

a series of fact sheets written
by experts in the field of liver
disease

HBV:

Drugs in Current Clinical Development (2008)

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In 2008, there were two types of drugs available to treat infection with the hepatitis B virus (HBV): interferons, which boost the immune system to fight the hepatitis B infection, and antiviral medications, which deliberately interfere with the virus's DNA so it can't reproduce efficiently. Below are the drugs that are currently approved by the U.S. Food and Drug Administration (FDA) to treat hepatitis B, and the up-and-coming drugs that may someday be used to eradicate a hepatitis B virus (HBV) infection.

Interferons

Interferon has an "immunomodulator effect," which means that it tweaks the immune system to produce lymphocytes (specialized immune cells) that either attack the virus' antigens directly by creating antibodies, or they attack the HBV-infected liver cells.

- B lymphocytes (B cells) are the immune cells responsible for the production of antibodies. They zero in on individual antigens, such as the HBV's surface, core or "e" antigens, by producing antigen-specific antibodies to combat and vanquish each antigen.
- Cytotoxic T cells (T cells) are specialized cells that recognize and kill HBV-infected liver cells and cancerous liver cells.

Interferons do something else that is very helpful. They enhance the "expression" or presence of certain antigens on the surface of HBV-infected liver cells. When these antigens are "expressed," the T cells can find them more easily and zero in and destroy the infected cells. This process is called enhanced cell surface expression of Class 1 Major Histocompatibility, or MHC.

Researchers are working to develop a variety of immune stimulants and enzymes that will trigger T cell, B cell and other immune cell production so these "soldier" cells will find and vanquish the HBV infection.

FDA-Approved Interferons

Today, there are two FDA-approved interferons to treat hepatitis B. One is called conventional interferon or interferon alpha 2b, which has been approved for the treatment of hepatitis B in adults and children. This interferon requires three injections each week and, unfortunately, has had limited treatment success.

Only about 37 percent of those who have the hepatitis B "e" antigen (HBeAg) are able to clear their bodies of HBV DNA (the genetic material that signals the presence of the virus in the blood), after treatment with interferon, and only 33 percent were reported to clear the "e" antigen. About 60 to 70 percent of those who are HBeAg-negative are able to achieve undetectable HBV DNA and normal ALT levels after treatment with conventional interferon. The second interferon is called pegylated interferon. It has been used with great success against hepatitis C and it requires only one injection each week. This interferon has a time-release formula so it remains present in the liver at a constant level to achieve a consistent "immune boosting" level. Pegylated interferon is also believed to more efficiently distribute itself throughout the liver, the main site of HBV infection, than conventional interferon. It appears that people with HBV strains or genotypes A and B may respond better to pegylated interferon than those with genotypes C and D.

According to research reports, 69 percent of HBeAg-positive people treated with pegylated interferon achieve undetectable viral load, 46 percent achieve normal ALTs, and about about 27 percent lose HBeAg and develop "e" antibodies. (Source: AASLD Treatment Guidelines for Hepatitis B, <https://www.aasld.org/eweb/docs/practiceguidelines/chronichepBcorrection.pdf>.)

Among people who are HBeAg-negative, and have never been treated, 87 percent treated with pegylated interferon achieve undetectable HBV DNA and 49 percent achieve normal ALTs.

There are other brands of interferon approved for HCV treatment, but the FDA has not approved them for hepatitis B treatment, they include Wellferon (Glaxo), Roferon (Hoffman-La Roche), and Infergen (Amgen).

Immune Stimulators (Similar to Interferons) Under Development

Immune enhancers or stimulators are similar to interferon, but they specifically help T cells find and fight tumors and viruses.

Zadaxin is thymosin alpha 1, a thymic hormone that enhances the maturation of T-cells. The drug's developer, SciClone Pharmaceuticals, reported that when this drug was combined with conventional interferon, it produced a 71 percent long-term sustained response rate in patients with difficult-to-treat hepatitis B after one year of treatment. This sustained response rate compares favorably to only 20 percent of patients using interferon alpha in combination with lamivudine, and 10 percent of patients using interferon alpha alone. After administration, thymosin alpha 1 circulates at 50 to 100 times its normal level in the body. Zadaxin has been approved for sale in more than 30 countries. This drug is currently in Phase II clinical trials for both hepatitis B and C.

Antiviral Medications or Nucleoside Analogs

Nucleoside analogs (also called nucleoside reverse transcriptase inhibitors, or NRTIs) and non-nucleoside antivirals prevent HBV from replicating. Most antiviral medications are pills that are taken daily. These drugs interfere with the HBV's DNA and the viral proteins that orchestrate its reproduction. As a result, the virus is unable to replicate in liver cells.

These antivirals are valuable because they lower the rate of HBV replicating in the liver. Generally, when viral load drops, liver damage declines because there are fewer viruses invading liver cells, and ALT levels also normalize. Researchers hope that one day a combination of immune enhancers and antiviral medications will be developed that can produce a strong immune response and lower viral load, and ultimately eradicate the infection.

FDA-Approved Antiviral Medications

There are four FDA-approved antiviral medications available to HBV-infected patients:

Lamivudine (brand name Epivir HBV): Administered as a daily pill or oral solution, lamivudine generally produces normal ALT levels and undetectable HBV DNA in about 60-75 percent of HBeAg-negative adults who take it. In HBeAg-positive patients, about 40-44 percent achieve undetectable HBV DNA, between 41-75 percent achieve normal ALT, and between 16-21 percent lose the HBeAg and develop the "e" antibody.

While lamivudine is safe and rarely causes side effects, like most antivirals, it is not a permanent or complete cure. It keeps the virus in check for only as long as it is taken. When treatment stops, HBV DNA and ALT levels usually rebound.

Some HBV with certain mutations are able to continue to reproduce despite lamivudine's antiviral punch. Over time, these lamivudine-resistant HBVs increase in number until viral load and ALT levels start to climb again. After four years of lamivudine treatment, more than 60 percent of patients develop lamivudine-resistant HBV.

Adefovir (brand name Hepsera): Adefovir appears to have all of lamivudine's antiviral clout, but it does not cause rapid viral resistance. About half of HBeAg-negative people who take adefovir achieve undetectable HBV DNA, and 72 percent develop normal ALT levels. About 21 percent of HBeAg-positive people who take adefovir achieve undetectable HBV DNA and 24 percent lose HBeAg, and 48 percent achieve normal ALTs. Like most antivirals, adefovir causes viral resistance at a rate of 3 percent after two years and 29 percent after five years.

Entecavir (ETV- brand name Baraclude) is a potent inhibitor of HBV replication. This antiviral has shown the ability to reduce viral CCC DNA levels, which are believed to promote development of liver cancer. Early studies also suggest that entecavir-treated patients had a more sustained response to the drug, even after treatment ended, including those with HBeAg-negative hepatitis B. About 67 percent of HBeAg-positive patients achieve undetectable HBV DNA following treatment with entecavir, 21 percent clear HBeAg, and 68 percent achieve normal ALTs. Among HBeAg-negative patients who have never been treated before, 90 percent achieve undetectable HBV DNA and 78 percent achieve normal ALTs.

Entecavir resistance is rare in those who have never been treated with an antiviral, remaining less than 1 percent after

one year; however in patients who have already developed lamivudine resistance, entecavir resistance reaches 43 percent after four years.

Telbivudine (brand name Tyzeka) is a nucleoside analog that has shown success in suppressing viral load and improvement of liver inflammation. One 52-week study that compared telbivudine to adefovir in 135 patients with HBeAg-positive hepatitis B and elevated ALT found it produced more significant declines in HBV DNA than adefovir. The daily dose is 600 mg/day. The most common side effects were elevated CPK (creatinine phosphokinase) About 60 percent of HBeAg-positive patients achieve undetectable HBV DNA following treatment with telbivudine, 22 percent clear HBeAg, and 77 percent achieve normal ALTs. Among HBeAg-negative patients who have never been treated before, 88 percent achieve undetectable HBV DNA and 74 percent achieve normal ALTs.

Telbivudine has a resistance rate of 3–4 percent after one year and 9–22 percent after two years.

Tenofovir (Viread): The newest antiviral, was approved by the FDA in August 2008. It has been used successfully against HIV for years. Viread (tenofovir disoproxil fumarate) is a nucleotide analog reverse transcriptase and HBV polymerase inhibitor that blocks an enzyme that the hepatitis B virus needs to replicate in liver cells. The recommended dose for chronic hepatitis B is one 300-mg tablet a day. Two ongoing Phase III clinical trials comparing Viread with Hepsera found that chronic hepatitis B patients on Viread achieved a higher rate of complete treatment response compared with patients taking Hepsera, according to the company, which says the two drugs should not be used together.

Antivirals in Development

There are several experimental antiviral medications currently in Phase III or late-stage clinical trials:

Emtricitabine (FTC, Emtriva), already approved by FDA for treatment of HIV, has been found to be effective in lowering HBV DNA. Gilead Sciences reported treatment with emtricitabine reduced liver fibrosis in 62 percent of patients who received the drug, compared to 25 percent of patients who received a placebo, and substantially lowered HBV DNA in 56 percent. However, researchers have found some instances of viral resistance to emtricitabine. A combination of emtricitabine and tenofovir has been effective against adefovir-resistant HBV. The drug is in Phase III trials.

Clevudine (L-FMAU) has demonstrated potent antiviral activity and the ability to produce a sustained response, even months after treatment has ended. In one study, 71 percent of patients who took clevudine maintained normal ALT levels six months after treatment ended, which is longer than with other antivirals. Clevudine, produced by Gilead, appeared to be well-tolerated with little resistance. The drug is now in Phase III trials.

BAM-205 (also NOV-205), developed by Novelos, also interferes with proteins involved in viral reproduction. BAM-205 was approved for use in Russia in 2001. Preclinical studies support BAM-205's anti-viral effects in more than 250 Russian hepatitis B patients studied. Viral load was reduced and ALT levels also declined.

For more information about hepatitis B, contact the following organizations:

- **Hepatitis B Foundation**
1-215-489-4900, www.hepb.org
- **Hepatitis B Support List**
www.hblist.org
- **Hepatitis Foundation International**
1-800-891-0707, www.hepfi.org

For more information about hepatitis C, hepatitis B and HCV coinfections, please visit www.hcvadvocate.org.

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