

# HBV JOURNAL REVIEW

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## Hepatitis B

Christine Kukka

### **When Lamivudine Resistance Occurs, Add Adefovir for Best Results**

Many people infected with the hepatitis B virus (HBV) quickly develop resistance to the antiviral lamivudine (Epivir-HBV) after a year or two of treatment. Lamivudine kills off the “wild” type or normal HBV, but the HBV with mutations are able to continue to replicate and the infection usually rebounds.

Researchers, reporting at the *American Association for the Study of Liver Disease* (AASLD) conference in Boston, studied whether 588 lamivudine-resistant patients should be switched to the antiviral adefovir (Hepsera), or if adefovir should be added to the ongoing

lamivudine treatment. All patients had hepatitis B “e” antigen (HBeAg)-negative hepatitis B.

They switched 303 patients to just adefovir and 285 to the adefovir and lamivudine combination and followed them for 24 months. The average age of those studied was 54, 85% were men, and 49% had cirrhosis (liver scarring).

About 68% of patients in both groups cleared HBV DNA, but more patients in the adefovir-only group experienced viral rebound (9% vs. 2%), and viral resistance to adefovir occurred more frequently in the adefovir-only group (5% vs 0.8%).

“In HBeAg-negative lamivudine-resistant patients, adefovir should be added to

lamivudine and both drugs should be continued to reduce the risk of adefovir-related secondary treatment failure,” researchers recommended.

In a separate AASLD report, researchers reported that a combination of adefovir and lamivudine worked best in HBeAg-negative patients with resistance to lamivudine, more than 80% maintained undetectable HBV DNA levels over 3.5 years.

### **Antiviral Telbivudine Lowers Viral Load Better than Adefovir after 52 Weeks**

Researchers, also reporting at the AASLD conference, unveiled their findings that the antiviral telbivudine (LdT) outperformed

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Executive Director  
Editor-in-Chief,  
HCSP Publications  
Alan Franciscus

Contributor  
Christine Kukka

Managing Editor,  
Webmaster  
C.D. Mazoff, PhD

Contact Information:  
The Hepatitis C Support Project  
PO Box 427037  
San Francisco, CA 94142

[www.hbvadvocate.org](http://www.hbvadvocate.org)

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adefovir over a 52-week study period of 135 patients with HBeAg-positive hepatitis B, elevated ALT and moderately high viral load.

Adefovir has been approved by the U.S. Food and Drug Administration for hepatitis B treatment, while LdT has been in Phase III clinical trials and has not been approved yet.

Patients initially received either adefovir (10 mg/day) or LdT (600 mg/day) for 24 weeks. Half of the adefovir recipients were then switched to LdT.

At Week 24, HBV DNA declines were significantly greater with LdT than adefovir. At 52 weeks, those switched from adefovir to LdT achieved greater HBV DNA reductions and loss of HBeAg (about 29% vs. 21% with adefovir).

In the group that switched from adefovir to LdT, average viral load decreased rapidly following the switch at week 24, and by week 40 the average viral load was similar to the group receiving LdT from the beginning.

“At 24 weeks, LdT produced significantly

greater and more consistent antiviral efficacy than adefovir,” the researchers reported. “At one year, patients treated continuously with LdT, or switched from adefovir to LdT, showed proportionally better results on all measures of antiviral efficacy compared to continuous adefovir.”

Earlier studies have demonstrated that LdT is far more effective than lamivudine.

### ***Adefovir Alone Causes Viral Mutations to Develop Sooner in Lamivudine-Resistant Patients***

Viral resistance to adefovir develops faster than expected in patients who have already developed resistance to lamivudine, according to a report by South Korean researchers in the October issue of *Gut*.

Among patients who have never been treated with lamivudine, adefovir resistance develops at a rate of about 2% and 5.9% respectively after 96 and 144 weeks of treatment.

Researchers studied 67 lamivudine-resistant patients and adefovir

resistance developed at months 12 and 24 at a rate of 6.4% and 25.4% respectively. This is higher than has been reported to date. The first cases of adefovir resistant mutations in HBV were detected as early as three months after adefovir treatment began in this group.

“Adefovir is useful for the treatment of lamivudine-resistant cases,” researchers noted, but resistance to one drug may make patients prone to emergence of resistance to other drugs, similar to what occurs in antiviral therapy of HIV.

### ***Tenofovir Has Limited Success Against Adefovir-Resistant HBV***

A small group of three HBV patients who had developed viral resistance first to lamivudine and then to the antiviral adefovir were switched to tenofovir (first developed to treat HIV infection) to see if that agent could vanquish adefovir-resistant HBV.

According to the researchers’ report, submitted at AASLD, about 28% of those treated with adefovir

develop mutations after five years and risk a resurgence of viral load and infection. Although tenofovir works similarly to adefovir, they hoped the higher tenofovir dosage would be potent enough to kill off the adefovir-resistant HBV.

The three HBeAg-positive patients, who had high viral loads and elevated ALT levels, unfortunately did not experience a drop in HBV DNA and did not respond to tenofovir. “Therefore, a combination of tenofovir plus a nucleoside analogue (i.e. lamivudine) seems to be a more promising therapeutic approach to address this clinical problem,” researchers concluded.

### ***No Viral Resistance Documented after Five Years of Tenofovir Treatment***

In another AASLD presentation, researchers reported they found no evidence of HBV resistance to the antiviral tenofovir after five years of treatment.

Sixty-nine patients with lamivudine-resistant HBV infection

were treated with 300 mg daily of tenofovir and followed for at least six and up to 59 months. Twenty-four of the 69 patients were coinfecting with HIV-HBV.

At the end of the observation period, HBV DNA became undetectable in 68 out of the 69 patients. The one patient with detectable HBV DNA received a reduced tenofovir dose due to kidney problems.

There was no evidence of viral resistance development (evidence by a resurgence of HBV DNA). HBeAg seroconversion was documented in 36% of the patients after 14 months of treatment, and HBsAg loss occurred in 8% after about 16 months on average.

**New Antiviral Appears Effective Against HBV that Are Resistant to Antivirals**

A new antiviral – called 2,4-diamino-6-[2-(phosphonomethoxy)ethoxy]-pyrimidine (PMEO) – appears to be effective against wild-type and lami-

vidine-resistant HBV.

Researchers, presenting their data at AASLD, investigated how effective PMEO was against lamivudine-resistant and wild HBV in comparison to lamivudine, adefovir, entecavir and tenofovir in the lab.

They report that PMEO may be a new candidate for treatment of drug-resistant and also as a player in combination therapy.

**Study Finds 3% of HBV-Infected Should Be Treated**

What percentage of those infected with HBV in the United States require treatment? Researchers, reporting at the annual AASLD conference, reviewed health records from 2.3 million patients enrolled in a northern California health care program for two years for a snapshot of how many with HBV infections should be treated under current guidelines.

Of the group, 9,362 (0.4%) had chronic hepatitis B. Of these, 4,723 (50.5%) were male and 4,926 (52.6%) were aged 18-

44 years. About 2,249 (24.5%) were Asian-American, 220 (2.4%) were co-infected with HIV, and 268 (2.9%) with hepatitis C virus. Fifty-two (0.6%) had liver cancer and 262 (2.8%) had severe cirrhosis.

Researchers reported that 2,832 (49.9%) of 5,713 patients followed had elevated ALT. Compared to those with normal enzymes, patients with elevated liver tests more frequently had liver cancer and decompensated cirrhosis. Evaluation of those with elevated liver enzymes included HBV DNA testing in 46.5%, HBeAg in 71.9% and liver biopsy in 11.8%.

In this diverse population, a wide spectrum of HBV infections were identified, with serious liver disease in about 3%. “These results highlight the large number of patients with chronic HBV who may be potential candidates for future therapy,” they noted.

**Should Hepatitis B Treatment Depend on HBV Genotypes? – A Hypothesis**

Researchers, report-

ing at the AASLD conference, studied more than 18 treatment reports to determine if treatment should be geared to genotype. They hypothesized:

1) When antivirals are used, HBV genotypes do not appear to respond dramatically differently.

2) When interferon is used in HBeAg-positive patients, HBeAg seroconversion (loss of HBeAg and gaining of the “e” antibody) occurs more often in patients with genotype A and B, when compared to genotypes D and C.

3) Loss of HBsAg after after interferon treatment is greater for genotype A than D. There appears to be no difference in HBsAg clearance between genotypes B vs. C.

**Can the Hepatitis B Vaccine Stop Infection with Lamivudine-Resistant HBV?**

The hepatitis B vaccine injects only the surface antigen (HbsAg) protein of the virus to “trick” the immune system into producing hepatitis B surface antibodies. It

works well against wild-type HBV, but what about HBV with antiviral-induced mutations, such as lamivudine-resistant HBV?

After prolonged treatment with lamivudine, for example, the only HBV that remain are those with mutations that allow them to replicate despite the presence of this antiviral. Sometimes, those mutations include changes to the HBsAg, the protein that encases the virus.

A group of researchers tried injecting two immunized chimpanzees with HBV that had antiviral resistance, a third chimpanzee served as a control.

According to their report at the AASLD conference, there was evidence of HBV infection in the two chimps infected with the mutated virus. While there was no HBV DNA or HBsAg detected, the chimps developed core antibodies.

The findings, “warrant further studies to evaluate the potential public health impact of emergence of drug-resistant mutants and protective efficacy of commercial HBV vaccination against

such mutants,” researchers reported.

**Entecavir Reduces HBV DNA Faster than Adefovir in Untreated HBeAg-Positive Adults**

Sixty-nine previously untreated HBeAg-positive patients received either adefovir or entecavir (Baraclude) for 52 weeks to see which antiviral reduced viral load more successfully.

At week 24, entecavir lowered viral load better, (as early as Day 10). Undetectable HBV DNA was achieved in 45% of entecavir patients, vs. 13 % of adefovir-treated patients.

**Pegylated Interferon Works 33% of the Time in Those Who Failed Lamivudine and Conventional Interferon**

A group of Dutch researchers, writing in the October 2006 issue of the *American Journal of Gastroenterology*, assessed how effective pegylated interferon is in patients who have failed to respond to either lamivudine or

standard interferon.

Pegylated interferon, injected once a week, boosts the immune system to fight HBV infection.

They analyzed 76 nonresponders who had failed to respond to interferon, lamivudine, or a combination of the two. The patients received 52 weeks of 100 mug Peg-IFN alpha2b weekly combined with either 100 mg lamivudine daily or a placebo. After therapy, patients were followed for 26 weeks.

Thirteen (35%) nonresponders to previous interferon, five (29%) nonresponders to lamivudine, and four (22%) nonresponders to both interferon and lamivudine responded to pegylated interferon.

No difference in response was found among those treated with pegylated interferon alone or in combination with lamivudine. However, those with elevated ALT levels at the start of treatment fared better.

**HBV Infection Falls 90% in Hawaii after Universal Infant Immunization**

HBV infections

among elementary school children in Hawaii fell by more than 90% after universal infant hepatitis B vaccination was implemented, according to a report in the

October issue of *Pediatrics*. Routine HBV immunization was first recommended in 1991.

The prevalence of chronic HBV infection decreased from 1.6% to 0.04% (a by 97% reduction), after routine HBV vaccination began, the authors report, and the prevalence of resolved infection fell by 90%, from 2.1% to 0.20%.

**Precore and HBsAg Mutations Found in Children after Taiwan’s Vaccination Program**

A group of Taiwanese researchers investigated the impact of HBV mutations on children. Most children, they reported in the September 2006 issue of the *Indian Journal of Pediatrics*, begin with “wild” or natural HBV. But over months and years of infection, mutations develop in the HBV’s precore region in about 10 to 24% of children

before HBeAg seroconversion, and in about half of these children after HBeAg seroconversion.

Occasionally, children may be infected primarily by mutant strains of HBV. They found that about 36% of children with fulminant hepatitis and 30% of children with acute hepatitis B were infected by precore mutants of HBV transmitted by their mothers or blood donors.

In addition, after universal HBV vaccination, HBV surface antigen (HBsAg) mutations develop either to avoid the immune system after immunization or preventive treatment with hepatitis B immune globulin.

The prevalence of HBsAg mutations increased from 7.8% before universal vaccination began in Taiwan to 19.6%, 28.1% and 23.1% at 5, 10 and 15 years after the program.

**Tenofovir as Effective as Tenofovir-Lamivudine Combination Among HIV-HBV Co-infected**

Researchers treated two groups of HIV-HBV coinfecting pa-

tients with either tenofovir alone, or a combination of tenofovir and lamivudine, to see which treatment was most effective.

One group, who had failed to improve when given lamivudine, was treated with just tenofovir, the other group was given the combination of lamivudine and tenofovir.

The researchers, reporting in the Oct. 3, 2006 issue of *AIDS*, found that 76% of the patients receiving both antivirals achieved undetectable HBV DNA, while 84% who received just tenofovir achieved undetectable viral load.

A loss of HBeAg was observed in 36% of patients on tenofovir plus lamivudine and in 24% on tenofovir.

Researchers concluded that after 116 weeks of treatment, tenofovir was as effective as tenofovir plus lamivudine.



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