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Hepatitis B and C Viruses

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Abstract

Hepatitis B and C viruses (HBV/HCV) are among the leading causes of liver disease. HBV is a partially double-stranded circular DNA virus whose genome is approximately 3200 bases with four overlapping open reading frames (ORFs) and belongs to *Hepadnaviridae* family. HBV prevalence varies worldwide, with high rates reported in low-income countries. Approximately 90% of HBV infections are acute, 10% progress to chronic infection among adult patients. Although HBV can be prevented by immunisation, there is no licenced HCV vaccine. HCV is a positive-sense single-stranded RNA (+ssRNA) virus belonging to *Flaviviridae* family. The HCV global epidemiology varies, with high prevalence rates reported in low-income countries. Approximately 80% of acutely HCV-infected individuals develop chronic hepatitis disease, while 20% resolve spontaneously. Both HBV and HCV infections can result in both acute and chronic hepatitis, ranging in severity from asymptomatic to a life-threatening disease. The HBV and HCV are transmitted through contact with contaminated blood or its products. As compared with mono-infection, HBV/HCV co-infection has higher risk of liver damage. Thus, individuals who have active HBV and HCV infections are likely to be HCV-dominant with a high HCV viral load and low or undetectable HBV DNA levels.

Keywords: viral hepatitis, hepatitis B virus, hepatitis C virus, epidemiology, pathogenesis, natural history, diagnosis, genotype, treatment, natural history

1. Hepatitis B virus

Hepatitis B virus (HBV) belongs to *Orthohepadnavirus* genus a member of the *Hepadnaviridae* family which includes other identified but less popular viruses such as *Pekin duck*, *woodchuck*, *Woolly monkey hepatitis B*, and *ground squirrel viruses*. There are some viral similarities in structure, size, nature, genetic replication, and ability to cause infection among these viruses, but HBV remains a major cause of chronic liver disease [1].

1.1 Properties

1.1.1 Structure

The HBV is a partially double stranded enveloped deoxyribonucleic acid (DNA) virus with an icosahedral symmetry that can be seen in three different forms and sizes [2]. The predominant form is a small, spherical particle (22 nm diameter), the other form has a diameter of 42 nm. Generally, the HBV virion is spherical, with a diameter of about 40–48 nm, and a length of about 3.2 kb [3]. Approximately 10^{14} HBV particles per millilitre can be present in the blood of an infected individual [4].

1.1.2 HBV genome organisation

The HBV genome is made up of a circular DNA which is partly single stranded and partly double stranded. The DNA is not fully double stranded; one strand is incomplete (short strand) whereas the other forms a full length strand (complete long strand). There are small molecules that are covalently linked to the 5' end of each HBV DNA strand. The short strand is capped with a ribonucleic acid (RNA), whereas the complete long strand is linked to a viral DNA polymerase [5]. The HBV DNA forms a circular conformation, and the full length strand together with the double stands form a short sequence of triple-stranded at the 5' ends. The HBV envelope comprises three proteins namely; small (S), medium (M), and large (L) that are expressed on the surface of the viral particle. The S protein is the most abundant of the three. The gene S encodes for the HBV surface antigen (HBsAg) [6].

1.1.3 Genetic variation

The HBV unique life cycle requires an error-prone reverse transcriptase for replication which results in genetic variation in the form of genotypes, sub-genotypes, and mutations. The relationship between HBV genetic variation and HBV-related pathogenesis has been described which determines the outcome of HBV exposure. The HBV genome has approximately 3200 bases with four overlapping open reading frames (ORFs) namely: pre-S/S (surface proteins), pre-C/C (pre-core/core), X (transcriptional co-activator) and P (DNA polymerase) [6, 7]. The pre-S/S ORF which encodes different structural envelope proteins (large, medium and small) is contained within the P ORF, the C ORF overlaps the P ORF by a quarter of its sequence length; whereas the X ORF overlap the P ORF by a third of its sequence length. From the above mentioned four ORFs, seven different proteins are translated [6].

1.1.4 Replication cycle

The HBV replication is initiated by the attachment of the viral particles to the target cells, in this instance, hepatocytes. A number of cellular receptors such as heparin sulfate proteoglycan (HSPG), and sodium taurocholate co-transporting polypeptide (NTCP) have been reported [8]. Following attachment to the hepatocytes, the viral particles fuse with the host cell's membrane and enter the cell through endocytosis. Following penetration into the cell, the virus uncoats releasing the genetic material (HBV DNA) into the cytoplasm, which is transferred into the nucleus through nuclear pores. In the nucleus, the genetic material is converted to a complete circular double stranded DNA (dsDNA) by the action of the host DNA polymerase. The dsDNA is then transformed into a covalently closed circular DNA (cccDNA) ring (an episomal viral genome) that serves as a template for transcription of five viral RNAs [6, 9, 10]. The dsDNA is very stable and can survive in the host nucleus for a long time. The cellular RNA polymerase transcribes the negative sense single stranded DNA (–ssDNA) to form a positive sense single stranded RNA (+ssRNA). The newly transcribed positive RNA strand leaves the nucleus and migrates to the cytoplasm for protein synthesis (translation). The reverse transcriptase enzyme converts the +ssRNA to form a –ssDNA (reverse transcription). The +ssRNA is flanked by a small fragment of DNA polymerase at the 5' end which primes the reverse transcription of $\frac{3}{4}$ of the +ssRNA but unable to complete the transcription of the remaining third. This results in the formation of dsDNA viral particles containing one partially complete strand. The mature viral particles exit the cell through budding and invade other hepatocytes and repeat the replication cycle [11–13].

1.2 Epidemiology

The HBV prevalence varies worldwide, with high rates reported in low income countries. The World Health Organisation (WHO) estimates that 6.1% of the African population, and 6.2% of the Western Pacific region are infected with HBV [1]. The HBV endemicity is heterogeneous due to variable multiple factors such as child vaccination, injection drug use, poor sensitisation campaigns among others [14].

Approximately over 250 million people are infected with HBV globally [15]. The risks of infection vary widely due to different behaviours that determine the rate of exposure. Uninfected laboratory personnel and other health-care workers are at risk of HBV exposure from infected patients, but the degree of risk depends on several factors such as the strength of their immunity, and nature of work performed [16]. Likewise, patients are also at risk from hospital staff when there are conducting their duties such as surgery, haemodialysis, and dentistry procedures.

1.3 HBV genotypes and their geographical distribution

HBV genotype plays a significant role in the clinical outcome following viral-host interaction. There are 10 different genotypes of HBV (from A to J), that determine the liver disease clinical progression, prognosis, and the response to antiviral therapy. Genotypes A, B, C, D, and F are associated with rapid progression to cirrhosis and hepatocellular carcinoma. The HBV genotypes A and B are commonly isolated in acute HBV infected individuals [17].

The HBV genotypes geographical distribution varies from one genotype and subtype to the other. The variations in the HBV genotype distributions are related to mode and route of transmission, where vertical transmissions are associated with genotypes B and C [17]. The HBV genotype A is prevalent in Africa, and North Europe; genotypes B and C are widespread in Asia; genotype D is also common in Africa, some parts of Europe, and Asia; genotype E is predominantly in West and Central Africa; genotype F is common in America; genotype G is common in Western countries; genotype H is found in Central and South America; genotype I was reported in Vietnam and Laos; while genotype J was reported in Japan [7, 18].

1.4 Transmission

The HBV cases usually occur in parenteral drug injection use through sharing of infected needles and other paraphernalia. Other risk factors include: sexual contact, transfusion of blood and/or its products, occupational exposure (e.g. laboratory, and other health-care workers, surgery, dental surgery, obstetrics and gynaecology procedures), and use of unsterile procedure when in contact with blood or body fluids. The HBV transmission routes are similar to most blood-borne viruses such as *Human immunodeficiency virus* (HIV) [7]. Transmission from mother-to-child is possible; therefore, early intervention at birth is important to protect the HBV infection. Efforts are on-going to achieve a 90% reduction in new chronic HBV infections [19].

1.5 Natural history

The natural history of chronic HBV infection (CHBV) varies and is dependent of the viral virulence factors and the host's immune response. Following exposure to HBV, some individuals (0.5–1% per year) clear the HBsAg spontaneously but remain anti-HBV positive, with undetectable HBV DNA in serum, whereas the majority progress to CHBV infection. The development of CHBV infection is determined by a complex set of interactions between the host (e.g. age, sex,

immune status, and other underlying infections) and the virus (e.g. infective dose, co-infection with other viruses, and viral genotype) [20].

The CHBV infection is characterised by elevated serum alanine aminotransferase (ALT), serum HBV DNA, and/or hepatitis B e antigen (HBeAg), HBsAg which determines the phase of infection and predicts the risk of disease progression to hepatocellular carcinoma (HCC) [21]. Five CHBV phases (1, 2, 3, 4 and 5) have been described based on HBeAg, ALT, and HBV viral load [22]. Phases 1 and 2 would be HBeAg-positive, whereas phases 3 and 4 would be considered to be HBeAg-negative. The chronic HBV phase 1 is also known as immune tolerance phase (HBeAg-positive chronic HBV infection), phase 2 (immune clearance phase or HBeAg-positive chronic hepatitis B), phase 3 (inactive carrier phase or HBeAg-negative chronic HBV infection), phase 4 (reactivation phase or HBeAg-negative chronic hepatitis B), and phase 5 (occult HBV infection or HBsAg-negative phase). During the early stages of CHBV infection, the serum ALT levels are normal or slightly elevated whereas the HBV DNA, and hepatitis B e antigen (HBeAg) levels are elevated in serum. This first stage is followed by a second phase where the HBeAg, HBsAg, and ALTs are elevated. After varying intervals, the ALT levels return to normal, and the HBV DNA reach undetectable levels or suppressed to low levels, resulting in an inactive HBV carrier state. The fourth phase is characterised by fluctuation of HBV diagnostic markers that include HBV DNA, ALTs and HBV antibody concentrations [21, 22]. The fifth phase is characterised by the presence of anti-HBc antibodies, absence of HBsAg, detectable or undetectable anti-HBs antibodies. Of note, not all HBV patients fit into these phases of disease progression. Chronic HBV infection does not always represent development of chronic hepatitis B disease. Thus, not all patients with HBV infection have hepatitis disease [22].

1.6 Clinical features

The possible outcome following HBV exposure depend on series of complex mechanisms that could lead to spontaneous clearance with detectable HBV antibodies, or establishment of chronic HBV infection (described in four phases). The HBV incubation period varies greatly often about 2–6 months, but shorter incubation periods have been observed related to high infective doses. Symptoms of HBV infection may include fever, nausea, vomiting, abdominal pain, dark urine, anorexia, myalgia, and jaundice (is the hallmark of severe liver disease). In some cases, arthralgia may occur, hepatocellular damage may be detected [7, 21].

1.7 Pathogenesis

1.7.1 Acute infection

It is estimated that approximately 90% of HBV infections are acute, where about 10% progress to chronic HBV infection among adult patients, whereas 30–50% for infection among under-5 children. The HBV replicates in hepatocytes following successful entry into the cell by binding the host cellular receptors. In acute infection before seroconversion, the HBV viral load is high before the host immune response kicks in. The viral markers such HBeAg, and HBsAg are expressed on the host cellular cytoplasmic membrane that trigger an adaptive immune response (both B and T cells) [6, 23].

Within hours following HBV exposure, the host innate immune response by releasing the interferon- α which modulate the immune system, and has a direct antiviral effect [24]. This is followed by a transient release of interleukin (IL)-6 to control the viral spread and virus-induced cellular apoptosis. The production of interferons and

other cytokines enhances the expression of major histocompatibility complex class I (MHC-I) that recognises the viral antigens which leads to lysis of infected hepatocytes. The subsequent activation of natural killer (NK) and cytotoxic killer cells may reduce the HBV viral load through secretion of different cytokines, which may lead to hepatocellular damage. An anti-inflammatory cytokine IL-10 suppresses the activation of NK T cells. The liver damage is less severe in the HBV acute infection [25–27].

1.7.2 Chronic infection

HBV persistence and development of chronic HBV infection is a result of neonatal tolerance to HBV if acquired vertically. The HBV precore antigen, HBeAg which crosses the placenta is able to induce neonatal tolerance to HBV *ex vivo*. The HBV adult infections have a low rate (<5%) of developing chronic HBV infection as compared to neonates. However, the mechanism that contributes to inadequate immune response a key feature of onset of chronic HBV in adults is unclear.

Of note, nearly 15–40% of HBV infected individuals are at risk of developing cirrhosis during their life time, and nearly 5% risk of HCC with cirrhosis. During the immune clearance phase (phase 2), the viral load is reduced due to the action of the cytotoxic T cells that destroy the infected hepatocytes. Since the action of NK and cytotoxic T cells in chronic HBV infection is inefficient, the destruction of hepatocytes happens for years which increases the possibility of reinfection [11, 15, 25, 26, 28].

The production of different HBV specific antibodies such as those against HBeAg, HBcAg, and HBsAg prevent the spreading of viral particles between hepatocytes. Ineffective viral suppression could lead to cirrhosis which is a prime factor for carcinogenesis. The integration of viral and host genome, and the formation of cccDNA during viral replication are essential steps towards development of hepatic carcinogenesis. Both B and T cell responses to HBcAg could be suppressed by secretion of some HBV antigens such as HBeAg, which results in inhibition of HBcAg-specific T cells to eliminate HBV infected hepatocytes. Likewise, increased levels of HBsAg also suppress the immune elimination of infected cells [9–11].

Increased risks of cirrhosis and HCC are associated with male gender, race, HIV, hepatitis C virus (HCV) co-infection, persistence of increased HBV viral load (high HBV DNA levels), HBeAg negative status, elevated ALTs, and the general impairment of host immune responses.

The HBV clinical outcomes are classified into: immune-tolerant, immune clearance, inactive and recovery phase. Occult HBV infection is a phenomenon that occurs in patients who receive HBV vaccine and/or hepatitis B immunoglobulin injection who may develop chronic HBV infection with PreS and/or S gene mutations. In these four clinical stages of HBV infection, the HBV DNA levels are high in immune tolerance and immune clearance stages, and become undetectable in inactive phase. HBV isolated from chemotherapy of immunocompromised patients show mutations in the PreS, S, basal core promoter (BCP) or Pre-C regions (**Figure 1**) (Adapted from [6]).

1.8 Laboratory diagnosis

1.8.1 Acute HBV infection

Nearly 90% of acute HBV infections in adults are self-limiting, with only a small proportion (<1%) progress to severe acute infection. Acute HBV infection presents with non-specific signs and symptoms. The HBV incubation period may be 6 weeks or more following exposure. Some of the signs and symptoms of acute HBV infection may include: malaise, fever, nausea, dark urine and anorexia. The majority of acute HBV infected individual are usually asymptomatic with elevated levels

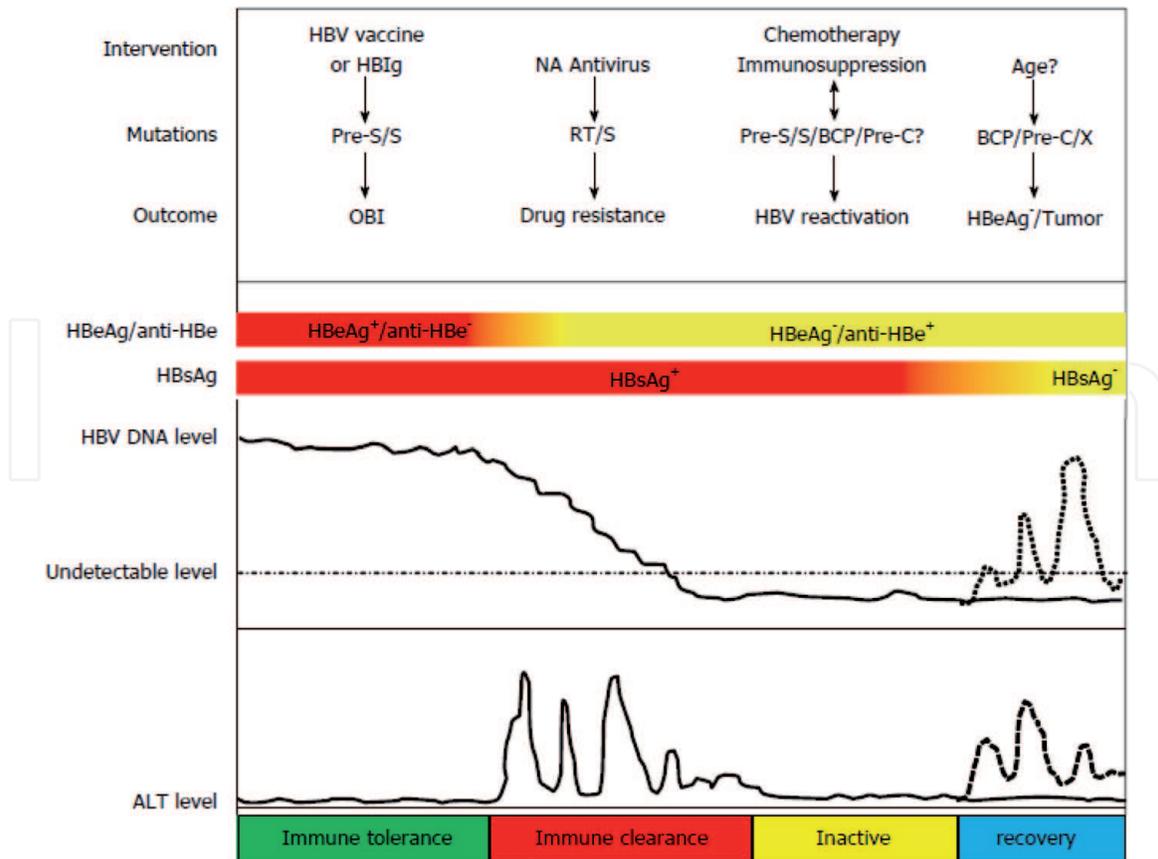


Figure 1.
HBV pathogenesis and clinical outcomes.

of ALT, total bilirubin, and total protein. The HBsAg positive test suggest an HBV infection, however it is advisable to repeat the test after 6 months to determine HBV spontaneous resolution or establishment of chronic infection [29].

1.8.2 Chronic HBV infection

The majority of acute HBV infected individuals clear the infection spontaneously, whereas 5–10% progress to develop chronic HBV infection. The majority of chronic HBV infected individuals are at risk of developing chronic active disease (HBV hepatitis) which may progress to cirrhosis and hepatocellular carcinoma. The development of chronic HBV infection does not follow clinical phases (1–5) in sequential order as described above. The HBV diagnostic markers vary from one clinical phase to another.

1.8.2.1 Immune-tolerance phase

During the immune-tolerance phase of chronic HBV infection, the virus is actively replicating, but there is a reduced inflammation response. The individuals who get HBV infection at birth stay in this phase for decades before progressing to the next phases of liver disease. The laboratory diagnosis markers that characterise the immune-tolerance phase include: increased HBV viral load (>million copies IU/ml), normal ALT, HBsAg positive test [22, 30].

1.8.2.2 Immune clearance phase

During the immune-active phase, the virus continues to replicate and cause noticeable liver damage. The host immune response activates the signalling cascade

that leads to inflammatory response, leading to liver fibrosis. The individuals who were HBV susceptible during childhood stay in this phase for decades but clinical feature manifest in mid-thirties. During this stage, the laboratory diagnostic features fluctuate from HBeAg positive to negative, with detectable anti-HBe antibodies. Classic HBV immune-active phase is characterised by the HBeAg seroconversion and detection of different anti-HBV immunoglobulins. The HBeAg seroconversion is associated with reduced disease progression rate to development of cirrhosis and end stage liver disease. The laboratory detection markers include: increased ALT levels, four-fold increase in HBV viral load, positive HBeAg, and liver fibrosis [22].

1.8.2.3 Inactive carrier phase

In this phase, the anti-HBe antibodies are detectable, whereas the ALT levels return to normal, and HBV viral load is suppressed and may be undetectable. The extent of liver damage depends on an inflammatory immune response, but liver fibrosis is noticeable if it was observed in the previous stage of liver disease. The majority (nearly 80%) of chronic HBV infected patients remain in this stage whereas nearly 20% may revert to the immune-tolerance phase. Some of the laboratory diagnostic markers of this stage include: Normal ALT, negative HBeAg, reduced or undetectable HBV viral load (<2000 copies IU/ml), and variable liver fibrosis [22].

1.8.2.4 Reactivation phase

This phase is also known as the immune reactivation phase where the chronic HBV is very active with detectable anti-HBe antibodies. Some of the diagnostic markers include: increased HBV viral load, elevated ALT, negative HBeAg, moderate-to-severe liver fibrosis, sometimes cirrhosis, and hepatocellular carcinoma. In this phase, people have seroconverted to anti-HBe positive, but their chronic HBV is very active. The ALT levels and HBV viral load are elevated. The liver inflammation and fibrosis levels are moderate to severe [22].

1.8.2.5 Occult HBV infection

This phase is also known as HBsAg-negative phase. During this phase the viral detection markers such as HBsAg, anti-HBs, and HBV DNA are usually negative. The anti-HBc antibodies are positive, and in rare cases, the anti-HBs could be positive. The serum ALT levels are usually normal, with detectable cccDNA copies [22].

1.9 Treatment, prevention, and control

The treatment and management efforts of HBV infection are aimed at reducing the incidence rates, prevent development of chronic HBV disease, progression to HCC, and obviously death from HBV-related liver disease. The decision to treat is based on clinical assessment of phases of HBV infection based primarily on the biochemical, virological, serological investigations, and the stage of liver disease [22].

Historically, the interferon-based therapy has been the principal treatment option for HBV infection. The current HBV treatment guidelines recommend treating patients with increased viral load, decompensated liver cirrhosis, and HCC. Treatment is less favourable in HBV infected individuals classified as belonging to first phase chronic HBV infection. The recommended standard treatment for HBV infection is the nucleoside analogues (NAs) and/or IFN-based therapy. The response to IFN-based therapy is robust which results in loss of HBeAg and HBsAg as opposed to NA monotherapy. However, IFN is less efficient at suppressing viral replication and

is reported to be associated with adverse effects compared to the NAs. The IFN- α has a direct antiviral effect through inhibition of viral assembly [8, 31].

The pegylated IFN- α administered parenterally, and the NAs (Entecavir and Tenofovir) are the first line antiviral drugs recommended for chronic HBV treatment. These drugs are hardly available in low income countries due to high costs. The most widely antiviral drug for HBV treatment is lamivudine which is a nucleoside analogue that inhibits the synthesis of HBV DNA *ex vivo*. The lamivudine course has resulted in a marked reduction in viral DNA, normal ALT levels, HBeAg-positive cases seroconverting to become anti-HBe positive. Other antiviral drugs that have been used to treat HBV infection include adefovir, emtricitabine, telbivudine, and clevudine. For end stage liver disease such as HCC, liver transplantation is recommended. There is an urgent need to develop alternative HBV therapeutic agents that can successfully suppress HBV replication and decrease the risk of disease progression to fibrosis and HCC [8, 31].

Several approaches can be employed for the prevention and control of HCV infection. Screening of blood donations has significantly reduced the risks of HBV transmission through transfusion of blood and/or its products [32]. Modification of risk behaviours proves to be an effective measure to prevent HBV transmission. Some essential approaches include voiding contact with blood and body fluids, practicing safe sexual contact, avoiding drug use (either injecting or snorting), and use of sterile needles when body piercing and acupuncture. The implementation of health and safety policies that include wearing personal protective equipment when performing risky procedures in the hospital or during accidents and emergencies [22].

Herd immunity can be provided through incorporation of HBV vaccine in the child immunisation schedule. Other important approaches to prevent HBV infection include: antenatal screening for identification of carrier mothers, and universal infant and adolescent vaccination. If universal vaccination is not implemented yet, HBV vaccine should be given to other groups at special risk of HBV exposure.

1.10 Vaccination

Hepatitis B is a vaccine preventable disease. In 1965, Dr. Baruch Blumberg and his team discovered the HBV vaccine which prevents the establishment of HBV infection and liver cancer [33].

1.10.1 Active immunisation

The current HBV vaccine is given in three doses as follows: first dose given within 24 hours, second dose given 1 month later, and a third booster dose given at 6 months of age. The HBV vaccine elicits humoral immune response that is mediated by secreted anti-HBs antibodies. Such an antibody-mediated response is influenced by several factors including age, sex, immune status, and underlined pathological conditions. High seroconversion rates of >90% are seen in young female adults as opposed to their male counterparts or older men, whereas lower rates are observed in immunosuppressed individuals [34].

The HBV vaccine was made available since 1982. In 1991, the WHO recommended that each country adopt and implement universal HBV vaccination programme. HBV vaccine is included in the new-born immunisation schedule where first dose is given shortly after birth, second dose at 1–2 months of age, and third dose at 6–18 months of age. A child born to a HBV-positive mother should receive the HBV vaccine and HBIG combination as early as within 12 hours after birth to

protect baby from HBV infection. The vaccine may cause swelling, soreness and redness on the site of injection, and a mild fever [35, 36].

1.10.2 Passive immunisation

The plasma-derived hepatitis B vaccine was licenced for human use in 1981. Hepatitis B immunoglobulin (HBIG) is an anti-HBs prepared from plasma of donors with high titres of antibodies of the HBsAg. The administration of anti-HBV immunoglobulins induces an adaptive immune response. Since the HBIG contains anti-HBV immunoglobulins, it offers an immediate short-term protection in risk population who have not yet received HBV vaccine. The HBIG half-life is estimated at 3 weeks, but long-term protection can be achieved by a combination of HBIG and HBV vaccine at the time of HBIG initial administration. Therefore, an HBIG booster dose is not necessary when a HBV vaccine is administered concurrently with HBIG [37, 38]. The HBIG dose of 300–500 IU in 3 ml is administered either intramuscularly (IM) or intravenously as a post-exposure prophylaxis, given to babies born to infected mothers, or prevention of the establishment of chronic HBV infection in liver transplants. HBIG should be administered 24–48 hours after a potential exposure to HBV, and a second dose 4 weeks later. An absolute protection against HBV is unlikely to be achieved but a vaccine efficacy of 76% has been reported, and the protection could last for at least 22 years [38]. In babies, a 6 month course of HBIG is initiated that offers nearly 70% efficacy. High rates (nearly 90%) are achieved when combining HBIG and HBV vaccine.

The HBIG side effects include allergic reactions, back pain, muscle pain, nausea, and general body pain.

1.10.3 Who should get vaccinated?

HBV vaccination is aimed at preventing HBV transmission to uninfected individuals, and ultimately eradicating the virus from the population. A small subset of HBV exposed individuals exist who have persistent HBV infection, could have undetectable or carry low levels of the HBV DNA; and are termed ‘inactive HBV carriers.’ The HBV carrier state is a potential reservoir for HBV transmission through contact with the infected body fluids.

The HBV vaccination is recommended in the following [16]:

- Newly born babies who could become long-term HBV carriers if not protected immediately after birth
- Commercial sex workers
- Intravenous drug users
- Occupational exposures (health care workers, laboratory personnel, Medical personnel, dental therapists, first aid providers)
- Anyone who comes in contact with infected blood
- Victims of sexual assault

The passive and active HBV immunisation is 95% effective in preventing establishment of chronic infection, but HBV reinfection is possible following continuous exposure to the virus.

2. Hepatitis C virus

Hepatitis C virus (HCV) belongs to the Flaviviridae family and the genus *Hepacivirus* [39]; and has evolved over hundreds and thousands of years with human as the only host. When HCV was first identified in 1989 [40] as the aetiological agent of non-A/non-B hepatitis the extent of the global health problem from HCV related cirrhosis and hepatocellular carcinoma was underestimated. Today HCV remains a global public health problem with a prevalence at 2.8%, with relatively low prevalence in Europe (0.6–5.6%), with pockets of high prevalence in Africa (Egypt has the highest prevalence rate estimated at 14% based on anti-HCV antibody testing) [41].

2.1 Discovery

HCV was discovered in 1989 [40]. It was thought to be the primary cause of transfusion-associated non-A/non-B hepatitis (NANBH). Following intensive search through development of different immunological and serological assays, an experimental chimpanzee model was utilised to identify the presence of an NANBH transmissible agent. Immunoscreening of bacterial complementary deoxyribonucleic acid (cDNA) obtained from chimpanzee blood samples that were infected with NANBH enabled the isolation of a single cDNA clone, and the translation of viral proteins was possible. On 21st April 1989, Michael Houghton and his colleagues in collaboration with Daniel Bradley announced the discovery of NANBH aetiological agent and named it '*Hepatitis C virus*' [40].

2.2 Properties

2.2.1 Structure

HCV is a small, enveloped virus that contains two viral glycoproteins expressed on the surface of the virus particle namely, E1 and E2 [42, 43]. The HCV is a positive-sense single-stranded RNA (+ssRNA) virus that has approximately 10,000 bases in length. Visualised viral particles are estimated to be between 40 and 60 nm [44]. The HCV gene sequence contains a single long open reading frame (ORF) that produces large polyprotein precursor of more than 3000 amino acids. The HCV ORF is flanked by 5' and 3' non-translated regions (NTRs). During and after translation, the polyprotein precursor is cleaved by the proteases for synthesis of mature structural and non-structural (NS) proteins [45].

2.2.2 Lipoviral particle

The hepatic portal vein and hepatic arteries circulate blood through the liver. The HCV particles circulating in the blood stream are reported to bind directly to low density lipoprotein (LDL), very low density lipoprotein (VLDL), chylomicrons, different types of apolipoproteins (apo) [46, 47]. The lipoviral particles (LVPs) are highly infectious viral particles that form a complex with VLDL composed of triglyceride-rich, and cholesterol-rich lipoproteins that are believed to contain apoA1, apoB, apoC1, and apoE [48, 49]. During the LVPs formation they also form a complex with viral envelope glycoproteins E1 and E2; and nucleocapsids [50–52]. It is believed that the LVPs facilitate the viral attachment and entry into the target host cell [53].

Figure 2 shows an HCV viral particle in association with lipoproteins in a structure termed 'lipoviral particle.' The viral envelope glycoproteins E1, and E2

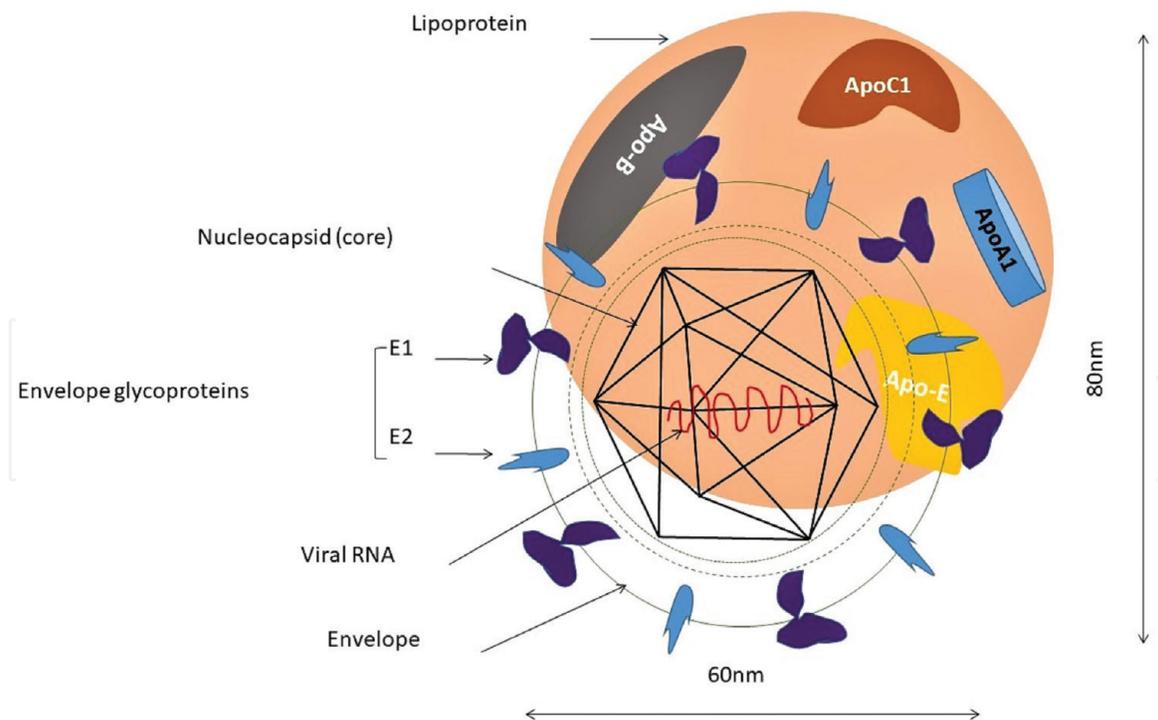


Figure 2.
Hepatitis C virus lipoviral structure.

help to attach the virus to the host cell receptors. The apolipoprotein components of the LVPs are also facilitate viral binding via cellular lipoprotein receptors. (Adapted from <https://pearl.plymouth.ac.uk/handle/10026.1/10386>).

2.2.3 Replication

The primary *in vivo* target of HCV replication are hepatocytes, however, lack of small animal model to propagate HCV hampers efforts to fully describe the HCV replication.

Following the formation of LVPs in vascular compartment, they travel to the liver for attachment to the hepatocytes utilising the viral envelope glycoproteins, and the lipoprotein plasma lipoproteins component of the LVPs. The HCV LVP levels determine viral persistence [54]. The viral particles utilise the virally encoded envelope glycoproteins E1 and E2, and different classes of apolipoproteins (apoA-1, apoB, apoC-1 and apoE) to bind to host cellular receptors, co-receptors, and entry factors to facilitate viral entry into the cell cytoplasm [53]. Some of the reported host cellular receptors and entry factors include: tetraspanin CD81, highly sulphated glycosaminoglycans (HS-GAGs) [55], low density lipoprotein receptor (LDLR), and Scavenger receptor class B type I (SR-BI) [56]. The viral entry involves clathrin-mediated endocytosis, and membrane fusion.

After entry, the viral RNA genome is translated for production of different viral proteins in endoplasmic reticulum (ER). Translation of the polyprotein from HCV RNA is an essential first step after releasing the viral genetic material into the host cytoplasm. Since the HCV RNA is a positive-sense single strand, it directly serves as a template for translation. The 5' NTR serves as the primary site where HCV RNA translation into polypeptides is initiated which results in expression of structural and NS viral proteins (NS1, 2, 3, 4 and 5) required for genome replication [52].

Several HCV NS proteins such as NS3/4A, NS4B, NS5A, and NS5B form part of a complex replication machinery which replicate a positive-sense RNA genome

through a negative-sense RNA intermediate which takes place in lipid droplets (LDs) [57]. The HCV replication process occurs in specialised membranous web on the endoplasmic reticulum membrane. Initiation of assembly of viral proteins requires release of viral genomes from the membranous web to the cytosolic site of the ER. Therefore, progeny viral assembly initiates in the cytosol followed by maturation and release of the viral particles on the luminal side of the ER membrane. During this process, the virions become lipidated through further interaction with the host lipid components, transported through the Golgi apparatus. After budding, the viral particles are transported to the extracellular environment through the lipid secretory channels [58].

2.3 HCV epidemiology, genotypes, and global distribution

HCV is one of the major causes of liver disease globally. Over the years HCV prevalence rates have increased to 2.8% worldwide, where an estimated 71 million people are reported to have chronic hepatitis C infection [59]. The World Health Organisation (WHO) estimates that nearly 399,000 people die annually due to HCV related liver disease. The HCV global distribution varies with high prevalence rates reported among people who inject drugs (PWIDs) [60]. Egypt has the highest burden of HCV infection due to use of non-sterile injecting needles during the mass treatment of schistosomiasis. In the 80s, the tartar emeric treatment was replaced by an oral drug, praziquantel for treatment of schistosomiasis [41].

Seven major HCV genotypes (1–7) were reported that comprise different subspecies [61]. Determination of HCV genotypes is essential and predicts the disease outcome, and treatment options. Globally, HCV genotype 1 is the most prevalence, followed by genotypes 3, 2, and 4. Genotypes 1, 2, and 3 have a worldwide distribution but predominantly highly prevalent in western countries [62, 63]. Genotype 4 is prevalent in Egypt and the middle-east, genotype 5 is prevalent in South Africa, and genotype is high in Hongkong. Genotype 6 is endemic in Southeast Asia [64, 65], whereas genotype 7 is was reported in central Africa [66].

The HCV nucleotide sequences show some genetic differences from one genotype to another. Genotypes show nearly 30% sequence diversity from each other [30, 67].

2.4 Transmission

HCV is primarily transmitted via parenteral exposure to the virus, though sometimes it can be transmitted sexually. Injection drug use (IDU) remains the highest risk factor for HCV infection in western countries. Some of the risk factors for HCV transmission include: blood transfusion before initiation of universal donor screening programme in 1991 [68], occupational exposure, tattooing, organ transplant from an infected donor, acupuncture, haemodialysis, and use of unsterilized razor blades and other paraphernalia for cultural rituals. Some studies have reported vertical transmission, as well as cell-to-cell transmission. The frequency of mother-to-child transmission is estimated at between 3 and 10% in some studies. The following factors have not been described to transmit HCV; hugging, kissing, hand shake, and/or sharing drinking bottles with an infected person [69].

2.5 HCV natural history

Exposure to HCV usually results in an asymptomatic acute HCV infection which is followed by three possible outcomes: clearance of the virus spontaneously

(15–25%), progression to chronic HCV infection (>80%), or remain uninfected without detectable HCV RNA and anti-HCV antibodies [70–72].

2.5.1 Acute HCV infection

Diagnosis of acute HCV infection is problematic because the majority of infected individuals are asymptomatic with only 20–30% go on to develop clinical signs and symptoms. An acute infection occurs during the first 6 months following exposure, and during this period few infected individuals complain of fever, fatigue, nausea, anorexia, vomiting, and sometimes mild jaundice appears [73].

The HCV incubation period ranges from 3 to 12 weeks. The development of clinical manifestations depends on multiple viral and host factors that may include: infective dose (viral load), viral genotype, route of transmission, gender, age, and host immune response among others. HCV seroconversion window period ranges between 8 and 12 weeks after viremia. Of note, acute HCV infection does not always lead to the development of chronic infection. Nearly 20% of acute HCV infected individuals resolve the infection spontaneously with detectable anti-HCV antibodies, but without HCV RNA [73].

2.5.2 Chronic HCV infection

Following the establishment of acute HCV infection, nearly 80% of infected individuals progress to develop chronic HCV infection. Persistent HCV infection is usually associated with progressive hepatitis disease, with detectable HCV RNA and anti-HCV antibodies. Despite detection of HCV markers in the blood, there is no correlation between viremia and disease severity. The majority of chronically infected individuals develop fibrosis, cirrhosis and hepatocellular carcinoma (usually after 20 or more years followed infection) if no antiviral treatment is initiated. Once cirrhosis develops, the situation is usually irreversible but further liver damage can be prevented with early diagnosis and treatment. The development of cirrhosis and HCC is accelerated by immunosuppression [74]. Chronic HCV infection causes several histological changes in the liver and classifies the disease into persistent HCV infection, and active HCV infection with or without cirrhosis.

HCV infected individuals do not realise that they are infected, until the following signs and symptoms appear: anorexia, vomiting, fever, dark urine, jaundice, weight loss, and myalgia.

2.6 Laboratory diagnosis

Since seroconversion takes 8–12 weeks after viremia, serological diagnosis of acute HCV infection is tricky. During the acute stage, molecular diagnostic methods are reliable where HCV RNA can be detected within 1–3 weeks after exposure. Anti-HCV antibodies can be detected at the onset of clinical signs and symptoms. The HCV laboratory diagnostic methods include detection of specific anti-HCV antibodies, quantification of HCV RNA, and characterisation of HCV biomarkers. Enzyme immunoassay (EIA), rapid diagnostic kits, and polymerase chain reaction (PCR) techniques are commonly used for HCV diagnosis. It is prudent that each facility should establish a testing algorithm that includes screening, supplementary, and confirmatory testing methods. Detection of HCV RNA confirms active infection, whereas detection of anti-HCV antibodies suggests clearance of HCV infection spontaneously or establishment of

chronic infection. It is advisable to confirm all anti-HCV positive test results with a nucleic acid test to rule-out spontaneous viral clearance [75]. Once chronic infection has been noted, further liver damage has to be assessed by performing liver function tests, liver biopsy, or other non-invasive procedures. In chronic HCV infection, the following markers are elevated: alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), total protein (TP), gamma-glutamyl transpeptidase (GGT), prothrombin time (PT), total bilirubin, and sometimes a fasting serum acid [76].

2.7 Treatment, prevention, and control

For the past few decades, the standard HCV treatment has been interferon based therapy but there were increased cases of adverse effects, and reduced sustained viral response rate (50%). It is not all HCV cases that require treatment, since some individuals are asymptomatic. When treatment is desirable, the primary goal is cure [77]. The arrival of direct acting antivirals (DAAs) since 2014 with a high rate of responses to this treatment has brought a great expectancy of the possible cure and eradication of HCV infection in the next future. The WHO recommends sofosbuvir, daclatasvir, and the sofosbuvir/ledipasvir combination that has a 95% reported cure rate. Detection of the HCV genotypes and subtypes is relevant to response to the DAAs. The DAAs disrupt viral replication which subsequent establishment of HCV infection [78]. The following classes of DAAs have been suggested: NS3/4A protease inhibitors, NS5A inhibitors, NS5B nucleoside polymerase (NS5B RNA-dependent RNA polymerase) inhibitors, and NS5B non-nucleoside polymerase inhibitors. The DAAs have reduced the treatment duration (12 weeks to achieve cure), changed the drug administration route, reduced adverse effects, improved efficacy, viral sustained response, and tolerability [30]. Access to DAAs is still limited in low income countries, but the introduction of generic versions of DAAs has reduced the production and consumption cost in low income countries. It is estimated that HCV viremic burden will decline by approximately 60% [79].

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