

# HBV JOURNAL REVIEW

Volume 1, Issue 1  
June 01, 2004

## Hepatitis B

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### Few Develop Viral Resistance to Adefovir after 2.7 Years

Hepatitis B patients face a 3.8% chance of developing viral resistance to adefovir (Hepsera), after 144 weeks of treatment, according to a Digestive Disease Week 2004 conference report.

Currently, there are two antivirals – lamivudine (Epivir-HBV) and adefovir – available that prevent hepatitis B viruses (HBV) from reproducing. However, with lamivudine, after four years a significant number of HBV are able to resist lamivudine’s antiviral effect.

Researchers studied 629, 293, and 167 patients treated with adefovir through 48, 96 and 144 weeks, respectively, to

determine when viral resistance to adefovir developed. They found no resistant mutations (labeled rtN236T and rtA181V) at 48 weeks, but six patients (2%) developed resistance after 96 weeks.

Three other patients developed adefovir resistance by week 144. All viral mutants occurred in patients receiving only adefovir (not in combination with lamivudine.) All patients with the rtN236T mutation and two of the three patients with the rtA181V mutation experienced an increase in viral load (HBV DNA).

Adefovir-resistant HBV appeared to be susceptible to lamivudine. The authors suggest that patients should be treated with both lamivudine and adefovir, if insurance companies will cover it, to prevent resistance to either antiviral from developing.

### Young Nonresponders to Interferon Do Better with Combination Treatment

In the May 2004 issue of the *Pediatric Infectious Disease Journal*, Turkish researchers reported that 36.8 percent of HBV-infected children who had previously not responded to interferon alpha treatment developed a virological response (usually defined as production of the “e” antibody and lowering of HBV DNA) when they were given lamivudine alone for three months (to lower viral load), followed by a six-month combination of interferon alpha and continued lamivudine treatment.

HBV Journal Review  
*A publication of the Hepatitis C Support Project*

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To date, more than half of HBV-infected children treated with interferon alpha do not respond.

Seven of the 19 children treated with the combination interferon and lamivudine achieved virologic response. "Lamivudine and interferon alpha combination therapy may represent an effective treatment option," researchers noted.

### Children Experience Minor Side Effects from Interferon

Researchers, who interviewed 100 HBV-infected children and their parents, concluded that side effects from interferon alpha treatment were minor, and primarily included "fever, flu-like symptoms and bone marrow suppression."

The side effects were also temporary, they noted in the May, 2004, issue of the *Journal of Paediatrics and Child Health*. In some adults, side effects from interferon can be severe and include anxiety and depression.

### Pegylated Interferon plus Lamivudine Better than Lamivudine Alone

Researchers at the Digestive Disease Week 2004 conference reported that the combination of pegylated interferon and lamivudine was substantially more effective against "e" (HBeAg)-positive hepatitis B than lamivudine treatment alone.

Researchers treated 50 HBeAg-

positive patients, who had never been treated for hepatitis B, with 32 weeks of pegylated interferon, followed by a 52-week course of lamivudine. Fifty other patients were treated only with a 52-week course of lamivudine.

Researchers were interested to see how many patients developed the "e" antibody and experienced a drop in HBV DNA 24 weeks after treatment ended. Historically, the combination of interferon alpha and lamivudine has not been highly effective against hepatitis B. Pegylated interferon, however, appears to be more effective against HBV infection than conventional interferon alpha.

Researchers found 36% of patients treated with pegylated interferon and lamivudine developed the "e" antibody and lower HBV DNA at 24 weeks after treatment, compared to 14% treated with just lamivudine. The group that received the combination treatment was less likely to develop lamivudine-resistant viruses (21% vs. 40%) when compared to the group treated with just lamivudine.

Researchers noted they did not study patients treated with only pegylated interferon. Because lamivudine has a high rate of drug resistance (over time it does not subdue HBV with mutations that enable them to "resist" lamivudine's antiviral effects), the addition of lamivudine to pegylated interferon may not ultimately be that beneficial over pegylated interferon treatment alone.

### Pegylated Interferon Better than Lamivudine for HBeAg-Negative HBV

A report presented at the 39th Annual European Association for the

Study of the Liver (EASL) conference in April 2004 found pegylated interferon to be more effective against HBeAg-negative hepatitis B than lamivudine by itself, or a lamivudine-and-pegylated-interferon combination.

Some people with chronic hepatitis B have viruses that are able to reproduce without secreting the "e" antigen (HBeAg). To date, lamivudine has not been very successful in the treatment of HBeAg-negative HBV.

Researchers treated 537 people with HBeAg-negative HBV with either pegylated interferon alone, a pegylated interferon plus lamivudine combination, or just lamivudine, for 48 weeks and followed them up for 24 weeks.

By week 72, the percentage of patients with normal ALT and low viral load (HBV DNA) was significantly higher in the pegylated interferon and pegylated-plus-lamivudine-treated groups, compared to the group treated with just lamivudine.

An improvement in liver tissue health was reported in 47% of patients receiving pegylated interferon alone, 37% receiving pegylated interferon plus lamivudine, and 39% receiving lamivudine.

Researchers concluded that a significantly higher sustained response rate was observed with pegylated interferon, compared with just lamivudine in the treatment of HBeAg-negative hepatitis B. The combination of lamivudine and pegylated interferon did not prove to be significantly more successful than pegylated interferon alone.

### Limited Success Found in Combo Treatment for HBeAg-Negative HBV

Researchers, writing in the April 2004 issue of *Liver International*, tried sequential, combination therapy using interferon alpha with either famciclovir or lamivudine to treat difficult-to-treat HBeAg-negative hepatitis B.

Fourteen patients were treated with antivirals – either famciclovir or lamivudine – for four weeks to reduce viral load, and then treated with a combination of the antiviral and interferon alpha until 16 weeks beyond the loss of detectible HBV DNA.

HBV DNA was undetectable and ALT levels normalized in all patients by end of treatment. Seven (50%) patients maintained a sustained response 12 months after treatment ended. Only two of them had been infected by HBV with the G1896A mutation. Most patients (five of seven) with the G1896A mutation in their HBV relapsed within four months after therapy ended.

### Peginterferon Improves Liver Histology, but Not Fibrosis

Dutch researchers treated 255 HBeAg-positive patients for 52 weeks with either pegylated interferon alone or in combination with lamivudine to study the two treatment regimens' impact on liver tissue health (histology).

The pegylated interferon dosage was

halved after 32 weeks of treatment. Liver biopsies were conducted before and after treatment and examined for fibrosis and inflammation.

The scores of the two treatment groups were comparable. Overall, the inflammation score improved and there was a slight progression in fibrosis. The fibrosis score improved more often in the combination group (17 patients vs. 13 patients).

In those who responded to treatment and seroconverted (producing the “e” antibody) at the end of follow-up, the inflammation score improved in 65%, compared to 38% of non-responders.

“In conclusion,” researchers wrote in *Gastroenterology and Hepatology*, “[pegylated interferon] therapy improves liver histology . . . . We found an improvement in necroinflammatory scores but no significant reduction of fibrosis in both treatment groups.”

### Assessing Cost Effectiveness of Adefovir, Lamivudine and Interferon Alpha

There are three therapies available to treat chronic hepatitis B. Interferon alpha has significant side effects. Lamivudine, though safe, is associated with a high rate of viral resistance. Adefovir is effective regardless of “e” (HBeAg) status, but it is more expensive than lamivudine.

Researchers at the Digestive Dis-

ease Week 2004 conference reported on their comparison of the cost-effectiveness of treating patients with interferon, or lamivudine—or first with lamivudine and then switching to adefovir (called “adefovir salvage” strategy) when viral resistance to lamivudine developed.

They calculated the cost-effectiveness of the treatment strategies for a group of 40-year-old patients with elevated ALTs and no cirrhosis. Estimates of treatment costs and long-term outcomes (including cirrhosis and related complications) were performed from a third party payer perspective and were obtained from Medicare and the Red Book. The primary outcome measure was cost per life year (LY).

#### The researchers found:

- Interferon (at a dose of 5 MU, three times/week for six and 12 months for HBeAg positive and negative patients respectively) cost \$18,607 per life year.
- Lamivudine (100 mg/day with discontinuation upon sustained virological response only) cost \$20,915 per life year.
- Lamivudine (100 mg/day) followed by 10 mg per day of adefovir salvage therapy if resistance developed cost \$28,362.

The interferon and lamivudine-only strategies provided 34.7 and 37.2 undiscounted life years respectively. The adefovir salvage strategy, researchers found, was most effective as it provided 38.9 life years.

Adefovir salvage became the dominant strategy when the cost of adefovir was \$300 per month, the cost of lamivudine was \$305 per month, and when less than 60% of the cohort was HBeAg negative.

The authors concluded, "Adefovir salvage therapy is more effective than both interferon and lamivudine monotherapy at an acceptable incremental cost. The salvage strategy becomes the preferred approach overall in patients with HBeAg-negative chronic hepatitis B, suggesting a possible key role in the management of this therapeutically resistant sub-group."

### **Telbivudine Superior to Lamivudine in Lowering HBV DNA and ALT**

After one year of treatment, telbivudine (LdT), a potent inhibitor of HBV replication, outperformed lamivudine in lowering viral load and normalizing ALT levels in 104 patients with chronic hepatitis B.

Patients treated with telbivudine experienced marked suppression of HBV replication, with a mean reduction in viral load of 6 log<sub>10</sub> or 1 million-fold. This was significantly greater than among patients who received lamivudine alone, who experienced a 4.57 log<sub>10</sub> reduction, or 50,000-fold drop in viral load.

The study compared the efficacy and safety of telbivudine 400 or 600 mg per day, and telbivudine 400 or 600 mg per day combined with lamivudine 100 mg per day, to lamivudine 100 mg per day by itself in adults with HBeAg-positive hepatitis

B and elevated ALT.

The study was presented at the April 2004 EASL by researchers from the UCLA School of Medicine's Division of Digestive Diseases, and one of the lead U.S. investigators in the Phase IIb clinical trial of telbivudine.

Residual viral load at Week 52 was highest in those treated with just lamivudine, while the median HBV DNA level in telbivudine-only-treated patients was undetectable.

Nearly twice the percentage of patients treated with just telbivudine experienced reductions in HBV DNA below the detection limit of a highly sensitive test, compared with patients receiving just lamivudine (61% and 32% respectively).

ALT levels became normal in significantly more patients in the telbivudine groups than patients in the lamivudine group (86% and 63% respectively).

### **Adefovir Successful in HBV-HIV Coinfected Patients over Four Years**

Researchers studied the success of adefovir treatment in 22 patients coinfecting with HIV and lamivudine-resistant hepatitis B over a four-year period. Adefovir had been added to the patients' anti-retroviral HIV therapies, which continued to include lamivudine.

In their report to the Digestive Disease Week 2004 conference, researchers said they found no indications of HBV that had genetic mutations that allowed them to resist adefovir at week 144. (Week 192 genotyping was not available.)

Of three patients who lost HBeAg and developed the "e" antibody at week 48, two had sustained this seroconversion at week 192. No evidence of nephrotoxicity or serious side effects related to adefovir occurred. HIV RNA and CD4 count remained stable.

Researchers concluded that long-term adefovir treatment, at least up to four years, was well-tolerated and resulted in sustained reductions in HBV DNA and ALT. "The magnitude of reduction in serum HBV DNA and ALT continues to increase with treatment duration," they noted.

### **High Viral Load May Increase Liver Cancer Risk**

A team of Japanese researchers say that high viral load, together with age and severe fibrosis, increased liver cancer in 73 patients with chronic hepatitis B over a 19-year period.

The researchers investigated the role high HBV DNA levels played in the development of liver cancer. In the June 2004 issue of the *Journal of Gastroenterology and Hepatology*, the team reported they examined the impact of age, sex, habitual drinking, ALT levels, HBV viral load, interferon treatment, and liver fibrosis and inflammation on development of liver cancer.

The patients received liver biopsies at five-, 10- and 15-year intervals. Liver cancer occurred in 14%, 29% and 48% of the patients respectively. High HBV DNA levels, together with age and severe fibrosis, was a critical risk

factor for cancer. The researchers recommended that patients with high viral load should be carefully screened for liver cancer.

### HBV Genotype and Treatment: Overview of 2003 Research

In the May 2004 issue of *Current Opinion in Gastroenterology*, Drs. Anna S. Lok and Scott K. Fung provided an overview of 40 significant studies about hepatitis B published in 2003.

They reported that among 700 patients studied in the United States, genotypes A and C were most common, followed by genotypes B and D. The prevalence of HBV genotypes varied by region and was related to patients' ethnicity and places of birth. Only 35% of the patients studied were born in the United States. "These data indicate that the epidemiology of HBV infection in the United States is strongly related to immigration patterns," they noted.

They also found a high prevalence of HBV precore and core promoter mutations, 27% and 44%, respectively, that cause "e" antigen (HBeAg)-negative hepatitis B. Given the widespread nature of these two mutations, the doctors recommend that physicians learn how to diagnose and treat HBeAg-negative hepatitis B.

On the treatment front, Drs. Lok and Fung reviewed a study of 82 Chinese patients who were monitored for 12 to 88 months after lamivudine-induced HBeAg sero-

conversion. They found that a sustained response was seen in only 52% of patients 12 months after treatment ceased. Sustained responders were more likely to be infected with HBV genotype B, to be age 36 or younger, and to have continued to receive lamivudine therapy at least eight months after HBeAg seroconversion. This was the first study, they noted, that demonstrated a genotype-related difference in the durability of response after lamivudine treatment ended.

The doctors also cited a study that looked at ALT flares in patients who develop resistance to lamivudine. The safety of lamivudine was analyzed in a study of 998 HBeAg-positive patients who received up to six years of lamivudine. Hepatitis flares were estimated to occur in 9%, 23%, 31%, 39%, and 43% of patients in years 1, 2, 3, 4, and 5, respectively. Patients with lamivudine-resistant mutations experienced significantly more hepatitis flares than did patients without these mutations.

While the study showed lamivudine's safety in patients with HBeAg-positive compensated liver disease, patients with long-standing lamivudine-resistant mutation may experience worsening liver disease.

Adefovir, the latest antiviral to be approved by the U.S. Food and Drug Administration, appears to be effective against nearly all hepatitis B viruses, including those with mutations that can resist lamivudine. However, a new virus with a mutation in the HBV DNA polymerase has been identified that could grow resistant to adefovir. However, this mutation is susceptible to lamivudine's antiviral effect.

### Prolonged Lamivudine Helps Few HBeAg-Negative Cirrhotic Patients

After five years of lamivudine treatment, only one-third of 44 patients with HBeAg-negative cirrhosis experienced prolonged lowered viral load, and only 10% enjoyed complete viral suppression.

After prolonged treatment, 21 patients (48%) maintained undetectable HBV DNA and normal ALT, while 22 patients (52%) developed lamivudine resistance, reported researchers at the April 2004 EASL. One patient never achieved any response.

The authors found HBV resistance to lamivudine was associated with increased risk of liver-related complications, particularly liver cancer. Sudden flares or increases in ALT levels have been reported in patients who abruptly stop lamivudine antiviral therapy. With no antivirals impeding reproduction of hepatitis B viruses, viral load and liver damage often rebound once treatment stops.

### Lamivudine-to-Entecavir Switch Poses No Risk

Researchers studied 181 patients for 85 weeks who had been treated with lamivudine, and found that the patients could be safely switched directly to the antiviral entecavir (ETV) (1.0 mg daily) without experiencing any severe ALT flares. No overlap treatment with lami-

ludine was necessary, according to researchers who reported their findings at the EASL conference in April 2004.

The authors concluded that continuation or overlap of lamivudine is not necessary when switching to entecavir at a dose of 1.0 mg daily, and subsequent ALT and HBV DNA reductions may “reflect a favorable response to therapy.”

### **Only One -Third of HIV-Infected Vaccinated against HBV**

An article in the May 2004 issue of *Clinical Infectious Diseases*, reported that only 32.4 percent of 612 people infected with HIV had received at least one dose of the three-dose hepatitis B vaccine, and only 23.3% had received the hepatitis A vaccine. Doctors recommend that everyone with HIV be immunized against both viral hepatitis infections.

HIV Outpatient Study (HOPS) investigators reported that HBV vaccination was more common in people with higher education levels and a track record of more clinic visits. The HOPS team found a better medical response to HBV vaccination in people with an undetectable HIV load and with a higher CD4 count, though people at all CD4 levels had some response to the vaccine.

The authors suggest that, “prompt efforts to vaccinate patients entering care, receipt of antiretroviral therapy, and practice reminder systems may enhance vaccination practices.”

### **Childhood Hepatitis B Vaccination Rates Dropped in 2000**

U.S. Centers for Disease Control and Prevention researchers, writing in the May 2004 issue of the *Journal of the American Medical Association*, estimated that 750,000 children may not have been immunized against hepatitis B in 2000.

In 1999, the vaccine was temporarily withdrawn from the market for three months due to concerns about a preservative used in its manufacture, and that may have resulted in many children not getting immunized against hepatitis B.

Vaccination guidelines recommend that children get three doses of the hepatitis B vaccine before they reach 19 months of age. The three-month suspension caused many parents to skip the hepatitis B vaccine series, with perhaps as many as 750,000 fewer children vaccinated in 2000 than in 1998, researchers reported.

The authors of the study urge officials and physicians to educate parents about the risks of hepatitis B and to encourage them to have their children vaccinated.

