

# HBV JOURNAL REVIEW

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## Hepatitis B

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### **Long-Term Antiviral Use May Impact Other Organ Functions, Careful Monitoring Encouraged**

Historically, researchers have identified few side effects resulting from antiviral treatment for hepatitis B virus (HBV) infection. Unlike interferon, which can cause fatigue and depression, antivirals appeared to cause few symptoms. But experts told a recent National Institutes of Health Consensus Conference on hepatitis B treatment that long-term antiviral treatment that spans years carries some risk of pancreatitis, myopathy (affecting skeletal muscles), neuropathy (affecting the nervous system), and other symptoms.

In addition to disrupting the reproduction of HBV, the antivirals appear to impact reproduction of other cells, which causes mitochondrial toxicity, that can affect organ, muscle, and nervous system tissue. Additionally, researcher pointed out that use of antiviral combinations may increase this toxicity at a greater rate.

The following is report on risks associated with individual antivirals:

- **Lamivudine (Epivir-HBV):** Generally well-tolerated, but are rare instances of reversible myopathy and neuropathy.
- **Adefovir (Hepsera):** Have been reports of reversible nephrotoxicity (affecting the kidneys), the risk is higher at higher adefovir doses.

Among 125 patients treated for up to five years, there was a 3% rate of nephrotoxicity problems.

- **Entecavir (Baraclude):** No mitochondrial toxicity was identified in patients treated for five years, however an increased incidence of tumors was noted in animals receiving high doses.
- **Telbivudine (Tyzeka):** A significantly high rate of creatine phosphokinase (CPK), an enzyme found mainly in the heart, brain, and skeletal muscle tissue, was found in 7.5% of patients treated with telbivudine after one year and in 12.9% after two years. As a result, monitoring for muscle and joint symptoms and testing CPK levels periodically is recommended.

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• **Tenofovir (Viread):** This newest antiviral, which has been used for many years successfully in HIV patients, has a good safety record. But researchers noted concerns about some impact on kidney function, and so recommended a urinalysis every three months to monitor kidney function. Additionally, there have been rare cases of reported declines in bone density.

**Increased Interest in Antivirals to Reduce Mother-to-Child HBV Infection, But No Firm Recommendations**

Currently, antivirals have been used effectively to prevent mother-to-child (perinatal) transmission of HIV infection, and increasingly researchers are investigating whether antivirals can be used in pregnant women with high viral loads to prevent perinatal infection. While immediate immunization and use of HBIG (hepatitis B antibodies) effectively prevents infection in 90% of cases, women who test positive for hepatitis B

“e” antigen (HBeAg) and have high viral load often transmit the infection.

Researchers presenting at the NIH conference reported that of the five approved antivirals, only telbivudine and tenofovir are “Category B” and ARE not known to cause birth defects. However, lamivudine has been used effectively in HIV-infected women without causing any birth defects during the third trimester of pregnancy.

“Because of the potential adverse effect of tenofovir on fetal bone growth, this drug should be avoided if possible,” the researchers reported. Additionally, all of the antivirals can be excreted in breast milk, and so breast-feeding should be avoided if the mother is taking antivirals.

**Experts Suggest Starting Antivirals One Month Before Beginning Chemotherapy or Immune-Suppressing Medication**

People who have resolved or inactive (undetectable viral load, normal liver en-

zymes) hepatitis B have been found to experience a reactivation of the infection – which can lead to life-threatening liver damage – when they are treated with immune-suppressing drugs such as chemotherapy, or have bone marrow transplants.

While use of antivirals before chemotherapy is recommended, when such treatment should start, in which patients, and for how long, has not been defined.

Speaking to the NIH consensus panel, experts suggested all patients with or without detectable hepatitis B surface antigen (HBsAg) undergoing chemotherapy should have their viral load and ALTs measured and then monitored during treatment. They suggested that because antivirals can take about a month to be effectively, such preventive treatment should start one month before chemotherapy begins.

How long they should be continued after chemotherapy ends remains controversial, with some evidence showing that HBV reactivation occurred months or years after

chemotherapy treatment.

**Cesarean Deliveries Lower Risk of Mother-to-Child HBV Transmission**

If an HBV-infected mother chooses a Cesarean delivery, the risk of transmitting HBV to the newborn is lower, according to a report by Chinese researchers in the August 2008 issue of *Virology Journal*.

Researchers reviewed evidence from four randomized controlled trials involving 789 women for any effect on the risk of transmission of HBV when Cesarean deliveries were used. They reported that the combined results showed the rate of mother-to-child transmission of HBV to be significantly lower at an average of 10.5% with Cesarean deliveries than after vaginal deliveries, which averaged 28%.

“If HBV DNA is less than 1,000 copies/mL, we suggest performing a vaginal delivery,” the researchers said, “If HBV DNA is more than 1,000 copies/mL, we recommend carrying out elective Cesarean sections.”

The researchers also

called for more studies to confirm their findings.

**Interferon or Antiviral Treatments Lower Liver Cancer Risk by 34% and 78% Respectively**

Hong Kong researchers reviewed 12 studies, which included 2,742 patients, to assess if either antiviral or interferon treatments lowered patients' risk of liver cancer. According to the report published in a recent issue of the journal of *Alimentary Pharmacology & Therapeutics*, treatment definitely lowered cancer risk, with interferon benefiting patients with cirrhosis, and antivirals benefiting HBeAg-positive patients and those without cirrhosis.

Based on the studies' results, interferon-treated patients' risk of liver cancer was reduced by 34%, compared to a control group. Patients with early cirrhosis appeared to benefit more than those without cirrhosis. Five studies, covering 2,289 patients treated with antivirals, found their risk of liver cancer

declined 78%.

HBeAg-positive patients showed more significantly reduced liver cancer risk with treatment. Patients without cirrhosis benefited more from antivirals than those with cirrhosis.

**How Long to Continue Adefovir after HBeAg Seroconversion?**

Researchers are struggling to define how long patients should continue to be treated with antivirals after they experience loss of HBeAg and develop the "e" antibody (seroconversion). If sustained, this seroconversion can lead to lower risk of liver damage from HBV infection.

In a recent study published in the October 2008 journal of *Clinical Infectious Diseases*, Chinese researchers followed 41 patients who experienced seroconversion while taking adefovir for up to 41 weeks after the event. Researchers reported that those who sustained their seroconversion had experienced the seroconversion more quickly after starting adefovir, and

they continued to take adefovir for up to 41 weeks after seroconversion.

"Prolonged adefovir therapy after HBeAg seroconversion appeared to increase the likelihood of sustained HBeAg seroconversion," they wrote.

**Development of More Sensitive Test for HBsAg Reveals More Infections**

Researchers recently developed a more sensitive test that could detect HBsAg at much lower concentrations than what is currently available at most labs, and tested 210 reportedly "normal" or uninfected volunteers. What they found surprised everyone.

According to the report published in a recent issue of the *Journal of Hepatology*, low HBsAg levels (at a concentration of 0.025 ng/mL) was found in: six (2.86%) of the 210 healthy volunteers. HBsAg was also found in five of 65 cirrhotic patients (7.69%) who previously tested negative for hepatitis B or C., in six of 62 (9.68%) liver cancer patients, in 12 of 134 hepatitis C patients (8.96%), and

in 11 of 107 patients (10.28%) who had hepatitis C-related liver cancer.

"Increasing the sensitivity of HBsAg detection to below the present limit has revealed that infection with HBV, including occult HBV, is far more endemic than suspected previously," the Japanese researchers reported.

**HBeAg-negative Patients with High-Normal or Variable ALT Levels May Require Treatment**

According to a report published in a recent issue of *Hepatology*, people who are HBeAg-negative, have normal ALT levels, and who also have a viral load of 20,000 IU/mL often require treatment – despite the lack of liver damage indicated by their normal ALT levels.

Greek researchers evaluated the severity of liver disease – through liver biopsies – of numerous HBeAg-negative patients, and clustered them by normal and elevated ALTs, and by viral load.

They compared 399 patients with elevated and variable ALT levels with 35 patients with normal ALT and low viral load (less than 2,000 IU/mL).

Liver damage, sufficient to require treatment, was evident in most of the patients with elevated ALTs (86%), but liver damage was also documented in 74% (58 of 78) of those with moderately-low ALT levels.

### **New HBV Genotype “I” Identified in People in Laos and Vietnam**

A team of researchers from Luxembourg have reported finding a new HBV strain or genotype in people living in Laos and Vietnam, according to their report published in the November 2008 issue of the journal of *Emerging Infectious Diseases*.

The team performed a molecular analysis of 18 HBV strains and identified them as belonging to a new genotype, which they labeled I. Currently there are eight identified HBV genotypes – A-H – and each develops differently and also responds to treatment

differently.

“This emerging new genotype likely developed outside Southeast Asia and is now found in mixed infections and in recombinations with local strains in a geographically confined region,” they reported.

In Laos, 8.7% of residents are chronically infected with HBV, and perinatal transmission is the most common route of infection. Past analysis of HBV genotypes in Laos revealed 42.2% strains were genotype B, and 55.4% were of genotype C.

Nineteen strains, including 15 complete sequences, did not group with any of the known genotypes A-H, researchers reported. With one exception, all genotype I strains were found in people living in Vientiane City in Laos. However, a genotype strain recovered from Hanoi, Vietnam, eight years ago also belongs to the genotype I family.

“A complex recombination pattern suggests that genotype I was formed by recombinations (of HBV) outside of Southeast Asia before spreading within Laos and Vietnam, and giving birth to a new genotype with sub-

genotypes, which later recombined with regional strains,” they wrote. “Identification and analysis of genotype I strains provide further evidence of the importance of recombination in the evolution and genesis of new HBV genotypes, a complexity not fully acknowledged by the current genotype classification.”

### **Researchers Still Worried That Hepatitis B Vaccine Protection May Wane with Time**

Following immunization – especially in infants – the number of hepatitis B antibodies wanes with time. Researchers assume the immune system still retains an “immune memory” and can spring into action to fight infection if exposure occurs. But a study by the U.S. Centers for Disease Control and Prevention found a waning in protection in teens 15 years after immunization.

They evaluated new infections and waning of antibodies in 105 teens who had been given the recommended series of three hepatitis B vaccine at

birth. Only eight showed evidence of a past hepatitis B infection, the authors report. But only seven of the other 97 teens still had relatively high antibody levels, the researchers reported in *The Pediatric Infectious Disease Journal*.

Less than half of the participants who received a booster dose of hepatitis B vaccine had an expected antibody response after 14 days, which could indicate waning immunity.

“At this point in time, we do not have any evidence from our surveillance systems of breakthrough hepatitis B virus infections occurring among vaccinated adolescents and therefore do not recommend additional doses of hepatitis B vaccine for adolescents or children who already received three doses of hepatitis B vaccine,” researchers said.

However, researchers stressed the need to continue to look for new cases of hepatitis B among vaccinated adolescents, before recommending additional doses of the vaccine.

