Hepatitis Viruses:

Many viruses cause hepatitis. Of these, five medically important viruses are commonly described as "hepatitis viruses" because their main site of infection is the liver. These five are hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV, delta virus), and hepatitis E virus (HEV) . Other viruses, such as Epstein-Barr virus (the cause of infectious mononucleosis), cytomegalovirus, and yellow fever virus, infect the liver but also infect other sites in the body and therefore are not exclusively hepatitis viruses.

Glossary of Hepatitis Viruses and Their Serologic Markers	
Abbreviation	**Name and Description**
HAV	Hepatitis A virus (enterovirus 72), a picornavirus (nonenveloped RNA virus)
IgM HAV Ab	IgM antibody to HAV; best test to detect acute hepatitis A
HBV	Hepatitis B virus, a hepadnavirus (enveloped, partially double-stranded DNA virus); also known as Dane particle
HBsAg	Antigen found on surface of HBV, also found on noninfectious particles in patient's blood; positive during acute disease; continued presence indicates carrier state
HBsAb	Antibody to HBsAg; provides immunity to hepatitis B
HBcAg	Antigen associated with core of HBV
HBcAb	Antibody to HBcAg; positive during window phase; IgM HBcAb is an indicator of recent disease
HBeAg	A second, different antigenic determinant in the HBV core; important indicator of transmissibility
HBeAb	Antibody to e antigen; indicates low transmissibility
Non-A, non-B	Hepatitis viruses that are neither HAV nor HBV
HCV	Enveloped RNA virus; one of the non-A, non-B viruses
HDV	Small RNA virus with HBsAg envelope; defective virus that replicates only in HBV-infected cells
HEV	Nonenveloped RNA virus; one of the non-A, non-B viruses

Important Properties of Hepatitis Viruses

Virus	Genome	Replication Defective	DNA Polymerase in Virion	HBsAg in Envelope	Virus Family
HAV	ssRNA	No	No	No	Picornavirus
HBV	dsDNA[1]	No	Yes	Yes	Hepadnavirus
HCV	ssRNA	No	No	No	Flavivirus
HDV	ssRNA[2]	Yes	No	Yes	Deltavirus
HEV	ssRNA	No	No	No	Hepeviridae

[1]Interrupted, circular dsDNA.

[2]Circular, negative-stranded ssRNA.

Hepatitis A Virus

Disease; HAV causes hepatitis A.

Important Properties; HAV is a typical **enterovirus** classified in the picornavirus family. It has a single-stranded RNA genome and a nonenveloped icosahedral nucleocapsid and replicates in the cytoplasm of the cell. It is also known as enterovirus 72. It has one serotype, and there is no antigenic relationship to HBV or other hepatitis viruses.

Summary of Replicative Cycle; HAV has a replicative cycle similar to that of other enteroviruses.

Transmission & Epidemiology; HAV is transmitted by the **fecal–oral** route. Humans are the reservoir for HAV. Virus appears in the feces roughly 2 weeks before the appearance of symptoms, so quarantine of patients is ineffective. **Children are the most frequently infected** group, and outbreaks occur in special living situations such as summer camps and boarding schools. Common-source outbreaks arise from fecally

contaminated water or food such as oysters grown in polluted water and eaten raw. Unlike HBV, HAV is **rarely transmitted via the blood,** because the level of viremia is low and chronic infection does not occur.

Pathogenesis & Immunity; The pathogenesis of HAV infection is not completely understood. The virus probably replicates in the gastrointestinal tract and spreads to the liver via the blood. Hepatocytes are infected, but the mechanism by which cell damage occurs is unclear. HAV infection of cultured cells produces no cytopathic effect. It is likely that attack by cytotoxic T cells causes the damage to the hepatocytes. The infection is cleared, the damage is repaired, and no chronic infection ensues. Hepatitis caused by the different viruses cannot be distinguished pathologically.

The immune response consists initially of IgM antibody, which is detectable at the time jaundice appears. It is therefore important in the laboratory diagnosis of hepatitis A. The appearance of IgM is followed 1 to 3 weeks later by the production of IgG antibody, which provides lifelong protection.

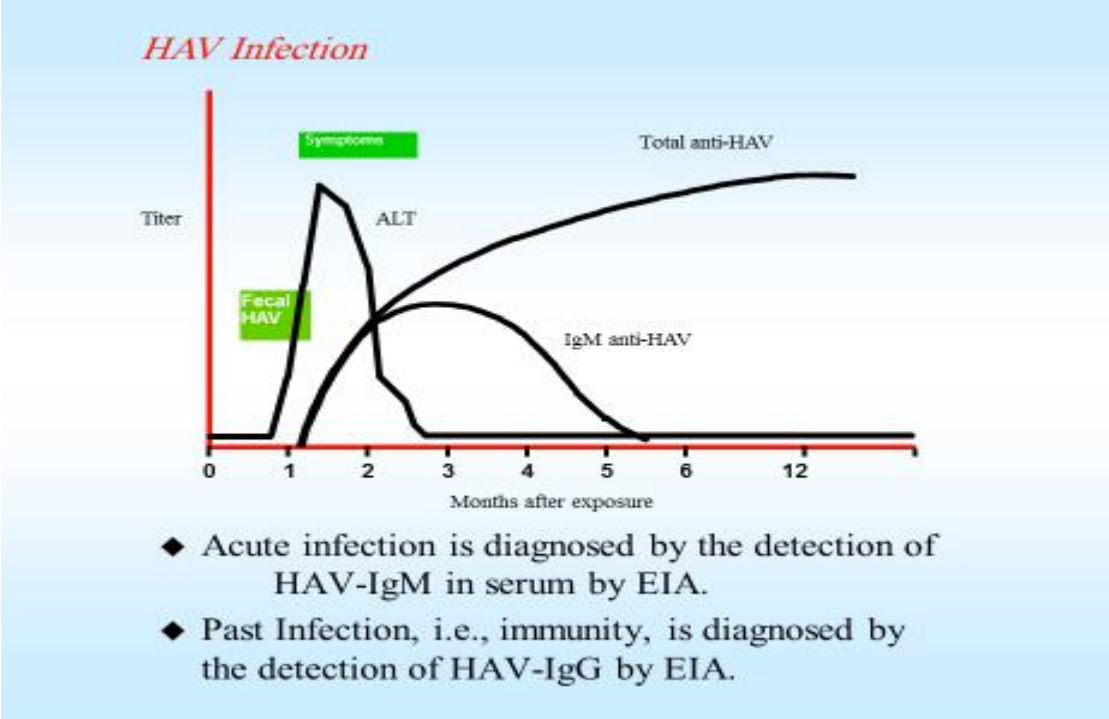
Clinical Findings; The clinical manifestations of hepatitis are virtually the same, regardless of which hepatitis virus is the cause. Fever, anorexia, nausea, vomiting, and jaundice are typical. Dark urine, pale feces, and elevated transaminase levels are seen. Most cases resolve spontaneously in 2 to 4 weeks. Hepatitis A has a short incubation period (3–4 weeks), in contrast to that of hepatitis B, which is 10 to 12 weeks. Most HAV infections are asymptomatic and are detected solely by the presence of IgG antibody. No chronic hepatitis or chronic carrier state occurs, and there is no predisposition to hepatocellular carcinoma.

Clinical Features of Hepatitis Viruses

Virus	**Mode of Transmission**	**Chronic Carriers**	**Laboratory Test Usually Used for Diagnosis**	**Vaccine Available**	**Immune Globulins Useful**
HAV	fecal–oral	No	IgM HAV	Yes	Yes
HBV	Blood, sexual, at birth	Yes	HBsAg, HBsAb, IgM HBcAb	Yes	Yes
HCV	Blood, sexual[1]	Yes	HCV Ab	No	No
HDV	Blood, sexual[1]	Yes	Ab to delta Ag	No	No
HEV	fecal–oral	No	None	No	No

[1]Sexual transmission seems likely but is poorly documented.

Laboratory Diagnosis; The detection of **IgM antibody** is the most important test. A fourfold rise in IgG antibody titer can also be used. Isolation of the virus in cell culture is possible but not available in the clinical laboratory.



Treatment & Prevention; No antiviral therapy is available. **Active immunization** with a vaccine containing inactivated HAV is available. The virus is grown in human cell culture and inactivated with formalin. Two doses, an initial dose followed by a booster 6 to 12 months later, should be given. No subsequent booster dose is recommended. The vaccine is recommended for travelers to developing countries, for children ages 2 to 18 years, and for men who have sex with men. If an unimmunized person must travel to an endemic area within 4 weeks, then passive immunization (see below) should be given to provide immediate protection and the vaccine given to provide long-term protection. This is an example of **passive–active immunization.**

Because many adults have antibodies to HAV, it may be cost-effective to determine whether antibodies are present before giving the vaccine. The vaccine is also effective in postexposure prophylaxis if given within 2 weeks of exposure. A combination vaccine that immunizes against both HAV and HBV called Twinrix is available. Twinrix contains the same immunogens as the individual HAV and HBV vaccines.

Passive immunization with immune serum globulin prior to infection or within 14 days after exposure can prevent or mitigate the disease. Observation of proper hygiene, e.g., sewage disposal and handwashing after bowel movements, is of prime importance.

Hepatitis E Virus

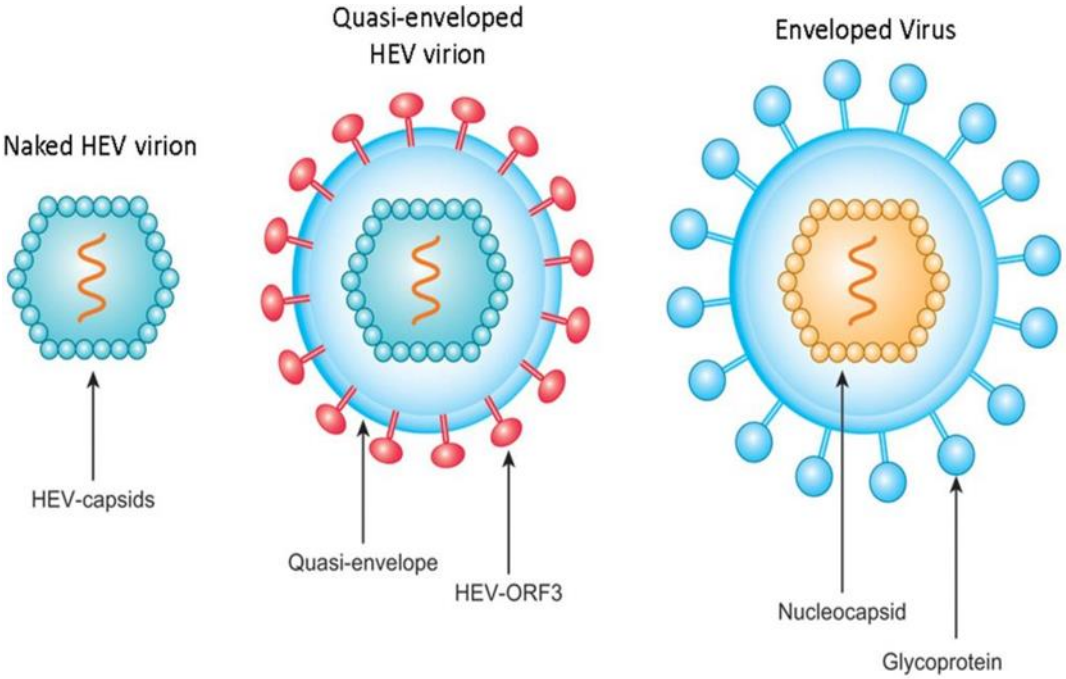
HEV is a major cause of enterically transmitted hepatitis. It is a common cause of waterborne epidemics of hepatitis in Asia, Africa, India, and Mexico but is uncommon in the United States. HEV is a unenveloped, single-stranded RNA virus classified as a member of the hepevirus family. Clinically the disease resembles hepatitis A, with the exception of a high mortality rate in pregnant women. Chronic liver disease does not occur, and there is no prolonged carrier state.

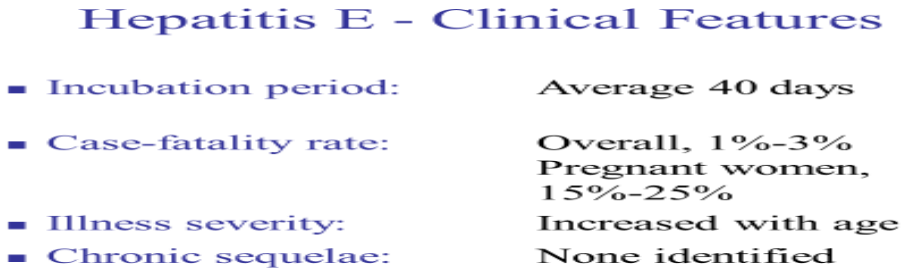
The test for HEV antibody is not readily available; the diagnosis is therefore typically made by excluding HAV and other causes. There is no antiviral treatment and no vaccine. Most outbreaks associated with faecally contaminated drinking water.

Several other large epidemics have occurred since in the Indian subcontinent and the USSR, China, Africa and Mexico.

Minimal person-to-person transmission.

Prevention and Control Measures for Travelers to HEV-Endemic Regions :Avoid drinking water (and beverages with ice) of unknown purity, uncooked shellfish, and uncooked fruit/vegetables not peeled or prepared by traveler.





Hepatitis B Virus

Disease; HBV causes hepatitis B.

Important Properties; HBV is a member of the hepadnavirus family. It is a 42-nm **enveloped** virion,[1] with an icosahedral nucleocapsid core containing a **partially double-stranded circular** DNA genome.

The envelope contains a protein called the **surface antigen** (HBsAg), which is important for laboratory diagnosis and immunization.[2]

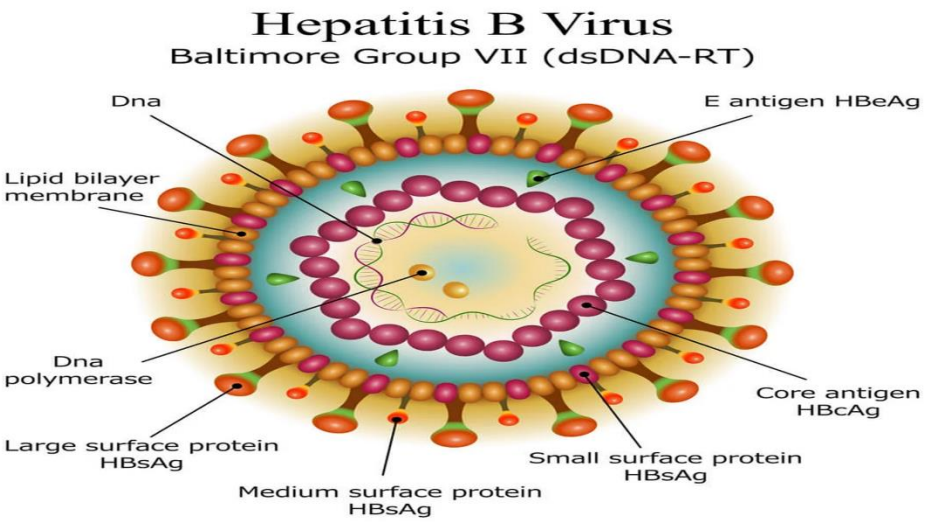
Within the core is a **DNA-dependent DNA polymerase.** The genome contains four genes (four open reading frames) that encode five proteins, namely, the S gene encodes the surface antigen, the C gene encodes the core antigen and the e antigen, the P gene encodes the polymerase, and the X gene encodes the X protein. The X protein is an activator of viral RNA transcription. The DNA polymerase has both RNA-dependent (reverse transcriptase) and DNA-dependent activity.

Electron microscopy of a patient's serum reveals three different types of particles: a few 42-nm virions and many 22-nm **spheres** and long **filaments** 22-nm wide, which are composed of surface antigen. HBV is the only human virus that produces these spheres and filaments in such large numbers in the patient's blood. The ratio of filaments and small spheres to virions is 1000:1.

In addition to HBsAg, there are two other important antigens: the **core antigen** (HBcAg) and the **e antigen** (HBeAg). The core antigen, as the name implies, forms the nucleocapsid core of the virion, whereas the e antigen is secreted from infected cells into the blood. The e antigen is an important indicator of **transmissibility.**

The specificity of HBV for liver cells is based on two properties: virus-specific receptors located on the hepatocyte cell membrane (facilitate entry) and transcription factors found only in the hepatocyte that enhances viral mRNA synthesis (act post entry).

Humans are the only natural hosts of HBV. There is no animal reservoir.



Summary of Replicative Cycle; After entry of the virion into the cell and its uncoating, the virion DNA polymerase synthesizes the missing portion of DNA and a double-stranded closed-circular DNA is formed in the nucleus. This DNA serves as a template for mRNA synthesis by cellular RNA polymerase. After the individual mRNAs are made, a full-length positive-strand transcript is made, which is the template for the minus strand of the progeny DNA. The minus strand then serves as the template for the plus strand of the genome DNA. This **RNA-dependent DNA synthesis** takes place within the newly assembled virion core in the cytoplasm. The RNA-dependent DNA synthesis that produces the genome and the DNA-dependent DNA synthesis that fills in the missing portion of DNA soon after infection of the next cell are carried out by the same enzyme, i.e., the HBV genome encodes only one polymerase.

Hepadnaviruses are the *only* viruses that produce genome DNA by reverse transcription with mRNA as the template. (Note that this type of RNA-dependent DNA synthesis is similar to but different from the process in retroviruses, in which the genome RNA is transcribed into a DNA intermediate.) Some of the progeny DNA integrates into the host cell genome, and this seems likely to be the DNA that maintains the carrier state. Progeny HBV with its HBsAg-containing envelope is released from the cell by budding through the cell membrane.

Transmission & Epidemiology; The three main modes of transmission are via blood, during sexual intercourse, and perinatally from mother to newborn. The observation that needle-stick injuries can transmit the virus indicates that only very small amounts of blood are necessary. HBV infection is especially prevalent in addicts who use intravenous drugs. Screening of blood for the presence of HBsAg has greatly decreased the number of transfusion-associated cases of hepatitis B.[3]

However, because blood transfusion is a modern procedure, there must be another, natural route of transmission. It is likely that **sexual** transmission and transmission from **mother to child** during birth or breast feeding are the natural routes. Note that enveloped viruses, such as HBV, are more sensitive to the environment than nonenveloped viruses and hence are more efficiently transmitted by intimate contact,

e.g., sexual contact. Nonenveloped viruses, such as HAV, are quite stable and are transmitted well via the environment, e.g., fecal–oral transmission.

Hepatitis B is found worldwide but is particularly prevalent in Asia. Globally, more than 300 million people are chronically infected with HBV and about 75% of them are Asian. There is a high incidence of **hepatocellular carcinoma (hepatoma)** in many Asian countries—a finding that indicates that HBV may be a human tumor virus .Immunization against HBV has significantly reduced the incidence of hepatoma in children. It appears that the HBV vaccine is the **first vaccine to prevent a human cancer.**

Pathogenesis & Immunity; After entering the blood, the virus infects hepatocytes, and viral antigens are displayed on the surface of the cells. Cytotoxic T cells mediate an immune attack against the viral antigens, and inflammation and necrosis occur. **Immune attack** against viral antigens on infected hepatocytes is mediated by cytotoxic T cells. The pathogenesis of hepatitis B is probably the result of this cell-mediated immune injury, because HBV itself does not cause a cytopathic effect. Antigen–antibody complexes cause some of the early symptoms, e.g., arthralgias, arthritis, and urticaria, and some of the complications in chronic hepatitis, e.g., glomerulonephritis, cryoglobulinemia, and vasculitis.

About 5% of patients with HBV infection become chronic carriers; in contrast, there is no prolonged carrier state in patients with HAV infection. A chronic carrier is someone who has **HBsAg persisting in their blood for at least 6 months.** The chronic carrier state is attributed to a persistent infection of the hepatocytes, which results in the prolonged presence of HBV and HBsAg in the blood. The main determinant of whether a person clears the infection or becomes a chronic carrier is the adequacy of the cytotoxic T-cell response. HBV DNA exists primarily as an episome in the cytoplasm of persistently infected cells; a small number of copies of HBV DNA are integrated into cell DNA.

A high rate of **hepatocellular carcinoma occurs in chronic carriers.** The HBV genome has no oncogene, and hepatocellular carcinoma appears to be the result of persistent cellular regeneration that attempts to replace the dead hepatocytes. Alternatively, malignant transformation could be the result of insertional mutagenesis, which could occur when the HBV genome integrates into the hepatocyte DNA. Integration of the HBV DNA could activate a cellular oncogene, leading to a loss of growth control.

Chronic carriage is more likely to occur when infection occurs in a newborn than in an adult, probably because a newborn's immune system is less competent than that of an adult's. Approximately 90% of infected neonates become chronic carriers. Chronic carriage resulting from neonatal infection is associated with a high risk of hepatocellular carcinoma.

Lifelong immunity occurs after the natural infection and is mediated by humoral antibody against HBsAg. Antibody against HBsAg (HBsAb) is protective because it binds to surface antigen on the virion and prevents it from interacting with receptors on the hepatocyte. (HBsAb is said to neutralize the infectivity of HBV.) Note that

antibody against the core antigen (HBcAb) is *not* protective because the core antigen is inside the virion and the antibody cannot interact with it.

Clinical Findings

Many HBV infections are asymptomatic and are detected only by the presence of antibody to HBsAg. The mean incubation period for hepatitis B is 10 to 12 weeks, which is much longer than that of hepatitis A (3–4 weeks). The clinical appearance of acute hepatitis B is similar to that of hepatitis A. However, with hepatitis B, symptoms tend to be more severe, and life-threatening hepatitis can occur. Most chronic carriers are asymptomatic, but some have chronic active hepatitis, which can lead to cirrhosis and death.

Patients coinfected with both HBV and HIV may have increased hepatic damage if human immunodeficiency virus (HIV) is treated prior to treating HBV. This occurs because the "immune reconstitution" that results when HIV is treated successfully leads to increased damage to the hepatocytes by the restored, competent cytotoxic T cells. For this reason, it is suggested that HBV be treated prior to treating HIV.

Laboratory Diagnosis; The most important laboratory test for the detection of early HBV infection is the immunoassay for **HBsAg.** HBsAg appears during the incubation period and is detectable in most patients during the prodrome and acute disease .It falls to undetectable levels during convalescence in most cases; its **prolonged presence** (at least 6 months) indicates the carrier state and the risk of chronic hepatitis and hepatic carcinoma. As described in Table –4, HBsAb is not detectable in the chronic carrier state. Note that HBsAb is, in fact, being made but is not detectable in the laboratory tests because it is bound to the large amount of HBsAg present in the blood. HBsAb is also being made during the acute disease but is similarly undetectable because it is bound in antigen–antibody complexes.

Table–4 Serologic Test Results in Four Stages of HBV Infection

Test	**Acute Disease**	**Window Phase**	**Complete Recovery**	**Chronic Carrier State**
HBsAg	Positive	Negative	Negative	Positive
HBsAb	Negative	Negative	Positive	Negative[1]
HBcAb	Positive[2]	Positive	Positive	Positive

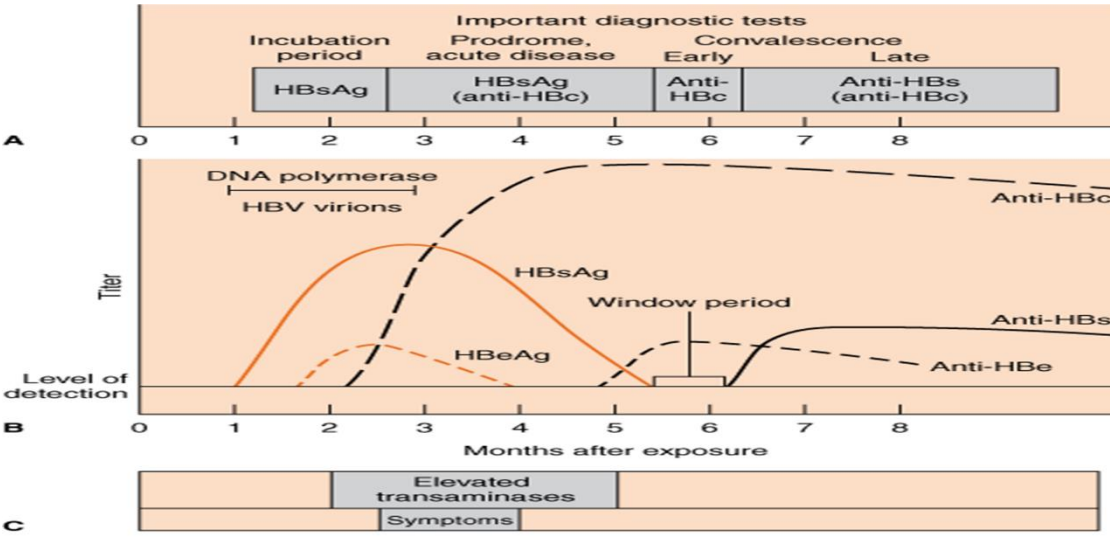
[1]Chronic carriers have negative antibody tests, but HBsAb is being made by these individuals. It is undetected in the tests because it is bound to the large amount of HBsAg present in the plasma. They are not tolerant to HbsAg.

[2]IgM is found in the acute stage; IgG is found in subsequent stages.

Note: People immunized with HBV vaccine have HBsAb but not HBcAb because the immunogen in the vaccine is purified HBsAg.

Note that there is a period of several weeks when HBsAg has disappeared but HBsAb is not yet detectable. This is the **window phase.** At this time, the HBcAb is always positive and can be used to make the diagnosis. HBcAb is present in those with acute infection and chronic infection, as well as in those who have recovered from acute infection. Therefore, it cannot be used to distinguish between acute and chronic infection. The IgM form of HBcAb is present during acute infection and disappears approximately 6 months after infection. The test for HBcAg is not readily available. Table –4 describes the serologic test results that characterize the four important stages of HBV infection.

HBeAg arises during the incubation period and is present during the prodrome and early acute disease and in certain chronic carriers. Its presence indicates a **high likelihood of transmissibility,** and, conversely, the finding of HBeAb indicates a lower likelihood, but transmission can still occur. DNA polymerase activity is detectable during the incubation period and early in the disease, but the assay is not available in most clinical laboratories. The detection of viral DNA in the serum is strong evidence that infectious virions are present.



Source: Levinson W: *Review of Medical Microbiology and Immunology, 11th Edition*: http://www.accessmedicine.com

Treatment & Prevention; Alpha interferon in the form of long-acting pegylated interferon (Pegasys) is clinically useful for the treatment of chronic hepatitis B infections. Some nucleoside analogues, such as lamivudine (Epivir-HBV), that inhibit the reverse transcriptase of HIV also are effective against the DNA polymerase of HBV. Adefovir (Hepsera) is a nucleotide analogue of adenosine monophosphate that also inhibits the DNA polymerase of HBV. Two drugs, entecavir (Baraclude), a deoxyguanosine analogue, and telbivudine (Tyzeka), a thymidine analogue, inhibit the DNA polymerase of HBV. They are useful in the treatment of HBV infection but are not used in the treatment of HIV. These drugs reduce hepatic inflammation and lower the levels of HBV in patients with chronic active hepatitis. Neither interferon nor the nucleoside analogues cure the HBV infection. In most patients when the drug is stopped, HBV replication resumes.

Prevention involves the use of either the **vaccine** or **hyperimmune globulin** or both.

1. The vaccine, e.g., Recombivax, contains HBsAg produced in yeasts by recombinant DNA techniques. The vaccine is highly effective in preventing hepatitis B and has few side effects. It is indicated for people who are frequently exposed to blood or blood products, such as certain health care personnel (e.g., medical students, surgeons, and dentists), patients receiving multiple transfusions or dialysis, patients with frequent sexually transmitted disease, and abusers of illicit intravenous drugs. Travelers who plan a long stay in areas of endemic infection, such as many countries in Asia and Africa, should receive the vaccine. The U.S. Public Health Service recommends that all newborns and adolescents receive the vaccine.

   At present, booster doses after the initial three-dose regimen are not recommended. However, if antibody titers have declined in immunized patients who are at high risk, such as dialysis patients, then a booster dose should be considered.

   Widespread immunization with the HBV vaccine has significantly reduced the incidence of hepatocellular carcinoma in children. A vaccine called Twinrix that contains both HBsAg and inactivated HAV provides protection against both hepatitis B and hepatitis A.

2. Hepatitis B immune globulin (HBIG) contains a high titer of HBsAb because it is prepared from sera of patients who have recovered from hepatitis B. It is used to provide immediate, passive protection to individuals known to be exposed to HBsAg-positive blood, e.g., after an accidental needle-stick injury.

However, the recommendation regarding one common concern of medical students, the needle-stick injury from a patient with HBsAg-positive blood, is that both the vaccine and HBIG be given (at separate sites). This is true even if the patient's blood is HBeAb positive. Both the vaccine and HBIG should also be given to a newborn whose mother is HBsAg-positive. These are good examples of **passive–active** immunization, in which both immediate and long-term protection are provided.

All blood for transfusion should be screened for HBsAg. No one with a history of hepatitis (of any type) should donate blood, because non-A, non-B viruses may be present.