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Hepatitis B Makeover: An Expert Panel Discussion

A Report From a Symposium Presented During the 58th Annual Meeting of the American Association for the Study of Liver Diseases
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1. Discuss the factors considered in the decision to commence treatment of patients with chronic hepatitis B infection.
2. Describe the relationship between hepatitis B infection, viral load, and progressive liver disease.
3. Apply treatment strategies to effectively suppress hepatitis B viral load and avoid the development of resistance.

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Hepatitis B Makeover

An Expert Panel Discussion

The following expert panel discussion was held on November 5, 2007, at the Sheraton Boston Hotel in Boston, Massachusetts, to share the latest findings and opinions on the management of patients with chronic hepatitis B virus (HBV) infection.

What is the natural history of chronic HBV infection?

Dr. F. Fred Poordad Our current understanding of the natural course of chronic HBV infection is that it occurs in four phases.[1] Phase 1, known as the immune tolerant phase, is characterized by a hepatitis B e antigen (HBeAg)-positive status, along with normal alanine aminotransferase (ALT) levels and high HBV DNA levels. On biopsy the liver has little to no evidence of disease or damage. Phase 1 typically occurs only in patients who acquired HBV through perinatal transmission. The length of this phase can vary greatly, lasting from 10 to 40 years. Several long-term studies have shown that during this time prognosis is generally favorable, despite the high HBV DNA levels.[2,3]

Phase 2 of chronic HBV infection, like phase 1, is characterized by an HBeAg-positive status and high or fluctuating HBV DNA levels. Unlike in phase 1, patients also exhibit either persistently or intermittently elevated ALT levels and the liver is actively inflamed. An important hallmark of this phase is flares in ALT levels. These ALT flares are thought to be due to the lysis of infected hepatocytes, which is brought on by an increase in the immune response to HBeAg. Because of this, phase 2 is also known as the immune clearance phase, although "immune active phase" may be a more appropriate term.[4,5] Because these flares are associated with hepatic decompensation, a longer duration of this phase has been clearly linked with an increased risk of developing liver disease complications such as cirrhosis and hepatocellular carcinoma (HCC). The end result of phase 2 is seroconversion, from HBeAg-positive to HBeAg-negative and anti-HBe–positive.

Patients in phase 3, the inactive hepatitis B surface antigen (HBsAg) carrier state, are HBeAg-negative, anti-HBe–positive, and have normal ALT levels with low or undetectable HBV DNA levels. The prognosis for patients in this phase is again relatively favorable, and liver biopsy generally reveals minimal fibrosis. Inactive cirrhosis may be present in patients who experienced severe liver injury during phase 2. Phase 3 may persist indefinitely, in which case patients have a relatively good prognosis. One study of 296 healthy patients in phase 3 of chronic HBV infection showed no difference in survival compared to healthy uninfected controls over a 30-year mean follow-up period.[6] However, some patients undergo viral reactivation, either spontaneously or as a result of immunosuppression.

Phase 4, the reactivation phase, is characterized by an HBeAg-negative and anti-HBe–positive status, with accompanying detectable levels of HBV DNA and elevated ALT levels. Patients in this phase may have significant fibrosis on liver biopsy, in spite of normal or mildly elevated ALT levels. As in phase 2, both HBV DNA levels and ALT levels characteristically fluctuate. Approximately one third of chronically infected HBV patients ultimately enter phase 4 and are defined as having HBeAg-negative disease. Once hepatic decompensation occurs in this stage, patient prognosis is poor, with 5-year survival rates as low as 14–28%.[7-10]

How do HBV DNA levels affect HBeAg seroconversion?

Dr. Nezam H. Afdhal Analysis of patients from a phase II study investigating extended lamivudine therapy for chronic HBV showed that HBeAg seroconversion took place only in patients whose HBV DNA levels were suppressed to less than 10,000 copies/mL.[11] However, adequate HBV DNA suppression is not solely able to dictate HBeAg seroconversion. Seroconversion requires, to some degree, an ability to stimulate the actual immune response to convert from the HBeAg to the HBe antibody.

What are the key prognostic factors associated with liver disease complications?

Dr. Ira M. Jacobson Several factors have been identified that are prognostic for the development of liver disease complications such as cirrhosis and HCC. The presence of either HBsAg or HBeAg was linked with the develop-

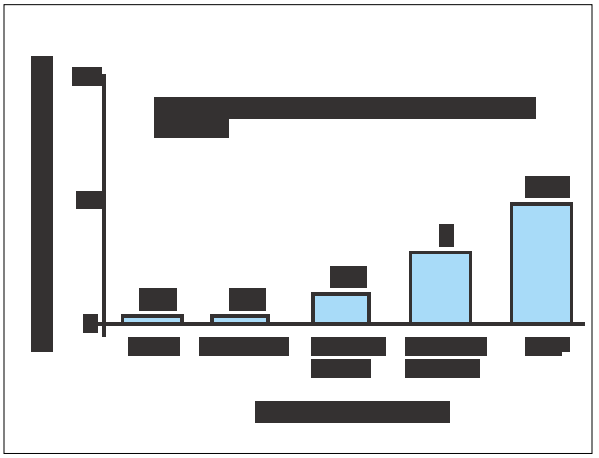

Figure 1. Hepatocellular carcinoma (HCC): association with baseline hepatitis B virus (HBV) DNA levels.

Adapted from Chen CJ, et al.[13]

ALT=alanine aminotransferase; HBeAg=hepatitis B e antigen.

ment of HCC in a large prospective study of 11,893 men throughout Taiwan.[12] Compared to men testing negative for both antigens, HBsAg-positive status was associated with a relative risk (RR) for the development of HCC of 9.6 (95% confidence interval [CI], 6.0–15.2) while a serum-positive test for both HBsAg and HBeAg correlated with a RR of 60.2 (95% CI, 35.5–102.1).

Recently, the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (REVEAL) study sought to determine if a link existed between HBV DNA levels and the risk of developing HCC.[13] In this long-term prospective study, 3,653 HBsAg-positive patients were followed over an average of 11.4 years and monitored for the development of HCC. There was a strong correlation between increasing levels of HBV DNA and the occurrence of HCC. Patients with baseline HBV DNA levels below 300 copies/mL had a cumulative HCC incidence of 1.3%, and this incidence became greater with increasing gradients of HBV DNA levels, starting at 10,000 copies/mL and culminating with a 14.9% cumulative HCC incidence rate in patients with HBV DNA levels greater than 1×10^6 copies/mL. This HCC incidence gradient was statistically significant ($P<.001$), even after adjustment for cofactors, including age, sex, smoking, and alcohol use. Additionally, the level of HBV DNA was a statistically significant prognostic factor regardless of HBeAg status, ALT levels, or evidence of cirrhosis. When only the patients negative for HBeAg with no liver cirrhosis and normal ALT levels were compared (n=2,925), the cumulative incidence increased from 0.74 among patients with less than 300 HBV DNA copies/mL to 13.5 in patients with HBV DNA levels greater than 1×10^6 copies/mL (Figure 1). Additionally, this long-term study found that patients with persistently elevated levels of HBV DNA faired the worst.

The REVEAL study likewise found a statistically significant correlation between increasing HBV DNA levels and the risk of developing cirrhosis.[14] When compared to patients with less than 300 HBV DNA copies/mL, patients with 1×10^4 to 1×10^5, 1×10^5 to 10^6, and more than 1×10^6 copies/mL had adjusted RRs (95% CI) of 2.5 (1.6–3.8), 5.6 (3.7–8.5), and 6.5 (4.1–10.2), respectively ($P<.001$ for all comparisons). HBV DNA levels remained a statistically significant independent risk factor for the development of cirrhosis even in HBeAg-negative patients with normal ALT levels.

The REVEAL study investigators recently published a revision to the data, using a more sensitive real-time polymerase chain reaction (PCR) method to requantify patient HBV DNA levels.[15] This allowed for a more exact distinction between the different HBV DNA–level groups. In this analysis, the hazard ratio (HR) for the development of HCC in patients with HBV DNA levels of 100–1,000 copies/mL was 1.2 (95% CI, 0.3–4.4) and 3.2 (95% CI, 1.5–7.1) for patients with HBV DNA measuring from 1,000 to less than 10,000 copies/mL. Importantly, even though this level of HBV DNA is below the cutoff of current guidelines, it still carries with it an increased risk of HCC progression. Therefore, the authors of the REVEAL study concluded that the therapeutic goal should be maximal and durable suppression of HBV DNA levels, as opposed to simply reducing HBV DNA levels to less than 10,000 copies/mL.

Do elevated ALT levels have an effect on liver disease progression or complications?

IJ A study in several hundred Chinese patients showed that while higher ALT levels correlated with progressive liver disease in both HBeAg-positive and -negative patients, liver disease can also occur in the setting of normal ALT levels.[16]

NA We recapitulated this study in a retrospective review of 192 patients with chronic HBV.[17] While subgroup analysis showed that the majority of patients with evidence of fibrosis had ALT levels on the higher end of normal, 18% of patients with persistently normal ALT levels had stage 2 or greater fibrosis and 34% had grade 2–3 inflammation. Overall, this study showed that 37% of patients with persistently normal ALT levels had evidence of significant fibrosis or inflammation. Based on this study, we recommended that a liver biopsy should be

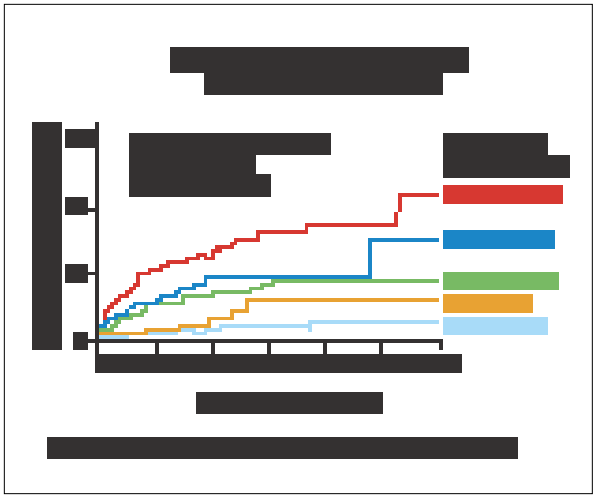

Figure 2. Alanine aminotransferase (ALT) activity is an unreliable predictor of disease progression.

Adapted from Yuen MF, et al.[18]

HBV=hepatitis B virus; HBeAg=hepatitis B e antigen; ULN=upper limit of normal.

considered for patients with high normal ALT levels who are older than 40 years, which is another risk factor for the development of liver disease.

IJ Another trial of 3,233 Chinese patients with chronic HBV showed that elevated ALT levels can significantly impact the risk of liver disease complications.[18] Importantly, this is true even for ALT levels that are within the published normal range. Compared with patients with ALT levels less than 0.5 times the upper limit of normal (ULN), those patients with ALT levels 0.5 to 1 3 ULN and 1 to 2 3 ULN both experienced a significantly increased risk of developing liver disease complications (P<.0001 for both; Figure 2). In this study, the ULN was defined as 53 IU/L for men and 31 IU/L for women. An important consideration to remember when interpreting the findings from this study is that the patients who exhibited the greatest risk of developing liver disease complications were patients with ALT levels 1 to 2 3 ULN, a group that current guidelines recommend be treated on a case-by-case basis or if a liver biopsy shows evidence of liver disease.[19]

Is there an association between HBV genotype and the risk for developing liver disease complications?

IJ A prospective study of 426 patients was performed to determine if HBV genotype impacts the risk of developing subsequent liver disease complications.[20] The majority (57%) of study patients had HBV genotype C, while most of the remaining patients (42%) had HBV genotype B. A total of 25 patients developed HCC over a median follow-up of 121 weeks (range: 14–236 weeks). A multivariate analysis was performed to identify factors that independently predict a risk for HCC development. As expected, cirrhosis was found to have a highly significant adjusted RR of 10.24 (95% CI, 4.39–23.89; P<.001). Interestingly, HBV genotype C was also shown to be independently associated with the development of HCC, with an adjusted RR of 2.84 (95% CI, 1.05–7.72; P=.040). Patients who were infected with genotype C were also found to more commonly have HBeAg-positive status and higher ALT levels.

The link between genotype C and liver disease progression was further confirmed in several other studies. In a cross-sectional study of 200 Taiwanese patients with chronic HBV, having genotype C carried an odds ratio (OR) of 2.87 (95% CI, 1.21–6.81; P=.017) for the development of liver cirrhosis.[21] This same study showed that two other factors, mutations at T1762/A1764 (OR: 11.11; 95% CI, 3.91–31.25; P<.001) and age of at least 35 years (OR: 3.42; 95% CI, 1.33–8.77; P=.011), also significantly predicted the development of liver cirrhosis. The majority (62.1%) of patients with all three of these factors had liver cirrhosis. Core promoter mutations continued to be an important predictor of cirrhosis development in a longitudinal study of the same Taiwanese population (HR: 5.54; 95% CI, 2.18–14.08; P<.001).[22] When only HBeAg-positive patients were considered (n=148), the OR for cirrhosis development was 10.17 (95% CI, 3.14–33.02; P<.001). Another longitudinal study, in 400 chronic HBV patients in the United States, also showed a statistically significant risk for development of HCC in both precore mutations (OR: 4.23; 95% CI, 1.53–19.58; P=.02) and basal core promoter mutations (OR: 2.93; 95% CI, 1.24–7.57; P=.02).[23]

Consideration of the genotype of a patient independent of other risk factors, especially age and histologic status, remains unclear. I have begun to routinely incorporate genotype testing into my practice. Although I do not use it as a decisive factor, I do consider the patient's genotype among many other factors when determining treatment decisions.

When should treatment be initiated in chronically infected HBV patients?

IJ As a result of an increasing number of published clinical studies investigating new antiviral agents to treat HBV, as well as an increased understanding of the natural history of the disease, several treatment guidelines have

Table 1. Summary of Treatment Guidelines: Patients Without Cirrhosis

	HBeAg-positive		HBeAg-negative	
	Keeffe EB, et al. 2006	**AASLD 2007**	**Keeffe EB, et al. 2006**	**AASLD 2007**
Monitor, do not treat	ALT normal HBV DNA <20,000 IU/mL (<10^5 copies/mL) Consider therapy in patients with significant histologic disease	ALT <1 3 ULN Consider biopsy if ALT fluctuates or minimally elevated, patient >40 years, or family history of HCC	ALT normal HBV DNA <2,000 IU/mL (<10^4 copies/mL) Consider therapy in patients with significant histologic disease	ALT ≤ 3 ULN HBV DNA ≤2,000 IU/mL (≤10^4 copies/mL) Observe. Treat if HBV DNA or ALT becomes higher
Consider treatment if disease	ALT normal HBV DNA ≥20,000 IU/mL (≥10^5 copies/mL) Consider biopsy, especially if patient >35 years; treat if disease. In absence of biopsy, observe for increase in ALT	ALT 1-2 3 ULN HBV DNA >20,000 IU/mL (>10^5 copies/mL) Consider biopsy if persistent or age >40 years; treat if disease	ALT normal HBV DNA ≥2,000 IU/mL (≥10^4 copies/mL) Consider biopsy; treat if disease. In absence of biopsy, observe for increase in ALT	ALT 1–>2 3 ULN HBV DNA >2,000 IU/mL (>10^4 copies/mL) Consider biopsy; treat if moderate/severe inflammation or significant fibrosis
Treat	ALT elevated HBV DNA ≥20,000 IU/mL (≥10^5 copies/mL)	ALT >2 3 ULN HBV DNA >20,000 IU/mL (>10^5 copies/mL)	ALT elevated HBV DNA ≥2,000 IU/mL (≥10^4 copies/mL)	ALT ≥2 3 ULN HBV DNA ≥20,000 IU/mL

Adapted from Lok ASF, et al[19] and Keeffe EB, et al.[24]

AASLD=American Association for the Study of Liver Diseases; ALT=alanine aminotransferase; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HBeAg=hepatitis B e antigen; ULN=upper limit of normal.

recently been updated (Table 1). According to the most recent practice guidelines released from the American Association for the Study of Liver Diseases (AASLD), HBeAg-negative patients with HBV DNA levels over 20,000 IU/mL and ALT levels greater than 2 3 ULN are clear candidates for treatment.[19] A liver biopsy should be considered for HBeAg-negative patients with HBV DNA levels greater than 2,000 IU/mL and slightly elevated ALT levels (1 to 2 3 ULN). If liver biopsy indicates moderate to severe necroinflammation or significant fibrosis, treatment should then be decided on an individualized basis. Finally, observation-only is recommended for HBeAg-negative patients with HBV DNA levels less than 2,000 IU/mL and normal ALT levels. Treatment should be initiated in these patients only upon elevation of HBV DNA or ALT levels.

Recently an alternative algorithm was developed for deciding when to initiate treatment in patients with chronic HBV infection.[24] Known as a US treatment algorithm because of its American authorship, these guidelines recommend treatment for HBeAg-negative patients with HBV DNA levels of 2,000 IU/mL or greater and elevated ALT levels. For patients with HBV DNA levels of 2,000 IU/mL or greater and normal ALT levels, the recommendation is for close monitoring of ALT or a biopsy, as determined on a case-by-case basis. Again, if the biopsy finds significant evidence of liver disease, treatment should be initiated. HBeAg-negative patients with HBV DNA levels below 2,000 IU/mL can be monitored every 6–12 months, with no treatment indicated.

Another important point is that both of these guidelines update the cutoffs for the ULN for ALT, reducing them to 30 IU/L for men and 19 IU/L for women.

To summarize both guidelines, the consensus is to initiate therapy for HBeAg-positive patients with persistently elevated ALT levels when accompanied by HBV DNA levels greater than 20,000 IU/mL. The consensus for therapy initiation in HBeAg-negative patients is not

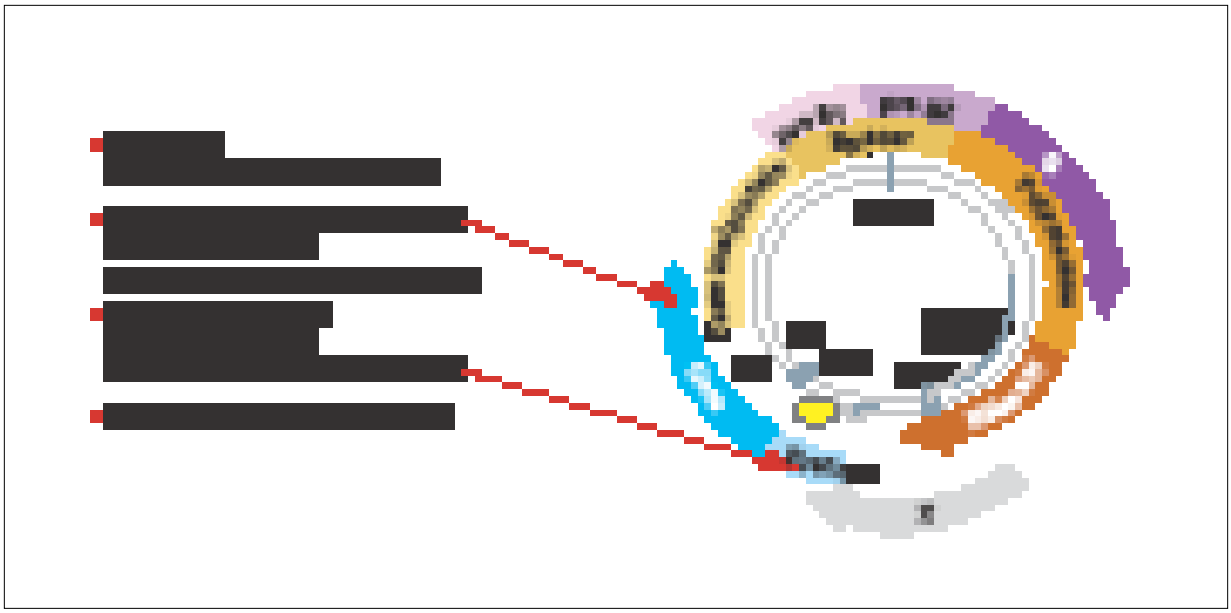

Figure 3. Hepatitis B virus variants.

Adapted from Buchwold VE, et al,[25] Chu C-J, et al,[26] and Hunt CM, et al.[27]

HBeAg=hepatitis B e antigen.

as clear, as the treatment threshold for HBV DNA levels differs between the two guidelines (2,000 and 20,000 IU/mL). In the AASLD guidelines, an ALT cutoff to define optimal treatment candidacy is more strictly defined in both HBeAg-positive and HBeAg-negative patients (≥2 × ULN).

What type of HBV viral variants occur?

FP The basal core promoter of the hepatitis B virion controls the transcription of both the precore viral RNA, which encodes the HBeAg, and the core viral RNA, which encodes the major core protein and DNA polymerase.[25] A nationwide study of 694 patients with chronic HBV infection detected precore mutations in 27% of patients and core mutations in 44% of patients.[26] Generally, patients with wild-type virus are HBeAg-positive while those with basal core mutations have a lower rate of HBeAg-positive status, and precore mutations generally abolish the production of HBeAg, creating an HBeAg-negative status (Figure 3).[27]

How do antiviral agents contribute to HBV viral resistance?

NA One definition of an antiviral drug is an agent that selects for resistance.[28] Under most conditions, the wild-type virus coexists with naturally occurring viral variants. However, because the wild-type virus exhibits superior replicative fitness, it becomes the predominant species. After exposure of the wild-type virus to a single-agent antiviral drug, primary mutations leading to drug resistance can occur. Although these mutations offer a selective advantage in the presence of the antiviral agent, the viral particles typically display a reduced fitness. However, subsequent secondary or compensatory mutations that occur under the selective pressure of the drug can restore the replicative fitness of the viral particle, allowing it to then become the predominant species. This occurs especially in the setting where viral replication has been inadequately suppressed.[29,30]

One important strategy to reduce the risk of developing antiviral drug resistance is to use the most potent agents possible, with very careful monitoring of the patient while on therapy. Agents with both a powerful antiviral activity (the degree to which the viral replication is suppressed) and a high genetic barrier to resistance (an increased number of genetic substitutions needed to induce resistance) are preferable.

According to the most recent AASLD guidelines, adefovir or entecavir are preferred over lamivudine or telbivudine as single-agent therapies because of the lower risk of resistance associated with these agents.[19] Notably, these guidelines now also recommend against the use of

lamivudine as a frontline agent, both because of its likelihood to develop resistance and the increased risk of cross-resistance that may result, eliminating possible future therapies. In the event that lamivudine or telbivudine are used as single-agent frontline therapies, patients should be carefully monitored to determine if effective virologic suppression is achieved. If not, an alternative treatment regimen should be considered.

The rates of resistance emergence associated with each of these antiviral drugs have been documented through several clinical studies in nucleoside-naïve patients. In 185 HBeAg-negative patients, long-term adefovir therapy resulted in the formation of resistance mutations in 5.9% of patients after 144 weeks.[31] A separate study of 673 individuals found that 2-year entecavir therapy resulted in resistance in only 0.1% of the patients.[32] In contrast, lamivudine produced resistance mutations in 24% of 335 patients after 1 year of therapy,[33] and telbivudine treatment leads to resistance in 5.3% and 11.4% of HBeAg-negative and -positive patients, respectively.[34]

Is combination antiviral therapy more effective than single-agent therapy in preventing resistance?

NA The three strategies using antiviral agents to treat HBV are monotherapy with sequentially sequenced agents, add-on combination therapy, and de novo combination therapy. The basis for selecting agents to add-on in combination is to avoid cross-resistance between two agents. For this reason, adefovir is a good choice for lamivudine-resistant HBV, whereas lamivudine may be effective against HBV resistant to adefovir or entecavir.[24,35] However, the most effective strategy to prevent the development of resistance is with the use of de novo combination therapy.

Several studies are now looking at de novo combination therapy to prevent lamivudine resistance. Combining lamivudine with adefovir reduced the risk of resistance from 20% with single-agent lamivudine to 2% with the combination.[36] A similar experience was noted when lamivudine was combined with pegylated interferon. In one study, the 1-year incidence of resistance was reduced from 18% to 1%, while a second study reported a reduction from 34% to 11%.[37,38] The addition of telbivudine to lamivudine also reduced resistance from 21% to 12%, but this was still higher than single-agent telbivudine-induced resistance, which was 5%.[39]

Likewise, the addition of lamivudine to adefovir therapy also reduces the risk of adefovir-induced resistance. A 5-year follow-up of single-agent adefovir therapy showed that the incidence of resistance increased from 0% to 3%, 11%, 19%, and 30% in Years 1 through 5, respectively. However, when adefovir was administered in combination with lamivudine, the incidence of resistance remained at 0% over the first 3 years of follow-up.[40]

In addition to the prevention of resistance, other advantages to de novo combination therapy include potentiation or synergy between the two drugs and enhanced durability of response. However, despite the promising results from de novo combination trials, what is yet to be determined is the patient population that is most likely to benefit from these combinations. Hopefully, this question will be clarified in future clinical trials.

Dr. Eugene R. Schiff I agree, and another important point is that the rates of resistance have not been determined in patients with normal ALT levels, mainly because these patients have not been followed in clinical trials.

What are the therapeutic options in treatment-naive patients who have progressed to cirrhosis?

Dr. Robert S. Brown, Jr. In a previously untreated patient with cirrhosis and no evidence of HCC, and no edema or encephalopathy, medical treatment should be initiated before considering transplant. However, the course of therapy must be considered carefully if the patient is HBeAg-positive and anti-HBe antibody negative, with a high viral load. The most important question is that of whether to choose between monotherapy or combination therapy with a nucleos(t)ide agent.

In a case such as this, the best course is the initiation of monotherapy in order to bring down the viral load and avoid the possible emergence of an untreatable resistant variant. If the patient responds well, a second, less potent, nucleos(t)ide agent can be added after the virus has been sufficiently suppressed, in the hopes of promoting improved liver function and reversal of fibrosis.

How does previous antiviral exposure affect the development of resistance to new antivirals?

FP An interesting study was reported at the 2007 European Association for the Study of the Liver.[41] In treatment-naïve patients, resistance rates to entecavir over a 4-year period remained very low (0.1%, 0.4%, 1.1%, 1.9%, for Years 1–4, respectively). However, in patients previously exposed to lamivudine, entecavir resistance rates were dramatically higher over the same 4-year period (6%, 14%, 32%, and 43%, respectively).

Viral load at the initiation of combination therapy also seems to be very important. For lamivudine-resistant patients with a low viral load at the time of adefovir ini-

tiation, the response is quick and robust. However, when viral load is high, especially above 1 million copies/mL, patients do not respond as well to therapy, with less than 80% achieving undetectable HBV DNA levels by 24 months of therapy (P<.0001).[42]

What is the consensus for managing chronic HBV infection in pregnancy?

FP Effectively managing HBV infection during pregnancy is an important component in preventing the vertical transmission of the virus from the mother to the infant perinatally. When no prophylactic methods are used, children of chronically infected women have a 70–90% chance of developing chronic HBV.[43] Fortunately, with the combination of both passive (hepatitis B immune globulin) and active (HBV vaccination) immunoprophylaxis, 90–95% of perinatal transmissions may be prevented.[44,45]

ES Several studies have now indicated that a higher viral load in a pregnant woman confers a greater risk of perinatal transmission.[46,47] In fact, HBV DNA levels greater than 1×10^8 copies/mL carry a greater risk of viral breakthrough even when effective prophylactic measures are taken.[48] For this reason, strategies to reduce viral load in pregnant women can also decrease the risk of perinatal transmission.[49] One way to do this is to initiate antiviral therapy during the third trimester. At present, most guidelines recommend using single-agent lamivudine in this setting, as this drug has been the most extensively studied in pregnant women. In a randomized, double-blind, placebo-controlled study of 120 HBV-infected pregnant women with high (>1,000 mEq/mL) HBV DNA levels, lamivudine administration during the third trimester showed no evidence of triggering birth defects.[50] Importantly, infants born to mothers receiving lamivudine were more likely to be HBsAg-positive (18%; P=.014) than those born to mothers receiving placebo, although all of the infants received immunoprophylaxis.

FP Despite the generally accepted use of lamivudine during the third trimester, there is currently no consensus on how the HBV infection should be effectively managed in women who become pregnant while receiving antiviral therapy. Several of the currently approved anti-HBV oral nucleos(t)ide analogs are designated as pregnancy category C by the Food and Drug Administration because of their teratogenicity or embryolethality in animal studies at very high doses. The pregnancy category C drugs include adefovir, entecavir, and lamivudine. However, it is important to note a study in 38 women who became pregnant while receiving lamivudine and elected to continue their therapy during pregnancy.[51] No pregnancy complications or developmental abnormalities were noted in the newborn infants of these women, and none tested positive for HBV. Telbivudine is classified as pregnancy category B, meaning it showed no teratogenicity in preclinical animal studies, but this has not been confirmed in adequate human trials. Likewise, tenofovir, currently approved for HIV but also active against HBV, is also category B.

The debate for clinicians is whether to stop therapy when the patient realizes she is pregnant or continue therapy during pregnancy, possibly switching to lamivudine or a category B drug. However, an important point to consider when choosing an appropriate agent is the likelihood of the mother requiring long-term antiviral therapy, in which case the risk of drug resistance must be factored in.

What is the evidence for the efficacy of clevudine against chronic HBV?

ES Several clinical trials have now investigated clevudine against HBV. One multicenter, randomized, placebo-controlled phase III study tested clevudine monotherapy in 243 chronically infected HBV patients.[52] After 24 weeks of therapy, clevudine produced statistically significant reductions in HBV DNA levels from baseline compared to placebo (-5.1 vs -0.27; P<.001). Similarly, 68% of patients receiving clevudine achieved normalized ALT levels, compared to only 18% of placebo-treated patients (P<.001). Importantly, clevudine produced a durable residual effect as well, compared to placebo. This was observed after 24 weeks of off-therapy follow-up in both the decrease from baseline HBV DNA levels (-2.02 vs -0.68; P<.001) and normalization of ALT levels (61% vs 28%; P<.001). This residual effect is an important and unique characteristic of clevudine.

When clevudine was investigated in a similar trial of 86 HBeAg-negative patients, it again produced statistically significant reductions in HBV DNA levels from baseline compared to placebo (-4.25 vs -0.48, respectively; P<.0001) and ALT normalization (75% vs 33%, respectively; P=.006).[53] Again, clevudine produced long-term durable effects compared to placebo, with a 24-week off-therapy follow-up revealing statistically significant reductions in HBV DNA levels from baseline (-3.11 vs -0.66, respectively; P<.0001) and ALT normalization (71% vs 29%, respectively; P=.007).

Recently, results of a 1-year follow-up of an open-label extension of the original phase III trial were reported.[54] In this extension study of 55 patients, 40 were HBeAg-positive and 15 were HBeAg-negative. After the first 24 weeks of clevudine at a dose of 30 mg/day, the dose was reduced to 10 mg/day for the subsequent

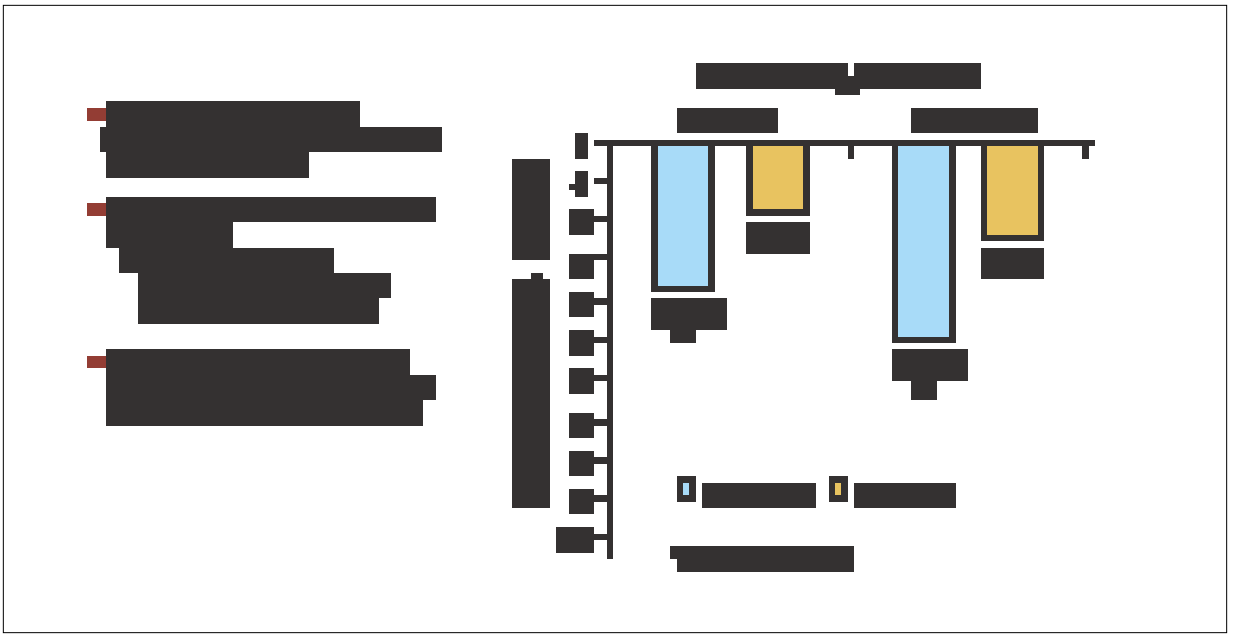

Figure 4. Tenofovir versus adefovir for lamivudine resistance.

Adapted from Hann HW. 40th European Association for the Study of the Liver meeting. April 13–17, 2005. Paris, France.

ALT=alanine aminotransferase; HBV=hepatitis B virus; HBeAg=hepatitis B e antigen.

24 weeks. After the cumulative 48 weeks of therapy, patients were then followed for an additional 12 weeks, during which time they received no additional antiviral therapy. When normalized to the HBeAg-negative patients, 68% of HBeAg-positive patients achieved HBV DNA levels below 300 copies/mL by the end of treatment and 23% maintained residual HBV DNA levels after the additional 12-week follow-up. After normalization to the HBeAg-negative population, 89% of HBeAg-positive patients had normalized ALT levels at the end of treatment, and this was maintained at a high level (86%) during the 12-week off-treatment follow-up.

The durability of the response to clevudine was also evident in a combination trial with emtricitabine.[55] In this trial, patients who had completed an emtricitabine monotherapy study were enrolled in a second 24-week study that randomized patients to receive either continued single-agent emtricitabine or emtricitabine with clevudine added on. After the 24-week treatment period, patients were followed for an additional 24 weeks off treatment. Although no significant difference was evident between the treatment arms at the end of the 24-week treatment period, patients in the clevudine combination arm exhibited statistically significant responses to therapy off treatment. During the follow-up period, 40% of patients in the combination arm and 23% of patients in the emtricitabine-only arm achieved HBV DNA levels less than 4,700 copies/mL (P=.025). Likewise, 63% of patients in the combination arm and 42% of patients in the emtricitabine-only arm achieved normalized ALT levels (P=.002).

What data are available for the use of emtricitabine in HBV patients?

ES Currently, emtricitabine is approved only for the treatment of HIV, but its activity against HBV has been clearly established in several clinical trials. In one controlled double-blind study of emtricitabine monotherapy versus placebo in 247 patients with chronic HBV, 56% of patients in the emtricitabine arm and 7% of patients in the placebo arm achieved undetectable HBV DNA levels, while 65% of patients in the emtricitabine arm and 25% of patients in the placebo arm achieved normalized ALT levels (P<.001 for both comparisons).[56] Importantly, 43% of the emtricitabine-treated patients had both undetectable HBV DNA levels and normalized ALT levels, compared with only 4% of the placebo group (P<.001). In this study, patients received treatment for a total of 48 weeks and resistance mutations were found in 12.6% of the emtricitabine-treated patients at the end of therapy.

Emtricitabine may also be efficacious in combination therapy with adefovir. In a small study of 30 HBeAg-positive patients randomized to receive either adefovir monotherapy or adefovir plus emtricitabine, although a trend of greater reduction in HBV DNA levels from baseline was noted in the combination arm at Week 24 of therapy (-3.19 for single agent vs -5.08 for combination), the difference was not statistically significant.[57] However, by 48 weeks, the combination arm produced statistically significantly superior reductions in HBV DNA levels from baseline compared to adefovir monotherapy (-5.44 vs -3.4; *P*<.03). Another interesting finding from this study was that by Week 12 of therapy, HBV DNA clearance was associated with an enhanced immune response to both hepatitis B core antigen and HBsAg.

What are the most current clinical data for tenofovir use in chronic HBV patients?

ES Like emtricitabine, tenofovir is currently approved only for HIV and is under investigation for HBV. One randomized study compared tenofovir versus adefovir in 109 lamivudine-resistant patients, assessing response at both 6 and 12 months of therapy.[58] In some patients, lamivudine was either maintained or added in. Although no differences were found in either normalization of ALT levels or HBeAg loss, tenofovir produced significantly superior reductions in HBV DNA levels from baseline compared to adefovir (-3.65 vs -1.94 at 6 months, -5.03 vs -2.36 at 12 months: *P*=.001; Figure 4).

Another trial of 106 lamivudine-resistant patients also showed that tenofovir produced superior reductions in HBV DNA levels compared to adefovir (-5.4 vs -3.4, respectively).[59] Although adefovir is efficacious in these patients, its effect is not as potent as tenofovir. Importantly, in this trial tenofovir was administered at 300 mg/day and adefovir was administered at 10 mg/day.

The results of a study of tenofovir in HBeAg-positive patients were presented at the 2007 AASLD meeting.[60] In this study, after a pretreatment liver biopsy, 266 patients were randomized to receive either 300 mg daily tenofovir or 10 mg daily adefovir. After 48 weeks of treatment, another liver biopsy was performed, after which patients were placed on open-label tenofovir, planned to be extended for 5 years. After the 48-week randomization period, 76% of patients in the tenofovir-treated arm exhibited HBV DNA levels less than 400 copies/mL, compared to only 13% in the adefovir-treated arm. This robust drop in HBV DNA levels did not correlate with a difference in HBeAg seroconversion (21% vs 18%, respectively; *P*=NS); however, there is an advantage to the rapid loss of HBV DNA, as it is more likely to result in reductions in liver inflammation and liver disease complications.

A similarly designed study in 376 HBeAg-negative patients was also performed.[61] At the end of the 48-week randomization period, a significantly higher percentage of patients in the tenofovir arm versus the adefovir arm achieved a complete liver response (70.8% vs 48.8%, respectively; *P*<.001), defined as at least a 2-point reduction in the Knodell necroinflammatory score, no worsening of existing fibrosis, and a decrease in HBV DNA levels to less than 400 copies/mL. Although tenofovir again produced statistically significant reductions in HBV DNA levels at 48 weeks (93% vs 63% of patients achieving <400 copies/mL; *P*<.001), the difference is not as dramatic as was seen in HBeAg-positive patients, most likely because of the already comparatively reduced levels of HBV DNA.

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Notes

Hepatitis B Makeover: An Expert Panel Discussion

CME Post-Test: *Circle the correct answer for each question below.*

1. A hallmark symptom of phase 2 of chronic HBV infection is flares in _____.

   a. HBV DNA levels
   b. ALT levels
   c. HBeAg levels
   d. HBsAg levels

2. According to Dr. Afdhal, a phase II study investigating extended lamivudine treatment showed that HBeAg seroconversion took place only in patients with HBV DNA levels _____.

   a. less than 2,000 copies/mL
   b. less than 5,000 copies/mL
   c. less than 10,000 copies/mL
   d. more than 10,000 copies/mL

3. The REVEAL study showed that HBV DNA levels were a prognostic indicator of HCC, finding that patients with HBV DNA levels of more than 1×10^6 had a cumulative HCC incidence of _____.

   a. 1.3% b. 2.7% c. 4.5% d. 14.9%

4. True or false? In the study of 426 HBV patients cited by Dr. Jacobson, patients with genotype C HBV were found to have relatively higher ALT levels.

   a. True b. False

5. Recently, the AASLD guidelines were updated to reflect lower ALT ULN cutoffs: _____ for men and _____ for women.

   a. 5 IU/L; 10 IU/L
   b. 19 IU/L; 30 IU/L
   c. 30 IU/L; 19 IU/L
   d. 24 IU/L; 12 IU/L

6. According to the most recent AASLD guidelines, _____ or _____ are preferred as single-agent therapies due to the lower risk of resistance associated with these agents.

   a. adefovir; lamivudine
   b. adefovir; entecavir
   c. entecavir; telbivudine
   d. lamivudine; telbivudine

7. In a study discussed by Dr. Poordad, the rate of resistance induced by 4 years of entecavir therapy in treatment-naïve patients was _____, dramatically lower than in patients with previous exposure to lamivudine.

   a. 1.9% b. 6% c. 14% d. 43%

8. When proper immunoprophylaxis is administered, _____ _____ of perinatal HBV transmission can be prevented.

   a. 30–35%
   b. 50–55%
   c. 70–90%
   d. 90–95%

9. In a placebo-controlled trial of emtricitabine monotherapy for chronic HBV, ____ of patients receiving active treatment achieved undetectable viral levels.

   a. 51% b. 56% c. 60% d. 67%

10. In a study of 266 HBeAg-positive patients discussed by Dr. Schiff, _____ of patients randomly assigned to receive tenofovir achieved HBV DNA levels less than 400 copies/mL after 48 weeks.

    a. 49% b. 57% c. 65% d. 76%

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Thank you for completing the evaluation form. Your evaluation of the activity and comments are important to us and will remain confidential.

Please answer the following questions by circling the number that best reflects your view.
(Scale: 1 = poor; 2 = fair; 3 = satisfactory; 4 = good; 5 = excellent)

1. Please rate how effectively you are able to:

a. Discuss the factors considered in the decision to commence treatment of patients with chronic hepatitis B infection. 1 2 3 4 5

b. Describe the relationship between hepatitis B infection, viral load, and progressive liver disease. 1 2 3 4 5

c. Apply treatment strategies to effectively suppress hepatitis B viral load and avoid the development of resistance. 1 2 3 4 5

2. Activity/Topic:

a. The extent this program met your continuing professional development goals 1 2 3 4 5
b. The overall quality of the activity 1 2 3 4 5
c. The overall format of the activity 1 2 3 4 5
d. The applicability/usefulness of the material to your practice Not in practice ☐ 1 2 3 4 5

3. Based on your previous knowledge and experience, this activity was:

Too basic ☐ Appropriate ☐ Too complex ☐

4. Do you feel that the activity was objective, balanced, and free of commercial bias? Yes No

If no, why? _____

5. Based on this activity, how might you change your practice management or patient care?

_____

6. Please list any speakers and/or topics you would like in future programs.

_____

7. Would a periodic review of this or related material be appropriate? Yes No

8. We welcome your comments _____

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