# Chronic Hepatitis B

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This guideline has been approved by the American Association for the Study of Liver Diseases and represents the position of the Association.

## Preamble

These guidelines have been written to assist physicians and other health care providers in the recognition, diagnosis, and management of patients chronically infected with the hepatitis B virus (HBV). These recommendations provide a data-supported approach. They are based on the following: (1) formal review and analysis of published literature on the topic – Medline search up to 2003 and meeting abstracts in 2001-2003; (2) American College of Physicians Manual for Assessing Health Practices and Designing Practice Guidelines[1] (3) guideline policies, including the AASLD Policy on the Development and Use of Practice Guidelines and the AGA Policy Statement on Guidelines[2] (4) the experience of the authors in hepatitis B. In addition, the proceedings of a recent National Institutes of Health workshop on the "Management of Hepatitis B" and the EASL International Consensus Conference on Hepatitis B were considered in the development of these guidelines.[2a,2b] These recommendations suggest preferred approaches to the diagnostic, therapeutic and preventive aspects of care. They are intended to be flexible. Specific recommendations are based on relevant published information. In an attempt to characterize the quality of evidence supporting recommendations, the Practice Guidelines Committee of the AASLD requires a category to be assigned and reported with each recommendation (Table 1). These guidelines may be updated periodically as new information becomes available.

## Introduction

An estimated 350 million persons worldwide are chronically infected with HBV.[3] In the United States, there are an estimated 1.25 million hepatitis B carriers, defined as persons positive for hepatitis B surface antigen (HBsAg) for more than 6 months.[4,5] Carriers of HBV are at increased risk of developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC).[6] Although most carriers will not develop hepatic complications from chronic hepatitis B, 15% to 40% will develop serious sequelae during their lifetime.[7] Recommendations in these guidelines pertain to (1) evaluation of patients with chronic HBV infection, (2) prevention of HBV infection, (3) role of HCC surveillance, and (4) treatment of chronic hepatitis B.

**Table 1**

**QUALITY OF EVIDENCE ON WHICH A RECOMMENDATION IS BASED**

| Grade | Definition |
|---|---|
| I | Randomized controlled trials |
| II-1 | Controlled trials without randomization |
| II-2 | Cohort or case-control analytic studies, |
| II-3 | Multiple time series, dramatic uncontrolled experiments |
| III | Opinions of respected authorities, descriptive epidemiology |

## Hepatitis B Virus

HBV belongs to the family of hepadnaviruses. The HBV genome is a relaxed circular, partially double stranded DNA of approximately 3,200 base pairs. There are 4 partially overlapping open reading frames encoding the envelope (pre-S/S), core (precore/core), polymerase, and X proteins.[8,9] The pre-S/S open reading frame encodes the large (L), middle (M), and small (S) surface glycoproteins. The precore/core open reading frame is translated into a precore polypeptide, which is modified into a soluble protein, the hepatitis B e antigen (HBeAg) and the nucleocapsid protein, hepatitis B core antigen. Mutations in the core promoter and precore region have been shown to decrease or abolish HBeAg production.[10,11] The polymerase protein functions as a reverse transcriptase as well as a DNA polymerase. The X protein is a potent transactivator and may play a role in hepatocarcinogenesis.

The replication cycle of HBV begins with the attachment of the virion to the hepatocyte. Inside the hepatocyte nucleus, synthesis of the plus strand HBV DNA is completed and the viral genome is converted into a covalently closed circular DNA (cccDNA). The cccDNA is the template for the pregenomic RNA, which is reverse transcribed into the minus strand HBV DNA. There are two sources of cccDNA: entry of new virus particles into the hepatocyte and translocation of newly synthesized HBV DNA from the hepatocyte cytoplasm. Most antiviral agents that have been examined so far have little or no effect on cccDNA.[12] This accounts for the rapid reappearance of serum HBV DNA after cessation of antiviral therapy.

## Epidemiology of Hepatitis B

Although persons chronically infected with HBV live in all parts of the globe, HBV is especially endemic in Asia, the South Pacific Region, sub-Saharan Africa, in certain indigenous population groups residing in the Arctic (Alaska, Greenland, and Northern Canada), Australia, New Zealand, and populations in South America and the Mid East.[7,13,14] HBV infection is

**Table 2**

**PREVALENCE OF HBV SEROLOGIC MARKERS IN POPULATION GROUPS WHO SHOULD BE TESTED FOR HBV INFECTION**

| | *Prevalence of HBV serologic markers (%)* | |
|---|---|---|
| **Population** | **HBsAg** | **Any marker** |
| *Persons born in high endemic areas** | 13 | 70-85 |
| *Men who have sex with men* | 6 | 35-80 |
| *Injecting drug users* | 7 | 60-80 |
| *Dialysis patients* | 3-10 | 20-80 |
| *HIV infected patients* | 8-11 | 89-90 |
| *Pregnant females (USA)* | 0.4-1.5 | |
| *Family/household and sexual contacts* | 3-6 | 30-60 |

*Africa; Southeast Asia, including China, Korea, Indonesia, and the Philippines; the Middle East, except Israel; south and Western Pacific islands; the interior Amazon River basin; and certain parts of the Caribbean (Haiti and the Dominican Republic)

also more prevalent in certain groups in developed countries, such as immigrants from endemic areas, men who have sex with men, injecting drug users, and persons with multiple sex partners.[5,15-19] In some parts of the world such as China and sub-Saharan Africa, HCC associated with HBV is one of the leading causes of cancer in men.[6,7] Table 2 displays the prevalence of HBV serologic markers in population groups that should be screened for HBV infection and immunized if seronegative.

HBV is transmitted by perinatal, percutaneous, and sexual exposure, as well as by close person-to-person contact presumably by open cuts and sores, especially among children in hyperendemic areas.[5,15-17] HBV can survive outside the body for prolonged periods, and carriers who are HBeAg positive can shed large quantities of viral particles ($10^{7-9}$) on environmental surfaces through open cuts or sores.[20,21] The risk of developing chronic HBV infection after acute exposure ranges from 90% in newborns of HBeAg-positive mothers to 25% to 30% in infants and children under 5 and less than 10% in adults.[22-26] In addition, immunosuppressed persons are more likely to develop chronic HBV infection after acute infection.[27,28]

### Recommendations for Persons Who Should Be Tested for HBV Infection

**1. The following groups should be tested for HBV infection: persons born in hyperendemic areas (Table 2), men who have sex with men, injecting drug users, dialysis patients, HIV-infected individuals, pregnant women, and family members, household members, and sexual contacts of HBV-infected persons. Testing for HBsAg and antibody to HBsAg (anti-HBs) should be performed, seronegative persons should be vaccinated (I) while HBsAg positive persons should be evaluated to assess activity of liver disease and need for antiviral therapy (II-3).**

## Terminology and Natural History of Chronic HBV Infection

The consensus definition and diagnostic criteria for clinical terms relating to HBV infection adopted at the National Institutes of Health (NIH) workshop on Management of Hepatitis B 2000 are summarized in Table 3.[2a]

The most commonly used definition of the carrier state is presence of HBsAg in serum for at least 6 months. It is important to recognize that occasionally it may take a few more months for some individuals to clear HBsAg, but HBsAg

**Table 3**

**GLOSSARY OF CLINICAL TERMS USED IN HBV INFECTION**

**Definitions**

***Chronic hepatitis B***

Chronic necroinflammatory disease of the liver caused by persistent infection with hepatitis B virus. Chronic hepatitis B can be subdivided into HBeAg positive and HBeAg negative chronic hepatitis B.

***Inactive HBsAg carrier state***

Persistent HBV infection of the liver without significant, ongoing necroinflammatory disease.

***Resolved hepatitis B***

Previous HBV infection without further virological, biochemical or histological evidence of active virus infection or disease.

***Acute exacerbation or flare of hepatitis B***

Intermittent elevations of aminotransferase activity to more than 10 times the upper limit of normal and more than twice the baseline value.

***Reactivation of hepatitis B***

Reappearance of active necroinflammatory disease of the liver in a person known to have the inactive HBsAg carrier state or resolved hepatitis B.

***HBeAg clearance***

Loss of HBeAg in a person who was previously HBeAg positive.

***HBeAg seroconversion***

Loss of HBeAg and detection of anti-HBe in a person who was previously HBeAg positive and anti-HBe negative.

***HBeAg reversion***

Reappearance of HBeAg in a person who was previously HBeAg negative, anti-HBe positive.

**Diagnostic criteria**

***Chronic hepatitis B***

1. HBsAg + > 6 months
2. Serum HBV DNA $>10^5$ copies/ml
3. Persistent or intermittent elevation in ALT/AST levels
4. Liver biopsy showing chronic hepatitis (necroinflammatory score ≥4)*

***Inactive HBsAg carrier state***

1. HBsAg+ > 6 months
2. HBeAg-, anti-HBe+
3. Serum HBV DNA $<10^5$ copies/ml
4. Persistently normal ALT/AST levels
5. Liver biopsy confirms absence of significant hepatitis (necroinflammatory score <4)*

***Resolved hepatitis B***

1. Previous known history of acute or chronic hepatitis B or the presence of anti-HBc ± anti-HBs
2. HBsAg-
3. Undetectable serum HBV DNA#
4. Normal ALT levels

* Optional # Very low levels may be detectable using sensitive PCR assays

should be undetectable 1 year after acute HBV infection.[25] During the initial phase of chronic HBV infection, serum HBV DNA levels are high and HBeAg is present. The majority of carriers eventually lose HBeAg and develop antibody to HBeAg (anti-HBe).[29-33] In most patients who have undergone seroconversion from HBeAg to anti-HBe, levels of HBV DNA decrease below detection by unamplified assays (~$10^5$ copies/mL), aminotransferase (ALT) levels normalize, and necroinflammation decreases.[29,32] However, in some patients, liver disease persists or relapses after a period of inactivity. Most of these patients have core promoter or precore variants.

Three serologic patterns of chronic HBV infection have been identified. In Asia and the South Pacific Islands, where at least 50% of chronic HBV infection is a result of perinatal transmission, persistence of HBeAg is longer and seroconversion does not occur in most persons until later in adulthood (pattern 1).[34,35] Among individuals with perinatally acquired HBV infection, a large percent of HBeAg-positive patients have high serum HBV DNA but normal ALT levels.[34,35] These patients are considered to be in the "immune tolerant" phase. Many of these patients develop HBeAg-positive chronic hepatitis B with elevated ALT levels described as pattern 2 in later life.[33,36,37] In sub-Saharan Africa, Alaska, and Mediterranean countries, transmission of HBV usually occurs from person to person in childhood, whereas perinatal transmission is less common (pattern 2).[25,38-40] In these populations most children who are HBeAg positive have elevated ALT levels and seroconversion to anti-HBe is common near or shortly after the onset of puberty. The third pattern is usually observed in individuals who acquired HBV infection during adulthood. This pattern is similar to pattern 2 and is most common in developed countries where sexual transmission is the predominant mode of spread (pattern 3).[15,41] Very little longitudinal data is available on the latter patients, but liver disease is generally present in patients with high HBV DNA levels.[30,32,42]

Among adults in Asia and the South Pacific Islands with elevated ALT levels and carriers of all ages with childhood or adult-acquired HBV infection, the rate of clearance of HBeAg averages between 8% and 12% per year.[29-33,43] The rate of clearance of HBeAg is much lower in Asian children (most of whom have normal ALT levels)[34,35] and in immunocompromised subjects.[28,44] The largest prospective follow-up study conducted in Alaska of 1,536 carrier children and adults, followed for 12 years, showed that spontaneous HBeAg clearance occurred in 45% of carriers in 5 years and in 80% after 10 years.[43] Similarly, 3- and 5-year HBeAg clearance rates of 50% and 70% were reported in untreated children with elevated ALT levels from Taiwan and Italy.[36,39] Older age and elevated ALT are predictive of HBeAg clearance. HBeAg clearance may follow an exacerbation of hepatitis, manifested by an elevation of ALT levels.[31,33]

After spontaneous HBeAg seroconversion, 67% to 80% of carriers remain HBeAg negative and anti-HBe positive with normal ALT levels and minimal or no necroinflammation on liver biopsy.[43, 43a] This has been referred to as the "inactive carrier state."[29,32,33,39,40,43,45] The course and outcome of the inactive HBsAg carrier state is generally but not invariably benign depending on the duration and severity of the preceding chronic hepatitis. Because fluctuations in ALT and HBV DNA levels are common during the course of chronic HBV infection, serial tests should be performed before patients are determined to be in an inactive carrier state and periodically thereafter. Up to 20% of carriers in the inactive state can have exacerbations of hepatitis, as evidenced by elevations of ALT levels to 5 to 10 times the upper limit of normal, with or without seroreversion to HBeAg.[33,37,46,47] Repeated exacerbations or reactivations can lead to progressive fibrosis.

HBeAg-negative chronic hepatitis B, characterized by HBV DNA levels detectable by nonamplified assays and continued necroinflammation in the liver, has been reported in all parts of the world but is more common in Mediterranean countries and Asia.[48-64] Most patients with HBeAg-negative chronic hepatitis B harbor HBV variants in the precore or core promoter region.[49-56,59,62-67] The most common precore mutation, $G_{1896}A$, creates a premature stop codon in the precore region thus abolishing production of HBeAg.[67] This variant is commonly found in association with HBV genotype D, which is prevalent in the Mediterranean basin and is rarely detected in association with HBV genotype A, which is prevalent in the United States and North-West Europe.[51,68] The most common core promoter mutations, $A_{1762}T$ + $G_{1764}A$, decrease transcription of precore messenger RNA and production of HBeAg.[11] There are also clinical differences between HBeAg-positive and HBeAg-negative chronic hepatitis B.[57] Patients with HBeAg-negative chronic hepatitis B tend to have lower serum HBV DNA levels (mean $10^5$ versus $10^8$ copies/mL) and are more likely to run a fluctuating course characterized by persistently elevated or fluctuating ALT levels.[57,60,62, 62a, 62b]

Approximately 0.5% of HBsAg carriers will clear HBsAg yearly; most will develop anti-HBs.[43,69,70] However, low levels of HBV DNA detectable only by polymerase chain reaction (PCR) assays can be found in up to half of these persons after disappearance of HBsAg.[71] The pathogenic significance of very low levels of HBV DNA is unknown.

One population-based study of HBsAg carriers found the incidence of decompensated cirrhosis to be 0.5 per 1,000 years.[43] In carriers referred to clinical centers, the reported incidence of cirrhosis is as high as 2% to 3% per year possibly because of underlying chronic hepatitis.[61,72-74] Prognostic factors for the development of cirrhosis include HBeAg positivity, older age, and elevated ALT levels.[72,73,75] For patients with compensated cirrhosis, the survival is 84% at 5 years and 68% at 10 years.[75,76] In carriers with decompensated cirrhosis, 5-year survival is only 14%.[76,77] In patients with cirrhosis, risk factors for decompensation include presence of HBeAg and failure to respond to interferon.[77,78] Patients with compensated cirrhosis who were HBeAg-negative had significantly better 5-year survival (97%) than those who were HBeAg-positive (72%).[76] Clearance of HBeAg, whether spontaneous or after antiviral therapy, reduces the risk of hepatic decompensation and improves survival.[72,74,76-81]

Risk factors for HCC in patients with chronic HBV infection include male gender, family history of HCC, older age, presence

of HBeAg in an adult, history of reversions from anti-HBe to HBeAg, presence of cirrhosis, and coinfection with hepatitis C virus (HCV).[6,7,43,77,82, 82a] Alcohol use has been reported to be associated with HCC in persons with hepatitis B in some studies,[82b, 82c] but not in others.[82d, 82e] Discrepancies in the conclusion may be related to the accuracy of the alcohol history. It is important to note that, although HCC is more common in persons with cirrhosis, 30% to 50% of HCC associated with HBV occurs in the absence of cirrhosis.[7] Clearance of HBsAg decreases the risk of hepatic decompensation and probably HCC,[69,83] but HCC can occur in long-term carriers who have cleared HBsAg.[43,70,84]

Coinfection with HCV or human immunodeficiency virus (HIV) is commonly seen in injecting drug users.[5] Coinfection with HIV is also seen in men who have sex with men. Persons who are chronically coinfected with HBV and HCV may have more rapid progression of liver disease[85] and a higher risk of developing HCC than carriers with HBV infection only.[7] Individuals with HBV and HIV coinfection tend to have higher levels of HBV DNA, lower rates of spontaneous HBeAg seroconversion,[28,44] and more severe liver disease.[86]

Hepatitis D virus (HDV) is a satellite virus, which is dependent on HBV for the production of envelope proteins.[87] HBV/HDV coinfection most commonly occurs in the Mediterranean area and parts of South America. The availability of HBV vaccines and public health education on prevention of transmission of HBV infection has led to a significant decline in the prevalence of HDV infection in the past decade.[88,89] HDV infection can occur in two forms. The first form is caused by the coinfection of HBV and HDV; this usually results in a more severe acute hepatitis with a higher mortality rate than is seen with acute hepatitis B alone,[87,90] but rarely results in chronic infection. A second form is a result of a superinfection of HDV in an HBV carrier. HDV superinfection can manifest as a severe "acute" hepatitis in previously asymptomatic HBV carriers or exacerbations of underlying chronic hepatitis B. Unlike coinfection, HDV superinfection in HBV carriers almost always results in chronic infection with both viruses. Although persons with chronic HBV/HDV infection can exhibit a wide spectrum of liver pathology, a higher proportion develops cirrhosis, hepatic decompensation, and HCC compared with those with chronic HBV infection alone.[91,92]

## Evaluation and Management of Patients with Chronic HBV Infection (Table 4)

### *Initial Evaluation*

The initial evaluation of patients with chronic HBV infection should include a thorough history and physical examination, with special emphasis on risk factors for coinfection, alcohol use, and family history of HBV infection and liver cancer. Laboratory tests should include assessment of liver disease, markers of HBV replication, and tests for coinfection with HCV, HDV, and HIV in those at risk (Table 4). Vaccination for hepatitis A should be administered as per Centers for Disease Control recommendations to persons with chronic hepatitis B.[93]

**Table 4**

**EVALUATION OF PATIENTS WITH CHRONIC HBV INFECTION**

**Initial evaluation**

1. History and physical examination
2. Laboratory tests to assess liver disease – complete blood counts with platelets, hepatic panel and prothrombin time
3. Tests for HBV replication – HBeAg/anti-HBe, HBV DNA
4. Tests to rule out other causes of liver disease – anti-HCV, anti-HDV (in persons from countries where HDV infection is common and in those with history of injection drug use)
5. Tests to screen for HCC – AFP and, in high risk patients, ultrasound
6. Liver biopsy to grade and stage liver disease - for patients who meet criteria for chronic hepatitis

***Suggested follow-up for patients not considered for treatment***

**HBeAg+ chronic hepatitis with HBV DNA >$10^5$ copies/ml and normal ALT**

- ALT q 3-6 months
- If ALT >1-2 x ULN, recheck ALT q1-3 months
- If ALT >2 x ULN for 3-6 months and HBeAg+, HBV DNA >$10^5$ copies/ml, consider liver biopsy and treatment
- Consider screening for HCC in relevant population

**Inactive HBsAg carrier state**

- ALT q 6-12 months
- If ALT >1-2 x ULN, check serum HBV DNA level and exclude other causes of liver disease
- Consider screening for HCC in relevant population

Prevaccination screening for antibody to hepatitis A (total) should be considered if the prevalence of infection in the population is likely to be greater than 33%.[93]

### Recommendations for Vaccinating Persons With Chronic HBV Infection Against Hepatitis A

**2. All persons with chronic hepatitis B not immune to hepatitis A should receive 2 doses of hepatitis A vaccine 6 to 18 months apart. (II-3)**

### HBV DNA Assays

The appropriate HBV DNA assay to use for initial evaluation of patients with chronic HBV infection has not been determined. An arbitrary value of >$10^5$ copies/mL was chosen as a diagnostic criterion for chronic hepatitis B at a recent NIH conference.[1] However, there are problems with this definition. First, assays for HBV DNA quantification are not well standardized (Table 5).[94-96] Second, some patients with chronic hepatitis B have fluctuating HBV DNA levels that may at times fall below $10^5$ copies/mL. Third, the threshold HBV DNA level that is associated with progressive liver disease is unknown. Quantitative amplification assays can detect HBV DNA levels as low as $10^2$ copies/mL but the results of these assays have to be interpreted with caution because of the uncertain clinical significance of low HBV DNA levels. Based on our current knowledge and definition of chronic hepatitis B, unamplified assays with detection limits of $10^5$ to $10^6$ copies/mL are adequate for the initial evaluation of patients with chronic HBV infection.

**Table 5**

**COMPARISON OF HBV DNA QUANTIFICATION ASSAYS***

| Assay (Manufacturer) | Volume of sample | Sensitivity@ pg/ml | copies/ml | Linearity copies/ml | Genotype independent | Coefficient of variation |
|---|---|---|---|---|---|---|
| Branched DNA (Bayer) | 10 ul | 2.1 | $7 \times 10^5$ | $7 \times 10^5$ – $5 \times 10^9$ | A,B,C,D,E,F | 6-15% |
| Hybrid capture (Digene) | 30 ul<br>1 ml | 0.5<br>0.02 | $1.4 \times 10^5$<br>$5 \times 10^3$ | 2 x 105 – 1 x 109<br>$5 \times 10^3$ – $3 \times 10^6$ | A,B,C,D | 10-15% |
| Liquid hybridization (Abbott) | 100 ul | 1.6 | $4.5 \times 10^5$<br>[$8 \times 10^6$]# | $5 \times 10^5$ – $1 \times 10^{10}$ | detects genotype D better than A | 12-22% |
| PCR - Amplicor (Roche) | 50 ul | 0.001 | $4 \times 10^2$<br>$2 \times 10^2$ | $4 \times 10^2$ – $1 \times 10^7$<br>Cobas: –$10^5$<br>Taqman^: - $10^{10}$ | A,B,C,D,E | 14-44% |
| Molecular Beacons | 10-50 ul | - | <50 | 50 – $1 \times 10^9$ | A-F | 5-10% |

* Adapted from Zuezem S (25)

@ 1 pg HBV DNA = 283,000 copies (~$3 \times 10^5$ viral genome equivalents)

^ 1 IU= 5.1 copies/mL # Revised limit of detection

**Liver Biopsy**

The purpose of a liver biopsy is to assess the degree of liver damage and to rule out other causes of liver disease. An international panel of experts recommended that the histologic diagnosis of chronic hepatitis should include the etiology, grade of necroinflammatory activity, and stage/extent of fibrosis.[97] Several numerical scoring systems have been established to permit statistical comparisons of necroinflammatory activity and fibrosis.[98-100] Histologic findings may help in predicting prognosis.[101] However, it must be recognized that liver histology can improve significantly in patients who have sustained response to antiviral therapy or spontaneous HBeAg seroconversion. Liver histology also can worsen rapidly in patients who have recurrent exacerbations or reactivations of hepatitis. Liver biopsies can be used for immunohistochemical staining for HBsAg and hepatitis B core antigen.

***Follow-up of Patients not considered for Treatment***

***HBeAg-Positive Patients with High Serum HBV DNA but Normal ALT Levels***

These patients should be monitored at 3- to 6-month intervals (Table 4). In general, liver biopsy is not necessary unless treatment is contemplated. More frequent monitoring should be performed when ALT levels become elevated. Exacerbations in liver disease have been reported in up to 40% of patients prior to spontaneous HBeAg clearance.[31,33,37,47] Patients who remain HBeAg positive with HBV DNA levels greater than $10^5$ copies/mL after a 3- to 6-month period of elevated ALT levels should be considered for liver biopsy and antiviral treatment.

***HBeAg-negative anti-HBe positive persons with normal ALT levels (Inactive HBsAg carriers)***

These persons should be monitored every 6-12 months with ALT determinations, since up to 30% may develop reactivation of hepatitis B with or without reversion to HBeAg.[36,37,43,43b,46,47,48] If ALT level is subsequently found to be elevated, more frequent monitoring is needed and an evaluation into the cause of ALT elevation should be initiated if it persists or recurs (see Table 4).

**Recommendations for Monitoring Patients with Chronic HBV Infection**

**3. HBeAg-positive patients with elevated ALT levels and compensated liver disease should be observed for 3 to 6 months for spontaneous seroconversion from HBeAg to anti-HBe prior to initiation of treatment (III).**

**4. Patients who meet the criteria for chronic hepatitis B (serum HBV DNA >$10^5$ copies/mL and persistent or intermittent elevation in aminotransferase levels) should be evaluated further with a liver biopsy (III).**

**5. Patients in the inactive HBsAg carrier state should be monitored with periodic liver chemistries every 6 to 12 months, as liver disease may become active even after many years of quiescence (III).**

## Counseling and Prevention of Hepatitis B

Patients with chronic HBV infection should be counseled regarding lifestyle modifications and prevention of transmission. There are no specific dietary measures that have been shown to have any effect on the progression of chronic hepatitis B. However, heavy use of alcohol (>40 g/d) has been associated with higher ALT levels[102,103] and development of cirrhosis.[104] In addition, the development of cirrhosis and HCC occurs at a younger age in heavy drinkers with chronic hepatitis B.[105,106]

Carriers of HBV should be counseled as to the risk of transmission to others. Counseling should include precautions to prevent sexual transmission, perinatal transmission, and risk of inadvertent transmission via environmental contamination from a blood spill. Household members are at increased risk of HBV infection and therefore should be vaccinated if they test negative for HBV serologic markers.[5] Testing should be

performed for HBsAg and anti-HBs. A positive result for antibody to hepatitis B core antigen (anti-HBc) does not differentiate between recovered and chronic infection. In addition, false-positive test results are not uncommon in persons with isolated antibodies to hepatitis B core antigen.[107,108] Vaccination of sexual partners has been shown to be effective in preventing sexual transmission of HBV.[5] Steady sexual partners should be tested and vaccinated against hepatitis B if found to be seronegative. For casual sex partners or steady partners who have not been tested or have not completed the full immunization series, barrier protection methods should be employed. HBsAg-positive women who are pregnant should be counseled to make sure they inform their providers so hepatitis B immune globulin (HBIG) and hepatitis B vaccine can be administered to their newborn immediately after delivery.[5] In addition, they should be informed that their infants need to complete the recommended vaccination schedule and have follow-up testing for HBsAg and anti-HBs at 9-15 months of age. HBIG and concurrent hepatitis B vaccine have been shown to be 95% efficacious in the prevention of perinatal transmission of HBV.[16,109] A recent study of 368 infants of HBsAg-positive women who received prophylactic HBIG and hepatitis B vaccination and were followed until 15 months of age, showed that breast-fed infants were at no additional risk of acquiring hepatitis B than formula-fed infants.[109a] Carriers should be advised to cover open cuts and scratches and clean up blood spills with bleach, because HBV can survive on environmental surfaces for at least 1 week.[20] It should be noted that carriers with high HBV DNA levels are more likely to be infectious, as evidenced by transmission from maternal carriers to infants.[110] Transmission of HBV from infected health care workers to patients has also been shown to occur in rare instances.[111,112] For HBV carriers who are health care workers, the Centers for Disease Control and Prevention recommends that those who are HBeAg-positive should not perform invasive procedures without prior counseling and advice from an expert review panel under what circumstances, if any, they should be allowed to perform these procedures.[113] These circumstances would include notifying prospective patients of their HBV status prior to procedures.

### Recommendations for Prevention of Transmission of Hepatitis B from Individuals With Chronic HBV Infection

**6. Carriers should be counseled regarding prevention of transmission of HBV. (I)**

**7. Sexual and household contacts of carriers should be tested for HBV (HBsAg and anti-HBs) and if negative receive hepatitis B vaccination. (II-2)**

**8. Newborns of HBV-infected mothers should receive HBIG and hepatitis B vaccine at delivery and complete the recommended vaccination series. (I)**

**9. Persons who remain at risk for HBV infection such as infants of HBsAg-positive mothers, health care workers, dialysis patients, and sexual partners of carriers should be tested for response to vaccination. Postvaccination testing should be performed 3-9 months after the last dose in infants of carrier mothers and 1-2 months after the last dose in other persons. (I) Follow-up testing of vaccine responders is recommended annually for chronic hemodialysis patients. (I)**

**10. Abstinence or only limited use of alcohol is recommended in hepatitis B carriers. (III)**

### *Periodic Screening for HCC*

In longitudinal prospective studies, carriers of HBV have clearly been shown to be at increased risk of developing HCC.[6,7,39] HCC may have a long asymptomatic stage lasting 2 years or longer.[114] In the majority of patients, the cancer begins as a single tumor that is often encapsulated. The doubling time of HCC has been estimated to range from 2 to 12 months with a median of 4 months.[115-117] There is considerable evidence that HCC can be detected early when persons with chronic HBV or HCV infection receive periodic screening. Five population-based screening studies using alpha-fetoprotein (AFP) have been published in HBV carriers, four involving periodic screening and one reporting a one-time mass screening.[118-121, 121a] Using AFP as a screening method, small HCC, defined as tumors with a diameter of less than 5 cm, were found in 37% to 77% of persons who had HCC. One large randomized trial in Shanghai involved 8,109 HBsAg carriers randomized to ultrasound (US) and AFP every 6 months and 9,711 carriers to no screening (control group).[121a] During a mean follow-up of 1.2 years (12,038 person years), HCC was found in 38 carriers in the screening group and 18 carriers in the control group. Most (77%) of the tumors in the screening group were small and 71% were resected compared with none of the tumors in the control group. Among those with HCC, the 1-year survival rate was 88% in the screening group and 0 in the control group. However, the improved survival in the screening group may be related to early detection of incident tumors and cannot be interpreted as evidence of a survival benefit due to the screening program. In addition, since this was a population-based study it may have included a large portion of persons without cirrhosis. Ultrasound appears to be less sensitive and specific in detecting HCC in cirrhotic livers because of increased echo-density of the liver and the presence of regenerative nodules. In clinic-based periodic screening studies involving persons with HBV utilizing both AFP and US small tumors were found in 57% and 83% of persons respectively with HCC.[122,123] Effective treatment modalities for small HCC have resulted in successful ablation of tumor and reports of long-term tumor-free survival.[124-129]

Patients with small HCC detected by AFP screening and surgically resected who have survived for more than 5 to 10 years have been reported in two population-based studies.[118,119] Duration of tumor-free survival of greater than 5 years would mean that lead time bias is unlikely to be a factor. One of these studies utilizing only AFP compared survival in screened patients with nonscreened historical controls from the same population and showed significant improvement in 5- and 10-year survival rates.[119] Other uncontrolled clinic-based studies have reported long-term survivors who had either surgery or percutaneous ethanol injection after detection of small HCC.[126] Although there is strong evidence that long-term survival can

occur in some patients with small HCC that are treated surgically, no randomized trials of carriers undergoing periodic screening compared with those not screened with adequate duration of follow-up have been reported. In addition, it is important to note that a high false-positive rate of AFP in HBV carriers with chronic hepatitis or cirrhosis may result in expensive evaluations such as radiographic procedures and liver biopsy.

Based on the risk factors discussed in the Natural History section, while it would be easy to identify groups of carriers to prioritize for screening (i.e., men >45 years of age, carriers with cirrhosis or a family history of HCC), carriers of any age, even asymptomatic persons with normal ALT levels and minimal or absent liver disease, can develop HCC. The study from Alaska showed a distinct survival advantage for younger patients detected with HCC, most of whom did not have cirrhosis.[119] However, most HCC develops after decades of chronic HBV infection. Thus, the optimal age to initiate periodic screening is not known.

Several prospective screening studies in HBsAg carriers using laboratory and radiographic tests have been performed.[119-123,130-134] Of the laboratory tests that have been used, AFP has been studied most extensively. The sensitivity of AFP testing depends on the cutoff level employed. The normal level of AFP is less than 8 to 12 ng/mL. If a level of 20 ng/mL is used, the sensitivity for small HCC ranges from 50% to 75%. The specificity of AFP is above 90% in studies that include not only individuals with chronic hepatitis or cirrhosis but also carriers in the inactive state. The negative predictive value is greater than 99%.[119, 122] However, the positive predictive value is low, ranging from 9% to 30%. AFP levels that rise in a step-like manner strongly suggest the presence of HCC, and persons with persistent mild elevation of AFP (<200 ng/mL) are at a higher risk of HCC than those with a single increased value.[119] Other markers that have been shown to be elevated in small HCC in cross-sectional studies include des-γ-carboxy prothrombin (DCP), serum-γ-glutamyl transferase isoenzyme II, and alpha-L-fucosidase.[135-140] Only DCP has been studied in a prospective manner. Several studies have shown that, while DCP can be elevated in small HCC, the sensitivity of DCP is less than AFP.[135-137] However, two recent studies using a more sensitive assay suggest that DCP and AFP are complimentary and result in a higher sensitivity than either test alone.[141,142] One study in the United States, found that DCP was more sensitive and specific than AFP in differentiating patients with HCC and those with cirrhosis and no HCC.[142a] However, very few patients in this study had hepatitis B. DCP assays are not commercially available in the United States and have not been evaluated as a screening tool.

US is the only radiographic test that has been prospectively studied as an imaging tool for HCC surveillance. Extracting data regarding US from clinic-based studies, the sensitivity for small HCC ranged from 68% to 87% and false-positive rate from 28% to 82%.[122,123,133,134,143] Regenerating nodules, seen in patients with cirrhosis, are the most common reason for false-positive results. US is considerably more expensive than AFP, and, in many developed countries, has to be performed by a radiologist. In addition, US is operator dependent and sensitivity of US in detecting small HCC varies depending on the skill of the ultrasound technologist and the radiologist. Furthermore, large body habitus can make visualization of the liver more difficult and detection of small tumors in cirrhotic livers can be a challenge. However, US is more sensitive for small HCC than AFP. The combination of AFP and US appears to be superior to either alone but only one randomized trial has been reported, and the number of cases detected and the follow-up period (36 months) were too short to determine if any difference in early detection existed.[122] No randomized trials examining the frequency of HCC surveillance in HBV carriers (or persons with other liver conditions at risk for HCC) have been reported. However, when reviewing the results of 6 clinic-based studies utilizing AFP and US, involving 140 to 1,069 patients with cirrhosis due to HBV or HCV, screening every 6 months appears superior to yearly screening in the detection of small HCC.[122,123,130-133] There appears to be no difference between screening every 3 or 6 months.

Few cost effectiveness studies on surveillance for HCC in patients with chronic HBV infection have been reported. One clinic-based study from Hong Kong, which has a socialized health care system, using AFP and US for all patients, and computerized tomography for those with AFP levels greater than 20 ng/mL, showed that the cost per tumor detected was $1,667.[144] In this study using AFP for initial screening 61% of HCC were discovered at a resectable stage. In the randomized study in Shanghai, the cost per tumor detected at an early stage was $1,500 but it must be stated that the cost of health care in China is significantly lower than that in western countries.[121a] In other studies the cost per tumor detected ranged from $11,800 to $25,000.[121,145] In the cohort of carriers from the Alaska study,[146] cost per quality adjusted life year saved ranged from $10,000 to $15,000, well below the widely accepted limit of $50,000 per quality adjusted life year gained. However, prospective studies on the cost effectiveness and impact of surveillance for HCC on survival need to be conducted before definitive recommendations on HCC surveillance can be made.

In conclusion, the data available which supports recommendations for HCC surveillance suggest the following: (1) Periodic testing can detect HCC at a resectable stage in greater than 50% of the instances. (2) Some carriers can experience long-term survival after resection of small HCC, and one study comparing screened cases to historical controls showed a significant survival advantage. (3) Screening with AFP alone has been shown to detect HCC early in some carriers from endemic areas where there is a high risk of perinatal or early childhood infection, and one population study in predominantly noncirrhotic carriers demonstrated 10-year tumor free survival in 27%. (4) US, while more costly, appears to be more sensitive than AFP and the combination of US and AFP may be best. (5) The sensitivity of AFP is less than US but the negative predictive value is high, 99% in low-risk carriers, suggesting that AFP could be used as an initial screening test in low-risk individuals without cirrhosis.[120,122,143] (6) While carriers at higher risk can be identified, all

carriers could benefit from periodic testing with AFP. The age to initiate screening for low-risk carriers and the frequency of testing is not known. Evidence to date suggests that carriers with low risk of HCC could be screened with AFP and those at high risk with AFP and US. (7) The age at which screening for HCC should begin is unknown. (8) The optimal frequency for surveillance appears to be every 6 months. The exact risk of HCC in nonendemic populations, such as adult-infected white carriers living in developed countries, has not been determined and the role of periodic screening in this population is not known.

### Recommendations for HCC Screening

**11. HBV carriers at high risk for HCC such as men over 45 years, persons with cirrhosis, and persons with a family history of HCC, should be screened periodically with both AFP and US. (III)**

**12. While there are insufficient data to recommend routine screening in low-risk patients with chronic HBV infection, periodic screening for HCC with AFP in carriers from endemic areas should be considered. (III)**

## Treatment of Chronic Hepatitis B

The aims of treatment of chronic hepatitis B are to achieve sustained suppression of HBV replication and remission of liver disease. The end points used to assess treatment response include normalization of serum ALT level, undetectable serum HBV DNA by an unamplified assay, loss of HBeAg with or without detection of anti-HBe, and improvement in liver histology. Inconsistencies in the definition of response, lack of standardization of HBV DNA assays, and heterogeneity in patient populations make it difficult to compare response rates in clinical trials of treatment of chronic hepatitis B. At the recent NIH workshop on Management of Hepatitis B, it was proposed that responses to antiviral therapy of chronic hepatitis B be categorized as biochemical (BR), virologic (VR), or histologic (HR), and as on-therapy or sustained off-therapy (Table 6).[2a] Currently, three therapeutic agents have been approved by the FDA for the treatment of chronic hepatitis B.

**Table 6**

**DEFINITION OF RESPONSE TO ANTIVIRAL THERAPY OF CHRONIC HEPATITIS B**

| | |
|---|---|
| **Category of response** | |
| ***Biochemical (BR)*** | Decrease in serum ALT to within the normal range |
| ***Virological (VR)*** | Decrease in serum HBV DNA to undetectable levels in unamplified assays (<$10^5$ copies/ml), and loss of HBeAg in patients who were initially HBeAg positive |
| ***Histological (HR)*** | Decrease in histology activity index by at least 2 points compared to pre-treatment liver biopsy |
| ***Complete (CR)*** | Fulfill criteria of biochemical and virological response and loss of HBsAg |
| **Time of assessment** | |
| **On-therapy** | During therapy |
| ***Maintained*** | Persist throughout the course of treatment |
| ***End-of-treatment*** | At the end of a defined course of therapy |
| **Off-therapy** | After discontinuation of therapy |
| ***Sustained (SR-6)*** | 6 months after discontinuation of therapy |
| ***Sustained (SR-12)*** | 12 months after discontinuation of therapy |

### *Interferon*

Interferons (IFNs) have antiviral, antiproliferative, and immunomodulatory effects. Interferon alfa (IFN-α) has been shown to be effective in suppressing HBV replication and in inducing remission of liver disease. However, its efficacy is limited to a small percentage of highly selected patients.

Efficacy in Various Categories of Patients

1.HBeAg-positive chronic hepatitis B with the following (Table 7A):

*a. Persistent or intermittent elevation in ALT.* This pattern is seen in "typical" chronic hepatitis B patients. A meta-analysis of 15 randomized controlled trials involving 837 adult patients found that a significantly higher percentage of IFN-α–treated patients had a virologic response compared with untreated controls.[147] High pretreatment ALT and lower levels of serum HBV DNA are the most important predictors of a response to IFN-α therapy.[148-150]

*b. Normal ALT.* This pattern is usually seen in children or young adults with perinatally acquired HBV infection. Virologic response to IFN-α therapy is observed in less than 10% of these patients.[150-153]

*c. Asian patients.* Trials in Asian patients with HBeAg-positive chronic hepatitis B found that while the response in patients with normal ALT was poor,[153] the response in patients with elevated ALT was similar to that in white patients.[150]

*d. Children.* The efficacy of IFN-α is similar to that in adults. Among children with elevated ALT, HBeAg clearance has been reported in 30% of those who received IFN-α compared with 10% of controls.[154-156] However, less than 10% of children with normal ALT levels, who received IFN-α cleared HBeAg.[151,152] One meta-analysis of 240 children found that IFN-α treatment increased HBV DNA clearance (odds ratio 2.2), HBeAg clearance (odds ratio 2.2), and ALT normalization (odds ratio 2.3) compared with untreated controls.[157] Adverse events were similar to those in adults.

2. HBeAg-negative chronic hepatitis B (Table 7B)

HBeAg loss or seroconversion cannot be used as an end point to assess response in these patients. Therefore, response is usually defined as undetectable serum HBV DNA by unamplified assays and normalization of ALT level. Analyses of the results of trials of IFN-α in HBeAg-negative chronic hepatitis B are complicated by the heterogeneity not just of the disease, but also the virus and study designs. Results of four randomized controlled trials involving a total of 86 IFN-α–treated patients and 84 controls showed that the end-of-treatment response ranged from 38% to 90% in treated patients compared with only 0% to 37% of controls. The 12-month sustained response rates varied from 10% to 47% (average 24%) among the treated patients and 0% in the controls.[158-161] Neither pretreatment factors nor IFN-α dose was predictive of response but longer duration of treatment (12 vs. <6 months) was associated with a

**Table 7a**

**COMPARISON OF THE RESPONSE TO TREATMENT OF HBeAg POSITIVE CHRONIC HEPATITIS B**

| | IFNα | | LAMIVUDINE | | ADEFOVIR | |
|---|---|---|---|---|---|---|
| | *12-24 wk* | *Control* | *52 wk* | *Control* | *48 wk* | *Control* |
| ***Loss of serum HBV DNA**** | 37% | 17% | 44% | 16% | 21% | 0 |
| ***Loss of HBeAg*** | 33% | 12% | 17-32% | 6-11% | 24% | 11% |
| ***HBeAg seroconversion*** | Difference of 18% | | 16-18% | 4-6% | 12% | 6% |
| ***Loss of HBsAg*** | 7.8% | 1.8% | <1% | 0 | 0 | 0 |
| ***Normalization of ALT*** | Difference of 23% | | 41-72% | 7-24% | 48% | 16% |
| ***Histologic improvement*** | NA | NA | 49-56% | 23-25% | 53% | 25% |
| ***Durability of response*** | 80-90% | | 50-80% | | NA | |

*IFN and Lamivudine – Hybridization or branched DNA assay, Adefovir – PCR assay
NA = not available

**Table 7b**

**COMPARISON OF THE RESPONSE TO TREATMENT OF HBeAg NEGATIVE CHRONIC HEPATITIS B**

| | IFNα | | LAMIVUDINE | | ADEFOVIR | |
|---|---|---|---|---|---|---|
| | *6-12 mo* | *Control* | *52 wk* | *Control* | *48 wk* | *Control* |
| ***Loss of serum HBV DNA*** | 60-70% | 10-20% | 60-70% (40-60%)* | NA | 51%* | 0 |
| ***Normalization of ALT*** | 60-70% | 10-20% | 60-70% | NA | 72% | 29% |
| ***Histologic improvement*** | NA | NA | 60% | NA | 64% | 33% |
| ***Durability of response*** | 20-25% | | <10% | | <10% | |

*PCR assay
NA = not available

doubling of the sustained response rates.[1,162,163] A major problem with IFN-α treatment of HBeAg-negative chronic hepatitis B is relapse; approximately half of the responders relapse when therapy is discontinued, and relapses can occur up to 5 years post-therapy.[164] Longer duration of treatment, up to 24 months, may improve the rate of sustained response.[164a, 164b] Overall, sustained response can be achieved in 15% to 30% of patients and long-term follow-up showed that 15% to 50% of sustained responders cleared HBsAg.[1,164, 164b]

3. Nonresponders to IFNα treatment

Most studies found that retreatment of IFN-α nonresponders with IFN-α alone was associated with a very low rate of response. However, a recent trial reported an HBeAg clearance rate of 33% among patients retreated with IFN-α versus 10% in untreated controls.[165] Unfortunately, this trial included patients who were previously treated with suboptimal doses of IFN-α and may have overestimated the benefits of IFN-α retreatment.

4.HBV DNA–positive clinical cirrhosis

Approximately 20% to 40% of patients with HBeAg-positive chronic hepatitis B develop a flare in their ALT values during IFN-α treatment. The flare is believed to be a reflection of IFN-induced immune-mediated lysis of infected hepatocytes and is considered to be a predictor of response. In patients with cirrhosis, the flare may precipitate hepatic decompensation. Two studies on IFN-α in patients with Child's class B or C cirrhosis reported no benefit. In addition, significant side effects due to bacterial infection and exacerbation of liver disease occurred even with low doses of IFN-α (3 MU every other day).[166,167] IFN-α is in general safe and may be effective in patients with clinically and biochemically compensated cirrhosis but there is a small risk of hepatic decompensation associated with IFN-α induced hepatitis flares. In clinical trials of patients with HBeAg-positive chronic hepatitis, up to 60% of patients included had histologic cirrhosis, less than 1% of patients who received standard doses of IFN-α developed hepatic decompensation.[149,150]

Dose Regimen

IFN-α is administered as subcutaneous injections. The recommended dose for adults is 5 MU daily or 10 MU thrice weekly and for children 6 MU/m$^2$ thrice weekly with a maximum of 10 MU. The recommended duration of treatment for patients with HBeAg positive chronic hepatitis B is 16 to 24 weeks. There are very little data on longer courses of treatment in patients with HBeAg-positive chronic hepatitis B.[168-170] One study found that the response was similar in patients who received 12 versus 24 weeks of IFN-α.[169] Another study reported that among patients who have not cleared HBeAg after 16 weeks of IFN-α, those randomized to continue treatment until

week 32 had significantly higher rates of HBeAg clearance compared with those who stopped treatment.[170] Current data suggest that patients with HBeAg-negative chronic hepatitis B should be treated for at least 12 months and longer duration of treatment may increase the rate of sustained response. While receiving IFN-α, patients should have liver chemistries and complete blood counts tested every 2 to 4 weeks.

Results of a phase II trial suggest that the efficacy of pegylated IFN-α may be greater than that of standard IFN-α.[170a] Clinical trials of pegylated IFN-α singly and in combination with lamivudine in patients with HBeAg positive and HBeAg negative chronic hepatitis B are ongoing. The role of pegylated IFN-α in the treatment of chronic hepatitis B and the optimal dose and duration remain to be determined.

Prednisone Priming

The rationale for administering a tapering course of steroids prior to antiviral therapy (prednisone priming) is that recovery of immune function following steroid withdrawal may be beneficial particularly if this is timed with the initiation of IFN-α therapy. A meta-analysis of 7 randomized trials of IFN-α with or without prednisone priming in 376 patients with HBeAg-positive chronic hepatitis failed to show a significant benefit of steroid pretreatment.[171] However, a subsequent study of 200 European patients reported that patients who received prednisone priming had a significantly higher rate of HBeAg seroconversion.[172] Although a small subset of patients may benefit from prednisone priming, there is a risk of fatal exacerbations in patients with underlying cirrhosis. Therefore, prednisone priming is not recommended as a primary treatment of chronic hepatitis B.

Adverse Events

IFN-α therapy is associated with many adverse effects. Of these, flu-like symptoms, fatigue, leucopenia, and depression are the most common. Most patients develop tolerance to the flu-like symptoms after the first week, but fatigue, anorexia, hair loss, and mood swings including anxiety, irritability, and depression may persist throughout the course of treatment and for a few weeks after discontinuation of therapy. IFN-α may also unmask or exacerbate underlying autoimmune disorders. An analysis of 9 randomized controlled trials with 552 patients showed that 35% of the patients treated with IFN-α required dose reduction and 5% required premature cessation of treatment.[173]

Durability of Response and Long-Term Outcome of IFN-α–T.reated Patients

IFN-α–induced HBeAg clearance has been reported to be durable in 80% to 90% of patients after a follow-up period of 4 to 8 years.[80,81,174-176] However, HBV DNA remained detectable in the serum from most of these patients when tested by PCR assays. Five studies in Europe and the United States reported that delayed clearance of HBsAg occurred in 12% to 65% of patients within 5 years of HBeAg loss, but delayed HBsAg clearance was not observed in 2 studies on Chinese patients.[78-81,174,175,177] Sustained virologic response is usually accompanied by a decrease in necroinflammation of the liver but residual hepatic injury is frequently present.[178] Several studies reported that the 5-year cumulative rates of HBeAg clearance were similar in treated patients and controls, but IFN-α–treated patients were more likely to have normal ALT levels and to clear HBsAg.[79,179] These findings suggest that the main role of IFN-α may be to reduce the duration of active liver disease by hastening viral clearance. Data on long-term clinical benefits of IFN-α treatment are limited because chronic hepatitis B is an insidious disease, and adverse outcomes such as progression to cirrhosis, hepatic decompensation, or HCC may not be evident until decades later. In addition, patients initially randomized to the control group frequently receive treatment after completion of the trial. There has been only one report comparing the outcome of treated patients and controls. An 8-year follow-up of 101 male patients who participated in a controlled trial of IFN-α therapy in Taiwan found that treated patients had a lower incidence of HCC (1.5% vs. 12%, P = .04) and a higher survival rate (98% vs. 57%, P = .02).[80] IFN-α has not been shown to decrease the incidence of HCC in European or North American patients probably because of the low rate of HCC in untreated patients.[79,81] Studies comparing the outcome of responders versus nonresponders found that patients who cleared HBeAg had better overall survival and survival free of hepatic decompensation.[78,80,81]

Data on long-term outcome of patients treated for HBeAg-negative chronic hepatitis B showed that 20-50% of long-term responders, defined by normal ALT levels and undetectable HBV DNA by hybridization assay cleared HBsAg after 5 years of follow-up.[1,164,164b] In addition, long-term responders appear to have reduced risks of progression to cirrhosis, HCC and liver-related deaths.[62b,164,164b]

### *Lamivudine (Epivir-HBV, 3TC)*

Lamivudine is the (-) enantiomer of 2`-3` dideoxy-3`-thiacytidine. Incorporation of the active triphosphate (3TC-TP) into growing DNA chains results in premature chain termination thereby inhibiting HBV DNA synthesis.

Efficacy in Various Categories of Patients

1. HBeAg-positive chronic hepatitis B with the following (Table 7A):

*a. Persistent or intermittent elevation in ALT.* Three clinical trials involving a total of 731 treatment naïve patients who received lamivudine for 1 year reported that HBeAg seroconversion (defined as the loss of HBeAg, detection of anti-HBe, and loss of serum HBV DNA based on non-PCR assays) occurred in 16% to 18% of patients compared with 4% to 6% of untreated controls.[180-182] Histologic improvement defined as a reduction in necroinflammatory score greater than or equal to 2 points was observed in 49% to 56% treated patients and in 23% to 25% of controls. Follow-up reports of the multicenter Asian study showed that HBeAg seroconversion rates increased with the duration of treatment from 17% at 1 year to 27%, 33%, 47%, and 50% at 2, 3, 4, and 5 years, respectively.[183-185,185a] Whether the incremental HBeAg seroconversion can be attrib-

uted to the additional years of lamivudine treatment is unclear because most of the patients randomized to placebo in the second year were transferred to open-label lamivudine treatment.

Pretreatment ALT has been found to be the most important predictor of response.[186] Pooled data from 406 patients who received lamivudine 100 mg daily for 1 year showed that HBeAg seroconversion occurred in 2%, 7%, 20%, and 42% of patients with pretreatment ALT levels within normal, 1-2 times normal, 2-5 times normal, and more than 5 times normal.[187] The corresponding figures for 196 patients in the placebo group were 0%, 5%, 9%, and 15%, respectively.

*b. Normal ALT levels.* HBeAg seroconversion rate after 1 year of treatment is less than 10% in patients with pretreatment ALT levels less than 2 times normal.[186,187]

*c. Asian patients.* Asians respond similarly to lamivudine as white patients. [187]

*d. Children.* Lamivudine has been shown to be safe and efficacious in children with chronic hepatitis B. One controlled trial involved 286 children, aged 2 to 17 years, with ALT levels greater than 1.3 times normal. The children were randomized in a 2:1 ratio to lamivudine (3 mg/kg/d up to 100 mg/d) or placebo. At week 52, HBeAg seroconversion was observed in 22% lamivudine-treated children versus 13% placebo controls (p=0.06), while HBeAg loss was observed in 26% and 15% of treated and control children, respectively, (p=0.03).[187a] As with adults, HBeAg seroconversion rate was higher among children with elevated pretreatment ALT levels. HBeAg seroconversion was observed in 12%, 12%, 31%, and 50% of lamivudine-treated children who had pretreatment ALT levels within normal, 1-2 times normal, 2-5 times normal, and >5 times normal, respectively. The corresponding figures in the control group were 14%, 7%, 12%, and 24%, respectively. The adverse event profile of the two groups was similar. Lamivudine-resistant HBV mutants were detected in 19% of treated children during the 1-year period. This trial indicates that lamivudine is safe and effective in children but the benefit must be carefully balanced against the risk of selecting drug resistant mutants.

2. HBeAg-negative chronic hepatitis B (Table 7B)

Lamivudine has been shown to benefit patients with HBeAg-negative chronic hepatitis B.[188-193] In one study, virologic and biochemical response was achieved in 34 of 54 (63%) patients who received 24 weeks of lamivudine therapy versus 3 of 53 (6%) patients on placebo (P < .001). Of the 54 patients who completed 1 year of lamivudine treatment, serum HBV DNA was undetectable by bDNA assay in 65% and by PCR assay in 39% of patients, and histologic improvement was observed in 60% of patients.[188] Other studies have reported similar 1-year response rates of 70%.[189,191,193] However, the vast majority (~90%) of patients relapsed when treatment was stopped.[194] Unfortunately, extending the duration of treatment resulted in progressively lower rate of response due to the selection of lamivudine-resistant mutants. In one study of 78 patients, virologic remission (undetectable HBV DNA by PCR assay) decreased from 77% at 12 months to 52% at 24 months, and 42% at 36 months, the corresponding rates of biochemical remission were 90%, 63%, and 53%, respectively.[194a]

3. Nonresponders to IFN-α treatment

In a multicenter trial on IFN-α nonresponders, 238 patients were randomized to receive lamivudine monotherapy for 52 weeks, lamivudine for 8 weeks followed by a combination of lamivudine and IFN-α for another 16 weeks, or no treatment. Patients who received lamivudine monotherapy had the highest HBeAg seroconversion rate, 18% compared with 12% and 13%, respectively, in the other groups (not significant).[195] These data suggest that patients who failed IFN-α treatment have a similar response to lamivudine as treatment-naive patients, and retreatment with combination of IFN-α and lamivudine did not confer any added benefit compared with retreatment with lamivudine monotherapy.

4. HBsAg-positive clinical cirrhosis

Studies of lamivudine in patients with decompensated cirrhosis showed that lamivudine treatment is well tolerated and results in clinical improvement in many patients.[196-199] In one study of 35 patients (10 with Child-Pugh class C and 25 with Child-Pugh class B), improvement in liver disease defined as a decrease in Child-Pugh score of greater than 2 was observed in 22 of 23 patients who received a minimum of 6 months treatment.[197] However, 7 patients had progressive liver disease necessitating liver transplant and an additional 5 died during the first 6 months. A major concern with early treatment is the selection of resistant mutants. In the study mentioned above,[197] 3 patients developed breakthrough infection. Although all 3 remained clinically stable, more data are needed to determine the long-term outcome of cirrhotic patients who develop lamivudine resistance, and their risks of recurrent hepatitis B after liver transplantation. On the other hand, delaying treatment until patients have very advanced liver failure is unlikely to be of benefit as improvement or stabilization of liver disease takes 3-6 months. Retrospective analysis of 154 patients with HBsAg-positive decompensated cirrhosis, who received lamivudine for a median of 16 months revealed a biphasic survival pattern with most deaths (25 of 32, 78%) occurring within the first 6 months.[199] The estimated 3-year actuarial survival of patients who survived at least 6 months was 88% on continued treatment. Multivariate analyses showed that elevated pretreatment bilirubin and creatinine levels as well as detectable serum HBV DNA (by bDNA assay) were significantly associated with 6-month mortality.

Adverse Events

In general, lamivudine is very well tolerated. Various adverse events including a mild (2- to 3-fold) increase in ALT level have been reported in patients receiving lamivudine, but these events occurred in the same frequency among the controls.[180-182]

Durability of Response

Follow-up of 40 patients in phase II or III lamivudine trials conducted in non-Asian countries reported that 30 of 39 (77%) patients with HBeAg seroconversion had durable response after a median follow-up of 37 months (range, 5-46 months).[200] ALT levels were normal in 25 (63%) patients. In addition, 8 (20%) patients had HBsAg seroconversion. The estimated durability of

lamivudine-induced HBeAg seroconversion was lower (69%, 64%, and 64% at 12, 24, and 36 months, respectively) if all 65 patients who had HBeAg seroconversion were included and the time of discontinuation of lamivudine used as the starting point in the analysis. Three studies from Asia reported lower rates of durable response, 38% to 83%.[185,201,201a] In one study from Korea, 34 patients had HBeAg seroconversion after a mean duration of treatment of 9.3 ± 3.0 months.[201] Post-treatment, the cumulative relapse rates at 1 and 2 years were 38% and 49%. Most (12 of 16) relapses occurred within the first 12 months after cessation of treatment. Multivariate analysis found that duration of additional lamivudine therapy after HBeAg seroconversion and pretreatment serum HBV DNA levels were independent predictors of post-treatment relapse.

A recent report compared durability of response in 130 patients from 24 centers, who had treatment-related HBeAg seroconversion: 59 received lamivudine, 49 received IFN-α, and 22 were treated with a combination of lamivudine and IFN-α. The 3-year cumulative relapse rates were 54% for lamivudine, 32% for IFN-α, and 23% for combination therapy (p=0.01).[201b] However, these results may be biased by differences in pre-treatment characteristics of the patients as well as differences in dose and treatment duration.

Lamivudine Resistance

Selection of lamivudine-resistant mutants is the main concern with lamivudine treatment. The most common mutation affects the YMDD motif of the HBV DNA polymerase (methionine to valine or isoleucine rtM204V/I, formerly M552V/I).[202,203] This mutation is frequently accompanied by a leucine to methionine substitution in an upstream region (rtL180M formerly L528M). Lamivudine resistance is usually manifested as breakthrough infection defined as reappearance of HBV DNA in serum using an unamplified assay on two or more occasions after its initial disappearance. However, breakthrough infection also can be a result of noncompliance. Genotypic resistance can be detected in 14% to 32% after 1 year of treatment.[180-182] In the Asian study, genotypic resistance increased from 14% in year 1 to 38%, 49%, 66%, and 69% after 2, 3, 4, and 5 years of treatment, respectively.[183-185a] The clinical course of patients with lamivudine-resistant mutants is variable and the long-term outcome remains to be determined. In some patients, emergence of lamivudine-resistant mutants may be accompanied by acute exacerbations of liver disease and rarely hepatic decompensation.[204-206] However, most patients who continue treatment have lower serum HBV DNA and ALT levels initially, compared with their pretreatment levels. The continued benefit may be related to the suppressive effect of lamivudine on residual wild-type virus and the impaired replication capacity of the mutants.[207,208] In addition, HBeAg seroconversion has been reported in approximately 25% of the patients who continued treatment after the detection of lamivudine-resistant mutants.[183,204] Long-term follow-up studies suggest that over time, the initial benefit of continued treatment is negated in patients with lamivudine-resistant mutants. In one study that compared liver histology in 63 patients prior to and after 3 years of lamivudine treatment, necroinflammatory scores were improved in 77%, and worsened in 5% of patients without lamivudine-resistant mutants, but improved in only 45% and worsened in 14% of those with lamivudine-resistant mutants.[204a] Not all persons in this study had follow-up biopsies so selection bias could have influenced the outcome.

The rates of lamivudine resistance in patients treated for HBeAg-negative chronic hepatitis B appear to be more variable (0% to 27% at 1 year and 10% to 56% at 2 years).[188-190,192] The optimal duration of lamivudine therapy in persons who have an initial response is unknown. Extended treatment is associated with increasing rate of resistance and decreasing rate of remission. On the other hand, relapse occurs in 90% of responders if treatment is withdrawn after one year.[194a]

Dose Regimen

The recommended dose for adults with normal renal function (creatinine clearance >50 mL/min) and no HIV coinfection is 100 mg orally daily. The recommended dose for children is 3 mg/kg/d with a maximum dose of 100 mg/d. Dose reduction is necessary for patients with renal insufficiency. Patients with HIV coinfection should be treated with twice daily 150-mg doses in addition to other anti-retroviral therapies.

The end point of treatment for HBeAg-positive patients is HBeAg seroconversion. In general, lamivudine should be administered for 1 year as a shorter duration of therapy is associated with lower rates of HBeAg seroconversion.[180-182,209,210] Liver chemistries and quantitative HBV DNA levels preferably using a PCR assay should be monitored every 3 months while on therapy, and HBeAg and anti-HBe tested at the end of 1 year of treatment and every 3-6 months thereafter. Treatment may be discontinued in patients who have completed 1 year of treatment and have persistent HBeAg seroconversion (HBeAg loss, anti-HBe detection, and serum HBV DNA undetectable by non-PCR assays on more than one occasion determined 2-3 months apart). Durability of response after cessation of treatment is expected to be 60% to 80%. Post-treatment relapse appears to be reduced in patients if treatment is continued for an additional 3-6 months after confirmed HBeAg seroconversion. It is not clear if lamivudine can be discontinued in patients who have completed 1 year of treatment and have sustained HBeAg loss but no detectable anti-HBe. Based on data from the Korean study,[201] it is not advisable to discontinue treatment before 1 year in patients who have early HBeAg seroconversion.

Treatment may be continued in patients who have not achieved HBeAg seroconversion and have no evidence of breakthrough infection as HBeAg seroconversion may occur with continued treatment.[183] However, the benefits of continued treatment must be balanced against the risks of resistant mutants. Monitoring of serum HBV DNA levels, preferably with PCR assays will permit detection of virologic breakthrough (redetection or >1 $\log_{10}$ increase in serum HBV DNA levels after initial suppression), which usually occurs before biochemical breakthrough (increase in ALT levels after initial suppression).

In patients who have breakthrough infection, testing for lamivudine-resistant mutants should be performed when

possible, as approximately 30% of breakthrough infection has been attributed to non-compliance, and resumption of lamivudine and enforcement of compliance will result in viral suppression. For patients with confirmed lamivudine-resistance, the options include: 1) discontinue treatment and monitor for hepatitis flares, 2) continue lamivudine treatment as long as benefit to the patient is maintained, or 3) switch to or add antiviral agents such as adefovir, which are effective in suppressing lamivudine-resistant HBV. Stopping lamivudine is a reasonable option in immunocompetent patients without cirrhosis as long as they are closely monitored. Two recent reports from Asia suggest that discontinuation of lamivudine in patients with resistant mutants is not associated with increased frequency of hepatitis flares or decompensation compared to those who continued to receive lamivudine.[210a,b] However, discontinuation of lamivudine should not be attempted in patients with underlying cirrhosis or immunosuppression unless they have already been placed on adefovir. Continuing lamivudine in persons who have developed resistance should only be undertaken if a clear benefit is demonstrated by ALT and HBV DNA levels that remain significantly lower than pretreatment values. In persons who have lamivudine resistance and worsening liver disease (increasing ALT with or without hepatic decompensation), in those who had decompensated cirrhosis or recurrent hepatitis B after liver transplant, and in persons who require immunosuppressive therapy, a switch to or addition of adefovir is the best option.

Acute exacerbations of hepatitis with or without hepatic decompensation may occur after discontinuation of lamivudine therapy. Exacerbations may occur even in patients who have developed HBeAg seroconversion and may occur up to 1 year (median 4 months) after cessation of treatment.[211] Thus, all patients should be closely monitored for at least 1 year after treatment is discontinued. Reinstitution of lamivudine treatment is usually effective in controlling the exacerbations in patients who have not experienced breakthrough infection and may result in subsequent HBeAg seroconversion.[211, 192]

The end point of treatment for HBeAg-negative chronic hepatitis B is unknown. Post-treatment relapse can occur even in patients with undetectable serum HBV DNA by PCR assay. Because of the high rate of relapse when treatment is discontinued after 1 year, longer duration of treatment may be needed. However, the initial benefits may be negated during extended treatment due to selection of lamivudine-resistant mutants.

***Adefovir Dipivoxil (bis-POM PMEA, Hepsera)***

Adefovir dipivoxil is an orally bioavailable pro-drug of adefovir, a nucleotide analog of adenosine monophosphate. It can inhibit both the reverse transcriptase and DNA polymerase activity and is incorporated into HBV DNA causing chain termination. In patients receiving adefovir, HBV DNA is reduced by 3.5 to 3.9 $\log_{10}$ from baseline.[211a, 211b]

Efficacy in various categories of patients

1. HBeAg positive chronic hepatitis B (Table 7A) – In the Phase III trial, 515 patients were randomized to receive 10 or 30 mg of adefovir or placebo for 48 weeks. Histologic response, defined as ≥2 point decrease in Knodell necroinflammatory score with no worsening of fibrosis, was observed in 25%, 53%, and 59% patients who received placebo, adefovir 10 mg and 30 mg, respectively ($p<0.001$).[211a] The corresponding figures for HBeAg loss were 11%, 24%, and 27% ($p<0.001$ for both treatment groups compared to placebo), and for HBeAg seroconversion was 6%, 12%, and 14% ($p=0.049$ and $p=0.011$ for adefovir 10 mg and 30 mg groups compared to placebo). Serum HBV DNA levels decreased by a mean of 0.6, 3.5, and 4.8 $\log_{10}$ copies/mL ($p<0.001$); and normalization of ALT levels were observed in 16%, 48%, and 55% ($p<0.001$) of patients who received placebo, adefovir 10 mg and 30 mg, respectively. The side effect profiles in the three groups were similar but 8% of patients in the adefovir 30 mg dose group had nephrotoxicity (defined as increase in serum creatinine by ≥0.5 mg/dL above the baseline value on two consecutive occasions). These data demonstrated that adefovir is beneficial in patients with HBeAg positive chronic hepatitis and that the 10-mg dose has a more favorable risk-benefit profile. Clinical trials directly comparing adefovir with lamivudine have not been performed, the rate of HBeAg seroconversion among patients who received 10 mg dose of adefovir (12%) in the phase III trial was similar to that reported in randomized trials using lamivudine 100 mg (16%).[180,181]

2. HBeAg negative chronic hepatitis (Table 7B) – In the Phase III trial, 184 patients were randomized in a 2:1 ratio to receive adefovir 10 mg or placebo. At week 48, the treated group had significantly higher rates of response than the placebo group: histologic response, 64% versus 33% ($p<0.001$); normalization of ALT, 72% versus 29% ($p<0.001$); and undetectable serum HBV DNA by PCR assay, 51% versus 0 ($p<0.001$).[211b] During year 2, patients who received adefovir in year 1 were randomized in a 2:1 ratio to continue adefovir 10 mg or to receive placebo.[211c] The proportion of patients with undetectable serum HBV DNA and normal ALT increased from 46% at week 48 to 51% at week 96 in the group that received extended treatment, and decreased from 59% to 3% in the group that stopped therapy. Two (2.5%) patients who received extended treatment had nephrotoxicity.[211d]

3. Children – Adefovir has not been studied in children.

4. Decompensated cirrhosis – Adefovir has not been evaluated as a primary treatment for patients with decompensated cirrhosis.

5. Lamivudine-resistant hepatitis B – Adefovir has been shown to be effective in suppressing not only wild-type HBV but also lamivudine-resistant HBV mutants in both *in vitro*[211e] and *in vivo* studies.

*a. Decompensated cirrhosis and liver transplant recipients* – In a compassionate use study involving 128 patients with decompensated cirrhosis and 196 patients with recurrent hepatitis B after liver transplant, addition of adefovir was associated with a 3-4 $\log_{10}$ reduction in serum HBV DNA levels, which was sustained throughout the course of treatment.[211f] Virologic response was accompanied by stable or decreased ALT and Child-Pugh score. At week 48, nephrotoxicity was observed in 28% and

12% of pre- and post- transplant patients, respectively. Whether the deterioration in renal function was related to adefovir or a result of the underlying liver disease or concomitant medications such as cyclosporine or tacrolimus is unclear.

*b. Compensated liver disease* – A pilot study compared the efficacy of adefovir 10 mg alone, combination of adefovir and lamivudine, and continued treatment with lamivudine 100 mg only, in 58 patients with compensated chronic hepatitis B and lamivudine resistance.[211g] At week 48, HBV DNA suppression and ALT normalization were achieved in similar proportions of patients who received adefovir alone or combination treatment, suggesting no advantage to continuing lamivudine in patients who developed resistance and have been switched to adefovir. However, patients who discontinued lamivudine were more likely to develop ALT flares during the first 12 weeks of adefovir monotherapy.

Adverse Events

Adefovir is well tolerated and has similar side effect profile as placebo in Phase III clinical trials. However, adefovir when used in high doses has been reported to be associated with renal tubular dysfunction resembling Fanconi syndrome as well as deterioration in renal function.[211h] Because of these concerns, only the 10 mg daily dose has been approved. At this dose, none of the patients in the two Phase III trials was observed to have renal tubular dysfunction or nephrotoxicity after 48 week of treatment.[211a,b] However, nephrotoxicity has been reported in 2.5% patients with compensated liver disease during the second year of adefovir therapy, and in 12% of transplant recipients and 28% of patients with decompensated cirrhosis during the first year of therapy.[211d,f] Thus, monitoring of renal function every 3 months is necessary for patients with medical conditions that predispose to renal insufficiency and in all patients on adefovir for more than 1-year. More frequent monitoring should be performed in patients with pre-existing renal insufficiency.

Durability of Response

Data on the durability of HBeAg seroconversion after adefovir is discontinued have not been presented. Preliminary data indicate that most patients with HBeAg negative chronic hepatitis will relapse when adefovir is withdrawn after 1 year.[211c]

Adefovir Resistance

Careful analyses of the HBV polymerase gene sequences before and at the end of 1 year of treatment in the patients who participated in the Phase III trials failed to reveal any adefovir associated resistant mutations.[211i] However, analysis of the year 2 samples from patients who received extended treatment in the trial on HBeAg negative patients found that 2 of 79 patients (2.5%) had breakthrough infection and a new mutation, asparagine to threonine (rtN236T), downstream of the YMDD motif.[211j] In vitro studies confirmed that this mutation confers resistance to adefovir.

Dose regimen

The recommended dose for adults with normal renal function (creatinine clearance >50 mL/min) is 10 mg orally daily. Dosing interval should be increased in patients with renal insufficiency. Adefovir has not been approved for use in children. Adefovir at the 10 mg dose is ineffective in suppressing HIV replication.

The optimal duration of treatment is unclear. For patients with HBeAg positive chronic hepatitis, treatment may be discontinued for patients who have completed 1 year of treatment and have confirmed HBeAg seroconversion, but the durability of response is unknown. Treatment may be continued in patients who have not achieved HBeAg seroconversion but the safety and efficacy of extended treatment has not been established.

For patients with HBeAg negative chronic hepatitis, preliminary data suggest that extended treatment (beyond 1 year) is needed to maintain the response.[211c] Whether the rate of response will increase with longer duration of treatment is unclear. Because of the occurrence, albeit at a low rate, of nephrotoxicity and adefovir-resistance during the second year,[211h,j] close monitoring is required. Further studies are needed to determine the optimal duration of therapy and to establish the efficacy and safety of long-term adefovir treatment.

For patients with lamivudine-resistant mutants, particularly those with decompensated cirrhosis or recurrent hepatitis B post-transplant, long-term treatment will be required. Data from a small number of patients with compensated liver disease suggest that patients with lamivudine resistance may discontinue lamivudine when adefovir is added. These data need to be confirmed in larger number of patients, and in patients with decompensated liver disease as well as in transplant recipients.

### *Other Therapies*

Famciclovir

Famciclovir is the oral prodrug of penciclovir. Clinical studies showed that famciclovir is well tolerated and effective in suppressing HBV replication but its antiviral effect is less potent than that of lamivudine. A phase III clinical trial of 417 patients with HBeAg-positive chronic hepatitis B found a higher rate of HBeAg seroconversion compared with controls, 9% versus 3%.[212] Resistance to famciclovir including L180M (L528M) mutation has been reported.[213] In view of the low efficacy, need for thrice daily administration, and potential for cross-resistance with lamivudine, it is unlikely that famciclovir will have a major role in the treatment of chronic hepatitis B.

Entecavir

Entecavir, a carbocyclic analogue of 2'-deoxyguanosine, inhibits HBV replication at three different steps: the priming of HBV DNA polymerase, the reverse transcription of the negative strand HBV DNA from the pregenomic RNA, and the synthesis of the positive strand HBV DNA. *In vitro* studies showed that entecavir is more potent than lamivudine and adefovir and is effective against lamivudine-resistant HBV mutants although the activity against the dual mutants is significantly less than that of wild-type HBV.[214]

Phase II clinical trials showed that entecavir in doses of 0.1

and 0.5 mg daily decreased serum HBV DNA levels by 4 $\log_{10}$ copies/mL compared to 3 $\log_{10}$ copies/mL with lamivudine 100 mg daily.[215, 215a] Adverse events were mild and similar to those of lamivudine. Phase III clinical trials are ongoing.

*In vivo* efficacy of entecavir in patients with lamivudine resistance was evaluated in a double-blind trial in which 181 patients with compensated liver disease and lamivudine resistance were randomized to receive entecavir (0.1, 0.5 or 1.0 mg) or lamivudine 100 mg daily.[215b] At week 48, serum HBV DNA decreased by 2.8, 4.4, 5.0, and 1.4 $\log_{10}$ copies/mL, respectively, in the four treatment groups. Entecavir was also reported to be safe and effective in a pilot study of 9 liver transplant recipients with allograft infection and lamivudine resistance.[215c]

Tenofovir

Tenofovir disoproxil fumarate (TDF) is an acylic nucleotide reverse transcriptase inhibitor, closely related to adefovir. It has been approved for the treatment of HIV infection. Tenofovir has been shown to have significant activity against HBV, both wild-type virus and lamivudine-resistant HBV mutants.

Tenofovir has not been systematically evaluated in patients with HBV infection alone. However, several studies have evaluated the effect of tenofovir in patients with HIV and HBV co-infection, particularly patients who have developed lamivudine resistance.[216, 216a, 216b] All studies showed that tenofovir in doses of 300 mg daily, decreased serum HBV DNA levels by 3-4 $\log_{10}$ copies/mL, and appeared to have similar efficacy against wild-type and lamivudine-resistant HBV.

Compared to adefovir, tenofovir has been regarded to be associated with a lower risk of nephrotoxicity although safety data of tenofovir beyond 24 weeks are limited. Cases of nephrotoxicity and even Fanconi syndrome have been reported[216c] but co-morbid conditions may have contributed to these problems in some of the patients.

The efficacy of tenofovir against HBV at the approved dose for HIV infection makes it the treatment of choice for patients with HBV and HIV coinfection who require anti-retroviral therapy, particularly those with lamivudine-resistant infection. Because of the paucity of data on long-term safety and efficacy of tenofovir in HBV infection, it should not be used as a first-line treatment for patients who are not coinfected with HIV.

Other Antiviral Agents

Other antiviral agents that have shown promise in clinical trials include emtricitabine (FTC),[217] b-L nucleosides (LdT and LdC),[218, 218a] and clevudine (L-FMAU).[219]

Thymosin

Thymic-derived peptides can stimulate T-cell function. Clinical trials have shown that thymosin is well tolerated but data on efficacy are conflicting.[220-223] Thus, more studies are needed before thymosin can be recommended for treatment of chronic hepatitis B.

### *Combination Therapies*

Combination therapies may have additive or synergistic antiviral effects and reduce or delay resistance. Combination therapies have been proven to be more effective in the treatment of chronic HCV and HIV infections. The potential disadvantages of combination therapies include added costs, increased toxicities, and drug interactions.

IFN-α and Lamivudine.

Combination therapy of IFN-α and lamivudine has been evaluated in several studies.

1. HBeAg positive patients – In one study, 226 treatment-naïve patients were randomized to receive lamivudine monotherapy for 52 weeks or IFN-α alone for 16 weeks or lamivudine for 8 weeks followed by lamivudine and IFN-α for 16 weeks. At week 52, the rates of HBeAg seroconversion were 18%, 19%, and 29% in the groups that received lamivudine monotherapy, IFN-α monotherapy, and combination therapy, respectively (not significant).[182] These data indicate that a 1-year course of lamivudine has similar antiviral efficacy to a 16-week course of IFN-α in treatment-naïve patients, and the combination of lamivudine and IFN-α does not seem to have any added benefit. Similar results were reported in the other study on IFN-α nonresponders.[195] However problems in the design of these two studies including sample size, shorter duration of lamivudine therapy (24 vs. 52 weeks) in the group that received combination therapy, and timing of the second biopsy (28 weeks post-treatment vs. on-treatment) prevent a definitive conclusion concerning the efficacy of combination therapy of IFN-α and lamivudine. Studies using other regimens are ongoing. Until further data are available, combination therapy of IFN-α and lamivudine is not recommended.

2. HBeAg negative patients – In one study, 50 patients were randomized to receive lamivudine (100 mg daily) alone or lamivudine plus IFN-α (5 MU three times weekly) for 12 months.[223a] While no significant differences were observed in initial response rates or relapse rates following discontinuation of therapy, fewer patients in the combination group developed lamivudine-resistant mutations during therapy.

Lamivudine and Famciclovir

In vitro and in vivo studies in woodchucks showed that lamivudine and penciclovir have additive or synergistic antiviral effects. A pilot study found that a short course of combination therapy of lamivudine and famciclovir have added antiviral efficacy.[224] Whether these effects will translate into higher rates of sustained antiviral response or lower rates of resistant mutants remain to be determined.

Lamivudine and Adefovir

Combination therapy of lamivudine and adefovir has been evaluated mostly in patients with lamivudine resistance. One double-blind trial randomized 115 HBeAg positive nucleoside-naïve patients to receive lamivudine (100 mg) alone or combination of lamivudine and adefovir (10 mg).[224a] Preliminary data at the end of 1 year found that combination therapy was not associated with a higher rate of response; HBeAg loss was observed in 19% in the combination group and in 20% in the lamivudine monotherapy group. However, combination therapy was associated with a significantly lower

rate of lamivudine resistance: 2% versus 20% in the lamivudine monotherapy group.

### *Coinfection with HBV and HDV*

The primary endpoint of treatment is the suppression of HDV replication, which is usually accompanied by normalization of ALT level and necroinflammatory activity on liver biopsy. In most countries, the only approved treatment of chronic hepatitis D is IFN-α. Data on the efficacy of IFN-α in chronic hepatitis D are limited. One trial on 61 patients comparing IFN-α in doses of 3 to 5 MU/m$^2$ 3 times a week for 12 months versus placebo found that there was no difference in sustained virologic response between treated patients and controls, and only 1 patient had sustained biochemical response.[225] Another randomized trial on 42 patients found that patients who received high dose (9 MU 3 times a week) IFN-α had higher rates of virologic and biochemical as well as histologic response than those who received IFN-α 3 MU 3 times a week or placebo.[226] Although most patients had virologic relapse, improvement in liver histology was maintained 10 years post-treatment among the patients who received high-dose IFN-α.[227]

Lamivudine has been evaluated in a small number of patients and found to be ineffective in inhibiting HDV replication.[228]

Based on available data, high-dose IFN-α (9 MU 3 times a week) for 1 year appears to have long-term beneficial effects in patients with chronic hepatitis D. Because of the rarity of hepatitis D, patients with chronic hepatitis D should be referred to specialized centers for treatment.

### *Antiviral Prophylaxis of Hepatitis B Carriers Who Receive Immunosuppressive or Cytotoxic Chemotherapy*

Reactivation of HBV replication with increase in serum HBV DNA and ALT level has been reported in 20% to 50% of hepatitis B carriers undergoing immunosuppressive or cancer chemo therapies. In most instances, the hepatitis flares are asymptomatic, but icteric flares, and even hepatic decompensation and death have been observed.[229-230] Reactivation of HBV replication is more common when chemotherapeutic regimens that include corticosteroids are used.[231] Uncontrolled studies showed that propyhlactic therapy with lamivudine can reduce the rate of HBV reactivation, severity of associated hepatitis flares and mortality.[232-234] Because of the potential for fatal hepatitis flares, HBsAg testing should be performed in persons who have high risk of HBV infection, prior to initiation of chemo or immunosuppressive therapy. It seems prudent to administer prophylactic antiviral therapy to hepatitis B carriers at the onset of cancer chemotherapy or a finite course of immunosuppressive therapy, and to maintain antiviral therapy for 6 months afterwards. The benefit versus risk of prophylactic antiviral therapy in hepatitis B carriers who require life-long immunosuppressive therapy is less certain. One approach would be to monitor these patients and initiate antiviral therapy when there is a significant increase in serum HBV DNA or ALT level but the threshold values for initiation of antiviral therapy are unclear. A recent study found that the vast majority (11/12) of HBsAg positive patients who were closely monitored after renal transplantation met pre-defined criteria for lamivudine treatment.[234] Studies to date have focused on lamivudine; adefovir may be used as an alternative treatment in patients who are not at risk of renal insufficiency. IFN-α should not be used in this setting because of its bone marrow suppressive effects and the risk of hepatitis flares.

While HBV reactivation can occur in persons who are HBsAg negative but anti-HBc and anti-HBs positive, this is infrequent, and there is not enough information to recommend prophylaxis for these individuals at this time.[229,230]

## Recommendations for the Treatment of Chronic Hepatitis B

*Who to treat and what treatment to use* (Table 8 and 9): Current therapy of chronic hepatitis B has limited long-term

**Table 8**

**COMPARISON OF THREE APPROVED TREATMENTS OF CHRONIC HEPATITIS B**

| | IFNα | LAMIVUDINE | ADEFOVIR |
|---|---|---|---|
| ***Indications*** | | | |
| HBeAg+, normal ALT | Not indicated | Not indicated | Not indicated |
| HBeAg+ chronic hepatitis | Indicated | Indicated | Indicated |
| HBeAg- chronic hepatitis | Indicated | Indicated | Indicated |
| ***Duration of treatment*** | | | |
| HBeAg+ chronic hepatitis | 4-6 months | ≥ 1 year | ≥ 1 year |
| HBeAg- chronic hepatitis | 1 year | > 1 year | > 1 year |
| ***Route*** | Subcutaneous | Oral | Oral |
| ***Side effects*** | Many | Negligible | Potential nephrotoxicity |
| ***Drug resistance*** | - | ~20%, year 1<br>~70%, year 5 | None, year 1<br>~3%, year 2 |
| ***Cost**** | High | Low | Intermediate |

**Based on treatment duration of 1 year*

**Table 9**

**RECOMMENDATIONS FOR TREATMENT OF CHRONIC HEPATITIS B**

| HBeAg | HBV DNA* | ALT | Treatment strategy |
|---|---|---|---|
| + | + | ≤2 x ULN | Low efficacy with current treatment.<br>Observe; consider treatment when ALT becomes elevated. |
| + | + | > 2 x ULN | IFNα , LAM or ADV may be used as initial therapy.<br>End-point of treatment – Seroconversion from HBeAg to anti-HBe<br>Duration of therapy<br>• IFNα: 16 weeks<br>• Lamivudine: minimum 1 year, continue for 3-6 months after HBeAg seroconversion<br>• Adefovir: minimum 1 year<br>IFNα non-responders / contraindications to IFNα → LAM or ADV.<br>LAM resistance → ADV. |
| - | + | > 2 x ULN | IFNα, LAM or ADV may be used as initial therapy, IFNα or ADV is preferred because of the need for long-term therapy.<br>End-point of treatment – sustained normalization of ALT and undetectable HBV DNA by PCR assay.<br>Duration of therapy<br>• IFNα: 1 year<br>• Lamivudine: > 1 year<br>• Adefovir: > 1 year<br>IFNα non-responders / contraindications to IFNα → LAM or ADV.<br>LAM resistance → ADV. |
| - | - | ≤ 2 x ULN | No treatment required. |
| +/- | + | Cirrhosis | Compensated: LAM or ADV<br>Decompensated: LAM, coordinate treatment with transplant center. Refer for liver transplant |
| +/- | - | Cirrhosis | Compensated: Observe.<br>Decompensated: Refer for liver transplant |

*HBV DNA >$10^5$ copies/ml, this value is arbitrarily chosen.

LAM = Lamivudine

ADV = Adefovir

efficacy. Thus, careful consideration of patient's age, severity of liver disease, likelihood of response, and potential adverse events and complications is needed before treatment is initiated. Except for patients with contraindications or previous non-response to specific therapy, either IFN-α, lamivudine or adefovir may be used as initial therapy for patients with compensated liver disease. The advantages of IFN-α include a finite duration of treatment, a more durable response and the lack of resistant mutants. The disadvantages of IFN-α are the costs and side effects. Lamivudine is more economical (if given for 1 year only) and well tolerated but the durability of response appears to be lower, and long-term therapy is associated with increasing risk of drug-resistant mutants which may negate the initial benefits and in some patients result in worsening of liver disease. The main advantages of adefovir include its activity against lamivudine-resistant mutants and a very low rate of adefovir resistance during initial therapy. However, adefovir is significantly more costly than lamivudine, and the durability of response, long-term safety and risk of drug resistance remain to be determined. In choosing which antiviral agent to use as the first-line therapy, consideration should be given to the costs of the medication, monitoring tests, and clinic visits; as well as patient and provider preferences.

**13. Patients with HBeAg-positive chronic hepatitis B**

***a. ALT greater than 2 times normal or moderate/severe hepatitis on biopsy.*** **These patients should be considered for treatment. Treatment should be delayed for 3 to 6 months in persons with compensated liver disease to determine if spontaneous HBeAg seroconversion occurs. Treatment may result in virologic, biochemical, and histologic response (I) and also appear to improve clinical outcome (II-3). Treatment may be initiated with IFNα,**

lamivudine, or adefovir as the 3 treatments have similar efficacy.

*b. ALT persistently normal or minimally elevated (<2 times normal).* These patients should not be initiated on treatment. Liver biopsy may be considered in patients with fluctuating or minimally elevated ALT levels, and treatment initiated if there is moderate or severe necroinflammation (I).

*c. Children with elevated ALT greater than 2 times normal.* These patients should be considered for treatment if ALT levels remain elevated at this level for longer than 6 months. (I). Both IFN-α and lamivudine are approved treatments for children with chronic hepatitis B.

14. Patients with HBeAg-negative chronic hepatitis B (serum HBV DNA $>10^5$ copies/mL, elevated ALT >2 times normal or moderate/severe hepatitis on biopsy) should be considered for treatment (I). Treatment may be initiated with IFN-α, lamivudine or adefovir (I for adefovir and II-1 for IFN-α and lamivudine). In view of the need for long-term treatment, IFN-α or adefovir is preferred.

15. Patients who failed to respond to prior IFN-α therapy may be retreated with lamivudine or adefovir if they fulfill the criteria listed above (I).

16. Persons who develop breakthrough infection while on lamivudine should be treated with adefovir especially if there is worsening of liver disease, if they had decompensated cirrhosis or recurrent hepatitis B after liver transplant, or if they require concomitant immunosuppressive therapy (II-2).

17. Patients with compensated cirrhosis are best treated with lamivudine or adefovir because of the risk of hepatic decompensation associated with IFN-α related flares of hepatitis.

18. Patients with decompensated cirrhosis should be considered for lamivudine treatment (III-3). Adefovir may be used as an alternative to lamivudine, although it has not been evaluated as a primary treatment in these patients. If adefovir is used, close monitoring of renal function with testing of BUN and creatinine every 1-3 months should be performed. Treatment should be coordinated with transplant centers. IFN-α should not be used in patients with decompensated cirrhosis (II-3).

19. In patients with inactive HBsAg carrier state antiviral treatment is not indicated.

*Dose Regimens*

20. IFN-α is administered as subcutaneous injections.

*a. The recommended IFN-α dose for adults is 5 MU daily or 10 MU thrice weekly (I).*

*b. The recommended IFN-α dose for children is 6 MU/m² thrice weekly with a maximum of 10 MU (I).*

*c. The recommended treatment duration for HBeAg-positive chronic hepatitis B is 16 weeks (I).*

*d. The recommended treatment duration for HBeAg-negative chronic hepatitis B is 12 months (II-3).*

(21). Lamivudine is administered orally.

*a. The recommended lamivudine dose for adults with normal renal function and no HIV coinfection is 100 mg daily (I).*

*b. The recommended lamivudine dose for children is 3 mg/kg/d with a maximum of 100 mg/d (I).*

*c. The recommended treatment duration for HBeAg-positive chronic hepatitis B is a minimum of 1 year.* Patients in whom HBeAg seroconversion has occurred should be maintained on treatment for 3-6 months after HBeAg seroconversion is confirmed (two occasions at least 2 months apart) to reduce post-treatment relapse. Treatment may be continued in patients who have not developed HBeAg seroconversion. Treatment may be continued in patients who have breakthrough infection due to lamivudine-resistant mutants as long as benefit to the patient (based on clinical assessment, ALT, and HBV DNA level) is maintained (I). Adefovir should be considered especially in patients with worsening of liver disease and in those who require immunosuppressive therapy.

*d. The recommended treatment duration for HBeAg negative chronic hepatitis B is longer than 1 year but the optimal duration has not been established (II-3).*

*e. The recommended dose of lamivudine for persons co-infected with HIV is 150 mg twice daily, along with other antiretroviral medications (I).*

(22). Adefovir is administered orally.

*a. The recommended adefovir dose for adults with normal renal function is 10 mg daily (I).*

*b. The recommended treatment duration for HBeAg positive chronic hepatitis B is a minimum of 1 year.* The benefits versus risks of longer duration of treatment are unknown (I).

*c. The recommended treatment duration for HBeAg negative chronic hepatitis B is longer than 1 year.* Longer duration of treatment is likely necessary for sustained response but the optimal duration of treatment and the benefits versus risks of longer duration of treatment remain to be determined (I).

*d. The recommended treatment duration for patients with lamivudine-resistant mutants has not been determined.* Long-term treatment is required particularly for patients with decompensated cirrhosis or allograft infection. There appears to be no advantage to continuing lamivudine therapy in patients with compensated liver disease who have been switched to adefovir (III).

### Recommendations for Antiviral Prophylaxis of Hepatitis B Carriers Who Receive Immunosuppressive or Cytotoxic Therapy

23. HBsAg testing should be performed in persons who have high risk of HBV infection, prior to initiation of chemotherapy or immunosuppressive therapy (III).

24. Prophylactic antiviral therapy with lamivudine is recommended for HBV carriers at the onset of cancer chemotherapy or of a finite course of immunosuppressive therapy and maintained for 6 months after completion of chemotherapy or immunosuppressive therapy (III).

## Appendix

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## Author Disclosures

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*Abbreviations:* HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HBeAg, hepatitis B e antigen; cccDNA, covalently closed circular DNA; anti-HBe, antibody to hepatitis B e antigen; ALT, alanine aminotransferase; anti-HBs, antibody to hepatitis B surface antigen; PCR, polymerase chain reaction; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HDV, hepatitis D virus; HBIG, hepatitis B immunoglobulin; AFP, alpha fetoprotein; US, ultrasonography; DCP, des-γ-carboxy prothrombin; IFN, interferon.

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