Chronic Viral Hepatitis at ESCMID 2026: From Molecular Biomarkers to Clinical Practice

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CHRONIC viral hepatitis remains a major global health burden, with ongoing challenges in both diagnosis and management despite significant therapeutic advances. In recent years, increasing attention has been directed towards translating mechanistic insights into clinically meaningful strategies, particularly in the context of hepatocarcinogenesis, viral reactivation, and emerging antiviral therapies. The session 'Turning Mechanisms into Clinical Strategies in Chronic Viral Hepatitis', presented at the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) 2026 Global Congress, brought together a series of studies addressing these key aspects, with a strong emphasis on biomarker discovery, risk stratification, and real-world clinical practice.

NOVEL LONG NON-CODING RNA BIOMARKERS IN HBV-RELATED POST-TRANSPLANT HCC RECURRENCE

One of the most concerning complications of chronic hepatitis B virus (HBV) infection is hepatocellular carcinoma (HCC), with HBV itself representing a major driver of hepatocarcinogenesis. In the first presentation, delivered by Secil Aksoy,[1] Near East University, Nicosia, Türkiye, the authors focused on HCC recurrence following liver transplantation. Building on a previous cohort of 132 HBV-related HCC cases, 20 patients with post-transplant HCC recurrence were selected for further analysis.[1]

The study aimed to identify novel prognostic biomarkers, specifically long non-coding RNAs (lncRNA), which regulate epigenetic and transcriptional processes associated with tumour progression. An *in vitro* HepG2 model with sodium taurocholate co-transporting polypeptide (NTCP) overexpression was used to investigate HBV infection, evaluating viral markers, tumour-related behaviour, and the expression of selected lncRNAs and microRNA-21. HBV infection in NTCP-expressing cells was associated with increased proliferative and migratory capacity, along with upregulation of oncogenic lncRNAs (*MALAT1*, *HULC*, and *PVT1*) and microRNA-21, while *SNHG16* expression remained unchanged.[1] This model therefore represents a promising translational platform for the functional validation of prognostic biomarkers and

the development of antiviral or epigenetic-targeted therapies. Notably, these findings highlight the growing relevance of non-coding RNA signatures as clinically meaningful tools that may help refine post-transplant risk stratification and guide more personalised surveillance strategies.

In the subsequent presentation, delivered by Ekta Gupta,[2] Institute of Liver and Biliary Sciences (ILBS), New Delhi, India, the authors focused on distinct HBV mutational patterns in HCC.[2] Similar to the previous study, the aim was to identify novel biomarkers by comparing mutational differences between patients with HCC and those with chronic hepatitis B (CHB) without malignancy. Mutations across different regions of the viral genome were evaluated as potential biomarkers of hepatocarcinogenesis. The study cohort included 10 patients with HCC (median age: 61 years; eight male) and seven patients with CHB (median age: 39.5 years; three male), with mutation frequencies assessed across 12 HBV genomic regions. Patients with HCC demonstrated significantly higher mutation frequencies in the reverse transcriptase and surface antigen regions compared with those with CHB, while the spacer region showed the highest overall mutation burden in both groups, albeit without statistical significance. Mutation hotspots in HCC predominantly involved the spacer, reverse transcriptase, surface antigen, and X protein regions, whereas in CHB they were more frequently observed in the spacer, RNase H, X protein, and reverse transcriptase regions. Notably, pre-core mutations were detected exclusively in patients with HCC, and immune escape mutations at position 120 were present in 60% of cases.[2]

Clinically, patients with HCC exhibited markedly higher liver stiffness and fibrosis scores, along with a higher prevalence of prior antiviral treatment. Overall, these findings indicate that distinct HBV mutational profiles, particularly involving the reverse transcriptase and surface antigen regions, may contribute to hepatocarcinogenesis through mechanisms related to viral replication and immune evasion. Importantly, integrating viral mutation patterns with clinical parameters may improve risk stratification and surveillance strategies in patients with chronic HBV infection.

HBV MUTATIONAL PROFILING AS A TOOL FOR HEPATOCARCINOGENESIS RISK STRATIFICATION

In the third presentation, Italian authors addressed an important and increasingly discussed topic: the prophylaxis of HBV reactivation (HBVr) in patients receiving immunosuppressive therapy. HBVr is a serious complication, defined by a sudden increase or reappearance of viral replication (HBV DNA >100 IU/mL) or re-detection of hepatitis B surface antigen (HBsAg) in individuals with previously undetectable levels, or at least a 10-fold rise in HBV DNA compared with baseline.[3] HBVr may lead to significant liver injury and, in severe cases, acute liver failure. Recent European Association for the Study of the Liver (EASL) guidelines stratify the risk of HBVr into high (>10%), intermediate (1–10%), and low (<1%) categories, based on the type of immunosuppressive therapy and the patient's HBsAg/hepatitis B core antibody (anti-HBc) status. Historically, lamivudine was widely used for prophylaxis; however, it is no longer recommended due to its low barrier to resistance compared with tenofovir or entecavir, which are currently preferred.[3]

In a single-centre study, Giuseppe De Simone,[4] Tor Vergata University of Rome, Italy, presented a cohort of 644 patients, including 515 with resolved HBV infection (HBsAg-negative/anti-HBc-positive) and 139 with indeterminate serological status (HBsAg-negative/anti-HBc-negative/antibody to hepatitis B surface antigen-positive, vaccine-naïve).[4] Notably, more than half of the cohort (55%) was classified as high risk for HBVr. A total of 97.7% of patients received prophylaxis against HBVr, predominantly lamivudine (91.4%). Prophylaxis was discontinued in a subset of patients after a median duration of 29 months, with subsequent reactivation events primarily occurring after withdrawal.

Overall, 50 viral episodes were identified, most commonly following discontinuation of prophylaxis, and predominantly in patients classified as high risk. HBV-breakthrough (defined as any detectable viraemia or HBsAg positivity during prophylaxis) was observed in 14 patients, occurring after a median of 11 months from the initiation of prophylaxis. HBV-reactivation after prophylaxis was observed in 31 patients, after a median of 7 months after discontinuation of therapy. HBVr without prophylaxis was observed in five cases. There were only two cases of hepatitis and no fatal events.[4]

Taken together, these findings suggest that while lamivudine prophylaxis was associated with a low rate of on-treatment breakthrough, the risk of HBVr remains significant after treatment discontinuation, underscoring the importance of prolonged post-prophylaxis monitoring. Notably, although current guidelines favour high-barrier agents such as tenofovir or entecavir, these real-world data indicate that lamivudine may still represent a pragmatic option in selected settings when combined with careful patient selection and structured follow-up. This presentation also prompted a broad discussion among the audience, with questions focusing on the optimal duration of prophylaxis, the frequency of monitoring, and the role of lamivudine. This highlights the need for future research to define the optimal duration of prophylaxis and post-treatment monitoring, as well as to identify novel biomarkers that could improve patient risk stratification and enable more individualised approaches to HBVr prophylaxis.

HCV REACTIVATION IN PATIENTS RECEIVING BTK INHIBITORS: A LOW BUT CLINICALLY RELEVANT RISK

In another presentation, authors from the University of Texas MD Anderson Cancer Center, Houston, USA, addressed an interesting and relatively underexplored topic: the potential for hepatitis C virus (HCV) reactivation in patients receiving Bruton's tyrosine kinase inhibitors (BTKI), which are commonly used in the treatment of B cell lymphomas. While BTKIs are associated with an intermediate risk of HBVr, data regarding HCV reactivation (HCVr) remain limited and less clearly defined. Although HCVr is rarely fatal, it is still essential to screen all patients for anti-HCV antibodies prior to initiating immunosuppressive therapy, followed by HCV RNA testing in those with positive serology. The advent of highly effective direct-acting antivirals has made it possible to cure nearly all patients with chronic hepatitis C; however, drug–drug interactions remain a key challenge, particularly in the context of concomitant administration with BTKIs.[5]

In the presented retrospective study, patients with cancer who were infected with HCV and receiving BTKIs were screened for anti-HCV antibodies. Among a large screened population (140,020 patients), only a small subset of patients (36; 0.02%) with anti-HCV positivity undergoing BTKI therapy was identified.[5] Most patients (29/36; 80.5%) had previously treated HCV, and, among those with active viraemia (6/36; 16.7%), the majority remained clinically stable during treatment, without hepatitis flare. HCV viral load tended to decrease during BTKI therapy, although complete viral suppression was not achieved. Median HCV RNA decreased from 6.11 $\log_{10}$ IU/mL before BTKI to 3.2 $\log_{10}$ IU/mL after BTKI. Notably, HCVr (increase in HCV RNA level >1 $\log_{10}$ IU/mL over baseline after starting cancer treatment) was rare, occurring in only one patient. This patient had lymphoma pre-treated with rituximab and ibrutinib followed by acalabrutinib for 2 months at the time of HCVr. During cancer treatment, alanine aminotransferase (ALT) levels remained persistently elevated and viral load tended to increase. Patient was successfully managed with direct-acting antiviral therapy without the need to interrupt BTKI treatment.[5]

In this first study evaluating the risk of HCVr in patients treated with BTKIs, findings suggest that BTKI therapy appears to be associated with a low risk of HCVr, although the limited sample size warrants

cautious interpretation. Nevertheless, they underscore the importance of systematic HCV screening and highlight that, when needed, direct-acting antiviral therapy can be safely and effectively co-administered without interrupting oncological treatment.

BULEVIRTIDE FOR CHRONIC HEPATITIS D: 12-MONTH REAL-WORLD EXPERIENCE FROM ROMANIA

In the final presentation of the session,[6] George Sebastian Gherlan, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, presented 12-month real-world experience with bulevirtide treatment for chronic hepatitis D, which has been available in Romania since July 2024. The study included 58 adult patients who received bulevirtide at a dose of 2 mg administered subcutaneously. At baseline, patients had a mean age of 51.5 years and showed elevated liver enzymes (aspartate aminotransferase median: 67.5 IU/L; ALT median: 106.5 IU/L), moderate fibrosis (median: 10.6 kPa), and high viral load (median: 6.4 $\log_{10}$ IU/mL).[6] While ALT levels did not decrease significantly after 1 month of treatment, a progressive and statistically significant reduction was observed from Month 2 onwards, with sustained improvement up to 12 months. In parallel, platelet counts and prothrombin index improved significantly over time, indicating better liver function. Viral load decreased at 6 and 12 months, with over half of patients achieving a ≥2 log reduction by 12 months. Liver stiffness also declined significantly, reflecting an improvement in fibrosis parameters. These findings are consistent with data from clinical trials, and the discussion also addressed concerns regarding potentially reduced treatment adherence related to the subcutaneous mode of bulevirtide administration.[6]

Taken together, the presented studies highlight the evolving landscape of chronic viral hepatitis management, where integration of molecular biomarkers, viral genetic profiling, and clinical parameters is becoming increasingly important. From improved risk stratification in HBV-related hepatocarcinogenesis, through optimisation of antiviral prophylaxis strategies, to emerging data on HBV and HCVr and novel therapies for hepatitis D, these findings underscore the shift towards more personalised and evidence-based care. Further research is warranted to refine these approaches and translate them into routine clinical practice.

References

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