Evolving insights into viral hepatitis: Advances, evidence, and expert perspectives from the ESCMID Study Group for Viral Hepatitis (ESGVH) – Part 2: hepatitis B, C, and delta

Oana Săndulescu[1,], Mojca Matičič[2], Federico Garcia[3], Marianne Alanko Blomé[4], Mario U Mondelli[5], William Irving[6], Snjezana Zidovec-Lepej[7], Anders Widell[8], Gülşen Özkaya Şahin[9], and on behalf of ESCMID Study Group for Viral Hepatitis (ESGVH)*

Abstract

Hepatitis B virus (HBV), hepatitis delta virus (HDV), and hepatitis C virus (HCV) remain leading drivers of chronic viral hepatitis, cirrhosis, hepatocellular carcinoma, and liver-related mortality. This ESCMID Study Group for Viral Hepatitis (ESGVH) narrative review summarizes recent advances and expert perspectives in the field. For HBV, emerging biomarkers such as quantitative HBs antigen, HBV RNA, and hepatitis B core-related antigen offer opportunities to refine monitoring and to individualize treatment. HDV epidemiology is evolving, and is being increasingly studied; in parallel, the approval of bulevirtide represents a major breakthrough in therapy, with further agents in the HDV pipeline. For HCV, direct-acting antivirals provide curative therapy and have made elimination a realistic goal, while identifying remaining gaps in diagnosis, linkage-to-care, and equitable access offers clear opportunities to accelerate progress. Together, these advances bring the goal of a hepatitis-free future closer than ever.

Keywords **Viral hepatitis, HBV, HCV, HDV, bloodborne viruses, liver.**

Introduction

Chronic viral hepatitis continues be a substantial driver of morbidity, mortality, and healthcare burden. Hepatitis B virus (HBV), hepatitis delta virus (HDV) and hepatitis C virus (HCV) are responsible for the majority of chronic viral hepatitis cases worldwide, driving the progression to cirrhosis, hepatocellular carcinoma, and liver-related deaths.

In recent years, progress in molecular diagnostics, antiviral development, and public health strategies has reshaped the landscape of

Received: 17 September 2025; revised: 27 September 2025; accepted: 28 September 2025.

[1]MD, PhD, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, and National Institute for Infectious Diseases "Prof. Dr. Matei Balş", Bucharest 021105, Romania, and Academy of Romanian Scientists, Bucharest, Romania, and Infection Science Forum, and Chair of ESCMID Study Group for Viral Hepatitis (ESGVH) Executive Committee; [2]MD, PhD, Clinic for Infectious Diseases and Febrile Illnesses, University Medical Centre Ljubljana, and Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia, and ESCMID Study Group for Viral Hepatitis (ESGVH) Executive Committee; [3]Pharm D, PhD, Hospital Universitario Clínico San Cecilio, Granada 18016, Spain, and Instituto de Investigación ibs.GRANADA, Granada, Spain, and Centro de Investigación Biomédica en Red de Enfermedades Infecciosas - CIBERINFEC, Spain, and Former President of SEIMC, and ESCMID Study Group for Viral Hepatitis (ESGVH); [4]MD, PhD, Department of Infectious Diseases, Skåne University Hospital, Malmö, Sweden, and Clinical Infection Medicine and Department of Translational Medicine, Lund University, Lund, Sweden, and Center for Communicable Disease Prevention and Control, Skåne Region, Sweden; [5]MD, PhD, Division of Clinical Immunology – Infectious Diseases, Fondazione IRCCS Policlinico San Matteo, and Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy, and ESCMID Study Group for Viral Hepatitis (ESGVH); [6]FRCPath, PhD, NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust, University of Nottingham, Nottingham, UK and ESCMID Study Group for Viral Hepatitis (ESGVH); [7]PhD, Associate Professor, Department of Immunological and Molecular Diagnostics, University Hospital for Infectious Diseases "Dr. Fran Mihaljevic", Mirogojska, Zagreb, Croatia, and ESCMID Study Group for Viral Hepatitis (ESGVH); [8]MD, PhD, Associate Professor, Senior virologist, retired from clinical work, Department of Translational Medicine, Clinical Virology, Lund University, Lund University Virus Centre, Wallenberg laboratory, Malmö 214 28, Sweden; [9]MD, PhD, Clinical Microbiology, Infection Prevention and Control, Office for Medical Services, Region Skåne, Lund, Sweden, and Division of Medical Microbiology, Department of Laboratory Medicine Lund, Medical Faculty, Lund University, Lund, Sweden, and ESCMID Study Group for Viral Hepatitis (ESGVH).

viral hepatitis management. The identification of novel biomarkers in HBV, the approval of new classes of therapies for HDV, and the remarkable efficacy of direct-acting antivirals for HCV have provided unprecedented opportunities to improve outcomes. Yet, challenges persist, including gaps in access to care, underdiagnosis, therapeutic limitations in special populations, and evolving epidemiological trends driven by migration, comorbidities, and changes in risk behavior.

Building on the first part of this ESCMID Study Group for Viral Hepatitis (ESGVH) series, which focused on hepatitis A and E and herpesvirus-associated hepatitis, the present narrative review summarizes contemporary advances in HBV, HDV and HCV. We highlight evolving concepts in virology, epidemiology, diagnostics, and therapy, while reflecting on the framework for elimination of viral hepatitis from the list of public health threats. By integrating scientific evidence with expert perspectives, this article aims to provide an updated, practice-oriented overview to support clinicians, researchers, and policymakers in the fight against viral hepatitis.

Hepatitis B virus

Novel tools for diagnosis and monitoring of HBV infection

Traditionally, the diagnosis and management of chronic hepatitis B (CHB) have relied on serologic markers such as hepatitis B surface antigen (HBsAg), hepatitis B e-antigen (HBeAg), and HBV DNA levels.[1] These markers have been instrumental in diagnosing infection, assessing viral replication, and monitoring treatment efficacy. However, they present limitations, including insufficient sensitivity to comprehensively predict disease progression or treatment response.[2]

*Corresponding author: Oana Săndulescu, oana.sandulescu@umfcd.ro

Article downloaded from www.germs.ro
Published September 2025

ISSN 2248 – 2997
ISSN – L = 2248 – 2997

There is a need for better biomarkers that can more accurately predict outcomes, reliably track long-term disease progression, and reflect the severity of organ damage, especially in chronic conditions like liver disease. Current biomarkers often fall short in these areas, making it difficult to assess a patient's future health and monitor treatment effects over time. Additionally, they lack the specificity needed for personalized treatment strategies, limiting their effectiveness in precision medicine.[3]

Recent advances have introduced promising new biomarkers for enhancing HBV management, with the aim of improving patient outcomes and optimizing treatment strategies. Among these key biomarkers are quantitative HBsAg (qHBsAg), HBV RNA, and hepatitis B core-related antigen (HBcrAg).

HBsAg levels fluctuate throughout the course of HBV disease, providing valuable insights for: a) more accurate identification of true inactive carriers,[4,5] with HBsAg <1000 IU/mL and HBV-DNA <2000 IU/mL identifying them with 94.7% accuracy; b) predicting the risk of hepatocellular carcinoma (HCC),[6] as HBsAg >1000 IU/mL is linked to higher HCC risk in HBeAg-negative patients; c) forecasting HBsAg clearance after discontinuing nucleos(t)ide analogue (NUC) therapy,[7] with rates ranging from 33% (HBsAg <100 IU/mL in Asian persons) to 41% (HBsAg <1000 IU/mL, in Caucasian persons) in HBeAg-negative patients; and d) predicting response to emerging therapies like bepirovirsen,[8] with a higher response at the end of treatment in patients who had HBsAg <1000 IU/mL at baseline.

Both HBV RNA and HBcrAg are closely linked to covalently closed circular DNA (cccDNA) transcriptional activity and may potentially be used in a similar manner to qHBsAg. The integration of these new biomarkers into clinical practice could significantly refine the management of HBV. By offering a more nuanced understanding of viral dynamics and immune responses, these markers enable personalized treatment approaches, potentially improving patient outcomes. However, there currently are limitations – such as availability, standardization, sensitivity, and

insufficient studies across diverse populations – that need to be addressed before HBV RNA and HBcrAg can be fully integrated into clinical practice.

As these new biomarkers become more accessible and standardized, they promise to transform HBV management from a one-size-fits-all approach to a more tailored and effective strategy. Their development and refinement underscore the dynamic and evolving nature of HBV research, paving the way for better diagnostic tools and therapeutic options that hold the potential to improve the lives of millions affected by this chronic infection.

Hepatitis delta virus

Changing epidemiology of HDV-infection: why and where?

Hepatitis delta virus (HDV) requires the assistance of hepatitis B virus (HBV) for complete replication. Infection can therefore only occur in the presence of HBV, either as a co-infection, or as a super-infection in a patient with chronic HBV infection. Chronic co-infection enhances progression of liver disease and is associated with an average progression to cirrhosis in 5 years and to hepatocellular carcinoma in 10 years.

Risk factors for acquisition of HDV infection include injecting drug use, exposure to other blood-contaminated needles, and sexual transmission. There is also evidence of intrahousehold transmission – there was a significant clustering of HDV infections within households as compared to HBV, HCV or HIV in a large study from Cameroon.[9] Other at-risk groups include individuals with HCV or HIV co-infection, and patients undergoing hemodialysis. Evidence for mother-to-child transmission is not convincing – 0/36 babies of mothers with HBV/HDV co-infection in France were anti-HDV positive at 2 years.[10] A rural village study in Cameroon identified 8 HDV infections out of 54 patients with HBV infection, 3 of whom were children, but intrahousehold transmission could not be ruled out.[11] Higher rates of HDV infection are also found in migrants from high prevalence countries, and patients with advanced liver disease.

There is some controversy over estimates of the global burden of HDV infection. Three large systematic reviews have appeared[12-14] with global burdens varying between 12 and 70 million people. Possible reasons for these widely varying results are slightly different statistical analyses, different selection criteria for inclusion over different periods of time (182 studies from 61 countries over 49 years;[12] 634 from 83 countries over 52 years;[13] 282 from 95 countries over 21 years[14]) being included in the analysis. Individual studies also vary according to which diagnostic marker and which assay was used to define HDV infection, whether studies were hospital- or community-based, and whether patients with HIV co-infection were included or not.

HDV epidemiology is changing over time as a result of universal HBV immunization, and migration from countries of high(er) endemicity to low endemic countries. Thus, in high income countries, there is a dual epidemiology with an "ageing cohort of domestic patients with advanced liver fibrosis [...] and [...] a younger generation of immigrants from endemic countries".[15] Despite all of the above, there is agreement that HDV infection is not rare; recognized hot spots include Mongolia, Pakistan, Tunisia, Niger, Moldova, Romania, Cameroon and Latin America. Barriers to understanding the true epidemiology of HDV include the absence of well-conducted population-based surveys, studies producing over-estimates due to testing of hepatology/referral clinics,[16] an unmet need for large sample sizes in low HBV prevalence settings, a lack of standardized and validated RNA assays and low global testing with difficulty in accessing tests. A number of recent studies have tried to produce more accurate estimates of the numbers of infected patients in the USA, Canada and across Europe.[17-20] HDV prevalence may vary widely within a country[21] and may not necessarily parallel HBV prevalence,[9] both factors rendering large scale estimations even more complicated.

Cell culture evidence suggests that HDV may utilize helper viruses other than HBV, including HCV, for replication,[22] raising the possibility of individuals with HDV infection being currently undiagnosed because they have no marker of HBV infection. Two possible such cases were

reported from Venezuela,[23] although a study of patients with HCV mono-infection in China failed to find any with HDV markers.[21] A study of French blood donors identified 14 anti-HBc negative donors with low level anti-HDV reactivity.[24] This issue has yet to be fully resolved.

Advances in the treatment of HDV infection

The landscape of HDV treatment is evolving rapidly with the introduction of new therapeutic agents. According to the EASL 2023 clinical practice guidelines on HDV, all patients with chronic HDV should be considered for antiviral treatment (level of evidence 3; strong recommendation).[25] The HDV lifecycle offers multiple therapeutic targets,[26] providing opportunities to inhibit viral replication through various mechanisms: blocking virus entry into hepatocytes by targeting the sodium taurocholate co-transporting polypeptide (NTCP) receptor (entry inhibitors); preventing the secretion of HBsAg, a key component of the HDV lifecycle (HBsAg secretion inhibitors); inhibiting farnesyl-transferase, which is essential for viral replication (prenylation inhibitors); and enhancing the immune response by activating the JAK-STAT pathway, leading to interferon-stimulated gene (ISG) production and antiviral activity (immune modulators). Additionally, blocking HBV itself could be a strategy to disrupt the HDV lifecycle.

Bulevirtide (BLV) marks a significant breakthrough as the first approved drug for HDV treatment in Europe. Derived from the NTCP binding domain of L-HBsAg,[27] BLV is the first-in-class entry inhibitor that blocks HDV from entering hepatocytes by targeting the NTCP receptor. This prevents the virus from infecting new liver cells, effectively halting viral spread at a critical juncture in the HDV lifecycle. By leveraging this unique mechanism, BLV distinguishes itself as a novel therapy for HDV, a disease that has long been associated with limited treatment options and progressive liver damage.

BLV has demonstrated promising efficacy in clinical trials[28] as well as real-world studies.[29,30] Data support the effectiveness of BLV 2 mg therapy over 96 weeks, showing virological response rates – defined as undetectable HDV RNA or a ≥2-log decline from baseline – ranging between 68-77%. ALT normalization was observed in 56-73% of patients, and combined virological response plus ALT normalization was achieved in 52-55% of cases.

Other HDV antiviral agents remain under investigation. Pegylated interferon alfa (Peg-IFNα, an immune modulator) and lonafarnib (a prenylation inhibitor) have shown lower efficacy compared to BLV in clinical trials [HIDIT-I[31] & II,[32] D-LIVR[33]], and they were associated with high rates of virological relapse following therapy discontinuation. Other agents under development include REP-2139 (HBsAg secretion inhibitor combined with NUC ± Peg-IFNα), which has shown lower efficacy than BLV, as well as HBV-DNA polymerase inhibitors (ATI-2173) and HBV-RNA interference molecules (JNJ-3989, VIR-2218).

The approval of BLV marks a pivotal shift in HDV treatment, addressing a previously unmet need for effective antiviral therapies. The ongoing development of new agents and combination regimens seeks to improve viral suppression, mitigate liver disease progression, and enhance patient outcomes. As the therapeutic arsenal expands, clinicians will be better positioned to tailor treatments to individual needs, optimizing both efficacy and adherence. This growing landscape of treatment options offers a more hopeful outlook for patients with HDV infection, with the potential to significantly transform the standard of care for this challenging viral infection.

Hepatitis C virus

Insights into HCV evolution

Despite exceptional research efforts in evolutionary biology that have been undertaken during the past decade, the origin of HCV still remains unknown. Nevertheless, development of novel approaches to nucleic acid sequencing and significant advances in bioinformatic tools used in evolutionary biology have led to the significant increase in knowledge in this field, particularly in the context of non-human hepatitis viruses.[34] Discovery of animal hepaciviruses has significantly re-shaped our understanding of the origin of HCV. Hepaciviruses have been

discovered and characterized in mammals, birds, reptiles, arthropods and fish species with a particularly extensive molecular diversity in bats and rodents.[35,36] Phylogenetic analyses of human and animal viruses belonging to the *Hepacivirus* genus have shown that equine hepacivirus (EqHV) is the closest known relative of HCV identified so far. These findings have led to the hypothesis of EqHV being the possible evolutionary origin of HCV.[35-37]

Although horses represent a natural host for EqHV, the virus is equally adapted to donkeys and can sporadically infect dogs, suggesting a potential for cross-species transmission.[37] Despite the well-established historical ecological link between humans and horses via animal domestication about 5,500 years ago, there is no evidence on the zoonotic transmission of this virus to humans so far.[37] In addition, molecular dating studies performed by using a variety of bioinformatic approaches that are beyond the scope of this summary have provided estimates of the time to the most recent common ancestor (TMRCA) of ~3000 years ago for the extant HCV genotypes (with a low-bound estimate of ~5000 years before present) and of ~800 years ago for equine/canine hepacivirus, excluding the possibility of EqHV as the evolutionary origin of HCV.[37,38] This observation is in concordance with the striking difference between the exceptionally high diversity of HCV and the very low molecular diversity of EqHV suggesting a rather short evolutionary history of EqHV.[39]

One of the logical assumptions in the field was that hepaciviruses described in non-human primates should be evaluated as predecessors of HCV due to the genetic relatedness of the hosts that can facilitate cross-species transmission. However, this hypothesis has been excluded based on data showing that hepaciviruses from non-human primates do not share a recent common ancestor with HCV. These studies suggested a more ancient origin of HCV.

Recent evidence suggests that the ancient origins of all hepatitis viruses in non-human hosts possibly date back to arthropods that evolved about 500 million years ago. The current hypothesis holds that arthropod-borne precursors of hepatitis viruses may have been transmitted to insectivorous mammals and that, possibly subsequent to intensive diversification, these ancient viruses were transmitted into humans directly or indirectly, via an unknown intermediate host.[35]

One of the most important steps in understanding the origin of viruses is the accurate estimation of the timescale for their evolution. Extensive research efforts have been focused on providing reliable estimates for all hepatitis viruses, including HCV, based on projections of MRCA but the results need to be carefully interpreted due to the application of various bioinformatic tools in published studies and sampling bias. By using a selection-informed evolutionary model, Forny et al. showed in 2018 that the common ancestor of extant HCV genotypes existed at least 3000 years ago (CI: 3192-5221 years ago), whereas EqHV origins were estimated around 1100 CE (CI: 291-1640 CE).[38] More recently, in 2021, Ghafari et al. used a new mechanistic bioinformatic model that re-estimated the date of diversification of HCV genotypes to around 423,000 years ago, that is to the time preceding the dispersal of modern humans out of Africa.[40] Overall, we can conclude that the timelines of *Hepacivirus* genus evolution and the molecular mechanisms behind it are still a matter of debate within the field. Future research should focus on identification of viral missing links in hepatitis virus evolution and identification of direct ancestors of human hepatitis viruses.

Elimination of hepatitis C: the remaining issues to be solved

In the post-COVID era, besides tuberculosis, hepatitis B and hepatitis C represent the most common causes of mortality due to infectious diseases, with mortality increasing over the past five years despite a decrease in their incidences.[41] In 2022, 244,000 HCV-related deaths were reported globally due to cirrhosis and hepatocellular carcinoma (HCC) which represents the only cancer with an increasing incidence over the past 10 years.[42]

With the introduction of curative treatment with direct acting antivirals (DAAs) a decade ago, in 2016 the World Health Organization (WHO)

adopted the Global Health Sector Strategy to eliminate viral hepatitis as a public health threat through a 90% decrease in HCV incidence and a 65% decrease in HCV mortality rate by 2030.[43] Since then, an impressive public health response to HCV infection has arisen by improving access to testing and curative treatment, and by optimizing the continuum of HCV care, but unfortunately the latter still represents quite a steep downward cascade.[41] In 2022, with an estimated 50 million people living with HCV worldwide, only 36% of cases had been diagnosed and 20% had received treatment.[41] Indeed, the tools to eliminate HCV are there, but their use still needs to be streamlined, with the biggest challenge represented by inequity among and within countries.[44]

Several high income countries are on track to meet the WHO targets by 2030, whereas progress in many middle- and low-income countries remains challenging.[41] Limited healthcare resources, lack of awareness and restrictions on access to DAAs led to a problematic situation of low treatment coverage.[45] Egypt is the country with globally the highest HCV burden and the only one to reach HCV macroelimination by a strong political awareness, will and strategy including a massive population-level HCV screening, generic DAAs and a test-and-treat approach.[46,47] However, the majority of countries adopted microelimination, a targeted strategy tailored to systematic HCV screening and linkage-to-care within specific regions, settings or key populations with high HCV infection rates, such as people who inject drugs (PWID).[48] The latter represent a priority population for the elimination of HCV in Europe where the overall HCV prevalence ranges from 0.04% to 2.3%, and at least 35.8% of it is attributed to PWID.[44,49]

Importantly, the poorest access to HCV testing and treatment services is often seen among the most vulnerable and underserved populations.[41] Scaling-up effective HCV interventions by introducing higher levels of combined prevention, a better access to point-of-care testing, linkage-to-care and DAA treatment, together with a decentralization of services involving non-specialist healthcare providers as well as the community, is needed.[50,51] The combination of an increase in awareness and advocacy, improved public health strategy and community action, fight against stigma and discrimination, as well as a strong political commitment will pave the road towards HCV elimination on the population level.[52]

On the individual level, modern generation DAA treatment associates an overall rate of >97% sustained virological response (SVR), allowing the virological cure of HCV infection in most patients. Remaining challenges include difficult-to-treat cases, in patients who have not achieved SVR following initial DAA treatment, such as those with decompensated cirrhosis, end-stage renal disease, NS5A-experienced patients and those with infection by rare HCV subtypes or subtypes harboring NS5A resistance associated variants; for these cases, a salvage voxilaprevir-based treatment could be considered.[53-55] Adherence to DAA treatment is paramount, and lack thereof requires special attention and care.[56] Importantly, HCV cure is now attainable for special populations such as children, the elderly and people living with HIV.[57-59] But even after achieving SVR, a residual mortality risk exists in some individuals due to either decompensated cirrhosis, extrahepatic manifestations, or development of HCC, so a lifelong follow-up in certain patient groups is warranted.[53] An increasing proportion of reinfections among PWID and people living with HIV across Europe urges for sustainable re-testing after achieving SVR in those who remain at risk, ensuring re-treatment of individuals with reinfection.[60,61]

To conclude, the remaining issues to be solved on the way to eliminate HCV demand complex activities on the population as well as on the individual level.

Point-of-care approaches for screening and diagnosis of HCV

Adapting testing to the setting provides a major contribution to hepatitis C elimination. Reduction of incident infections by 90% by 2030 poses several challenges. Prevalence data is often accessed through assessments that are limited time- and population-wise. PWID are at risk for HCV and several other health hazards, and better targeting of harm-reduction interventions for

these risks are called for.[62] For reliable incidence data, testing should occur repeatedly at regular intervals at high-risk settings and be readily available upon risk incidents or for contact tracing of each incident case. Injection drug use is the main route of HCV transmission in most of the European region, estimated to contribute to 72.9% (58.3-78.6%) of incident infections.[41] Yet sustainable access to testing can be challenging to establish for this population at risk through conventional health care platforms. Information campaigns and increased overall awareness are needed to reach ever-injectors who might have been infected a long time ago, and do not have ongoing risk behavior. The infection – often being asymptomatic in both the acute and chronic phases before considerable liver damage is present – might easily go undiagnosed. Testing for HCV (as well as HBV and HIV) should therefore be readily available at healthcare settings, hospitals and outpatient clinics, specialized and primary healthcare settings alike. Here traditional testing with venipuncture, with initial assessment of anti-HCV antibodies at the hospital laboratories, followed by reflex testing for HCV RNA, can still be feasible.

However, to increase access to testing for people with ongoing injection drug use, the group at highest risk of incident infections, decentralization of testing services is a prerequisite. With the aid of adequate technical and human resources, matching of the testing modality to the setting is key.[63] Several examples of innovative HCV models of care have been described.[64] For screening in prisons or opiate agonist therapy (OAT) clinics, point-of-care (PoC) testing for HCV-antibody followed by HCV RNA detection on site via dry blood spot (DBS) tests or PoC-RNA could be the most efficient options. DBS testing has been suggested as a helpful and reliable tool to diagnose HCV infection, to assess cure and reinfection after on-site treatment, and to discern between reinfection and treatment failure.[65,66] For testing at settings with a very high expected HCV RNA prevalence (>74%), such as needle syringe programs or shelters, testing directly with PoC-RNA without antibody testing could be an option.[67] At such settings, if run by non-governmental organizations or non-healthcare staff, outreach testing by mobile healthcare staff units experienced in diagnostics and liver assessment can offer not only testing, but also assessment and treatment initiation on site. Such mobile units should visit at regular intervals to enable collection of prevalence and incidence data as well as data on treatment outcomes. As more patients are treated and obtain SVR, the larger the pool of susceptible individuals will become, which further emphasizes the need for regular testing at high-risk settings. Peer involvement will improve access to key populations and the establishment of sustainable alliances. Requirements according to local infrastructure should be taken into consideration, adjusted after the differences in need between urban and rural settings and specific subpopulations.

Harm reduction interventions: almost 4 decades of needle exchange in Skåne Region, Sweden

Skåne Region, the southernmost region in Sweden, has been a forerunner in Sweden in establishing access to healthcare for people who inject drugs, by operating needle exchange programs (NEPs) for almost four decades now, 25 years longer than the rest of the country. All four NEPs in Skåne (Malmö, Lund, Helsingborg and Kristianstad) are part of an infectious disease department. The NEP in Lund was established in 1986 and early evaluations found it to be efficient in HIV prevention.[68] Thereafter the Malmö NEP (MNEP, 1987) has become a base for translational research. Transmission of HIV has remained very low, while HBV prevalence and incidence declined among the participants after the introduction of vaccination in 1994.[69] However, HCV prevalence (>90% in 1990-1993) and incidence (31.5/100 person years at risk in 1997-2005) remained high during these earlier study periods, emphasizing the need for specific action aimed at HCV.[70]

A study introduced in 2011 promoted direct and fast referral of MNEP participants to OAT with high retention rates, setting the base for multidisciplinary collaboration between ID and addiction care.[71] In 2018 the ACTIONNE-study was launched, including 50 MNEP participants

with chronic HCV infection. They received a fixed combination of glecaprevir/pibrentasvir for 8 weeks (non-cirrhotic) or 12 weeks (cirrhotic). The study proved to be successful, with 47/50 (94%) completing treatment and 45 tested for SVR12, all without viremia (SVR rate per intention to treat was 90% and per protocol 96%).[72] The cohort was followed for detection, treatment and contact tracing of reinfections and subsequently all 4 NEPs started treating participants for HCV on site. HCV treatment has also been offered at the OAT clinics in the region, providing a basis for elimination. Regional guidelines for testing for all three bloodborne viruses (HIV, HBV and HCV) are applied at all NEPs and OAT clinics.

In addition to liver related morbidity, PWID are at risk of opioid overdose related mortality. Thus, the regional Take Home Naloxone project was launched in 2018, gathering all four NEPs, >25 OAT clinics and several other addiction care facilities (50 units in total). The participants receive education on handling acute overdose situations and tailored kits with naloxone for nasal administration. To date, more than 2700 participants have been included and the kits have been used in more than 900 overdose incidents. Deaths associated with overdose decreased from 3.9 to 2.8 per 100,000 inhabitants/year during the intervention period (a marked decrease observed among men, from 6.7 to 4.3, but not among women, from 1.2 to 1.3).[73]

Such multidisciplinary collaboration is now essential in implementing the national hepatitis elimination plan on a regional level.

Conclusions

The past decade has witnessed remarkable advances in our understanding and management of HBV, HDV and HCV. Novel biomarkers such as quantitative HBsAg, HBV RNA, and HBcrAg promise to refine HBV monitoring and guide individualized treatment strategies. The approval of bulevirtide has transformed the therapeutic landscape of HDV, a long-neglected infection, while additional agents targeting distinct viral and host pathways are under active development. For HCV, the advent of highly effective direct-acting antivirals has made elimination a realistic goal; identifying and addressing gaps in diagnosis, linkage-to-care, and treatment access offers opportunities to accelerate progress and overcome barriers, particularly in resource-limited settings and among vulnerable populations such as people who inject drugs.

Sustained progress will require coordinated global action, combining scientific innovation with strong political commitment and health system strengthening. Integration of point-of-care testing, harm reduction strategies, and decentralized care models can help close equity gaps and ensure that advances translate into real-world impact.

By bringing together updated evidence and expert insights, this review underscores both the achievements and the unfinished agenda in the field of viral hepatitis. Continued collaboration among clinicians, researchers, public health authorities, and patient communities will be key to turning the vision of hepatitis elimination into reality.

Author contributions: Conceptualization: OS and GOŞ; writing – original draft: OS, MM, FG, MAB, MUM, WI, SZ-L, AW, GOŞ; writing - review & editing: OS, MM, FG, MAB, MUM, WI, SZ-L, AW, GOŞ. Supervision: OS and GOŞ. All authors read and approved the final version of the manuscript.

Conflicts of interest: All authors – none to declare.

Funding: None to declare.

Ethics approval: Not applicable for review papers.

Data availability: This article is a narrative review and does not involve the generation or analysis of new datasets. All data discussed are drawn from previously published studies, which are cited within the manuscript.

References

1. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370-98. https://doi.org/10.1016/j.jhep.2017.03.021
2. 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;67:1560-99. https://doi.org/10.1002/hep.29800
3. Charre C, Levrero M, Zoulim F, Scholtes C. Non-invasive biomarkers for chronic hepatitis B virus infection management. Antiviral Res. 2019;169:104553.

https://doi.org/10.1016/j.antiviral.2019.104553
4. Brunetto MR, Oliveri F, Colombatto P, et al. Hepatitis B surface antigen serum levels help to distinguish active from inactive hepatitis B virus genotype D carriers. Gastroenterology. 2010;139:483-90. https://doi.org/10.1053/j.gastro.2010.04.052
5. Cornberg M, Wong VW, Locarnini S, Brunetto M, Janssen HLA, Chan HL. The role of quantitative hepatitis B surface antigen revisited. J Hepatol. 2017;66:398-411. https://doi.org/10.1016/j.jhep.2016.08.009
6. Tseng TC, Liu CJ, Yang HC, et al. High levels of hepatitis B surface antigen increase risk of hepatocellular carcinoma in patients with low HBV load. Gastroenterology. 2012;142:1140-9 e3; quiz e13-4. https://doi.org/10.1053/j.gastro.2012.02.007
7. Jeng WJ, Chen YC, Chien RN, Sheen IS, Liaw YF. Incidence and predictors of hepatitis B surface antigen seroclearance after cessation of nucleos(t)ide analogue therapy in hepatitis B e antigen-negative chronic hepatitis B. Hepatology. 2018;68:425-34. https://doi.org/10.1002/hep.29640
8. Yuen MF, Lim SG, Plesniak R, et al. Efficacy and safety of bepirovirsen in chronic hepatitis B infection. N Engl J Med. 2022;387:1957-68. https://doi.org/10.1056/NEJMoa2210027
9. Besombes C, Njouom R, Paireau J, et al. The epidemiology of hepatitis delta virus infection in Cameroon. Gut. 2020;69:1294-300. https://doi.org/10.1136/gutjnl-2019-320027
10. Sellier PO, Maylin S, Brichler S, et al. Hepatitis B virus-hepatitis D virus mother-to-child co-transmission: A retrospective study in a developed country. Liver Int. 2018;38:611-8. https://doi.org/10.1111/liv.13556
11. Pinho-Nascimento CA, Bratschi MW, Hofer R, et al. Transmission of hepatitis B and D viruses in an African rural community. mSystems. 2018;3. https://doi.org/10.1128/msystems.00120-18
12. Chen HY, Shen DT, Ji DZ, et al. Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis. Gut. 2019;68:512-21. https://doi.org/10.1136/gutjnl-2018-316601
13. Miao Z, Zhang S, Ou X, et al. Estimating the global prevalence, disease progression, and clinical outcome of hepatitis delta Virus infection. J Infect Dis. 2020;221:1677-87. https://doi.org/10.1093/infdis/jiz633
14. Stockdale AJ, Kreuels B, Henrion MYR, et al. The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. J Hepatol. 2020;73:523-32. https://doi.org/10.1016/j.jhep.2020.04.008
15. Rizzetto M, Hamid S, Negro F. The changing context of hepatitis D. J Hepatol. 2021;74:1200-11. https://doi.org/10.1016/j.jhep.2021.01.014
16. Tharwani A, Hamid S. Elimination of HDV: Epidemiologic implications and public health perspectives. Liver Int. 2023;43 Suppl 1:101-7. https://doi.org/10.1111/liv.15579
17. Wong RJ, Brosgart C, Wong SS, et al. Estimating the prevalence of hepatitis delta virus infection among adults in the United States: A meta-analysis. Liver Int. 2024;44:1715-34. https://doi.org/10.1111/liv.15921
18. Wong RJ, Hirode G, Feld J, et al. An updated assessment of hepatitis delta prevalence among adults in Canada: A meta-analysis. J Viral Hepat. 2024;31:324-41. https://doi.org/10.1111/jvh.13939
19. Polaris Observatory Collaborators. Adjusted estimate of the prevalence of hepatitis delta virus in 25 countries and territories. J Hepatol. 2024;80:232-42. https://doi.org/10.1016/j.jhep.2023.10.043
20. Demirel A, Uraz S, Deniz Z, et al. Epidemiology of hepatitis D virus infection in Europe: Is it vanishing? J Viral Hepat. 2024;31:120-8. https://doi.org/10.1111/jvh.13899
21. Roggenbach I, Chi X, Lempp FA, et al. HDV seroprevalence in HBsAg-positive patients in China occurs in hotspots and is not associated with HCV mono-infection. Viruses. 2021;13. https://doi.org/10.3390/v13091799
22. Perez-Vargas J, Amirache F, Boson B, et al. Enveloped viruses distinct from HBV induce dissemination of hepatitis D virus in vivo. Nat Commun. 2019;10:2098. https://doi.org/10.1038/s41467-019-10117-z
23. Chemin I, Pujol FH, Scholtes C, et al. Preliminary evidence for hepatitis delta virus exposure in patients who are apparently not infected with hepatitis B virus. Hepatology. 2021;73:861-4. https://doi.org/10.1002/hep.31453
24. Cappy P, Lucas Q, Kankarafou N, Sureau C, Laperche S. No evidence of hepatitis C virus (HCV)-assisted hepatitis D virus propagation in a large cohort of HCV-positive blood donors. J Infect Dis. 2021;223:1376-80. https://doi.org/10.1093/infdis/jiaa517
25. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on hepatitis delta virus. J Hepatol. 2023;79:433-60. https://doi.org/10.1016/j.jhep.2023.05.001
26. Gilman C, Heller T, Koh C. Chronic hepatitis delta: A state-of-the-art review and new therapies. World J Gastroenterol. 2019;25:4580-97. https://doi.org/10.3748/wjg.v25.i32.4580
27. Kang C, Syed YY. Bulevirtide: First Approval. Drugs. 2020;80:1601-5. https://doi.org/10.1007/s40265-020-01400-1
28. Wedemeyer H, Aleman S, Brunetto M, et al. Bulevirtide monotherapy in patients with chronic HDV: Efficacy and safety results through week 96 from a phase III randomized trial. J Hepatol. 2024;81:621-9. https://doi.org/10.1016/j.jhep.2024.05.001
29. Degasperi E, Anolli MP, Uceda Renteria SC, et al. Bulevirtide monotherapy for 48 weeks in patients with HDV-related compensated cirrhosis and clinically significant portal hypertension. J Hepatol. 2022;77:1525-31. https://doi.org/10.1016/j.jhep.2022.07.016

30. Dietz-Fricke C, Degasperi E, Jachs M, et al. Safety and efficacy of off-label bulevirtide monotherapy in patients with HDV with decompensated Child-B cirrhosis-A real-world case series. Hepatology. 2024;80:664-73. https://doi.org/10.1097/HEP.0000000000000847
31. Wranke A, Hardtke S, Heidrich B, et al. Ten-year follow-up of a randomized controlled clinical trial in chronic hepatitis delta. J Viral Hepat. 2020;27:1359-68. https://doi.org/10.1111/jvh.13366
32. Wedemeyer H, Yurdaydin C, Hardtke S, et al. Peginterferon alfa-2a plus tenofovir disoproxil fumarate for hepatitis D (HIDIT-II): a randomised, placebo controlled, phase 2 trial. Lancet Infect Dis. 2019;19:275-86. https://doi.org/10.1016/S1473-3099(18)30663-7
33. Etzion O, Hamid SS, Asselah T, Gherlan GS, Turcanu A, Petrivna, T et al. Week 48 results of the phase 3 D-LIVR study, a randomized double-blind, placebo-controlled trial evaluating the safety and efficacy of lonafarnib-boosted with ritonavir with or without peginterferon alfa in patients with chronic hepatitis delta. J Hepatol. 2023; 78(S1):S10. https://doi.org/10.1016/S0168-8278(23)00451-8
34. Cagliani R, Forni D, Sironi M. Mode and tempo of human hepatitis virus evolution. Comput Struct Biotechnol J. 2019;17:1384-95. https://doi.org/10.1016/j.csbj.2019.09.007
35. Rasche A, Sander AL, Corman VM, Drexler JF. Evolutionary biology of human hepatitis viruses. J Hepatol. 2019;70:501-20. https://doi.org/10.1016/j.jhep.2018.11.010
36. Moreira-Soto A, Arroyo-Murillo F, Sander AL, et al. Cross-order host switches of hepatitis C-related viruses illustrated by a novel hepacivirus from sloths. Virus Evol. 2020;6:veaa033. https://doi.org/10.1093/ve/veaa033
37. Pacchiarotti G, Nardini R, Scicluna MT. Equine hepacivirus: A systematic review and a meta-analysis of serological and biomolecular prevalence and a phylogenetic update. Animals (Basel). 2022;12:2486. https://doi.org/10.3390/ani12192486
38. Forni D, Cagliani R, Pontremoli C, et al. Evolutionary analysis provides insight into the origin and adaptation of HCV. Front Microbiol. 2018;9:854. https://doi.org/10.3389/fmicb.2018.00854
39. Walter S, Rasche A, Moreira-Soto A, et al. Differential infection patterns and recent evolutionary origins of equine hepaciviruses in donkeys. J Virol. 2017;91. https://doi.org/10.1128/JVI.01711-16
40. Ghafari M, Simmonds P, Pybus OG, Katzourakis A. A mechanistic evolutionary model explains the time-dependent pattern of substitution rates in viruses. Curr Biol. 2021;31:4689-96 e5. https://doi.org/10.1016/j.cub.2021.08.020
41. World Health Organization (WHO). Global hepatitis report 2024: action for access in low- and middle-income countries. Geneva: WHO; 2024.
42. Vargas-Accarino E, Higuera M, Buti M, Minguez B. Hepatitis-C-related hepatocellular carcinoma, still a relevant etiology beyond a hepatitis C infection cure. Cancers (Basel). 2024;16:1521. https://doi.org/10.3390/cancers16081521
43. World Health Organization (WHO). Global health sector strategies on viral hepatitis, 2016-2021. Towards ending viral hepatitis. Geneva: WHO; 2016.
44. European Centre for Disease Prevention and Control (ECDC). Monitoring of the responses to the hepatitis B and C epidemics in EU/EEA countries, 2023. Stockholm: ECDC; 2024.
45. Marshall AD, Willing AR, Kairouz A, et al. Direct-acting antiviral therapies for hepatitis C infection: global registration, reimbursement, and restrictions. Lancet Gastroenterol Hepatol. 2024;9:366-82. https://doi.org/10.1016/S2468-1253(23)00335-7
46. Hassanin A, Kamel S, Waked I, Fort M. Egypt's ambitious strategy to eliminate hepatitis C virus: A case study. Glob Health Sci Pract. 2021;9:187-200. https://doi.org/10.9745/GHSP-D-20-00234
47. Sandulescu O, Dudman SG, Gmizic I, et al. Global hepatitis C elimination: Updates, challenges, and opportunities from real-world experiences in Europe and North America. Hepatology. 2025. https://doi.org/10.1097/HEP.0000000000001548
48. Lazarus JV, Wiktor S, Colombo M, Thursz M, EASL International Liver Foundation. Micro-elimination - A path to global elimination of hepatitis C. J Hepatol. 2017;67:665-6. https://doi.org/10.1016/j.jhep.2017.06.033
49. Thomadakis C, Gountas I, Duffell E, et al. Prevalence of chronic HCV infection in EU/EEA countries in 2019 using multiparameter evidence synthesis. Lancet Reg Health Eur. 2024;36:100792. https://doi.org/10.1016/j.lanepe.2023.100792
50. Martinello M, Solomon SS, Terrault NA, Dore GJ. Hepatitis C. Lancet. 2023;402:1085-96. https://doi.org/10.1016/S0140-6736(23)01320-X
51. Maticic M, Pirnat Z, Leicht A, et al. The civil society monitoring of hepatitis C response related to the WHO 2030 elimination goals in 35 European countries. Harm Reduct J. 2020;17:89. https://doi.org/10.1186/s12954-020-00439-3
52. Buti M, Craxi A, Foster GR, et al. Viral hepatitis elimination: Towards a hepatitis-free world. J Hepatol. 2022;77:1444-7. https://doi.org/10.1016/j.jhep.2022.06.034
53. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: Final update of the series. J Hepatol. 2020;73:1170-218. https://doi.org/10.1016/j.jhep.2020.08.018
54. Manns MP, Maasoumy B. Breakthroughs in hepatitis C research: from discovery to cure. Nat Rev Gastroenterol Hepatol. 2022;19:533-50. https://doi.org/10.1038/s41575-022-00608-8
55. Devan P, Tiong KLA, Neo JE, et al. Treatment outcomes of sofosbuvir/velpatasvir/voxilaprevir in direct-acting antiviral-experienced hepatitis C virus patients: A systematic review and meta-analysis. Viruses. 2023;15. https://doi.org/10.3390/v15071489

56. Drysdale K, Ntuli Y, Bestwick J, et al. English hepatitis C registry data show high response rates to directly acting anti-virals, even if treatment is not completed. Aliment Pharmacol Ther. 2020;52:168-81. https://doi.org/10.1111/apt.15780
57. Jarasvaraparn C, Hartley C, Karnsakul W. Updated clinical guidelines on the management of hepatitis C infection in children. Pathogens. 2024;13:180. https://doi.org/10.3390/pathogens13020180
58. Pugliese N, Calvaruso V, Masarone M, et al. Glecaprevir/pibrentasvir is safe and effective in Italian patients with chronic hepatitis C aged 75 years or older: A multicentre study. Liver Int. 2023;43:1440-5. https://doi.org/10.1111/liv.15599
59. Ambrosioni J, Levi L, Alagaratnam J, et al. Major revision version 12.0 of the European AIDS Clinical Society guidelines 2023. HIV Med. 2023;24:1126-36. https://doi.org/10.1111/hiv.13542
60. Yeung A, Palmateer NE, Dillon JF, et al. Population-level estimates of hepatitis C reinfection post scale-up of direct-acting antivirals among people who inject drugs. J Hepatol. 2022;76:549-57. https://doi.org/10.1016/j.jhep.2021.09.038
61. Hosseini-Hooshyar S, Hajarizadeh B, Bajis S, et al. Risk of hepatitis C reinfection following successful therapy among people living with HIV: a global systematic review, meta-analysis, and meta-regression. Lancet HIV. 2022;9:e414-e27. https://doi.org/10.1016/S2352-3018(22)00077-7
62. Degenhardt L, Webb P, Colledge-Frisby S, et al. Epidemiology of injecting drug use, prevalence of injecting-related harm, and exposure to behavioural and environmental risks among people who inject drugs: a systematic review. Lancet Glob Health. 2023;11:e659-e72. https://doi.org/10.1016/S2214-109X(23)00057-8
63. Ivanova Reipold E, Shilton S, Donolato M, Fernandez Suarez M. Molecular point-of-care testing for hepatitis C: Available technologies, pipeline, and promising future directions. J Infect Dis. 2024;229:S342-S9. https://doi.org/10.1093/infdis/jiad463
64. Biondi MJ, Feld JJ. Hepatitis C models of care: approaches to elimination. Can Liver J. 2020;3:165-76. https://doi.org/10.3138/canlivj.2019-0002
65. Not A, Saludes V, Galvez M, et al. Usefulness of dried blood spot samples for monitoring hepatitis C treatment outcome and reinfection among people who inject drugs in a test-and-treat program. J Med Virol. 2023;95:e28544. https://doi.org/10.1002/jmv.28544
66. Conway A, Valerio H, Alavi M, et al. A Testing campaign intervention consisting of peer-facilitated engagement, point-of-care HCV RNA testing, and linkage to nursing support to enhance hepatitis C treatment uptake among people who inject drugs: The ETHOS Engage Study. Viruses. 2022;14. https://doi.org/10.3390/v14071555
67. Feld J. Innovations in HCV testing and practical implications for enhancing care. INHSU 2023, Geneva, Switzerland.
68. Ljungberg B, Christensson B, Tunving K, et al. HIV prevention among injecting drug users: three years of experience from a syringe exchange program in Sweden. J Acquir Immune Defic Syndr (1988). 1991;4:890-5. https://doi.org/10.1097/00126334-199109000-00010
69. Mansson AS, Moestrup T, Nordenfelt E, Widell A. Continued transmission of hepatitis B and C viruses, but no transmission of human immunodeficiency virus among intravenous drug users participating in a syringe/needle exchange program. Scand J Infect Dis 2000;32:253-8. https://doi.org/10.1080/00365540050165875
70. Alanko Blome M, Bjorkman P, Flamholc L, Jacobsson H, Widell A. Vaccination against hepatitis B virus among people who inject drugs - A 20year experience from a Swedish needle exchange program. Vaccine 2017;35:84-90. https://doi.org/10.1016/j.vaccine.2016.11.041
71. Braback M, Ekstrom L, Troberg K, et al. Malmo treatment referral and intervention study-high 12-month retention rates in patients referred from syringe exchange to methadone or buprenorphine/naloxone treatment. Front Psychiatry. 2017;8:161. https://doi.org/10.3389/fpsyt.2017.00161
72. Blome MA, Braback M, Alsterberg S, Jerkeman A. Hepatitis C treatment at a Swedish needle exchange program, a successful model of care - the ACTIONNE study. Int J Drug Policy. 2021;96:103407. https://doi.org/10.1016/j.drugpo.2021.103407
73. Hakansson A, Alanko Blome M, Isendahl P, Landgren M, Malmqvist U, Troberg K. Distribution of intranasal naloxone to potential opioid overdose bystanders in Sweden: effects on overdose mortality in a full region-wide study. BMJ Open. 2024;14:e074152. https://doi.org/10.1136/bmjopen-2023-074152

Please cite this article as:
Săndulescu O, Matičič M, Garcia F, Alanko Blomé M, Mondelli MU, Irving W, Zidovec-Lepej S, Widell A, Şahin GÖ. Evolving insights into viral hepatitis: Advances, evidence, and expert perspectives from the ESCMID Study Group for Viral Hepatitis (ESGVH) – Part 2: hepatitis B, C, and delta. GERMS. 2025;15(3):263-273. doi: 10.18683/germs.2025.1473