

Hepatitis B

Winter 2000

Reviewed by Dr. Gary Garber, University of Ottawa

What is Hepatitis B?

Hepatitis B is a liver disease caused by the hepatitis B virus (HBV). Like HIV, HBV is spread through contact with the blood or body fluids of an infected person. HBV infection is common in HIV-positive people.

Usually, a healthy immune system can fight off HBV infection. However, some people become chronically infected with HBV. That means their bodies can't effectively control the virus, and HBV can continue to replicate. About 10 per cent of HIV-positive people who are infected with HBV develop chronic hepatitis. People with chronic HBV infection often feel completely healthy, even though they carry the virus. They can, however, transmit HBV to others who come in contact with their blood, semen, vaginal fluid, breast milk and saliva.

HBV and Liver Disease

Chronic HBV infection can lead to serious liver damage, but it may take many years, even decades, for this to happen. The liver damage seems to be caused by the body's response to HBV and not by the virus itself. Immune system cells, called cytotoxic T lymphocytes (CTLs) or killer T-cells, fight HBV by killing infected liver cells. Although the liver has the ability to replace damaged or dead cells, repeated injury can cause permanent damage over time. Instead of regrowing healthy tissue, damaged cells are replaced with fibrous scar tissue. Cirrhosis is the term used to describe scarring that has developed throughout the liver.

Because the liver performs hundreds of essential functions, damage to it can be life-threatening. The liver transforms glucose into glycogen and stores it as the source of energy for every cell in the body. It stores fats and vitamins, produces proteins that allow blood to clot and transforms harmful agents into substances that are safe for the body.

HBV and HIV

It's not clear exactly how these two viruses may interact. Research suggests that HBV does not affect HIV infection and does not cause a faster progression to AIDS. However, HIV may influence HBV. In chronic HBV infection, much of the damage to the liver is caused by the immune system as it tries to fight the virus. Because HIV suppresses the immune system, there may be a weaker immune response to HBV. As a result, people living with both viruses (co-infected) may have higher levels of HBV in their blood for longer periods. In theory, because of HIV-related immune suppression, co-infected people may actually have less liver damage than those who are HIV-negative. At the same time, if HBV is not controlled with treatment, very high levels of virus in the body means it can be easily transmitted to someone else.

Symptoms

Many people have no symptoms when they're first infected with HBV. Others may feel like they have the flu, with fever, fatigue, loss of appetite, nausea and vomiting, diarrhea, weight loss and aching joints and muscles. A few people may develop jaundice — a condition in

which the skin and the whites of the eyes turn yellow.

Similarly, people living with chronic HBV infection often feel perfectly healthy. Others may experience bouts of fatigue, lost appetite and nausea.

Diagnosis and Monitoring

There are several tests that doctors can use to find out if a patient has been exposed to HBV, if it's a new (acute) or old (chronic) infection and if HBV is affecting the liver.

- **HBsAg.** This test identifies the hepatitis B surface antigen (HBsAg), a part of the outer coat of the virus. This is the most common test used to find out if someone has been exposed to HBV.
- **HbeAg.** This test identifies the hepatitis B e antigen (HbeAg), another part of the virus. If this antigen is found, it means the patient is contagious and can pass the virus on to someone else.
- **Antibody tests.** These tests can identify several different antibodies, including the hepatitis B surface antibody (HBsAb), the hepatitis B core antibody (HBcAb) and the hepatitis B e antibody (HBeAb). If antibodies are found, it means the immune system is able to fight the virus either because the patient has been vaccinated against HBV or because the body has recovered from HBV infection.
- **ALT and AST.** Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are liver enzymes that are normally present in the blood. A higher-than-normal amount of these enzymes in a sample of blood can be a sign of liver damage.
- **Liver biopsy** is the removal of a tiny piece of tissue from the liver. The biopsy sample is examined under a microscope to see if scar tissue is present. A biopsy can indicate if scarring is present, what type of cells are involved and how far the scarring has spread. Although it is an invasive procedure, a liver

biopsy is a fast and safe way to assess liver damage in most people. For hemophiliacs, however, there is always the risk of serious bleeding.

Doctors may classify chronic HBV infection as “replicative” or “non-replicative.” In replicative infections (also known as chronic active hepatitis), the virus is replicating at a high rate, HBV viral load is usually high, and the “e” antigen (HBeAg) is present in the blood. In non-replicative infections (chronic persistent hepatitis), the virus is still replicating but at a fairly low level. HBV viral load is generally low and the “e” antigen is not found.

Generally, people with non-replicative hepatitis are at much lower risk of developing serious liver damage than those with replicative infection. However, because their immune systems are compromised, HIV-positive people may find that their HBV status can change from non-replicative to replicative infection.

Treatment

Treating HBV and HIV can be tricky: there are no clear guidelines, and research on the drugs has been done only in small groups of people. Co-infected patients may have to consult both an HIV specialist and a liver specialist as well as their primary care doctor to manage both conditions.

Treatment for HBV is aimed at improving the body's ability to control the infection. Generally, treatment is offered only to those with replicative infection who are at high risk of developing liver damage. HBV treatment is judged successful if all of the following occur:

- The “e” antigen (HBeAg) disappears.
- The “e” antibody (HBeAb) develops.
- HBV viral load is cleared from blood.
- Liver enzyme (AST and ALT) levels normalize.

The anti-HIV drug 3TC (lamivudine) is licensed for the treatment of chronic HBV

infection. It can lower the amount of HBV in blood and reduce inflammation of the liver. However, when 3TC is stopped, levels of HBV in the blood often rise again, signs of inflammation (elevated levels of liver enzymes) reappear and symptoms can occur. Furthermore, when 3TC is used alone (monotherapy), viral resistance can develop, and this occurrence causes the drug to stop working. As a result, co-infected people should never use monotherapy to treat either HIV or HBV.

Interferon-alpha (sometimes called alpha-interferon) is a cytokine — a protein messenger produced by the immune system in response to infection. Interferon-alpha may work both by slowing HBV replication and by improving the immune response to the virus. Interferon-alpha is taken as a subcutaneous (under the skin) injection. The standard dose is either 9- to 10-million units (MU) three times a week or 5 MU to 6 MU daily for four months. Interferon-alpha is effective for about 17 to 33 per cent of HIV-negative people with chronic HBV. It can cause such severe flu-like symptoms, including fevers, chills, shaking and fatigue, that the dosage may have to be reduced.

HBV and HAART

Protease inhibitors and non-nucleoside reverse transcriptase inhibitors (non-nukes) are processed by the liver. Because both types of drugs can cause inflammation and liver damage, there is concern that using HAART could increase HBV-related liver damage. Many co-infected people are able to use HAART without serious problems, but the rate of HAART-related liver toxicity is about seven times higher in co-infected people than in those living with HIV alone.

A team of French researchers enrolled 17 patients in a study of HAART. All were co-infected with HIV and HBV, 41 per cent also had HCV, and 35 per cent had hepatitis D virus (HDV). Six had no symptoms of HIV infection, while the remaining 11 were living with an AIDS diagnosis. Before entering the

study, their median HIV viral load was 98,180 copies, and median CD4+ count was 245. All patients received 3TC and indinavir along with either AZT or d4T. After six months of HAART, 94 per cent had cleared HBV from their blood. Seven patients saw the “e” antigen (HBeAg) disappear from their blood, and five of them developed the “e” antibody (HBeAb). Blood levels of ALT became normal in six patients. After two years of HAART, 82 per cent have maintained their HBV response, and 29 per cent carry the “e” antibody.

Experimental Treatments

Several of the drugs being studied as treatments for chronic HBV are also used to treat HIV and herpes (HSV). Most researchers believe that combination therapy will be the most effective way to treat HBV.

1. Interferon-alpha is usually given for four months and then stopped, even if there are still signs of HBV. However, some doctors believe eight months of treatment may improve success rates.
2. Pegylated interferon is an experimental form of interferon-alpha, in which the drug is encased in a fat bubble of polyethylene glycol. Pegylated interferon lasts much longer in the body, which means it may only have to be taken once a week. Hoffmann LaRoche is developing Pegasys, a pegylated form of interferon-alpha-2a, and Schering Plough is working on Peg-Intron, pegylated interferon-alpha-2b.
3. Development of adefovir dipivoxil (Preveon) as an anti-HIV drug has stopped, but trials of adefovir as a treatment for hepatitis B continue. A small trial of adefovir in 53 HIV-negative subjects with chronic HBV compared the effects of a placebo with either 5 mg, 30 mg or 60 mg of adefovir taken once a day. After 24 weeks, eight of the 30 subjects who received either 30 mg or 60 mg lost the HBe-antigen, and six of the 30 tested positive for the HBe-antibody.
4. Famciclovir (Famvir) is an anti-herpes drug approved for sale in Canada. Phase III trials of

famciclovir as a treatment for HBV are under way. On its own, famciclovir has a modest effect against HBV. A very small trial of five HIV-negative men with chronic HBV studied famciclovir in combination with interferon-alpha. The subjects took 500 mg of famciclovir three times a day for a month before adding 5 MU of interferon-alpha. On famciclovir alone, their HBV viral load fell by a factor of 10; when interferon-alpha was added, viral load dropped by a factor of 100. After 12 weeks of combination treatment, famciclovir was stopped, and interferon-alpha continued for another four weeks. By the end of the study, two of the five men had normal ALT levels and undetectable HBV viral load; biopsies of their livers showed improvement as well.

5. Thymosin alpha 1 (Zadaxin) is a manufactured form of a protein produced by the thymus gland. It stimulates the growth of natural killer cells and T-cells and improves their ability to recognize antigens and fight infection. Zadaxin is approved for the treatment of chronic hepatitis B in nine countries. It is manufactured by SciClone Pharmaceuticals of San Mateo, California.

A placebo-controlled study of Zadaxin was conducted in 98 HIV-negative subjects with chronic hepatitis B. They were divided into three groups and randomly assigned to receive one of the following:

- 1.6 milligrams of Zadaxin by subcutaneous (under the skin) injection twice a week for 26 weeks
- 1.6 mg Zadaxin twice a week for 52 weeks
- A placebo

When their treatment ended, 40.6 per cent of subjects on the 26-week treatment, 26.5 per cent on the 52-week treatment, and 9.4 per cent on placebo had undetectable HBV viral load, and the “e” antigen (HBeAg) had disappeared from their blood.

Diet

Because even small amounts of alcohol can damage the liver, it is recommended that people living with chronic hepatitis stop drinking.

Nutritional approaches to chronic hepatitis are controversial because it's not clear if changes in diet really make a difference. Some of the common dietary recommendations may not be appropriate for people living with HIV. Anyone considering making changes to their diet should consult a nutritionist with experience in HIV.

For people with chronic hepatitis but no cirrhosis, a low-salt, low-fat, low-carbohydrate diet that maintains their body weight is often suggested.

For people with chronic hepatitis and cirrhosis, it is sometimes recommended that protein (mostly from plant sources) be limited to a daily intake of 80 to 100 grams, and that complex carbohydrates (such as vegetables) should be chosen over simple carbohydrates (breads, pastas, starchy vegetables such as potatoes). Instead of two or three large meals a day, five smaller, well-balanced meals may be easier on the liver.

Supplements

There are a wide variety of liver “detoxifying” products and supplements available. Supplements can vary widely in quality and price. It may be best to talk with a doctor of naturopathy or an experienced staff person at a well-regarded health food store before trying a supplement. A few of these products have been studied, but most of the research has been done in test tubes or on rats. In separate studies, vitamin E and sho-saiko-to (a Japanese combination of herbs) have reduced scar tissue in the livers of rats by as much as 25 per cent.

Silymarin is the general name given to the active ingredients (including silybin, silydianin and silychristine) of the milk thistle plant. It is commonly used in Europe to treat liver diseases related to alcoholism, including

cirrhosis. Most of the research on silymarin has been done in Austria and Hungary; although the results have been published, the papers have not been translated into English. Generally, European studies feature a standardized preparation containing 70 to 80 per cent silybin. At a dose of 420 mg daily for six months, silymarin seems to reduce levels of liver enzymes (including AST, ALT and GGT) in the blood. Silymarin may have a laxative effect at doses over 1,500 mg daily. A study of silymarin done on mice has shown that it is processed by the same liver enzymes that metabolize many drugs, including protease inhibitors and non-nukes. Therefore, there is the potential for interactions between silymarin and other drugs.

Availability

Several slightly different interferons are manufactured: Intron A (interferon-alpha 2-b, made by Schering Plough); Roferon A (interferon alpha-2a, made by Hoffmann LaRoche); and Wellferon (interferon-alpha n-1, made by Glaxo Wellcome). Intron A is the most widely studied version for the treatment of chronic hepatitis.

Famciclovir and 3TC are approved for sale in Canada. Adefovir is currently being studied in clinical trials.

Thymosin-alpha 1 (Zadaxin) is approved in several countries. It may be available through the larger American buyers' clubs.

Useful Web Sites

The Canadian Association for the Study of the Liver: www.lhsc.on.ca/casl

The Canadian Liver Foundation: www.liver.ca

Hepnet — The Hepatitis Information Network, sponsored by Schering Plough Canada: www.hepnet.com

References

Akbar SM, Yamamoto K, Abe M, et al. Potent synergistic effect of sho-saiko-to, a herbal medicine, during vaccine therapy in a murine model of hepatitis B virus carrier. *European Journal of Clinical Investigation* 1999 Sep;29(9):786-92.

Bessesen M, Ives D, Condreay L, et al. Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance

to or withdrawal of lamivudine. *Clinical Infectious Diseases* 1999 May;28(5):1032-5.

Carton JA, Maradona JA, Asensi V, et al. Lamivudine therapy for chronic hepatitis B and HIV coinfection. *AIDS* 1999 May 28;13(8):1002-3.

Chien RN, Liaw YF, Chen TC, et al. Efficacy of thymosin alpha 1 in patients with chronic hepatitis B: a randomized, controlled trial. *Hepatology* 1998 May;27(5):1383-7.

Ferenci P, Dragosics B, Dittrich H, et al. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *Journal of Hepatology* 1989;9:105-113.

Janssen HL, Gerken G, Carreno V, et al. Interferon alfa for chronic hepatitis B infection: increased efficacy of prolonged treatment. The European Concerted Action on Viral Hepatitis (EUROHEP). *Hepatology* 1999 Jul;30(1):238-43.

Marques AR, Lau DT, McKenzie R, et al. Combination therapy with famciclovir and interferon alpha for the treatment of chronic hepatitis B. *Journal of Infectious Diseases* 1998 78(5):1483-7.

Zylberberg H, Adda C, Nalpas B, et al. Incidence and predictors of acute hepatitis occurring under antiretroviral therapy including a protease inhibitor. [Abstract 698] *50th annual meeting of the American Association for the Study of Liver Diseases*. Dallas, TX; November 5-9, 1999.

Bertrand Toulouse and Deirdre Maclean

Disclaimer

The Community AIDS Treatment Information Exchange (CATIE) provides information resources to help people living with HIV/AIDS who wish to manage their own health care in partnership with their care providers. We do not recommend or advocate particular treatments and we urge users to consult as broad a range of sources as possible. Although we update our material regularly, users should be aware that information changes rapidly. Additional information may be available from CATIE at 1-800-263-1638 or on our Web site at <http://www.catie.ca>. Users relying on the information do so entirely at their own risk. Neither CATIE nor Health Canada accepts responsibility for any damage that may result from the use or misuse of this information. The views expressed herein are solely those of the authors and do not necessarily reflect the official policy of the Minister of Health Canada. Decisions about particular treatments should be made in consultation with a health-care professional knowledgeable about HIV-related illnesses and the treatments in question.

Permission to Reproduce

This document is copyrighted. It may be reprinted and distributed in its entirety for non-commercial purposes without prior permission, but permission must be obtained to edit its content. The following credit must appear on any reprint: *This information was provided by the Community AIDS Treatment Information Exchange (CATIE). For more information, contact CATIE at 1-800-263-1638.*

Contact CATIE

by telephone

1-800-263-1638
(416) 203-7122

by fax

(416) 203-8284

by e-mail

info@catie.ca

on the Web

<http://www.catie.ca>

by mail

555 Richmond Street West, Suite 505, Box 1104
Toronto, Ontario M5V 3B1
Canada

Funding has been provided by the HIV/AIDS Care, Treatment and Support Program, Health Canada, under the Canadian Strategy on HIV/AIDS.

