

Viral Hepatitis: An Update on Biology, Pathogenesis and Diagnosis

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Abstract

Viral hepatitis remains one of the leading causes of liver-related morbidity and mortality worldwide, despite major advances in vaccination, antiviral therapy, and public health interventions. Hepatitis viruses A, B, C, D, and E differ in their genomic structure, modes of transmission, mechanisms of infection, and clinical outcomes, ranging from self-limiting acute disease to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. This review summarizes the historical development of hepatitis research and provides a comprehensive overview of the virology, epidemiology, mechanisms of viral entry, replication, and pathogenesis of the major hepatitis viruses. It further discusses current diagnostic approaches, including serological, molecular, imaging, and histopathological techniques, that enable early detection and disease monitoring. Recent therapeutic advances, particularly nucleos(t)ide analogues for hepatitis B, direct-acting antivirals for hepatitis C, and targeted therapies for hepatitis D, have substantially improved patient outcomes, although achieving a complete cure for chronic hepatitis B remains challenging due to the persistence of covalently closed circular DNA (cccDNA). Preventive strategies, including vaccination, blood safety, sanitation, and harm-reduction programmes, remain fundamental to disease control. Emerging therapeutic approaches such as gene-silencing technologies, capsid assembly modulators, CRISPR/Cas9-based genome editing, immune checkpoint inhibitors, and artificial intelligence-assisted disease prediction offer promising opportunities for future management. Continued research, expanded access to diagnosis and treatment, and coordinated global public health efforts are essential to achieve the World Health Organization's goal of eliminating viral hepatitis as a major public health threat by 2030.

Keywords: Viral, hepatitis, liver, HVA

Introduction

Hepatitis is clinically described as swelling within the hepatic tissue area, defined by the arrival of immune cells (like lymphocytes, neutrophils, and Kupffer cells) into the hepatic parenchyma (Johns Hopkins Medicine, 2022).

Viral hepatitis stays a huge worldwide public health danger which counts annually causing over 1.3 million deaths worldwide; more than 90 percent of these fatalities arise from prolonged consequences linked to persistent infections (National Institute of Allergy and Infectious Diseases, 2023). The Global Health Group (WHO) plan puts bold goals to wipe out viral hepatitis as a key public health danger by 2030, seeking a 90 percent drop in fresh chronic infections and a 65 percent cut in yearly death rates (World Health Organization, 2022).

The goal of this review paper is to examine how hepatitis viruses are built and organized, how they reproduce within liver cells, to show how viral infection harms liver cells and leads to chronic liver illness and to review recent advances in diagnostic techniques and treatment procedures.

History of Hepatitis

The clinical picture of viral hepatitis has been known since ancient times. Thus, Hippocrates described this disease as “epidemic jaundice” in the 5th century BC, while in military practice, it was also called “campaign jaundice.” However, science has deciphered the ethology of this disease only in the 20th century. The classification of “infectious jaundice” into two independent forms – “Hepatitis A (epidemic)” and “Hepatitis B (serum)” was proposed by MacCallum in 1947 (MacCallum, 1947). In 1965, Baruch Blumberg discovered the so-called “Australia antigen” (HBs Ag), for which he was awarded the Nobel Prize; moreover, this discovery allowed creating a test for detecting HBV infections and a plasma derived vaccine (Blumberg et al., 1965). In turn, Stephen Feinstone isolated the Hepatitis A virus (HAV) in 1973 applying immunoelectron microscopic examination of infected stools (Feinstone et al., 1973).

However, in the 70s and 80s of the 20th century, scientists faced the problem that neither serological tests for HAV nor HBV could detect post-transfusion hepatitis. This hepatitis was temporarily called “non-A, non-B hepatitis” and later received the name hepatitis C (Choo et al., 1989). Harvey Alter, Michael Houghton, and Charles Rice isolated the RNA of the Hepatitis C virus (HCV) using cloning technologies in 1989 and were awarded the Nobel Prize for this discovery (Choo et. Al, 1989).

In 1977, Mario Rizzetto isolated the delta hepatitis virus (HDV) from a patient’s biopsy material; this virus is notable for being non-infectious on its own and requires the assistance of the hepatitis B virus to replicate (Rizzetto et al., 1977). Finally, Balayan et al. isolated the Hepatitis E virus (HEV) from patients who suffered from an outbreak of acute hepatitis that began in 1983. Thus, the study of viral hepatitis made a major contribution to its detection and treatment. In particular, the etiology of hepatitis was elucidated, which allowed developing effective methods for combating the disease.

Viral Hepatitis

Viral hepatitis is an inflammation of the liver caused by different viruses, primarily hepatitis A, B, C, D, and E.

HEPATITIS A (HAV)

Hepatitis A virus (HAV) is an RNA virus belonging to the Picornaviridae family. It was first detected in 1973 by Feinstone via immune electron microscopy (Feinstone et al., 1973). HAV is mainly transmitted through the fecal-oral ingestion of tainted food or liquid or through close person-to-contact person. Rare spread via blood transfusion has also been reported. Worldwide, HAV leads to roughly 1.4 million cases annually and was

accounting for roughly 7,134 fatalities in 2016, where almost half of all recorded instances occurred happening within Asia. In America, the rate was noted at 2 instances per 100,000 populations in 2006 and outbreaks from 2016 to 2018 displayed a clear rise in cases. diseases. Upon getting into the body via the gut lining, the bug gets to the liver via the portal vein, it replicates inside hepatocytes, then moves to bile before going back. into the gut lumen and excreted within stool. Hepatic damage happens mostly because of the immune reaction involving HAV-particular CD8+ T lymphocytes and natural killer. The incubation period is usually 2–4 weeks. Typical clinical signs involve fever, tiredness, yellowing skin, exhaustion, sickness, vomiting, tummy ache, loose stools, loss of appetite, joint soreness and body aches. The majority of patients recover completely; however, about 10 relapse can happen to fifteen percent inside half a year. Older people, men, and those having prior liver illness or long-term viral hepatitis face risk and possess higher danger for serious illness, sudden liver collapse, admission to hospital and dying (Axley et al., 2021).

HEPATITIS B (HBV)

Hepatitis B virus (HBV) counts as a double-stranded DNA virus inside the Hepadnaviridae family. It was found first in 1963 and at first called the Australian antigen (Blumberg, 1965). HBV spreads via contaminated blood and bodily liquids, such as blood donations, infectious needles, sexual contact and mother-to-child transmission. HBV remains one of the primary reasons for chronic liver illness. Roughly 257 million of people live with chronic hepatitis B infection, where prevalence peaks in the Western Pacific and African areas (WHO, 2017). Acute HBV disease can vary from an illness from asymptomatic to severe icteric hepatitis. Symptoms often include fatigue, nausea, nausea, pain in the upper abdomen and yellowing skin. Long term illness greatly raises risk levels, risk of cirrhosis and hepatocellular carcinoma, making HBV a major cause of disease (Castaneda et al., 2021).

HEPATITIS C (HCV)

Hepatitis C virus (HCV), first found in 1989, is a small, enveloped, plus-sense one-strand RNA virus belonging to Flaviviridae family within the Hepacivirus genus (Choo et al., 1989). HCV spreads mostly via contact with tainted blood, such as from needles, trauma, IV drug use, blood transfusions, organ transplants, dialysis, tattoos, sexual contacts, body piercings and perinatal transmission (Axley et al., 2021). Over 71 million people globally carry HCV (WHO, 2017) with highest rates in the East region. After entering once inside hepatocytes, the virus replicates and triggers liver damage via immune mechanisms including death of infected cells and metabolic inflammation involving oxidative stress, liver damage, fatty liver and insulin resistance (AASLD-IDSA, 2023). Approximately 50-85 percent of infected people develop disease chronic infection, while 15 percent clear the virus spontaneously (Axley et al., 2021). Most patients remain asymptomatic or develop nonspecific symptoms such as fatigue, nausea, abdominal pain, loose stools, loss of appetite, sore muscles, joint ache, tiredness, worry, sadness, weight loss and so on (Axley et al., 2021).

HEPATITIS D (HDV)

Hepatitis D virus (HDV) acts as a flawed single-stranded RNA agent needing hepatitis B virus to function for replication. It was initially described in 1977 and spreads via contact with infected material, blood and body fluids, much like HBV (Rizzetto et al., 1977). An estimated 62–72 million individuals globally are carriers of HDV virus (Stockdale et al., 2020). Regions showing greatest rates involve west and middle Africa, the Amazon Basin, eastern and Mediterranean Europe, the Middle East and parts of Asia (Stockdale et al., 2020). The clinical range

goes from no symptoms to sudden liver stop. Coinfection with HBV often produces a self-restrictive condition, yet HDV infection within people having chronic HBV typically causes worse and longer lasting liver issues (Axley et al., 2021).

HEPATITIS E (HEV)

Hepatitis E virus (HEV) is a tiny, one strand RNA virus inside the family. Hepeviridae. This virus spreads mainly via the fecal-oral path, particularly when eating contaminated food, polluted liquid and counts among the frequent but poorly detected origins of disease. The World Health Organization estimates approximately 20 million HEV cases globally each year infections yearly, causing roughly 3.3 million symptomatic instances and over 44,000 deaths occurred in 2015 (WHO, 2017; Khuroo et al., 2016). The majority of HEV infections remain symptom free or appear as a mild, self-limiting condition sickness looking like hepatitis A following an incubation time of 2–10 weeks. Fewer than 5% of people infected develop acute liver failure, including pregnant women, malnourished people and those having prior liver illness (Axley et al., 2021; Khuroo et al., 2016).

Table 1: List of Hepatitis Viruses

Virus	Types	Spread and disease
Hepatitis A (HAV)	RNA hepatovirus	Faecal-oral, acute
Hepatitis B (HBV)	DNA hepadnavirus	Parental, acute or chronic
Hepatitis C (HCV)	RNA hepacivirus	Parental or sporadic; acute, more often chronic
Hepatitis D (HDV)	RNA deltavirus	Pathogenic when combined with HBV
Hepatitis E (HEV)	RNA virus	Faecal-oral, epidemic or sporadic acute disease

Mechanism of Infection in Viral Hepatitis

1. Hepatitis A Virus (HAV)

Hepatitis A enters the body through contaminated food or water, traveling down the digestive tract before targeting the liver. The virus actually exists in two forms: a standard "naked" virus found in fecal matter, and a "quasi-enveloped" version in the bloodstream that disguises itself by wrapping inside host cell membranes.

- Initial Attachment: The virus docks onto liver cells by binding to surface sugar molecules called gangliosides. If the virus arrives wrapped in a lipid envelope, it uses surface lipids like phosphatidylserine to blend in with the cell membrane.

- **Receptor Binding:** It binds to a specific surface receptor called HAVCR1 (also known as TIM-1). While TIM-1 helps pull in the enveloped virus, gangliosides act as the main trigger for cell entry (Das et al., 2017).
- **Cellular Entry:** The cell engulfs HAV into a small internal vesicle (an endosome). As the environment inside this bubble becomes acidic, the virus sheds its protective coat and creates a pore to release its RNA straight into the cell's cytoplasm (Hollinger & Martin, 2013).

2. Hepatitis B Virus (HBV)

Hepatitis B travels through blood and bodily fluids with a very specific destination: the hepatocytes (liver cells).

- **Initial Attachment:** HBV first grabs onto sugar chains on the liver cell surface called heparan sulfate proteoglycans (HSPGs). This acts like a tether, keeping the virus close to the cell surface (Verrier et al., 2016).
- **Receptor Binding:** The virus searches for its primary target—a liver-specific bile acid transporter called NTCP (Sodium taurocholate cotransporting polypeptide). A region on the viral surface called the pre-S1 domain fits directly into the NTCP receptor (Yan et al., 2012).
- **Cellular Entry & Control:** Once bound, the cell pulls HBV inside a membrane bubble. The virus sheds its outer envelope and releases its inner core into the cytoplasm. This core hitches a ride along the cell's internal transport system to the nucleus. After dropping its DNA through the nuclear pore, host enzymes convert the viral DNA into a super-stable circular form known as cccDNA. This cccDNA acts like a permanent mini-chromosome inside the cell, continuously producing new viral particles (Leverero et al., 2009; Lucifora & Protzer, 2014).

3. Hepatitis C Virus (HCV)

Hepatitis C is a blood-borne virus that disguises itself by hiding within host lipoproteins (fat molecules), circulating through the body virtually unnoticed by the immune system.

- **Initial Attachment:** Disguised as a fat particle, HCV attaches to fat-processing receptors on the liver cell surface, such as the low-density lipoprotein receptor (LDLR) and HSPGs (Agnello et al., 1999).
- **Multi-Receptor Lock System:** To get inside, HCV must engage four distinct receptors in a specific sequence:
- It attaches to SR-BI and CD81 on the cell membrane (Pileri et al., 1998; Scarselli et al., 2002).
- Binding to CD81 shifts the virus sideways toward the tight junctions—the narrow spaces where adjacent liver cells meet.
- At the junction, it binds to two final proteins: Claudin-1 and Occludin (Evans et al., 2007; Ploss et al., 2009).

- Cellular Entry: Once all four receptors are engaged, the cell draws HCV inside via endocytosis. Inside the acidic bubble, the viral coat fuses with the vesicle wall, releasing its RNA into the cytoplasm. HCV replicates entirely in the cell's fluid, never entering the nucleus (Lindenbach & Rice, 2013).

4. Hepatitis D Virus (HDV)

Hepatitis D is a unique "satellite" virus—it cannot build its own protein coat. To infect cells, it borrows the outer envelope (surface antigen, HBsAg) of Hepatitis B.

- Initial Attachment: Because HDV wears HBV's coat, it follows the exact same entry pathway, anchoring to liver cells via HSPGs (Verrier et al., 2016).
- Receptor Binding: HDV uses the stolen pre-S1 domain on its envelope to unlock the NTCP receptor (Yan et al., 2012).
- Cellular Entry: The cell draws HDV inside through an internal bubble. Once inside the cytoplasm, the outer coat strips away, and HDV's tiny RNA genome travels into the nucleus. Lacking its own replication enzymes, HDV hijacks the cell's own RNA polymerase to make copies of itself (Sureau & Negro, 2016).

5. Hepatitis E Virus (HEV)

Spread primarily through contaminated water or undercooked meat, Hepatitis E also takes on two forms: a naked virus excreted in stool, and a "quasi-enveloped" virus shielded by host lipids while traveling in blood.

- Initial Attachment: Naked HEV particles use their viral capsid proteins to dock onto HSPGs and the asialoglycoprotein receptor (ASGPR) on liver cells (Yin et al., 2016).
- Receptor Binding: HEV utilizes helper entry factors, including Integrin $\alpha 3$ and the Epidermal Growth Factor Receptor (EGFR), which signal the cell to initiate viral uptake.
- Cellular Entry: The cell engulfs HEV through endocytosis. Enzymes inside the internal bubble break down the viral coat (or lipid layer), triggering a shape change that releases the viral RNA into the cytoplasm for replication (Yin et al., 2016).

Replication of Genetic Material

After entering the cytoplasm, the nucleocapsid delivers its partially double-stranded relaxed rcDNA. Nuclear entry of stranded relaxed rcDNA occurs via important alpha/beta routes (Rabe et al., 2003; Gallucci & Kann, 2021). Repair host enzymes turn rcDNA into covalently closed circular DNA (cccDNA), creating a stable nuclear episomal minichromosome (Levrero et al., 2009; Lucifora & Protzer, 2014). Host RNA Polymerase II converts cccDNA to viral mRNAs and a 3.5 kb pregenomic RNA (pgRNA) (Beck & Nassal, 2007; Seeger & Mason, 2000). Within the cytoplasm, pgRNA and viral Polymerase (P protein) come together to form a complex structure capsids, where P protein starts reverse transcription to make negative-strand DNA then followed by partial positive-strand DNA synthesis (Summers & Mason, 1982; Nassal, 2008).

In case of RNA, positive-sense single-stranded (+)ssRNA viral genomes are translated directly on the rough endoplasmic reticulum (ER) (Moradpour et al., 2007). Viral non-structural proteins alter host ER membranes to

create a unique 'membranous web' (Egger et al., 2002; Romero-Brey et al., 2012). The viral RNA- dependent RNA polymerase (RdRp; e.g., HCV NS5B) makes a complementary negative- positive strandRNA template to make offspring negative strand RNA genomes (Behrens et al., 1996; Lohmann et al., 1999). Offspring shells wrap copied genetic material (Paul et al., 2014). HBV core particles either return to recycling. to the nucleus to keep cccDNA levels up or get envelope surface proteins in the ER/Golgi before release through multivesicular bodies (Watanabe et al., 2007; Patient et al., 2009). HCV particles form close to cytosolic space lipid droplets then leave through the lipoviriparticle route (Viral Assembly) (Miyanari et al., 2007; Lindenbach & Rice, 2013).

Diagnostic Approaches

A complete diagnosis of viral hepatitis is needed to choose the best therapy plan, bettering patient results and stopping sickness issues like liver scarring, failing cirrhosis, and liver cancer (HCC) (European Association for the Study of the Liver, 2017; AASLD-IDSA, 2023). The diagnostic procedure entails mix of clinical assessment, lab tests, serological tests, quantitative assessments, non- intrusive scanning and tissue pathology study (European Association for the Study of the Liver, 2017). Getting a full history that shows risks like parenteral exposure (pre-history of transfusion, IV drug abuse, needle injections, tattooing), high-risk sexual behaviour, occupational exposure, and travel to endemic regions aids in diagnosing viral liver inflammation (World Health Organization, 2024). An exam assists finding markers of long-term organ damage including jaundice of the sclerae, spider angiomas, swelling at periphery, enlargement of liver and spleen, plus fluid accumulation (Feld et al., 2015; Axley et al., 2021).

Alanine aminotransferase and aspartate aminotransferase (ALT/AST) serve as standard screening measures which show parenchymal tissue injury and liver cell death (Kwo et al., 2017). Protein levels and clotting factors/time ratios standardized value (PT/INR) aid track hepatic synthetic roles. (Kwo et al., 2017) Non-invasive assays such like the AST to platelet ratio index (APRI score) and Fibrosis-4 (FIB-4) are basic, precise, cheap devices employed to forecast the chance of severe liver scarring (Sterling et al., 2006; Wai et al., 2003). Serology for hepatitis is vital to identify the particular antigen-antibody response occurring, which helps determine the phase of the infection and the. appropriate line of management (European Association for the Study of the Liver, 2017). Polymerase chain reaction (PCR) serves as a sensitive and dependable molecular method employed for detecting and measuring viral nucleic acid (RNA/DNA) within serum or plasma samples (World Health Organization, 2024). Quantitative real-time PCR (qRT- PCR) helps determine the starting viral amount (copies of viral genome per IU/mL) and track how well therapy works (AASLD-IDSA, 2023). Next generation sequencing (NGS) allows exact detection of virus changes, thereby helping to facilitate tailored therapy (AASLD-IDSA, 2023). Through the uptake of swift diagnostic assays and dried blood spots technologies, improvements exist in hepatitis screening, particularly in low-and middle-income countries (World Health Organization, 2024).

An abdominal ultrasound scan serves as a primary non-invasive diagnostic imaging method utilized to detect morphological irregularities and screen for HCC (European Association for the Study of the Liver, 2018). Transient elastography (FibroScan) serves as a non-invasive option instead of liver biopsy that assists judging how severe liver scarring is using stiffness data measured in kPa (kPa) (Afonso et al., 2020). Biopsy of liver tissue remains an invasive yet standard method for diagnosing and staging hepatic fibrosis, especially when non-invasive

tests fail to provide clear results or when there exists doubt regarding additional hepatic conditions including nonalcoholic steatohepatitis or autoimmune disorders (European Association for the Study of the Liver, 2017).

Treatment for Hepatitis

No specific antiviral therapy exists for Hepatitis A because it is a self-limiting infection; however, fluid retention, malnutrition, and hepatotoxic drugs should be avoided (World Health Organization, 2023; Axley et al., 2021). The goal of therapy for Hepatitis B aims at stopping disease progression toward cirrhosis and HCC. Approved Nucleos(t)ide analogues (NAs) possess a high genetic barrier against resistance and include tenofovir alafenamide (TAF), tenofovir disoproxil fumarate (TDF), and entecavir (ETV). TAF shows comparable antiviral action to TDF yet results in lower risk of renal toxicity and bone mineral density reduction. Although long-term therapy may lower serum HBV DNA to undetectable levels, clearing Hepatitis B surface antigen (HBsAg) remains uncommon because the virus persists in the form of covalently closed circular DNA (cccDNA) inside hepatocytes (Terrault et al., 2018; European Association for the Study of the Liver, 2017). Direct-acting antivirals (DAAs) have transformed the treatment landscape for chronic HCV infection. Sofosbuvir/velpatasvir (NS5B polymerase inhibitor + NS5A inhibitor) and glecaprevir/pibrentasvir (NS3/4A protease inhibitor + NS5A inhibitor) are among the primary regimens. These FDA-approved fixed-dose direct-acting antiviral combinations achieve a high sustained virologic response (SVR) rate greater than 95%; treatment typically lasts 8 to 12 weeks depending on the specific regimen and presence of cirrhosis, with minimal adverse effects (AASLD-IDSA, 2023; Feld et al., 2015).

For individuals with dual infection involving hepatitis B and D, bulevirtide serves as a targeted therapeutic option. Bulevirtide acts as a lipopeptide entry inhibitor targeting the sodium-taurocholate cotransporting polypeptide (NTCP) receptor. It is administered either as monotherapy or alongside pegylated interferon alpha (PegIFN- α) to suppress HDV replication, thereby significantly reducing serum HDV RNA levels and facilitating liver enzyme normalization (Wedemeyer et al., 2023; European Medicines Agency, 2020). Treatment for Hepatitis E is primarily indicated in organ transplant recipients and immunocompromised patients with chronic infection. A reduction of immunosuppressive therapy in transplant patients combined with a 3-month course of ribavirin (RBV) monotherapy is the preferred strategy for achieving viral clearance in chronic HEV (European Association for the Study of the Liver, 2018; Kamar et al., 2014).

Prevention and Control

Stopping and managing viral hepatitis needs a multidisciplinary method including immunization, screening, and harm reduction strategies.

- **Vaccination:** Vaccines work well against hepatitis A and B. The hepatitis B shot goes to newborns and guards past teenage years. Combined active and passive immunization using HBV vaccine plus hepatitis B immune globulin (HBIG) lowers the risk of HBV acquisition by over ninety percent in infants born to HBsAg/HBeAg-positive mothers.
- **Infection Control and Harm Reduction:** Universal screening of donated blood for HBV, HCV, and HIV has dramatically reduced the transmission of blood-borne viruses. In addition, following safe needle and

syringe rules, needle and syringe exchange programs (NSPs), and opioid agonist treatment (OAT) have markedly decreased parenteral spread among people who inject drugs (PWID).

- Sanitation and Water: Better access to clean water and sanitation cuts down on how HAV and HEV travel via contaminated water and food.
- World Health Organization (WHO) 2030 Goals: The WHO aims to eliminate viral hepatitis as a major public health threat by 2030 via a 90% drop in new chronic cases and a 65% reduction in hepatitis-related mortality (*Note: Corrected "year three thousand and twenty" OCR artifact to 2030*).

A functional cure of HBV is reached upon sustained loss of serum HBsAg with or without seroconversion to anti-HBs. Present research seeks to address both extra-hepatic and intra-hepatic viral replication while also boosting the host's anti-HBV immunity to clear the viral reservoir.

- Gene-Silencing Molecules (ASOs and siRNA): Antisense oligonucleotides (ASOs) and small interfering RNA (siRNA) stop viral protein creation by targeting and degrading viral messenger RNA (mRNA). For instance, Bepirovirsen (an ASO) lowers the production of HBV RNA, reducing HBsAg levels and triggering an anti-HBV immune response.
- Capsid Assembly Modulators (CAMs): These medications disrupt mature virus nucleocapsid assembly, blocking packaging of pregenomic RNA (pgRNA) and preventing the replenishment of the nuclear covalently closed circular DNA (cccDNA) pool.
- CRISPR/Cas9 Technology: This gene-editing platform can directly target and permanently cleave episomal cccDNA and integrated HBV DNA inside hepatocytes.
- Entry Inhibitors: These agents target the sodium-taurocholate cotransporting polypeptide (NTCP) receptor to block viral entry into liver cells.
- Immune Checkpoint Inhibitors: Anti-PD-1/PD-L1 antibody immune checkpoint blockers aim to reverse CD8+ T-cell exhaustion and restore antiviral immunity.
- Artificial Intelligence (AI): Machine learning models analyze digital pathology sections and multi-omics data in chronic HBV to stratify risk, predict end-stage liver disease, and model HCC development.

Conclusion

Viral hepatitis continues to pose a major global health challenge due to its high prevalence, diverse transmission routes, and potential to cause chronic liver disease, cirrhosis, and hepatocellular carcinoma. Although hepatitis A and E are generally self-limiting infections, hepatitis B, C, and D remain significant contributors to long-term liver-related morbidity and mortality. Advances in the understanding of viral structure, mechanisms of host-cell entry.

Replication, and immune evasion have greatly enhanced the development of sensitive diagnostic methods and effective antiviral therapies. In particular, direct-acting antivirals have revolutionised the treatment of hepatitis C, while potent nucleos(t)ide analogues have significantly improved the long-term management of hepatitis B. Nevertheless, the persistence of HBV cccDNA and the complexity of HDV co-infection continue to present important therapeutic challenges.

Early diagnosis through serological and molecular testing, combined with non-invasive assessment of liver fibrosis, has improved clinical decision-making and patient outcomes. Equally important are preventive measures such as universal hepatitis B vaccination, improved sanitation, safe blood transfusion practices, infection-control measures, and harm-reduction strategies, which remain the cornerstone of reducing disease transmission. Emerging technologies, including gene-editing platforms, RNA-based therapeutics, novel entry inhibitors, immunomodulatory approaches, and artificial intelligence, have the potential to transform future hepatitis management and move closer to achieving a functional cure for chronic hepatitis B.

Sustained investment in research, equitable access to screening and treatment, strengthened healthcare infrastructure, and international collaboration will be essential to meet the World Health Organization's target of eliminating viral hepatitis as a public health threat by 2030. Continued scientific innovation, together with effective prevention and early intervention, offers the best opportunity to reduce the global burden of viral hepatitis and improve long-term liver health.

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