Recent Advances in the Diagnosis and Management of Viral Hepatitis

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ABSTRACT

Viral hepatitis, caused by hepatitis A, B, C, D and E viruses, remains one of the leading causes of chronic liver disease, cirrhosis and hepatocellular carcinoma worldwide, with hepatitis B and C viruses together responsible for the overwhelming majority of hepatitis-related mortality. Over the past few years, the field has moved rapidly on three fronts: diagnosis, drug discovery and vaccination. Point-of-care nucleic acid and antigen assays have shortened the gap between testing and treatment, while quantitative biomarkers such as HBV RNA and hepatitis B core-related antigen are being explored as tools to guide therapy and predict outcomes. Direct-acting antivirals have transformed hepatitis C into a curable infection, and the first targeted therapy for hepatitis D, the entry inhibitor bulevirtide, has moved from conditional approval to full regulatory approval in multiple regions. For hepatitis B, novel classes of agents including small interfering RNA therapeutics, capsid assembly modulators and immune-modulatory approaches are advancing through clinical trials in pursuit of a functional cure, defined as sustained loss of hepatitis B surface antigen. Vaccine science continues to evolve alongside these therapeutic advances, with high global coverage of the conventional hepatitis B vaccine, ongoing development of messenger RNA-based prophylactic and therapeutic hepatitis B vaccines, and progress toward wider licensure of the only approved hepatitis E vaccine. This review summarises recent advances in the diagnosis and management of viral hepatitis, with particular emphasis on drug discovery and vaccine development, and outlines the challenges that remain on the path to the World Health Organization's 2030 hepatitis elimination targets.

KEYWORDS: Viral hepatitis, diagnosis, antiviral therapy, drug discovery, vaccines, elimination

INTRODUCTION

Viral hepatitis continues to be one of the world's foremost public health challenges. Hepatitis B virus (HBV) and hepatitis C virus (HCV) together account for the great majority of hepatitis-related deaths globally, causing chronic infection, cirrhosis, liver failure and hepatocellular carcinoma in hundreds of millions of people. Hepatitis A virus (HAV) and hepatitis E virus (HEV) are transmitted predominantly through the faecal-oral route and are usually self-limiting, though HEV can cause severe disease in pregnant women and in patients with pre-existing liver disease. Hepatitis D virus (HDV) is a defective virus that requires the presence of HBV for replication and produces the most aggressive form of chronic viral hepatitis.[1]

The World Health Organization has set an ambitious target of eliminating viral hepatitis as a public health threat by 2030, defined as a 90% reduction in new chronic infections and a 65% reduction in mortality compared with a 2015 baseline. Meeting this target depends on progress in three interlinked areas: earlier and simpler diagnosis, more effective and accessible drug therapy, and broader vaccine coverage, including the development of new prophylactic and therapeutic vaccines. Considerable progress has been reported in each of these areas over the past few years, and this review brings together recent developments with an emphasis on drug discovery and vaccines.[1,2]

RECENT ADVANCES IN DIAGNOSIS

Timely diagnosis remains the single largest gap in the global hepatitis response, since a substantial proportion of people living with chronic HBV or HCV infection remain undiagnosed. Traditional laboratory-based serological and nucleic acid testing requires trained personnel, dedicated infrastructure and, often, more than one clinic visit, all of which limit access in resource-limited and community settings.[1,22]

- **Point-of-care (POC) testing:** High-sensitivity point-of-care nucleic acid tests for HCV RNA can now deliver a qualitative result within about 40 to 60 minutes, enabling single-visit test-and-treat strategies in primary care, harm-reduction and community outreach settings. Point-of-care HBsAg and anti-HCV antibody assays have also seen wider adoption, substantially improving screening efficiency.[19,20]
- **Reflex and multiplex testing:** Reflex testing algorithms, in which a reactive antibody screen automatically triggers nucleic acid testing on the same sample, reduce loss to follow-up between screening and confirmation of active infection.[19]
- **Novel HBV biomarkers:** Quantitative HBV RNA and hepatitis B core-related antigen (HBcrAg) are being investigated as surrogate markers of residual viral transcriptional activity in patients on nucleos(t)ide analogue therapy. Emerging evidence suggests that persistently detectable HBV RNA correlates with a higher risk of disease progression and hepatocellular carcinoma, making it a candidate biomarker for treatment monitoring and risk stratification, although it is not yet part of routine clinical practice.[10]
- **Simplified algorithms:** The World Health Organization has consolidated more than eighty evidence-based recommendations on hepatitis B, C and D testing and treatment (2015 to 2025) into a single implementation handbook, promoting the use of point-of-care and reflex testing and simplified, decentralised treatment pathways suitable for delivery outside specialist liver centres.[2,5,6]

ADVANCES IN DRUG DISCOVERY

Hepatitis C

The introduction of direct-acting antivirals (DAAs) has already transformed chronic hepatitis C from a lifelong illness into a curable infection, with cure rates exceeding 95% after eight to twelve weeks of oral therapy. Current efforts are focused less on new drug classes and more on simplifying treatment delivery: pan-genotypic regimens that remove the need for genotype testing, shortened treatment courses, and decentralised test-and-treat models that pair point-of-care RNA testing with same-day treatment initiation. Cumulatively, more than twenty million people have now received DAA therapy worldwide, and treatment costs in low- and middle-income countries have fallen substantially, improving access.[1,3]

Hepatitis B

Nucleos(t)ide analogues such as entecavir and tenofovir remain the backbone of chronic HBV therapy, suppressing HBV DNA to undetectable levels in the great majority of treated patients and allowing regression of fibrosis and cirrhosis with long-term use. However, these agents do not eliminate the covalently closed circular DNA (cccDNA) that persists in the nucleus of infected hepatocytes, so treatment is typically lifelong and true functional cure - sustained loss of hepatitis B surface antigen (HBsAg) with anti-HBs seroconversion - is achieved in only a small minority of patients. This has driven an active pipeline of more than thirty investigational agents directed at three broad strategies:[28,29,30,31]

- **Inhibition of viral replication and antigen production:** small interfering RNA (siRNA) therapeutics delivered via GalNAc-conjugate or lipid nanoparticle platforms silence HBV transcripts and have shown substantial, sustained reductions in HBsAg in early and mid-phase trials, with some agents also inducing anti-HBs seroconversion in a subset of patients when combined with pegylated interferon or capsid assembly modulators.[8,9,12,13]
- **Capsid assembly modulators:** these small molecules interfere with the correct assembly of the HBV nucleocapsid, blocking replication and, in combination regimens with siRNA agents, have produced deeper and more durable antigen suppression than either class alone.[11]
- **Immune modulation:** therapeutic strategies aimed at restoring HBV-specific T-cell and antibody responses, including therapeutic vaccination and checkpoint-directed approaches, are being combined with antiviral agents in an effort to achieve durable, treatment-free control of infection.[10,23,24]

Hepatitis D

Chronic hepatitis D, the most severe form of viral hepatitis, has historically been treated with pegylated interferon alpha alone, with limited efficacy and considerable toxicity. Bulevirtide, a first-in-class entry inhibitor that blocks the sodium taurocholate co-transporting polypeptide (NTCP) receptor used by both HBV and HDV to enter hepatocytes, received conditional approval in the European Union in 2020 and full approval in 2023 to 2024; it is now approved in several jurisdictions, including recent approval in the United States, marking the first dedicated therapy for this disease. Long-term data show that a large majority of patients who achieve undetectable HDV RNA at extended treatment durations maintain this response after stopping therapy. Combination regimens pairing bulevirtide with pegylated interferon, and newer investigational combinations pairing monoclonal antibodies against

HBsAg with siRNA agents, are in active clinical development and have shown encouraging virological and biochemical response rates.[14,15,16,17,18]

Hepatitis A and E

No specific antiviral therapy is approved for HAV or HEV infection; management remains supportive, since both infections are typically self-limiting in immunocompetent individuals. Ribavirin has shown benefit in selected cases of chronic HEV infection in immunosuppressed patients, such as solid organ transplant recipients, and remains the main pharmacological option in that setting.[1]

Prevention of mother-to-child transmission

Maternal antiviral prophylaxis has become a key strategy for eliminating HBV mother-to-child transmission, which remains the dominant route of new chronic infections in high-endemicity settings. Randomised and cohort data show that tenofovir disoproxil fumarate given during the third trimester to mothers with high viral loads, combined with timely birth-dose vaccination and hepatitis B immunoglobulin in the infant, reduces residual transmission to below 1%, and updated national and international guidelines now recommend maternal tenofovir prophylaxis as standard of care in this population.[32,33,34,35]

VACCINE DEVELOPMENT

Hepatitis B vaccine coverage

The recombinant hepatitis B vaccine remains one of the most successful vaccination programmes in history. Global three-dose coverage in infants has now surpassed 90%, and hepatitis B surface antigen prevalence among children under five years has fallen below the World Health Organization's 2025 target of 0.5% in most regions, reflecting the impact of the birth-dose strategy combined with the routine infant series. Coverage among healthcare workers, including dental and other allied health personnel, remains more variable, ranging from below 20% in some low-resource settings to over 75% in high-income countries, underscoring a persistent gap in occupational protection.[1,4]

Therapeutic and next-generation hepatitis B vaccines

Because existing prophylactic vaccines do not benefit those already chronically infected, considerable research is now directed at therapeutic vaccination as a component of functional-cure regimens. Messenger RNA (mRNA) platforms encoding HBV core, polymerase and surface antigens, delivered in lipid nanoparticles, have shown the ability to induce polyfunctional, antigen-specific T-cell responses and antibody production in preclinical models, and several mRNA-based therapeutic vaccine candidates have now entered early-phase clinical trials. These approaches are generally being explored in combination with antiviral agents such as siRNA therapeutics or capsid assembly modulators, on the premise that durable immune control is unlikely to be achieved by any single modality alone.[23,24]

Hepatitis E vaccine

Hecolin, a recombinant, alum-adjuvanted vaccine based on a capsid protein of HEV genotype 1, remains the only licensed hepatitis E vaccine worldwide. It is administered as three intramuscular doses and has demonstrated high efficacy with evidence of cross-genotype protection. The vaccine is licensed in China and Pakistan, with registration under way in other HEV-endemic countries; however, it has not yet received World Health Organization

prequalification, which remains a major barrier to global access, particularly for use in maternal immunisation programmes in endemic regions where HEV infection during pregnancy carries a high risk of severe disease.[7,25,26,27]

Hepatitis A and C vaccines

Inactivated hepatitis A vaccines remain highly effective and are recommended in national immunisation schedules in many endemic and high-risk settings. No vaccine currently exists for hepatitis C, owing to the high genetic diversity of the virus and its ability to evade neutralising antibody responses; several candidate vaccines targeting conserved viral epitopes remain in early-phase development.[1]

EMERGING THERAPEUTIC AND PREVENTIVE AGENTS

Table 1: summarises selected agents that illustrate the current direction of drug discovery and vaccine development in viral hepatitis.

Agent / Class	Target Virus	Mechanism	Development Status
Nucleos(t)ide analogues (e.g., entecavir, tenofovir)	HBV	Inhibit viral polymerase; suppress HBV DNA replication	Approved; standard of care
siRNA therapeutics (e.g., GalNAc-conjugated agents)	HBV	Silence viral transcripts; reduce HBsAg production	Phase II / III trials
Capsid assembly modulators	HBV	Disrupt nucleocapsid assembly and replication	Phase II trials, often combined with siRNA agents
Bulevirtide	HDV (with HBV)	NTCP entry-receptor blockade; prevents hepatocyte infection	Approved (EU, UK, Switzerland, Australia, USA)
Direct-acting antivirals (pan-genotypic regimens)	HCV	Inhibit NS3/4A, NS5A and NS5B viral proteins	Approved; curative in over 95% of patients
mRNA therapeutic vaccine candidates	HBV	Induce HBV-specific T-cell and antibody responses	Preclinical / early-phase clinical trials
Hecolin (HEV239)	HEV	Recombinant capsid protein; induces neutralising antibodies	Licensed in China and Pakistan; awaiting WHO prequalification

CHALLENGES AND FUTURE DIRECTIONS

- **Diagnostic gap:** the majority of people living with chronic HBV or HCV infection worldwide remain undiagnosed, limiting the reach of even highly effective therapies.[1,21,22]

- **Access and affordability:** newer HBV and HDV agents, and mRNA-based vaccine platforms, remain expensive and are largely confined to high-income settings, mirroring earlier disparities seen with DAA rollout for hepatitis C.[1,3]
- **Combination regimen complexity:** achieving functional cure in HBV is likely to require rational combinations of antiviral, immune-modulatory and vaccine-based approaches, raising questions of sequencing, duration and long-term safety that are still being worked out in ongoing trials.[10,11]
- **Regulatory and manufacturing barriers:** the hepatitis E vaccine's continued lack of World Health Organization prequalification illustrates how regulatory pathways can delay global access to an already-effective product.[7,25]
- **Occupational and healthcare-setting transmission:** sustained attention to infection-control practice and healthcare-worker vaccination coverage remains essential even as new drugs and vaccines are developed, since prevention of transmission in clinical settings continues to reduce the overall burden of disease.[4]

CONCLUSION

The diagnosis and management of viral hepatitis has advanced considerably in recent years. Point-of-care and simplified testing strategies are narrowing the diagnostic gap; hepatitis C has effectively become a curable disease; the first targeted therapy for hepatitis D has reached regulatory approval; and an expanding pipeline of siRNA, capsid assembly and immune-based agents is bringing a functional cure for hepatitis B within closer reach. Vaccine science continues to underpin prevention, with high global hepatitis B vaccine coverage, active development of mRNA-based prophylactic and therapeutic hepatitis B vaccines, and incremental progress toward wider licensure of the hepatitis E vaccine. Translating these scientific advances into equitable global access - through affordable diagnostics, simplified treatment delivery and broader vaccine availability - will determine whether the World Health Organization's 2030 hepatitis elimination targets can be met.

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