

# HEPATITIS D

## The Most Virulent Hepatitis Virus Of All

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The hepatitis D virus is perhaps the most unique of all hepatitis viruses, and also the most virulent.

As a virus, it is flawed. The hepatitis D virus (HDV) cannot replicate and infect someone unless the person is already infected with the hepatitis B virus (HBV). The hepatitis D virus requires the outer coating of the hepatitis B virus—called the surface antigen—in order to reproduce itself in a human host.

The virus currently infects 15 million worldwide, nearly all adults, and it is most common among injecting drug user populations and in countries bordering the Mediterranean Sea. Most children with HDV infection live in Italy and Greece, with a few in northern Africa. There are no reports or estimates of the number of children infected with HDV worldwide.

Despite widespread hepatitis B in Asian populations, HDV infection is virtually unknown there and appears primarily in injecting drug user populations.

HDV is transmitted through blood and body fluids, similar to the hepatitis B virus. Hepatitis D symptoms are similar to other viral hepatitis diseases and include jaundice, fever, malaise, dark urine and nausea. Although symptoms are similar, patients are more ill with hepatitis D than with hepatitis B alone.

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There are two types of HDV infection, coinfection and super-infection:

- Coinfection occurs when a patient is simultaneously infected with HDV and HBV. The majority of these patients completely recover but there is a higher rate of fulminant hepatic failure and death than with HBV infection alone.
- Super-infection occurs when someone with an existing chronic HBV infection becomes infected with HDV. These patients usually experience a sudden worsening of liver disease. Patients with hepatitis B who become chronically infected with HDV experience a very high rate of cirrhosis and end stage liver disease, which makes this super-infection a very dangerous disease.

with a super-infection are scarce, but doctors say the disease in children follows a similar pattern as in adults with rapidly developing liver disease. Most children with only chronic HBV infection are asymptomatic with no signs of liver damage. When additionally infected with HDV, they develop significant liver damage as a result of the super-infection.

### **What Is the Hepatitis D Virus?**

Dr. Mario Rizzetto of Italy identified the hepatitis D virus in 1977. He was examining liver cells from patients with chronic HBV infection when he observed a new antigen (a harmful, foreign substance) that was not one of HBV's three main antigens, which include the surface, core and e antigen.

After several years of testing and isolating the virus in chimpanzees, scientists finally named this new virus hepatitis D. This virus is a defective single-stranded RNA virus. In RNA viruses, the genetic information is stored in the RNA, while in cells and some other viruses, that information is stored in the DNA.

The virus has the smallest genome (genetic material) among all known animal viruses. The hepatitis D virus requires a particle from the hepatitis B virus—the hepatitis B virus's outer coating called the surface antigen—to synthesize its own outer protein coat to encapsulate its genetic core. The hepatitis D virus can still successfully replicate in people whose hepatitis B surface antigen level has dropped below detectable levels.

Like HBV, the hepatitis D virus inserts its genetic material into liver cells and uses the liver cells' resources to replicate itself. What is unique about HDV is that it replicates in a way similar to how plant viruses replicate. When the virus's genetic material is assembled in the "host" liver cell, the virus completes itself by incorporating hepatitis B surface antigen into its cytoplasm, then it is released from the host cell as a whole hepatitis D virus capable of infecting a new cell.

Researchers believe the hepatitis D virus directly harms liver cells. This is different from HBV infections, in which most of the damage to the liver is caused by the body's own immune system's efforts to eradicate the infected cells.

To date, researchers have identified three genotypes or regional variations of HDV around the world. Genotype 1 is widely distributed around the world, Genotype 2 is a unique genotype found only in Japan and Genotype 3, from South America, is associated with a severe form of HDV infection characterized by high mortality and a lesion in the liver called a morula cell.

A team of Canadian gastroenterologists have isolated and closely studied the molecular biology through nucleotide sequencing of a hepatitis D virus. They discovered a certain area of the virus was able to mutate easily. Researchers suspect this virus is capable of mutating rapidly and producing a much larger variety of HDV genotypes than has been identified to date.

### **Where Do HDV Infections Occur?**

In general, HDV infection reflects the epidemiology of HBV prevalence, but with some unique variations.

In countries with a low rate of chronic or long-term HBV infection, HDV also has a low prevalence among those chronically infected with HBV. HDV infection in these countries occurs most commonly among injecting drug users and persons with hemophilia.

In countries with moderate to high levels of chronic HBV infection, the prevalence of HDV varies. In southern Italy and in parts of Russia and Romania, the prevalence of HDV is very high among both asymptomatic HBV carriers and among patients with acute HBV.

However, in most of Southeast Asia, Taiwan and China, where the prevalence of chronic HBV infection is extremely high, hepatitis D virus infection is quite uncommon.

In some South American countries in the Amazon River Basin, periodic epidemics of HDV infection have occurred among people with chronic HBV infection in relatively isolated regions. During these HDV outbreaks, patients have progressed to life-threatening fulminant hepatitis and the death rate has been between 10 to 20 percent.

It is not clear why HDV is so frequent and lethal in the Amazon Basin, non-existent in Asia and fairly benign in Greece and the South Pacific. Researchers suspect different HDV genotypes cause varying degrees of liver damage.

There are low rates of HDV infection in most of Western Europe, the United States and Australia. In the United States, HDV most commonly occurs in people who are exposed to blood or blood products, such as medical personnel, injecting drug users and hemophiliacs who receive clotting factor concentrates.

## **How It Is Transmitted**

Hepatitis D is a bloodborne disease and is transmitted primarily by exposure to an infected person's blood or body fluids. Unlike hepatitis B, sexual transmission appears to be a less efficient mode of transmission though it can still be transmitted by barrier-free sexual activity.

According to the California Pacific Medical Center, sexual transmission of HDV is less common than sexual transmission of the hepatitis B virus. Researchers base that conclusion on the fact that the incidence of HDV infection is far lower among homosexuals than among injecting drug users. Both groups are at high risk of HBV infection.

Vertical (mother-to-infant) transmission is rare. A study, conducted in 1981, found of five babies born to hepatitis B surface antigen positive mothers with hepatitis D antibodies, only one baby showed evidence of hepatitis D infection. That baby was born to a mother with the hepatitis B e antigen, while the other mothers had developed antibodies to the e antigen. Individuals with e antigens generally have more viruses circulating in the bloodstream.

Scientists estimate the incubation period for HDV ranges between 21 and 90 days, but it may be shorter in cases of super-infection.

Blood is potentially infectious during all phases of acute hepatitis D, but an individual is probably most infectious just prior to onset of illness and symptoms. A chronically infected person's blood may continue to be infectious.

## **Hepatitis B and D Coinfection**

A coinfection occurs when a person is initially infected with both hepatitis B and D at the very same time.

A hepatitis B and D coinfection is more severe than other reported forms of single viral hepatitis infections. Death rates and liver failure are much higher than with hepatitis B alone.

Although the illness is more severe than most single viral hepatitis infections, the majority of adults will experience an acute infection and their immune system will successfully fight off HBV infection. Once hepatitis B viruses are eliminated, hepatitis D viruses cannot replicate without the hepatitis B's surface antigen and they also disappear.

In 90 to 95 percent of cases of adult coinfection, the malady begins with acute, self-limited hepatitis, followed by clearance of hepatitis B and D viruses, and finally development of hepatitis B surface antibodies, which confer protective immunity against hepatitis B.

Most cases of hepatitis B and D coinfection resolve themselves, only 2.4 to 4.7 percent of adults coinfecting with B and D simultaneously become chronic hepatitis carriers and risk serious liver damage, according to the National Centers for Disease Control and Prevention (CDC).

Though they have few numbers to judge, doctors expect children to be more susceptible to developing long-term or chronic HDV infection when exposed simultaneously to hepatitis B and D viruses in a coinfection situation.

Doctors expect that children's immune systems would not be as aggressive as adults in fending off a coinfection. They expect the younger the child is, the more prone he or she may be to developing a chronic HDV infection. This vulnerability to chronic infection mirrors the response young children experience when exposed to the hepatitis B virus.

In the case of a coinfection, IgM (Immune Globulin Class M) is the first antibody to be generated by the immune system to fight hepatitis D viruses, followed by IgG (Immune Globulin Class G). However in about 15 percent of patients, the only evidence of HDV infection may be the detection of either IgM antibody alone during the early acute period of illness or IgG antibody alone during convalescence.

Hepatitis D antibodies generally decline to sub-detectable levels after the infection is resolved and there is no indication in a person's blood to show that the patient was ever infected with HDV. Hepatitis D antigen can be detected in serum (blood) in only 25 percent of patients with a hepatitis B and D coinfection.

### **Hepatitis B and D Super-infection**

A super-infection occurs when someone who is already chronically infected with HBV becomes infected with the hepatitis D virus.

HDV infection is most virulent in adults and children who have hepatitis B surface antigen already circulating in their livers. Even when there are just small quantities of HBV surface antigen present and the person is asymptomatic, the hepatitis D virus can quickly replicate using the available hepatitis B surface antigen. The ensuing HDV infection can quickly induce acute hepatitis, with accompanying liver damage.

When an otherwise healthy person with chronic HBV infection begins to experience acute hepatitis symptoms, doctors should test for HDV. Adults with HDV super-infection usually develop chronic HDV infection. In long-term studies, 70 to 80 percent of patients with HDV super-infection will develop chronic liver disease and cirrhosis, as opposed to the 15 to 30 percent with HBV infection alone.

Though the study numbers are few, doctors report that HDV super-infection in children is similarly aggressive—perhaps even more aggressive because children’s immune systems are still developing—with rapidly developing liver disease. However, there are no available statistics on what percentage of children with HDV infection advance to cirrhosis.

According to Dr. Howard Worman of the Columbia University Division of Gastroenterology:

“Hepatitis D virus super-infection should be suspected in a patient with chronic hepatitis B whose condition suddenly worsens. There is usually an obvious history of continued exposure to blood or blood products (eg. an active intravenous drug user). Coinfection or super-infection with hepatitis D virus in a patient with hepatitis B is diagnosed by the presence of antibodies against the hepatitis D virus. IgM antibodies indicate acute infection.”

When children and adults with chronic HBV infections are infected with HDV in a super-infection scenario, the levels of HBV surface antigen decline as hepatitis D antigens appear, which sometimes masks the presence of hepatitis B when tests are conducted.

The hepatitis D antigens and hepatitis D RNA remain detectable because chronic HDV infection generally occurs in most patients with hepatitis B and D super-infection. High levels of both IgM and IgG hepatitis D antibodies are detectable, and will persist indefinitely.

In the case of super-infection, there is a quick rise in liver enzymes, which signals liver damage.

### **When to Test for HDV Infection**

There is no national standard or recommendation for when to test for hepatitis D antigens or antibodies. Generally, doctors test for hepatitis D only in patients who already have chronic or long-term hepatitis B and who have acute worsening of their

liver disease. It has been suggested that all patients with chronic HBV infection be tested for HDV infection, especially if there is a sudden worsening. Others recommend testing of injecting drug users who experience jaundice, whether or not they are hepatitis B surface antigen positive, because hepatitis D can mask or suppress hepatitis B surface antigens in many conventional lab tests.

If and when a liver biopsy is performed, the specimen can be tested for the hepatitis D antigen.

### **Preventing HDV Infections**

Because the hepatitis D virus is dependent on the hepatitis B virus for replication, hepatitis D can be prevented by preventing hepatitis B through routine vaccination or by administering the vaccine and hepatitis B immune globulin or HBIG, which contains high levels of hepatitis B antibodies, to anyone who has been exposed to HBV.

However, no vaccine exists that prevents hepatitis D super-infection in people chronically infected with HBV. As a result, preventing hepatitis D super-infection depends on reducing exposure to blood and body fluids that may contain the hepatitis D virus. This can be accomplished through safer sex practices, standard precautions to prevent contact with blood and other body fluids and not sharing injecting drug paraphernalia.

### **Symptoms of HDV Infection**

HDV infection symptoms are similar to those of hepatitis B. The onset of symptoms is usually abrupt and includes fatigue, poor appetite, fever, vomiting and occasionally joint pain, hives or rash. Urine may become dark in color, and then jaundice (a yellowing of the skin and whites of the eyes) may appear.

There may be no fever in children, but fever may be present in adolescents.

According to studies of adults, cirrhosis develops in 60 to 70 percent of those infected with HDV, a rate far higher than that observed with hepatitis B or C. The disease can be rapidly progressive, with cirrhosis developing within one to two years following acute hepatitis in 15 percent of patients.

## **Treating Hepatitis D**

Historically, there has been minimal research, and minimal success, in finding effective treatments to combat HDV infection.

To date, most of the research has taken place in the Mediterranean region where there is a higher rate of HDV infection in adults and children. Given its severity, hepatitis D responds poorly to treatment, reactivates readily and can lead to liver failure.

Interferon alpha is currently one of the few drugs used in children and adults that appear to help in the treatment of hepatitis D. However, it has limitations. About half of patients do not respond to interferon therapy, and relapse is common when the 48-week treatment is discontinued.

According to Dr. Patrizia Farci of the Institute of Internal Medicine at the University of Cagliari in Italy, interferon alpha remains the more effective known agent against hepatitis D. Pilot studies using the antiviral agent ribavirin failed to inhibit hepatitis D virus replication.

The experience with combination therapy has been limited in the treatment of chronic hepatitis D. In one study using acyclovir for two weeks followed by a four-month course of interferon alpha, the results did not differ from those obtained with the same dose of interferon alpha alone, Dr. Farci reported. Similar results were found in studies looking at combination therapy with lamivudine and interferon.

Dr. Farci and scientists in another medical center in Italy conducted two major studies using varying levels of interferon treatment in adults with hepatitis D in Italy and Sardinia, where the disease is endemic. They found that treatment with higher doses of interferon produced significant improvement in liver function and inflammation.

However, both this study and others in adults demonstrated a high rate of relapse once interferon was discontinued. Dr. Farci noted that in this study, a sustained biochemical response was observed in only 35 percent of the patients treated with the higher dose of interferon.

Dr. Farci suspects there are genetic variants of the hepatitis D virus that cause different degrees of liver damage. She suggested that interferon alpha, when it works, reduces hepatitis D virus replication to a level that does not cause liver damage, but never eradicates it completely.

Dr. Farci reported that, “despite the encouraging results of the high-dose regimens, it is clear that interferon is not a curative treatment for hepatitis D, as indicated by the lack of virus eradication even in patients with sustained biochemical responses.”

Dr. Farci also suggested that early recognition and treatment of chronic HDV infection (within two years of infection) may lessen or slow liver damage. She has found no demographic factors such as age, gender or ethnicity that impact how patients respond to therapy.

Dr. Farci recommends high-dose treatment with interferon alpha of 9 million IU three times a week for at least one year for adults. While 5 million IU daily is better tolerated, the response is not as good, she noted.

Before treatment, a liver biopsy should be performed to assess the progression of the disease.

Researchers have reported that the response to interferon treatment is slower in chronic HDV infection, taking up to 10 months after start of treatment versus one to three months for chronic hepatitis B or C. They recommend that treatment be stopped if there is no response within one year.

Interferon is not recommended in immunosuppressed patients and those who have decompensated cirrhosis.

### **Treatment in Children**

During the late 1990s, doctors at the Department of Internal Medicine and Pediatrics at the University of Ioannina in Greece followed seven children chronically infected with HDV. They were treated with interferon alpha three times weekly.

While their alanine aminotransferase (ALT) levels (liver enzymes that are released when liver cells are damaged) declined during the treatment period in all seven children, the level of hepatitis D antibodies and hepatitis D IgG antibodies remained positive in all children. In four children, hepatitis D RNA remained positive. None of the children seroconverted or lost their hepatitis B surface antigen or developed surface antibodies as a result of treatment. The doctors considered the findings disappointing.

The interferon alpha treatment caused mild fever and malaise, but the children remained active and continued to attend school during this study period. A couple actually gained weight during the study.

“This study indirectly indicates that more effective agents and new approaches at the molecular level of the hepatitis D virus genome are urgently warranted for its control in individuals already infected with the virus,” the researchers concluded. “Finally, the poor therapeutic results ... further enhance the necessity of the expanded vaccination against hepatitis B virus.”

### **Liver Transplant as Treatment**

To date, liver transplants in patients with HDV infection have produced mixed and inconclusive results.

According to a report by Dr. Sean R. Lacey of the Department of Gastroenterology at Case Western Reserve University/University Hospitals of Cleveland, liver transplants in patients with hepatitis B and D super-infections have not been encouraging. He found “... fulminant (life-threatening) hepatitis from recurrent hepatitis B and D infection in the transplanted liver has resulted in patient death or the need to re-transplant.”

Other researchers have found that hepatitis D reappears in previously infected people who receive a liver transplant. Though there appears to be no evidence of hepatitis B surface antigens following the transplant, just a few intact hepatitis D-infected liver cells are sufficient to cause a reoccurrence of hepatitis D.

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