronic HBV infection to remain vigilant about monitoring for flare-ups of hepatitis, liver damage, or cirrhosis, and to schedule regular screenings for liver cancer (p. 16).[1,2]

Elevated ALT indicates liver damage.

ALT blood test – every 6 months

The ALT (alanine transaminase) test is one of the most useful and low cost tests to assess whether treatment against HBV is needed. An elevated ALT level is indicative of active liver damage. If ALT is normal, there is no evidence to support HBV treatment (unless patient is undergoing cancer chemotherapy or has cirrhosis, see p. 17).[1,2]

HBV DNA indicates if liver damage is due to HBV, and helps evaluate treatment response.

Additional tests

HBV DNA level by PCR

The HBV DNA test is a direct measure of HBV viral load. It is a recommended baseline test after initial diagnosis of chronic hepatitis B. If your patient's ALT level is elevated, the HBV DNA test will help verify whether his/her liver damage is caused by HBV infection, and determine whether HBV treatment is appropriate. HBV DNA levels that become undetectable or decrease significantly are a good measure of treatment response.[1,2] HBV DNA should be measured every 6-12 months to monitor for the emergence of antiviral drug resistant mutant HBV.

HBeAg and anti-HBe help monitor treatment response.

HBeAg and anti-HBe tests

HBeAg is a recommended baseline test after initial diagnosis of chronic HBV infection. HBeAg is a marker of a high degree of HBV infectivity and indirect measure of viral load (though some mutant HBV strains have high viral load but negative HBeAg). If HBeAg is positive, the test should be repeated yearly. HBeAg seroconversion, which is the loss of HBeAg (hepatitis B e antigen) and development of anti-HBe (hepatitis B e antibodies), is a sign of favorable response to treatment. This seroconversion can take years. The development of anti-HBe does not mean that your patient is cured and does not mean that treatment is unnecessary. Some individuals carry mutant HBV strains that do not secrete HBeAg; thus, the HBV DNA test is preferred when measuring HBV viral load.[1,2]

Platelet count and albumin monitor for cirrhosis.

Platelet count and albumin

A low platelet count (generally less than 150,000 platelets/mm^3) combined with a low albumin level (3.5 gm/dL or lower), with or without prolonged prothrombin time, are signs suggestive of cirrhosis with impaired liver function.[1,2]

Liver biopsy is an invasive procedure that should not be done routinely. It is sometimes recommended to determine whether a person with mildly elevated ALT and DNA level is a candidate for antiviral treatment. Liver biopsy is unnecessary if there is a clear cut indication for antiviral treatment.

Screening for Liver Cancer

Screen for liver cancer regularly

The World Health Organization estimates that 70% of deaths associated with chronic HBV infection are due to hepatocellular carcinoma (HCC). Regular liver cancer screening involving both AFP and ultrasound tests is essential because *liver cancer can occur even in patients without cirrhosis* and in the presence of normal ALT levels. AFP is elevated in only 40–60% of liver cancers. Ultrasound tests miss about 20% of liver cancers, especially in patients who are obese or have heterogeneous livers due to fatty liver or cirrhosis. Therefore, it is important for both tests to be performed regularly.[1,2]

Hepatocellular carcinoma is the primary cause of death for patients with chronic hepatitis B.

AFP blood test – every 6 months

The AFP (alpha-fetoprotein) test is the most widely used blood test for liver cancer. A rising AFP level on serial measurements or an AFP level >500 ng/ml is usually associated with liver cancer (normal range is <10 ng/ml). Since AFP levels may appear normal in 40% of liver cancers, an ultrasound is needed to help detect tumors.[1,2]

Both the AFP and ultrasound tests must be done regularly because either test alone can miss the cancer.

Ultrasound – every 6-12 months

Ultrasound is used to screen for liver tumors. Since use of ultrasound can catch only 80% of liver cancers, it must be performed along with the AFP test. If the ultrasound result is inconclusive (common in patients with cirrhosis or fatty liver) or your patient shows rising AFP levels, you should evaluate using a triphasic spiral CT scan or MRI scan of the liver or refer him/her for further assessment. A lesion that enhances on the arterial phase and washes out to become less dense than the rest of the liver in the delayed venous phase of scanning is characteristic of HCC (see example at right). A patient with a new lesion detected on ultrasound or CT scan and/or rising AFP levels should be referred immediately for liver cancer evaluation and treatment.[1,2]

Family history and cirrhosis increase the risk of liver cancer

If your patient develops cirrhosis or has a family history of liver cancer, an ultrasound or triphasic spiral CT scan of the liver should be performed every 6 months regardless of age.[1,2]

Early Detection is Key to Improving Survival

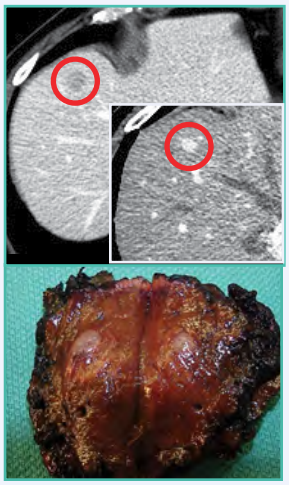
Liver cancer caused by chronic HBV infection often develops between 30 to 65 years of age, when people are maximally productive and have family responsibilities. It is reasonable to start regular ultrasound screenings in men at the age of 30 years and at the age of 50 years for women.[1,2]

Late diagnosis of liver cancer is often the reason for the 6 to 12-month average survival time following diagnosis. It also explains the approximate 10% survival rate of liver cancer patients. However, regular screening to detect the cancer while it is small can lead to successful treatment by surgical and nonsurgical treatments, resulting in long-term survival.[1,2,20]

Liver cancer screening is important because:[1,2]

- Most patients have the appearance of perfect health without showing any symptoms until it is already too late.
- Small tumor lumps are impossible to feel because of the shielded location of the liver underneath the ribs.
- Pain is uncommon until the tumor is large; even then, some tumors do not cause pain.
- Liver cancers can grow rapidly.

1.2 cm liver cancer detected by ultrasound screening, confirmed by triphasic CT scan and successfully removed. In this case AFP level was normal.



Principles of Drug Treatment for Chronic HBV

Initiation of HBV treatment is appropriate if ALT and HBV DNA levels are elevated, your patient with normal ALT has cirrhosis, or he/she is undergoing cancer chemotherapy.

Rationale for treatment

Although **there is no cure for hepatitis B**, effective treatment can reduce liver damage and decrease the risk of cirrhosis and liver cancer. Regular screening for liver damage is necessary to determine if and when initiation of HBV treatment is appropriate (p. 15-16).

Not every patient with chronic hepatitis B needs to be on treatment.

Patients should be informed about the treatment rationale, as well as options, side effects, and risks associated with each treatment.

When is treatment for chronic HBV infection appropriate?

HBV treatment NOT indicated

Normal ALT (<30 U/L for men, <19 U/L for women)
There is no evidence to support treatment of these patients, regardless of their HBV DNA or HBeAg status. However, they are still at risk for liver cancer and flare-up of hepatitis, and should be screened regularly (p. 15-16). **Exceptions** are patients with cirrhosis or patients initiating chemotherapy (see below).

Elevated ALT (>2x normal)
Low or undetectable HBV DNA
HBeAg (–)
Liver damage in these patients is not caused by HBV. You should investigate other possible causes for the elevated ALT, including hepatitis C virus infection, steatohepatitis (fatty liver), drug use, or heavy alcohol consumption.

HBV treatment indicated

Elevated ALT (>2x normal)
Elevated HBV DNA (>20,000 IU/mL)
HBeAg (+)
These chronic HBV patients show signs of active liver damage associated with high viral activity. It is reasonable to consider treatment by oral antivirals or injection immunostimulators (p. 18).

Elevated ALT (>2x normal)
Elevated HBV DNA (>20,000 IU/mL)
HBeAg (–)
These chronic HBV patients show signs of active liver damage caused by a mutant strain of HBV that does not secrete HBeAg. It is reasonable to consider treatment by oral antivirals or injection immunostimulators (p. 18).

Cirrhosis (Compensated or decompensated)
Normal or elevated ALT, Detectable HBV DNA
For patients with compensated or uncompensated cirrhosis consider HBV treatment by oral antivirals (p. 18), regardless of HBeAg status.

Immunosuppressive or cancer chemotherapy
When the immune system is suppressed during cancer chemotherapy, flare-up of the HBV infection can lead to fulminant hepatitis and death. Therefore, HBsAg-positive patients undergoing chemotherapy should be placed on prophylactic oral antiviral treatment (p. 18), regardless of pre-treatment ALT or HBV DNA levels or HBeAg status.

For more detailed information refer to the current practice guidelines released by the American Association for the Study of Liver Diseases[2].

There are currently 7 FDA-approved drugs to treat chronic HBV infection

Oral Antivirals

Oral antivirals inhibit replication of HBV. Patient compliance in taking the medication daily is important to minimize the development of mutant or drug-resistant viruses. Treatment with oral antivirals will likely require long-term suppressive therapy.[2]

- **Lamivudine** (Epivir-HBV, approved 1998)
  Pill or oral solution taken once a day.
- **Adefovir** (Hepsera, approved 2002)
  Pill taken once a day; need to monitor renal function (test for blood levels of blood urea nitrogen and creatinine).
- **Entecavir** (Baraclude, approved 2005)
  Pill or oral solution taken once a day.
- **Telbivudine** (Tyzeka, approved 2006)
  Pill taken once a day.
- **Tenofovir** (Viread, approved 2008)
  Pill taken once a day; need to monitor renal function (test for blood levels of blood urea nitrogen and creatinine).

Injection Immunostimulators

These stimulate the immune system to kill liver cells infected with HBV. This class of drugs generally has a low response rate in patients with low pre-treatment ALT levels, high viral load, and long duration of chronic infection (common in Asians). They are not recommended for elderly patients and patients with decompensated cirrhosis. Injection immunostimulation usually consists of a 6-12 month course of treatment.[2]

- **Interferon alfa-2b** (Intron A, approved 1991)
  Administer by subcutaneous injection 3-5 times a week.
- **Peginterferon alfa-2a** (Pegasys, approved 2005)
  Administer by subcutaneous injection once a week.

Possible side effects

For oral antivirals, side effects are uncommon and usually mild. Adefovir and Tenofovir have potential renal toxicity, though it is uncommon.[2]

For injection immunostimulators, side effects may be severe and include flu-like symptoms, hair loss, leukopenia, and psychiatric effects.[2]

Favorable responses to HBV treatment

- Sustained viral suppression: loss or marked reduction of HBV DNA levels
- Normalization of serum ALT levels
- HBeAg seroconversion: loss of HBeAg, development of anti-HBe
- Improvement in liver inflammation and fibrosis
- Long-term reduction in the risk of liver cancer

Note: There are no large-scale clinical studies that support combining the use of oral antivirals and injection immunostimulators in chronic HBV treatment.[2]

What about herbal treatments?

Herbal treatments have not been proven to prevent or treat HBV infection. The hepatitis B vaccine is the safest and most effective way to protect against HBV.

Frequently Asked Questions

Q: My doctor told me that I have hepatitis B, but that I have normal liver function tests and am a "healthy carrier." What does this mean?

A: The term "healthy carrier" is misleading and should be discontinued. An HBV carrier is someone who has chronic HBV infection. Many chronically infected patients do not show symptoms and have normal liver function tests, but are still at increased risk for liver cancer and liver damage. Therefore, it is critical to remain vigilant about regular screening for liver damage (with ALT tests every 6 months) and liver cancer (with AFP tests every 6 months and an ultrasound every year).

Q: Isn't hepatitis B transmitted through contaminated food and water?

A: No. HBV is transmitted like HIV: from an infected mother to her child at birth, through contaminated blood, or through unprotected sex. A different virus, the hepatitis A virus, is spread through food and water contaminated by human fecal waste.

Q: If I have hepatitis B, am I going to die from liver cancer or liver failure?

A: People with chronic hepatitis B can lead completely normal and active lives. With regular ALT and AFP tests every 6 months and an ultrasound every year, liver disease can be detected early and treated quickly to prevent further damage, which will increase the probability of long-term survival.

Q: If I am pregnant and have chronic hepatitis B, will my child be infected as well?

A: Hepatitis B is NOT a hereditary disease. Mothers with high HBV DNA levels or who test positive for HBeAg are at the greatest risk of infecting their newborns. HBsAg-positive mothers can protect their newborns from becoming chronically infected with HBV if the newborn receives the first dose of the hepatitis B vaccine and the hepatitis B immune globulin (HBIG) shot within 12 hours of birth, and completes the hepatitis B vaccination series. This will be more than 95% effective in preventing HBV transmission from the infected mother to her child.

Q: I have already received my 3-shot hepatitis B vaccination. Do I need a booster shot?

A: The CDC does not recommend a routine booster shot of the hepatitis B vaccine. Successful completion of the 3-shot vaccination series provides long-term protection against HBV in most of those vaccinated.

Q: Why is hepatitis B so common in Asians?

A: There is no clear explanation for the endemic persistence of HBV in Asia, though lack of symptoms, testing, vaccination, and awareness are all contributing factors. Because mother-to-child transmission is common in Asians, HBV infection is often passed silently from generation to generation. However, anyone (regardless of race or gender) without proper vaccination is susceptible to HBV infection.

Glossary of Key Terms

Acute HBV infection	Initial infection with hepatitis B virus. May result in liver failure and sometimes death, but over 90% of adult cases will recover completely and develop immunity.
AFP	Alpha-fetoprotein. Elevated or rising AFP levels can indicate liver cancer.
ALT	Alanine transaminase (or alanine aminotransferase). Elevated ALT levels can indicate active liver damage. Also referred to as SGPT (serum glutamate pyruvate transaminase).
Anti-HBc or HBcAb	Hepatitis B core antibody. Its presence can indicate past or current infection with HBV. Not a protective antibody.
Anti-HBe or HBeAb	Hepatitis B e antibody. Its presence can indicate a positive response to the treatment of chronic hepatitis B. Not a protective antibody.
Anti-HBs or HBsAb	Hepatitis B surface antibody. Levels ≥10 mIU/mL indicate protection against HBV.
Chronic HBV infection	Clinical term used to describe lifelong HBV infection, indicated by presence of hepatitis B surface antigen (HBsAg) in the blood for more than six months.
Cirrhosis	Severe scarring of the liver that can lead to liver failure and death. Common causes include chronic hepatitis B, chronic hepatitis C, and excessive alcohol consumption.
HBeAg	Recommended baseline test after initial diagnosis of chronic HBV infection. HBeAg is a marker of a high degree of HBV infectivity and indirect measure of viral load (though some mutant HBV strains have high viral load but negative HBeAg). If HBeAg is positive, the test should be repeated yearly.
HBeAg seroconversion	Loss of HBeAg and development of anti-HBe, a favorable response to HBV treatment.
HBIG	Hepatitis B immune globulin. Provides short-term protection against HBV and is given in combination with the 3-dose hepatitis B vaccine, especially to unprotected individuals exposed to HBV or newborns born to chronically infected mothers.
HBsAg	Hepatitis B surface antigen. Its presence for at least six months after initial infection indicates chronic HBV infection.
HBV DNA	Hepatitis B virus deoxyribonucleic acid. The basis of the most direct blood test used to measure the hepatitis B viral load. It is used to assess and monitor the treatment of chronic HBV patients.
Hepatitis	General term meaning "inflammation of the liver," which can be caused by bacterial infections, trauma, adverse drug reactions, and a range of viruses including hepatitis A, B, C, D, and E.
Hepatitis A	Disease of the liver caused by infection with the hepatitis A virus (HAV). HAV is transmitted through food or water contaminated by fecal matter from humans infected with HAV. It is vaccine-preventable.
Hepatitis B	Disease of the liver caused by infection with the hepatitis B virus (HBV). Chronic infection with HBV can lead to death caused by cirrhosis, liver failure, or liver cancer. It is vaccine-preventable.
Hepatitis C	Disease of the liver caused by infection with the hepatitis C virus (HCV). Largely a bloodborne infection that can also cause liver cancer and cirrhosis, but there is currently no vaccine.
Hepatocellular carcinoma (HCC)	Most common type of malignant primary liver tumor, otherwise known as liver cancer. Worldwide, an estimated 78% of HCC is caused by chronic HBV or HCV infection.[15] Cirrhosis due to long-term heavy alcohol consumption is also a common cause of HCC in the Western world.
Vaccination for HBV	3-shot vaccine series that provides >95% of individuals with long-term protection against HBV.

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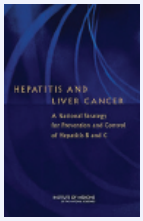
Additional Resources

U.S. Centers for Disease Control and Prevention



Division of Viral Hepatitis

- Hepatitis B Information for Health Professionals in the United States
- Available at www.cdc.gov/hepatitis/HBV/index.htm

Institute of Medicine of the National Academies

Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C

- Report released January 11, 2010
- Available at www.iom.edu/Reports/2010/Hepatitis-and-Liver-Cancer-A-National-Strategy-for-Prevention-and-Control-of-Hepatitis-B-and-C.aspx

World Health Organization

Western Pacific Regional Office

- News and press releases, current data and statistics, and publications regarding WHO region bearing the highest burden of chronic hepatitis B
- Available at www.wpro.who.int/topics/hepatitis/en/

American Association for the Study of Liver Diseases

Current Practice Guidelines

- Annually updated guidelines for treatment and management of chronic hepatitis B
- Available at www.aasld.org/practiceguidelines/Pages/default.aspx

Asian Liver Center at Stanford University

- The first non-profit organization in the United States that addresses the high incidence of hepatitis B and liver cancer in Asians and Asian Americans
- More information available at liver.stanford.edu and www.hepbmoms.org

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