

HIV

**GUIDE TO
HEPATITIS B
FOR PEOPLE
LIVING WITH
HIV**

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GUIDE TO HEPATITIS B FOR PEOPLE LIVING WITH HIV

TAG

Treatment Action Group

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For Martin Delaney

**Thanks to TAG's board, staff, and generous donors.
This work would not be possible without your support.**

Treatment Action Group is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS.
TAG works to ensure that all people with HIV receive lifesaving treatment, care, and information.

We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions.

TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end AIDS.

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Disclaimer: *Information in this guide is not intended to replace information from your doctor or other health-care providers. Decisions related to your treatment should be made in consultation with your doctor.*

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TABLE OF CONTENTS

Section 1: First Questions	1
Section 2: Transmission and Prevention	7
Section 3: Natural History	13
Section 4: HBV Disease Progression and the Impact of HIV Coinfection	17
Section 5: Diagnostics	21
Section 6: HBV Treatment for HIV-Positive People	31
Section 7: HIV/HBV Treatment for People Who Use Drugs	39
Section 8: Research into New HBV Therapies	41
Section 9: Managing Cirrhosis	43
Section 10: Living with Chronic HBV	45
Section 11: Other Viral Hepatitis	51
Section 12: Resources	53
Appendix: Treatment for HBV Monoinfection	55
Glossary	66

INTRODUCTION

Welcome to this treatment guide for HIV-positive people who also have hepatitis B (HBV). This guide provides information on the prevention, care, and treatment of HBV, and the impact of HBV on HIV disease. It is designed to be accessible to people with no medical training. Where medical terms are used, they are explained in detailed but simple language.

Because HIV and hepatitis viruses are transmitted in similar ways, having both HIV and hepatitis B (known as HIV/HBV coinfection) is possible. This guide focuses on coinfection with HIV and hepatitis B, but since most of our understanding of hepatitis B comes from research studies done in people without HIV, most of the information provided here should also be useful for people who have HBV alone.

While people with HIV/HBV coinfection are living longer and healthier lives with effective HIV treatment, slower-progressing liver disease caused by hepatitis B, such as liver cancer and liver failure, are now emerging as major health concerns. There are many complicating factors in HIV/HBV coinfection that can change disease progression, depending on when you're infected with these viruses and how long you've had them. These factors underscore the importance of an individual approach to your own health care. Being informed about the range of care and treatment choices available to you may help you feel more in control of your health-care decisions.

At the end of this guide, we have included a list of organizations that can provide support, financial assistance, and current medical information. We have also included a glossary that defines some of the medical terms used in this guide.

Hepatitis B treatment options have greatly expanded in the last ten years, and our understanding of chronic HBV disease is likely to change as new research findings emerge. Please check online for updates at www.treatmentactiongroup.org.

You can request additional printed copies free of charge, or download the guide as a PDF from our website. A version in Spanish is also available.

SECTION 1: FIRST QUESTIONS

Learning more about hepatitis B will help you better understand the complexities of this condition and become a more informed partner with your doctor in making health-care decisions. Following are some basic questions you might have about HBV and HIV/HBV coinfection. You can find more detailed discussions of these questions in later chapters.

What Is Hepatitis B?

Hepatitis B (HBV) is a virus that infects liver cells. Once inside the liver, HBV can reproduce in large numbers while causing no liver damage for years to decades. In fact, many people with HBV are healthy and will never need treatment. But in about one out of four people, as they live with the infection longer and by reasons still unclear, their immune system will start to recognize the infection and activate by attacking and killing HBV-infected liver cells, slowly causing liver inflammation and scarring (called **fibrosis**). Eventually, HBV can lead to more serious liver scarring (called **cirrhosis**), liver failure, or liver cancer (**hepatocellular carcinoma**, or **HCC**).

How Did I Get HBV?

Because they usually have no symptoms when they are first infected, people with HBV are often surprised when they find out they have it. HBV can be passed from mother to infant at birth or during early childhood; in parts of the world where HBV is common (Africa and Asia), most people with HBV were infected at birth and may not know they have it. Adults can get HBV through unprotected sex or sharing injection drug equipment with someone who is infected. Since these are also HIV transmission routes, HIV/HBV coinfection is common with these risk activities.

The good news is that HBV can be prevented. There is an effective preventive vaccine, and the use of condoms and clean drug injection equipment greatly reduces the risk of transmission. For more information about HBV transmission and how to protect yourself and others, see Section 2 (page 7) on Transmission and Prevention.

How Serious Is HBV?

Hepatitis B infection is a very complicated condition, and researchers are still trying to understand why the disease is more serious in some people than in others. For example, when healthy adults are first infected (**acute infection**), only about 30–50% will experience symptoms, and the vast majority (more than 95%) will be able to clear the virus on their own (**spontaneous clearance**) within the first three months. HIV-positive adults, due to their weakened immune system, are significantly less able to clear HBV on their own. Infants and young children usually experience no symptoms during acute infection, but since their immune systems are not yet fully functional, only about 10% will clear HBV. If infection is cleared, the immune system develops antibodies that provide protection from becoming infected again. If the infection is not cleared, it becomes chronic (or lifelong).

Since physical symptoms are rare until extensive liver damage has developed in this slow progressing illness, most people who were infected at birth may not experience any serious health problems until they are in their thirties to fifties.

The risk of chronic HBV progression varies, based on many factors. People are at higher risk for developing serious disease if they:

- Have been infected for a long time (at birth vs. as adults);
- Are men over 40 or women over 50 years old;
- Are overweight;
- Drink a lot of alcohol;
- Have a family history of liver disease, abnormal cholesterol, or diabetes; or
- Have a weakened immune system (people who are HIV-positive, have other conditions that affect their immune system, or are taking immunosuppressive drugs).

Because there are so many complicating factors, it is difficult to generalize about the likelihood of disease progression; therefore, it is important to consider your own specific situation and to make your health-care decisions accordingly. For more information on how to do this, see Section 3 (page 13) on Natural History.

How Common Are HBV Infection and HIV/HBV Coinfection?

Worldwide, at least 350 million people are chronically infected with HBV. In the United States, an estimated 2 million people are living with chronic HBV infection. Since HIV and HBV are transmitted in similar ways, coinfection is common: an estimated 10% of the 36 million HIV-positive people worldwide are coinfecting with HBV. Globally about 50% of reported cases of cirrhosis and 30% of liver cancer are HBV-related, and over 500,000 people die from them each year.

Since the mid 1980's, universal HBV vaccine programs for newborns have been highly successful in lowering HBV infection rates in countries that have implemented them, while countries that have not put programs in place are seeing their HBV epidemic continue to grow. Decades later, people without access to HBV vaccination and those born before the vaccine became widely available are now starting to develop serious liver disease.

HIV-positive people who have access to treatment are living longer, but are now experiencing liver damage caused by viral hepatitis, including HBV. **End-stage liver disease (ESLD)** from viral hepatitis coinfection is now a leading cause of death among people with HIV.

Will HIV Make My HBV Worse?

HIV worsens HBV infection because HIV weakens the immune system, making it harder for HIV-positive people to clear an acute HBV infection. In chronic HBV, HIV induced immune dysfunction can increase the risk of liver damage caused by episodes of immune activation that targets HBV infected liver cells. Coinfected people are more likely to experience faster

HBV disease progression and sustain more liver damage than those with HBV alone. HIV coinfection also increases the risk of developing HBV-related liver cancer later in life.

It is very important for all HIV-positive people to be screened for HBV before starting their HIV treatment for the first time, because coinfection impacts treatment decisions. This is because some HIV drugs are also effective against HBV, while others are not. If a chosen HIV drug combination lacks the ability to control HBV at the same time, as people's immune system improves with HIV treatment (**immune reconstitution**) while their HBV is left unchecked, previously unnoticed HBV infection may now be recognized by the improved immune system and trigger a strong immune response, potentially causing rapid and severe liver damage that can be fatal.

This is especially important for coinfecting people starting treatment with a low CD4 cell count ($<200/\text{mm}^3$) as they may have a much higher level of HBV in the body, which can trigger a more severe immune response. Your doctor should watch out for rapid and high liver enzyme elevations during the first few months after starting HIV treatment.

Caution should also be taken when coinfecting people stop or switch their HIV regimen. Stopping HBV treatment can cause a viral rebound, an increased HBV viral load that can trigger an immune response and cause liver damage. This is called an **HBV flare**. Likewise, switching to another HIV regimen without a HBV active drug can also cause an HBV flare. For more information, see Section 4 (page 17) on HBV Disease Progression and the Impact of HIV Coinfection.

Will HBV Make My HIV Worse?

It isn't clear that HBV infection has any direct impact on HIV disease progression; however, many HIV drugs can be broken down properly only if the liver is healthy. HIV-positive people with HBV-related liver damage may be unable to process the drug efficiently, and may experience more severe side effects caused by higher drug concentrations left in the body. Some HIV drugs can also cause liver damage directly. These drugs should be avoided in people coinfecting with HBV. Ask your doctor to prescribe medications that are less likely to cause liver injury.

What Tests Should I Have, and What Do the Results Mean?

Doctors use many different tests to regularly monitor the activity of HBV, watch for signs of disease activation, and measure degrees of liver damage. These tests can provide important information about the current state of your HBV disease and are used as guideposts for HBV treatment initiation, as well as measurements of your response to treatment. These test results can show fluctuations (irregular swings/changes) in the amount of virus in the blood and changes in liver inflammation frequently seen in chronic HBV, so you will need to track them over time in order to see a clear pattern that will give you enough information to make treatment decisions. To understand more about these tests and what they tell you, see Section 5 (page 21) on Diagnostics.

Can HBV Be Cured, and How Do I Know If I Need Treatment?

It is not currently possible to cure HBV with treatment, since small particles of the virus (**cccDNA**) inserts itself inside the nucleus of liver cells, where the drugs cannot reach it; but drugs can control HBV in order to prevent or delay the development of liver damage. Some HIV-negative people who have successfully controlled HBV with treatment may be able to stop treatment and rely on their immune system alone to keep the virus in check. Most people, however, will need to stay on HBV treatment indefinitely.

Although there have been encouraging improvements in HBV treatment over the last ten years, making treatment decisions can be complicated. Doctors and researchers are still trying to find better indicators for the need to start treatment, but in general they agree that people can benefit from treatment when their HBV is actively replicating, and there are signs of ongoing or existing liver inflammation or scarring. Since HBV treatment is not always necessary, deciding whether to wait and see, or to start treatment, can be difficult, especially considering the potential long-term treatment side effects and the high cost of lifelong therapies.

There are now six different drugs available to treat HBV. There are major concerns about the emergence of **drug resistance**, as some of these drugs are more effective than others in controlling drug-resistant HBV mutations. For more information about HBV treatment and current guidelines on when to start, see Section 6 (page 31) on HBV Treatment.

What Should I Do First After Learning I Have HBV?

For some people, joining a support group makes sense. Talking to others and sharing your experiences can make you feel less isolated. Dealing with difficult issues, such as disclosing your status, and recommending HBV testing and vaccination to your family or to sex and drug-use partners, can be more manageable when you hear about how others have dealt with these situations.

Finding a doctor who is experienced in treating both HIV and HBV is an important next step. Many people have negative feelings about hospitals, clinics, and doctors' offices, perhaps from traumatic experiences in the past. One thing to keep in mind is that with managing a chronic disease like HBV, you might go through many years of monitoring your condition with just routine blood tests and office visits without the need for treatment. Working with a doctor you like and trust, and taking charge of your own health-care decisions, can be empowering and positive experiences. You may want to see a liver expert (a hepatologist or a gastroenterologist) in addition to your HIV caregiver.

When you are ready for treatment, an important step is finding health-care coverage. If you have an HBV diagnosis, health insurance can be expensive and hard to get. This can be a difficult issue to tackle, but it may be the most important thing to sort out first, as HBV treatment is costly. HIV-positive people usually have better access to treatment than people who don't have HIV, through publicly funded programs that were created through

advocacy by people living with HIV in the 1980's. There may be state funded government assistance programs where you live, and drug company discount programs that can help defray some of the costs for your HBV treatment and lab tests. For more information about where to find support, information, and financial assistance, see Section 12 (page 53) on Resources.

Are There Other Hepatitis Viruses I Should Know About?

In addition to HBV, here are several other viruses that infect the liver. They are named alphabetically (A, C, D, and E) in the order in which they were discovered. All HIV-positive people should be tested for these viral hepatitis infections. Although all of these viruses infect the liver, each virus is different, and some are more serious than others. Being coinfecting with more than one virus can further complicate your health and cause more rapid liver damage. For more information about other viral hepatitis coinfections, please see Section 11 on Other Viral Hepatitis (page 51).

SECTION 2: HBV TRANSMISSION AND PREVENTION

Coming to terms with your HBV infection sometimes involves telling family members, sexual or drug-use partners, and other people close to you about your status. It may be very helpful for you to know how HBV is transmitted so that you can protect others from exposure and educate them about how to prevent becoming infected.

HBV is transmitted through blood, semen, and other body fluids. HBV is 50–100 times more infectious than HIV and can survive outside the body for up to seven days.

HBV is most commonly transmitted through:

- Birth, from an infected mother to her infant;
- Having unprotected anal or vaginal sex with someone who has HBV; the risk from unprotected oral sex is unclear;
- Sharing drug injection equipment, including needles, cookers, ties, cotton, straws, water, and even measuring syringes;
- Sharing personal-care items that may have blood on them, such as razors or toothbrushes;
- Getting a tattoo with any shared, unsterilized equipment, such as needles, ink, and inkwells;
- Getting a medical procedure with unsterilized equipment; and
- Accidental needlestick injuries or other occupational hazards involving exposure to blood from an infected person.

HBV cannot be transmitted through casual contact such as kissing, shaking hands, hugging, or sharing drinking glasses or eating utensils.

HBV Testing and Vaccination

People who are at risk for HBV infection should get a simple blood test to find out if they have ever been exposed to HBV or if they need to be vaccinated against HBV. The test looks for small pieces of HBV called **antigens**, and **antibodies** produced by the immune system to fight off HBV. The tests look for the presence (positive) or absence (negative) of three things:

HBV surface antigen (HBsAg): Small proteins on the surface of HBV.

HBV surface antibody (anti-HBs): Antibody targeting the surface antigen.

HBV core antibody (anti-HBc): Antibody targeting the core antigen.

HBV Screening Test Results Chart

HBsAg	Anti-HBs	Anti-HBc	What It Means
Negative	Negative	Negative	The person has never been infected and needs to get vaccinated against HBV.
Negative	Positive	Negative or Positive	The person has been vaccinated, or has successfully fought off an earlier infection, and is now protected against HBV. This person cannot spread the virus to others and does not need to be vaccinated.
Negative	Negative	Positive	Unclear. The person may have occult HBV and will need an HBV viral load (HBV DNA) test to confirm. The person may also be fighting off an acute HBV infection; another test in six months can confirm.
Positive	Negative	Negative or Positive	The person may have acute or chronic HBV. The person can spread the virus to others and needs further testing to determine whether or not HBV has become chronic.

HBsAg (Hepatitis B Surface Antigen)

HBsAg are small protein particles on the surface of the hepatitis B virus. HBsAg can be detected and measured by a blood test. HBsAg testing is commonly used to screen for HBV infection and to diagnose chronic HBV. Test results are usually reported as positive (reactive) or negative (non-reactive), though sometimes in a research setting HBsAg is measured in quantities and reported in IU/mL (international units per milliliter). People who are HBsAg-positive have some level of ongoing HBV viral replication, even when their disease is inactive, and they can transmit the virus to others.

Some people may get a negative result from their HBsAg test but still have detectable hepatitis B virus in their blood. This is called **occult HBV**. HIV-positive people have a higher rate of occult HBV than people without HIV. It is not clear if occult HBV infection causes liver damage.

It is a good idea for people who are at risk of HBV infection to also be tested for hepatitis C (HCV) and HIV, because these viruses are transmitted in similar ways. There are no preventive vaccines for HCV or HIV, but these viruses are treatable, and in the case of HCV, curable.

HBV Vaccine

The HBV vaccine was created in the early 1980s. It is made with a small part of the virus that is not infectious. Once the vaccine is injected, the immune system responds to the viral particle in the vaccine by producing antibodies that protect against HBV. The vaccine is safe and more than 90% effective in people without HIV; it is given as a series of three shots over

a six-month period. Some medical providers will give the first dose of vaccine at the same time as the HBV test, as the vaccine is not harmful to people who are already infected or already have antibody protection, although this practice has not been formally recommended in prevention and treatment guidelines. The HBV vaccine is also available in a combination shot with the vaccine for hepatitis A (Twinrix).

Who Should Get It?

Since the early 1990s, vaccination programs for newborns of mothers with chronic hepatitis B have greatly reduced mother-to-child transmission of HBV. In addition, according to recommendations from public health authorities, the following people should be vaccinated: children; and all those who are at risk for HBV, such as people who have a family member with HBV; health-care workers; people with end-stage renal (kidney) disease who are on dialysis; people with hemophilia (a hereditary blood-clotting disease); HIV-positive people; people who engage in high-risk sexual activities (unprotected vaginal and anal sex); injection drug users; and people with hepatitis C or other types of liver disease.

In the United States, the Centers for Disease Control and Prevention (CDC) also recommends that people born in geographic regions with HBsAg prevalence of greater than 2%, and children of immigrants from these regions should be tested and vaccinated. This includes many countries in Eastern Europe, Asia, Africa, the Middle East, and the Pacific Islands. For a complete list, see: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm#tab3>.

How Long Does It Work?

The protective effect of the HBV vaccine may wear off over time, so if you were vaccinated more than ten years ago, it is a good idea to ask your doctor to do a test (called an anti-HBs immunizing antibodies **titer**) to see if you need a booster shot (another shot of the vaccine) to maintain the protection.

Vaccination for HIV-Positive People

All HIV-positive people should be vaccinated against HBV and the hepatitis A virus (HAV) if they have never been infected before. Your doctor can check to see if you need to be vaccinated.

Some HIV-positive people will need to repeat the vaccination series or use a higher dose of the vaccine to produce enough antibodies to protect against HAV and HBV. Because these vaccines require the immune system to be healthy in order for them to be effective, if your CD4 cell count is under 200/mm³, some experts think it may be better to start HIV treatment first and then be vaccinated later, when your immune system is stronger.

After vaccination, be sure to have your clinic check your antibody titer levels annually to see if you have sufficient protection. A booster shot may be needed to restore your antibody titer level.

Preventing Mother-to-Child Transmission

HBV can be passed easily from mother to infant. Globally, the majority of people with chronic HBV were infected at birth. About 90% of babies born to mothers with HBV will become chronically infected. Since mother-to-child transmission of HBV can be prevented, it is important for all pregnant women to be screened for HBV.

Mothers with HBV can protect their babies by making sure that their newborn gets a shot of hepatitis B immune globulin (HBIG—a product made from blood plasma that contains antibodies that protect against HBV) and the first dose of HBV vaccine within 12 hours of birth. Two to three more shots (depending on vaccination for HBV alone or in combination with other vaccines) are needed to complete the series over the first year. This strategy is about 95% effective in protecting the infant from HBV, but the success rate is lower when the mother has a high HBV viral load. Ask your doctor how many more shots your baby will need and when you should come back to get them.

There has not been sufficient research on the risk of birth defects in infants or on the reduction of transmission with HBV treatment during pregnancy. However, data from the Antiretroviral Pregnancy Registry to date has shown no additional risk of birth defects in infants born from mothers who were on HBV treatment during pregnancy than in the general population.

Pregnant women who are HIV/HBV-coinfected should be on HIV/HBV treatment (see Section 6 (Page 31) on HBV Treatment for HIV-Positive People for more information); this will help prevent the transmission of HIV to the baby. For more information about HIV and pregnancy, see the i-Base guide available online at <http://www.i-base.info/guides/pregnancy/index.html>.

Some Important Considerations About the Use of HIV Drugs for HIV Prevention

Sometimes people are given HIV drugs to prevent HIV, such as people accidentally exposed to HIV, or HIV-positive pregnant women who would not otherwise need treatment (to prevent mother-to-child transmission). Two of the drugs used in these circumstances are lamivudine and tenofovir, which are also used for HBV treatment.

It is very important to test for HBV before giving anyone lamivudine or tenofovir to prevent HIV.

People who have HBV need to avoid using these two drugs for HIV prevention, because stopping them can cause serious, possibly life-threatening HBV flares.

Other HIV drugs with no effect on HBV should be used instead.

Breastfeeding

HBV has been found in breast milk, but studies have shown that it is safe to breastfeed when the baby is vaccinated against HBV at birth; however, since HIV can be passed from mother to infant through breast milk, breast-feeding is not recommended for HIV-positive mothers, although this might not be feasible in poorer countries where infant formulas are not available.

Preventing Sexual Transmission of HIV and HBV

HIV and HBV can both be transmitted sexually via the same body fluids (semen, vaginal fluid, and blood), but different sex acts carry different degrees of risk. For example, mutual masturbation and body rubbing are zero-risk, and oral sex is very low-risk. On the other hand, anal, or vaginal sex without a condom is high-risk. Having a high HIV- and/or HBV viral load (the amount of virus circulating in the blood) increases the risk of infecting one's sex partner with HIV and/or HBV. People with untreated sexually transmitted diseases (STDs, such as herpes, gonorrhea, and syphilis) are more likely to transmit, and more likely to become infected with HIV and HBV. This is because their immune systems might be weakened by the STD infection or they might have open sores. Consistent and correct use of condoms every time you have sex greatly reduces the risk of HIV and HBV transmission.

HBV and Injection Drug Use

The hepatitis B virus can remain alive in syringes and other objects for days. This is why it's important to talk to people you get high with about how to make sure you're getting high safely, and in a way that protects everyone. People who inject drugs should be tested and vaccinated for HBV.

Cleaning syringes with bleach reduces the risk for HIV transmission, but may be less effective in preventing HBV- and HCV transmission. If you're getting high, use a new set of syringes and equipment each time you inject. If you're injecting drugs with other people, mark your equipment and be sure that everyone has his/her own spoon or cooker. Using clean needles and your own works each time you inject stops HIV, HBV, and HCV transmission.

SECTION 3: NATURAL HISTORY

HBV infection primarily affects the liver, the largest organ inside the human body, found on the right side, underneath the rib cage. Your liver works as a filter and processing plant: anything you eat, drink, or inhale passes through the liver. Your liver also breaks down drugs, herbal remedies, and vitamins.

Each day, your liver:

- filters waste from the blood;
- stores vitamins, minerals, and iron;
- changes food into energy;
- makes bile (a liquid that your body uses to digest fat);
- helps balance sugar and hormone levels;
- makes cholesterol; and
- creates many of the proteins needed for blood clotting.

HBV and Liver Damage

The hepatitis B virus infects liver cells, where it reproduces. Newly made hepatitis B virus particles, called virions, are released into the blood stream and in turn infect more liver cells. The hepatitis B virus does not directly cause liver damage. Instead, your immune system tries to prevent HBV from infecting other cells by surrounding already-infected liver cells and walling them off, causing liver scarring.

As the scarring worsens over time, the liver hardens and becomes less elastic, making it increasingly difficult for blood and other fluids to flow freely through it. Serious liver damage makes it difficult for the liver to regulate sugar-, hormone-, fat-, and platelet levels. As the liver slowly loses its ability to filter waste products, they can build up to toxic levels in your bloodstream.

Liver damage from HBV happens slowly, usually over decades in people without HIV. HIV-positive people, especially those who have lower CD4 cell counts, can develop liver damage faster. Even though a damaged liver can keep working, the ongoing inflammation and scarring can slowly interfere with liver function and lead to additional health complications.

Acute HBV

The first six months of HBV infection are referred to as the acute phase; during this phase, about 30–50% of infected people will experience symptoms. Symptoms usually appear between one and three months after people are infected—symptoms that can include nausea; vomiting; appetite loss; fever; fatigue; abdominal and joint pain; liver swelling; and jaundice (yellow skin and eyes). In very rare cases (<1%), these symptoms can arise very rapidly and severely (this is known as **fulminant hepatitis**) and can be fatal. People experiencing severe symptoms should seek medical attention immediately.

HBV treatment is usually not recommended in the acute phase, as it is not effective and might interfere with the natural immune process and cause chronic disease. However, treatment may be used in some acute cases when liver transplantation is considered in patients with fulminant hepatitis B.

Spontaneous Clearance

During acute HBV infection, some people will eliminate the virus from the blood (HBsAg **seroconversion** from positive to negative, meaning HBsAg can no longer be detected in the blood) and develop antibodies (anti-HBs) that protect against future HBV infection. This is called **spontaneous clearance**. During spontaneous clearance, the immune system recognizes HBV and responds by marking and destroying HBV in the blood, and by killing off infected liver cells.

The rate of HBV spontaneous clearance differs, depending on the robustness of your immune system when you were infected.

HBV Infection at Birth

Because the immune system takes many years to mature enough to recognize HBV infection passed on by the mother, infants and children cannot clear the virus as successfully; 90% will develop chronic (lifelong) HBV infection.

HBV Infection in Adults

Most adults with acute HBV will spontaneously clear the virus. Less than 1% of adults with a healthy immune system will develop chronic disease.

HIV-Positive Adults

People with weakened immune systems have a harder time clearing the virus. HIV-positive adults who become infected with HBV are significantly more likely to develop chronic disease than people without HIV.

Chronic HBV

If there is no spontaneous clearance, the HBV infection becomes chronic (lifelong). Having chronic HBV does not always mean that you will have serious liver damage or that you'll need treatment. Some people live with chronic HBV for many years and will never have serious liver damage. If HBV is untreated, the lifetime risk of death from serious HBV-related liver disease is about 25–40% among people without HIV.

Spontaneous clearance still happens at the rate of 1–2% per year during chronic HBV; one large study from Asia reported that 45% of people spontaneously cleared HBV over a 25-year period in younger adults. The reason for this is not clear, but is likely due to the maturing of the immune-system. This group of people generally has an excellent long-term outcome and will stay disease-free. Spontaneous clearance is less likely to happen in people over 35 years old.

HIV-coinfected people have a higher risk of developing serious liver disease without treatment; however, since effective treatment became available in the mid-1990s, the prognosis for coinfecting people has significantly improved. When their regimens include drugs that are also active against HBV, HIV/HBV-coinfected people respond just as well to their HIV drugs as do people with HIV alone. Studies have also found that treating HIV and HBV can lower the risk of HBV disease progression, and in some cases, even reverse liver damage from HBV.

Liver Damage Progression

While some people never develop serious liver damage from HBV, others may develop mild-to-moderate liver scarring, called **fibrosis**. They may experience symptoms such as fatigue, depression, and confusion; however, some people who have liver fibrosis will experience no symptoms. There does not seem to be a clear relationship between symptoms and the degree of liver damage.

Having HBV and being overweight can cause fat to build up in the liver, a condition called **steatosis**. Some HIV drugs (especially zidovudine, didanosine, and stavudine) can also cause steatosis. People with steatosis are at higher risk for liver damage.

Serious liver scarring is called **cirrhosis**. **Compensated cirrhosis** means the liver is still able to function even though it is scarred. People with compensated cirrhosis are at risk for developing liver failure and other serious complications.

Liver failure, also called **decompensated cirrhosis**, or **end-stage liver disease (ESLD)**, means that the liver can no longer do its job, and that a liver transplant may be necessary.

Liver cancer (also called **hepatocellular carcinoma**, or **HCC**) is a very serious complication of HBV infection. It is very difficult to treat successfully, especially if it is not caught early.

SECTION 4: HBV DISEASE PROGRESSION AND THE IMPACT OF HIV COINFECTION

One of the most perplexing aspects of HBV infection is its disease progression. In fact, researchers still don't fully understand why some people with HBV have no associated health problems, while others progress to serious liver disease; however, we do know that HBV disease progression is driven by the immune system's ability to control HBV replication, and that damages to the liver result from this dynamic process.

HIV worsens HBV because HIV directly attacks the immune system and gradually suppresses immune function by lowering the CD4 cell count. HIV infection also triggers persistent immune activation, which causes low-level inflammation throughout the body. These immune dysfunctions alter HBV disease progression.

Chronic HBV disease progression varies widely among individuals, but in general there are four distinct disease phases. Not everyone will go through every phase, and there can be fluctuations and reversions.

Phase 1: Immune Tolerant

During this phase, HBV is infecting liver cells and replicating at a very high rate, but the immune system either does not recognize the infection or is incapable of mounting an effective defense—the immune system is tolerating the virus. Since there is little-to-no immune response, the risk of liver damage is very low, and treatment is not recommended.

Primarily seen in people infected at birth or in early childhood, the immune tolerant phase can last decades, so most people can remain in this phase until their twenties and thirties. People infected as adults usually will not have an obvious immune tolerant phase.

The impact of HIV infection on the immune tolerant phase is not clear. Since HIV disease progresses faster than HBV-related liver damage can develop, the immune tolerant phase will not make a difference in treatment decisions in HIV/HBV coinfection.

Phase 2: Immune Clearance

Researchers are still not sure what triggers the immune system to activate and attempt to control a previously unnoticed HBV infection, but when it does, the immune-clearance phase has begun. During this phase, the immune system and HBV battle for control. The amount of virus in the body will rise and fall in response to the intensity of the immune activation. This phase can last from years to decades, primarily in people younger than 35, during which time liver damage can develop. Because of the risk of liver damage, people in the immune clearance phase are often recommended to go on treatment.

During immune clearance, HIV-positive people have more HBV in the body than people without HIV; at the same time, their immune responses to HBV are less intense. This makes it harder for them to clear HBV infection without treatment. As a result, they are more likely to remain in the immune clearance phase for a longer period of time. As their weakened immune systems attempt to control HBV repeatedly and without success, causing low but persistent liver inflammation, HIV-positive people are more likely to develop serious liver damage during the immune clearance phase.

Phase 3: Inactive

When the immune system is able to gain the upper hand, people with HBV will pass into an inactive disease phase. There may still be some very low-level HBV replication, but it will elicit little or no immune response and will not cause liver damage. Chronic HBV is considered to be in remission. In some people, especially those who did not develop liver damage during the immune clearance phase, HBV stays in remission indefinitely; nonetheless, those people still have a low risk of developing liver cancer as they age, possibly because of previous liver damage or other unknown effects of prolonged HBV infection.

Since the inactive phase is dependent on immune control of HBV, immune suppression caused by HIV will upset this balance. As HIV disease progresses, people will likely lose the ability to control HBV. HIV-positive people are unlikely to stay in remission without treatment and may revert to the immune clearance phase or progress to the next phase: reactivation.

Phase 4: Reactivation

Chronic HBV can reactivate in some people after a period of inactivity. This generally starts to occur as men reach the age of 40 and women reach the age of 50 who have been infected at birth, and the likelihood of reactivation increases as they get older. Researchers believe this is caused by the combined effects of the loss of immune function associated with aging, and naturally occurring HBV mutations (in the **pre-core** or **basal-core** regions of the viral genome). As the weakened immune system cannot recognize and sufficiently control these HBV mutations, more viral replication follows.

During reactivation, a moderate rise in HBV levels triggers an immune response, causing liver damage. Reactivation increases the risk for serious liver damage and liver cancer.

Another type of reactivation is seen in people who have cleared HBV either spontaneously or with treatment. This can happen when the immune system is affected by chemotherapy, high-dose steroids, or other immunosuppressive therapies such as those commonly used during bone-marrow and stem-cell

transplantation. Rarely, people have become infected with HBV after liver transplantation with an organ from a previously infected donor, even when the donor had cleared HBV spontaneously.

Reactivation can be more severe in HIV-positive people and rapidly cause serious liver damage. It is also possible for HBV to reactivate in HIV-positive people who have spontaneously cleared HBV in the past. As immune function often fluctuates in HIV disease, repeated episodes of reactivation are more likely in HIV/HBV coinfection; these can cause more liver scarring, speed up liver damage, and lead to a higher rate of developing cirrhosis. It is difficult to provide a more precise risk ratio of liver damage in HIV/HBV coinfection, since the availability of treatment has largely been effective in halting HBV disease progression.

SECTION 5: DIAGNOSTICS

Since the discovery of HBV, researchers have identified various ways to measure the rate of viral replication; signs of liver inflammation; degrees of liver damage; different strains of HBV; and evolution of chronic disease. Together, these tests can help identify which phase of chronic HBV disease you might be in, and are essential tools for monitoring disease progression and guiding treatment decisions.

HBeAg (Hepatitis B “e” Antigen)

HBeAg is a protein produced during the HBV replication process, then released into the bloodstream from infected liver cells. People infected at birth who have detectable HBeAg in the body (known as being **HBeAg-positive**) are in the first two phases of chronic HBV (immune tolerant to immune clearance), and most of them are younger than 35.

During the immune clearance phase, the immune system can develop antibodies to HBeAg (anti-HBe) to get rid of HBeAg in the blood. This is called HBeAg **seroconversion** (converting from positive to negative; at this point, HBeAg is no longer detectable in the blood) and is one indication that the immune system is gaining control over HBV. HBeAg status should be checked every one to two years to watch for HBeAg seroconversion.

HBeAg seroconversion happens at about 2–15% per year without treatment, and two-thirds of those who have seroconverted can remain that way and will not have disease progression nearly a decade later, greatly reducing their risk of serious liver damage.

HIV-positive people are less likely to have HBeAg seroconversion. The rate is reduced by about 60% as compared to people without HIV, at 3% in two years, and 11% in five years. HIV-positive people are also more likely to revert to being HBeAg-positive than are people without HIV.

The presence of HBeAg was first thought to be a clear indication of active HBV replication. More recently, however, researchers discovered HBV mutations (called **pre-core** and **basal-core** mutations) that are capable of replication without also making HBeAg. People with a detectable HBV viral load who are **HBeAg-negative** have likely developed these mutations. Researchers believe these mutations are more likely to develop with longer duration of HBV infection, as they are usually detected in people older than 40 who were infected at birth. People with these mutations have an increased risk for HBV reactivation and serious liver damage.

Regular Monitoring Tests for Chronic HBV

It is very important to get regular blood tests to monitor HBV progression. These tests can determine when a person should start HBV treatment, thereby preventing or delaying liver damage or liver cancer. Doctors check for two main indicators: activity of the hepatitis B virus (by measuring the amount of HBV in the blood [**HBV DNA**]) and amount of liver inflammation (by measuring the level of a liver enzyme [**ALT**]). HBV-DNA and liver-enzyme levels can fluctuate, so one-time measurements don't provide enough information for a definitive diagnosis on the phase of HBV disease or indicate the need for treatment. These tests need to be performed regularly (every three to six months) in order to show persistent elevations, a clearer indication of active viral replication and corresponding immune activation.

HBV DNA (Viral Load)

This test finds and measures the amount of HBV in the blood. Viral load can range from undetectable (not enough to show up on the test) to very high (up to billions of HBV in one drop of blood). A high viral load means the virus is actively replicating. Viral-load levels differ depending on the phase of chronic HBV disease. People who are HBeAg-positive generally have a higher viral load than people who are HBeAg-negative.

HBV viral loads are measured in International Units per milliliter (IU/mL); sometimes they are also reported in number of copies. Different labs use different viral-load tests, and there are differences in conversion rates from copies to IU. As a rough guide, five copies converts to one IU. Check with your lab to find out their exact conversion rate.

- A viral load greater than 20,000 IU/mL (100,000 copies) is considered high in HBeAg-positive people;
- A viral load greater than 2,000 IU/mL (10,000 copies) is considered high in HBeAg-negative people.

While a high viral load does not in itself cause liver damage, a recent large-scale and long-term study from Taiwan has shown that people with higher viral loads are more likely to develop cirrhosis and liver cancer later in life. Although there are some limitations to the study (only Chinese patients, most of whom had genotypes B and C exclusively, were studied), this finding has elevated the importance of HBV viral load in predicting disease progression, and viral suppression (lowering the viral load) is becoming a significant treatment goal.

To get a better picture of chronic HBV disease in addition to viral load, people will also need other important tests—those that measure liver-enzyme levels.

Liver Enzyme Tests: ALT and AST

Liver enzymes are proteins that have specific functions. When the liver is injured, some of these enzymes leave the liver and enter the bloodstream. Several things can cause liver enzyme levels to rise abnormally, such as **liver toxicity** from prescription and over-the-counter medications, herbs, vitamins, and supplements; exposure to toxic fumes; heavy alcohol consumption; acute or chronic viral hepatitis; and detoxifying from drugs and/or alcohol. Many HIV medications cause liver enzyme elevations—usually not to dangerous levels. In some cases, people may need to switch or discontinue certain drugs.

Liver enzymes are measured through a group of blood tests. Although they are often referred to as Liver Function Tests (LFTs), these tests do not actually measure how well the liver is working.

Alanine aminotransferase (ALT) and **aspartate aminotransferase (AST)** are two important liver enzymes.

ALT is an enzyme that usually resides inside the liver; it is released from the liver into the bloodstream when liver cells are injured. Increases in ALT are usually a signal of liver inflammation or damage; however, since liver-enzyme levels often fluctuate, ALT levels are not a reliable predictor of disease progression, nor do they indicate the severity of liver disease. ALT levels are also influenced by age, gender, and body weight. HIV-positive people may also develop liver damage when they have low or near-normal ALT levels.

ALT levels should be monitored every three to six months, since persistently increasing levels may suggest HBV disease progression. It's especially important for coinfecting people on treatment—or taking any other drugs known to be hard on the liver—to have liver enzyme levels measured routinely.

AST is made in the heart, intestines, and muscles, so it is not a sensitive marker for liver injury. AST levels are often used to monitor liver inflammation and damage (in combination with other tests). In monitoring of chronic HBV progression, ALT is used instead of AST, although these tests are usually done together.

ALT is measured in U/L (units per liter). Normal ALT levels are different in men and women, and liver inflammation is indicated by ALT levels above the upper limit of normal (ULN). Individual laboratories set their own ULN levels, but recently researchers have recommended a standardized and slightly lower ULN to more accurately reflect inflammation:

- ULN for men: ALT = 30 U/L
- ULN for women: ALT = 19 U/L

The results of an ALT test alone, however, are not enough to decide if someone needs treatment.

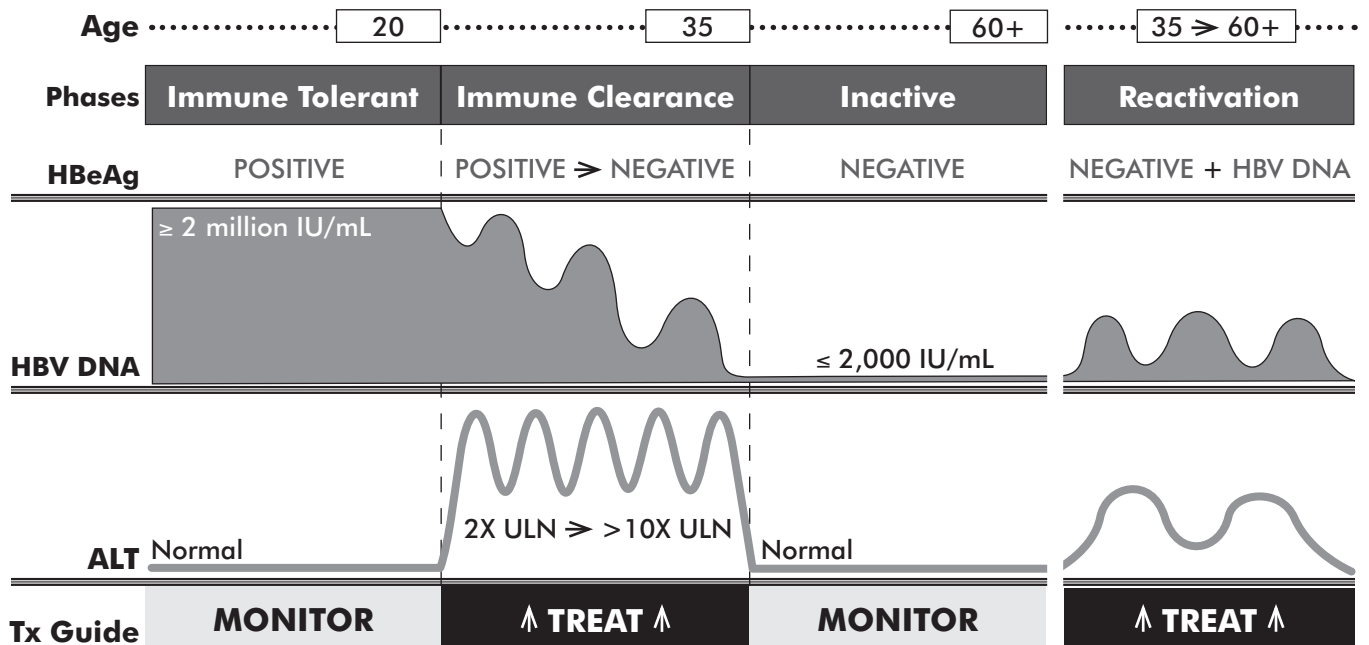
- An elevated ALT level might be due to liver inflammation from causes other than HBV, such as drinking alcohol or taking some drugs and herbs; and
- A normal ALT level doesn't always mean the liver is healthy; there might be existing liver damage but no elevated ALT because there is no current inflammation (25% of people with normal ALT levels may have existing liver fibrosis).

Liver-enzyme levels often fluctuate or are persistently elevated in people with chronic HBV. Sometimes these fluctuations are referred to as **HBV flares** or liver enzyme flares. Low-level flares often will cause no symptoms and might not cause liver damage; it is very high levels, persistent elevations, or dramatic changes that doctors are concerned about.

Liver-enzyme levels may be elevated during HBsAg- or HBeAg seroconversion, either spontaneously or during treatment, sometimes to very high levels (more than ten times the ULN). But liver-enzyme levels usually fall back within the normal range shortly after seroconversion. Studies have also shown that HBV treatments are more effective in people who have elevated ALT levels when they start treatment.

In the previous section on HBV natural history, we discussed the four phases of chronic HBV disease. The following graphic illustrates how test results on HBeAg, HBV viral load, and ALT are used to determine which phase of chronic HBV you are in and when treatment is indicated.

Chronic HBV Disease Progression



Other Liver Enzymes: ALP, GGT, Bilirubin, Albumin, and Prothrombin Time

It is important for people with HBV and HIV/HBV to undergo routine monitoring of ALP, GGT, bilirubin, albumin, and prothrombin time. Results from each test should be evaluated in relation to other information.

Alkaline phosphatase (ALP) is present in tissues throughout the body, including the liver. Many different conditions can cause increased ALP levels in the bloodstream. Elevated ALP may be a sign of blocked bile ducts (cholestasis). Some medications, including the HIV protease inhibitors atazanavir and indinavir can cause ALP elevations.

Gamma glutamyl transferase (GGT) may be elevated when bile ducts are blocked. GGT elevations may be due to liver disease, and/or heavy drinking, and use of some medications.

Bilirubin is a by-product from the breakdown of red blood cells. Bilirubin levels go up in advanced liver disease (direct bilirubin); jaundice, dark urine, and pale stool are common signals of elevated bilirubin. Some drugs, including the HIV protease inhibitors atazanavir and indinavir, can cause elevated bilirubin levels, but this is indirect bilirubin and does not indicate liver injury.

Albumin is a protein made by the liver. It carries drugs, hormones, and waste products through the bloodstream and maintains fluid levels within the body. Abnormally low levels of albumin can be a sign of serious liver damage or, in HIV-positive people, of malnutrition.

PT (prothrombin time; ProTime) testing measures the amount of time it takes for blood to clot. When the liver is damaged, its ability to make clotting factors is impaired. A prolonged PT interval indicates decreased liver function.

HBV Genotype

There are eight different HBV strains, or genotypes (from type A to type H), distributed worldwide. Due to global immigration patterns, different regions in the world have a variety of genotypes. HBV genotype can affect disease progression and response to some treatments, but research into the significance of HBV genotypes is still ongoing, and current knowledge may still change when new information comes to light. A blood test exists that can tell you which HBV genotype you have. Although this information can be useful, genotype testing is very expensive and is not critical in making treatment decisions in most cases.

Genotype A: Most common in the United States, Northern Europe, India, Africa, Spain, and Brazil. Recent studies have shown that people with genotype A have the best response to immune-based treatment (i.e., pegylated interferon; see Appendix on HBV Treatment for more information).

Genotypes B and C: Most common in Asia and the Pacific regions, and among immigrants and their children from these regions now living in Western countries. In studies from Asia, people with genotype C tend to have more severe liver disease and are at higher risk of developing liver cancer than those with genotype B, but it is not clear if treatment should start earlier in people with genotype C.

Genotype D: Most common in the Mediterranean, the Middle East, and India. People with genotype D develop pre-core mutations at a higher rate than do those with other genotypes, and are at increased risk for HBV disease progression.

Genotypes E, F, G, and H: Studies on these genotypes are lacking. Genotype E is most common in West Africa; genotype F in South and Central America; genotype G in the United States and France; and genotype H in Mexico and South America.

Liver Biopsy

Before recommending HBV treatment, some doctors want to perform a liver biopsy on their patients to get more information on the amount of liver damage their patients have. During liver biopsy, a needle is inserted between the ribs and into the liver to remove a small sample of liver tissue. The sample is sent to a lab, where it is examined under a microscope for cell abnormalities. Liver biopsy is uncomfortable, occasionally painful, and carries a small risk of complications (1–3%), such as puncturing adjoining organs or hemorrhage (bleeding), and a much, much smaller risk of death. Many people with HBV are reluctant to have one. Although some doctors will recommend a liver biopsy, particularly in people with ALT persistently just below the level that clearly indicates liver inflammation, it is not always a requirement for determining HBV treatment.

Still, a liver biopsy is considered the diagnostic gold standard for assessing liver disease because it is the most reliable way to learn both the **stage** (amount of scarring that has already occurred) and the **grade** (amount of inflammation, which drives future scarring) of liver disease. It can also identify other causes of liver disease that are not HBV-related.

Biopsy, however, is not perfect; it is subject to errors in sampling and in reviewing. Results may be inaccurate when a sample is either too small or comes from a part of the liver that is either less or more damaged than the rest. Samples need to be studied by a pathologist (the person who looks at your biopsy) with expertise in evaluating liver disease. In addition, biopsy is an expensive procedure, though it is covered by Medicaid in the U.S. For these reasons, some doctors might not recommend the procedure, especially if they are not liver specialists.

A biopsy should be performed only by an experienced doctor with a good record of successful biopsies. Also, if your pathologist is not a liver expert, he or she may make an error; ask to have your results reviewed by a pathologist experienced in liver disease. If you are concerned about pain, ask your doctor about your options for pain management during and after the procedure. Ask around, it may be easier to find a good doctor by talking with people who have had a biopsy.

Researchers are looking at less invasive alternatives to biopsy (see below).

Interpreting Biopsy Results

There are different systems for measuring liver inflammation and fibrosis. All go from zero to a maximum score; the higher the number, the more inflammation or fibrosis. The Ishak scale measures inflammation on a scale of 0 to 18, and fibrosis on a scale of 0 to 6. The METAVIR scale measures inflammation on a scale of A0 to A3 (“A” is for activity), and fibrosis on a scale of F0 to F4 (“F” is for fibrosis).

Guidelines define mild liver damage as a modified Ishak score of 3 or less, and a fibrosis score of 2 or less; and moderate liver damage as an inflammation score of 4 or more and/or a fibrosis score of 3 to 5. Sometimes your doctor might describe the condition of your liver instead of using a score.

Scale	Inflammation	Fibrosis
Ishak	0–18	0–6
METAVIR	A0–A3	F0–F4
Knodell	0–18	0–4

When Should You Get a Biopsy?

Having a biopsy can help you make a treatment decision by identifying how much liver inflammation and how much liver damage is present. Despite the discomfort and risk of complications it involves, biopsy is still an important test for assessing the need for treatment and for monitoring HBV progression over time. It is therefore recommended before deciding to start treatment (more frequently for HIV/HBV-coinfected people than for those with HBV alone).

Alternatives to a Biopsy: Non-invasive Markers of Liver Disease

There is new research to see whether results from blood tests instead of a biopsy can be used to assess liver damage. This area of research is important, as it could change how HBV is managed in the future.

Recent studies evaluating combinations of these blood tests suggest they are useful for identifying serious liver damage in HCV- and HBV-infected people, but it remains controversial whether they are yet a reliable substitute for liver biopsy.

Measuring Liver Stiffness (“FibroScan”)

FibroScan is a non-invasive approach already showing promising results. FibroScan measures the stiffness of the liver using an ultrasound probe on a vibrating apparatus to create waves and measure their speed. Wave speed reflects liver stiffness; the harder the liver tissue, the more rapidly the waves will pass through it.

Although FibroScan is much less sensitive in detecting mild or moderate liver damage, it is very sensitive to severe damage and can identify people who may need treatment urgently. FibroScan is not painful or invasive, but the machines are expensive and are available in only a few clinics. Furthermore, FibroScan may not be accurate in obese people (body mass index [BMI] over 30). You can find out your BMI at: www.nhbisupport.com/bmi/.

Non-invasive Biomarkers of Liver Disease (Blood Tests)

Combinations of blood tests are being used to assess liver damage. These tests are most useful for identifying or ruling out cirrhosis rather than mild-to-moderate liver damage. These tests include:

- SHASTA Index;
- FibroTest;
- Hepascore; and
- Fibrometer.

Regular Screening for Early Signs of Liver Cancer

People with chronic HBV are at high risk of developing liver cancer, sometimes even if they have no liver damage. Therefore it is very important to regularly (at least once a year) check for signs of liver cancer. The prognosis of liver cancer is much better when it is found early.

The **AFP (alpha-fetoprotein)** test looks for a type of protein in the blood that can be found at higher-than-normal levels ($> 10 \mu\text{g/L}$) in people who have different kinds of cancers, including liver cancer. Sometimes, however, AFP may be elevated when a person's liver is inflamed even if they don't have liver cancer. In addition, some people with liver cancer may have normal AFP levels, so AFP testing alone is not totally reliable.

Ultrasound testing is the main method used for early detection of liver cancer. More sensitive cancer screening tests are still being developed.

Track Your Lab Work

You might want to bring this worksheet with you to your doctor's appointments and record your lab results. Tracking these results over time will give you a better picture of your HIV/HBV disease progression and can tell you if your treatment is working.

Date						Ranges
CD4 cell count						From 0 to 1,600 cells/mm ³ . HIV treatment is recommended when CD4 falls below 350 cells/mm ³ .
HIV RNA (viral load)						From undetectable to over 1 million copies/mL.
HBV DNA (viral load)						From undetectable to over 1 trillion IU/mL
ALT						ULN (upper limit of normal): Women: 19 units/L Men: 30 units/L
AST						Women: 9–25 units/L Men: 10–40 units/L
ALP						Women: 30–100 units/L Men: 45–115 units/L
GGT						Women: <45 U/L Men: <65 U/L
Bilirubin (direct)						0.0–0.4 mg/dl (U.S.) 0–7 umol/L (SI units)
Bilirubin (total)						0.0–1.0 mg/dl (U.S.) 0–17 umol/L (SI units)
Albumin						3.1–4.3 g/dl (U.S.) 31–43 g/L (SI units)
PT						11–13.5 seconds (INR < 1.3)
AFP						<10 µg/L

SECTION 6: HBV TREATMENT FOR HIV-POSITIVE PEOPLE

Because HBV disease progresses faster in HIV-positive people, treating HIV/HBV coinfection is different than treating HBV in people without HIV. For a more detailed discussion on treating HBV monoinfection, please see the appendix.

Treating HBV and HIV can be complicated; people may not need to treat both at the same time. For example, if you were infected with HIV and HBV at the same time, or if you were already immunosuppressed when you were coinfecting with HBV, both viral infections will need to be treated at the same time. On the other hand, if you already have chronic HBV (e.g., if you were infected at birth) and then were infected with HIV, your chronic HBV might need to be treated first before HIV treatment is needed.

HBV treatment guidelines for people without HIV are based on HBV viral load and ALT levels; these guidelines are not very useful in HIV coinfection. HIV/HBV-coinfecting people usually have higher HBV viral loads; they can also develop liver damage with less liver inflammation, making ALT levels a less reliable indicator of the need for HBV treatment. For these reasons, researchers recommend that HIV/HBV treatment should start earlier in HIV/HBV-coinfecting people. Some HIV treatment guidelines have begun to recommend starting treatment at higher CD4 cell counts (>350 cells/mm³).

Since coinfection with HIV speeds up HBV disease progression, starting HIV treatment earlier may delay or prevent liver damage from HBV. HIV-positive people, even those with higher CD4 cell counts, also have persistent low levels of inflammation; this may contribute to ongoing liver damage in people coinfecting with HBV. There may be additional benefits to starting HIV treatment earlier; however, other factors—such as adherence and long-term drug toxicity—need to be considered.

Goals of HBV Treatment for HIV-Positive People

The primary goal of HBV treatment is to bring viral load down and to keep it suppressed, which can prevent, delay, stop, and in some cases reverse liver damage. Another goal is to stimulate the immune system to control the infection, although this approach has not been very successful to date. Following are some measurable goals based on test results.

Undetectable HBV Viral Load: When the amount of virus in your blood drops to a level that cannot be detected, it means the virus is under control, even though a small amount of HBV may still be present. While any drop in viral load is good, having a detectable viral load after one year of treatment increases the risk of developing HBV drug resistance. This is particularly important because HBV drug resistance can develop faster in HIV-positive people.

Normalization of ALT: After the viral load becomes undetectable, the immune system will stop killing infected liver cells, and ALT levels fall back within the normal range; this means that HBV infection has stabilized. However, HIV-positive people often experience ALT elevations caused by some HIV drugs even when their HBV infection is under control, so this measure might be less useful in HIV-positive people.

HBeAg Seroconversion: In people who are HBeAg-positive, HBV treatment can stimulate the immune system to eliminate HBeAg in the blood and produce HBeAg antibodies (anti-HBe); this is called HBeAg seroconversion. HIV-positive people on treatment can achieve HBeAg seroconversion at about the same rate as people without HIV, but the long-term benefit of this has not been studied in HIV coinfection.

HBsAg Seroconversion: After HBeAg seroconversion, some people can go on to achieve HBsAg seroconversion. HIV-positive people are less likely to develop antibodies to HBV surface antigen (anti-HBs) and become HBsAg-negative on treatment. HBsAg seroconversion provides the strongest control of the virus and is the closest thing to a cure at present, but the risk of HBV reactivation is higher in HIV-positive people. Due to this increased risk, HIV-positive people should not switch their HIV/HBV treatment even if they have achieved HBsAg seroconversion.

Current HBV treatment cannot get rid of the virus completely. This is because HBV inserts small pieces of its DNA (**cccDNA**) inside liver cells, where drugs cannot reach. People with chronic HBV need lifelong monitoring with HBV viral-load and ALT tests.

HBV treatment works better when the baseline (meaning pretreatment) viral load is lower and when there is less liver damage. Doctors recommend starting HBV treatment before the development of serious liver damage.

There are two types of HBV treatment:

1. Pegylated Interferon (Peg-IFN)

Interferon is a protein made by the human body; it sends virus-fighting messages to the immune system. HBV treatment involves a large dose of man-made interferon, much more than the human body produces on its own. This treatment is not recommended for people with decompensated cirrhosis.

Peg-IFN is rarely used to treat HBV in HIV-positive people. It is recommended only for coinfecting people with a CD4 cell count above 350 cells/mm³ who do not need to start HIV treatment. It has not been studied in people coinfecting with HIV, but about one in ten people who are HIV/HBV-coinfecting can achieve HBeAg seroconversion using the older form of interferon, according to one study. Peg-IFN is more effective for people who are HBeAg-positive and have an elevated ALT level at the start of treatment.

A major drawback of Peg-IFN is its severe side effects. For a more detailed discussion of Peg-IFN, please see the appendix.

2. Antiviral Drugs

Antivirals help control the virus by interfering with the HBV life cycle so the virus cannot make more copies of itself; these drugs are taken once a day by mouth.

There are currently six HBV antivirals:

- Lamivudine (Epivir HBV), approved in 1989;
- Adefovir (Hepsera), approved in 2002;
- Entecavir (Baraclude), approved in 2005;
- Telbivudine (Tyzeka), approved in 2006;
- Tenofovir (Viread), approved in 2008; and
- Tenofovir/emtricitabine (Truvada) (not yet approved as a treatment for HIV/HBV coinfection; it is currently being tested as a combination therapy drug).

Three of these drugs are also effective against HIV: **tenofovir**, **lamivudine**, and **emtricitabine**. People coinfecting with HIV and HBV should choose a drug combination of tenofovir plus either emtricitabine or lamivudine, with a third HIV drug from a different class.

The HBV drug entecavir should not be used as an HBV monotherapy in HIV-positive people since it has a very weak effect on HIV and has been linked to the development of lamivudine resistance to HIV.

Telbivudine and adefovir may also have a weak effect against HIV; further studies are needed to determine this.

Large-scale clinical trials comparing the effectiveness of these drugs in people with HIV vs. people without HIV are still ongoing. Small studies have shown similar response rates regardless of HIV coinfection. Tenofovir is the preferred drug; about 90% of people are able to bring their HBV viral load down to undetectable levels after one year of treatment. Response rates to lamivudine are only about 40%, and it is not recommended except in combination with tenofovir. Emtricitabine has very similar response rates to lamivudine, and it is being tested as a combination pill with tenofovir.

Antivirals are better at controlling the virus in HBeAg-negative people than in people who are HBeAg-positive; treatment outcome does not vary by HBV genotype.

Drug Resistance

One major limitation of HBV and HIV treatment with antiviral drugs is the development of drug resistance. Drug resistance can happen because HIV and HBV replicate rapidly and can make many mistakes in the process of replication; these mistakes are called mutations.

Unfortunately, some mutations can prevent drugs from blocking HIV and HBV replication. When people start on treatment, the drugs will be able to stop most of the normal HBV and HIV (called wild-type virus) from reproducing. Over time, the drugs can control wild-type viruses, but some mutated viral strains can still replicate during treatment, and these mutated viruses will eventually take over, causing the viral load to increase. This is called drug resistance.

Most people taking oral drugs will likely develop drug resistance eventually, but some drugs are harder to develop resistance to than others (called having a higher resistance barrier). Studies have shown that, after four years on lamivudine, 94% of HIV/HBV-coinfected people will develop HBV mutations that are resistant to it. Tenofovir has a much higher resistance barrier than lamivudine. To date, no tenofovir-resistant mutations have been shown to cause the drug to lose effectiveness in clinical trials, but it has only been studied for two years. Coinfected people develop HBV drug resistance faster than those with HBV alone, so using two drugs that are active against HBV in your HIV regimen will help to prevent or delay development of HBV drug resistance.

Drug resistance can also develop when there is not enough drug in the body to control the virus. This happens when people don't take the pills every day or skip doses; as a result, drug levels become too low to block viral replication. It is very important to take HIV/HBV drugs as they are prescribed to avoid drug resistance.

Managing Drug Resistance

When people develop drug resistance, they will need to either switch to a newer, more potent drug or add a second drug. Unfortunately, given that there are only three drugs that work against both HIV and HBV, alternative treatment options are sorely needed. Studies have shown that using two drugs instead of one can prevent or delay the development of resistant mutations, but combination therapy does not make the treatment more effective in bringing down viral load.

Long-Term Outcomes of Antiviral Treatment

Given the slow progression of chronic HBV disease, the long-term benefits of antiviral therapy are hard to measure. Since all of these drugs were approved within the last decade, long-term follow-up is limited. Some small studies of older drugs are reporting that long-term use can prevent, and in some cases reverse, liver damage from HBV; however, the ability of antiviral drugs to prevent the development of liver cancer is still unclear (this is especially true of the newer and more potent antivirals). More long-term and large-scale studies are needed to provide this vital information.

Immune Reconstitution Inflammatory Syndrome (IRIS)

Coinfected people with fewer than 200 CD4 cells/mm³ need to be monitored for potentially fatal flares of hepatitis B more frequently (every week) when they start HIV (and HBV) treatment. Flares can happen when a weakened immune system recovers enough to respond to hepatitis B. Once HIV treatment starts, the immune system will start to restore itself and become stronger; this is called immune reconstitution, or **IRIS (Immune Reconstitution Inflammatory Syndrome)**. A stronger immune system can start to respond to HBV by attacking infected liver cells. This response can be very intense and may lead to rapid liver failure, a life-threatening condition.

HIV/HBV-coinfected people with fewer than 200 CD4 cells/mm³ who are starting antiretroviral therapy should be on the lookout for these symptoms: nausea; vomiting; appetite loss; fever; fatigue; abdominal and joint pain; liver swelling; and jaundice (yellow skin and eyes). If these symptoms develop, contact your doctor immediately; you probably need to stop taking your drugs immediately. Immune reconstitution flares can be prevented by including HBV-active agents in your HIV treatment regimen.

Stopping or Switching HBV Treatment

There is a risk of severe HBV flares when people stop taking oral antivirals. If you have to stop taking your HIV drugs or change them for any reason, be very careful and talk to your doctor beforehand. Since these drugs are controlling HIV and HBV, stopping or changing them can cause HBV reactivation, which can quickly lead to severe liver damage and life-threatening liver failure.

For HIV/HBV-coinfected people who cannot use tenofovir because of kidney damage, adding entecavir, adefovir, or telbivudine in addition to a three-drug HIV combination might be a potential strategy to treat HBV at the same time. This approach, however, has not been studied.

Antiviral Treatment Side Effects

Side effects from HBV antiviral drugs are usually mild; many people don't have any. Common side effects include: dizziness, nausea, vomiting, headache, fatigue, stomach pain, itchiness, weakness, diarrhea, and indigestion.

In rare cases, there may be some serious side effects, especially if a person has serious liver damage or has kidney disease, since HBV antivirals are broken down by the kidneys. Most of these drugs are very new, so potential long-term side effects are not known yet.

Some of these rare side effects can be halted and sometimes reversed when you stop taking the drug, but going off the drug can itself be a serious problem because of the risk of HBV reactivation and the lack of alternative treatment options. If you experience these symptoms, do not stop taking the drug without consulting with your doctor.

These rare but serious side effects may include:

- **Peripheral neuropathy:** damage to the nerves in the hands and feet. Symptoms are burning, tingling, or numbing sensations in the hands and feet; these can be very painful. This condition can be debilitating and may become irreversible, so it is very important to change your treatment regimen as soon as you start to experience symptoms.
- **Lactic acidosis:** an abnormal buildup of lactic acid in the bloodstream. People with liver damage—especially cirrhosis—are most susceptible. Symptoms include weakness and fatigue; muscle weakness or tenderness; trouble breathing; stomach and/or liver pain; nausea and vomiting; feeling cold (especially in your arms and legs); dizziness or lightheadedness; and fast or irregular heartbeat. If you are experiencing any of these symptoms, contact your doctor immediately; you may need to stop taking medication right away. A blood test can confirm whether you have lactic acidosis.
- **Kidney damage:** All approved HBV drugs are eliminated from the body by the kidney. Tenofovir and adefovir in particular can cause severe kidney damage (**nephrotoxicity**), especially in people who already have kidney problems. Kidney damage can be reversed quickly when the drug that's causing it is stopped or the dose is reduced. Kidney function should be checked before starting treatment with any HBV drug and monitored regularly during treatment by assessing **creatinine clearance rate**. Creatinine is a natural waste product produced by the body and processed by the kidney. A low creatinine clearance rate can mean the kidney is not functioning properly.
- **Bone loss:** There is a concern about potential loss of bone density from long-term use of tenofovir and adefovir. In clinical trials, HIV-positive people taking tenofovir have been observed to experience bone loss, but it is still unclear if the loss is due to the drug itself. There are ongoing studies examining this issue in HIV-negative people with chronic HBV.
- **Myopathy:** Telbivudine can cause myopathy (muscle weakness) in some people during the first few months on therapy. Myopathy is reversible when you stop taking telbivudine. If you experience muscle tenderness or weakness, telbivudine might have to be discontinued.

HIV Drugs and Liver Toxicity

Many HIV drugs are broken down by the liver; these can sometimes cause damage to it (referred to as **liver toxicity**). Liver toxicity is more likely for coinfecting people with serious liver damage, because a damaged liver is not fully functional, and these drugs add an extra burden to it. Having liver-enzyme levels checked regularly is very important for coinfecting people who are on treatment because they are vulnerable to liver problems caused by HIV drugs and/or other factors.

Nevirapine is known to cause liver toxicity in some coinfecting people due to a hypersensitivity reaction to the drug, though some have used it without having any problem. Stavudine and didanosine can cause damage to the part of liver cells that produces energy; these are called **mitochondria**. Because of these toxicities, nevirapine, didanosine, and stavudine should be avoided by people who are coinfecting.

Protease inhibitors such as lopinavir, ritonavir, tipranavir, and darunavir also cause liver toxicity. Careful monitoring of liver-enzyme levels is recommended for people using these drugs.

Because a damaged liver works less efficiently, the amount of drug in the blood could increase to dangerous levels and should (ideally) be checked using **therapeutic drug monitoring (TDM)** so that the dose can be modified if necessary.

TDM is a blood test that checks whether you are getting adequate levels of a **protease inhibitor**, an **NNRTI**, and possibly the **entry inhibitor** enfurvitide. Doses for HIV drugs are worked out for an average person as a one-size-fits-all solution; however, individual differences in absorption can vary considerably in real life—especially in people with reduced liver function related to HBV coinfection. TDM is currently available only in research settings and certain clinics in the U.S., but it may be an important option if you're coinfecting and having problems with your HIV regimen.

Interferon and CD4 Cell Count

Interferon can dramatically lower a person's white blood cell count, including CD4 cells, even when they are on HIV treatment; however, because the total number of white blood cell count lowers, the percentage of CD4 cells stays stable or may increase. Researchers believe this means your level of immune protection is not affected, and clinical trials have not reported more opportunistic infections in people who had a decrease in CD4 cells from taking interferon. Seeing your CD4 cell count plummet can be frightening, but it is temporary—the CD4 cell count goes back up after stopping interferon.

SECTION 7: HIV/HBV TREATMENT FOR PEOPLE WHO USE DRUGS

Injection drug users are often discriminated against in health-care settings. Often they don't receive adequate care and are denied medical treatment, even when they need it. Fortunately, this has begun to change. Experience with HIV treatment confirms that it is possible for drug users to adhere to therapy and that they do respond to treatment at rates similar to non-users.

Don't avoid medical care just because you are using.

Many drug users with HBV are being monitored regularly for disease progression and some have begun, and are staying on, treatment. It is important to find a doctor who is willing and able to work with drug users. Ask other drug users to recommend a doctor—or to warn you about which ones to avoid.

Try hard not to miss medical appointments, since some doctors will use missed appointments as part of the criteria for deciding whether or not they will treat you. Even if you think your treatment side effects are insignificant, discuss them with your doctor and ask up front how he or she plans to help you manage these side effects so you can get through treatment.

If you need pain medication, anti-anxiety drugs, or other medications sometimes associated with "drug use/abuse," discuss this openly with your doctor before you begin treatment. Be assertive and make an agreement on how the two of you will handle this should the issue arise.

Depression and other mental health diagnoses are much more common among people with HIV and drug users than in the general population. Many of these conditions can be treated successfully.

People with a history of depression are more likely to develop depression during Peg-IFN treatment, although it can happen to people who have not been depressed in the past. If you are concerned about the psychiatric side effects of Peg-IFN, consider working with a mental health care provider.

Some people can manage treatment while they are using drugs; others have found that stopping or cutting down on drug use help them prepare for, and stay on, treatment because they feel more stable. Some therapy choices may include a self-help program; counseling; drug treatment; heroin substitution; methadone maintenance; naltrexone implants; and buprenorphine.

If you are still injecting drugs, ask your doctor or local syringe-exchange program for information on safer injection practices to lower your risk of HCV and other infections.

Working with Your Clinicians

- Make sure to work with health-care providers that take the time to answer your questions about treatment and side effects.
- Make a list of questions before going to the doctor and bring someone with you if possible.
- Keeping medical appointments is especially important after you start your treatment; your doctor needs to be able to regularly monitor your health and help you with side effects.
- If you need pain medication or other medications with abuse potential, discuss this with your doctor; make an agreement on how the two of you will handle this.
- Identify people in your life who are, or will be, a good source of support for you.
- Consider joining a support group.

Concerns for People in Recovery

Some people are concerned about self-injecting Peg-IFN for various reasons. Sometimes the once-weekly injections can be given at a doctor's office or clinic to avoid triggering a relapse to injection drug use; however, some insurers may not cover this service.

SECTION 8: RESEARCH INTO NEW HBV THERAPIES

Currently approved treatments are unable to completely cure HBV infection. The rate of HBsAg seroconversion, the closest measure to a cure, is less than 10%, and most people will need to stay on treatment for life. When people need to stay on therapy for decades, the development of drug resistance will likely be inevitable. New, more potent drugs with high resistance barriers are needed.

Research into HBV is difficult because the virus cannot be grown in laboratories in an efficient manner. This limitation has resulted in an incomplete understanding of the HBV viral life cycle, which makes it harder to develop new drugs that can suppress HBV in different ways. Right now, all of the approved antivirals block viral replication at the same site; this is why combinations of HBV antiviral therapies do not improve efficacy, unlike in HIV, where drugs targeting different steps in the viral replication process can be combined into effective regimens.

Since the immune system plays such an important role in HBV disease progression, there is a critical need for research into what triggers immune response in the acute-infection, immune-clearance, and reactivation phases of chronic HBV. A complete HBV cure is likely to depend on a better understanding of these mechanisms.

There is a new **HBV Clinical Research Network** being set up by the National Institutes of Health. This network is likely to focus on treatment strategies, such as the best use of current drugs in different phases of chronic HBV disease progression, and different drug combination strategies with newer and more potent drugs. While this development is encouraging, funding for this network is not sufficient for researchers to adequately address most of the unanswered questions in chronic HBV. The network's website is at: www.hepbnet.org

Public investment in HBV research lags behind that for HIV and HCV. A more vocal approach to HBV research advocacy is needed to bring more attention to, and increase funding for, this disease.

Where to Find Information on New HBV Drugs

An update on HBV drugs in clinical development is included in the *TAG Pipeline Report*, available for download as a PDF file from the TAG website: www.treatmentactiongroup.org

Reports relating to new HBV treatment are also regularly on the National AIDS Treatment Advocacy Project (NATAP) website: www.natap.org

An ongoing, detailed list of HBV drugs in development is also available on the Hepatitis B Foundation website: http://www.hepb.org/professionals/hbf_drug_watch.htm

SECTION 9: MANAGING LIVER CIRRHOSIS

A damaged liver can still function, but people who have developed cirrhosis are at risk for liver failure and other serious, life-threatening complications. People with compensated cirrhosis should be screened for liver cancer and monitored regularly for decreasing liver function and **varices** (stretched and bursting veins in the esophagus or stomach). Beta blockers can help prevent varices. **Variceal hemorrhaging** is managed with medication and endoscopic intervention (banding and injection). In some patients, a procedure called **TIPSS (Transjugular Intrahepatic Portasystemic Stent Shunt)**, insertion of a metal mesh tube (stent) through the liver to relieve blood pressure by connecting two large veins, may be recommended.

Changing your diet may help to manage some of the complications of cirrhosis. Cutting down on salt and eating many small light meals per day, with protein from vegetables and dairy products rather than meat, can help redress nutritional imbalances. A nutritionist and your doctor can help you plan a healthy diet.

When liver function has deteriorated and hepatic decompensation occurs, a liver transplant becomes necessary.

Liver Transplant in People with HIV/HBV Coinfection

In people with severe decompensated liver disease, a liver transplant is the final option.

This is a major operation, and success rates vary. It is also complicated by a scarcity of donor organs that are available for transplant.

For many years, transplant services actively avoided transplanting organs into HIV-positive people. This was due to several factors: discrimination from some surgeons who did not want to operate on HIV-positive people; the poor long-term prognosis for HIV-positive people before effective HIV treatment was available, which meant that a donor organ would provide fewer years of additional life than it might to a person without HIV or other medical conditions; and concerns about using immunosuppressive drugs in HIV-positive people.

The effectiveness of HIV drugs has changed this. HIV is no longer an exclusion criterion for transplantation in some places. Centers in the U.S., Spain, France, and the U.K. have transplanted livers into HIV-positive candidates; results have been mixed. Some centers have reported no significant difference in survival according to HIV status, but medical management remains complex due to drug interactions between immunosuppressants and protease inhibitors; graft rejection; reactivation of HBV; and difficulty in tolerating HIV- and HBV treatment after transplantation.

SECTION 10: LIVING WITH CHRONIC HBV

Probably the most important aspect of dealing with any medical condition is having the time and support to become better informed about choices that affect your health.

Many people who are diagnosed with a chronic disease take the opportunity to examine their lives in order to reduce stress and improve both their quality of life and their general health.

Some of the lifestyle changes discussed below can reduce the risk of HBV progression—especially cutting down on or avoiding alcohol. Stopping smoking; eating better; resting properly; exercising; and other forms of stress reduction are important for everyone’s health.

Alcohol and HBV

Heavy drinking is known to be harmful to the liver. Alcohol intake in amounts of more than 50 grams per day (four or five glasses of wine, beer, or mixed drinks) for men and more than 30 grams per day (two or three glasses of wine, beer, or mixed drinks) for women is clearly associated with more rapid development of liver disease. Alcohol harms the liver by increasing both inflammation and scarring. Since no one has determined what amount of alcohol is not harmful to people with liver disease, the less you drink, the better for your liver. Many doctors recommend abstinence.

Alcohol and Liver Damage

Alcohol is broken down mainly by the liver, and this process creates by-products that damage the liver more than the alcohol itself does. Prolonged inflammation from long-term alcohol use causes an overproduction of molecules called **free radicals** that can destroy healthy liver tissue, subsequently impairing liver function.

Alcohol can also disrupt the production of **antioxidants**, which defend the body against free-radical damage. The combination of overproduction of free radicals and loss of antioxidants can contribute to liver damage.

Women may be more prone than men to the damaging effects of alcohol. Drinking less—or not at all—can be very difficult. Some people cut down or quit on their own, while others find that support groups, counseling, and/or pharmacotherapy work best for them. A list of resources is provided on the next page.

Recreational Drugs

The liver is the organ that processes most recreational drugs. These drugs are likely to contain impurities and unspecified ingredients. If you are injecting drugs, use new, sterile equipment—needle, cooker, filter, water, tie, and measuring syringe—each time to protect yourself from hepatitis C and other infections.

Support Organizations

Alcohol and Drugs

Organizations that provide information and support for people who want to reduce or stop their use of alcohol and/or drugs include:

Alcoholics Anonymous: www.alcoholicsanonymous.org

Buprenorphine FAQs: <http://buprenorphine.samhsa.gov/faq.html>

Buprenorphine Physician and Treatment Locator:
http://buprenorphine.samhsa.gov/bwns_locator/index.html

FAQs: A Quick Guide to Finding Effective Drug and Alcohol Treatment (from SAMHSA): <http://csat.samhsa.gov/faqs.aspx>

Fact Sheets on Recreational Drugs:
www.aidsmap.com/cms1045198.asp

Referral to a Therapist : 1-888-227-7542

Moderation Management: www.moderation.org

Narcotics Anonymous: www.na.org

Opioid Treatment Program Directory:
<http://dpt2.samhsa.gov/treatment>

Substance Abuse Treatment Facility Locator:
<http://findtreatment.samhsa.gov>

Harm Reduction Resources

Directory of Syringe-Exchange Programs and Other Resources by State
www.harmreduction.org/article.php?id=530

Harm Reduction Psychotherapy and Training Associates
www.harmreductioncounseling.com/index.html

People who are regular users of recreational drugs may not be getting enough sleep or eating well, and may be under a great deal of stress. For these reasons, recreational drug use—especially on a daily basis—can have a negative impact on a person’s health; however, there is not enough research on whether this kind of drug use can actually cause or worsen liver damage in people with chronic hepatitis.

Street Drugs and the Liver

Since cocaine, heroin, methamphetamine, GHB (gammahydroxybutyrate), ketamine, and ecstasy are illegal, there is very little research or information on whether these drugs cause liver damage in people with chronic hepatitis. Most research on “street drugs” (illegal drugs) has been done in mice or in a test tube, not in humans. What happens inside the human body is often very different than what happens in an animal or a test tube, so it is hard to know how the results from these studies relate to what actually happens in a person’s body.

The purity of street drugs varies. The other substances that are added to street drugs may be harmful to the liver, although the drug itself may not be; this makes it more difficult to know if using street drugs has an effect on chronic hepatitis.

Regular use of marijuana (one joint or more per day over several years) accelerates the progression of fibrosis in people with chronic HBV and HCV, but occasional use of marijuana has not been found to be harmful.

You can find more detailed information about street drugs and HIV at www.aidsmap.com/cms1045198.asp.

Some people are comfortable with their drug use, while others might find it problematic. If you want to stop using recreational drugs, there are places where you can get help. Please see the resources listed in the sidebar.

Prescription Drug Use

Some people use prescription drugs to get high. This can be risky because the drugs may interact with other medications, causing lowered or increased drug levels in a person’s body. If drug levels are too low, medications may stop working, and in some cases—such as with HIV medications and antibiotics—resistance can develop. Drug levels that are too high can also be dangerous, since they can increase drug toxicity and side effects, or cause an overdose.

For example, midazolam interacts with alcohol; caffeine; sleeping pills; some antidepressants and anti-anxiety drugs; hormonal contraception (birth control pills); some of the drugs used to treat TB fungal infections, high blood pressure, heart problems; and even cold medications (among others).

Benzodiazepines, a family of drugs that includes midazolam, diazepam, rohypnol, and alprazolam, are addictive. Withdrawal symptoms include seizures, psychosis, and the

“rebound effect,” where insomnia or anxiety return and are worse than what someone experienced before they started using these drugs.

Drug Overdose

The risk of overdosing on certain prescription drugs (alprazolam, diazepam, midazolam, triazolam, fentanyl, and lidocaine) may be higher in people with cirrhosis from chronic hepatitis, since some drugs are broken down by the liver.

Smoking

Smoking has a negative impact on everyone’s health. Research on the impact of smoking on HBV disease progression has shown unclear results because most people in the studies also drank alcohol, making it hard to tell how much smoking mattered.

Stopping smoking is not easy. Giving up cigarettes may be a long-term goal for many people; it may not always be a person’s most important short-term priority. If you feel ready to stop smoking, talk with your doctor about ways to make quitting easier.

Diet

A healthy and balanced diet is important for general good health. Liver abnormalities are more common in people who are overweight; these abnormalities may include liver **steatosis** and inflammation.

Liver problems are also more common among people with diabetes, and being overweight is a risk factor for developing diabetes. When overweight people lose weight, their liver condition is likely to improve.

All foods and fluids pass through the liver to be broken down. Avoiding things that are hard for the liver to break down supports liver health.

The most appropriate diet for you depends on a number of factors including age, weight, extent of liver damage, and current symptoms. With advanced liver disease, avoiding or reducing the amount of certain foods may be important. These may include:

- Fried foods;
- Foods with a high fat content, especially if they contain saturated or hydrogenated fats (trans fats);
- Very high-protein diets;
- Foods with a high iron content, and iron supplements, unless your liver specialist recommends these;

- Processed food and “junk” food;
- Caffeine in coffee, tea, and some carbonated drinks;
- Salt, especially if you have advanced liver disease;
- Foods containing additives and pesticides; and
- Sugar, since diabetes is more common among people with chronic HBV; eat less food containing processed sugar, and switch from white bread and pasta to whole wheat bread and pasta.

If you find it hard to lose weight or want more information on a healthier diet, ask your doctor about seeing a nutritionist.

Herbal Medicine

Herbal remedies have been used for centuries to treat liver disease, but they cannot cure hepatitis B. So far, no clinical trials have demonstrated that herbal remedies are safe and effective against hepatitis B. Many people use these nonetheless: some because conventional treatment has not worked for them, others because of concerns about the side effects of HBV therapy. Keep in mind that even natural or herbal products may cause stress to the liver.

Milk thistle (silymarin) is often used to treat hepatitis B, though clinical trials have not found any benefit. Research on milk thistle and viral hepatitis is ongoing.

Licorice root (glycyrrhizin) has been used to treat HBV in Japan. There is very little information from clinical trials on its effectiveness; however, long-term use can cause side effects such as high blood pressure and fluid retention, which are especially serious for people with cirrhosis.

Many other combinations of herbs are being sold to treat HBV or benefit the liver. Unfortunately, these products are unregulated, and they differ in purity and strength. Some may actually be harmful to the liver, and others may interact with HIV drugs and other medications. It is important to discuss the use of any herbs or supplements with your doctor.

SECTION 11: OTHER VIRAL HEPATITIS

Hepatitis A (HAV)

HAV is found in feces (stool). People become infected when feces from a person who is infected with HAV enters their mouth. This may occur when food (including raw or undercooked shellfish) or water is contaminated with sewage; when an infected person handles food without washing his/her hands after using the bathroom; through oral-anal sex with an infected person (also known as rimming); and, rarely, from blood transfusions.

A vaccine is available to prevent HAV infection, and every person with HIV or HBV should be vaccinated (though it may be less effective in people with low CD4 cell counts.)

Some people with HAV—especially children—don't feel sick at all; others have symptoms including nausea, vomiting, diarrhea, fever, fatigue, rash, jaundice, liver pain, and dark brown urine. There is no treatment for HAV itself, but the symptoms can be treated.

HAV is not a chronic infection—it goes away by itself, usually within two months. A person can be infected with HAV only once.

Hepatitis C (HCV)

HCV is found in blood (very small amounts have been found in semen and vaginal fluid). You can get HCV from:

- Sharing drug-use or tattoo equipment, including needles; measuring syringes; water; cookers; cotton; and tattoo ink and inkwells;
- Unprotected sex (especially if you have a sexually transmitted infection such as herpes, syphilis, or HIV) that involves blood: rough anal or vaginal sex, and fisting, are riskier;
- Mother to child during birth; and
- Sharing personal-care items that may have blood on them, such as razors and toothbrushes.

You can get HCV more than once, even if you already cleared it with treatment or through your own immune response.

Most people have no symptoms when they are first infected; about 20% will experience nausea, abdominal pain, appetite loss, fatigue, jaundice (yellow skin and eyes), and dark urine. HCV infection can become chronic (lifelong) in 55–85% of people; the rest clear the virus without treatment.

About 20–30% of chronically infected people will develop cirrhosis over the decades. Each year, 1–5% of people with cirrhosis develop liver cancer.

HCV can be treated—and cured—with a combination of pegylated interferon and ribavirin, but HCV treatment does not always get rid of the virus, and the side effects can be severe. New therapies are currently in development.

Recent outbreaks of sexually transmitted HCV have been reported in HIV-positive gay men in the U.S., some European cities, and Australia. A cluster of risk factors has been identified, including non-injection drug use; group sex; rough, long-lasting anal sex; fisting; and being HIV-positive.

All HIV-positive people should be screened for HCV. HIV makes HCV worse: it is more likely to be chronic, progresses more quickly, and is harder to treat. Hepatitis C is worse in people who are coinfecting with hepatitis B.

There is less research on HIV coinfection with these viral hepatitis infections:

Hepatitis D (HDV) – a virus that infects only people with hepatitis B. HDV increases the risk of cirrhosis and the rate of liver disease progression for people with HBV. HIV coinfection may also accelerate HDV-related disease progression. A vaccine protecting against HBV also protects against HDV infection. Treatment options are very limited; research into this area is ongoing.

Hepatitis E (HEV) – an infectious virus with characteristics similar to hepatitis A. HEV will clear without treatment over several weeks to months. There is no vaccine for HEV. You can be infected with this virus only once. People with underlying liver disease may be more susceptible to serious liver damage and liver failure.

SECTION 12: RESOURCES

The following websites include excellent resources for support and further information.

Support

The Hepatitis B Information and Support List: www.hblist.org

This online e-mail list was begun in 1998. It provides invaluable resource information and support to persons with hepatitis B and/or their family and friends. Members sign up from countries all over the world, including, but not limited to: China, India, Pakistan, Vietnam, France, Germany, the United Kingdom, the United States, Malaysia, Denmark, Australia, Canada, Brazil, Egypt, Israel, Indonesia, and the Philippines. Physicians and members of the pharmaceutical industry provide information and assistance to its members.

Financial Assistance

Needy Meds: www.needymeds.org

If you need financial assistance for care and treatment, this website is a good place to start. You can find patient assistance programs offered by individual pharmaceutical companies that can provide free medication for uninsured people who meet their eligibility criteria. There is also a section on government programs sponsored by individual states and the federal government.

Positively Aware

www.positivelyaware.com/2009/news_briefs/news_briefs_09_02_03.shtml

As the cost of medication continues to increase, health insurance companies have begun raising patient co-payments. Several drug manufacturers have started providing co-pay assistance to those who qualify. This website provides up-to-date information on these programs.

Information

Treatment Action Group (TAG): www.treatmentactiongroup.org

TAG is an HIV activist group based in New York City that reports new data on the epidemiology and natural history of HBV, HCV, and HIV coinfection, and on the development of new treatments. TAG works with drug companies, government agencies, researchers, and other treatment activists. TAG also educates members of the HIV community about coinfection with HIV and viral hepatitis.

TAG produces the Pipeline Report, which includes a review of new research.

HCV/HBV Advocate: www.hbvadvocate.org

A nonprofit organization founded in 1997 by people living with hepatitis C, HCV/HBV Advocate provides a wide range of HCV, HBV, and HIV coinfection information online, including helpful fact sheets.

HIV i-Base: www.i-base.info

HIV i-Base is an advocacy organization set up in April 2000 by HIV-positive advocates. HIV i-Base produces a monthly publication for doctors, and four non-technical treatment guides, all of which are available free both in print and online.

Hepatitis B Foundation: www.hepb.org

Founded in 1991, the Hepatitis B Foundation is dedicated to finding a cure for HBV and improving quality of life for those affected by hepatitis B worldwide. Its services include funding focused research; promoting disease awareness; supporting immunization and treatment initiatives; and serving as the primary source of information for patients and their families, the medical and scientific community, and the general public.

National AIDS Treatment Advocacy Program (NATAP): www.natap.org

NATAP is a treatment information and advocacy project that provides wide coverage of news about HIV, HCV, HBV, and other related issues. The website and e-mail lists include postings of conference presentations and full journal articles that are otherwise inaccessible due to journal subscription requirements.

HIV and Hepatitis.com: www.HIVandHepatitis.com

This is a medical website that includes research reports on viral hepatitis, particularly as it relates to HIV coinfection. On this site, it is easy to search for articles by subject.

Medical Conferences

Most of the major HIV conferences also include presentations and research relating to HIV/ HBV coinfection. Hepatitis conferences tend to be less focused on coinfection. Many HIV organizations and websites cover reports from these meetings, including NAM (www.aidsmap.com), HIV and Hepatitis.com (www.hivandhepatitis.com), HIV i-Base (www.i-base.info), and NATAP (www.natap.org).

APPENDIX: TREATMENT FOR HBV MONOINFECTION

There are many treatment guidelines published by doctors and researchers advising when to start HBV treatment. There are some minor variations, but they generally recommend treatment for people with a high viral load and elevated ALT levels, and for people with moderate-to-severe fibrosis or any cirrhosis.

Treatment Guidelines Comparison Table

HBeAg Status	Positive		Negative	
	HBV DNA	ALT	HBV DNA	ALT
EASL ₁	2,000 IU/mL	>ULN	2,000 IU/mL	> ULN
U.S. Panel ₂	20,000 IU/mL	>ULN	2,000 IU/mL	> ULN
Asian-Pacific Panel ₃	20,000 IU/mL	>2X ULN	2,000 IU/mL	>2X ULN
AASLD ₄	20,000 IU/mL	>2X ULN	2,000 IU/mL	>2X ULN

Sources:

1. European Association for the Study of the Liver. *Clinical Practice Guidelines: Management of chronic hepatitis B*. 2009
2. *A treatment algorithm for the management of chronic hepatitis B virus infection in the United States*. 2008
3. ACT-HBV Asia-Pacific Steering Committee Members. *Chronic hepatitis B: treatment alert*. 2006
4. American Association for the Study of Liver Disease. *Chronic hepatitis B*. 2007

Deciding when to start treatment is rarely easy; there are many considerations that may influence your decision. For most people with chronic HBV, especially those who are HBeAg-negative, starting treatment means taking medications for the rest of their lives, because the virus will likely reactivate once they stop. This can be a hard pill to swallow, especially considering the expense of these therapies. The potential for long-term drug toxicities is also an unknown risk.

On the other hand, currently available treatments are highly effective, are generally well tolerated, and have been shown to provide long-term benefits. The pendulum also swings towards favoring treatment when you have other risk factors that can lead to liver damage, such as:

- Being infected for a long time (at birth vs. as an adult);
- Being male over 40-year-old or female over 50-year-old;
- Being overweight, and/or drinking a lot of alcohol;
- Having a family history of liver disease, abnormal cholesterol, or diabetes; and
- Having a weakened immune system (this includes people who are HIV-positive with low CD4 cell counts (<200/mm³); people with other conditions that suppress the immune system; or people taking immunosuppressive drugs).

Goals of HBV Treatment

The primary goal of HBV treatment is to bring viral load down and to keep it suppressed, which can prevent, delay, stop, and in some cases reverse liver damage. Another goal is to stimulate the immune system to control the infection. Here are some measurable goals based on test results:

Undetectable HBV Viral Load: When the amount of virus in your blood drops to a level that cannot be detected, it means the virus is under control, even though a small amount of HBV may still be present. Viral suppression starts to happen anytime within the first three months after starting treatment, and may take more than a year to reach the undetectable level. While any drop in viral load is good, having a detectable viral load after one year of treatment increases the risk of developing HBV drug resistance.

Normalization of ALT: After the viral load becomes undetectable, the immune system will stop killing infected liver cells, and ALT levels will fall back within the normal range; at this point, the disease has stabilized. Sometimes when people begin HBV treatment, their ALT level may rise while their viral load drops. This can be an indication that the treatment is working and HBV is being cleared; ALT levels should eventually return to normal.

HBeAg Seroconversion: In people who are HBeAg-positive, HBV treatment can stimulate the immune system to eliminate HBeAg in the blood and produce HBeAg antibodies (anti-HBe); this is called HBeAg seroconversion. When a person seroconverts and has an undetectable hepatitis B viral load and normal ALT after one to two years on treatment, he/she may be able to stop treatment. Unfortunately, there have not been enough long-term studies to determine how long the benefit of HBV treatment lasts after a person has stopped, or even if stopping can be done safely. It is still important to regularly monitor HBV viral load and ALT every six to twelve months to watch for reactivation, or for the development of **pre-core** and **basal-core mutations**.

HBsAg Seroconversion: After HBeAg seroconversion, some people can go on to achieve HBsAg seroconversion. Even with treatment, however, only a very small percentage of people (<10%) will develop antibodies to HBV surface antigen (anti-HBs) and become HBsAg-negative. HBsAg seroconversion provides the strongest control of the virus and is the closest thing to a cure at present, but there remains a risk of HBV reactivation. People on HBV treatment should check their HBsAg every one to two years and may safely stop treatment if they've seroconverted.

Current HBV treatment cannot get rid of the virus completely. This is because HBV hides small pieces of its DNA (**cccDNA**) inside liver cells, where drugs cannot reach. People with chronic HBV need lifelong monitoring with HBV viral-load and ALT tests.

HBV treatment works better when the baseline (meaning pretreatment) viral load is lower and when there is less liver damage. Doctors recommend starting HBV treatment before the development of serious liver damage.

There are two types of HBV treatment:

- 1. Antivirals:** These are drugs that help control the virus by interfering with the HBV life cycle, so the virus cannot make more copies of itself. These drugs are taken once a day by mouth. Treatment period is at least one or two years for HBeAg-positive people; most HBeAg-negative people will need to stay on treatment indefinitely, possibly for life.
- 2. Pegylated Interferon (Peg-IFN):** Interferon is a man-made form of a natural protein that stimulates the immune system to fight against HBV. Pegylation is a process that keeps the drug in the body longer. Pegylated interferon is taken once a week by injection; the recommended treatment duration is one year.

Antiviral Drugs

There are currently six HBV antivirals:

- Lamivudine (Epivir HBV), approved in 1989;
- Adefovir (Hepsera), approved in 2002;
- Entecavir (Baraclude), approved in 2005;
- Telbivudine (Tyzeka), approved in 2006;
- Tenofovir (Viread), approved in 2008; and
- Tenofovir/emtricitabine (Truvada) (not yet approved as a treatment for HIV/HBV coinfection; it is currently being tested as a combination therapy drug).

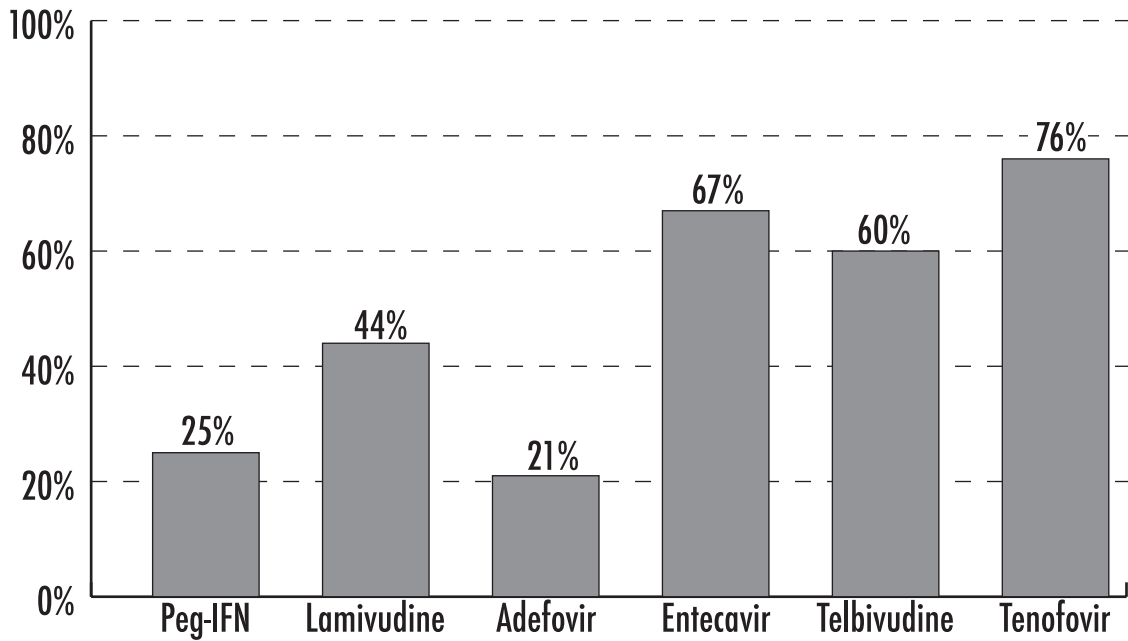
When these drugs are effective in controlling HBV, they bring the viral load down to undetectable levels and keep it there. Once the virus is under control, people usually will see their ALT levels return to normal. These drugs work equally well regardless of your HBV genotype; some are more potent than others in bringing down HBV viral load.

Antivirals are better at controlling the virus in HBeAg-negative people than in people who are HBeAg-positive, but they are not very effective in achieving HBsAg seroconversion (<2% after one year of treatment). Nonetheless, new data on long-term treatment outcomes are still emerging, and there are encouraging signs about a possible increased rate of HBsAg seroconversion after several years on therapy.

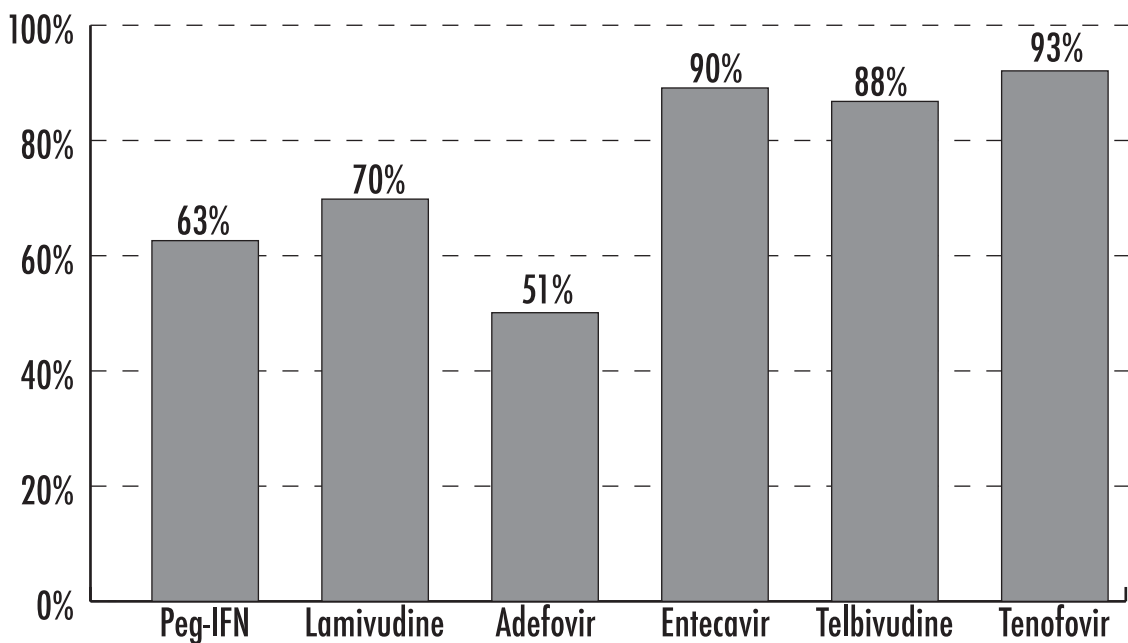
Comparison of Effectiveness of HBV Drugs

Percentage of people who have undetectable HBV viral load after one year on treatment

Response Rates for HBeAg-Positive People



Response Rates for HBeAg-Negative People



HBV Drug Resistance

One major limitation of HBV treatment with antiviral drugs is the development of drug resistance. Drug resistance can happen because HBV makes billions of copies of new virus each day (when the disease is active) and can make many mistakes in the process; these mistakes are called mutations. Unfortunately, some HBV mutations can prevent drugs from blocking HBV replication. When people start on HBV treatment, the drugs will be able to stop most of the normal HBV (called wild-type virus) from reproducing. Over time, the drugs can control wild-type HBV; however, some mutated strains of HBV can still replicate during treatment, and these mutated viruses will eventually take over, causing the viral load to increase. This is called drug resistance. Most people taking oral drugs will likely develop drug-resistant HBV eventually, but some drugs are harder to develop resistance to than others (called having a higher resistance barrier).

Drug resistance can also develop when there is not enough HBV drug in the body to control the virus. This happens when people don't take the pills every day or skip doses; as a result, drug levels become too low to block HBV replication. It is very important to take HBV drugs as they are prescribed to avoid drug resistance.

Comparison of Development of Drug Resistance

Drug	Year 1	Year 2	Year 3	Year 4	Year 5
Lamivudine	24%	38%	49%	67%	NA
Adefovir	0%	3%	11%	18%	29%
Entecavir	<1%	<1%	<1%	<1%	<1%
Telbivudine	5%	22%	NA	NA	NA
Tenofovir	0%	0%	0%	NA	NA

Choosing the Right Drug When You First Start Treatment

Treatment guidelines recommend the use of drugs that are both potent in controlling the virus by lowering hepatitis B viral load, and have a high drug-resistance barrier to development of HBV mutations. Using these criteria, tenofovir and entecavir are the two optimal drugs at present. Adefovir is the least effective in lowering viral load, and lamivudine and telbivudine have the lowest drug-resistance barrier.

All the current HBV drugs interfere with viral replication in very similar ways. This means that once drug-resistant mutations develop, the same mutation might also be resistant to other HBV drugs, or make it easier for a person to develop resistance to the new drug. If people start treatment using a drug with a low resistance barrier, the next drug might also become less effective; this effect is called **cross resistance**.

Many people who began HBV treatment with weaker drugs like lamivudine or adefovir will have fewer treatment options after developing resistance to these drugs, because stronger and newer drugs are not as effective against the mutated HBV. This is why it is very important to start treatment with the strongest drugs first, so they will control HBV and prevent the development of drug resistance for as long as possible.

Managing Drug Resistance

When people develop drug resistance, they will need to either switch to a newer, more potent drug or add on a second drug. Studies have shown that using two drugs instead of one can prevent or delay the development of new resistant mutations, but combination therapy does not make the treatment more effective in bringing down viral load. The decision to switch or add depends on which drug the person has already developed resistance to, and if there is another drug to which it does not have cross-resistance.

Cross Resistance and Drug Sequencing

Drug Resistance	Switch to a Different Drug or a Different Combination	Add a Second Drug
Lamivudine resistance	Switch to emtricitabine+tenofovir	Add adefovir or tenofovir
Adefovir resistance	Switch to entecavir	Add entecavir
Lamivudine+adefovir resistance	Switch to emtricitabine+tenofovir	Add lamivudine or telbivudine
Entecavir resistance	Switch to adefovir or tenofovir; Switch to emtricitabine+tenofovir	Add adefovir or tenofovir
Telbivudine resistance	Switch to emtricitabine+tenofovir	Add adefovir or tenofovir

Stopping Treatment

There is a risk of severe HBV flares when people stop taking oral antivirals. Flares occur when the drugs are no longer controlling the virus and the immune system reacts by mounting an intense response to the sudden spike in HBV viral load. HBV flares can be very dangerous, so people should be closely monitored for elevated ALT levels for several months after stopping treatment.

Long-Term Outcomes of Antiviral Treatment

Given the slow progression of chronic HBV disease, the long-term benefits of antiviral therapy are hard to measure. Since all of these drugs were approved within the last decade, long-term follow-up is limited. Some small studies of older drugs are reporting that long-term use can prevent, and in some cases reverse, liver damage from HBV; however, the ability of

antiviral drugs to prevent the development of liver cancer is still unclear (this is especially true of the newer and more potent antivirals). More long-term and large-scale studies are needed to provide this vital information.

Antiviral Treatment Side Effects

Side effects from HBV drugs are usually mild; many people don't have any. Common side effects include: dizziness, nausea, vomiting, headache, fatigue, stomach pain, itchiness, weakness, diarrhea, and indigestion.

In rare cases, there may be some serious side effects, especially if the person has serious HBV-related liver damage or has kidney disease, since HBV antivirals are broken down by the kidneys. Most of these drugs are very new, so potential long-term side effects are not known yet.

Some of these rare side effects can be halted and sometimes reversed when you stop taking the drug, but going off the drug can itself be a serious problem because of the risk of HBV reactivation and the lack of alternative treatment options. If you experience these symptoms, do not stop taking the drug without consulting your doctor.

These rare but serious side effects may include:

- **Peripheral neuropathy:** damage to the nerves in the hands and feet. Symptoms are burning, tingling, or numbing sensations in the hands and feet; these can be very painful. This condition can be debilitating and irreversible, so it is very important to change your treatment regimen as soon as you start to experience symptoms.
- **Lactic acidosis:** an abnormal buildup of lactic acid in the bloodstream. People with liver damage—especially cirrhosis—are most susceptible. Symptoms include weakness and fatigue; muscle weakness or tenderness; trouble breathing; stomach and/or liver pain; nausea and vomiting; feeling cold (especially in your arms and legs); dizziness or lightheadedness; and fast or irregular heartbeat. If you are experiencing any of these symptoms, contact your doctor immediately; you may need to stop taking medication right away. A blood test can confirm whether you have lactic acidosis.
- **Kidney damage:** All approved HBV drugs are eliminated from the body by the kidney. Tenofovir and adefovir in particular can cause severe kidney damage (**nephrotoxicity**), especially in people who already have kidney problems. Kidney damage can be reversed quickly when the drug is stopped or the dose is reduced. Kidney function should be checked before starting treatment with any HBV drug and monitored regularly during treatment by assessing **creatinine clearance rate**. Creatinine is a natural waste product produced by the body and processed by the kidney. A low creatinine clearance rate can mean the kidney is not functioning properly.

Bone loss: There is a concern about potential loss of bone density from long-term use of tenofovir and adefovir. In clinical trials, HIV-positive people taking tenofovir have been observed to experience bone loss, but it is still unclear if this loss is due to the drug itself. There are ongoing studies examining this issue in HIV-negative people with chronic HBV.

- **Myopathy:** Telbivudine can cause myopathy (muscle weakness) in some people during the first few months on therapy. Myopathy is reversible when you stop taking telbivudine. If you experience muscle tenderness or weakness, telbivudine might have to be discontinued.

Pegylated Interferon (Peg-IFN)

Interferon is a protein made by the human body. It sends virus-fighting messages to the immune system. HBV treatment involves a large dose of man-made interferon, much more than the human body produces on its own. Pegylation is a process that keeps interferon in the body longer, making it more effective. Before interferon was pegylated, people had to inject it three times per week (for up to 48 weeks). Peg-IFN is given once a week by injection for 12–72 weeks.

There are two different brands of Peg-IFN, but only one is currently approved for the treatment of HBV (Pegasys, by Roche, approved in 2005). Peg-IFN needs to be refrigerated. It is contraindicated for people with decompensated cirrhosis. Standard, non-pegylated interferon is no longer the standard of care and should not be used.

Peg-IFN is more effective for people who are HBeAg-positive with an elevated ALT level at the start of treatment. It has not been studied in people coinfecting with HIV, but about one in ten people who are HIV/HBV-coinfecting can achieve HBeAg seroconversion using the older form of interferon, according to one study.

The major advantages of this treatment are the short duration (one year) and lack of drug resistance. Studies have shown that some people who have achieved HBeAg seroconversion and maintain it are able to keep the virus under control, and some can even achieve HBsAg seroconversion several years after the end of treatment. For these lucky few, it is still important to keep monitoring HBV every six to twelve months to make sure it doesn't reactivate.

Peg-IFN treatment is more likely to work in some people than in others. Before choosing this treatment, people should talk to their doctor and decide if this treatment is right for them. Peg-IFN works better for people who:

- Are younger than 40;
- Are HBeAg-positive;
- Are infected with HBV genotype A;
- Have a lower viral load (<2 million IU/mL); and
- Have higher ALT levels (>3 times ULN) at the start of treatment.

About one in three people with chronic HBV can achieve **HBeAg seroconversion** with Peg-IFN. This treatment effect has been found to be sustainable in about 80% of people three years after treatment. The sustained rate is higher in people with genotype A, at about 96%.

Peg-IFN is more effective than antivirals in achieving **HBsAg seroconversion**. Response rates are different according HBV genotype: 14% for genotype A, 9% for genotype B, 3% for genotype C, and 2% for genotype D. This response rate is sustained in about 30% of people three years after treatment. The sustained rate is higher in people with genotype A, at about 60% after three years.

Early Predictors of Response to Treatment with Peg-IFN

If hepatitis B viral load does not drop by at least 1 log (a ten-fold decrease; for example, from 20,000 down to 2,000) after three months of treatment with Peg-IFN, it is not likely to be effective, and treatment should be switched to oral drugs.

Measuring the amount of HBsAg (quantitative testing) may help predict a person's response to Peg-IFN. In people who are HBeAg-positive, those with a lower level of pretreatment HBsAg are more likely to achieve HBeAg seroconversion. After three months of treatment, people with the lowest HBsAg levels are more likely to have HBsAg clearance at the end of full year of treatment.

Long-Term Outcomes of Peg-IFN Treatment

Since Peg-IFN was not approved until 2005 for treating chronic HBV, there are no long-term follow-up data, but information from older trials using standard interferon can shed some light. In Western studies, people who achieved HBeAg seroconversion while on interferon treatment have improved survival and lower rates of liver damage than untreated people. In a study conducted in China, however, no improvements were seen after nine years. This might be due to the study's Chinese volunteers having different HBV genotypes, or to other factors. It is not clear whether Peg-IFN treatment will prevent development of liver cancer.

Peg-IFN Side Effects

The major disadvantages of Peg-IFN are serious side effects and cost. In the beginning, most people will experience symptoms that can make it difficult for them to stay on treatment, but symptoms usually get better after the first few months. People have found it helpful to know the side effects they may experience before they start treatment, and to take steps that can help lessen the symptoms.

Peg-IFN side effects include:

- Flulike symptoms (feeling weak or feverish; having muscle and joint pain);
- Headache, nausea, and appetite loss;
- Fatigue/low energy;
- Anxiety, irritability, insomnia, mania, and mood swings;
- Mild-to-serious depression, including (in rare case) suicidal thoughts;
- Low white blood cell counts (neutropenia);
- Low red blood cell counts (anemia);
- Low platelets (thrombocytopenia);
- Weight loss; and
- Emergence of autoimmune disease (e.g., thyroid disease).

These side effects can be uncomfortable, sometimes debilitating, and—rarely—even life-threatening. People who are coinfecting with HIV and HBV may have more severe side effects. There are ways to manage these side effects, which will be discussed below.

It can be very helpful to talk with people who have been on Peg-IFN, and to ask your doctor how he/she will treat your side effects. With the right planning and support, many side effects can be managed. Support from other people with HBV, friends, and family before and during treatment plays a key role in coping with side effects.

Depression, Anxiety, and Other Psychiatric Side Effects

Depression and anxiety are commonly reported side effects of interferon treatment. In rare cases, people have reported that they've felt like taking their own lives, and a few people have committed suicide during their treatment. People with a history of depression are at greater risk for developing these side effects, although depression and anxiety have also been reported in people who never experienced them before. Interferon can also cause irritability, insomnia, mania, mood swings, and psychosis.

It's important to have access to mental health care before and during treatment so that, if it becomes necessary, psychiatric side effects can be treated promptly and appropriately.

Starting an antidepressant before going on Peg-IFN can help to prevent depression. Antidepressants and other psychiatric medications have their own side effects, however, so some experts think it is better to provide these drugs only if and when people need them. It is important to correctly diagnose and properly address these treatment-related psychiatric symptoms.

Flulike symptoms (fever, aches and pains, headache, chills, and nausea) are common side effects of interferon. Taking the pegylated interferon shot in the evening helps. You can also reduce your symptoms by taking a low dose of acetaminophen or a non-steroidal antiinflammatory agent, as well as an anti-nausea medication and/or dronabinol (also called Marinol, a derivative of marijuana). Drinking plenty of water also helps to lessen flulike symptoms.

Weight loss often occurs during treatment because people on Peg-IFN may lose their appetite, have diarrhea, and/or feel nauseated. People who experience these symptoms should try to eat many small, light meals to keep their energy up. Dronabinol may also help by stimulating the appetite.

Fatigue is also common during HCV treatment; napping, and doing regular, light exercise (when possible), can help. Some doctors are treating fatigue with methylphenidate (Ritalin).

HIV-positive people may have low white and/or red blood cell counts; anemia, neutropenia, and thrombocytopenia sometimes develop in persons with advanced HIV disease. Regular monitoring of white and red blood cell counts during Peg-IFN treatment is especially important for coinfecting people, since they are at greater risk for anemia, neutropenia, and thrombocytopenia.

Anemia (an abnormally low red blood cell count) is a side effect of Peg-IFN because it suppresses the growth of bone marrow, where blood cells develop. The most common symptom of anemia is fatigue. Anemia is a common problem for HIV-positive people, and can be caused by AZT. If possible, coinfecting people should avoid taking AZT, especially during Peg-IFN treatment. Combivir and Trizivir both contain AZT.

It is possible to treat anemia with injections of a red-cell growth factor called Epogen, which improves fatigue and helps people to stay on treatment.

Neutropenia is an abnormally low amount of neutrophils in the blood; neutrophils are the white blood cells that fight bacterial infections. Peg-IFN can cause neutropenia. The risk of developing bacterial infections is higher in people with neutropenia. If the neutrophil count drops during treatment, the dose of Peg-IFN may be reduced. Neutropenia is treated with injections of a white-cell growth factor called Neupogen.

Thrombocytes are platelets that help stop bleeding by clotting the blood.

Thrombocytopenia (low platelet count) can be caused by serious liver damage (because platelets are made in the liver). It can also be caused by other medical conditions, including HIV itself, and by pegylated interferon. Severe thrombocytopenia can have life-threatening consequences, such as intracranial hemorrhage. If severe thrombocytopenia develops, Peg-IFN treatment is usually discontinued.

GLOSSARY

Acute infection – with hepatitis B, this refers to the first six months after infection.

AFP (alpha-fetoprotein) – a protein found in the blood, commonly used to detect early signs of liver cancer.

Albumin – a protein made by the liver that carries drugs, hormones, and waste through the bloodstream, and helps maintain fluid levels within the body. Abnormally low levels of albumin can signal serious liver damage.

ALP (alkaline phosphatase) – a liver enzyme also found in tissues throughout the body. ALP should be monitored regularly during HIV treatment and in persons with hepatitis B.

ALT (alanine transaminase) - also called serum glutamate pyruvate transaminase, or SGPT; a key liver enzyme produced in liver cells. ALT should be monitored regularly during HIV treatment and in persons with hepatitis B.

Antigen – a substance foreign to the body, such as protein particles from a virus.

Antibodies – a substance produced by the immune system to fight off infections.

Antioxidant – a substance that reduces oxidative damage (damage due to oxygen), such as that caused by free radicals (see definition below).

Ascites – an abnormal accumulation of fluid in the abdomen; a sign of serious liver damage in people with hepatitis B.

AST (aspartate aminotransferase) – also called serum glutamic oxaloacetic transaminase, or SGOT; an enzyme made in many places throughout the body (heart, intestines, muscle). AST should be monitored regularly during HIV treatment and in persons with hepatitis B.

Bilirubin – a yellowish byproduct from the breakdown of old red blood cells; jaundice occurs if certain drugs, or bile-duct or liver damage, cause bilirubin to build up in the bloodstream.

Biopsy – taking a small sample of body tissue for examination and testing in the laboratory.

cccDNA (covalently closed circle DNA) – genetic coding of the hepatitis B virus.

CD4 Cells – a type of white blood cell that is an important part of the immune system. Low CD4 cell count indicates a weakened immune system.

Chronic infection – a persistent condition; with hepatitis B, this means any time following the acute phase.

Cirrhosis – severe scarring of the liver that makes it difficult for the liver to carry out its functions (see Fibrosis).

Coinfection – infection with more than one virus.

Compensated cirrhosis – a scarred liver that is still able to function.

Cross resistance – HBV mutations that are resistant to more than one drug.

Cryoglobulinemia – increased blood levels of a protein that can cause inflamed blood vessels and thicken blood.

Decompensated cirrhosis – when liver scarring prevents the liver from functioning.

Diabetes – an illness related to the inability to regulate sugar in the blood.

Drug Resistance - when a drug is no longer effective against a virus with genetic mutations.

Encephalopathy – degenerative brain function or disease.

End-stage liver disease (ESLD) – liver failure.

Enzyme – a protein in the body that speeds up other chemical reactions.

Fibrosis – mild-to-moderate scarring of the liver (see Cirrhosis).

FibroTest – a test that uses results from blood tests to predict liver damage; this test may become an alternative option to liver biopsy for some patients.

FibroScan – a non-invasive ultrasound scan that measures the elasticity or stiffness of the liver.

Free radical – a chemical produced after a molecular reaction, often containing oxygen, that has one free (unpaired) electron on its outer surface—this makes it able to react to and damage other cells. Free radicals may perhaps increase progression of cardiovascular disease, cancers, and aging.

Fulminant hepatitis – sudden, rapid disease progression related to liver failure.

Genotype – a category for different strains of the hepatitis B virus; there are at least six HBV genotypes.

GGT (gamma glutamyl transferase) – a liver enzyme made in the bile ducts. GGT levels may be abnormally high as a result of liver disease, heavy drinking, or some medications.

Grade/Grading – The grade of hepatitis infection refers to the amount of liver inflammation found by a biopsy. It is usually measured on the Ishak scale from 1 to 18, where 0 is none and 18 is the maximum.

HBeAg (Hepatitis B “e” Antigen) – a protein produced by hepatitis B in its replication. People who are HBeAg-positive and HBeAg-negative have different disease progressions.

HBsAg (Hepatitis B surface Antigen) – A protein on the surface of HBV; positive HBsAg means someone is infected with HBV.

HBV DNA (viral load) – a blood test that measures the amount of hepatitis B in the blood.

HBV flare – an increase replication of the hepatitis B virus that triggers an immune response, causing an elevation of liver enzymes, a sign of liver inflammation.

Hepatocellular carcinoma (HCC) – liver cancer.

IRIS (Immune Reconstitution Inflammatory Syndrome) – when the immune system recovers as the result of effective HIV treatment and starts responding to an infection, causing an inflammation.

Interferon – a chemical messenger produced by the human body; it can also be man-made. Interferon stimulates the immune system to fight viruses.

Jaundice – a common symptom of hepatitis where increased levels of bilirubin (see definition above) lead to a yellowing of the skin or eyes.

Lactic acidosis – abnormal buildup of lactate in the blood, caused by cellular damage associated with the use of nucleoside reverse transcriptase inhibitors (NRTIs; see definition below); if untreated, it can be fatal.

Liver toxicity – When a drug or chemical cannot be adequately processed by the liver, causing a build-up of toxins in the blood.

Lipoatrophy – fat loss, especially in the arms, legs, cheeks, and buttocks.

Lipodystrophy – abnormal fat accumulation or fat loss.

Mitochondria – part of a cell that produces energy in the body.

Monoinfection – infection with one virus.

Myopathy – muscle weakness.

Nephrotoxicity – kidney toxicity.

NRTI (Nucleoside reverse transcriptase inhibitor) – a type of HIV and HBV drug, also called nucleosides, or Nukes.

NNRTI (Non-nucleoside reverse transcriptase inhibitor) – a type of HIV drug.

Occult HBV – a form of HBV infection when the hepatitis B surface antigen can no longer be detected in a blood test, despite the presence of HBV in the blood.

Pancreatitis – inflammation of the pancreas; it can be painful and life-threatening if not treated.

PI (Protease inhibitor) – a type of HIV drug.

Peripheral neuropathy – nerve damage in the hands and feet.

Portal hypertension – increased blood pressure (hypertension) in the vein carrying blood to the liver.

Pre-core or basal-core mutations – naturally occurring HBV mutations that can still replicate without producing HBeAg.

Reactivation – When HBV starts replicating again after a period of inactivity.

Remission – When HBV infection is under control and not triggering an immune response.

Seroconversion – When an antigen is no longer detected in the blood, and the body produces antibodies to the antigen. A sign that the immune system has gained control of an infection.

SGOT – see AST.

SGPT – see ALT.

Spontaneous clearance – when the immune system is able to rid the body of the hepatitis B virus; if this occurs, it will be shortly after infection (usually within six months).

Stage/Staging – the stage of hepatitis infection refers to the amount of liver scarring (fibrosis) detected by biopsy. It is usually measured by either the METAVIR scale of 0 to 4, where 0 represents no scarring and 4 cirrhosis, or by the Knodell scale of 0 to 6, where 0 represents no scarring and 6 cirrhosis.

Steatosis – abnormal fat deposits in the liver.

Therapeutic drug monitoring (TDM) – a blood test that measures the level of certain drugs in the blood.

Titer – a measure of the concentration of antibodies to a specific antigen in a person's blood.

TIPSS (Transjugular Intrahepatic Portasystemic Stent Shunt) – a medical procedure inserting a metal mesh tube (stent) to connect two large veins in the liver used to treat portal hypertension.

Upper limit of normal (ULN) – the normal level of the liver enzyme ALT, above which can be an indication of liver inflammation.

Variceal hemorrhaging – bleeding caused by bursting veins (see Varices).

Varices – extended or swollen veins that can burst; a complication of cirrhosis.

TAG

Treatment Action Group