

NOVEMBER 2008

# POST AASLD\* American Association for the Study of Liver Diseases 2008 CME/CE UPDATE Assessing Best Practices in HBV Therapy

## INTENDED AUDIENCE

This program will be of interest to primary care providers and infectious disease specialists who provide care to patients with hepatitis B.

## LEARNING OBJECTIVES

Upon the completion of this CME activity, the participant should be able to:

- Discuss significant developments in the diagnosis and management of hepatitis B
- Summarize new drugs and treatment strategies for hepatitis B
- Describe recent hepatitis therapy toxicity, drug interaction and side effect data and strategies for management
- Identify new therapeutic strategies to avoid or overcome antiviral resistance
- Highlight diagnosis and management approaches for hepatitis B in individuals co-infected with HIV

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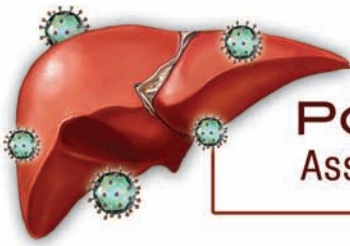


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## POST AASLD\* 2008 CME/CE UPDATE

### Assessing Best Practices in HBV Therapy

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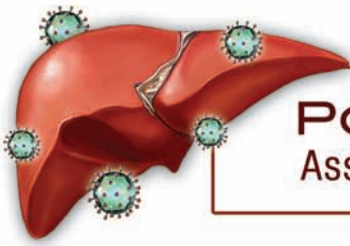
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### Assessing Best Practices in HBV Therapy

#### INTRODUCTION

The 59th Annual Meeting of the American Association for the Study of Liver Diseases was held in San Francisco, California from October 31–November 4, 2008. Presentations at this conference, which is the premier meeting in the science and practice of hepatology, provided some significant new insights into the treatment of patients infected with hepatitis B virus, the most important of which are briefly summarized in this newsletter.

#### THERAPIES FOR CHRONIC HEPATITIS B INFECTION

##### Tenofovir

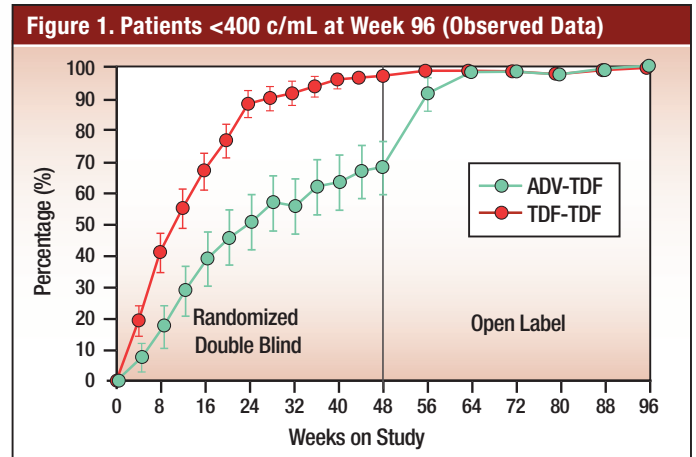
##### *Tenofovir and Adefovir Comparison in Asian Patients with Chronic Hepatitis B Infection*

Because of the high prevalence of chronic hepatitis B infection (CHB) among Asians, researchers analyzed the efficacy and safety of tenofovir (TDF) in Asian patients with CHB. [Abst. 980] A total of 189 Asian CHB patients were enrolled in two phase 3 trials, Study 102 (HBeAg-negative patients) and Study 103 (HBeAg-positive patients), and randomized 2:1 to receive TDF 300 mg or adefovir (ADV) 10 mg once daily (QD) for 48 weeks. At week 48, 85% of patients treated with TDF had an HBV DNA level <400 c/mL, compared with 42% of patients taking ADV ( $p < 0.001$ ). Further, 72% of patients taking TDF had normal ALT levels, compared with 65% of patients taking ADV; and histologic response was seen in 77% of patients taking TDF, compared with 71% of patients taking ADV. Therefore, TDF was superior to ADV in this group of Asian patients.

##### *Tenofovir and Adefovir Comparison in HBeAg-negative Chronic Hepatitis B Infection*

A randomized, double-blind trial enrolled 375 patients with HBeAg-negative CHB to receive either TDF 300 mg (N=250) or ADV 10 mg (N=125) QD. [Abst. 146] After 48 weeks, biopsied patients were switched to open-label TDF for up to an additional 7 years, with the option to initiate combination emtricitabine (FTC) + TDF treatment at or after week 72 for a confirmed HBV DNA  $\geq 400$  c/mL (69 IU/mL). Of the patients who had originally been randomized to ADV and initiated TDF at week 48, all who remained on therapy at week 96 had an HBV DNA < 400 c/mL. (Figure 1) Patients who had an HBV DNA  $\geq 400$  c/mL after 48 weeks of ADV (n=35) and patients stable on ADV (n=77) with an HBV DNA < 400 c/mL both responded favorably to the switch to TDF. For patients treated with TDF during the first 48 weeks, 98% of those on therapy at week 96 had an HBV DNA < 400 c/mL. (Figure 1) Mean ALT values were similar at week 96 for ADV-TDF and TDF-TDF patients with an overall mean ALT value of 37 U/mL. Overall, very few (~1%) initiated open-label FTC+TDF at or after week 72. This study revealed that TDF produced considerable and persistent viral suppres-

sion and was well tolerated through week 96 with no resistance observed and 99% of individuals having an HBV DNA <400 c/mL.

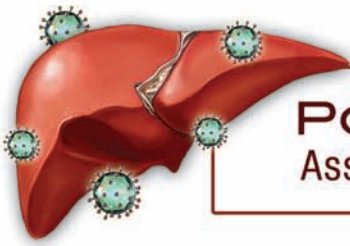


##### *TDF Resistance Surveillance*

To evaluate amino acid changes within the HBV pol/RT following treatment with TDF and to determine the potential association of these changes with resistance to TDF, investigators conducted two studies, GS-US-174-0102 (HBeAg-negative patients) and GS-US-174-0103 (HBeAg-positive patients). [Abst. 977] Sequencing of the serum hepatitis B virus pol/RT was performed for all patients at baseline and at 96 weeks for viremic subjects (HBV DNA  $\geq 400$  c/mL). Of the 389 patients who entered the second year of the studies, 5 with HBV DNA  $\geq 400$  c/mL at week 96 and 19 who discontinued TDF monotherapy between week 48 and week 96 with an HBV DNA  $\geq 400$  c/mL were evaluated for genotypic resistance. All other patients had HBV DNA <400 c/mL at their last visit. Of the 19 patients who discontinued TDF, 2 had conserved site changes in HBV pol/RT in the absence of virologic breakthrough and both had achieved  $>6 \log_{10}$  c/mL decline from baseline in HBV DNA and were still declining when the changes were detected. Of the 5 subjects who experienced virologic breakthrough during the second year of the studies; 3/5 had no changes in pol/RT and 2/5 had polymorphic site changes. The incidence of these polymorphisms in patients at baseline ranged from 6% to 60% and did not have an impact on the antiviral response to TDF. The majority of the subjects with virologic breakthrough had a history of noncompliance. The investigators concluded that conserved site changes in HBV pol/RT were rare and did not result in virologic breakthrough among patients treated with TDF. This prospective study, with an adequate methodology, showed that TDF has an excellent resistance profile when used in monotherapy for 2 years.

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### Tenofovir in HIV-HBV co-infected Individuals

A study investigated the impact of TDF on liver fibrosis dynamics in patients with HIV/HBV co-infection. [Abst. 914] A total of 130 patients who were HIV/HBV co-infected were treated with TDF and followed for a median of 29.4 months. At baseline, 74 patients presented with Fibrometer® stage F0-F1-F2 and 56 patients with stage F3-F4. Among patients with F3-F4 baseline fibrosis stages, there was a considerable decline in fibrosis score at 12 months (-0.126; 95% CI: -0.209, -0.044;  $p=0.003$ ), followed by a slow and stable decline at 24 and 36 months of treatment (-0.149; 95% CI: -0.250, -0.049;  $p=0.004$  and -0.171; 95% CI: -0.329, -0.013;  $p=0.03$ , respectively). Patients with F0-F1-F2 baseline fibrosis remained consistently stable over time. This study revealed that TDF induces a significant decrease in fibrosis level in HIV/HBV co-infected patients with fibrosis at baseline, including those with advanced fibrosis.

A retrospective study compared the early virologic response in HIV/HBV co-infected patients of de novo combination therapy with TDF plus either lamivudine (LAM) or emtricitabine (FTC) (Group I,  $n=15$ ) versus add-on therapy with TDF added to ongoing LAM therapy (Group II,  $n=46$ ). [Abst. 922] All Group I patients achieved early virologic response ( $<3 \log \text{ IU/mL}$ ) at month 6 vs. 75% of patients in Group II ( $p=0.035$ ). Fourteen Group II patients met criteria for primary non-response (HBV DNA decrease  $<1 \log \text{ IU/mL}$  at 6 months of TDF); 7 were non-adherent by drug level measurement and the 7 remaining patients achieved a delayed response to TDF after a median of 20 months of TDF therapy. In this cohort of HIV/HBV co-infected patients, de novo combination therapy with TDF plus either LAM or FTC appeared to lead to a better earlier virologic response than add-on therapy, and should strongly be considered in HIV/HBV co-infected individuals.

### Entecavir

#### Long-term Entecavir Treatment in Chronic Hepatitis B Patients

Researchers assessed histologic improvement in CHB patients in Japan who had evaluable liver biopsies after receiving at least 3 years of entecavir (ETV) therapy during the open-label, rollover study ETV-060 that was performed following two phase II studies (ETV-053 and ETV-052). [Abst. 889] In ETV-053, 66 nucleoside-naïve patients received ETV 1.0 mg or 0.5 mg for 52 weeks; in study ETV-052, 84 LAM-refractory patients received these same ETV regimens. In ETV-060, patients received ETV 0.5 mg (naïve) or ETV 1 mg (LAM-refractory) for  $>96$  weeks. The investigators performed liver biopsies on 37 naïve patients and 27 LAM-refractory patients at three time points. At week 148, there were significant improvements from baseline in Knodell necroinflammation and fibrosis for both naïve and LAM-refractory patients. (Table 1) Also, at week 148, 95% of naïve and 56% of LAM-refractory patients had an HBV DNA level  $<400 \text{ c/mL}$ ; and 95% of naïve and 93% of LAM-refractory patients had normalized ALT levels. In summary,

both naïve and LAM-refractory CHB patients demonstrated significantly improved liver histology after three years of ETV therapy.

**Table 1. Liver Histology Improvement on ETV in ETV-060**

	Week 48	Week 148
<b>Naïve patients</b>		
Improvement in Knodell NI score, n/n (%)	31/37 (84)	37/37 (100)*
Improvement in Knodell fibrosis score, n/n (%)	6/36 (17)	17/36 (47) <sup>†</sup>
<b>LAM-refractory patients</b>		
Improvement in Knodell NI score, n/n (%)	15/26 (58)	23/26 (89)*
Improvement in Knodell fibrosis score, n/n (%)	3/25 (12)	8/25 (32) <sup>‡</sup>

\* $p < 0.0001$  compared to baseline

<sup>†</sup> $p = 0.0002$  compared to baseline

<sup>‡</sup> $p = 0.043$  compared to baseline

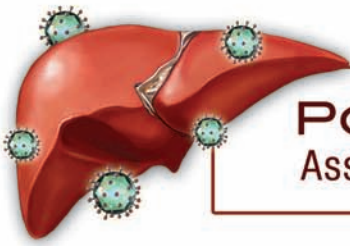
#### Long-term ETV Therapy in HBeAg-positive Chronic Hepatitis B Patients

A study documented the efficacy and safety results of ETV in nucleoside-naïve, HBeAg-positive patients who received a total of five years of continuous ETV treatment in studies ETV-022/-901. [Abst. 893] A total of 146 ETV-treated patients from study -022 enrolled in study -901, through which they continued to receive ETV (1 mg QD) for up to a total of 5 years. Investigators noted that of the 94 patients that remained on ETV therapy at the end of 240 weeks, 94% had an HBV DNA  $<300 \text{ c/mL}$ , 80% had an ALT  $\leq 1 \times \text{ULN}$ , 41% had HBeAg loss and 17% had HBeAg seroconversion. Further, 63 patients in ETV-022/-901 with an HBV DNA  $<300 \text{ c/mL}$  at the end of 240 weeks of therapy were evaluated for histologic changes. [Abst. 894] A significant number of patients experienced histologic improvements (96%), improvements in Ishak fibrosis score (88%  $\geq 1$  point), and ALT normalization (86%). Five patients had baseline cirrhosis (Ishak fibrosis score  $\geq 5$ ), four of whom had evaluable long-term biopsies and all four demonstrated a  $\geq 1$  point improvement in Ishak fibrosis score with a median change from baseline of -3 (range: -1 to -4). These analyses indicate that long-term treatment with ETV results in profound and durable virologic suppression and histologic improvement, with regression of fibrosis.

#### ETV in Patients who Failed LAM-ADV Sequential Therapy

While ETV is recommended for CHB patients who are resistant to LAM or ADV, the efficacy of ETV in patients who previously failed LAM-ADV sequential therapy is unclear. To test this, researchers compared the efficacy of ETV monotherapy in patients who showed viral breakthrough or non-response during LAM-ADV sequential therapy ( $n=39$ ) or LAM monotherapy ( $n=31$ ). [Abst. 948] In this study, patients were treated for at least 24 weeks with ETV 1 mg QD. At week 24 of ETV therapy, the mean decrease in serum HBV DNA was significantly higher in the LAM monotherapy group compared with the sequential LAM-ADV group ( $-3.97$  vs.  $-1.42 \log_{10} \text{ c/mL}$ ,  $p < 0.001$ ).





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In addition, more patients in the LAM monotherapy group had an HBV DNA level  $<10^4$  c/mL (48.4% vs. 20.5%,  $p=0.021$ ), despite having a greater baseline level. An undetectable HBV DNA was seen exclusively in 5 of the LAM monotherapy patients, but the rates of HBeAg seroconversion and loss or ALT normalization did not differ significantly between the two groups. The investigators concluded that switching to ETV as rescue therapy is less effective in patients with LAM-ADV resistance following LAM-ADV sequential therapy than in those who have failed only LAM monotherapy. This study confirmed that sequential monotherapy exposes patients to multiple failures and viral resistance. It strengthens the argument that, in general, sequential monotherapy should be avoided and that, in the event a patient develops resistance on monotherapy, add on therapy is the best approach.

#### Telbivudine

##### *Long-term Telbivudine in HBeAg-positive Patients*

Investigators analyzed the response at 3 years in HBeAg-positive, CHB patients who had achieved an undetectable HBV DNA and HBeAg seroconversion after two years of telbivudine (LdT) treatment. [Abst. 942] At year 3, all 87 patients in this study maintained HBeAg loss, 93.1% maintained HBeAg seroconversion, and 88% maintained ALT normalization. In 90.8% of patients, both HBeAg loss and serum HBV DNA  $<10^3$  c/mL were present at year 3. For 9.2% of patients, the serum HBV DNA was between  $10^3$  and  $10^5$  c/mL. This study showed that continued LdT in patients who achieve HBeAg seroconversion can effectively maintain control of HBV replication.

#### Interferon

##### *Hepatitis B Virus Genotypes and Interferon Treatment*

Investigators designed a study to determine the influence of HBV genotypes on treatment outcomes in 1,229 CHB patients treated with interferon- $\alpha$ . [Abst. 883] Patients infected by HBV genotype A ( $n=174$ ), genotype B ( $n=245$ ), genotype C ( $n=464$ ) and genotype D ( $n=346$ ) were treated with standard interferon- $\alpha$ , pegylated interferon- $\alpha$ , or a combination of pegylated interferon- $\alpha$  with LAM for 6 to 12 months. A sustained virological response (SVR, defined as ALT normalization with a decrease of HBV DNA to  $<20,000$  c/mL and, in HBeAg-positive patients, HBeAg seroconversion) was seen in 35.6% of patient with HBV genotype A, 24.9% of patients with genotype B, 27.8% of patients with genotype C, and 19.6% of patients with genotype D ( $p<0.001$ ). SVR for HBeAg-positive and -negative patients, respectively, were 36.3% and 34.0% for genotype A, 21.1% and 32% for genotype B, 18.5% and 50.4% for genotype C, and 14.6% and 21.4% for genotype D ( $p<0.001$ ). HBV genotypes, HBeAg status, and ALT level were independent predictors for SVR. This study revealed that HBV genotype is the strongest predictor for response to interferon- $\alpha$  with genotype C having a high response in HBeAg-negative individuals.

#### COMBINATION THERAPY WITH APPROVED AGENTS

##### *Entecavir Plus Tenofovir for Treatment of Chronic Hepatitis B Infection*

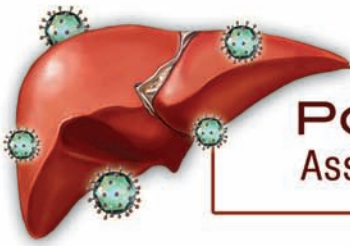
TDF and ETV are very potent HBV antiviral therapies with relatively high genetic barriers to resistance. While extensively studied as monotherapy in persons who are treatment-naïve, no data has been available on the combination of these two agents in treatment-experienced, CHB patients. Despite this paucity of data, experts have speculated that combination therapy with ETV + TDF may be highly effective due to non-overlapping resistance pathways. Accordingly, this small, open-label study is important in that it evaluated a combination therapy strategy for the treatment of CHB. The investigators studied the efficacy and safety of TDF (245 mg) and ETV (1 mg) QD in 12 male, treatment-experienced patients with multidrug resistant HBV and established cirrhosis (9 HBeAg-positive). [Abst. 985] Patients were treated with the combination therapy for a median of 6 months. The median HBV DNA drop was 4.6  $\log_{10}$  c/mL (range 1.7-7.8  $\log_{10}$  c/mL;  $p<0.0001$ ) and in 9 patients HBV DNA was  $<400$  c/mL. Patients also experienced a significant decline in ALT levels (median 1.2xULN; range 0.44-4.2;  $p=0.001$ ). No patient experienced hepatic decompensation and no treatment related adverse effects were observed. Although limited, these data demonstrate the potential effectiveness and tolerability of combination therapy with TDF plus ETV in extensively treated patients. Additional research is needed to assess the long-term safety and antiviral efficacy of this regimen.

##### *Adefovir plus Lamivudine Following Lamivudine Monotherapy Failure*

The strategy of "rescuing" patients failing LAM monotherapy due to resistance with the addition of ADV has been supported by multiple short-term studies demonstrating low rates of viral breakthrough. Four year follow-up data were provided from a study in which 143 LAM-resistant patients were treated with the addition of ADV (10 mg) QD to ongoing LAM (100 mg) QD. [Abst. 906] Overall, 116 (81%) of patients achieved an undetectable HBV DNA, with year 1 through 5 clearance rates of 58%, 68%, 78%, 88%, and 86%, respectively. No virologic or clinical breakthrough was observed and no patient developed ADV resistant mutations at position 236 (N $\rightarrow$ T). Interestingly, among 6 patients with mutations at position 181 (implicated in resistance to ADV), 5 achieved an undetectable HBV DNA during therapy while the remaining patient had an incomplete response after 36 months requiring switch of ADV to TDF. Serum creatinine increases  $>0.5$  mg (compared to baseline) were observed in 23 patients which stabilized or improved following adjustment of ADV dosing to every other day. Thus, "Add-on" ADV in LAM-resistant patients was effective and prevented virologic breakthrough up to 4 years.

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#### *Adefovir plus Lamivudine De Novo Combination Therapy*

To prevent multidrug resistant HBV from developing, researchers tested the potential of de novo combination therapy with ADV plus LAM. [Abst. 930] In this retrospective study, 201 patients with CHB receiving LAM plus ADV were split into 2 groups: de novo combination LAM plus ADV and add-on ADV to LAM. At month 3, more patients in the de novo group achieved an undetectable HBV DNA (35% vs 10%,  $p=0.01$ ). At month 6, similar proportions had an undetectable HBV DNA, but fewer de novo patients had non-response ( $<1 \log_{10}$  c/mL HBV decline) (4% vs 15%,  $p<0.001$ ). At month 18, more de novo patients experienced an undetectable HBV DNA (63% vs 35%,  $p=0.04$ ) and fewer had non-response (0 vs 12%,  $p<0.01$ ). The mean decrease in HBV DNA ( $\log_{10}$  c/mL) was greater in de novo patients than add-on patients at all time points (month 3,  $3.4\pm 0.1$  vs.  $2.0\pm 0.4$ ,  $p<0.001$ ; month 6,  $4\pm 0.2$  vs.  $2.1\pm 0.3$ ,  $p<0.001$ ; month 12,  $4.2\pm 0.2$  vs.  $2.3\pm 0.3$ ,  $p=0.004$ ; month 18,  $4.1\pm 0.7$  vs.  $2.4\pm 0.5$ ,  $p=0.02$ ) and only add-on patients ( $n=5$ ) had viral breakthrough. In summary, this study found that de novo LAM plus ADV was more effective than adding ADV to LAM.

#### *Peginterferon alfa-2a plus Ribavirin for Chronic Hepatitis B Infection*

Ribavirin (RBV) substantially increases the effectiveness of IFN-alfa in the treatment of hepatitis C; its role in the treatment of CHB is unknown. In an international, multicenter trial, HBeAg-negative patients were randomized to receive PegIFN alfa-2a 180 mcg weekly + Placebo ( $n=69$ ) or PegIFN alfa-2a + RBV 1000 or 1200 mg per day ( $n=64$ ) for 48 weeks. [Abst 991] Twenty-four weeks after discontinuation of therapy, no difference was observed with respect to durable HBV DNA suppression (9% PegIFN vs. 6% PegIFN/RBV) or ALT normalization (41% PegIFN vs. 52% PegIFN/RBV). HBsAg seroconversion was observed in only 1 patient. Treatment discontinuations were similar in both groups. The addition of RBV to PegIFN did not improve virologic or immunologic outcomes in HBeAg-negative CHB patients.

### **COST EFFECTIVENESS**

#### *Cost-effectiveness of Antiviral Drugs in HBeAg-negative Patients with Chronic Hepatitis B*

A simulation analysis using a Markov model was designed to estimate the impact of initiating treatment with TDF, LAM, ADV, and ETV on cost and quality of life in HBeAg-negative patients in the United States. [Abst. 976] The model was used to predict the incidence and cost of disease-related complications according to levels of HBV DNA over time, and an analysis was conducted based on a population of 1,000 simulated patients per treatment over a period of 20 years. Patients were assumed to be treatment-naïve at the time that their treatment was initiated, and if they became resistant, they could switch or add-on another treatment. Patients who also developed resistance to

subsequent treatments were assumed to discontinue treatment. Patients who developed decompensated cirrhosis or hepatocellular carcinoma were eligible for liver transplants. The model indicated that patients who initiated treatment with TDF would generate lower pharmacy and medical costs than LAM, ADV and ETV and have a greater (LAM and ADV) or similar (ETV) number of quality-adjusted life years. (Table 2) These findings resulted from a low expected resistance rate for TDF compared with LAM and a lower acquisition cost than ETV and ADV. Although the long-term medical costs associated with care and treatment of HBeAg-negative patients are not completely known, this study suggests that TDF is a more cost-effective treatment than LAM, ADV, and ETV.

**Table 2. HBV Antiviral Cost-Effectiveness**

	TDF	LAM	ADV	ETV
Total pharmacy and medical cost per patient (US\$)	117,794	152,336	138,950	141,409
Cost of initial and subsequent HBV treatments (US\$)	94,781	101,990	105,449	117,648
Quality-Adjusted Life Years	10.28	8.93	9.72	10.28

### **NOVEL AGENT: CLEVDUDINE**

#### *48 week Clevudine Therapy in Chronic Hepatitis B Patients*

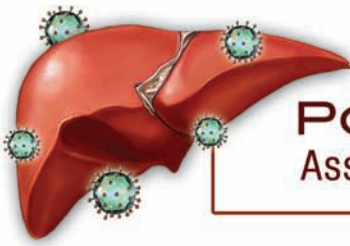
Clevudine (CLV) is a pyrimidine nucleoside analogue with previously reported potent antiviral activity over 24 weeks of therapy. In an open-label study of 34 treatment-naïve patients with CHB, the efficacy and resistance profile of CLV (30 mg) QD over 48 weeks was assessed. [Abst. 943] Among 24 HBeAg-positive patients, HBV DNA decreased by a mean of  $4.7\pm 0.7 \log_{10}$  c/mL, HBV DNA was undetectable in 75%, serum ALT levels normalized in 83%, and HBeAg loss was observed in 3 patients. In 10 HBeAg-negative patients, HBV DNA was undetectable in all patients, and serum ALT levels were normalized in 80%. Two HBeAg-positive patients showed viral breakthrough and had HBV polymerase mutation rtM204I. No adverse events were reported. These data suggest that CLV is effective in HBeAg-negative and -positive patients; however, resistance was observed in ~8% of HBeAg-positive patients. The observed polymerase mutation (rtM204I) would be expected to confer cross-resistance to LAM and LdT and decreased sensitivity to ETV.

#### *Clevudine Therapy in Lamivudine-experienced Patients*

Researchers evaluated the efficacy of "switching" 116 patients with CHB who were failing LAM therapy to treatment with CLV. [Abst. 902] The median change in HBV DNA after 36 weeks and 48 weeks of treatment was 3.0 ( $n=88$ ) and 4.5  $\log_{10}$  c/mL ( $n=28$ ), respectively. Viral breakthrough ( $> 1 \log_{10}$  c/mL increase from nadir) during CLV therapy was reported in 5 subjects (resistance mutations not reported).

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The authors concluded that CLV demonstrated potent antiviral activity in LAM-experienced patients. Nonetheless, the observation of viral breakthrough in 5 subjects and the previously reported cross-resistance of LAM and CLV resistance variants indicate that this type of “switch” strategy would be expected to be inferior to a strategy of combination therapy with CLV and a nucleotide analogue (ADV or TDF).

### *Clevudine versus Lamivudine in treatment-naïve patients*

An ongoing randomized, controlled trial compared the efficacy and safety of CLV versus LAM administered for 48 weeks in HBeAg-positive, CHB patients in Hong Kong. [Abst. 911] Eligible subjects were HBeAg-positive with a HBV DNA levels > 3 million c/mL and ALT > ULN. To date, 55 subjects have completed 48 weeks of therapy: 29 in the CLV group and 26 in the LAM group. At week 48, the CLV arm had a significantly greater decline in HBV DNA than the LAM arm (-4.7 vs. -3.2 log<sub>10</sub> c/mL, *p* < 0.01). In the CLV and LAM arms, respectively, at week 48 72% and 46% achieved a serum HBV DNA levels <300 c/mL and 17% and 8% had HBeAg seroconversion. LAM-resistant mutations were detected in 9 patients in the LAM group compared with none in the CLV group. The preliminary results from this study suggest that CLV therapy is superior to LAM therapy for HBeAg-positive, CHB patients with greater viral suppression and lower incidence of resistance over 48 weeks.

## RESISTANCE ISSUES

### *Tenofovir-associated Resistance Mutations*

A retrospective study evaluated the development of mutations in CHB patients during TDF treatment. [Abst. 913] The study included 48 CHB patients treated with TDF (300 mg) QD for ≥ 12 months. Prior to TDF treatment, 43 patients had been treated with LAM and 33 patients with ADV for a mean duration of 27 and 13 months, respectively. At baseline, 20 patients had wild type HBV, 22 patients had genotypic resistance to LAM, and six had genotypic resistance to ADV. In all patients with initial ADV resistance, mutations associated with ADV resistance remained detectable during TDF treatment and only one patient achieved an HBV DNA <400 c/mL at month 12 (*p* < 0.0001). In four patients without genotypic resistance to ADV at baseline, ADV resistant variants (rtA181T, rtA181V, rtA181T+rtN236T) became detectable between months 5 and 11 of TDF treatment, however, after 12 months of TDF treatment, three of the four patients achieved an HBV DNA level <400 c/mL. No new mutations or an increase of HBV DNA levels was observed during TDF treatment. Therefore, while HBV variants associated with resistance to ADV and LAM can become detectable during TDF treatment, this does not seem to influence response to TDF. Follow-up is needed to confirm that ADV mutations that arise during TDF treatment do not influence the long-term efficacy of TDF.

### *Primary Resistance Mutations in Treatment-naïve Patients*

A study was designed to determine the occurrence of primary resistance mutations in treatment-naïve, CHB patients taking nucleos(t)ide analogues and the association of these mutations with viral genotypes. [Abst. 884] Among 288 patients, the distribution of HBV genotypes was: 56.9% D, 28.8% A, 5.6% C, 4.2% E, 2.7% B, and 0.7% G. Primary resistance mutations were observed in 9.3% when polymorphisms (at nucleotides 215 and 217) are excluded and in 34.7% when polymorphisms are included. (Table 3) Primary resistance mutations, not including polymorphisms, were detected at a rate of 8.2% in genotype A, 20.8 % in genotype B/C, 10.4 % in genotype D and 0% in genotype E. Polymorphisms at nucleotide 217 were highly associated with genotype A, and polymorphisms at nucleotide 215 with genotype D. Patients with primary resistance mutations were less frequently HBeAg-positive compared with patients without primary resistance mutations (25% vs. 44%; *p* < 0.008). However, these patients did not differ in ALT levels and viral load. This study found that about 10% of all treatment-naïve patients were diagnosed with primary resistance mutations against nucleos(t)ide analogues.

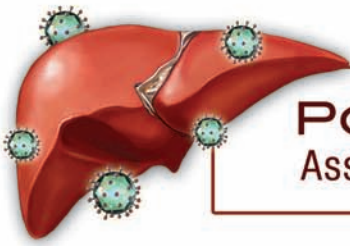
**Table 3. Frequency of Specific Resistance Mutations**

	V173L/M	L180M	A181S/V/T	T184I	A194G/T	M204I	M204V	I233V/K/R	N236D
n	1	3	3	1	3	2	2	11	1
[%]	0.3	1.0	1.0	0.3	1.0	0.7	0.7	4.0	0.3

Another study documented the prevalence of antiviral resistance mutations among treatment-naïve, CHB patients using a sensitive line probe assay. [Abst. 888] A total of 209 treatment-naïve, adult CHB patients were tested. The prevalence of spontaneous antiviral resistance mutations was: rtL180M 10%; rtM204V/I 12%; rtL80V/I 9%; rtV173L 3%; rtA181V/T 0%; rtN236T 0%. Patients with high HBV DNA levels and male gender were more likely to harbor these mutants. Among patients with LAM-resistance at baseline, three patients received LAM 100 mg QD (mean duration 11 months); one had primary non-response, while two had virologic breakthrough. However, in three patients treated with ADV 10 mg QD or TDF 300 mg QD (mean duration 7 months), all had undetectable viral DNA at last follow-up.

These data suggest that baseline resistance to nucleosides (LAM, FTC, ETV, d4T) may be more common than nucleotides (TDF and ADV) and that antiviral resistance testing among treatment-naïve patients is important in order to tailor therapy and optimize treatment response. However, further studies are required to determine the role of testing in routine clinical practice.

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#### TREATMENT TO PREVENT COMPLICATIONS AND IMPROVE QOL

##### *Therapy to Prevent Hepatocellular Carcinoma*

A total of 203 CHB patients diagnosed with cirrhosis were enrolled in a study to determine the relationship between the level of HBV DNA and hepatocarcinogenesis. [Abst. 895] The incidence rates of hepatocellular carcinoma (HCC) were 13% at the 5th year and 32% at the 10th year. High HBV DNA levels ( $\geq 5 \log_{10}$  c/mL, relative risk 2.97,  $p=0.0194$ ), age ( $\geq 50$  years, relative risk 2.44,  $p=0.0064$ ) and platelet count ( $<100,000/\mu\text{l}$ , relative risk 3.16,  $p=0.0003$ ), were independent and significant risk factors for HCC. Among patients with high HBV DNA levels ( $\geq 5 \log_{10}$  c/mL), the cumulative HCC incidence rate of patients who underwent nucleoside analogue (NA) therapy was 8% at the 5th year, compared with 26% among non-therapy patients ( $p=0.0157$ ). This study found that the HCC rate of patients who underwent NA therapy was significantly lower than that of non-therapy patients and that NA therapy was an independent predicting factor for lower hepatocellular carcinogenesis among patients with high viral load ( $p=0.0027$ ; relative risk 0.26). Thus, appropriate use of NA therapy has the potential to decrease the risk of HCC.

##### *On-treatment Virologic Response Predicts Development of Hepatocellular Carcinoma*

To assess the incidence, clinical patterns, and risk factors for HCC in patients with CHB treated with oral antiviral agents, investigators reviewed the medical records of the 874 patients who were diagnosed with liver disease and treated with LAM and/or ADV over one year. [Abst. 1448] Among these patients, 562 were treated with LAM only, 228 switched to ADV after the development of LAM resistance, and 84 added ADV after LAM resistance. HCC developed in 55 patients (6.7%), whose mean duration of follow-up was  $4.5 \pm 2.3$  years. Compared with patients who did not develop HCC, patients who developed HCC were older (47.8 years vs. 40.0 years,  $p<0.001$ ), more likely to have cirrhosis (87.3% vs. 44.7%,  $p<0.001$ ), and had lower albumin and platelet levels ( $p<0.001$ ). In addition, the sustained viral suppression was only 10.9% in the group that developed HCC compared with 44.6% in the group that did not ( $p<0.001$ ). Among patients ( $n=310$ ) with Child-Pugh A liver cirrhosis, HCC developed in 2.8% (3/108) of those with sustained viral suppression and in 13.4% (27/202) of those without sustained viral suppression ( $p=0.002$ ). The risk factors for the development of HCC by the Cox regression model were age ( $p<0.001$ ), cirrhosis ( $p=0.009$ ), and on-treatment virologic response ( $p=0.034$ ). This study, like the prior study, indicates the importance of antiviral therapy in preventing HCC.

#### ALTERNATIVES TO LIVER BIOPSY

##### *Serum Markers as Indicators of Liver Cirrhosis*

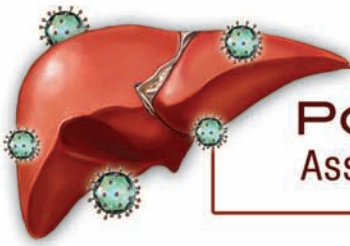
While liver biopsy is considered the gold standard for evaluating cirrhosis, it has several shortcomings including its invasive nature, its potential to cause complications of bleeding and infection, and its limited accuracy. Therefore, researchers tested the potential of certain serum markers as non-invasive predictors of cirrhosis in CHB patients. [Abst. 846] Among the 125 patients with CHB in this study, 34 patients (27.2%) were diagnosed with cirrhosis on liver biopsy. Age, platelet count, WBC count, AST, ALT, haptoglobin, apo-A1, MMP-2, and YKL-40 were significantly different between patients with chronic hepatitis and patients with cirrhosis by univariate analysis. By multivariate analysis, platelet count, AST, haptoglobin, and apo-A1 were independent predictive factors for cirrhosis. With these four factors, the investigators created a scoring system called the PAHA index. PAHA indices were significantly different between patients with chronic hepatitis and patients with cirrhosis ( $3.6 \pm 2.3$  and  $6.8 \pm 1.9$ , respectively;  $P<0.001$ ). Area under the ROC curve of PAHA index for predicting cirrhosis was 0.85 (95% CI, 0.78-0.92). With a cut-off value of 5.5, sensitivity, specificity, positive predictive value and negative predictive value were 75.8%, 81%, 60.9%, and 89.5%, respectively. In summary, the PAHA index including platelet count, AST, haptoglobin, and apo-A1 was useful for predicting cirrhosis in patients with CHB. Therefore, the PAHA index might help reduce the need for liver biopsies.

##### *Liver Stiffness as an Indicator of Liver Cirrhosis*

While transient Elastography (TE) is a reliable non-invasive predictor of hepatic fibrosis, data on that procedures use in patients with CHB are limited. A prospective study was designed to evaluate the accuracy of TE for diagnosis of hepatic fibrosis in these patients. [Abst. 899] The study included 104 patients who underwent liver biopsy prior to antiviral therapy. Liver stiffness measured with TE (Fibroscan®) as well as liver histology graded by METAVIR classification were performed on the same day. Spearman rank correlation was used to evaluate the association between liver stiffness and liver histology.

The median liver stiffness was 6.9 kPa, which correlated with histological fibrosis grade ( $r=0.719$ ,  $p<0.001$ ) and necroinflammation activity ( $r=0.656$ ,  $p<0.001$ ). Area under the ROC curve for diagnosis of significant fibrosis was 0.757 (95% CI: 0.66, 0.84) and advanced fibrosis was 0.793 (95% CI: 0.70, 0.87). Optimal liver stiffness value was 6.9 kPa for diagnosis of significant fibrosis, which yielded a sensitivity of 70%, specificity of 79%, positive predictive value of 82%, and negative predictive value of 66%. Optimal liver stiffness value was 7.3 kPa for diagnosis of cirrhosis, which provided a sensitivity of 93%, specificity of 61%, positive predictive value of 31%, and negative predictive value of 98%. This study revealed that liver stiffness is a reliable predictor of hepatic fibrosis in patients with CHB and that this non-invasive procedure could help identify significant fibrosis in these patients.





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### NEED FOR LIVER BIOPSY

#### *Histological Characteristics of HBeAg-negative Chronic Hepatitis B Patients with Normal ALT Levels*

Because information on HBeAg-negative carriers with persistently normal ALT levels is limited, a study assessed the histological features of these patients and the factors influencing their disease progression. [Abst. 838] A total of 154 HBeAg-negative, CHB patients who underwent percutaneous liver biopsies were enrolled, 56 with abnormal ALT levels and 98 with persistently normal ALT levels. When evaluating liver pathology by Ishak scoring system, investigators found that patients with persistently normal ALT levels had lower histological activity index and fibrosis scores than those with abnormal ALT levels (0 vs. 5.5,  $p=0.000$ ; 0 vs. 3,  $p=0.000$ ). However, 22.4% and 17.3% of patients with persistently normal ALT levels had histological activity index scores  $\geq 4$  and fibrosis scores  $\geq 3$ , respectively. Patients with ALT  $>0.50 \times \text{ULN}$  had a significantly higher rate of these histological findings than those with ALT  $<0.50 \times \text{ULN}$  (36.4% vs. 11.1%,  $p=0.003$ ; 27.3% vs. 9.3%,  $p=0.019$ ). Also, patients older than 45 years had a higher proportion of fibrosis scores  $\geq 3$  than younger patients (33.3% vs. 13.4%,  $p=0.027$ ). Fibrosis and an increase in age by a decade were independent predictors of histological activity index scores  $\geq 4$  (OR=2.584,  $p=0.000$ ; OR=2.410,  $p=0.023$ ), while histological grade was the only independent predictor of fibrosis scores  $\geq 3$  (OR=2.179,  $p=0.000$ ). HBV DNA was detectable ( $\geq 10^3$  c/mL) in 91.3% of individuals with persistently normal ALT levels. In patients with HBV DNA  $<10^4$  c/mL, 14.9% had histological activity index scores  $\geq 4$  and 12.8% had fibrosis scores  $\geq 3$ . While liver histology is worse in HBeAg-negative CHB patients with an abnormal ALT, even patients with a persistently normal ALT may have abnormal histology and benefit from liver biopsy.

#### *Need for Liver Biopsy in HBeAg-negative Chronic Hepatitis B Patients with HBV DNA $<20,000$ IU/mL*

A study was designed to evaluate the severity of liver histology in HBeAg-negative CHB patients with HBV DNA  $<20,000$  IU/mL [Abst. 840]. Liver biopsies were performed in 105 HBeAg-negative patients with increased ALT levels and an HBV DNA of 80-20,000 IU/mL (group A) and in 35 HBeAg-negative patients with persistently normal ALT levels and an HBV DNA 2,000-19,999 IU/mL (group B). Patients in group A had higher ALT levels, worse grading score (6.1 vs 2.9,  $P<0.001$ ), and worse stage (2.6 vs 1.0,  $p<0.001$ ) than patients in group B. Histological treatment indication was present in 70% of group A patients and in only 17% of group B patients. The study found no substantial differences between HBeAg-negative CHB patients with elevated ALT levels and hepatitis B virus DNA  $<2,000$  or 2,000-20,000 IU/mL. The data indicate that liver biopsy is required for all HBeAg-negative patients with elevated ALT levels regardless of viremia. However, immediate liver biopsy is not required for HBeAg-negative patients with persistently normal ALT levels and hepatitis B virus DNA 2,000-20,000 IU/mL.

#### *Liver Biopsy in Patients with Normal ALT Levels*

A study investigated the prevalence of advanced fibrosis in patients with normal and near-normal ALT levels in a non-Asian setting [Abst. 973]. Investigators retrospectively analyzed 252 patients with chronic, replicative hepatitis B who underwent liver biopsy, finding that 38 had normal and 214 had elevated ALT levels, with 84 of those with an elevated ALT  $<2 \times \text{ULN}$ . A significant portion of the patients with normal or slightly elevated transaminases were found to have advanced liver fibrosis or cirrhosis. (Table 4) Therefore, these data indicate that liver biopsy should be considered for patients with normal or near normal ALT levels.

**Table 4. Rates of Liver Disease**

Parameter	Normal ALT (n=38)	ALT $<2 \times \text{ULN}$ (n=84)	ALT $>2 \times \text{ULN}$ (n=130)
Significant liver fibrosis $\geq \text{F3}$	16/38 (42%)	45/84 (54%)	82/130 (63%)
Liver cirrhosis	9/38 (24%)	21/84 (25%)	28/130 (22%)
Significant inflammation $\geq \text{G2}$	7/27 (26%)	34/66 (52%)	71/104 (68%)

### HEPATITIS B VIRUS PATIENT EPIDEMIOLOGY AND PERCEPTIONS

#### *Chronic Hepatitis B Prevalence in Foreign-Born Individuals in the US*

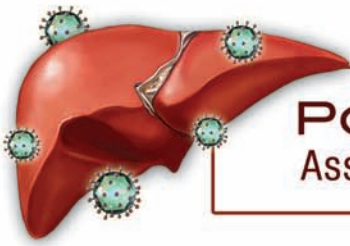
Groups at an elevated risk for CHB are excluded or under-represented in government reports of individuals in the US living with this disease. Therefore, a study was designed to estimate the prevalence of foreign-born individuals in the US living with CHB [Abst. 853]. US Census data were used to estimate the number of foreign-born persons from 93 countries/regions living in the US in 2008, and published CHB prevalence rates by country/region were reviewed. The number of foreign-born persons with CHB was estimated by multiplying each population by its prevalence rate. Investigators found that the number of foreign-born individuals with CHB in the US ranges from 850,000 to 2,240,000 persons. Over half are from Asia, 13-15% are from Africa, 9-18% are from Central America. The average prevalence rate among the foreign-born was estimated at between 2.0% and 5.4%. The authors noted that knowledge of key foreign-born CHB populations will help develop programs for prevention, diagnosis, and care.

#### *Perception of Chronic Hepatitis B in Asian Communities*

There is a high prevalence of CHB infection among the Asian population in the United States, but little is known about this population's awareness of the disease and its treatments. Researchers conducted telephone interviews of 600 Chinese, Korean or Vietnamese individuals between the ages of 18 and 65 years who were first generation immigrants or, if born in United States, able to read or write their native language "natively" or "very well" [Abst. 941]. The researchers found that overall

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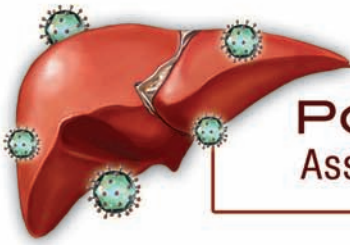




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hepatitis B awareness was high but its unaided mention is under 20%, ranking under diabetes (43%), hypertension (40%), and cancer (21%). Eighty percent of respondents agree that CHB causes liver damage and 78% agree that it could slowly progress to liver cancer if untreated. However, only about half of surveyed individuals agree that it is easily transmittable or that there are effective drugs to treat it. While 61% of those who tested negative claim to have been vaccinated, lack of information is one of the main reasons claimed by those who have not received the vaccine. This survey results indicate that more education about CHB, especially how it is transmitted and treated, is needed.





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