

# HBV JOURNAL REVIEW

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## Hepatitis B

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### Tenofovir Better than Adefovir against Lamivudine-Resistant HBV

Tenofovir (Viread), an antiviral medication used to treat HIV, appears to be highly effective against hepatitis B virus (HBV) that are able to resist the antiviral effects of lamivudine (Epivir-HBV).

Lamivudine was the first antiviral medication approved by the U.S. Food and Drug Administration (FDA) to treat hepatitis B, and it is commonly used. Antivirals work by tampering with the virus's genetic material so it cannot replicate. However, some strains

or mutations of HBV can replicate despite lamivudine's antiviral effects.

Adefovir (Hepsera), the only other FDA-approved antiviral available to treat hepatitis B, has shown some effectiveness against lamivudine-resistant HBV. However, researchers attending the 55th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) in late October reported tenofovir to be even more effective against lamivudine-resistant HBV than adefovir.

Of 55 lamivudine-resistant patients, 19 were treated with adefovir and 36 were treated with tenofovir for at least three months. When measured at the six-month

point, HBV DNA (viral load) became negative in 69% of patients treated with tenofovir, compared to 37% treated with adefovir.

ALT decline was significantly faster in patients treated with tenofovir than those treated with adefovir.

### Lamivudine In Late Pregnancy Cuts Mother-to-Child HBV Infection

Researchers report that treating pregnant, HBV-infected women with lamivudine for eight weeks, starting at week 32, substantially cut the rate of mother-to-child transmission of

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hepatitis B.

Today, despite immediate immunization and treatment with hepatitis B antibodies (hepatitis B immunoglobulin or HBIG) at birth, some newborns born to HBV-infected mothers still contract hepatitis B due to prenatal infection or because of the mother's high viral load.

Treating pregnant, HIV-infected women with antivirals has greatly reduced mother-to-child (vertical) transmission of HIV. Researchers hoped lamivudine treatment in late pregnancy would similarly reduce vertical HBV infection.

Researchers, working primarily in China, treated 56 pregnant, HBV-infected women with lamivudine and 58 with placebo. All newborns were immunized and received HBIG at birth. Researchers monitored the two groups of infants for one year to compare HBV infection rates.

At week 52, researchers tested the 116 infants for hepatitis B surface antigen (HBsAg) and measured viral load. They found,

“The rate of HBV vertical transmission was significantly reduced in infants receiving HBV vaccine and HBIG whose mothers received lamivudine in the eight weeks (+/- 2 weeks) prior to delivery compared to those whose mothers received placebo.”

Of the 56 infants born to lamivudine-treated mothers, 10 tested positive for HBsAg at 52 weeks. Of the 59 infants born to mothers who did not receive lamivudine, 23 tested positive for HBsAg.

There were no adverse effects from lamivudine treatment in either mothers or infants.

### **Adefovir Plus Emtricitabine (FTC) Faster, Superior to Adefovir Alone**

Hepatitis B patients treated with a combination of the experimental antiviral emtricitabine (FTC) and adefovir experienced a faster decline in

their viral load than patients treated with just adefovir, according to a randomized, double-blind study reported at the AASLD conference.

Thirty patients who had the “e” antigen (HBeAg) and who had never been treated were divided into two groups, 14 received adefovir plus FTC, and 16 received adefovir and a placebo over 48 weeks.

At week 24, the group receiving adefovir and FTC showed a 1,000-fold reduction in HBV DNA, compared to the adefovir-only group, which experienced a 100-fold reduction.

Loss of HBeAg and production of the “e” antibody occurred in two patients received the combination antiviral treatment, compared to one in the adefovir-only group. “The adefovir plus FTC combination therapy shows faster and greater HBV suppression in comparison with adefovir alone,” the researchers wrote.

### **Researchers Study HBV Genotypes and Subtypes by Region for Clues**

A team of international researchers, writing in the November 2004 issue of the *Journal of Viral Hepatitis*, explored the molecular make-up of the eight genotypes and nine subtypes of the hepatitis B viruses found worldwide and discovered that amino acid sequences were unique to regions and ethnic groups, as well as within subtypes.

Specific nucleotide sequences were common among Korean, Indian, Chinese, Italian and Pacific region HBV samples. The researchers also found amino acid sequences that were common to Southeast Asian and Western populations, irrespective of subtype. “We believe that HBV strains spread within constrained ethnic groups, result in selection pressures that define sequence variability within each sub-

type,” the researchers wrote. “It suggests that particular T cell epitopes (the part of an antigen to which the antibody binds) are specific for geographical regions, and thus ethnic groups; this may affect the design of immunomodulatory therapies.”

### “Pulse” Lamivudine Therapy Promising in Patients with Low ALT and HBeAg

Currently, treatment is not generally recommended for patients whose alanine aminotransferase (ALT) levels are less than twice normal, but a new sequence of lamivudine treatment shows promise in this population.

ALT, a liver enzyme that is released when liver cells are damaged or die, increases when the immune system is destroying HBV-infected liver cells. Doctors assume ele-

vated ALT levels indicate the immune system is primed to vanquish the virus, and would be helped by the addition of antiviral medication or interferon, which boosts the immune system.

But researchers, reporting in the November 2004 issue of the *Journal of Viral Hepatitis*, treated 27 patients who had HBeAg and ALT levels that were only 1.5-times the normal level with four weeks of lamivudine treatment. They then stopped treatment for two weeks, and then restarted medication for the next two more years. They wanted to see if this “pulse” of lamivudine would spur the immune system to begin fighting the HBV infection more aggressively.

Lamivudine withdrawal, after four weeks of treatment, led to a rise in ALT levels in 11 (42.3%) patients at six weeks. Seven of them (63.6%) lost HBeAg compared with only two of the 15 patients in whom ALT levels did not rise.

Ultimately, eight (31%) patients responded to lamivudine pulse ther-

apy. Responders had a higher albumin level, a lower fibrosis score, and relatively high baseline ALT levels than the nonresponders. YMDD mutations developed in three patients and none of them responded.

The researchers conclude lamivudine pulse therapy, “has potential in converting HBeAg-positive,” patients who would normally not be treated because of their low ALT levels.

### Surface Antigen Mutations Induce DNA Damage and Could Lead to Cancer

Taiwanese researchers, writing in the 2004 issue of *Carcinogenesis*, examined the role that mutations in the HBV surface antigen (called pre-S) play in inducing DNA damage and causing liver cancer.

Ground glass hepatocytes (liver cells called GGHs) are the hallmarks in the late stages of hepatitis B, when there is extensive liver

damage. The researchers identified two types of GGHs that contained two mutant types of large HBV surface antigens (HBsAg) with pre-S mutations. They determined the two surface antigen mutations caused stress and DNA damage, which in the late stages of hepatitis B can lead to cancer.

### Tenofovir Withdrawal Can Cause HBV Exacerbations in HIV-HBV Coinfected

The FDA recently revised tenofovir’s safety labeling to caution patients coinfecting with hepatitis B and HIV that withdrawal of this antiviral could cause severe HBV exacerbations.

The FDA approved revisions to the safety labeling for tenofovir disoproxil fumarate to warn patients and doctors that the drug is not currently approved by FDA to treat chronic hepatitis B (though it has been used in clinical trials) and that its

safety and efficacy have not been studied in patients coinfecting with HIV and HBV.

The warning was issued after FDA received reports of severe acute HBV exacerbations—marked by a resurgence of viral load and liver damage—in coinfecting patients when they stopped taking tenofovir. The agency advises close monitoring of liver function for at least several months in coinfecting patients.

Tenofovir is currently used in combination with other antiretroviral agents to treat HIV-1 infection. The FDA recommends that all patients with HIV be tested for HBV infection before beginning antiretroviral therapy.

### Researchers Focus on T-Cells for Clues to Effective HBV Eradication

When researchers examined how 22 chronically-infected children responded to standard interferon treatment,

they discovered that children age 5 or younger responded far better than older children and teens.

Writing in *The Journal of Pediatrics*, a team of U.S. and European pediatric hepatologists examined the charts of children treated with interferon who ranged in age from 17 months to 17 years, including 14 males and eight females.

Ten patients (48%) responded to interferon, achieving HBeAg conversion, undetectable HBV DNA and normal ALT and aspartate aminotransferase (AST) six months after treatment. Five cleared the infection and produced surface antibodies.

Seven of nine patients (78%) who were 5 years of age responded (five of them cleared surface antigen). Three of 13 patients (23%) who were older than age 5 responded. Younger patients clearly responded better to interferon than older children and teens.

AST, ALT, and HBV DNA at the start of treatment were not dif-

ferent between responders and nonresponders. The doctors concluded interferon treatment may be more effective in younger children with chronic hepatitis B.

### HIV- and HBV-Infected Men Are Often Consistent Users of Condoms

A study of more than 7,000 men who had multiple sex partners over an eight-year period found that men who had sex with men (MSM), and were infected with HIV or chronic hepatitis B were more likely to consistently use condoms than uninfected, married men.

Writing in Volume 16 of *AIDS Care*, researchers reported that men who were not infected with HIV or HBV used condoms inconsistently due to alcohol consumption, injecting drug use and being married.

Among the 508 hepati-

tis B carriers in the study, consistent condom users were generally unmarried and not injecting drug users.

Researchers concluded that only a small number of HIV positive men report unsafe sex with multiple partners, and that health education activities should be directed at this group.

### Correlation Between HBsAg and HBV DNA Levels Studied

Researchers studying the relationship between HBV DNA and hepatitis B surface antigen (HBsAg), measured the two in 67 asymptomatic hepatitis B carriers to see if there was a correlation between the two. Researchers wonder if ultimately only surface antigen could be measured to determine viral load.

They divided the patients into four groups, three were negative for the “e” antigen (HBeAg) and had low to undetectable HBV

DNA levels. The fourth group had high viral load and the “e” antigen.

Writing in the November 2004 issue of the *European Journal of Gastroenterology* and *Hepatology*, the researchers reported that there was a direct relationship between HBsAg levels and HBV DNA in all four groups.

They concluded, “Quantitative measurement of HBsAg titres may be an easy and economical reference for HBV replication in HBV carriers.

### **In Cases of HBV-HCV Coinfection, the Hepatitis B Virus Often Dominates**

Researchers compared the genetic variability and reproduction rate of the hepatitis C virus (HCV) in patients infected with only HCV or HBV, and those coinfecting

with both HBV and HCV.

Writing in the October 2004 issue of the *Archives of Virology*, researchers reported they studied 37 patients with HBV-HCV coinfection, 33 with HBV and 25 with HCV.

HBV genomes were detected in all 37 coinfecting patients, 19 of them also had circulating HCV particles but HCV particles were undetectable in the other 18.

HBV viral load was similar in the coinfecting and HBV-only infected groups.

“Our data indicate ... HBV can suppress HCV replication to undetectable levels, whereas HCV may reduce but does not abrogate the replication capacity of HBV.

Furthermore in the cases of HCV dominance, circulating HBV genomes did not have a significant effect on the viral heterogeneity of HCV,” researchers noted.

### **HBV Genetic Evolutions Happen Early and Impact a Patient’s Recovery**

Writing in the October 2004 issue of *Gastroenterology*, researchers compared when HBV genetic material evolved during the early phase of hepatitis B infection in patients who experienced a short-term hepatitis B infection and those who could not clear the infection and became chronic carriers.

They found that rapid reaction by the patient’s immune system dictates whether a person can clear HBV, even when there are HBV mutations that can escape the watchful eye of the immune system.

“Overall, genetic evolution of the hepatitis B virus differs at early time points between patients who experience acute resolving hepatitis B and those who progress to chronicity,” they noted.

### **Occult, or HBsAg-negative Hepatitis B More Prevalent Than Expected**

Researchers have long wondered why so many hemodialysis patients, who use machines to clean wastes from their blood after their kidneys fail, develop hepatitis B.

A team of Canadian researchers, reporting in the October 2004 issue of *Hepatology*, tested the blood of 241 hemodialysis patients for the surface antigen (HBsAg), as well as HBV DNA, to see how many of these patients had “occult” hepatitis B, which occurs when HBV DNA is present though HBsAg is not.

Two of the 241 patients were HBsAg positive. Of the remaining 239 HBsAg-negative patients, nine patients (3.8%) tested positive for HBV DNA. Viral loads in these individuals were low. Demographic, biochemical, and HBV serological testing did not help identify those with occult hepatitis B infections.

They concluded that “occult” HBV infection in adult hemodialysis patients was about four to five times higher than standard HBsAg testing would suggest.

### **Lamivudine Slows Liver Disease and Cancer Risks in Late-Stage HBV Patients**

Continuous treatment with lamivudine over nearly three years significantly reduced liver disease and the risk of liver cancer in hepatitis B patients with advanced liver fibrosis or cirrhosis. A team of researchers, reporting in the October 2004 issue of the *New England Journal of Medicine*, treated 651 Asian patients who had advanced hepatitis B with either lamivudine (436 patients) or a placebo (215 patients). Over three years of treatment, liver damage increased in

3.4 percent of lamivudine-treated patients compared to 8.8 percent of those receiving placebo. Liver cancer occurred in 3.9 percent of the lamivudine group, and in 7.4 percent of the placebo group.

HBV resistance to lamivudine developed in 49 percent of the patients treated with lamivudine, and liver damage was more likely to increase in patients with these mutations than in the other patients treated with lamivudine.

About 12 percent of patients in the lamivudine group and 18 percent of patients in the placebo group reported serious adverse events from treatment.

Continuous treatment with lamivudine delays progression of liver disease and significantly reduces the incidence of liver failure and liver cancer, the researchers concluded.

### **Clevudine Shows Promise in Phase II Clinical Trials**

The nucleoside analogue clevudine effectively suppressed HBV DNA levels and normalized ALT levels in Phase II clinical trials, according to reports presented at the 12th United European Gastroenterology Week.

The multicenter, randomized, double-blind, placebo-controlled study investigated the efficacy of clevudine over a 12-week treatment period, with a 24-week follow-up period. The 99 patients, nearly all male and Korean, were positive for HBeAg, had detectable HBV DNA levels and had never been treated with any antiviral before.

There were three treatment groups: 33 received placebo, 32 received clevudine at 30 mg daily, and 34 received a 50 mg dose.

HBV DNA levels dropped by half in the two clevudine-treated groups and these patients continued to have sustained decreases in their viral load 24 weeks after treatment ended.

Half of the two clevudine-treated groups achieved normal ALTs. While ini-

tial loss of HBeAg was greater for the clevudine groups, by the end of treatment and follow-up period all three groups had experienced a 20% rate at developing the “e” antibody.

The incidence of adverse events were similar for all three groups. A larger clinical trial of clevudine is underway.

### **Clevudine’s Prolonged Antiviral Action Raises Hopes and Concerns**

Hepatitis B expert Dr. Robert Perrillo, writing about the Phase II clinical trial of the antiviral clevudine (L-FMAU) in the 2004 issue of *Hepatology*, praised its unique ability to cause a sustained decline in viral load 24 weeks after treatment ended.

The drop in HBV DNA levels after 12 weeks of clevudine treatment was similar to the decline seen after one year of lamivudine or adefovir treatment. “This prolonged effect on HBV DNA has not been

seen to the same extent with any of the other nucleoside analogues (antiviral),” he noted.

Usually, when lamivudine or adefovir treatment ends, 20 to 25% of patients experience a sharp rise in HBV DNA and ALT levels as HBV replication rebounds.

While no one knows why clevudine suppresses HBV replication long after treatment ends, Perrillo noted its, “more potent inhibition of the covalently closed circular form of HBV DNA or immunomodulatory properties of the drug may explain its prolonged action.”

Its potentially long half-life in liver cells could be beneficial, resulting in a less-than-daily dosing schedule. But, “...drug accumulation could potentially occur with prolonged daily therapy, and this may alter its safety,” Perrillo cautioned. “Thus, it is important that more prolonged dosing studies be conducted before any conclusions can be made about the ultimate safety of clevudine.”

### **HIV-Hepatitis Coinfected Face Higher Liver Failure Rates, But Same Death Rates**

Writing in the October 2004 issue of *AIDS*, a group of researchers compared survival in patients infected with only HIV to those coinfecting with HIV and either hepatitis B or C. They found HIV deaths were similar in patients co-infected with viral hepatitis compared to those with only HIV.

In the study group, 72 patients were coinfecting with HIV-HBV, 256 had HIV and HCV, 18 had HIV and HCV and HBV, and 126 were infected with only HIV.

Researchers reported 134 patients died during follow-up. Liver death occurred in 55 patients, representing 12% of the entire group and 41% of those who died. Survival rates were similar in patients with HIV alone and those coinfecting with viral hepatitis.

Those who died from

liver failure were similar in the HIV-HBV and HIV-HCV groups.

In coinfecting patients, initial higher CD4 cell count and use of highly active antiretroviral therapy (HAART) experienced higher survival rates and fewer deaths from liver failure.

### **Women at Risk of HIV and Syphilis Also at Risk of Hepatitis B**

A survey of 1,500 HIV-infected women and 461 uninfected women revealed a high rate of hepatitis B infection – 43% and 22% respectively – according to a study published in the journal of *Clinical Infectious Diseases*.

A history of injecting drug use and infection with herpes simplex virus 2 increased the rate of HBV infection dramatically. A history of syphilis in the non-injecting drug use group increased their risk of hepatitis B infection.

“Sexual transmission of HBV, particularly in

those with a history of genital ulcer disease, should be a major focus of education in all high-risk groups,” researchers recommended.

### **FDA Warns Against Possible, Severe HBV Exacerbation After Stopping Adefovir**

Severe exacerbation of hepatitis B has been reported in up to 25% of patients who discontinued use of the antiviral medication adefovir, according to a labeling change reported by the U.S. FDA's MedWatch program.

As a result, adefovir's label now includes a warning advising that liver function should be monitored for at least several months after treatment is stopped.

A total of 492 patients from two clinical trials were followed after they stopped taking adefovir. Within 12 weeks, up to 25% experienced a rebound of HBV DNA, and ALT

level increases that exceeded 10 times the normal range.

HBeAg seroconversion did not generally result during these exacerbations. Although severe (decompensated) liver damage did not result during the exacerbations in either HBeAg-positive or negative patients with relatively healthy livers, these studies did not include patients with advanced liver disease or cirrhosis, who may be at higher risk for liver damage and failure during an HBV exacerbation.

Most exacerbations were self-limited or were resolved by resuming adefovir use.

**Four Years of Lamivudine Leads to HBeAg Seroconversion in 47% of Chinese**

Despite the presence of HBV with YMDD-variant mutations that can resist lamivudine's antiviral effects, 47% of HBV-infected Chinese patients lost the

HBeAg and developed the "e" antibody after four years of lamivudine treatment.

The rate of HBeAg seroconversion in these patients increased with prolonged lamivudine treatment, and when patients had high ALT levels at the start of treatment, according to a report published in the November 2004 issue of Journal of Gastroenterology and Hepatology.

The YMDD-variant HBV was detected in 67% of the 58 patients studied, and 33% of the patients with YMDD-variant HBV achieved HBeAg seroconversion. The seroconversion rate increased to 57% in 14 patients who had elevated ALT levels at the start of treatment. The number of patients with normal ALT increased from 29% at the start of therapy to 69% after four years of treatment. This included 68% of patients with YMDD-variant HBV.

All 58 patients experienced reduced viral load despite the emergence of YMDD-variant HBV in 39 patients.



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