AMERICAN JOURNAL OF APPLIED MEDICAL SCIENCE
ISSN: 2996-5101 (online) | ResearchBib (IF) = 10.81 IMPACT FACTOR
Volume-4| Issue-3| 2026 Published: |30-03-2026

UDC: 616.36-002.2-022-036.22-07-085

CHRONIC VIRAL HEPATITIS: MODERN PERSPECTIVES ON EPIDEMIOLOGY, PATHOGENESIS, DIAGNOSTICS AND ANTIVIRAL TREATMENT STRATEGIES (A COMPREHENSIVE SCIENTIFIC REVIEW)

https://doi.org/10.5281/zenodo.19060552

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Abstract

Background: Chronic viral hepatitis, caused predominantly by hepatitis B virus (HBV) and hepatitis C virus (HCV), constitutes one of the most significant infectious disease burdens globally, accounting for an estimated 1.1 million deaths annually. Despite the availability of effective antiviral therapies and a prophylactic vaccine for HBV, the majority of infected individuals remain undiagnosed and untreated, perpetuating the hepatic sequelae of progressive fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).

Objective: This review critically synthesizes contemporary research on the epidemiology, molecular pathogenesis, diagnostics, and therapeutic strategies for chronic HBV and HCV infection, with emphasis on evidence published between 2015 and 2024.

Key Findings: Global HBV prevalence remains approximately 254 million infections, while HCV affects approximately 50 million individuals worldwide, with pronounced regional heterogeneity. Advances in understanding viral-immune interactions have illuminated mechanisms of immune tolerance, T-cell exhaustion, and epigenetic regulation underlying viral persistence. Diagnostic innovation, including point-of-care nucleic acid testing and transient elastography, has substantially improved staging accuracy. The introduction of pan-genotypic direct-acting antivirals (DAAs) for HCV has transformed clinical outcomes, achieving sustained virological response (SVR) rates exceeding 95% in most populations. For HBV, long-term nucleos(t)ide analogue (NA) therapy suppresses viral replication

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but rarely achieves functional cure, with covalently closed circular DNA (cccDNA) persistence representing a fundamental barrier.

Scientific Significance: This review identifies critical gaps in global access to diagnostics and treatment, highlights emerging therapeutic targets including HBV cccDNA silencing and capsid assembly modulators, and underscores the urgency of achieving the WHO 2030 viral hepatitis elimination targets. These insights carry direct implications for global hepatology research, clinical practice, and public health policy.

Keywords

chronic hepatitis; hepatitis B virus; hepatitis C virus; liver fibrosis; antiviral therapy; hepatocellular carcinoma; global epidemiology; direct-acting antivirals; viral persistence; liver cirrhosis

Introduction

Chronic viral hepatitis remains among the most consequential infectious diseases of the modern era. The two dominant etiological agents — hepatitis B virus (HBV) and hepatitis C virus (HCV) — together account for approximately 96% of all hepatitis-related deaths worldwide, surpassing the combined mortality attributable to HIV, tuberculosis, and malaria in several global regions [1]. The clinical trajectory of chronic HBV and HCV infection is insidious: decades of smoldering hepatic inflammation and progressive fibrosis culminate in cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC), the fourth leading cause of cancer-related death globally [2].

The World Health Organization (WHO) has promulgated an ambitious hepatitis elimination strategy, targeting a 90% reduction in new infections and a 65% reduction in mortality by 2030 relative to 2015 baselines [3]. As of 2022, global progress toward these targets was profoundly inadequate, with only a fraction of infected individuals diagnosed and an even smaller proportion receiving guideline-concordant treatment [4]. This diagnostic and therapeutic gap reflects a complex interplay of structural, socioeconomic, and scientific barriers that demand coordinated intervention across multiple levels.

The scientific landscape of chronic viral hepatitis has been substantially reshaped over the past decade. The development of pan-genotypic direct-acting antivirals has rendered HCV curable in the vast majority of patients, fundamentally altering the disease's natural history in high-income settings [5]. For HBV, nucleos(t)ide analogues achieve durable virological suppression, yet functional cure remains elusive due to the persistence of intrahepatic covalently closed circular DNA (cccDNA), which serves as the viral transcriptional template and

cannot be eradicated by current antivirals [6]. These unresolved biological challenges underscore the need for continued investment in basic hepatology research alongside strengthened public health infrastructure.

This review synthesizes contemporary evidence across the full spectrum of chronic HBV and HCV disease — from molecular pathogenesis and population-level epidemiology to state-of-the-art diagnostics and antiviral therapy — with the aim of informing clinicians, researchers, and policymakers navigating an increasingly complex field.

Global Epidemiology of Chronic Hepatitis

Hepatitis B Virus

The global burden of chronic HBV infection is staggering in scale. A 2019 systematic review and modeling study estimated 257 million people living with chronic HBV infection (defined as hepatitis B surface antigen [HBsAg] positivity), corresponding to a global prevalence of 3.5% [7]. The epidemiological distribution is markedly heterogeneous: sub-Saharan Africa and the Western Pacific region together account for approximately 68% of the global HBV burden, with seroprevalence rates exceeding 8% in certain West African and East Asian populations [7]. By contrast, Western Europe and North America maintain low-endemicity profiles, largely attributable to the implementation of universal infant vaccination programs beginning in the 1980s and 1990s.

Transmission dynamics diverge substantially by region. In high-endemicity settings, perinatal and early childhood transmission predominate, establishing chronic infection in 80–90% of neonates born to HBeAg-positive mothers [8]. This vertical transmission route is particularly consequential given that perinatally acquired infection carries the highest lifetime risk of cirrhosis and HCC. In low-endemicity regions, horizontal transmission via sexual contact, injecting drug use, and healthcare-associated exposures accounts for the majority of new infections, predominantly affecting adults who typically clear the virus [9]. The global incidence of new HBV infections has declined considerably following vaccine scale-up, yet approximately 1.5 million new infections occur annually, reflecting persistent coverage gaps and ongoing transmission among unvaccinated adults [3].

Hepatitis C Virus

Recent WHO estimates place the global HCV burden at approximately 50 million individuals with chronic infection, a figure substantially revised downward from earlier projections partly due to direct-acting antiviral (DAA) treatment scale-up and refined seroprevalence modeling [4]. HCV seroprevalence is highest in the Eastern Mediterranean and European regions, particularly in Egypt, Pakistan, Russia, and parts of Central Asia. Egypt historically harbored the world's highest

national HCV prevalence (exceeding 10% in some studies), largely a consequence of large-scale parenteral antischistosomal treatment campaigns conducted between the 1960s and 1980s [10]. Injecting drug use represents the principal transmission route in most high-income countries, while unsafe therapeutic injections, unscreened blood transfusions, and inadequately sterilized medical equipment remain dominant drivers in resource-limited settings [11].

Unlike HBV, HCV does not integrate into host hepatocytes, and the absence of a prophylactic vaccine, combined with the silent progression of liver disease, has rendered population-level screening and case-finding critically important. An estimated 80% of HCV-infected individuals globally remain unaware of their diagnosis [4], a figure that impedes both treatment scale-up and transmission interruption. Socioeconomic marginalization — including poverty, incarceration, and homelessness — strongly predicts both infection risk and suboptimal engagement with care, highlighting the necessity of equity-centered approaches to elimination.

Molecular Pathogenesis and Disease Progression

HBV Replication and Immunobiology

HBV is a partially double-stranded DNA virus belonging to the Hepadnaviridae family. Following hepatocellular entry via the sodium-taurocholate cotransporting polypeptide (NTCP) receptor, the viral relaxed circular DNA (rcDNA) is transported to the nucleus, where host repair mechanisms convert it to cccDNA — an episomal minichromosome that serves as the transcriptional template for all viral RNAs [6]. The cccDNA pool is remarkably stable, with an estimated intrahepatic half-life ranging from weeks to potentially decades, and is largely refractory to current antiviral agents. Additionally, HBV DNA can integrate into host chromosomes, a process that does not contribute to productive replication but plays a significant role in HCC pathogenesis through insertional mutagenesis and promotion of genomic instability [12].

The immunopathogenesis of chronic HBV infection is fundamentally shaped by the host immune response and the developmental timing of infection. The predominant mechanism of hepatic injury is immune-mediated rather than directly cytopathic: HBV-specific CD8+ T cells recognize viral peptide-MHC class I complexes on hepatocyte surfaces and induce apoptosis through perforin/granzyme and Fas-FasL pathways [13]. In chronic infection, prolonged antigen exposure drives HBV-specific T cells toward exhaustion, characterized by upregulation of inhibitory receptors including PD-1, TIM-3, CTLA-4, and LAG-3, and a progressive loss of polyfunctional cytokine secretion capacity [13]. This T-cell exhaustion is reinforced by a tolerogenic hepatic microenvironment and elevated

levels of circulating HBsAg, which can desensitize and delete antigen-specific T cells.

HBV encodes several immunomodulatory proteins that facilitate immune evasion. The hepatitis B e antigen (HBeAg), a secreted form of the core protein, exerts tolerogenic effects, particularly in neonatal infection. HBsAg-containing subviral particles, produced in vast excess over complete virions, act as decoys that sequester neutralizing antibodies and exhaust B-cell responses [14]. The HBV X protein (HBx) functions as a transcriptional transactivator that dysregulates host gene expression, impairs proteasomal degradation of cccDNA-associated proteins, and promotes hepatocyte survival signaling — all properties with direct relevance to oncogenesis.

HCV Replication and Immune Evasion

HCV is a positive-sense single-stranded RNA virus of the Flaviviridae family, comprising seven major genotypes (1–7) with distinct geographic distributions and differential responsiveness to interferon-based therapy [15]. The viral life cycle encompasses receptor-mediated entry (involving CD81, SR-BI, claudin-1, and occludin), cytoplasmic replication within membranous web structures, and secretion via the very-low-density lipoprotein pathway. HCV replicates exclusively in the cytoplasm and does not establish a nuclear reservoir analogous to HBV cccDNA, which is why viral eradication is achievable with DAAs.

Chronic HCV infection results from the virus's extraordinary capacity to evade innate and adaptive immune responses. HCV employs multiple strategies to antagonize interferon signaling: the NS3/4A protease cleaves the mitochondrial antiviral signaling (MAVS) protein and TRIF, disrupting RIG-I- and TLR3-mediated interferon induction, respectively [15]. The viral NS5A protein further interferes with PKR-mediated antiviral responses. Genetic hypervariability in the HCV E1/E2 envelope proteins, driven by error-prone replication (estimated mutation rate 10^-4 substitutions per nucleotide per replication cycle), enables rapid escape from neutralizing antibodies [16]. At the adaptive immune level, HCV-specific CD4+ and CD8+ T cells exhibit functional exhaustion patterns similar to, yet mechanistically distinct from, those observed in HBV infection.

Fibrogenesis and Oncogenesis

Regardless of etiology, the fibro-inflammatory cascade represents the final common pathway of hepatocellular injury in chronic viral hepatitis. Activated hepatic stellate cells (HSCs), in response to pro-fibrogenic signals including TGF-beta1, PDGF, and angiotensin II, undergo phenotypic transformation to myofibroblasts, secreting extracellular matrix components — predominantly type I and III collagens — that progressively replace functional hepatic parenchyma [17].

Concurrently, portal myofibroblasts and bone marrow-derived fibrocytes contribute to the fibrotic matrix. The METAVIR system (F0–F4) provides standardized histological staging of fibrosis severity, with F4 (cirrhosis) defining the threshold at which portal hypertension and its complications become clinically manifest.

Hepatocellular carcinoma arises through a multistep oncogenic process driven by chronic inflammation, oxidative stress, and direct viral oncogenic mechanisms. In HBV-associated HCC, HBV DNA integration into the host genome activates proto-oncogenes (notably hTERT and CCNE1) and disrupts tumor suppressors (TP53, RB1), independent of cirrhosis [12]. In HCV-associated HCC, carcinogenesis is predominantly cirrhosis-dependent, mediated through sustained oxidative stress, IL-6/STAT3 signaling, and Wnt/beta-catenin pathway activation [17]. Remarkably, HCV cure with DAAs substantially reduces but does not eliminate HCC risk in patients with established cirrhosis, necessitating continued surveillance.

Advances in Diagnostic Methods

Serological Diagnostics

The initial serological diagnosis of HBV infection relies upon detection of HBsAg, anti-HBc antibodies (total and IgM), and HBeAg, together with their respective antibody responses. The pattern of serological markers enables classification of disease phase: immune-tolerant, immune-active (HBeAg-positive or -negative), inactive carrier, and resolved infection [18]. Third-generation enzyme-linked immunosorbent assays (ELISA) and chemiluminescent immunoassays achieve HBsAg sensitivity thresholds of 0.05 IU/mL, sufficient for routine clinical diagnosis. Quantitative HBsAg (qHBsAg) measurement has emerged as a clinically meaningful biomarker: qHBsAg levels below 1,000 IU/mL in HBeAg-negative patients identify inactive carriers with high accuracy, while a decline below 100 IU/mL during treatment is associated with higher probability of HBsAg clearance [18].

For HCV, the diagnostic cascade begins with anti-HCV antibody detection, which becomes reactive approximately 8–12 weeks following infection. Rapid diagnostic tests (RDTs) employing immunochromatographic platforms have achieved sensitivity and specificity values exceeding 98% in meta-analyses, enabling deployment in decentralized settings [19]. However, anti-HCV positivity cannot distinguish active from resolved infection, necessitating confirmatory HCV RNA quantification by nucleic acid testing (NAT). A reactive anti-HCV with undetectable HCV RNA indicates spontaneous or treatment-mediated clearance, while a detectable HCV RNA confirms current infection requiring treatment.

Molecular Diagnostics and Viral Quantification

Quantitative HBV DNA measurement by real-time polymerase chain reaction (qPCR) is indispensable for treatment eligibility assessment, therapeutic monitoring, and resistance surveillance. Current commercial assays (Roche COBAS AmpliPrep/COBAS TaqMan, Abbott RealTime HBV) have lower limits of detection of approximately 10–20 IU/mL and dynamic ranges spanning 1–9 log10 IU/mL, with excellent interlaboratory reproducibility using WHO-standardized international units [20]. HBV genotyping — performed by direct sequencing, restriction fragment length polymorphism, or line probe assays — informs prognosis and regional epidemiology but has limited therapeutic implications in the era of potent NAs. Resistance genotyping assumes critical importance when virological breakthrough occurs, as mutations in the polymerase gene (rtM204I/V, rtN236T) confer cross-resistance patterns relevant to second-line drug selection.

HCV RNA quantification by qPCR serves as the definitive confirmatory test for active infection, informs treatment eligibility, and constitutes the primary efficacy endpoint — sustained virological response (SVR12, defined as undetectable HCV RNA 12 weeks post-treatment) equates to virological cure [5]. HCV genotyping, historically essential for treatment regimen selection with interferon-based therapies, retains relevance for certain pan-genotypic regimens in treatment-experienced patients and resource-limited settings. Next-generation sequencing (NGS) platforms have enabled comprehensive resistance-associated substitution (RAS) profiling, providing insights into NS5A, NS5B, and NS3 RAS patterns that may inform retreatment decisions in DAA failures [16].

Non-Invasive Liver Fibrosis Assessment

Liver biopsy, long considered the gold standard for fibrosis staging, is associated with significant limitations including sampling variability, procedure-related complications (pain in up to 30%, major bleeding in 0.5% of cases), and poor patient acceptability [21]. The development and validation of non-invasive fibrosis assessment methods has fundamentally changed clinical practice. Transient elastography (FibroScan, Echosens) measures liver stiffness by quantifying shear wave propagation velocity through hepatic parenchyma; stiffness correlates strongly with METAVIR fibrosis stage (AUROC 0.85–0.92 for F4 diagnosis) and is now recommended as the preferred staging modality in multiple international guidelines [21]. Magnetic resonance elastography (MRE) offers superior accuracy across all fibrosis stages, with AUROC values of 0.93–0.97, and has been validated across diverse hepatic conditions, though its widespread adoption is constrained by cost and scanner availability.

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Serum-based fibrosis indices, including the FIB-4 index (calculated from age, ALT, AST, and platelet count) and the APRI score, offer practical, low-cost screening tools with acceptable diagnostic performance for excluding advanced fibrosis (AUROC 0.77–0.85 for F3–F4) in resource-limited settings [21]. Enhanced Liver Fibrosis (ELF) panel, measuring direct markers of matrix remodeling (PIIINP, HA, TIMP-1), provides additional diagnostic specificity. Emerging proteomic and glycomic biomarker panels, including the Mac-2 binding protein glycosylation isomer (M2BPGi), have demonstrated promising performance characteristics and may supplement or supplant current indices in future clinical algorithms [22].

Modern Antiviral Treatment Strategies

Chronic Hepatitis B

The therapeutic landscape for chronic HBV has been shaped by two principal modalities: pegylated interferon alfa (PEG-IFN) and oral nucleos(t)ide analogues (NAs). The preferred NAs — tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), and entecavir (ETV) — are recommended as first-line agents by all major hepatology societies (EASL, AASLD, APASL) due to their high barrier to resistance, potent viral suppression, and favorable long-term safety profiles [23]. TDF and ETV achieve HBV DNA undetectability in approximately 67–76% of HBeAg-positive and 90–93% of HBeAg-negative patients at 48 weeks, with sustained suppression rates approaching 100% after 5 years [23]. TAF, a prodrug with enhanced intrahepatic delivery, achieves equivalent antiviral efficacy to TDF at one-tenth the plasma dose, with significantly lower rates of renal tubular dysfunction and bone mineral density reduction — a critical advantage in patients with pre-existing nephropathy or osteoporosis.

Despite their virological efficacy, NAs suppress but do not eliminate intrahepatic cccDNA, resulting in HBsAg clearance rates of less than 1–3% per year on long-term therapy [23]. This biological reality underscores the inherent limitation of current HBV treatment: prolonged — in many cases indefinite — therapy is required to prevent virological relapse and disease progression. PEG-IFN offers a finite treatment course (48 weeks) and the possibility of immune-mediated HBsAg clearance, but is associated with substantial adverse effects (flu-like symptoms, cytopenias, neuropsychiatric toxicity), requires parenteral administration, and achieves HBsAg loss in only 3–7% of treated patients [24]. However, PEG-IFN-induced HBeAg seroconversion, achieved in approximately 27–32% of treated patients, can permit treatment discontinuation with durable virological control in appropriately selected individuals.

The concept of functional cure — defined as HBsAg loss with or without anti-HBs seroconversion — has emerged as the new treatment endpoint for HBV

therapy, analogous to SVR in HCV [6]. Novel therapeutic strategies targeting this goal include RNA interference (siRNA and antisense oligonucleotides) to suppress HBsAg production, capsid assembly modulators (CAMs) to disrupt core protein polymerization, entry inhibitors (bulevirtide, recently approved in Europe), and innate immune agonists (TLR7/8 agonists, RIG-I agonists) to restore intrahepatic antiviral immunity. Combination approaches pairing antigen reduction with immune stimulation represent the most promising avenue toward achieving functional cure [6].

Chronic Hepatitis C

The therapeutic revolution in HCV management, achieved through the development and clinical deployment of direct-acting antivirals, represents one of the most transformative advances in modern infectious disease medicine. DAAs target three viral non-structural proteins: NS3/4A serine protease (inhibitors: glecaprevir, grazoprevir, voxilaprevir), NS5A replication complex protein (inhibitors: pibrentasvir, elbasvir, velpatasvir, ledipasvir), and NS5B RNA-dependent RNA polymerase (inhibitors: sofosbuvir [nucleotide], dasabuvir [non-nucleoside]) [5]. Pan-genotypic regimens — notably sofosbuvir/velpatasvir (Epclusa), sofosbuvir/ledipasvir, and glecaprevir/pibrentasvir (Mavyret) — achieve SVR12 rates of 95–99% across all HCV genotypes in treatment-naive patients without cirrhosis in 8–12-week regimens [5].

DAA efficacy is maintained in clinically challenging populations including patients with compensated cirrhosis, advanced chronic kidney disease, prior treatment failure, and HIV co-infection, though certain combinations require dose adjustment or are contraindicated in the setting of hepatic decompensation [15]. The NS5A inhibitor-dominant resistance-associated substitutions (RASs) — particularly at positions Y93 and L31 in NS5A — can reduce SVR rates in some genotype 1a and 3 patients receiving NS5A-containing regimens, with clinical significance that varies by specific drug combination and baseline viral load [16]. In patients with NS5A RAS-harboring viruses who fail first-line therapy, retreatment with sofosbuvir/velpatasvir/voxilaprevir (Vosevi) for 12 weeks achieves SVR12 in approximately 96% of cases [5].

Despite the remarkable clinical efficacy of DAAs in clinical trial settings, the global reach of these therapies remains profoundly unequal. High-income countries have achieved substantial treatment uptake among diagnosed populations, yet many low- and middle-income countries (LMICs) face prohibitive drug costs, inadequate diagnostic infrastructure, and shortages of trained hepatology providers [4]. Generic DAA production, facilitated by voluntary licensing agreements and Medicines Patent Pool participation, has substantially reduced

costs in many LMIC settings, and pan-genotypic simplified treatment algorithms — removing the requirement for genotyping, resistance testing, and specialist oversight — have enabled task-shifted delivery through primary care platforms in several pioneering programs [11].

Complications and Long-Term Outcomes

The natural history of untreated or inadequately treated chronic viral hepatitis culminates in progressive hepatic fibrosis, cirrhosis, and its life-threatening complications. The annual rate of cirrhosis development in HBeAg-positive chronic HBV infection is approximately 2–5%, substantially higher in HCV (3–5% per year) and further accelerated by co-factors including alcohol consumption, metabolic-associated fatty liver disease, age, and HIV co-infection [17]. Once cirrhosis is established, annual rates of hepatic decompensation (ascites, variceal hemorrhage, spontaneous bacterial peritonitis, hepatic encephalopathy) are approximately 5–7%, with 5-year survival dropping to 50–60% following the first decompensation event.

Hepatocellular carcinoma represents the most feared complication of chronic viral hepatitis, accounting for approximately 72% of all HCC cases worldwide [2]. The annual HCC incidence in HBV-related cirrhosis ranges from 2% to 5%, while in HCV-cirrhosis, rates of 3–8% per year have been reported. Critically, HBV-associated HCC can develop in the absence of cirrhosis, with approximately 20–30% of HBV-related HCC cases arising in non-cirrhotic livers — a unique oncological risk profile attributed to direct viral oncogenesis via HBV DNA integration [12]. HCC surveillance with hepatic ultrasound and serum alpha-fetoprotein (AFP) every 6 months is recommended in all cirrhotic patients and in high-risk non-cirrhotic HBV carriers, based on evidence that surveillance reduces HCC-related mortality by approximately 37% [2].

The efficacy of antiviral therapy in modifying long-term outcomes is well-established. Long-term NA therapy for HBV (5–10 years) reduces hepatic decompensation rates, HCC incidence, and liver-related mortality in multiple large cohort studies and randomized controlled trials [23]. In HCV, SVR achievement is associated with a 71% reduction in all-cause mortality, an 84% reduction in liver-related mortality, and a 76% reduction in HCC risk in meta-analyses [5]. However, even after HCV cure, residual HCC risk persists in patients with advanced fibrosis, particularly among those with metabolic co-morbidities, necessitating indefinite surveillance in the post-treatment period.

Liver transplantation remains the definitive treatment for end-stage liver disease secondary to viral hepatitis, with 5-year post-transplant survival rates of 70–80%. Universal NA prophylaxis with TDF or ETV, combined with hepatitis B immunoglobulin (HBIG) in the immediate post-transplant period, has reduced

HBV recurrence rates to below 5% in contemporary cohorts [24]. In HCV, all patients awaiting or undergoing transplantation should receive DAA therapy; post-transplant treatment of HCV reinfection achieves SVR rates equivalent to pre-transplant treatment. Living-donor liver transplantation from HCV-positive donors, followed by DAA therapy, is now practiced in experienced centers, expanding the donor pool.

Prevention and Global Control Strategies

Universal HBV vaccination represents one of the most cost-effective public health interventions ever implemented. The three-dose recombinant HBsAg vaccine confers protective anti-HBs antibody titers in approximately 95% of immunocompetent adults and 98% of infants, with immunological memory persisting for at least 30 years and likely lifelong in most individuals [8]. Global WHO-recommended immunization schedules include a birth dose (ideally within 24 hours of delivery) to prevent perinatal transmission, followed by two or three additional doses in the first year of life. Birth dose coverage has increased substantially but remains below 50% in several high-burden African countries, primarily due to home delivery rates and cold-chain logistics [3]. Combination interventions — antiviral prophylaxis with TDF in HBeAg-positive mothers during the third trimester, combined with birth dose vaccination and HBIG administration — reduce perinatal HBV transmission to below 1% and represent the current standard of care [8].

HCV prevention remains dependent on harm reduction and behavioral interventions in the absence of a licensed vaccine. Needle and syringe programs (NSPs) for people who inject drugs reduce HCV incidence by 50–70% in modeling estimates, and opioid agonist therapy (OAT) provides complementary protection [11]. Universal blood supply screening with NAT has virtually eliminated transfusion-transmitted HCV in countries with robust screening infrastructure. Healthcare-associated transmission prevention requires stringent injection safety standards, single-use equipment policies, and healthcare worker training — interventions that are cost-effective and technically feasible but require sustained implementation quality.

The WHO's Global Health Sector Strategy on Viral Hepatitis articulates a phased approach to elimination, requiring scale-up of prevention, testing, and treatment simultaneously [3]. Integrated models of care — embedding hepatitis testing and treatment within HIV, tuberculosis, antenatal care, and primary care services — have demonstrated feasibility and cost-effectiveness in diverse settings. National hepatitis plans with dedicated funding, country-specific epidemiological surveillance, and political commitment are essential enabling conditions. The WHO

"triple P" framework emphasizes prevention, diagnosis (People know their status), and treatment access as the three fundamental pillars of the elimination response.

Discussion

A critical examination of contemporary hepatitis research reveals both remarkable therapeutic achievements and persistent structural failures. The contrast between the biomedical and public health dimensions of viral hepatitis is perhaps nowhere more striking than in HCV: a disease now biologically curable in virtually all patients, yet affecting 50 million individuals who remain largely untreated globally [4]. The DAA revolution has, paradoxically, exposed the inadequacy of existing diagnostic and healthcare delivery infrastructure. In many high-burden countries, awareness campaigns, simplified testing algorithms, and task-shifted treatment delivery have demonstrated that community-based models can dramatically accelerate case-finding and treatment initiation — yet these models require sustained political and financial commitment that frequently exceeds available resources [11].

For HBV, the scientific challenge is more fundamental: current therapeutics do not achieve viral eradication in the overwhelming majority of patients. The cccDNA problem — the persistence of transcriptionally active viral episomes in the nucleus of infected hepatocytes — is the central unsolved problem in HBV therapy. While the intrahepatic cccDNA pool slowly declines under long-term NA therapy due to hepatocyte turnover, mathematical modeling suggests that complete cccDNA elimination through NA therapy alone would require several decades [6]. Multiple approaches to cccDNA degradation or silencing are under investigation, including targeted epigenetic silencing via CRISPR-based mechanisms and zinc finger nucleases, but translational barriers remain substantial [6]. A critical appraisal of the functional cure concept must acknowledge that even HBsAg loss — the current operational definition — does not guarantee complete intrahepatic cccDNA clearance, and reactivation can occur under profound immunosuppression.

Diagnostic limitations continue to constrain clinical practice. Transient elastography, while significantly more accurate and acceptable than liver biopsy, is affected by confounders including hepatic steatosis, extrahepatic cholestasis, and non-fasting states that can spuriously elevate liver stiffness measurements [21]. The "grey zone" of liver stiffness values (7–10 kPa for HCV, 8–12 kPa for HBV) remains problematic, often requiring confirmatory biopsy or sequential non-invasive assessment. Point-of-care nucleic acid testing holds particular promise for decentralized hepatitis diagnosis in resource-limited settings, but cost barriers and laboratory infrastructure requirements have delayed widespread adoption.

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ISSN: 2996-5101 (online) | ResearchBib (IF) = 10.81 IMPACT FACTOR
Volume-4| Issue-3| 2026 Published: |30-03-2026

The significant treatment outcome disparities between high-income and low-income settings remain ethically untenable and epidemiologically consequential. HCV DAA treatment costs in the United States, while dramatically reduced from early pangenotypic regimen launch prices, remain orders of magnitude higher than production costs and generic prices available in some low-income countries [4]. The Medicines Patent Pool and voluntary licensing frameworks have improved generic access in certain LMICs, but middle-income countries — which harbor a disproportionate share of the global HCV burden — often fall outside generic access agreements, creating a "middle-income trap" in hepatitis elimination financing. Research gaps include robust data on hepatitis burden in many sub-Saharan African countries, the cost-effectiveness of newer HBV biomarker combinations in treatment eligibility stratification, long-term HCC risk modeling after HCV SVR in LMICs, and implementation science for integrated hepatitis care delivery.

Future Perspectives

The trajectory of HBV therapy is clearly oriented toward functional cure. Several agents in phase 2 and 3 clinical trials represent genuinely novel mechanisms of action: siRNA molecules (JNJ-3989, AB-729) potently reduce HBsAg levels by post-transcriptionally silencing HBV mRNA derived from both cccDNA and integrated templates, achieving mean HBsAg reductions of 2–3 log10 IU/mL in phase 2 studies [6]. Capsid assembly modulators (vebicorvir, ABI-H0731) target HBV core protein, interfering with both pgRNA encapsidation and cccDNA replenishment. Innate immune activators including TLR8 agonists selectively stimulate intrahepatic Kupffer cells and NK cells, potentially restoring the innate immune environment suppressed by chronic infection. The prevailing scientific consensus is that combination regimens — pairing HBsAg suppression with immune stimulation — will be required to achieve immunological control enabling finite treatment.

In HCV, the elimination of viral replication as a scientific challenge has shifted research priorities toward population-level elimination strategies and long-term outcomes research. Mathematical modeling studies indicate that achieving the WHO 2030 elimination targets will require simultaneous scale-up of all elimination pillars — not sequential implementation — and sustained political and financial commitment beyond current trajectories [3]. Simplified, decentralized treatment models ("simplified HCV care") have demonstrated non-inferiority to specialist-delivered care in randomized trials, with profound implications for task shifting in primary care and community settings [11]. Retreatment strategies for the small proportion of DAA-experienced patients with persistent infection continue to

evolve, with triple-DAA regimens including voxilaprevir demonstrating high efficacy even in the presence of multiple resistance-associated substitutions.

Precision medicine approaches are beginning to reshape hepatology practice. Polygenic risk scores incorporating host genetic variants — particularly HLA class I and II alleles associated with HBV-specific T-cell response magnitude — may identify individuals most likely to benefit from immunomodulatory therapies [13]. Liquid biopsy technologies detecting circulating cell-free HBV DNA and viral cccDNA-derived markers promise less invasive intrahepatic viral activity assessment. Multi-omics integration — combining transcriptomics, proteomics, and metabolomics of the liver microenvironment — is generating mechanistic insights into fibrosis regression and HCC risk stratification that may yield new predictive biomarkers and therapeutic targets. Finally, digital health technologies including mobile-based adherence support, telemedicine, and AI-assisted image analysis of hepatic ultrasound are increasingly being evaluated in hepatitis care delivery, with potential to extend specialist expertise to underserved populations.

Conclusion

Chronic viral hepatitis caused by HBV and HCV remains a defining global health challenge of the 21st century, despite revolutionary scientific advances that have rendered HCV curable and established effective long-term suppressive therapy for HBV. The WHO 2030 elimination targets represent an achievable but deeply aspirational goal that requires simultaneous progress on epidemiological surveillance, vaccination coverage, diagnostic scale-up, equitable treatment access, and health system strengthening.

For clinicians, the evidence reviewed here supports adoption of non-invasive fibrosis staging as the standard of care, prioritization of pan-genotypic DAA regimens for HCV, and long-term NA therapy with regular HCC surveillance for appropriate HBV patient populations. The evolving landscape of HBV functional cure strategies warrants participation in clinical trials by specialized hepatology centers and informed counseling of patients regarding realistic treatment expectations.

For researchers, critical priorities include elucidating the mechanisms governing cccDNA biology and persistence, developing immunological correlates of protective anti-HBV immunity applicable to therapeutic vaccine design, and conducting rigorous implementation science to optimize hepatitis care delivery in resource-limited settings. Robust data generation from under-represented high-burden regions — particularly sub-Saharan Africa — is essential to close epidemiological knowledge gaps.

For global public health policymakers, the evidence overwhelmingly supports investment in universal HBV birth dose vaccination, expansion of HCV harm reduction infrastructure, negotiation of accessible DAA pricing for all LMICs, and integration of viral hepatitis services within existing primary care and HIV platforms. Without commensurate political will and financing commitments, the biological advances described in this review will remain inaccessible to the billions of individuals who bear the greatest burden of this preventable and increasingly treatable disease.

REFERENCES:

1. GBD 2019 Hepatitis Collaborators. Mortality due to cirrhosis and liver cancer attributable to hepatitis B and C in 195 countries, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Gastroenterol Hepatol. 2022;7(9):796-829. doi:10.1016/S2468-1253(22)00144-4

2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249. doi:10.3322/caac.21660

3. World Health Organization. Global Health Sector Strategies on, Respectively, HIV, Viral Hepatitis and Sexually Transmitted Infections for the Period 2022-2030. Geneva: WHO; 2022.

4. World Health Organization. Hepatitis C. WHO Fact Sheet. 2023. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c

5. Pawlotsky JM. Treatment of chronic hepatitis C virus infection in the era of direct-acting antiviral agents. J Hepatol. 2023;78(5):1054-1063. doi:10.1016/j.jhep.2022.12.014

6. Lok AS, Zoulim F, Dusheiko G, Ghany MG. Hepatitis B cure: from discovery to regulatory approval. J Hepatol. 2017;67(4):847-861. doi:10.1016/j.jhep.2017.05.008

7. Razavi-Shearer D, Gamkrelidze I, Nguyen MH, et al. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol. 2018;3(6):383-403. doi:10.1016/S2468-1253(18)30056-6

8. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012;30(12):2212-2219. doi:10.1016/j.vaccine.2011.12.116

9. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-398. doi:10.1016/j.jhep.2017.03.021

10. Ray Kim W. Global epidemiology and burden of hepatitis C. Microbes Infect. 2002;4(12):1219-1225. doi:10.1016/S1286-4579(02)01649-0

11. Lazarus JV, Safreed-Harmon K, Hetherington KL, et al. Consensus statements on reorienting health and social systems to optimise hepatitis C elimination. J Hepatol. 2021;74(3):489-498. doi:10.1016/j.jhep.2020.10.038

12. Levrero M, Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. J Hepatol. 2016;64(1 Suppl):S84-S101. doi:10.1016/j.jhep.2016.02.021

13. Bertoletti A, Ferrari C. Adaptive immunity in HBV infection. J Hepatol. 2016;64(1 Suppl):S71-S83. doi:10.1016/j.jhep.2016.01.026

14. Rehermann B, Thimme R. Insights from antiviral T cell responses in acute and chronic hepatitis B and C virus infection. Gastroenterology. 2019;156(2):369-383. doi:10.1053/j.gastro.2018.10.024

15. Manns MP, Buti M, Gane E, et al. Hepatitis C virus infection. Nat Rev Dis Primers. 2017;3:17006. doi:10.1038/nrdp.2017.6

16. Pawlotsky JM. Hepatitis C virus resistance to direct-acting antiviral drugs in interferon-free regimens. Gastroenterology. 2016;151(1):70-86. doi:10.1053/j.gastro.2016.04.003

17. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet. 2014;383(9930):1749-1761. doi:10.1016/S0140-6736(14)60121-5

18. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560-1599. doi:10.1002/hep.29800

19. Chevaliez S, Pawlotsky JM. New virological tools for screening, diagnosis and monitoring of hepatitis B and C in resource-limited settings. J Hepatol. 2018;69(4):916-926. doi:10.1016/j.jhep.2018.05.017

20. Germer JJ, Beito TL, Espy MJ, et al. Comparison of the COBAS AmpliPrep/COBAS TaqMan hepatitis B virus (HBV) test and COBAS AmpliPrep/COBAS TaqMan HBV test v2.0 for quantification of HBV DNA. J Clin Microbiol. 2012;50(3):1045-1048. doi:10.1128/JCM.05773-11

21. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388-1402. doi:10.1016/j.jhep.2015.11.004

22. Toshima T, Shirabe K, Ikegami T, et al. A novel serum marker, glycosylated Wisteria floribunda agglutinin-positive Mac-2 binding protein (WFA+-M2BP), for assessing liver fibrosis in non-alcoholic fatty liver disease. PLoS One. 2015;10(3):e0121197. doi:10.1371/journal.pone.0121197

23. Lampertico P, Agarwal K, Berg T, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-398. doi:10.1016/j.jhep.2017.03.021

24. Loomba R, Liang TJ. Hepatitis B reactivation associated with immune suppressive and biological modifier therapies: current concepts, management strategies, and future directions. Gastroenterology. 2017;152(6):1297-1309. doi:10.1053/j.gastro.2017.02.009

25. Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. Nat Rev Gastroenterol Hepatol. 2013;10(9):553-562. doi:10.1038/nrgastro.2013.107

26. Thursz M, Fontanet A. HCV transmission in industrialized countries and resource-constrained areas. Nat Rev Gastroenterol Hepatol. 2014;11(1):28-35. doi:10.1038/nrgastro.2013.179

27. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. Clin Infect Dis. 2018;67(10):1477-1492. doi:10.1093/cid/ciy585

28. Younossi ZM, Tanaka A, Eguchi Y, et al. The impact of hepatitis C virus outside the liver: evidence from Asia. Liver Int. 2017;37(2):159-172. doi:10.1111/liv.13167

29. Dusheiko G, Aghemo A, Bhagat S, et al. New approaches to achieving a cure for hepatitis B. J Hepatol. 2024;80(3):483-495. doi:10.1016/j.jhep.2023.10.026

30. Thursz MR, Gane E, Schwabe R, Hellard M, Estes C. New challenges, new approaches: roadmap for the elimination of viral hepatitis. J Hepatol. 2021;74(Suppl 1):S52-S68. doi:10.1016/j.jhep.2021.01.014

31. Рахматуллаева, Ш. Б., Муминова, М. Т., Нурматов, А. Х., & Саъдуллаев, С. Э. (2023). Особенности течения COVID-19 у детей с коморбидной патологией. *Педиатрия. Восточная Европа,(3 Часть 12)*, 436-442.

32. Матякубов, Б. Б., & Ниязметов, Р. Э. СОВРЕМЕННЫЕ АСПЕКТЫ ЛЕЧЕНИЯ МАССИВНОГО АКУШЕРСКОГО КРОВОТЕЧЕНИЯ В ИССЛЕДУЕМОЙ ГРУППЕ. *МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ УЗБЕКИСТАН РЕСПУБЛИКАНСКИЙ СПЕЦИАЛИЗИРОВАННЫЙ НАУЧНО-ПРАКТИЧЕСКИЙ МЕДИЦИНСКИЙ ЦЕНТР АКУШЕРСТВА И ГИНЕКОЛОГИИ АССОЦИАЦИЯ ВРАЧЕЙ ЧАСТНОЙ ПРАКТИКИ УЗБЕКИСТАНА КЛИНИКА «MAHLIYO-SHIFO» & V*, 23.

33. NIYAZMETOV, R., MATYAKUBOV, B., NAZAROV, B., & USINOVA, Z. MASSIVE OBSTETRIC BLEEDING: OPTIMIZATION OF TOTAL HYSTERECTOMY SURGERY TECHNIQUE AND CONSERVATIVE

TREATMENT. *INFUSION & CHEMOTHERAPY Учредители: Communicable Diseases Intensive Care Association*, (3.1), 55-56.

34. Максумова, Н. Б., Ниязметов, Р. Э., Матякубов, Б. Б., & Усинова, З. Б. (2019). РОЛЬ МЕСТНОГО ИСПОЛЬЗОВАНИЯ КОНЪЮГИРОВАННОГО ЭСТРОГЕНА В УЛУЧШЕНИИ ИСХОДОВ ОПЕРАТИВНОГО ЛЕЧЕНИЯ ПРОЛАПСА ГЕНИТАЛИЙ. *Innova*, (2 (15)), 20-23.

35. Matyakubov, B. B., Niyazmetov, R. E., Khabibullaev, D. M., & Usinova, Z. B. (2021). SURGICAL TACTICS FOR MASSIVE OBSTETRIC BLEEDING. *European Journal of Molecular and Clinical Medicine*, *8*(2), 594-600.