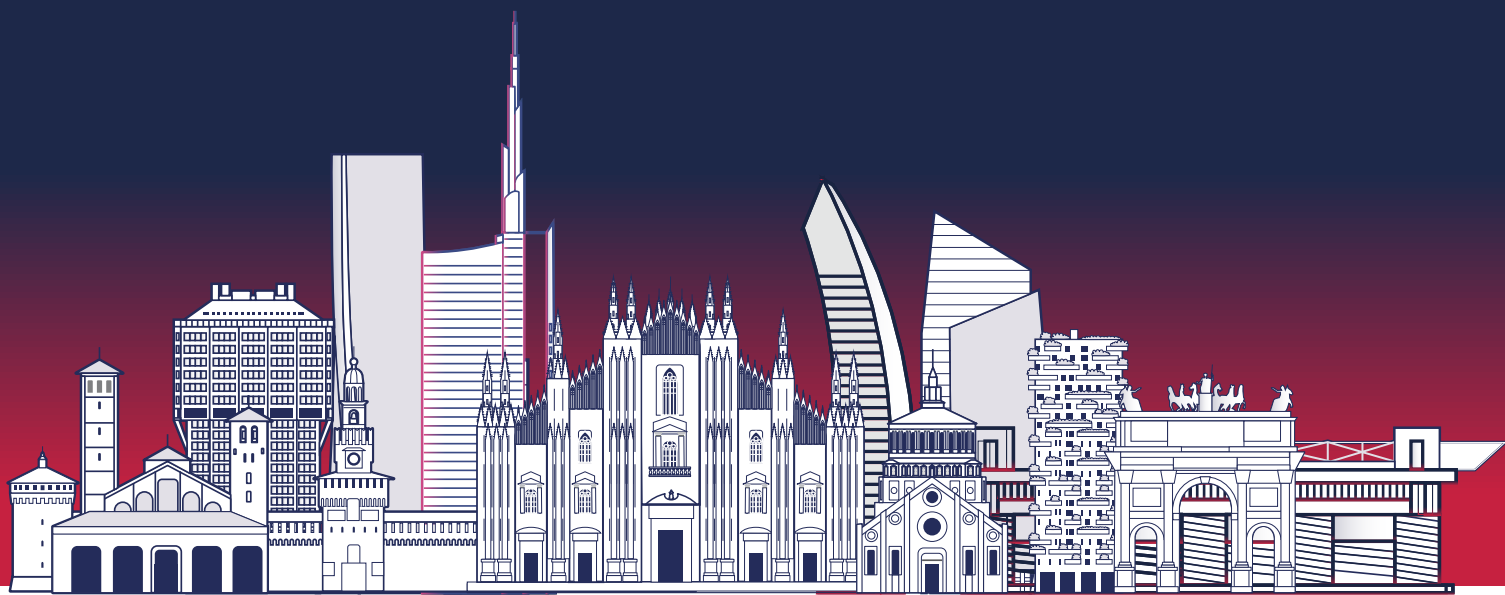


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ABSTRACT BOOK

OCTOBER 15-16 2026 MILAN, ITALY



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EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

GLOBAL AND LOCAL EPIDEMIOLOGY

OP01 HIGH PREVALENCE OF HDV AND HBV DETECTED AMONGST HOUSEHOLD CONTACTS OF HDV POSITIVE INDIVIDUALS IN RURAL SINDH

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Background: Hepatitis D virus (HDV) infection continues to impose a substantial clinical and public health burden in Pakistan, particularly in rural settings where hepatitis B virus (HBV) remains endemic. While intrafamilial transmission of HBV is well recognized, the importance of household transmission for HDV infection has not been well described.

Objectives: To determine the prevalence of HBV and HDV among household contacts of HDV-positive index cases and to identify patterns suggestive of horizontal, and possible vertical transmission in rural Sindh.

Methods: This cross-sectional observational study enrolled consenting HDV RNA positive individuals from rural Sindh and screened their household members for HBV and HDV infection. All adults and children > 1 year of age, living in the same housing unit were tested. Household contacts were first tested for hepatitis B surface antigen (HBsAg) using WHO prequalified rapid diagnostic tests; HBsAg positive individuals were then tested for antibodies to hepatitis D virus (anti-HDV antibodies total) using an enzyme-linked immunosorbent assay (ELISA) at the central laboratory at Aga Khan University. Moreover, clinical, laboratory, and demographic data were collected.

Results/Outcomes: A total of 257 HDV-positive index cases and 1,462 household contacts were enrolled. Overall, 166 (11.4%) household members were HBsAg positive, of whom 121 (72.9%) were also anti-HDV antibody positive. HDV antibody prevalence among HBsAg+ spouses were 28/30 (93.3%), 34/61 (55.7%) among children, and 59/75 (78.6%) among extended family members. These findings suggest ongoing intrafamilial transmission through both horizontal and possible vertical routes. Fig. 1. Currently, genomic analysis of the collected samples is ongoing, and the results will be shared upon completion.

Conclusions: These findings suggest that intrafamilial transmission of HDV infection is common among HBV infected family members. Household contacts of HDV-positive individuals are at high-risk for HBV and HDV infection in rural Pakistan. Integrating routine household screening, improving HBV vaccination coverage, and ensuring timely referral to care are critical steps toward reducing HDV transmission and disease burden in endemic regions. Targeted household screening and preventive strategies should be prioritized within national hepatitis control programs.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

OP02 PAIRED LIVER AND SERUM DEEP SEQUENCING REVEALS DIFFERENCES BETWEEN CIRCULATING HDV AND INTRAHEPATIC VIRAL POPULATIONS

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Background: Hepatitis D virus (HDV) sequencing is typically performed on serum HDV RNA, assuming that circulating virus reflects the intrahepatic viral population. However, this has not been systematically evaluated. We investigated the relationship between intrahepatic and circulating HDV quasispecies, and its evolution in serum over time, using deep sequencing of liver and serum samples.

Material and methods: Paired serum and liver samples were obtained from four patients with chronic hepatitis D, that had undergone liver transplantation, and longitudinal sera from an additional 6 patients monitored for chronic HDV in routine care. A total of 30 serum samples were included. From each explanted liver, ten spatially separated tissue pieces were analyzed to assess intrahepatic viral diversity. HDV RNA was amplified using PCR targeting a 284-nt region spanning the 3' end of the HDAg ORF and deep sequenced on the Ion Torrent platform. Species carrying minor variants were identified using CliqueSNV, which reconstructs variant haplotypes and estimates their frequencies. Variant species with frequencies between 0.5% and 50% were included, hereafter called minor species.

Results: Consensus nucleotide sequences of HDV were almost identical in all tissue pieces within each patient, but had differences compared with the consensus sequences in serum samples taken at transplantation at 0–5 positions (mean 2.25). Among the four liver explants, 564 minor species were detected, of which 96% were not identified in matched serum samples. Seventy-nine percent of all minor variants were detected in only one of the ten tissue pieces. In serum, 42 of 63 minor variant species (71%) were not identified in the corresponding liver tissue. One transplanted patient had no detectable minor species in serum, interestingly, this patient had the highest number of consensus sequence differences compared with the liver. The mean frequency of all minor species was 3% in liver and 4% in serum. Minor species detected in both compartments generally occurred at lower frequencies in serum than in liver, in mean 2% and 4%, respectively ($P=0.04$). Longitudinal serum samples demonstrated different compositions of minor species over time, but the consensus was typically well-conserved.

Conclusions: Our findings agree with the idea that HDV in serum might not be representative for HDV in the liver, although circulating HDV should represent the average genetic variation of HDV secreted from the liver to blood. Recent studies have shown that HDV RNA can be present in hepatocytes without HBsAg production, unable to secrete HDV particles. Thus, both serum samples and liver biopsies likely underestimate the complexity of intrahepatic HDV diversity. These findings may have implications for molecular studies of HDV, including investigations of treatment- or immune-associated selection, cell division-mediated spread and the design of experimental constructs based on serum-derived HDV sequences.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

IMMUNOLOGY UPDATE AND SPATIAL TRANSCRIPTOMICS

OP03 IDENTIFICATION OF GBP3 AS A NOVEL HOST FACTOR REQUIRED FOR HEPATITIS DELTA VIRUS RECOGNITION BY HEPATOCYTES

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Background: Following entry into hepatocytes, the hepatitis D virus (HDV) ribonucleoprotein complex is sensed by the cytosolic RNA receptors MDA5 and LGP2, leading to the activation of type I and III interferon (IFN) responses.

Material and methods: Although differentiated HuH7.5-NTCP cells responded to stimulation with an MDA5 ligand (high-molecular-weight poly(I:C)), they failed to mount an IFN response following HDV infection, even upon ectopic MDA5 overexpression. These observations suggested the involvement of an additional, as yet unidentified, host factor in HDV recognition. To identify such factor(s), we analyzed transcriptomic data comparing gene expression profiles of differentiated HuH7.5-NTCP and dHuH7-NTCP cells, the latter being capable of mounting a robust IFN response upon HDV infection. Among the differentially expressed genes, we identified the guanylate-binding protein 3 (GBP3). Using dHepaRG and dHuH7-NTCP cells, we observed a significant reduction in HDV-induced expression of the interferon-stimulated gene RSAD2 following GBP3 knockdown by RNA interference. This reduction was comparable to that observed following LGP2 knockdown.

Results: Conversely, we found that co-expression of MDA5, LGP2 and GBP3 restored the IFN response to HDV infection in non-responsive cells (undifferentiated HuH7-NTCP cells). Mechanistically, immunoprecipitation assays revealed associations between GBP3 and MDA5, GBP3 and LGP2 as well as between GBP3 and HDV RNAs. In addition, rather than promoting the association of MDA5 with HDV RNAs, we found that GBP3 enhanced MDA5 oligomerization, thereby promoting downstream IFN pathway activation.

Conclusions: In conclusion, we identify GBP3 as a novel host factor required for innate sensing of HDV by infected hepatocytes, uncovering a previously unrecognized mechanism regulating MDA5 activation during HDV infection.



DIAGNOSIS AND NATURAL HISTORY

DIAGNOSTICS UPDATE

OP04 QUANTITATIVE ANTI-HDV MEASUREMENT AS A DIAGNOSTIC SURROGATE OF HDV REPLICATION

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Background: Detection of serum HDV-RNA confirms active HDV replication and points to severe hepatitis D. However, HDV-RNA testing is technically demanding and often unavailable in resource-limited settings, where diagnosis may rely on anti-HDV alone. We assessed whether anti-HDV titers may serve as a diagnostic surrogate for high-level HDV viremia and explored whether anti-HDV kinetics during bulevirtide (BLV) therapy reflect the depth of virological suppression.

Materials and methods: We considered 450 untreated HBsAg/anti-HDV-positive patients from the Italian HDV DESCRIBE cohort (Caviglia 2025). Median age was 56 years, 282 (62.7%) were male, and 373 (82.9%) were HDV-RNA-positive (median HDV-RNA: 5.02, 3.22–6.03 Log IU/mL). Total anti-HDV was measured with the LIAISON XL Murex Anti-HDV assay and quantified by endpoint titration using serial ten-fold dilutions; titers were calculated by multiplying the signal obtained at the last reactive dilution by the corresponding dilution factor and expressed as AU/mL. Clinical phenotypes were defined according to the HDV DESCRIBE classification: patients were first stratified by cirrhosis status, while non-cirrhotic chronic hepatitis D and inactive/mild disease were defined by HDV-RNA >3 or ≤3 Log IU/mL, respectively. Among them, 69 patients subsequently treated with BLV were evaluated longitudinally up to week (w) 48, including 45 with w96 samples.

Results: Anti-HDV titers correlated with HDV-RNA levels ($rs=0.595$; $p<0.001$), more strongly in non-cirrhotic patients than in those with cirrhosis ($rs=0.706$ vs $rs=0.481$; $p<0.001$). Among viremic patients, anti-HDV titers were higher in those with high-level than low-level viremia (4.77 vs 3.32 Log AU/mL; $p<0.001$; AUC=0.828). A cut-off >4 Log AU/mL identified high-level viremia with 86.6% sensitivity and 65.6% specificity. Anti-HDV titers ≤4 Log AU/mL predominated in inactive/mild disease (79.2%), whereas titers >4 Log AU/mL predominated in non-cirrhotic chronic hepatitis D (85.7%) and cirrhosis (80.2%; $p<0.001$). During BLV therapy, 10/69 patients had HDV-RNA <20 IU/mL and 4/69 achieved target-not-detected (TND) at w48; at w96, 6/45 had HDV-RNA <20 IU/mL and 8/45 achieved TND. Anti-HDV



kinetics showed a delayed on-treatment decline compared with HDV-RNA; baseline titers did not differ according to w96 virological outcome ($p=0.708$), whereas median titers at w48/w96 were 4.06/3.81 Log AU/mL in patients with persistent quantifiable viremia, 3.63/3.41 in those with HDV-RNA <20 IU/mL, and 3.13/2.76 in those achieving TND, respectively ($p=0.017$ at w48 and $p<0.001$ at w96). W48 anti-HDV titers correlated with w96 HDV-RNA levels ($r_s=0.460$; $p=0.001$), while w96 titers showed a stronger correlation with w96 HDV-RNA levels ($r_s=0.667$; $p<0.001$).

Conclusions: Quantitative anti-HDV closely reflects HDV replication and may serve as a diagnostic surrogate to identify high-level HDV viremia. During BLV therapy, anti-HDV kinetics may provide information on the depth of virological suppression.



DIAGNOSIS AND NATURAL HISTORY

NATURAL HISTORY

OP05 PREDICTORS OF ADVANCED CHRONIC LIVER DISEASE (ACLD) IN PATIENTS WITH HEPATITIS DELTA VIRUS (HDV) INFECTION: DOES THE GENOTYPE MATTER?

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Background: Hepatitis delta virus (HDV) infection causes the most severe form of viral hepatitis. Whether disease severity differs according to HDV genotype remains uncertain. We aimed to compare the clinical features of patients chronically infected with different HDV genotypes, and identify predictors of advanced chronic liver disease (ACLD).

Methods: Prospective, multicenter observational study across 15 Portuguese centers. Adults with chronic hepatitis B and positive anti-HDV antibodies were enrolled between March 2024 and June 2026. Additionally, patients with stored blood samples collected within the preceding 3 years were included retrospectively. HDV RNA was determined by RT-PCR, and positive samples underwent sequencing, genotyping, phylogenetic analysis, and viral load quantification. Demographic, virological, and clinical characteristics were analyzed. Predictors of ACLD were evaluated.

Results: 156 patients were included (age 44±11 years; 56% male). Participants originated from Portugal (25.0%), Africa (63.5% - of whom 77.8% from Guinea-Bissau), Eastern Europe (9.0%), Asia (1.9%), and South America (0.6%). Most patients were HBeAg-negative (86.8%) and 59.6% were receiving nucleos(t)ide analogue therapy. HCV and HIV coinfections were present in 17.9% and 20.9% of patients, respectively. HDV RNA was detectable in 65 patients (41.7%), of whom 25 (38.5%) were infected with HDV-1, 34 (52.3%) with HDV-5, and 6 (9.2%) with HDV-8. HDV-5 was detected predominantly in patients from Guinea-Bissau and HDV-8 in those from Angola. ACLD was present in 33.3% of patients, including 15 with clinically significant portal hypertension, 6 with decompensated cirrhosis, and 5 with primary liver cancer. Compared with patients with undetectable HDV RNA, viraemic patients were younger, more frequently female, and had higher rates of ACLD (49.2% vs. 22.0%; $p < 0.001$). For genotype comparisons, patients with negative HDV RNA were assigned a presumed HDV genotype based on country of birth, reflecting the near-perfect correlation between genotype and geographic origin observed among patients with detectable HDV RNA. Compared with HDV-5/8, patients with HDV-1 were older, more frequently male, had higher rates of intravenous drug use, HCV and HIV coinfection, and ACLD (48.3% vs. 24.4%; $p = 0.003$). Detectable HDV RNA was the strongest independent predictor of ACLD (aOR 7.6, 95% CI 2.9–20.0; $p < 0.001$). Detectable HBV DNA was independently associated with lower odds of ACLD (aOR 0.37, 95% CI 0.14–0.94; $p = 0.04$). HDV-1 showed a borderline independent association with ACLD (aOR 2.9, 95% CI 0.98–8.39; $p = 0.055$).

Conclusions: In this cohort of patients infected with different HDV genotypes, detectable HDV RNA was the strongest independent predictor of ACLD. Patients with HDV-1 infection also showed a trend towards greater disease severity than those with HDV-5/8 infection, supporting a potential role of HDV genotype in modulating the clinical course of HDV infection.



CURRENT AND NEW ANTIVIRAL TREATMENTS

LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

OP06 CLINICAL AND ECONOMIC VALUE OF EARLY TREATMENT WITH BULEVIRTIDE IN CHRONIC HEPATITIS DELTA VIRUS

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Background: Chronic hepatitis D is associated with accelerated fibrosis progression, hepatic decompensation, and premature mortality. Bulevirtide (Hepcludex®) is currently the only approved therapy for chronic HDV. This study evaluates the clinical and economic benefits of bulevirtide in terms of avoided clinical complications and associated costs, comparing its use in the early versus advanced stages of liver fibrosis in a Spanish cohort with chronic HDV infection.

Methods: A validated economic model was used to simulate the natural history of the disease, including liver disease progression and associated cost. The analysis compared bulevirtide treatment at F0-F2 (early-stage treatment) versus F3-F4 (advanced-stage treatment), each assuming a cohort of 2,173 patients. Model inputs were obtained from available literature, including efficacy informed by the MYR301 study using the combined response rate at 144 weeks. The liver complications assessed were decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), liver transplantation (LT), and liver-related death. Clinical events and costs were evaluated from the perspective of the Spanish National Health Service, applying a 3% discount rate over a lifetime horizon. A subgroup analysis within the early-stage population compared treatment initiation at F0-F1 versus F2.

Results: In simulated model analyses of a cohort of 2,173 patients, early-stage treatment with bulevirtide was associated with 392 fewer cases of DC (-63%), 120 fewer cases of HCC (-18%), 24 fewer LTs (-52%), and 620 fewer liver-related deaths (-45%) compared with treatment initiation in advanced-stage disease. These clinical benefits resulted in total lifetime cost savings of €26.1 million (-50%) with early-stage treatment. In an additional subanalysis within the early-stage population, treatment initiation at the earliest stages of fibrosis provided additional clinical benefits compared with delaying treatment until F2, avoiding 123 cases of DC (-40%), 68 cases of HCC (-12%), 8 LTs (-29%), and 222 liver-related deaths (-24%), with corresponding to cost savings of €8.7 million (-27%) over the lifetime-horizon of the model.

Conclusions: Early initiation of bulevirtide in chronic HDV infection substantially reduces liver-related complications, mortality, and healthcare costs compared with delayed treatment, as estimated in a lifetime-horizon. These findings support treatment initiation at the earliest stages of fibrosis to maximize both clinical and economic benefits in the Spanish healthcare setting.



CURRENT AND NEW ANTIVIRAL TREATMENTS

LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

OP07 HEPATIC RECOMPENSATION ACCORDING TO BAVENO VII IN DECOMPENSATED CHRONIC HEPATITIS DELTA TREATED WITH BULEVIRTIDE: A MULTICENTER EXPERIENCE

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Background: Bulevirtide (BLV) is actually approved only for compensated chronic hepatitis D (CHD). Whether it can induce hepatic recompensation, as defined by Baveno VII, in decompensated CHD remains unknown.

We assessed the rate of Baveno VII recompensation in decompensated CHD patients treated with BLV, and also compared them to an untreated control cohort with comparable disease severity.

Materials and methods: We performed a retrospective multicenter study of CHD patients with detectable HDV-RNA and decompensated cirrhosis Child-Pugh (CP) B or C with ascites, variceal bleeding or hepatic encephalopathy under evaluation or listed for liver transplantation (LT). The BLV group received BLV 2 mg/day, initiated between 2020 and 2023, with follow-up extending to 2026. The untreated control group comprised patients with detectable HDV-RNA and decompensated cirrhosis listed and transplanted between 2014 and 2021. Baveno VII recompensation required undetectable HDV-RNA, resolution of ascites off diuretics, of encephalopathy off lactulose/rifaximin, and absence of recurrent variceal bleeding for ≥ 12 months, together with stable improvement of liver function to Child-Pugh A.

Results: Twenty-nine patients were included: 11 BLV-treated and 18 controls. Groups were comparable for age (46 vs 46 years, $p=0.84$), male sex (64% vs 39%, $p=0.26$), CP score (10 vs 10, $p=0.85$), MELD (15 vs 18, $p=0.30$), bilirubin (43 vs 57 $\mu\text{mol/L}$) and platelets (35 vs 59 $\times 10^9/\text{L}$, $p=0.08$); controls had lower albumin (27 vs 30 g/L, $p=0.02$) and slightly higher baseline HDV-RNA (5.3 vs 3.7 $\log_{10}$ IU/mL, $p=0.17$). In the BLV group over 22 (2–67) months, 7/9 evaluable patients achieved undetectable HDV-RNA by week 48, MELD improved from 15 to 13 and CP A was reached in 5/9. Baveno VII recompensation occurred in 1/11 (9%) BLV-treated patients versus 0/18 (0%) controls ($p=0.38$). Delisting after clinical improvement occurred in 3/11 (27%) BLV versus 0/18 (0%) controls ($p=0.045$), and LT in 7/11 (64%) BLV versus 18/18 (100%) controls ($p=0.014$); untreated controls were transplanted within a median of 3 months (0.2–16) from listing.

Conclusions: Formal Baveno VII recompensation in decompensated CHD was rare under BLV (9%) and absent in the control group (0%), underscoring how rarely full recompensation is reached in this population. Nonetheless, BLV was associated with MELD and CP improvement, suggesting that it may defer transplantation and improve clinical outcome.



CURRENT AND NEW ANTIVIRAL TREATMENTS

OTHER THERAPEUTIC APPROACHES FOR HDV

OP08 PREDICTING TIME TO CURE IN HDV PATIENTS TREATED WITH BULEVIRTIDE AND PEGYLATED INTERFERON-ALPHA IN THE SEE-D TRIAL

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Background and Aims: Bulevirtide (BLV) was recently approved by the U.S. Food and Drug Administration for the treatment of patients living with compensated chronic hepatitis D without a defined length of therapy. In the MYR 204 trial, a 48 week combination therapy with BLV and pegylated Interferon-alpha (peg-IFN) showed higher rates of on-treatment undetectable HDV RNA compared to either drug as monotherapy. The SEE-D trial investigates the effect of BLV (2mg/day) and peg-IFN (180 µg weekly, reduced to 135 µg from week 48) combination therapy. We aim to use mathematical modeling to explain HDV-host dynamics and predict time to cure in the SEE-D trial.

Method: 31 patients with chronic hepatitis D were enrolled at Karolinska University Hospital, Sweden (EU no. 2023-504414-29-00). They received 96-weeks of combination treatment with BLV (2 mg/day) and peg-IFN. One early dropout and one participant without quantifiable HDV RNA values were excluded. We used our recent mathematical model (DOI: 10.1016/j.antiviral.2026.106489) accounting for both blocking of viral production (peg-IFN efficacy, ϵ) and blocking of infection (BLV efficacy; η), with total efficacy of $\epsilon\eta$. Due to parameter identifiability issues, BLV efficacy was fixed at 80% as recently estimated under BLV monotherapy (Antiviral Res. 2026 Jul 17:106489). The critical drug efficacy (CDE) was estimated, such that for $\epsilon\eta > \text{CDE}$, HDV is ultimately cleared (i.e., cure), while $\epsilon\eta < \text{CDE}$ results in a new lower viral plateau or viral breakthrough. We also assumed that cure is reached when there is < 1 infectious virus particle in the extracellular body fluid (approximately 13.5 L), which corresponds to one virion/13 500 mL = 7×10^{-5} .

Results: The 29 participants initially showed a rapid first-phase HDV RNA decline ($-0.91 \log_{10} \text{ IU/mL/month}$), followed by undetectability ($n=26$; Fig.1A), or a plateau close to LLoQ ($n=3$; Fig. 1B) followed by viral breakthrough (VB, Fig.1C). The model reproduced the observed HDV kinetics and estimated $\epsilon\eta$ of 96% (95% CI 95 – 98), which exceeded CDE in 90% of the participants (Fig. 1A) but was below the CDE in the three participants who reached a lower plateau (Fig 1B), and a VB (Fig. 1C). The model predicted that 20/29 (69%) patients could reach cure (Fig. 1A), with a median time of 76 weeks (IQR: 61 - 101). ALT normalization (Fig. 1) was explained by a decline in HDV-infected cells. HBsAg kinetics were explained by a constant number of HBsAg-producing hepatocytes during treatment (Fig. 1), except for in 3 participants who exhibited a $>1 \log$ HBsAg decline from baseline, which may reflect loss of HBsAg-producing cells and/or interferon-mediated inhibition of HBsAg production.

Conclusion: Modeling predicts that in the SEE-D trial, the combination of BLV and peg-IFN therapy has sufficient total antiviral efficacy to achieve HDV cure with a prolonged course of therapy in most patients with continuous undetectable HDV RNA on treatment.



CURRENT AND NEW ANTIVIRAL TREATMENTS

OTHER THERAPEUTIC APPROACHES FOR HDV

OP09 HISTOLOGIC IMPROVEMENT AND REDUCTION IN NECROINFLAMMATION WITH LONAFARNIB-BASED THERAPY IN CHRONIC HEPATITIS DELTA: PHASE 3 D-LIVR TRIAL

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Background: Lonafarnib (LNF) pharmacokinetically boosted with ritonavir (LNF/RTV) remains the only late-stage oral agent under development for the treatment of chronic hepatitis D virus (HDV). By inhibiting host farnesyltransferase, LNF disrupts HDV virion assembly in infected hepatocytes and promotes immune modulation. LNF/RTV is being advanced as a 48-week treatment regimen for patients living with HDV, administered as monotherapy or in combination with peg-interferon alfa-2a (PEG). Improvement in the Ishak Histologic Activity Index (HAI) and its subdomains were evaluated to provide mechanistic insight into treatment effects on liver health.

Method: D-LIVR is the largest Phase 3 randomized placebo-controlled HDV study (N=407) to date, evaluating LNF/RTV with or without PEG. The primary efficacy composite endpoint was defined as a ≥ 2 log reduction in HDV RNA and ALT normalization compared to baseline at Week 48 (end of treatment [EOT]).

D-LIVR also included a large paired-biopsy population (N=229 with baseline and EOT samples). Histologic responders were defined as ≥ 2 point improvement in the modified Ishak HAI score without worsening of fibrosis. Effects of treatment on Ishak HAI subcomponents most directly impacted by the health of infected hepatocytes were evaluated in exploratory analyses: focal lytic necrosis, apoptosis, and inflammation (FLNAI) which reflects ongoing hepatocyte injury and immune surveillance, and periportal/periseptal interface hepatitis (PPIH) which reflects ongoing necroinflammation and fibrosis advancement.

Results: The primary composite endpoint at 48 weeks was met by both LNF/RTV ($p = 0.004$) and LNF/RTV+PEG ($p < 0.0001$) treatment groups. LNF/RTV+PEG also resulted in improvement of the histological endpoint in a significant proportion of patients (35 of 125, $p = 0.01$) and LNF/RTV monotherapy improved histology in many patients (35 of 178, NS).

Among the paired-biopsy population, the FLNAI subdomain score was improved compared to baseline by treatment with both LNF/RTV (-0.42, 95%CI: -0.65 to -0.19, N=108) and LNF/RTV+PEG (-0.74, 95%CI -1.1 to -0.41, N=66). Similarly, the PPIH subdomain score improved significantly compared to baseline in both LNF/RTV (-0.32, 95%CI: -0.54 to -0.11, N=108) and LNF/RTV+PEG (-0.65, 95%CI -0.98 to -0.32, N=66) treatment groups. Placebo-treated patients did not experience subdomain improvement. Improvements in FLNAI and PPIH subdomains were significant among patients who achieved a composite response at any time during the study, irrespective of response status at EOT.

Conclusions: In the D-LIVR study, LNF/RTV-based therapy, with or without PEG, improved inflammatory HAI subdomains, consistent with reduced hepatocyte injury and necroinflammation. LNF/RTV is a first-in-class oral HDV therapy with efficacy and safety in HDV patients, and histologic evaluation supports the continued development of LNF-based therapy as a 48-week treatment regimen for HDV with definitive impact on liver tissue health.



CURRENT AND NEW ANTIVIRAL TREATMENTS

OTHER THERAPEUTIC APPROACHES FOR HDV

OP10 THE EFFICACY AND SAFETY OF SIRNA OZISIRAN IN PATIENTS WITH CHRONIC HEPATITIS D: INTERIM RESULTS THROUGH TREATMENT WEEK 36 FROM THE PHASE 2A RC04T001 TRIAL

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Background: Ozisiran (RBD1016) is a small interfering RNA (siRNA) that suppresses HBsAg production. We evaluated the efficacy and safety of ozisiran in combination with a nucleotide analogue in patients with chronic hepatitis D (CHD), with interim analysis through Week 36.

Material and Methods: This Phase 2a trial includes a randomized, single-blind, placebo-controlled exploratory phase and enrolled 14 participants with CHD at Karolinska University Hospital and Danderyd Hospital, Stockholm, Sweden. Eligible participants were non-cirrhotic, with liver stiffness < 10 kPa and HBsAg levels < 10,000 IU/mL. Participants were allocated to an active treatment group (n=9) or a deferred treatment group (n=5), with the latter receiving placebo for 16 weeks before active treatment. Ozisiran 300 mg was administered subcutaneously at Weeks 0, 4, 8, 12, 36 and 48. All participants received tenofovir alafenamide (TAF). ALT flares were defined as ALT ≥ 3x the upper limit of normal (ULN) and ≥ 2x the nadir value, or ALT ≥ 3x ULN at baseline. In this interim analysis, safety and efficacy were evaluated through Week 36, including four doses of ozisiran over 12 weeks followed by a 24-week dose-free interval.

Results: Baseline characteristics are shown in Table 1. Mean (SD) log₁₀ HDV RNA decreased from 4.6 (1.7) at baseline to 3.9 (1.7) at Week 24 and remained at 3.9 (1.9) at Week 36. Mean (SD) log₁₀ HBsAg decreased from 3.5 (0.8) at baseline to 2.0 (0.7) at Week 24 and was 2.6 (1.0) at Week 36, with 7/14 (50%) participants achieving HBsAg < 200 IU/mL at Week 36. Most adverse events were mild, with the exception of Grade 2-4 ALT elevations. ALT flares occurred in 8 (57%) participants. No serious adverse events occurred. Two participants developed Grade 4 ALT elevations (> 20 x ULN) at treatment Weeks 22 and 26, respectively, and received bulevirtide (BLV) 2 mg SC QD. ALT levels normalized to < ULN within 6-8 weeks after BLV initiation, allowing both participants to continue ozisiran without recurrent ALT elevations. One participant with a moderate ALT-flare discontinued ozisiran at Week 36 at the investigator's discretion because of suspected autoimmune hepatitis (AIH). ANA and SMA positivity and elevated IgG were already present at baseline, with IgG increasing from 18.3 to 23.3 g/L by Week 27. Liver biopsy showed grade 2 inflammation and stage 1 fibrosis (Batts-Ludwig), without specific findings supporting AIH. Among participants without ALT flares (n=6), mean (SD) log₁₀ HDV RNA decreased from 3.7 (2.1) at baseline to 2.4 (1.3) at Week 24 and was 3.0 (1.8) at Week 36, and mean (SD) log₁₀ HBsAg decreased from 3.0 (1.0) at baseline to 1.4 (0.5) at Week 24 and 1.6 (0.6) at Week 36.

Conclusions: Ozisiran resulted in reductions in HDV RNA and HBsAg through Week 36 in this Phase 2a trial, with a substantial proportion of the participants achieving low HBsAg levels of < 200 IU/mL. The few cases of high-grade ALT flares were successfully managed with BLV therapy.



CURRENT AND NEW ANTIVIRAL TREATMENTS

BLV IN CLINICAL TRIALS

P01 IMMUNOLOGICAL PREDICTIVE FACTORS FOR TREATMENT RESPONSE DURING BULEVIRTIDE THERAPY IN HBV-HDV COINFECTED PATIENTS

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Background: Chronic Hepatitis Delta (HDV) represents the most aggressive form of viral hepatitis, leading to accelerated liver disease progression, cirrhosis, and hepatocellular carcinoma (HCC). Active HDV replication triggers intense innate immune activation, causing persistent liver inflammation and elevated cytokine production. The entry inhibitor Bulevirtide (BLV) has been approved for the treatment of chronic HDV infection. However, validated non-invasive biomarkers to predict individual treatment responses remain limited in clinical practice. This study aimed to analyze inflammatory and pro-fibrotic cytokine profiles in HBV-HDV coinfecting patients to identify potential immunological predictors of response to BLV therapy.

Material and methods: Twenty-six consecutive patients with chronic HBV-HDV hepatitis receiving daily BLV (2 mg) were longitudinally evaluated at baseline (T0) and at weeks 4, 12, 24, and 48. A control group of 20 healthy donors was included for baseline comparisons. Biochemical, virological, and immunological parameters were assessed. Serum concentrations of IL-6, IL-8, TNF- α , CXCL10 and IFN- γ were quantified using the automated Simple Plex™ platform. Combined response at week 48 was defined as the simultaneous achievement of virological response (HDV-RNA decline ≥ 2 log₁₀ or undetectable HDV-RNA) and biochemical response (ALT normalization) according to EASL guidelines. Statistical analyses included Principal Component Analysis (PCA) and univariable logistic regression.

Results: Among the 26 patients enrolled the median age was 50 [47–59] years, most of them were female (54%) and came from Eastern European countries (73%). Most of the patients were cirrhotic (65.4%, all Child-Pugh A), 23.5% with esophageal and/or gastric varices and 1 had history of resection for HCC. At T0 median ALT levels was 88 U/L [56–113]; HDV-RNA was 4.83 log₁₀ cp/mL [3.46–5.76]. After 48 weeks of BLV therapy, 13 (50%) patients achieved a combined response, 53.8% a virological response and 65.4% a biochemical response. PCA analyses demonstrated that CXCL10, anti-HBc IgG and IFN- γ were the primary drivers discriminating responders from non-responders. Univariable logistic regression identified higher baseline CXCL10 levels as a significant predictor of combined response at week 48 (OR = 1.12 per 10-unit increase, 95% CI: 1.04–1.27, p = 0.019). Conversely, higher baseline anti-HBc IgG levels were significantly associated with lower odds of response (OR = 0.88, 95% CI: 0.79–0.96, p = 0.007) (Table 1).

Conclusions: These preliminary findings identify baseline CXCL10 as a potential predictor of response to BLV therapy. Elevated baseline CXCL10 levels characterize a subgroup of patients with an activated interferon-driven immune profile, which may be associated with a higher likelihood of treatment response. Further studies are warranted to validate CXCL10 as a non-invasive biomarker to support personalized therapeutic approaches in chronic HDV.



CURRENT AND NEW ANTIVIRAL TREATMENTS

BLV IN CLINICAL TRIALS

P02 DISCONTINUATION OF BULEVIRTIDE MONOTHERAPY IN PATIENTS WITH CHRONIC HEPATITIS D: A PROSPECTIVE MULTICENTER STUDY (D-SOLVE BUL-STOP)

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Background: For patients with chronic hepatitis D (CHD), long-term treatment with bulevirtide (BLV) is currently the recommended approach. However, preliminary findings from the pivotal MYR-301 study and limited real-world experience suggest that a finite duration of BLV therapy may be sufficient for a small subset of patients. At the same time, uncontrolled discontinuation of BLV has been associated with severe hepatitis flares and episodes of hepatic decompensation, underscoring the need for an evidence-based withdrawal strategy. The BUL-STOP study was designed to assess the safety of BLV discontinuation in carefully selected patients with CHD and to identify biomarkers predictive of sustained HDV control after treatment cessation, supporting improved patient selection and individualized treatment approaches.

Material and methods: BUL-STOP is an investigator-initiated multicenter study performed in Germany and Italy and supported by the EU-funded D-SOLVE consortium (project 10105791), and the HEP-NET Study House. Patients with CHD and compensated liver disease were eligible if they had been treated with BLV for at least 48 weeks and had achieved HDV RNA levels below 100 IU/ml for a minimum of 24 weeks. After cessation of BLV therapy, patients were monitored for up to 48 weeks, with serial biomarker assessments including fine-needle aspiration. Follow-up continued until completion of the 48-week observation period or until re-initiation of BLV treatment was deemed necessary.

Results: Twenty-one patients were enrolled. Three patients did not fulfill all inclusion criteria, resulting in a study population of 18 patients who were followed after treatment cessation (10 females, 8 males). Baseline characteristics included a median age of 57 years (range 34–75 years), a median ALT level of 26 U/L (range 14–39 U/L), and liver stiffness measurements >10.2 kPa in two patients, one of whom had a value >15.2 kPa, while all other patients had values ≤10.2 kPa. Median BLV therapy prior to treatment discontinuation was 144 weeks (range 53–250 weeks). HDV RNA was not detectable (TND) in 13/18 patients at baseline, 10/18 at week 4, 6/15 at week 12, 4/9 at week 24 and 5/8 at week 48. Three patients (17%) had persistently undetectable HDV RNA at all assessments during the 48 weeks. Ten patients (56%) were retreated with BLV or entered another clinical trial. Four patients experienced ALT elevations of more than three times ULN. No cases of hepatic decompensation were observed throughout the study period.

Conclusions: Controlled discontinuation of BLV monotherapy appears feasible in a subset of patients with CHD, suggesting that finite treatment may be achievable in carefully selected individuals. Nevertheless, relapse following treatment withdrawal can be associated with hepatitis flares and may require prompt re-initiation of therapy. Further biomarker analyses aim to identify predictors of sustained HDV control after BLV discontinuation.



CURRENT AND NEW ANTIVIRAL TREATMENTS

BLV IN CLINICAL TRIALS

P03 INTEGRATED EFFICACY ANALYSIS BY HDV AND HBV GENOTYPES IN PATIENTS WITH CHRONIC HEPATITIS DELTA RECEIVING BULEVIRTIDE

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Background: The 8 hepatitis delta virus (HDV) genotypes (GT1–8) and 8 hepatitis B virus (HBV) GT (A–H) have distinct geographical distributions, with HDV GT1 and HBV GTD being the most prevalent globally. Based on its efficacy and safety profile in clinical trials, bulevirtide (BLV), a first-in-class entry inhibitor, is approved in the US, EU and other regions for treatment of patients (pts) with chronic hepatitis delta. This analysis evaluated the efficacy of BLV by HDV and HBV GT.

Material and methods: Data were included from pts in the phase 3 MYR301 (NCT03852719) and phase 2 MYR204 (NCT03852433) studies through Week (W) 96 receiving BLV 10 mg alone, or (MYR204 only) with pegylated interferon alfa-2a (PegIFN) for the first 48 weeks (wks). Efficacy assessments included virologic response (VR; undetectable HDV RNA [uHDV] or ≥ 2 log₁₀ IU/mL decline in HDV RNA from baseline [BL]), alanine aminotransferase (ALT) normalisation, uHDV and HDV RNA change from baseline.

Results: For BLV 10 mg, 129 (86%) pts had HBV GTD, 12 (8%) HBV GTA and 9 (6%) HBV GT other (Table 1). BL characteristics were similar between GTD, GTA and GT other: cirrhosis was present in 41%, 50% and 67%; mean (SD) HDV RNA was 5.1 (1.4), 5.7 (1.5) and 5.6 (0.9) log₁₀ IU/mL; mean (SD) ALT was 108 (89), 109 (68) and 106 (46) U/L, respectively. GT distribution and BL characteristics were similar between treatment groups. As $\geq 94\%$ of pts per group had HDV GT1, results by HDV GT are not presented.

In the BLV 10 mg group, ALT normalisation at W48 was similar by HBV GT (GTD: 57%; GTA: 42%) and maintained through W96 (GTD: 61%; GTA: 58%); similar results were observed for the BLV + PegIFN HBV GT groups at W48, and W96 rates increased for GTD and were maintained for GTA.

For BLV 10 mg, HBV GTD had higher VR and uHDV rates vs. HBV GTA at W48 (VR: 88% vs. 17%; uHDV: 20% vs. 8%); through W96, VR rates were maintained for HBV GTD and increased for HBV GTA (87% vs. 50%). Mean change from BL in HDV RNA (log₁₀ IU/mL) at W48 had larger declines for HBV GTD vs. GTA (−3.4 vs. −1.3) and through W96, both GT continued to decline (−3.9 vs. −2.0). For BLV 10 mg + PegIFN, VR and uHDV rates at W48 were similar between HBV GT. Rates at W96 were maintained or increased for GTD and maintained for GTA.

Conclusions: BLV had long-term efficacy over 96 wks across HDV and HBV GT, consistent with overall trial results; however, a limitation was the small size of the cohort with HBV GTA. ALT normalisation was similar across GT, suggesting BLV effectiveness in preventing new hepatocyte infection and necroinflammation. Faster virologic declines with HBV GTD vs. GTA for BLV alone may be due to differences in cell turnover kinetics between HBV GT, as no differences in BLV activity have been observed due to its mechanism of action in binding the host NTCP receptor. Addition of PegIFN may lead to more rapid clearance of infected cells regardless of HBV GT.



CURRENT AND NEW ANTIVIRAL TREATMENTS

BLV IN CLINICAL TRIALS

P04 LONG-TERM TREATMENT WITH BULEVIRTIDE 2 MG IMPROVES FATIGUE SEVERITY SCALE SCORES IN PATIENTS WITH CHRONIC HEPATITIS DELTA VIRUS: RESULTS FROM AN EXPLORATORY ANALYSIS OF THE PHASE 3 MYR301 TRIAL

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Background: Infection with hepatitis delta virus increases the risk of developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma. In MYR301, a Phase 3, randomised, multicentre, open-label study, bulevirtide (BLV) monotherapy improved health-related quality of life in patients with chronic hepatitis delta (CHD) at 24 and 48 weeks vs untreated patients. Here, we present results of an exploratory analysis of patient-reported outcomes (PROs) from MYR301, assessed using the Fatigue Severity Scale (FSS) at baseline and week 144.

Material and methods: Adult patients with CHD and compensated liver disease were enrolled in the Phase 3 MYR301 study; details of the study design have been previously published. In this analysis, we report results from patients receiving BLV 2 mg. Fatigue was assessed using the FSS, a 9-item PRO measure with scores ranging from 1 to 7, where higher scores indicate greater fatigue severity. Patients completed the questionnaire on their own at prespecified time points, including baseline, week 96, and week 144. The clinical threshold of ≥ 0.7 points was applied to consider a minimum clinically important difference (MCID) in fatigue. Mixed-effects models for repeated measures were used to calculate least-squares means (LSM) and 95% CIs in the analysis of change from baseline. A subgroup analysis of patients by liver cirrhosis was performed.

Results: Patients were mostly male (61%) and White (84%), with a mean (SD) age of 44 (9.0) years; 47% had cirrhosis at baseline. Mean (95% CI) FSS scores decreased from 3.6 (3.18, 4.09) at baseline to 2.6 (2.25, 3.04) at week 144, and patients receiving BLV achieved a statistically significant LSM (95% CI) change from baseline in FSS score of -1.0 (-1.55 , -0.49 ; $P < .001$; Figure 1). In addition, patients with and without cirrhosis had significantly reduced LSM FSS scores at week 144. In patients with cirrhosis, the LSM (95% CI) change from baseline to week 144 in FSS score was -1.3 (-1.88 , -0.76 ; $P < .001$); in patients without cirrhosis, the LSM change from baseline (95% CI) to week 144 in FSS score was -1.0 (-1.71 , -0.34 ; $P = .004$; Figure 1). Of note, LSM FSS scores surpassed the MCID threshold.

Conclusions: Overall, patients with CHD treated with BLV for 144 weeks experienced clinically significant improvements in fatigue scores, regardless of cirrhosis status.



CURRENT AND NEW ANTIVIRAL TREATMENTS

BLV IN CLINICAL TRIALS

P05 NO IMPACT OF ANTIDRUG ANTIBODIES ON THE EFFICACY OF BULEVIRTIDE IN CHRONIC HEPATITIS DELTA: INSIGHTS FROM A 96-WEEK INTEGRATED ANALYSIS

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Background: Antidrug antibodies (ADAs) may affect the efficacy of biologic therapies. For bulevirtide (BLV), which is approved for the treatment of chronic hepatitis delta, the clinical relevance of ADA development remains incompletely characterised. This integrated analysis assessed efficacy outcomes by ADA status in patients receiving BLV monotherapy.

Materials and Methods: To increase sample size, data were pooled across BLV dose groups and across the MYR301 (NCT03852719) and MYR204 (NCT03852433) studies; pooling across dose groups was supported by similar ADA incidence between the BLV 2 mg and 10 mg groups. The analysis included patients who received subcutaneous BLV 2 mg or 10 mg once daily as monotherapy for 96 weeks and had ≥ 1 postbaseline ADA result. Treatment-emergent ADA positivity (ADA+) was defined as ADA negative or missing at baseline with postbaseline presence of ADAs, or baseline presence of ADAs with a ≥ 4 -fold postbaseline titre increase. ADA incidence was assessed using a 3-tiered electrochemiluminescence assay. Week 96 efficacy outcomes included virologic response (undetectable hepatitis delta virus [HDV] RNA or ≥ 2 log₁₀ IU/mL decline), undetectable HDV RNA, biochemical response (alanine aminotransferase normalisation), combined response (virologic plus biochemical response), and change from baseline in liver stiffness. For efficacy, the missing-equals-failure approach was used; for change from baseline in liver stiffness, the missing values remained missing.

Results: Overall, the pooled BLV monotherapy population across dose groups and studies was 199 patients, of which 13 had presence of ADAs at baseline; 197 had postbaseline data and were included in this analysis. Treatment-emergent ADAs developed in 69% (135/197) of patients through Week 96. At Week 96, efficacy outcomes were broadly similar by ADA status. Combined response was achieved by 50% of ADA+ patients vs 63% of ADA- patients, virologic response by 82% vs 81%, biochemical response by 56% vs 74%, and undetectable HDV RNA by 33% vs 32%, respectively. Mean change from baseline in liver stiffness was similar between ADA+ and ADA- patients (-4.3 vs -4.0 kPa). ADA onset generally occurred by Week 16, with maximum ADA titres observed by Week 24, and declined thereafter through 96 weeks.

Conclusions: In this pooled Week 96 analysis of patients receiving BLV monotherapy, ADA development was not associated with a clinically meaningful reduction in efficacy outcomes. These findings support sustained BLV efficacy regardless of ADA status.



CURRENT AND NEW ANTIVIRAL TREATMENTS

LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

P06 PREGNANCY OUTCOMES FOLLOWING BULEVIRTIDE EXPOSURE DURING PREGNANCY: AN ANALYSIS OF CLINICAL TRIAL AND POSTMARKETING DATA

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Background: Bulevirtide (BLV), a first-in-class entry inhibitor, is approved in the European Union (EU), United States (US) and other regions for the treatment of chronic hepatitis delta. No data have been previously published on pregnancy outcomes following BLV exposure during pregnancy. Nonclinical studies in rats and rabbits have shown no effect of BLV on embryofetal development, fertility and pre- and postnatal development at exposure margins of 4- and 37-fold, respectively, relative to exposures at the highest dose studied in humans. This analysis characterises pregnancy outcomes following BLV exposure during pregnancy, based on data from clinical trials and postmarketing BLV exposure of around 14,000 patient-years in Europe and other regions.

Material and methods: A search of the Gilead global safety database (containing cases from clinical trials, managed access programs and postmarketing spontaneous and solicited cases) was performed to identify BLV 2 mg pregnancy cases cumulative to 20 February 2026.

Results: Twenty-six BLV pregnancy cases were identified. Five of these cases (3 from Phase 2 study MYR204, 2 from Phase 3 study MYR301) were excluded from the analysis, as 1 participant was never dosed with BLV, and 4 participants became pregnant in the posttreatment period (at least 10 weeks to 8 months post-BLV) with no maternal exposure to BLV (terminal plasma half-life is 3–4 hours). Of the remaining 21 cases where patients were exposed to BLV during pregnancy, 19 were from the postmarketing setting (including 1 case from a Registry Study 6206), and 1 each were from Study MYR301 and a pre-approval compassionate use program. Seventeen pregnancy cases were prospectively reported and 4 were retrospectively reported. Of the 17 prospective pregnancy cases, pregnancy outcome was reported in 4 cases: 2 live births, 1 induced abortion and 1 spontaneous abortion; all 4 cases involved first trimester exposure to BLV with no reported congenital anomalies. Pregnancy outcome was unknown in 13 prospective cases (7 with first trimester exposure, 6 with unknown trimester of exposure). Of the 4 retrospective pregnancy cases, there were 2 live births and 2 induced abortions; no congenital anomalies were reported. Three cases had first trimester exposure to BLV; 1 had unknown trimester of exposure.

Conclusions: While the number of pregnant women exposed to BLV in clinical studies and the postmarketing setting is limited, review of the 21 cases with BLV exposure during pregnancy in this analysis found no safety signals for pregnancy outcomes, which is consistent with the absence of reproductive safety concerns with BLV in nonclinical studies.



CURRENT AND NEW ANTIVIRAL TREATMENTS

LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

P07 BULEVIRTIDE MONOTHERAPY PREVENTS LIVER DECOMPENSATION BUT NOT HCC IN PATIENTS WITH HDV-RELATED CIRRHOSIS: 3-YEAR RESULTS FROM AN INVERSE PROBABILITY-WEIGHTED EUROPEAN CASE-CONTROLLED STUDY

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Background and aims: While Bulevirtide (BLV) monotherapy induces strong virological and biochemical responses in



chronic hepatitis delta (CHD), its impact on hard clinical outcomes remains poorly characterized. **Methods:** This retrospective European cohort study included consecutive CHD patients with cirrhosis treated with BLV monotherapy for up to 3 years. BLV-treated patients were compared against pooled historical data from two BLV-untreated cohorts. The primary endpoint was the 3-year incidence of de novo liver-related events (LREs), defined as decompensation and hepatocellular carcinoma (HCC). Risk-adjusted analyses were performed using inverse probability of treatment weighting (IPTW), Cox proportional hazards regression, and competing risks models.

Results: A total of 642 patients were evaluated: 344 BLV-treated and 298 untreated controls. At baseline, BLV-treated patients were significantly older (50 vs. 40 years, $p < 0.0001$), more frequently female (38% vs. 22%, $p = 0.001$), Caucasian (84% vs. 62%, $p < 0.0001$), on nucleos(t)ide analogues (91% vs. 40%, $p < 0.0001$), and had higher baseline HDV RNA (5.4 vs. 4.9 Log₁₀ IU/mL, $p = 0.002$). Rates of baseline clinically significant portal hypertension, previous decompensation, and HCC were balanced between groups.

The 3-year cumulative incidence of LREs was significantly lower in the BLV-treated cohort compared to untreated controls: 8.9% (95% CI 4–12%) vs. 16.2% (95% CI 11–22%), respectively ($p = 0.03$). These figures were driven by a reduction in clinical decompensation (2.7% [95% CI 1–4%] vs. 11.3% [95% CI 7–16%], $p = 0.001$), whereas the 3-year cumulative incidence of HCC remained similar between cohorts (6.1% [95% CI 3–8%] vs. 6.6% [95% CI 3–11%], $p = 0.49$).

In the IPTW-adjusted Cox regression analysis, BLV treatment was associated with a significantly lower risk of overall LREs (HR 0.44, 95% CI 0.27–0.72, $p = 0.001$) and decompensation (HR 0.16, 95% CI 0.07–0.36, $p < 0.0001$). These findings were confirmed by an IPTW-adjusted competing risks regression model (SHR 0.16, 95% CI 0.06–0.40, $p < 0.0001$). No difference in HCC risk was observed. Lower baseline albumin levels independently predicted LRE development in both the BLV group (HR 0.22, $p = 0.006$) and the untreated group (HR 0.38, $p = 0.002$). BLV exhibited a favorable safety profile; the most common adverse events were mild pruritus (10%) and injection site reactions (3%).

Conclusions: In CHD patients with cirrhosis, 3 years of Bulevirtide monotherapy significantly reduced the risk of decompensation, but not of HCC compared to an IPTW-matched untreated population.



CURRENT AND NEW ANTIVIRAL TREATMENTS

LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

P08 LONG-TERM CLINICAL AND VIROLOGICAL OUTCOMES OF BULEVIRTIDE MONOTHERAPY UP TO 4 YEARS IN CHD PATIENTS WITH CIRRHOSIS: THE SAVE-D STUDY

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Background and Aim: Bulevirtide (BLV) is EMA and FDA-approved for chronic hepatitis Delta (CHD); however, data regarding long-term clinical and virological outcomes in patients with cirrhosis remain limited. This study evaluated the long-term efficacy, safety, and clinical events in CHD patients with cirrhosis treated with BLV within a large, real-world cohort.

Methods: We analyzed CHD patients with cirrhosis receiving BLV 2 mg/day monotherapy from the multicenter SAVE-D study (65 centers). Endpoints included virological response (VR: undetectable HDV RNA or ≥ 2 Log₁₀ decline from baseline), biochemical response (BR: ALT <40 U/L), combined response (CR: VR + BR), virological breakthroughs (VBK: ≥ 1 Log₁₀ HDV RNA increase from nadir), and de novo liver-related events (LREs). Clinically significant portal hypertension (CSPH) was defined using Baveno VII criteria.

Results: The study included 424 patients treated with BLV for up to 192 weeks (W). At baseline, median age was 50 years, 61% men, ALT 78 (51-128) U/L, liver stiffness measurement (LSM) 16.5 (12.6-25.3) kPa, platelets 101 (68-149) x10⁹/L, 96% CPT score A, 51% with varices, 9% with previous decompensation, 90% on NUC. Baseline HDV-RNA was 5.4 (4.2-6.3) Log₁₀ IU/mL and qHBsAg 3.7 (3.2-4.1) Log₁₀ IU/mL. At week 144, rates of VR, BR, CR, and undetectable HDV RNA were 73%, 69%, 54%, and 35%, respectively. In the subgroup of 59 patients with week 192 data, the corresponding figures were 79%, 71%, 59%, and 41%, respectively. Patients with <1 Log₁₀ HDV RNA decline vs. baseline decreased from 20% at week 48 to 14% at week 144. VBK occurred in 7% of patients between weeks 48–96 (77% with normal ALT) and in 9% between weeks 96–144 (70% with normal ALT). Non-invasive Baveno VII criteria for CSPH showed an improvement in up to 40% of patients. During follow-up, 29 patients developed an LRE (9 decompensation, 20 HCC), corresponding to a 3-year cumulative incidence of 2.3% (95% CI 1–4%) for decompensation and 6.8% (95% CI 3–9%) for HCC. Lower baseline albumin independently predicted decompensation, whereas older age, higher BMI, and lower albumin predicted HCC development. Eight patients underwent liver transplantation (6 for HCC, 2 for decompensation) and 5 patients died (3 due to LREs). Treatment retention was high, with 93% remaining on therapy; 30 patients discontinued BLV (7 transitioned to IFN add-on, 2 due to skin allergy, 2 due to decompensation, 3 with undetectable HDV RNA, 3 due to non-compliance, 2 due to non-response, 2 entered clinical trials, 1 achieved HBsAg loss) and 8 were lost to follow-up.

Conclusions: In CHD patients with cirrhosis, long-term BLV monotherapy up to 192 weeks demonstrated sustained safety and effectiveness. Rates of de novo liver-related events remained low, especially liver decompensation.



CURRENT AND NEW ANTIVIRAL TREATMENTS

LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

P09 CHARACTERIZATION OF VIROLOGICAL BREAKTHROUGHS UNDER BULEVIRTIDE MONOTHERAPY: COMBINED DATA FROM THE SAVE-D AND D-SHIELD COHORTS

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Background and aim: Bulevirtide (BLV) 2 mg/day is approved for the treatment of chronic hepatitis Delta (CHD), but real-world data on virological breakthroughs (VBK) during long-term BLV monotherapy remain scarce. This study assessed the incidence, timing, and clinical outcomes of VBK during BLV monotherapy using data from two large, multicenter, real-life cohorts (SAVE-D and D-SHIELD).

Methods: We analyzed CHD patients from the retrospective/prospective SAVE-D and D-SHIELD studies who received BLV 2 mg/day monotherapy and had complete, paired data from baseline up to weeks 24, 48, 72, or 96. VBK was defined as a confirmed increase in HDV RNA of ≥ 1 Log10 from the lowest previous value (nadir). Virological response (VR: undetectable HDV RNA or ≥ 2 Log10 decline vs. baseline), biochemical response (BR: ALT < 40 U/L), combined response (CR: VR + BR), HDV RNA undetectability, and liver-related events were also assessed.

Results: Among 900 CHD patients enrolled, 276 patients with complete baseline-to-week 72 data (including 111 with week 96 data) were analyzed. At baseline, median age was 52 years, 55% were male, 73% had cirrhosis, median ALT 81 (45-144) U/L, liver stiffness measurement (LSM) 14.0 (6.1-25.0) kPa, HBsAg 3.7 (3.2-4.2) Log10IU/mL, and



median HDV RNA was 5.3 Log₁₀ IU/mL. At week 48, rates for VR, BR, CR, and undetectable HDV RNA were 68%, 67%, 52%, and 28%, respectively; at week 96, the corresponding figures were 68%, 65%, 50%, and 38%. VBK occurred in 15 patients (5%) at week 48, 24 (9%) at week 72, and 8 (3%) at week 96. At the time of VBK, biochemical response was preserved in 7/15 (47%) patients at week 48, 10/24 (42%) at week 72, and 7/8 (87%) at week 96. The onset of VBK was not significantly influenced by baseline ALT ($p=0.08$), HDV RNA ($p=0.72$), or cirrhosis status ($p=0.15$). VBK persisted across two consecutive timepoints in 7 patients (15%), while it was transient and resolved spontaneously in the remaining cases. No patients experiencing a VBK developed de-novo liver-related events.

Conclusions: Virological breakthroughs occurred in 17% of CHD patients treated with BLV 2 mg/day monotherapy up to 96 weeks. However, the majority of VBK were transient and did not cause ALT elevations.



CURRENT AND NEW ANTIVIRAL TREATMENTS

LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

P10 BULEVIRTIDE PROVIDES COMPARABLE VIROLOGICAL CONTROL REGARDLESS OF CIRRHOSIS STATUS: ANALYSIS OF TREATMENT RESPONSE AND BREAKTHROUGHS FROM THE D-SHIELD MULTICENTER PROSPECTIVE STUDY

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Background: Whether compensated cirrhosis influences the durability of antiviral response during bulevirtide (BLV) therapy remains uncertain. We evaluated the impact of cirrhosis status on treatment outcomes during BLV monotherapy in the prospective multicenter D-SHIELD study.

Methods: Consecutive patients with chronic hepatitis delta initiating BLV monotherapy (2 mg/day) were prospectively enrolled across 46 Italian centers. Clinical, virological and biochemical assessments were performed at baseline and every three months thereafter. Virological response (VR) was defined as a ≥ 2 log IU/mL decline in HDV RNA from baseline or undetectable HDV RNA. Biochemical response (BR), combined response (CR), virological breakthrough (VBK; >1 log IU/mL increase in HDV RNA from the previous visit), biochemical breakthrough (BKK; ALT increase $>1.5\times$ from nadir in patients without BR, or loss of BR with ALT $>1.5\times$ ULN in patients previously achieving BR), and safety were compared according to cirrhosis status.

Results: Among 501 patients receiving BLV monotherapy, 358 (72%) had compensated cirrhosis and 142 did not. At



baseline, patients with cirrhosis were older, more frequently receiving nucleos(t)ide analogues, and had higher liver stiffness but lower platelet count, HBsAg and HDV RNA levels than non-cirrhotic patients. Response rates increased steadily during treatment in both groups without significant differences at any study visit. At week 96, BR was achieved in 70% versus 69% ($p=1.00$), VR in 75% versus 83% ($p=0.72$), and CR in 61% versus 58% ($p=0.85$) among patients with and without cirrhosis, respectively. HDV RNA undetectability differed only at week 72 (32% vs. 12%, $p=0.005$), with no significant differences at the remaining time points. Overall, 46 patients (9.2%) experienced a VBK, predominantly between weeks 48 and 72 (80%), with identical incidence according to cirrhosis status (9.2% vs. 9.1%, $p=1.00$); among patients with available follow-up, 44% remained persistent VBK through week 96. Fourteen patients (2.8%) developed a BKK, again without differences between cirrhotic and non-cirrhotic individuals (3.5% vs. 2.5%, $p=0.55$). Most BKKs occurred between weeks 48 and 72 (75%), and 25% persisted until week 96. 8 patients experienced both virological and biochemical breakthroughs. The frequency of adverse events was identical in both groups (15% vs. 15%, $p=1.00$), with transient pruritus and injection-site reactions representing the most common treatment-related events. As expected, serum bile acid concentrations remained consistently higher in patients with cirrhosis throughout follow-up ($p<0.001$ at all time points).

Conclusions: In this large prospective real-world cohort, compensated cirrhosis did not adversely affect the efficacy, durability of virological and biochemical responses, or safety of Bulevirtide monotherapy. These findings support the use of BLV across the spectrum of compensated CHD, irrespective of cirrhosis status.



CURRENT AND NEW ANTIVIRAL TREATMENTS

LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

P11 EARLY GAMMA-GLUTAMYL TRANSFERASE DECLINE MIRRORS VIROLOGICAL RESPONSE DURING BULEVIRTIDE THERAPY IN CHRONIC HEPATITIS D: A REAL-WORLD LONGITUDINAL STUDY

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Background: Monitoring treatment response in chronic hepatitis D (CHD) relies primarily on serial HDV-RNA measurements, which may not always be readily available in clinical practice. Accessible biochemical surrogate markers of antiviral efficacy remain a still unmet goal. While baseline gamma-glutamyl transferase (GGT) has been associated with biochemical response to bulevirtide (BLV) in real-world cohorts, on-treatment GGT kinetics as a correlate of virological response has not been properly characterized. We evaluated longitudinal changes in biochemical markers during BLV therapy and their correlation with virological response in a real-world CHD cohort.

Methods: Retrospective single-centre study of consecutive CHD patients treated with BLV. GGT, alkaline phosphatase (ALP) and aminotransferases were assessed at baseline, 6, 12 and 24 months. The relationship between absolute GGT and ALP decline and log₁₀ HDV-RNA reduction at 6 months was evaluated by Spearman's correlation. Longitudinal GGT changes were analysed using a linear mixed-effects model including time, virological response (VR) and their interaction.

Results: Fourteen patients were included. Median GGT declined from 49 U/L at baseline to 28.5 U/L at 6 months and 28 U/L at 12 months; among patients completing 24 months (n=7), median GGT reached 20 U/L (>50% overall reduction) (Figure 1). Absolute GGT decline showed a strong positive correlation with log₁₀ HDV-RNA reduction at 6 months (Spearman's $\rho=0.906$, $p<0.001$), suggesting early biochemical improvement closely mirrors antiviral efficacy (Figure 2). Individual GGT trajectories are shown in Figure 3. Aminotransferases declined in virological responders, consistently with previously reported real-world data. ALP changes did not correlate with virological response in the overall cohort, likely reflecting the lower specificity of this marker for hepatic necroinflammatory activity. Mixed-effects analysis confirmed a significant GGT decline over time ($\beta=-1.21$ U/L/month, $p=0.004$); no significant time-by-response interaction was observed, likely due to the limited number of non-responders.

Conclusions: BLV therapy was associated with an early, constant and progressive GGT reduction closely mirroring virological response. On-treatment GGT kinetics may represent a practical and accessible monitoring option in clinical settings where serial HDV-RNA testing is not readily available, supporting a dynamic on-treatment role rather than a prognostic one. However, clinicians should exercise caution in interpreting GGT trends in the presence of concurrent conditions independently affecting liver enzyme levels, such as alcohol use or hepatotoxic co-exposures, which may confound its reliability as a surrogate of antiviral efficacy. Larger prospective studies are needed to confirm these preliminary observations.



CURRENT AND NEW ANTIVIRAL TREATMENTS

LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

P12 IMPROVEMENT OF NON-INVASIVE FIBROSIS TESTS AND CLINICALLY SIGNIFICANT PORTAL HYPERTENSION ACCORDING TO BAVENO VII CRITERIA DURING BULEVIRTIDE MONOTHERAPY IN PATIENTS WITH HDV-RELATED CIRRHOSIS: A LONGITUDINAL ANALYSIS OF THE SAVE-D STUDY

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Background: Non-invasive tests (NITs) of liver fibrosis are established predictors of clinical outcomes and surrogate tools to assess clinically significant portal hypertension (CSPH), however data specifically in chronic hepatitis Delta (CHD) are limited. This real-world study aimed to investigate the role and dynamic changes of NITs and CSPH in patients with CHD and cirrhosis treated with Bulevirtide (BLV) monotherapy.

Methods: CHD patients with compensated cirrhosis (and no history of decompensation) enrolled in the SAVE-D study and treated with BLV 2 mg/day were analyzed. Liver stiffness measurement (LSM), APRI, and FIB-4 were assessed at baseline and on-treatment. CSPH risk was stratified according to Baveno VII criteria: rule-out (LSM ≤ 15 kPa + PLT ≥ 150 10⁹/L), rule-in (LSM > 25 kPa), and grey zone (all other patients).

Results: 348 patients treated with BLV for up to 144 weeks were included. At baseline (BLV start), median age was 49 (IQR 40-58) years, 62% men, ALT 80 (51-128) U/L, PLT 112 (76-154) 10⁹/L, 46% with varices, LSM 16.3 (12.5-24.7) kPa, APRI 1.8 (1.1-3.8), FIB-4 3.6 (2.1-6.0), HDV-RNA 5.4 (4.2-6.3) Log₁₀ IU/mL. At baseline, 84/348 (24%) patients fulfilled the Baveno VII rule-in criteria, 58 (17%) the rule-out and 206 (59%) were in the grey zone. During 144 weeks of BLV, all NITs significantly declined: LSM to 13.5 kPa (W48) vs. 11.3 (W96) vs. 12.0 (W144); APRI 0.9 vs. 0.8 vs. 1.0; FIB-4 2.7 vs. 2.6 vs. 3.3 ($p < 0.01$ for all comparisons vs. baseline). A $> 30\%$ LSM decline was observed in 35% (W48), 46% (W96) and 51% (W144) of patients; the corresponding figures were 69%, 76%, 75% (APRI) and 34%, 44%, 49% (FIB-4), respectively. Paired data analysis showed improvements in CSPH risk categories: at W48 ($n=158$), 50% (18/36) of baseline rule-in patients improved to rule-out (8%) or grey zone (42%); 12% in the grey zone shifted to rule-out, while 5% worsened to rule-in. At W96 ($n=96$), 63% (15/24) of baseline rule-in patients improved (rule-out 13%, grey zone 50%); 9% in the grey zone worsened to rule-in. At W144 ($n=70$), 67% (12/18) of baseline rule-in patients improved (rule-out 11%, grey zone 56%); 4/44 (9%) in the grey zone worsened to rule-in. None of the 52 baseline rule-out patients with available paired data worsened to rule-in throughout 144 weeks. Between BLV week 48 and 144, 10 de-novo liver-related events (LREs) occurred (6 HCC and 4 decompensations): all except one patient who developed LREs were in the baseline CSPH rule-in ($n=4$) or grey zone ($n=5$) categories, while the only rule-out patient developed HCC. No patient with CSPH improvement at W48 developed LREs afterwards. NIT values at BLV start, but not at W48, predicted LREs.

Conclusions: In a real-world cohort of CHD patients with cirrhosis receiving BLV monotherapy up to 144 weeks, NITs and CSPH categories improved, mainly during the first 48 weeks of therapy. Except for a single case of HCC, no LREs occurred in the CSPH rule-out category.



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P13 BULEVIRTIDE DISCONTINUATION AFTER LONG-TERM HDV RNA SUPPRESSION IN PATIENTS WITH CHD: IMPACT OF DIFFERENT HDV RNA ASSAYS ON PATIENT SELECTION AND VIROLOGICAL OUTCOMES (ROBOGENE 2.0 VS. ALTOSTAR 1.5)

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Background and Aim: Prolonged HDV RNA undetectability during bulevirtide (BLV) monotherapy may identify patients who can maintain negative viremia after withdrawal. However, HDV RNA undetectability is assay-dependent, and stopping data were generated with Robogene 2.0. We evaluated if patients' selection and virological outcomes after BLV withdrawal could be affected by the assay.

Methods: In this retrospective single center study, we evaluated patients with CHD discontinuing BLV after achieving long-term virological suppression by Robogene HDV RNA Quantification Kit 2.0 (Roboscreen GmbH; lower limit of detection [LOD] 6 IU/mL). Stored samples were subsequently re-tested with AltoStar HDV RT-PCR RUO Kit 1.5 (Altona Diagnostics GmbH; LOD 1.1 IU/mL, lower limit of quantification [LLOQ] 20 IU/mL). Patients were followed for up to 48 weeks after BLV stop.

Results: 10 patients (80% with cirrhosis, of whom 40% with CSPH and 13% with previous HCC) discontinued BLV monotherapy after 34 (IQR 23–47) months: 7 (70%) had HDV RNA TND with Robogene 2.0, 3 (30%) < LOD. Table 1 shows HDV RNA in the 18 months prior BLV discontinuation. During 48 weeks of post BLV follow-up, 3 patients experienced a virological and biochemical rebound (pt 1 at wk8: HDV RNA 499 IU/mL and ALT 69 U/ml; pt3 at wk12: HDV RNA 74,833 and ALT 470 U/L, pt 8 at wk12: HDV RNA 315 IU/mL and ALT 79 U/L), and 3 patients had a virological rebound only (pt 2 at wk8: HDV RNA 4,925 IU/mL; pt 9 wk24 HDV RNA 119 U/L, pt 10 wk8 HDV RNA 207 U/L). The first 3 patients rapidly responded to BLV retreatment, for the last 3 no follow-up is available yet (Figure 1). Pt 5 experienced a transient virological rebound at wk24 (HDV RNA 399 IU/mL) followed by HDV RNA < LOD at wk 36 and HDV RNA TND at wk48. In the remaining 3 (30%) patients, HDV RNA remained TND and ALT < ULN up to 48 weeks of follow-up (Figure 1). 3/4 of patients with sustained off-therapy virological response (SVR) had >18 months on-therapy HDV RNA TND/< LOD by Robogene 2.0, all 4 12 months of HDV RNA TND (Table 1). When samples were retested by AltoStar 1.5 assay, 3/7 (43%) patients classified as HDV RNA TND by Robogene 2.0 at BLV discontinuation showed detectable residual viremia with AltoStar 1.5 (3–25 IU/mL), while 2/3 HDV RNA < LOD with Robogene 2.0 tested >LOD with AltoStar 1.5 (20 and 25 IU/mL). 5/6 patients with HDV rebound had HDV RNA >LOD at BLV stop with AltoStar 1.5, 4/6 6 months before, all 6 had it 12 months before BLV stop, 5/6 18 months before. Among 4 SVR patients by Robogene 2.0, one (pt 7) had HDV RNA TND 18 months before BLV stop, another (pt 6) from 12 months before, 2 (pt 4 and 5) 6 months before (Table 1).

Conclusions: BLV discontinuation may be feasible after prolonged virological suppression in selected patients, even with advanced liver disease. However, assay-dependent detection of low-level HDV RNA may influence patient selection and relapse-risk assessment.



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P14 INTEGRATED PHARMACOGENETIC, PHARMACOKINETIC, AND CLINICAL EVALUATION OF BULEVIRTIDE IN PATIENTS WITH CHRONIC HEPATITIS D

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Background: Bulevirdide is the first approved entry inhibitor for HDV treatment. Its antiviral activity is mediated through inhibition of the sodium taurocholate co-transporting polypeptide (NTCP), thereby preventing viral entry into hepatocytes. To date, data on the variability of bulevirdide plasma concentrations and the contribution of host genetic polymorphisms remain limited. This study aimed to characterize bulevirdide plasma concentrations together with biochemical and virological parameters over the course of treatment, and to investigate the potential influence of NTCP genetic variants on therapeutic outcomes, with particular emphasis on virological and biochemical responses at week 60 (W60).

Materials and methods: Patients receiving bulevirdide were enrolled. Bulevirdide plasma concentrations, together with biochemical and virological parameters, were assessed at baseline and at weeks (W) 4, 12, 24, 36, 48, and 60 using liquid chromatography. Two NTCP single nucleotide polymorphisms, rs8011311 and rs2296651, were genotyped using PCR-based methods.

Results: Seventeen patients were initially enrolled, of whom five were excluded because of incomplete follow-up and poor treatment adherence. The final analysis included 12 patients, 75% of whom were male. The median age was 51.5 years, the median body mass index (BMI) was 24.5 kg/m², and cirrhosis was present in 50% of the cohort. At baseline, the median alanine aminotransferase (ALT) level was 80.5 IU/L and the median HDV RNA was 5.3 log. Liver stiffness significantly declined at week 48 compared with baseline ($p = 0.041$). Lipid profiles remained unchanged throughout treatment, whereas bile acid levels showed a slight but non-significant increase. No treatment-related adverse events were observed. At week 60 (W60), virological, biochemical, and combined responses were achieved in 4 (33.3%), 4 (33.3%), and 3 (25.0%) patients, respectively. Median bulevirdide plasma concentrations were 0.4 ng/mL (IQR, 0.3–0.5) at W4, 0.9 ng/mL (IQR, 0.4–1.9) at W12, 0.6 ng/mL (IQR, 0.3–1.6) at W24, 1.0 ng/mL (IQR, 0.5–1.3) at W36, 1.2 ng/mL (IQR, 0.5–7.2) at W48, and 0.7 ng/mL (IQR, 0.3–2.1) at W60. Concomitant medications were not associated with significant differences in bulevirdide exposure. In contrast, patients with liver stiffness values >12 kPa exhibited significantly different plasma drug concentrations, particularly at W12 ($p=0.026$). Pharmacogenetic analysis showed that carriers of the NTCP rs8011311GC/CC genotype had significantly lower bulevirdide plasma concentrations than patients with the GG genotype at W4 ($p=0.047$).

Conclusions: This exploratory study characterizes bulevirdide plasma concentrations during 60 weeks of treatment, evaluating the potential influence of host genetic variability, despite the limited sample size. These preliminary findings provide a basis for future larger-scale studies aimed at clarifying the pharmacokinetic and pharmacogenetic determinants of bulevirdide exposure.



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P15 VIRAL KINETICS MODELLING OF INITIAL AND RETREATMENT IN HDV PATIENTS UNDER BULEVIRTIDE MONOTHERAPY

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Background: Bulevirtide (BLV) was recently approved in the United States for the treatment of chronic hepatitis D. We used mathematical modelling to compare changes in HDV-RNA, qHBsAg and ALT levels during initial BLV treatment in the MYR 301 trial to those measured during subsequent BLV retreatment.

Methods: 15 patients received initial treatment with 144 weeks of BLV (2 mg/d, n=3; 10 mg/d, n=12) as part of the MYR-301 trial. After a median of 28 weeks (range: 6-64) from completion of initial treatment, patients were retreated with BLV 2mg/d for 48 weeks. HDV RNA, ALT, and qHBsAg were measured every 8 weeks. The recent model by Mhlanga/Shekhtman et al. (Antiviral Res. 2026 Jul 17:106489) was used to fit initial and retreatment data. The model includes HDV-infected cells, serum ALT and HDV virions dynamics in blood, and HDV-free target cells (HBsAg producing cells).

Results: Twelve patients (80%) had a similar HDV decline under both treatments (Fig. 1A), one patient responded only to retreatment (Fig. 1B), one patient had a breakthrough under both treatments at around 24 weeks of therapy (Fig. 1C), and one patient responded to initial treatment but had a breakthrough after 24 weeks of retreatment. ALT levels normalized during initial treatment and also declined under retreatment. Pretreatment viral load V_0 was 5.6 ± 1.0 log IU/ml at start of initial treatment and 5.3 ± 1.8 log IU/ml at start of retreatment. Despite similar decline patterns during treatment and retreatment in many patients (Fig. 1A), some patients had an increase in BLV efficacy (Fig. 1A-B) while others had a decline in efficacy during retreatment (Fig. 1C). Overall BLV efficacy (η) remained largely similar with a median of 91% [IQR: 72%–99%] for the initial treatment and 98% [IQR: 77%–99%] for retreatment. In contrast, the cell death rate of HDV-infected cells (δ) under initial treatment was a median 0.05 1/day [IQR: 0.02–0.08] and increased to 0.08 1/day [IQR: 0.02–0.16] at the beginning of retreatment ($p=0.044$). The corresponding HDV half-lives were 9.9 and 5.3 days for initial and retreatment respectively. The estimated median baseline ALT (A_0) of 107 IU/mL [IQR: 67–194] for initial treatment trended lower ($p=0.095$) compared to the median ALT of 160 IU/mL [IQR: 57–567] at the beginning of retreatment. The within-patient change in δ correlated with A_0 changes ($p=0.039$), suggesting higher A_0 is associated with cell death (δ).

Conclusion: While viral declines and BLV efficacy were mostly similar between initial treatment and retreatment, modeling suggested that cell death rates and ALT levels may increase during treatment interruption, warranting further investigation into whether HDV rebound during BLV interruption increases HDV-infected cell turnover in some patients.



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LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

P16 REAL-WORLD EFFECTIVENESS AND SAFETY OF BULEVIRTIDE IN PATIENTS WITH CHRONIC HEPATITIS D: A SINGLE-CENTER COHORT FROM ROMANIA

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Background and aims: Romania remains one of the European countries with the highest burden of chronic hepatitis B, resulting in a substantial population at risk for hepatitis D virus (HDV) infection. Bulevirtide (BLV), the first approved entry inhibitor targeting HDV, has demonstrated promising efficacy in clinical trials; however, real-world data from Eastern Europe remain scarce. We aimed to evaluate the effectiveness and safety of BLV therapy in patients with chronic hepatitis D managed in a Romanian tertiary referral center.

Methods: We performed a retrospective single-center study including consecutive adults with chronic HDV infection who initiated BLV therapy between August 2024 and July 2026 at the National Institute for Infectious Diseases "Prof. Dr. Matei Bals", Bucharest. Demographic, clinical, biochemical, virological and fibrosis-related parameters were collected. Biochemical response (BR) was defined as ALT normalization, while virological response (VR) was defined as undetectable HDV-RNA or a $\geq 2 \log_{10}$ IU/mL decline from baseline after 48 weeks of treatment. Statistical analyses were performed using SPSS version 26.

Results: Thirty-eight patients were included (median age 46 years, IQR 26; female predominance, male-to-female ratio 0.81:1), of whom 42% had compensated cirrhosis and one patient had HIV co-infection. Baseline median ALT was 76 U/L, AST 54 U/L, APRI 0.78, FIB-4 1.55, HBV-DNA 11.5 IU/mL and HDV-RNA 277,134 IU/mL. Among the 35 patients (92%) completing 24 weeks of BLV treatment, administered 2 mg once daily either as monotherapy or combined with nucleos(t)ide analogues (42%), biochemical response was achieved in 51%, whereas 57% demonstrated a $\geq 2 \log_{10}$ IU/mL decline in HDV-RNA. Patients achieving biochemical response had significantly lower APRI (median 0.36; $p=0.014$) and FIB-4 scores (median 1.42; $p=0.022$) in 40% cases, suggesting greater treatment benefit in individuals with less advanced liver disease.

Thirty patients (79%) completed 48 weeks of BLV without treatment-limiting adverse events. Biochemical response was observed in 57% cases, virological response in 57% cases, and a combined biochemical and virological response in 30% of patients after 48 weeks, irrespective of baseline fibrosis stage.

Conclusions: In this real-world Romanian cohort, Bulevirtide demonstrated sustained biochemical and virological efficacy together with an excellent safety profile over 48 weeks of treatment. These findings reinforce the effectiveness of BLV outside the setting of clinical trials and provide valuable real-world evidence from a region with one of Europe's highest HDV burdens. Longer prospective studies are warranted to determine the durability of virological control and the impact of BLV on fibrosis progression and liver-related clinical outcomes.

Keywords: chronic hepatitis D; hepatitis delta virus; bulevirtide; real-world evidence; virological response; biochemical response



CURRENT AND NEW ANTIVIRAL TREATMENTS

LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

P17 CORRELATION BETWEEN HDV RNA AND ANTI-HDV DYNAMICS IN CHRONIC HEPATITIS D PATIENTS TREATED WITH BULEVIRTIDE

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Background: Treatment monitoring in chronic hepatitis D (CHD) relies on serum HDV RNA and ALT. Serum anti-HDV levels correlated with response to Interferon, but their kinetics during Bulevirdide (BLV) therapy remained unexplored. We studied the relationship between HDV RNA and anti-HDV serum levels in long-term BLV treated CHD patients (pts).

Methods: HDV RNA (AltoStar HDV-RT-qPCR Kit 1.5; LOD 1.12 IU/mL) and anti-HDV (CLIA, LIAISON XL Murex anti-HDV, DiaSorin; 10-fold endpoint dilutions expressed as Log AU/mL after multiplying AU/mL by dilution factor) were quantified in 28 consecutive CHD pts treated with 2 mg BLV whose baseline (BL) and follow-up (fu) samples were available. Virological Response (VR) was defined as ≥ 2 Log HDV RNA decline/undetectability and Combined Response (CR) as VR plus normal ALT.

Results: Their median age was 48.5 years, 46.4% males, 85.7% cirrhotics; median on BLV-fu 144 (72.6-222.6) weeks (wks). VR rates were 71.4%, 71.4%, 64.0% and 78.6% at wks 48, 72, 96 and 144, respectively; at the same timepoints, ALT normalization occurred in 92.6%, 85.7%, 88.0% and 92.9%; CR rates were 64.3%, 64.3%, 56.0% and 71.4%. At the end of follow-up [EOF; median 102 (66-171) wks], 19/28 (67.9%) pts achieved VR [13/28 (46.4%) with ≥ 2 Log HDV RNA decline and 6/28 (21.4%) pts with undetectable HDV RNA]; ALT normalized in 23/28 (82.1%) and 16/28 (57.1%) pts achieved CR. At BL, median HDV RNA and anti-HDV levels were 5.57 (1.70-7.20) Log IU/mL and 3.82 (3.38-4.71) Log AU/mL, with 17/28 (60.7%) anti-HDV-positive at the 1:1,000 dilution and 11/28 (39.3%) at 1:10,000. HDV RNA and anti-HDV levels did not correlate at BL ($p=0.015$; $p=0.942$) but did it significantly at wk 72 ($p=0.547$; $p=0.003$) and wk 96 ($p=0.529$; $p=0.007$) of treatment. The best correlation ($p=0.598$, $P=0.001$) was observed at EOF in responders (anti-HDV titers were 1:10 in 1, 1:100 in 4, and 1:1,000 in 14) whereas all non-responders showed anti-HDV titers $\geq 1:1,000$ (8 at 1:1,000 and 1 at 1:10,000). Consistently, anti-HDV serum levels were significantly lower in responders [3.12 (1.48-3.85) vs 3.74 (3.07-4.23) Log AU/mL; $P=0.004$] with the lowest levels in 6 pts with undetectable HDV RNA [3.04 (2.13-3.36) Log AU/mL, $P=0.010$] (Figure 1). Similarly, 16 pts with CR at EOF showed significantly lower anti-HDV (3.12 [1.48-3.85] vs 3.58 [3.01-4.23] LogAU/mL, $P=0.023$). At ROC-analysis wk 72 anti-HDV levels predicted VR at EOF (AUC=0.807) with 3.47 Log AU/mL cut-off maximizing sensitivity and specificity: anti-HDV ≤ 3.47 Log AU/mL in 13/19 (68.4%) responders and >3.47 Log AU/mL in 8/9 (88.9%) non-responders.

Conclusions: HDV RNA and anti-HDV levels were significantly correlated in BLV-treated CHD patients. Progressive anti-HDV decline mirrored an increasing viral suppression, consistently with previous observations in interferon-treated pts. These findings suggest that monitoring anti-HDV kinetics may provide an additional tool for assessing treatment response and discontinuation strategies.



CURRENT AND NEW ANTIVIRAL TREATMENTS

LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

P18 BULEVIRTIDE TREATMENT IS ASSOCIATED WITH IMPROVEMENTS IN DISEASE SEVERITY IN PATIENTS WITH DETECTABLE HEPATITIS DELTA VIRUS RNA: RESULTS FROM A REAL-WORLD STUDY IN EUROPE

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Background: Detectable hepatitis delta virus (HDV) RNA is associated with a higher risk of progression to severe liver disease than undetectable HDV RNA. However, HDV RNA is an imperfect surrogate of intrahepatic disease activity; undetectable HDV RNA achieved during chronic therapy may not reflect clearance of infected hepatocytes and should be interpreted in the context of treatment mechanism and durability of response. We evaluated the association between detectable HDV RNA and disease severity and explored disease severity differences according to patient bulevirtide (BLV) treatment status in a real-world setting.

Materials and Methods: Data were drawn from the Adelphi Real World Hepatitis II Disease Specific Programme, a cross-sectional survey with retrospective data collection of physicians and their patients with HDV infection from Jun–Dec 2024. Physicians reported on up to 4 patients (2 prescribed BLV and 2 regardless of treatment status) consulting for routine care. Patients in the non-BLV cohort received interferon, peginterferon, or other antiviral treatments or were antiviral treatment naïve. Descriptive analyses focused on physician-reported patient demographics and physician-perceived disease severity. Disease severity considered patient fibrosis and cirrhosis status and was reported as mild, moderate, or severe at diagnosis (a proxy for baseline) and at the survey date. The associations of BLV treatment and detectable HDV RNA with disease severity were evaluated using ordinal logistic regression analyses (reporting odds ratios) and Mann-Whitney U tests, as appropriate.

Results: In total, 164 physicians (France, 36; Germany, 40; Italy, 41; Spain, 32; UK, 15) reported data on 553 patients (France, 120; Germany, 135; Italy, 144; Spain, 71; UK, 83). Most patients were male (379/548; 69%), White (309/433; 71%), and had detectable HDV RNA (255/351; 73%). Detectable HDV RNA was associated with worsening disease severity from diagnosis to the survey date (odds ratio, 0.39; 95% CI, 0.21–0.71; $P = .002$; $n = 332$). Among patients with detectable HDV RNA, a significant difference was found in disease severity between BLV-treated patients and patients not taking BLV ($P = .008$; Figure 1). Overall, 70/159 (44%) BLV-treated patients and 20/72 (28%) patients not taking BLV who had detectable HDV RNA experienced improvements in disease severity.

Conclusions: Among patients with detectable HDV RNA, BLV treatment was associated with greater improvement in disease severity vs no BLV treatment, demonstrating that clinical benefit is not contingent on achieving HDV RNA undetectability. The clinical relevance of HDV RNA undetectability may vary according to treatment mechanism and whether it reflects on-treatment suppression or sustained off-treatment clearance. Undetectability attained on chronic therapy should not be assumed to confer a benefit equivalent to durable off-treatment clearance, and disease severity remains an essential real-world endpoint.



CURRENT AND NEW ANTIVIRAL TREATMENTS

LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

P19 ASSOCIATION OF BULEVIRTIDE USE WITH CHANGES IN ALT: RESULTS FROM A REAL-WORLD STUDY IN EUROPE

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Background: Bulevirtide (BLV) is approved for the treatment of chronic hepatitis delta virus (HDV) infection in the United States, the European Economic Area, and several other countries. In both real-world and clinical trial settings, BLV treatment is associated with decreases in alanine aminotransferase (ALT). Here, we describe the effect of BLV on ALT in a real-world setting among patients receiving BLV or untreated patients.

Material and methods: Data were drawn from the Adelphi Real World Hepatitis II Disease Specific Programme, a cross-sectional survey with retrospective data collection of physicians and their patients with HDV infection from Jun to Dec 2024. Physicians provided data on up to 4 patients (2 prescribed BLV and 2 regardless of treatment status) seen during routine care. Descriptive analyses included physician-reported patient demographics and changes in ALT levels from diagnosis to the survey date. All data were collected at the survey date with no follow-up data recorded. Patients in the BLV group were receiving BLV at the survey date. Untreated patients were defined as those not receiving BLV, pegylated interferon, or interferon alfa-2b at the survey date or as their most recent treatment regimen; however, prior HDV antiviral therapy was not captured and cannot be excluded. Patients may or may not have been receiving nucleos(t)ide analogue therapy. The effect of BLV therapy on the change in ALT level was assessed using univariate and multiple linear regression. Covariates for multiple linear regression included age, sex, comorbidities (Charlson Comorbidity Index [CCI]), and body mass index.

Results: In total, 185 physicians (France, 43; Germany, 40; Italy, 41; Spain, 39; UK, 22) reported data on 306 patients (France, 73; Germany, 59; Italy, 91; Spain, 44; UK, 39). Most patients were male (222/306; 73%) and White (166/233; 71%), with a mean (SD) age of 43 (12.7) years. Overall, 210 (69%) patients were prescribed BLV and 96 (31%) were untreated. Physician-reported patient demographics and disease characteristics for each group are reported in Table 1. At the time of HDV diagnosis, mean (SD) ALT levels were 410.6 (460.08) U/L and 212.1 (249.29) U/L among BLV-treated and untreated patients, respectively; at the survey date, ALT levels were 102.3 (100.92) U/L and 78.3 (100.75) U/L. BLV treatment was associated with a greater reduction in ALT by univariate ($\beta = -175.9$, $P = .001$, $n = 307$) and multiple ($\beta = -130.8$, $P = .003$, $n = 306$) linear regression analyses. Variables such as age ($\beta = 4.4$, $P = .042$), sex (male vs female; $\beta = -105.2$, $P = .006$), and comorbidities (CCI; $\beta = 21.4$, $P = .021$) were significantly associated with changes in ALT levels.

Conclusions: In this real-world cohort including patients from 5 countries, BLV therapy was associated with significantly decreased ALT levels from the time of HDV diagnosis to the survey date, reflecting improvements in liver necroinflammation and disease activity.



CURRENT AND NEW ANTIVIRAL TREATMENTS

LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

P20 REAL-WORLD 72-WEEK VIROLOGICAL AND BIOCHEMICAL RESPONSES TO BULEVIRTIDE IN ROMANIAN PATIENTS WITH CHRONIC HEPATITIS D: DATA FROM A MULTICENTRE REGISTRY

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Background and aims: Clinical trials and Western European real-world cohorts have shown the effectiveness of bulevirtide in chronic hepatitis D, but data from large Eastern European populations remain limited. We assessed 72-week virological and biochemical outcomes and baseline predictors of response in a Romanian multicentre cohort.

Methods: We prospectively analysed 306 patients with chronic hepatitis D treated with bulevirtide. The primary virological response was an HDV RNA decline $\geq 2 \log_{10}$ IU/mL from baseline or undetectable HDV RNA; a broader endpoint was a decline $\geq 1 \log_{10}$ IU/mL. Biochemical response was ALT normalisation in patients with elevated baseline ALT. Predictors were assessed by logistic regression adjusted for centre.

Results: Median age was 49 years (IQR 40–64), 53.4% were male, and 61.0% had liver stiffness ≥ 12 kPa. Median baseline HDV RNA was 5.45 $\log_{10}$ IU/mL, and 55.4% received nucleos(t)ide analogue co-therapy. Primary virological response rates were 42.9%, 57.9%, and 53.8% at weeks 24, 48, and 72; HDV RNA was undetectable in 11.0% at week 48. For the $\geq 1 \log_{10}$ endpoint, response rates were 65.9%, 72.7%, and 73.1%, respectively. Among patients with at least two on-treatment HDV RNA measurements, 61.5% maintained response, 20.9% remained non-responders, and 12.6% had virological breakthrough, defined as an increase $\geq 1 \log_{10}$ IU/mL from nadir. Biochemical response increased from 60.7% at week 24 to 70.8% at week 48 and 77.2% at week 72; median ALT fell from 68 U/L at baseline to 32 U/L at week 48. Older age independently predicted primary virological response (OR 1.05/year, 95% CI 1.02–1.08; $p=0.002$). Liver stiffness, cirrhosis, HBV DNA, and nucleos(t)ide analogue co-therapy were not associated with response. The apparent association of higher baseline HDV RNA with response disappeared among patients with baseline HDV RNA $\geq 4 \log_{10}$ IU/mL ($p=0.36$), suggesting a floor effect from the $\geq 2 \log_{10}$ definition. No deaths or liver transplantations occurred. Bulevirtide-related adverse events were reported in 5.6%.

Conclusions: In this large Romanian real-world cohort, bulevirtide produced increasing biochemical response rates, reaching 77.2% at week 72. At week 72, 53.8% met the primary virological endpoint and 73.1% achieved an HDV RNA decline $\geq 1 \log_{10}$ IU/mL. Response was independent of fibrosis severity, cirrhosis, HBV DNA, and nucleos(t)ide analogue co-therapy.



CURRENT AND NEW ANTIVIRAL TREATMENTS

LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

P21 HEALTH-RELATED QUALITY OF LIFE DURING BULEVIRTIDE TREATMENT IN A ROMANIAN COHORT

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Background and aims: Patient-reported outcomes during bulevirtide treatment remain insufficiently characterised. We assessed longitudinal changes in health-related quality of life (HRQoL) and adherence and explored their relationship with virological response.

Methods: Patients enrolled in a Romanian multicentre bulevirtide registry completed the Hepatitis Quality of Life Questionnaire at baseline and after 6 and 12 months, together with the 8-item Morisky Medication Adherence Scale (MMAS-8). In an exploratory analysis, questionnaire items were grouped into 12 conceptually defined domains scored from 0 to 100, with higher scores indicating better HRQoL. Internal consistency was acceptable to excellent (Cronbach's α 0.70–0.93). Paired comparisons used the Wilcoxon signed-rank test.

Results: Baseline questionnaires were available for 114 patients; 79 baseline-to-6-month and 43 baseline-to-12-month paired assessments were analysable. At 6 months, 18 of 51 items changed significantly after correction for multiple testing. Median perceived general health improved from 35 to 50 points (adjusted $p=0.0001$), with 64.1% of patients improving. Positive well-being increased from 35 to 40 points (adjusted $p=0.0023$), with improvement in 64.5%. Conversely, limitations in daily activities attributable to emotional problems increased, reflected by a score reduction from 66.7 to 50.0 points (adjusted $p=0.0069$). Physical functioning, bodily pain, limitations due to physical health, and social functioning did not change significantly. At 12 months, no domain remained significant after multiple-testing correction. Hepatitis-specific distress showed the largest numerical improvement (+10 points), with 65.1% improving (adjusted $p=0.055$). Adherence was high and showed limited variability: median MMAS-8 scores were 7.0 at 6 months and 8.0 at 12 months, and only 1 of 109 patients scored below 6. Adherence was not associated with virological response ($p=0.36$). Week-48 virological response was associated with greater improvement in vitality (+6.2 vs 0.0 points; $p=0.009$) and positive well-being (+15.0 vs +5.0 points; $p=0.041$), but not in perceived general health ($p=0.56$), which improved similarly in responders and non-responders.

Conclusions: During the first year of bulevirtide treatment, HRQoL improvements mainly involved perceived general health and psychological well-being, without measurable gains in physical functioning. Virological response may reinforce vitality and positive well-being by providing tangible evidence of treatment benefit. However, worsening emotionally driven limitations in daily activities may reflect the burden of daily injections and an undefined treatment endpoint, even among responders. This interpretation is hypothesis-generating because treatment expectations and injection-related burden were not assessed directly. Adherence was uniformly high, limiting evaluation of its association with treatment response.



CURRENT AND NEW ANTIVIRAL TREATMENTS

LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

P22 HEPATIC RECOMPENSATION ACCORDING TO BAVENO VII IN DECOMPENSATED CHRONIC HEPATITIS DELTA TREATED WITH BULEVIRTIDE: A MULTICENTER EXPERIENCE

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Background: Bulevirtide (BLV) is actually approved only for compensated chronic hepatitis D (CHD). Whether it can induce hepatic recompensation, as defined by Baveno VII, in decompensated CHD remains unknown.

We assessed the rate of Baveno VII recompensation in decompensated CHD patients treated with BLV, and also compared them to an untreated control cohort with comparable disease severity.

Materials and methods: We performed a retrospective multicenter study of CHD patients with detectable HDV-RNA and decompensated cirrhosis Child-Pugh (CP) B or C with ascites, variceal bleeding or hepatic encephalopathy under evaluation or listed for liver transplantation (LT). The BLV group received BLV 2 mg/day, initiated between 2020 and 2023, with follow-up extending to 2026. The untreated control group comprised patients with detectable HDV-RNA and decompensated cirrhosis listed and transplanted between 2014 and 2021. Baveno VII recompensation required undetectable HDV-RNA, resolution of ascites off diuretics, of encephalopathy off lactulose/rifaximin, and absence of recurrent variceal bleeding for ≥ 12 months, together with stable improvement of liver function to Child-Pugh A.

Results: Twenty-nine patients were included: 11 BLV-treated and 18 controls. Groups were comparable for age (46 vs 46 years, $p=0.84$), male sex (64% vs 39%, $p=0.26$), CP score (10 vs 10, $p=0.85$), MELD (15 vs 18, $p=0.30$), bilirubin (43 vs 57 $\mu\text{mol/L}$) and platelets (35 vs 59 $\times 10^9/\text{L}$, $p=0.08$); controls had lower albumin (27 vs 30 g/L, $p=0.02$) and slightly higher baseline HDV-RNA (5.3 vs 3.7 $\log_{10}$ IU/mL, $p=0.17$). In the BLV group over 22 (2–67) months, 7/9 evaluable patients achieved undetectable HDV-RNA by week 48, MELD improved from 15 to 13 and CP A was reached in 5/9. Baveno VII recompensation occurred in 1/11 (9%) BLV-treated patients versus 0/18 (0%) controls ($p=0.38$). Delisting after clinical improvement occurred in 3/11 (27%) BLV versus 0/18 (0%) controls ($p=0.045$), and LT in 7/11 (64%) BLV versus 18/18 (100%) controls ($p=0.014$); untreated controls were transplanted within a median of 3 months (0.2–16) from listing.

Conclusions: Formal Baveno VII recompensation in decompensated CHD was rare under BLV (9%) and absent in the control group (0%), underscoring how rarely full recompensation is reached in this population. Nonetheless, BLV was associated with MELD and CP improvement, suggesting that it may defer transplantation and improve clinical outcome.



CURRENT AND NEW ANTIVIRAL TREATMENTS

LONG-TERM OUTCOMES IN BLV-TREATED PATIENTS

P23 MATHEMATICAL MODELING OF 144-WEEK BULEVIRTIDE MONOTHERAPY IN HDV-INFECTED PATIENTS WITH COMPENSATED CIRRHOSIS AND CSPH

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Background and Aims: The entry inhibitor bulevirtide (BLV) was approved in 2023 for the treatment of patients living with compensated chronic hepatitis D by the European Medicines Agency and in 2026 by the U.S. Food and Drug Administration. However, detailed kinetic analysis and dynamic understanding of HDV, HBsAg and ALT kinetics during 3 years of BLV (2 mg/day) monotherapy in patients with compensated cirrhosis and clinically significant portal hypertension (CSPH) are lacking.

Methods: 38 patients were included. All patients received nucleos(t)ide analogues for HBV. Blood samples were collected at weeks 0, 4, 8, 16, 24, 32, 40, 48 and every 12 weeks thereafter. We used our recently developed mathematical model that includes HDV-free and HDV-infected HBsAg-producing hepatocyte dynamics [Mhlanga et al.10.1016/j.antiviral.2026.106489] to explain observed HDV, ALT and HBsAg kinetics for up to 3 years of BLV treatment using a nonlinear mixed-effects approach. The critical drug efficacy (CDE) was estimated for each patient, such that for BLV efficacy (η) > CDE, HDV is ultimately cleared (i.e., cure), while η < CDE results in a new lower viral plateau or viral breakthrough.

Results: 7 patients were non-responders (less than 1.6 log HDV decline from baseline) by BLV week 144. After an initial decline, the 31 responder patients exhibited 3 different kinetic patterns (Fig. 1): a flat partial response (Fig. 1A), where the viral kinetics reached a new lower plateau (FPR, n=19); a biphasic response (Fig. 1B) with a second slower phase of HDV decline (BP, n=4); or a viral breakthrough (Fig. 1C) marked by a 1.6 log HDV kinetic increase from nadir (VB, n=8). The model reproduced the observed HDV, ALT and HBsAg kinetic patterns well in all responders (Fig. 1A, B and C) and the non-responders (Fig. 1D). Modeling indicated that BLV inhibited infection of hepatocytes with overall efficacy of 73% (95% CI: 52 – 87%) and estimated an HDV-infected cell half-life, $t_{1/2}$, of 8.3 (95% CI: 4.0 – 12.5) days. BLV efficacy (η) was < CDE in 15 FPR and all VB cases. Modeling explained VB by an increase of susceptible cells (i.e., HDV-free hepatocytes), ALT normalization by a decline in HDV-infected cells, and stable HBsAg by an overall constant number of HBsAg-producing hepatocytes during treatment.

Conclusion: This is the first report analyzing and modeling HDV RNA, HBsAg and ALT kinetics measured under BLV 2 mg/day monotherapy administered for 144 weeks in patients with HDV-related compensated cirrhosis and CSPH. The findings support the prediction that the efficacy of BLV 2 mg/day < CDE required for HDV cure in many patients with compensated cirrhosis and CSPH, highlighting the potential need for higher doses or combination therapy.



CURRENT AND NEW ANTIVIRAL TREATMENTS

ANTI-HBS AND SIRNA COMBINATION

P24 SOLSTICE WEEK 48 SUBGROUP ANALYSIS: IMPACT OF BMI ON ALT NORMALIZATION AFTER SUCCESSFUL VIRAL CONTROL IN PARTICIPANTS WITH CHRONIC HEPATITIS DELTA VIRUS INFECTION TREATED WITH ELEBSIRAN AND TOBEVIBART

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Background and Aims: Hepatitis delta virus (HDV) infection is the most severe form of chronic viral hepatitis with limited treatment options. The ongoing phase 2 SOLSTICE study is investigating the antiviral activity and safety of the small interfering RNA elebsiran in combination with the monoclonal antibody tobevibart or tobevibart alone in participants with chronic HDV infection, with or without compensated cirrhosis, on NRTI therapy (NCT05461170). ALT normalization is used to assess resolution of inflammation during antiviral treatment, but is non-specific, multifactorial, and may be influenced by factors beyond HDV viremia in infected persons. Here we sought to examine additional factors impacting ALT normalization.

Method: A subgroup analysis of ALT normalization was performed based on baseline participant and disease characteristics after 48 weeks of therapy with elebsiran 200 mg and tobevibart 300 mg subcutaneously (SC) every 4 weeks (elebsiran and tobevibart Q4W; N=32).

Results: After 48 weeks, HDV RNA decreased by ≥ 2 log₁₀ from baseline in 97% (31/32) of participants receiving elebsiran and tobevibart Q4W and HDV RNA target not detected (TND) was achieved by 66% (21/32) of participants. Most participants receiving elebsiran and tobevibart Q4W had reductions in ALT values compared to baseline, with ALT normalization observed in 56% (18/32) of participants at week 48. In the full cohort, there was a trend towards lower baseline BMI in those who achieved ALT normalization at week 48. Of the 21 participants receiving elebsiran and tobevibart Q4W who achieved HDV RNA TND at week 48, median baseline ALT was 2.2x ULN, 2.0x ULN, and 1.3x ULN in BMI subgroups <25, 25-29.9, and ≥ 30 , respectively. Among those achieving TND, ALT normalization was achieved by 80% (4/5), 64% (7/11), and 20% (1/5) in BMI subgroups <25, 25-29.9, and ≥ 30 , respectively. Across the BMI subgroups, treatment-emergent adverse events (TEAEs) were primarily Grade 1-2 and transient in nature. No treatment-related serious adverse events occurred.

Conclusion: At 48 weeks, participants receiving elebsiran and tobevibart Q4W therapy achieved high rates of HDV RNA TND. ALT normalization at week 48 was more frequently observed in participants with lower baseline BMI, which suggests that elevated BMI could be independently contributing to elevated ALT even in participants achieving HDV RNA TND receiving elebsiran and tobevibart therapy.



CURRENT AND NEW ANTIVIRAL TREATMENTS

ANTI-HBS AND SIRNA COMBINATION

P25 EFFICACY AND SAFETY OF ELEBSIRAN (VIR-2218) IN COMBINATION WITH TOBEVIBART (VIR-3434) OR TOBEVIBART ALONE IN PARTICIPANTS WITH CHRONIC HEPATITIS DELTA VIRUS INFECTION: WEEK 96 ENDPOINT RESULTS FROM THE PHASE 2 SOLSTICE TRIAL

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Background and Aims: Hepatitis delta virus (HDV) infection causes the most severe form of chronic viral hepatitis with limited treatment options. The ongoing phase 2 SOLSTICE study is investigating the antiviral activity and safety of the small interfering RNA (siRNA) elebsiran in combination with the monoclonal antibody tobevibart or tobevibart alone in participants with chronic HDV infection, with or without compensated cirrhosis, on NRTI therapy (NCT05461170).

Methods: Safety and efficacy, including trends in HDV and HBV antiviral activity and biochemical markers, were assessed in participants receiving either elebsiran 200 mg and tobevibart 300 mg subcutaneously (SC) every 4 weeks (elebsiran and tobevibart Q4W) or tobevibart 300 mg SC every 2 weeks (tobevibart Q2W) for 96 weeks.

Results: At week 96, HDV RNA TND (target not detected, no amplification on PCR) was achieved by 88% (28/32) and 53% (17/32) of participants receiving elebsiran and tobevibart Q4W and tobevibart Q2W, respectively. ALT normalized in 53% (17/32) and 63% (20/32) of participants receiving elebsiran and tobevibart Q4W and tobevibart Q2W at week 96, respectively. At week 96, 88% (28/32) of elebsiran and tobevibart Q4W participants and 25% (8/32) of tobevibart Q2W participants had HBsAg <10 IU/mL. Treatment-emergent adverse events (TEAEs) were primarily Grade 1-2. The most common TEAE was flu-like symptoms, which were mild to moderate, transient, and only occurred beyond the first dose in 3% (1/32) and 15% (5/33) of participants receiving elebsiran and tobevibart Q4W and tobevibart Q2W, respectively. No treatment-related serious adverse events occurred.

Conclusions: Participants receiving elebsiran and tobevibart Q4W showed numerically greater rates of HDV RNA TND and HBsAg <10 IU/mL at week 96 than those receiving tobevibart Q2W monotherapy. HDV RNA TND rates increased over time with combination therapy, while rates plateaued with monotherapy. Adverse events were generally mild to moderate and transient. These results support further development of elebsiran and tobevibart Q4W, which is now being evaluated in the registrational ECLIPSE program for chronic HDV infection.



CURRENT AND NEW ANTIVIRAL TREATMENTS

OTHER THERAPEUTIC APPROACHES FOR HDV

P26 LIBEVITUG TREATMENT IN CHRONIC HEPATITIS D: VIROLOGIC, BIOCHEMICAL, AND BIOMARKER IMPROVEMENTS THROUGH 48 WEEKS

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Background: Chronic hepatitis D virus (HDV) infection is the most severe form of viral hepatitis and is associated with rapid progression to cirrhosis, hepatocellular carcinoma, and liver-related mortality. Libevitug (HH-003) is a human monoclonal antibody that targets the hepatitis B virus (HBV)/HDV PreS1 domain and blocks sodium taurocholate cotransporting polypeptide (NTCP)-mediated entry pathway. In the randomized, controlled phase 2b trial (HH003-204, NCT05861674), 48 weeks of libevitug treatment demonstrated significant anti-HDV efficacy and a favorable safety profile in patients with chronic HDV infection. To further characterize the biological impact of treatment response, we evaluated changes in liver function and disease biomarkers through Week 48 according to treatment response status in HH003-204.

Methods: Data were analyzed from the phase 2b trial in 100 patients with chronic HDV infection randomized 2:2:1 to libevitug 20 mg/kg, libevitug 10 mg/kg, or tenofovir alafenamide fumarate (TAF) alone. In addition to standard assessments of virologic response (defined as $\geq 2.0 \log_{10}$ IU/mL HDV RNA decline or $<$ lower limit of quantification [LLOQ]), alanine aminotransferase (ALT) normalization, and combined response, changes in liver function and disease biomarkers through Week 48 were evaluated according to treatment response status. Longitudinally assessed parameters included aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), aspartate aminotransferase-to-platelet ratio index (APRI), liver stiffness measurement by transient elastography, alpha-fetoprotein (AFP), interferon gamma-induced protein 10 (IP-10), and interferon γ (IFN- γ).

Results: At Week 48, combined response rates were 42.5% in the libevitug 20 mg/kg group and 44.1% in the libevitug 10 mg/kg group, significantly higher than 5% in the TAF alone group ($P < 0.01$ for each comparison); the corresponding virologic response rates were 60.0%, 50.0% and 5.0%, respectively ($P < 0.001$ for each comparison); the corresponding ALT normalization rates were 70.0%, 55.9%, and 10.0%, respectively ($P < 0.0001$ and $P = 0.0012$, respectively). These efficacy responses were accompanied by consistent improvements in liver-related biomarkers. Compared with patients with limited HDV RNA decline ($< 1 \log_{10}$ decrease; non-responder), Week 48 virologic responders, defined as patients with an HDV RNA decline $> 2 \log_{10}$ with or without ALT normalization, demonstrated greater reductions in AST and GGT, along with improvements in non-invasive fibrosis markers, including APRI and liver stiffness, and reductions in AFP and IP-10 levels through Week 48.

Conclusion: Stronger HDV RNA suppression was associated with coordinated improvements in virologic, biochemical, hepatic, fibrosis-related, oncofetal, and immune-inflammatory markers through Week 48. These findings support the potential of libevitug to modify disease activity in patients with chronic HDV infection.



CURRENT AND NEW ANTIVIRAL TREATMENTS

OTHER THERAPEUTIC APPROACHES FOR HDV

P27 HISTOLOGIC IMPROVEMENT AND REDUCTION IN NECROINFLAMMATION WITH LONAFARNIB-BASED THERAPY IN CHRONIC HEPATITIS DELTA: PHASE 3 D-LIVR TRIAL

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Background: Lonafarnib (LNF) pharmacokinetically boosted with ritonavir (LNF/RTV) remains the only late-stage oral agent under development for the treatment of chronic hepatitis D virus (HDV). By inhibiting host farnesyltransferase, LNF disrupts HDV virion assembly in infected hepatocytes and promotes immune modulation. LNF/RTV is being advanced as a 48-week treatment regimen for patients living with HDV, administered as monotherapy or in combination with peg-interferon alfa-2a (PEG). Improvement in the Ishak Histologic Activity Index (HAI) and its subdomains were evaluated to provide mechanistic insight into treatment effects on liver health.

Method: D-LIVR is the largest Phase 3 randomized placebo-controlled HDV study (N=407) to date, evaluating LNF/RTV with or without PEG. The primary efficacy composite endpoint was defined as a ≥ 2 log reduction in HDV RNA and ALT normalization compared to baseline at Week 48 (end of treatment [EOT]).

D-LIVR also included a large paired-biopsy population (N=229 with baseline and EOT samples). Histologic responders were defined as ≥ 2 point improvement in the modified Ishak HAI score without worsening of fibrosis. Effects of treatment on Ishak HAI subcomponents most directly impacted by the health of infected hepatocytes were evaluated in exploratory analyses: focal lytic necrosis, apoptosis, and inflammation (FLNAI) which reflects ongoing hepatocyte injury and immune surveillance, and periportal/periseptal interface hepatitis (PPIH) which reflects ongoing necroinflammation and fibrosis advancement.

Results: The primary composite endpoint at 48 weeks was met by both LNF/RTV ($p = 0.004$) and LNF/RTV+PEG ($p < 0.0001$) treatment groups. LNF/RTV+PEG also resulted in improvement of the histological endpoint in a significant proportion of patients (35 of 125, $p = 0.01$) and LNF/RTV monotherapy improved histology in many patients (35 of 178, NS).

Among the paired-biopsy population, the FLNAI subdomain score was improved compared to baseline by treatment with both LNF/RTV (-0.42, 95%CI: -0.65 to -0.19, N=108) and LNF/RTV+PEG (-0.74, 95%CI -1.1 to -0.41, N=66). Similarly, the PPIH subdomain score improved significantly compared to baseline in both LNF/RTV (-0.32, 95%CI: -0.54 to -0.11, N=108) and LNF/RTV+PEG (-0.65, 95%CI -0.98 to -0.32, N=66) treatment groups. Placebo-treated patients did not experience subdomain improvement. Improvements in FLNAI and PPIH subdomains were significant among patients who achieved a composite response at any time during the study, irrespective of response status at EOT.

Conclusions: In the D-LIVR study, LNF/RTV-based therapy, with or without PEG, improved inflammatory HAI subdomains, consistent with reduced hepatocyte injury and necroinflammation. LNF/RTV is a first-in-class oral HDV therapy with efficacy and safety in HDV patients, and histologic evaluation supports the continued development of LNF-based therapy as a 48-week treatment regimen for HDV with definitive impact on liver tissue health.



CURRENT AND NEW ANTIVIRAL TREATMENTS

OTHER THERAPEUTIC APPROACHES FOR HDV

P28 POST-TREATMENT RESPONSE FOLLOWING 48 WEEKS OF LONAFARNIB THERAPY: ANALYSIS OF 24-WEEK FOLLOW-UP IN THE PHASE 3 D-LIVR TRIAL IN CHRONIC HEPATITIS DELTA

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Background: The durability of treatment response following therapy cessation remains an important consideration in the management of chronic hepatitis D virus (HDV) infection. Lonafarnib (LNF) pharmacokinetically boosted with ritonavir (LNF/RTV) remains the only late-stage oral agent under development for the treatment of chronic hepatitis D virus (HDV) and is being advanced as a 48-week oral treatment for patients living with HDV. By inhibiting host farnesyltransferase, LNF disrupts HDV virion assembly in infected hepatocytes and promotes immune modulation and has been evaluated as monotherapy or in combination with peg-interferon alfa-2a.

Method: D-LIVR is the largest randomized placebo-controlled clinical trial in HDV patients to date (N=407), evaluating LNF/RTV with or without PEG for 48 weeks, followed by a 24-week off-treatment follow-up period to evaluate durability of treatment response. The primary composite efficacy endpoint was a composite response defined as a ≥ 2 log reduction in HDV RNA and ALT normalization compared to baseline at 48-weeks on-treatment (end of treatment [EOT]). Patients achieving viral loads below the lower limit of quantification (<LLOQ, 40 IU/mL, target detected and target not detected) were also assessed.

Post-treatment analyses included durability of composite response among EOT responders, emergence of new composite responders during follow-up among patients who had not achieved response at EOT, and virologic suppression (<LLOQ) at EOT and EOS.

Results: Both LNF-containing regimens met the primary composite efficacy endpoint compared to placebo (LNF/RTV: $p = 0.004$, LNF/RTV + PEG: $p < 0.0001$). Composite response at EOS was achieved in 14.2% of patients treated with LNF/RTV oral therapy and in 26.4% treated with LNF/RTV + PEG treatment arm. There were no EOS composite responses in the placebo group.

EOT composite responses were durable through EOS in 44.4% and 41.7% of EOT composite responders in the LNF/RTV and LNF/RTV + PEG treatment arms, respectively. In addition, among patients who were not composite responders at EOT, newly emergent composite response was achieved in 10% of the LNF/RTV treatment group and 22.8% of the LNF/RTV + PEG treatment group.

HDV RNA <LLOQ was achieved in 8.4% (15 of 178) LNF/RTV patients at EOT and 6.1% (9 of 148) at EOS, 3 of which represent durable response. Viral suppression was stronger in the LNF/RTV + PEG combination group, with HDV RNA <LLOQ achieved in 20.8% (26 of 125) of patients at EOT and 22.7% (25 of 110) of patients at EOS, 13 of which were durable from EOT. Corresponding rates in the placebo group were 3.8% (2 of 52) at EOT and 2.6% (1 of 39) at EOS.

Conclusions: Oral LNF/RTV is a first-in-class HDV therapy with efficacy and safety in HDV patients and substantial benefit after treatment cessation. Among patients treated with LNF/RTV or LNF/RTV + PEG composite treatment response after a 48-week treatment course was durable through a 24-week follow-up and some non-responders achieved composite response off treatment. This analysis of off-treatment response supports the continued development of lonafarnib-based therapy as a 48-week treatment regimen for HDV either with or without PEG.



CURRENT AND NEW ANTIVIRAL TREATMENTS

OTHER THERAPEUTIC APPROACHES FOR HDV

P29 CLINICAL SIGNIFICANCE OF ALT DYNAMICS FOLLOWING LONAFARNIB TREATMENT CESSATION IN THE PHASE 3 D-LIVR TRIAL

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Background: Alanine aminotransferase (ALT) elevations have been reported following treatment discontinuation of currently available chronic hepatitis D virus (HDV) infections, but their clinical significance remains uncertain. Lonafarnib (LNF), an oral host-targeting farnesyltransferase inhibitor being advanced as a 48-week treatment regimen for the treatment of HDV has been associated with transient ALT elevations following treatment cessation in phase 2 studies. Exploratory analysis of phase 3 D-LIVR study data seeks to characterize post-treatment ALT elevations to define their clinical significance.

Method: D-LIVR is a Phase 3 randomized placebo-controlled HDV study (N=407) evaluating LNF/RTV with or without peginterferon alfa-2a (PEG), with primary composite endpoint defined as a ≥ 2 log reduction in HDV RNA and ALT normalization compared to baseline at 48-weeks (end of treatment [EOT]). D-LIVR also included a 24-week off-treatment follow-up period to evaluate post-treatment efficacy and safety after treatment cessation (end of study [EOS]).

As part of the predefined analysis, ALT elevations were flagged based on $> 3 \times \text{ULN}$ and $> 10 \times \text{ULN}$ thresholds. The frequency, severity, association with other laboratory abnormalities (INR $> 2 \times \text{ULN}$ or bilirubin $> 2.5 \times \text{ULN}$), and associated viral load kinetics were evaluated to characterize their impact on overall LNF risk/benefit profile.

Results: Both LNF-containing regimens met the primary composite efficacy endpoint compared to placebo (LNF/RTV: $p = 0.004$, LNF/RTV + PEG: $p < 0.0001$).

Post-treatment ALT elevations were reported among LNF-treated patients. $> 3 \times \text{ULN}$ elevations were reported in 47% (70 of 148) and 41% (45 of 110) of patients in the LNF/RTV and LNF/RTV + PEG groups, respectively, and were not more common among cirrhotic patients. ALT $> 10 \times \text{ULN}$ were less frequent, reported in 7.4% (11 of 148) and 6.4% (7 of 110) of patients in the LNF/RTV and LNF/RTV + PEG groups. No post-treatment ALT elevations were associated with concurrent laboratory abnormalities of interest, and there were no reports of hepatic decompensation among study participants, regardless of cirrhosis status at baseline.

Of the $> 10 \times \text{ULN}$ elevations reported in D-LIVR, none were associated with subsequent increases in HDV RNA ($> 1 \log_{10} \text{ IU/mL}$), whereas most (71% and 66% in LNF/RTV and LNF/RTV + PEG, respectively) were associated with a subsequent decline in HDV RNA ($> 1 \log_{10} \text{ IU/mL}$).

Conclusions: Lonafarnib remains the only late-stage oral agent under development for the treatment of chronic hepatitis D virus (HDV). Post-treatment ALT elevations following lonafarnib-based treatment cessation were generally transient, infrequently severe, and were not associated with evidence of clinically significant liver injury or hepatic decompensation. Their frequent association with subsequent declines in HDV RNA, together with independent review by a hepatic adjudication committee, suggests that these events may reflect a favorable host response rather than treatment-related hepatotoxicity.



CURRENT AND NEW ANTIVIRAL TREATMENTS

OTHER THERAPEUTIC APPROACHES FOR HDV

P30 BRELOVITUG MONOTHERAPY FOR THE TREATMENT OF CHRONIC HEPATITIS D: PRIMARY 24 WEEK EFFICACY AND SAFETY RESULTS FROM THE AZURE-1 PHASE 2B STUDY

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Background: Chronic Hepatitis D (CHD) is the most severe form of viral hepatitis, and current treatments are limited. Brelovitug (BJT-778) is a fully human monoclonal antibody against Hepatitis B surface antigen. Brelovitug is currently being evaluated in AZURE-1(NCT06907290), a global, randomized, Phase 2b/3 trial vs delayed treatment (DT) in adults with CHD. Here we report on the primary 24-week efficacy and safety results from AZURE-1 phase 2b.

Methods: Participants were randomized 2:2:1 to receive brelovitug 300 mg subcutaneous (SC) weekly (QW) self-administered at home, 900 mg SC every 4 weeks (Q4W) administered in clinic, or DT for 24 weeks followed by brelovitug 300mg QW. Key inclusion criteria included hepatitis D virus (HDV) RNA >500 IU/mL, ALT >upper limit of normal (ULN), and Child–Turcotte–Pugh (CTP) Score <7; HIV co-infection and compensated cirrhosis with or without clinically significant portal hypertension (CSPH) were allowed. There were no exclusion criteria for liver stiffness, bilirubin, albumin, INR or maximum ALT. The primary endpoint (PE) was a composite of virologic response (HDV RNA ≥ 2 log₁₀ IU/mL decline or <LLOQ/TND) and ALT normalization at W24.

Results: A total of 53 participants were randomized and dosed; 21 to 300 mg QW, 20 to 900 mg Q4W, and 12 to DT. Mean (SD) age overall was 46 (8.2) years, 49 (92%) were White, 37 (70%) were male, and 28 (53%) had cirrhosis. Mean (SD) baseline HDV RNA was 5.5 (0.83) log₁₀ IU/mL and ALT was 124 (95.3) U/L, including 11 (21%) with ALT $\geq 5 \times$ ULN, 8 (15%) with liver stiffness >25kPa, and 2/28 (7%) with cirrhosis had a CTP score of 6. There were 14 (26%) participants with probable CSPH by Baveno VII criteria (LSM 15–20 kPa with platelets <110,000/ μ L or LSM 20–25 kPa with platelets <150,000/ μ L or LSM ≥ 25 kPa). Virologic response and ALT normalization at 24 weeks are shown in Table 1. ALT normalization at any time up to and including Week 24 occurred in 60% (12/20) and 50% (10/20) of the 300 mg QW and 900 mg Q4W groups, respectively. Seven participants (13%) reported mild injection site reactions and 1 reported mild flu-like syndrome. There was 1 SAE of hospitalization of liver cirrhosis, class B, in a participant with a recent history of ascites and hypoalbuminaemia, not related and resolved. There were no treatment-related SAEs, Grade ≥ 3 AEs, or AEs leading to study discontinuation.

Conclusions: In individuals with CHD, brelovitug demonstrated significant improvements in both HDV RNA and ALT (combined endpoint) and was well-tolerated at 24 weeks. The AZURE-1 Phase 3 trial and other phase 3 trials for brelovitug in CHD patients are ongoing.



CURRENT AND NEW ANTIVIRAL TREATMENTS

OTHER THERAPEUTIC APPROACHES FOR HDV

P31 BRELOVITUG MONOTHERAPY FOR THE TREATMENT OF CHRONIC HEPATITIS D: PRIMARY 24-WEEK EFFICACY AND SAFETY RESULTS IN PATIENTS WITH BASELINE PLATELET COUNTS <100,000/ML FROM THE AZURE-1 PHASE 2B STUDY

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Background: Chronic Hepatitis D (CHD) is the most severe form of viral hepatitis with limited treatments. Brelovitug (BTG), a fully human monoclonal antibody against hepatitis B surface antigen, is being evaluated in AZURE-1 (NCT06907290), a global, randomized, Phase 2b/3 trial vs delayed treatment (DT) in adults with CHD. We report a subanalysis of AZURE-1 phase 2b evaluating 24-week efficacy and safety outcomes in patients with a baseline (BL) platelet count <100,000/ μ L, a surrogate for portal hypertension.

Methods: Participants were randomized 2:2:1 to receive BTG 300 mg subcutaneous (SC) weekly (QW) self-administered at home, 900 mg SC every 4 weeks (Q4W) administered in clinic, or DT for 24 weeks followed by BTG 300mg QW. Key inclusion criteria included hepatitis D virus (HDV) RNA >500 IU/mL, ALT >upper limit of normal (ULN), and CTP Score <7; HIV co-infection and compensated cirrhosis with or without portal hypertension were allowed. There were no exclusion criteria for liver stiffness, bilirubin, albumin, INR or maximum ALT. The primary endpoint was a composite of virologic response (HDV RNA ≥ 2 log₁₀ IU/mL decline or <LLOQ/TND) and ALT normalization at W24.

Results: A total of 53 participants were randomized; 21 to 300 mg QW, 20 to 900 mg Q4W, and 12 to DT. Of these, 11 (21%) participants assigned to 300 mg, 900 mg, or DT arms had baseline platelet counts <100,000/ μ L and 10 had post baseline data. In this subgroup (n=10), mean (SD) age was 48.5 (6.92) years, 10 (100%) were White, 7 (70%) were male, and 9 (90%) had cirrhosis. Mean (SD) baseline HDV RNA was 5.0 (1.05) log₁₀ IU/mL and ALT was 107 (80.0) U/L, including 2 (20%) with ALT ≥ 5 x ULN; 4(40%) had liver stiffness (LS) >25 kPa, and 1/9 (11%) with cirrhosis (LS ≥ 12.5 kPa) had a CTP score of 6 at screening or baseline. Mean (SD) platelet count was 75.6 (20.8) at baseline and 71.1 (19.0) at Week 24. Virologic response and ALT normalization at Week 24 are shown in Table 1. BTG was safe and well-tolerated in participants with baseline platelets <100,000/ μ L. All AEs were grade 1 or 2 in severity similar to the overall cohort. One participant (900 mg), with baseline CTP 6 and recent history of ascites and hypoalbuminemia, reported an SAE of hospitalization for liver cirrhosis class B, which was considered not related to study drug and resolved. None reported flu-like illness.

Conclusions: Brelovitug demonstrated robust antiviral and biochemical activity and favorable safety profile in individuals with fully compensated cirrhosis, including those with portal hypertension, supporting its potential as a treatment option in this high-risk population from the AZURE-1 Phase 2b study. Platelet counts remained unchanged through Week 24. The AZURE-1 Phase 3 trial and other phase 3 trials for brelovitug in CHD patients are ongoing.



CURRENT AND NEW ANTIVIRAL TREATMENTS

OTHER THERAPEUTIC APPROACHES FOR HDV

P32 EFFICACY AND SAFETY OF PEGYLATED INTERFERON ALFA-2A IN PATIENTS WITH CHRONIC HEPATITIS DELTA IN MONGOLIA

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Background & Aims: Mongolia has the highest global prevalence of Hepatitis Delta Virus (HDV), with approximately 60% of HBsAg-positive individuals co-infected with HDV—far exceeding the global average of 4–5%. This translates to a severe public health burden, as HDV drives the most aggressive course of viral hepatitis, characterized by rapid progression to cirrhosis and hepatocellular carcinoma. Despite this high prevalence, treatment data from Mongolian patients remain limited, and peg-IFN (48 weeks only). This study aims to evaluate the real-world efficacy and safety of Peg-IFN-alpha-2a in patients with chronic HDV infection in Mongolia.

Methods: A total of 84 patients with chronic hepatitis Delta (excluded patients received combined treatments of peg-IFN with Bulevirtide) had been received peg-interferon with or without Bulevirtide for a duration of 2-106 weeks since 2023 at the Liver Center, Ulaanbaatar Mongolia. A total of 74 patients received peg-IFN for durations ranging from 2 to 106 weeks. The cirrhosis rate (liver stiffness >12.5 kPa) was 14.9% (11/74). Of the 74 patients, 43 patients are still using peg-IFN or discontinued the treatment before 48 weeks. The remaining 31 patients have been treated with peg-IFN for 48 weeks or more (65.3±15.6 wks). The virological, biochemical, and liver stiffness parameters had been collected during treatment. Safety was assessed by monitoring adverse events.

Results: Main analysis was performed using data of these 31 patients. Mean age was 42.4 ± 7.6 and 24 (77.4%, 24/31) were male. Biochemical and virological parameters during treatment are summarized in Table 1. Baseline ALT declined through week 24, with a mild rebound to 75.7 U/L at week 48. Dose modifications due to leukopenia and neutropenia required in 12.9% (4/31) of patients. At baseline, 35.5% (11/31) of patients had detectable HBV-DNA (>10 IU/mL); by week 48, all patients had achieved undetectable HBV-DNA. HBeAg positivity decreased from 25.8% (8/31) at baseline to 12.9% (4/31) by week 24. Serum HBsAg levels declined modestly, but a >2 log reduction observed in only one patient. Baseline HDV-RNA was high (6.1 log₁₀ IU/mL) but declined steadily at week 48. The proportion of patients achieving undetectable HDV-RNA increased progressively over time: 3.2% (1/31) at week 12, 19.4% (4/31) at week 24, and 29.0% (5/31) at week 48. Despite undetectable HDV-RNA, ALT failed to normalize, suggesting that MASLD and elevated ferritin—potentially related to high red meat intake—should be assessed in these patients.

Conclusion: Peg-IFN achieved potent antiviral effects, HDV-RNA clearance in nearly one-third by week 48 (mean 2.2 log₁₀ reduction). However, biochemical improvements lagged—ALT failed to normalize despite viral suppression. The persistent ALT and GGT elevation despite undetectable HDV-RNA warrants evaluation for MASLD and hyperferritinemia (high red meat intake) as potentially modifiable contributors.



CURRENT AND NEW ANTIVIRAL TREATMENTS

OTHER THERAPEUTIC APPROACHES FOR HDV

P33 MATHEMATICAL MODELING REVEALS MECHANISMS OF RESPONSE TO PEGYLATED INTERFERON-ALPHA IN CHRONIC HEPATITIS D: INSIGHTS FROM THE D-LIVR STUDY

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Background: Even in the era of emerging therapies for chronic HDV, pegylated-interferon-alpha (IFN) may retain a role as a component of combination regimens. Understanding the mechanisms of IFN in the treatment of HDV will be important to optimize patient selection and inform combination strategies. However, longitudinal data with frequent sampling suitable for kinetic analysis during IFN monotherapy, is scarce. The Phase 3 D-LIVR trial, provides a unique opportunity for HDV kinetic analysis and mathematical modelling under IFN.

Methods: D-LIVR (NCT03719313) included 52 patients treated with IFN plus oral placebo for 48 weeks. HDV RNA, quantitative HBsAg, and ALT were measured at treatment weeks 1, 2, 4 of therapy and every 4 weeks thereafter, through end of treatment. Consistent with our previous study [Hepatology 2014;60:1902–1910], we focused on the first 24 weeks of therapy. We applied a recently developed mathematical model incorporating target cell dynamics [Antiviral Res. 2026 Jul 17:106489]. Of 52 patients, 29 were excluded because of treatment discontinuation (n=11), inadequate response or dose reduction (n=10) or an HDV RNA decline <1.6 log, that was insufficient for reliable kinetic parameter estimation (n=8).

Results: Among 23 evaluable patients, seven (30%) had an initial HDV RNA decline followed by a plateau (Fig. 1A), two (9%) had a monophasic decline (Fig. 1B), 10 (43%) exhibited a biphasic decline (Fig. 1C-D), and four (17%) experienced viral increase, on treatment, termed herein breakthrough (Fig. 1E). Among those with a biphasic HDV RNA decline, four had declining HBsAg (Fig. 1C) and six had stable HBsAg (Fig. 1D); one participant with a monophasic decline also had declining HBsAg. The model estimated a median delay of 10 days (IQR, 3.8–15) before HDV RNA decline and a median 97% inhibition of HDV production (IQR, 89%–99.8%). HBsAg decline began in 5/23 patients (22%) after a median of 81 days (IQR, 80–83) and was explained by a delayed secondary effect of IFN, with a median 97% inhibition of HBsAg production (IQR, 92%–99.6%). Stable HBsAg in 18/23 patients (78%) was consistent with maintenance of the HBsAg-producing cell population.

Conclusions: A model incorporating target cell dynamics reproduced the observed HDV and HBsAg kinetic patterns and indicated that IFN primarily acts as a potent inhibitor of HDV production. A subset (22%) of patients had a delayed HBsAg decline, which modeling explained by reduced HBsAg production without infected-cell loss, consistent with findings in HDV/HBV-coinfected humanized mice [Virus Res 2024;349:199451]. Five of 12 patients with mono- or biphasic HDV declines subsequently experienced on-treatment breakthrough or post-treatment rebound, supporting further evaluation of combination regimens.



CURRENT AND NEW ANTIVIRAL TREATMENTS

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P34 A 2LOG DECREASE IN HDV RNA PLUS NORMAL ALT 6 MONTHS POST LONAFARNIB-BASED THERAPY FOR HEPATITIS DELTA VIRUS (HDV) IS SUFFICIENT FOR LONG-TERM CLINICAL BENEFIT

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Background: Lonafarnib (LNF) is in advanced clinical development for hepatitis delta virus (HDV), the most severe form of human viral hepatitis.

Material and methods: A recent long-term follow-up assessment of multiple phase 2 and 3 studies revealed that patients achieving a composite endpoint ($\square$ 2 log drop in HDV RNA or undetectable HDV RNA + ALT normalization) 6 months post-treatment (6MPT) of any LNF-based therapy (monotherapy, combination with ritonavir, interferon alfa or lambda, of 2, 3, 6, or 12 months duration) experienced no major clinical event (liver decompensation, hepatocellular cancer (HCC), transplantation, or death) in up to over 10 years of follow-up. Although undetectable HDVRNA off treatment may appear as a reasonable surrogate marker of treatment efficacy, there is no defined efficacy threshold for HDVRNA levels in preventing these clinical events in patients receiving finite treatment for HDV-induced chronic liver disease.

Results: In patients with hepatitis B virus (HBV) or HDV-induced liver disease, finite treatment necessitates a drug with immune-stimulatory properties. The farnesyl transferase inhibitor LNF both directly inhibits release of infective virions and leads to the stimulation of the immune system, including interferon-stimulated gene expression. This study retrospectively assessed the phase 2 LOWR1, LOWR 2 and LIFT studies performed in Ankara, Turkey and Bethesda, USA, and the phase 3 D-LIVR study center in Istanbul, Turkey. HDVRNA levels were measured with an in-house real-time PCR assays in Ankara and one commercial assay in Istanbul with different assay sensitivities (LLQ was 3.8 log IU/mL in Ankara and 1.6 log IU/mL in Istanbul, respectively). 14 patients reached the co-primary endpoint. 10/14 patients (71%) achieving the composite endpoint 6MPT of LNF-based therapy had HDV RNA <LLOQ, but 4/14 (29%) patients did not, and had just $\square$ 2 log drop in HDV RNA. It is important to note that in LOWR 1 and 2 studies, of 5 patients with the composite endpoint, 4(80%) had 6MPT undetectable HDVRNA levels with the inhouse PCR assay (LLOQ: 3.8logs IU/mL), whereas of 4 patients with the composite endpoint in the D-LIVR study only one patient had undetectable HDVRNA with the commercial assay (LLOQ: 1.6 logs IU/mL), raising the potential possibility that an even greater percentage of the 14 patients may not have achieved undetectability with a more sensitive assay.

Conclusions: We conclude that ALT normalization plus a >2log (IU/mL) decrease in HDVRNA as composite response appears to be sufficient for prediction of long-term clinical benefit following LNF-based finite therapy.



CURRENT AND NEW ANTIVIRAL TREATMENTS

OTHER THERAPEUTIC APPROACHES FOR HDV

P35 THE EFFICACY AND SAFETY OF SIRNA OZISIRAN IN PATIENTS WITH CHRONIC HEPATITIS D: INTERIM RESULTS THROUGH TREATMENT WEEK 36 FROM THE PHASE 2A RC04T001 TRIAL

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Background: Ozisiran (RBD1016) is a small interfering RNA (siRNA) that suppresses HBsAg production. We evaluated the efficacy and safety of ozisiran in combination with a nucleotide analogue in patients with chronic hepatitis D (CHD), with interim analysis through Week 36.

Material and Methods: This Phase 2a trial includes a randomized, single-blind, placebo-controlled exploratory phase and enrolled 14 participants with CHD at Karolinska University Hospital and Danderyd Hospital, Stockholm, Sweden. Eligible participants were non-cirrhotic, with liver stiffness < 10 kPa and HBsAg levels < 10,000 IU/mL. Participants were allocated to an active treatment group (n=9) or a deferred treatment group (n=5), with the latter receiving placebo for 16 weeks before active treatment. Ozisiran 300 mg was administered subcutaneously at Weeks 0, 4, 8, 12, 36 and 48. All participants received tenofovir alafenamide (TAF). ALT flares were defined as ALT ≥ 3x the upper limit of normal (ULN) and ≥ 2x the nadir value, or ALT ≥ 3x ULN at baseline. In this interim analysis, safety and efficacy were evaluated through Week 36, including four doses of ozisiran over 12 weeks followed by a 24-week dose-free interval.

Results: Baseline characteristics are shown in Table 1. Mean (SD) log₁₀ HDV RNA decreased from 4.6 (1.7) at baseline to 3.9 (1.7) at Week 24 and remained at 3.9 (1.9) at Week 36. Mean (SD) log₁₀ HBsAg decreased from 3.5 (0.8) at baseline to 2.0 (0.7) at Week 24 and was 2.6 (1.0) at Week 36, with 7/14 (50%) participants achieving HBsAg < 200 IU/mL at Week 36. Most adverse events were mild, with the exception of Grade 2-4 ALT elevations. ALT flares occurred in 8 (57%) participants. No serious adverse events occurred. Two participants developed Grade 4 ALT elevations (> 20 x ULN) at treatment Weeks 22 and 26, respectively, and received bulevirtide (BLV) 2 mg SC QD. ALT levels normalized to < ULN within 6-8 weeks after BLV initiation, allowing both participants to continue ozisiran without recurrent ALT elevations. One participant with a moderate ALT-flare discontinued ozisiran at Week 36 at the investigator's discretion because of suspected autoimmune hepatitis (AIH). ANA and SMA positivity and elevated IgG were already present at baseline, with IgG increasing from 18.3 to 23.3 g/L by Week 27. Liver biopsy showed grade 2 inflammation and stage 1 fibrosis (Batts-Ludwig), without specific findings supporting AIH. Among participants without ALT flares (n=6), mean (SD) log₁₀ HDV RNA decreased from 3.7 (2.1) at baseline to 2.4 (1.3) at Week 24 and was 3.0 (1.8) at Week 36, and mean (SD) log₁₀ HBsAg decreased from 3.0 (1.0) at baseline to 1.4 (0.5) at Week 24 and 1.6 (0.6) at Week 36.

Conclusions: Ozisiran resulted in reductions in HDV RNA and HBsAg through Week 36 in this Phase 2a trial, with a substantial proportion of the participants achieving low HBsAg levels of < 200 IU/mL. The few cases of high-grade ALT flares were successfully managed with BLV therapy.



UNMET NEEDS IN HDV

GLOBAL MODELING OF HDV ANTIVIRAL THERAPY IMPACT

P36 CLINICAL IMPACT OF MULTIDISCIPLINARY CARE IN AN ONCOLOGY PATIENT WITH HIV AND CHRONIC VIRAL HEPATITIS RECEIVING CHEMOTHERAPY

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Background: Viral coinfections remain a challenging and highly relevant issue for infectious disease specialists, particularly in clinical settings where immunomodulatory therapies are required. These conditions demand careful evaluation of viral reactivation risks, drug–drug interactions, and patient adherence to antiviral regimens.

Materials and Methods: We describe the clinical case of a 43-year-old Ukrainian man with HIV infection diagnosed in 2002, historically poorly adherent to antiretroviral therapy. His medical history included HCV co-infection treated with interferon and ribavirin, chronic HBV infection with HBcAb positivity, and active alcohol consumption.

Results: At presentation to our center, the patient was receiving HAART with raltegravir/emtricitabine/tenofovir disoproxil fumarate, with documented poor adherence. In September 2025, due to detectable HIV viremia, resistance testing was performed through viral genome amplification and Sanger sequencing. Therapy was subsequently switched to bicittegravir/emtricitabine/tenofovir alafenamide, resulting in rapid viral load reduction.

In January 2026, the patient was diagnosed with metastatic cholangiocarcinoma and evaluated for chemotherapy with cisplatin, durvalumab, and gemcitabine. Infectious disease consultation included assessment of potential interactions between antiretrovirals and oncologic agents. Updated viral screening revealed reappearance of HBsAg positivity and HDV co-infection, with detectable HDV DNA. Antiviral therapy with bulevirtide was initiated, while the existing HAART regimen—also active against HBV—was maintained.

Pharmacological evaluation: indicated no clinically significant interactions between BIC/FTC/TAF and gemcitabine or durvalumab. A potentially beneficial interaction with cisplatin was noted: bicittegravir inhibits OCT2, reducing cisplatin uptake into renal tubular cells and potentially lowering nephrotoxicity risk. However, cisplatin-related renal impairment could affect emtricitabine elimination, warranting close monitoring of creatinine clearance. No significant interaction was expected with tenofovir alafenamide.

Given the patient's improved adherence, declining HIV RNA levels, persistently undetectable HBV DNA, and initiation of HDV targeted therapy, infectious disease specialists authorized chemotherapy, with strict monitoring of HIV, HBV, and HDV viral loads in accordance with EACS and EASL recommendations.

Conclusion: The patient died in March 2026 due to severe complications and multiorgan failure related to terminal oncologic disease. Although the clinical outcome was unfavorable, this case underscores the crucial role of multidisciplinary collaboration—infectious disease physicians, oncologists, and clinical pharmacologists—in managing highly complex patients with multiple viral co-infections undergoing immunomodulatory cancer therapy.



UNMET NEEDS IN HDV

GLOBAL MODELING OF HDV ANTIVIRAL THERAPY IMPACT

P37 BEYOND FIBROSIS: CHRONIC HEPATITIS D IS ASSOCIATED WITH WORSE PATIENT-REPORTED OUTCOMES AND A DISTINCT CLINICAL BURDEN COMPARED WITH HEPATITIS B

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Background: Chronic hepatitis D virus (HDV) infection is uncommon, but contemporary data on disease severity and patient experience are sparse. We aimed to characterize the clinical profile and patient-reported outcomes (PROs) of patients with chronic HDV and compare them with hepatitis B virus (HBV) mono-infection.

Methods: Adults with HDV and HBV enrolled in the Global Liver Registry were included in this analysis. Advanced fibrosis was defined as a liver stiffness measurement (LSM) ≥ 8 kPa. Clinical parameters and PROs (CLDQ-HBV, FACIT-F, WPAI:HBV) were compared between the HDV and HBV groups.

Results: We included 210 subjects with HBV infection (N=46 with HDV co-infection; N=164 with HBV mono-infection). Patients with HDV had a mean (SD) age of 47.7 (11.3) years; 58.7% were male, 64.4% were on antiviral treatment, and 62.8% had detectable HDV viremia. Compared with HBV, HDV was associated with higher ALT and AST, lower platelet count, higher FIB-4 score (2.55 (2.87) vs. 1.46 (1.50)), and higher LSM (15.7 (17.4) vs. 6.2 (4.6) kPa) (all $p < 0.0001$). Advanced fibrosis was present in 56.8% of patients with HDV vs. 15.1% of HBV mono-infection ($p < 0.0001$). HDV remained independently associated with advanced fibrosis after adjustment for confounders (OR 11.3, 95% CI 4.3–29.9). Furthermore, in the HDV patients, detectable HDV RNA was independently associated with advanced fibrosis (79.2% viremic among those with advanced fibrosis vs. 38.9% among those without; adjusted OR 7.9, 95% CI 1.6–38.2). Beyond liver-related outcomes, patients with HDV had lower CLDQ-HBV Worry domain scores (5.5 (1.4) vs. 6.0 (1.3), $p = 0.011$) and greater activity impairment by WPAI (0.20 (0.30) vs. 0.06 (0.18), $p < 0.0001$). Emotional well-being (FACIT-F) in HDV was lower than the general population norm (18.6 vs. 19.9, $p = 0.039$). In multivariate analysis, HDV was independently associated with lower CLDQ-HBV Sleep ($\beta = -0.61 \pm 0.24$, $p = 0.012$) and Worry domain scores ($\beta = -0.40 \pm 0.20$, $p = 0.049$), and with greater activity impairment ($\beta = +0.14 \pm 0.03$, $p < 0.001$). Among patients with HDV, male sex was associated with better PROs, whereas a history of type 2 diabetes, fatigue, anxiety, depression, and sleep apnea were associated with PRO impairment (all $p < 0.05$).

Conclusion: Patients with HDV have substantially greater liver disease severity and impaired patient-reported outcomes compared with those HBV mono-infected. These findings emphasize the need for earlier diagnosis and effective HDV-directed therapies aimed not only at preventing cirrhosis but also at improving patients' quality of life.



UNMET NEEDS IN HDV

MASLD/MASH IN HBV AND HDV

P38 CARDIOMETABOLIC PROFILE OF EUROPEAN PATIENTS WITH CHRONIC HEPATITIS DELTA: INSIGHTS FROM THE SAVE-D AND D-SHIELD COHORTS

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Background and Aim: Metabolic dysfunction is increasingly recognized as an important modifier of disease progression and treatment outcomes in chronic liver diseases. However, the burden of cardiometabolic comorbidities and their influence on antiviral therapy in chronic hepatitis delta (CHD) remain largely unexplored. This study investigated the prevalence of cardiometabolic risk factors in European patients with CHD and assessed their association with response to Bulevirtide (BLV).

Methods: Patients enrolled in the multicenter retrospective European SAVE-D study and the multicenter prospective Italian D-SHIELD study receiving BLV monotherapy (2 mg/day) were included. Baseline prevalence of arterial hypertension (AHTN), type 2 diabetes mellitus (T2DM), overweight/obesity, body mass index (BMI), and hepatic steatosis assessed by controlled attenuation parameter (CAP) on Fibroscan® were evaluated. Their association with



virological and biochemical treatment outcomes at week 48 was analyzed.

Results: The study included 828 patients (median age 52 [IQR 42–60] years; 57% male), of whom 698 (84%) had cirrhosis. Median BMI was 24.8 (22.7–27.4) kg/m². T2DM was present in 39 patients (5%), arterial hypertension in 126 (15%), and obesity (BMI ≥30 kg/m²) in 85 (10%), including 13 (15%) with grade II and 2 (2%) with grade III obesity. CAP measurements were available in 484 patients (59%), with a median value of 209 (181–238) dB/m. Hepatic steatosis (CAP >275 dB/m) was identified in 50 patients (5%), who had a median BMI of 28.4 kg/m²; among them, 12% had T2DM and 22% had arterial hypertension. Patients with T2DM had lower baseline ALT (62 vs. 79 U/L, $p=0.04$) and GGT (44 vs. 58 U/L, $p=0.03$) than those without diabetes. At multivariable analysis, higher CAP values were the only baseline variable associated with biochemical response at week 48 (OR 1.01, 95% CI 1.00–1.02; $p=0.02$). No association was observed between cardiometabolic risk factors, BMI, or CAP and virological response, combined response, or HDV RNA undetectability after 48 weeks of BLV monotherapy.

Conclusions: Cardiometabolic comorbidities were infrequent in this large European CHD cohort, confirming a distinct metabolic profile, compared with other chronic liver diseases. Baseline metabolic risk factors did not adversely influence virological or combined treatment outcomes during the first year of Bulevirtide monotherapy.



UNMET NEEDS IN HDV

LIVER TRANSPLANTATION FOR HDV

P39 HDV INFECTION IN THE LIVER TRANSPLANTATION SETTING: LESS RARE THAN EXPECTED BUT ASSOCIATED WITH EXCELLENT OUTCOMES

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Background and aims: HDV infection is the most severe form of viral hepatitis. The burden of HDV in the liver transplantation (LT) setting and post-transplant outcomes in HDV-recipients remain incompletely defined. We aimed to assess the prevalence of HDV among HBsAg-positive LT recipients and to evaluate post-LT survival, HBV recurrence, and HCC recurrence.

Methods: This is a subanalysis of a previously published retrospective multicentre study including HBsAg positive patients with/without HDV and with/without HCC who underwent LT across 20 Italian LT centres between 2010 and 2021. Pre-transplant characteristics, post-transplant antiviral prophylaxis regimens and outcomes were compared between HDV- and HBV-recipients. Cox regression models were used to identify factors associated with post-LT outcomes.

Results: A total of 1357 LT recipients were included, of whom 53.5% had HDV. At LT, HDV-patients were younger (55 vs. 58 years, $p < 0.001$), had more advanced liver disease (Child C 34% vs. 25%, $p < 0.001$), lower prevalence of HCC (53.5% vs. 68.9%, $p < 0.001$) and lower tumour burden than HBV-patients. Unadjusted HCC-recurrence was lower in HDV-patients than in HBV-patients (7.8% vs. 13.6%, $p = 0.010$). However, after multivariable Cox regression analysis, HDV status was not independently associated with HCC-recurrence, whereas microvascular invasion remained the strongest predictor of recurrence (adjusted HR 2.92, 95% CI 1.60–5.33, $p < 0.001$). After LT, HDV-patients more frequently received lifelong combined HBIG+NUCs prophylaxis than HBV-patients (92% vs. 82%, $p < 0.001$). Lifelong HBIG+NUC prophylaxis was associated with the lowest risk of HBV-recurrence compared to HBIG-free or HBIG short-course regimen (aHR 0.19, 95% CI 0.08–0.44, $p < 0.001$) (Figure 1). Post-LT HBV-recurrence was similar in HDV- and HBV-patients (2.2% vs. 2.5%, respectively).

Five- and 10-year post-LT patient survival was 91.0% and 85.0% in HDV-patients versus 83.7% and 72.1% in HBV-patients ($p < 0.001$). The survival advantage of HDV-patients remained both in patients without HCC (5- and 10-year



survival: 94.2% and 86.9% vs. 85.1% and 77.8%; $p=0.001$) and in those with HCC (88.2% and 83.4% vs. 82.9% and 69.3%; $p=0.010$) (Figure 2A, 2B and 2C). In HDV-patients, the use of life-long HBIG was independently associated with improved survival both in HCC (aHR 0.41 95%CI 0.20-0.87, $p=0.019$) and non-HCC patients (aHR 0.26 95%CI 0.11-0.59, $p=0.001$).

Conclusions: Although HDV is associated with more severe liver disease, post-LT outcomes are excellent. HDV was not associated with increased HBV-recurrence, HCC-recurrence, patient mortality, or graft loss after LT. Lifelong HBIG +NUC prophylaxis was associated with the lowest HBV-recurrence risk and improved survival in HDV-patients with and without HCC. These findings support the importance of optimized long-term HBV prophylaxis after LT in HDV-recipients.

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UNMET NEEDS IN HDV

LIVER TRANSPLANTATION FOR HDV

P40 HEPATITIS D AND LIVER TRANSPLANTATION OVER TWO DECADES: YOUNGER RECIPIENTS, MORE DECOMPENSATED DISEASE, BUT SUPERIOR POST-TRANSPLANT SURVIVAL. A STUDY FROM THE ELTR (EUROPEAN LIVER TRANSPLANT REGISTRY)

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Background: Hepatitis D virus (HDV) related liver disease is an uncommon but clinically important indication for liver transplantation (LT). In the era of emerging HDV-directed therapies, understanding the long-term outcomes of patients requiring liver transplantation is critical to defining the future burden of end-stage HDV liver disease. We compared the clinical presentation and post-transplant outcomes of LT recipients with HDV coinfection versus those with HBV mono-infection.

Methods: Adult LT recipients with HBV infection were identified from the European Liver Transplant Registry (ELTR, 2000–2022). Clinical parameters and post-LT mortality were summarized according to the presence of HDV coinfection, as determined by the listing diagnosis.

Results: Among 9,405 HBV-infected recipients, 2,230 (24%) had HDV coinfection (HDV group) and 7,175 (76%) had HBV mono-infection (HBV group). The proportion of HDV among HBV-infected LT recipients rose from 19% in 2000 to a peak of 30% in 2014, then declined to 25% in 2021. Compared with the HBV group, HDV patients were younger (48 ± 10 vs. 53 ± 10 years), had lower BMI (25.3 ± 3.9 vs. 26.3 ± 4.2), and were less often male (68% vs. 84%; all $p < 0.0001$) and had higher pre-transplant MELD scores (17.4 ± 7.2 vs. 15.9 ± 7.6 , $p < 0.0001$) and more frequent pre-transplant ascites (65% vs. 50%) and hepatic encephalopathy (29% vs. 21%; both $p < 0.0001$). Fewer HDV patients were listed with hepatocellular carcinoma (HCC) (27% vs. 45%, $p < 0.0001$), although the proportion of HCC in the HDV group increased over time (22% in 2000–2004 vs. 27% in 2018–2022, $p = 0.003$). Despite this more severe pre-transplant phenotype, patients with HDV experienced significantly lower post-transplant mortality than those without HDV, with cumulative mortality of 14% versus 26% over a median (IQR) follow-up of 3 (1–9) years. Mortality rates at 1, 3, 5, and 10 years were 8% versus 14%, 14% versus 24%, 19% versus 32%, and 32% versus 46%, respectively (all $p < 0.01$). Similar trends were observed among patients without HCC (1-year 8% vs. 16%, 3-year 12% vs. 25%, 5-year 16% vs. 31%, 10-year 28% vs. 46%; all $p < 0.01$), whereas differences among patients with HCC were less pronounced (1-year 10% vs. 12%, 3-year 19% vs. 23%, 5-year 25% vs. 32%, 10-year 39% vs. 47%; all $p > 0.01$). Older age was the only significant predictor of post-transplant mortality in the HDV group (aHR 1.03 per year, 95% CI 1.01–1.05, $p = 0.002$).

Conclusion: Compared with HBV mono-infected patients, HDV patients are younger but more often listed for decompensated liver disease, underscoring the need for effective therapies to suppress HDV replication. Nonetheless, HDV patients achieve similar or more favorable post-transplant outcomes than those transplanted for HBV mono-infection.



UNMET NEEDS IN HDV

LIVER TRANSPLANTATION FOR HDV

P41 EXCELLENT LONG-TERM SURVIVAL AND LOW VIRAL RECURRENCE AFTER LIVER TRANSPLANTATION FOR HBV/HDV COINFECTION

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Background/Objectives: Hepatitis D virus (HDV) is hyperendemic in Romania and causes the most aggressive form of chronic viral hepatitis, yet single-centre outcomes after liver transplantation (LT) for HBV/HDV coinfection from this region are lacking. We report ten-year outcomes of one of the largest single-centre coinfecting cohorts.

Methods: We retrospectively studied 236 patients transplanted for HBV/HDV-related cirrhosis. Overall survival was estimated by the Kaplan–Meier method (patients censored at last contact) and predictors were assessed by Cox regression.

Results: Hepatocellular carcinoma (HCC) was an indication in 36.5% patients, predominantly within the Milan criteria (72.3%). Under immunoprophylaxis, HBV recurrence occurred in 3.4% and HDV recurrence in only 0.9%; seven of the eight patients with HBsAg reappearance had been transplanted for HCC. Anti-HBs titres peaked early (mean ≈510 IU/L at 1 week) and plateaued at ≈120–140 IU/L beyond the first year, with ≈60% of patients above 100 IU/L in the long term. Overall survival was 88.6% at 1 year, 84.5% at 5 years and 81.7% at 10 years; among 90-day survivors it reached 92.9% and 89.8% at 5 and 10 years. Fifty-four percent of deaths occurred within 90 days, mainly from sepsis and surgical complications, whereas viral recurrence rarely caused death, and no baseline variable independently predicted survival.

Conclusions: LT for HBV/HDV cirrhosis in a Romanian HDV-endemic setting yields excellent ten-year survival with very low viral recurrence. Prognosis is governed by perioperative events rather than viral or tumour biology and reappearance of HBsAg was strongly associated with a history of HCC.



UNMET NEEDS IN HDV

AI-BASED APPROACHES FOR LIVER DISEASES: LESSONS LEARNED

P42 SYNTHETIC DATA GENERATION BY ARTIFICIAL INTELLIGENCE PREDICTS CLINICAL OUTCOMES IN UNTREATED AND BULEVIRTIDE-TREATED PATIENTS WITH CHRONIC HEPATITIS DELTA

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Background and Aim: Bulevirtide (BLV) monotherapy induces virological and biochemical responses in patients with chronic hepatitis Delta (CHD). However, evaluating its long-term impact on clinical outcomes remains challenging due to the lack of comparable untreated controls. Since synthetic data (SD) mimic the properties of real patients, they can potentially overcome this limitation. We aimed to generate and validate high-fidelity SD to evaluate clinical outcomes in BLV-treated versus untreated cirrhotic CHD patients.

Methods: Clinical data from 344 cirrhotic CHD patients treated with BLV (SAVE-D study) and two historical untreated cohorts from Italy and France (n=298) were used to train AI models. Two distinct settings were evaluated: A) a 1:1 generation of both cohorts to assess clinical fidelity and privacy; B) generation of balanced, augmented cohorts (n=3,000/group) to reproduce clinical endpoints and address matching challenges. SD were validated using the SAFE framework against a real-data pool excluded from training. Fidelity and privacy were assessed via the Clinical Synthetic Fidelity (CSF) score and the Nearest Neighbour Distance Ratio (NNDR; optimal range: 0.65-0.85). Propensity score matching (PSM) aligned baseline covariates (SMD <0.1). The primary endpoint was the 3-year incidence of liver-related events (HCC and hepatic decompensation).

Results: In setting A, the synthetic cohorts demonstrated high fidelity and privacy (BLV-treated/untreated: CSF 90% /94%, NNDR 0.71/0.85). In setting B, PSM successfully paired 624 matched couples from the augmented pool. The 3-year cumulative incidences of decompensation and HCC were highly consistent between real and synthetic data: decompensation 2.7% vs. 4.2% (BLV-treated) and 11.3% vs. 10.0% (untreated), HCC 6.6% vs. 8.5% (BLV-treated) and 3.6% vs. 4.8% (untreated), respectively. Notably, the synthetic cohort significantly enhanced statistical power and robustness due to the larger sample size of perfectly matched individuals (Real-data p-values: 0.054 and 0.378 vs. Synthetic-data p-values: 0.039 and 0.546).

Conclusions: High-fidelity synthetic patient-level data accurately replicate clinical outcomes in cirrhotic CHD patients, regardless of BLV treatment status. This AI-driven approach represents a powerful strategy to overcome sample size limitations and control-matching challenges in rare diseases.



UNMET NEEDS IN HDV

AI-BASED APPROACHES FOR LIVER DISEASES: LESSONS LEARNED

P43 ARTIFICIAL INTELLIGENCE AND SYNTHETIC DATA TO INVESTIGATE PREDICTORS OF CLINICAL OUTCOMES IN BULEVIRTIDE-TREATED PATIENTS WITH CHRONIC HEPATITIS DELTA

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Background and Aim: Predicting clinical outcomes in chronic hepatitis Delta (CHD) is challenging due to the disease's rarity and limited cohort sizes. Synthetic data (SD) generation can overcome these limitations. We aimed to evaluate predictors of clinical outcomes in a real-world cohort of Bulevirtide (BLV)-treated CHD patients with cirrhosis compared to an AI-augmented cohort.

Methods: Clinical data from 344 CHD patients with cirrhosis treated with BLV monotherapy up to 3 years (SAVE-D study) were used to train a Conditional Tabular Wasserstein GAN with Gradient Penalty (CT-WGAN-GP) model and generate an augmented cohort (n=2,000/group). Synthetic data quality was validated via SAFE framework, providing normalized aggregated scores across 3 core dimensions. Statistical fidelity assesses univariate distributions, pairwise correlations and PCA. Clinical utility evaluated the replication of Kaplan-Meier curves across overall cohorts and clinical subgroups. Privacy preservation was evaluated via DCR and NNDR. Predictors of de-novo liver-related events (decompensation and HCC) were analysed using time-dependent Cox regression analysis in both real and synthetic cohorts.

Results: SAFE validation confirmed high data quality, achieving a Clinical Synthetic Fidelity score of 0.92 and a Privacy Synthetic score of 0.94, while a Survival score of 1 confirmed that Kaplan-Meier curves were faithfully replicated. In the real BLV-treated cohort, de-novo decompensation occurred in 7 patients and HCC in 14. The corresponding 3-year cumulative incidences were 2.7% for decompensation and 6.6% for HCC. At multivariable analysis, decompensation was predicted by lower baseline albumin (HR 0.15, 95% CI 0.05-0.44, p=0.005), while HCC by higher BMI (HR 1.09, 95% CI 1.01-1.19, p=0.04). In the synthetic augmented BLV-treated cohort, 43 decompensation and 87 HCC cases were recorded, with 3-year incidences comparable to the real cohort (3.5% and 7.8%, respectively). Multivariable Cox regression analysis confirmed lower baseline albumin to predict decompensation (HR 0.68, 95% CI 0.49-0.93, p=0.01), while identified as emergent predictors higher LSM (HR 1.01, 95% CI 1.00-1.03, p=0.04) and history of prior HCC (HR 3.38, 95% CI 1.64-6.97, p=0.001). Higher baseline BMI (HR 1.05, 95% CI 1.02-1.08, p=0.003) was confirmed to predict HCC also in the synthetic cohort, together with additional predictors: higher LSM (HR 1.02, 95% CI 1.01-1.03, p=0.004), higher bilirubin (HR 1.34, 95% CI 1.10-1.63, p=0.003), lower albumin levels (HR 0.73, 95% CI 0.56-0.96, p=0.03), lower HDV RNA levels (HR 0.89, 95% CI 0.80-0.98, p=0.01) and history of previous decompensation (HR 2.16, 95% CI 1.43-3.24, p=0.002).

Conclusion: Synthetic patient-level data can successfully replicate clinical outcomes in CHD patients with cirrhosis. By increasing sample size and statistical power, SD generation allows for a more comprehensive predictor analysis, thus overcoming the limitations inherent to rare diseases



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

GLOBAL AND LOCAL EPIDEMIOLOGY

P44 HEPATITIS D REMAINS OVERREPRESENTED AND UNDERTREATED IN PRISON POPULATIONS: DATA FROM CATALONIA, SPAIN

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Background and objectives: The rate of hepatitis D among prisoners is estimated to be high, although the exact figure is unknown. The aim of this study was to determine the prevalence, determinants of hepatitis D viremia (HDV) and the rate of treatment with bulevirtide in the prison population of Catalonia, Spain.

Methods: A 16-month prospective study was conducted from January 2024 to April 2025 to determine the prevalence of HDV infection among inmates of nine Catalan prisons using a double-reflex test for anti-HDV antibodies and HDV RNA. Additional analytical, demographic, epidemiological, and clinical-therapeutic data were collected. The study aimed to establish whether there were descriptive and clinical differences, and differences in access to treatment, between inmates and non-inmates.

Results: Of 18,116 samples analysed, 289 (1.6%) tested positive for HBsAg. Of these, 71 (24.6%) had anti-HDV antibodies, and 10 (14.8%) detectable viremia. The prevalence of HDV RNA in inmates was 0.55 per 1,000, and 14.8 per 1,000 among those who were HBsAg-positive; both figures are around 2.5 times higher than the corresponding rates in the general population. The infection most frequently affected middle-aged male migrants, many of whom were injection drug users. No inmates received treatment with bulevirtide, but 46.1% of non-inmates were administered this drug ($p < 0.001$). The reasons for not treating inmates were their short prison stay and, above all, the social complexities and factors that hinder adherence.

Discussion: The prison setting provides an opportunity for detecting and monitoring infectious diseases, including hepatitis D. In this study, HDV prevalence was higher among prisoners than among non-prisoners, predominantly affecting middle-aged immigrant men; however, no inmates received bulevirtide treatment. These findings highlight the need for targeted HDV screening programs in prisons as well as the design of strategies to enhance access to antiviral therapy.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

GLOBAL AND LOCAL EPIDEMIOLOGY

P45 INTEGRATION OF REFLEX HEPATITIS D VIRUS SCREENING INTO THE NATIONAL VIRAL HEPATITIS ELIMINATION PROGRAMME IN UZBEKISTAN

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Background: In accordance with the Presidential Decree of the Republic of Uzbekistan, a comprehensive National Viral Hepatitis Elimination Programme is being implemented, providing for the phased expansion of hepatitis B and C screening to cover 2 million people. Between 2022 and the first half of 2026, 2,376,839 individuals were screened for hepatitis B and 2,371,951 for hepatitis C. To assess the national burden of hepatitis D virus (HDV) infection and develop measures for its elimination, the results of a nationwide seroepidemiological study were analysed.

Materials and Methods: The analysis is based on data from a nationwide cross-sectional seroepidemiological study conducted in 2022 among the adult population in 7 of the 14 regions of Uzbekistan (n = 9,063), as well as the National Strategy and Action Plan for the Elimination of Parenteral Viral Hepatitis for 2026–2030.

Results: The seroepidemiological study showed that the prevalence of HBsAg among the examined adults was 5.3% (95% CI 4.4–6.5%). Among HBsAg-positive individuals, antibodies to HDV were detected in 17.7%, while HDV RNA was detected in 13.0%, indicating active viral replication and a high risk of severe liver disease progression. Extrapolation to the national population aged ≥5 years (31.3 million people) allowed us to estimate that approximately 168,000 individuals (95% CI 101,000–269,000) have active HDV infection, compared with an estimated 1,292,000 people living with chronic HBV infection. However, systematic HDV screening is not currently implemented nationwide, and testing for HBV DNA and HDV markers, as well as subsequent treatment, must be paid for out-of-pocket by patients. Therefore, reflex testing for hepatitis D was incorporated into the National Viral Hepatitis Elimination Strategy.

Conclusions: Implementation of reflex anti-HDV testing for all HBsAg-positive individuals, followed by HDV RNA testing in those with positive anti-HDV results, will enable the establishment of the world's largest national registry of patients with HDV infection by 2030. Given the emergence of new therapies for hepatitis D, such a registry will have substantial scientific and public health value. The National Strategy and Action Plan for the Elimination of Parenteral Viral Hepatitis for 2026–2030 aims to achieve 100% coverage of HDV screening among all HBsAg-positive individuals by 2030.

Programme targets for 2026–2030: 100% coverage with reflex anti-HDV screening among HBsAg-positive individuals by 2030. 23,000 rapid tests annually among high-risk groups for the early detection of hepatitis D during 2026–2030. Identification of more than 100,000 patients with hepatitis D within five years.

Keywords: hepatitis D virus, HDV, HBV/HDV coinfection, Uzbekistan, viral hepatitis elimination.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

GLOBAL AND LOCAL EPIDEMIOLOGY

P46 SINGLE-CENTER EXPERIENCE ON RATES OF HEPATITIS D TESTING AND ELECTRONIC MEDICAL RECORD CODING IN PATIENTS WITH KNOWN HEPATITIS B INFECTION

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Background:

Despite evidence that hepatitis D virus (HDV) accelerates morbidity and mortality in patients with hepatitis B virus (HBV), gaps in testing persist. This single-center retrospective study examines the rate of HDV testing in patients with known HBV, evaluates the accuracy of HDV coding, and assesses factors that impact testing.

Materials and Methods: We conducted a retrospective chart review of adults with HBV documented in the electronic medical record (EMR) problem list at Rush University Medical Center (RUMC) since January 2020. Patients without laboratory confirmed HBV infection were excluded. Charts were reviewed for HBV and HDV diagnostic codes, dates of code entry, viral testing, and testing dates. When available, risk factor data was collected. The primary endpoint was the percentage of patients with hepatitis D specific ICD codes in the EMR who had positive serological testing for HDV, as defined by positive anti-HDV serology or HDV RNA, any time prior to the HDV-code entry.

Results: 188 patients with HBV ICD codes entered into their EMR problem list and serologically confirmed HBV infection were included. 5 patients had an HDV-specific ICD code. Of these five, 4 (80.0%; 95% CI, 28.4%–99.5%) had laboratory-confirmed HDV infection documented prior to code assignment. Of all 188 patients, 145 (77.1%; 95% CI, 70.5%–82.7%) were tested for HDV. Of those 145 tested for HDV, 53 had concurrent HBV and HDV testing, 18 patients had HDV testing prior to documented HBV positivity at RUMC, and 74 had stepwise testing (positive HBV serology followed by HDV testing). Among the 74 tested in a stepwise approach, the median time to testing was 71 days (IQR, 17–431 days). 170 of the 188 patients had hepatology follow up. Patients followed by hepatology were significantly more likely to undergo HDV testing than those without hepatology follow-up (83.5% vs. 16.7%; OR, 24.7; 95% CI, 6.4–142.1; $p < 0.001$). Among the 188 patients, 50 (26.6%) had at least one documented HDV risk factor. The most common risk factors were origin from an HDV-endemic region (60.0%), HIV coinfection (12.0%), injection drug use (12.0%), history of incarceration (8.0%), HCV coinfection (4.0%), and high-risk sexual behavior (4.0%). Notably, 14 of 50 patients with documented HDV risk factors (28.0%) did not undergo HDV testing. Among the 5 patients with confirmed HDV infection, 3 (60.0%) had at least one documented risk factor, whereas 2 (40.0%) had no charted risk factors.

Conclusion: In this retrospective single-center study, HDV screening rates were higher than published benchmarks. The small sample size was a limitation and may have been influenced by incomplete HBV documentation in the EMR problem list. The median time to screening was 71 days. Many patients with HDV infection lacked documented risk factors, supporting universal, rather than risk based, HDV screening among patients with known hepatitis B and standardized screening pathways as HDV therapies emerge.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

GLOBAL AND LOCAL EPIDEMIOLOGY

P47 HIGH PREVALENCE OF HDV AND HBV DETECTED AMONGST HOUSEHOLD CONTACTS OF HDV POSITIVE INDIVIDUALS IN RURAL SINDH

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Background: Hepatitis D virus (HDV) infection continues to impose a substantial clinical and public health burden in Pakistan, particularly in rural settings where hepatitis B virus (HBV) remains endemic. While intrafamilial transmission of HBV is well recognized, the importance of household transmission for HDV infection has not been well described.

Objectives: To determine the prevalence of HBV and HDV among household contacts of HDV-positive index cases and to identify patterns suggestive of horizontal, and possible vertical transmission in rural Sindh.

Methods: This cross-sectional observational study enrolled consenting HDV RNA positive individuals from rural Sindh and screened their household members for HBV and HDV infection. All adults and children > 1 year of age, living in the same housing unit were tested. Household contacts were first tested for hepatitis B surface antigen (HBsAg) using WHO prequalified rapid diagnostic tests; HBsAg positive individuals were then tested for antibodies to hepatitis D virus (anti-HDV antibodies total) using an enzyme-linked immunosorbent assay (ELISA) at the central laboratory at Aga Khan University. Moreover, clinical, laboratory, and demographic data were collected.

Results/Outcomes: A total of 257 HDV-positive index cases and 1,462 household contacts were enrolled. Overall, 166 (11.4%) household members were HBsAg positive, of whom 121 (72.9%) were also anti-HDV antibody positive. HDV antibody prevalence among HBsAg+ spouses were 28/30 (93.3%), 34/61 (55.7%) among children, and 59/75 (78.6%) among extended family members. These findings suggest ongoing intrafamilial transmission through both horizontal and possible vertical routes. Fig. 1. Currently, genomic analysis of the collected samples is ongoing, and the results will be shared upon completion.

Conclusions: These findings suggest that intrafamilial transmission of HDV infection is common among HBV infected family members. Household contacts of HDV-positive individuals are at high-risk for HBV and HDV infection in rural Pakistan. Integrating routine household screening, improving HBV vaccination coverage, and ensuring timely referral to care are critical steps toward reducing HDV transmission and disease burden in endemic regions. Targeted household screening and preventive strategies should be prioritized within national hepatitis control programs.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

GLOBAL AND LOCAL EPIDEMIOLOGY

P48 REAL-WORLD ADHERENCE TO HDV REFLEX TESTING AMONG HBSAG-POSITIVE PATIENTS IN PAKISTAN: ARE WE MISSING HDV?

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Background: Hepatitis D virus (HDV) is the most severe form of chronic viral hepatitis and markedly accelerates progression to cirrhosis, hepatic decompensation, and hepatocellular carcinoma in individuals with chronic hepatitis B (HBV). International guidelines recommend universal HDV screening for all HBsAg-positive patients using anti-HDV antibody testing followed by confirmatory HDV RNA testing in seropositive individuals. However, real-world adherence to this diagnostic pathway remains poorly characterized in Pakistan. Aim To evaluate adherence to guideline-recommended HDV reflex testing and describe referral pathways associated with HDV screening among HBsAg-positive patients in routine clinical practice.

Methods: A prospective observational study was conducted at the hepatology outpatient department of AIMS Hospital, Hyderabad, Pakistan, between 2023 and 2026. Consecutive HBsAg-positive patients were included. HDV reflex testing was defined as anti-HDV antibody testing in all HBsAg-positive patients followed by HDV RNA testing in anti-HDV-positive individuals. Demographic characteristics, referral source (general physicians, consultant physicians, gastroenterologists/hepatologists, Free Hepatitis Prevention Program, or combined referrals), and completion of the diagnostic pathway were analyzed.

Results: Among 2,642 HBsAg-positive patients, only 502 (19.0%) underwent guideline-recommended HDV reflex testing, whereas 2,140 (81.0%) had no documented HDV evaluation. Of the screened patients, 230 (46%) were referred by gastroenterologists/hepatologists, 150 (30%) through the Free Hepatitis Prevention Program, 50 (10%) by consultant physicians, 50 (10%) by general physicians, and 22 (4%) through combined referral pathways. The mean age was 35.0 ± 12.7 years, and 74.9% were male. Anti-HDV antibodies were detected in 235/502 (46.8%) patients. Among anti-HDV-positive patients, 200 (85.1%) underwent confirmatory HDV RNA testing, with active infection confirmed in 165/200 (82.5%). The median HDV RNA level was 64,353 IU/mL (IQR 388–764,527 IU/mL).

Conclusions: Only one in five HBsAg-positive patients received guideline-recommended HDV testing, demonstrating substantial missed opportunities for diagnosis. Referral pathways differed considerably, with most testing initiated by hepatology specialists or the national hepatitis program rather than primary care physicians. Strengthening physician awareness and integrating standardized HDV reflex testing into routine HBV care could substantially improve early HDV detection and linkage to treatment in Pakistan.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

GLOBAL AND LOCAL EPIDEMIOLOGY

P49 GLOBAL BURDEN AND GEOGRAPHIC CONCENTRATION OF HEPATITIS DELTA VIRUS INFECTION ACROSS 195 COUNTRIES IN 2020: A MODELING STUDY

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Background: Hepatitis delta virus (HDV) is the most severe form of viral hepatitis. Previous studies have provided global, regional, or selected-country estimates, but comparable national estimates of active infection remain unavailable for many countries. We integrated published country-specific and regional evidence to generate harmonized estimates of anti-HDV positivity and active HDV infection across 195 countries in 2020.

Methods: We combined published country-specific estimates from the Polaris Observatory and Stockdale et al. with country-level epidemiologic characteristics and WHO estimates of hepatitis B surface antigen (HBsAg)-positive populations. Bayesian hierarchical models accounting for regional and geographic variation predicted anti-HDV positivity among HBsAg-positive people and, separately, HDV RNA positivity among anti-HDV-positive people. Predictive performance was evaluated through cross-validation and compared with regional extrapolation. Predictions were applied to WHO HBsAg-positive populations and United Nations population denominators to estimate national infection counts and general-population prevalence. Uncertainty in source estimates, model predictions, and population inputs was propagated through 100,000 Monte Carlo iterations to generate 95% uncertainty intervals.

Results: Among 280.15 million HBsAg-positive individuals worldwide in 2020, an estimated 11.11 million (95% UI, 10.32–17.00 million; 3.97%) had anti-HDV antibodies and 6.19 million (5.59–9.67 million; 2.21%) had detectable HDV RNA. Corresponding national general-population prevalences were 141.6 (131.5–216.7) and 78.9 (71.3–123.2) per 100,000, respectively. The WHO African, Western Pacific, and Eastern Mediterranean regions accounted for 34.5%, 32.5%, and 18.8% of the global RNA-positive population, respectively; the African Region also had the highest regional prevalence, at 186.0 per 100,000. Pakistan, Viet Nam, China, Nigeria, and the Democratic Republic of the Congo had the largest RNA-positive populations and collectively accounted for 51.0% of the global burden. The highest modelled RNA-prevalence point estimates per 100,000 population were observed in Mongolia (3,513.5), Togo (955.3), Mauritania (892.6), Guinea-Bissau (841.3), and Kiribati (789.9) (Figure 1).

Conclusions: This analysis provides a harmonized, country-level atlas of anti-HDV positivity and detectable HDV RNA. Active infection was geographically concentrated, with 51.0% of the estimated global population with detectable HDV RNA residing in just five countries. These findings can inform targeted testing and treatment planning, while the substantial reliance on regional extrapolation highlights priority countries for strengthened HDV surveillance.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

GLOBAL AND LOCAL EPIDEMIOLOGY

P50 CLINICAL PHENOTYPE OF HEPATITIS D ACCORDING TO HIV SEROSTATUS: RESULTS FROM THE NATIONWIDE DDR SPAIN COHORT

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Background: HIV coinfection is common among people with hepatitis D virus (HDV) infection because of shared transmission routes, yet its impact on the clinical phenotype of HDV remains poorly defined. We compared the epidemiological, virological and liver disease characteristics of anti-HDV-positive individuals according to HIV serostatus and assessed liver disease severity among patients with active HDV infection.

Material and methods: Prospective multicentre study within the nationwide DDR Spain cohort including anti-HDV-positive individuals enrolled between April 2024 and March 2026 across 70 Spanish hospitals. Baseline characteristics were compared according to HIV serostatus using Mann–Whitney U and chi-square tests. Liver-related outcomes according to HIV status were assessed in a secondary analysis restricted to patients with detectable HDV-RNA. In the overall population with available HIV and HDV-RNA results, logistic regression was used to assess whether HIV modified the association between active HDV infection and liver disease severity, adjusting for age, sex and anti-HCV status. CD4 count and HIV-RNA were unavailable.

Results: Among 944 anti-HDV-positive individuals, 189 (20%) were HIV-positive. Compared with HIV-negative



patients, they were older (59 vs 51 years; $p < 0.001$), more often male (78% vs 57%; $p < 0.001$), born in Spain (77% vs 39%; $p < 0.001$), people who inject drugs (82% vs 59%; $p = 0.007$), and anti-HCV-positive (65% vs 10%; $p < 0.001$). They more frequently received HBV antiviral therapy (75% vs 47%; $p < 0.001$), mainly tenofovir, and had lower HBV-DNA levels. Active HDV infection (47% vs 43%; $p = 0.327$) and HDV-RNA levels (4.0 vs 4.2 log IU/mL; $p = 0.368$) were similar. Among 387 patients with detectable HDV-RNA, liver disease severity was comparable regardless of HIV status, including advanced fibrosis (57% vs 60%; $p = 0.617$), cirrhosis (43% vs 36%; $p = 0.346$), liver stiffness measurement (LSM) (10.0 vs 9.9 kPa; $p = 0.455$), LSM 7–<10 kPa (26% vs 25%; $p = 0.886$), LSM ≥ 10 kPa (51% vs 49%; $p = 0.805$), and previous hepatic decompensation (32% vs 25%; $p = 0.397$). FIB-4 was higher in HIV-positive patients (2.50 vs 1.80; $p = 0.002$), but this association disappeared after adjustment for age and sex. Active HDV infection was associated with advanced fibrosis in both HIV-positive (aOR 2.78, 95% CI 1.15–6.72) and HIV-negative patients (aOR 6.84, 95% CI 4.09–11.43), without significant interaction ($p = 0.082$).

Conclusions: HIV-positive individuals had a distinct epidemiological profile but a similar frequency of active HDV infection. Among patients with active infection, liver disease severity was comparable irrespective of HIV status, with no evidence that HIV modified the impact of HDV replication. These findings support systematic anti-HDV screening with reflex HDV-RNA testing in all HBsAg-positive individuals, regardless of HIV status.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

GLOBAL AND LOCAL EPIDEMIOLOGY

P51 WHERE SHOULD WE LOOK FOR HEPATITIS D? COMMUNITY VERSUS HOSPITAL-BASED SCREENING IN ROMANIAN MIGRANTS IN CATALONIA, SPAIN.

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Background and Aims: Universal hepatitis D virus (HDV) screening is recommended for all people with chronic hepatitis B (CHB), but the most effective setting for case finding remains unclear. Romanian migrants represent one of the largest populations from an HDV-endemic country living in Catalonia. We compared the effectiveness of community and hospital-based HDV screening in this high-risk population.

Methods: We compared two HDV screening strategies conducted in Catalonia. The first was a community-based screening program targeting Romanian adults between June 2025 and June 2026. The second included Romanian HBsAg-positive individuals attending outpatient healthcare services between January 2024 and April 2025, where systematic anti-HDV screening and reflex HDV-RNA testing was implemented. HBV and HDV prevalence, as well as the clinical characteristics of patients diagnosed with HDV, were analyzed.

Results: A total of 420 Romanian individuals (56% women, and median age 50 years (IQR 43-58)) participated in the community screening program. Overall, five individuals (1.2%) tested positive for HBsAg, only one showing detectable HBV-DNA, and no cases of HDV infection were identified. In contrast, among 611 HBsAg-positive patients evaluated in healthcare services, 41 Romanian patients (6.7%) were diagnosed with HDV infection (27% women and median age 40 years (IQR 36-49)), of whom 24 (58.5%) had detectable HDV-RNA. Most patients had advanced liver disease at diagnosis (39% liver cirrhosis, 15% decompensated cirrhosis, 5% hepatocellular carcinoma), requiring specialist care, and nine initiated treatment with bulevirtide.

Conclusions: Community-based screening did not identify any cases of HDV in this high-risk migrant population, whereas systematic hospital-based screening detected a substantial number of patients with active infection, many with advanced liver disease. This difference may reflect the distinct populations reached by each strategy. Community-based screening primarily engages with younger, apparently healthy individuals, while hospital-based screening includes patients with underlying health conditions and additional risk factors, increasing the likelihood of detecting an advanced HDV infection. These findings suggest that the two strategies address different objectives along the care pathway; community-based screening may contribute to broaden viral hepatitis awareness, while systematic HDV screening in hospital care appears particularly effective for case detection. Larger studies are needed to confirm these results.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

GLOBAL AND LOCAL EPIDEMIOLOGY

P52 NATIONAL REGISTRY OF PATIENTS WITH HEPATITIS D: REAL-WORLD CLINICAL PRACTICE DATA IN SPAIN

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Background: Chronic hepatitis D (CHD) is the most aggressive form of chronic viral hepatitis. In Spain, HDV infection is estimated to affect approximately 5% of patients with chronic HBV infection, reflecting both historical parenteral transmission and migration from HDV-endemic regions. Bulevirtide (BLV) became available in Spain in February 2024. We aimed to characterize the nationwide clinical profile of patients with HBV/HDV coinfection and evaluate the early real-world use and outcomes of BLV.

Material and methods: This multicenter registry included anti-HDV-positive patients followed at 48 Spanish centres. Data were collected at diagnosis and the latest visit; Progression comprised new cases of cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), or liver transplantation (LT). BLV-treated patients were assessed through weeks 24, 48 and 96. Combined response was defined as ALT < UNL plus a >2-log₁₀ HDV RNA decline or undetectability.

Results: The cohort included 621 anti-HDV patients, 39% were female and the median age was 42(32-50) years. Two epidemiological profiles emerged: 49% were Spanish-born and 26% originated from Eastern Europe, predominantly Romania (18% overall). Spanish-born patients were older (46 vs 37 years) and more frequently had HCV or HIV coinfection and injecting drug use ($p < 0.01$), consistent with historical parenteral exposure. At diagnosis, HDV RNA was positive in 287/418 (69%) and cirrhosis was already present in 38%. Over a median follow-up of 5.1 (1.6–10.2) years in the overall cohort, 62/348 (18%) at-risk patients developed cirrhosis, 27/411 (7%) decompensation, 29/564 (5%) HCC, and 68/597 (11%) underwent LT. HDV RNA positivity was associated with progression (71% vs 54%; OR 2.16, 95% CI 1.29–3.63; $p = 0.003$). BLV 2mg monotherapy is reimbursed in Spain since Feb/24. Up to date, BLV treatment has been initiated in 143 patients included in the registry. Of these, 69% had cirrhosis (8 patients had previous decompensation, and 7 had HCC). Most received concomitant nucleos(t)ide analogues (92%), while 43% had previously received interferon. Baseline ALT was 65 (41–100) IU/L and HDV RNA 5.07 (3.87–5.82) log₁₀ IU/mL. Among 79 patients with week 48 data, 20/69 patients (29%) achieved undetectable HDV RNA and 29/68 (43%) achieved the combined response. Six patients had clinical events during BLV follow-up: ascites ($n = 2$), HCC ($n = 3$), or LT ($n = 2$; one overlapping event).

Conclusions: These real-world data from the Spanish HDV registry show that BLV has a safety profile consistent with that reported in clinical trials. Ongoing HDV viraemia was associated with liver disease progression, making systematic HDV RNA testing, early diagnosis, and timely treatment urgent national priorities. Since reimbursement, BLV has been initiated in almost one-quarter of registry patients and yielded a 43% combined response at week 48, despite 69% having cirrhosis at treatment initiation, signaling a major shift in HDV care in Spain.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

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P53 EPIDEMIOLOGY AND CLINICAL CHARACTERISTICS OF HEPATITIS DELTA VIRUS INFECTION IN BELGIUM: FINAL RESULTS OF A NATIONWIDE DOUBLE HDV REFLEX TESTING STUDY

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Background: With new treatment options for chronic hepatitis delta virus (HDV) infection emerging, it is crucial to optimize screening and linkage to care. This prospective study aims to provide national estimates of HDV seroprevalence, viremia, and circulating genotypes (gt) in a representative sample of hepatitis B surface antigen positive (HBsAg+) patients in Belgium using a standardized double HDV reflex testing approach. In addition, the performance of anti-HDV testing in immunocompromised patients was evaluated.

Materials and methods: From 16 large Belgian clinics, a total of 2073 samples testing positive for HBsAg during the study period (2024/11/25 – 2026/03/06), were sent to Sciensano (National Reference Center for Viral Hepatitis). Here, double HDV reflex testing was performed (HDVAb total: ELISA assay DiaSorin; HDV PCR: Realstar® kit Altona Diagnostics; in house HDV genotyping). Irrespective of the anti-HDV result, HDV RNA screening was performed for all immunocompromised patients, based on co-medication or HIV-status. Advanced fibrosis was defined based on elastography (HBV > 8 kPa; HDV > 10.4 kPa), histology and clinical criteria.

Results: HDV seroprevalence is 5.9% (122/2073; 95% CI: 4.9–7.0%). Of 122 anti-HDV-positive patients, 46 tested positive for HDV viremia (46/122, 37.7%). The overall cohort included 224 immunocompromised patients, two of whom were anti-HDV-negative but HDV RNA-positive: one patient with HBV/HIV coinfection (HDV RNA, 5.5 IU/mL) and one patient with rheumatological disease receiving corticosteroids and methotrexate (HDV RNA, 24.1 IU/mL). Overall, HDV viremia was 2.3% (n=48/2073; 95% CI 1.7–3.1%) with predominant genotype 1 (n=38) and genotype 5 (n=8). Most HDV viremic patients were born in Eastern Europe (41.5%, predominantly in Romania), Sub-Saharan Africa (39.0%), and Asia (17.1%). Six of eight patients with HDV genotype 5 were born in Sub-Saharan Africa. Patients with active HDV infection were more likely to be HCV seropositive (12.8% vs 2.2%, p = 0.002). HDV RNA-positive patients had higher FIB-4 scores, GGT (gamma-glutamyl transferase), bilirubin, and INR levels (international normalized ratio), and lower albumin levels (table 1). Anti-HDV positive patients more often had a history of injecting drug use (14.6% vs 3.0%, p = 0.003) and HDV viremia was strongly associated with advanced fibrosis (adjusted OR 11.0, 95% CI 4.7–25.7, p < 0.001), independently of BMI and alcohol consumption. Seven patients with active HDV infection were newly diagnosed through double HDV reflex testing (diagnosis rate: 7/46 or 15.2%).

Conclusions: Active HDV co-infection presents with more advanced liver disease and is expected in around one in every 40 HBsAg-positive patients in Belgium. These findings support broader implementation of double HDV reflex testing in Belgium to improve HDV case finding and linkage to specialist care.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

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P54 SEROPREVALENCE AND VIRAL BIOMARKER CHARACTERIZATION OF HEPATITIS D INFECTION IN TREATMENT NAIVE-INFECTED BLOOD DONORS WITH HEPATITIS B IN CAMEROON

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Background: Hepatitis delta virus (HDV) infection causes the most severe form of chronic viral hepatitis, yet it remains significantly under-researched in Sub-Saharan Africa (SSA). In Cameroon, data on HDV prevalence and its interaction with hepatitis B virus (HBV) biomarkers are scarce, hindering effective public health interventions and clinical trials. Our study investigated the HDV seroprevalence and HBV biomarker characterization of HDV infection among HBsAg positive blood donors in Yaoundé, Cameroon.

Method: In this cross-sectional study, sera were collected from 2023-2025 in Yaounde-Cameroon (ethical approval n°: 002382/CRERSHC/2025). Rapid screening of HBsAg was done onsite. In Leipzig, Anti-HDV antibodies detection with rapid test (LFA, Heidelberg-Germany), HDV RNA quantification on anti-HDV+ sera using RoboGene HDV 2.0 and 3.0 (RoboScreen, Germany) and HBV characterization were conducted. HDV RNA (IU/mL) and HBV DNA (IU/mL) were categorized as not detected, low and medium/high: <Lower limit of detection (LLOD), $\leq 10^4$, $> 10^4$ and <LLOD (HBV DNA-), <2000, > 2000, respectively.

Results: Out of 200 HBsAg-positive blood donors, overall seroprevalence of anti-HDV was 25% (50/200). HDV RNA quantification showed higher sensitivity with the RoboGene HDV 3.0 assay detecting forty-three HDV RNA-positive cases compared with thirty-seven by RoboGene 2.0. However, correlation of both kits was high ($r=0.996$; $p<0.0001$). Based on HDV 3.0 results, 62% (31/50), 24% (12/50) and 14% (7/50) of anti-HDV+ had a medium/high ($>10^4$), low ($<10^4$) and undetectable HDV RNA (IU/mL), respectively. Overall, median HDV RNA (log IU/mL) was 0, 3.2 and 5.7 in not detected, low and medium/high, respectively. Median HBV DNA (log IU/mL) and HBV RNA (log cp/mL) were relatively low in all groups (<3.3 log and ~ 0 , respectively, $p=ns$). In contrast, HBsAg levels (log IU/mL) were medium/high (>3 log, $p=ns$). According to HBV DNA breakdown, undetectable HBV DNA ($<LLOD$ (1.4log), HBV DNA-) were highest in medium/high HDV RNA (41.9% vs. 16-28% others co-infected, $p=0.08$), suggesting HDV suppression of HBV replication. Stratified analyses showed significant high levels of HBV DNA and HBV RNA in mono- and co-infected subjects with medium/high HBV DNA (>2000) while HBsAg levels remains similar.

Conclusion: This study revealed a substantial seroprevalence of anti-HDV antibodies (25%) with predominant medium-to-high rate of HDV replication in apparently healthy blood donors in Cameroon, underscoring the urgent need to implement systematic HDV screening and establish specialized treatment pathways in Cameroon to mitigate the severe health outcomes associated with hepatitis delta. Key words: Seroprevalence, viral biomarker, hepatitis D, treatment naive-infected blood donors, hepatitis B, Cameroon.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

GLOBAL AND LOCAL EPIDEMIOLOGY

P55 REFLEX TESTING REVEALS A SIGNIFICANT HDV BURDEN ACROSS EUROPE AND INCREASES HDV DIAGNOSIS AT AN EARLY STAGE

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Background: Hepatitis D virus (HDV) causes the most severe form of viral hepatitis but often remains underdiagnosed. We evaluated HDV testing coverage and anti-HDV positivity in HBsAg-positive individuals across Europe and Middle East before (2021-2023) and after (2024-2025) implementation of double reflex testing (DRT) was promoted. DRT consists of automatic anti-HDV screening (if unknown HDV serostatus), followed by HDV-RNA testing in those who tested anti-HDV positive.

Material and methods: This multicenter study included 25,527 individuals with a positive HBsAg test from 22 centres, including 15,483 evaluated in 2021-2023 and 10,044 in 2024-2025. Testing uptake and clinical and virological characteristics were compared between the two periods.

Results: Overall, 57% were male, with a median age was 49 years and 28% received NUC-treatment. Anti-HDV testing coverage increased from 56% before DRT to 92% after implementation ($p < 0.001$), while anti-HDV positivity among those tested slightly decreased from 6% to 4% ($p < 0.001$). Among anti-HDV-positive individuals, HDV-RNA testing increased from 81% to 94% ($p < 0.001$). Detectable HDV RNA decreased but remained substantial, 47% vs 39% ($p = 0.04$). Compared with individuals identified before DRT, those identified after implementation more frequently had ALT < 40 U/l (66% vs 33%, $p < 0.001$) and F0-F1 fibrosis (94% vs 33.8%, $p < 0.001$). Among 343 viremic individuals, median HDV-RNA was 5.2 log IU/ml. Compared with those identified before DRT, individuals identified after implementation had lower median qHBsAg (2,313 vs 5,158 IU/ml), HBV-DNA (30 vs 131 IU/ml), and ALT (45 vs 79 U/L) ($p < 0.001$ for all).

Conclusions: Promoting DRT among participating centres markedly improved HDV testing and diagnosis with a substantial proportion of anti-HDV-positive individuals having active infection. Lower ALT levels and less advanced fibrosis after DRT were consistent with earlier-stage detection. These findings support DRT adoption to improve HDV case ascertainment and enable earlier clinical evaluation.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

GLOBAL AND LOCAL EPIDEMIOLOGY

P56 SEARCHING FOR HDV TO FIND HBV INFECTION; IMPACT OF HDV SCREENING IN DETECTING NEW HBV INFECTIONS

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Background: Hepatitis Delta virus (HDV) infection is strictly dependent on the presence of hepatitis B virus (HBV). In the last years, efficacy of interferon treatment has always been limited, as HDV-RNA test availability. In 2020, Bulevirtide (BLV) was conditionally approved as first HDV antiviral drug for treatment of chronic delta hepatitis (CHD) and since 2023, AIFA reimbursement was obtained. The increased focus on the delta virus has also raised attention on tracking HBsAg positive patients particularly in age groups at risk. However, in clinical practice, screening strategies aimed at searching for HDV can serve as an effective reflex diagnostic tool capable of uncovering previously unknown or underdiagnosed HBV cases. Patients admitted to an Internal Medicine ward typically present with high clinical complexity, multimorbidity, and systemic conditions that require a holistic approach rather than one limited to a single organ or system. In many of these patients, it is not common to test for hepatitis virus infection in the absence of specific alterations in liver function tests (patients with specific age, origin from endemic areas, anamnestic risk factors, and presence of pathologies that could be extrahepatic manifestations of hepatitis (renal pathologies, vasculitis, etc.) and subjects who needed to start immunosuppressive treatment. Aim of our study was to evaluate the incidence of delta virus infection and submerged/occult HBV infection in an internal medicine department, testing potential new cases of HBV infection, previously not evaluated in the hepatology specialist setting.

Materials and methods: We evaluated the incidence of HBV infection in patients admitted to Our Internal Medicine unit in the last 2 years.

In 3855 hospitalized people, we performed 1138 tests, in 740 men, aged between 17 and 98 years old; we excluded patients who were definitely vaccinated and who were known to be HBsAg positive. All patients underwent all HBV infection markers testing and after also anti-delta testing and, if indicated, quantitative HDV RNA testing with the Elitech bosphore test.

Results: We found 65 (5,7%) new HBV positives (48 Men, age range 40 - 68), 36 of whom had normal transaminases. 5 patients older than 75 years, 12 were from endemic areas, 14 with anamnestic risk factors, 18 subjects who needed to start immunosuppressive treatment, 16 with pathologies that could be extrahepatic manifestations. Two thirds of these patients, on the basis of transaminase and HBV DNA values, were placed on antiviral treatment.

Three patients tested positive for anti-delta and two also for HDV RNA, for which treatment with bulevirtide was started.

Conclusion: In our experience, availability of BLV and a reliable HDV RNA test on-site, has increased attention to submerged/occult HBV infection in patients admitted to internal medicine departments with characteristics potentially at risk of infection.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

GLOBAL AND LOCAL EPIDEMIOLOGY

P57 HEPATITIS DELTA SCREENING AND TREATMENT CASCADE AMONG PEOPLE WITH HIV AND CHRONIC HEPATITIS B IN MILAN

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Background: Hepatitis D virus (HDV) infection accelerates liver disease progression in people with chronic hepatitis B, including people with HIV (PWH). Anti-HDV screening followed by confirmatory HDV RNA testing is essential to identify active infection and enable timely treatment. We assessed the HDV screening and treatment cascade among PWH with chronic hepatitis B.

Material and methods: This retrospective, single-centre study included PWH receiving care at IRCCS San Raffaele Scientific Institute, Milan, with a positive last available HBsAg result and available anti-HDV serology. Among anti-HDV-positive individuals, the availability and results of HDV RNA testing were assessed. Among those with detectable HDV RNA, linkage to care and bulevirtide uptake were evaluated. Demographic and clinical characteristics at the last available visit were described by anti-HDV status.

Results: Overall, 163 PWH were included; 31/163 (19.0%) were anti-HDV positive and 147/163 (90.2%) were male. Demographic and clinical characteristics by anti-HDV status are shown in Table 1. HDV RNA testing was available for 20/31 (64.5%) anti-HDV-positive individuals: 9/20 (45.0%) had detectable HDV RNA and 11/20 (55.0%) tested negative. HDV RNA was not assessed or was missing in 11/31 (35.5%); nine were lost to follow-up. Among the nine individuals with active infection, 2/9 (22.2%) initiated bulevirtide and both showed a favorable response (improved liver function, overall well-being and no METAVIR worsening); 2/9 (22.2%) were lost to follow-up. In the remaining five, treatment initiation remained under discussion, with dosing frequency and route of administration reported as the main barriers (Figure 1).

Conclusions: Anti-HDV seropositivity was frequent among PWH with chronic hepatitis B. Substantial gaps remained in retention in care and treatment uptake. Systematic screening, reflex testing and structured linkage-to-care pathways are needed to improve the HDV care cascade, while treatment acceptability remains a challenge.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

GLOBAL AND LOCAL EPIDEMIOLOGY

P58 OPPORTUNISTIC HEPATITIS SCREENING REVEALS A HIDDEN BURDEN OF HEPATITIS D AND ADVANCED LIVER FIBROSIS AMONG HBSAG-POSITIVE PATIENTS PRESENTING WITH GASTROINTESTINAL SYMPTOMS IN PAKISTAN

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Background: Pakistan continues to face a substantial burden of viral hepatitis despite ongoing elimination efforts. Hepatitis B and D may remain clinically silent until significant liver disease develops. Gastroenterology services may provide an opportunity for opportunistic hepatitis case-finding among patients presenting with nonspecific gastrointestinal (GI) symptoms. We evaluated the burden of HDV and advanced liver fibrosis identified through hepatitis screening in HBsAg-positive patients presenting to a tertiary gastroenterology service.

Methods: We conducted a cross-sectional study of 1,170 consecutive adults presenting with GI symptoms who were identified as HBsAg-positive during clinical evaluation at a tertiary hepatology center in Hyderabad, Pakistan. Patients underwent further assessment for HDV and liver disease severity, including transient elastography. Demographic, clinical, metabolic and laboratory data were analyzed. Advanced fibrosis was defined as liver stiffness ≥ 10 kPa (F3–F4).

Results: The mean age was 48.1 ± 13.4 years, 50.9% were female, and 81.7% resided in rural areas. Among the 1,170 HBsAg-positive patients, 543 (46.4%) were anti HDV-positive, revealing a substantial hidden burden of HDV in this gastroenterology population. Patients commonly presented with nonspecific upper GI symptoms, including early satiety, nausea, epigastric pain, bloating and burning sensation. Transient elastography demonstrated F0 in 23.2%, F1 in 6.3%, F2 in 34.7%, F3 in 30.3%, and F4 in 5.5%; consequently, 35.8% had advanced fibrosis at initial specialist assessment. Compared with patients with F0–F2 fibrosis, those with F3–F4 were older and had higher AST, triglycerides, FIB-4, APRI and AST/ALT ratio, with lower platelet counts (all $p < 0.05$). On multivariable analysis, increasing age (adjusted OR 1.10, 95% CI 1.084–1.119), higher AST (adjusted OR 1.07, 95% CI 1.061–1.080), lower platelet count (adjusted OR 0.98, 95% CI 0.972–0.979), and higher triglycerides (adjusted OR 1.004, 95% CI 1.001–1.007) were independently associated with advanced fibrosis.

Conclusions: Opportunistic hepatitis screening among patients presenting with nonspecific GI symptoms uncovered a substantial hidden burden of HDV and advanced liver fibrosis in this predominantly rural Pakistani cohort. Nearly half of HBsAg-positive patients were HDV-positive, while more than one-third already had advanced fibrosis at first specialist assessment. These findings highlight gastroenterology services as a potential setting for systematic HBV/HDV case-finding and early fibrosis assessment, particularly in resource-limited settings where undiagnosed HDV may contribute to preventable progression of liver disease.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

GLOBAL AND LOCAL EPIDEMIOLOGY

P59 THE ECONOMIC BURDEN OF CHRONIC HEPATITIS DELTA TREATMENT IN MONGOLIA

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Background: Chronic Hepatitis Delta (HDV) represents a critical public health challenge in Mongolia, which bears one of the highest global burdens of the disease. High co-infection rates with Hepatitis B drive an elevated incidence of liver cancer. While novel treatments demonstrate clinical efficacy, their real-world value is contingent upon financial accessibility. This study evaluates the economic burden of treating this patient population in Mongolia.

Methods: This economic analysis compares the annual costs of available and emerging HDV therapies—pegylated interferon (PEG-IFN), bulevirtide, and libevitug—against Mongolia's average gross annual salary of \$8,580–\$9,600 USD.

Results: In 2024, the Mongolian government allocated \$5.6 million USD (11.7% of all health insurance prescription funding) to cover approximately 360 HDV patients. However, all evaluated therapies impose substantial economic strain. PEG-IFN costs \$3,840 annually, consuming 40–45% of an average salary. Libevitug, currently unregistered and purchased out-of-pocket in China, costs approximately \$7,680 annually (80–90% of salary). Bulevirtide presents the most prohibitive burden; while a government initiative reduced its annual cost to \$10,200 (106–119% of salary), its previous commercial price reached \$32,500 (340–380% of salary).

Conclusion: The high costs of HDV therapies pose a major barrier to access in Mongolia, forcing potential catastrophic health expenditures that risk pushing families into poverty. Without substantial government subsidies or comprehensive insurance, these therapies remain financially unsustainable. Balancing clinical need against fiscal feasibility is paramount for equitable and sustainable disease management.

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EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P60 PRECISION-CUT LIVER SLICES AS A MODEL FOR EVALUATING THERAPEUTIC AGENTS AGAINST HBV AND HDV

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Background: Developing new therapeutic strategies against hepatitis B virus (HBV) and hepatitis delta virus (HDV) is essential to cure these infections. Yet evaluation of host-targeting agents (HTAs) with in vitro/in vivo models remains challenging. Therefore, we assessed precision-cut liver slices (PCLS) as an HBV/HDV co-infection model to study virus-host interactions and HTAs.

Material and methods: We generated PCLS from human liver resections and infected them ex vivo with HBV and HDV. Tissue viability and architecture were monitored by intracellular ATP, secreted albumin, and multiplexed immunofluorescence. Viral markers were assessed by quantitative PCR, western blot, and light-sheet microscopy in infected slices following treatment with a sodium taurocholate co-transporting polypeptide (NTCP)-targeting peptide, lonafarnib, or the Toll-like receptor 8 agonist selgantolimod. Single-cell RNA sequencing was performed to characterize the cellular responses to selgantolimod (Fig. 1).

Results: Here we show that our ex vivo infection protocol allows to establish HBV and HDV infection within the liver's three-dimensional architecture. Treatment with three well-characterized HTAs produced distinct antiviral effects consistent with each mechanism: an NTCP-targeting peptide blocked entry; lonafarnib induced intracellular hepatitis delta antigen accumulation; selgantolimod showed anti-HBV activity not previously seen in cultured hepatocytes, indicating cross-talk between immune and infected cells within liver slices.

Conclusions: These results provide the characterization of PCLS as an ex vivo model of HBV/HDV co-infection and antiviral testing. In the future, PCLS could contribute to expediting pre-clinical characterization of HTAs and to exploring alternatives to animal experimentation.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P61 INTERFERON RESPONSE AND CELL DIVISION-MEDIATED SPREAD OF PATIENT-DERIVED HEPATITIS D VIRUS STRAINS

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Introduction: Hepatitis D virus (HDV), a satellite virus of hepatitis B virus (HBV) spreads through two distinct mechanisms: infection of hepatocytes through binding of HBsAg to the NTCP receptor and transmission of the viral genome during division of infected hepatocytes, termed cell division-mediated spread (CDMS). Interferon (IFN) efficiently inhibits CDMS of HDV RNA in vitro by a yet unknown mechanism. Previous experiments with HDV-like agents suggest that resistance to IFN relies within structural features of replicating RNA. Although specific HDV strains have been associated with IFN sensitivity or resistance, data on patient-derived strains with known clinical treatment outcomes remain limited.

Methods: We analyzed serum samples from 35 patients with chronic HDV infection from Germany and Sweden who had received IFN treatment. Patients were classified as IFN responders or non-responders based on whether they achieved a ≥ 2 -log₁₀ reduction in HDV RNA. HDV genomes were sequenced using Nanopore technology, and single-nucleotide variants (SNVs) were analyzed. Twelve consensus sequences were synthesized, cloned, and their replication capacity and IFN sensitivity were assessed in HuH7 cells. A previously characterized IFN-sensitive HDV strain and an IFN-resistant woodchuck delta-like agent strain were included as controls. CDMS was assessed by splitting the cells at day five and elucidating the capacity to form HDV-positive colonies.

Results: Analysis of minor variants identified an association between A-to-G substitutions and clinical response to IFN treatment. These substitutions may reflect IFN-induced editing by adenosine deaminase acting on RNA (ADAR), which converts adenosine to inosine and is detected as an A-to-G substitution during sequencing. The A282G substitution showed the strongest association with IFN response ($p < 0.001$). SNVs associated with treatment response were predicted to alter the secondary structure of HDV RNA. In addition, the HDAg amino acid residues D47, S159, V188, N191, and A202 were significantly associated with IFN treatment response.

In vitro, IFN sensitivity and CDMS varied among strains derived from both responders and non-responders. Across all these strains, IFN treatment reduced the mean proportion of HDV-positive cells by 73% (SD, 45 percentage points). This heterogeneity suggests that strain-intrinsic IFN sensitivity alone may not fully explain treatment response in vivo.

Conclusion: HDV SNVs may predict clinical response to IFN. However, IFN-mediated restriction of CDMS varied substantially among strains from both IFN responders and non-responders, indicating considerable strain-specific heterogeneity. Additional experiments are needed to validate these phenotypes and identify the viral and host factors associated with IFN resistance.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P62 A NOVEL IN VITRO HEPATOCYTE MODEL OF CHRONIC PROPAGATIVE HEPATITIS DELTA VIRUS INFECTION FOR LONG-TERM ANTIVIRAL EVALUATION AND HOST FACTOR DISCOVERY

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HDV infects hepatocytes through the Na⁺/taurocholate co-transporting polypeptide (NTCP) receptor and depends on the hepatitis B virus (HBV) surface antigens for virion assembly, release, and propagation. The development of new antiviral therapies and study of HDV persistence are hindered by the lack of robust cellular models supporting efficient viral spreading. Using a clonal HuH7-NTCP cell line transduced with a lentiviral vector allowing stable stoichiometric expression of all HBV surface proteins, we derived the here-after called HuH7-NTCP-HBs cell line, which mimic HBV integration into host genome. Over a 49-day time course, HuH7-NTCP-HBs cells maintained a stable replication of HDV in contrast to the parental HuH7-NTCP cells suggesting HDV propagation in HuH7-NTCP-HBs cells. This propagation-driven maintenance of HDV replication was significantly impaired when PreS1 peptide/NTCP-entry inhibitor, PEG-IFN- α or Lonafermin treatments were applied at different time after the initial round of infection. Interestingly, the model allowed to test the effect of combination therapies including molecules with different mode of action. Importantly, the model also enabled monitoring of viral rebound following withdrawal of treatment, providing a unique platform to evaluate the durability of antiviral responses. Unlike currently available in vitro HDV infection models, chronic HDV infection could be established in HuH7-NTCP-HBs cells without the use of polyethylene glycol (PEG), providing a more relevant system to study HDV infection. We further demonstrated that the interferon response to HDV infection, assessed through ISG expression, did not prevent the viral persistence within the culture. Moreover, we observed a correlation between virions infectivity and secretion of apolipoprotein E (ApoE) by HuH7-NTCP-HBs cells and knock down of ApoE, through RNA interference, strongly impaired HDV chronic infection. Altogether, these results highlight the importance of this host factor in HDV propagation. Finally, HuH7-NTCP-HBs cells were readily infected with HDV derived from patient sera, demonstrating the suitability of the system for studying clinically relevant viral isolates. In conclusion, we established a unique in vitro platform that faithfully supports chronic propagative HDV infection and enables (i) long-term evaluation of antiviral efficacy, including combination therapies and prediction of viral rebound after treatment withdrawal, (ii) infection with patient-derived HDV isolates and (iii) identification of host factors regulating viral propagation. This versatile and relevant model will allow to investigate HDV persistence and accelerate the preclinical development of curative antiviral strategies.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P63 A NEW HUMANIZED MOUSE MODEL DEMONSTRATES HBV DNA INTEGRATION-DRIVEN HDV SPREAD MIMICKING CHRONIC HEPATITIS D

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Background: HDV replicates independently of HBV in infected hepatocytes but depends on HBV surface proteins (HBs) for release and spread. Recent patient data suggests that HDV also utilizes HBs expressed from HBV DNA integrations (iHBV), a common feature of acute and chronic HBV infection associated with hepatocarcinogenesis. However, the role of iHBV in HDV spread and persistence remains poorly understood due to a lack of suitable experimental models. We aimed to establish a human liver chimeric mouse model harboring iHBV sequences and investigate their role in supporting HDV infection and persistence.

Material and methods: Primary human hepatocytes (PHH) were transduced ex vivo with lentiviral vectors encoding a prototypic iHBV sequence (HBs and HBx ORFs under endogenous promoters, with a downstream eGFP reporter gene). Human liver chimeric urokinase-type plasminogen activator/severe combined immunodeficiency/beige/interleukin 2 receptor γ $^{-/-}$ (USG) mice were reconstituted with transduced PHHs, yielding a high liver repopulation with approximately 21% iHBV-positive cells. Mice were inoculated with cell culture-derived HDV GT-1 (Giersch, JHEP Reports 2023) and sacrificed 2, 4, 6 and 8 weeks (n=12) after HDV infection. Viral and host markers were assessed by qPCR, immunofluorescence (IF), and RNA in situ hybridization (RNA-ISH). HBV-infected USG mice superinfected with HDV for 10 weeks served as controls (n=6).

Results: Serum HDV titers developed in the first 4 weeks (median HDV RNA = 1×10^6 copies/mL) and plateaued thereafter. Intrahepatic HDV RNA reached levels comparable with HBV/HDV-superinfected mice. IF and RNA-ISH analyses detected HDV antigens and HDV genomic RNA in iHBV-carrying PHH, consistent with intrahepatic HDV spread. In the same liver, a large proportion of iHBV-negative PHHs were HDV-monoinfected. In line with HBV/HDV-superinfected controls, human innate immune genes were upregulated.

Conclusions: This study demonstrates the successful establishment of HDV infection in the presence of HBV DNA integrations supporting the release of HDV particles and occurrence of new infections. The model provides a novel in vivo platform to study the role of iHBV in HDV spread, immunopathogenesis, and therapeutic settings.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P64 KINETICS OF HBCRAG DURING BULEVIRTIDE MONOTHERAPY IN PATIENTS WITH HDV-RELATED CIRRHOSIS: A SINGLE-CENTER REAL-WORLD STUDY

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Background and aim: While serum HBcrAg is a well-established biomarker for managing chronic hepatitis B, its clinical utility in patients with chronic hepatitis Delta (CHD) undergoing Bulevirtide (BLV) therapy remains uncharacterized. This study aimed to investigate the dynamics of HBcrAg levels in CHD patients receiving BLV monotherapy.

Methods: We evaluated CHD patients with cirrhosis treated with BLV 2 mg/day monotherapy from a single center of the retrospective SAVE-D study. Serum HBcrAg was quantified using the LUMIPULSE® G HBcrAg assay (Fujirebio Europe, LLOQ 3 Log₁₀ U/mL). Virological (VR: HDV-RNA undetectable or ≥ 2 Log₁₀ decline vs. baseline), biochemical (BR: ALT<40 U/L), combined response (CR: VR + BR) and HDV RNA undetectability were assessed.

Results: A total of 405 longitudinal serum samples from 79 patients treated with BLV up to week 144 were analyzed. At baseline (BLV start), median age was 55 years, 53% were male, 100% had cirrhosis (87% Child-Pugh A), 100% NUC-treated, median ALT 97 (52-151) U/L, HBsAg 3.7 (3.4-3.9) Log₁₀U/mL, 92% HBeAg-negative, 90% HBV DNA undetectable, median HDV RNA 5.5 (4.2-6.2) Log₁₀U/mL. Baseline HBcrAg was positive in 63 patients (80%), with a median value of 4.0 (3.5-4.8) Log₁₀ U/mL. Baseline HBcrAg levels correlated positively with HBsAg ($r=0.37$, $p=0.002$) and HDV RNA ($r=0.30$, $p=0.01$), but showed no correlation with ALT or HBV DNA. At week 144, rates for VR, BR, CR, and undetectable HDV RNA were 70%, 64%, 52%, and 33%, respectively. HBcrAg levels significantly decreased during treatment, with a median decline of -0.31 Log₁₀ at week 48 ($p=0.02$), -0.63 Log₁₀ at week 96 ($p=0.003$), and -0.62 Log₁₀ at week 144 ($p=0.01$). On-treatment HBcrAg did not correlate with concurrent HDV RNA levels but maintained a strong positive correlation with HBsAg throughout the study (W48: $r=0.35$, $p=0.007$; W96: $r=0.45$, $p=0.006$; W144: $r=0.50$, $p=0.01$). Neither baseline nor longitudinal HBcrAg levels were predictive of VR or HDV RNA undetectability. Overall, 10 patients achieved negative HBcrAg by week 144 ($n=5$ at week 48, $n=3$ at week 96; $n=2$ at week 144). At the time of HBcrAg negativity, 7 had achieved a virological response (HDV RNA undetectable in 3), while 3 patients were suboptimal responders (< 2 Log₁₀ HDV RNA decline). Conversely, 5 patients who tested at baseline HBcrAg negative experienced low-level HBcrAg positivity (< 3.5 Log₁₀ U/mL in all cases; $n=4$ at week 48, $n=1$ at week 144): at the time of positive HBcrAg, 3 had achieved a virological response (HDV RNA undetectable in $n=2$), while 2 patients were suboptimal responders. No significant changes in HBsAg levels were observed during the study period.

Conclusions: In CHD patients with cirrhosis treated with BLV monotherapy for up to 144 weeks, HBcrAg was detectable in most patients at baseline and correlated with both HBsAg and HDV RNA. During therapy, HBcrAg levels progressively declined in parallel with HBsAg levels, but not with HDV virological outcomes.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P65 HOST IMMUNOGENETICS AND FIRST SEQUENCING-BASED CHARACTERIZATION OF HDV IN UZBEKISTAN

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Background: Uzbekistan is a high-burden country for HDV infection, with previous studies reporting anti-HDV positivity in 80.7% of HBsAg-positive patients with liver cirrhosis. Despite this substantial disease burden, molecular epidemiological data remain limited. The introduction of novel anti-HDV therapies has increased the importance of molecular characterization of both host and viral factors for improved patient stratification. HLA class I molecules, acting as ligands for killer-cell immunoglobulin-like receptors (KIRs), regulate natural killer cell activity and may contribute to differences in HDV disease progression. This study investigated HLA immunogenetic profiles in patients with chronic hepatitis and HDV-associated cirrhosis and performed pilot sequencing of HDV isolates.

Materials and methods: This exploratory study included 41 patients: 19 with chronic hepatitis and 22 with HDV-associated cirrhosis (Child-Pugh A-C). HLA typing was performed using 5-colour multiplex RT PCR (HISTO TYPE Rainbow CFX, BAG Diagnostics). HLA-B Bw4/Bw6 and HLA-C C1/C2 KIR-ligand profiles, together with HLA allele groups, were compared between clinical groups using Fisher's exact test with odds ratios (ORs) and 95% confidence intervals (CIs). Also for 4 HDV samples obtained targeted sequencing of a 650 bp genomic region for genotyping using an in-house protocol provided by Hannover Medical School. Sequencing was performed on the MinION Mk1C platform, data were analyzed using EPI2ME, and genotypes were assigned by BLAST of the NCBI GenBank database.

Results: Distinct immunogenetic patterns were observed between the clinical groups. Bw4/Bw4, C1/C2, HLA-C04, HLA-DQB105 and HLA-DRB114 were more frequent in patients with cirrhosis, whereas Bw4/Bw6, C2/C2 and HLA-DQB102 predominated in chronic hepatitis. HLA-C*04 showed the strongest exploratory association with cirrhosis (45.5% vs 15.8%; OR 4.44, 95% CI 1.00-19.75; $p=0.052$), although none of the comparisons reached conventional statistical significance (Figure 1). Sequencing identified HDV genotype 1 in all 4 samples. This finding is consistent with previous PCR-based data from Uzbekistan and reports from neighboring Central Asian countries and represents, to our knowledge, the first sequencing-based characterization of HDV clinical isolates from Uzbekistan.

Conclusions: Distinct HLA immunogenetic profiles were observed between patients with chronic hepatitis and HDV-associated cirrhosis, supporting a potential role of host genetic factors in disease progression. Although exploratory, the enrichment of Bw4/Bw4, C1/C2, HLA-C04, HLA-DQB105 and HLA-DRB1*14 in cirrhosis warrants validation in larger cohorts. Sequencing confirmed HDV genotype 1 in 4 isolates, providing the first sequencing-based molecular evidence from Uzbekistan and supporting previous epidemiological observations. Continued recruitment and expanded molecular analyses will further improve understanding of host-virus interactions in HDV infection.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P66 ASSOCIATION OF IL28B GENE POLYMORPHISMS RS8099917 AND RS12979860 WITH PROGRESSION OF CHRONIC HEPATITIS D

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Background: In addition to viral factors, host genetic variation may contribute to variability in the clinical course of chronic HDV infection. The IL28B gene, which encodes interferon- λ 3, plays an important role in regulating the innate antiviral immune response. The IL28B polymorphisms rs8099917 and rs12979860 have been extensively investigated in chronic hepatitis C, where they have been associated with disease progression and response to antiviral therapy. However, data regarding their role in the progression of chronic HDV infection and the development of liver cirrhosis remain limited and inconsistent. Therefore, the aim of this study was to evaluate the association of the IL28B polymorphisms rs8099917 and rs12979860 with chronic HDV infection and progression to liver cirrhosis.

Material and methods: The study included 243 patients with chronic HDV infection, including 134 patients without liver cirrhosis and 109 with liver cirrhosis, as well as 40 healthy controls. Genotyping of the IL28B rs8099917 and rs12979860 polymorphisms was performed using real-time PCR. Genotype and allele frequency distributions were compared between the study groups. Statistical analysis included assessment of Hardy–Weinberg equilibrium, the χ^2 test, calculation of odds ratios (ORs) with 95% confidence intervals (95% CI), and dominant model analysis.

Results: Genotype distributions of both polymorphisms were in Hardy–Weinberg equilibrium in all study groups ($p > 0.05$). Comparison of healthy controls with the combined group of patients with chronic HDV infection (with and without liver cirrhosis) showed no significant differences in genotype distribution for either rs8099917 ($\chi^2 = 1.483$; $p = 0.476$) or rs12979860 ($\chi^2 = 0.354$; $p = 0.838$). By contrast, genotype distribution differed significantly between patients with and without liver cirrhosis only for rs8099917 ($\chi^2 = 6.718$; $p = 0.035$). The frequency of the rs8099917 G allele was higher in patients with liver cirrhosis (14.7%) than in those without cirrhosis (7.8%) and was associated with increased odds of liver cirrhosis (OR=2.02; 95% CI 1.13–3.62; $p = 0.024$). Dominant model analysis showed that carriers of the TG/GG genotypes had 2.27-fold higher odds of liver cirrhosis than carriers of the TT genotype (OR=2.27; 95% CI 1.20–4.26; $p = 0.011$). No significant associations were observed for rs12979860 in genotype distribution ($\chi^2 = 2.948$; $p = 0.229$), allele analysis (OR=1.11; 95% CI 0.72–1.70; $p = 0.645$), or dominant model analysis.

Conclusions: These findings suggest that carriage of the G allele of the IL28B rs8099917 polymorphism may be associated with increased odds of liver cirrhosis in patients with chronic HDV infection. These findings require confirmation in larger independent studies to further clarify the role of IL28B polymorphisms in the progression of chronic HDV infection.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P67 ONE PROTEIN, MANY ROLES: LARGE HDAG CONTROLS VIRAL ASSEMBLY, REPLICATION AND CYTOPATHIC EFFECTS TO SUSTAIN VIRAL PERSISTENCE

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Introduction: Intracellular HDV RNA replication is HBV-independent and modulated by a balanced expression of small and large HDV antigen (S- and L-HDAg). L-HDAg is synthesized upon an ADAR1-mediated editing of antigenomes, leading to a C-terminal extension of the HDAg comprising a farnesylation motif which is recognized and modified by host farnesyltransferase. It is noteworthy that prenylated and non-prenylated L-HDAg may serve diverse effects on packaging and replication. Both unedited and edited genomes can be packed, resulting in secretion of HDV encoding either S-HDAg or L-HDAg, respectively. Since infection at increasing viral titers of such heterogeneous HDV preparations results in an unexpected restriction of infection rates we analyzed the effects of genome editing, L-HDAg expression and farnesylation on HDV infection and the host cell.

Methods: To remove the negative regulation by farnesylated L-HDAg, we applied farnesyltransferase inhibitors (e.g. Lonafarnib), or infected cells with HDV mutants incapable of expressing prenylated L-HDAg either by mutating the editing site (amber/W) or the prenylation motif (C211). To examine the relevance of innate immunity, we used innate immune (in)competent cell lines and applied the JAK1/2 inhibitor Ruxolitinib.

Results: While infections with increasing titers of heterogeneous HDV led to an increase of HDAg-positive cells until saturation at 20-30%, no such restriction was observed in the absence of farnesylated L-HDAg. This effect of overcoming self-restriction could be observed in the presence of Lonafarnib or when infecting with HDV carrying mutations of the editing or prenylation motif. As previously reported, obstruction of the negative regulatory effect of the prenylated L-HDAg led to a strong induction of HDV replication. Strikingly, this resulted in cell death during long term infections of HepG2-NTCP and HepaRG-NTCP cells, but not Huh7-NTCP cells. This suggested a connection to innate immunity, as Huh7-NTCP cells are unable to sense HDV. Additionally, the unrestricted replication of HDV in HepG2-NTCP and HepaRG-NTCP cells resulted in elevated expression of ISGs. Knocking out the sensors of HDV RNA (MDA5 or LGP2), or treatment with Ruxolitinib resulted in reduced cytotoxicity, highlighting the contribution of interferon signaling.

Conclusion: Our findings indicate that farnesylated L-HDAg expressed from edited HDV represses viral replication and this repression is released upon inhibition of farnesyltransferase. The interplay between HDV replication and innate immune stimulation modulates cytopathic effects of HDV. By balancing its own replication, HDV might avoid excessive ISG induction and cytotoxicity. These findings might provide a new rationale for the application of farnesyltransferase inhibitors, e.g. in combination with an entry inhibitor.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P68 CELL PROLIFERATION REDUCES INNATE ANTIVIRAL DEFENSES AND PROMOTES HDV SPREAD IN PRIMARY HUMAN HEPATOCYTES IN VIVO

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Introduction and aim: Previous studies in humanized mice have demonstrated that HDV can persist through hepatocyte division (Giersch, Gut 2018). In vitro data further showed that interferon (IFN) treatment efficiently suppresses this mode of viral dissemination (Zhang, JHepatol 2022). This study aimed to investigate the intrahepatic mechanisms that support HDV spread via cell division in proliferating primary human hepatocytes (PHH) in vivo and to assess the impact of pegIFN α treatment.

Methods: uPA/SCID/IL2R γ -/- (USG) mice were transplanted with PHHs (n=15) derived from a donor mouse stably infected with HBV (1.7x10⁹ copies/mL) and HDV (5.3x10⁸ copies/mL). One week post-transplantation, a group of mice received pegIFN α for 8 weeks. PHH proliferation and virological markers were assessed by ELISA, qPCR, immunohistology, RNA-ISH, and RNA sequencing. A separate uninfected cohort received a single pegIFN α dose at week 1 and was sacrificed after 24 hours.

Results: pegIFN α treatment produced a substantially greater antiviral effect in a proliferative liver environment ($\geq 4\log_{10}$ reduction) compared with stably repopulated and HBV/HDV-infected mice ($-0.5\log_{10}$), leading to undetectable HDV viremia, intrahepatic HDV RNA, and HDAg-positive hepatocytes. At 1 week post-transplantation, ~45% of PHHs were Ki67-positive, indicating active proliferation, and immunofluorescence confirmed the presence of proliferating HDAg-positive cells in vivo. At this time point, qPCR analyses showed reduced expression of ISGs, stress-response factors, and metabolic regulators, alongside upregulation in cell-cycle-associated cyclins. Decreased ISG expression was confirmed by in situ hybridization. Notably, pegIFN α -treatment of proliferating PHHs induced robust expression of human ISGs, indicating that proliferating hepatocytes retain the capacity to mount antiviral responses.

Conclusion: Although PHHs remain IFN-competent, active proliferation is associated with downregulation of ISGs and antiviral effectors. This transient reduction in antiviral defenses may facilitate HDV spread through cell division and enhance sensitivity to pegIFN α treatment.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P69 PRE-TREATMENT AND ON-TREATMENT MARKERS OF HBV CCCDNA TRANSCRIPTION PREDICT VIROLOGICAL RESPONSE IN CHRONIC HEPATITIS D TREATED PATIENTS WITH PEGYLATED-INTERFERON OR BULEVIRTIDE

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Background: Hepatitis delta (HDV) is a satellite virus that requires the envelope proteins of HBV (HBs) for cell entry. Bulevirdide blocks virion engagement with NTCP receptors and achieves undetectable HDV RNA (sustained, off-treatment) in approximately 20% of patients. Pegylated interferon (IFN) exerts pleiotropic antiviral effects, including on cccDNA episomes. We compared peripheral biomarkers of HBV infection (HBsAg, HBcrAg, pgRNA and HDV genotype) during IFN vs. BLV therapy and assessed their temporal relationship to serum HDV RNA.

Methods: We analysed 51 patients with HBV/HDV co-infection (median age 42 yrs, 31 males, 55% compensated cirrhosis). 33 patients were treated with IFN for 48 weeks (+ 24 wks follow up) and 18 patients were treated with BLV monotherapy for at least 72 weeks. The following biomarkers were measured at start-of-treatment, week 24, 48 & 72: HBcrAg [CLEIA Fujirebio, log₁₀ U/ml, LLOQ 3.0 log₁₀ U/ml], pgRNA [RealTime RUO, Abbott Diagnostics, LLOQ= 0.49 log₁₀ U/ml], HBsAg quant [Abbott ARCHITECT, LLOQ 0.05 IU/ml], HDV RNA [RealTime RUO, Abbott Diagnostics, LLOQ 5 IU/ml], and HDV genotyping (direct sequencing). Treatment response was defined as undetectable HDV RNA on therapy (BLV cohort) or 24 weeks after end-of-therapy (IFN cohort).

Results: 19 (58%) IFN patients achieved HDV RNA loss vs 7 (39%) patients on 72 weeks of BLV therapy. While lower pre-treatment HDV RNA (<100 000 IU/ml), HBsAg (<5 000 IU/ml), pgRNA (<1.75 LogU/mL), & HBcrAg (<3.5 LogU/mL) and genotype 5 (OR 1.45) were predictive of response in IFN patients, only HDV RNA <50000 IU/ml and HBsAg <7000 IU/ml predicted BLV-induced HDV RNA loss. Patients without cirrhosis were more likely to respond (OR 1.93). Irrespective of treatment modality, a higher proportion of responders had HBcrAg and/or pgRNA < LLOQ at start-of-treatment vs non-responders (HBcrAg 23% vs 0%; pgRNA 16% vs 6%). The proportion of patients with HBcrAg or pgRNA < LLOQ increased during therapy with both treatments, but only amongst responders (week 72: HBcrAg 83%; pgRNA: 76%). During therapy, non-responders showed strong correlations between HDV RNA and HBsAg, and between HBcrAg and pgRNA (week 72: R=0.711, p<0.01 and R=0.64, p<0.01, respectively). In contrast, responders demonstrated a different pattern, with a strong correlation observed only between HBsAg and pgRNA (week 72: R=0.59, p<0.01). HBsAg declines were exclusively encountered in the IFN-treatment cohort (-973 IU/ml/year), of whom 4 patients (12%) achieved HBsAg seroclearance (this was more pronounced in genotype 5 as there were strong correlations between HBsAg and HBcrAg and pgRNA levels during therapy suggestive of an impact on cccDNA transcription).

Conclusion: Baseline levels of HBV cccDNA transcription were predictive of response to IFN, but not BLV, probably reflecting the distinct mechanisms of action. Changes in HBcrAg and pgRNA were more pronounced in responders irrespective of therapy. There is a need for therapy focused studies.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P70 COMPARATIVE LABORATORY EVALUATION OF THE ROBOGENE HDV RNA QUANTIFICATION KIT 2.0 FOR QUANTITATIVE DETECTION OF HEPATITIS D VIRUS RNA

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Background: Reliable detection and quantification of hepatitis D virus (HDV) RNA are crucial for laboratory diagnosis and monitoring of HDV infection. This study aimed to evaluate the diagnostic and analytical performance of the RoboGene HDV RNA Quantification Kit 2.0 (ROBOSCREEN DIAGNOSTICS) versus the AmpliSens® HDV-Monitor-FL PCR assay used in the routine diagnostics in the Reference Laboratory of the Research Institute of Virology, Uzbekistan.

Methods: The comparative evaluation included 110 plasma samples: 97 HDV RNA-positive and 13 HDV RNA-negative samples characterized using a routine method. RNA extraction and quantitative real-time RT-PCR were performed according to the manufacturers' instructions. The RoboGene HDV RNA Quantification Kit 2.0 and AmpliSens® HDV-Monitor-FL were used in parallel for each sample. Quantitative results were expressed in IU/mL. The WHO International Standard for HDV RNA NAT (PEI 7657/12; assigned concentration 575,000 IU/mL) was also tested for quantitative comparability.

Results: Among HDV RNA-positive samples, 93 of 97 results were concordant, corresponding to 95.87% positive agreement. All 13 HDV RNA-negative samples were concordant, corresponding to 100% negative agreement. The observed quantitative range of the RoboGene assay was 11 to 100,000,000 IU/mL. Viral load measurements obtained with the two assays demonstrated comparable quantitative performance across samples with different HDV RNA concentrations. Analysis of the WHO International Standard demonstrated close agreement of the obtained results within the expected logarithmic range, considering differences in plasma input volumes and RNA extraction procedures. The evaluated workflow provided complete RNA extraction and amplification; however, the extraction procedure required additional reagents and longer processing time than the routinely used extraction method.

Conclusions: The results of comparative laboratory evaluation demonstrated showed that the RoboGene HDV RNA Quantification Kit 2.0 and AmpliSens® HDV-Monitor-FL were highly concordant and equivalent in terms of HDV RNA quantification. The data confirm that both kits are suitable for the laboratory diagnosis of hepatitis D virus infection and the quantitative monitoring of viral load. Thus, the use of these test systems can facilitate the diagnosis and laboratory monitoring of patients with HDV infection in Uzbekistan. Keywords: hepatitis D, HDV, laboratory diagnosis and monitoring of HDV infection, PCR diagnostics of HDV.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P71 HEPATITIS-B CORE-RELATED ANTIGEN (HBcRAG), PHOSPHORYLATED HBcAg, AND HBsAg ISOFORMS AS BIOMARKERS OF VIRAL ACTIVITY IN CHRONIC HDV INFECTION: DO THEY MIRROR HDV RNA STATUS?

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Background & Aims: Hepatitis delta virus (HDV) is a defective satellite virus that depends on hepatitis B virus (HBV) for propagation, requiring HBV envelope proteins (HBsAg) to enter hepatocytes. HBsAg is produced from both covalently closed circular DNA (cccDNA) and integrated HBV DNA, and comprises three isoforms—large (L HBs), middle (M HBs), and small (S HBs). L HBs mediates HBV (and thus HDV) attachment to the NTCP receptor. HBV biomarkers such as hepatitis B core-related antigen (HBcRAg) and pregenomic RNA (pgRNA) reflect cccDNA transcriptional activity and are elevated in HDV RNA-positive individuals. Phosphorylation of HBcAg regulates pgRNA encapsidation: phosphorylated HBcAg (p HBcAg) is the dominant HBcAg protein found in empty and pgRNA containing HBV capsids. Its relevance in HDV infection remains poorly defined. This study compared levels of key HBV virological markers: HBV DNA, HBsAg, HBcRAg, p HBcAg, and HBsAg isoforms (L HBs, M HBs, S HBs), in sequential samples from two groups: individuals with active chronic hepatitis D (HDV RNA-positive) and individuals with past HDV exposure (anti HDV-positive, HDV RNA-negative).

Methods: We analysed samples from 130 HBsAg positive, anti HDV-positive patients (median age 47 years; 62% male; 40% with compensated cirrhosis; 83% receiving nucleos(t)ide analogue [NUC] therapy, 5% HBeAg+). Seventy six patients were HDV RNA-positive, and 54 had undetectable HDV RNA. The following biomarkers were quantified: HBV DNA (real-time PCR, Cobas®, LLOQ 10 IU/ml), HBcRAg (CLEIA, Fujirebio; log₁₀ U/mL; LLOQ 3.0 log₁₀ U/mL), HBsAg (Abbott ARCHITECT; LLOQ 0.05 IU/mL), HDV RNA (RealTime RUO, Abbott; LLOQ 5 IU/mL), HDV genotype (direct sequencing), p HBcAg (Abbott RUO CMA; log₁₀ U/mL) and HBsAg isoforms (Abbott RUO assay; S/Co). Comparisons were stratified by HDV RNA status.

Results: The proportion of patients with undetectable HBcRAg was substantially higher in the HDV RNA-negative group (HBcRAg: 55% vs. 17%, $p < 0.01$). Although HDV RNA-positive patients showed significantly higher levels of several HBV markers (HBcRAg, HBsAg, and HBsAg isoforms), these HBV marker levels did not differ according to HDV genotype (genotype 1 vs. genotype 5) or HBeAg status (Table 1). In contrast, HBV DNA and p-HBcAg were lower in HDV RNA-positive patients. Among the 108 patients receiving NUC therapy, HBV DNA suppression was the only marker significantly influenced by treatment; other HBV biomarkers did not differ according to treatment status.

Conclusions: HBcRAg, a marker reflecting cccDNA transcriptional activity — along with HBsAg isoforms including L-HBs were consistently higher in patients with active HDV infection. Elevated levels of HBsAg isoforms, but lower p-HBcAg (representing empty or pgRNA containing capsids) highlight the potential utility of these emerging HBV biomarkers in characterising HDV associated viral activity.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P72 CLINICAL AND VIROLOGICAL CHARACTERISTICS OF PATIENTS WITH LOW HDV RNA: HBV TRANSCRIPTIONAL ACTIVITY PERSISTS DESPITE MINIMAL REPLICATION

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Background: Increasing use of highly sensitive HDV RNA assays has identified a subgroup of patients with low level HDV viraemia, yet the clinical significance of this state remains unclear. Low or intermittently detectable HDV RNA generally reflects reduced replication, but even minimal HDV activity can drive hepatic inflammation and fibrosis. Patients with HDV RNA below typical clinical trial thresholds (<500 IU/mL) may still experience disease progression. We have examined whether a composite of HBV related biomarkers—including HBcrAg, pgRNA, total HBsAg, and HBsAg isoforms – (by inference, production of Large HBs protein) are pivotal for cellular propagation and sustained active infection. These markers may therefore help characterise HBV transcriptional activity capable of sustaining HDV mediated liver injury despite low HDV RNA. This study compared two cohorts stratified by HDV RNA (<500 vs. >500 IU/mL), assessing HBV virological markers alongside indicators of liver disease activity (ALT, AST, FIB 4, FibroScan) to determine whether low level HDV replication is associated with distinct HBV biomarkers patterns, or differences in hepatic injury.

Methods: Samples from 72 HDV RNA–positive patients (median age 47; 63% male; 50% compensated cirrhosis; 97% on nucleos(t)ide analogue therapy; 8% HBeAg positive) were analysed. Patients were categorised as low HDV RNA (<500 IU/mL; n=24) or high HDV RNA (>500 IU/mL; n=48). We compared HBV DNA [rt PCR, Cobas®, LLOQ 10 IU/ml), HBcrAg (CLEIA, Fujirebio; log₁₀ IU/mL; LLOQ 3.0 log₁₀ IU/mL), pgRNA (RealTime RUO, Abbott; LLOQ 0.49 log₁₀ IU/mL), HBsAg (Abbott ARCHITECT; LLOQ 0.05 IU/mL), HDV RNA (RealTime RUO, Abbott; LLOQ 5 IU/mL), HDV genotype (direct sequencing), phosphorylated -(p)-HBcrAg (Abbott RUO CLEIA; log₁₀ IU/mL) and HBsAg isoforms (Abbott RUO assay; S/Co) in the two groups. Inflammatory activity and hepatic fibrosis was assessed using ALT, AST, bilirubin, albumin, INR, platelets, FIB-4, and FibroScan.

Results: Higher HDV RNA concentrations was associated with significantly higher HBV related biomarkers, particularly HBcrAg, total HBsAg, and HBsAg isoforms, while HBV DNA and p-HBcrAg did not differ. ALT, AST, and platelet counts were higher in the high HDV RNA group, but FibroScan liver stiffness and FIB 4 scores were similar (Table 1). Concurrent HBcrAg and pgRNA positivity was more frequent in high HDV RNA patients (54% vs. 40%, p=0.03), as was HBcrAg positivity alone (44% vs. 21%, p=0.008), whereas isolated pgRNA positivity did not differ statistically (12.5% vs. 25%, p=0.16).

Conclusions: High HDV RNA levels and hepatic inflammation were associated with markers of active cccDNA transcription, but not hepatic fibrosis in this cross-sectional cohort. This discordance suggests that enhanced HBV cccDNA transcriptional activity is more likely in high HDV RNA patients, and is associated with active hepatic inflammation. Our analysis does not allow for the assessment of ultimate hepatic fibrosis or prognosis.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P73 PAIRED LIVER AND SERUM DEEP SEQUENCING REVEALS DIFFERENCES BETWEEN CIRCULATING HDV AND INTRAHEPATIC VIRAL POPULATIONS

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Background: Hepatitis D virus (HDV) sequencing is typically performed on serum HDV RNA, assuming that circulating virus reflects the intrahepatic viral population. However, this has not been systematically evaluated. We investigated the relationship between intrahepatic and circulating HDV quasispecies, and its evolution in serum over time, using deep sequencing of liver and serum samples.

Material and methods: Paired serum and liver samples were obtained from four patients with chronic hepatitis D, that had undergone liver transplantation, and longitudinal sera from an additional 6 patients monitored for chronic HDV in routine care. A total of 30 serum samples were included. From each explanted liver, ten spatially separated tissue pieces were analyzed to assess intrahepatic viral diversity. HDV RNA was amplified using PCR targeting a 284-nt region spanning the 3' end of the HDAg ORF and deep sequenced on the Ion Torrent platform. Species carrying minor variants were identified using CliqueSNV, which reconstructs variant haplotypes and estimates their frequencies. Variant species with frequencies between 0.5% and 50% were included, hereafter called minor species.

Results: Consensus nucleotide sequences of HDV were almost identical in all tissue pieces within each patient, but had differences compared with the consensus sequences in serum samples taken at transplantation at 0–5 positions (mean 2.25). Among the four liver explants, 564 minor species were detected, of which 96% were not identified in matched serum samples. Seventy-nine percent of all minor variants were detected in only one of the ten tissue pieces. In serum, 42 of 63 minor variant species (71%) were not identified in the corresponding liver tissue. One transplanted patient had no detectable minor species in serum, interestingly, this patient had the highest number of consensus sequence differences compared with the liver. The mean frequency of all minor species was 3% in liver and 4% in serum. Minor species detected in both compartments generally occurred at lower frequencies in serum than in liver, in mean 2% and 4%, respectively ($P=0.04$). Longitudinal serum samples demonstrated different compositions of minor species over time, but the consensus was typically well-conserved.

Conclusions: Our findings agree with the idea that HDV in serum might not be representative for HDV in the liver, although circulating HDV should represent the average genetic variation of HDV secreted from the liver to blood. Recent studies have shown that HDV RNA can be present in hepatocytes without HBsAg production, unable to secrete HDV particles. Thus, both serum samples and liver biopsies likely underestimate the complexity of intrahepatic HDV diversity. These findings may have implications for molecular studies of HDV, including investigations of treatment- or immune-associated selection, cell division-mediated spread and the design of experimental constructs based on serum-derived HDV sequences.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P74 DISCORDANCE BETWEEN TWO PERIPHERAL BIOMARKERS OF CCCDNA TRANSCRIPTIONAL ACTIVITY, NAMELY HBV CORE RELATED ANTIGEN AND HBV RNA, IN HBV-HDV CO-INFECTION

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Background: HBV core related antigen (HBcrAg) and HBV RNA have been proposed as surrogate biomarkers of cccDNA transcriptional activity; however, recent work from our group and others has noted a discordance between these two parameters in HBV/HDV co-infection. These studies lacked a comparator HBV mono-infected cohort.

Materials and Methods: The aim of our cross-sectional study was to compare the profile of HBcrAg and HBV RNA in three patient cohorts: (1) HBV mono-infection (n=351), (2) Resolved HDV infection (n=100) and (3) HBV-HDV co-infection (n=94). HBcrAg was measured using chemiluminescent microparticle technology (Fujirebio G-HBcrAg, LLOQ 3.0 log₁₀ U/ml), whilst HBV RNAs were quantified using a dual-target RTqPCR assay (Abbott v2, LLOQ 0.80 log₁₀ U/ml). HDV RNA levels were measured using a RealTime HDV RNA assay (Abbott, LLOD 5 IU/ml).

Results: The median age of our HBV-HDV co-infected cohort was 40 years (IQR 34-48) and 81.9% were receiving long-term nucleos(t)ide analogue therapy. 51.1% had historical exposure to pegylated interferon and HDV genotype was available in 59/94 cases. The most common genotypes were HDV-1 (34 out of 59) and HDV-5 (24 out of 59). Most of our "resolved HDV cohort" had spontaneously resolved HDV and < 10% were exposed to pegylated interferon. The median age of our HBV mono-infected cohort was 42 years (IQR 36-49) and 94.9% were in the HBeAg negative phase of infection. Overall, there was no significant difference in peripheral HBV RNA titres across the three cohorts (p=0.31). However, median HBcrAg titres were significantly higher in the setting of HDV: HBV-HDV co-infection (3.7 log₁₀ U/ml) vs HBV mono-infection (2.5 log₁₀ U/ml) vs resolved HDV infection (0.0 log₁₀ U/ml) (p<0.0001). 25.5% of our HBV-HDV co-infected cohort had quantifiable HBcrAg (≥3.0 log₁₀ U/ml) but HBV RNA < LLOQ. The proportion of HBcrAg POS HBV RNA NEG cases was similar across different HBV-HDV subgroups, irrespective of HDV genotype, concurrent NA therapy or prior exposure to pegylated interferon. For comparison, the proportion of patients with HBcrAg ≥ LLOQ plus HBV RNA < LLOQ in HBV mono-infection was 3.4% (and 3.0% in resolved HDV infection). Next, we performed logistic regression modelling to identify variables associated with a divergent HBcrAg/HBV RNA profile. In the multivariate analysis, two variables were independently predictive of HBcrAg POS/HBV RNA profile, namely (i) HDV co-infection (OR 4.87, 95% CI 1.33 – 19.3, p=0.02), and (ii) Undetectable serum HBV DNA (OR for detectable HBV DNA was 0.22, 95% CI 0.08 = 0.59, p=0.003) (Figure 1). A logistic regression model incorporating these two variables could predict HBcrAg POS/HBV RNA NEG profile with an AUROC of 0.77.

Conclusion: In summary, co-infection with HDV was associated with discordance between serum HBcrAg and HBV RNA. Delineating the underlying mechanism(s) would be informative and may uncover novel therapeutic targets.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P75 HEALTH CARE RESOURCE UTILISATION AND COSTS BY DISEASE STATE IN ADULTS WITH HEPATITIS DELTA VIRUS IN THE UNITED STATES

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Background: Hepatitis delta virus (HDV) infection increases the risk of advanced liver disease. This study evaluated health care resource utilisation (HCRU) and costs in adults with HDV and evidence of progressive disease in inpatient and outpatient settings in the United States.

Material and methods: Adult patients (aged ≥18 years at index) in the PharMetrics database with an HDV diagnosis during the study period (first diagnosis between 01/01/2006 and 31/08/2022 with ≥12 months of continuous enrolment pre-index) with ≥1 inpatient or ≥2 outpatient claims ≥30 days apart were identified. Mean per-patient-per-month (PPPM) HCRU was assessed for patients with noncirrhotic disease (NCD), compensated cirrhosis (CC), decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), or liver transplant (LT). Descriptive statistics were summarised, and comparisons between disease states were evaluated using chi-square and Mann-Whitney U tests.

Results: Among 272,148,753 patients identified in the database, 1,952 adults with HDV were included. Patients had a mean (SD) age of 48.2 (11.05) years and were predominantly male (59%). The proportions of patients within each disease state at baseline were NCD, 1,365/1,952 (70%); CC, 102/1,952 (5%); DC, 340/1,952 (17%); HCC, 80/1,952 (4%); and LT, 65/1,952 (3%). The mean number of all-cause inpatient visits PPPM was significantly higher for patients with DC, HCC, and LT compared with NCD ($P < .0001$) and CC ($P < .0001$). A significantly higher mean number of all-cause inpatient visits PPPM was observed for patients with HCC ($P = .0062$) and LT ($P < .0001$) compared with DC, and for those with LT compared with HCC ($P = .0013$; Table 1). The mean number of all-cause outpatient visits PPPM was significantly higher for patients with CC ($P = .0044$), DC, HCC, and LT compared with NCD ($P < .0001$). For patients with HCC and LT, the mean number of all-cause outpatient visits PPPM was significantly higher compared with CC ($P < .0001$) and DC ($P < .0001$), and also significantly higher for patients with LT compared with HCC ($P = .0032$). Mean all-cause total costs PPPM were significantly higher for CC ($P = .0002$), DC, HCC, and LT compared with NCD ($P < .0001$). Significantly higher mean all-cause total costs PPPM were observed for patients with HCC and LT compared with CC ($P = .0013$ and $P < .0001$, respectively) and DC ($P < .0001$). Inpatient costs PPPM were significantly higher for patients with DC, HCC, and LT compared with patients in the NCD ($P < .0001$) and CC ($P < .0001$) groups, higher for patients with HCC ($P = .0045$) and LT ($P < .0001$) compared with DC, and higher for those with LT compared with HCC ($P = .0068$), contributing to higher all-cause total costs.

Conclusions: In the US, patients with HDV who have progressed to more advanced liver disease stages have higher HCRU and costs compared with those with NCD, highlighting the need for early detection and treatment of HDV to mitigate disease progression and reduce HCRU and costs.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P* WHAT IS THE RELATIONSHIP BETWEEN HBV DNA, HDV RNA AND LIVER FIBROSIS AMONG PERSONS WITH HBV/HDV CO-INFECTION IN ETHIOPIA?

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Background: Co-infection of hepatitis B virus (HBV) and hepatitis D virus (HDV) represents the most severe form of viral hepatitis. However, the interplay of these two viruses is poorly characterized, especially in Africa. We assessed the association between HBV DNA, HDV RNA and liver fibrosis among individuals with HBV/HDV co-infection in Ethiopia.

Methods: A multicenter, cross-sectional study was conducted at four public hospitals in Ethiopia from December 2021 to December 2023. Baseline data included clinical characteristics, liver enzymes, viral markers and non-invasive liver fibrosis markers (aspartate aminotransferase to platelet ratio index; APRI). Total anti-HDV antibody was tested using an ELISA method and HBV DNA and HDV RNA were quantified using commercial PCR assays. Logistic regression models were used to analyze associations with significant liver fibrosis.

Results: In total, 362 HBsAg and anti-HDV positive individuals were included; median age was 30 years (interquartile range [IQR] 25-40) and 241/362 (66.6%) were males. The proportion with significant fibrosis (APRI >0.5) increased with increasing HDV RNA levels. In multivariable analysis, adjusted for age and sex, HBV DNA >20,000 IU/ml (compared to <2000 IU/ml; adjusted odds ratio [aOR] 4.8; 95% CI 2.6-9.3), and HDV RNA 3-5 log₁₀ IU/ml (compared to undetectable; aOR 2.9; 95% CI 1.6-5.1) were strong predictors of liver fibrosis. A complex interaction was observed between HBV DNA and HDV RNA, in which the highest prevalence of liver fibrosis was observed among patients with high HBV DNA and low HDV RNA, and the lowest prevalence in those with low HBV DNA and low HDV RNA. Patients with HDV RNA level >3 log₁₀ IU/ml had an intermediate prevalence of liver fibrosis, which was independent of HBV DNA level.

Conclusions: In HBV/HDV co-infected patients, liver fibrosis is strongly associated with both HBV DNA and HDV RNA levels, with a complex interaction between the two viruses. Individuals with HBV DNA <2000 IU/ml and HDV RNA <3 log₁₀ IU/ml appeared to have the most favorable profile.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P76 TREATMENT OF HBV-HDV HEPATITIS IN A SOLID ORGAN TRANSPLANT RECIPIENT PATIENT: A CASE REPORT

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Background: J.H., 57 years old, had a kidney transplant in 2002, for an unspecified renal pathology present since his youth and diagnosed in his Country of origin, Albania, where he was undergoing dialysis treatment. In anamnesis there was HBV-HCV related hepatitis, treated with Interferon in 1998, following a liver biopsy, which found chronic active hepatitis. Abdominal ultrasound shows liver with thickened echostructure, regular spleen; a liver Transient Elastography shows stiffness of 5.8 KPa. Persistent positivity of HBsAg is found, with HBVDNA values <10 or not detected. Last determination of HBVDNA in September 2023 was 66 copies/mL. HCVRNA was non-reactive on 11/3/2023; transaminase values persistently altered. She starts therapy with Entecavir 0.5mg 1 cp/day with persistent negativization of HBV viremia and normalization of transaminases. On 10/16/2023, a search for total anti-HDV Ig was performed, with positive results of HDVRNA (3222911 copies/mL). A diagnosis of HBV and HDV co-infection was therefore made.

Materials and methods: The introduction of Bulevirtide into therapy was therefore evaluated. The patient was already in therapy with: Cyclosporin 50 mg every 12 hours; Prednisone 5 mg/die; Mycophenolate 360 mg every 12 hours; Pantoprazole 40 mg every 12 hours; Bisoprolol 2.5 mg 1 + ½ tablet/die; Ezetimibe/Atorvastatin 10/10 mg7die; Amlodipine 5 mg/die; Lormetazepam 1 mg/die; Levothyroxine 50 mcg/die; Escitalopram 20 mg/die; Alprazolam 15 drops/die; Febuxostat 80 mg/die; Cardioaspirin 100 mg/die; Ferrous sulfate 1 tablet/die; Cholecalciferol 10000 IU 20 drops/week.

Results: Potential clinically significant interactions between Bulevirtide and Atorvastatin and between Bulevirtide and Levothyroxine were detected; furthermore, absolute contraindication to coadministration of Bulevirtide and cyclosporine and Bulevirtide and ezetimibe was detected. We decided to modify the immunosuppressive therapy, suspending Cyclosporine, and introducing Tacrolimus 2 mg every 12 h, taking into account the possible interactions also present between Bulevirtide and Tacrolimus. Based on the tacrolemia values on January 2024 (12.4 ng/mL), the Tacrolimus dosage was reduced to 2 mg in the morning and 1 mg in the evening. With a tacrolemia of 10.2 ng/mL on February 2024 and 6.2 ng/mL on March 2024. The tacrolemia values were then constantly maintained within the desired ranges, without requiring further dosage adjustments. Furthermore, the lipid-lowering therapy was modified, suspending Ezetimibe/Atorvastatin and introducing Simvastatin 20 mg/die. On 21.02 antiviral therapy for delta hepatitis was started with Bulevirtide 2 mg/die subcutaneously.

Conclusion: The drug is well tolerated with a progressive reduction in HDV viremia until it became negative. Our case highlights the need for careful evaluation of drug interactions, especially with immunosuppressant drugs, and the importance of close monitoring of their serum levels.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P77 PHYLOGEOGRAPHY AND EPIDEMIOLOGICAL HISTORY OF HEPATITIS DELTA VIRUS GENOTYPE 3 IN SOUTH AMERICA

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Background: Hepatitis delta virus genotype 3 (HDV-3) predominates in the Amazon Basin and is associated with severe and fulminant hepatitis. Despite clinical recognition, its evolutionary origin, dissemination routes and long-term maintenance remain poorly resolved. We integrated newly generated HDV-3 genomes with public data, Bayesian phylogeography, a historical review and surveillance records to reconstruct its evolutionary and epidemiological history in South America.

Material and methods: This cross-sectional study included 215 HBsAg-positive and anti-HDV-positive individuals followed in Amazonas, Rondônia and Acre from January 2016 to February 2024. HDV RNA was tested with the Abbott RealTime HDV RNA assay. Complete genomes were generated on the Illumina NovaSeq 6000 platform and HDAg fragments by Sanger sequencing. New sequences were combined with dated, georeferenced GenBank data, yielding datasets of 186 complete genomes and 309 HDAg sequences. Discrete and continuous Bayesian phylogeographic analyses in BEAST X v10.5.0 inferred ancestral locations, migration, spatial diffusion, dispersal velocity, lineage persistence, source–sink dynamics and demographic history. Sampling bias was assessed by tip-state-swap analyses and adjusted Bayes factors. Findings were contextualized through a systematic review and 3,537 laboratory-confirmed cases reported to Brazil's National Notifiable Diseases Information System (SINAN) from 2007 to 2023.

Results: We obtained 85 new complete HDV-3 genomes and 29 new HDAg sequences, representing 46% of all complete genomes and 9% of all HDAg sequences in GenBank. The most recent common ancestor was dated to 1808 for complete genomes and 1862 for HDAg sequences. Amazonas was the most probable ancestral location in both datasets, although sampling-adjusted support was retained only in the complete-genome analysis. Continuous phylogeography indicated slow, structured expansion along the Amazonas–Acre–Rondônia axis, with dispersal velocities of 8.8–11.2 km/year and a reach of 1,950 km by 2024. Lineage residence time and net migration identified Amazonas as the main reservoir and exporter, whereas Acre and Rondônia were mainly sink regions. Skygrid suggested twentieth-century population growth followed by a recent decline, consistent with reduced confirmed SINAN cases despite increased testing. Historical evidence documented confirmed HDV circulation dating to the 1930s–1940s, consistent with introductions preceding molecular surveillance.

Conclusions: HDV-3 emerged, diversified and persisted within the Amazon Basin before spreading slowly through Amazonian territories. Amazonas was the central axis of HDV-3 history, acting as the most probable ancestral location, main long-term reservoir and dominant source of dissemination. These findings reinforce the need for sustained molecular surveillance, expanded HDV screening among HBsAg-positive individuals and targeted prevention across the Amazon Basin.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

VIROLOGY: THE LATEST INSIGHTS

P78 PHYLOGEOGRAPHIC RECONSTRUCTION REVEALS RECENT AFRICAN-ATLANTIC DISPERSAL OF HEPATITIS DELTA VIRUS GENOTYPE 8

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Background: Hepatitis delta virus (HDV) causes the most severe form of chronic viral hepatitis. However, the historical processes shaping its diversity and spread remain poorly understood. HDV genotype 8 (HDV-8) has been reported mainly in Africa and, unexpectedly, in Brazil, suggesting possible trans-Atlantic transmission linked to long-standing connections between West-Central Africa and South America. The historical pathway through which HDV-8 reached Brazil remains undetermined and has not been formally evaluated using phylogeographic methods that infer the origin, timing and routes of viral spread.

Material and methods: We analysed 44 publicly available HDV-8 sequences from GenBank, sampled between 1999 and 2019 in ten countries, including eight sequences from Brazil. Bayesian phylogenetic analyses were performed in BEAST X v10.5.0, with discrete phylogeographic reconstruction at country and regional levels under an asymmetric diffusion model. Migration pathways, lineage residence times and transition histories were assessed using adjusted Bayes factors, Markov rewards and stochastic-history jumps. Inferred transitions were assigned to time windows corresponding to the trans-Atlantic slave trade, late slavery and post-abolition, African decolonization and contemporary mobility.

Results: Africa-to-Brazil transitions were infrequently associated with periods compatible with the active slave trade. Their posterior probability was <0.3% before 1850 and <1.5% before 1888. In contrast, 46–50% of the transition probability was assigned to periods after 1960, with median first-entry dates in Brazil between 1963 and 1966. Gabon had the highest inferred lineage residence time and was frequently reconstructed as a source of entry into other locations, although this may reflect broader West-Central African diversity rather than the definitive origin of HDV-8. Skygrid analyses supported a twentieth-century increase in effective population size, consistent with post-1960 dispersal. A supported Brazil-to-Namibia route was also identified, occurring approximately 46 years after the first inferred entry of HDV-8 into Brazil.

Conclusions: Our findings support a deeply African lineage of HDV-8 shaped by West-Central African persistence, regional circulation and subsequent transcontinental movement. The presence of HDV-8 in Brazil remains historically compatible with Africa-to-South America transmission. The dated phylogeographic signal points to twentieth-century, post-colonial mobility rather than a predominant slave-trade-era introduction of HDV-8 to Brazil. A subsequent HDV-8 transition from South America back toward Africa was also inferred, although unsampled intermediate locations cannot be excluded. Together, these findings provide a formal phylogeographic framework for understanding how African–Atlantic historical processes influenced the intercontinental distribution of HDV-8.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

IMMUNOLOGY UPDATE AND SPATIAL TRANSCRIPTOMICS

P79 IDENTIFICATION OF GBP3 AS A NOVEL HOST FACTOR REQUIRED FOR HEPATITIS DELTA VIRUS RECOGNITION BY HEPATOCYTES

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Background: Following entry into hepatocytes, the hepatitis D virus (HDV) ribonucleoprotein complex is sensed by the cytosolic RNA receptors MDA5 and LGP2, leading to the activation of type I and III interferon (IFN) responses.

Material and methods: Although differentiated HuH7.5-NTCP cells responded to stimulation with an MDA5 ligand (high-molecular-weight poly(I:C)), they failed to mount an IFN response following HDV infection, even upon ectopic MDA5 overexpression. These observations suggested the involvement of an additional, as yet unidentified, host factor in HDV recognition. To identify such factor(s), we analyzed transcriptomic data comparing gene expression profiles of differentiated HuH7.5-NTCP and dHuH7-NTCP cells, the latter being capable of mounting a robust IFN response upon HDV infection. Among the differentially expressed genes, we identified the guanylate-binding protein 3 (GBP3). Using dHepaRG and dHuH7-NTCP cells, we observed a significant reduction in HDV-induced expression of the interferon-stimulated gene RSAD2 following GBP3 knockdown by RNA interference. This reduction was comparable to that observed following LGP2 knockdown.

Results: Conversely, we found that co-expression of MDA5, LGP2 and GBP3 restored the IFN response to HDV infection in non-responsive cells (undifferentiated HuH7-NTCP cells). Mechanistically, immunoprecipitation assays revealed associations between GBP3 and MDA5, GBP3 and LGP2 as well as between GBP3 and HDV RNAs. In addition, rather than promoting the association of MDA5 with HDV RNAs, we found that GBP3 enhanced MDA5 oligomerization, thereby promoting downstream IFN pathway activation.

Conclusions: In conclusion, we identify GBP3 as a novel host factor required for innate sensing of HDV by infected hepatocytes, uncovering a previously unrecognized mechanism regulating MDA5 activation during HDV infection.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY
IMMUNOLOGY UPDATE AND SPATIAL TRANSCRIPTOMICS

P80 BULEVIRTIDE TREATMENT REDUCES ACTIVATION OF T CELLS IN CHRONIC HDV INFECTION

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Background: Infection with the hepatitis D virus (HDV) induces the most severe form of chronic viral hepatitis. Liver disease pathogenesis has been associated with bystander activation of CD8⁺ T-cells, which upregulate NKG2D, allowing them to interact with NKG2D ligands on hepatocytes, and contributing to liver immunopathology. Bulevirtide (BLV) is a novel antiviral drug that inhibits HDV infection by blocking its entry into hepatocytes. Since improvement in liver function tests has been observed under BLV treatment, we aim to identify if this is mediated by reduced bystander activation of CD8⁺ T cells.

Materials and Methods: Peripheral blood mononuclear cells (PBMCs) and plasma samples were isolated from HDV-infected patients (n=21) before (baseline) and at week 48 of BLV treatment (TW48). Single-cell RNA sequencing (scRNA Seq) and 34-color spectral flow cytometry were performed to assess gene expression and immune-cell phenotypes over time. A 48-plex immunoassay was conducted on plasma samples to assess circulating cytokine levels.

Results: Under BLV treatment, HDV-infected patients exhibit a decline in liver transaminases, aspartate transaminase to platelet ratio index, and fibroscan values. This is coupled with a significant reduction in circulating chemokines CXCL9, CXCL10, and CCL3, reflecting decreased inflammation and type I interferon signaling. CD4⁺ and CD8⁺ central memory T-cell frequencies were low at baseline, but recovered at TW48. Interestingly, although reduced in numbers at baseline, these cells displayed higher levels of activation at the transcriptomic and proteomic level, as gene signatures associated with mitochondrial activity, oxidative stress, and interferon-stimulated genes were significantly upregulated compared to TW48. Furthermore, CD8⁺ T-cells revealed an elevated bystander activation signature at baseline, which decreased with BLV treatment, and was accompanied by significant reduction of NKG2D expression on T cells and its ligands on HDV-infected Huh7NTCP cells, indicating a decline in NKG2D/NKG2D-ligand interaction.

Conclusions: BLV therapy decreases bystander activation of CD8⁺ T cells at TW48, suggesting that treatment reduces NKG2D-mediated signaling, which may explain the improvement in liver function.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

IMMUNOLOGY UPDATE AND SPATIAL TRANSCRIPTOMICS

P81 IDENTIFICATION OF PERIPHERAL IMMUNE CELL POPULATIONS IN HDV UNTREATED AND BULEVIRTIDE-TREATED PATIENTS.

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Background and Aims: The outcomes of HDV infection are heterogeneous, ranging from viral control to persistent viremia. Similarly, treatment response varies, with a subset of patients failing to achieve response. While the immune system plays a central role in infection control, few data are available regarding the immune dynamics in HDV infection. This study aims to characterize peripheral blood immune cell populations associated with virological control and treatment response.

Methods: Immune cells profiling was performed using high-dimensional spectral flow cytometry with a 38-markers panel covering T cells (including $\gamma\delta$), B cells, NK cells, monocytes and dendritic cells. Peripheral blood mononuclear cells (PBMCs) were obtained from 26 individuals living with HDV. Of these, 12 were untreated and grouped according to their HDV RNA and ALT levels: undetectable HDV RNA (n=4), persistent viremia with normal ALT (n=4) and patients with chronic hepatitis (persistent viremia and high ALT, n=4). The remaining 14 were treated with Bulevirdide (BLV) and stratified in responders (n=7) and non-responders (n=7) based on their combined response (HDV RNA drop >2log or undetectable plus ALT normalization) at 1 year of treatment (T1). For treated patients, samples were analyzed at baseline (start-of-treatment; SOT) and T1.

Results: Unsupervised multidimensional analysis revealed that untreated patients with active chronic hepatitis exhibited a distinct immune profile. Compared with the other two sub-groups, these patients showed an expansion of tissue-homing (CXCR3+, CXCR6+) $\gamma\delta$ T-cells with an exhausted phenotype (PD1+, TIGIT+); p<0.05. Among BLV-treated patients, responders displayed a higher proportion of mature (CD57+), cytokine-responsive (CD161+) NK cells at both SOT and T1 compared to non-responders (p<0.05). Conversely, non-responders maintained a distinct population of tissue-homing, exhausted CD8+ TEMRA cells displaying an NK-like phenotype (CD56dim, NKG2D+; p<0.05).

Conclusion: Distinct peripheral immune signatures characterize HDV infection outcomes and responsiveness to BLV. The interplay between functional innate responses and exhausted immune populations may represent a pivotal factor driving the lack of immunological control in HDV infection. Identifying these circulating immune profiles may facilitate early risk stratification in patients with HDV. Study supported by the project PI23/01065, funded by Instituto de Salud Carlos III and co-funded by European Union (ERDF, "A way to make Europe").



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY

IMMUNOLOGY UPDATE AND SPATIAL TRANSCRIPTOMICS

P82 BULEVIRTIDE INCREASES TAUROCHOLIC ACID IN HEPATITIS D PATIENTS LEADING TO REDUCED NK CELL PROLIFERATION CAPACITY

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Introduction and specific aims: The antiviral therapy Bulevirtide (BLV) inhibits HBV/HDV entry by blocking Na⁺ taurocholate co-transporting polypeptide (NTCP) expressed on hepatocytes. This leads to decline of viral load and reduction of ALT. By the mode of action, bile acids (BAs) was increased in the blood of most BLV-treated patients. As a signaling molecule, BAs are known to regulate lipid metabolism. The disruption of BA metabolism may link to liver diseases. Furthermore, it has been reported that hepatitis B patients' derived natural killer (NK) cells exposed with taurocholic acid (TCA) has the impaired cytotoxic function. Thus, this study aims to analyze the in-vitro effect of TCA on NK cell functionality.

Methods

Profiling of serum BAs was done using liquid chromatography and mass spectrometry (LC-MS). We selected the specific BAs and analyzed their effects on NK cells by using high-dimensional flow cytometry and in-vitro functional assays.

Results: The BAs profiling results showed the elevated TCA concentration in non-cirrhotic patients during BLV therapy. TCA exposure has minor changes on NK cell cytokine secretion and cytotoxicity. However, Ki67 expression and the frequency of divided NK cells were significantly reduced upon the exposure of physiological dose of TCA, suggesting that the metabolism changes and proliferation capacity were negatively affected by TCA.

Conclusion: Our study identifies BAs and selected TCA as our focus in this study. TCA increased statistically significant in the patients during BLV therapy. The in-vitro functional analysis also implicated the functional effect of TCA on NK cells, especially the proliferation capacity. Further in-vitro functional assay and RNA sequencing analysis will be performed to confirm the study.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY
IMMUNOLOGY UPDATE AND SPATIAL TRANSCRIPTOMICS

P83 AN IMMUNOCOMPETENT SYRIAN HAMSTER MODEL OF PERSISTENT HDV MONO-INFECTION VALIDATED FOR ANTIVIRAL TESTING

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Background: Hepatitis D virus (HDV) mono-infection models have been restricted to SCID human-liver xenograft mice due to the highly restricted host range of HDV. While the discovery of hNTCP as the entry receptor has allowed for hNTCP-expressing mouse models, these produces only a transient, short-lived mono-infection. This contrasts with the human setting, where HDV mono-infection can establish a reservoir with the risk of reactivation upon HBV superinfection. Here, we present the Syrian hamster (*Mesocricetus auratus*) as a robust *in vivo* model that supports prolonged hepatic HDV infection. Furthermore, we validate this platform for preclinical screening using both host- and direct-acting therapeutics.

Materials and methods: Five-week-old female wild-type Syrian hamsters were transduced with an adeno-associated viral vector expressing hNTCP under a liver-specific promoter. One week post-transduction, animals were challenged with HDV. To assess viral kinetics, hamsters were sacrificed at various intervals up to 56 days post-infection (dpi). Liver tissues were analyzed via RT-qPCR for HDV RNA and hNTCP transcripts, alongside immunohistochemistry (IHC). For antiviral validation, a separate cohort received treatment starting one day prior to HDV inoculation. Interventions included Bulevirtide (2 mg/kg/day, SC) or recombinant hamster IFN- α (5 μ g/kg/day, IP) from day -1 to 2 dpi, or a single dose of Tobeivart (5 mg/kg, SC) on day -1. Animals were monitored for body weight and euthanized at 6 dpi for analyses.

Results: Hepatic hNTCP transcript levels were uniform across subjects, confirming consistent AAV-hNTCP transduction and receptor availability. Following HDV challenge, intrahepatic HDV RNA levels exhibited an initial surge and plateaued, maintaining stable titers up to 56 dpi. This persistence was confirmed by IHC, demonstrating sustained HDAG presence within hNTCP-expressing hepatocytes. In the antiviral efficacy study, systemic treatments were generally well-tolerated. The IFN- α cohort exhibited a transient, expected weight loss, which rebounded upon cessation of therapy. At termination, all therapeutic interventions yielded statistically significant reductions in intrahepatic HDV RNA compared to vehicle controls. Tobeivart exhibited the highest prophylactic efficacy with a >2.5-log reduction ($p=0.0012$). This was followed by Bulevirtide (2-log reduction, $p=0.0048$) and IFN- α (1.5-log reduction, $p=0.0205$).

Conclusions: Following hNTCP-expression, wild-type, immunocompetent Syrian hamsters are highly susceptible to HDV mono-infection and support a persistent viral reservoir in the absence of HBV. This model mirrors the persistence seen in human-liver xenograft mice and overcomes the rapid viral clearance observed in hNTCP-murine models. The hNTCP Syrian hamster serves as a physiologically relevant and robustly predictive preclinical platform for the *in vivo* evaluation of both host-directed and direct-acting antiviral therapies.



EPIDEMIOLOGY, VIROLOGY AND IMMUNOLOGY
IMMUNOLOGY UPDATE AND SPATIAL TRANSCRIPTOMICS

P84 A HIGH-CONTENT IMAGING-COMPATIBLE INNATE IMMUNE RESPONSE-BASED REPORTER SYSTEM FOR HDV ANTIVIRAL SCREENING

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Background: In vitro screening of antivirals against hepatitis D virus (HDV) currently relies on low-throughput, labor-intensive methods such as immunofluorescence or RT-qPCR. Developing recombinant HDV reporter strains remains technically challenging due to the virus's intricate genomic architecture. To overcome this bottleneck, we developed a reporter cell line that leverages the host's innate immune response. By exploiting the intracellular sensing of viral RNA by the pathogen recognition receptors, our system utilizes an interferon-stimulated response element (ISRE) to drive the expression of mNeonGreen (mNG). This enables direct, fluorescence-based monitoring of viral infection and the subsequent validation of antiviral hits.

Materials and methods: A lentiviral vector was engineered with an expression cassette encoding mNG under the control of an ISRE promoter and a nuclear fluorescent protein (mRFP670) for cell identification. Polyclonal reporter lines were generated via lentiviral transduction of HEK293T-AD, HepG2, and Calu-3 cells. ISRE promoter activity was validated by high-content imaging following stimulation with type I and III interferons, as well as synthetic PAMPs. The system's capacity to detect RNA virus infection was initially benchmarked using a yellow fever 17D-mCherry (YF17D-mCherry) reporter virus, both in the presence and absence of the reference antiviral NITD008. To enable the sensing of HDV replication, cells were further transduced to overexpress MDA5, challenged with HDV, and assessed for the coexpression of mNG and with HDAg by immunofluorescence assay (IFA).

Results: Stable reporter cell lines derived from HEK293T-AD, HepG2, and Calu-3 cells were successfully established. Exogenous interferon stimulation induced robust mNG expression in HEK293T-AD and Calu-3 cells, whereas the HepG2 clone remained unresponsive. Profiling of PRR pathways using synthetic agonists revealed functional deficiencies in multiple sensors in HEK293T-AD and HepG2 cells; conversely, Calu-3 cells exhibited intact TLR3, MDA5, and cGAS-STING signalling. Despite these baseline innate immune variations, YF17D-mCherry infection successfully triggered ISRE-driven mNG expression across all cell lines, with strict coexpression of mNG and viral mCherry signals. Treatment with NITD008 effectively abrogated the mNG signal, validating the platform's predictive utility for antiviral screening. In addition, MDA5-expressing reporter cell lines successfully sensed HDV replication, evidenced by expression of mNG in HDAg-positive cells.

Conclusions: We developed and validated a high-content imaging-compatible reporter cell system that utilizes the host MDA5-ISRE signalling axis to sense viral infection. This innate immune-based approach successfully circumvents the need for recombinant HDV reporter strains, offering a robust, high-throughput phenotypic platform for the discovery and evaluation of novel anti-HDV therapeutics.



DIAGNOSIS AND NATURAL HISTORY

DIAGNOSTICS UPDATE

P85 PAN-GENOTYPIC DETECTION AND WHOLE-GENOME SEQUENCING OF HEPATITIS D VIRUS USING THE ILLUMINA VIRAL SURVEILLANCE PANEL V2

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Background: Hepatitis D virus (HDV) exhibits high genetic diversity, with eight recognised genotypes distributed worldwide. Accurate detection and comprehensive genomic characterisation of HDV-RNA (1.680nt genome) are essential for molecular surveillance and epidemiological studies. We evaluated the performance of the Illumina Viral Surveillance Panel v2 (VSP2) for both HDV detection and whole-genome sequencing across all known HDV genotypes.

Material and Methods: A validation panel including 24 HDV RNA-positive samples representing the eight HDV genotypes and two HDV RNA-negative controls was analysed using the VSP2 target-enrichment workflow followed by NGS. HDV viral loads ranged from 2.7 to 6.1 log IU/mL. Assay performance was assessed for HDV detection, genome coverage and sequencing depth. Consensus sequences generated by the VSP2 bioinformatic software (Dragen®) were compared to reference sequences previously obtained by Sanger sequencing. Phylogenetic analyses were performed to evaluate sequence concordance and genotype assignment.

Results: HDV-RNA was successfully detected in all 24 positive samples with a median of 0.5M HDV reads per sample. Both negative controls remained negative, with only 6 and 10 HDV reads detected respectively, below the threshold. HDV genomes coverage ranged from 91% to 100%. For all samples except the two HDV-3 strains, comparison with Sanger sequences demonstrated high concordance, with a median of 7.5 nucleotide differences per genome. Phylogenetic analysis confirmed correct clustering with the corresponding Sanger references and accurate genotype assignment. The Illumina Dragen® application failed to correctly reconstruct the two HDV-3 genomes, generating consensus sequences that were discordant with the Sanger references and incorrectly positioned within the phylogenetic tree. Reanalysis of the raw FASTQ files using an in-house workflow successfully recovered the expected HDV-3 genomes, demonstrating that this limitation was due to the Dragen® pipeline rather than to sequencing performance. Improvements to this pipeline are currently underway. Of note, HBV-DNA was simultaneously detected in 7 samples, highlighting the ability of the assay to detect HBV/HDV co-infections when both are actively replicating.

Conclusion: The Illumina VSP2 assay demonstrated excellent performance for HDV detection and whole-genome sequencing, achieving 100% detection of positive samples across all eight known HDV genotypes and high genome coverage over a broad range of viral loads. Consensus sequences showed strong concordance with Sanger references for all genotypes except HDV-3. Reconstruction of HDV-3 genomes from raw sequencing data using an home-made pipeline confirmed that the observed limitation was related to the current Illumina bioinformatics pipeline rather than to assay performance. These findings support the use of VSP2 for HDV molecular screening, genomic epidemiology and characterization of HBV/HDV co-infections.



DIAGNOSIS AND NATURAL HISTORY

DIAGNOSTICS UPDATE

P86 GLOBAL PRACTICE PATTERNS IN HEPATITIS D VIRUS SCREENING AND MANAGEMENT: RESULTS FROM AN INTERNATIONAL SURVEY OF HEALTHCARE PROVIDERS

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Background: Despite recent therapeutic advances and updated international guidelines recommending universal HDV screening in all HBsAg-positive individuals, real-world implementation remains heterogeneous worldwide. We aimed to evaluate healthcare providers' knowledge and practice patterns regarding HDV screening and treatment.

Methods: An international expert panel from the Global Liver Council developed a 37-item anonymous online survey, distributed between June and September 2025, to assess clinicians' HBV/HDV management patterns. Multivariable logistic regression identified factors associated with HDV screening, HDV RNA testing access, and treatment recommendations, including demographics, professional and geographic characteristics.

Results: Overall, 611 clinicians from seven global regions completed the survey (hepatologists/gastroenterologists 68%, infectious disease specialists 11.5%, other specialties 20.5%). EASL guidelines were most frequently followed (46%), followed by AASLD (21%), WHO (12.6%), APASL (10.1%), and other guidelines (10%). Among 559 respondents evaluating HDV screening, 257 (46.0%) reported universal screening of all HBsAg-positive patients, while only 29 (5.2%) had implemented reflex anti-HDV testing. Another 116 (20.8%) supported universal screening but reported inconsistent implementation, while 157 (28.1%) continued to use a risk-based screening strategy. Risk-based screening was more common among gastroenterologists than hepatologists or infectious disease specialists (45.9% vs. 38.2% vs. 1.9%, $P < 0.001$). In multivariable analysis, clinicians from South Asia (OR 0.24, 95% CI 0.12–0.46; $P < 0.001$), Southeast Asia (OR 0.08, 95% CI 0.05–0.14; $P < 0.001$), and following AASLD guidelines (OR 0.41, 95% CI



0.24–0.68; $P=0.001$) were less likely to implement universal HDV screening whereas infectious disease specialists were more likely to recommend universal screening (OR 3.59, 95% CI 1.03–12.56; $P=0.046$). HDV RNA testing access was limited, with only 271 (48.5%) respondents reporting test availability and 146 (26.1%) reporting reimbursement. Most clinicians (444/546, 81.3%) supported treatment of all patients with chronic Hepatitis D, whereas 102 (18.7%) restricted treatment to those with at least moderate fibrosis. In multivariable analysis, clinicians practicing in Southeast Asia (OR 0.37, 95% CI 0.24–0.59; $P<0.001$) and male clinicians (OR 0.60, 95% CI 0.37–0.97; $P=0.038$) were less likely to recommend treatment irrespective of fibrosis stage, reflecting a greater tendency to adopt a fibrosis-based treatment strategy.

Conclusions: Despite broad support for universal HDV screening and treatment, gaps between guideline recommendations and real-world practice remain. Universal screening is inconsistently implemented, reflex anti-HDV testing is rarely available, and reimbursed HDV RNA testing and medications remain limited. Improving diagnostic access and targeted education are essential for evidence-based HDV care worldwide.



DIAGNOSIS AND NATURAL HISTORY

DIAGNOSTICS UPDATE

P87 EVALUATION OF DRIED BLOOD SPOTS FOR AUTOMATED HEPATITIS D NUCLEIC ACID TESTING

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Background: In low- and middle-income countries, where access to molecular diagnostics is often limited, dried blood spots (DBS) provide a practical alternative to conventional plasma or serum samples, enabling simplified specimen collection, storage, and longer transportation without the need for an uninterrupted cold chain. Objective: This study aims to evaluate the feasibility of using DBS for the molecular detection of HDV RNA utilizing the AltoStar® Automation System AM16 in combination with the AltoStar® HDV RT-PCR Kit 1.5 (off-label use).

Material and Methods: A total of 10 DBS were prepared from whole blood samples of patients with active HDV infection (high viral load). In parallel, 25 DBS were prepared using a serial dilution of whole blood with defined HDV RNA concentrations (1st WHO International Standard for HDV RNA). All DBS were kept at room temperature for drying before processing while the corresponding patient samples and serial dilutions were stored at -20°C. All DBS samples (patient samples plus serial dilution samples) were pre-treated according to the user manual of the AltoStar® Automation System AM16 and were processed together with the samples stored at -20°C on the instrument and amplified using the AltoStar® HDV RT-PCR Kit 1.5 assay reagents.

Results: HDV RNA was quantifiable in all DBS specimens from patients with active infection, although viral load levels were lower than in plasma and whole blood.

Conclusions: Automated molecular testing of HDV RNA from DBS in countries with minimal laboratory infrastructure could significantly improve hepatitis D surveillance, facilitate timely diagnosis, and support the expansion of antiviral treatment programs in underserved populations.



DIAGNOSIS AND NATURAL HISTORY

DIAGNOSTICS UPDATE

P88 LONGITUDINAL HDV RNA MONITORING REVEALS VIROLOGICAL REBOUND DESPITE SUSTAINED HIV AND HBV SUPPRESSION IN A CIRRHOTIC PATIENT

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Background: Chronic hepatitis D is the most severe form of viral hepatitis. It is associated with accelerated progression to cirrhosis and liver-related complications. HDV screening is recommended in all HBsAg-positive individuals. HDV RNA should be monitored every 6 months to define response to treatment¹.

Case presentation: A 65-year-old man was diagnosed with HIV infection (HIV RNA 133,522 copies/mL; CD4 nadir 256 cells/ μ L; CDC stage C2), chronic HBV and HDV infection, previous resolved HCV infection (HCV RNA has always been undetectable) and compensated cirrhosis. Liver disease was complicated by portal hypertension, splenomegaly, severe portal hypertensive gastropathy and F1 esophageal varices. Antiretroviral therapy (ART) with bicitgravir/emtricitabine/tenofovir alafenamide was started. Baseline abdominal CT showed hepatomegaly and irregular liver margins. Baseline and follow-up elastographies showed a liver stiffness of 17.9 kPa, consistent with advanced fibrosis (METAVIR F4). After ART initiation, HIV RNA rapidly became undetectable and remained suppressed thereafter. One year after diagnosis HBV DNA also became undetectable, while HBsAg remained detectable. Child-Pugh class remained A throughout follow-up. In parallel, HDV RNA measured 724 IU/mL at diagnosis and one year after increased to 12,550 IU/mL, despite persistently normal liver enzymes and stable liver function, prompting initiation of bulevirtide. After four months of treatment, HDV RNA declined to 7,114 IU/mL, while AST and ALT remained within the normal range. At the last follow-up, two years after, biochemical remission persisted (ALT 18 U/L; AST 24 U/L) and the HDV RNA became 692 IU/mL. The patient is still taking bulevirtide and ART despite suboptimal adherence to scheduled outpatient visits.

Conclusions: Sustained HIV suppression, persistent HBV DNA suppression under tenofovir-containing ART and normal aminotransferases do not necessarily reflect HDV virological activity. The increase in HDV RNA despite biochemical quiescence supported treatment initiation with bulevirtide and emphasize the importance of serial HDV RNA monitoring in patients with chronic hepatitis D, particularly in those with advanced liver disease and HIV coinfection.^{1,2} Moreover HDV virological activity occurred despite persistently normal aminotransferases and stable Child-Pugh class A, suggesting that biochemical remission may underestimate ongoing viral replication. These findings reinforce the importance of serial HDV RNA monitoring and support the need for HDV-specific therapy in selected patients despite optimal HBV suppression, supporting the concept that HBV DNA suppression alone is insufficient to control HDV infection especially if HBsAg is detectable throughout follow-up.

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DIAGNOSIS AND NATURAL HISTORY

DIAGNOSTICS UPDATE

P89 DEVELOPMENT OF A LOCAL PANEL FOR QUALITY CONTROL OF HEPATITIS DELTA VIRUS PCR DIAGNOSTIC KITS

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Background: Quantitative measurement of HDV RNA by real-time PCR represents the gold standard for evaluating viral activity, establishing indications for therapy, and monitoring antiviral treatment efficacy. The analytical sensitivity and reproducibility of molecular diagnostic methods directly depend on the quality of diagnostic kits. Implementing internal and external quality control systems allows effective monitoring at pre-analytical and analytical stages. However, routine reliance on imported reference panels is frequently constrained by high costs and supply chain logistics. Therefore, the development and validation of local reference samples is of high practical importance. **Aims:** To develop a local PCR reference panel for HDV RNA detection and to evaluate its efficacy within a quality control system for molecular diagnostic assays. **Materials and Methods:** Blood plasma samples obtained from HDV-positive patients served as the initial material. All samples were confirmed for HDV viral load presence. The panel was established using 12 samples covering a linear concentration range from 10^2 – 10^7 IU/mL. Samples were aliquoted into 150 μ L volumes and stored at -20°C . Each sample was tested in triplicate using the AmpliSens® HDV-Monitor-FL reagent kit. Analytical performance was evaluated based on cycle threshold (Ct) values and standard deviation (SD).

Results: All samples of the established panel were successfully amplified in all replicates. A strong inverse linear relationship was demonstrated between HDV RNA concentration and Ct values: sample D1 (10^2 IU/mL) yielded a Ct of 29.08 ± 0.60 , whereas sample D11 (10^7 IU/mL) yielded a Ct of 15.37 ± 0.55 . Low variance and minimal SD values across parallel replicates confirmed high homogeneity of the prepared aliquots and method reproducibility. Negative control samples showed no amplification across all runs, ruling out contamination.

Conclusions: The developed local reference panel demonstrates high analytical stability across a wide dynamic range (10^2 – 10^7 IU/mL). This panel is suitable for lot-to-lot verification of diagnostic kits, validation of new PCR testing kits, and implementation as an internal quality control material in routine diagnostic workflows.

Key words: HDV, Quality control, HDV PCR testing.



DIAGNOSIS AND NATURAL HISTORY

DIAGNOSTICS UPDATE

P90 VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY SHOWS A HIGH DIAGNOSTIC VALUE IN THE EXCLUSION OF CIRRHOSIS AND THE DETECTION OF SIGNIFICANT FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS D VIRUS INFECTION

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Background: Non-invasive tests (NITs), including serological tests and vibration-controlled transient elastography (VCTE) have been proposed as alternatives to liver biopsy for staging fibrosis and cirrhosis. However, large-scale cohort data remains scarce for patients with chronic hepatitis D (CHD).

Material and methods: In this retrospective study, individual patient data from 506 CHD patients of two previously published European multicenter studies were pooled to evaluate the diagnostic performance of VCTE, AAR (serum AST to ALT Ratio), APRI (AST to platelet ratio index), and FIB-4 (Fibrosis 4 index) for the staging of liver disease. Patients were randomly assigned to derivation (n=359) and validation (n=147) cohorts, stratified by histological METAVIR stage and ALT levels.

Results: In the derivation cohort, median VCTE values increased progressively with METAVIR stage, from 7.2 kPa for F0/1, to 8.9 kPa for F2, 10.4 kPa for F3, and 17.4 kPa for F4 (all $p < 0.01$). VCTE outperformed other NITs for detecting significant fibrosis ($\geq F2$; AUC: VCTE: 0.75, AAR: 0.51, APRI: 0.62, FIB-4: 0.63), advanced fibrosis ($\geq F3$; AUC: VCTE: 0.78, AAR: 0.52, APRI: 0.66, FIB-4: 0.70), and cirrhosis (F4; AUC: VCTE: 0.83, AAR: 0.59, APRI: 0.70, FIB-4: 0.76). Similar diagnostic performance was observed after excluding patients with ALT or GGT levels $>3x$ or $>5x$ the upper limit of normal, respectively.

Optimal VCTE cutoffs, determined using the Youden index and selected based on sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV), were >8.5 kPa for significant fibrosis ($\geq F2$; Se: 73.4%, Sp: 65.4%, PPV: 83.3%, NPV: 51.1%), >10.2 kPa for advanced fibrosis ($\geq F3$; Se: 69.8%, Sp: 70.5%, PPV: 62.7%, NPV: 76.7%), and >15.2 kPa for cirrhosis (F4; Se: 61.0%, Sp: 90.3%, PPV: 64.9%, NPV: 88.7%). These thresholds correctly classified 71%, 70% and 84% of patients when stratifying according to significant fibrosis, advanced fibrosis and cirrhosis, respectively. Comparable classification accuracies were observed in the validation cohort (F2: 71%, F3: 65%, F4: 76%).

Conclusion: VCTE demonstrates strong diagnostic performance for staging liver disease in patients with CHD, particularly for detecting significant fibrosis and excluding cirrhosis. However, in patients with discordant clinical and NIT results, further diagnostics, including liver biopsy, remains necessary.



DIAGNOSIS AND NATURAL HISTORY

DIAGNOSTICS UPDATE

P91 IMPLEMENTATION OF REFLEX TESTING FOR HEPATITIS DELTA INTO UZBEKISTAN'S NATIONAL STRATEGY AND ACTION PLAN FOR THE ELIMINATION OF PARENTERAL VIRAL HEPATITIS (2026–2030): VALIDATION OF DIAGNOSTIC SCREENING TOOLS

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Background: Uzbekistan carries one of the world's highest burdens of hepatitis D. A nationwide serosurvey found anti-HDV antibodies in 17.7% of HBsAg-positive individuals. Uzbekistan's National Strategy and Action Plan for the Elimination of Parenteral Viral Hepatitis (2026–2030) therefore includes reflex testing for hepatitis D: by 2030, the program must reach 100% anti-HDV reflex screening coverage among HBsAg-positive patients and identify over 100,000 hepatitis D patients within five years. Achieving this goal requires validated diagnostic tests that enable large-scale reflex screening in regional laboratories: anti-HDV testing after every positive HBsAg result, followed by HDV RNA testing when anti-HDV is positive.

Material and methods: The Reference Laboratory of the Institute of Virology validated rapid anti-HDV tests for the reflex algorithm. The first anti-HDV rapid test available on the Uzbek market was the LUCA HDV Ab Rapid Kit (LUCA AICeLL); the laboratory evaluated it on 70 plasma samples (50 HDV RNA/anti-HDV-positive, 20 negative). The reference methods were ELISA (DS-EIA-ANTI-HDV, RPS Diagnostics), which had earlier shown 99% concordance in sensitivity and specificity with the DiaPro HDV Ab ELISA kit, and PCR (AmpliSens® HDV-Monitor-FL). The second stage evaluated the domestic rapid test HDV IgG Ekspress Test Kasseta (NAM BIOTEST, Uzbekistan) on 150 plasma samples (71 HDV RNA/anti-HDV-positive, 79 negative).

Results: The LUCA HDV Ab Rapid Kit reached 100% sensitivity, 95% specificity, 98% positive predictive value, and 100% negative predictive value. The HDV IgG Ekspress Test Kasseta (NAM BIOTEST) reached 97.18% sensitivity, 96.20% specificity, 95.83% positive predictive value, and 97.43% negative predictive value. Both tests meet the national screening-test criteria (≥95%).

Conclusions: Test validation is an important step in implementing the reflex testing algorithm as part of Uzbekistan's National Strategy and Action Plan for the Elimination of Parenteral Viral Hepatitis (2026–2030). The performance characteristics of the domestically produced test support its suitability for use in the national program; its implementation could reduce reliance on imported diagnostic tests and help support the achievement of the National Strategy's target for 2026-2030

Keywords: Hepatitis Delta, HDV, reflex testing, Uzbekistan, rapid diagnostics.



DIAGNOSIS AND NATURAL HISTORY

DIAGNOSTICS UPDATE

P92 PERFORMANCE EVALUATION OF THE COBAS HDV ASSAY FOR AUTOMATED HDV RNA DETECTION AND QUANTIFICATION: IMPLICATIONS FOR CLINICAL DIAGNOSTICS AND TREATMENT MONITORING IN PATIENTS WITH HDV INFECTION

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Background: Accurate HDV RNA quantification is central to diagnosing HDV infection and monitoring antiviral treatment response. Yet, access to automated, WHO-standardised assays with broad genotype coverage remains limited. This study assessed the analytical and clinical performance of the CE-IVD-cleared Cobas® HDV assay (dual-target; compatible with Cobas 5800/6800/8800 systems) for diagnosis and treatment monitoring in patients with HDV infection.

Methods: Serum and plasma from anti-HDV-positive individuals (with and without detectable HDV RNA) were tested in parallel with the fully automated Cobas HDV assay and the RoboGene HDV RNA Quantification Kit 2.0 (manual extraction). LOD, LLOQ, clinical sensitivity and specificity were determined across HDV genotypes; quantitative agreement and comparison of longitudinal HDV RNA trajectories were performed in a treated cohort, with non-inferiority of response rates, as measured by the Cobas HDV assay compared to the RoboGene assay, as a pre-specified endpoint. ALT/AST were tracked as inflammatory surrogate markers.

Results: Serum LOD for HDV genotypes 1, 2, and 6–8 was 9.91 IU/mL, with approximately 3-fold higher LODs for genotype 3 (29.73 IU/mL) and 1.5-fold higher for genotypes 4 and 5 (14.85 IU/mL). Plasma LOD for genotypes 1, 2, and 5–8 was 3.34 IU/mL, again with elevated LODs for genotypes 3 (3×; 10.02 IU/mL) and 4 (1.5×; 5.01 IU/mL). LLOQ of the Cobas HDV assay for genotype 1 (plasma and serum) was 25 IU/mL. Among 199 anti-HDV-positive patients (135 HDV RNA-detectable, 64 HDV RNA-undetectable), clinical sensitivity and specificity of Cobas HDV were 97.8% (95% CI: 93.7–99.2) and 92.2% (95% CI: 83.0–96.6), respectively. Quantitative agreement (serum and plasma samples) between Cobas HDV and RoboGene HDV RNA Quantification Kit 2.0 was excellent (mean difference: $-0.005 \log_{10}$ IU/mL; 95% CI: -0.081 to 0.071). In 302 samples from treated patients with chronic hepatitis D (CHD), concordance reached 100% (95% CI: 98.7–100), with parallel HDV RNA decline trajectories confirming non-inferiority. ALT/AST reduction kinetics closely mirrored the observed decrease in HDV RNA titers.

Conclusion: The Cobas HDV assay offers reliable, automated HDV RNA detection and quantification across genotypes, supporting its use in both diagnosis and long-term management of patients with CHD.



DIAGNOSIS AND NATURAL HISTORY

DIAGNOSTICS UPDATE

P93 POSITIVE IMPACT OF ANTI-HDV REFLEX TESTING IN ALL HBSAG+ PATIENTS

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Introduction: Hepatitis D virus (HDV) infection remains the most aggressive form of chronic viral hepatitis, accelerating progression to cirrhosis, hepatic decompensation, hepatocellular carcinoma and liver-related mortality compared with HBV mono-infection. Recent international guidelines recommend universal HDV screening in all HBsAg-positive individuals; however, implementation remains inconsistent, resulting in substantial underdiagnosis and delayed referral for specialist assessment and treatment. Reflex testing strategies have emerged as a potential approach to improve the HDV care cascade by increasing screening uptake and facilitating earlier identification of patients eligible for antiviral therapy.

Materials and Methods: A retrospective single-centre study was conducted at Coimbra Local Health Unit (ULS Coimbra) to evaluate the impact of implementing an automated anti-HDV reflex testing strategy among HBsAg-positive individuals. The intervention resulted from a multidisciplinary collaboration involving Infectious Diseases, Serology and Virology Laboratories. Since March 2025, anti-HDV serology is automatically performed whenever HBsAg is positive, without requiring an additional clinical request. Two periods were compared: pre-implementation (January 2019–December 2024) and post-implementation (March 2025–May 2026). HBsAg testing was performed using Abbott Alinity i® chemiluminescent microparticle immunoassay or Roche Cobas® electrochemiluminescence immunoassay platforms. Anti-HDV antibodies were determined using the LIAISON® XL chemiluminescence assay. Outcomes included the proportion of HBsAg-positive individuals screened for HDV and anti-HDV seropositivity rates. Additionally in all anti-HDV positives, HDV-RNA was analysed to look for active hepatitis delta infection.

Results: During the pre-implementation period, 84,135 patients underwent HBsAg testing, of whom 1106 (1.3%) were HBsAg-positive. Anti-HDV serology was performed on 72% of the patients, of whom 21 were positive (2.6%). Following implementation of reflex testing, 29,418 patients were screened for HBsAg and 604 (2.1%) were positive. Anti-HDV testing was performed in 100% of the HBsAg positive patients, identifying 19 anti-HDV-positive individuals (3.1%). HDV-RNA was performed in 15 individuals and 40% had detectable viraemia.

Conclusions: Discussion Automated anti-HDV reflex testing successfully standardized HDV screening in HBsAg-positive patients and eliminated important gaps in the diagnostic pathway. By ensuring universal screening and facilitating earlier identification of HDV coinfection, this strategy may improve linkage to specialist care, accelerate treatment evaluation and contribute to better long-term liver outcomes. Reflex testing should be considered a key component of HDV elimination efforts and optimization of the HBV-HDV care cascade.



DIAGNOSIS AND NATURAL HISTORY

DIAGNOSTICS UPDATE

P94 INADEQUATE HDV SCREENING AMONG PATIENTS WITH HBV IN PREGNANCY AND ASSOCIATION OF HDV WITH ADVERSE PREGNANCY OUTCOMES: RESULTS FROM A MULTICENTER RETROSPECTIVE STUDY

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Background: Universal screening for HBV is recommended among all pregnant women in the US during pregnancy, but no pregnancy-specific recommendation on HDV screening exists, even though pregnancy offers an opportunity for widespread HDV screening. HDV course is not well understood in the context of pregnancy. We aimed to characterize real-world HDV testing patterns in the pregnant population, prevalence of HDV coinfection, and compare pregnancy outcomes between women with HDV and HBV.

Material and methods: We conducted a retrospective cohort study leveraging the TriNetX Research Network, which contains electronic health records from 118 contributing health care organizations. Pregnant patients were identified using previously validated ICD-10 codes and all patients who had a positive hepatitis B surface antigen (HbsAg) test result were included in the analysis. We determined prevalence of HDV antibody (HDV Ab) testing and determined prevalence of HDV based on positive HDV Ab test result and/or HDV ICD-10 diagnosis code. We compared pregnancy outcomes between those with and without evidence of HDV.

Results: We identified over 6 million pregnant patients and 3,676 pregnant patients who were HbsAg-positive, a prevalence of about 0.06%. Of patients with HBV, 365 (9.9%) had evidence of HDV Ab testing. A total of 88 patients were documented to have HDV based on laboratory results or diagnosis codes. Only 9 patients had HDV Ab-positive results available, and 1 of those 9 had evidence of HDV RNA testing (Figure 1). When comparing pregnancy outcomes between HDV coinfecting and HBV cohorts, HDV coinfection was associated with higher risk of intrahepatic cholestasis of pregnancy (10.2% vs 4.6%; OR 2.37, p=0.035) (Figure 2). No other adverse pregnancy outcome differed significantly, including spontaneous abortion (12.5% vs 10.4%), preeclampsia/eclampsia (8.0% vs 8.7%), gestational diabetes (12.5% vs 12.6%), and preterm birth (4.5% vs 7.2%) (Figure 2).

Conclusion: Testing for HDV occurred in < 10% of pregnant HBV-positive population despite guidelines to screen for HDV among all HBV-positive patients. HDV confirmatory RNA testing was very rare, suggesting lack of awareness of appropriate testing recommendations. The perinatal care period represents a missed opportunity to screen for HDV and link patients to follow-up care. These testing patterns underscore a need for improved adherence to HDV screening guidelines, especially given the potential association between HDV and intrahepatic cholestasis of pregnancy, an outcome associated with fetal and maternal morbidity, which should be explored further.



DIAGNOSIS AND NATURAL HISTORY

DIAGNOSTICS UPDATE

P95 QUANTITATIVE ANTI-HDV MEASUREMENT AS A DIAGNOSTIC SURROGATE OF HDV REPLICATION

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Background: Detection of serum HDV-RNA confirms active HDV replication and points to severe hepatitis D. However, HDV-RNA testing is technically demanding and often unavailable in resource-limited settings, where diagnosis may rely on anti-HDV alone. We assessed whether anti-HDV titers may serve as a diagnostic surrogate for high-level HDV viremia and explored whether anti-HDV kinetics during bulevirtide (BLV) therapy reflect the depth of virological suppression.

Materials and methods: We considered 450 untreated HBsAg/anti-HDV-positive patients from the Italian HDV DESCRIBE cohort (Caviglia 2025). Median age was 56 years, 282 (62.7%) were male, and 373 (82.9%) were HDV-RNA-positive (median HDV-RNA: 5.02, 3.22–6.03 Log IU/mL). Total anti-HDV was measured with the LIAISON XL Murex Anti-HDV assay and quantified by endpoint titration using serial ten-fold dilutions; titers were calculated by multiplying the signal obtained at the last reactive dilution by the corresponding dilution factor and expressed as AU/mL. Clinical phenotypes were defined according to the HDV DESCRIBE classification: patients were first stratified by cirrhosis status, while non-cirrhotic chronic hepatitis D and inactive/mild disease were defined by HDV-RNA >3 or ≤3 Log IU/mL, respectively. Among them, 69 patients subsequently treated with BLV were evaluated longitudinally up to week (w) 48, including 45 with w96 samples.

Results: Anti-HDV titers correlated with HDV-RNA levels ($r_s=0.595$; $p<0.001$), more strongly in non-cirrhotic patients than in those with cirrhosis ($r_s=0.706$ vs $r_s=0.481$; $p<0.001$). Among viremic patients, anti-HDV titers were higher in those with high-level than low-level viremia (4.77 vs 3.32 Log AU/mL; $p<0.001$; AUC=0.828). A cut-off >4 Log AU/mL identified high-level viremia with 86.6% sensitivity and 65.6% specificity. Anti-HDV titers ≤4 Log AU/mL predominated in inactive/mild disease (79.2%), whereas titers >4 Log AU/mL predominated in non-cirrhotic chronic hepatitis D (85.7%) and cirrhosis (80.2%; $p<0.001$). During BLV therapy, 10/69 patients had HDV-RNA <20 IU/mL and 4/69 achieved target-not-detected (TND) at w48; at w96, 6/45 had HDV-RNA <20 IU/mL and 8/45 achieved TND. Anti-HDV



kinetics showed a delayed on-treatment decline compared with HDV-RNA; baseline titers did not differ according to w96 virological outcome ($p=0.708$), whereas median titers at w48/w96 were 4.06/3.81 Log AU/mL in patients with persistent quantifiable viremia, 3.63/3.41 in those with HDV-RNA <20 IU/mL, and 3.13/2.76 in those achieving TND, respectively ($p=0.017$ at w48 and $p<0.001$ at w96). W48 anti-HDV titers correlated with w96 HDV-RNA levels ($r_s=0.460$; $p=0.001$), while w96 titers showed a stronger correlation with w96 HDV-RNA levels ($r_s=0.667$; $p<0.001$).

Conclusions: Quantitative anti-HDV closely reflects HDV replication and may serve as a diagnostic surrogate to identify high-level HDV viremia. During BLV therapy, anti-HDV kinetics may provide information on the depth of virological suppression.



DIAGNOSIS AND NATURAL HISTORY

DIAGNOSTICS UPDATE

P96 LONGITUDINAL COMPARISON OF ROBOGENE HDV RNA QUANTIFICATION KIT 2.0 AND 3.0 AND AN IN-HOUSE HDV RNA ASSAY DURING BLV AND PEG-IFN TREATMENT

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Background & Aims: Accurate HDV RNA quantification is essential for monitoring treatment response of Chronic hepatitis D (CHD). While the new RoboGene HDV RNA Quantification Kit 3.0 (RG_HDV3.0) has demonstrated improved analytical performance, data comparing its clinical performance with RoboGene 2.0 (RG_HDV2.0) and established lab-developed tests during antiviral therapy are limited. We therefore compared the performance of three HDV RNA test in CHD patients receiving bulevirtide (BLV) or pegylated interferon (PEG-IFN).

Methods: 43 serum samples (from 2005 – 2024) of 19 CHD patients treated with either BLV (n=8 2mg/d for a median follow up time of 16 (10-26) months) or PEG-IFN (n=9; 180 µg/week for a median of 48 (48-72) weeks) were pre-analyzed with a lab-developed HDV RNA test and treatment outcome (i) HDV RNA TND or (ii) HDV RNA detectability at last FU were assessed using in-house test data. Additionally, all samples have been re-analyzed with RG_HDV2.0 and RG_HDV3.0 and detectability and quantifiability rates were compared.

Results: The in-house assay was able to detect HDV RNA in 67% (29/43), in comparison the RG_HDV2.0 HDV RNA in 84% (36/43) and the RG_HDV3.0 in 88% (38/43) of the samples, respectively (p=0.13 and p=0.03). 2/10 patients under PEG-IFN achieved HDV RNA TND with the in-house test, however one of those patients showed detectable HDV RNA levels with RG_HDV2.0 and RG_HDV3.0 tests at last FU. In BLV-treated CHD, 5/10 achieved HDV RNA TND, however in 3/5 patients, detectable HDV RNA levels were found with RG_HDV2.0 (0.83 log IU/mL), while in 4/5 patients were found detectable HDV RNA levels with the RG_HDV3.0 assay (1.16 log IU/mL) at last FU. Thus, in 5 of 7 patients with previously assessed HDV RNA TND, detectable levels of HDV RNA were found using the RG_HDV3.0 assay (p=0.02) Furthermore, RG_HDV3.0 quantified HDV RNA in 32/43 (74.4%) samples compared with 29/43 (67.4%) using RG_HDV2.0, reducing the number of samples reported below the LLOQ from 13 to 10. These differences were primarily observed in samples with low-level viremia during prolonged antiviral therapy.

Conclusions: RG_HDV3.0 and RG_HDV2.0 identified HDV RNA in a higher proportion of samples than the in-house assay and provided a higher proportion of quantifiable results. The improved detection and quantification of low-level HDV RNA may facilitate longitudinal treatment monitoring in patients receiving BLV and PEG-IFN. These findings support the implementation of RG_HDV3.0 in clinical practice while highlighting the importance of assay consistency when interpreting HDV RNA responses during long-term therapy.



DIAGNOSIS AND NATURAL HISTORY

DIAGNOSTICS UPDATE

P97 DIAGNOSTIC AND CARE PATHWAY DELAYS AMONG CHRONIC HEPATITIS D PATIENTS IN PAKISTAN: A MIXED-METHODS STUDY

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Background: Hepatitis D virus (HDV) co-infection with hepatitis B (HBV) is the most severe form of viral hepatitis, accelerating progression to cirrhosis and hepatocellular carcinoma. Pakistan carries a high burden of HDV, particularly in Sindh and Balochistan. Yet, no empirical data exist describing the diagnostic and care pathway or the delays and barriers patients face in reaching appropriate care.

Materials and methods: A sequential explanatory mixed-methods design was used. In the quantitative phase, 157 confirmed chronic HDV patients from two tertiary care centres in Karachi (Ziauddin Hospital and Jinnah Postgraduate Medical Centre) completed a structured survey that captured the dates of five pathway milestones: symptom onset, first healthcare contact, HBV diagnosis, HDV diagnosis, and referral to tertiary care. Time intervals (delays) were summarised using medians and interquartile ranges (IQR) and compared using non-parametric tests. In the qualitative phase, four focus group discussions with 18 purposively selected participants were analysed thematically following Braun and Clarke's six-phase framework.

Results: Participants were predominantly male (80.3%), rural (80.3%), and without formal education (58.6%). Delay data were available for 143/157 patients (91.1%). The longest interval was between HBV and HDV diagnosis (median 5.0 years, IQR 4, range 0-10), followed by referral to tertiary care after HDV diagnosis (median 2.0 years, IQR 1, range 0-3). Median total pathway delay from symptom onset to tertiary care was 9.0 years (IQR 7, range 1-23). Rural residence was significantly associated with delay to first healthcare contact ($p=0.007$); no significant differences were found by gender or education level. Thematic analysis identified six barriers: misattribution of symptoms and delayed help-seeking, primary care diagnostic failures, financial and logistical constraints, knowledge gaps about hepatitis, structural health-system dysfunction, and patient calls for free, decentralised hepatitis services.

Conclusions: Chronic HDV patients in Pakistan experience substantial, largely avoidable delays across the diagnostic and care pathway, with the greatest gap occurring between HBV and HDV diagnosis, reflecting a missed reflex-testing opportunity. These findings support universal HDV reflex testing for all HBsAg-positive individuals, primary care provider training on HDV, decentralisation of hepatitis services to high-prevalence districts, and reduction of financial barriers to diagnosis and treatment.

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DIAGNOSIS AND NATURAL HISTORY

DIAGNOSTICS UPDATE

P98 CLINICAL PERFORMANCES OF THE ROCHE COBAS HDV RNA QUANTIFICATION ASSAY IN UNTREATED AND BULEVIRTIDE-TREATED CHD PATIENTS: A 4-ASSAY COMPARATIVE STUDY

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Background and Aim: HDV RNA quantification is crucial in the management of patients with chronic hepatitis Delta (CHD), but standardisation remains undefined. We aimed to assess the clinical performance of the new Roche Cobas® HDV assay in CHD and compare it with results generated by 3 other popular commercially available assays.

Methods: Frozen plasma samples from untreated and BLV-treated CHD patients were tested in parallel on the same day by 4 sensitive commercially available assays: Robogene HDV-RNA Quantification Kit 2.0 [Roboscreen GmbH; Lower Limit of Detection (LOD) 6 IU/mL], Robogene Quantification Kit 3.0 [Roboscreen GmbH; LOD 0.82 IU/mL, Lower Limit of Quantification (LLOQ) 10 IU/mL], AltoStar HDV RT-PCR RUO Kit 1.5 (Altona Diagnostics GmbH, LOD 1.1 IU/mL, LLOQ 20 IU/mL), and Roche Cobas® HDV (Roche Diagnostics, Basel, Switzerland, LOD not specified, estimated LLOQ 25 IU/mL). Robogene 2.0 and 3.0 had manual nucleic acid extraction, while AltoStar 1.5 and Roche had automated extraction.

Results: 200 plasma samples from 69 untreated and BLV-treated (42 samples from untreated patients, 158 from BLV-treated patients) CHD patients were tested by all 4 assays (overall 800 tests). Overall, median HDV RNA levels measured by Robogene 2.0, Robogene 3.0, AltoStar 1.5, and Roche were 3.4 (2.7–5.1), 3.5 (2.8–5.4), 3.3 (2.6–5.0), and 3.1 (2.4–5.0) log IU/mL, respectively (Friedman test, $p < 0.001$). Pairwise comparisons showed higher HDV RNA values by Robogene 3.0 than with Robogene 2.0, Roche, and AltoStar 1.5 (all $p < 0.001$). Roche yielded significantly lower HDV RNA values than Robogene 2.0 and AltoStar 1.5 (both $p < 0.001$) while no significant difference was observed between AltoStar 1.5 and Robogene 2.0 ($p = 0.861$). Overall, a decreasing trend in HDV RNA levels was observed across assays: Robogene 3.0 > Robogene 2.0 > AltoStar 1.5 > Roche. Robogene 2.0 and Roche reported comparable proportions of positive samples (64.0% vs. 64.5%). Cohen's κ values ranged from 0.210 to 0.642 (all $p < 0.001$), highest for Robogene 2.0 and Roche ($\kappa = 0.642$), whereas the highest agreement was observed between Robogene 3.0 and AltoStar 1.5 (84.5%). Detection rates (HDV RNA < LOD or positive) differed significantly (Cochran's $Q = 66.158$, $df = 3$, $p < 0.001$): 94% for Robogene 3.0, 80.5% for AltoStar 1.5, 79% for Roche, and 73% for Robogene 2.0. Robogene 3.0 showed the lowest proportion of TND samples (6%), while the other assays reported comparable proportions (27% for Robogene 2.0, 19.5% for AltoStar 1.5, 21% for Roche) (Figure 1). Robogene 3.0 reported HDV RNA ranging 1-98 IU/mL in samples testing TND with Robogene 2.0, AltoStar 1.5 and Roche.

Conclusions: The new fully automated Roche Cobas HDV RNA assay showed overall good agreement with established commercially available assays providing consistent quantitative HDV RNA assessment in both untreated and BLV-treated patients. Robogene 3.0 yielded the lowest HDV RNA undetectability (TND) rates.



DIAGNOSIS AND NATURAL HISTORY

NATURAL HISTORY

P99 LANDMARK MACHINE LEARNING ANALYSIS TO IDENTIFY ONE-YEAR RISK OF ADVANCED LIVER DISEASE IN INDIVIDUALS WITH HEPATITIS DELTA VIRUS INFECTION

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Background: Previous analyses suggest substantially higher risk of liver-related events (LREs; cirrhosis, liver decompensation, hepatocellular carcinoma [HCC], and liver transplant) among individuals infected with both hepatitis B virus (HBV) and hepatitis delta viruses (HDV) versus those with HBV mono-infection (hazard ratios from 1.41 – 2.08). Identifying patients with HDV infection at high near-term LRE risk could inform clinical management (e.g., closer monitoring and timely HDV treatment). This study aimed to develop a novel machine learning (ML) model using routinely available clinical data to identify non-cirrhotic HDV patients at high risk of developing incident LRE within one year.

Material and Methods: Individuals with HDV infection in the PharMetrics® Closed Health plan claims database (Oct2015–Mar2026) were identified. Index date was defined as the first inpatient or first of two outpatient HDV claims ≥30 days apart. Included individuals had ≥183 days of continuous enrollment and no evidence of LRE before index. A landmark analysis incorporating both time-based (every six months) and event-based landmarks was conducted. At each landmark, those who remained free of LREs were included, and baseline covariates were reassessed. Subsequent risk of LREs was evaluated over a 1-year follow-up period.

Candidate predictors were identified through literature review and expert consultation. ML models were developed with an 80/20 train–test split and 5-fold cross-validation. Models incorporated demographics, dispensing, and comorbidity data from the 6 months preceding each landmark.

Model performance was evaluated using the area under the precision–recall curve (AUPRC) relative to baseline LRE prevalence. The probability threshold that maximized the harmonic mean of precision and recall (F1 score) was identified, with individuals above this threshold classified as high risk. Key model features were examined as potential predictors of LRE risk.

Results: A cohort of 14,136 individuals with non-cirrhotic HDV was identified (46% male, mean age 51 years at baseline). Among candidate ML models, the distributed random forest model demonstrated the highest performance. Model precision was 26%, recall was 37%, and AUPRC was 0.26, representing a 6.5-fold improvement in identifying patients with an LRE within one year (Figure 1).

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DIAGNOSIS AND NATURAL HISTORY

NATURAL HISTORY

P100 LONG-TERM NATURAL HISTORY AND PROGNOSTIC FACTORS IN PATIENTS WITH CHRONIC HEPATITIS DELTA: A SINGLE-CENTER RETROSPECTIVE LONGITUDINAL STUDY.

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Background: Hepatitis Delta Virus (HDV) worsens disease progression in Hepatitis B Virus (HBV) carriers, increasing the risk of cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC). However, long-term longitudinal outcome data remain limited. This study evaluated the long-term clinical course and identified independent predictors of adverse outcomes in chronic HBV-HDV coinfection compared with a matched HBV-monoinfected cohort.

Material and methods: In this retrospective longitudinal study (1975–2026), 67 anti-HDV-positive patients with chronic HBV-HDV hepatitis were matched for sex, age and baseline cirrhosis with 64 anti-HDV-negative chronic HBV controls at Policlinico Umberto I, Rome. Patients with HCV/HIV coinfection or alcohol-related liver disease were excluded. All patients received standard-of-care treatment for chronic viral hepatitis and liver cirrhosis according to the international guidelines applicable during the period of follow-up. Overall survival and progression to cirrhosis, decompensation, and HCC were evaluated. Independent predictors of mortality and HCC development were identified using multivariable Cox proportional hazards regression models.

Results: At baseline, the two groups (HDV-positive and HDV-negative) did not differ significantly in clinical characteristics and liver disease severity. During a comparable follow-up (73.1 ± 88.6 vs. 84.6 ± 80.7 months, $p=0.342$), HDV-positive patients experienced significantly worse clinical outcomes: higher prevalence of Child-Pugh B/C (76.4% vs. 38.6%, $p<0.001$), higher MELD score (16.1 ± 8.2 vs. 10.6 ± 3.8 , $p=0.001$), greater hepatic decompensation (73.1% vs. 42.2%, $p<0.005$), and increased HCC incidence (30.0% vs. 10.9%, $p=0.007$). Overall survival was significantly lower in HDV-positive patients (251.1 vs. 367.8 months, log-rank $p=0.011$). In multivariable Cox models, HDV status remained independently associated with mortality (HR=5.26, 95% CI: 1.20–23.10, $p=0.028$) after adjustment for baseline Child-Pugh class (HR=3.07, 95% CI: 1.33–7.10, $p=0.009$), and baseline HCC (HR=7.29, 95% CI: 1.55–34.43, $p=0.012$). Furthermore, HDV positivity was an independent risk factor for HCC occurrence (HR=4.44, 95% CI: 1.24–8.77, $p=0.016$) after adjustment for baseline cirrhosis (HR=7.37, 95% CI: 2.03–25.55, $p=0.002$).

Conclusions: HDV coinfection independently drives liver disease progression and is associated with significantly increased risks of hepatic decompensation, HCC, and mortality compared with HBV monoinfection. These findings support systematic anti-HDV screening in all HbsAg-positive to enable earlier diagnosis and timely therapeutic intervention.



DIAGNOSIS AND NATURAL HISTORY

NATURAL HISTORY

P101 A PEDIATRIC CASE OF CHRONIC HEPATITIS B/D RECEIVING MULTIPLE COURSES OF ANTIVIRAL THERAPY

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Background: Pediatric cases of chronic hepatitis B virus (HBV)/hepatitis D virus (HDV) coinfection are rare and poorly characterized. We report a 12-year-old Mongolian boy with chronic hepatitis B/D; who has undergone both treatment with pegylated interferon-alpha2a (peg-IFN-a), and bulevirtide (BLV).

Materials and methods: We report a pediatric chronic hepatitis B/D patient, including clinical history and serum analyses. HDV RNA was quantified using an in-house PCR assay, HBV and HDV genotyping was performed with nested PCR followed by Sanger sequencing. Infection assays were performed in HuH7-NTCP and HepG2-NTCP cell lines, and analysed by immunofluorescence staining, as well as in-cell Western Blots. Anti-BLV antibodies were evaluated with an indirect ELISA. Atto488-coupled BLV was used to assess neutralization capacities of the antibodies.

Results: The 12-year-old Mongolian boy was diagnosed with HBV/HDV coinfection at age 3 following presentation with headaches and fever. His mother was also diagnosed with chronic hepatitis B/D. Despite two 48-week courses of peg-IFN-a with background tenofovir alafenamide (TAF) therapy, he demonstrated unusually rapid progression to advanced fibrosis within a decade. Further treatment courses included BLV 2 mg and peg-IFN-a + BLV, with or without TAF. Triple antiviral therapy yielded ALT normalization, and a marked decrease in HDV RNA, however no elimination of HDV. Serum analyses revealed HDV genotype 1. In vitro, the virus showed dose-dependent infectivity. It was sensitive to BLV, as well as to peg-IFN-a in dividing cells. Interestingly, the boy had very high levels of anti-BLV antibodies, which did not seem to neutralize BLV. The patient currently struggles to continue BLV therapy, as his family cannot afford the cost of the drug.

Conclusions: Further analyses of the patients' virus' properties and antibodies are ongoing. This case illustrates an aggressive course of pediatric HBV/HDV coinfection and the diagnostic, therapeutic, and prognostic challenges in endemic regions. It underscores the need for early family screening, improved molecular diagnostics, expanded pediatric access to emerging agents, and close non-invasive monitoring with HCC surveillance.



DIAGNOSIS AND NATURAL HISTORY

NATURAL HISTORY

P102 DISCORDANCE BETWEEN LIVER STIFFNESS MEASUREMENT AND FIB-4 AND ITS IMPACT ON THE LONG-TERM RISK OF LIVER-RELATED EVENTS IN CHRONIC HEPATITIS D

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Background: Liver stiffness measurement (LSM) by vibration-controlled transient elastography performs well for ruling-out advanced fibrosis and cirrhosis in chronic hepatitis D (CHD). However, the frequency of discordance between LSM and Fibrosis-4 score (FIB-4) score, and the clinical significance of this discordance for long-term liver-related events (LREs), remain unknown.

Methods: We conducted a retrospective cohort study of adult patients with confirmed CHD (HDV RNA ≥ 50 IU/mL) attending a liver center in Mongolia between 2015 and 2025. Patients with prior LREs (liver decompensation, hepatocellular carcinoma, or liver transplantation) or history of anti-HDV therapies were excluded. FIB-4 was categorized using standard cutoffs: low (<1.3), indeterminate (1.3 - 2.67) and high-risk (>2.67) groups. LSM served as the outcome reference, with thresholds of <6.5 kPa defining low-risk of clinically significant fibrosis, and ≥ 10 kPa defining high-risk of advanced fibrosis or cirrhosis. Factors associated with FIB-4 misclassifications were identified by logistic regression analysis, and the cumulative incidence of composite LREs according to the concordance or discordance between the two non-invasive tests was estimated by the Kaplan-Meier methods.

Results: Overall, 2,447 patients were included with: median age 40.3 years, 56.1% females, 9.2% diabetes, median HDV RNA 5.3 log₁₀ IU/mL, and 23.6% with cirrhosis at baseline. Among 1400 patients classified as low risk by FIB-4, 442 (31.6%) had LSM ≥ 10 kPa, and 563 (40.2%) had LSM between 6.5- <10 kPa (misclassified as low risk). Univariable logistic regression analysis showed that younger age, male sex, smoking, alcohol overconsumption, ALT, AST, GGT and diabetes were all significantly associated with low-risk misclassification by FIB-4 (all $p < 0.05$). In multivariable analysis, male sex (adjusted odds ratio [aOR]=1.56, 1.2-2.00), elevated AST (aOR=1.32, 1.01-1.76), elevated GGT (aOR=2.20, 1.72-2.81) and diabetes mellitus (aOR=1.60; 1.08-2.35) independently predicted low-risk misclassification by FIB-4. During a median follow-up of 7.3 years, the highest cumulative incidence of composite LREs occurred in patients with both FIB4 >2.67 and LSM ≥ 10 kPa, while the lowest incidence was observed in those with FIB4 <1.3 and LSM <6.5 kPa. Within the indeterminate FIB-4 group, patients with LSM ≥ 10 kPa identified patients with significantly worse outcomes.

Conclusion: In chronic hepatitis D, FIB-4 demonstrates suboptimal accuracy for risk stratification, while liver stiffness more reliably identified patients at higher risk, particularly within the indeterminate FIB-4 range. These findings support the need for HDV-specific non-invasive scores and cautious interpretation of conventional FIB-4 cutoffs in this population.



DIAGNOSIS AND NATURAL HISTORY

HCC IN HDV: PATHOGENESIS, INCIDENCE AND PREDICTORS

P103 HEPATOCELLULAR CARCINOMA IN CHRONIC HEPATITIS D: A NATIONWIDE BENCHMARK PRE-BULEVIRTIDE ERA FROM THE ITALIAN PITER COHORT

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Background and aims: Chronic hepatitis D is an uncommon but severe form of viral hepatitis in Europe. With the introduction of bulevirtide, the natural history of HDV infection is expected to change substantially. Contemporary data describing hepatocellular carcinoma (HCC) before the availability of bulevirtide are therefore essential to establish a benchmark for future therapeutic evaluation. We compared the clinical features and outcomes of HDV-related and HBV-related HCC in the nationwide Italian PITER-B cohort. Methods: HCC cases were retrospectively identified within the PITER-B cohort, which prospectively enrolled consecutive HBsAg-positive individuals from 58 Italian centres between 2019 and 2024, regardless of HDV status, treatment eligibility, or treatment indication.

Results: Among 6,031 HBsAg-positive patients, 4,572 were tested for anti-HDV. HCC was diagnosed in 51 of 596 patients with chronic HDV infection and in 140 of 3,976 patients with HBV mono-infection (8.6% vs 3.5%; $p < 0.001$). A total of 178 patients with HCC were included in the analysis: 42 with HDV-related HCC and 136 with HBV-related HCC. HDV RNA was detectable in 29 of 36 tested patients with HDV (80.6%). At enrolment in the PITER cohort patients with HDV-related HCC had a more advanced liver disease compared to patients with HBV-related HCC, as reflected by lower platelet counts, higher AST, ALT and GGT values, more advanced Child–Pugh class, and a higher prevalence of clinically significant portal hypertension (CSPH). A sub-analysis of more recently diagnosed cases confirmed the findings. Compared with HBV-related HCC, HDV-related HCC developed at a younger age (60 vs 65 years; $p = 0.009$), particularly among women (57 vs 71 years; $p = 0.031$). The macro-pathological features of tumours at diagnosis and the proportion of patients who were Milan criteria-in were comparable between groups. Liver transplantation was performed more frequently in patients with HDV-related HCC (23.8% vs 7.3%; $p = 0.009$). Mortality rates were higher in HDV-related HCC (11.0 vs 4.3 per 100 person-years). After multivariable adjustment, associated to death was CSPH but not HDV infection while surgical treatments (LT or resection) and being Milan-in were negatively associated. Conclusions: Compared with HBV mono-infection, HDV-related HCC occurs at a younger age despite a similar tumour burden. Patients with HDV-related HCC have more advanced liver disease than those with HBV-related HCC. These findings provide an important pre-bulevirtide benchmark against which the impact of disease-modifying therapies on HCC presentation, treatment allocation, and survival can be evaluated.



DIAGNOSIS AND NATURAL HISTORY

HCC IN HDV: PATHOGENESIS, INCIDENCE AND PREDICTORS

P104 HCC RISK STRATIFICATION DURING LONG-TERM BULEVIRTIDE THERAPY: PERFORMANCE OF PAGE-B AND AMAP IN COMPENSATED HDV CIRRHOSIS

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Background and Aim: Reliable risk stratification is essential to optimize hepatocellular carcinoma (HCC) surveillance in patients with chronic hepatitis delta (CHD), particularly during long-term antiviral treatment. Although PAGE-B and AMAP are widely used HCC prediction models in chronic hepatitis B, their performance in patients with HDV-related cirrhosis receiving Bulevirtide (BLV) has not been characterized. We evaluated the ability of these scores to stratify HCC risk during prolonged BLV monotherapy.

Methods: Patients with compensated HDV-related cirrhosis enrolled in the multicenter retrospective European SAVE-D study who received BLV monotherapy were included. Individuals with a previous history of HCC were excluded. PAGE-B and AMAP scores were calculated at treatment initiation according to established definitions. Patients were categorized into standard risk classes, and HCC incidence during follow-up was compared across risk groups. Baseline predictors of de novo HCC were also assessed.

Results: A total of 391 patients with cirrhosis were included (median age 49 [IQR 40–57] years; 60% male; median platelet count $102 [69–148] \times 10^9/L$) and followed for up to 240 weeks of BLV monotherapy. According to PAGE-B, 117 patients (30%) were classified as low risk, 255 (65%) as intermediate risk, and 19 (5%) as high risk. Patients in the high-risk PAGE-B category had a median age of 64 (62–67) years and a median platelet count of $75 (60–90) \times 10^9/L$. AMAP score was available for 387 patients, identifying 10 (3%) as low risk, 84 (22%) as intermediate risk, and 293 (76%) as high risk. During follow-up, 17 patients developed de novo HCC, after a median of 11 (10–25) months. 2 (12%) HCC developed in the PAGE-B low-risk group, 11 (65%) in the intermediate-risk group, and 4 (24%) in the high-risk group. PAGE-B cumulative 240-week incidences were of 2.2%, 5.7%, and 30.9% in the low-, intermediate-, and high-risk groups, respectively. Similarly, cumulative HCC incidence according to AMAP risk categories was 0%, 1.3%, and 7.7%, with 16 of 17 HCC cases (94%) occurring in the high-risk group and none among low-risk patients. No HCC developed in the four patients with unavailable AMAP score. albumin, bilirubin, platelets and liver stiffness values were associated with de-novo HCC at univariate analysis, but only albumin was confirmed at multivariate analysis (HR 0.22 [0.09–0.53], $p < 0.001$).

Conclusions: Both PAGE-B and AMAP successfully identified distinct HCC risk categories in patients with compensated HDV-related cirrhosis receiving long-term BLV therapy, supporting their use in routine clinical practice. Nevertheless, the development of dedicated HDV-specific prediction models may further improve personalized HCC surveillance in this high-risk population.



DIAGNOSIS AND NATURAL HISTORY

HCC IN HDV: PATHOGENESIS, INCIDENCE AND PREDICTORS

P105 MANAGEMENT OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CHRONIC HBV-HDV INFECTION UNDERGOING BULEVIRTIDE THERAPY

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Background: Chronic HBV-HDV infection is associated with the highest risk of hepatocellular carcinoma (HCC) development of all chronic liver diseases, especially in patients with advanced fibrosis. Current national and international guidelines recommend Bulevirdide as the only therapeutical option, in association with pegylated interferon or nucleotide/nucleoside analogues (NUC). The impact of Bulevirdide on the development and management of HCC in a real-world setting is yet to be determined. The aim of this study is to analyze the short and mid-term evolution of patients undergoing local therapies for HCC, while under Bulevirdide therapy.

Material and methods: This is a prospective study including patients with chronic HBV-HDV infection, undergoing treatment with Bulevirdide and NUC, referred to our tertiary center for local interventional procedures for newly diagnosed HCC. Patients with recurrent HCC or other liver tumors were excluded from the study. We recorded data regarding demographic features, laboratory tests and evolution at 1 and 6 months after the procedure.

Results: The study included 13 patients with a mean age of 45.48 years (38 – 64 years); 8 patients (61%) were male. Mean duration of Bulevirdide therapy was 7.3 months (3-12 months). The majority of patients had F4 fibrosis (8/12 patients). All patients had significant decrease of ALT levels from Bulevirdide initiation (mean decrease 45.8%, $p=0.02$, CI95%) but 5 patients still had ALT above normal limits. HDV-RNA decreased by 2log in 9/12 patients. 7 patients underwent transarterial chemoembolization (TACE) and 5 patients underwent local radiofrequency ablation (RFA). Bulevirdide was administered in the morning of the procedure and was not interrupted. After TACE 2 patients presented post-embolization syndrome (with inflammatory syndrome and AT increased 5 fold from baseline), remitted under supportive care. At 1-months follow-up none of the patients had discontinued Bulevirdide and all patients presented complete response of the nodule. Persistently increased transaminases was noted in 3/12 patients. At 6-months follow-up 2 patients presented HCC recurrence; the patients had previously underwent TACE and had persistently elevated transaminases at 1 month follow-up. Overall, 11/12 patients achieved undetectable HDV-RNA at 6 months follow-up. Normal levels of ALT were noted in 10/12 patients.

Conclusion: While performed on a small number of patients, this study demonstrated that Bulevirdide is safe and effective to use in patients diagnosed with HCC. Furthermore, performing local therapies for HCC in patients under Bulevirdide therapy is not associated with risks regarding liver decompensation. Persistently increased transaminases under antiviral therapy could indicate the presence of HCC and extensive screening by high-performance imaging.



DIAGNOSIS AND NATURAL HISTORY

HCC IN HDV: PATHOGENESIS, INCIDENCE AND PREDICTORS

P106 HEPATITIS D IN HEPATITIS B-ASSOCIATED HEPATOCELLULAR CARCINOMA: A REAL-WORLD PAKISTANI COHORT REVEALS A HIGH BURDEN AND ADVANCED PRESENTATION

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Background: Hepatitis D virus (HDV) accelerates the course of chronic hepatitis B (HBV) and is associated with severe liver disease and hepatocellular carcinoma (HCC). However, real-world data describing the burden and clinical characteristics of HDV-associated HCC in Pakistan remain limited. We evaluated the burden of HDV among HBV-associated HCC and characterized disease stage, vascular involvement, treatment patterns, and short-term outcomes.

Methods: We retrospectively evaluated 1,097 consecutive patients with HCC managed at a tertiary hepatology center in Hyderabad, Pakistan. Patients were categorized as non-HBV/HDV, HBV only, or HBV/HDV co-infection. Demographics, Barcelona Clinic Liver Cancer (BCLC) stage, portal vein thrombosis (PVT), HCC treatment, and 6- and 12-month outcomes were assessed. Associations between etiology and categorical clinical variables were evaluated using chi-square testing.

Results: The cohort was predominantly male (79.6%), with 43.0% aged 50–60 years and 36.1% aged >60 years. HBV-associated HCC was identified in 209/1,097 (19.1%) patients, including 56 (26.8%) with HBV/HDV co-infection. Among HBV/HDV-associated HCC, only 4/56 (7.1%) presented with BCLC A, whereas 44/56 (78.6%) presented with BCLC C/D disease. PVT was documented in 20/56 (35.7%) patients with HBV/HDV-associated HCC; the distribution of PVT status differed significantly across etiologic groups ($\chi^2=10.65$, $p=0.031$). At 6 months, 24/56 (42.9%) HBV/HDV patients had died and 28/56 (50.0%) had worsened; by 12 months, 44/56 (78.6%) had died. HCC-directed treatment was not received by 28/56 (50.0%) patients; 12 (21.4%) received sorafenib, 8 (14.3%) referred for TACE, and 8 (14.3%) referred for liver transplantation. Etiology was significantly associated with BCLC stage, treatment pattern, and 6- and 12-month outcomes ($p < 0.05$).

Conclusions: HDV co-infection was present in more than one-quarter of HBV-associated HCC cases in this large real-world Pakistani cohort, demonstrating a substantial burden of HDV among patients with HBV-related HCC. Nearly four-fifths of HBV/HDV-associated HCC presented with advanced BCLC C/D disease, with very poor short-term outcomes and nearly four-fifths dying within one year. These findings underscore the need for systematic HDV detection among HBV-infected individuals, effective HCC surveillance, and earlier linkage to specialist care before advanced disease develops.



DIAGNOSIS AND NATURAL HISTORY

BAVENO VIII UPDATE

P107 BAVENO CRITERIA IN HDV-RELATED CIRRHOSIS: TOWARD A DISEASE-SPECIFIC MODEL TO SAFELY AVOID SCREENING ENDOSCOPY (BAVENO-HDV)

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Background and Aim: Current international recommendations, including the Baveno consensus and the AASLD 2024 guidance, endorse non-invasive criteria to identify patients with compensated cirrhosis who can safely defer screening endoscopy for high-risk varices (HRV). However, these criteria have not been specifically evaluated in Chronic Hepatitis Delta (CHD) patients, a population characterized by distinct disease severity and portal hypertension. We assessed the diagnostic performance of currently recommended criteria in HDV-related cirrhosis and developed optimized disease-specific thresholds (Baveno-HDV).

Methods: This multicenter study included untreated patients with compensated HDV-related cirrhosis enrolled in the SAVE-D and D-SHIELD cohorts who underwent both liver stiffness measurement (LSM) and esophagogastroduodenoscopy (EGD). The Baveno VI and AASLD 2024 "avoid endoscopy" criteria were evaluated



using the recommended combination of LSM <20 kPa and platelet count (PLT) $>150 \times 10^9/L$. Alternative HDV-specific LSM and platelet thresholds were identified through grid-search optimization and internally validated using nonparametric bootstrap resampling.

Results: A total of 347 patients were analyzed (median age 54 years; 56% male). Median LSM was 16.7 (11.8–25.2) kPa, platelet count was 95 (65–147) $\times 10^9/L$, and spleen diameter 14 (12–17) cm. Overall, 156 patients (45%) had gastroesophageal varices, including 93 (27%) with HRV. Application of the Baveno VI/AASLD 2024 criteria would have avoided screening endoscopy in 19% of patients while missing 4 HRV cases (6.2%), corresponding to a sensitivity of 95.7% and a negative predictive value (NPV) of 93.8%. Bootstrap analysis demonstrated considerable uncertainty around the false-negative estimate (BC 95%: 1.15%–13.88%). Since only 2 patients had a platelet count exactly equal to $150 \times 10^9/L$, both with LSM >20 kPa, no differences in patient classification emerged between the Baveno VI and AASLD 2024 recommendations. An HDV-specific model ("Baveno-HDV"), based on a grid search derived combination of LSM ≤ 19 kPa and PLT $\geq 110 \times 10^9/L$, improved clinical performance by reducing missed HRV to 3.6%, while increasing the proportion of patients safely spared from endoscopy from 19% to 32% (sensitivity 95.7%, NPV 96.4%). Internal validation confirmed greater robustness, with a narrower BC-CI for the false-negative rate (0.87%–7.76%).

Conclusions: Baveno VI and AASLD 2024 criteria appear insufficiently calibrated for untreated HDV-related compensated cirrhosis, leading to potentially unsafe misclassification of patients with HRV. HDV-tailored non-invasive thresholds (Baveno-HDV) improved both safety and efficiency by decreasing missed HRV while allowing substantially more patients to avoid unnecessary screening endoscopy.

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