Editorial

HBV in the era of metabolic liver disease

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When viral quiescence meets metabolic injury: Rethinking risk and treatment at the intersection of MASLD and chronic hepatitis B

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The past three decades have transformed the landscape of chronic liver disease. Universal hepatitis B virus (HBV) vaccination programs and the widespread use of potent nucleos(t)ide analogues have dramatically reduced the incidence of HBV-related cirrhosis and hepatocellular carcinoma (HCC). In parallel, the advent of curative direct-acting antivirals for hepatitis C virus (HCV) has reshaped expectations for viral hepatitis elimination. Yet, despite these achievements, liver-related morbidity and mortality remain unacceptably high worldwide, accounting for nearly two million deaths annually. This gap between virological success and clinical outcomes has led to a rethinking of the factors driving liver disease progression today.

Increasingly, the answer lies not in viral hepatitis alone, but in its convergence with metabolic dysfunction-associated steatotic liver disease (MASLD). Rather than replacing viral hepatitis, MASLD is overlapping with it, creating a dual-etiology state in which metabolic and viral insults interact within the same liver. This emerging reality challenges long-standing disease constructs and exposes important gaps in current clinical algorithms. In the era of MASLD, virological inactivity can no longer be equated with clinical safety.

In this context, the two studies published in the January 2026 issue of Hepatology Forum—the narrative review by Ejaz and colleagues[1] and the original cohort study by Bodakci and colleagues[2]—provide complementary and timely insights into this evolving paradigm. Together, they highlight not only the scale of the MASLD–viral hepatitis overlap, but also the clinical ambiguities that arise when traditional virological definitions are applied to metabolically injured livers.

The Expanding Overlap of MASLD and Viral Hepatitis

Ejaz et al. comprehensively describe the growing epidemiological convergence between MASLD and chronic viral hepatitis. MASLD now affects approximately 30% of the global adult population, with substantially higher prevalence among individuals with diabetes mellitus, hypertension, and obesity.[3] However, like viral hepatitis, MASLD exhibits marked geographic heterogeneity, with substantial variation across and within regions, as highlighted by Ejaz et al.[1] At the same time, hundreds of millions of people still live with chronic HBV or HCV. These epidemics increasingly overlap, especially in regions long affected by viral hepatitis, such as East and South Asia and sub-Saharan Africa.

Several forces underpin this convergence. First, antiviral therapies have converted HBV and HCV into chronic, manageable conditions, allowing affected populations to age and accumulate metabolic comorbidities. Second, rapid urbanization and westernization of dietary patterns have accelerated the rise of obesity and insulin resistance in HBV-endemic regions. As a result, an increasing proportion of patients now present with dual pathology, in which viral persistence coexists with metabolic lipotoxicity.

Importantly, this overlap is not benign. Epidemiological studies consistently demonstrate that MASLD amplifies the risk of fibrosis progression, cirrhosis, and HCC in patients with viral hepatitis, even when viral replication is low or suppressed.[4] These observations suggest that metabolic injury may lower the threshold at which viral signals translate into clinically meaningful liver damage.

Steatosis in Chronic HBV: Friend, Foe, or Both?

While Ejaz et al.[1] frame the problem at a population level, Bodakci et al.[2] illuminate its clinical complexity. In their long-term, biopsy-based cohort of patients with chronic HBV infection, hepatic steatosis was independently associated with higher rates of hepatitis B surface antigen (HBsAg) seroclearance, an outcome often regarded as a functional cure of HBV. Paradoxically, the same patients exhibited greater fibrosis progression and higher liver stiffness over time.

This apparent contradiction encapsulates the central dilemma of MASLD–HBV coexistence. On the one hand, metabolic inflammation may enhance certain immune pathways that facilitate viral antigen clearance. On the other hand, lipotoxicity, oxidative stress, and chronic low-grade inflammation promote fibrogenesis and structural liver injury. This discordance between virological control and histological progression indicates that a favorable viral response does not always translate into long-term clinical improvement.

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Crucially, Bodakci et al.[2] demonstrate that this paradox is not theoretical. Even in patients who achieve HBsAg loss, advanced fibrosis may continue to evolve, underscoring that functional cure does not equate to biological quiescence when metabolic injury persists.

Mechanistic Convergence: Beyond Additive Risk

From a biological standpoint, the coexistence of MASLD and chronic viral hepatitis likely creates a permissive milieu for synergistic liver injury.[5,6] Chronic viral infection establishes a background of immune dysregulation and low-grade inflammatory signaling, while metabolic dysfunction introduces lipotoxicity, oxidative stress, and mitochondrial injury.[7] When these processes converge, hepatocytes and non-parenchymal cells may be exposed to parallel profibrotic and pro-oncogenic stimuli. Importantly, metabolic inflammation may lower the threshold at which residual viral signals become biologically relevant, even in the setting of virological quiescence.[8] This integrated framework provides a plausible mechanistic explanation for clinical observations in which favorable virological endpoints coexist with ongoing fibrosis progression and persistent hepatocellular carcinoma risk in patients with concomitant MASLD.[9]

Diagnostic Challenges

Beyond management, the coexistence of MASLD and chronic viral hepatitis introduces important diagnostic challenges. Non-invasive fibrosis assessments, including liver stiffness measurements, may reflect the cumulative impact of metabolic inflammation and viral injury, making it difficult to attribute fibrosis progression to a single etiology. Normal aminotransferase levels may provide false reassurance in this setting, as significant fibrotic remodeling can occur in the absence of biochemical activity.[10] Similarly, commonly used non-invasive scores were largely derived from single-etiology populations and may have reduced specificity in dual-etiology disease. Consequently, discordance between virological markers, biochemical indices, and fibrosis assessments is common, and liver biopsy may still play a role in selected cases to clarify disease drivers and inform risk stratification.

The Clinical Blind Spot: Inactive HBV in a Metabolically Injured Liver

Perhaps the most pressing implication of this dual-etiology framework emerges in daily clinical practice. Consider the increasingly common patient with chronic HBV infection who meets virological criteria for an inactive carrier state—low HBV DNA levels and normal aminotransferases—yet demonstrates advanced fibrosis in the setting of concomitant MASLD. Non-invasive stiffness measurements or liver biopsy may reveal significant fibrotic remodeling, while existing HBV treatment algorithms provide little practical guidance.

Current international guidelines anchor treatment decisions primarily in viral replication thresholds and biochemical activity, whereas MASLD guidelines often exclude patients with chronic viral hepatitis altogether.[11,12] The result is a growing population of patients who fall into a guideline blind spot: virologically "inactive," metabolically high-risk, and histologically advanced.

In such cases, the clinical question is no longer whether antiviral therapy is indicated by classical HBV criteria alone, but whether persistent viral signaling can be safely ignored in a metabolically primed, fibrotic liver. Emerging observational data suggest that MASLD may amplify the fibrogenic and oncogenic consequences of even low-grade viral persistence,[6,13] raising the possibility that traditional HBV DNA cutoffs, largely derived from metabolically healthier populations, may be biologically insufficient in this context.

While antiviral therapy does not treat MASLD per se, it may reduce the background viral "noise" that contributes to immune activation and long-term oncogenic risk. In the absence of prospective trials, available evidence supports a more individualized, risk-based approach, particularly in patients with advanced fibrosis, where the margin for error is small.[12,14] Antiviral treatment alone, however, is unlikely to sufficiently mitigate long-term risk and should be complemented by aggressive lifestyle modification and evidence-based metabolic pharmacotherapy. Importantly, management decisions should integrate fibrosis stage, metabolic risk profile, and patient-specific factors, rather than relying solely on traditional virological thresholds.

Implications for Guidelines and Future Research

The convergence of MASLD and viral hepatitis exposes fundamental limitations in current disease frameworks. Single-etiology thinking no longer reflects clinical reality. Risk stratification tools that rely exclusively on viral or metabolic parameters in isolation fail to capture the integrated nature of liver injury. Strict adherence to current HBV treatment algorithms may inadvertently delay intervention in a growing subgroup of high-risk patients.

Future guidelines must move toward dual-risk assessment models that account for both viral persistence and metabolic dysfunction. Prospective studies are urgently needed to determine whether antiviral therapy confers incremental benefit in metabolically driven fibrosis, even in the setting of low-level viremia. Equally important is the development of integrated management strategies that address metabolic risk factors alongside viral suppression.

Conclusion: Toward a Dual-Etiology Paradigm in Hepatology

The studies by Ejaz et al.[1] and Bodakci et al.[2] mark an important step in reframing chronic liver disease for the modern era. They remind us that virological quiescence does not equate to biological inactivity, and that metabolic injury fundamentally alters the risk landscape of viral hepatitis. As MASLD and viral hepatitis increasingly converge, hepatology must evolve beyond siloed disease constructs toward an integrated, patient-centered paradigm. For clinicians, this means moving beyond viral replication and aminotransferase thresholds alone and incorporating fibrosis burden and metabolic risk into routine decision-making. For guideline committees, this underscores the need to revisit treatment algorithms that were developed in single-etiology populations and may underestimate risk in metabolically injured livers. For future trials, priority should be given to prospective studies evaluating whether antiviral therapy provides incremental benefit in patients with MASLD-driven fibrosis, even in the setting of low-level viremia.

Key takeaways for the clinician

Clinical domain	Key insight and recommendation
Epidemiology	A substantial proportion (≈30–50%) of viral hepatitis patients have concurrent MASLD, with particularly high prevalence among individuals with diabetes and other metabolic risk factors.
Pathophysiology	Dual "hits" from virus and fat create synergistic inflammation and fibrosis. Steatosis induces ER stress which may suppress HBV replication.
Diagnosis	Normal enzymes do not rule out disease. Use CAP/FibroScan for staging but interpret LSM with caution. Biopsy remains the gold standard for discordant cases.
Prognosis	Be aware of the "steatosis paradox": a fatty liver may help clear HBsAg (functional cure), but it will accelerate fibrosis progression if metabolic factors are not controlled.
Treatment	Antiviral therapy (TDF/TAF/ETV) in virologically inactive patients with MASLD-related fibrosis should be considered but is unlikely to be sufficient as a standalone strategy. Aggressive lifestyle modification and evidence-based metabolic pharmacotherapy are essential, with careful attention to potential drug–drug interactions.

MASLD: Metabolic dysfunction-associated steatotic liver disease; ER: Endoplasmic reticulum; HBV: Hepatitis B virus; CAP: Controlled attenuation parameter; LSM: Liver stiffness measurement; TDF: Tenofovir disoproxil fumarate; TAF: Tenofovir alafenamide; ETV: Entecavir.

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