

HEPATITIS VIRUS ALPHABET: AN INTRODUCTION TO HEPATITIS VIRUSES A THROUGH G

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- Hepatitis A (HAV)
- Hepatitis B (HBV)
- Hepatitis C (HCV) (updated 11/14/2005 from Annual AASLD Meeting)
- Hepatitis D (HDV)
- Hepatitis E (HEV)
- Hepatitis G (HGV)

Viral hepatitis is a disease as old as the history of Medicine. Hepatitis was described in the Babylonian Talmud in the Fifth Century BC, and was referred to by Hippocrates over 2000 years ago. Despite this ancient knowledge, it was not until 1969 that the first human hepatitis virus was isolated, Hepatitis B. This was followed quickly by the purification of Hepatitis A in 1973, and more recently by the isolation of viruses C, D, E, and G. This is an introduction to the 6 major human hepatitis viruses—Viruses A through G.

Although Viruses A through E are often discussed, there are more than twenty other viruses which infect the human liver. These are not considered "hepatitis viruses" as these other viruses tend to infect organs other than the liver more seriously. These include common viruses such as cytomegalovirus, mumps, and rubella, as well as rare ones such as Lassa Fever and Yellow Fever viruses.

Incidentally, not all "hepatitis" is caused by viruses. "Hepatitis" means "inflammation of the liver", and can be caused also by other types of infection (bacteria, fungal, TB, etc.); toxic drugs; poisons; alcoholism; vascular disorders; and immune system diseases.

Hepatitis A (HAV)

Hepatitis A (HAV) is caused by a RNA virus which is found in feces, saliva, semen, and blood of infected people. It is transmitted primarily by the fecal, oral or sexual contamination, but can be passed rarely by blood transfusion or contaminated needles.

The illness typically begins with jaundice (yellow skin), fever, and weakness occurring six weeks after the time of infection. Prior to the onset of jaundice, there is often a period of mild illness for several days resembling the "flu" with tender lymph nodes (especially in the neck), mild cough, mild diarrhea, or upper abdominal pain. Symptoms of hepatitis usually resolve in two to six weeks.

Rarely, patients experience relapses (restarting of symptoms) for up to a year after the first illness; or there may be a prolonged phase with jaundice lasting for 6 months. Rarely, a fulminate acute hepatitis occurs which often ends in death. Chronic Hepatitis A does NOT occur.

Efforts to prevent Hepatitis A focus upon limiting exposure to the virus and giving a gamma globulin (antibody) injection to people exposed to the virus. Vaccination to prevent Hepatitis A is very effective and is required for all school children in the United States. We recommend that all adults be vaccinated (two injections are given into muscle), especially those likely to travel to endemic areas such as Latin America, Africa, Eastern Europe, and Asia.

Treatment of Hepatitis A includes rest, plenty of fluids, and avoidance of medications or herbs which might injure the liver. Patients with fulminate liver failure are referred for emergency liver transplantation.



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Hepatitis B (HBV)

Hepatitis B remains one of the major causes of human suffering in the world despite a thorough understanding of its transmission and prevention. It is a DNA virus and there are many serotypes (subtypes). Fortunately, antibody to the protein called "B surface antigen" gives a person immunity to most HBV's subtypes.

HBV can be acquired parenterally (blood transfusions, contaminated needles) or sexually. The acute illness (jaundice, weakness, fever, nausea) typically resolves after 2-4 weeks. In under one percent of cases, fulminate hepatitis occurs which is often fatal. One in twenty infections results in chronic hepatitis, defined as persistent hepatitis virus six months after the onset of the acute illness.

Chronic HBV infection can be entirely benign with normal liver blood tests ("chronic carrier state") or may be an aggressive inflammatory process ("chronic active hepatitis") which can lead to severe scarring ("cirrhosis"). The risk of liver cancer (hepatoma) is high in cirrhosis caused by HBV.

The 3-injection vaccine for HBV is recommended for all school-aged children, for people exposed to HBV, and for some health care workers. These vaccines are not derived from patients and carry NO RISK of giving someone hepatitis or AIDS virus.

Acute exposures, such as needle stick injuries, infants born to infected mothers, and rape victims, are managed with the Hepatitis B vaccine and, in addition, with Hepatitis B high-titer Immune Globulin injection (HBIG).

Interferon has been approved for the treatment of biopsy-proven chronic active

HBV. This treatment is administered as injections given daily or three times a week for four months.

Lamivudine, An oral agent has been used now for several years in the treatment of hepatitis B. Two early studies investigated if in combination with interferon there might be better outcomes. Such seems not the case. At present, much investigation is directed at Lamivudine in a mono-therapy role. A recent article published in the New England Journal of Medicine by the US Lamivudine Investigator Group (Dienstag et al. Lamivudine as Initial Treatment for Chronic Hepatitis B in The United States NEJM 1993;41(17):1256-1269) suggest that one year of mono therapy with Lamivudine had positive effect with respect to histology, virulence and biochemical features. The down side with Lamivudine, many patients after a year will develop a resistance to it, and the Hepatitis B virus may form mutations making it more difficult to treat. Because of this, many liver doctors are advocating the use of newer oral drugs in the treatment of hepatitis B. One of these drugs is Hepsara (Adefovir Dipivoxil). This agent was first used in AIDS patients, but now is being used by many as a first line oral agent in the treatment of Hepatitis B. Unfortunately, with more use, this drug is also showing some risk of the development of resistance and mutation. An even newer drug has come to market in the fight against chronic B, called Baraclude (Entecavir). Baraclude thus far looks like a good alternative to current oral agents, but data is limited. This is an interesting time in the management of chronic Hepatitis B in that there are several new drugs in the pipeline.

Hepatitis C (HCV)

Hepatitis C (HCV) is a single-stranded RNA virus. In 1990, the partial genetic sequence of the virus was reported and the first diagnostic test became available to detect antibodies to the virus in blood. These antibodies are not protective against the virus but are a helpful marker of infection in that most people with HCV antibodies are actively infected and contagious. HCV is responsible for most cases of what was previously called "Non-A, Non-B Hepatitis".

Risk Factors For Transmission:

- Blood Exposure, Needle Stick Injury or Transfusion
- Illegal Drug Use, Including "snorting"
- Tattoos or Body Piercing
- Sexually Active with Multiple Partners
- Transmission of HCV can occur by blood transfusions (now very rare)
- Needle stick injuries to health care workers
- Drug abuse through sharing of infected needles (most common).

One of the mysteries surrounding HCV is that the mode of transmission is not identified in more than 20% of cases. The spouses of infected people are at slightly

increased risk although the mechanism of transmission to spouses is not known. Transmission to spouses during intercourse is so rare that condom use is usually NOT advised for a patient who is in a long-term relationship with one partner. Certainly HCV is in blood, and sexual behavior should be considered dangerous where blood may be spread such as when there is a cut or sore in the genital areas.

Acute Hepatitis C develops approximately 6 to 10 weeks after infection. Patients may experience no symptoms or merely a mild flu-like illness lasting a few days or weeks and usually without jaundice (yellow skin and eyes). Usually, liver blood tests are not measured and Hepatitis C is not suspected or diagnosed until years or decades later.

Chronic Hepatitis C disease occurs in 50-62% of cases; most of these people remain contagious for life. The majority of those with chronic HCV have a relatively mild form, which seldom progresses; though the natural history is mild HCV is still under study. Of those who develop chronic hepatitis, many develop aggressive hepatitis with gradual progression to cirrhosis (permanent scarring) and liver failure. Unfortunately, most people with aggressive HCV disease have no symptoms until the late stages of cirrhosis.

The diagnosis of HCV is usually an accident. Typically, a routine liver blood test will be found to be abnormal, and the physician then orders the Hepatitis C antibody blood test. The virus itself can also be measured (HCV RNA), and this test has become helpful to gastroenterologists managing drug therapy for HCV (see below). Liver biopsy, the most precise way to evaluate the severity of HCV infection, is required for all patients prior to starting drug therapy.

Many studies have shown that a medicine called interferon, given as an injection three times a week for 6 - 12 months, can improve liver blood tests and the appearance of liver tissue when seen through a microscope (histology). This is the current standard treatment for aggressive hepatitis C.

Therapy for Hepatitis C

Many studies have shown that a medicine called interferon, given as an injection three times a week for 6 - 12 months, can improve liver blood tests and the appearance of liver tissue when seen through a microscope (histology).

Four brands of interferon are available in the United States. This therapy is prescribed by liver specialists and requires careful patient education and monitoring to be administered safely. The form of interferon used most often is Interferon alpha-2B (Intron-A). Approximately one half of subjects treated with Intron-A respond with normalization or near-normalization of liver blood tests by six months. Unfortunately, most will relapse by two years after completion of therapy, and many require long term low-dose treatment, or other options. The long term, virus-free success rate with Intron-A is well under 10%.

Combination therapy with two or more medicines is under intense study. In an article published in the New England Journal of Medicine (McHutchinson et al. NEJM 1998:339(21) 1485-1550) McHutchinson's investigators reported undetectable serum virus levels 24 weeks after treatment with patients treated for 24 weeks with interferon alone at 6% and for patients treated with combination therapy (Interferon and Ribavirin) to be 31%. In this same study, in-patients who were treated for 48 weeks with either form of therapy, the results were 13% for mono-therapy with interferon and 38% for patients treated with combination therapy.

In general, the trend in viral therapy seems to be directed at present with investigating different forms of combination therapy. Of note, several large multi-center studies investigating the effectiveness of combination therapy will be releasing their data in the next year, and we look forward to this data to better explain the added role of Ribavirin. At present, the combination of Ribavirin with Interferon has replaced mono-therapy with interferon, but as with all things in medicine, there will most likely be a different approach to therapy in the near future. Although not yet proven, the hope is that interferon therapy will prevent the progression of the disease to cirrhosis and death.

Two years ago the FDA approved a new form of interferon which was time released called peginterferon Alpha 2b, thus allowing patients once a week injections vs. three times a week as had been the case . Until recently only one manufacture, Sherring pharmaceuticals had FDA approval for this new form of long acting self released interferon, but as of last month Hoffman-LaRoche pharmaceuticals introduced peginterfeon Alpha-2a, and in a recent clinical trial published in the New England Journal of Medicine dated September 26th, 2002 (Vol.347,no.13,975-982), researchers Fried et al. compared these two different manufactures interferon in hepatitis C patients. Early data may suggest improved response with peginterferon Alpha-2a, though as has been the case with all new clinical trials with interferon based treatments, larger study groups will be needed before the final answer is out. We are pleased now to have other pharmaceutical companies getting involved in the treatment of hepatitis C, since the competitiveness between companies may extend new treatments to our patients with better and more effective treatments in the future.

This year (Nov 11-15th,2005 in San Francisco) at the AASLD annual liver meeting, Several new study drugs were presented. VX-950 a highly selective peptidomimetic inhibitor being investigated by Vertex Pharmaceuticals was presented. This , their final results of a phase 1B Study. VX-950 was well tolerated with little significant side effects, and at a dose of 800 mg TID produced a significant log drop of HCV RNA at wk 2. Current phase 2 studies with vx-950 are underway. An other study drug SCH 503034 had early data presented. This is a HCV protease inhibitor from Shering-Plough Research Institute. This was a multi-dose , double blinded study which showed few side effects, and 1.5- 2 fold log drop of HCV RNA at a dose of 400mg TID in patients who had previously failed Interferon therapy. Future phase 3 studies are on the way with this drug. Another investigational drug NM283 (Valopicitabine) of Idenix Pharmaceuticals was presented. This was a phase 2b study

in which previous non responders to Interferon and Ribavirin were randomized to several treatment arms. The final results suggest that NM283 along with pegulated interferon had significantly better results in re treatment vs. pegulated interferon with ribaviron.

[Click Here for more information from the 2005 Liver Meetings!](#)

One of the newest areas of interest, are those patients in whom some form of long term interferon based therapy has been given in advanced cases of fibrosis. There is some early evidence that the use of interferon in such patients may retard...at least for a while. the eventual progression to cirrhosis and decompensated liver disease and hence the need for transplantation. While it is too early to say if long term administration of interferon based therapy may succeed in this, there are on going trials in the U.S. to study this.

As with all clinical studies, if one is considering becoming a participant, one should be cautious of several things. First, is study participation in any way going to interfere with your health care insurance contract? Many HMO's and PPO's will not cover clinical research trials, and if you become ill during such a clinical trial, your insurance carrier may not cover those medical cost incurred by yourself. Be sure to have clarification of this point, and inquire whether the clinical trial that you are going to participate in will cover such costs if needed. Second, many drug studies are in fact pseudo-marketing ventures with the investigators and the drug manufactures, inquire about the type of study that you are considering with the investigator. Do they have a financial incentive to enroll patients? Studies are designated as Phase 1, 2, 3 and 4. Phase 4 studies tend to be post drug (FDA) approval studies, and these you should be most leery of, since they tend to be marketing studies usually funded by the marketing arms of the pharmaceutical industry and not by the research sides of the industry. Phase 2 and 3 studies are usually pre-approval studies, and most often are funded by the research divisions of the pharmaceutical industry. These studies ask such questions as to whether the drug really does what it is intended to do, and what are the appropriate doses.

At present, all patients who have chronic Hepatitis C should be vaccinated for both Hepatitis A and B if they do not already have immunity. This , per a recommendation of the NIH and most leading experts in the field of hepatology.

The diagnosis of Hepatitis C and all of these treatments are available from Borland-Groover Clinic physicians and their expert staff.

Treatment with interferon, ribavarin, and other medicines is very difficult and expensive. For patients requiring therapy but unable to afford the medications, many of the pharmaceutical companies involved in therapy have provided ways to get medications for free, one needs to ask ones physician if this is an issue.

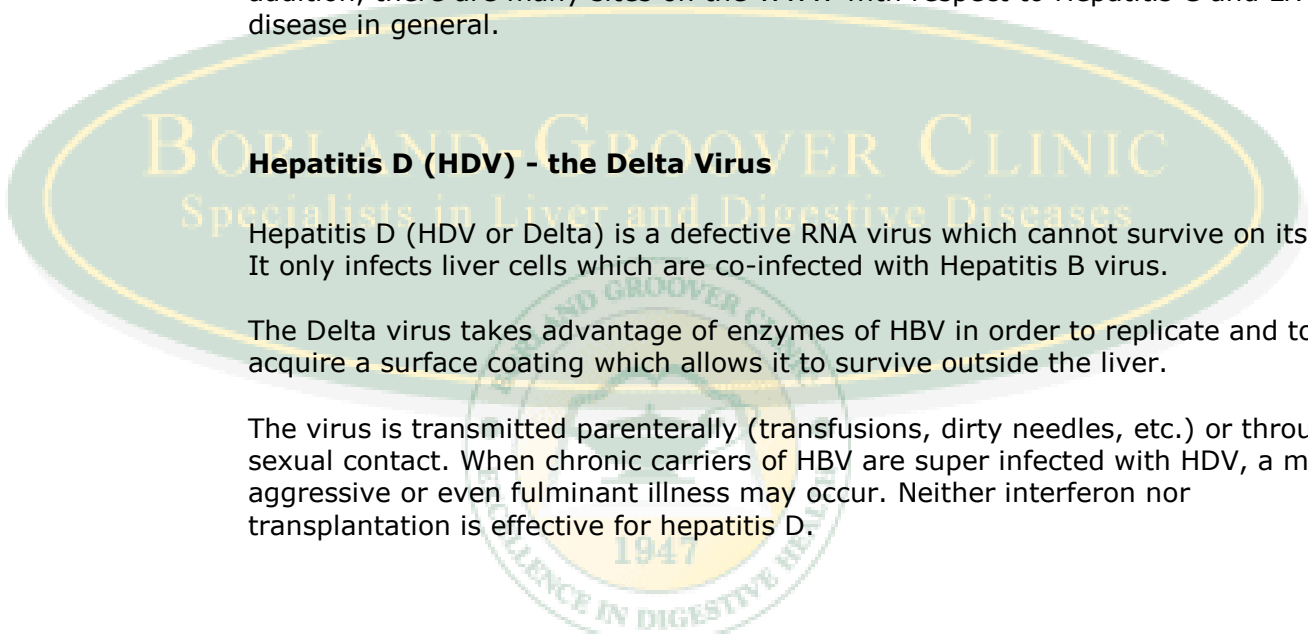
All patients have complications, sometimes severe, while taking these drugs. Unfortunately, for patients with aggressive hepatitis C there often is no good

alternative as other approaches (diets, herbs, exercise etc.) are ineffective. People with hepatitis C should discuss these issues in detail with their primary care physician or Board-certified gastroenterologist.

Liver transplantation is considered when hepatitis C results in end stage cirrhosis and liver failure. The time from initial infection to liver failure is 20- 40 years.

Recently, Treatment for patients with Hepatitis C and HIV is now being considered, for more information [click here](#).

Patients with Hepatitis C who are on or not on therapy often have many issues that they have to face, and family and friends can also feel the effects of this disease. To help, many communities such as ours have support groups that can help. In addition, there are many sites on the WWW with respect to Hepatitis C and Liver disease in general.



Hepatitis D (HDV) - the Delta Virus

Hepatitis D (HDV or Delta) is a defective RNA virus which cannot survive on its own. It only infects liver cells which are co-infected with Hepatitis B virus.

The Delta virus takes advantage of enzymes of HBV in order to replicate and to acquire a surface coating which allows it to survive outside the liver.

The virus is transmitted parenterally (transfusions, dirty needles, etc.) or through sexual contact. When chronic carriers of HBV are super infected with HDV, a more aggressive or even fulminant illness may occur. Neither interferon nor transplantation is effective for hepatitis D.

Hepatitis E (HEV)

The first reports of the isolation and partial molecular sequencing of Hepatitis E were published in 1990. HEV is similar to hepatitis A in many respects: it is an RNA virus, is transmitted by the fecal-oral routes, and causes acute (but not chronic) illness. This agent appears to be the principle cause of epidemic, water-borne hepatitis in the Third World. A few cases have been reported in the United States among travelers recently returned from Mexico or Asia. Generally a benign illness, the greatest risk is to pregnant women for whom the case fatality rate is approximately 20%. A 1997 report suggests that a strain of HEV may be a rare cause fatal fulminant hepatitis in the United States.

Hepatitis G (HGV)

No Hepatitis F virus has been named, but Hepatitis G (HGV) was newly described in 1995.

This virus is very similar to the Hepatitis C (HCV) : both are RNA viruses and 25% of their molecular structures are identical. HGV is transmitted from person-to-person by the same methods as HCV (see above), and approximately one in five people infected with HCV also carries HGV.

Fortunately, it appears that HGV is an "innocent" virus in that it is commonly found in livers but does not seem to cause disease or lead to complications. Patients with HCV and HGV confection are no more ill than those with HCV infection alone.

Blood tests are available to detect antibodies to HGV but these are ordered rarely by physicians. No therapy has been described although it does not appear that therapy is necessary.

The Future - Hepatitis H?

The next five years should bring more widespread use of the Hepatitis A and Hepatitis B vaccines, and progress towards the development of a HCV vaccine. There will be better medication regimens for HCV, with options using 2 or more medicines in combination. Long term survival rates will improve for liver transplantation.

Lastly, most experts believe that more viruses remain to be discovered to explain the 10 to 15% of patients whose chronic hepatitis is unexplained. One of these is likely to be named the new Hepatitis H virus.