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Hepatitis B

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Doctors Recommend Pegylated Interferon, Entecavir or Tenofovir as First-choice Treatment

With the availability of highly sensitive molecular tests that can detect trace levels of HBV DNA in blood samples, Stanford University Medical Center researchers reviewed the available antiviral and interferon treatments and have recommended three front-line treatments to manage hepatitis B.

They suggest doctors use the highly-sensitive tests to establish a baseline level of HBV DNA (viral load) in each patient, and then carefully monitor HBV DNA to assess the patient's response to treatment and to quickly identify the development of drug resistance.

While convention and pegylated interferon, lamivudine (Epivir-HBV), adefovir (Hepsera), entecavir (Baraclude), telbivudine (Tyzeka), and tenofovir (Viread) have been approved for treating infection with the hepatitis B virus (HBV), the doctors suggest the, "preferred first-line treatment choices are entecavir, pegylated interferon, and tenofovir," according to their report in the journal of *Clinical Gastroenterology and Hepatology*.

Continuous Antiviral Treatment Needed to Sustain HBeAg Seroconversion

Researchers monitored patients who experienced hepatitis B "e" antigen (HBeAg) seroconversion (loss of HBeAg and development of the "e" antibody) during and after

28 weeks of antiviral treatment to determine how permanent the seroconversions were. Among the patients, 69 were treated with lamivudine, 35 with adefovir, 18 with entecavir, and 6 with tenofovir.

HBeAg returned in 65% of the patients, including 73% treated with lamivudine, 60% treated with adefovir, and half of those treated with entecavir. None of the tenofovir-treated patients experienced a return of HBeAg.

Many of the relapses occurred during treatment, often due to development of viral resistance to antivirals. Other relapses occurred between six to 12 months after treatment ended.

Researchers, reporting at the annual American Association for the Study of Liver Disease (AASLD) conference in

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Boston in early November, concluded that, “long-term continuation of treatment with (antivirals) after HBeAg seroconversion appears necessary.”

Are HBeAg-negative Patients with Normal ALTs at Risk for Liver Damage?

Researchers performed liver biopsies on 56 HBeAg-negative patients with elevated alanine aminotransferase (ALT) levels, which indicate that liver damage is occurring, and 98 HBeAg-negative patients with normal ALTs to compare the degree of liver damage. Those with normal ALTs had less fibrosis, however one-third still had some liver damage.

Patients with ALTs in the upper normal range had a markedly higher rate of fibrosis and mild liver damage than those with low or normal ALTs. Viral load was not a reliable indicator of liver damage in those with normal ALTs. A liver biopsy remains the best tool for recognizing liver damage and identifying patients who need treatment, researchers noted, according to the AASLD conference report.

Estimates of HBV-Infected U.S. Residents Rise to 3 Million

The U.S. Centers for Disease Control (CDC) estimate that between 800,000 to 1.4 million U.S. residents are chronically infected with HBV, but increasingly researchers are challenging that estimate and one report presented at the AASLD conference suggested the number may be as high as 3 million if foreign-born residents are included.

CDC estimates are based on surveys that historically do not include people who are at high risk of HBV infection, including institutionalized people, Asians immigrants and Native Americans. Between 1990 and 2008, the number of foreign-born residents increased from 20 million to 41 million. Half of this population is from Asia, and about 14% are from Africa, where HBV infection is also prevalent.

Researchers estimate that between 2% to 5.4% of foreign-born residents are chronically infected, and when combined with the U.S. citizens infected with HBV, researchers suggest the more accurate estimate could be as high as 3 million.

Many Parents Use Alternative Therapies on HBV-Infected Children

Researchers surveyed 68 families to see how prevalent the use of complementary and alternative medicine (CAM), which included milk thistle, was among families with children infected with either HBV or the hepatitis C virus (HCV). They found that 46% of the families employ some type of CAM.

The most common CAM therapies used were: milk thistle (21%), essential fatty acids (14.7%), self-prayer/spiritual healing (13.2%), deep breathing exercises (11.7%), probiotics (8.8%) and massage (8.8%). CAM use was more common if the child had been treated with antivirals, or if parents themselves used CAM. Only 32.3% of parents reported they, “always disclosed their child’s CAM use to the child’s doctor,” and only 12% of doctors reportedly asked parents about CAM use during appointments.

Researchers at AASLD encouraged doctors to inquire about CAM use, given its high and undisclosed usage by parents.

Tenofovir Treatment News from AASLD:

Tenofovir highly effective in HBeAg-positive patients: A study that followed 176 HBeAg-patients treated with tenofovir over 96 weeks found the antiviral to be highly effective, resulting in HBeAg seroconversion in 26 patients, HBsAg loss in six, and undetectable viral load and normal ALT levels in all treated patients.

Tenofovir most cost-effective antiviral treatment for hepatitis B: Researchers analyzed the pharmacy and medical costs and quality-adjusted life years of 1,000 hepatitis B patients who were treated for 20 years with either tenofovir, lamivudine, adefovir or entecavir to see which treatment was the most cost effective. They found that tenofovir was most cost effective due to its treatment success and lack of viral resistance.

They found that patients who began treatment with tenofovir had lower pharmacy and medical costs and had greater number of quality-adjusted life years than patients treated with lamivudine and adefovir.

Compared to entecavir, patients treated with tenofovir were expected to

generate lower pharmacy and medical costs while yielding similar number of quality-adjusted life years. These results were due to the expected low viral resistance rate for tenofovir, and its lower cost, when compared to entecavir and adefovir.

(See cost comparison chart below.)

Tenofovir safe in cirrhotic patients with viral resistance: Researchers treated 12 male cirrhotic patients—with high viral loads and elevated ALT levels—who had developed resistance to at least two other antivirals (commonly lamivudine and adefovir) with a combination of tenofovir (245mg) and entecavir (1mg) over six months.

Average HBV-DNA levels dropped significantly (4.6-fold) and nine of the 12 patients had undetectable viral load (less than 400 copies/ml). ALTs also declined, and

no patients developed liver cancer or worsening liver damage. Despite the decline in viral load, none of the patients lost HBeAg or HBsAg.

Tenofovir effective with all HBV genotypes: In a laboratory-based experiment, researchers tested the antiviral clout of tenofovir in HBV genotypes or strains A through H. Statistical analysis showed tenofovir was equally effective in all genotypes.

Lamivudine resistance increases risk of tenofovir resistance: Another study found that patients who had previously developed antiviral resistance to lamivudine, or who were HBeAg-positive, had a slightly higher risk of developing viral resistance to tenofovir. Three of seven lamivudine-resistant male patients developed some resistance to tenofovir, as did seven of 20

HBeAg-positive patients. HBeAg-positive patients with normal ALTs had a 66 percent higher rate of tenofovir mutations than HBeAg-negative patients.

Tenofovir superior to adefovir in Asian patients: Tenofovir appeared superior to adefovir in Asian patients with genotypes B or C. After 48 weeks of tenofovir treatment in 127 patients and adefovir treatment in 62, 85% of tenofovir patients had undetectable viral load compared to 42% of adefovir patients, and 72% of tenofovir patients had normal ALTs compared to 65% on adefovir. The rates of HBeAg seroconversion (loss of HBeAg and development of “e” antibodies) were equal in both treatment groups.

Antiviral Resistance Updates from AASLD

About 10% of HBV patients have antiviral resistant HBV before treatment begins: Researchers studied the prevalence of HBV that had mutations that could “resist” antivirals such as lamivudine, telbivudine, adefovir and possibly entecavir and tenofovir in patients who had never been treated with any of these antivirals. To their surprise, they found that

10% of these treatment-naïve patients already had these antiviral-resistant mutations. A patient’s genotype also dictated what percentage of HBV had mutations also.

Researchers reported that primary resistance mutations were detected at a rate of 8.2% in genotype A, 20.8 % in genotype B and C, 10.4 % in genotype D and 0% in genotype E. “Since these findings have an impact on therapeutic decisions, newly-diagnosed patients should receive a primary resistance testing,” the researchers recommended, to identify the pre-existing viral-resistant mutations.

Interferon Treatment Updates from AASLD

HBV genotypes dictate interferon treatment success: Researchers followed 1,229 patients treated with standard interferon (298), pegylated interferon (491) or a combination of pegylated interferon with lamivudine (440) for six to 12 months to determine what role HBV genotypes played in causing a sustained virologic response (SVR), defined as achieving normal ALT, low viral load, and HBeAg seroconversion in HBeAg-positive

Cost Comparison Chart

| | Tenofovir | Lamivudine | Adefovir | Entecavir |
|--|-----------|------------|-----------|-----------|
| Total pharmacy and medical cost per patient | \$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 |

patients. Researchers reported the overall SVR rate was 26%. It was 35.6% for genotype A, 24.9% for genotype B, 27.8 % for genotype C, and 19.6 % for genotype D. SVR for HBeAg-positive and negative patients were 36.3 % vs. 34.0% for HBV genotype A, 21.1 % vs. 32% for HBV genotype B, 18.5 % vs. 50.4 % for genotype C and 14.6 % vs. 21.4% for HBV genotype D.

Rapid drop in HBsAg indicates good response to pegylated interferon: Researchers followed seven patients treated with pegylated interferon to assess the relationship between a decline in HBsAg and the patients' response. They reported that within three months of starting interferon therapy, six of seven of the patients who ultimately cleared HBsAg, showed a rapid decline in antigen. The seventh patient who cleared HBsAg had a slower decline in HBsAg.

Rapid loss of HBeAg indicates interferon treatment success: Researchers followed 172 HBeAg-positive patients treated with pegylated interferon and found that the 27% who lost HBeAg rapidly, within 32 weeks of the start of treatment, had a higher

rate of achieving undetectable HBV DNA (47% vs. 21%) and also clearing HBsAg (36% vs. 4%).

Lamivudine-resistant, HBeAg-positive patients benefit from interferon: Researchers compared success rates of 150 HBeAg-positive, many of whom had lamivudine resistance, when treated with pegylated interferon. The overall HBeAg seroconversion rate was 27% and there was no significant difference among patients who had lamivudine resistance. A separate study found that treating lamivudine-resistant patients with interferon was more effective than treating them with adefovir.

Entecavir Update from AASLD

Long-term entecavir treatment effective in HBeAg-positive patients: A five-year study of 146 HBeAg-positive patients, who had not been treated in the past, who were treated with entecavir for up to five years showed promising results. About 94% achieved undetectable viral load during the five years of continuous entecavir treatment and only one patient developed entecavir resistance during the long-term study. Most maintained normal

ALT levels during the 96 weeks, and 31% achieved HBeAg seroconversion and 5% lost hepatitis B surface antigen (HBsAg).

Health Care Workers Continue to Be At Risk of Blood-borne Infections

A CDC study that tracked health care worker mortality from 1984 to 2004, published in the *American Journal of Industrial Medicine*, reports that health care workers continue to face infection and death from bloodborne diseases such as HIV, HBV and HCV.

The study also found that male health care workers face a two-fold risk of dying from HIV/AIDS-related causes. Accidental needle sticks and other workplace accidents put health care workers at an increased risk of exposure to bloodborne diseases. The study examined 248,550 deaths from HIV/AIDS, hepatitis B and C, liver cancer and cirrhosis and found that male workers faced a doubled risk of dying from HIV/AIDS and hepatitis B, while female health care workers had a higher rate of HCV infections than their male counterparts.

Researchers could not determine how much of the increased risk of infection for male workers was due to occupational or non-occupational exposure. The researchers wrote, "The greatest limitation to our study was that information was not available on possible confounding factors, such as sexual risk behaviors, history of blood transfusions, intravenous drug use and alcohol use."

HBV Found in Tears of Infected Patient

Taiwanese researchers, writing in the German journal *Ophthalmologica*, reported they have detected HBV in the tears (aqueous humor) of a chronically-infected person. Earlier studies reported the detection of only HBsAg in tears. Researchers examined the tears of an HBV-infected patient using a detailed test and found HBV, which suggests ophthalmologists may be at risk of contracting HBV infection if exposed to patients' tears through an open sore or cut.

