THE FORUM FOR COLLABORATIVE RESEARCH

HBV FORUM 16

Executive Summary

26th May 2026
Barcelona

1608 Rhode Island Avenue NW
Washington, DC 20036
www.forumresearch.org

THE FORUM
For Collaborative Research℠
Berkeley's Hub for Regulatory Science

UC Berkeley Public Health

CONTENTS

SESSION I: UPDATES

Industry Updates: Summaries are provided only for presentations without slides, as all shared slides are available on our website.

- **Precision Biosciences**: Biopsy data showed that PBGENE-HBV directly targets cccDNA, validating its mechanism of action. The ongoing Phase 1 trial is evaluating safety, efficacy, and dose optimization in HBeAg-negative patients on NUC therapy.
- **Tune Therapeutics**: Tune-401 Phase 1b/2a clinical trial data are now available, including results from the fourth single-ascending-dose cohort and second multiple-ascending-dose cohort as of December 2024.

European Medicines Agency HBV Guideline Review Update:
The HBV Steering Committee has submitted its formal comments for the EMA HBV Guideline consultation. The recommendations are organized into four key categories: ensuring consistency across terminology and definitions, refining clinical trial populations and endpoints, clarifying treatment discontinuation protocols, and addressing special populations, particularly pediatric clinical trials.

Feedback from the World Hepatitis Summit, Bangkok
The summit, organized in collaboration with the Ministry of Public Health of Thailand and WHO, focused on the public health approaches to viral hepatitis. The WHO Global Hepatitis Report highlighted that HBV and HCV together are now the world's deadliest communicable diseases. Key sessions covered HBV guidelines, functional cure research, HDV, liver cancer, treatment access, HCV in pregnancy, prevention of mother-to-child transmission, and hepatitis care in conflict settings.

Standardizing HBV Nomenclature, Update from societies

An initiative to standardize HBV nomenclature has officially launched with the signing of Memorandum of Understanding by five major regional liver societies: AASLD, EASL, APASL, ALEH, and SOLDA. The steering committee met at EASL 2026 to establish the necessary organizational framework and aims to deliver a final consensus by APASL next year. The initiative will focus on three areas: standardizing the clinical phases of HBV infection, defining HBV cure terminology for global use, and aligning therapeutic endpoints.

SESSION II: HBV AND METABOLIC ASSOCIATED STEATOTIC LIVER DISEASE

The writing group has finalized the consensus manuscript, which is being revised for submission. The paper recognizes CHB with metabolic dysfunction-associated steatotic liver disease (MASLD) as a unique hybrid condition, affecting more than 35% of patients with CHB globally. Concurrent CHB-MASLD is characterized by an uncoupling of the relationship between HBV viremia and liver disease severity, an increased risk of adverse liver-related outcomes including hepatocellular carcinoma and altered responses to antiviral therapy. These unique clinical features highlight the need for specific clinical trials for co-affected patients. Such studies could improve patient recruitment, enhance the generalizability of findings, and better capture liver-related outcomes. However, trial design is complicated by the overlapping effects of CHB and MASLD on ALT, liver

stiffness, and HBV DNA, as well as persistent HCC risk and potential drug-drug interactions. Careful study design, including specific eligibility criteria for co-affected patients and endpoint selection, will therefore be essential when enrolling patients with CHB-MASLD into either CHB or MASLD clinical trials.

Discussion

Integrating MASLD into CHB management and clinical trial design introduces considerable complexity, underscoring the need for pragmatic, streamlined approaches. Although available evidence suggests that steatotic liver disease may modestly increase the likelihood of HBsAg loss, the magnitude and clinical significance of this association remain uncertain. Interpretation of existing data is further complicated by the retrospective nature of most studies and the frequent use of metabolic therapies, including statins and antidiabetic medications, which make it difficult to establish a causal relationship between steatotic liver disease and HBV outcomes. Distinguishing metabolic dysfunction-associated steatohepatitis (MASH) from MASLD in patients with CHB also remains challenging, as HBV-related inflammation can confound histological assessment.

There was broad agreement that Phase 3 CHB trials should not require MASLD-specific stratification or dedicated sub-studies. Given the high prevalence of metabolic comorbidities, appropriate randomization is expected to balance these factors while avoiding unnecessary regulatory, logistical, and financial burdens. Instead, participants emphasized collecting baseline metabolic and liver-related measures, including BMI, GGT, and metabolic biomarkers, to enable retrospective subgroup analyses, improve interpretation of ALT normalization, and monitor potential drug-drug interactions and treatment-related toxicities.

From a clinical perspective, the management of patients with low HBV viremia and concurrent MASLD or diabetes remains a gray area, particularly as WHO treatment guidelines expand antiviral eligibility in resource-limited settings. Although these comorbidities are associated with worse liver-related outcomes, it remains unclear whether antiviral therapy meaningfully reduces risks driven primarily by metabolic disease. Overall, the group concluded that MASLD should be recognized as a common but distinct comorbidity that warrants careful characterization, without introducing disease-specific trial endpoints that could unnecessarily complicate studies or delay access to effective HBV therapies.

SESSION III: HEPATITIS DELTA THERAPEUTICS: CLINICAL TRIAL ENDPOINTS

The HDV Clinical Trial Endpoints Working Group aims to develop recommendations for future HDV clinical trial endpoints, with a consensus manuscript planned for early 2027. The initiative has been driven by recent advances in the field, including FDA approval of 10 mg bulevirtide (BLV), emerging long-term outcome data, extended follow-up from interferon studies, and the development of next-generation Phase 3 therapies pursuing functional cure.

The group reviewed the current combined endpoint of ≥2 log10 HDV RNA reduction and ALT normalization, focusing on the limitations of ALT as a confounding marker in patients with underlying metabolic liver disease and whether endpoint selection should vary according to treatment mechanism or duration. There is a growing interest in HDV RNA target-not-detected (TND), with or

without ALT normalization, as a preferred endpoint. However, uncertainty remains regarding whether serum HDV RNA accurately reflects reductions in infected hepatocytes. There is also a need for more sensitive and standardized HDV RNA assays, given the variability in undetectability rates across currently available commercial tests.

Beyond traditional virologic and biochemical endpoints, the group discussed incorporating patient-reported outcomes, which remain underutilized despite the substantial quality-of-life burden associated with HDV infection. Additional endpoints under consideration included HBsAg reduction and non-invasive biomarkers, although both present interpretation challenges. The working group also considered whether finite and chronic therapies require different endpoints or evaluation timepoints and discussed challenges in resource-limited settings, including diagnostic and treatment gaps, population heterogeneity, and varying risks of disease progression and of liver cancer. Key priorities for future work include identifying the primary drivers of HDV disease progression, determining whether TND should replace current virologic thresholds, establishing predictors of durable response after finite therapy, evaluating whether endpoints should differ by mechanism of action, and clarifying the interpretation of ALT in patients with coexisting metabolic liver disease.

Discussion

The participants deliberated whether future HDV clinical trials should adopt Target Not Detected (TND) as a simplified primary endpoint or retain the traditional combined endpoint of ≥2-log decline in HDV RNA plus ALT normalization. Supporters of TND argued that advances in standardized, highly sensitive HDV RNA assays have made absolute viral suppression a practical and objective endpoint, consistent with treatment paradigms in HIV and HCV. Others emphasized that endpoint selection should reflect a therapy's mechanism of action, noting that agents such as Bulevirtide can substantially improve liver-related outcomes and normalize ALT despite infrequently achieving TND. As such, relying solely on TND could underestimate the value of therapies that primarily improve clinical outcomes by reducing liver injury rather than completely suppressing viral replication.

Long-term follow-up data were also cited in support of the traditional combined endpoint, demonstrating its prognostic value for predicting reduced progression to hepatocellular carcinoma and end-stage liver disease. However, participants noted that increasingly sensitive PCR assays may detect residual non-replicating viral RNA, complicating interpretation of TND and highlighting the need for standardized testing methodologies across laboratories.

The discussion also distinguished between finite curative therapy and chronic viral suppression. Although HDV is theoretically curable because it does not integrate into the host genome, demonstrating durable off-treatment responses remains challenging and costly. A pragmatic development strategy was proposed in which chronic suppressive therapies are first brought into clinical practice, followed by studies that define treatment discontinuation strategies and identify patients most likely to achieve sustained remission. Participants also emphasized that finite therapies are preferable from both patient and health system perspectives, particularly in resource-limited settings where lifelong treatment imposes substantial financial and quality-of-life burdens and complex endpoint assessments may further limit access to care.

SESSION IV: ADVANCING HBV TREATMENT IN SUB-SAHARAN AFRICA

There is a paradigm shift toward an integrated chronic care model, the "2for1 Project," in sub-Saharan Africa, which integrates HBV care into existing HIV and non-communicable disease programs. This model aims to address longstanding barriers to HBV care, including poor linkage to care, limited retention, and fragmented healthcare delivery. A pilot implementation in Uganda demonstrated its feasibility by improving healthcare workforce capacity and patient experience while reducing per-patient costs through shared infrastructure, low-cost tenofovir, and expanded WHO treatment guidelines. Future efforts will focus on scaling the model beyond Uganda and Kenya, generating evidence on cost-effectiveness, overcoming data integration challenges, and supporting sustainable implementation through domestic financing.

Discussion

Despite HBV prevalence in sub-Saharan Africa being approximately three times higher than HIV, individuals with HBV monoinfection remain substantially underdiagnosed and undertreated compared with those with HIV-HBV coinfection. Participants emphasized that expanding integrated chronic care models could help address this gap by improving the detection of diabetes and hypertension, reducing stigma through general chronic care clinics, and strengthening patient retention.

Key implementation challenges include inconsistent procurement and distribution of HBV medications, shortages of tenofovir monotherapy, and continued reliance on HIV procurement systems to secure treatment access. Participants therefore identified sustainable pooled procurement strategies, particularly for future long-acting therapies and novel HBV treatments, as a priority for ensuring equitable and sustainable access across the region.

SESSION V: HEPATOCELLULAR CARCINOMA: GAPS AND OPPORTUNITIES FOR EARLY DETECTION

Universal HBV treatment continues to face important implementation barriers, particularly in remote and resource-limited settings such as Alaska. Limited access to specialized care, insufficient long-term evidence supporting lifelong antiviral therapy, and gaps in provider knowledge remain major obstacles, contributing to suboptimal HCC surveillance uptake and delayed early-stage tumor detection in many HBV-endemic regions. While expanding antiviral therapy may reduce HCC incidence, further work is needed to optimize surveillance through individualized risk assessment incorporating factors such as HBV genotype, alcohol consumption, and metabolic comorbidities.

The Asia-Pacific region accounts for more than 70% of global HBV-related HCC cases, yet HBV diagnosis, treatment, and HCC surveillance remain inadequate. Current surveillance relies on ultrasound and alpha-fetoprotein, while emerging biomarkers, including circulating cell-free DNA and

quantitative HBsAg, may improve early detection and support more individualized surveillance strategies. Expanding HBV diagnosis and treatment, increasing surveillance participation, and validating novel biomarkers were identified as key regional priorities.

In sub-Saharan Africa, HCC surveillance is limited by competing public health priorities, constrained healthcare infrastructure, and restricted access to curative therapies. Although ultrasound remains the primary surveillance tool, variable imaging quality, limited risk stratification, and logistical barriers reduce its effectiveness. Opportunities to improve HCC care include artificial intelligence-assisted ultrasound, telemedicine, workforce development, expanded access to local ablative therapies, and timely HBV birth-dose vaccination.

In the Americas, strengthening HCC surveillance requires improving the entire HBV care cascade, from diagnosis to surveillance and timely follow-up of abnormal findings. Existing surveillance methods remain limited by operator dependence and suboptimal sensitivity, highlighting the need for more accurate approaches, including multi-marker panels, circulating tumor DNA, and abbreviated MRI. Future surveillance strategies should transition from the current one-size-fits-all approach to risk-stratified models supported by population health management tools and standardized quality metrics.

Discussion

Universal HBV treatment should be considered within the context of regional healthcare resources, particularly in low- and middle-income countries where limited access to surveillance and biomarker testing makes individualized risk stratification difficult. Discussion centered on whether simplified "treat-all" strategies or risk-based approaches are more appropriate. Some favored treating all patients except those at clearly low risk, arguing that simplified strategies may be more feasible. Others supported risk-based treatment based on HBV DNA level, viral genotype, age, and predicted HCC risk, noting that patients with HBV DNA levels below 2,000 IU/mL generally have a lower risk of HCC and may not require immediate antiviral therapy. Expanding access to point-of-care HBV DNA testing, particularly by leveraging existing HIV testing infrastructure in Africa, was viewed as a practical strategy to facilitate better HBV DNA testing and patient monitoring.

Participants also noted that current treatment guidelines exclude many patients who may benefit from future functional cure therapies. In contrast, many investigational therapies are being developed for only a small subset of patients. Treating patients with lower viral loads was recognized to increase the number needed to treat to prevent one case of HCC, underscoring the importance of balancing clinical benefit, cost-effectiveness, and regional resource availability. Regardless of treatment strategy, antiviral therapy was recognized to reduce, but not eliminate, the risk of HCC, making continued HCC surveillance essential.