SSR Journal of Medical Sciences (SSRJMS)

OPEN ACCESS

Volume 2, Issue 4, 2025 Journal homepage: https://ssrpublisher.com/ssrjms/ ISSN: 3049-0375
Email: office.ssrpublisher@gmail.com

The Impact of Hepatitis B Virus on Liver Disease and Liver Cancer: Molecular Mechanisms and Clinical Implications

Papka I. M.*[1]; Mangga H. K.[2]; Oyebode, S. A.[2]; Bukbuk D. N.[2] and Ladan J.[3]

[1]Department of Microbiology, Faculty of Science, Adamawa state University, Mubi, PMB 25, Adamawa state, Nigeria.
[2]Department of Microbiology, Faculty of Life Sciences, University of Maiduguri, P.M.B. 1069, Bama Road, Maiduguri, Borno Sate, Nigeria.
[3]National Primary Health Care Development Agency, Abuja.

Received: *14.07.2025* | ***Accepted:*** *26.07.2025* | ***Published:*** *31.07.2025*

***Corresponding author:** Papka I. M

DOI: *10.5281/zenodo.16646437*

Abstract **Review Article**

An estimated 257 million people worldwide suffer from chronic hepatitis B virus (HBV) infection, making it a major public health concern. Due to its association with chronic liver disease and hepatocellular carcinoma (HCC), the most prevalent type of primary liver cancer, HBV continues to cause significant morbidity and mortality even in the face of an effective preventive vaccine and strong antiviral treatments. Hepatocyte regeneration, chronic inflammation, and immune-mediated liver damage are all components of the complicated, multifactorial process that leads to fibrosis, cirrhosis, and malignant transformation in cases of chronic HBV infection. This article offers a thorough summary of the molecular and cellular processes via which HBV aids in the development of liver illness and cancer.

The pleiotropic functions of the HBx protein, which modify host transcription, cell cycle regulation, and apoptosis; the integration of HBV DNA into the host genome, which causes genomic instability and disrupts essential regulatory genes; and extensive epigenetic modifications, such as DNA methylation, histone modifications, and dysregulation of non-coding RNAs, are important pathogenic features. Furthermore, HBV causes chronic inflammation and oxidative stress, which worsen liver damage and promote neoplastic transformation.

The pathophysiology of HBV has significant clinical ramifications for diagnosis, treatment, and disease surveillance. Covalently closed circular DNA (cccDNA), the viral minichromosome that causes persistent infection, is not eliminated by nucleos(t)ide analogues, despite the fact that they successfully inhibit viral replication. Therefore, the risk of HCC is decreased but not eliminated by current therapies. Promising new therapeutic approaches, such as gene editing, immune-based strategies, and epigenetic modulators targeted at eradicating or silencing HBV reservoirs, have been made possible by advances in molecular biology.

To sum up, a better comprehension of the molecular processes behind HBV-related liver disease is essential for creating novel treatment approaches and honing public health initiatives. To overcome the obstacles of viral persistence, stop the progression of the disease, and eventually find a functional or sterilizing treatment for HBV infection, more research is required.

Keywords: Hepatitis B Virus (HBV), Liver Disease, Liver Cancer, Hepatocellular Carcinoma (HCC), Molecular Mechanisms, Viral Pathogenesis, HBV Infection, Chronic Hepatitis B, Liver Fibrosis, Cirrhosis, Oncogenesis, Viral Integration, Immune Response, Clinical Implications, Biomarkers, Antiviral Therapy, HBV DNA, HBV Proteins (e.g., HBx), Inflammation Viral Replication.

Citation: Papka, I. M., Mangga, H. K., Oyebode, S. A., Bukbuk, D. N., & Ladan, J. (2025). The impact of Hepatitis B virus on liver disease and liver cancer: Molecular mechanisms and clinical implications. *SSR Journal of Medical Sciences (SSRJMS)*, *2*(4), 14-24.

1. INTRODUCTION

A substantial and long-lasting global health burden, hepatitis B virus (HBV) infection affects an estimated 257 million people globally. HBV-related liver disease, such as liver cirrhosis and hepatocellular carcinoma (HCC), is responsible for over 820,000 deaths per year (WHO, 2024; Schweitzer *et al*., 2015). The distinctive 3.2-kilobase partly double-stranded DNA genome of HBV, a member of the Hepadnaviridae family, replicates by reverse transcription of an RNA intermediary (Seeger and Mason, 2015). The sodium taurocholate co-transporting polypeptide (NTCP) receptor on the liver cell membrane is the main way that the virus infects hepatocytes, causing both acute and chronic infection (Yan *et al*., 2012).

A number of host and viral variables, such as age at infection, immunological status, and viral genotype, influence the clinical outcome of HBV infection. The majority of adults may recover from acute infections, but vertical or early-life horizontal transmission frequently results in chronic infections, which are linked to a significant risk of developing liver disease and ultimately developing cancer (McMahon, 2009). In the dynamic disease known as chronic hepatitis B (CHB), the host immune response causes liver inflammation and fibrosis during the phases of immunological tolerance, immune clearance, and immune control or reactivation (Lok *et al.*, 2016).

The development of covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes is a defining feature of HBV's persistence. It is challenging to achieve a functional cure because this episomal form, which is the transcriptional template for viral replication, endures even after long-term antiviral therapy (Revill *et al*., 2016). HBV induces oxidative stress, produces the oncogenic HBx protein, integrates its DNA into the host genome, modifies host immune responses, and induces epigenetic remodeling in addition to its replicative strategies, all of which contribute to hepatocarcinogenesis (Tu *et al*., 2017; Zhang *et al*., 2022).

Hepatocellular carcinoma ranks third in terms of cancer-related mortality and is the fifth most prevalent type of cancer worldwide. Over 50% of HCC cases globally are caused by chronic HBV infection, especially in endemic regions like East Asia and sub-Saharan Africa (El-Serag, 2012; Perz *et al.*, 2006). Notably, HBV is a direct carcinogen: HCC can arise without cirrhosis, highlighting the virus's capacity to cause cancer through non-cirrhotic pathways such HBx-mediated gene deregulation and HBV DNA integration (Levrero & Zucman-Rossi, 2016).

Although entecavir and tenofovir, two modern nucleos(t)ide analogue therapies, can successfully inhibit HBV replication and lower the risk of cirrhosis and HCC, they do not eradicate integrated viral DNA or cccDNA, which are important sources of viral persistence and carcinogenic activity, (Yuen *et al.*, 2018). Furthermore, the need for novel therapeutic approaches that target the molecular underpinnings of HBV persistence and oncogenesis is highlighted by the current antiviral medicines' poor ability to induce HBsAg reduction, a sign of functional cure.

Therefore, improving patient outcomes requires a thorough knowledge of the molecular processes via which HBV contributes to the development of cancer and the progression of liver disease. With an emphasis on viral integration, HBx function, immune-mediated liver injury, epigenetic alterations, and clinical implications, this study examines the main virological characteristics of HBV and their pathological effects. By doing this, it hopes to contribute to the development of future diagnostic, treatment, and public health approaches for the treatment of chronic HBV infection and liver cancer linked to HBV.

2. HBV VIROLOGY AND LIFECYCLE

The prototype member of the *Hepadnaviridae* family, which is categorized under the *Orthohepadnavirus* genus, is the tiny, enveloped DNA virus known as the Hepatitis B virus (HBV). The virus primarily infects human and other species' hepatocytes due to its severe *hepatotropism*. HBV has a sophisticated replication mechanism that enables it to survive in infected persons and avoid immune clearance, despite its small genome and dependence on host cellular machinery. HBV's ability to produce liver inflammation, oncogenesis, and chronic infection is supported by some features of its virology and life cycle.

2.1 Viral Structure and Genome Organization

- HBV virions, sometimes referred to as Dane particles, have a diameter of about 42 nm and are made up of an inner nucleocapsid that contains viral polymerase, hepatitis B core antigen (HBcAg), and a partially double-stranded relaxed circular DNA (rcDNA) genome (~3.2 kb). The outer lipid envelope is embedded with hepatitis B surface antigens (HBsAg). The main viral proteins are encoded by four overlapping open reading frames (ORFs) in the small genome:
- **S gene**: encodes the small (S), medium (M), and large (L) surface proteins,
- **C gene**: encodes core (HBcAg) and e antigen (HBeAg),
- **P gene**: encodes the viral polymerase with reverse transcriptase and RNase H activity,
- **X gene**: encodes HBx, a multifunctional regulatory protein implicated in transcriptional activation, apoptosis, and carcinogenesis, (Seeger & Mason, 2015; Locarnini *et al.*, 2013).

2.2 Viral Entry and Uncoating

Viral attachment to hepatocytes marks the start of the HBV lifecycle. Heparan sulfate proteoglycans on the hepatocyte surface interact with HBsAg to mediate the first low-affinity binding. The sodium taurocholate co-transporting polypeptide (NTCP), a bile acid transporter that is exclusively produced on the basolateral membrane of hepatocytes, binds to the L-HBsAg with high affinity through the preS1 domain (Yan *et al.*, 2012). HBV enters the host cell through clathrin-mediated endocytosis after binding to its receptor.

Following internalization, the nucleocapsid is released into the cytoplasm when the viral envelope and endosomal membrane combine. According to Urban *et al.* (2014), the capsid is subsequently transported to the nuclear pore complex, where it disassembles and releases rcDNA into the nucleus.

2.3 cccDNA Formation and Maintenance

Covalently closed circular DNA (cccDNA), a very stable episomal DNA structure that acts as the transcriptional template for all viral RNAs, is created inside the nucleus when the rcDNA is repaired by the host. Establishing a persistent infection requires this stage. Host histones and non-histone proteins organize cccDNA, which takes the shape of a chromatinized minichromosome (Lucifora *et al*., 2014). HBV cccDNA contributes to the virus's long-term persistence in

hepatocytes because, although non-integrative by nature, it is extremely resistant to antiviral treatment and immune-mediated clearance.

2.4 Transcription and Translation

The cccDNA is transcribed by host RNA polymerase II to produce five major viral transcripts:

- 3.5 kb pgRNA (pregenomic RNA) and precore RNA,
- 2.4 kb preS1 mRNA,
- 2.1 kb preS2/S mRNA,
- 0.7 kb HBx mRNA.

Covalently closed circular DNA (cccDNA), a very stable episomal DNA structure that acts as the transcriptional template for all viral RNAs, is created inside the nucleus when the rcDNA is repaired by the host. Establishing a persistent infection requires this stage. Host histones and non-histone proteins organize cccDNA, which takes the shape of a chromatinized minichromosome (Lucifora et al., 2014). HBV cccDNA contributes to the virus's long-term persistence in hepatocytes because, although non-integrative by nature, it is extremely resistant to antiviral treatment and immune-mediated clearance.

2.5 Genome Replication by Reverse Transcription

Newly generated capsids are where genome replication takes place. Initiating reverse transcription, the HBV polymerase attaches itself to a stem-loop structure (ε) on the pgRNA. The RNA strand is broken down as the polymerase creates a minus-strand DNA copy of the pgRNA first. The characteristic rcDNA genome present in mature virions is the result of the subsequent, typically partial, synthesis of the plus-strand DNA (Tavis *et al*., 2019). Even though HBV is a DNA virus, its reverse transcription method is comparable to that of retroviruses.

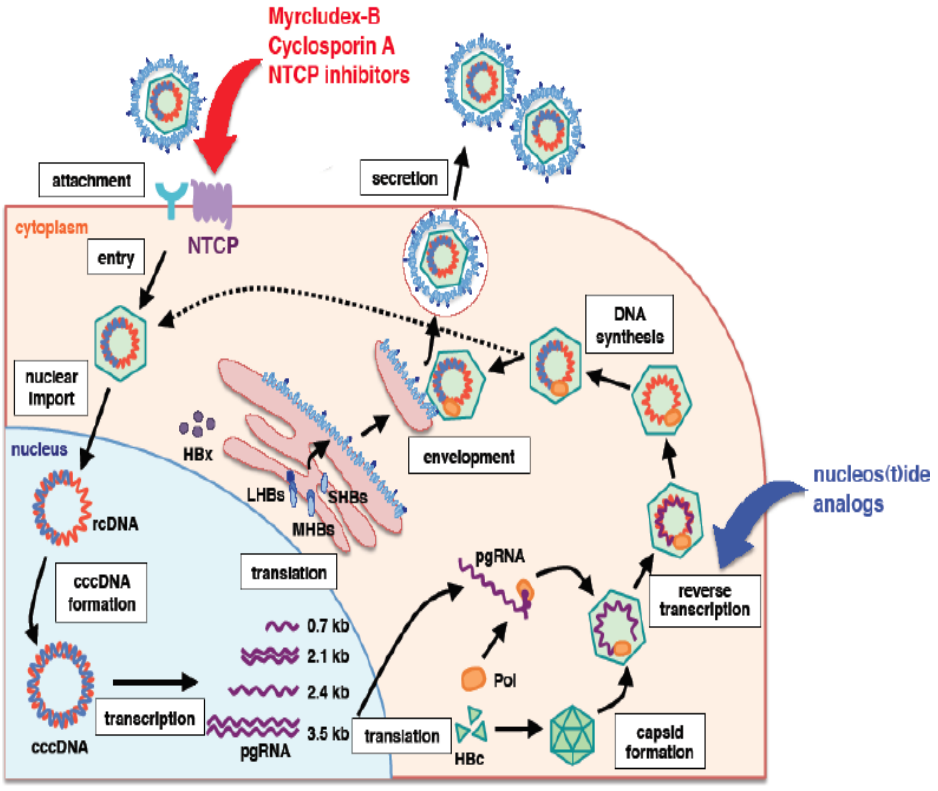
2.6 Virion Assembly and Release

Before being released as mature virions, the viral core particles are encased in lipid membranes that contain HBsAg in the Golgi complex and endoplasmic reticulum (ER). Intracellular amplification is the mechanism by which a portion of the freshly created nucleocapsids are returned to the nucleus to replenish the cccDNA pool. In order to control immune responses and avoid antibody neutralization, infected hepatocytes also release a lot of non-infectious subviral particles (SVPs), which are made up of HBsAg without viral DNA (Seeger and Mason, 2015).

2.7 HBV DNA Integration

Integration into the host genome is not necessary for HBV replication, but it usually happens during a long-term infection. Although integrated HBV DNA is frequently flawed and incapable of replication, it can nonetheless play a role in pathogenesis. In addition to disrupting host genes, activating oncogenes, or promoting genomic instability—all of which are key processes in HBV-induced hepatocellular carcinoma—it may produce shortened or altered viral proteins, (Tu *et al.*, 2017; Zhang *et al*., 2022).

HBV Lifecycle Diagram (Textual Description)



- [Departure] → [Endocytosis] → [Nuclear Import & Uncoating] → [CccDNA Formation] → [Transcript] → [Translation]: → [Reverse Transcription] → [Assembly] → [cccDNA Recycling OR secrecy] (Sung et al., 2012).
- **Attachment**: Binding to NTCP on hepatocyte membrane.
- **Entry**: Endocytosis and fusion.
- **Uncoating**: Capsid disassembles, rcDNA enters nucleus.
- **cccDNA Formation**: rcDNA repaired to form episomal cccDNA.
- **Transcription**: cccDNA transcribed to viral RNAs.
- **Translation**: Viral proteins synthesized in cytoplasm.
- **Replication**: pgRNA reverse transcribed to DNA inside capsids.
- **Assembly**: Mature virions formed.
- **Egress or Recycling**: Virions secreted or capsids return to nucleus.

3. MOLECULAR MECHANISMS OF DISEASE AND CARCINOGENESIS

Globally, hepatitis B virus (HBV) infection is a major contributor to hepatocellular carcinoma (HCC) and chronic liver disease. Viral components and host cellular and immunological responses interact intricately in the multifactorial pathophysiology of HBV-induced liver damage and carcinogenesis. Chronic inflammation, genomic instability, and cellular transformation are all fueled by this complex interaction, which eventually leads to the development of HCC and progressive liver fibrosis and cirrhosis.

3.1 Immune-Mediated Inflammation and Liver Injury

The host immunological response to infected hepatocytes is the main cause of liver damage in HBV infection. The immune system's killing of HBV-infected cells is primarily responsible for liver damage; the virus itself is not very cytopathic. CD8 cytotoxicity sub>+ T lymphocytes (CTLs) use the major histocompatibility complex (MHC) class I molecules to identify viral peptides that are presented by hepatocytes. They then use the Fas/FasL and perforin/granzyme release pathways to cause necrosis and apoptosis, (Rehermann, 2013). Furthermore, $CD4^+$ By releasing pro-inflammatory cytokines including interleukins, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), T cells and natural killer (NK) cells contribute to inflammation.

Hepatocyte turnover and fibrogenesis persist as a result of chronic immunological activation. The two main risk factors for HCC, cirrhosis and fibrosis, are brought on by the overabundance of extracellular matrix components deposited by activated hepatic stellate cells (HSCs), (Friedman, 2008). Additionally, by producing reactive oxygen and nitrogen species, the inflammatory microenvironment encourages oxidative stress, which results in DNA damage and mutagenesis that aid in oncogenic transformation, (Yang *et al.*, 2015).

3.2 HBV DNA Integration and Genomic Instability

Integration into the host genome is not necessary for HBV replication, in contrast to retroviruses. Nonetheless, integration is found in more than 80% of HBV-associated HCC tumors and happens often during chronic infection, (Zhao *et al.*, 2020). This process, which contributes to chromosomal instability, is largely random but preferentially targets fragile sites, repetitive DNA sequences, and transcriptionally active regions.

For instance, integration near the telomerase reverse transcriptase (TERT) promoter causes its overexpression, conferring replicative immortality (Zhang et al., 2019). Other common targets include CCNE1, MLL4, and the cyclin-dependent kinase inhibitor CDKN2A. The viral-host junction sequences may also produce chimeric transcripts encoding truncated viral proteins or fusion proteins with oncogenic potential, (Sung *et al.*, 2012). Integrated HBV DNA can cause insertional mutagenesis, disrupting tumor suppressor genes, or increasing oncogene expression.

Furthermore, integration events result in structural chromosomal changes like deletions, translocations, and amplifications, all of which promote tumorigenesis; integrated HBV DNA is a source of persistent viral antigen expression, maintaining immune-mediated liver inflammation and additional genomic damage, (Tu *et al.*, 2017).

3.3 HBx Protein: A Central Modulator of Oncogenesis

- A multifunctional regulatory protein, the HBV X protein (HBx) is essential for viral replication and pathogenesis, particularly carcinogenesis. HBx localizes in the mitochondria, nucleus, and cytoplasm, where it modifies a variety of biological pathways:

Disruption of DNA Repair and Cell Cycle Regulation: By preventing DNA binding and transcriptional activation, HBx disrupts the activity of the tumor suppressor protein p53. As a result, genetic mutations can accumulate because p53-mediated apoptosis and DNA repair are compromised, (Feitelson & Lee, 2007). By interacting with repair enzymes including poly(ADP-ribose) polymerase 1 (PARP1) and thymine-DNA glycosylase (TDG), HBx also inhibits the nucleotide excision repair (NER) and base excision repair (BER) pathways, which promotes mutagenesis (Zhang *et al.*, 2013).

Activation of Proliferative and Survival Signaling: HBx triggers several carcinogenic signaling cascades, such as the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways, nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/Akt, and Wnt/β-catenin. These enhance angiogenesis and metastasis, suppress apoptosis, and regulate cell proliferation, (Bouchard and Schneider, 2004; Waris *et al.*, 2001).

Epigenetic Reprogramming: HBx modifies histone modifications and DNA methylation to change the host chromatin landscape. It causes the transcriptional silencing of tumor suppressor genes like p16^INK4A and E-cadherin by attracting DNA methyltransferases (DNMT1, DNMT3A/B) to their promoter regions (Zhou *et al.*, 2011). Additionally, histone-modifying enzymes including histone acetyltransferases (HATs) and histone deacetylases (HDACs) interact with HBx to alter chromatin structure in a way that promotes the expression of oncogenes, (Deng *et al.*, 2013).

Regulation of cccDNA Transcription: By targeting the restriction factor that inhibits cccDNA transcription, the host structural maintenance of chromosomes 5/6 complex (Smc5/6), HBx promotes transcription from viral cccDNA. According to Decorsière et al. (2016), HBx-mediated ubiquitination and degradation of Smc5/6 enable persistent viral replication and persistence.

3.4 Oxidative Stress and Mitochondrial Dysfunction

Through a variety of mechanisms, HBV infection causes oxidative stress. HBx targets mitochondria, causing electron transport chain components to be disrupted and an increase in the production of reactive oxygen species (ROS). This mitochondrial dysfunction leads to DNA strand breaks, lipid peroxidation, and the activation of pro-survival signaling pathways, (Kuo *et al*., 2009).
Furthermore, the unfolded protein response (UPR), which is triggered by the aggregation of viral surface proteins in the endoplasmic reticulum, exacerbates oxidative stress and encourages inflammation and hepatocyte death, (Brouwer *et al.*, 2013). If left unfixed, ROS-induced DNA damage encourages chromosomal instability and mutations, which in turn leads to neoplastic transformation.

3.5 Dysregulation of Non-coding RNAs

Recent studies highlight the importance of non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), in HBV-associated hepatocarcinogenesis.

- MicroRNAs: HBx modifies the expression of several miRNAs, upregulating oncogenic miRNAs like miR-21 and miR-221 and downregulating tumor-suppressive miRNAs like miR-122 and miR-223. For example, tumor growth and metastasis are increased when miR-122, which typically inhibits proliferation and encourages apoptosis, is downregulated, (Cai *et al.*, 2012).
- Long Non-Coding RNAs: According to Wang *et al.*, (2016), HBx triggers the production of oncogenic lncRNAs including UCA1 and HULC (Highly Upregulated in Liver Cancer), which control signaling pathways and epigenetic modifiers to encourage invasion, proliferation, and the epithelial-to-mesenchymal transition (EMT).

These ncRNAs interact together to create a complex regulatory network that alters gene expression both post-transcriptionally and epigenetically, which promotes the development of cancer.

Summary

HBV causes liver disease and HCC through the following molecular mechanisms: HBV DNA integration leading to genomic instability, persistent immune-mediated liver inflammation and fibrosis:
• The HBx protein's several carcinogenic roles;
• DNA damage brought on by oxidative stress and mitochondria;
• Dysregulated non-coding RNA networks.
Even in patients without cirrhosis, these processes work together to provide a pro-tumorigenic hepatic milieu, which supports the high prevalence of HCC in chronic HBV infection.

4. CLINICAL IMPLICATIONS

Significant therapeutic ramifications throughout the spectrum of therapy result from the deep molecular understanding of the pathophysiology of HBV infection and its progression to liver disease and hepatocellular carcinoma (HCC). These include better prognostic and diagnostic instruments, customized treatment plans, and improved monitoring techniques. The translational bridge from bench to bedside is reflected in the following sections, which go into greater detail about these topics.

4.1 Diagnosis and Disease Monitoring

Accurate diagnosis and ongoing monitoring are the first steps towards managing a chronic HBV infection effectively. In order to determine infection phase, viral replication status, and infectivity, routine screening uses serological markers such as hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), antibody profiles (anti-HBs, anti-HBc), and quantitative HBV DNA viral load assays (European Association for the Study of the Liver [EASL], 2017).
Since HBV covalently closed circular DNA (cccDNA) and viral integration are known to play a crucial role in hepatocarcinogenesis, emerging diagnostic techniques are concentrating on surrogate biomarkers of these processes. For example, circulating HBV RNA transcripts and serum levels of hepatitis B core-related antigen (HBcrAg) indicate cccDNA activity, offering a more direct indicator of the viral reservoir than HBV DNA alone, (Yuen *et al.*, 2018). These indicators enhance the evaluation of illness prognosis and treatment effectiveness, especially in patients receiving antiviral therapy.
Furthermore, liver biopsy has been supplanted by non-invasive liver fibrosis evaluation methods including transient elastography (FibroScan) and serum fibrosis panels (e.g., FibroTest) as standard procedures for staging cirrhosis and fibrosis, which are important indicators of HCC risk, (Castera *et al.*, 2019). A thorough and dynamic assessment of the course of the disease is made possible by the integration of molecular data with imaging and serum indicators.

4.2 Antiviral Therapy: Impact and Limitations

According to Terrault et al. (2018), nucleos(t)ide analogues (NAs) like entecavir and tenofovir continue to be the cornerstone of chronic HBV treatment because of their strong suppression of viral replication and high barrier to resistance. Research from clinical trials and real-world investigations consistently demonstrates that long-term viral suppression lowers the incidence of HCC, fibrosis development, and hepatic inflammation, (Kim *et al*., 2016).

However, the persistence of cccDNA and integrated viral DNA, which continue to drive oncogenic processes through HBx expression and chromosomal instability, makes complete eradication of HBV rare even with effective viral suppression. This explains why patients receiving antiviral medication, particularly those with cirrhosis or a history of infection, have a decreased but not completely abolished risk of HCC, (Yuen *et al.*, 2018).

Novel therapeutic approaches beyond viral suppression are desperately needed, as evidenced by the ongoing carcinogenic stimulation from integrated HBV DNA and HBx protein. These include substances that target the transcriptional activity of cccDNA, the functions of HBx proteins, and the epigenetic makeup of infected hepatocytes. There are encouraging paths toward a functional cure thanks to current research on CRISPR/Cas9-mediated genome editing, small molecules that block HBx-DNA interactions, and epigenetic modifiers like histone deacetylase inhibitors, (Block *et al*., 2017; Revill *et al.*, 2019).

4.3 Surveillance and Early Detection of Hepatocellular Carcinoma

In individuals with a chronic HBV infection, surveillance for HCC is essential for early tumor diagnosis, which greatly enhances prognosis and increases available treatments. According to international guidelines, individuals at high risk, such as those with cirrhosis, a family history of HCC, or higher HBV DNA levels, should have a biannual abdominal ultrasonography with or without a serum alpha-fetoprotein (AFP) measurement (EASL, 2018).

In order to improve surveillance accuracy, new molecular biomarkers are being assessed in light of the sensitivity and specificity limitations of AFP and ultrasonography. There is potential for non-invasive, early HCC identification by circulating microRNAs like miR-122 and miR-21, tumor suppressor gene methylation patterns, and next-generation sequencing of cell-free DNA to find HBV integration signals, (Huang *et al.*, 2019). By combining these biomarkers with imaging techniques, a precision medicine strategy to surveillance might be introduced.

4.4 Risk Stratification and Personalized Medicine

More accurate risk stratification frameworks have been made possible by the molecular characterisation of HBV infection. For instance, individuals with high serum HBsAg levels and persistent viral replication, or those infected with HBV genotype C, are more likely to develop HCC (Yuen et al., 2018). Risk profiles are further altered by host genetic variations that impact fibrosis and immune response pathways (Marques *et al*., 2017).

Targets for customized medicine therapy are also identified by the biochemical pathways that are changed by the HBx protein and viral integration. A paradigm change towards immunotherapy, immune checkpoint drugs, such pembrolizumab and nivolumab, which alter the PD-1/PD-L1 pathways, have shown promise in treating HBV-related HCC (El-Khoueiry *et al.*, 2017). In therapeutic trials, epigenetic medications that target HBx-induced aberrant chromatin remodeling may be used in conjunction with immunological modulation and antiviral treatment.

Treatment customization based on host genetic background, virus genotype, and molecular biomarker profiles has the potential to maximize positive results, reduce side effects, and effectively allocate medical resources.

4.5 Preventive Strategies: Vaccination and Novel Therapeutics

Globally, particularly in endemic areas, the implementation of universal HBV vaccination programs has significantly decreased the incidence of HBV-related HCC and HBV prevalence (Schillie et al., 2018). Since early childhood infections and vertical transmission are closely linked to chronicity and carcinogenesis, neonatal vaccination continues to be the most effective preventive strategy. Therapeutic vaccines that aim to restore HBV-specific immune responses in patients with chronic infection are complementing current vaccination regimens.

The goal of these vaccinations is to prevent immune evasion caused by HBx and persistent antigen exposure. Therapeutic vaccines, either by themselves or in combination with antiviral drugs, have demonstrated promising immunogenicity and viral load reduction in early clinical trials, (Revill *et al*., 2019). The development of new antiviral drugs that target cccDNA, viral entry receptors (such as NTCP inhibitors), and host factors crucial for viral replication is also guided by our understanding of the molecular biology of HBV. According to Block *et al.*, (2017), these medicines are necessary to prevent HCC and accomplish the HBV functional cure, which is sustained HBsAg loss with or without anti-HBs seroconversion.

Summary

The molecular pathophysiology of HBV has clinical implications for liver disease and HCC diagnosis, therapy, surveillance, and prevention. While antiviral medications lessen the viral burden but do not completely eradicate the carcinogenic hazards connected to viral integration and HBx, developments in biomarker discovery enhance diagnostic accuracy and risk assessment. This emphasizes the necessity of developing new treatment approaches that focus on these pathways. Early HCC identification is promised by surveillance programs that use molecular biomarkers, and customized

therapy strategies based on host and viral molecular profiling are starting to take shape.
In addition to developing therapeutic vaccinations and new antivirals targeted at functional cure, preventive vaccination is still crucial. Improving outcomes for HBV-infected patients and lowering the worldwide burden of HBV-related liver disease require a bridge between genetic research and clinical practice.

5. PUBLIC HEALTH STRATEGIES

Controlling the worldwide burden of hepatitis B virus (HBV) infection and its aftereffects, such as chronic liver disease and hepatocellular carcinoma (HCC), continues to depend heavily on public health initiatives. Vertical transmission, which historically accounted for a sizable share of chronic infections globally, has been significantly reduced with the introduction and use of neonatal HBV vaccine and maternal screening with prompt immunoprophylaxis. However, there are still issues, especially with increasing screening and connecting adults to care and boosting vaccine coverage in high-prevalence areas, (Sung *et al*., 2012).

5.1 Neonatal Vaccination and Maternal Screening

One of the most successful public health initiatives in the fight against infectious diseases is the implementation of universal newborn HBV immunization programs. In order to finish the immunization series, the World Health Organization (WHO) advises giving the first dose of the HBV vaccine within 24 hours of birth, followed by additional doses (WHO, 2022). The bulk of chronic HBV infections in endemic areas are caused by mother-to-child transmission (M, TCT), which can be avoided with this early immunization, (Shin *et al.,* 2016).
Simultaneously, HBV-infected moms can be identified through maternal screening for HBV surface antigen (HBsAg) during pregnancy. Timely hepatitis B immunoglobulin (HBIG) administration in conjunction with the vaccine is beneficial for infants born to HBsAg-positive mothers, particularly those with high virus loads or HBeAg positivity. This combined prophylactic approach lowers MTCT rates to less than 1% (Pan et al., 2016). In nations with high vaccination rates, like Taiwan and China, these integrated programs have resulted in notable drops in the incidence of childhood HCC and HBV prevalence, (Chang *et al.,* 2018).

5.2 Challenges in Vaccination Coverage and Access

Despite these achievements, there are still significant vaccine coverage gaps, especially in low- and middle-income (LMIC) nations where the prevalence of HBV is still high. Obstacles include inadequate maternal health service utilization, vaccination stockouts, delayed birth dose administration, and a lack of adequate healthcare infrastructure, (Cutts *et al.,* 2016).
Although overall HBV vaccination coverage has increased, according to global estimates, only over 43% of babies in the WHO African Region receive the timely birth dose, while over 80% in the Western Pacific Region do so (WHO, 2022). Additionally, the COVID-19 pandemic interfered with regular immunization services, which could undo improvements, (Causey *et al.,* 2021). Community engagement, education initiatives, combining HBV vaccination with other maternal-child health services, and innovations like controlled temperature chain (CTC) vaccine formulations that enable cold-chain-independent delivery are some ways to increase coverage, (Martinez *et al*., 2019).

5.3 Adult Screening and Linkage to Care

Expanding adult screening, especially in high-risk populations (e.g., drug injectors, immigrants from endemic regions, and those with HIV co-infection), is crucial for early detection and linkage to care, even though neonatal vaccination targets new infections. National guidelines increasingly recommend universal or targeted HBV screening programs integrated into primary care and community health settings, (Simmons *et al*., 2020). However, a significant reservoir of chronically infected adults remains worldwide, and many are unaware of their infection due to the asymptomatic nature of early HBV disease, delaying diagnosis and treatment initiation (Lin & Kao, 2017).
But these initiatives are hampered by obstacles like stigma, lack of awareness, restricted access to healthcare, and inadequate funding. To address these issues, creative models that make use of digital health platforms, point-of-care testing, and community health workers are being tested (Kowdley *et al.,* 2019).

5.4 Prevention of Horizontal Transmission and Public Awareness

Apart from vertical transmission, horizontal transmission by mucosal or percutaneous exposure is still important, particularly in adults through sexual intercourse, blood transfusions, and hazardous injections. Comprehensive HBV control must include condom use, safe injection techniques, harm reduction initiatives, and strengthened blood safety, (WHO, 2017).
To de-stigmatize HBV infection, encourage testing and immunization, and inform people about the disease's transmission pathways and available treatments, public awareness campaigns are crucial. In order to meet elimination targets, the WHO Global Hepatitis Strategy 2016–2021 places a strong emphasis on community involvement and multisectoral collaboration, (WHO, 2016).

Summary

With the help of maternal screening with immunoprophylaxis and neonatal immunization, which drastically lower perinatal transmission, public health initiatives aimed at preventing HBV have made impressive strides. To stop the global HBV epidemic, however, issues with adult screening, vaccination coverage, and care linkage must be resolved. The WHO's goal of eradicating viral hepatitis as a public health threat by 2030 depends on bolstering healthcare infrastructure, increasing targeted

screening, raising public awareness, and incorporating innovative delivery models.

6. RESEARCH DIRECTIONS

The distinctive virological characteristics of HBV, especially its persistence as covalently closed circular DNA (cccDNA) and incorporation into the host genome, make it a significant worldwide health concern even with the advancements in antiviral therapy. These characteristics not only fuel viral chronicity but also neoplastic transformation via immunological modulation, chromosomal instability, and HBx-mediated epigenetic dysregulation. The goal of current research is to identify the molecular and genetic foundations of HBV pathogenesis in order to create tailored treatment plans, curative medicines, and predictive biomarkers.

6.1 Epigenomic Profiling and Biomarkers for Hepatocarcinogenesis

Finding molecular biomarkers that can forecast the development of hepatocellular carcinoma (HCC) is a crucial component of research on HBV-related liver cancer. Because chronically infected people have varying clinical outcomes, epigenomic profiling has become a potent tool for differentiating between high-risk and low-risk patients. By interacting with chromatin remodeling complexes, DNA methyltransferases (DNMTs), and histone-modifying enzymes, HBV, especially through the HBx protein, modifies the epigenetic landscape of host hepatocytes (Li *et al.*, 2021).

These alterations impact the expression of genes related to immune evasion, apoptosis, and cell cycle regulation. Certain patterns, such as hypermethylation of tumor suppressor genes (e.g., CDKN2A, GSTP1) and hypomethylation of oncogenes, have been found to be associated with the risk and progression of HCC by genome-wide methylation studies, (Guo *et al.*, 2020). As early indicators of malignant transformation, chromatin accessibility and histone modification signatures (such as H3K27ac and H3K4me3) are also being investigated. Enhancer areas and transcriptional networks causing oncogenesis in HBV-infected livers have been identified thanks to high-throughput methods like ATAC-seq and ChIP-seq, (Nault and Villanueva, 2021).

Furthermore, there is ongoing research into the use of circulating epigenetic biomarkers, such as methylation DNA fragments and non-coding RNAs (such lncRNAs like HULC and miR-122), as minimally invasive methods for the early diagnosis and prognosis of HBV-related HCC (Huang *et al.*, 2019).

6.2 Therapeutics Targeting cccDNA, HBx, and Integrated Viral DNA

- The persistence of cccDNA, a stable episomal viral minichromosome that acts as the transcriptional template for viral RNAs, is one of the main barriers to the treatment of chronic HBV infection. Most patients require lifelong therapy since current nucleos(t)ide analogues reduce HBV DNA synthesis but have little effect on cccDNA, (Revill *et al.*, 2019). Novel therapeutic approaches seek to specifically target, eradicate, or mute cccDNA. These consist of:
- **Gene editing technologies** such as CRISPR/Cas9, which can be designed to target and cleave cccDNA, although delivery and off-target effects remain significant challenges (Lucifora et al., 2021).
- **cccDNA epigenetic silencing agents**, such as small-molecule inhibitors of histone acetyltransferases or DNMTs, which aim to induce transcriptional dormancy of cccDNA, (Trepo *et al.*, 2014).
- **RNA interference (RNAi)** therapies, including siRNAs and antisense oligonucleotides that degrade viral transcripts and reduce antigen burden, potentially restoring immune function, (Yuen *et al*., 2022).
- Being a multipurpose regulator, HBx is still a desirable yet elusive target. Small compounds that disrupt HBx interactions with host epigenetic regulators and DDB1-containing E3 ligase complexes have been discovered recently, (Decorsière *et al.*, 2016). By focusing on these interactions, host restriction mechanisms may be restored and HBx-mediated degradation of Smc5/6 prevented.
  Targeting integrated HBV DNA, which is frequently transcriptionally active and plays a role in the formation of HBsAg and hepatocarcinogenesis, is another frontier. Emerging methods, such as site-specific recombinases and engineered nucleases, provide viable ways to inactivate or remove integrated sequences, even though they are currently irreversible, (Yang and Kao, 2021).

6.3 Personalized Medicine and Host-Viral Genomic Integration

An emerging concept in HBV care is personalized medicine, which uses genomic information from both the virus and the host to provide customized risk assessment, therapy, and surveillance plans. Analysis of viral mutations and genotyping sheds light on the course of the disease and the effectiveness of treatment. For example, basal core promoter mutations are linked to immune escape and liver injury, whereas genotype C is linked to an increased risk of HCC, (Yuen *et al.*, 2018). The selection of antiviral medications can be influenced by changes in the reverse transcriptase domain linked to resistance.

According to Marques *et al*., (2017), host genetic variants, including those in the HLA locus, IFNL3/4, and PNPLA3, have been linked to the formation of HCC, fibrosis progression, and vulnerability to chronic infection. Multiple SNP-integrated polygenic risk scores (PRS) are being created to stratify patients and customize the level of screening.

Predictive models of illness development and treatment outcomes are increasingly being constructed using multi-omics techniques, which combine genomics,

transcriptomics, proteomics, and metabolomics. Large-scale HBV data sets are being subjected to machine learning and artificial intelligence techniques in order to find trends that conventional approaches might miss, (Oikonomou *et al*., 2022).

Ultimately, the integration of host and viral molecular profiles into clinical decision-making tools could revolutionize HBV care, transitioning from population-based to precision medicine models.

Summary

Three transformative directions will drive future HBV research: (1) finding strong molecular and epigenetic biomarkers predictive of hepatocarcinogenesis and disease progression; (2) creating treatments that target cccDNA, HBx, and integrated HBV DNA; and (3) advancing personalized medicine through thorough host and viral genomic profiling. By offering specialized, long-lasting, and reasonably priced treatments, these research initiatives seek to not only enhance therapeutic results but also support international HBV eradication objectives.

REFERENCES

Block, T. M., Mehta, A., Fimmel, C., & Jordan, R. (2017). Molecular viral oncology of hepatocellular carcinoma. *Oncogene*, 36(33), 4722–4732. https://doi.org/10.1038/onc.2017.137

Bouchard, M. J., & Schneider, R. J. (2004). The enigmatic X gene of hepatitis B virus. *Journal of Virology*, 78(23), 12725–12734. https://doi.org/10.1128/JVI.78.23.12725-12734.2004

Brouwer, W. P. (2013). Unfolded protein response in HBV infection and disease progression. *Journal of Hepatology*, 58(6), 1231–1233. https://doi.org/10.1016/j.jhep.2013.01.027

Cai, X. (2012). miR-122 inhibits proliferation and tumorigenesis of hepatocellular carcinoma by downregulation of ADAM17. *Oncology Reports*, 27(5), 1715–1722. https://doi.org/10.3892/or.2012.1729

Castera, L., Friedrich-Rust, M., & Loomba, R. (2019). Noninvasive assessment of liver disease in patients with hepatitis B or C. *Gastroenterology*, 156(2), 293-310.e7. https://doi.org/10.1053/j.gastro.2018.08.060

Causey, K., Fullman, N., Sorensen, R. J., Galles, N. C., Zheng, P., Aravkin, A. Y., and Mokdad, A. H. (2021). Estimating global and regional disruptions to routine childhood vaccine coverage during the COVID-19 pandemic in 2020: A modelling study. *The Lancet*, 398(10299), 522-534. https://doi.org/10.1016/S0140-6736(21)01337-4

Chang, M. H., Chen, C. J., Lai, M. S., Hsu, H. M., Wu, T. C., Kong, M. S. and Chen, D. S. (2018). Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *New England Journal of Medicine*, 336(26), 1855-1859. https://doi.org/10.1056/NEJM199706263362602

Cutts, F. T., Izurieta, H. S., & Rhoda, D. A. (2016). Measuring coverage in MNCH: Design, implementation, and interpretation challenges associated with tracking vaccination coverage using household surveys. *PLoS Medicine*, 13(4), e1002028. https://doi.org/10.1371/journal.pmed.1002028

Decorsière, A. (2016). Hepatitis B virus X protein identifies the Smc5/6 complex as a host restriction factor. *Nature*, 531(7594), 386–389. https://doi.org/10.1038/nature17170

Decorsière, A., Mueller, H., van Breugel, P. C., Abdul, F., Gerossier, L., Beran, R. K. and Strubin, M. (2016). Hepatitis B virus X protein identifies the Smc5/6 complex as a host restriction factor. *Nature*, 531(7594), 386–389. https://doi.org/10.1038/nature17170

Deng, L., et al. (2013). Epigenetic regulation of HBV replication by histone modification and chromatin remodeling. *Current Opinion in Virology*, 3(6), 644–650. https://doi.org/10.1016/j.coviro.2013.09.005

El-Khoueiry, A. B., Sangro, B., Yau, T., Crocenzi, T. S., Kudo, M., Hsu, C. and Melero, I. (2017). Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *The Lancet*, 389(10088), 2492-2502. https://doi.org/10.1016/S0140-6736(17)31046-2

El-Serag, H. B. (2012). Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology*, 142(6), 1264–1273.

European Association for the Study of the Liver (EASL). (2017). EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *Journal of Hepatology*, 67(2), 370–398. https://doi.org/10.1016/j.jhep.2017.03.021

European Association for the Study of the Liver (EASL). (2018). EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *Journal of Hepatology*, 69(1), 182–236. https://doi.org/10.1016/j.jhep.2018.03.019

Feitelson, M. A., & Lee, J. (2007). Hepatitis B virus HBx and hepatocarcinogenesis. *Cancer Letters*, 254(2), 160–170. https://doi.org/10.1016/j.canlet.2007.03.028

Friedman, S. L. (2008). Hepatic fibrosis — overview. *Toxicology*, 254(3), 120–129. https://doi.org/10.

Guo, Y., Ren, J., Wang, X., Qu, Z., & Liu, Y. (2020). DNA methylation in hepatocellular carcinoma: Mechanisms and clinical significance. *Clinical Epigenetics*, 12(1), 105. https://doi.org/10.1186/s13148-020-00894-6

Huang, A., Zeng, Y., & Yan, Y. (2019). Circulating microRNAs as biomarkers for early detection of hepatocellular carcinoma: A meta-analysis. *Scientific Reports*, 9(1), 5887. https://doi.org/10.1038/s41598-019-42299-1

Huang, A., Zeng, Y., & Yan, Y. (2019). Circulating microRNAs as biomarkers for early detection of hepatocellular carcinoma: A meta-analysis. *Scientific Reports*, 9(1), 5887. https://doi.org/10.1038/s41598-019-42299-1

Kim, G. A., Lim, Y. S., Han, S., Choi, J., Shim, J. H., Kim, K. M., and Lee, Y. S. (2016). High risk of hepatocellular carcinoma and death in patients with immune-tolerant phase chronic hepatitis B. *Gut*, 66(9), 1706–1712. https://doi.org/10.1136/gutjnl-2015-310691

Kowdley, K. V., Wang, C., Welch, S., Roberts, H., & Brosgart, C. L. (2019). Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. *Hepatology*, 60(1), 200-209. https://doi.org/10.1002/hep.27438

Levrero, M., & Zucman-Rossi, J. (2016). Mechanisms of HBV-induced hepatocellular carcinoma. *Journal of Hepatology*, 64(1), S84–S101.

Li, M., Sun, R., Xu, W., and Liu, Y. (2021). Epigenetic regulation of HBV cccDNA: Implications for novel biomarkers and therapeutic targets. *Frontiers in Genetics*, 12, 667153. https://doi.org/10.3389/fgene.2021.667153

Lin, C. L., & Kao, J. H. (2017). The global burden of hepatitis B virus infection and impact of vaccination. *Journal of Hepatology*, 68(4), 691-699. https://doi.org/10.1016/j.jhep.2017.11.016

Lok, A. S. F., Zoulim, F., Dusheiko, G., & Ghany, M. G. (2016). Hepatitis B cure: From discovery to regulatory approval. *Journal of Hepatology*, 67(4), 847–861.

Lucifora, J. (2014). Specific and nonhepatotoxic degradation of nuclear hepatitis B virus cccDNA. *Science*, 343(6176), 1221–1228.

Lucifora, J., Xia, Y., Reisinger, F., Zhang, K., Stadler, D., Cheng, X., ... & Protzer, U. (2021). Specific and nonhepatotoxic degradation of nuclear hepatitis B virus cccDNA. *Science*, 346(6205), 1221–1225. https://doi.org/10.1126/science.1261755

Marques, A. H. (2017). Host genetic factors and risk of hepatocellular carcinoma in chronic hepatitis B. *World Journal of Hepatology*, 9(4), 174–183. https://doi.org/10.4254/wjh.v9.i4.174

Marques, A. (2017). Host genetic factors and risk of hepatocellular carcinoma in chronic hepatitis B. *World Journal of Hepatology*, 9(4), 174–183. https://doi.org/10.4254/wjh.v9.i4.174

Martinez, J. C., Hartigan-Go, K. (2019). Controlled temperature chain (CTC) vaccines: A review of the landscape. *Vaccine*, 37(5), 695-702. https://doi.org/10.1016/j.vaccine..12.021

McMahon, B. J. (2009). The natural history of chronic hepatitis B virus infection. *Hepatology*, 49(S5), S45–S55.

Nault, J. C., & Villanueva, A. (2021). Biomarkers for hepatobiliary cancers. *Hepatology*, 73(S1), 115–127. https://doi.org/10.1002/hep.31478

Oikonomou, A., Karanikas, C. A., & Tzovaras, D. (2022). Machine learning in chronic liver disease: Applications in diagnosis and prognosis. *Liver International*, 42(2), 249–259. https://doi.org/10.1111/liv.15087

Pan, C. Q., Duan, Z., Dai, E., Zhang, S., Han, G., Wang, Y., and Zou, H. (2016). Tenofovir to prevent hepatitis B transmission in mothers with high viral load. *New England Journal of Medicine*, 374(24), 2324-2334. https://doi.org/10.1056/NEJMoa1508660

Perz, J. F., Armstrong, G. L., Farrington, L. A., Hutin, Y. J., & Bell, B. P. (2006). The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *Journal of Hepatology*, 45(4), 529–538.

Revill, P. A., Chisari, F. V., Block, J. M., Dandri, M., Gehring, A. J., Guo, H., ... & Zoulim, F. (2019). A global scientific strategy to cure hepatitis B. *The Lancet Gastroenterology & Hepatology*, 4(7), 545–558. https://doi.org/10.1016/S2468-1253(19)30119-0

Revill, P. A., Chisari, F. V., Block, J. M., et al. (2016). A global scientific strategy to cure hepatitis B. *Lancet Gastroenterology & Hepatology*, 1(6), 403–404.

Revill, P., Testoni, B., Locarnini, S., & Zoulim, F. (2019). Global strategies are required to cure and eliminate HBV infection. *Nature Reviews Gastroenterology & Hepatology*, 16(4), 239–250. https://doi.org/10.1038/s41575-019-0125-5

Schillie, S., Vellozzi, C., Reingold, A., Harris, A., Haber, P., Ward, J. W., & Nelson, N. P. (2018). Prevention of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Recommendations and Reports*, 67(1), 1–31. https://doi.org/10.15585/mmwr.rr6701a1

Schweitzer, A., Horn, J., Mikolajczyk, R. T., Krause, G., & Ott, J. J. (2015). Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between

1965 and 2013. *The Lancet*, 386(10003), 1546–1555.

Seeger, C., & Mason, W. S. (2015). Molecular biology of hepatitis B virus infection. *Virology*, 479–480, 672–686.

Seeger, C., & Mason, W. S. (2015). Molecular biology of hepatitis B virus infection. *Virology*, 479–480, 672–686.

Shin, H., Kim, J., & Yim, H. J. (2016). Mother-to-child transmission of hepatitis B virus and prevention strategies. *Clinical and Molecular Hepatology*, 22(3), 294-302. https://doi.org/10.3350/cmh.2016.22.3.294

Simmons, B., Saleem, J. J., Hill, A., Riley, S., & Cooke, G. S. (2020). Hepatitis B testing and treatment coverage in low- and middle-income countries, 2016 to 2019: A systematic review and meta-analysis. *PLoS Medicine*, 17(7), e1003060. https://doi.org/10.1371/journal.pmed.1003060

Tavis, J. E. (2019). The antiviral potential of targeting the HBV core protein. *Viruses*, 11(8), 660.

Terrault, N. A., Lok, A. S. F., McMahon, B. J., Chang, K. M., Hwang, J. P., Jonas, M. M., ... & Yawn, B. P. (2018). Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*, 67(4), 1560–1599. https://doi.org/10.1002/hep.29800

Trepo, C., Chan, H. L. Y., & Lok, A. (2014). Hepatitis B virus infection. *The Lancet*, 384(9959), 2053–2063. https://doi.org/10.1016/S0140-6736(14)60220-8

Tseng, T. C., Liu, C. J., Yang, H. C., Su, T. H., Wang, H. Y., Chen, C. H., ... & Chen, D. S. (2020). Serum hepatitis B surface antigen levels and risk of hepatocellular carcinoma: A systematic review and meta-analysis. *Hepatology Communications*, 4(3), 453–462. https://doi.org/10.1002/hep4.1462

Tu, T., Budzinska, M. A., Shackel, N. A., & Urban, S. (2017). HBV DNA integration: Molecular mechanisms and clinical implications. *Viruses*, 9(4), 75.

Tu, T., et al. (2017). HBV DNA integration: Molecular mechanisms and clinical implications. *Viruses*, 9(4), 75.

Urban, S., et al. (2014). The HBV life cycle: Entry and morphogenesis. *Viruses*, 6(2), 682–705.

WHO. (2024). *Updated Guidelines on the Prevention and Management of Chronic Hepatitis B Infection*. Geneva: World Health Organization.

Wieland, S. F., & Chisari, F. V. (2005). Stealth and cunning:

World Health Organization (WHO). (2016). Global hepatitis report 2016. https://apps.who.int/iris/handle/10665/246177

World Health Organization (WHO). (2017). Guidelines on hepatitis B and C testing. https://www.who.int/publications/i/item/9789241549981

World Health Organization (WHO). (2022). Hepatitis B vaccines: WHO position paper, July 2022. *Weekly Epidemiological Record*, 97(27), 301-320. https://www.who.int/publications/i/item/who-wer9727-301-320

Yan, H., Zhong, G., Xu, G. (2012). Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. *eLife*, 1, e00049.

Yang, H. C., & Kao, J. H. (2021). Persistence of hepatitis B virus covalently closed circular DNA in hepatocytes: Molecular mechanisms and clinical significance. *Emerging Microbes & Infections*, 10(1), 407–415. https://doi.org/10.1080/22221751.2021.1890134

Yuen, M. F., Chen, D. S., Dusheiko, G. M. (2018). Hepatitis B virus infection. *Nature Reviews Disease Primers*, 4(1), 18035.

Yuen, M. F., Chen, D. S., Dusheiko, G., Janssen, H. L., Lau, D. T., Locarnini, S. & Zoulim, F. (2018). Management of chronic hepatitis B: consensus statement from the Asian Pacific Association for the Study of the Liver. *Hepatology International*, 12(6), 421–441. https://doi.org/10.1007/s12072-018-9886-4

Yuen, M. F. (2018). Management of chronic hepatitis B: 2018 update from the Asian Pacific Association for the Study of the Liver (APASL). *Hepatology International*, 12(6), 421–441. https://doi.org/10.1007/s12072-018-9886-4

Yuen, M. F., Gane, E., Kim, D. J., Weilert, F., Yoon, J. H., Kudo, M., and Janssen, H. L. A. (2022). Antiviral activity of small interfering RNA against hepatitis B virus in patients with chronic hepatitis B infection. *Journal of Hepatology*, 77(3), 759–768. https://doi.org/10.1016/j.jhep.2022.03.032

Zhang, Y., Zhang, L., & Yu, C. (2022). Epigenetic regulation in HBV-related hepatocellular carcinoma: From basic mechanisms to clinical implications. *Biomolecules*, 12(3), 387.