

Precision Medicine in Viral Hepatitis: Current Advances, Challenges and Future Perspectives

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Doi: <https://doi.org/10.5281/zenodo.22301138>

Received: 6 July 2026

Accepted: 16 July 2026

Abstract

Viral hepatitis is a major global health problem, being the leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma. The World Health Organization (WHO) has reported that hepatitis B and C viruses cause 1.34 million deaths yearly, and despite the availability of effective vaccines and treatments, the infections remain a significant health hazard. The application of conventional “one-size-fits-all” treatment and prevention methods cannot be efficient enough in the context of the identified genetic, immunological, and biochemical variability, which may affect individual response to treatment. The precision medicine paradigm aims to account for this complexity in order to individualize prevention, diagnosis, and treatment. This review discusses the state-of-the-art of precision medicine in the context of viral hepatitis. For instance, in the case of hepatitis B, the discussion revolves around the potential of quantitative HBs antigen, hepatitis B core-related antigen, and HBV RNA as biomarkers of treatment cessation and functional cure, as well as gene-editing and RNA-based therapies targeting the hepatitis B covalently closed circular DNA (cccDNA). Turning to hepatitis C, it is noted that, despite the advent of pangenotypic direct-acting antiviral agents (DAAs), the individualization of treatment still requires consideration of IL28B polymorphisms, NS5A resistance-associated substitutions, and other host and viral biomarkers. The first entry inhibitor for hepatitis D, bulevirtide, has also been highlighted, alongside the importance of pharmacogenetic-guided ribavirin dosing, which is still relevant in certain cases. The role of artificial intelligence in precision oncology was also discussed in the context of liver cancer risk prediction, with a particular focus on hepatocellular carcinoma. Among the key challenges in the field are the high costs of individualized therapies and the insufficient consideration of host responses in low- and middle-income countries (LMICs), as well as the lack of high-quality biomarkers for hepatitis E in LMICs, which hinders the personalized approach to prevention and treatment there. The key future directions for precision medicine in viral hepatitis include multi-omics studies, single-cell technologies, artificial intelligence-assisted

precision prevention and treatment, and the implementation of these innovations in public health and population health approaches to viral hepatitis elimination by 2030, as envisioned by the WHO.

Keywords: Hepatitis, Viral; Precision Medicine; Hepatitis B virus; Hepatitis C virus; Pharmacogenomics; Biomarkers; Antiviral Agents; Genotype

1. Introduction

Viral hepatitis represents a huge public health burden. The World Health Organization (WHO) Global Hepatitis Report 2024 estimates chronic hepatitis B infection as 254 million worldwide and 50 million for chronic hepatitis C, while viral hepatitis is the second highest communicable disease death cause after tuberculosis, resulting in approximately 3,500 deaths every day (1). New surveillance data show that 287 million people worldwide are estimated to be living with chronic hepatitis B or C infection in 2024, with these two virus forms accounting for 95% of total hepatitis mortality, with ten countries being responsible for 69% of hepatitis B fatalities (2). In 2016, the World Health Assembly set elimination targets for 2030 by reducing new infection cases by 90% and mortality by 65% compared to the 2015 baseline (1). Since then, hepatitis B incidence has decreased by 32%, and mortality from hepatitis C has decreased by 12%, while 85 countries have achieved the pediatric hepatitis B prevalence target (2). However, independent expert assessment shows that only 15% and 14% of countries are on track to meet the 2030 hepatitis C mortality and incidence targets, respectively, with significant regional variations (3). Finally, precision medicine offers a way to achieve an accelerated hepatitis elimination by focusing limited resources on those patients who are most likely to benefit from a specific form of intervention.

The conventional approach to managing viral hepatitis has been based on the use of standardized treatment algorithms that primarily focused on the level of viral load and liver enzymes with the addition of genotype-specific recommendations. Such a strategy has been enormously successful in the case of hepatitis C, where pangenotypic direct-acting antiviral agents (DAAs) enable achieving a sustained virological response (SVR) in almost all treated patients. However, it has proved largely ineffective in the case of hepatitis B, D, and E, with no reliable predictors of functional cure, reactivation, and progression to cirrhosis or hepatocellular carcinoma (HCC). Applying the concept of precision medicine (PM) which assumes the consideration of a patient's

individual characteristics, including genetic, environmental and lifestyle factors, and focuses on the prediction of individual clinical outcomes based on this information rather than the analysis of pooled populations (4,5) can help bridge this gap. Several reports suggest that PM and its analysis of host and viral determinants have significant implications for hepatitis treatment. Indeed, the editorial board of Hepatology has openly stated that PM is critical to the WHO strategy to eliminate viral hepatitis by focusing on host- and virus-specific signatures associated with treatment response and reactivation of the virus (6).

This scoping review aims to assess the existing evidence in the field by summarizing the published data on the potential of applying PM to different forms of viral hepatitis, highlighting the available molecular tools that can be employed to identify predictive and prognostic biomarkers, discussing some of the key controversies in the field, and providing an outlook on the clinical implementation of PM. Particular attention will be paid to the issues of applicability in low and middle-income countries which are the epicenters of the hepatitis epidemic.

2. Overview of Viral Hepatitis

Five hepatotropic viruses, namely hepatitis A (HAV), B (HBV), C (HCV), D (HDV) and E (HEV), differ substantially regarding their virology, transmission routes and persistence. HAV and HEV are transmitted by the faeco-oral route and usually cause an acute, self-limiting hepatitis, but HEV is associated with high risk of mortality in pregnant women and chronic liver disease in immunosuppressed hosts (7,8). In contrast to the RNA structure of HAV, HEV is a small, positive-sense RNA virus of the family Hepeviridae that infects humans via a zoonotic route; genotypes 1-2 are associated with endemic outbreaks in developing countries, whereas 3-4 are maintained in animal reservoirs (particularly pigs) in developed countries (7,9).

HBV is a partially double-stranded DNA hepadnavirus that employs an RNA intermediate for transcription, and establishes persistent infections mediated by stable cccDNA minichromosomes in the nucleus, thereby presenting particular challenges for definitive cure (10). At least ten HBV genotypes (A-J) have been identified that differ in geographical distribution, association with liver fibrosis progression, risk of hepatocellular carcinoma (HCC) and response to treatment with interferons (11-13). Finally, HCV is an enveloped positive-sense RNA flavivirus with extraordinary sequence diversity that traditionally dictated genotype-specific therapies, although

cross-genotypic direct-acting antivirals (DAAs) have since been developed (14). HDV, a defective RNA virus, only infects humans in the presence of HBV envelope proteins and causes more aggressive forms of hepatitis with increased risk of cirrhosis and HCC compared to HBV mono-infection (15). All three viruses, chronically infecting hepatocytes, share the ability to promote liver fibrosis, cirrhosis and HCC, the ultimate manifestation being the second highest cancer mortality worldwide.

3. Concept of Precision Medicine

The US National Human Genome Research Institute defines precision medicine as an approach “to use information from an individual’s genome, environment and lifestyle to make decisions about their medical care,” particularly to allow “more accurate prevention, diagnosis, and treatment” (4). The concept was popularised by the 2011 National Research Council report “Toward Precision Medicine”, which proposed to stratify patients into molecularly defined categories based on their individualised risk profiles or treatment response, to both better target those who stand to benefit while minimising toxic or unnecessary interventions for the rest (5).

“Precision” and “personalised” are often used interchangeably; the National Research Council even mentions ‘personalised medicine’ as an alternative term for the same concept (4). However, some authors make a distinction between the two, arguing that while the term precision medicine is about categorising individuals into biologically informative subgroups, personalised medicine implies a more bespoke, individual approach, which the National Research Council aims to move away from (5,14). The broader P4 paradigm (predictive, preventive, personalised, participatory) also contains elements of predictive analytics and systems biology requiring high-throughput multi-omics data for post-genomic era analyses (14). On the other hand, some authors argue that this trend discounts the importance of socioeconomic risk factors,

which may dominate in many low- and middle-income countries due to the disease's strong socioeconomic determinants (2,14). The field of hepatology and its understanding of hepatitis has since the 2000s been transformed by the advent of next-generation sequencing and genome-wide association studies, and more recently driven by the rise of artificial intelligence in the field.

4. Molecular Basis of Precision Medicine

Host genome-wide association studies initially established the value of this approach in predicting treatment outcomes, as single nucleotide polymorphisms in IL28B / IFNL4 were the most powerful pretreatment predictors of hepatitis C virus (HCV) clearance (15,16); screening of ITPA variants provided critical information on ribavirin-induced anemia risk (17). Intrahepatic viral genome sequencing allows the identification of hepatitis B virus (HBV) genotype and quantitative assessment of the basal core promoter, precore, and polymerase mutants associated with viral replication capacity, immune evasion, and drug resistance (11,13). For HCV, treatment guidelines recommend resistance-associated substitutions (RAS) testing in NS3, NS5A, and NS5B, including NS5A Y93H, to inform retreatment after direct-acting antiviral (DAA) failure.

In terms of therapy, the clinical development of finite-persistence regimes leading to functional cure is ongoing. Specifically, the antisense oligonucleotide bepirovirsen produced serological response (loss of HBsAg / HBV DNA) in 9-10% of patients in the phase IIb trial; in the phase III B-Well trials, which enrolled 1,838 patients from 29 countries, 19-20% of patients who received the drug achieved functional cure at week 72, compared to 0% in the placebo group – the first functional cure ever reported in a phase III trial (25,26). The CRISPR-Cas9 system targeting cccDNA can effectively edit the viral genome in cell-based and humanized mouse models, demonstrating a reduction in cccDNA levels and the appearance of mutated viral genomes (28,29). However, the clinical application of this technology is limited by the need to deliver it to a significant proportion of infected hepatocytes (30,31). Therapeutic vaccination also holds promise, as the combined HBsAg / HBcAg nasal vaccine NASVAC produced an antiviral response in patients with different genotypes, with a prolonged HBeAg loss and, in a five-year follow-up study, serological conversion to anti-HBs in some patients; however, these results were modest compared to preclinical studies (32,33). Artificial intelligence models of HCC have demonstrated promising results in predicting tumorigenesis: in the development of a machine learning algorithm based on computed tomography imaging biomarkers (PLAN-B-DF), the prediction of HCC was more accurate than conventional clinical staging models in a cohort of 5,585 patients (34). At the

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(DAA) failure.

Transcriptomic and proteomic studies of liver-infiltrating immune cells and peripheral blood mononuclear cells decipher immune signatures of HBV control/persistence, while a metabolomics-based machine learning approach has distinguished hepatocellular carcinoma (HCC) from cirrhosis in HCV patients by non-invasive biomarker panels (18). Epigenetic regulation of host and cccDNA chromatin and microRNAs represent additional candidate mechanisms; immune checkpoint profiling of exhausted HBV-specific T cells is further advanced by single-cell approaches (Section 9).

5. Precision Medicine in Hepatitis B

The management of chronic hepatitis B has shifted from long-term suppression to strategies tailored to patients' clinical features in the context of nucleos(t)ide analogues (NA) with high barrier to resistance. With effective suppression of HBV replication, the focus of treatment has shifted to the management of concomitant morbidity, HCC prevention, and cure (10). Notably, genotype differences reported in clinical outcomes are relevant to precision medicine: compared to genotype A, genotypes C and D were associated with delayed HBeAg seroconversion, a higher frequency of basal core promoter mutations, and increased cirrhosis/HCC risk (12,13). Moreover, these genotypes showed reduced response to interferon (IFN), although comparable NA efficacy was reported across all genotypes (13). Indeed, large-scale HBV sequence analyses revealed that immune escape, resistance-conferring, and HCC-associated substitutions were not randomly distributed across genotypes (13,19).

Clinical biomarkers in serum are central to precision management of chronic HBV infection. Specifically, quantitative HBsAg allows the estimation of the risk of clinical endpoints during the natural history of infection, serological clearance, relapse after NA discontinuation, and HCC development (20). Meanwhile, the level of HBcrAg, a marker of cccDNA transcriptional activity, independently predicted virological relapse after nucleos(t)ide analogue discontinuation; in a meta-analysis including 13 studies and 1,529 patients, the overall sensitivity and specificity were

0.81 and 0.72, respectively, while the summary area under the curve (AUC) was 0.83 (21,22). In the Hepatitis B Research Network Immune Active study, quantification of end-of-treatment HBV RNA was associated with a reduced likelihood of achieving a sustained partial response compared to undetectable HBsAg (<100IU / mL; odds ratio: 0.03): 73% of patients who achieved virological response versus 3% of patients with detectable HBV RNA at the end of therapy had sustained partial response (23). In any case, the value of HBcrAg and HBV RNA as independent predictors was modest compared to standard clinical and laboratory variables, and assays remain inadequately standardized (23,24).

same time, a cross-ethnic algorithm using machine learning also demonstrated good accuracy in predicting HCC; however, the results require further validation (35).

6. Precision Medicine in Hepatitis C

Pan-genotypic direct-acting antivirals (DAAs) have changed hepatitis C virology fundamentally, curing most treated patients and diminishing the need for genotype-specific regimens. IL28B (IFNL3) genotype

was the most important pretreatment predictor of sustained virological response (SVR) during interferon-based therapy; favourable CC rs12979860 genotype was associated with 2- to 3-fold higher SVR compared to CT/TT (15,36). With first-generation protease inhibitors, this association was slightly attenuated (37). Within the DAA era, there is conflicting evidence on the value of IL28B in predicting either efficacy or safety of DAA therapy. While Egyptian genotype

4 cohort did not find an association of IL28B genotype with either outcomes (38), zinc supplementation on top of therapy allowed achieving 100% SVR in patients with CC genotype compared to 54% in those with CT/TT (11). By contrast, IL28B gene–FOXP3 interaction predicted DAA response with 76.2% sensitivity and 91.9% specificity (39). Similarly inconsistent were the findings on other genetic variants; thus, interferon-era pharmacogenetics have limited utility in the DAA era.

Pharmacogenetic testing remains relevant in treatment algorithms for hepatitis C that include ribavirin (genotype 3 retreatment, resource-limited settings). Genome-wide screening identified ITPA rs1127354 variant associated with lower ribavirin-induced haemolysis; this functional polymorphism was confirmed in Japanese, Austrian and Egyptian populations, with CC genotype being associated with significantly lower change in haemoglobin levels during treatment (40,41,43). A similar protective effect was reported for rs6051702 (41) that may help identify patients at greatest risk of anemia even in interferon-free regimens (41). Ribavirin transporter polymorphisms (SLC28A2/3, SLC29A1) can be used to further stratify patients based on anemia risk, potentially allowing individualization of RBV dosing; a combined screening of multiple polymorphisms may yield better results than testing for individual variants (43,44).

Resistance-associated substitutions (RAS) are present in a significant proportion of treatment-naïve patients failing DAA therapy due to NS5A inhibitors (most commonly Y93H in genotype 1b, conferring resistance to elbasvir and velpatasvir) or NS3 protease inhibitors; such substitutions

can be detected even after treatment discontinuation and inform retreatment decisions. However, baseline RASs have limited role in guiding treatment choice due to reduced impact on response rates and lack of universal recommendations; thus, it is unclear if a potentially valuable precision medicine tool will see widespread adoption.

7. Precision Medicine in Hepatitis D

HDV is the only virus causing hepatitis, and previous lack of HDV-specific drugs limited treatment options to interferon-based regimens. The recent discovery of sodium taurocholate co-transporting polypeptide (NTCP) as entry receptor for both HBV and HDV enabled the development of bulevirtide – a lipopeptide inhibitor of NTCP that binds to pre-S1 domain of HDV envelope protein. In the phase 3 MYR301 study, 150 patients with chronic hepatitis D (with or without compensated cirrhosis) received either 2 mg or 10 mg of bulevirtide or deferred treatment for 144 weeks; at week 48, the composite endpoint of HDV RNA reduction with normalization of aminotransferases was achieved in 45% and 48% of patients who received 2 mg and 10 mg bulevirtide, respectively, versus 2% in the control group (45,46). Bulevirtide was generally well-tolerated, with asymptomatic bile-acid elevations (dose-dependent) and transient pruritus seen in 14% of cases; no evidence of cholestatic hepatitis was observed (46). Combination of bulevirtide with pegylated

interferon alfa-2a is currently evaluated in phase 2b trial to improve response rates and reduce treatment duration (47).

Unlike for HBV and HCV, there are limited HDV-specific biomarkers suitable for routine clinical practice (Table 2). Quantification of HDV RNA is informative but suffers from lack of standardization across assays. Predictors of treatment response to bulevirtide are not yet established, and it remains unknown if response rates can be predicted at the time of treatment discontinuation. Due to interplay between HDV and HBV, it is unclear if HBV genotype or cccDNA-targeted biomarkers can be leveraged in HDV management (45).

8. Precision Medicine in Hepatitis E

HEV is unique among viral hepatitis agents in terms of both epidemiology and natural history. Infection in the third trimester of pregnancy – more commonly genotype 1 in endemic areas – is associated with increased perinatal and maternal mortality, although there are no validated

biomarkers to identify high-risk pregnancies (7,48). Chronic HEV infection occurs in immunosuppressed hosts, including solid-organ transplant recipients, in whom it causes more aggressive fibrosis progression comparable to hepatitis C (49). There is no effective treatment for chronic HEV infection; ribavirin remains the treatment of choice for acute hepatitis, acute-on-chronic liver failure or extrahepatic manifestations (48). Pegylated interferon alfa-2a is considered an option in ribavirin-relapsed or -resistant cases, with sofosbuvir showing promise as adjunctive therapy (8). Duration of therapy is typically 3 months for chronic HEV infection, whereas acute infections are treated for 12 weeks (8). Genotype 3 – the main zoonotic genotype circulating in industrialized nations – is associated with higher risk of chronicity compared to genotypes 1-2, that typically cause self-limited infections (8,50).

There are limited biomarkers to guide management of HEV infection. As with HBV, HEV serology shows wide inter-laboratory variability; HEV IgM positivity is not predictive of acute infection in pregnant women (51). Screening of immunosuppressed patients for HEV may be guided by degree of immunosuppression: a pooled analysis of HEV-infected inflammatory bowel disease patients found that seropositivity rates in European countries were similar to those of general population (51). Notably, intensified immunosuppression was associated with higher risk of HEV infection (51); therefore, the functional state of the immune system, rather than the underlying diagnosis, may determine HEV risk. The HEV 239 (Hecolin) vaccine is available in China for prevention of hepatitis E; its role in immunosuppressed or pregnant populations has not been established (52). Overall, hepatitis E virology remains understudied compared to other hepatitis viruses, and its management lags behind in terms of precision-medicine opportunities.

9. Role of Artificial Intelligence

Machine-learning algorithms increasingly enable clinicians to exploit the power of big data in genomics, transcriptomics, connectomics and other domains (53). In particular, artificial intelligence assists in mining complex data and identifying patterns that cannot be captured by traditional statistical methods. In chronic

hepatitis B, extreme-gradient-boosting machine learning algorithm allowed to build a clinically applicable model that successfully stratified patients according to risk of hepatocellular carcinoma (HCC) development (54). Similar approach improved surveillance of patients with chronic hepatitis C through the development of CT-based

PLAN-B-DF algorithm which incorporated deep learning to identify tumours not picked up by conventional morphology-based assessment (34). In patients with established HCC, machine learning survival analyses achieved recall rates of up to 91% for six-month survival prediction in early-stage disease and up to 92% three-year survival prediction in advanced HCC (55). AutoML combined with TreeSHAP explainable AI software identified metabolomic signatures that discriminated between HCC and cirrhosis in patients with chronic HCV infection (18). Of note, many algorithms originate from single-centre studies and require external validation. Another important consideration is the choice of training sets; currently, most algorithms are trained on data from a single ethnic group or country, and their performance in other populations may not be comparable (35,53).

10. Biomarkers

Biomarkers can be used for diagnostic, predictive or prognostic purposes. In hepatitis B, quantitative HBsAg, HBcrAg and HBV RNA comprise the key serum biomarkers that are relatively simple to measure but have important clinical implications. For example, HBsAg can be positive in patients with low-level viremia due to transcription from integrated HBV DNA (20,23,24). By comparison, HBcrAg assays are hampered by lack of standardization between manufacturers (24). Finally, while HBV RNA is a sensitive and specific marker of cccDNA and viral replication, its measurement requires specialized and thus often unavailable techniques (23). In hepatitis C, IL28B genotype and ITPA polymorphisms have predictive value in selecting patients for ribavirin-containing regimens, while NS5A/NS3 resistance-associated substitutions inform on treatment failure after DAA therapy (15,40,41). Liquid-core technologies enable isolation of cell-free DNA and RNA for non-invasive HCC screening: in particular, a signature of 9 exosomal RNA species discriminated between patients with and without HCC with an overall accuracy of approximately 85% in a large discovery cohort (56). However, most liquid biopsies remain in the realm of research; additional studies are needed before any biomarker can be incorporated in routine clinical practice.

11. Pharmacogenomics

Genetic variants influencing response to hepatitis medications have been extensively characterized, and such data can guide individualized treatment selection in some scenarios. For ribavirin, genome-wide association studies identified ITPA rs1127354 variant associated with impaired inosine triphosphate pyrophosphatase activity, which in turn decreases bioavailability of ribavirin and reduces anemia risk (17,42). This germline polymorphism was associated with lower decrease in hemoglobin levels during RBV-containing treatment for hepatitis C (40,41,42). The same applies to rs6051702, except that it can be used to identify patients at highest risk of severe anemia even during DAA treatment (41). Other ribavirin transporter polymorphisms (SLC28A2/3, SLC29A1) can also be considered when developing individualized treatment plans for patients receiving RBV (43,44). Outside of interferon-containing regimens, pharmacogenomics

have limited role in hepatitis management. For example, there are no established relationships between genetic variants and entecavir/tenofovir dosing in patients with renal dysfunction or between CYP or P-glycoprotein polymorphisms and DAA metabolism. Nevertheless, genotype-guided dosing of ribavirin remains a useful example of precision medicine in hepatitis.

12. Precision Therapeutics

The antiviral therapeutic arsenal is undergoing rapid change and expansion. Targeting of HBV RNA with antisense molecules (bepirovirsen) allows to degrade both cccDNA- and integrated HBV transcripts, thereby reducing HBsAg levels and, importantly, inducing functional cure in a sizeable fraction of patients. In phase 3 clinical trials, bepirovirsen administered as 12-week course decreased HBsAg levels by over 2-log and resulted in 18-25% of patients achieving treatment response at week 72 (25-27). Similar reductions in HBsAg levels were observed with other RNA-targeting therapeutics (28). More direct approaches that utilize CRISPR-Cas9 to cleave cccDNA and integrated HBV DNA also demonstrate promise, although in vivo studies in humanised mice have so far shown only partial suppression of antigen expression and cccDNA clearance (28)(29)(30). Therapeutic vaccination represents another promising area, with modified antigen-antibody complexes and intranasal administration of HBsAg/HBcAg shown to induce HBeAg seroconversion and, in some cases, HBsAg loss upon long-term follow-up (32,33,57). For hepatitis D, bulevirtide is the first targeted entry inhibitor that demonstrated significant improvements in HDV RNA clearance and liver biochemistry; its combination with pegylated interferon is currently investigated to shorten treatment duration and improve response rates (45,46,47).

Nanomedicine-based formulations are being explored to increase bioavailability of nucleos(t)ide analogues and improve delivery of gene-silencing therapeutics to hepatocytes. Polymeric and lipid-based nanocarriers or ligands that target asialoglycoprotein receptor can be used to deliver lamivudine (60) or other nucleoside analogues to increase their antiviral efficacy while reducing off-target toxicity (58,59). Similarly to small-molecule carriers, nanoparticles can enhance the potency of various biologics; this approach is particularly promising for gene-editing and RNAi therapeutics. At present, most nanomedicine developments are at pre-clinical stage; however, their successful application in other disease domains suggests that they will see utility in the treatment of viral hepatitis in the next 5-10 years. Overall, the next decade will see rapid progress in all spheres of precision medicine, from biomarker discovery to novel therapies.

13. Current Challenges

Translation of precision medicine into routine clinical practice is hindered by multiple factors. The most important consideration is economics: next-generation sequencing, HBcrAg testing, or novel therapeutics such as RNAi or gene-editing will be inaccessible to most hepatitis carriers, many of whom are in low- and middle-income countries (1,2). Equally important are practical considerations, such as availability of resources to perform next-generation sequencing in low-and middle-income countries. Genotype-guided

treatment of chronic hepatitis B is limited to resource-rich settings, despite clear clinical benefit in patients with genotype A (13,19). Additionally, integration of large-scale genetic data into routine practice requires ethical considerations and appropriate consent procedures; these topics have received limited attention within hepatology literature. Another challenge is regulatory environment, which will be crucial in determining the pace of gene-editing therapeutics development. Finally, all precision-medicine advancements reviewed here are challenged by the “research vs. practice” dichotomy. There is a need for broader adoption of validated biomarkers, tests, and therapeutics across different healthcare settings – this applies to non-invasive HCC screening tests and HBeAg-negative chronic hepatitis B management, among others (6).

14. Future Perspectives

Multi-omics approaches have the potential to facilitate precision medicine in viral hepatitis by combining information from multiple sources, thus increasing the predictive power. Early studies in HBV-associated HCC have demonstrated that combining genetic, transcriptomic and metabolomic data can improve biomarker discovery (61). Single-cell RNA-sequencing of fine-needle aspirates allows to dissect the heterogeneity of immune response to HBV infection and differentiate between various T-cell subsets that are important in HBV control or liver fibrosis progression (62)(63)(64). These insights can be leveraged to develop novel immunotherapeutics or treatment monitoring tools that can be applied in low- and middle-income countries: fine-needle aspiration and RNA sequencing has already been successfully employed in Zambia to delineate HBV-related chronic hepatitis (65). AI-guided decision-support systems will become increasingly important in routine clinical practice, although their role should be envisioned in combination with genotype- and biomarker-guided approaches. Development of simpler diagnostic assays will be critical to ensure equitable healthcare: Point-of-care testing will allow to streamline management of chronic hepatitis B, while community-based screening can support hepatitis elimination efforts. New therapeutic modalities, such as capsid assembly modifiers, will generate additional treatment options, while personalized vaccination strategies are particularly pertinent for high-risk groups (hepatitis E). Finally, it is important to recognize that the role of precision medicine in viral hepatitis depends on its integration into national healthcare systems; its future success will be determined by opportunities for implementation in different economic settings.

15. Critical Analysis of Current Literature

Several tensions can be drawn from this literature. Firstly, the depth of evidence is uneven across different viruses, as hepatitis B and C have been subjected to extensive research leading to an abundance of validated biomarkers and therapeutic options with high cure rates, whereas hepatitis D and E are understudied, pointing to the need for more research into these areas (7,45). Secondly, the host genetic predictors of response to DAA therapy for hepatitis C are inconsistent, ranging from no predictive power to over 75% sensitivity and specificity, potentially explaining by population differences, small sample sizes, and DAA’s overwhelming clinical benefit masking minor genetic effects, therefore rendering these findings difficult to generalize (11,38,39). Thirdly,

while being consistently associated with outcomes of clinical relevance, HBcrAg and HBV RNA only

provide modest predictive gains on top of standard of care markers in multivariable models, suggesting that their value in clinical practice is limited unless further refined into composite scores (23,24). Fourthly, the AI models to predict the risk of HCC represent an important step forward, though they have been trained on data from a single country and require external validation before their application in diverse populations can be considered (35,53,55). Lastly, it is clear that in order to truly impact the control and management of viral hepatitis, future studies and clinical practice should be focused on implementing precision medicine approaches that have been demonstrated to work across different settings, particularly with respect to the needs of disadvantaged populations and the viral hepatitis other than hepatitis B and C.

16. Conclusion

Precision medicine is beginning to transform the management of viral hepatitis, shifting the paradigm from one-size-fits-all treatments to therapies that take into account the unique characteristics of individual patients, such as the hepatitis genotype, host genetics, serum biomarkers, and AI-driven models. The most promising areas of research are found in the management of hepatitis B, where a functional cure is being actively pursued by investigating biomarkers and therapies such as gene editing or RNAi, and hepatitis C, where pharmacogenomic-guided treatment and resistance testing continue to play an important role alongside direct-acting antiviral medications. The addition of bulevirtide to the hepatitis D treatment armamentarium represents an important step forward in the management of this challenging infection, while hepatitis E remains the weakest link in our precision health strategies, with the most impactful interventions needed for pregnant women and immunocompromised individuals, who are particularly vulnerable to this infection. The outlined areas of research and clinical practice will contribute to the global control of viral hepatitis and the realization of the WHO's 2030 elimination goals. However, there are several challenges and limitations to the widespread implementation of the discussed approaches, namely their high costs and complexity. Therefore, future research should be focused on developing comprehensive, multi-marker tests, implementing the most promising interventions in the low and middle-income countries, and continuing the investigation into the mechanisms and therapies for other hepatitis viruses.

Table 1: Characteristics of the Major Hepatotropic Viruses

Virus	Family / Genome	Transmission	Chronicity	Key Complications
HAV	Picornaviridae; +ssRNA	Faecal-oral	None (acute only)	Rarely fulminant hepatitis
HBV	Hepadnaviridae; partly dsDNA (cccDNA)	Blood, perinatal, sexual	High in perinatal infection	Cirrhosis, HCC, reactivation
HCV	Flaviviridae; +ssRNA	Bloodborne (injection drug use)	~55-85% if untreated	Cirrhosis, HCC, extrahepatic disease

HDV	Defective RNA satellite (requires HBsAg)	Blood, sexual (HBV-dependent)	High; accelerates HBV course	Rapid cirrhosis, HCC, ACLF
HEV	Hepeviridae; +ssRNA	Faecal-oral, zoonotic (GT3/4)	Only in immunocompromised hosts	Fulminant hepatitis in pregnancy; chronic hepatitis post-transplant

Table 2: Selected Biomarkers Used in Precision Management of Viral Hepatitis

Biomarker	Virus	Clinical Application	Key Limitation
Quantitative HBsAg	HBV	Phase staging, seroclearance and HCC risk prediction (20)	May remain elevated from integrated DNA-derived antigen
HBcrAg	HBV	Predicts relapse after NA withdrawal (21,22)	Limited cross-manufacturer standardisation
HBV RNA (pgRNA)	HBV	Predicts sustained partial/functional cure (23)	Investigational; no reference standard
IL28B (IFNL3) genotype	HCV	Predicted interferon-era SVR; residual DAA-era relevance (15,36-39)	Attenuated predictive value with modern DAAs
ITPA rs1127354/rs6051702	HCV	Predicts ribavirin-induced anaemia (17,40,41)	Relevant only where ribavirin is used
NS5A RAS (e.g., Y93H)	HCV	Guides salvage regimen after DAA failure	Uncertain value in treatment-naïve patients
HDV RNA	HDV	Monitors bulevirtide response (45,46)	Assay standardisation limited

Table 3: Selected Approved or Guideline-Endorsed Antiviral Therapies Relevant to Precision Management

Agent	Target Virus	Mechanism	Status
Entecavir / Tenofovir	HBV	Nucleos(t)ide analogue; reverse transcriptase inhibition	Guideline first-line (10)
Pegylated interferon alfa-2a	HBV, HDV, HCV(hx)	Immunomodulation, antiviral	Approved / off-label for HDV (47)
Sofosbuvir-based DAA regimens	HCV	NS5B/NS5A/NS3 inhibition	Guideline first-line, pangenotypic
Ribavirin	HCV, HEV	Broad-spectrum nucleoside analogue	Adjunct / first-line for severe HEV (8)
Bulevirtide	HDV	NTCP entry inhibitor	Approved (EMA); phase 3 confirmed (45,46)

Table 4: Emerging Precision Therapeutics in Viral Hepatitis

Modality	Virus Target	Mechanism	Stage	Representative Agent
Antisense oligonucleotide	HBV	Degrades all HBV transcripts, reduces HBsAg	Phase 3 (26,27)	Bepirovirsen
CRISPR-Cas9 gene editing	HBV	Direct cccDNA/integrated DNA disruption	Preclinical / early clinical (10,28-31)	PBGENE-HBV
Therapeutic vaccination	HBV	Restores HBV-specific T-cell immunity	Phase 2-3 (32,33,57)	NASVAC / HeberNasvac
NTCP entry inhibition	HDV	Blocks hepatocyte viral entry	Approved/Phase 3 (45-47)	Bulevirtide
Nanoparticle drug delivery	HBV, HCV	Hepatocyte-targeted, controlled antiviral release	Preclinical (58-60)	Galactose-targeted nanocarriers

Table 5: Selected Clinical Trials Relevant to Precision Medicine in Viral Hepatitis

Trial / Registry	Virus	Intervention	Phase	Primary Endpoint
MYR301 (NCT03852719)	HDV	Bulevirtide 2 mg / 10 mg	Phase 3 (45,46)	Combined HDV RNA decline + ALT normalisation
B-Well 1 / B-Well 2 (NCT05630807/20)	HBV	Bepirovirsen + NA therapy	Phase 3 (26,27)	Functional cure at week 72
B-Clear (NCT04449029)	HBV	Bepirovirsen (weekly)	Phase 2b (25)	HBsAg and HBV DNA loss
ELIMINATE-B	HBV	PBGENE-HBV (CRISPR gene editing)	Phase 1/2 (10)	Safety and viral marker reduction

MYR301-linked combination study	HDV	Bulevirtide + peginterferon alfa-2a	Phase 2b (47)	Virologic response at end of treatment
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