

# Prevention, Diagnosis, and Treatment Strategies for Viral Hepatitis: A Comprehensive Review

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## Abstract

Viral hepatitis, caused principally by hepatitis A, B, C, D, and E viruses, remains one of the leading infectious causes of morbidity and mortality worldwide, responsible for approximately 1.3 million deaths annually, a burden comparable to tuberculosis and HIV/AIDS. Hepatitis B and C together account for more than 95% of hepatitis-related deaths, driven largely by the long, often silent natural history of chronic infection that progresses to cirrhosis, hepatic decompensation, and hepatocellular carcinoma. This review synthesizes current evidence and international guidance on the prevention, diagnosis, and treatment of the five major hepatitis viruses. Preventive strategies discussed include universal hepatitis B birth-dose and infant vaccination, hepatitis A and E vaccination in endemic and outbreak settings, safe injection and blood-transfusion practices, harm-reduction programmes for people who inject drugs, and antenatal screening with tenofovir-based prophylaxis to interrupt mother-to-child transmission. Diagnostic advances reviewed include serological and molecular assays, point-of-care and reflex RNA testing algorithms for hepatitis C, non-invasive fibrosis assessment, and the expanding role of simplified testing in decentralized and primary-care settings. Treatment strategies encompass nucleos(t)ide analogue therapy and emerging finite regimens aiming at functional cure for hepatitis B, and pangenotypic direct-acting antiviral regimens that now cure more than 95% of hepatitis C infections. The review also addresses persistent gaps in diagnosis and treatment coverage, particularly in low- and middle-income countries and the WHO African and Western Pacific regions, and outlines priority actions required to meet the World Health Organization's 2030 hepatitis elimination targets. Continued investment in vaccination, decentralized testing, affordable antivirals, and integrated service delivery is essential to close the gap between available tools and their equitable global deployment.

**Keywords:** viral hepatitis; hepatitis B; hepatitis C; direct-acting antivirals; nucleos(t)ide analogues; vaccination; elimination; diagnosis

## **1. Introduction**

Viral hepatitis refers to inflammation of the liver caused by one of five distinct hepatotropic viruses — hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV). Although these agents differ in structure, mode of transmission, and natural history, together they constitute one of the most significant infectious disease burdens globally. According to the World Health Organization's most recent Global Hepatitis Report, hepatitis B and C alone claimed an estimated 1.34 million lives in 2024, with more than 4,900 new infections occurring every day, underscoring that transmission continues despite the availability of effective vaccines and curative therapies.

Chronic hepatitis B and C are responsible for over 95% of viral hepatitis mortality, largely through their long asymptomatic phase, during which progressive liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) can develop undetected for decades. As of 2022, approximately 254 million people were living with chronic hepatitis B and 50 million with chronic hepatitis C worldwide, yet only 13% of people with hepatitis B and 36% of people with hepatitis C had been diagnosed, and treatment coverage was even lower, at 3% and 20% respectively. These figures fall far short of the WHO 2025 interim targets of 60% diagnosed and 50% treated, illustrating a persistent and consequential gap between the tools available and their real-world deployment.

Hepatitis A and E, by contrast, are typically transmitted through the faecal-oral route via contaminated food and water and usually cause self-limited acute illness, although hepatitis E can cause severe disease in pregnant women and hepatitis A can occasionally cause fulminant hepatic failure. Hepatitis D is a satellite virus that requires co-infection with HBV to replicate and produces the most severe form of chronic viral hepatitis; WHO designated hepatitis D as carcinogenic in 2025 in recognition of its markedly accelerated risk of cirrhosis and liver cancer compared with HBV mono-infection.

The global response to viral hepatitis has entered a pivotal decade. WHO's elimination strategy, endorsed by member states, targets a 90% reduction in new chronic infections and a 65% reduction in mortality by 2030, relative to a 2015 baseline. Meeting these targets will require substantial scale-up of vaccination, blood and injection safety, harm reduction, simplified diagnostic algorithms, and affordable antiviral treatment, delivered through integrated and decentralized health services. This review provides a structured synthesis of current prevention, diagnosis, and treatment strategies for each of the five hepatitis viruses, drawing on recent WHO guidance, clinical practice guidelines from AASLD, IDSA, and EASL, and the contemporary peer-reviewed literature, with the aim of providing clinicians, public health practitioners, and researchers with an integrated, up-to-date reference.

## **2. Main Review**

### **2.1 Hepatitis A**

Hepatitis A virus is transmitted via the faecal-oral route, most commonly through ingestion of contaminated water or food, or through close person-to-person contact. Infection confers lifelong immunity and does not become chronic, but can cause prolonged or relapsing illness and, rarely, acute liver failure, particularly in older adults or those with pre-existing liver disease.

**Prevention** - The cornerstone of hepatitis A prevention is a safe and highly effective inactivated vaccine, administered as part of routine childhood immunization in many endemic countries or targeted to high-risk groups (travellers to endemic regions, men who have sex with men, people who use drugs, and people with chronic liver disease) in others. Improved water, sanitation, and hygiene infrastructure, together with food-safety practices, remain equally important for reducing transmission, especially in outbreak settings such as those linked to contaminated shellfish or produce.

**Diagnosis** - Acute hepatitis A is diagnosed serologically by detection of anti-HAV immunoglobulin M (IgM), which appears at symptom onset and typically persists for three to six months; anti-HAV immunoglobulin G (IgG) indicates past infection or vaccination and confers long-term immunity. Liver enzymes (ALT, AST) are typically markedly elevated during acute infection.

**Treatment** - There is no specific antiviral therapy for hepatitis A; management is supportive, focusing on rest, adequate nutrition and hydration, and avoidance of hepatotoxic substances including alcohol and certain medications. Hospitalization is reserved for patients with severe or fulminant disease.

## **2.2 Hepatitis B**

Hepatitis B virus is transmitted through perinatal exposure, percutaneous or mucosal contact with infected blood or body fluids, and sexual contact. The age at infection strongly determines chronicity risk: perinatal and early childhood infection carries a 80–90% risk of progression to chronic infection, whereas infection acquired in adulthood becomes chronic in less than 5% of cases, making prevention of mother-to-child and early childhood transmission the single highest-yield intervention.

**Prevention** - The hepatitis B vaccine, first licensed in the 1980s, is 90–95% effective in preventing infection when the birth dose is administered within 24 hours of delivery, followed by two or three additional doses in infancy. Global coverage of the three-dose infant series has surpassed 90% in many regions, but birth-dose coverage remains only around 43% globally and as low as 17% in the WHO African Region, leaving a substantial gap in perinatal protection. For pregnant women with high viral load (HBV DNA generally above 200,000 IU/mL) or HBeAg positivity, WHO and professional society guidelines recommend antiviral prophylaxis with tenofovir disoproxil fumarate during the third trimester in addition to infant vaccination and hepatitis B immunoglobulin where available, to further reduce residual transmission risk. Antenatal screening policies for hepatitis B have now been adopted by 129 countries, though implementation and birth-dose coverage remain uneven. Additional preventive measures

include blood and organ donor screening, safe injection practices, and harm-reduction services for people who inject drugs.

**Diagnosis** - Initial screening relies on detection of hepatitis B surface antigen (HBsAg); a positive result persisting beyond six months defines chronic infection. Further characterization includes HBeAg/anti-HBe status, quantitative HBV DNA, liver enzymes, and assessment of liver fibrosis using non-invasive tools such as transient elastography (FibroScan) or serum fibrosis indices (e.g., APRI, FIB-4), reducing reliance on liver biopsy. WHO's 2024 hepatitis B guidelines expanded treatment eligibility criteria to simplify decision-making in resource-limited settings, recommending treatment initiation based on a combination of HBV DNA level, ALT, and evidence of fibrosis or cirrhosis, rather than requiring extensive staging in all patients.

**Treatment** - First-line therapy for chronic hepatitis B consists of nucleos(t)ide analogues (NAs) with a high genetic barrier to resistance, principally tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), or entecavir. These agents durably suppress HBV DNA replication, normalize liver enzymes, and reduce the risk of cirrhosis and hepatocellular carcinoma, but rarely eliminate covalently closed circular DNA (cccDNA) in hepatocytes, meaning treatment is generally lifelong. Comparative studies suggest tenofovir-based regimens may achieve somewhat greater HBsAg decline and virological response than entecavir, with a favourable resistance profile, although TAF offers improved renal and bone safety relative to TDF. Because current NAs rarely achieve a 'functional cure' — defined as sustained loss of HBsAg with undetectable HBV DNA off treatment — substantial research effort is directed at novel strategies, including RNA interference agents, capsid assembly modulators, and immunomodulatory approaches such as therapeutic vaccines and toll-like receptor agonists, several of which are in phase II/III clinical trials. Pegylated interferon-alfa remains an option for selected patients, particularly those seeking a finite treatment course, though its use is limited by tolerability. Regular monitoring for hepatocellular carcinoma with ultrasound (with or without alpha-fetoprotein) is recommended for patients with cirrhosis or other high-risk features.

## 2.3 Hepatitis C

Hepatitis C virus is transmitted primarily through percutaneous exposure to infected blood, most commonly via unsafe injection practices, inadequately screened blood products, and injection drug use; sexual transmission occurs less efficiently but is important among certain populations, including men who have sex with men living with HIV. Unlike hepatitis B, there is no vaccine currently available for hepatitis C, making risk-reduction, screening, and treatment-as-prevention central to control efforts.

**Prevention** - Preventive measures include rigorous blood and organ donor screening, infection control and safe injection practices in healthcare settings, and harm-reduction programmes for people who inject drugs, including needle and syringe exchange and opioid agonist therapy. Because treatment now cures the great majority of infections, 'treatment as prevention' — identifying and curing infected individuals to interrupt onward transmission — has become a core pillar of elimination strategy, particularly within harm-reduction and correctional settings.

**Diagnosis** - Testing follows a two-step algorithm: an initial anti-HCV antibody test to identify prior or current exposure, followed by a quantitative HCV RNA (or core antigen) test in antibody-positive individuals to confirm active viraemia, since roughly one-quarter of infections resolve spontaneously and remain antibody-positive without ongoing infection. Point-of-care antibody and RNA assays and dried blood spot testing have expanded access to diagnosis in decentralized and low-resource settings. Non-invasive fibrosis staging using transient elastography or serum biomarkers guides assessment of disease severity and post-treatment monitoring, particularly for cirrhosis-related hepatocellular carcinoma surveillance.

**Treatment** - The development of pangenotypic direct-acting antivirals (DAAs) has transformed hepatitis C from a difficult-to-treat, often chronic infection into a curable disease, with sustained virologic response (cure) rates exceeding 95% after 8–12 weeks of oral therapy. Current first-line regimens recommended in AASLD/IDSA and EASL guidance include sofosbuvir/velpatasvir and glecaprevir/pibrentasvir, both effective across HCV genotypes without the need for genotype testing in most treatment-naïve patients, greatly simplifying care pathways. For the small proportion of patients who fail first-line DAA therapy, salvage regimens such as sofosbuvir/velpatasvir/voxilaprevir achieve high cure rates. Between 2014 and 2023, a cumulative 12.7 million people worldwide received DAA therapy, yet this still represents a minority of the estimated 50 million people living with chronic infection, reflecting persistent gaps in diagnosis, linkage to care, and treatment affordability, particularly in low- and middle-income countries. Special considerations apply to patients with decompensated cirrhosis, HIV or hepatitis B co-infection, end-stage renal disease, or prior liver transplantation, who should be managed in consultation with a hepatology specialist; treatment is generally deferred in pregnancy given limited safety data.

## 2.4 Hepatitis D

Hepatitis D virus is a defective RNA virus that can only replicate in the presence of HBV, occurring either as simultaneous co-infection or as superinfection of a person already chronically infected with HBV. Chronic hepatitis D produces the most rapidly progressive form of viral hepatitis, with markedly accelerated rates of cirrhosis, hepatic decompensation, and hepatocellular carcinoma compared with HBV mono-infection; WHO classified hepatitis D as carcinogenic in 2025 in recognition of this risk.

**Prevention** - Because HDV cannot establish infection without HBV, hepatitis B vaccination is fully protective against hepatitis D and remains the most effective preventive measure, particularly when delivered as part of universal infant immunization.

**Diagnosis** - All patients with HBsAg positivity should be considered for anti-HDV antibody screening at least once, with confirmation by HDV RNA quantification in antibody-positive individuals, since not all anti-HDV-positive patients have active viraemia.

**Treatment** - Historically, pegylated interferon-alfa was the only available therapy, with limited efficacy and poor tolerability. Bulevirtide, an entry-inhibitor that blocks the HBV/HDV shared receptor, has been approved in

several jurisdictions for chronic hepatitis D and represents a significant therapeutic advance, often used alone or in combination with pegylated interferon, though relapse after treatment discontinuation is common and long-term efficacy data continue to mature.

## 2.5 Hepatitis E

Hepatitis E virus is transmitted principally through the faecal-oral route via contaminated water in endemic regions of Asia and Africa (genotypes 1 and 2), and through consumption of undercooked meat from infected animals in industrialized countries (genotypes 3 and 4), where it is increasingly recognized as a zoonotic infection. Most infections are self-limited, but hepatitis E carries a case fatality rate of up to 20–25% in pregnant women, particularly during the third trimester, and can cause chronic infection in immunosuppressed individuals, including solid-organ transplant recipients.

**Prevention** - Prevention in endemic settings relies on safe water and sanitation infrastructure and food safety. A recombinant hepatitis E vaccine (HEV 239) has been licensed and used in outbreak response and for high-risk groups in China, though it is not yet in widespread global use; WHO has recommended its consideration for outbreak control and for protecting pregnant women in high-burden settings.

**Diagnosis** - Diagnosis relies on detection of anti-HEV IgM in acute infection, with HEV RNA testing used to confirm active infection, particularly in immunosuppressed patients who may not mount a robust antibody response, and to identify chronic infection.

**Treatment** - Most cases require only supportive care. In chronic hepatitis E, typically seen in transplant recipients, reduction of immunosuppression is the first step, with ribavirin therapy used in cases that do not resolve, since no HEV-specific antiviral is currently approved.

## 2.6 Cross-Cutting Strategies and Remaining Challenges

Beyond virus-specific measures, several cross-cutting strategies underpin progress toward hepatitis elimination. Simplified and decentralized testing — including point-of-care serology and RNA/DNA assays, reflex testing algorithms, and integration of hepatitis testing into HIV, primary care, antenatal, and harm-reduction services — is essential to close the diagnosis gap, given that most people with chronic hepatitis B or C remain undiagnosed. As of 2025, 123 countries had developed national hepatitis strategic plans, and hepatitis services had been integrated into primary health care in 80 countries and into HIV programmes in 128 countries, but integration into harm-reduction services remained limited to only 27 countries, a significant gap given the elevated burden of hepatitis C among people who inject drugs.

Affordability and supply of vaccines, diagnostics, and antivirals remain major barriers in low- and middle-income countries, where the burden of disease, particularly hepatitis B in the WHO African Region and hepatitis B and C in the Western Pacific Region, is highest. Continued price negotiation, generic manufacturing, and simplified

WHO-recommended treatment algorithms that reduce the need for specialist referral and extensive laboratory monitoring are central to expanding access. Stigma, limited awareness, and workforce constraints further impede case-finding and linkage to care in many settings.

Surveillance and monitoring have also improved, with WHO's Global Hepatitis Reporting System receiving data from 140 member states in the most recent 2025 reporting round, up from 113 in 2023, enabling more precise tracking of progress toward the 2030 targets of a 90% reduction in incidence and 65% reduction in mortality relative to 2015. Sustaining and accelerating this progress will require coordinated investment across vaccination, blood and injection safety, harm reduction, decentralized diagnosis, and affordable curative and suppressive therapy.

### **3. Conclusion**

Viral hepatitis remains a major, largely preventable and treatable cause of global mortality, with hepatitis B and C accounting for the overwhelming majority of disease burden through their capacity to establish chronic infection and silently progress to cirrhosis and hepatocellular carcinoma. Substantial biomedical progress has been achieved over the past two decades: hepatitis B vaccination has become one of the most successful immunization programmes in history, and pangenotypic direct-acting antivirals have transformed hepatitis C into a curable infection in the great majority of cases. Emerging therapies, including entry inhibitors for hepatitis D and novel agents pursuing a functional cure for hepatitis B, promise further gains. However, persistent and substantial gaps in diagnosis, treatment coverage, and equitable access — particularly birth-dose vaccination coverage, antenatal screening, and integration of services into harm-reduction and primary care — continue to undermine progress toward the World Health Organization's 2030 elimination targets. Achieving elimination will require sustained political commitment, affordable and simplified diagnostic and treatment pathways, expanded decentralized testing, and integration of hepatitis services across the continuum of primary care, maternal health, HIV, and harm-reduction programmes. Continued research into finite, curative regimens for hepatitis B and D, together with global scale-up of existing effective tools, offers a credible pathway to substantially reducing the burden of viral hepatitis over the coming decade.

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