Chronic Hepatitis B: Update of Recommendations

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An estimated 350 million persons worldwide and 1.25 million in the United States are infected with hepatitis B virus (HBV). Hepatitis B carriers are at risk for development of cirrhosis and hepatocellular carcinoma (HCC). The natural history of chronic HBV infection is variable. Persons with chronic HBV infection need lifelong monitoring to determine if and when intervention with antiviral therapy is needed and to observe for serious sequelae. These guidelines were developed under the auspices of, and approved by, the Practice Guidelines Committee of the American Association for the Study of Liver Diseases. The original guidelines were published in HEPATOLOGY 2001;34:1225–1241.[1] In light of recent progress, particularly in the treatment of chronic hepatitis B, these guidelines were updated in September of 2003. A complete version of the updated guidelines, including a review of recently published literature, can be found at the AASLD web site, www.aasld.org. Following is a summary of the updated recommendations for treatment of chronic hepatitis B. The recommendations were graded as 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), and III (opinions of respected authorities, descriptive epidemiology).

Summary of Recent Literature on the Treatment of Chronic Hepatitis B

Lamivudine

Approved for Use in Children. In a controlled trial that involved 286 children aged 2 to 17 years, randomized to lamivudine (3 mg/kg/d up to 100 mg/d) or placebo, hepatitis B e antigen (HBeAg) seroconversion was observed in 22% lamivudine-treated children versus 13% placebo controls ($P = .06$), while HBeAg loss was observed in 26% and 15%, respectively ($P = 0.03$).[2] HBeAg seroconversion rate was higher among children with elevated alanine aminotransferase (ALT) levels. Lamivudine-resistant mutation was detected in 19% of treated children during the 1-year period.

Durability of HBeAg Seroconversion. Among patients who experienced HBeAg seroconversion during lamivudine treatment, the durability of response after cessation of therapy has ranged from 38% to 77%.[3–5] The 3-year cumulative relapse rate varied from 36% to 54%, with most of the relapses occurring during the first year posttreatment.

Lamivudine Resistance. The risk of developing lamivudine resistance increases with the duration of therapy. In a study from Asia, genotypic resistance increased from 14% in year 1 to 38%, 49%, 66%, and 69% after 2, 3, 4, and 5 years, respectively, of treatment.[6] Long-term follow-up studies showed that over time, the initial benefit 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.[7]

For patients with confirmed lamivudine-resistance, the options include continuing lamivudine treatment as long as benefit to the patient (based on clinical assessment, ALT, and HBV DNA levels) is maintained; discontinuing treatment and monitoring for hepatitis flares; or switching to other antiviral agents such as adefovir, which are effective in suppressing lamivudine-resistant HBV. 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 with those who continued to receive lamivudine.[8,9] Thus, stopping lamivudine is a reasonable option for immunocompetent patients without cirrhosis, as long as they are closely monitored; but patients with underlying cirrhosis or immunosuppression should be switched to adefovir before stopping lamivudine.

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase; IFN-α, interferon alfa; HBsAg, hepatitis B surface antigen.

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Adefovir Dipivoxil

Adefovir dipivoxil is an orally bioavailable prodrug of adefovir, a nucleotide analog of adenosine monophosphate that inhibits both HBV reverse transcriptase and DNA polymerase activity. Adefovir has been shown to be effective in suppressing not only wild-type HBV but also lamivudine-resistant HBV mutants.

HBeAg-Positive Patients. In a randomized trial of 515 patients with HBeAg-positive chronic hepatitis B treated with 30-mg or 10-mg doses of adefovir or placebo for 48 weeks, a significantly higher proportion of adefovir-treated patients had histologic response, HBeAg loss, normalization of ALT levels, and reduction of HBV DNA, compared with those who received placebo (all $P < .001$).[10] HBeAg seroconversion was observed in 12% of the adefovir and 6% of the placebo groups ($P = .049$).

HBeAg-Negative Patients. In a trial of 184 patients with HBeAg-negative chronic hepatitis B who were randomized to receive adefovir 10 mg or placebo for 48 weeks, histologic response, normalization of ALT, and undetectable serum HBV DNA by polymerase chain reaction assay were observed significantly more frequently in the treatment group (all $P < .001$).[11] During year 2, the proportion of patients with undetectable serum HBV DNA and normal ALT levels increased from 46% at week 48 to 51% at week 96 among those who continued treatment, and decreased from 59% to 3% among those in whom therapy was stopped.[12]

Patients With Lamivudine Resistance. In a compassionate-use study involving 128 patients with decompensated cirrhosis and 196 patients with recurrent hepatitis B after liver transplant, with lamivudine resistance, 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.[13] Virologic response was accompanied by stable or decreased ALT and Child-Pugh score. A pilot study in 58 patients with compensated chronic hepatitis B and lamivudine resistance found that adefovir alone had similar efficacy as combination treatment of lamivudine and adefovir in suppressing replication of lamivudine-resistant HBV.[14]

Safety. Adefovir has not been evaluated in children. Nephrotoxiciy (increase in serum creatinine by $\geq$0.5 mg/dL above baseline values on two consecutive occasions) was observed in 8% of patients who received adefovir 30 mg for 1 year and in none of the patients with compensated liver disease who received adefovir 10 mg for 1 year. However, nephrotoxicity has been reported in 2.5% of patients with compensated liver disease who received 2 years of adefovir 10 mg, and in 12% of transplant recipients and 28% of patients with decompensated cirrhosis who received 1 year of adefovir 10 mg.[13,15]

Dose Regimen. The recommended dose of adefovir for adults with normal renal function is 10 mg daily orally. Dosing interval should be increased in patients with renal insufficiency. The optimal duration of adefovir treatment is unclear. Data on the durability of HBeAg seroconversion after adefovir is discontinued have not been presented. Preliminary data indicate that patients with HBeAg negative chronic hepatitis will require long-term treatment as most patients will relapse when adefovir is withdrawn after 1 year.[14] Based on experience with lamivudine, consideration should be given to treating patients in whom HBeAg seroconversion has occurred for an additional 3 to 6 months after HBeAg seroconversion is confirmed (two occasions at least 2 months apart) to reduce post-treatment relapse. Long-term treatment will also be required for patients with lamivudine-resistant mutants, particularly those with decompensated cirrhosis or recurrent hepatitis B posttransplant.

Adefovir Resistance. A major advantage of adefovir is the lack of resistance after the first year of therapy, but drug-resistant mutation, asparagine to threonine (rtN236T), downstream of the YMDD motif, has been reported in 2 of 79 (2.5%) patients with HBeAg-negative chronic hepatitis B during the second year of therapy.[16] *In vitro* studies confirmed that this mutation confers resistance to adefovir, but the resistant mutant appears to be susceptible to lamivudine and entecavir.

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

Reactivation of HBV replication with hepatitis flares and rarely hepatic decompensation have been reported to occur in 20% to 50% of hepatitis B carriers undergoing immunosuppressive or cancer chemotherapies, especially when corticosteroids are included.[17,18] Administration of lamivudine has been reported to reduce the frequency and severity of the hepatitis flares, and to improve survival compared to historical controls.[17,19]

Recommendations for Monitoring Patients With Chronic HBV Infection

1. 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 HBe antibody prior to initiation of treatment (III).

2. 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).

3. Patients in the inactive hepatitis B surface antigen (HBsAg) carrier state should be monitored with periodic

Table 1. Comparison of Three Approved Treatments of Chronic Hepatitis B

	IFN-α	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 ~70%, year 5	None, year 1 ~3%, year 2
Cost*	High	Low	Intermediate

Abbreviations: IFN-α, interferon alfa; HBeAg, hepatitis B e antigen.
*Based on treatment duration of 1 year.

liver chemistries every 6 to 12 months, as liver disease may become active even after many years of quiescence (III).

Recommendations for the Treatment of Chronic Hepatitis B

Who to treat and what treatment to use (Tables 1 and 2). Current therapy of chronic hepatitis B has limited long-term efficacy. Thus, careful balance of patient 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 nonresponse 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, 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 an increasing risk of drug-resistant mutants that 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. Adefovir is significantly more costly than lamivudine, and the durability of response and its long-term safety and risk of drug resistance remain to be determined. All three medications are FDA approved as first-line therapy. In choosing which antiviral agent to use as the first-line therapy, consideration should be given not only to long-term safety and efficacy but also the costs of the medication, monitoring tests, and clinic visits, as well as patient and provider preferences.

Table 2. Recommendations for Treatment of Chronic Hepatitis B

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

Abbreviations: HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase; ULN, upper limit of normal; IFN-α, interferon alfa; LAM, lamivudine; ADV, adefovir; PCR, polymerase chain reaction.
*HBV DNA > 10^5 copies/mL; this value is arbitrarily chosen.

4. 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 whether 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 IFN-α, 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 (I). Liver biopsy may be considered in patients with fluctuating or minimally elevated ALT levels and treatment initiated if there is moderate or severe necroinflammation.
   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.

5. 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 IFNα and lamivudine). In view of the need for long-term treatment, IFNα or adefovir is preferred.

6. 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).

7. Persons who develop breakthrough infection while on lamivudine should be treated with adefovir 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).

8. 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.

9. 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 blood urea nitrogen and creatinine every 1 to 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).

10. For patients with an inactive HBsAg carrier state, antiviral treatment is not indicated.

Dose Regimens

11. IFN-α is administered as subcutaneous injections.
   A. *The recommended IFN-α dose for adults is 5 million units (MU) daily or 10 MU thrice weekly (I).*
   B. *The recommended IFN-α dose for children is 6 MU/m^2 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).*
12. 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 (I).* Patients in whom HBeAg seroconversion has occurred should be maintained on treatment for 3 to 6 months after HBeAg seroconversion is confirmed (two occasions at least 2 months apart) to reduce posttreatment 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 level, and HBV DNA level) is maintained.
   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 coinfected with HIV is 150 mg twice daily, along with other antiretroviral medications (I).*
13. 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. For patients with compensated liver disease, there appears to be no advantage to continuing lamivudine therapy in patients switched to adefovir but an overlap period of 2–3 months is advisable to minimize the risk of hepatitis flares during the transition (III).

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

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

15. 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).

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