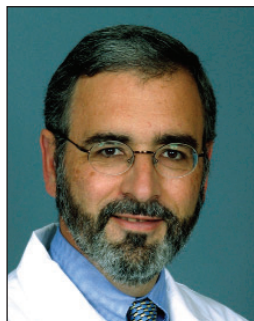


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Chronic Hepatitis B: Who and How to Treat



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INTRODUCTION

Chronic hepatitis B (HBV) is a potentially serious disease that can lead to cirrhosis, liver failure, and hepatocellular carcinoma. It is estimated that 350-400 million people worldwide are infected with chronic HBV (1) with 500,000 deaths per year due to complications (2). In the United States there are an estimated 1.25 million people with chronic HBV, but this estimate fails to take into account immigrants from endemic regions and persons who are incarcerated (3). Chronic HBV is diagnosed by the presence of hepatitis B surface antigen (HBsAg) in serum on two occasions separated by six months.

Several effective pharmacologic therapies are available for use in treatment; however, who and how to treat can be complicated and confusing given the variability in disease progression, variable individual patient response, and the different advantages and disadvantages of each treatment modality. Patient selection is the key to having the best chance at a remission or cure with treatment. Which patients to treat is further complicated by several recent consensus statements and the 2007 AASLD guidelines, all of which have subtle differences

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on who and how to treat (4–8). Additionally, a recent appraisal of treatment strategies for hepatitis B found disagreement even among experts in the field (9). The criteria used to select patients for treatment are based on serologic, virologic, and histologic parameters.

NATURAL HISTORY

Hepatitis B is spread parenterally. This can occur through perinatal transmission, or through contact with infected blood or body fluids. Risk factors include high-risk sexual behavior, intravenous drug use, children of mothers with HBV, and those who are exposed to blood products. The age at which one becomes infected determines presence of symptoms and chance of progression to chronic disease. In children less than five years old, jaundice occurs in less than 10%, while 30%–90% of those infected will progress to chronic HBV. In patients over the age of five, jaundice is more frequent, occurring in 30% to 50%, and only 2% to 10% of those infected develop chronic HBV. Acute HBV has a case-fatality rate of 0.5% to 1%, and 15% to 25% of all who are infected develop pre-mature mortality from chronic liver disease. Patients with chronic HBV progress through 4 stages (discussed later) with 15% to 40% progressing to cirrhosis, hepatocellular carcinoma, or liver failure.

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PATIENT EVALUATION

The initial approach to chronic HBV patients should be systematic and organized. It should include a thorough history and physical examination with special focus on risk factors for co-infection, alcohol use, and family history of HBV infection and liver cancer. Laboratory tests should include assessment of liver disease, HBV-DNA level by polymerase chain reaction, assays for hepatitis B e-antigen (HBeAg), hepatitis B e-antibody (HBeAb), and tests for co-infection with HCV or HIV. For those at risk, such as intravenous drug users or persons from endemic areas, testing for hepatitis D co-infection is recommended. Vaccination for hepatitis A should also be administered to those not already immune.

After establishing a diagnosis of chronic hepatitis B infection based on two separate positive HBsAg six months apart, and the results of the above tests, patients can be divided into one-of-four groups based on virologic and serologic markers. 1) Immune tolerant 2) Immune reactive 3) Inactive carrier 4) e-Antigen negative reactivation. Once patients are categorized into one of the above groups rational decisions for treatment can be made. The characteristics of these phases are summarized in Table 1.

IMMUNE TOLERANT PHASE

This phase is characterized by high levels of circulating viral DNA (>20,000 IU/mL or >100,000 copies/mL), normal ALT levels, positive e-antigen, negative e-antibody, and minimal to no inflammatory changes on liver biopsy. This period may vary from decades in those infected at birth to only a few weeks in those infected as adults. In acute infections this is considered the incubation period. During this time, the infected hepatocytes are not recognized by the immune system so minimal if any damage occurs to the liver. Patients in this phase usually do not progress to severe liver disease and have less than a 5% a year risk of developing cirrhosis (10).

Since there is a very weak or no immune system recognition in this phase, current treatment options cannot effectively control viral replication and rarely induce long-term remission. For this reason treatment is not recommended in this phase. Patients in this phase who have a fluctuating or minimally elevated ALT may be considered for liver biopsy. A biopsy may also be

considered in patients with a viral load >20,000 IU/mL, in patients over 40-years-of-age, or in those patients with ALT levels in the upper limits of normal. If moderate necroinflammation or significant fibrosis is present then treatment should be considered. It should be understood however, that treatment in this scenario will require long-term therapy (years) with little chance of achieving a sustained remission. Although the natural history of the immune tolerant patient has traditionally been considered benign, recent data suggests otherwise: Data from the REVEAL-HBV study group, which followed 3,500 Taiwanese patients with chronic HBV for a mean of 11 years in respect to natural history, found that the risk of both hepatocellular carcinoma and cirrhosis increased as viral loads increased, independently of other risk factors, including patients with normal ALT levels (35,36) Currently there is no recommendation to treat based on viral load if transaminases and biopsy are normal.

During the course of chronic HBV, for unknown reasons, patients in this phase will enter the immune reactive phase signaled by an increase in transaminases, inflammation on biopsy, and a decrease in viral load. It is this time that treatment offers the best chance at a sustained response.

IMMUNE REACTIVE PHASE

This phase represents the immune system recognition and lysis of infected hepatocytes. Characteristic findings are elevated liver enzymes and necroinflammatory activity on liver biopsy. Viral load can fluctuate but is generally high (>20,000 IU/mL). This phase has a variable time length and may last from months to years. The severity and duration of this phase determines the risk of liver disease progression. These patients are the most likely to benefit from treatment. The active immune response increases the likelihood of obtaining a durable remission with antiviral therapy. If left untreated, the ongoing inflammation puts these patients at increased risk for cirrhosis and complications such as hepatocellular carcinoma. While patients with both high viral load and persistent high ALT have an increased chance at spontaneous seroconversion, they also have the highest risk of disease progression and are the best candidates for antiviral treatment.

Table 1
Phases of Chronic Hepatitis B

<i>Phase</i>	<i>Immune Tolerant</i>	<i>Immune Reactive</i>	<i>Inactive Carrier</i>	<i>e-Antigen Reactivation</i>
ALT	Normal (<1X ULN [#])	Elevated (>2X ULN)	Normal (<1X ULN)	Elevated (>1-2X ULN)
HBV DNA	>20,000 IU/mL (>10 ⁵ copies/mL)	>20,000 IU/mL (>10 ⁵ copies/mL)	<2000 IU/mL (<10 ⁴ copies/mL)	>2000 IU/mL (>10 ⁴ copies/mL)
e-antigen	Positive	Positive	Negative	Negative
e-antibody	Negative	Negative	Positive	Positive
Liver Biopsy	Inactive	Active	Inactive	Active
Treatment	Not Recommended*	Recommended	Not Recommended	Recommended

Adapted from Herrera. The ACG 2006 Annual Postgraduate course syllabus, 201-207.

[#] Upper limit of Normal.

* Unless active biopsy with fibrosis, then consider treatment.

Liver biopsy is not necessary prior to initiating treatment in patients in the immune reactive phase, but should be considered to assess the degree of fibrosis or identify cirrhosis if present. This has important implications on treatment choices and duration which are discussed later. Liver biopsy may also be useful in patients who have minimal or modest elevations in transaminases, but low levels of virus (200–2,000 IU/mL), as active necroinflammatory changes or fibrosis would influence decisions for treatment.

INACTIVE CARRIER PHASE

Patients who successfully exit the immune reactive phase, either spontaneously or as a result of antiviral therapy, will enter the inactive carrier phase. These patients are characterized by low (<2,000 IU/mL) or undetectable hepatitis B virus DNA and persistently normal ALT. Liver biopsy is usually not necessary, but if performed it will show no necroinflammatory activity, slight fibrosis, or possibly inactive cirrhosis in patients who had severe disease in the immune reactive phase. Once in this phase the majority of patients have a benign course with a sustained remission. Some patients in this group may undergo reactivation spontaneously or as a result of immunosuppression. During the inactive carrier phase, the risk of developing hepatocellular carcinoma is low but screening with ultrasound and alpha fetoprotein is recommended. As long as the patient remains HBsAg positive, periodic moni-

toring with liver enzymes levels and viral load should be performed as reactivation is often asymptomatic but can lead to significant liver damage. Antiviral treatment is not needed during the inactive carrier phase because the goal of treatment has already been reached. Hepatitis B surface antigen seroconversion, manifested as clearance of the HBsAg and appearance of HBsAb is the ideal goal, but occurs only at a rate of 1%–2% annually in these patients (11).

e-ANTIGEN NEGATIVE REACTIVATION PHASE

During the inactive carrier phase, mutations in the core or core promoter regions of the HBV genome can develop, giving rise to e-antigen negative mutants that escape immune surveillance and cause reactivation of chronic HBV. The most frequent mutation is a G to A change at nucleotide 1896 (G1896A) which produces a stop codon. The development of e-antigen negative reactivation is a late event in the natural history of chronic hepatitis B, thus, patients with e-antigen mutant strains tend to be older, and have more advanced disease. Serologically, these patients have elevated HBV DNA (>2,000 IU/mL), are HBeAg negative and HBeAB positive, with fluctuating levels of liver enzymes; the HBV viral loads are typically lower than seen in e-antigen positive disease. Patients with e-antigen negative disease are less likely to obtain a sustained remission, and are at increased risk for complications. Treatment does result in viral suppression and

serologic and histologic improvement, but lifelong treatment is often needed as even after prolonged periods of non-detectable HBV DNA, reactivation is common when discontinuing therapy.

Transition to e-antigen negative hepatitis must be differentiated from seroconversion and transition to the inactive carrier state, or remission. Both are e-antigen negative, e-antibody positive, but inactive carriers have persistently normal transaminases and low level (<2,000 IU/mL) or undetectable viral load. In contrast, e-antigen negative reactivation is characterized by higher and fluctuating levels of ALT and HBV-DNA (often >2,000 IU/mL), and active inflammation on biopsy.

TREATMENT GOALS

HBV integrates its genome with the host genome in the form of covalent closed circular DNA (cccDNA). This makes total eradication of the virus impossible. This is evidenced by the fact that even HBsAg-negative HBsAb-positive patients can have reactivation during periods of immunosuppression, and organ donations from these patients can transmit HBV to recipients (12). The ideal goal of antiviral therapy is to achieve HBsAg seroconversion, however, this is seldom achieved with current therapies. The highest rates of HBsAg seroconversion are seen with interferon based therapies, but this only occurs in <8% of patients and it is usually delayed by months to years after successful e-antigen seroconversion. Based on these factors, HBsAg seroconversion, while important, is an unrealistic and seldom achievable goal.

The ultimate goal of treatment is to prevent progressive liver disease, cirrhosis, and hepatocellular carcinoma. This is achieved through sustained viral suppression. Seroconversion of e-antigen to e-antibody with a decrease in viral load to low or undetectable levels, normalization of ALT, and histologic improvement on biopsy signal this end-point. Once this endpoint has been achieved and maintained for at least six-to-12 months on therapy, long lasting remission is the rule, and in most cases, therapy may be discontinued.

In e-antigen mutant infection, e-antigen seroconversion is no longer an attainable goal and as a result there is no clear endpoint at which time therapy can be

discontinued. Reactivation of disease in this group of patients is common even with virus levels that have been undetectable for years on therapy. Reactivation can result in flares that are life-threatening in these patients (13). Thus, life-long therapy is usually recommended in patients with e-antigen negative disease.

In patients who have already progressed to cirrhosis treatment must be more aggressive with life-long therapy as the rule. The goal in compensated patients is to prevent fatal flares and decompensation, hepatocellular carcinoma, and prolong time until liver transplant. All patients with viral load above 2,000 IU/mL should be treated regardless of e-antigen status. The goal in both compensated and decompensated cirrhosis patients is an undetectable viral load with serologic normalization. Ideally, with treatment these patients will clinically improve and may eventually be removed from the transplant list (7). In compensated cirrhosis, life-long treatment is recommended. Treatment discontinuation may be considered if HBsAg seroconversion is achieved.

TREATMENT OPTIONS

Currently six therapies are approved by the FDA for treatment of chronic hepatitis B. There are also promising medications currently in phase III trials. Only FDA approved therapies will be discussed here. These therapies are listed in Table 2.

Interferon Alfa-2b

The first approved treatment for chronic hepatitis B and of historical interest only. Recent trials show that pegylated interferon alfa is more efficacious and better tolerated so regular interferon will not be discussed further.

Pegylated Interferon Alfa (14,15)

Interferon therapy is the only therapy with a finite course of treatment. It is the also the only therapy which stimulates the immune response in addition to inhibiting viral replication. The enhanced immune response increases the likelihood of e-antigen seroconversion and also has the highest likelihood of HBsAg conversion. Thirty-two percent of patients treated with 48 weeks of peg inter-

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Table 2
Therapy for Chronic Hepatitis B (34)

Therapy	Dose	Efficacy* HBeAg (+)	Efficacy** HBeAg (-)	Advantages	Disadvantages
Pegylated Interferon Alfa	180 mcg weekly	30%	60%–70%	Finite Duration No resistance Possible HBsAg seroconversion	Contraindicated in advanced liver disease Broad adverse event profile Injection therapy
Lamivudine	100mg@ daily	16%–18%	50%–80%	Least expensive oral agent Potent viral suppression Effective for adefovir resistant mutants	Very high resistance rates: 20% year one, 70% at year five
Adefovir dipivoxil	10mg@ daily	12%	51%	Low resistance rates Effective for lamivudine resistant mutants	Weak antiviral effect Cost Renal toxicity 25% resistance rate in HBeAg negative hepatitis after five years
Entecavir	0.5mg@# daily	21%	90%	Potent antiviral effect No resistance during first year Effective for lamivudine resistant mutants	No long term safety data Most expensive agent Must be taken on empty stomach
L-deoxythymidine (Telbivudine)	600mg@ daily	26%	88%	Potent antiviral agent Well tolerated	High resistance rates: 4% at year one, 21% at year two No long term safety data

Adapted from Wang and Lok. *Arch Intern Med*, 2006;166:9-12

@ In patients with normal renal function; adjustment required for renal insufficiency.

In lamivudine resistant patients use 1mg/day.

* Efficacy in HBeAg positive hepatitis = HBeAg seroconversion.

** Efficacy in HBeAg negative hepatitis = undetectable DNA at end of treatment.

feron achieved e-antigen seroconversion compared with 19% of those who received lamivudine alone. Of those who achieved e-antigen seroconversion on interferon therapy, 3% achieved HBsAg seroconversion compared with none in the lamivudine group. Combination therapy using interferon and lamivudine does not improve long-term response, but does appear to decrease lamivudine resistance. At this time, however, combination therapy with interferon and lamivudine is not recommended. Predictors of response to interferon include elevated ALT, low viral DNA, and active necroinflammatory changes on biopsy. Hepatitis B virus genotypes A and to

a lesser extent genotype B may be more responsive to treatment with interferon than genotypes C and D (16).

Advantages of interferon-based therapy include finite duration of therapy (one year), increased rates of e-antigen seroconversion, lack of resistance, and increased but low likelihood of HBsAg seroconversion. Disadvantages include a broad side effect profile, need for injection therapy, frequent laboratory monitoring, and cost. Interferon therapy should not be used in patients with decompensated disease or cirrhosis, as it can cause ALT elevations and hepatitis flares that could be severe.

Lamivudine (17–19)

Lamivudine was the first oral nucleoside analogue approved for treating chronic hepatitis B. Only 15%–18% of patients treated with lamivudine will achieve e-antigen seroconversion during the first year of therapy. The major advantage is its excellent tolerability and relative low cost compared with other therapies. These advantages are offset by the rapid development of viral resistance. Approximately 20% of patients will develop resistance at one year and this increases to >70% at four years. Lamivudine resistance also makes resistance to other therapies more likely. Because of the high rate of resistant mutants, lamivudine should not be used as first line therapy or as single-agent therapy. Lamivudine dose must be adjusted for renal insufficiency. Lamivudine should be avoided in patients co-infected with HBV and HIV if they do not require HAART therapy to prevent selection of mutations in the HIV genome.

Adefovir Dipivoxil (20–22,37)

Adefovir dipivoxil is the pro-drug of adefovir, an oral nucleotide analogue of adenosine monophosphate. It suppresses replication by inhibiting the HBV DNA polymerase. Adefovir has weaker antiviral activity than lamivudine, but has a much more favorable resistance profile. One year of therapy results in e-antigen seroconversion in 12% of patients, increasing to 40% by year three in e-antigen positive patients. In e-antigen negative patients when adefovir was compared to placebo at 48 weeks, ALT normalization was achieved in 72% versus 29% respectively; histologic improvement was noted in 64% versus 33% respectively; and viral load was reduced to less than 400 copies/mL in 51% versus 0% respectively. At five years 67% of adefovir-treated patients had ALT normalization; 83% had histologic improvement; 67% had HBV DNA levels less than 1,000 copies/mL.

Adefovir is generally well tolerated with a side effect profile similar to placebo. The approved dose is 10 mg/day. It was noted that in higher doses (30 mg/day) 8% of patients developed nephrotoxic side effects. The risk of nephrotoxic effects with the 10 mg dose are markedly reduced; however, caution should be used when patients are taking other medications associated with nephrotoxicity, the creatinine should

be periodically monitored, and patients with pre-existing renal insufficiency should have the dose adjusted. It has been reported that with the 10 mg dose 20%–50% of patients have primary non-response (<4_{log} copies/mL decrease after six months of therapy) indicating the current dose may be suboptimal (23). Failure of the baseline HBV-DNA to decrease below 2,000 IU/mL by one year of therapy usually signals the need to add a second drug or change to an alternate antiviral medication.

The resistance profile of adefovir is much more favorable than lamivudine with an annual incidence of 1.5%–2%. Patients who maintained an HBV-DNA of >10³ copies/mL after 48 weeks of adefovir therapy are more likely to develop resistance with continued therapy. The rate of resistance to adefovir is higher when patients with lamivudine resistance are switched to adefovir monotherapy (24). While adefovir is the treatment of choice for lamivudine resistance, it should be added to lamivudine rather than replace lamivudine in this situation.

Adefovir dipivoxil at the 10mg dose has negligible activity against HIV, so it may be considered in co-infected patients who do not require HAART therapy.

Entecavir (25–28)

Entecavir is a potent suppressor of viral replication, inhibiting HBV replication at three different steps. It achieves rapid viral suppression with greater serologic and histologic improvement when compared with lamivudine; however, e-antigen seroconversion is similar in both groups. Of e-antigen positive patients 20% had e-antigen seroconversion after 48 weeks. Entecavir is also effective for e-antigen negative mutants; 90% of e-antigen negative patients were HBV DNA undetectable after 52 weeks of therapy, with 48 % of those responders exhibiting a sustained response 24 weeks after discontinuing treatment. The approved dose for naïve patients is 0.5 mg/day. This is generally well tolerated with a side effect profile similar to that of placebo, however long-term efficacy and safety beyond three years has not been carefully studied.

No resistance to entecavir is evident during the initial 48 weeks of treatment, with a very low resistance rate of 1.1% after three years. High-dose entecavir (1

mg/day) is effective against lamivudine resistant strains, but it has significantly reduced effectiveness, and up to 7% of lamivudine resistant patients may be cross-resistant to entecavir. For this reason, entecavir is not the treatment of choice for lamivudine resistant strains.

Although early data suggested that entecavir had no activity against HIV, more recent reports have found some anti-HIV activity. Caution is urged when using entecavir in HIV patients who are not currently receiving HAART therapy as HIV mutations resistant to other agents may be selected.

L-deoxythymidine (Telbivudine) (29–33)

Telbivudine is the newest agent approved for treatment of chronic hepatitis B. It is an oral L-nucleoside analogue that rapidly suppresses viral replication. In a phase III trial it was shown to be more potent than lamivudine: 60% versus 40% respectively of e-antigen positive patients had undetectable virus DNA at the end of one year. It is also effective in treating e-antigen negative chronic hepatitis.

Telbivudine selects for mutations in the YMDD motif, similar to lamivudine. Thus, lamivudine resistant mutants are also resistant to telbivudine. The resistance profile of telbivudine is less favorable than adefovir or entecavir. The observed resistance is 4.4% at one year, but increases exponentially after the first year of treatment. After two years the observed resistance was 21.6%. A low viral DNA (<103 copies/mL) at 24 weeks of therapy may be associated with lower rates of resistance (4% at week 96). Although the rates of resistance are lower than lamivudine, initial or monotherapy with telbivudine is not recommended, as other available agents have a more favorable resistance profile.

CHOOSING A THERAPY

When deciding on a therapy, each patient must be taken as an individual as there is no “standard therapy.” The advantages, disadvantages, duration of treatment, and likelihood of a sustained response should be discussed with each patient in whom treatment is considered. The treatment endpoints should be carefully assessed based on e-antigen status and histology. Current published treatment guidelines are shown on Table 3.

For patients in the immune active stage with significantly elevated ALT, who have compensated liver disease and do not have contraindications to interferon therapy, a one year course of pegylated interferon offers the highest likelihood of both e-antigen seroconversion and surface-antigen seroconversion. This is especially true of genotype A. Oral agents are also effective in these patients, but prolonged therapy may be needed to achieve similar results.

For patients who cannot take interferon, the most potent oral agent with the lowest rates of resistance should be used, recognizing that prolonged or indefinite therapy may be needed. Adefovir, although not the most potent agent, should be considered among the first-line agents in that it has a favorable resistance profile and long-term safety and efficacy data available. Entecavir has the most powerful antiviral activity of the currently approved agents, and a very favorable short-term resistance rate profile, but long-term data is not yet available. In e-antigen negative mutants the agent with the lowest rate of resistance should be chosen as multi-year or indefinite therapy is likely necessary.

Patients with compensated cirrhosis should be treated when ALT levels are elevated greater than twice normal, and in patients with normal ALT levels who have circulating viral DNA 2,000 IU/mL or higher, some recommend treating all patients with cirrhosis and detectable HBV-DNA regardless of level. Inter-

Table 3
Treatment Guidelines: Recommendations in Chronic Hepatitis B Patients without Cirrhosis

Immune Reactive and e-Antigen negative reactivation Chronic HBV

- Treatment may be delayed in e-Antigen positive patients who are compensated for three-to-six months to allow for spontaneous HBeAg seroconversion
- Patients with icteric flares should be treated
- PegIFN- α , adefovir, or entecavir preferred as first-line therapy (all approved as monotherapy only)
- Lamivudine should not be used first line due to high rate of resistance
- Above guidelines developed prior to telbivudine FDA approval

Adapted from Keeffe. *Clin Gastroenterol Hepatol*, 2006;4:936-962.

Table 4
Treatment Guidelines: Recommendations in Chronic Hepatitis B Patients with Cirrhosis

Compensated Cirrhosis

- Adefovir or entecavir are preferred first-line options
- Interferon not used due to risk of hepatitis flares and decompensation
- Lamivudine not a good choice due to high rate of resistance

Decompensated Cirrhosis

- Combination therapy with lamivudine and adefovir
- Telbivudine may be substituted for lamivudine but data in decompensated cirrhosis is lacking
- Sequential monotherapy is not recommended
- Entecavir may also be used, but data in decompensated cirrhosis is limited

Adapted from Keeffe. *Clin Gastroenterol Hepatol.* 2006;4:936-62.

feron based therapy should not be used in these patients because of risk of fatal hepatitis flares. Adefovir or entecavir are preferred first-line choices since long-term therapy is needed. In patients with decompensated cirrhosis rapid viral suppression is needed. Lamivudine is preferred to adefovir monotherapy for its potent antiviral action; however, because of the high risk for resistance, it should be used in combination with adefovir to reduce resistance. Entecavir may also be an acceptable choice to use in combination with lamivudine, but data in decompensated cirrhosis is limited. Telbivudine may also be substituted for lamivudine, but it also lacks data in decompensated cirrhosis and its resistance profile is inferior to entecavir or lamivudine-adevovir combination therapy. Recommendations for patients with cirrhosis are summarized in Table 4.

When a patient develops resistance on the current therapy, the agent chosen to treat the resistant strain should be added to current therapy rather than simply switching agents (sequential monotherapy). This will help to prevent multidrug resistant strains. In patients with lamivudine resistance, the addition of adefovir will control the lamivudine resistant mutants, while continuing lamivudine will prevent adefovir-resistant mutants from arising. High dose (1 mg/d) entecavir is also an alternative, recognizing that lamivudine resistance is a

Table 5
Treatment Guidelines: Endpoints

e-Antigen Positive Chronic HBV

- e-Antigen seroconversion: Treat additional 6–12 months then stop
- No seroconversion: Continue treatment, consider alternative medications for suboptimal response

e-Antigen Negative Chronic HBV

- Treat indefinitely, consider alternative medications for suboptimal response

Cirrhosis

- Treat until HBsAg seroconversion
- Treatment discontinuation may be considered in HBeAg (+) patients who achieve HBeAg seroconversion and complete 6 months of consolidation therapy

Adapted from Lok and McMahon. AASLD Practice Guidelines: Chronic Hepatitis B. *Hepatology*, 2007;507-539

prerequisite for entecavir resistance. The efficacy and potency of entecavir is inferior when used in lamivudine-resistant patients. Telbivudine or entecavir resistant strains are responsive to adefovir or tenofovir therapy.

SUMMARY

The goal of treatment for chronic HBV is to prevent progressive liver disease, cirrhosis, and hepatocellular carcinoma. These are accomplished through suppression of viral replication. Decisions on who to treat are based on circulating viral DNA levels, transaminase levels, and histologic evidence of inflammation or fibrosis on liver biopsy. Currently, a viral DNA of 20,000 IU/mL or higher, with elevated transaminases warrants treatment in e-antigen positive patients. In e-antigen negative patients these threshold values are lower. An individual approach should be taken with each patient, and biopsy should be considered in patients with elevated viral loads and normal transaminases, to evaluate for inflammation and fibrosis. After identifying a patient as requiring treatment, decisions must then be made on which antiviral agent to use and what course length of therapy will likely be required. If no contraindications are present, interferon therapy

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offers the highest chance of sustained response and offers a finite course of therapy. Nucleos(t)ide analogues often need long-term (years) therapy but have a favorable adverse affect profile making them the choice for cirrhosis and e-antigen negative hepatitis. In patients who have progressed to cirrhosis, treatment is more aggressive to achieve undetectable viral DNA levels. Combination therapy is used for patients with decompensated cirrhosis to rapidly suppress viral replication and decrease emergence of resistance. ■

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