



## Hepatitis B Virus

Hepatitis B infection is caused by the hepatitis B virus (HBV), a small enveloped DNA virus belonging to the *Hepadnaviridae* family. Hepatitis B virus infection is a major global public health concern. Worldwide it is estimated that there are 240 million chronically infected people of which 20%- 30% will progress to develop major complications such as cirrhosis and hepatocellular carcinoma (HCC).

Chronic HBV infection is a dynamic process due to the interactions of the host immune response and the replication status of the Hepatitis B virus. As such, there are defined phases of HBV infection that reflect the different stages of disease progression. The phases are not necessarily sequential and patients can cycle between them for many years before reaching a stable status. It is worth noting that **not all patients with chronic infection have chronic hepatitis.**

Due to the nature of HBV infection a complete sterilising cure is unlikely to be attainable and thus the main end goal of treatment is a functional cure; this is defined as the induction of long term suppression of HBV replication and loss of serum HBsAg.

### Phases of HBV infection:

**Phase 1: HBeAg- positive chronic HBV infection** (previously termed “immune-tolerant phase”. This is characterised by the presence of HBeAg and high levels of HBV DNA; there is little or no immune recognition of HBV so inflammatory activity is low and ALT levels are persistently within normal range. During this phase the rate of spontaneous HBeAg loss is very low. This phase is more frequent and more prolonged in those infected perinatally or in the first years of life. These carriers are highly infectious.

**Phase 2: HBeAg- positive chronic hepatitis** (previously termed “immune-reactive phase”. This phase is characterised by the presence of HBeAg in the serum, high levels of HBV DNA and raised ALT levels. During this phase the immune system recognizes the virus and tries to eradicate it. There is moderate or severe liver necroinflammation and more rapid progression to fibrosis compared to the previous phase. Most patients can achieve seroconversion and enter the HBeAg- negative infection phase. This phase may last for several weeks to several years. Patients in this phase are infectious.

**Phase 3: HBeAg- negative chronic HBV infection** (previously termed “inactive-phase”). This is characterised by the presence of anti-HBe in the serum and undetectable or low HBV

DNA levels (<2000 IU/ mL). ALT levels are normal and inflammatory activity in the liver decreases. This state suggests a favourable long-term outcome with a very low risk of cirrhosis or HCC in the majority of patients. HBsAg loss and seroconversion to HBsAb may occur spontaneously in ~1-3% of cases per year, usually following several years of undetectable HBV DNA. Patients remain infectious but at a lower level.

**Phase 4: HBeAg negative chronic HBV.** This is characterised by periodic reactivation with fluctuating levels of HBV DNA and aminotransferases and active hepatitis. There is usually a lack of serum HBeAg and detectable levels of anti-HBe. Most of these patients harbour HBV variants with nucleotide substitutions in the precore and/or basal core promoter regions and are either unable to express HBeAg or express low levels. Patients in this phase are infectious.

**Phase 5: HBsAg negative phase** (also known as “occult HBV infection”). This phase is characterised by negative serum HBsAg and positive serum anti-HBc with or without anti-HBs. In this phase HBV DNA is generally undetectable in serum and ALT levels are normal. HBsAg loss is associated with a reduced risk of cirrhosis, decompensation and HCC. The clinical relevance of Occult HBV where HBV DNA continues to be detectable in the liver in such patients is unclear. Immunosuppression may lead to reactivation in these patients. Patients are considered non-infectious.

## The Interpretation of Diagnostic Blood Tests for Hepatitis B Virus (HBV)

### HBsAg - Hepatitis B surface antigen

- Presence indicates infection with HBV
- Is **DETECTED** in both acute cases and in HBV carriers
- Persistence for six months defines carrier status
- Levels may reflect the amount of virus in the liver and may provide useful information during treatment monitoring
- A decline in levels may predict eventual clearance of HBsAg

### HBeAg - Hepatitis B e antigen

- Can be **DETECTED** in the early phase of HBV infection (usually short lived, 3-6 weeks)
- Becomes **UNDETECTABLE** in acute HBV as the virus clears and HBeAb is **DETECTED**
- Can persist in carriers and is usually associated with **DETECTABLE** HBV DNA
- During the immune-active phase in HBV carriers a seroconversion occurs when HBeAg becomes **NOT DETECTED** as HBeAb becomes **DETECTED**
- It is possible for HBeAg and HBeAb to be both **DETECTED** at the same time or both **NOT DETECTED** but this is uncommon
- **NB:** Presence of HBeAg is not required for infectivity or replication. It is not part of the structure of the virus. Some patients with active viral replication do not produce HBeAg due to the presence of HBV variants

### HBeAb - Hepatitis B e antibody - anti-HBe

- Appearance in acute cases likely to be indicative of spontaneous resolution

- Carriers who are HBeAg **NOT DETECTED**, HBeAb **DETECTED** and HBV DNA **NOT DETECTED** are considered to be in the inactive phase. Liver function tests are usually normal in these cases and they are of low infectivity
- Carriers who are HBeAg **NOT DETECTED**, HBeAb **DETECTED** and HBV DNA **DETECTED** usually have abnormal liver function tests and are an infection risk

### HBV DNA - Hepatitis B virus DNA

- Presence indicates infectivity and active viral replication
- HBV DNA levels in the blood are essential for the diagnosis, decision to treat and monitoring of patients
- $<10^3$  IU/ml is likely to be associated with disease resolution
- High levels may be present in carriers with no evidence of liver damage
- May be **NOT DETECTED** in blood but **DETECTABLE** in the liver
- Presence in the liver of individuals with **UNDETECTABLE** HBsAg in blood defines Occult HBV

### HBV genotype and subtypes

- Eight genotypes defined, designated A,B,C,D,E and F with a number of subtypes
- Associated with distinct geographical areas
- Different genotypes may respond differently to anti-viral treatment
- May influence the severity of liver disease, disease progression and clinical outcome

### HBsAb - Hepatitis B surface antibody - anti-HBs

- Is usually, but not always, **DETECTED** after the disappearance of HBsAg in acute infection
- Is sometimes **DETECTED** in HBV carriers
- Is the **ONLY** antibody produced by successful vaccination

### HBcAb - Hepatitis B core antibody - anti-HBc

- **DETECTED** in anyone who has been previously exposed or is currently, infected with HBV
- In acute infection appears after the appearance of HBsAg and usually before a rise in liver enzymes
- Its persistence in all those who have been exposed to HBV makes it a useful epidemiological marker
- Is **NOT DETECTED** in those who have been vaccinated against HBV and have never been infected with the virus

### HBcAb IgM - IgM anti-HBc

- Routinely used to confirm the diagnosis of acute HBV infection
- May be the only marker present in cases of acute liver failure where HBsAg has already become **NOT DETECTABLE** and anti-HBc is not yet **DETECTED** but this is uncommon
- Levels may be elevated in HBV carriers with an active immune response to the virus such as those undergoing seroconversion

**Note:**

- Transfused blood or transplanted organs of people who are HBsAg NOT DETECTED, HBcAb DETECTED may transmit HBV to the recipients
- People who are HBsAg NOT DETECTED, HBcAb DETECTED may reactivate and become HBsAg DETECTED again if they become immune compromised
- HBcAg - Hepatitis B core antigen cannot be DETECTED in the blood but can be DETECTED in the liver

**Reference**

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection, European Association for the Study of the Liver, Journal of Hepatology 2017 vol. 67 j 370–398