

Evolving Landscape of Precision Medicine in Viral Hepatitis: Comparative Genomics, Biomarkers, Multi-Omics, Artificial Intelligence, and Personalized Therapeutics Across DNA and RNA Hepatitis Viruses

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ABSTRACT

Background: Viral hepatitis still brings great burden to all lands. It is a chief cause of long sickness of the liver, of hardening, and of liver cancer. In old times physic was given the same to all. New knowledge of the body's inner workings lets us shape physic to each man.

Objectives: This writing tells of new work in special physic for liver sickness from DNA and RNA germs. We speak of comparing kinds of germs, the blood of the host, signs in the body, many kinds of study, thinking engines, and physic made for one man.

Recent Advances: The book of the germ has shown how it moves, changes, and fights physic. Studies of messages, proteins, humours, marks on blood, and single cells show the fight between man and germ. Thinking engines now help find sickness, tell what may come, weigh hardening of the liver, watch for cancer, and guide the healer. So, we have vaccines for kinds, physic for the host, CRISPR tools, physic of RNA, and cures matched to the germ's kind.

Key Findings: When learning of body, germ, and reckoning meet, we can sort sickness better and give physic to the one. Yet gold, tools, and law still keep this from all men.

Future Perspectives: By men working in all lands and using true thinking engines, the hope of full cure draws near. Special liver physic shall be the base of care to come.

Keywords: Viral hepatitis, Precision physic, Comparing of kind, CRISPR, Special liver physic.

2. INTRODUCTION

2.1 Global Burden of Viral Hepatitis

Viral hepatitis remains a significant global health challenge, with hepatitis B virus (HBV) and hepatitis C virus (HCV) accounting for most chronic infections and affecting more than 300 million people worldwide. Hepatitis A virus (HAV), hepatitis D virus (HDV), and hepatitis E virus (HEV) continue to contribute substantially to acute hepatitis and regional outbreaks ⁽¹⁾. Collectively, viral hepatitis causes approximately 1.3 million deaths annually, primarily due to cirrhosis and hepatocellular carcinoma, making it one of the leading causes of infection-related mortality worldwide ⁽²⁾. Beyond mortality, chronic hepatitis imposes substantial healthcare, social, and economic burdens, particularly in low- and middle-income countries ^(3,1). The World Health Organization aims to eliminate viral hepatitis as a public health threat by 2030 through expanded vaccination, early diagnosis, effective treatment, and integrated public health strategies ⁽⁴⁾.

2.2 Precision Medicine: An Emerging Paradigm

Precision medicine is an individualized healthcare approach that integrates genetic, molecular, environmental, and lifestyle factors to improve disease prevention, diagnosis, and treatment ^(5,6). Advances in next-generation sequencing, genome-wide association studies, multi-omics technologies, and bioinformatics have transformed precision medicine into an important clinical strategy ⁽⁷⁾. In viral hepatitis, differences in viral genotypes, host genetics, immune responses, and biomarker profiles strongly influence disease progression and therapeutic outcomes ⁽⁸⁾. Integrating viral and host genomic information with biomarkers and AI enables accurate patient stratification, prediction of treatment response, optimized antiviral selection, and continuous disease monitoring, facilitating the transition from conventional management to personalized hepatology ⁽⁹⁾.

2.3 Hepatitis Viruses (DNA and RNA)

HBV is a partially double-stranded DNA virus belonging to the *Hepadnaviridae* family that establishes persistent infection through covalently closed circular DNA (cccDNA), making complete viral eradication difficult ⁽¹⁰⁾. HCV is a positive-sense single-stranded RNA virus characterized by extensive genetic diversity but is highly curable with direct-acting antivirals ⁽¹¹⁾. HAV is a non-enveloped RNA virus responsible for self-limiting acute hepatitis and is effectively prevented by vaccination ⁽¹²⁾. HEV is an RNA virus causing sporadic and epidemic hepatitis, with severe disease occurring mainly in pregnant women and immunocompromised individuals ⁽¹³⁾. HDV is a defective RNA virus that depends on HBV surface antigen for replication and causes the most severe form of chronic viral hepatitis ⁽¹⁴⁾.

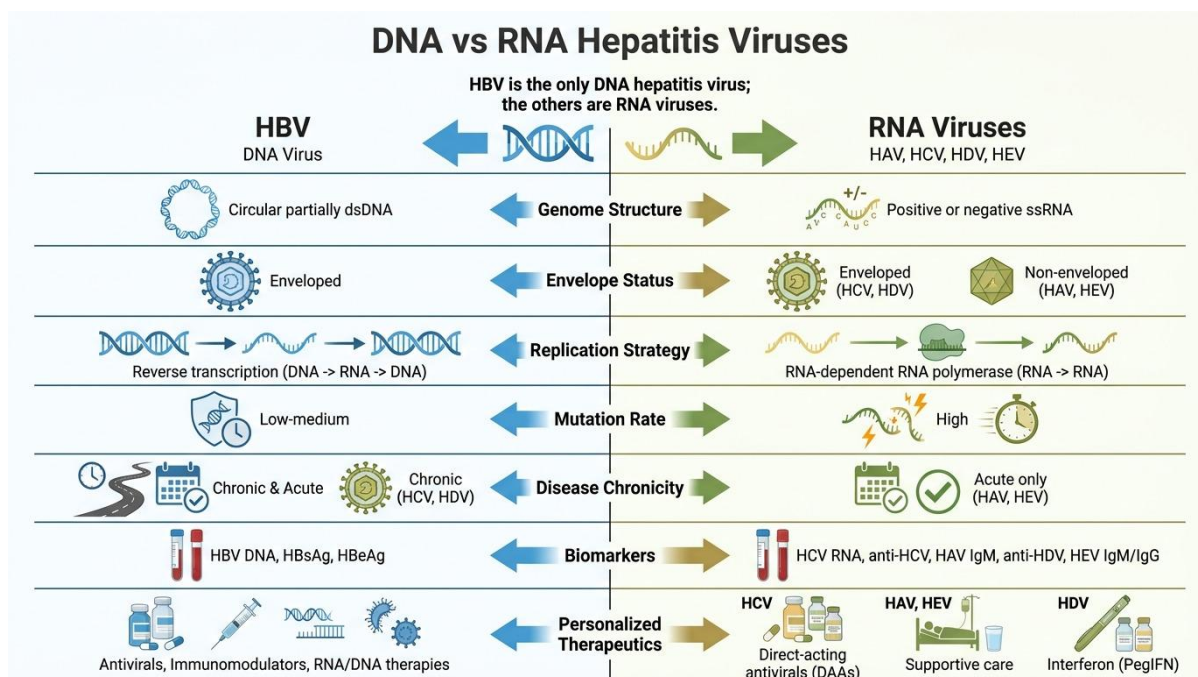


Figure 1: Comparison of DNA & RNA hepatitis viruses

2.4 The scope and objectives of the review

This review examines recent advances in precision medicine across DNA and RNA hepatitis viruses by integrating evidence from comparative genomics, host genetics, biomarkers, multi-omics technologies, artificial intelligence, and personalized therapeutics. It further discusses current clinical applications, translational challenges, and future research directions that may improve individualized diagnosis, treatment, and prevention of viral hepatitis.

3. BIOLOGY & COMPARATIVE GENOMICS OF HEPATITIS VIRUSES

3.1 Classification of Hepatitis viruses

Although all human hepatitis viruses exhibit hepatic tropism, they belong to distinct viral families and differ considerably in genomic structure, replication strategy, and clinical behavior. HBV belongs to the Hepadnaviridae family, HCV to Flaviviridae, HAV to Picornaviridae, HEV to Hepeviridae, and HDV to the genus Deltavirus, which requires HBV surface antigen (HBsAg) for replication and transmission^(15,16). These taxonomic differences

underlie variations in viral persistence, pathogenicity, therapeutic targets, and preventive strategies, forming the basis for precision medicine across hepatitis viruses.

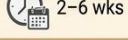
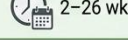
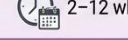
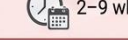
	HAV	HBV	HCV	HDV	HEV
Viral Family	Picornaviridae	Hepadnaviridae	Flaviviridae	Deltaviridae	Hepeviridae
Genome Type	 ssRNA(+), linear	 dsDNA, circular	 ssRNA(+), linear	 ssRNA(-), circular	 ssRNA(+), linear
Envelope Status	 Non-enveloped	 Enveloped	 Enveloped	 Enveloped	 Non-enveloped
Transmission Route	 Fecal-oral	 Blood, sexual	 Blood	 With HBV (blood)	 Fecal-oral
Incubation Period	 2–6 wks	 4–24 wks	 2–26 wks	 2–12 wks	 2–9 wks
Disease Outcome	 Acute, rare chronic	 Often chronic, cirrhosis, cancer	 Often chronic, cirrhosis, cancer	 Superinfection, severe	 Acute, severe in pregnancy

Figure 2: Major hepatitis viruses & Key Characteristics

3.2 Organization of Viral Genome

The genomic organization of hepatitis viruses differs substantially despite their shared affinity for the liver. HBV possesses a compact 3.2 kb partially double-stranded circular DNA genome that replicates through reverse transcription, whereas HCV, HAV, and HEV contain positive-sense single-stranded RNA genomes of approximately 9.6 kb, 7.5 kb, and 7.2 kb, respectively ^(17,18). HDV has the smallest known human pathogenic viral genome, consisting of a 1.7 kb circular negative-sense RNA genome that depends on HBV-derived HBsAg for virion assembly ⁽¹⁹⁾.

Comparative genomic studies demonstrate marked differences in genetic diversity among hepatitis viruses. HBV comprises at least ten genotypes (A–J) associated with variations in disease progression, geographic distribution, and treatment response ⁽¹⁷⁾. HCV exhibits extensive genetic heterogeneity with eight major genotypes and numerous subtypes, contributing to immune escape and differences in antiviral susceptibility ⁽²¹⁾. In contrast, HAV remains genetically stable because of highly conserved antigenic regions, allowing effective universal vaccine protection ⁽¹²⁾. HEV displays moderate diversity, with genotypes 1 and 2 restricted to humans, whereas genotypes 3 and 4 are zoonotic ⁽²⁹⁾. HDV contains eight genotypes that differ in geographic distribution and clinical severity despite its small genome ⁽²⁴⁾.

Distinct evolutionary mechanisms further influence viral diversity. HBV evolves through error-prone reverse transcription, generating quasispecies that promote immune escape, persistence, and antiviral adaptation ^(25,26). HCV evolves even more rapidly because its RNA-dependent RNA polymerase lacks proofreading activity, facilitating resistance development and immune evasion ⁽²⁷⁾. HAV and HEV evolve more slowly owing to greater genetic constraints, although adaptive mutations remain important for host adaptation ⁽²⁸⁾. HDV also demonstrates

rapid intra-host evolution despite its limited genome, affecting viral replication and disease severity⁽²⁹⁾. Understanding these genomic and evolutionary differences is fundamental for genotype-based diagnosis, biomarker discovery, therapeutic stratification, and precision-guided management of viral hepatitis⁽³⁰⁾.

3.3 Drug Resistance Mutations

Drug resistance remains a major challenge in precision antiviral therapy, particularly in chronic HBV and HCV infections. Long-term Nucleoside analogue therapy in HBV may select polymerase mutations, including rtM204V/I, rtL180M, and rtA181T/V, reducing susceptibility to lamivudine and related antivirals, whereas resistance to tenofovir remains uncommon⁽³¹⁾. In HCV, resistance-associated substitutions (RASs) within the NS3, NS5A, and NS5B regions may compromise the effectiveness of direct-acting antivirals in selected patients^(32,33). Clinically significant antiviral resistance has not been established for HAV or HEV, while HDV management

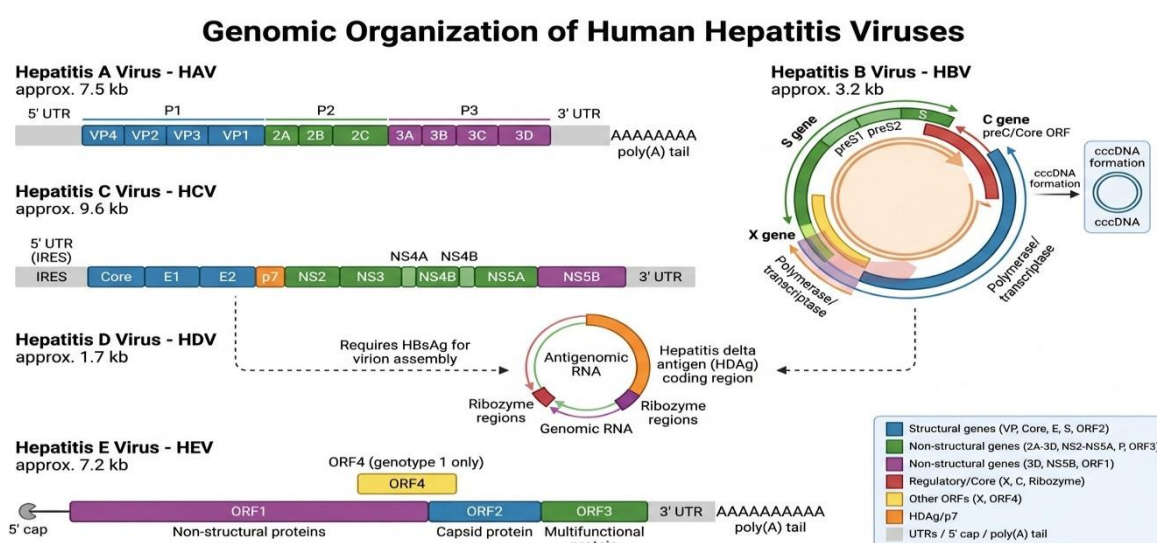


Figure 3: Genomic Organisation of Hepatitis viruses

is primarily limited by the availability of effective therapies rather than resistance mutations⁽³⁴⁾. Advances in viral genomics have enabled genotype-informed clinical management by supporting individualized risk assessment, treatment selection, and disease monitoring⁽³⁵⁾. HBV genotypes and specific genomic mutations are associated with differences in fibrosis progression, hepatocellular carcinoma risk, and antiviral response⁽³⁶⁾. Although pangenotypic direct-acting antivirals have reduced the routine need for HCV genotyping, viral genotype and resistance profiling remain valuable in complex clinical situations, including treatment failure and resistant infections⁽³⁷⁾. Integration of viral genomic information with host genetic markers, molecular biomarkers, and artificial intelligence further strengthens precision diagnosis, prognostic assessment, and personalized therapeutic decision-making in viral hepatitis⁽⁹⁾.

4. HOST GENETICS & PRECISION MEDICINE

4.1 Genetic Variability in Humans

Host genetic diversity greatly influences susceptibility to viral hepatitis, spontaneous viral clearance, disease progression, and treatment outcomes by influencing innate and adaptive immune responses⁽³⁹⁾. Genome-wide

association studies have found several host genetic variations that impact antiviral immunity, fibrosis progression, and treatment success, establishing human genetics as a vital component of precision medicine and tailored therapy of viral hepatitis ^(40,41).

4.2 Polymorphism of HLA

Antiviral immunity is mostly determined by human leukocyte antigen (HLA) polymorphisms, which affect antigen presentation, T-cell activation, viral clearance, and persistence in hepatitis virus infections ⁽⁴²⁾. Genome-wide association studies have consistently linked certain HLA class I and II alleles, such as HLA-DP, HLA-DQ, and HLA-DR variations, to the risk of hepatocellular cancer, spontaneous viral clearance, and chronic HBV infection ⁽⁴³⁾. Polymorphic HLA alleles influence adaptive immune responses in HCV infection and influence treatment results and spontaneous viral clearance ⁽⁴⁴⁾. Emerging data indicates that host HLA associations for HAV, HEV, and HDV are involved in immune modulation and disease severity, despite the fact that these relationships have not been thoroughly described ⁽⁴⁵⁾. Thus, HLA profiling is a viable biomarker for precision hepatology and personalized risk prediction ⁽⁴⁶⁾.

4.3 IL28B & Other Predictive Genes

Because they can predict viral clearance, illness progression, and therapeutic response in chronic viral hepatitis, host genetic indicators have become essential to precision medicine ⁽⁴⁷⁾. Among these, SNPs adjacent to the closely related IFNL4 and IL28B (IFNL3) genes are highly linked to good responses to interferon-based therapy and spontaneous HCV clearance, making them one of the first clinically useful genetic predictors in hepatology ⁽⁴⁸⁾. In addition to IL28B, variations in PNPLA3, TM6SF2, MBOAT7, and HSD17B13 have been associated with cirrhosis, fibrosis advancement, hepatocellular carcinoma, and hepatic steatosis in chronic viral hepatitis, underscoring the role of host genetics in disease heterogeneity ^(49,50). Individualized risk assessment, prognosis evaluation, and treatment decision-making are made possible by combining these predictive genes with viral genomic data and molecular biomarkers, supporting the shift toward precision hepatology and customized patient care ^(51,52).

4.4 Pharmacogenomics

Pharmacogenomics advances personalized treatment of viral hepatitis by using host genetic information to optimize drug selection, dosage, therapeutic efficacy, and safety ⁽⁵³⁾. Host genetic diversity still affects antiviral pharmacokinetics, immunological responses, and treatment outcomes in some patient populations, even though direct-acting antivirals have diminished the therapeutic significance of pharmacogenomic testing in HCV ⁽⁵⁴⁾. Combining host genomic profiles with viral genotypes and molecular indicators in chronic HBV infection may improve functional cure techniques and enable tailored treatment plans ⁽⁹⁾. In future clinical practice, it is anticipated that emerging pharmacogenomic models in conjunction with multi-omics and artificial intelligence would improve patient categorization, forecast adverse drug responses, and facilitate precision-guided antiviral therapy ^(56,57). Viral hepatitis outcomes are significantly influenced by gene-environment interactions, with host genetic susceptibility altered by co-infections, alcohol use, metabolic disorders, obesity, and environmental exposures ⁽⁵⁸⁾. Precision therapy approaches, tailored risk prediction, and prevention may all benefit from the integration of genetic and environmental factors ⁽⁵⁹⁾.

5. BIOMARKERS IN VIRAL HEPATITIS

5.1 Diagnostic Biomarkers

For the precise identification and categorization of viral hepatitis, diagnostic biomarkers are still essential. HBsAg, HBeAg, HBV DNA, and anti-HBc for HBV; anti-HCV antibodies and HCV RNA for HCV; anti-HAV IgM for acute HAV infection; anti-HEV IgM/IgG and HEV RNA for HEV; and anti-HDV antibodies and HDV RNA for HDV diagnosis are examples of established indicators ^(60,37). Precision-based clinical care and early diagnosis are made possible by advances in highly sensitive molecular assays, which have further increased diagnostic accuracy ⁽⁶²⁾.

5.2 Prognostic Biomarkers

By identifying patients at higher risk of cirrhosis, hepatic decompensation, fibrosis progression, and hepatocellular carcinoma (HCC), prognostic biomarkers are essential in precision hepatology ⁽⁶³⁾. Hepatitis B core-related antigen (HBcrAg), serum HBV RNA, and quantitative hepatitis B surface antigen (qHBsAg) all correlate with intrahepatic viral activity in chronic HBV infection and independently predict the development of HCC and disease progression ^(64,65). Sustained virological response significantly improves prognosis in HCV infection; nevertheless, biomarkers such as fibrosis-associated indicators, liver stiffness assessment, and alpha-fetoprotein (AFP) are still useful for identifying people who need ongoing HCC surveillance ⁽⁶⁶⁾. In patients with viral hepatitis, the integration of viral biomarkers with host molecular signatures and clinical characteristics improves individualized prognostic classification, enabling prompt treatment intervention and long-term risk prediction ⁽⁶⁷⁾.

5.3 Predictive Biomarkers

By identifying patients who are most likely to respond to particular antiviral or newly developed immunomodulatory treatments, predictive biomarkers facilitate tailored therapeutic decision-making ⁽⁶⁸⁾. Hepatitis B core-related antigen (HBcrAg), hepatitis B e antigen (HBeAg), serum HBV RNA, and baseline quantitative HBsAg (qHBsAg) status all predict treatment response, HBeAg seroconversion, and the possibility of obtaining a functional cure with nucleotide analogues or innovative therapeutic approaches in chronic HBV infection ^(69,70). Despite the availability of pangenotypic direct-acting antivirals, viral genotype, resistance-associated substitutions (RASs), and host biomarkers in HCV infection have historically guided interferon-based therapy and continue to drive treatment optimization in certain clinical contexts ⁽³⁷⁾.

5.4 Biomarkers for Treatment Monitoring

For the purpose of assessing antiviral efficacy, identifying virological relapse, and directing customized therapeutic choices along the course of disease care, biomarkers for therapy monitoring are crucial ⁽⁶⁰⁾. Hepatitis B core-related antigen (HBcrAg), serum HBV RNA, quantitative HBsAg (qHBsAg), and serial quantification of HBV DNA provide complementary information on viral replication, transcriptional activity, and treatment response in chronic HBV infection, supporting decisions about treatment discontinuation and functional cure prediction ^(65,76). While HDV RNA is the primary biomarker for evaluating treatment response in chronic hepatitis D, undetectable HCV RNA following therapy confirms sustained virological response in HCV infection ⁽⁷⁷⁾. It is

anticipated that new multiplex biomarker approaches that incorporate viral, host, and immunological markers would enhance dynamic treatment monitoring and enable precision-guided management of viral hepatitis ⁽⁷⁸⁾.

5.5 Emerging Biomarkers: By enabling earlier disease detection, better prognostic evaluation, and customized therapy monitoring beyond traditional viral indicators, emerging biomarkers are broadening the scope of precision hepatology ⁽⁷⁹⁾. Hepatocyte damage is reflected in cell-free DNA (cfDNA), which has demonstrated promise for non-invasive evaluation of the course of liver illness and the risk of hepatocellular carcinoma ⁽⁸⁰⁾. Viral nucleic acids, proteins, and immunological mediators are transported by extracellular vesicles, especially exosomes, which mimic host-virus interactions and may function as sensitive biomarkers for disease activity and treatment response ^(81,82). Additionally, circulating RNAs, such as circular RNAs, long non-coding RNAs, and microRNAs, control immunological responses, hepatocarcinogenesis, and viral replication, providing interesting targets for future precision medicine applications in viral hepatitis ^(83,84).

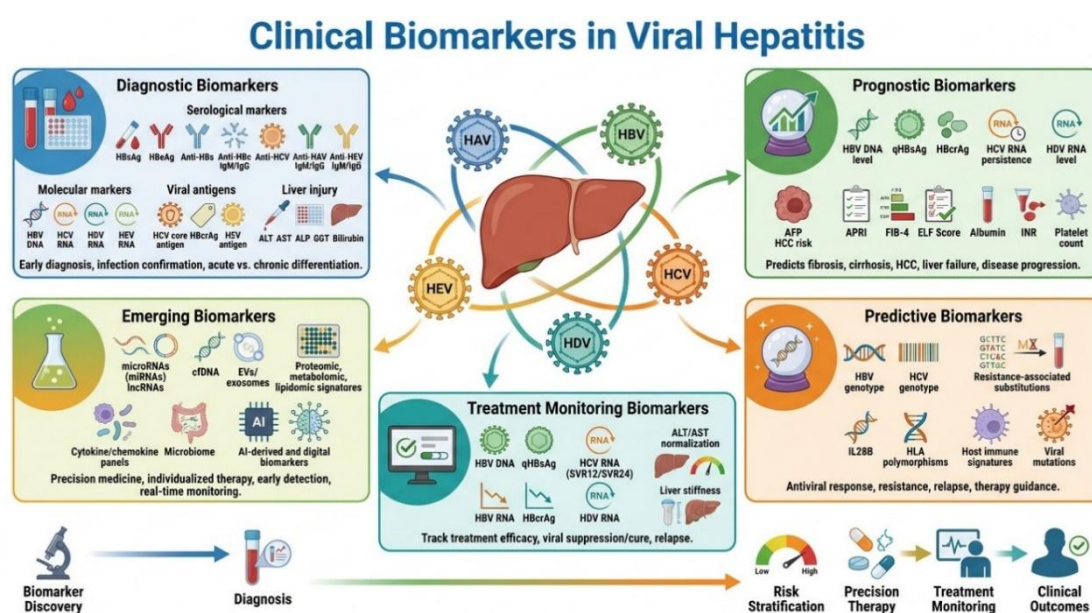


Figure 4: Overview of clinical biomarkers used for the diagnosis, prognosis, treatment monitoring, and precision management of viral hepatitis.

6. MULTI-OMICS APPROACHES

6.1 Genomics

By thoroughly defining viral and host genetic diversity linked to disease susceptibility, progression, and therapeutic response, genomics serves as the basis for precision medicine ⁽⁸⁵⁾. High-resolution investigation of hepatitis virus genomes has been made possible by developments in next-generation sequencing, which has made it easier to identify genotypes, detect mutations, track transmission, and find genomic biomarkers that support tailored therapeutic treatment ⁽³⁵⁾.

6.2 Transcriptomics

By measuring coding and non-coding RNA transcripts at the cellular level, transcriptomics offers thorough insights into alterations in gene expression that occur during viral hepatitis ⁽⁸⁷⁾. Biomarker discovery and precision-

based patient classification across hepatitis virus infections have been made easier by the identification of transcriptional signatures linked to viral persistence, immunological activation, fibrosis progression, and treatment response by high-throughput RNA sequencing ⁽⁸⁸⁾.

6.3 Proteomics

Proteomic profiling has found potential biomarkers linked to viral replication, immune dysregulation, fibrosis progression, and hepatocellular carcinoma, supporting disease stratification and precision therapeutic development in viral hepatitis ⁽⁹⁰⁾. Proteomics allows large-scale characterization of protein expression, post-translational modifications, and host–virus interactions that cannot be deduced from genomic data alone ⁽⁸⁹⁾.

6.4 Metabolomics

Metabolomics provides a functional readout of disease activity by thoroughly characterizing small-molecule metabolites that represent dynamic changes in host metabolism during viral hepatitis ⁽⁹¹⁾. In chronic viral hepatitis, distinct metabolic patterns linked to cirrhosis, fibrosis, inflammation, and hepatocellular cancer have shown promise for early diagnosis, prognostic evaluation, treatment monitoring, and biomarker-guided precision medicine ⁽⁹²⁾.

6.5 Microbiomics

By regulating immunological responses, hepatic inflammation, and metabolic balance, changes in the gut microbiota have a substantial impact on viral hepatitis through the gut–liver axis, according to microbiomics ⁽⁹³⁾. The gut microbiome is a viable target for biomarker identification and precision treatments since microbial dysbiosis has been linked to the development of fibrosis, cirrhosis, hepatocellular cancer, and antiviral therapy results ⁽⁹⁴⁾.

6.6 Epigenomics

By revealing heritable but reversible changes that control gene expression without changing the underlying DNA sequence, epigenomics has become a crucial part of precision hepatology ⁽⁹⁵⁾. DNA methylation, histone modifications, and chromatin remodeling are among the epigenetic changes brought on by viral hepatitis that affect hepatocarcinogenesis, fibrosis development, immunological evasion, and viral persistence ⁽⁹⁶⁾. Furthermore, host-virus interactions are modulated by dysregulated microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), which have shown significant promise as biomarkers for diagnosis, prognosis, and treatment ⁽⁸³⁾. Novel prospects for patient categorization, biomarker discovery, and precision-targeted therapies in viral hepatitis are presented by the integration of epigenomic markers with genomic and transcriptome data ⁽³⁵⁾.

6.7 Single-cell Omics

By providing high-resolution analysis of specific cellular populations inside the infected liver, single-cell omics has transformed precision hepatology by revealing cellular heterogeneity that is obscured by traditional bulk sequencing ⁽⁹⁹⁾. Different hepatocyte, immunological, and stromal cell subsets linked to virus persistence, immune

dysfunction, fibrosis progression, and the development of hepatocellular carcinoma have been found using single-cell RNA sequencing⁽¹⁰⁰⁾. Biomarker discovery and the creation of customized treatment plans for viral hepatitis are made easier by the integration of single-cell transcriptomic, epigenomic, and immune profiling, which offers previously unheard-of insights into host–virus interactions, therapeutic response, and mechanisms of disease progression^(101,102).

6.8 Spatial Omics

By maintaining the spatial organization of cells while concurrently characterizing transcriptomic and proteomic profiles within liver tissue, spatial omics has emerged as a transformative technology⁽¹⁰³⁾. Unlike traditional omics approaches, spatial technologies reveal the precise localization of infected hepatocytes, immune cells, and stromal populations, providing crucial insights into host–virus interactions, fibrosis progression, and hepatocellular carcinoma evolution⁽¹⁰⁴⁾. Combining spatial molecular data with histopathology improves the development of precision diagnostics and targeted therapeutic approaches for viral hepatitis⁽¹⁰⁵⁾.

6.9 Integration of Multi-Omics

To obtain a thorough understanding of viral hepatitis pathogenesis and therapeutic response, multi-omics integration integrates genomic, transcriptomic, proteomic, metabolomic, epigenomic, microbiomic, and geographical datasets⁽¹⁰⁶⁾. Disease-specific biomarkers, molecular subtypes, and regulatory networks that cannot be identified using individual omics platforms alone can be found using multi-layered molecular profiling⁽¹⁰⁷⁾. Accurate patient stratification, disease progression prediction, and individualized treatment selection are made possible by combining multi-omics data with AI and machine learning⁽¹⁰⁸⁾. Multi-omics is a key component of next-generation precision hepatology and customized clinical decision-making, and integrative analytical frameworks further speed up biomarker identification, functional validation, and precision medication development^(109,110).

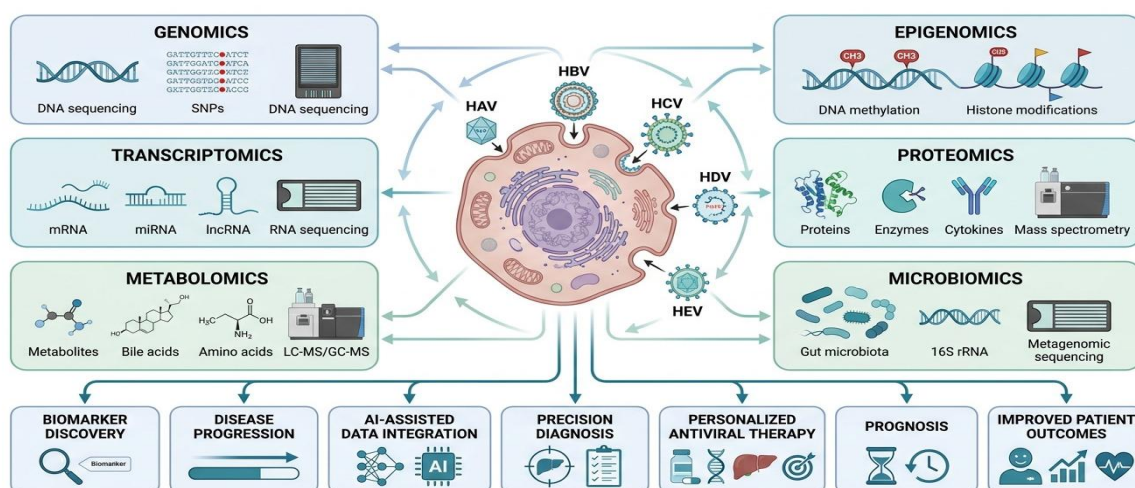


Figure 5: Multi -Omics approaches in precision medicines for viral hepatitis.

7. ARTIFICIAL INTELLIGENCE IN PRECISION HEPATOLOGY

Precision hepatology now heavily relies on machine learning (ML), which finds intricate patterns in clinical, imaging, and molecular datasets that are difficult to spot with traditional statistical methods ⁽¹¹¹⁾. ML algorithms enhance individualized clinical decision-making, prognostic evaluation, and illness classification in the treatment of viral hepatitis ⁽¹¹²⁾. Multilayered neural networks are used by deep learning (DL), a specialized area of machine learning, to automatically extract complicated features from imaging, histopathological, genomic, and clinical datasets ⁽¹¹³⁾. DL has improved disease staging, predictive modeling, and diagnostic accuracy in viral hepatitis, facilitating individualized patient treatment and precision-based clinical decision-making ⁽¹¹⁴⁾. By combining clinical characteristics, laboratory biomarkers, imaging data, and electronic health records, artificial intelligence has greatly enhanced the early diagnosis of viral hepatitis ⁽¹¹⁵⁾. By detecting subtle imaging and histological characteristics linked to hepatic inflammation, fibrosis, and early hepatocellular carcinoma, deep learning algorithms further improve diagnostic accuracy and enable prompt intervention and precision-based therapeutic care ^(116,117).

7.1 AI in Disease Prediction

By combining clinical, laboratory, imaging, genomic, and multi-omics datasets to create personalized risk prediction models, artificial intelligence has significantly improved illness prediction in viral hepatitis ⁽¹¹⁸⁾. Hepatic decompensation, cirrhosis, fibrosis progression, antiviral therapy response, and long-term clinical outcomes are all reliably predicted by machine learning algorithms, which often exceed traditional statistical models ^(119,115). By continuously analyzing electronic health records and longitudinal patient data, deep learning models further enable dynamic risk stratification, making it easier to identify high-risk individuals early on ⁽¹²¹⁾. It is anticipated that the combination of explainable AI and precision medicine will improve clinical interpretability, facilitate tailored treatment choices, and improve prognosis for all viral hepatitis patients ⁽¹²²⁾.

7.2 AI for Fibrosis Assessment

Artificial intelligence has enhanced non-invasive fibrosis assessment by combining imaging, elastography, histology, and clinical biomarkers into highly accurate predictive models ⁽¹²³⁾. Deep learning algorithms facilitate personalized risk assessment, treatment planning, and long-term monitoring in patients with viral hepatitis by improving fibrosis staging, lowering interobserver variability, and supporting early detection of advanced liver disease ⁽¹²⁴⁾.

7.3 AI for HCC Prediction

By incorporating laboratory measurements, imaging results, molecular biomarkers, and longitudinal clinical records into reliable risk prediction models, artificial intelligence has significantly improved the prediction of hepatocellular carcinoma (HCC) ⁽¹¹⁸⁾. Personalized surveillance techniques and early treatment intervention are made possible by the precise identification of patients at high risk for the development of HCC by machine learning and deep learning algorithms ⁽¹²⁶⁾. Additionally, radiomics-based AI algorithms enhance early HCC identification and prognostic evaluation by extracting quantitative imaging signals beyond human interpretation ⁽¹²⁷⁾. It is anticipated that the combination of AI and multi-omics biomarkers will improve precision oncology and tailored HCC prediction for patients with chronic viral hepatitis ⁽¹²⁸⁾.

7.4 AI in Drug Discovery

Antiviral drug discovery is accelerated by artificial intelligence, which integrates genetic, structural, chemical, and pharmacological databases to uncover novel therapeutic targets and optimize lead compounds ⁽¹²⁹⁾. Machine learning algorithms enable virtual screening, prediction of drug-target interactions, and drug repurposing, significantly lowering the time and expense involved with traditional drug development ⁽¹³⁰⁾. De novo molecular design and candidate optimization are further supported by generative artificial intelligence, providing new avenues for the development of precision treatments against hepatocellular carcinoma and chronic viral hepatitis ^(131,132).

7.5 Digital Health & Remote Monitoring

By facilitating ongoing remote monitoring via telemedicine, wearable technology, mobile health apps, and electronic patient-reported outcomes, digital health technologies have increased precision hepatology ⁽¹³³⁾. For

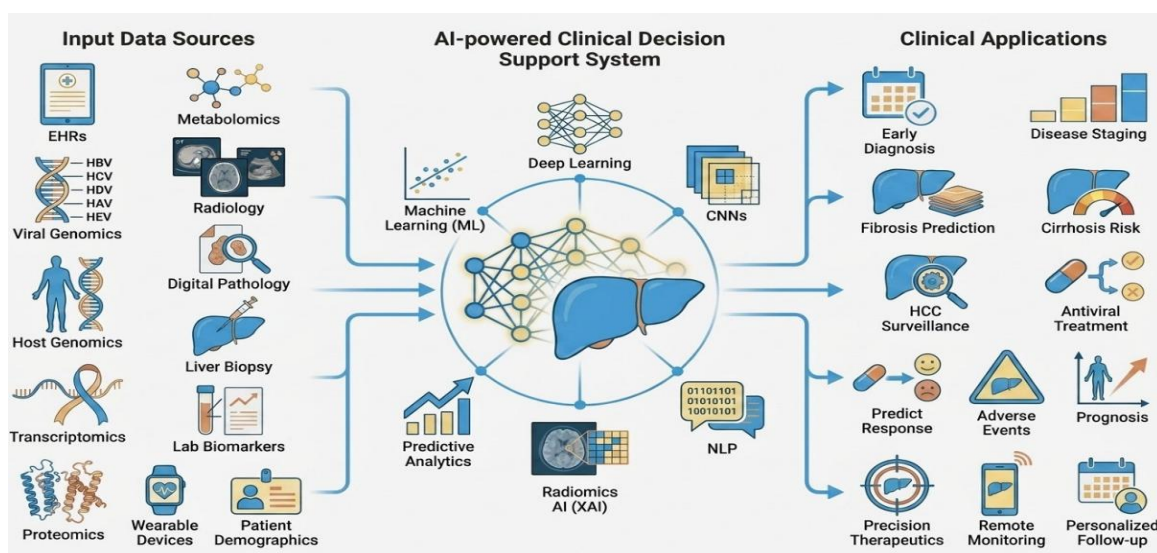


Figure 6: AI-powered clinical decision support system for precision management of viral hepatitis

patients with chronic viral hepatitis, integrating digital biomarkers with artificial intelligence promotes early clinical deterioration diagnosis, increases medication adherence, enables customized follow-up, and improves long-term disease management ^(134,135).

8. PERSONALIZED THERAPEUTICS

8.1 Personalized Antiviral Therapy

In order to maximize therapeutic efficiency and minimize side effects, personalized antiviral medication integrates host genetic variables, illness stage, virus genotype, resistance mutations, and molecular biomarkers ⁽⁶⁰⁾. HBV DNA, quantitative HBsAg, HBcrAg, and viral resistance profiles are used in customized approaches for chronic HBV infection to direct nucleoside analogue selection and assess the possibility of a functional cure ^(9,69). Pangenotypic direct-acting antivirals have made managing HCV easier, but patients with severe liver disease, resistance-associated substitutions, prior treatment failure, or viral coinfections still need customized care ⁽³⁷⁾.

Despite the advent of pangenotypic direct-acting antivirals, viral genotyping is still crucial for tailored treatment planning because it predicts antiviral response, resistance patterns, and disease progression, especially in chronic HBV and certain HCV clinical settings ⁽³⁷⁾. Using therapeutic vaccines, immune checkpoint inhibitors, tailored cytokines, and T-cell-based tactics, precision immunotherapy aims to restore virus-specific immune responses. Treatment selection is increasingly influenced by host immunological biomarkers and molecular profiling ^(141,142). In order to concurrently limit viral replication, rebuild antiviral immunity, and raise the possibility of obtaining a long-lasting functional cure in chronic hepatitis B, combination therapy combines direct-acting antivirals with immune-modulating or host-targeted drugs ⁽⁹⁾.

Instead of focusing only on viral proteins, host-directed therapy is a promising precision medicine approach that targets host cellular pathways crucial for viral reproduction and immune control ⁽¹⁴⁴⁾. In order to restore efficient antiviral responses, therapeutic strategies include entrance inhibitors, immunological modulators, toll-like receptor agonists, therapeutic cytokines, and drugs that target innate immune signalling ^(145,141). In order to achieve functional cure and prolonged immunological control in chronic HBV infection while lowering the danger of antiviral resistance, host-directed treatments are being studied more and more in conjunction with direct-acting antivirals ⁽⁹⁾.

8.2 Precision Vaccines

By combining viral genomes, host immunological profiles, and cutting-edge vaccination platforms to provide customized and long-lasting immune responses, precision vaccines are revolutionizing the prevention and treatment of viral hepatitis ⁽¹⁴⁸⁾. Therapeutic vaccinations, in contrast to traditional preventive vaccines, are intended to enhance persistent viral control in chronic HBV infection and restore virus-specific T-cell immunity ^(142,9). A promising approach to functional cure and precision vaccinology, emerging mRNA-based and customized neoantigen vaccination platforms provide increased flexibility, improved immunogenicity, and opportunities for combination with immunomodulatory treatments ⁽¹⁵¹⁾.

8.3 CRISPR gene editing

By directly targeting the viral genome, gene editing technologies in particular, the CRISPR/Cas system have become revolutionary therapeutic platforms for obtaining a functional or sterilizing cure for chronic hepatitis B ⁽¹⁵²⁾. In preclinical research, CRISPR-mediated cleavage of integrated HBV DNA and covalently closed circular DNA (cccDNA) has shown encouraging antiviral effectiveness, decreasing viral replication and antigen expression ^(153,35). While reducing off-target impacts, improvements in base editing, prime editing, and optimized delivery systems have increased editing precision ⁽¹⁵⁵⁾. Despite these developments, issues with long-term efficacy, safety, immunogenicity, and delivery efficiency continue to be significant obstacles to clinical translation ⁽¹⁵⁶⁾. By specifically inhibiting viral gene expression and altering host pathways associated with chronic hepatitis B infection, RNA therapies have become a key component of precision medicine ⁽¹⁵⁷⁾. Functional cure options are improved by small interfering RNAs (siRNAs), antisense oligonucleotides (ASOs), and messenger RNA (mRNA)-based treatments that successfully lower viral transcripts, hepatitis B surface antigen expression, and viral replication ^(158,159). A promising strategy for individualized therapy of viral hepatitis is the combination of RNA therapies with immunomodulatory and antiviral drugs ⁽³⁵⁾. New tailored strategies for treating advanced liver

disease and reestablishing antiviral immunity include adoptive CAR-T, NK-cell, and stem cell-based treatments (161,162)

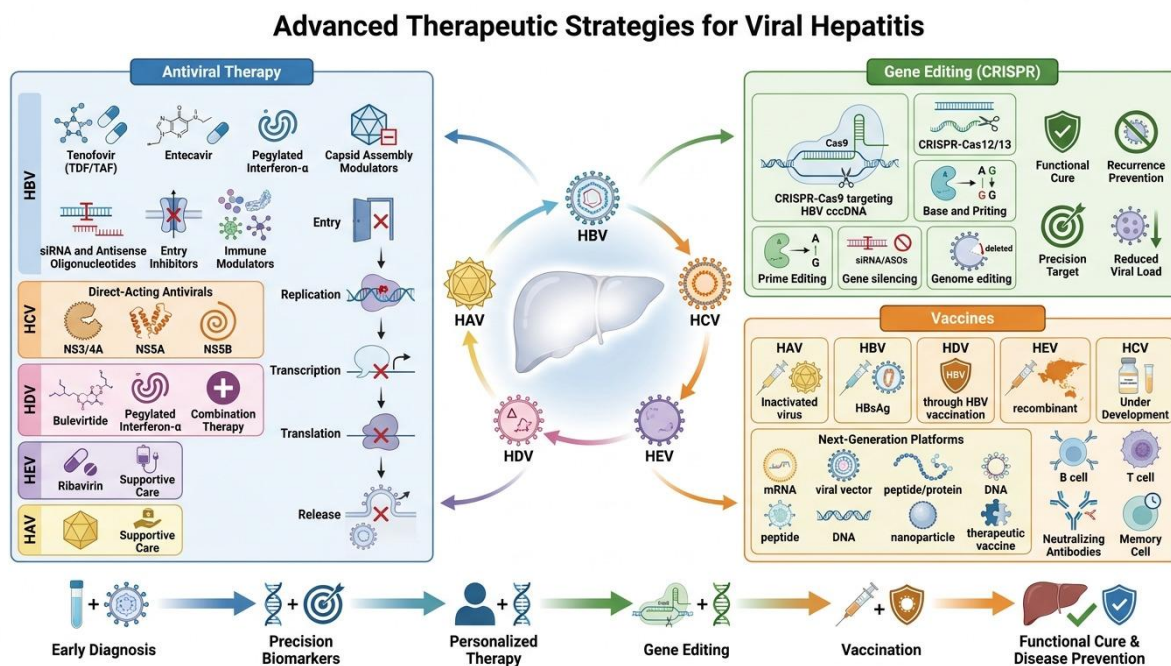


Figure 7: Emerging therapeutic strategies for viral hepatitis

Table 1: COMPARISON OF PRECISION MEDICINE ACROSS HEPATITIS VIRUSES

Feature	HBV	HCV	HDV	HAV	HEV
Genome	DNA	RNA	Defective RNA	RNA	RNA
Biomarkers	HBV DNA, HBsAg, HBcrAg, HBV RNA	HCV RNA, RASs	HDV RNA	Anti-HAV IgM	Anti-HEV IgM, HEV RNA
Host Genetics	HLA Polymorphisms	IL28B/IFNL4	Limited evidence	Minimal role	Emerging evidence
Multi-Omics	Extensive	Extensive	Emerging	Limited	Investigational
AI	Functional Cure	Fibrosis	Limited	Outbreak	Epidemiology

Applications	HCC, Fibrosis Prediction	Staging outcome Prediction		Surveillance	Monitoring
Personalized Therapy	Nucleostide analogues, RNA Therapeutics, CRISPR	DAAs	Entry Inhibitors immunotherapy	Supportive Care	Ribavirin in selected cases
Vaccines	Prophylactic & Therapeutic	None	Prevention via HBV vaccination	Effective Prophylactic	Available in selected cases
Future Direction	Functional Care	Ai guided long term	Immune based Therapies	Rapid Diagnostics	Precision diagnostics and vaccines

Comparing Precision Medicine for Different Hepatitis Viruses: Precision medicine varies among hepatitis viruses due to differences in viral genome, biomarkers, host genetics, and therapy techniques. HDV is a faulty RNA virus that depends on HBV, whereas HCV, HAV, and HEV are RNA viruses and HBV is a DNA virus. While HCV depends on HCV RNA and resistance-associated substitutions, HBV biomarkers include HBV DNA, HBsAg, HBcrAg, and HBV RNA. HDV RNA, anti-HAV IgM, and anti-HEV IgM/HEV RNA are used to monitor HDV, HAV, and HEV, respectively. For HBV and HCV, multi-omics and host genetic research are well-established; however, there are still few for the other hepatitis viruses. Artificial intelligence is being used more and more to forecast functional cures for HBV and evaluate fibrosis in HCV. Direct-acting antivirals for HCV, investigational treatments for HDV, supportive care for HAV, nucleostide analogues and RNA-based methods for HBV, and ribavirin in certain HEV cases are examples of personalized therapeutics. Future developments will concentrate on precision vaccines, immune-based treatments, AI-guided diagnostics, and better patient outcomes.

10. CLINICAL TRANSLATION & REALWORLD APPLICATIONS

By combining viral genomics, host genetics, molecular biomarkers, and clinical data to customize diagnosis, therapy choice, and disease monitoring, precision medicine is becoming more and more integrated into clinical hepatology⁽⁶⁰⁾. Patient classification and antiviral medication optimization are supported by biomarkers such HBV DNA, quantitative HBsAg, HBcrAg, serum HBV RNA, HCV RNA, and resistance-associated mutations⁽³⁷⁾. To improve treatment choices, artificial intelligence-based clinical decision support systems incorporate imaging,

viral genomes, laboratory results, and electronic health records ⁽³⁵⁾. Despite greater initial implementation costs, telemedicine, wearable technology, and digital health technologies further improve long-term monitoring and medication adherence, increasing clinical results ⁽¹⁶⁶⁾.

11. CHALLENGES & LIMITATIONS

Despite significant progress, precision medicine in viral hepatitis faces several challenges. High costs of genomic sequencing, multi-omics technologies, and targeted therapies limit accessibility, particularly in low- and middle-income countries ⁽⁶⁹⁾. Limited infrastructure, inadequate bioinformatics resources, and lack of standardized biomarkers hinder routine clinical implementation ⁽³⁷⁾. Ethical concerns regarding genomic data privacy, cybersecurity, and algorithmic bias in AI also remain important barriers ⁽¹⁶⁹⁾. Addressing these limitations through international collaboration, standardized protocols, and equitable healthcare access is essential for broader clinical adoption ⁽¹¹⁵⁾.

12. FUTURE PERSPECTIVES

In order to enhance illness prediction and tailored treatment, future developments in precision hepatology will depend on combining multi-omics technologies, artificial intelligence, and molecular biomarkers ⁽¹²¹⁾. There is hope for a functional cure with emerging RNA treatments, CRISPR-based gene editing, therapeutic vaccinations, and host-directed medicines ⁽¹³³⁾. Accelerated biomarker validation and equitable application of precision medicine in viral hepatitis will be made possible by the development of global genomic databases, digital health technology, and international cooperation ⁽¹⁷³⁾.

13. CONCLUSION

To improve the treatment of viral hepatitis, precision medicine combines comparative genomes, host genetics, biomarkers, multi-omics, artificial intelligence, and customized treatments. Through sustainable research, accessible healthcare, international partnerships, and innovation, ongoing multidisciplinary collaboration, equitable implementation, and technological innovation will speed up functional cure strategies, enhance clinical outcomes, and strengthen precision hepatology globally for future generations.

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