The five hepatitis viruses (HAV–HEV) belong to five different virus families and are genomically distinct with different replication strategies. They also have different clinical features and outcomes.

Hepatitis A virus (HAV) and hepatitis E virus (HEV) infections are transient and are transmitted by the oro–faecal route. Hepatitis B virus (HBV) and hepatitis C virus (HCV) and hepatitis delta virus (HDV) can be transient or chronic, and are transmitted by the parenteral route. There are also differences in the mechanisms of infection; for example they use different receptors to gain entry into the hepatocytes, use different mechanisms to establish chronic infection, and their mechanisms of pathogenicity differ.

In the acute phase there is typically a 2–6 weeks period when many hepatocytes are infected and shed virus in the blood stream or bile canaliculi depending on whether the virus is released from the basal (HBV, HCV, HDV) or apical (HAV, HEV) surface of the hepatocyte. During this period a major immune response is not apparent. Ultimately as the immune system respond virus production slows, and elimination of the virus by a combination of cell killing and cell recovery begins. Liver disease may result from the direct effects of viral proteins on the cells but is mostly due to cell killing by the immune response of the host. When the immune system fails to clear the virus it results in chronic liver disease. Liver disease resulting from chronic infection also reflects different effects of viral proteins on the infected hepatocytes.

Hepatitis A Virus

HAV (Fig. 1) is an enteric picornavirus [1–3] readily transmitted in settings of overcrowding and poor sanitation. The primary source of infection is faecal matter that can contain large quantities (up to $10^9$ virus/g) during the incubation phase. In developing countries where HAV is endemic infection generally occurs in childhood without serious consequences. Rarely a severe and fulminant, often fatal, hepatitis
develops. In up to 20% of patients a relapse may follow the apparent recovery from the symptomatic phase of infection.

HAV has a high degree of stability upon exposure to low pH and heat [4]. The primary target of HAV is hepatocytes. A ubiquitously expressed membrane protein is the cell surface receptor of HAV. Following entry into the host cell and uncoating of the viral RNA translation of the viral protein occurs. Once sufficient quantities of viral genomic RNA and structural proteins have been made virion assembly occurs. Liver disease is a consequence of host immune response during the recovery phase when virus production is largely shut down. Thus clinical jaundice and raised levels of alanine aminotransferase follow the end stage of viral production.

**Hepatitis B virus**

Transmission of HBV (Fig. 2) is primarily from blood or blood-derived products and perinatally. HBV is the most prevalent of the three viruses known to ensure chronic hepatitis (HCV and HDV) being the other two.

HBV has a double shell. The outer shell is the viral envelope consisting of HBsAg. The inner shell consists of hepatitis B core antigen (HBcAg) enclosing the viral genome. HBV is abundant in the blood during infection and in some stages of chronic infection with titres of up to $10^{10}$/ml. The most abundant viral particles are not the virion but non-infectious particles made up entirely of HBsAg. These are generally in at least 100-fold excess over virions. They are found as spherical and filamentous structures. They do not contain any DNA and are not infectious (Fig. 3).

Upon infection the viral core particle is transported to the nucleus and viral DNA is released. The transcription of the HBV mRNA is regulated by liver specific transcription factors that explain why HBV replicates mainly in the liver. Hepatocyte

![Fig. 2. Prevalence of Hepatitis B.](image)

![Fig. 3. Spherical and filamentous structures.](image)
destruction is the result of the anti viral response of the host. During transcription the e-antigen is released from infected cells. Presence of e-antigen in the serum is thus a marker of virus replication, and the appearance of antibodies to e-antigen is an indicator that virus replication is ceased or slowed down. The e-antigen has a role in perinatal transmission by suppression of cellular immune response to the nucleodapsid subunit of the virus [5].

After infection HBV remains quiescent for some weeks with low levels of HBV–DNA in the circulation \( (10^2–10^4 \text{ genome equivalents/ml}) \) before starting a rapid replication leading to plasma levels of \( 10^9–10^{10} \) copies/ml and infection of most hepatocytes. In self limited infection HBV–DNA falls by >90% within 2–3 weeks after peak of viral replication and before antigen-specific CD8 response and liver damage as indicated by rise in alanine aminotransferase levels. CD4 and CD8-mediated response specific to HBV becomes detectable soon after the increase in HBV replication.

An important feature of HBV replication is the ability to maintain a chronic productive infection of the hepatocytes without killing the host cells. Infections usually clear after 3–6 months generally with a neutralizing antibody response that protects against re-infection. [6]. Progression to chronic infection, as defined by the presence of HBsAg in the serum for more than a year, is related to host’s inadequate immune response during the first weeks following exposure to the virus. Of those infected before 1 year of age 90% become chronic carriers compared to 5% in adults (Fig. 4). Chronic infection may involve two stages—an early one in which the virus is produced at high titre by the hepatocytes with levels of up to \( 10^{10} \) ml of serum, and a late stage in which most hepatocytes have lost viral DNA and technically no longer infected although HBsAg production may continue. A significant proportion of subjects fail to complete e-antigen seroconversion and go through repeated cycles of ineffective clearance. The repeated cycles of inflammation, hepatocyte death and fibrosis predisposes them to cirrhosis or hepatocellular cancer. Genotype C HBV is associated with delayed HBeAg seroconversion, increased viral load and increased risk of fibrosis and hepatocellular cancer.

**Hepatitis C virus**

Most HCV infections are chronic. HCV belongs to hepacivirus genus of Flaviviridae which includes yellow fever, dengue, West Nile and Japanese encephalitis viruses. They possess much similarity in their genomic structure and replication strategy.

HCV has 6 major genotypes with HCV1b being most prevalent, and at least 20 subtypes [7, 8]. HCV infections are restricted to humans and chimpanzees targeting primarily hepatocytes. About 50% of patients infected with HCV1b fail treatment with IFN-\( \alpha \) whereas about 90% of those infected with genotype 2 or 3 can be cured (Fig. 5).

Diagnosis of HCV is based on detection of IgG antibodies by ELISA. The antibodies are detected 2–4 months post exposure at the same time as levels of alanine aminotransferase rise. Determination of viral genotype is helpful in deciding the outcome of treatment, and quantification of viral RNA in the serum by PCR helps in assessing the efficacy of treatment. [9].

**Hepatitis Delta Virus**

HDV does not encode its own envelope protein and depends on HBV for its transmission. It has an outer coating of HBsAg underneath which is HDVAg protein and RNA. Based on the genetic sequence HDV has been classified into three genotypes [10–12]. Genotype I is global, and has been associated with hepatitis of varying severity. Genotype II is found mainly in Asia (Taiwan and Japan) and causes relatively mild hepatitis. Genotype III is mainly in South America and is associated with fulminant hepatitis. In recent years more genetically distinct HDV strains have been isolated from Africa.

HDV uses the same receptor as HBV to infect liver cells. Once inside the cell HDV can replicate in the absence of HBV. Also unlike HBV it can replicate in
cell cultures of non-hepatic origin indicating that HDV RNA does not require liver-specific factors for replication. HDV utilizes HBsAg as its envelope protein and so HDV virion assembly cannot occur in the absence of HBV coinfection. HBV vaccination is the most effective way of controlling HDV so that since the advent of the vaccine HDV prevalence has dropped.

Acute HDV hepatitis should be suspected in every case of fulminant hepatitis, and when HBV carriers develop recurrence of acute hepatitis. Treatment with interferon-α is the treatment of choice but requires higher doses than used in HBV infection and does not prevent relapse.

HEV infects other primates, pigs and rats who may serve as reservoirs of human infections [13–14].

HEPATITIS E virus

HEV has been responsible for major outbreaks of acute hepatitis in developing countries. A unique characteristic of HEV infection is high mortality in among pregnant women in third trimester.