Hepatitis B: The Other Hepatitis Virus

Part Two

Treatment for HBV

by James Learned

Part One of this article in the March/April issue of *Positively Aware* discussed that infection with hepatitis B virus (HBV) is a significant problem for many people with HIV. Up to 10% of HIV-positive people in the U.S. are co-infected with chronic HBV.

HBV can cause short-term (acute) and long-term (chronic) infection. The immune system usually fights off (clears) HBV within six months of infection. If you clear the virus within that time, the antibodies that your immune system creates in response to the infection protect you in the future.

If the virus *doesn't* clear within six months, you have chronic HBV. The virus continues to reproduce in the liver, which can lead to inflammation, severe liver damage—including cirrhosis (scarring) and liver cancer—and, possibly, death.

People with weakened immune systems are more likely to develop chronic infection, and HIV/HBV co-infection can cause more problems than chronic HBV alone (monoinfection), including difficulty tolerating some HIV medications, faster progression of liver disease, and higher rates of liver failure.

Treatment for acute hepatitis B infection

Many people infected with HBV don't have noticeable symptoms and only learn that they've been infected if they have bloodwork done. During acute infection, you can transmit the virus to others—primarily through unprotected sex or sharing injection drug equipment. There's no treatment available for acute HBV except to rest, drink plenty of fluids, and take medications to help ease the flu-like symptoms.

If you know that you were exposed to the virus and less than two weeks have passed from the time of exposure, a hepatitis B immune globulin (HBIG) injection may prevent the development of HBV infection or reduce the length and severity of illness. But HBIG provides only temporary protection, so the hepatitis B vaccination series is started at the same time to provide long-lasting immunity.

Chronic hepatitis B infection

Hepatitis B is a complicated virus, and complex factors contribute to disease progression. Once HBV enters the liver, the virus inserts itself into the nucleus of liver cells, which makes it very difficult to eliminate. In co-infection, complex interactions occur between the two viruses.

Not everyone with chronic HBV needs treatment. The decision is made on a case-by-case basis, taking into account the following factors:

- HBV-DNA levels (hepatitis B viral load);
- liver function test results, especially ALT levels;
- the presence of hepatitis B envelope antigen (HBeAg)—fragments of the virus;
- the degree of liver damage as measured by imaging (ultrasound, CT, or MRI scans) or biopsy;
- benefits vs. risks of treatment (such as side effects);
- alcohol use;
- age;
- family history of HBV infection and liver cancer;
- the effect of symptoms on quality of life;
- other medical conditions, including HIV; and

- willingness to take HBV treatment.

Although chronic HBV is usually a slowly progressive disease, liver damage often occurs more quickly and is more serious in co-infected people. Even if you're not taking treatment for HBV, it's still important to have hepatitis B viral load and liver function checked regularly by a knowledgeable healthcare provider.

Goals of HBV treatment

The main goal of treatment for chronic HBV is to suppress viral replication and stop liver disease progression. Higher blood HBV-DNA levels predict a higher probability of developing liver cancer. Suppressing HBV-DNA to undetectable or very low levels reduces the likelihood of developing cirrhosis, liver cancer, and liver failure.

In addition to achieving undetectable HBV-DNA, successful HBV treatment is measured by normalized ALT levels, the loss of HBeAg, and a less damaged liver. If consistently elevated ALT levels prior to treatment become consistently within normal ranges, it's a good sign of decreased liver damage.

The presence of HBeAg usually means that HBV is replicating in liver cells. If HBeAg is no longer found during treatment, it's an indication that treatment has been successful, especially if the hepatitis B e antibody (anti-HBe)—produced by the immune system in response to HBeAg—wasn't present before starting treatment and then becomes present. HBV treatment is usually stopped in patients who maintain these antibodies for at least six months.

Treatment is continued indefinitely for people who are HBeAg-negative with detectable HBV-DNA.

When to begin HBV treatment

There are no absolutes about when to begin HBV treatment or who should be on treatment. Many factors need to be considered when making the decision.

The American Association for the Study of Liver Diseases (AASLD) Practice Guidelines currently recommend offering treatment to people who are HBeAg-positive *or* who have HBV-DNA levels above 100,000 copies/mL and liver damage determined by consistently elevated ALT levels (two times or more above the upper limit of normal) or liver biopsy.

For people who are HBeAg-negative, treatment is recommended if HBV-DNA levels are above 10,000 copies/mL.

Generally, people are less likely to have a successful response to HBV treatment if ALT levels are relatively low (*less* than two times above the upper limit of normal) when they begin treatment.

Since recent research indicates that the risk of liver cancer increases with higher HBV-DNA levels—regardless of ALT levels—the AASLD is considering recommending that treatment be initiated based only on HBV-DNA.

If HBV-DNA levels don't reach undetectable, getting below 100,000 copies/mL usually slows the progression of liver disease, although some people with HBV-DNA levels consistently below 100,000 have severe liver disease. An undetectable HBV-DNA level is important because it reduces the development of drug-resistant HBV. Less HBV replication allows less opportunity for resistance to develop.

Treatment for chronic HBV

There are many questions concerning the best treatment for chronic HBV infection—and the issue is more complicated in co-infection. Little consistent or comparative information exists about the individual drugs, partly because they've been studied in people with different categories of chronic HBV (with or without HBeAg and higher or lower HBV-DNA levels, for example).

Two types of HBV treatment are approved by the Food and Drug Administration: injectable immunomodulators that indirectly inhibit viral replication, and oral antivirals that directly inhibit viral replication. Approved immunomodulators are Intron A (interferon alfa-2b) and Pegasys (pegylated interferon alfa-2a). Approved oral antiretrovirals are Epivir-HBV (lamivudine, 3TC), Hepsera (adefovir dipivoxil), and Baraclude (entecavir).

None of these drugs are actually approved to treat HBV in co-infection (although they can still be used), and some need to be used very carefully in people with HBV and HIV. They vary in how well they work, durability of response after treatment, side effects, the development of HBV resistance, length of treatment, and their effect on HIV.

Immunomodulators

Most people treated with interferon (standard or pegylated) experience difficult side effects, and, for some people, these side effects are unbearable.

Intron A (interferon alfa-2b), or standard interferon, was approved in 1992 as the first treatment for chronic HBV, but is rarely used now due to its low response rate, inconvenience, and the availability of better therapies.

Pegasys (pegylated interferon alfa-2a) achieves higher sustained response rates for both HBeAg-positive and HBeAg-negative people than standard interferon. Pegylated interferon is injected subcutaneously (under the skin) once a week. Treatment lasts a year, and if you achieve a successful response (low HBV-DNA levels, normalized ALT levels), it tends to last once you finish treatment.

So far, there are no data showing the effect of pegylated interferon on HBV in co-infected people, but a few such studies are ongoing.

Oral antivirals

These drugs are taken once a day, have few side effects, and generally provide strong activity against HBV while you're on treatment. Unfortunately, they rarely lead to a long-lasting response. When you stop the drug, HBV-DNA and ALT levels usually return to where they were before you began treatment. This is unlikely to occur if you convert from being HBeAg-positive to HBeAg-negative and develop anti-HBe antibodies that are maintained for at least six months.

Most often, taking one of these drugs is a long-term deal. Stopping can cause sudden increased ALT levels, usually accompanied by rising HBV-DNA levels and, sometimes, serious physical symptoms. Liver function should be monitored closely for several months after stopping treatment with any of the following drugs.

Epivir-HBV (lamivudine, 3TC), a safe drug with few side effects, was developed to treat HIV. It's also active against HBV, decreasing HBV-DNA levels and significantly reducing liver damage and the risk of liver cancer. Lamivudine is effective for the treatment of both HBeAg-positive and HBeAg-negative chronic HBV.

Unfortunately, the effect of Epivir-HBV is severely limited by the development of drug-resistant HBV. The frequency of drug resistance increases over time—up to 70% after four years of treat-

ment. And resistance develops in as many as 90% of HIV/HBV co-infected people after four years of treatment.

Epivir-HBV should never be used as monotherapy (by itself) to treat HBV if you're co-infected. The dose of lamivudine in Epivir-HBV is too low for HIV. If lamivudine is taken by someone with HIV/HBV co-infection, the HIV dose (300 mg once a day or 150 mg every 12 hours) should be used as part of combination HIV therapy.

Hepsera (adefovir dipivoxil) suppresses replication of HBV without any mutations that cause drug resistance (wild-type virus) as well as lamivudine-resistant HBV. Clinical trials found Hepsera to be tolerable and safe, and side effects were similar to those seen in people taking placebo. It's important to monitor kidney function in anyone taking Hepsera. People with kidney problems may need a dose adjustment.

Studies of people who took Hepsera every day found significant decreases in HBV-DNA levels, liver improvement, normalization of ALT levels, and the loss of HBeAg in many participants after a year of treatment. These benefits were maintained—but didn't improve—in people who continued treatment for a total of four years. Like Epivir-HBV, Hepsera is effective for the treatment of both HBeAg-positive and HBeAg-negative chronic HBV.

HBV resistance to Hepsera is much lower than that for lamivudine. In 2005, researchers combined data from five studies to determine the likelihood of developing resistance to Hepsera over time. The probability of developing resistance after taking Hepsera as monotherapy for four years was 15% compared to 70% of people developing lamivudine-resistance after taking Epivir-HBV monotherapy for the same amount of time. The study also found that the probability of developing Hepsera-resistance after four years was 0% for people taking a combination of Hepsera and Epivir-HBV.

Baraclude (entecavir) was approved in 2005, so we don't have as much long-term data about it as we do for Epivir-HBV and Hepsera. Like Hepsera, Baraclude suppresses replication of wild-type HBV as well as HBV that's resistant to lamivudine. Results of a small study in people with HIV/HBV coinfection are promising.

The drug is safe and well tolerated. In clinical trials comparing Baraclude to Epivir-HBV or placebo (dummy pill), the frequency of side effects was similar in people taking either drug or the placebo.

Two large trials comparing Baraclude to Epivir-HBV in people who hadn't taken HBV treatment before—one of HBeAg-positive people and one of HBeAg-negative people showed positive results. After a year of treatment, Baraclude was more effective than Epivir-HBV in terms of improved liver damage and lower HBV-DNA levels.

Baraclude seems to have a very low rate of resistance, especially compared to Epivir-HBV. So far, only a few people have developed HBV that's resistant to Baraclude, but we only have two years of follow-up data from studies of Baraclude. Hepsera's resistance profile looked good after two years, too. It wasn't until we had four or five years of follow-up data that we learned that resistance to Hepsera can and does occur. One thing we *do* know is that people with HBV resistant to Epivir are more likely to develop resistance to Baraclude.

Treatment considerations in HIV/HBV co-infection

Three HIV medications are active against HBV—Emtriva (emtricitabine), Epivir (lamivudine, 3TC), and Viread (tenofovir). Various studies indicate that Viread is effective in people with lamivudine-resistant HBV, and one study suggests that Viread is more effective against HBV than Hepsera.

Emtriva and Epivir are very similar drugs, and HBV resistance to Emtriva (as with Epivir) limits the drug's ability to suppress HBV replication. These factors make it tricky to figure out how best to treat people with HIV/HBV co-infection.

Treatment for people with co-infection needs to be individualized based on the progression of their HBV infection, HIV disease, and other factors. The following are treatment considerations for people with HIV/HBV co-infection.

If treatment is needed for HIV but not for HBV

Avoid using Viread, Emtriva, or Epivir as the only drug with anti-HBV activity in an HIV combination. Use two of these drugs in the combination or save them all for later, when treating the HBV infection might be necessary.

If treatment is needed for HBV but not for HIV

Consider using pegylated interferon, Baraclude, or Hepsera to treat HBV. Combining Baraclude and Hepsera may be the best bet. Avoid Epivir-HBV, since Epivir monotherapy is very likely to cause Epivir- and Emtriva-resistant HIV. Epivir should only be used as part of a strong HIV combination unless your HIV is already resistant to the drug.

If treatment is needed for both HIV and HBV

Use Viread with either Epivir or Emtriva as part of your HIV regimen, since each of these drugs is active against HBV. Truvada combines Viread and Emtriva in a single, convenient pill.

When stopping an HIV drug with activity against HBV

If someone with HIV/HBV co-infection stops taking Epivir, Viread or Emtriva for any reason, liver function should be carefully monitored. Taking Hepsera may prevent hepatitis B flares. The formulations Combivir, Trizivir, Epzicom, and Truvada contain two or more HIV drugs, at least one of which is also active against HBV. Stopping any of these formulations could cause hepatitis B flares as well.

The future of HBV treatment in co-infection

Much progress has been made in treating chronic HBV over the last few years. Although information about the effectiveness of these treatments in co-infection is far from complete, many co-infection trials are now enrolling. At least 20 drugs are being studied to treat chronic HBV. Viread (tenofovir) may be the most promising.

It's possible that the future of HBV treatment is combination therapy. At least nine combination therapy trials are ongoing. With high rates of HBV-resistance to the oral antivirals over the long-term, the use of two or more drugs might be the way to go. Although there's little information available to support this strategy yet, considering what we know about the development of drug resistance using monotherapy in HIV, it makes sense. The potential benefits of combination therapy for HBV—especially with drugs that are relatively safe—deserve attention. Stay tuned!

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