

RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF HEPATITIS B VIRUS INFECTION

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Abstract

Hepatitis B and C viruses (HBV and HCV) are the primary causes of end-stage liver disease—liver failure and cirrhosis—worldwide. Although an effective vaccine against HBV exists, many new cases of infection are reported annually, particularly in resource-limited regions with weak vaccination policies. Furthermore, since there is no cure for HBV and chronic infection is lifelong, vaccines cannot treat individuals who are already infected. Research focused on an in-depth study of HBV biology and pathogenesis is limited, and much remains unknown about its genetic characteristics and their role in establishing and maintaining infection. The impact of these characteristics on disease progression and treatment response, especially in areas with a high prevalence of the virus, has not been fully explored. This underscores the need for in-depth research into the virus's biology, primarily to develop better management strategies for infected individuals and create effective prevention measures for others. Such information could also pave the way for finding a cure. In this article, we discuss the progress made in understanding the genetic basis of viral activity, which determines the complex interaction between the virus and the host, and the effects of co-infections.

Keywords

Viral hepatitis; Hepatitis B virus; Hepatitis D virus; Human immunodeficiency virus (HIV); vaccination; Ghana; liver cancer; hepatocellular carcinoma; liver coinfections; Plasmodium infections.

The liver is one of the body's essential multifunctional organs, playing a crucial role in metabolism, detoxification, and immune processes. Therefore, impaired liver function or its structural changes can lead to severe and life-threatening clinical complications. Although various treatment methods exist for liver diseases, liver transplantation is one of the most effective treatments for end-stage liver damage. Nevertheless, liver transplantation is associated with several serious challenges, including a shortage of donor organs, the difficulty of

determining human leukocyte antigen (HLA) compatibility, postoperative immunological complications, and significant financial costs. Furthermore, transplantation does not always ensure long-term patient survival. Disruptions in the regulatory systems that control the inflammatory process within liver tissue are among the key pathogenetic markers characteristic of chronic infections, autoimmune diseases, and malignant neoplasms. In various liver diseases, this process occurs through complex and intersecting signaling pathways. Dysregulation of immunoregulation is considered not only a critical link in pathogenesis but also a therapeutic target. In some liver pathologies, an imbalance of the immune system is observed, resulting in the body's response to damaging factors becoming excessive or bypassing control mechanisms and persisting for a long time. At the same time, the phenomenon of "secondary injury" occurs, in which heightened immune mechanisms damage healthy cells. In some cases, although the immune response may not exhibit severe hyperactivation, its long-lasting and persistent nature causes the gradual destruction of hepatocytes and the formation of fibrous tissue. Amidst ongoing cellular damage, the body's reparative and regenerative mechanisms are unable to compensate adequately. As a result, progressive structural and functional changes occur in the liver parenchyma. The term "hepatitis" is used as a general concept for inflammatory processes occurring in liver tissue. Although damage to the liver parenchyma can sometimes be caused by overactivation of the immune system, it most often develops under the influence of external pathogenic factors of viral etiology. During the virus's life cycle, especially at the replication stage, its structural elements trigger the activation of both the innate and acquired immune systems. As a result, the infectious process may manifest in an acute form or transition to a chronic stage over time. The clinical manifestations of the disease and its final outcomes largely depend on the characteristics of the pathogen and the reactivity of the host's immune system. The Hepatitis B virus (HBV) is one of the most common causes of viral hepatitis and is considered a major etiological factor in the development of severe liver diseases such as liver failure and hepatocellular carcinoma worldwide. Although a highly effective vaccine has been developed to prevent HBV infection, cases of the disease are still being observed. This is attributable, on the one hand, to insufficient vaccination coverage in areas with a high epidemiological burden and the fact that vaccines are not equally available or economically accessible to all population segments. On the other hand, it is explained by the virus's ability to partially evade the effects of immunoprophylaxis. Studies show that approximately 5% of infants who receive the initial dose of the anti-HBV vaccine in a timely manner after birth may still develop the infection. Moreover, vaccination provides no therapeutic

benefit to individuals who already have the disease. Therefore, to completely eradicate the infection, it is crucial to implement preventive vaccination in conjunction with patient detection and treatment strategies. The World Health Organization and its partners have developed the Global Health Sector Strategy (GHSS) on viral hepatitis. One of the strategy's main objectives is to reduce the incidence of new infections by 90% and the mortality rate by 65% compared to 2015 levels. Implementing these strategic goals requires establishing a real-time epidemiological database, timely introducing targeted interventions, and expanding early detection programs. This further underscores the need to launch proactive screening programs, improve the quality of clinical care, and promote widespread HBV vaccination. Studying the biological and molecular-genetic characteristics of the virus, as well as its complex interaction with the host immune system, will provide a scientific basis for developing more effective therapeutic strategies. This review examines current knowledge of HBV biology, its complex interactions with other infections, and the scientific gaps that hinder the effective implementation of control measures. Globally, approximately 30 million people are infected with HBV annually, and 296 million people are currently registered with chronic infection. Of this group, 2.7 million are coinfecting with the Human Immunodeficiency Virus (HIV). Approximately 1 million people die annually from HBV-related complications; nevertheless, fewer than 10% of those infected are diagnosed, and only about 1% have access to treatment. The disease burden is disproportionately distributed regionally, with the African and Asia-Pacific regions bearing the largest share of the global burden. This situation is explained, on one hand, by the insufficiently rigorous implementation of vaccination policies in high-risk groups and, on the other hand, by the lack of a continuous epidemiological monitoring and screening system in Africa's most affected regions. More than 60 million people on the African continent are infected with hepatitis B, causing over 60,000 deaths annually. The majority of infections occur in early childhood: transmitted vertically from an infected mother to her child or horizontally during the first five years of life from infected family members or close contacts. According to a 2006 study by Candotti et al., the distribution of HBV genotypes across Africa had not been sufficiently studied, despite high endemicity. Observations in Ghana showed that HBV genotype E was predominant among blood donors, detected in 87% of cases; genotypes A and D were found in 10% and 3% of cases, respectively. The detection of mixed infections of genotypes A and E confirms that coinfection or superinfection with multiple strains can occur. Recent epidemiological observations confirm that the predominance of genotype E is also found in neighboring countries and large areas of West Africa, particularly in the region from Senegal to

Angola. In the serum of infected individuals, HBV exists in three different virion forms. Among these, the infectious virion – the "Dane particle" – has a diameter of 42–45 nm and an outer envelope containing the surface antigen (HBsAg) within a lipid layer. Inside the viral lipid envelope is a nucleocapsid, which contains the nucleic acid and the reverse transcriptase enzyme. The other two particle types are subviral, with a size of around 22–24 nm, and are filamentous or spherical in shape. They consist of HBsAg embedded in a lipid membrane derived from the host cell but do not contain viral DNA. Subviral particles are found in the bloodstream in significantly greater numbers – from 100 to 100,000 times more – than infectious virions and play an immunomodulatory and immunosuppressive role. The genetic material of this virus, whose biological and pathogenetic significance has been analyzed in detail in separate studies, consists of a circular, partially double-stranded DNA molecule of approximately 3.2 kb. The genome consists of four partially overlapping open reading frames (ORFs), each with its own promoter but sharing a common polyadenylation sequence. The ORFs encode the surface antigen (HBsAg), core antigen (HBcAg), polymerase, and X protein (HBxAg). The small size of the viral genome necessitates that proteins are produced from overlapping translational frames, and regulatory elements are located within the protein-coding sequences. The error-prone polymerase enzyme present in HBV virions brings its mutation rate to 2.0×10^{-5} per nucleotide position per year. Given the small genome size, the partial overlap of ORFs, and the high functional importance of each nucleotide position, such a high mutation rate could theoretically have a negative impact on the virus's viability. HBV maintains its replicative competence and ensures biological stability even under conditions where genome restructuring is possible. Based on the presentation of antigenic epitopes in its outer envelope proteins, HBV is classified into four serotypes: adr, adw, ayr, and ayw. The virus also has eight main genotypes (A–H), and differences between genotypes affect disease severity, course, likelihood of complications, treatment response, and vaccine efficacy. The current classification of HBV includes at least 10 genotypes, designated A to J, which are distinguished by a sequence divergence of more than 8%. Several sub-genotypes have been identified with sequence divergences of 4–8%. These sub-genotypes have different geographical distributions and may also differ in the course and clinical features of the infection. It has been observed that infection transmission mechanisms can be specific to regions characteristic of certain genotypes. In the context of natural HBV infections, non-infectious subviral particles (SVPs) that lack a viral capsid are common, and their quantity is significantly higher than that of infectious virions. Subviral particles can contain the L, M, and S forms of the HBV envelope proteins. All proteins share a common C-

terminus, with the M protein containing a pre-S2 domain relative to S, and the L protein containing a pre-S1 domain relative to M. Research shows that during the infection process, the pre-S1 domain of the L protein plays a central role in binding to as-yet-unidentified host receptor (s). The binding of the L protein's pre-S1 domain to host receptors is necessary for viral entry into the cell and the initiation of infection. Meanwhile, the interaction between viral proteins and the innate immune response is of key importance in developing therapeutic approaches against HBV and HDV. Studies, including experimental infection systems and clinical data, indicate that HBV typically has the ability to evade the innate immune response, whereas coinfection with HDV leads to complex and profound changes in infected liver tissue. In 2021, research by Dandri et al. revealed that HBV/HDV coinfection leads to increased production of inflammatory cytokines and chemokines, along with an enhanced antigen presentation capacity. Thus, immune cells' ability to detect infected cells is improved, liver inflammation increases, and pathogenetic processes accelerate. Scientific observations have established the function of HBV and HDV proteins in regulating antiviral responses in infected liver cells, as well as the crucial role of the virus in suppressing the host's primary immune mechanisms. HBV is recognized as the primary prototype virus of the Hepadnaviridae family; other viruses in this family are pathogenic to birds (Avihepadnavirus) and mammals (Orthohepadnavirus). Recent studies have also reported the identification of hepadnaviruses specific to fish and amphibians. These viruses exhibit similarities in their genome structure and replication strategies, with sequence divergence among orthohepadnaviruses reaching approximately 40%, and up to 20% in avihepadnaviruses. The presence of three types of virion particles in the blood of individuals infected with HBV has been commonly noted. The infectious virion, known as the Dane particle, is 42–45 nm in diameter, with its lipid envelope containing HBsAg and surrounding the nucleocapsid. The nucleic acid within the nucleocapsid is bound to reverse transcriptase. The other two particle types – subviral particles – are 22–24 nm in diameter, filamentous and spherical in shape, coated with HBsAg, but do not contain viral DNA. Interestingly, they are found in the bloodstream 100 to 100,000 times more frequently than infectious virions and perform immunomodulatory and immunosuppressive functions. Their functions have been extensively analyzed in scientific research. The viral DNA is partially double-stranded and circular, with a size of approximately 3.2 kb. The genome is divided into four partially overlapping ORFs, each with its own promoter but sharing a common polyadenylation sequence. Each ORF encodes a surface antigen (HBsAg), a core antigen (HBcAg), a polymerase, and an X protein (HBxAg). Due to the small genome size, viral proteins are encoded in overlapping

translational frames, and regulatory elements are located within the protein-coding sequences. Furthermore, the viral polymerase is error-prone, increasing the annual substitution rate at each nucleotide position to 2.0×10^{-5} . Due to the overlapping ORFs and the crucial functional role of the nucleotides, the virus's high mutation rate could theoretically limit its viability. Nevertheless, HBV can maintain stable survival without losing its replicative ability, even when there is a risk of genome rearrangement.

Four serotypes of HBV – adr, adw, ayr, and ayw – are identified based on the characteristics of their antigenic epitopes. Additionally, there are eight genotypes (A–H) that influence the course of the disease, its severity, the likelihood of complications, response to therapy, and the effect of vaccination. The genetic diversity of HBV comprises at least 10 genotypes (A–J), which are distinguished by a sequence difference of over 8%. Furthermore, there are several sub-genotypes with a 4–8% sequence difference. Genotypes have specific geographical distributions and exhibit different natural courses of infection. Also, in certain regions, infection mechanisms specific to particular genotypes are observed. In a natural HBV infection, there is an excess of non-infectious subviral particles (SVPs) that lack a viral capsid. Subviral particles can contain three types of viral envelope proteins – L, M, and S. While each shares a common C-terminus, the M protein contains a pre-S2 domain relative to the S protein, and the L protein contains a pre-S1 domain relative to the M protein. Scientific research confirms that the pre-S1 domain of the L protein binds to as-yet-unidentified host receptors during the process of viral entry into a cell. The interplay between viral proteins and innate immune responses plays a central role in the development of curative therapies for HBV and HDV. Experimental infection models and clinical observations confirm that HBV is poorly recognized by the innate immune system, whereas co-infection with HDV leads to profound intrahepatic pathological changes. A study by Dandri et al. (2021) observed that in HBV/HDV co-infection, an increase in the production of chemokines and inflammatory cytokines, along with an enhanced antigen-presenting capacity, improves the ability of immune cells to detect infected cells, which in turn intensifies liver inflammation and accelerates disease pathogenesis. Experimental and clinical studies confirm the role of HBV and HDV proteins in regulating antiviral responses in infected liver cells, as well as the virus's impact in suppressing the host's first line of defense. However, many uncertainties remain regarding the details of the HBV genome and its functional role in initiating and sustaining infection. A thorough study of the molecular epidemiology of HBV in hyperendemic regions is a critical factor in assessing the natural course of the disease and therapeutic response. An article published by Lemoine et al. (2023)

noted the inadequate management of hepatitis B in Africa and emphasized the need to prevent infections by introducing the Birth Dose Vaccine (BDV) for newborns. The authors note that the current model—characterized by repeated laboratory tests, complex criteria for initiating antiviral therapy, and high diagnostic costs—serves as a barrier for patients in need of treatment. They also highlighted issues such as insufficient public awareness, limited access to laboratory and diagnostic services, and a lack of uninterrupted access to effective medicines, problems that are particularly acute in resource-limited areas. It is crucial to expand healthcare access by decentralizing medical services, integrating them, and implementing task-sharing, as well as by adequately funding the necessary infrastructure. New strategies, particularly the "Treat-All" and "Beyond-Treat-All" approaches, require scientific research on their practical implementation, as well as studies on their acceptance and evaluation by patients and policymakers.

HBV is transmitted primarily through two main routes: the perinatal route, meaning transmission from an infected mother to a newborn (the most common globally), and the horizontal route, which involves transmission through blood, bodily fluids, needle injections, tattoos, or other invasive procedures. In general, the mechanisms of HBV entry into hepatocytes and its intracellular spread are not yet fully understood. During this infection process, heparan sulfate proteoglycans, the sodium taurocholate co-transporting peptide (NTCP), and the epidermal growth factor receptor mediate the virus's entry into the hepatocyte, though the existence of other receptors is not excluded. These receptors—NTCP and HSPGs—are found exclusively in hepatocytes, which helps explain the virus's selective targeting of liver cells. An in-depth study of the mechanisms between HBV and its receptors could make a key contribution to creating therapeutic approaches aimed at halting the virus's spread within liver cells. Recent studies have shown that certain chemical compounds can selectively suppress the virus-receptor interaction via NTCP. Once HBV enters a hepatocyte, its nucleocapsid is released into the cytoplasm, and the genome is subsequently transported into the hepatocyte's nucleus. HBV's partially double-stranded DNA is repaired using the viral polymerase and host cell repair mechanisms, resulting in the formation of covalently closed circular DNA (cccDNA). This cccDNA serves as a template for the synthesis of subgenomic and pregenomic RNAs (sgRNA and pgRNA). The nucleocapsid contains the viral DNA, which also includes a DNA polymerase that functions as a reverse transcriptase. The outer envelope contains proteins involved in the virus's attachment to and entry into cells. HBV is one of the smallest enveloped viruses found in animals. Virions with a diameter of 42 nm are called "Dane particles" and are capable of infecting hepatocytes. In addition to Dane

particles, the blood serum of infected individuals also contains non-nucleated filamentous and spherical particles. These non-nucleated particles are not infectious and are composed of a lipid envelope and surface antigens (HBsAg). During viral replication, these subviral particles are produced in excess, affecting the immune system by creating an antigenic "decoy." The highly stable nature of cccDNA allows it to persist in hepatocytes for a long time, serving as a constant template for sg/pgRNA production and thereby increasing the virus's survival within the cell. While sgRNA is used to synthesize viral proteins, pgRNA is packaged into the nucleocapsid along with the polymerase. This pgRNA is then reverse-transcribed into a negative-strand DNA, which subsequently forms rcDNA, ensuring the stability of the viral genome within the cell. Nucleocapsids are either re-imported into the nucleus for cccDNA synthesis or are enveloped by the outer shell via the endoplasmic reticulum, creating the potential to infect other hepatocytes. In acute HBV infection, the elimination of the virus from hepatocytes occurs through the coordinated activity of cytotoxic CD8⁺ T-cells and helper CD4⁺ T-cells. CD8⁺ T-cells contribute to viral eradication by destroying infected hepatocytes, while CD4⁺ T-cells support the humoral immune response by stimulating antibody production. Much remains unknown about the role of these immune cells in chronic HBV infection; the mechanisms of their functional impairment and their impact on the duration of the infection have not yet been fully elucidated scientifically. A precise analysis of the antiviral immune response mechanisms and the process of cellular damage will enable the optimization of clinical management and treatment approaches. Acute hepatitis B infection often does not require a specific therapeutic approach, as adults frequently clear the infection through their own immune response. For patients with very severe symptoms or immunodeficiency, drug treatment for acute hepatitis B may be necessary, but this applies to only a small population, less than 1% of individuals. In patients with chronic HBV infection and persistently high blood levels of alanine aminotransferase (ALT), antiviral therapy is recommended to reduce the risk of liver damage and prevent the development of cirrhosis and liver cancer. The duration of treatment typically ranges from six months to one year, determined by the type of antiviral drug selected and the characteristics of the HBV genotype. Although modern therapeutic drugs cannot completely eradicate the infection, they do inhibit viral replication and help reduce hepatocyte damage. Treatment options include nucleoside/nucleotide analogs – lamivudine, adefovir, tenofovir disoproxil and alafenamide, telbivudine, entecavir – as well as immune-stimulating drugs, specifically interferon alpha-2a and its PEGylated form. In 2015, the World Health Organization recommended tenofovir and entecavir as the primary first-line drugs for treating patients with

HBV. Along with HBV, other viruses can also infect liver tissue, including the hepatitis A, C, D, and E viruses. Patients with HBV infection may also develop other forms of liver disease, particularly steatohepatitis and alcohol-related liver damage. Additionally, certain parasitic factors that negatively affect liver function—such as liver flukes or bacterial infections of the bile ducts—may occur, though such cases are rare. Plasmodium parasites, the etiological agent of malaria, undergo a liver stage in the human body, which is where their asexual development takes place. While the impact of these parasites on liver function is not often associated with severe hepatocyte damage, the immune response that develops against them in the liver tissue may modulate the immune mechanisms against HBV to some extent. Studies on HBV and malaria co-infection show that the biological interaction between the two pathogens is complex and manifests in various ways. Therefore, this section will examine the impact of other liver infections on the outcomes of HBV infection.

Thus, biochemical analyses are performed to assess liver function, where an increase in blood bilirubin levels and elevated ALT and AST (transaminase) enzymes indicate liver cell damage. If necessary, viral DNA can also be detected using the PCR (polymerase chain reaction) method, which is important for assessing the stage of the disease and the viral load. The treatment for hepatitis B depends on the form of the disease. While the acute form is managed primarily with symptomatic and supportive care, the chronic form is treated with antiviral drugs that suppress viral replication and prevent liver damage. However, this treatment requires long-term and regular monitoring. The most effective preventive measure is vaccination; the recombinant hepatitis B vaccine has high immunogenicity and creates long-term protection in the body. Vaccination programs have been implemented in many countries, which are significantly reducing the spread of the disease. The recombinant hepatitis B vaccine is included in Uzbekistan's national immunization schedule, with the first dose administered to infants within 12–24 hours after birth, and subsequent doses at 2 and 6 (or 9) months of age. As a result of vaccination, protective immunity is formed for at least 5 years and often longer. We consider the timely and high-quality implementation of vaccination and revaccination processes to be a crucial factor in preventing serum hepatitis.

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