

## Chronic Hepatitis B

### What is in our treatment armamentarium?

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Chronic hepatitis B affects more than 350 million people worldwide.<sup>1</sup> The Centers for Disease Control and Prevention reports an average of 60,000 newly infected cases per year.<sup>1</sup> In the United States, 1.25 million people are affected by this disease. Although a large percentage of cases occur among immigrants to the United States, 20-30% of the new cases in our country result from maternal transmission.<sup>1</sup> The prevention and treatment of hepatitis B is of utmost importance due to the association with serious long-term sequelae including cirrhosis and hepatocellular carcinoma. The purpose of this article is to discuss recently updated guidelines for treatment of chronic hepatitis B published by the American Association for the Study of Liver Diseases (AASLD).<sup>2</sup> In addition, our aim is to provide a rationale for choosing initial therapy based on efficacy, safety, incidence of resistance, and cost to our institution.

Chronic hepatitis B disease is defined as hepatitis B surface antigen (HBsAg) positive for >6 months, HBV DNA >20,000 copies/mL, persistent or intermittent elevation in alanine aminotransferase (ALT) levels, and liver biopsy indicating chronic hepatitis. Due to the high rate of viral replication and low fidelity polymerase, some HBV mutations develop independent of treatment. One of the most common mutations is a G-to-A substitution, resulting in a stop codon in the precore region, which prevents HBeAg production. Another common mutation is a dual mutation involving 2 nucleotide substitutions (A-to-T at position 1762 and G-to-A position 1764) leading to down-regulation of HBeAg production. Both these mutations produce what is termed a precore/core mutant. Hence, in the diagnosis of hepatitis B, it is useful to differentiate between HBeAg-positive and HBeAg-negative disease. Historically, seroconversion, from HBeAg positive to negative, was used as a method for characterizing response to therapy. Due to the presence of precore/core mutants, however, today the best way to assess response to therapy is to check serum hepatitis B viral titers.<sup>3</sup>

The AASLD guidelines published in January of this year strongly recommend avoiding unnecessary treatment in order to decrease the risk of resistance development from patient non-adherence to therapy. Of the available agents, peginterferon alfa-2a, adefovir, and entecavir are preferred for initial therapy (see figure 1).<sup>2</sup> Interferon alfa-2b has been replaced in practice by peginterferon alpha-2a due a more favorable pharmacokinetic profile which allows for less frequent dosing and better patient tolerability. Lamivudine is no longer recommended as a first-line therapy due to the increasing incidence of resistance seen in association with prolonged therapy. Likewise, telbivudine, the most recently approved agent is not preferred for initial therapy due to the high rate of resistance reported during clinical trials.<sup>2</sup>

Lamivudine (Epivir<sup>®</sup>) was the first agent to be approved for treatment of chronic hepatitis B. For many years, it was considered an optimal agent for first-line therapy due

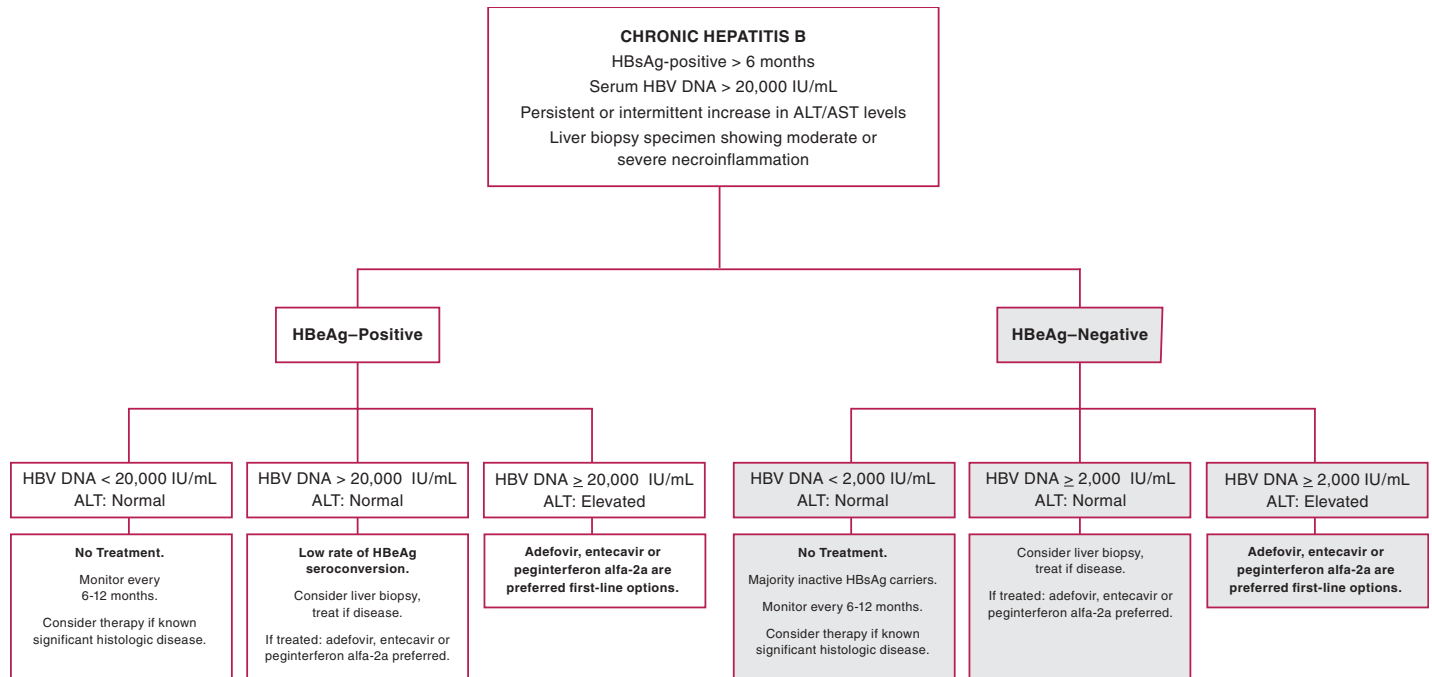
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Figure 1: Treatment Algorithm for Chronic Hepatitis B



**Hepatitis B virus-related hepatocellular carcinoma is the third most common cause of death in the Asia-Pacific region.<sup>1</sup>**

**Patients who fail lamivudine monotherapy are at higher risk for developing entecavir resistance.<sup>7</sup> The recommendation is to use 0.5mg of entecavir daily for nucleoside-naive patients and to double the dose to 1mg daily when entecavir is used for lamivudine-resistant disease or when entecavir is co-administered with lamivudine.**

its favorable side-effect profile and oral bioavailability. Unfortunately, the rate of resistance after 1 year of monotherapy is 18-20%, increasing to ~70% after 4 years (see Table I).<sup>4</sup> Resistance to lamivudine is due to a YMDD mutation (tyrosine-methionine-aspartate-aspartate) in the P gene associated with the active site of HBV DNA polymerase.<sup>3</sup> In patients who develop resistance while on lamivudine monotherapy, the AASLD guideline recommends adding adefovir or tenofovir or switching from lamivudine to another agent such as entecavir or Truvada<sup>®</sup> (emtricitabine combined with tenofovir).<sup>2</sup>

Adefovir (Hepsera<sup>®</sup>) was the second oral agent to be approved for treatment of chronic hepatitis B. Although it is relatively well tolerated, the development of nephrotoxicity can limit its use. The resistance profile of adefovir, reported to be 2% at 1 year and 18% after 4 years, is superior to that of lamivudine.<sup>4</sup> The mechanism of adefovir resistance differs from that of lamivudine resistance and is a result of A181V/T and/or N236T in the B- and D-domain of reverse transcriptase.<sup>3</sup> Cross-resistance between lamivudine and adefovir appears to be less than that for other agents;<sup>2</sup> therefore, it is reasonable to use these 2 agents in combination for patients who have previously failed monotherapy with either agent. In patients who develop resistance while on adefovir monotherapy, the AASLD guideline recommends adding lamivudine or switching from adefovir to another agent, such as entecavir or Truvada<sup>®</sup> (emtricitabine combined with tenofovir).<sup>2</sup>

Entecavir (Baraclude<sup>®</sup>) was FDA approved in 2005 as the third oral agent for the treatment of chronic hepatitis B. Data for the resistance profile of entecavir in treatment-naive patients is 3% at 96 weeks.<sup>2</sup> The 4-year resistance to entecavir is yet to be quantified. Entecavir may be associated with a relatively low rate of resistance due to its unique mechanism of action which inhibits 3 phases of viral replication: HBV DNA polymerase priming, reverse transcription, and the synthesis of positive-stranded DNA.<sup>5</sup> In patients with pre-existing lamivudine resistant mutations (I169, T184, S202, and M250), resistance to entecavir has been observed to be 16% at 96 weeks.<sup>2</sup> It seems that clinical evidence of resistance to entecavir requires more than 1 mutation, whereas resistance to either lamivudine or adefovir only requires a single amino acid change.<sup>5</sup> In addition to a superior resistance profile, seroconversion

Drugs	1 year e-antigen sero-conversion rate	Resistance		
		1 year	2 year	4 year
Adefovir	12-14%	2%	-	18%
Entecavir	21%	0%	-	N/A
Lamivudine	12-18%	18-20%	-	70%
Peginterferon alfa-2a	25-32%	0%	-	0%
Telbivudine	23%	-	17.8%	-

data for entecavir appear to be more favorable than for adefovir (21% vs. 12-14%) in treatment-naive patients with HBeAg-positive chronic hepatitis B.<sup>2</sup>

Among the available agents, peginterferon alpha-2a (Pegasys<sup>®</sup>) has the highest rate of seroconversion (27-33%) and best durability of response.<sup>2</sup> Unfortunately, use of peginterferon alpha-2a is limited by its less favorable side-effect profile, the inconvenience of weekly subcutaneous administration, and high cost, estimated to be approximately \$53,724 for 48 weeks of therapy (see Table II). In addition to the commonly reported “flu-like” symptoms, depression was reported in 18% of patients receiving peginterferon alpha-2a

therapy at the dose of 180mcg per week during clinical trials.<sup>6</sup> Despite these disadvantages, peginterferon alpha-2a therapy offers patients a defined duration of treatment (48 weeks) and the therapy is not associated with the development of resistance by the virus.

Telbivudine (Tyzeka<sup>®</sup>), the newest agent approved for treatment of chronic hepatitis B, is not on the UW Medicine Drug Formulary. Telbivudine works similarly to the other existing oral agents, as a nucleoside analog targeting the inhibition of HBV DNA synthesis. Results of Phase III studies have shown telbivudine 600mg per day to be superior to lamivudine 100mg per day in terms of viral load reduction.<sup>7</sup> Although preliminary data suggest that telbivudine may be a more potent inhibitor of HBV DNA than adefovir at 24 weeks, the genotypic resistance rate was 4.7% by 1 year, increasing to 21.5% by 2 years of treatment.<sup>7</sup> Telbivudine, like lamivudine, selects for the YMDD mutation and 1 trial has shown therapy using telbivudine in combination with lamivudine to be inferior to telbivudine monotherapy.<sup>2</sup> Therefore, combination therapy with these 2 agents should be avoided.

We are fortunate to have 6 options in our armamentarium for the treatment of chronic hepatitis B. Which of these options represents the best treatment choice for patients should logically be based on underlying patient characteristics, drug efficacy, patient tolerability, length of therapy, and cost. Important patient characteristics to consider include: HBV DNA levels, HBeAg status, serum ALT trends, liver biopsy findings, and the genotype of the virus. Taking all of these factors into account, it is reasonable to prefer peginterferon alpha-2a as initial therapy for the average patient. This regimen has the highest seroconversion rate (27-33%) and is not associated with the development of viral resistance during therapy. However, the cost may be prohibitive for patients without means. For these patients, and for patients who prefer an oral regimen, either adefovir or entecavir are preferable for initial treatment. The main disadvantage of adefovir is the risk of nephrotoxicity (2% after 2 years of treatment).<sup>8</sup>

Regrettably, patients treated for chronic hepatitis B are rarely cured of this disease. Experience with lamivudine suggests that the efficacy of our current antiviral treatment options is likely to erode over time because of the development of resistance. Our success with HAART therapy for chronic HIV suppression suggests that therapeutic regimens of the future will likely consist of multi-drug cocktails aimed at curbing the ability of the virus to develop resistance and thereby preserving the efficacy of the agents in our armamentarium. However, until highly reliable virologic eradication is within our grasp, prolonged drug therapy will remain necessary to reduce the sequelae of cirrhosis and carcinoma resulting from long-term infection. Hope for the future, therefore, lies in strategies that include new drug combinations, sequential treatment regimens, the discovery of highly

**Emtricitabine (Emtriva<sup>®</sup>) and tenofovir (Viread<sup>®</sup>), 2 antiretroviral agents indicated for HIV infection, are currently under investigation for the treatment of chronic hepatitis B infection.<sup>5</sup>**

**Hope for the future treatment of chronic hepatitis B disease lies in strategies that include new drug combinations, sequential treatment regimens, and discovery of novel agents.**

**Table II: UWMC Charge to Patient for each 30-day supply**

Drug	Dose	Cost
Adefovir	10mg q day	\$590
Entecavir (Current UW Medicine Formulary Status: Restricted to 2nd line therapy for chronic hepatitis B)	0.5mg q day	\$892
	1mg q day	\$892
Peginterferon alfa-2a	180mcg subQ q week x 48	\$4,477
Telbivudine (nonformulary)	600mg q day	\$630

## Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s), & Cost <sup>‡</sup>	Therapeutic Classification	Use	Usual Adult Starting Dose*
<b>Budesonide (Entocort EC)</b>	Capsule: 3mg	Corticosteroid	Crohn's disease	9mg once daily.
	Added to formulary limited to use by the Bone Marrow Transplant services for patients with gastrointestinal manifestations of graft-versus-host disease.			
<b>Etonogestrel implant system (Implanon)</b>	Implant: 68mg	Progestin	Contraceptive	Delivers 60mcg daily for 3 years.
	Use is restricted by the manufacturer to authorized prescribers.			

\* Refer to product labeling for full prescribing information. ‡ Contact pharmacy for information on drug costs.

### Chronic Hepatitis B: What is in our treatment armamentarium?

(continued)

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active viricidal agents, and other novel techniques targeting virus eradication.

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