abstracts book

Chairs:
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CURRENT AND NEW ANTIVIRAL TREATMENTS

OP Efficacy and safety of tobevibart (VIR-3434) alone or in combination with elebsiran (VIR-2218) in participants with chronic hepatitis delta virus infection: preliminary results from the Phase 2 SOLSTICE trial in non-cirrhotic and compensated cirrhotic participants

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Background and Aims:
Hepatitis D virus (HDV) infection is the most severe form of viral hepatitis with limited treatment options. The phase 2 SOLSTICE study is investigating the antiviral activity and safety of the monoclonal antibody tobevibart (VIR-3434) alone and in combination with the silencing RNA elebsiran (VIR-2218) in chronic HDV infection (NCT05461170).

Method:
Participants with chronic HDV infection, with or without compensated cirrhosis (CPT-A) on NRTI therapy, were randomized 1:1 to receive either tobevibart 300 mg plus elebsiran 200 mg subcutaneously (SC) every 4 weeks (Combo Q4W) or tobevibart 300 mg SC every 2 weeks (tobevibart Q2W) for 96 weeks. The primary endpoint is a combined response (CR) defined as a virologic response plus normalization of ALT at week 24. A virologic response was defined as HDV RNA less than limit of detection (LOD, 14 IU/mL) or a decrease of ≥ 2 log10 IU from baseline. Lower limit of quantification (LLOQ) for HDV RNA was 63 IU/mL.

Results:
Preliminary results from all participants completing 12 weeks of Combo Q4W (n = 18, 50% CPT-A) and tobevibart Q2W (n = 15, 27% CPT-A) are presented. Five participants who received tobevibart or elebsiran monotherapy for 12 weeks and failed to achieve virologic response (n = 3) or normalize ALT (n = 2) transitioned to Combo Q4W. Week 40 results on combination treatment for these participants are reported.
After 12 weeks of Combo Q4W treatment, 100% (18/18) of participants achieved a virologic response with 50% (9/18) < LOD, mean ALT decreased from 87 ± 53 IU/mL at baseline to 48 ± 30 U/L, 39% (7/18) achieved ALT normalization, 39% (7/18) achieved the CR and 28% (5/18) achieved HDV RNA < LLOQ + ALT normalization.
Among tobevibart Q2W participants, 80% (12/15) achieved a virologic response with 13% (2/15) < LOD, mean ALT decreased from 56 ± 22 U/L at baseline to 36 ± 12 U/L, 60% (9/15) achieved ALT normalization, 40% (6/15) achieved the CR and 13% (2/18) achieved HDV RNA < LLOQ + ALT normalization after 12 weeks. ALT and HDV RNA declines, and CR were comparable among non-cirrhotic and compensated cirrhotic participants in both cohorts and no ALT flares were observed.
All Combo roll-over Q4W participants (5/5) who have completed 40 weeks of combination therapy had HDV RNA < LOD.
Both regimens were well tolerated with no reported serious adverse events, Grades 3 and 4 treatment-emergent adverse events (TEAEs) or TEAEs leading to discontinuations.

Conclusion:
After 12 weeks of treatment, high rates of virologic response were observed in tobevibart and elebsiran combination therapy and tobevibart monotherapy cohorts. Reductions in ALT values occurred over time with no ALT flares. Similar results were observed in participants with non-cirrhotic and cirrhotic chronic HDV infection. Additional 12- and 24-week data will be presented. These results support continued development of tobevibart alone or in combination with elebsiran.

CURRENT AND NEW ANTIVIRAL TREATMENTS

OP Efficacy and safety of BLV monotherapy for chronic hepatitis delta: post treatment results through 24 weeks after the end of treatment from an interim analysis of a randomized Phase 3 study MYR301

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Background:
Bulevirtide (BLV, Hepcludex®) is a first-in-class entry inhibitor approved in Europe for chronic hepatitis delta (CHD). Results from MYR301 (NCT03852719), a phase 3 randomized study, showed monotherapy with BLV 2 mg/day (d) or 10 mg/d to be efficacious and safe through 144 weeks (w) of treatment. Here we present results from MYR301 through 24 weeks after end of treatment (FU24).

Methods:
150 CHD patients were randomized (stratification by presence/absence of compensated cirrhosis) in a 1:1:1 ratio to Arm A: no active anti-HDV treatment for 48 weeks followed by BLV 10 mg/d for 96 weeks (n=51), Arm B: BLV 2 mg/d (n=49) or Arm C: BLV 10 mg/d (n=50) for 144W. Patients are followed for 96 weeks after the end of tre ment (EOT).
Endpoints include: combined response (CR) defined as virologic response (VR; undetectable HDV RNA or a decrease by ≥ 2 log10 IU/mL from baseline) and ALT normalization, VR, ALT normalization, undetectable HDV RNA, liver stiffness (LS), and liver related outcomes.

Results:
Demographic and baseline (BL) characteristics were similar across groups and included: mean (SD) age 42 (8.4) years, 57% male, 83% White, 47% with compensated cirrhosis, mean (SD) HDV RNA 5.04 (1.34) log10 IU/mL, ALT 111 (69.0) U/L, LS 14.7 (8.8) kPa and 61% were on concomitant nucleos(t)ide analogues (NA) therapy. Most patients (83%) remained in the study at FU24. Efficacy and safety results are summarized below (Fig.1). Response rates decreased after treatment discontinuation due to either viral relapses or rebounds. CR and ALT normalization rates were similar between groups at EOT and numerically higher in the BLV 10 mg group at FU24. Undetectable HDV RNA rates at FU24 were numerically higher with BLV 10 mg compared to BLV 2 mg or DT to BLV 10 mg. One ontreatment liver related event of ascites was reported in a patient (from Arm A) with cirrhosis at BL. Safety during the post-treatment period was similar between Arms B and C, with slightly higher rates of serious adverse events (SAEs) and grade > 3 AEs in Arm A; the majority were associated with increased transaminases (ALT, AST). There was one previously reported death in Arm A due to plasma cell myeloma after the patient discontinued BLV, unrelated to BLV. Of the 9 patients who reported a posttreatment SAE, 8/9 experienced hepatic SAEs associated with increases in ALT and HDV RNA, 5/8 were cirrhotic, at least 6/8 started commercial BLV; 1 patient (Arm A) with BL cirrhosis experienced a posttreatment liver-related event of ascites (nonserious). Overall, 12/140 (9%) of patients (including 7 with hepatic SAEs) had post-treatment ALT > 10 x upper limit of normal (ULN).

Conclusion:
A subset of patients treated with BLV monotherapy for 2-3 years maintained virological and biochemical responses 24 weeks after stopping BLV. Post-treatment SAEs and ALT elevations >10 x ULN were observed in the 24-week posttreatment period. Assessment of durability of response at 48 and 96 weeks after EOT is planned

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

OP Hepatitis delta virus (HDV) replication through HBV integrants in HCC recurrence after liver transplantation

L. Di Marco[1,2], N. De Maria[3], A. Pivetti[3], A. Colecchia[3], A. Romanzi[3], A. Spallanzani[1], G. Guaraldi[4], G. Dolci[4], G. Ciusa[5], F. Di Benedetto[6], P. Magistri[6], S. Di Sandro[6], E. Degasperi[7], M.P. Anolli[7], P. Lampertico[7], D. Giosa[8], D. Lombardo[9], G. Raimondo[9], T. Pollicino[9]

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A PWID man, HCV/HBV-HDV/HIV-infected, underwent liver transplantation (LT) for HCC in 2012 at the age of 52 years. HCC tissue showed high HDV-RNA (88,400 copies/cell), low total HBV-DNA (0.00001 c/c), and HBVcccDNA0.00008 c/c), without detectable HBV-RNA. High-throughput HBV integration sequencing (HBIS) identified 657 HBV integration sites.HBV integrants were predominantly represented by HBx gene sequences. After LT, Tacrolimus, Bictegravir/Emtricitabine/TAF, and anti-HBs immunoglobulin were administered, yielding HBsAg, HDV-RNA, and HCV-RNA negativity.

In 2018, HBsAg reversion was observed with undetectable HBV-DNA and HDV-RNA >19,000 c/ml.

In 2019, HDV-related hepatitis occurred. Intrahepatic HBcAg, HBsAgHBV DNA, HBVcccDNA, and HBV-RNA were undetectable. HDV RNA concentrations were very high in the liver (3,920,000 c/c) but low in the serum (214 IU/mL).

CT scan (CTs) suspected an isolated HCC recurrence in the left adrenal gland, confirmed by adrenalectomy. Realtime PCR in the tumor from the adrenal gland revealed high levels of HDV RNA (5.5 c/c) but low levels of HBV DNA (0.00009 c/c) and HBVcccDNA (0.00001 c/c). HBV RNA was undetectable. HBIS identified 3497 HBV integrations, most of which included HBs gene sequences. After adrenalectomy, HBsAg and HDV-RNA became undetectable. Anti-HBs immunoglobulin was continued with Everolimus. In 2021, CTs showed two HCC nodules in the liver and one in the right adrenal gland. TACE was performed, and TKI therapy was started.

In 2023, new HDV hepatitis occurred, with HDV-RNA>3,631,360 UI/ml and HBV-DNA <10UI/ml. For the progression of HCC, RFA on the right adrenal gland was performed, and Bulevirtide was started. After 3 months, HDV-RNA was 48,638 c/ml, and transaminases were normal.

This case demonstrates HDV replication in extrahepatic HCC recurrence, despite low levels of HBVcccDNA. The decreased HDV RNA levels after RFA and BLV therapy suggest that HCC metastases may serve as HBsAg production sites following HBV integration.

VIROLOGY AND PATHOGENESIS

OP Integrative transcriptomics and epigenomics reveals a viral footprint of chronic HDV infection in HBV co-infected chimeric livers

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Chronic infection with Hepatitis D virus (HDV) causes the most severe form of viral hepatitis with accelerated progression to liver fibrosis, cirrhosis, and hepatocellular carcinoma. Antiviral therapy with bulevirtide reduces HDV load in patients with encouraging effects on liver disease parameters. However, effective chemo-preventive strategies to attenuate liver disease progression as well as reliable biomarkers are urgently needed to improve disease management. Chronic diseases are often driven by epigenetic regulation including histone modifications. Indeed, we have previously demonstrated that chronic hepatitis C infection induces a pro-fibrotic transcriptional signature, which is epigenetically regulated and partially persistent after anti-viral therapy (Lupberger et al. Gastroenterology 2019; Hamdane et al. Gastroenterology 2019; Jühling et al. Gut 2021).

Here we aim to identify the impact of chronic HDV infection on liver transcriptomics and epigenetics to identify molecular circuits of liver disease development, candidate biomarkers for liver disease progression and to characterize their response to antiviral treatment. Thereto, we infected human chimeric mice (FRG-NOD mice transplanted with human hepatocytes) with mock, HBV alone, or HDV/HBV. Snap-frozen liver tissues were analyzed 4 weeks post infection by bulk RNA-seq and ChIP-seq for histone marks associated with active transcriptional enhancers (H3K27ac and H3K4me1) and a mark for transcriptional repression (H3K27me3).

Moreover, we validated predicted biomarker candidates in the blood of infected chimeric mice and patients by ELISA.
We identified 748 unique transcripts in the livers of HDV/HBV-infected mice as compared with HBV mono-infected and mock-infected animals. Notably, most of these transcripts were highly upregulated by HDV infection and enriched by genes involved in HDV replication, inflammation, fibrosis, and cancer risk. Consistently, most of the genes coding for these transcripts are also associated with at least one histone mark linked to active enhancers and thus potentially representing a persistent viral footprint in the infected liver. Interestingly, 110 transcripts of this HDV signature potentially encoded secretory proteins based on signal peptide prediction. Top ranking candidate markers are positively correlated with the transcript levels and elevated in blood of HDV-infected mice and patients.

Overall, we revealed a HDV-specific transcriptional signature which is potentially part of a persistent epigenetic viral footprint. Signature components are differentially secreted to the blood of infected animals and therefore may serve as risk marker for disease progression and fibrosis. Further work is ongoing to address whether these proteins may serve as a prognostic biomarker for disease progression and/or therapeutic response such as bulevirtide and to predict and validate compounds able to reverse risk-associated transcriptional signatures

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P1 Nearly One-Third of Veterans with Hepatitis Delta Virus Infection in the United States Have Already Developed Cirrhosis or Hepatocellular Carcinoma at Time of Diagnosis

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Background:
Hepatitis delta virus (HDV) infection is associated with more rapid disease progression to cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality. Delays in timely diagnosis and treatment of HDV contribute to more severe liver disease at presentation. We aim to evaluate the prevalence and predictors of advanced liver disease (AdvLD) at presentation among a national cohort of United States (U.S.) Veterans co-infected with chronic hepatitis B (CHB) and HDV.

Methods:
Using longitudinal data on all Veterans receiving care within Veteran health systems in the U.S. (1/1/2010 -12/31/2023), we evaluated the prevalence of cirrhosis (including cirrhosis related complications such as ascites and hepatic encephalopathy) and HCC at time of HDV diagnosis. HDV diagnosis was confirmed on laboratory testing (HDV antibody and HDV RNA). Prevalence of AdvLD (cirrhosis, cirrhosis-related complications, or HCC) at time of HDV diagnosis was compared between groups using chi-square testing. We performed a sensitivity analysis focusing specifically on patients with documented viremic HDV (detectable HDV RNA).

Results:
Among 29,061 CHB patients, 3,571 (12.3%) completed HDV testing, among whom 109 (3.1%) were positive and 3,462 (96.9%) were negative. Compared to HDV negative, HDV positive patients were more likely to be black/African American (55.8% vs. 43.0%) or Hispanic (6.7% vs. 4.3%), less likely to be Asian (8.7% vs. 15.3%), $p<0.05$. HDV positive patients were more likely to have concurrent HCV infection (55.0% vs. 19.1%, $p<0.01$). When evaluating risk behaviors, compared to HDV negative, HDV positive patients were more likely to have high risk alcohol use (17.3% vs. 12.1%, $p<0.05$), current or past history of drug use (25.7% vs. 12.8%, $p<0.01$), and active tobacco use (53.8% vs. 39.9%, $p<0.01$). At the time of diagnosis, HDV positive patients had greater prevalence of cirrhosis (25.7% vs. 11.5%) or HCC (7.3% vs. 2.0%), $p<0.01$, compared to CHB patients without HDV. Overall, 29.4% of HDV positive patients had AdvLD at presentation, the prevalence of which was higher in black/African American vs. Hispanics (31.0% vs. 14.3%) and trended higher among those with concurrent HCV infection (31.7% vs. 26.5% in HCV negative) or concurrent HIV infection (100% vs. 28.7%), $p=0.12$). HDV patients who reported concurrent high-risk alcohol use also trended towards greater prevalence of AdvLD compared to low risk alcohol use (22.2% vs. 17.4%, $p=0.13$). On sensitivity analyses of viremic HDV patients only, 36.4% had AdvLD at presentation, with similar trends seen across subgroup comparisons.

Conclusion:
Among a national cohort of US Veterans with CHB and HDV, nearly 1 in 3 had already developed cirrhosis or HCC at time of HDV diagnosis, reflecting dangerous delays in diagnosis and treatment. Implementing effective programs for early HDV detection are urgently needed to facilitate timely linkage to care and treatment to prevent liver-related morbidity and mortality.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P2 Quantification of plasma HDV RNA in untreated and bulevirtide-treated patients with CHD: a comparison between robogene 2.0, Eurobioplex and altostar

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Background and Aim:
Accurate HDV-RNA quantification is crucial for diagnosis and management of chronic hepatitis Delta (CHD), yet a significant variability between assays exists. We compared three methods to quantify HDV-RNA levels in untreated and Bulevirtide (BLV)-treated CHD patients.

Methods:
Frozen plasma from untreated and BLV–treated CHD patients were tested in a single-center retrospective study by 3 different assays: Robogene HDV-RNA Quantification Kit 2.0 (Roboscreen GmbH; LOD 6 IU/mL on 7500 Fast Real-Time PCR System [Applied Byosystem]), EurobioPlex HDV PCR quantitative (Eurobio Scientific, LOD 100 IU/m) on CFX96™ real-time PCR detection system [Bio-Rad]) and AltoStar HDV RT-PCR RUO Kit 1.5 (Altona Diagnostics, estimated LOD <10 IU/mL) on the AltoStar®AM16 .

Results:
Overall, 431 plasma samples from 130 CHD (69 untreated and 61 BLV-treated) patients were studied.
Compared to Robogene, EurobioPlex reported higher HDV RNA levels [3.78 (0.70-7.99) vs. 4.69 (2.00-8.19) Log IU/mL, p<0.0001], with viremia higher than >0.5 Log in 160 (69%). Likewise, HDV RNA levels were higher with Altostar than with Robogene 2.0 [3.32 (0.70-7.37) vs. 3.91 (0.19-7.54) Log IU/mL, p<0.0001], with AltoStar reporting HDV-RNA levels >0.5 Log in 127 (52%). Although virological response rates (≥2 log decline vs. baseline) at week 24 (Robogene 2.0 vs. EurobioPlex and AltoStar) and 48 (Robogene 2.0 vs. AltoStar) were similar across assays, rates of HDV RNA undetectability significantly differed between the three assays at week 24 and 72 (p=0.003 and p=0.02)

Conclusions:
HDV-RNA levels quantified by EurobioPlex and Altostar were 1 and 0.5 logs higher than Robogene 2.0, respectively. HDV-RNA undetectability rates during BLV treatment were assay-dependent

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P3 Value and kinetics of virological markers in the natural course of chronic hepatitis D virus infection

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Objectives:
Chronic hepatitis D virus (HDV) infection can cause severe liver disease. In the light of new treatment options, it is of particular importance to identify patients at risk for liver-related complications. We aimed to investigate the kinetics and predictive value of novel virological and immunological markers in the natural course of chronic HDV infection.

Methods:
HBcrAg, HBV RNA and quantitative anti-HBc were analyzed in samples from patients with chronic HDV infection at three consecutive time points to study kinetics in the natural course of infection. Results were linked to clinical outcome by univariable and multivariable analyses. The primary endpoint was the composite endpoint of any liver-related event (hepatic decompensation, hepatocellular carcinoma, liver transplantation or liver-related death).

Results:
Samples from 190 individual patients were available for analysis with a total median follow-up time of 2.69 (IQR 1.13-6.51) years. The majority of patients had cirrhosis (98/190, 52%) and the primary endpoint occurred in 33% (62/190) of patients. In the univariable analysis, age, cirrhosis, lower levels of quantitative anti-HBc, higher ratio of HBcrAg/anti-HBc and detectable HDV RNA were associated with the primary endpoint. In the multivariable analysis, only presence of liver cirrhosis (HR 7.74, p<0.001) and age (1.06, p<0.001) remained independently associated with the primary endpoint. Kinetics of virological parameters during follow-up were similar between the groups. Quantitative anti-HBc was significantly lower in patients with liver cirrhosis (687 (IQR 188-3388) IU/ml vs. 309 (IQR 82-924) IU/ml, p<0.0004) and lower levels were independently associated with the development of the primary endpoint in this subgroup (HR 1.0, p=0.014).

Conclusion:
In chronic HDV infection, neither baseline values nor kinetics of HBV RNA, HBcrAg and anti-HBc were independently associated with clinical outcome, while stage of liver disease and age were predictors of liver-related events.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P4 Hepatitis delta virus (HDV) replication through HBV integrants in HCC recurrence after liver transplantation

L. Di Marco[1,2], N. De Maria[3], A. Pivetti[3], A. Colecchia[3], A. Romanzi[3], A. Spallanzani[1], G. Guaraldi[4], G. Dolci[4], G. Ciusa[5], F. Di Benedetto[6], P. Magistri[6], S. Di Sandro[6], E. Degasperi[7], M.P. Anolli[7], P. Lampertico[7], D. Giosa[8], D. Lombardo[9], G. Raimondo[9], T. Pollicino[9]

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A PWID man, HCV/HBV-HDV/HIV-infected, underwent liver transplantation (LT) for HCC in 2012 at the age of 52 years. HCC tissue showed high HDV-RNA (88,400 copies/cell), low total HBV-DNA (0.00001 c/c), and HBVcccDNA0.00008 c/c), without detectable HBV-RNA. High-throughput HBV integration sequencing (HBIS) identified 657 HBV integration sites.HBV integrants were predominantly represented by HBx gene sequences. After LT, Tacrolimus, Bictegravir/Emtricitabine/TAF, and anti-HBs immunoglobulin were administered, yielding HBsAg, HDV-RNA, and HCV-RNA negativity.

In 2018, HBsAg reversion was observed with undetectable HBV-DNA and HDV-RNA >19,000 c/ml.

In 2019, HDV-related hepatitis occurred. Intrahepatic HBcAg, HBsAgHBV DNA, HBVcccDNA, and HBV-RNA were undetectable. HDV RNA concentrations were very high in the liver (3,920,000 c/c) but low in the serum (214 IU/mL). CT scan (CTs) suspected an isolated HCC recurrence in the left adrenal gland, confirmed by adrenalectomy. Real-time PCR in the tumor from the adrenal gland revealed high levels of HDV RNA (5.5 c/c) but low levels of HBV DNA (0.00009 c/c) and HBVcccDNA (0.00001 c/c). HBV RNA was undetectable. HBIS identified 3497 HBV integrations, most of which included HBs gene sequences. After adrenalectomy, HBsAg and HDV-RNA became undetectable. Anti-HBs immunoglobulin was continued with Everolimus.

In 2021, CTs showed two HCC nodules in the liver and one in the right adrenal gland. TACE was performed, and TKI therapy was started.

In 2023, new HDV hepatitis occurred, with HDV-RNA>3,631,360 UI/ml and HBV-DNA <10UI/ml. For the progression of HCC, RFA on the right adrenal gland was performed, and Bulevirtide was started. After 3 months, HDV-RNA was 48,638 c/ml, and transaminases were normal.

This case demonstrates HDV replication in extrahepatic HCC recurrence, despite low levels of HBVcccDNA. The decreased HDV RNA levels after RFA and BLV therapy suggest that HCC metastases may serve as HBsAg production sites following HBV integration.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P5 Development and implementation of an hepatitis D detection and linkage to care program in Catalonia. Preliminary results.

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Introduction:
Hepatitis D virus (HDV) infection still remains underdiagnosed, although most guidelines recommend anti-HDV testing in all HBsAg-positive individuals. In Spain, HBsAg estimated prevalence is 0.22%, with a 7.7% of anti-HDV+. This project aims to develop and implement an hepatitis D detection program for all HBsAg-positive samples that are collected in public healthcare centers of Catalonia (>95% population coverage).

Patients and methods:
Prospective study including all HBsAg+ samples collected in 7 laboratories of the Catalan healthcare system. Double anti-HDV reflex testing was conducted, including a centralized HDV-RNA quantification.
Medical records of anti-HDV positive patients were examined and registered in a digital platform (demographics, epidemiology, clinical data, laboratory data, and linkage to care status).Linkage to care was ensured for all HDV-RNA positive individuals.

Results:
From January to June of 2024, HBsAg was tested in 144,166 samples and 3,633 (2.5%) were HBsAg+. Anti-HDV was tested in 3,215 (88%), a total of 149 (4.6%) were anti-HDV positive, and 83 (56%) were HDV-RNA positive (Figure).
Out of the 149 anti-HDV+, clinical data was collected in 80 subjects. Anti-HDV+ subjects were mainly male (61%), with a median age of 53 (42-58) years, and foreign (55%). Risk factors were reported in 35% of individuals, (21% parenteral transmission, from which 11% were PWID, 6% sexual risk behavior), with median ALT levels of 33 (20-59) IU/ml. Regarding liver disease, 26% had liver cirrhosis, 8% had history of liver-related decompensation, and 3% had history of hepatocellular carcinoma.
The program allowed testing 1,490 (46%) HBsAg+ samples not previously tested for anti-HDV, and detected 44 (3%) new cases of anti-HDV+, 11 (25%) of them being HDV-RNA positive. All of them have been linked to care and are now under evaluation for treatment.

Conclusions:
The development and implementation of a regional hepatitis D program has proven to be feasible and has a wide acceptance amongst all microbiology and liver units. Our preliminary results show that hepatitis D detection programs linked to the general healthcare system are crucial for optimal diagnosis and linkage to care of these patients.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P6 THE WHO HDV RNA International Standard does not reflect variability of real-world samples

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Introduction:
Reliable diagnosis of hepatitis D virus (HDV) infection and detection and quantification of HDV RNA is the basis for initiating and guiding antiviral therapies. The WHO HDV standard should allow standardization of quantitative HDV RNA values across different assays. However, comparison of different HDV RNA assays that all have been calibrated against the WHO standard revealed remarkable differences in quantitative HDV RNA values of real-world samples in several studies.

Methods:
Dilutions of the WHO standard as well as 28 plasma samples collected during routine management of hepatitis D patients were studied. All samples were tested at the same time with four different approaches: RoboGene HDV RNA Quantification Kit 2.0 or the newly developed RoboGene HDV RNA Quantification Kit 3.0 (CE-IVD pending) in combination with automated (INSTANT Virus RNA/DNA Kit – FX 2.0) or manual (INSTANT Virus RNA/DNA Kit Protocol 2 or 3, as recommended) extraction (all Roboscreen GmbH, Leipzig, Germany). All combinations were tested against each other and the WHO standard was included in all runs.

Results:
Quantitative RNA values were comparable with minor discrepancies when different dilutions of the WHO standard were tested. Substantial variabilities became evident for several but not all plasma samples collected during real-life conditions. Quantitative HDV RNA levels varied by < 1 log IU/ml in 43% (n=12/28) of plasma samples, while 57% (n=16/28) of samples showed a variation by > 1 log IU/ml. There was no association between the viral load level of the plasma sample and the degree of variability. The proportion of low viremic samples was similar in the samples with a variability < 1 log IU/ml (17%) and > 1 log IU/ml (19%).

Conclusion:
Calibrating HDV RNA assays based on the WHO standard alone may miss substantial differences between assays that become evident only when clinical samples are tested. The reason for heterogeneity of samples requires further investigation.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P7 Bulevirtide: a success case after pegINFα failure

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Bulevirtide is still a therapy under study, as the duration is not yet well defined and it is not clear whether a combination therapy is necessary. It is important to collect as much data as possible on bulevirtide treatment to observe its efficacy and its limits in real life.

At our centre we followed an Albanian 34-year-old man to whom an HBV hepatitis with HBeAg positive with HDV coinfection was diagnosed at the age of 29. At diagnosis, elastography was with stiffness of 8.8 Kpa (METAVIR F3), HBV DNA 9830 UI/ml, HBsAg 23996 UI/ml, HDV RNA 29475 copies/ml, GOT 45 U/l, GPT 92U/l.

At 4 months after diagnosis, therapy with tenofovir disoproxil fumarate 245 mg/day was started and after one month HBV-DNA was15 IU/ml; and at 7th month after disgnosis therapy with pegINFα 180 mcg/week was initiated. After 5 months of pegINFα treatment, HDV was 111000 copies/ml with GOT 84U/l and GPT 199U/l. At the end of treatment (48 weeks) HDV RNA was 435 copies/ml. At the next checks, there was an increase in HDV RNA values, confirmed at several times (March 2023: HDV 51060 copies/ml, July 2023: HDV 391890 copies/ml).

As side effects of pegINFαonly arthralgias and an episode of fever were reported.
In November 2023 he started treatment with bulevirtide 2mg/sc/day, continuing TDF. Already after two months of treatment, HDV viremia has decreased and transaminases have normalised. After eight months of therapy, transaminases are within normal values and HDV viremia is undetectable with the current method.

He did not complain of any systemic disorders or local skin and subcutaneous reactions.
This case shows how bulevirtide was effective in reducing viral replication of HDV and reducing liver damage following pegINFα failure. Bulevirtide is also well tolerated.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P8 The prevalence and characteristics of hepatitis B/D in 48,522 HBsAg tested individuals in Mongolia

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Background and Aims:
The prevalence of chronic hepatitis B/D virus (HBV/HDV) co-infection has been previously shown to be high in Mongolia. Characterization of HBV/HDV co-infected persons in a large cohort with comparison to mono-HBV infected or those with resolved HDV is lacking in the literature. We have therefore analyzed the prevalence of HBV/HDV and characteristics of individuals who have undergone HBsAg testing in Mongolia.

Method
This is a cross-sectional analysis of all individuals, who have been screened for HBsAg during the years 2015 - 2023 at the Liver Center, Ulaanbaatar, Mongolia. Persons ≥ 18 years were divided into three groups according to their first test results: 1. HBV/HDV co-infection: HBsAg+/HDV RNA+ (defined as ≥ limit of detection of 50 IU/ml); 2. HBV infection with resolved HDV ("resolved HDV"): HBsAg+/anti-HDV+/HDV RNA-; 3. HBV mono-infection: HBsAg+/anti-HDV-. The first performed tests of ALT, viral load and liver stiffness were analyzed.

Results
We have identified 51,113 attendees who have undergone HBsAg testing, and after exclusion of persons missing date of birth, sex, those <18 years, 48,522 individuals remained. 15,046 (31.0%) were found to be HBsAg+. 8318 (55.3%) underwent an anti-HDV test, and 5390 (35.8% among all HBsAg+) were anti-HDV+. The prevalence of HBV/HDV coinfection, resolved HDV and HBV mono-infection was 8.2% (n=3,970), 0.8% (n=388) and 5.9% (n=2,879), respectively. An increasing trend of the proportion of HDV RNA+ among HBsAg+ persons was seen across the study period, with the rate reaching 26.1% in 2022-23 compared to 11.2% in 2015 (p=<0.001). Persons with HBV/HDV coinfection were significantly older (mean ±SD; 43.4±10.7 vs. 37.5±10.2) and had more prevalent women (54.4% vs 48.4%) compared to HBV mono-infected (P=<0.001). HBV/HDV co-infected persons had significantly higher ALT levels than the other two groups (p<0,001). ALT level ≥ 1x upper limit of normal (ULN, adjusted for sex), ≥ 2x ULN, ≥ 5x ULN and ≥ 10x ULN was seen in 77.8%, 39.3%, 8.3% and 1.3%, respectively among HBV/HDV co-infected. The median HBV DNA level was 2.2, 2.4 and 3.2 log10 IU/ml, while HBsAg level of 3.8, 2.8 and 3.3 log10 IU/ml, respectively, in HBV/HDV co-infected, resolved HDV and HBV mono-infected persons. The (median, IQR) HDV RNA level was 5.3 (4.2-6.1) log10 IU/ml for HBV/HDV co-infected. The rate of liver stiffness level ≥15.2 Kpa was significantly higher among HBV/HDV co-infected at 14.5% than 4.8% in mono-HBV infected (P=<0.001) but similar to those with resolved HDV.

Conclusion
In this large-scale study of HBsAg tested in Mongolia, a high rate of HBV/HDV co-infected with an increasing rate of HDV RNA+ among HBsAg+ was present. Among 3970 HBV/HDV co-infected persons, higher rate of ALT elevation and advanced fibrosis than mono-HBV infected was seen, with 77.8% having increased ALT level. Further studies are needed to understand the pathogenesis of HBV/HDV co-infection.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P9 Validation of Streamlined serodiagnosis of hepatitis delta virus

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Background:
Hepatitis Delta Virus (HDV), the most severe form of viral hepatitis in humans, exacerbates the liver disease caused by Hepatitis B Virus (HBV). Despite an estimated global prevalence of 12 million, HDV infections often go under-diagnosed due to insufficient training, testing, and funding. To address this challenge, we are validating an anti-HDV Antibody Rapid Diagnostic Test (RDT) developed by LUCA AICell. The test leverages the lateral flow assay (LFA) technique to detect antibodies against Hepatitis Delta antigen (anti-HDV) in serum and plasma. The LFA operates in a streamlined mechanism. When a sample, such as serum or plasma, is applied it migrates via capillary action, encountering reagents including antibodies labeled with colored particles. These particles bind to any present anti-HDV, producing a test line indicating a positive result. A control line further validates this procedure.

Aim:
We aim to validate the LUCA AICell anti-HDV Antibody RDT on a higher study population. Previously, we validated the accuracy of the test on a small sample size of 200. This is the follow-up validation study. For this purpose, prototypes of the RDTs have been provided by LUCA AICell to the Liver Center.
Methods. The study was conducted on 2 cohorts. The first cohort contained 110 samples and the second cohort contained 897 samples. The total population of 1007, 548 HDV-RNA positives, 138 HDV-RNA negative but HBsAg positives, and 201 healthy patients, was collected from the blood bank of the Liver Center. Reference ELISA tests were performed prior to the study. Reference HDV-RNA tests were performed using an in-house developed RT-PCR.
To ensure the validity of the results some samples were randomized prior to testing. Only 702 samples from the second cohort were randomized. The tests were then conducted in groups of 10 according to the manufacturer's instructions. The results were examined by 3 different people after 15 minutes, and by 1 person after 20 and 25 minutes. Results were recorded by photo at all minute marks. The test conductor and examiners had no knowledge of the ELISA and qPCR test results. The results were compared to conventional HBsAg and anti-HDV ELISA tests, as well as HDV-RNA qPCR kits.

Results:
The test results show there to be 547 true positive, 444 true negative, 15 false positive, and 1 false negative sample. Furthermore, the RDT showcased 99.82% sensitivity, 96.73% specificity, and 98.41% accuracy compared to conventional anti-HDV and HBsAg ELISA tests, as well as HDV-RNA qPCR kits.

Conclusion:
The LUCA HDV Ab Rapid diagnostic test offers an inexpensive, accurate and highly accessible tool for HDV diagnosis. This study validates its high performance, and we believe it has the potential to significantly improve HDV diagnosis.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P10 Limited use of established risk scores for the prediction of hepatocellular carcinoma in patients with chronic hepatitis D virus infection

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Background and Aims:
Patients with chronic HDV infection (CHD) are at risk of developing hepatocellular carcinoma (HCC). In chronic HBV or HCV infection, risk scores are commonly used to predict HCC, but none has been validated in CHD. Here, we aim to validate existing HCC risk scores for their predictive potential in patients with CHD.

Method:
Data from patients with CHD and a minimum follow-up (FU) of 6 months were retrospectively collected at Hannover Medical School from 1990 to 2023. Patients with HCC development (CHD-HCC) during FU were identified and matched to patients without HCC development (CHD-non-HCC) based on sex, age, INR, and bilirubin in a 1:2 ratio. Time points for data collection were first visit to the clinic (BL), 12 (HCC-12) and 6 months (HCC-6) prior to HCC development, as well as at HCC diagnosis (HCC). Comparable time points were selected for the matched CHD-non-HCC cohort with the last one defined as the last available visit. The following validated HCC risk scores were calculated and compared between the cohorts: PAGE-B (platelets, age, sex), aMAP (age, sex, albumin/bilirubin, platelets), Toronto HCC Risk Index (age, etiology, sex, platelets), REAL-B (age, sex, alcohol, cirrhosis, diabetes, platelets, alpha-fetoprotein (AFP)), CAMD (cirrhosis, age, sex, diabetes), AASL (age, albumin, sex, cirrhosis) and ADRES-HCC (sex, FIB-4 index, AFP).

Results:
We retrospectively identified 251 CHD patients of whom 14 % (36/251) were diagnosed with HCC during FU. At BL, the majority of CHD-HCC patients were male (75 %), cirrhosis was present in 89% of patients and median time to HCC diagnosis was 3.42 years (IQR 1.4 – 6.96). The prevalence of liver cirrhosis, hepatic comorbidities and prior interferon treatment was similar to the matched 72 CHD-non-HCC patients. When comparing HCC prediction scores between the cohorts, overall test performance was poor. At BL, the REAL-B score reached the highest AUC with 0.65, followed by CAMD (AUC = 0.61) and aMAP (AUC = 0.61). Slightly weaker test performance was detected at HCC-12, with the three best performing tests being REAL-B (0.61), CAMD (AUC = 0.59) and ADRES-HCC (AUC = 0.56). At HCC-6, ADRES-HCC (AUC = 0.67), REAL-B (AUC = 0.64) and aMAP (AUC = 0.61) performed best. At HCC diagnosis, ADRES-HCC (AUC = 0.68) and aMAP (AUC = 0.66) were the two best scores to distinguish between patients with and without HCC. Interestingly, AFP alone outperformed all scores at every time point with an AUC of 0.69, 0.64, 0.75, and 0.78 at BL, HCC-12, HCC-6 and HCC, respectively. AFP and Albumin independently showed a predictive potential in univariate comparison, but not in multivariate analysis.

Conclusion:
In our cohort, none of the analyzed scores predicted HCC development with sufficient accuracy and consistency. However, HCC risk stratification is essential for the management of CHD patients. Thus, the development of a valid HCC risk score should be addressed in future studies.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P11 Is there a Hepatitis Delta Virus variant in West Africa, not detected by current serological diagnostic tests?

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The Hepatitis Delta Virus (HDV) causes the most severe form of viral hepatitis with a rapid progression to cirrhosis and hepatocellular carcinoma. Usually, the diagnosis of HDV is based on the detection of anti-HDV antibodies (HDVAb) by serological tests in all HBs antigen (HBsAg)-positive patients. For those with positive HDV-Ab, the virological profile must be completed with the measurement of HDV RNA in order to determine active viral replication. Last year, a study described the presence of HDV RNA in several Gambian patients with negative HDV-Ab (International DeltaCure 2023 meeting, poster 20). Although these results suggested false-negative serological results due to a possible HDV variant, a contamination during amplification could not be formally excluded. At the same period, we conducted an epidemiological study of HBV and HDV in Senegal (SEN-B), a neighboring country of the Gambia.

Therefore, we aimed to investigate this hypothesis of an HDV variant in our SEN-B cohort.
SEN-B enrolled 914 persons positive for HBsAg between 2019 and 2023 in Senegal. The median age was 32 years, and 475 (52%) were male. Patients were all diagnosed and followed at Dakar Fann University Hospital. HDV-Ab were found in 13 of 914 individuals (1.4%), using the HDV-Ab Liaison®XLMurex Anti-HDV assay. We then evaluated the presence of HDV RNA in all samples of the remaining 901 anti-HDV negative individuals. HDV-RNA extraction was realized with the m2000sp automatic device (Abbott Diagnosis) from 500µl of plasma, allowing a high sensitivity of detection. Then, we performed the conventional "R0"-RT-PCR as previously developed in our lab, using pan-genotypic primers defined in the most conserved region of the HDV genome, able to detect all described HDV-(sub)genotypes.

The sensitivity of our assay is around 20 IU/mL, according to the WHO-HDV-standard. In addition, in each amplification series, we included both a negative control and a very low positive control to confirm the efficacy, the sensitivity as well as the absence of contamination over the amplification process. We found no HDV RNA positive sample in the 901 negative HDV-Ab samples. Therefore, there is no evidence in this part of Africa, that HDV variants, undetectable by current serological assays exist. Our results strengthen our position in favour of a systematic screening of HDV infection with a double reflex diagnostic testing (i) by serological anti-HDV screening in all persons with HBV, (ii) followed by the quantification of HDV viral load by RT-qPCR to determine HDV replication among those with positive HDV-Ab.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P12 Novel anti-HDV therapies require reliable quantification of plasma HDV RNA: A European multicenter study

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Background:
Quantification of plasma HDV RNA is the essential tool for patient management under anti-HDV therapy and during follow up. Quantification of HDV RNA may vary depending on the efficiency of HDV RNA extraction.
Objectives: To investigate the comparability of quantification and sensitivity reported by different European laboratories using the new RoboGene HDV RNA Quantification Kit 3.0 (Roboscreen GmbH) with different manual or automated nucleic acid extraction protocols/platforms and amplification/detection devices in comparison with the commonly used RoboGene HDV RNA Quantification Kit 2.0.

Methods:
Eight study centers using 8 different combinations of NA extraction platforms and amplification devices participated in this study. For harmonization of HDV RNA concentrations obtained by different protocols, correction factors (CF's) were determined using the 1st WHO International Standard (IS) for HDV RNA. The limit of detection (LOD) was determined by analyzing dilution series of the 1st WHO IS for HDV RNA. For accuracy testing of each protocol, reference material was used. Furthermore, clinical samples were analyzed and results were compared.

Results:
CF's ranged from 14 to 10000 depending on the combination of NA extraction platform and amplification device used. Calculated CF's were applied for subsequent quantification. Depending on the combination used, LOD's ranged from below 2 to approximately 1000 IU/ml. When accuracy was tested, external quality control samples containing low HDV RNA concentrations were not detected by that protocol with the highest LOD. When dilutions of clinical samples were tested, the lower the HDV RNA concentration, the less quantifiable data sets were obtained.

Conclusion:
To ensure reliability in quantification of HDV RNA, any modification of the extraction and amplification/detection protocol validated by the manufacturer requires revalidation. With the 1st WHO IS for HDV RNA, CF's and LOD's could easily be calculated in this study leading to harmonization of quantitative results and verification of sensitivity. Both are essential for accurate monitoring of viral response to existing anti-HDV treatment as well as for comparability of study results investigating novel anti-HDV drugs during treatment and follow up after end of treatment.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P13 The asymmetry of the liver and spleen stiffness measures between patients with chronic hepatitis B and D reflects important clinic-pathologic differences

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Background:
Chronic HDV infection causes an additional pathologic burden in patients (pts) with chronic HBV infection that accounts for their worse clinical outcome. We studied the relative differences in liver (LSM) and spleen stiffness measurements (SSM) in a single center cohort of pts with chronic hepatitis B (CHB) and D (CHD), in order to point out potential added values of the SSM in this clinical setting.

Methods:
We studied 119 HBsAg+ pts, 71 CHB and 48 CHD [30(42.3%) and 27(56.3%) with cirrhosis, respectively] undergoing regular follow-up at the Hepatology Unit of Pisa University Hospital. Fifty-two (73.2%) CHB were on NUC and 15 (31.3%) CHD pts on Bulevirtide (BLV) therapy. Physical examination, ultrasound scan (US), LSM and SSM (FibroScan®, Echosens, France) were performed on the same day, liver biochemistry and virological assays within one week

Results:
Table 1 shows the comparison of demographic, clinical and laboratory characteristics in CHB and CHD pts. Median LSM was lower in CHB than in CHD pts [6.2(2.8-71) vs 8.1(2.8-33.1) kPa (p=0.004)], whereas SSM was similar [25.6 (9.3-87.6) vs 26.8 (4.8-100) kPa (p=0.569)]; accordingly, median SSM/LSM ratio was lower in CHD than in CHB [2.98 (1.00-9.64) vs 3.88 (1.09-16.25), p=0.003). Median spleen diameter (SD) was 11.0 (7.0-18.0) cm in CHB and 12.0 (6.5 -23.0) cm in CHD (p=0.079). CHD pts showed a significantly lower SD/LSM ratio [1.33(0.36-3.89) vs 1.78(0.21-4.08), p=0.007], but similar SD/SSM ratio [0.44 (0.14-2.06) vs 0.43 (0.14-1.07), p=0.688]. Also among pts diagnosed with cirrhosis,median LSM was significantly lower in CHB than in CHD [9.7(3.7-71) vs 13.3 (5.6-33.1) kPa, p=0.022], whereas SSM was similar [34.0(9.9-87.6) vs 33.3(14.5-100) kPa, p=0.842]. The SD/LSM ratio showed a trend to be lower in cirrhotic CHD [0.92 (0.36-2.09) vs 1.20 (0.21-2.89), p=0.054]. In CHD, as compared to CHB pts, SSM correlated better with LSM, overall (r=0.761 vs r=0.465) and in cirrhotics (r=0.799 vs r=0.432); with SD overall (r=0.643 vs r=0.489) and in cirrhotics (r=0.647 vs r=524) and with platelets count overall (r=-0.617 vs r=-0.498) and in cirrhotics (r=-0.726 vs r=-0.638).

Conclusion:
The combined measure of liver and spleen stiffness provides a useful differential clinic pathologic characterization of liver disease in patients with chronic HBV and HDV infection. The significantly lower SD/LSM ratio found in CHD pts, suggests underlines the specific role of HDV induced necro-inflammation as a driver of disease progression with splenomegaly and platelet count reduction. Longer follow up in CHD treated patients are needed to define the curative impact of the current antivirals.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P14 Diagnostic performances of different HDV RNA quantification assays used in clinical practice in Italy: results from a national quality control multicenter study

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Background and Aim:
A reliable quantification of serum HDV-RNA is essential for monitoring patients under antiviral therapy. This quality control study aimed at comparing the diagnostic performances of different quantitative HDV-RNA assays, used in clinical practice.

Methods:
2 HDV-RNA panels were quantified at 30 Italian labs by 6 commercial assays: RoboGene (#1, N=9 labs), Eurobio on Elitech platforms (#2, N=7), Altona RealStar (#3, N=5), Anatolia Bosphore (#4, N=3), Diapro. (#5, N=2), NuclearLaserMedicine (#6, N=1) and in-house assays (#7, N=3). Panel A comprised 8 serial dilutions of WHO HDV standard from 5 to 0.5 logIU/ml, while Panel B included 20 clinical samples with HDV-RNA from 6 to 0.5 logIU/ml. The labs quantified each sample of Panel A and B 9 and 5 times, respectively (3 independent runs). Panel A was used to define assay sensitivity by the 95%LOD (limit of detection) and the accuracy (by the differences between expected and observed values). Panel B was used to evaluate the assay precision by intra-run and inter-run coefficient of variation (CV) and the rate of false negative results. Results from both panels were used to define assays' linearity by linear regression analysis.

Results:
By Panel A, 95%LOD varied across the assays highlighting different sensitivities: assay #3 had the lowest median 95%LOD (10[min-max:3-316]IU/ml), followed by #1 (31[3-316] IU/ml), #6 (31IU/ml) and #2 (100[100-316] IU/ml). The remaining 3 assays had a median 95%LOD ranging from 316 to 1000IU/ml.
Moreover, 5 assays (#1, 2, 3, 6 and 7) showed a <0.5logIU/ml difference between expected and observed HDV-RNA values for all dilutions. Conversely, #4 and #5 exceeded 0.5logIU/ml (mean differences ranging from -1.3 to 1.2 and from -1.8 to -1.2logIU/ml, respectively), showing a substantial HDV-RNA underestimation.
By Panel B, different reproducibility was observed: assays #2 and #3 had a mean intra-run CV<20% for each tested concentration. Differently, #1 and #6 showed a mean intra-run CV<30%. Lastly, for #4, #5 and #7, the mean intra-run CV is <30% with specific concentrations showing CV>50%. Inter-run CV values were higher for all assays with only #3, #6 and #2 maintaining mean inter-run CVs<25%.
Furthermore, all panel B concentrations >100 IU/ml were detected in all replicates by all assays. Conversely, most assays showed a progressive increase in the rate of false negative results for HDV-RNA <100 IU/ml.
Finally, assays #1, 3, 2, 6, and 7 showed a good linearity (R2 >0.9), while a drop was observed for the concentrations <1000IU/ml, with only #3 and #1 maintaining a R2>0.85.

Conclusions:
This study underlines different levels of sensitivities (inter- and intra-assays), that could hamper the proper detection of low-level HDV-RNA. There is a need to improve the accuracy in the quantification of HDV-RNA at both low and high viral load for most assays. These results should be carefully considered for the proper monitoring of virological response to anti-HDV drugs.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P15 Hepatitis Delta Virus RNA quantification: a story about fruitful collaboration between private company and academic laboratory

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HBV-HDV co-infection is responsible for the most severe form of viral hepatitis. For patients with positive anti-HDV antibodies, HDV RNA detection and quantification in plasma is mandatory to identify an active infection, and to monitor the response to antiviral treatment. Several commercial or in-house RT-qPCR tests are used worldwide, but some tests encounter difficulties to quantify all HDV strains, due to the high genetic diversity (8 genotypes and multiple subgenotypes) and strong secondary structure of HDV RNA.

Altona Diagnostics, a renowned company, asked in mid-2022 the French National Reference Centre for HDV (F-NRC) to evaluate its RealStar HDV RT-PCR kit 1.0. The tests were overall very satisfactory. However, when testing the FNRC pangenotypic panel of HDV strains, 3 strains of HDV-1 (African origin) were severely underquantified. Because the quantification of more than twenty other African HDV-1 samples was correct, the matter was not pursued at that time.

In mid-2023, altona again asked the F-NRC to evaluate its new, all-automated, AltoStar HDV RT-PCR 1.5 kit.

Surprisingly, whereas the results were similar to those expected, the same 3 African HDV-1 samples from the panel were again severely underquantified.
This result prompted the F-NRC and altona Diagnostics' R&D Department to initiate a serious investigation on the subject. A random technical problem was easily dismissed (reproducible results on new aliquots of the panel).

Phylogenetic analysis allowed to confirm the 3 strains belonged to the same HDV-1d subgenotype. Complete sequence was available for the 3 panel strains, and altona verified their primers and probe primary sequences were a 100% match for the HDV-1d sequences. The F-NRC then tested 50 HDV-1 samples from its collection, choosing specifically patients born in sub-Saharan Africa, and 3 new problematic samples, which came out very close to HDV -1d on the phylogenetic tree, were identified.

A default of amplification due to a specific secondary structure of HDV-1d RNA was then mentioned. altona's R&D team worked on the different parameters of its kit (PCR protocol, reagents concentration) to improve the detection/quantification of the HDV-1d strains without affecting the overall performances of the kit.
The updated version of the AltoStar kit was finally tested by the F-NRC at the end of 2023, and the HDV-1d strains from the panel and 23 samples from the F-NRC collection were quantified correctly (with a mean difference of 0.3 log IU/mL vs EurobioPlex EBX-071).

This story underlines how academic and private labs can collaborate in an exemplary manner to provide clinicians and patients the best biological tools.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P16 Clinical evaluation of the Altostar HDV RT-PCR Kit 1.5

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Background and Aims:
Detection and quantification of hepatitis D virus (HDV) RNA is essential for diagnosis and treatment management of chronic HDV infection. The aim of this study was to evaluate the diagnostic performance of the Altostar HDV RT-PCR Kit 1.5 in real-world clinical samples with and without treatment with bulevirtide (BLV).

Methods:
A total of 54 plasma samples of 40 individual patients with chronic HDV infection were analyzed with the Altostar HDV RT-PCR Kit 1.5 (extraction kit: AltoStar Purification Kit 1.5, sample volume 500 µl, elution volume 80 µl) and compared to the local quantification standard, the RoboGene HDV RNA Quantification Kit 2.0 (extraction kit: QIAamp DNA Blood Mini Kit, sample volume 200 µl, elution volume 100 µl). Samples with different viral load (target not detected, below the lower limit of quantification and detectable) based on the local quantification standard were included. Additionally, 43 corresponding serum and plasma samples from the same time point were analyzed and compared. Baseline (BL) and on-treatment (FU) plasma samples of 20 patients receiving BLV treatment were analyzed to compare virological treatment response rates based on the quantification assay used.

Results:
Overall, mean HDV RNA levels of plasma samples with detectable HDV RNA quantified by the Altostar HDV RT-PCR Kit 1.5 were similar compared to the quantification with the local standard (5.04x105 IU/ml [± 1.12x106] vs. 1.72x106 IU/ml [± 4.44x106], p=0.07). Two of five samples were undetectable by the local standard, but were detected and quantifiable by Altostar 1.5. When comparing quantitative results of HDV RNA levels from corresponding plasma and serum samples (paired samples) by Altostar 1.5, the log10 mean difference between serum and plasma samples was 0.11 log10 IU/ml (± 0.08 log10 IU/ml) , showing no significant difference between the samples. In the subgroup of patients receiving BLV treatment, mean HDV RNA levels at baseline and after 56 to 65 weeks of treatment were comparable between Altostar 1.5 and the local standard (BL: 1.66x106 IU/ml [± 2.81x106] vs. 2.25x106 IU/ml [± 6.6x106], p=0.72; FU: 2.17x104 IU/ml [± 5.81x10] vs. 3.25x104 IU/ml [± 9.05x104] p=0.66). All eight samples that were undetectable with the local standard after 56-65 weeks of treatment were detectable with Altostar 1.5. There was no significant difference in the proportion of patients with virological response, defined as undetectable HDV RNA or HDV RNA decline ≥2 log10 IU/ml, as quantified by Altostar 1.5 (n=15/20, 75%) or the local standard (n=14/20, 70%).

Conclusion:
HDV RNA levels quantified by the Altostar HDV RT-PCR Kit 1.5 are comparable to the local quantification assay with a higher sensitivity for low viremic samples. Importantly, evaluation of treatment response during BLV treatment was not influenced by the type of quantification assay.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P17 Hepatitis Delta infection in individuals living with HIV – multicentric portuguese study

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Background and Aims:
Hepatitis Delta virus (HDV) infection is the most severe form of viral hepatitis. Data from prevalence among persons living with HIV (PLHIV) varies across different countries due to several reasons, namely lack of awareness and standardizing diagnostic tools. Features and outcomes of coinfection in PLHIV are scarce and prevalence is thought to be rising in many areas of the world due to increased risk factors as also to immigration from areas of high endemicity.

Methods:
To bettter know the prevalence of HDV among PLHIV, data from five portuguese centers was collected.
Coinfected with a positive hepatitis B surface antigen, followed during 2023 and june 2024 were included, and demographic and clinical characteristics were analised. All were tested with anti-HDV antibodies and in those positive, HDV RNA was performed. Degree of fibrosis, treatment for HDV and for the other coinfections were assessed.

Results:
We included 234 HIV/hepatitis B virus (HBV) coinfected individuals (2% from the total of PLHIV). Prevalence of HDV coinfection was 14,5 %, ranging from 12,7% in north/center (18 /141) to 17,2% in south area of the country (16/93). From the total, 85,3% were male, average age was 40 yrs, and the geographical origin was as followed:
Portugal- 55,9%, Guinea Bissau-29,4%, Angola-8,8%, and others-5,9%. Regarding HIV transmission group, IVDU represented 55,9%. HDV RNA was only avalilable in 72,7 % with evidence of active infection in 62,5 %. In those in which fibrosis assessment was performed, 50% evidenced advanced fibrosis (F3-F4). HBV DNA and HIV RNA were undetectable in 87,8% and 93,9% respectively, all with TDF/TAF+XTC as backbone. Only 46,6% had been treated (Pegylated Interferon) or are under treatment (Bulevirtide) for HDV.

Conclusions:
In this sample, prevalence of HDV infection in HIV infected individuals was 14,5%, mainly represented by IVDU and sexual transmission, in this latter case, migrant population playing an importante role. They represent a key population that we must focus on. Advanced liver fibrosis in this triple coinfection, highlight the need of HDV screening of all HIV/HBV-coinfected patients, close monitoring and treatment. More data should be provided to enrich this sample.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P18 HDV RNA assay sensitivity is critical for determining a correct outcome during Bulevirtide antiviral therapy

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Sensitive and pan-genotypic assays are critical for diagnosis and monitoring of response to antiviral therapy in patients with chronic hepatitis delta (HDV). Bulevirtide (BLV) mimics a pre-S1 HBsAg protein and blocks viral entry to hepatocytes. NICE (National Institute for Health and Clinical Excellence) recommends that therapy with BLV should be continued for as long it is associated with a clinical benefit. Currently there are no futility stopping rules in HDV EASL guidelines, but accurate determination of on-treatment response would guide the field. Variability in RNA extraction methods, different primer/probe design, lack of standardization contribute to substantial variability in performance characteristics of research-based and commercial HDV RNA assays. We aimed to compare the performance of our inhouse real-time PCR assay (LLoQ 640 copies/ml) (Shah et al J of Virological Methods 2012) and a research use only assay – HDV RNA test mRealTime by Abbott Diagnostics (LLoQ 5 IU/ml) (Coller KE et al Scientific Reports 2018) in a cohort of patients receiving BLV to determine their virological response.

Methods:
Blood samples were collected from 10 HBV/HDV co-infected patients treated with BLV (all HDV RNA positive at baseline, median age 48 years, males n=6, 90% compensated cirrhosis; 90% genotype 1 & 10% genotype 5). Plasma was collected at baseline, week 12 and 24, and HDV RNA was measured by two methods: Abbott Diagnostics research use only HDV mRealTime assay (LLoQ =5 IU/ml) and in-house real-time PCR (LLoQ=640 copies/ml). The response to BLV was categorised as: Responder (R) - >2 log10 IU/ml, partial responder (PR) 1-2 log10 IU/ml and non-responder (NR) < 1 log10 IU/ml at week 12 and week 24.

Results:
At start of therapy: HDV RNA levels by the Abbott assay were slightly higher than in-house assay (median: 5.4 log10 IU/ml vs. 4.7 log10 copies/ml, p=0.76). Start of therapy vs week12: HDV RNA declined significantly (p=0.025), but HDV RNA levels were higher in the Abbott assay (4.4 log10 IU/ml vs. 3.7 log10 copies/ml, p=0.86). The categorisation of response varied between assays: while only 1 patient achieved a response vs 4 patients (40%) with PR and 5 patients (50%) were non-responders by the Abbott assay. There were 3 (30%) responders and 7 (70%) non-responders by in-house assay. Start of therapy vs week24: HDV RNA declined significantly (p=0.001) in both assays and HDV RNA levels were higher in Abbott assay (3.6 log10 IU/ml vs 3.3 log10 copies/ml, p=0.89), but the number of patients categorised as responders were similar by both assays – 4 (40%) R by Abbott assay and in-house assay. In the Abbott assay there were 5 (50%) PR & 1 NR vs only 2 (20%) PR and 4 (40%) NR determined by inhouse assay. Two patients had undetectable HDV RNA by in-house assay, but were detected by Abbott assay.

Conclusion:
HDV RNA assays with high sensitivity and accuracy are critical for determining a correct outcome and management during BLV antiviral therapy

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P19 Treatment with pegIFNα inhibits cell division-mediated spread of HDV in a humanized mouse model supporting cell proliferation

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Background and Aims:
Previous studies in HDV-infected humanized mice demonstrated that pegylated interferonalpha (pegIFNα) treatment reduces HDV viremia (Giersch, J HEP Reports 2023). In vitro, IFNα exerts stronger anti-HDV activities in hepatoma cells undergoing cell division (Zhang, JHepatol 2022). This study aimed to investigate the impact of pegIFNα on the proliferation capacity of primary human hepatocytes (PHH) and HDV persistence in an experimental setting enabling cellular proliferation in vivo.

Methods:
uPA/SCID/IL2Rα-/- (USG) mice were transplanted either with uninfected PHHs (n=19) or with PHHs (n=15) isolated from a mouse stably infected with HBV and HDV (HBV viremia 1.7x109; HDV 5.3x108). 1 week post transplantation, both groups of mice were treated with or without pegIFNα for 8 weeks to assess cell proliferation.
Additionally, stably repopulated mice were superinfected with HDV after HBV establishment and treated with pegIFNα for 8 weeks. Virological markers were analyzed using ELISA, qPCR, and immunohistology.

Results:
In an environment supporting compensatory cell proliferation, transplanted PHHs underwent a strong expansion in vivo during the first 5 weeks, as demonstrated by the increase of human serum albumin, increased genome copy number, and the cellular proliferation marker Ki67 irrespective of pegIFNα treatment. In the absence of pegIFNα treatment, mice transplanted with infected PHH showed 1.6Log10 increase in intrahepatic HDV RNA and HDAg+ cells during cellular proliferation, while HDV RNA amounts per cell remained unchanged. PegIFNα administration strongly reduced intrahepatic HBV RNA (≥2.2log10). Strikingly, pegIFNα had a much more profound effect on HDV RNA levels (≥-4log10) in a setting promoting cellular proliferation than previously observed in stably repopulated mice (-0,5 log10), resulting in undetectable levels of HDV viremia, HDV RNA, and HDAg-positive PHHs.

Conclusion:
This study shows that pegIFNα does not hinder PHH proliferation in vivo. In line with previous studies, HDV can persist and spread among PHH undergoing cell division in vivo, but treatment with pegIFNα in an environment supporting cell proliferation potently reduced the amount of HDV-infected cells.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P20 Chronic delta hepatitis without efficient treatment poses a greater risk for hepatocellular cancer development than chronic hepatitis B with efficient treatment

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Background and Aims:
The risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB), treated with entecavir (ETV) or tenofovir (TDF) has been explored in large cohort studies. However, data in chronic hepatitis D (CDH) patients are limited. Aim of this study was to compare well-defined CDH and CHB cohorts with respect to HCC development.

Methods:
We searched our CHB and CDH databases for patients who had received treatment for CHB and CDH. 124 CDH patients (88M/36F; mean age: 40.3) had received at least 6 months and up to a cumulative duration of 10 years of IFN. In the CHB group, 238 chronic CHB patients (164M/74F; mean age: 48.5) were included. Of 238 patients in CHB cohort, 65 patients had a history of IFN and/or lamivudine and/or adefovir treatments. Of the 124 CDH patients, 40 had a maintained virological response (MVR) which was defined as durable negative HDV RNA for at least 2 years of post-treatment follow-up.

Results:
The 2 groups were similar for baseline clinical characteristics except for age (48.5 vs 40.3; p<0.01), HBeAg positivitity (32.6% vs 16.9% p<0.01), platelet numbers (188±76 vs 162±55 ; p<0.01) ,ALT levels (80±113 vs 103±101; p=0.05) and GGT levels (51±70vs. 80±75; p:0.001) for CHB and CDH patients, respectively. HCC developed in 21 (8.8%) of CHB and in 21 (16.9%) of CDH patients during the 144 months of FU. Cumulative probability of HCC development was 0.4%, 3.8%; 7.2%, 8.2%, 10.0%, 10.0% and 0.8%, 4.9%, 9.3%, 11.2%, 18% and 23.2% at 12, 36, 60, 84,120 and 144 months of follow-up for CHB and CDH patients, respectively. Development of HCC was more common in CDH compared to CHB patients (p:0.04). The yearly incidence rate was 1.28% and 1.92% within 60 months and 0.76% and 1.99% after the first 60 months of FU for CHB and CDH patients respectively. However, when CHB patients were compared to CDH patients with an MVR, the cumulative probability of HCC development did not differ (10% for HBV and 8.8% for HDV at the end of 144 months of FU, p:0.71). By multivariate analysis, age [95% CI OR: 1.09 (1.05-1.14);p<0.01], presence of CHD [95% CI OR: 5.29 (2.11-13.3);p<0.01] and GGT levels [95% CI OR: 1.010 (1.006-1.014);p<0.001] and to have a cirrhosis [95% CI OR: 2.77 (1.28-6.06);p:0.01] were independent predictors of HCC development. Propensity match scoring analysis showed that failure to achieve MVR in delta hepatitis was an independent predictor of HCC development (p:0.006).

Conclusions:
The data suggest that patients with CDH carry a very high risk for HCC development as with durable IFN virologic response is achieved in only about 15-20% of patients. HCC was more often seen in CDH patients despite CHB being,a known independent risk factor for HCC development. The importance of virologic response is highlighted by the disappearance of the difference of HCC development when comparison to CHB is confined to CDH patients with a MVR. The results underline the urgent need for new drug development in CDH.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P21 Complexities of Hepatitis Delta Virus Testing in a High HBV Prevalence Setting in London

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Background:
Historically, HDV testing of individuals with chronic hepatitis B virus (HBV) infection has not been systematically implemented and both antibody and RNA assays have shown inconsistent performance. This study aimed to evaluate the prevalence of anti-HDV in a North London population with high rates of chronic HBV infection and determine the proportion of individuals with anti-HDV that also had detectable HDV RNA before the (as yet limited) introduction of Bulevirtide.

Method:
We identified all positive HBsAg tests obtained between 2018 and 2022 (5 years) in the National Health System (NHS) diagnostic laboratory of the North Middlesex University Hospital in North London, with sources largely comprising the specialist hepatitis service, other outpatient services, emergency department opt-out testing, the sexual health service, and primary care. Unique HBsAg positive records were cross-referenced with anti-HDV antibody and HDV RNA tests. Demographic and clinical data were retrieved from electronic patient records. Antibody testing initially used the Diasorin ETI-AB-DELTAK2 assay, transitioning to the Liaison® XL Murex Anti-HDV assay in March 2019.
HDV-RNA detection employed an in-house real-time PCR assay. As part of the study, HDV RNA negative samples underwent retesting for anti-HDV by the Liaison assay and retesting for HDV RNA by a different in-house assay at the UK Health Security Agency reference laboratory.

Results:
Between 2018 and 2022, 1822 individuals had a positive HBsAg test. Of these, 970 (53.2%) had a record of undergoing testing for anti-HDV, with testing uptake being almost complete within the specialist hepatitis service and largely absent in other settings. A total of 48/970 (4.9%) individuals had ≥1 reactive anti-HDV result. These individuals were mostly women (30/48, 62.5%) with a median age of 46 years (IQR 38-55) and diverse backgrounds (Black African n=19; Eastern/Southern Europe n=18; South/East Asia n=5). In 12 (25%) of these 48 individuals, the initial positive Diasorin result did not confirm upon retesting with the Liaison assay; all lacked detectable HDV-RNA. HDV seroprevalence was therefore 36/970 (3.7%; 95% CI 2.6-5.1%). HDV RNA was detected in 7/36 (19.4%) individuals with anti-HDV reactivity.

Conclusion:
Our data indicate incomplete HDV testing in individuals with HBsAg, but highlight that testing is now routine within the hepatitis service. The population with HDV test results was therefore typically already engaged with HBV care. At 3.7%, HDV seroprevalence was in line with our previous estimates for the UK (2.1 to 5.3%; Stockdale et al. J Hepatol 2020). In this cohort, only 1 in 5 individuals with anti-HDV also had detectable HDV RNA, which is a lower prevalence of viraemia than we expected based on data from other cohorts. Given the diversity of the population with anti-HDV in our study, the lack of detectable HDV RNA warrants confirmation with additional assays.

DIAGNOSIS, STAGING, HCC RISK AND ANTIVIRAL THERAPY

P22 High frequency of liver cirrhosis in European patients with hepatitis D: Data from a large multi-centre study (D-SOLVE and HDV-1000 consortia)

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Background and Aims:
Infection with the hepatitis D virus (HDV) can lead to hepatitis delta, which is associated with a high risk of developing liver-related complications, including hepatic decompensation and hepatocellular carcinoma (HCC). The global epidemiology and disease severity of hepatitis delta is highly heterogeneous and disease presentation has changed over the last decades. There is limited knowledge on disease pathophysiology and hostvirus interactions explaining the large inter-individual variability in the course of the disease. We aim to screen a large multicentre cohort of well-defined HDV infected patients from different European countries to better understand not only the epidemiology but also to identify individual factors that determine the outcome of infection, thus providing the basis for an individualised treatment approach.

Method:
We report first findings from an observational, non-interventional, cross-sectional multicentre cohort with the aim of enrolling 1000 European HDV-infected patients from England, France, Italy, Germany, Romania and Sweden.
Patients with detectable anti-HDV for at least 6 months can be included. Retrospective data is obtained from databases and patient records for each patient's most recent visit that is eligible for inclusion (index visit). Available biosamples are used for virological and immunological analyses.

Results:
To date, 847 patients have been included (England 18 %, Italy 23 %, Germany 14 %, Romania 21 %, Sweden 24 %). The majority of patients is male (55 %) with a median age of 49 years (IQR 20 66). The top three countries of birth were Romania (27 %), Italy (11 %) and Mongolia (10 %). Two out of five patients were classified as having cirrhosis at the index visit (42 %, 351 / 840), of whom 8 % (56 / 708) and 17 % (120 / 691) presented with ascites or esophageal varices while only few patients had signs of hepatic encephalopathy (2 %, 14 / 717). A history of previous hepatic decompensation was documented in 13 % (104 / 822) of patients. HCC was reported for only 53 patients (6 %) at the index visit. 57 % of patients (480 / 847) received antiviral treatment at the index visit, of whom only 5 % were receiving IFN-based treatment. Nucleos(t)ide analogues were used in 94 % (452 / 480) of treated patients and bulevirtide (BLV) in 22 % (104 / 480). The latter is likely to underestimate the number of patients actually treated with BLV, as patients included in other registries and/or clinical trials were excluded. Anti-HCV antibodies were present in 10 % of cases, while HCV RNA was not detected in any of the patients. HDV RNA was detected in 53 % of patients, respectively.

Conclusion:
This study has the potential to elucidate HDV epidemiology, disease burden and cascades of HDV care in a large multicentre cohort. Data collection is still ongoing and the results from the final dataset will be presented at the conference.

CURRENT AND NEW ANTIVIRAL TREATMENTS

P23 Bulevirtide for patients with chronic hepatitis D (CHD) in Italy: a multicenter prospective nationwide real-life study (D-SHIELD)

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Background:
Bulevirtide (BLV) is the only approved drug for patients with chronic hepatitis delta (CHD) in EU. In Italy this drug has been available since May 2023, but no studies so far have addressed the demographic, virological and clinical features of patients treated with BLV as well as they response to treatment.

Methods:
Consecutive HDV patients with chronic hepatitis Delta (CHD) starting BLV 2 mg/day as monotherapy or in combination with pegIFNα were included in a multicenter real-life Italian study (D-SHIELD). Patients' characteristics before and during BLV treatment were collected. Virological, biochemical, clinical features were assessed.

Results:
315 patients with CHD from 27 centers were enrolled in this ongoing study. 99% received BLV 2 mg/day monotherapy: median age 54 (28 -82) years, 56% men, 96% of European origin, 78% with cirrhosis, 7% HIV-coinfected. Among patients with cirrhosis, 29% had varices, 9% had a history of HCC (active in 67%), 8% had a history of ascites (50% persistent), 3% with previous varices hemorrhage, 6% had decompensated (CPT-B) cirrhosis. At BLV start, median ALT were 75 (16 -1,074) U/L, liver stiffness measurement (LSM) 13.3 (3.6-68.1) kPa, platelets 118 (14-377) 103/mm3, 97% patients were on NUC therapy, 90% HBeAg negative. Median HDV RNA was 5.3 (1.5-8.2) log IU/mL and HBsAg 3.7 (0.6-4.7) log IU/mL. As of June 2024, 126 patients have reached week 32 of treatment. ALT and HDV RNA levels significantly declined: ALT from 75 (16-1,074) at baseline to 37 (11-173) at week 24 and 36 (12-213) U/L at week 32 and HDV RNA from 5.3 (1.5-8.2) to 3.3 (0.3-7.0) and 2.7 (0.2-7.2) Log IU/mL, respectively ($p<0.0001$). Virological, biochemical and combined response were achieved by 46%, 64% and 34% of patients at week 24 of treatment, respectively. At week 32, these responses were achieved by 63%, 63% and 42% of patients, respectively. Among patients not achieving a virological response, 58% and 50% achieved a partial virological response (HDV RNA decline >1 but <2 Log IU/mL, compared to baseline) at week 24 and 32, respectively. Moreover, 13% and 20% of patients achieved HDV RNA undetectable at week 24 and 32, respectively.

Conclusions:
D-SHIELD is the largest single country study on BLV treatment for CHD in Europe. Almost all Italian patients started BLV as monotherapy. Virological, biochemical and combined response rates at week 32 compare favorably with previous small retrospective studies.

CURRENT AND NEW ANTIVIRAL TREATMENTS

P24 Virological and clinical outcomes of patients with HDV-related cirrhosis treated with bulevirtide monotherapy for up to 96 weeks: a multicenter european study (SAVE-D)

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Background and Aims:
Bulevirtide (BLV) 2 mg/day is EMA approved for treatment of compensated chronic hepatitis due to Delta virus (HDV) infection, however real-life data in large cohorts of patients with cirrhosis are lacking.

Methods:
Consecutive HDV-infected patients with cirrhosis starting BLV 2 mg/day since September 2019 were included in a European retrospective multicenter real-life study (SAVE-D). Patient characteristics before and during BLV treatment were collected. Virological, biochemical, combined responses, adverse events and liver-related events (HCC, decompensation, liver transplant) were assessed.

Results:
244 patients with HDV-related cirrhosis receiving BLV monotherapy for a median of 92 (IQR 71-96) weeks were included: at BLV start, median (IQR) age was 49 (40 -58) years, 61% men, ALT 80 (55-130) U/L, liver stiffness measurement (LSM) 18.3 (13.0-26.3) kPa, platelets 94 (67 -145) x 103/mm3, 54% with esophageal varices, 95% Child Pugh score A, 10% HIV-coinfected, 92% on NUC, median HDV RNA 5.4 (4.1-6.5) Log10 IU/mL, HBsAg 3.8 (3.4-4.1) Log10 IU/mL. At weeks (W)48 and 96, virological, biochemical and combined responses were observed in 65% and 79%, 61% and 64%, 44% and 54% of patients, respectively. AST, GGT, albumin, IgG and LSM values significantly improved throughout treatment. Serum bile acid levels increased in most patients, only 10% patients reported mild and transient pruritus, independently of bile acid levels. The W96 cumulative risk of de-novo HCC and decompensation was 3.0% (95% CI 2-6%) and 2.8% (95% CI 1 -5%), respectively. Thirteen (5%) patients underwent liver transplantation (n=11 for HCC, n=2 for decompensation).

Conclusion:
BLV 2 mg/day monotherapy up to 96 weeks was safe and effective in patients with HDV-related cirrhosis. Virological and clinical responses increased over time. Liver-related complications were few.

CURRENT AND NEW ANTIVIRAL TREATMENTS

P25 Bulevirtide monotherapy prevents liver decompensation in patients with HDV-related cirrhosis: a case control study with propensity score weighted analysis

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Background and Aim:
Bulevirtide (BLV) monotherapy yields high rates of virological and biochemical response in hepatitis Delta (HDV) cirrhotic patients, however clinical benefits on hard outcomes remain unknown.

Methods:
Patients with HDV-related cirrhosis treated with BLV monotherapy in a retrospective multicenter European study (SAVE-D) were compared with untreated HDV cirrhotic patients enrolled in a previous cohort study (Romeo, Gastroenterology 2009). Liver-related events (LRE: HCC, decompensation) and overall mortality were compared by inverse probability treatment weighting (IPTW) analysis.

Results:
The BLV-treated cohort included 176 patients: at BLV start, median age was 49 (39-59) years, 59% men, ALT 77 (53-127) U/L, albumin 4.0 (3.7-4.4) g/dL, 100% CPT score A, 55% with varices. The untreated cohort included 140 patients: at study entry, median age was 40 (34-49) years, 78% men, ALT 102 (57-176) U/L, albumin 3.9 (3.6-4.3) g/dL, 100% CPT score A, 46% with varices. Overall, the 2-year cumulative probabilities of LRE were 7.3% (95% CI 3-13%) in the BLV-treated cohort vs. 15.6% (95% CI 9 -22%) in untreated patients (p=0.02): 3.7% vs. 6.6% for de-novo HCC (p=0.34) and 3.6% vs. 9.1% for decompensation (p=0.06), respectively. By IPTW analysis adjusted for confounding baseline factors and competing mortality risks, the BLV-treated cohort had a significantly decreased risk of all-type liver-related events (HR 0.38; 95% CI 0.23-0.62, p<0.0001) and decompensation (HR 0.32; 95% CI 0.16-0.63, p=0.001) compared to untreated patients. Conversely, the HCC risk was similar (HR 0.50; 95% CI 0.24-1.06, p=0.07).

Conclusions:
Compared to an untreated matched control group, a 2-year course of BLV monotherapy significantly reduced the risk of decompensation but not of HCC in HDV patients with compensated cirrhosis.

CURRENT AND NEW ANTIVIRAL TREATMENTS

P26 Continued Treatment of Early Virologic Non-responders or Partial Responders With Bulevirtide Monotherapy for Chronic Hepatitis Delta Leads to Improvement in Virologic and Biochemical Responses. Results From an Integrated Analysis at Week 96

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Bulevirtide (BLV), a novel hepatitis delta virus (HDV) entry inhibitor, is approved in Europe for the treatment of chronic hepatitis delta (CHD). In clinical studies, virologic response (VR) was defined as undetectable HDV RNA or ≥2 log10 IU/mL decline from baseline (BL). The optimal BLV monotherapy duration for CHD is unknown; whether continued therapy will benefit patients with early virologic nonresponse (NR) or partial response (PR) is also unclear. This integrated analysis evaluated continued BLV monotherapy in patients without VR after week (W) 24.

Results from patients who completed BLV monotherapy for 96W in the Phase 3 (MYR301; NCT03852719) and Phase 2 (MYR204; NCT03852433) studies were included. NR and PR were defined as HDV RNA declines of <1 log10 IU/mL and ≥1 but <2 log10 IU/mL, respectively. Rates of biochemical response (alanine aminotransferase [ALT] within normal limits [WNL]) were compared.

A total of 141 patients with CHD were evaluated (BLV 2 mg, n = 47; BLV 10 mg, n = 94). At BL, 67% were male, 87% were White, 43% had cirrhosis, 40% received concomitant nucleos(t)ide analogue therapy, and 50% had prior interferon exposure. Mean (standard deviation [SD]) HDV RNA was 5.2 (1.3) log10 IU/mL; median (quartile [Q]1, Q3) ALT was 94 (64, 136) U/L.

At W24, 92/141 (65%) patients had VR (53 [58%] with ALT WNL), 34/141 (24%) had PR (19 [56%] with ALT WNL), and 15/141 (11%) had NR (2 [13%] with ALT WNL) (Table).

There were 49 patients with NR or PR at W24. Of the 34 PR patients at W24, 25 (74%) had VR and 24 (71%) had ALT WNL by W96. Of the 15 NR patients at W24, 7 (47%) had VR and 3 (20%) had PR by W96. A higher proportion of patients with NR at W24 achieved VR at W96 among those receiving BLV 10 mg (4/5, 80%) vs BLV 2 mg (3/10, 30%).

Among patients with NR or PR at W24, mean BL HDV RNA did not predict VR at W96. Median (Q1, Q3) BL ALT (U/L) was higher in patients with NR (138 [112, 196]) vs VR (79 [53, 113]) and PR (95 [56, 150]) at W96. The mean (SD) HDV RNA change at W96 among VR/PR/NR was −3.6 (1.1), −1.4 (0.3), and −0.2 (0.7) log10 IU/mL for VR, PR, and NR at W96. Median (Q1, Q3) ALT change at W96 among VR/PR/NR was −48 (−73, −12), −42 (−83, −6), and −67 (−102, −33) U/L, respectively. Among all NR at W96, ALT declined >50% from BL in 7/11 (3/11 achieved ALT WNL).

Of 49 patients without VR at W24, the majority with PR and nearly half with NR were able to achieve VR at W96. ALT improved in all VR groups, including patients with NR. These results provide evidence for continuing BLV therapy despite early (W24) suboptimal VR.

CURRENT AND NEW ANTIVIRAL TREATMENTS

P27 Efficacy and Safety of 144 Weeks of Bulevirtide 2 mg or 10 mg Monotherapy From the Ongoing Phase 3 Study MYR301

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Bulevirtide (BLV) is a first-in-class entry inhibitor approved in Europe for the treatment of chronic hepatitis delta (CHD).

In a Phase 3 study over 96 weeks (W), BLV 2 mg or 10 mg monotherapy was effective and safe. Here, we present W144 results.

In this analysis, 150 patients with CHD were randomised: arm A (delayed treatment): observed for 48W followed by BLV 10 mg/d for 96W (n = 51); arm B: BLV 2 mg/d for 144W (n = 49); arm C: BLV 10 mg/d for 144W (n = 50). All patients were followed for 96W posttreatment. W144 efficacy endpoints included virologic response (VR; undetectable hepatitis delta virus (HDV) RNA or ≥2 log10 IU/mL decline from baseline [BL]), alanine aminotransferase (ALT) normalisation, combined response (CR; VR and ALT normalisation), and undetectable HDV RNA (target not detected). Univariate logistic regression was used to discern if any BL characteristics predicted undetectable HDV RNA at W144 for patients in Arms B/C who completed W144 and had BL HDV RNA ≥250 IU/mL. Predictors with a P <.05 were considered significant.

BL characteristics were previously published. At W144, 96% (49/51), 91.8% (45/49), and 88% (44/50) in arms A, B, and C remained in study. Arms B and C had similar rates of CR, VR, and ALT normalisation; rates increased through W96 and were maintained through W144. At W144, 57%, 73%, 59% (arm B) and 54%, 76%, 60% (arm C) of patients achieved CR, VR, and ALT normalisation. Undetectable HDV RNA rates continually increased with BLV treatment and were 29% in arm B and 50% in arm C at W144. Time to first reaching undetectable HDV RNA (mean [SD] wk) was faster in arm C (69.3 [41.2]) vs arm B (77.3 [44.5]). BL predictors of W144 undetectable HDV RNA were lower HDV RNA (BLV 2 mg: odds ratio (OR) 2.9, P = 0.0145; BLV 10 mg: OR 2.1, P = 0.0258) and lower hepatitis B surface antigen (HBsAg) levels (BLV 2 mg: OR 5.1, P = 0.0319; BLV 10 mg: OR 6.0, P = 0.0390). W144 HBsAg (mean [SD] change from BL, log10 IU/mL) was −0.36 (0.596) and −0.19 (0.39) with BLV 2 mg and BLV 10 mg. At W144 in arm A (96W of BLV), rates of CR, VR, ALT normalisation, and undetectable HDV RNA were 56%, 92%, 58%, and 52%.

There was no progression to liver-related outcomes over 144W except for 1 case of mild ascites in arm A (patient with BL cirrhosis). Platelet count and liver chemistries remained stable and/or improved including in patients with cirrhosis.
Through 144W of BLV therapy, there were no drug discontinuations, serious adverse events, or deaths attributed to BLV; the safety profiles were similar for BLV 2-mg and 10-mg doses. Dose-dependent increases in bile acids remained asymptomatic.

Long-term therapy with BLV therapy over 144W remains safe and effective. Improvements in biochemical, fibrosis, and virologic markers, including increased rates of undetectable HDV RNA, as well as low occurrence of liver-related events support the potential clinical benefits of long-term BLV therapy.

CURRENT AND NEW ANTIVIRAL TREATMENTS

P28 Forty-Eight-Week Off-Therapy Efficacy and Safety of Bulevirtide in Combination With Pegylated Interferon Alfa-2a in Patients With Chronic Hepatitis Delta: Final Results From the Phase 2b, Open-Label, Randomised, Multicentre Study MYR204

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Bulevirtide (BLV) is an entry inhibitor approved in Europe for the treatment of chronic hepatitis delta (CHD). This Phase 2b study (MYR204; NCT03852433) evaluated the safety and efficacy of BLV (2 mg and 10 mg) with or without pegylated interferon alfa-2a (PegIFN) in patients with compensated CHD. Here we present the results at 48 weeks (W) post–end of treatment (EOT).

Patients with CHD (N = 174) were randomised (1:2:2:2) and stratified based on the absence or presence of compensated cirrhosis to receive (A) PegIFN for 48W; (B) BLV 2 mg + PegIFN then 48W of BLV 2 mg monotherapy; (C) BLV 10 mg + PegIFN for 48W then 48W with BLV 10 mg monotherapy; or (D) BLV 10 mg for 96W. All patients were followed for up to 48W post–EOT (FU-48). The primary endpoint was the proportion who achieved undetectable HDV RNA (< lower limit of quantification [LLOQ] with target not detected; LLOQ = 50 IU/mL, limit of detection = 6 IU/mL) at W24 post-EOT (FU-24) with a predefined comparison between arms C and D. The composite response wa defined as undetectable HDV RNA and alanine aminotransferase (ALT) normalisation; other endpoints included ALT normalisation, change in liver stiffness (LS) by transient elastography, and hepatitis B surface antigen (HBsAg) loss.

Baseline characteristics were similar between arms: mean (standard deviation [SD]) age of 41 (8.7) years, 71% male, and 87% White. Overall, 34% had compensated cirrhosis with mean (SD) LS of 13.1 (7.7) kPa, HDV RNA of 5.3 (1.2 log10 IU/mL, and ALT of 114 (94.8) U/L; 48% were on nucleos(t)ide analogue therapy; and 48% were interferon experienced. At FU-24, undetectable HDV RNA was achieved in 17% (4/24) of arm A, 32% (16/50) of arm B, 46% (23/50) of arm C, and 12% (6/50) of arm D (arm C vs D, P = 0.0003; arm C vs A, P = 0.0197; arm B vs D, P = 0.0283).

By FU-48, undetectable HDV RNA was achieved in 25% (6/24) of arm A, 26% (13/50) of arm B, 46% (23/50) of arm C, and 12% (6/50) of arm D (arm C vs D, P = 0.0003). At FU-48, ALT normalisation and the composite endpoint were achieved by 42% and 25% in arm A, 38% and 22% in arm B, 46% and 40% in arm C, and 22% and 8% in arm D (arm C vs D, P <0.05), respectively. At FU-48 in the BLV-treated arms, least-square mean LS was improved compared with baseline (arm A, −0.3; arm B, −2.4; arm C, −2.5; arm D, −0.8). HBsAg loss at FU-48 was only observed in BLV treatment arms (arm A, 0%; arm B, 10% [5/50]; arm C, 4% [2/50]; arm D, 2% [1/50]). Overall, BLV was well tolerated: 1 patient discontinued BLV due to an adverse event related to BLV, and 3 patients experienced BLV-related serious adverse events post-EOT.

Combination therapy with BLV 10 mg and PegIFN resulted in the highest rates of undetectable HDV RNA at EOT and FU-24, which was sustained through FU-48, providing a viable finite treatment option for patients with compensated CHD.

CURRENT AND NEW ANTIVIRAL TREATMENTS

P29 Treatment of chronic hepatitis D with bulevirtide: 1st year report

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Introduction:
In July 2020, the EMA conditionally approved bulevirtide (BLV) for the treatment of adult patients with compensated chronic hepatitis D (CHD); this means that further evidence on efficacy and safety of BLV is awaited. The most frequently reported adverse reactions with this therapy in registering trials were itching due to increased bile ducts (very common), headache (very common), and injection site reactions (common). From May 2023, we started treating our patients with BLV.

Aim:
To report our experience on the use of BLV in real practice, at 1 year.

Materials and Methods:
Data were extracted from the cohort of patients attending the hepatology clinic of MED1 at AOU Maggiore della Carità of Novara. In the last 10 years, 20 patients have been identified as positive for both HBsAg and anti-HDV. Only 3 patients were found to be candidates for therapy with BLV (Table 1). All patients received a standard dose of BLV and underwent preliminary, ongoing, and 1-year testing after starting BLV.

Results:
Of the three patients, two were native Italians, and one was from Eastern Europe. All three patients underwent centralized serum HDV-RNA assessment (RoboGene® v2) and HDV genotyping (direct sequencing). The only genotype found was HDV-1. Table 2 shows data before and after 1 year of therapy. All patients adhered to the therapy regularly. Regarding side effects, no patient developed itching or headache. Two patients developed skin reactions at the injection site (Figure 1). One did not require any intervention and experienced spontaneous resolution, while the other required chronic antihistamine therapy to control symptoms. Notably, the latter patient was already being treated with monoclonal antibodies (mepolizumab) due to a history of hyper-eosinophilic asthma. All patients showed an improvement in transaminases, and two had a significant reduction in viremia. Except for one patient, all showed improvement in both liver stiffness and APRI.

Conclusions:
BLV treatment was safe and well-tolerated. Adherence to therapy in the patient without virological response is under investigation.

CURRENT AND NEW ANTIVIRAL TREATMENTS

P30 Bulevirtide monotherapy in patients with compensated cirrhosis and CSPH: a 96-week interim kinetic analysis of real-life setting

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Background:
Bulevirtide (BLV) was recently approved for treatment of hepatitis D in Europe. We aim to characterize HDV, HBsAg and ALT kinetics under BLV monotherapy in patients with compensated cirrhosis and clinically significant portal hypertension (CSPH).

Methods:
Thirty-eight patients with HDV-related compensated cirrhosis and CSPH were treated with BLV 2 mg/day monotherapy. All patients received TDF or ETV for HBV. Blood samples were collected at treatment initiation, weeks 4, 8, 16, 24, 32, 40, 48 and every 12 weeks thereafter. Fifteen (39%) patients did not reach 96 weeks of therapy: 3 had liver transplantation (week 48, 60, or 72), 1 stopped treatment (week 48), and 11 are still ongoing (range: week 60 -84). HDV RNA was measured using Robogene 2.0 (lower limit of detection, LLD= 6 IU/mL). ALT normalization was defined as 41 U/L and 59 U/L for women and men, respectively.

Results:
Mean baseline HDV RNA, HBsAg and ALT levels were 4.89 ± 1.23 log IU/mL, 3.55 ± 0.67 log IU/mL, and 114.4 ± 76.5 U/L respectively. Five (13%) patients were non-responders (<1.6 log IU/ml decline from baseline throughout treatment). All responders (n=33) experienced an initial rapid viral decline (0.19 ± 0.12 log/wk) followed by: (i) flat partial response with viral plateau (FPR) (n=19, Fig.1a), (ii) FPR and breakthrough (B) (n=3, Fig.1b), (iii) FPR and viral decline (n=3, Fig.1c), (iv) second slower phase, biphasic (BP) (n=2, Fig.1e), (v) BP + B (n=4, Fig.1d), or (vi) transient increase, TP (n=2, Fig.1f). ALT normalization was achieved in 28 (76%) patients at 7.9 ± 6.5 weeks (Fig.1). HBsAg remained at pre-treatment levels (Fig.1).

Conclusion:
Interim analysis finds that 22 patients (67% of responders) reached a low viral plateau (3.2 ± 1.1 log IU/mL below baseline) that lasted 56.4 ± 11.2 weeks (i.e., FPR in Fig.1 a, b & c), of whom 3 patients had a further decline (Fig.1c).Thus far, 7 (18%) of responders had viral breakthrough (Fig.1 b & e), 2 patients had a sustained 2nd decline phase (Fig.1d), and only 3 patients (8%) achieved sustainable HDV RNA TND (≥24 weeks) at the end of week 96 (Fig.1 c & f).

CURRENT AND NEW ANTIVIRAL TREATMENTS

P31 Improvement in Liver Histology Is Observed in Most Patients With Chronic Hepatitis Delta After 48 Weeks of Bulevirtide Monotherapy

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Bulevirtide (BLV) 2 mg/d is approved in the European Union for treatment of chronic hepatitis delta (CHD) with compensated liver disease. In the Phase 3 MYR301 study (NCT03852719), BLV 2 or 10 mg resulted in a virologic response (VR) in 76% to 82%, normalisation of alanine aminotransferase (ALT) in 63% to 64%, and a combined response (ALT normalisation + virologic response) in 55% to 56% of patients after 96 weeks (W).

This analysis evaluated the correlation of biochemical, virologic, and histologic parameters in patients with CHD treated with BLV monotherapy for 48W. Data up to 48W from patients with paired (baseline [BL] and 48W) liver biopsies in the ongoing MYR301 study were included. At 48W, there were 3 study arms: BLV 2 mg, BLV 10 mg, and a delayed-treatment arm with no anti–hepatitis delta virus (HDV) therapy (control). Virologic response groups were defined as follows: VR = HDV RNA decline of ≥2 log10 IU/mL from BL or undetectable HDV RNA; partial response (PR) = HDV RNA decline of ≥1 but <2 log10 IU/mL from BL; nonresponse (NR) = HDV RNA decline of <1 log10 IU/mL from BL. Histologic analysis included the following parameters: histologic activity index (HAI; 0–18), HAI category (0–4), and Ishak fibrosis score (IFS; 0–6). Improvement at 48W was defined as ≥1-point change from BL. Histologic improvement was defined as ≥2-point change in HAI with no worsening of IFS. ALT normalisation was defined at Russian sites as ≤31 U/L for females and ≤41 U/L for males and at all other sites as ≤34 U/L for females and ≤49 U/L for males. Overall, 83 patients were included: 56 treated with BLV (45 VR, 6 PR, and 5 NR) and 27 control. Greater median changes in ALT levels from BL were observed among BLV-treated patients vs the control group at 48W. Similar median changes in ALT levels were observed across virologic response groups among patients treated with BLV.

Decreases in ALT levels and HAI were observed in most patients treated with BLV. The degree of improvement in HAI and ALT levels did not correlate. There was no consistent pattern of HAI or ALT level change in the control group.

Among VR, PR, NR, and control patients, HAI improved in 80%, 100%, 40%, and 56%, and IFS improved in 58%, 33%, 25%, and 30%, respectively. HAI improvement was seen in 31 of 39 patients (79%) with ≥50% decline in ALT and in 13 of 17 patients (76%) with <50% ALT decline. Improvements in HAI category and histology were more frequent among patients with VR and PR.

Improvement in liver histology was observed in most patients after 48W of BLV treatment. Decreases in ALT levels and/or HAI were observed in most patients treated with BLV. The degrees of improvement in HAI and ALT levels did not correlate. Histologic and HAI or HAI category improvements occurred more frequently among patients with VR or PR. Improvement in fibrosis occurred most frequently in patients with VR. No consistent pattern of HAI, ALT level, or fibrosis change was observed in the control group

CURRENT AND NEW ANTIVIRAL TREATMENTS

P32 Rapid reductions of HDV RNA and ALT with the monoclonal antibody, BJT-778: results from a phase 2 study

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Background and Aims:
BJT-778 is a fully human anti-HBsAg monoclonal antibody that exhibits potent antiviral activity against HBV and HDV in vitro. BJT-778 is currently being evaluated in a Phase 1/2 study, BJT-778-001, for the treatment of chronic hepatitis B and chronic hepatitis D (CHD). We report the preliminary safety and efficacy results from the phase 2 portion of the study, where BJT-778 administered subcutaneously (SC) for a duration of up to 48 weeks in subjects with CHD.

Methods:
Approximately 10 subjects per arm were to be enrolled into: Arm 1: BJT-778 300 mg SC once weekly (QW); Arm 2: BJT-778 600 mg SC QW for 12 weeks followed by Q2W; and Arm 3: BJT-778 900 mg SC Q2W for 4 weeks followed by Q4W. Primary end points are safety and tolerability. Efficacy end points include absolute reductions and changes from baseline in HDV RNA and ALT levels, and the proportion of subjects achieving (i) virologic response defined as ≥2 log10 HDV RNA IU/ml reduction from baseline or below the limit of detection (BLD), (ii) ALT normalization (defined as ≤ULN in subjects with >ULN at baseline), and (iii) composite response (defined as virologic response and ALT normalization). Eligible patients have quantifiable HDV RNA, HBsAg levels of ≥10 IU/ml and HBV DNA <100 IU/ml on nucleos(t)ides. Arm 1 limited enrolment to non-cirrhotic patients, whereas Arms 2 and 3 included patients with compensated cirrhosis.

Results:
10 subjects were enrolled into Arm 1 and 11 subjects into Arm 2. Recruitment for Arm 3 is ongoing. All subjects in Arm 1 have completed 16 weeks of treatment, with the data presented here.

Baseline characteristics:
Median (range) age of 41 years (31 to 47), ALT of 54 U/L (19 to 117), HDV RNA of 5.3 (2.9 to 7.1) log10 IU/ml, and HBsAg of 4.2 (3.8 to 4.9) log10 IU/ml. Six were men and all were Caucasian. In Arm 1, by Week 28, 100% of the subjects achieved a virologic response, with 60% (6 out of 10) falling below the limit of quantification (BLQ, <10 IU/mL). Additionally, 67% (6/9) achieved ALT level normalization and composite response. One subject had a normal ALT at baseline, which remains normal. The mean reduction in HDV RNA at Week 24 was 3.6 logs (IU/mL). Across all treatment arms, BJT-778 at doses up to 900 mg have been well tolerated, with no reported serious or Grade 3/4 adverse events, and no treatment discontinuations in any of the arms. Available data from all arms will be presented.

Conclusion:
Monotherapy with BJT-778 was safe and well-tolerated and achieved rapid virologic responses with ALT normalization in most subjects with CHD.

CURRENT AND NEW ANTIVIRAL TREATMENTS

P33 Treatment of chronic hepatitis delta with bulevirtide in Portugal: data from a real-life cohort

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Background and Aims:
Hepatitis delta virus (HDV) infection is considered the most severe form of viral hepatitis. Treatment with bulevirtide (BLV) for adult patients with chronic hepatitis delta (CHD) and compensated liver disease became available in Portugal in 2022, through an early access program. Patients were eligible for treatment if they presented at least advanced fibrosis, and either previous exposure or a contraindication to interferon (IFN).

Methods:
We performed a multicentric observational study of patients who started BLV treatment for CHD between January 2022 and January 2024. All patients were treated with BLV monotherapy 2 mg SC per day. Follow-up visits were scheduled at the physician's discretion, usually every 8-12 weeks, and HDV RNA was determined locally. We collected epidemiological, clinical and virological variables at baseline and during follow-up. Virological response (VR) was defined as undetectable HDV RNA or ≥ 2 log10 decline from baseline, biochemical response (BR) as ALT < 40 IU/L, and complete response (CR) as VR and BR.

Results:
We included 14 patients (age at BLV start 40 ± 10 years; 57% female) from 7 centres, with a median followup on-treatment of 59 weeks. Most patients were immigrants from Africa (50%, most from Guinea-Bissau) or Eastern Europe (21%), while 29% originated from Portugal. Genotype (GT) was available in 7/14 patients (GT5: 5; GT1: 2).
Most patients were HBeAg-negative (79%). All but one were on nucleos(t)ide analogs for HBV. Co-infection with HIV was present in 36% patients. Median liver stiffness was 17.3 kPa and 71% patients (n=10) were cirrhotic (Child-Pugh A): 3 with varices and 1 with previous ascites. One patient had hepatocellular carcinoma (HCC) treated with chemoembolization. Half of the patients had previous exposure and 64% had a current contraindication to IFN.
Treatment was discontinued in 4 patients, due to adverse events (n=2; macopapular rash: 1; nausea and malaise: 1), loss of follow-up (n=1), and non-compliance (n=1). HDV RNA assays were non-standardized in 5 patients and 1 had only qualitative RNA positivity at baseline.
BR at w24, w48 and w72 were 50.0% (4/8), 71,4% (5/7) and 83.3% (5/6). VR and CR at w24, w48 and w72 were 42.9% (3/7), 42.9% (3/7) and 66.7% (4/6), and 28.6% (2/7), 28.6% (2/7), 66.7% (4/6), respectively.
The patient with previous ascites developed recurring septic arthritis and recurrent ascites, resulting in death from sepsis at w69.
The patient with HCC started atezolizumab-bevacizumab due to tumour progression and eventually died at w72 from a ruptured gastric varix.

Conclusion:
In this real-life experience with BLV in Portugal, both biochemical and virological responses increased over time, with virological response lagging behind biochemical response. Heterogenous HDV RNA assays, lacking standardization in some centers, may have hindered this assessment. Adherence to treatment is an issue that needs to be addressed in the future.

CURRENT AND NEW ANTIVIRAL TREATMENTS

P34 Detection and characterization of anti-preS1 antibodies in HDV-infected patients under Bulevirtide treatment

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Bulevirtide (BLV) has recently been approved in Europe for treatment of patients chronically infected with HDV. BLV is a viral entry inhibitor that binds with high affinity to the sodium taurocholate co-transporting polypeptide (NTCP), the cell receptor for HBV and HDV. BLV is a synthetic, myristoylated peptide specific of the N-terminal preS1 sequence of the HBV large envelope protein. Since HDV virions use preS1 as a receptor binding domain (RBD), the binding of BLV to NTCP blocks the virion entry pathway.

In this study funded by ANRS MIE, we sought to establish the anti-preS1 antibody status of 21 BLV-treated patients who were included in the BuleDelta observatory cohort (ANRS HD EPO1). Anti-preS1 antibody levels were measured using an in-house peptide-based ELISA. A total of 160 plasma samples were tested, including a sample at baseline for each patient, and samples covering both the treatment and post treatment periods for up to 168 weeks.

Our hypothesis was that BLV-induced anti-preS1 antibodies could play an ambivalent role in patients, either by binding to HDV virions and thus increasing the antiviral effect of BLV or, by binding to BLV itself, hence reducing the antiviral effect. The effectiveness of the treatment would eventually depend on the ratio of anti-preS1/BLV concentrations, and the levels of anti-preS1 antibodies could serve as marker for compliance to medication.

The results of our longitudinal analysis show that:
i) For most patients, anti-preS1 antibodies were detected early after daily injection of BLV (18 mean fold-increase at week 12), reaching a peak at week-48, followed by a decline that initiated during or after treatment;
ii) Both IgM and IgG antibodies were detected during the on- and off-treatment periods, with variable IgMs/IgGs ratios. High levels of both IgMs and IgGs were maintained during and post treatment for some patients, whereas in others, IgMs, or IgGs were pre-dominant.
iii) The mapping of the anti-preS1 specific epitopes showed that most BLV-induced antibodies were directed to, or near, the preS1 RBD.

Our results show that daily injection of BLV can elicit the production of anti-preS1 antibodies that have virusneutralization potential. This will be tested in an in vitro infection assay.

CURRENT AND NEW ANTIVIRAL TREATMENTS

P35 Treatment of HDV infection in Solid Organ Transplant with Bulevirtide: a case report

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Background:
HDV infection poses a significant challenge in solid organ transplant recipients due to its aggressive nature and limited therapeutic options. Bulevirtide, a novel antiviral agent, approved by the European Medicines Agency in 2020 for the treatment of HDV infection, has limited data on its use in solid organ transplant recipients.
In this report, we present what is to our knowledge the first case of a kidney transplant patient with HBV-HDV coinfection receiving treatment with entecavir and bulevirtide over a six-month management and observation period.

Case Presentation:
A 42-year-old male kidney transplant patient with HBV-HDV co-infection underwent a kidney transplant in September 2023. He was in treatment with entecavir 1 mg/day, due to prior lamivudine experience, and he had never been treated for HDV.
In January 2024, the patient began therapy with bulevirtide 2 mg/day administered via subcutaneous injection.
The clinical-laboratory controls consisted of a thorough clinical examination and comprehensive blood tests, evaluating the following parameters: hematological indices, coagulation profile, liver function and cytolysis tests, metabolic markers and serum levels of immunosuppressants (Tacrolemia and Everolemia). (see Table 1)
We underline the rapid virological and biochemical response observed in our patient just two months after initiating bulevirtide therapy. Achieving both negative serum HDV-RNA levels and normalization of transaminases within such a short timeframe reveals a profound antiviral effect of bulevirtide in our patient. (see Table 1)

With respect to tolerability, it is noteworthy that the stabilization of bile acid levels over the six-month treatment period, without causing itching, aligns with existing literature on the effects of bulevirtide therapy.
Moreover, the preservation of renal function despite bulevirtide therapy is also a significant finding, especially considering the patient's status as a kidney transplant recipient with baseline mild altered renal function.
Six months after the start of antiviral therapy with bulevirtide, the patient did not present any particular adverse reactions, but reported increased tenderness at the injection site over time. Additionally, starting from the fourth month of therapy, he experienced mild but tolerable asthenia, which did not deter him from continuing the treatment. This mild symptomatology was not associated with laboratory changes. The patient reported no other symptoms or adverse reactions during the six months of antiviral therapy.
As of now, the patient is still continuing his current therapy with bulevirtide.

Conclusions:
This case underscores the importance of individualized treatment approaches and highlights the potential efficacy of bulevirtide in solid organ transplant recipients with HDV infection. Further research is warranted to better understand management factors in this patient population.

CURRENT AND NEW ANTIVIRAL TREATMENTS

P36 Patient-Reported Outcomes Among Patients With Chronic Hepatitis Delta Treated With Bulevirtide 2 mg: A Long-Term Analysis of the Phase 3 MYR301 Trial at 96 Weeks

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Patients with chronic hepatitis delta (CHD) are at substantial risk of developing liver-related complications, including cirrhosis, hepatic decompensation, hepatocellular carcinoma, a need for liver transplant, and death.[1,2] Compared to a control group, bulevirtide (BLV) improved health-related quality of life among patients with CHD at both 24 and 48 weeks (W).[2,3] This study explored Hepatitis Quality of Life Questionnaire (HQLQ) outcomes in patients with CHD following 96W of treatment with BLV in the ongoing MYR301 trial.

MYR301 (NCT03852719) is a Phase 3, randomised, multicentre, open-label, parallel-group clinical trial, in which 150 patients with CHD were enrolled. Patients were randomised (1:1:1) to receive 1 of 3 treatments: BLV 2 mg (n = 49) for 144W, BLV 10 mg (n = 50) for 144W, or delayed treatment (n = 51) for 48W followed by BLV 10 mg for 96W. Patients completed the HQLQ, comprising the 36-Item Short Form Health Survey questionnaire and 4 hepatitis-specific (HS) health domain scores (15 supplemental items), independently at baseline (BL), 24W, 48W, and 96W. Higher scores on the HQLQ (range 0–100) indicated better health-related quality of life. The data were analysed using a mixedmodel repeated-measures method to estimate the least squares mean change from BL at different time points for the BLV 2 mg group, which is the dose approved for use in Europe.

Demographic characteristics were similar at BL across groups. Less than 10% of patients dropped out of the BLV 2 mg group by 96W. Compared to their BL scores, patients who received BLV 2 mg exhibited statistically significant improvements in all HQLQ domains at 96W. The least squares mean score improvements from BL were ≥5 points in all domains except the physical functioning and physical component summary domains (Figure). Substantial improvements (>10 points) were observed in the HS health domains—HS limitations and HS health distress. The HQLQ improvements observed at 24W and 48W with BLV 2 mg were sustained at 96W, emphasising its enduring efficacy as a monotherapy.

Patients with CHD treated with BLV 2 mg for 96W demonstrated improvements across all domains of the HQLQ, particularly in 2 HS health domains, which were sustained or enhanced from 24W and 48W of treatment, demonstrating the long-term benefits of BLV 2 mg monotherapy.

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CURRENT AND NEW ANTIVIRAL TREATMENTS

P37 Real life experience of HBV/HDV-related compensated cirrhosis treatment in an Italian prison. A case report.

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Background and Aim:
HDV infection affects approximately 12 million to 72 million people worldwide and is associated with more rapid progression to cirrhosis and liver failure and higher rates of hepatocellular carcinoma than infection with HBV alone. Bulevirtide is the first entry inhibitor with specific antiviral activity in subjects infected with both HBV and HDV. The objective of this study was to analyse the efficacy of Bulevertide and its safety in a difficult-to-treat condition such as a prison regime.

Case report:
We presented a case of a 59-year-old Caucasian male restricted in an Italian prison in Terni, Umbria, HBV infected under tenofovir disoproxil fumarate (TDF; 245mg once per day orally)therapy with HBV-DNA consistently undetectable (<10 IU/mL). At the end of 2022 during blood test routine test we found an impaired liver function: alanine aminotransferase (ALT)64 UI/l and aspartate transaminase (AST)62 UI/l. Autimmune test was negative. Virus Delta positive.HDV RNA 4 log IU/ml. In may 2023 2 mg subcutaneous bulevirtide once per day with TDF was approved by EMA for HBV/HDV-related compensated cirrhosis. Clinical evaluation,liver function test,alphafetoprotein and bile acid levels at baseline and after months 1,2,3,4,5 and 6 of treatment. HDV-RNA, HBV-DNA, hepatitis B surface antigen (HBsAg) quantification at the baseline and after month 4 and 6 of treatment. Liver and spleen stiffness assessment using Fibroscan©(Echosens, France). Magnetic resonance imaging(MRI) with contrast enhancemnet after 6 month of therapy to excluded hepatocellular carcinoma(HCC). Esophagogastroduodenoscopy (EGDS) to exlcuded esophageal varices. A combined response was defined as undetectable HDV RNA or ≥2 log IU/mL decline at week 24 versus baseline and ALT normalization.After six month a virological response was observed.HDV-RNA 2 log IU/mL decline.

ALT decline was evident at month 2; while platelet count was unchanged. Serum bile acid increases >2 versus baseline during treatment was indirect confirmation of treatment adherence. In the meantime INR value decline and alphafetoprotein negative. HBV-DNA remained undetectable (<10 IU/mL) at baseline and at all time points. At 6 month liver stiffness unchanged. At MRI no sign of HCC. No portal hypertension. No esophageal varices. No missing doses were recorded. Patient no reported systemic itching,liver decompensation,major complications or drug-related serious adverse events. No reaction at the injection site. No substantial changes in Child–Pugh class or Model for End-stage Liver Disease(MELD)-Na score were observed during bulevirtide treatment.

Conclusions:
Our data show the efficacy of subcutaneous bulevirtide monotherapy 2mg/day in reducing HDV-RNA and no changes in Child-Pugh class and MELD score. Adherence and treatment retention are important issues in long-term pharmacotherapy. Prison regime seems to be a place to insure adherence to bulevirtide 2 mg/day monotherapy administration because there is no self-administration but due to nurse staff.

CURRENT AND NEW ANTIVIRAL TREATMENTS

P38 Undetectable HDV RNA at 24 Weeks of Treatment With Bulevirtide and Pegylated Interferon Alfa-2a Combination Therapy Is an Important Predictor of Maintained Response Off-Therapy

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Chronic hepatitis delta (CHD) is the most severe form of viral hepatitis. Bulevirtide (BLV) 2 mg/d is approved for treatment of compensated CHD in the European Union. Suppression of hepatitis delta virus (HDV) RNA is associated with lower risk of disease progression. The MYR204 Phase 2b study (NCT03852433) assessed BLV with or without pegylated interferon alfa-2a (Peg-IFNα). Combination treatment showed higher virologic response rates posttreatment compared with either monotherapy at 24 weeks after the end of treatment (EOT).

This subanalysis used a logistic regression model to identify baseline (BL) characteristics or on-treatment clinical characteristics that predict EOT or posttreatment responses with combination treatment of BLV (2 or 10 mg) + Peg- IFNα. Additional analysis of early on-treatment viral kinetics was performed on a subset of patients who achieved undetectable HDV RNA at EOT. Composite response was defined as undetectable HDV RNA and alanine aminotransferase normalisation.

BL disease characteristics were well balanced across BLV doses. Both the 2- and 10-mg BLV doses with Peg-IFNα showed similar trends in off-treatment HDV RNA undetectability and composite response. Among patients with undetectable HDV RNA at EOT, the proportion of patients with viral relapse did not change between follow-up at week 24 (FU-24) and at week 48 (FU-48) after EOT. At EOT, potential BL predictors of undetectable HDV RNA were the absence of cirrhosis, HDV RNA levels that were less than the median and less than quartile (Q) 3, and lower liver stiffness. Similar trends were observed for the composite endpoint. At FU-24, potential BL predictors of undetectable HDV RNA were HDV RNA levels that were less than the median and less than Q3, lower hepatitis B surface antigen levels, no previous IFN therapy, and lower liver stiffness. Previous IFN therapy was not a predictor of composite response at FU-24. At FU-48, potential predictors of nonrelapse among patients with undetectable HDV RNA at EOT were BL HDV RNA levels that were less than the median and shorter time to onset and longer duration of HDV RNA undetectability on treatment. Notably, 23 of 25 patients with undetectable HDV RNA at week 24 on treatment did not relapse by FU-48.

Among patients with CHD treated with BLV (2 or 10 mg) + Peg-IFNα, key potential predictors of undetectable HDV RNA and of the composite endpoint at EOT and in the posttreatment period included lower BL HDV RNA levels and lower BL liver stiffness. Among a subset of patients who achieved undetectable HDV RNA at EOT, key on-treatment predictors of nonrelapse in the posttreatment period were earlier onset of undetectability and longer duration of undetectable HDV RNA status. Early undetectable HDV RNA at week 24 on treatment is an important predictor of nonrelapse in the posttreatment period.

CURRENT AND NEW ANTIVIRAL TREATMENTS

P39 Undetectable HDV RNA Defined as Target Not Detected at the End of Treatment With Bulevirtide and/or Pegylated Interferon Alpha-2a Is an Important Predictor of 48 Weeks Sustained Virologic Response in Chronic Hepatitis Delta

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Chronic hepatitis delta (CHD) infection is the most severe form of viral hepatitis. Bulevirtide (BLV) 2 mg/d is approved for treatment of compensated CHD in Europe. Virologic suppression of hepatitis delta virus (HDV) RNA, defined as below the lower limit of quantification (<LLOQ), is associated with lower risk of disease progression. Improved HDV RNA detection technologies have a more stringent definition of "undetectable HDV RNA": patients who achieve <LLOQ and target not detected (TND). The clinical relevance of TND vs <LLOQ (target detected [TD]) for HDV RNA levels is unknown.

The MYR204 Phase 2b study (NCT03852433) evaluated BLV with or without pegylated interferon alpha-2a (Peg-IFNα) in patients with compensated CHD. This subanalysis sought to establish the clinical relevance of undetectable HDV RNA, defined as <LLOQ with TND, for the following treatment regimens: Peg-IFNα, BLV 2 mg + Peg-IFNα, BLV 10 mg + Peg-IFNα, and BLV 10 mg. The primary endpoint was the proportion of patients who achieved undetectable HDV RNA at 24 weeks after end of treatment (EOT). Response categories at EOT and follow-up at weeks 24 and 48 after EOT (FU-24 and FU-48) included undetectable HDV RNA (<LLOQ, TND), low-positive viraemia (<LLOQ, TD), and HDV RNA ≥LLOQ.

Baseline disease characteristics were well balanced between treatment regimens. The highest rate of undetectable HDV RNA after EOT was observed in patients treated with BLV 10 mg + Peg-IFNα. The proportions of patients who achieved HDV RNA <LLOQ status remained similar between FU-24 and FU-48. The highest rate of HDV RNA <LLOQ after EOT was observed with BLV 10 mg + Peg-IFNα. Among patients with TND at EOT, 60% maintained undetectability at FU-48, while 73% of those with low-positive viraemia at EOT rebounded to HDV RNA ≥LLOQ.
Among patients with low-positive viraemia (<LLOQ, TD) at EOT, 24 of 33 (73%) experienced viral rebound by FU-48.
Only 2 of 33 (6%) patients with low-positive viraemia at EOT achieved undetectable status at FU-48 following BLV + Peg-IFNα treatment. Among patients with low-positive viraemia at EOT, nearly half, 15 of 33 (45%), had received BLV 10 mg monotherapy. At FU-48, 13 of these 15 patients (87%) experienced viral rebound. The other 2 patients maintained low-positive viraemia at FU-48.
The majority of patients with undetectable HDV RNA at EOT, 44 of 73 (60%), maintained undetectable status at FU-48; 33 of these 44 patients (75%) were treated with the combination of BLV + Peg-IFNα. Moreover, 4 of the 73 patients (5%) had low-positive viraemia at FU-48. Among patients with undetectable HDV RNA (<LLOQ, TND) at EOT, 21 of 73 (29%) experienced viral rebound by FU-48.

Among patients with compensated CHD receiving finite therapy, achieving on-treatment undetectable HDV RNA with TND is an important predictor of maintaining off-treatment response. Most patients with low-positive viraemia (HDV RNA <LLOQ, TD) at EOT had viral rebound in the posttreatment period.

CURRENT AND NEW ANTIVIRAL TREATMENTS

P40 High Rates of Adherence to Bulevirtide Monotherapy for Chronic Hepatitis Delta Through 96 Weeks: Results From an Interim Analysis of the Phase 3 Study MYR301

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Bulevirtide (BLV) 2 mg/d is approved in the European Union for treatment of chronic hepatitis delta (CHD) with compensated liver disease. In the open-label, randomised, Phase 3 study MYR301 (NCT03852719), BLV 2 or 10 mg/d was safe and effective through 96 weeks (W) based on the combined endpoint of virologic response (undetectable or a ≥2 log10 IU/mL decline in hepatitis delta virus [HDV] RNA from baseline) and biochemical response (alanine aminotransferase [ALT] normalisation).

This analysis describes patient adherence to, and efficacy and safety of, BLV monotherapy through 96W in MYR301.
Three cohorts were evaluated: a delayed-treatment arm not receiving anti-HDV therapy for 48W followed by BLV 10 mg for 96W and BLV 2 mg/d or BLV 10 mg/d for 144W. BLV 10 mg was self-administered as 2 subcutaneous (sc) injections of BLV 5 mg, while BLV 2 mg was given as a single injection. Data were included from all patients randomised to BLV 2 or 10 mg up to W96. Treatment adherence was assessed at each visit based on patient diaries and study drug accountability (ie, the number of dispensed vs returned vials [used and unused] of the study drug).

Adherence to BLV was computed as the ratio of the cumulative dose of BLV administered to the planned total dose at a particular time point. ALT upper limit of normal was defined at Russian sites as ≤31 U/L for females and ≤41 U/L for males and at all other sites as ≤34 U/L for females and ≤49 U/L for males.

In the BLV 2 and 10 mg groups, 47 of 49 (96%) and 47 of 50 (94%) patients completed 96W of treatment. Reasons for study discontinuation included withdrawal of consent (2 each from BLV 2- and 10-mg groups [n = 4]) and physician decision (BLV 10-mg group [n = 1]). Mean adherence rates exceeded 95% for BLV 2- and 10-mg groups at 24W and 48W and were higher in the BLV 2-mg group. At 96W, mean adherence rates were 98% and 95% for the BLV 2- and BLV 10-mg groups, respectively. The number of missed injections per patient was 4.4 in the BLV 2-mg group and 6.1 in the BLV 10-mg group. Among patients who completed 96W, mean adherence rates were >99% in both groups.

Combined response rates increased through 96W for BLV 2 and 10 mg. Treatment with BLV through 96W was associated with improvements in virologic and biochemical responses in most patients, with response rates increasing over time. BLV was safe and well tolerated; no serious adverse events were attributed to BLV or led to discontinuation. Injection-site reactions were mild to moderate in severity and occurred more frequently in the BLV 10-mg group vs the BLV 2-mg group.

High adherence rates were observed through 96W among patients with CHD self-administering BLV. Treatment with BLV monotherapy resulted in continued improvement in responses with maintained safety. Virologic and biochemical responses were observed in most patients after 96W of treatment with BLV monotherapy.

CURRENT AND NEW ANTIVIRAL TREATMENTS

P41 Improvements in Fibrosis and Necroinflammation With Bulevirtide Combined With Pegylated Interferon for Chronic Hepatitis Delta

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Background:
Hepatitis delta virus (HDV) is associated with the worst viral hepatitis prognosis with increased morbidity and mortality compared to monoinfection with hepatitis B. Bulevirtide is beneficial in normalizing liver function tests and decreasing HDV viral load; however, limited data exist on its effect on liver fibrosis and histological findings.

Methods:
In MYR204, a phase 2b open-label trial, patients were randomized to receive pegylated interferon alfa-2a alone for 48 weeks (Group A), bulevirtide 2 mg (Group B) or 10 mg (Group C) with pegylated interferon alfa-2a for 48 weeks followed by bulevirtide 2 or 10 mg alone for 48 weeks, or bulevirtide 10 mg alone for 96 weeks (Group D).
Patients who had paired biopsied available at baseline and Week 24 posttreatment were included in this subanalysis.
The changes in fibrosis were evaluated with Ishak fibrosis score (0–6), and METAVIR fibrosis score (F0–F4). The change in necroinflammation was assessed by the histological activity index (HAI; 0–18) and METAVIR activity grade.
Histological improvement was defined as decrease >2 points from baseline in HAI without worsening of Ishak fibrosis score at follow-up Week 24.

Results:
Fifty-eight of 174 patients (33%) had paired biopsy data available to assess liver fibrosis and changes in HAI (7 of 24 [29%] in Group A, 19 of 50 [38%] in Group B, 16 of 50 [32%] in Group C, and 16 of 50 [32%] in Group D [Table 1]). At baseline (n=58), mean age 42 years, 78% were males, 91% were White, 21% had compensated cirrhosis, 28% had previous interferon therapy, and 40% were on concomitant nucleos(t)ide analogue therapy. Mean HDV RNA and median ALT, HAI, and Ishak fibrosis score were 4.99 log10 IU/mL, 84 U/L, 9, and 3, respectively.
In the subset of participants with available data, the proportion who had improvements (decrease of >1 point from baseline) or no change in the fibrosis parameters (Ishak and METAVIR fibrosis scores) at follow-up Week 24 were 71% for Group A, ranged from 68% to 74% for Group B, 94% to 100% for Group C, and 81% for Group D across the 2 methods of scoring. In the same subset of participants with histological activity stage parameters (HAI and METAVIR activity grade, respectively), the proportion who had necroinflammation improvement (decrease of >1 point) or no change at follow-up Week 24 were 86% and 71% for Group A, 84% and 95% for Group B, 88% and 94% for Group C, and 94% and 100% for Group D.
The proportion of participants who had a histological improvement were numerically greatest in Group D, although the sample size was small (5 of 7 [71%] in Group A, 10 of 19 [53%] in Group B, 9 of 16 [56%] in Group C, and 12 of 16 [75%] in Group D.

Conclusions:
Treatment of chronic HDV infection with bulevirtide and pegylated interferon alfa-2a was associated with improvements in fibrosis and histologic activity at Week 24 posttreatment.

VIROLOGY AND PATHOGENESIS

P42 HIV-HBV-HDV co-infection. Case presentation.

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Introduction:
HIV infection is a global health problem. In Romania in December 2023, there were 18282 people living with HIV out of a cumulative total of 27897 people registered since 2015. Unfortunately, we do not have statistics on HIV-HBV-HDV co-infected patients in our country so far. However, our medical practice recommends testing HBsAg positive patients for HIV and HDV. Both HIV and hepatitis viruses give the patient a special profile from a psychological and medical point of view.

Case presentation:
We would like to present the case of a 34 years old male, diagnosed in 2023 in his home town with HIV immunological stage C3 and liver cirrhosis with B and D. The patient received antiretroviral therapy (Dolutegravir/Lamivudine) with virological response but without immunological improvement. He is referred to our clinic for further investigation and identification of therapeutic solutions.

Results:
The patient presented casectic, pale, with alopecia areas on the scalp, vulgar warts on the upper limbs, giant genital condylomatosis, inguinal and axillary adenopathies. From a virological viewpoint the HIV-RNA and HBV-DNA were undetectable, HDV-RNA= 6 log IU/ml. Immunologically the CD4+ cell count=18cells/mm3.
Established diagnoses were AIDS, liver cirrhosis with HBV and HDV (Child-Pugh B), portal hypertension with esophageal varices stage II Dogradi, hypersplenism with severe thrombocytopenia. Inguinal lymph node biopsy revealed metastases of moderately differentiated squamous cell carcinoma.

Discussion:
Immunological mechanisms in HIV infection are today increasingly well understood: destruction of lymphoid tissue architecture, action on LyT CD4+, LyB hyper-reactivity, behavior on Mo-Ma as an important factor for viral reservoir formation, Ag-presenting cells. Regarding HDV infection, both the pathophysiology of infection and the interaction between virus and host are being understood. In our patient's case, at this moment, the difficulty is related to the management of HDV infection. The patient receives antiretroviral therapy according to current guidelines, receives oncological support for carcinoma. We remain vulnerable in terms of antiviral control for HDV.

Conclusions:
HBsAg positive patients should be tested for HDV and HIV. Early diagnosis could offer a therapeutic opportunity for patients with HIV-HBV-HDV coinfection.
An estimate of the number of patients with HIV-HBV-HDV co-infection in Romania is not established.
Understanding the immunological impact and the HIV-HBV-HDV viral interaction is of interest for physicians treating such patients given the severity of the co-infection Therapeutic solutions at this time for our patient do not confer control of all diagnoses.

VIROLOGY AND PATHOGENESIS

P43 Differential patterns of HBV rna and HBcrAG levels in a large european cross-sectional study of untreated patients with chronic hepatitis delta

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Background and Aim:
Serum HBV RNA and HBcrAg levels have been proposed as useful biomarkers in the management of HBV patients, however their role in HDV infected patients is currently unknown.

Methods:
Consecutive untreated CHD patients were enrolled in a cross-sectional study in three EU centers. Clinical and virological characteristics were collected. Serum HBV RNA and HBcrAg levels were quantified by an automated realtime investigational assay (Cobas® 6800, Roche Diagnostics, Pleasanton, Ca, USA) and by LUMIPULSE® G HBcrAg assay (Fujirebio Europe), respectively. In a subset of patients, intrahepatic analyses were performed.

Results:
Overall, 240 HDV patients were enrolled: median age 46 years, 62% males, 53% cirrhotics, 57% NUC-treated, median ALT 70 U/L, HBsAg 3.8 log10 IU/mL, 88% HBeAg-negative, median HDV RNA 4.9 log10 IU/mL. HBV RNA tested positive (>10 cp/mL) in only 8% of the patients [median 40 (13-82,000) cp/mL], whereas HBcrAg was ≥3 log10 U/mL in 77% [median 4.2 (3.0-8.0) log10 U/mL]. By combining these biomarkers, 3 categories were identified: 23% double negative, 9% double positive and 68% negative for HBV RNA but positive for HBcrAg. HBV RNA levels were associated with male sex and detectable HBV DNA, while HBcrAg positivity correlated with higher HBsAg levels. Double positive patients were younger, non-European, with higher ALT and HDV RNA levels and detectable HBV DNA. Intrahepatic HDV RNA and HBV RNA were positive in most samples, while intrahepatic levels of cccDNA were low.

Conclusions:
In untreated CHD patients, HBV RNA and HBcrAg show a divergent pattern: most patients had undetectable HBV RNA but quantifiable HBcrAg in the absence of HBeAg. Additional studies aimed to unravel the molecular mechanisms underlying these findings are warranted.

VIROLOGY AND PATHOGENESIS

P44 HELZ2 is an interferon stimulated gene with antiviral properties against Hepatitis Delta Virus

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Patients chronically co-infected by Hepatitis B Virus (HBV) and Hepatitis D Virus (HDV) suffer from the most aggressive form of viral hepatitis leading to severe liver disease such as cirrhosis, hepatocellular carcinoma and liver decompensation. Treatments options are very limited with only two drugs used in clinic (IFN-α and Bulevertide) that rarely allow viral clearance. The molecular mechanisms leading to inhibition of HDV by IFN-α (in patients but also in vitro) are not known and mechanisms behind treatment failures in patients also remain elusive. Here we aimed at the identification of interferon stimulated genes (ISGs) that can specifically inhibit intracellular HDV replication.

Whereas IFN-α was known to have antiviral effect on both HBV and HDV in co-infected PHH and dHepaRG, we found that IFN-α was only able to inhibit HDV (but not HBV) in co-infected dHuH7.5-NTCP cells. We hypothesized that ISGs responsible for the antiviral effect of HDV should be upregulated in both dHepaRG and dHuH7.5-NTCP cells upon treatment with IFN-α. To identify these ISGs, dHuh7.5-NTCP and dHepaRG cells were stimulated with IFN-α for 8h and 150 genes were found to be significantly commonly upregulated in both cell lines after RNA sequencing analyses.
After an extensive review of the literature, we focused on candidate ISGs known to interfere with host/viral RNA metabolism and confirmed their upregulation in both cell lines through kinetics analyses upon interferon stimulation.

We next screened 14 candidate ISGs for their antiviral efficacy against HDV by gain of function assays using HDV replicating cells. We identified 4 ISGs with a strong antiviral effect on HDV by this approach. Among them, we confirmed the antiviral efficacy of HELZ2 in various in vitro models including HDV-infected primary human hepatocytes. Over-expression of several HELZ2 mutants indicated that neither the helicase or 3'-5' exoribonuclease activities of HELZ2 are involved in its antiviral activity against HDV. However, preliminary results from RNA-protein immunoprecipitation suggest that HELZ2 interacts with the HDV ribonucleoprotein and may thereby exert its antiviral activity.

The identification of HELZ2 protein as an IFN-α antiviral effector may provide a new target to develop improved antiviral strategies for HDV/HBV co-infected patients.

VIROLOGY AND PATHOGENESIS

P45 Hospitalised Adults With Hepatitis Delta Virus Infection Have Higher Risk of Disease Progression Than Those With Hepatitis B Virus Monoinfection in Italy

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Hepatitis delta virus (HDV) infection carries a greater risk of morbidity and mortality compared with hepatitis B virus monoinfection (HBV only). This retrospective study compared rates of disease progression between patients with HDV infection vs HBV only among hospitalised adults in Italy.

In Italy, data from healthcare resources and services reimbursed by the National Health System are maintained in administrative databases from local health units covering approximately 12 million patients. From these data, adult patients aged 18 years or older with at least 1 documented HDV or HBV hospital discharge diagnosis code (using ICD -9-CM) between 1 Jan 2009 and 30 Jun 2022 were screened. Patients with an HDV or HBV only diagnosis between 1 Jan 2010 and 30 Jun 2021 (identification period), no previous diagnosis, and at least 12 months of continuous enrolment before and after diagnosis were identified, with their first diagnosis defined as their index date. Propensity scores were generated for patients with HDV infection and HBV only based on baseline demographics and clinical characteristics assessed 12 months prior to the index date. Inverse probability of treatment weighting, based on propensity scores, was used to adjust for measured confounders between patients with HDV and patients with HBV only. Cox proportional hazard regression was performed to compare the risk of disease progression from noncirrhotic disease (NCD), compensated cirrhosis (CC), decompensated cirrhosis (DCC), or hepatocellular carcinoma (HCC) to greater disease severity, liver transplantation (LT), or death between cohorts.

Among 15,628 hospitalised patients, 14,238 patients were screened for HDV infection or HBV only, and 9,945 were included (HDV cohort, n = 556; HBV only cohort, n = 9,389). The mean (SD) age was similar between cohorts (HDV, 56.5 [16.3]; HBV only, 56.7 [16.4]; P = 0.763), as was the male to female ratio (approximately 2:1). Patients with HDV infection were more likely to progress from NCD to CC (hazard ratio [HR], 1.45; 95% CI, 1.04–2.02; P = 0.027), CC to DCC (HR, 3.50; 95% CI, 1.56–7.84; P = 0.002), CC to LT (HR, 9.02; 95% CI, 2.11–38.50; P = 0.003), CC to death (HR, 1.70; 95% CI, 1.03–2.81; P = 0.040), DCC to HCC (HR, 2.80; 95% CI, 1.16–6.79; P = 0.022), DCC to LT (HR, 4.98; 95% CI, 2.11–11.74; P <0.001), and HCC to LT (HR, 6.86; 95% CI, 2.59–18.13; P <0.001) compared to patients with HBV only.

Across local health units in Italy, patients with HDV infection have a significantly increased risk of progressing to greater liver disease severity compared to patients with HBV only in the inpatient setting. These data emphasise the need for early screening, diagnosis, and treatment of HDV to slow future disease progression.

VIROLOGY AND PATHOGENESIS

P46 Baseline characteristics and risk of liver-related events in hepatitis B and C coinfection with and without hepatitis D infection

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Background:
The prevalence of coinfection with hepatitis B and C viruses (HBV, HCV) ranges from 1 – 15% globally, and is associated with an increased risk of liver-related events when compared to mono-infection with either virus.
Limited research is available describing the consequences of infection with hepatitis delta virus (HDV) among those with HBV/HCV coinfection. In this analysis we describe baseline characteristics and risk of liver-related events in individuals with HBV/HCV infection with and without HDV.

Methods:
A retrospective cohort study was conducted using HealthVerity Marketplace data from October 2015 to March 2024 that includes medical and pharmacy claims and electronic health records for more than 100 million patient lives in the US. Those included were 18+ years at cohort entry with one year of prior continuous insurance enrollment and at least one day of follow-up. HBV, HCV, and HDV were identified with one inpatient or two outpatient ICD10 codes at least 30 days apart. A propensity score (PS) model was constructed using baseline demographics, clinical characteristics, and treatment history, and was used to estimate hazard ratios (HRs) with 95% confidence intervals (CI) comparing risk of advanced liver disease events (compensated and decompensated cirrhosis (CC, DC), hepatocellular carcinoma (HCC), and liver transplant (LTx)) among individuals with HBV/HCV coinfection with and without HDV.

Results:
We identified 34,893 individuals with HBV/HCV coinfection with no evidence of HDV, and 1,994 with triple infection (HBV/HCV/HDV). The distributions of age and sex were similar (both cohorts were 60-65% male, mean age 52-55 years). At baseline, those with HDV had significantly ($p< 0.01$) more claims for severe liver disease (CC: 39.3 vs 27.6%; DC: 28.8 vs 20.5%; HCC: 8.5 vs 4.5%; and LTx: 4.8 vs 2.1%) and were more likely to have initiated treatment with hepatitis B nucleos(t)ide analogues (36.5 vs 18.3%). However, dispensing claims for HCV DAA treatment (21.5 vs. 21.8%) and available follow up time (~2.3 years) were similar across cohorts. Baseline evidence of mental health issues, smoking, and substance abuse was significantly higher in individuals without HDV ($p<0.01$) while alcohol use was at parity for the cohorts. After PS weighting and excluding individuals with advanced liver disease at baseline, no difference in the risk of CC (HR: 1.03, CI: 0.87 – 1.21) or any liver-related event (HR: 0.97 (0.84 – 1.11)) was observed. In addition, no difference was observed with vs without HDV in the risk of DC, HCC or LTx among those with CC at baseline: HR: 0.96, CI:(0.74 – 1.25).

Conclusion:
Among individuals with HBV/HCV coinfection, those with HDV infection had evidence of more advanced liver disease at baseline. Over approximately 2 years of follow-up, no increased risk of incident liver-related events associated with HDV infection was observed, highlighting the complex interplay of multiple viral hepatitis infections.

VIROLOGY AND PATHOGENESIS

P47 TIGIT-expression on natural killer cell subsets correlate with liver inflammation and bulevirtide treatment response in chronic hepatitis D

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In 2023, Bulevirtide therapy completed a Phase 3 trial for the treatment of CHD patients. The study demonstrated a favorable risk-benefit ratio with significantly decreased HDV RNA and serum Alanine Aminotransferase (ALT) levels at 48 weeks of treatment. However, some patients were not fully responding.

The effects on circulating immune cells during the therapy was not clear yet.

The role of natural killer (NK) cells in bulevirtide treated patients is unknown. NK cells are an essential component of the innate immune system and play an important role in viral hepatitis. In this study, we performed an in-depth investigation of NK cell immunotypes in a patient cohort treated with bulevirtide. We longitudinally analyzed clinical parameters and PBMCs from a cohort of 20 patients with CHD at the time point of baseline (BL), therapy week 3 (TW3), and therapy week 48 (TW48) by spectral flow cytometry followed by high dimensional data processing. A cohort of 9 chronic HCV-infected patients treated with direct-acting antivirals (DAA) was used as reference.

The results showed although overall NK cell frequencies remained stable in all patients over time, we identified characteristic NK cell immunotype subsets that were prominent in biochemical responders (BR).
TIGIT-expression increased during the course of bulevirtide treatment and correlated with ALT levels in BR. A high frequency of TIGIT- CD57+ CD56dim NK cells and TIGIT- CD56bright NK cells at BL and low levels during therapy were indicative of a biochemical response.

We show that bulevirtide treatment affects NK cell immunotypes, depending on the biological response.
Furthermore, we suggest that TIGIT-expression patterns on NK cell subsets may play a role as an early predictive surrogate marker in CHD patients under bulevirtide treatment.

VIROLOGY AND PATHOGENESIS

P48 Adenine Base editing of Hepatitis B surface antigen potently inhibits HDV

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Chronic hepatitis B (HBV) and hepatitis D (HDV) viruses infections represent an unmet medical need that calls for novel therapeutics. For its propagation, HDV exploits HBV envelope proteins (HBsAg) derived from both cccDNA and HBV integrated sequences, thus allowing HDV replication also in patients with very limited intrahepatic HBV reservoir.

Base editing (BE) introduces precise mutations in DNA in a guide RNA (gRNA)-dependent manner without causing DNA double-strand breaks. In previous work, we demonstrated that introducing mutations in HBV genes by cytosine and adenine base editors could inhibit HBV replication and exhibit sustained HBsAg reduction in different cell culture and in vivo models. In this study, we aimed to explore the potential of editing HBs to impact HDV.

First, we performed base editing to introduce missense mutations in HBs ORF within PLC/PRF/5 cells, where HBsAg is exclusively produced by naturally HBV integrated sequences. These cells were first transfected with the HDV encoding plasmid, pSVLD3, to initiate HDV replication. Subsequent treatment with adenine base editor (ABE) encoding mRNA and HBs-targeting gRNA (gRNAS1 or gRNA S2) resulted in marked reduction of both intra- and extra-cellular HBsAg levels and extracellular HDV RNA. Similar results were obtained when HDV replication was initiated after base editing of HBV genome.

To further validate the effect of ABE-derived HBs mutations, we employed plasmids expressing mutant HBs to mimic the base-edited HBs sequences. Expression analysis revealed a robust inhibition of both extracellular and intracellular HBsAg by western blot and ELISA assays. Additionally, co-transfecting Huh7 cells with pSVLD3 and HBs mutant plasmids led to a drastic reduction in extracellular HDV yield, resulting in a decreased HDV infectivity in primary human hepatocytes.

Altogether, our results suggest that targeting the HBs coding sequence by adenine base editing is a promising strategy to inhibit HDV release and spread.

VIROLOGY AND PATHOGENESIS

P50 Deciphering the cellular response to IFN treatment in HDV-infected cells

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Chronic Hepatitis D, caused by the co-infection of hepatocytes by hepatitis B and D viruses (HBV, HDV) is the most aggressive form of chronic viral hepatitis. So far, no treatment allows viral clearance in patients and improved therapeutic strategies are urgently needed. Current available antiviral therapies in Europe include the entry inhibitor bulevirtide and pegylated interferon alpha (PEG-IFNα), used as a standard treatment for decades.

However, the efficacy of PEG-IFNα is limited, and interestingly, HDV replication is only moderately affected by endogenous or exogenous IFNα both in vivo and in vitro. The interplay between HDV infection and the innate immune response is complex. It has notably been shown that the ability of type I IFN to trigger ISG expression is impaired in HDV-infected cells, both in vivo and in vitro. However, the molecular mechanisms of this inhibition are still unknown.

Here, we analysed the whole transcriptome of HDV-infected differentiated HepaRG (dHepaRG) cells stimulated by either IFNα (type I-IFN) or IL-29 (type III-IFN) by RNA sequencing.

We observed a strong reduction of ISG induction in HDVinfected
cells treated with IFNα compared to non-infected cells, confirming the previous reports. Moreover, we show that the refractoriness to IFNα treatment was not observed in cells expressing the HDAg alone as well as in HDV infected cells impeded for HDV-induced innate immune responses.

This firmly confirmed previous reports suggesting that the refractoriness to IFNα was due to the pre-activation of the innate immune response by HDV. Interestingly, the treatment of HDV-infected dHepaRG cells with the type III IFN IL-29 showed an additive induction of ISG. This suggests that the transduction of type III-IFN signaling is not affected by the cellular response to virus infection and questions the molecular mechanism leading to specific inhibition of type I-IFN signal transduction in infected cells. In this context, proof-of-concept assays show that USP18 overexpression during HDV infection induces a selective refractoriness to IFNα treatment, but not IL-29 treatment in HDV-infected cells.

Taken together, our data provide an exhaustive list of ISG that are modulated by type I and type III IFN treatment in the context of HDV infection. We demonstrated that the cellular refractoriness to IFNα treatment in HDV-infected cells is due to the pre-activation of the innate response by HDV, independent of the expression of viral proteins, and specific to type-I IFN pathway, suggesting the existence of independent pathways in the control of innate immune response.

Our results pave the way to a better understanding of the treatment response in HDV patients and to novel therapeutic strategies against HDV infection.

VIROLOGY AND PATHOGENESIS

P51 Epidemiology and natural history of chronic hepatitis B and D infections in France from 2013 to 2022

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Background:
Limited data are available regarding epidemiology and natural history of chronic viral hepatitis.
Understanding the epidemiology of HBV and HDV infections will enable evidence-based and cost-effective public health and clinical interventions within countries and at the global level.

Methodology:
The French National Health Data System (SNDS) is a unique claim database covering continuously around 99% of the French population, i.e. more than 67 million people. It contains sociodemographic and medical information on all inpatient and outpatient services reimbursed by the French National Health Insurance since 2008, including dates of medical or paramedical visits, drugs and medical devices dispensed, the realization (but not the results) of laboratory tests, imaging procedures and other complementary exams, long-term diseases (LTDs) status.
Two algorithms, previously validated on a historic French HBV and HDV cohort, were used to identify patients with chronic HBV (with or without HDV infection) and the subpopulation of patients with HDV, defining the high range (HR) HBV and HDV prevalence for our study. Both algorithms were adjusted excluding patients with potential challenging coding for HDV and without health consumption during the last two years, defining low range (LR) prevalence for our study.

Results:

HBV and HDV prevalent populations and patient characteristics:
In 2023, between 90,505 (LR) and 104,562 (HR) patients were identified as patients with prevalent chronic HBV infection. Among them, between 3,421 (LR) and 6,934 (HR) were chronically HBV/HDV coinfected patients (Table 1)

Natural history:
A higher proportion of outcomes in relation with disease evolution was observed during the follow-up among patients with HDV/HBV coinfection than among HBV mono-infected patients (Table 2).

Conclusion:
The preliminary data obtained at the French national level, inform for the importance of HBV and HDV infection and the high proportion of severe outcomes notably among patients co-infected with the two viruses. There is a need for increasing education and HDV screening among HBV population.

VIROLOGY AND PATHOGENESIS

P52 Healthcare Resource Utilisation and Costs Among Terminal, Hospitalised Adults With Hepatitis Delta Virus or Hepatitis B Virus Monoinfection in Italy

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Hepatitis delta virus (HDV) infection increases the risk of liver-related morbidity and mortality compared to hepatitis B virus monoinfection (HBV only). In this study, terminal healthcare resource utilisation (HCRU) and costs were compared between adults with HDV vs HBV only in the inpatient setting in Italy.

Administrative databases of local health units in Italy (>12 million individuals) were screened for adult patients with an inpatient claim (using ICD-9-CM) between 1/1/2009 and 30/6/2022. Included patients had an HDV or HBV only diagnosis between 1/1/2010 and 30/6/2021, no prior diagnosis, and ≥12 months of continuous capture before and after diagnosis. Baseline (BL) characteristics were assessed over the 12-month period before each patient's first diagnosis. Inverse probability of treatment weighting (IPTW) was calculated using a propensity score (probability of having HDV vs HBV only, given BL variables) to generate weights. In terminal patients, the all-cause and diseasespecific HCRU and costs were compared via Mann-Whitney U test in the 12- and 6-month periods before death; descriptive statistics were summarised.

Of all included terminal patients with HDV vs HBV only (before IPTW: HDV, n = 161; HBV only, n = 2,553; after IPTW: HDV, n = 2,891; HBV only, n = 2,717), there were minimal differences in the age or number of males between groups (before IPTW: standardised difference [STD] = 0.117 and 0.081, respectively; after IPTW: STD = 0.033 and 0.089). In the year before death, the all-cause inpatient length of stay (LOS; days, mean [95% CI]) for patients with HDV vs HBV only was 109.5 (105–114.1) and 111.7 (107.1–116.3; P = .624); disease-specific inpatient LOS for patients with HDV vs HBV only was 30 (27.5–32.4) and 31.1 (28.7–33.5; P = .174). In patients with HDV vs HBV only, all-cause mean total costs per patient (PP; €, 95% CI) were 45,819.9 (44,056.3–47,583.5) and 49,419.5 (47,192.0–51,647.1; P = .679); disease-specific total costs PP were 9,641.4 (8,977.9–10,304.8) and 10,137.3 (9,425.8–10,848.8; P = .500).
In the 6 months before death, the all-cause inpatient LOS (days, mean [95% CI]) for patients with HDV vs HBV only was 61.7 (59.4–64.0) and 65.6 (63.1–68.0; P = .569); disease-specific inpatient LOS for patients with HDV vs HBV only was 16.3 (15.0–17.5) and 19.6 (18.2–21.0; P = .380). In patients with HDV vs HBV only, all-cause mean total costs PP (€, 95% CI) were 30,340.9 (28,979.2–31,702.7) and 31,607.9 (30,208.4–33,007.4; P = .625); diseasespecific total costs PP were 7,082.1 (6,479.9–7,684.4) and 6,974.6 (6,419.9–7,529.3; P = .653) (Table).

In Italy, the HCRU, including LOS, and costs were similarly high in terminal patients with HDV vs HBV only. These results highlight the need for enhanced screening/treatment practices to offset the high economic and health-related burden associated with HDV and HBV; future research should evaluate the impact of novel treatments for HDV and HBV on HCRU and costs.

VIROLOGY AND PATHOGENESIS

P53 Rational immunotherapy design for clinical development against HDV using a synthetic DNA-prime and protein-boost strategy

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Background:
Long-term treatment with bulevirtude provides significant clinical benefit to patients with hepatitis D, but only rarely results in HDV cure even after several years of treatment. We have developed a new DNA prime/protein boost immunotherapy for chronic HDV infection that combines effective inhibition of HDV viral entry by inducing neutralizing antibodies with enhancement of the T-cell responses to both preS1 and the HDAg. Our original vaccine designs were based on plasmid DNA encoding multiple preS1 and HDAg sequences and a polypeptide incorporating the same sequences that was unsuited for large-scale manufacture.

Methods:
pDNA was manufactured in E. coli using standard methods, and a synthetic DNA containing the same sequence (doggy-bone DNA, dbDNA) was manufactured enzymatically (Touchlight, UK). Protein expression studies were performed in E. coli. Protein purity was assessed using standard chromatographic and electrophoretic methods and by reverse phase ultra-performance liquid chromatography combined with mass spectrometry. Immunogenicity studies were performed in C57BL/6 mice and analyzed by ELISA and ELISpot assays.

Results:
The protein polypeptide could only be expressed with yields of <1mg/L. Based on the crystal structure of HDAg, each of the four HDAg sequences were expressed separately as an HDAg-preS1 fusion protein from a single operon, resulting in expression at >2g/L. Immunoprecipitation and UPLC-MS analysis showed that the resulting 29kDa monomers are expressed intact and hetero-oligomerize into a single protein with an apparent molecular weight of >600kDa. To facilitate clinical development, we also evaluated the use of dbDNA as the priming component in the immunotherapy, since the enzymatic production is more cost-effective and quicker, and the use of dbDNA means that no selectable marker (antibiotic resistance gene) is needed. The new oligomeric protein was shown to be fully immunogenic as part of a prime-boost immunization with pDNA when adjuvanted with QS21. Subsequent comparison of the immunogenicity of dbDNA and pDNA, either alone or followed by boosting with adjuvanted oligomeric protein, showed that the dbDNA was fully comparable to bacterially fermented pDNA. The PreS1 antibody levels averaged from 104-105 after DNA prime and one or two protein booster doses irrespective of the DNA production method.
Interestingly, the PreS1-specific T cell responses were maintained at a high level using a 10-fold lower dose of dbDNA as compared to pDNA.

Conclusions:
This new immunotherapy for chronic HDV infections comprises one or more doses of synthetic DNA encoding PreS1 and HDAg, followed by one or more doses an adjuvanted oligomeric PreS1-HDAg fusion protein produced in E.coli. The two components of the vaccine are ready for manufacturing of lots for GLP safety studies and a Phase 1 clinical study.

VIROLOGY AND PATHOGENESIS

P54 Development of a rapid test for HDV-specific T cell characterization in whole blood

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Background and Aims:
The ability to cure HBV and HBV-HDV co-infection is linked with the presence of functional virus-specific T cells that directly recognize and lyse infected cells (CD8 T cells) and help the production of high-affinity antibodies (CD4 T cells). Yet, clinical management of patients with chronic HBV-HDV co-infection (CHB/HDV) relies exclusively on the assessment of virological and biochemical biomarkers. We aimed to develop a robust and simple assay to measure in parallel HBV and HDV-specific T cell frequency and function with efficient throughput and minimal invasiveness to allow integration of these immunological biomarkers in CHB/HDV clinical management.

Method:
We designed and synthesized 15-mers peptides covering the sequence of Small HDV Ag (SHDVAg) of Genotypes 1, 2 and 4 (109 peptides) and of the Large HDV Ag (LHDV Ag-covers the 19 AA C-terminal extension - 6 peptides). The 109 SHDVAg and the 6 LHDVAg peptides were pooled in two distinct peptide mixtures and used to stimulate whole blood (400 □l of whole blood for each peptide pool) of 17 HBV-HDV chronically co-infected patients and 12 healthy controls. In parallel, peptide pools covering the envelope, core, polymerase, and X proteins of different HBV genotypes were also used to stimulate whole blood and measure HBV-specific T cells. After overnight incubation, supernatants were collected and analyzed for the production of different cytokines (IFN-γ, IL-2, IL-10, Granzyme B, TNF- , IL-4).

Results:
HBV peptide pools stimulated the secretion of T cell cytokines (IFN-γ, IL-2, and Granzyme B) in the whole blood of HBV-HDV co-infected patients, while the SHDVAg peptide pool did not activate such secretion. Only the LHDVAg peptide pool stimulated the production of cytokines (mainly Granzyme B) in 3 out of the 17 HBV-HDV chronically co-infected patients.
The quantity and ratio of the different cytokines stimulated by HBV peptide pools in HBV-HDV co-infected patients reveal a high production of Granzyme B over IL-2 and IFN-γ. This cytokine secretion profile is different from what is detected in CHB patients.
SHDVAg and LHDVAg peptide pools stimulated cytokines (IFN-γ and IL-2) in 1 out of the 12 healthy controls.

Conclusion:
We demonstrated that we can assess the quantity and multi-functionality of HBV- and HDV-specific T cells with minimal invasiveness and without complex in-vitro manipulation in a small volume of whole blood (total 3.6 ml). The assay suggests that HBV-HDV coinfected patients possess mainly HBV-specific T cells even though we detected in a minority of patients T cells specific for the 19 AA C-terminal extension of Large HDV antigen. The preferential production of Granzyme B by HBV-specific T cells of HBV-HDV co-infected patients suggests that inflammatory events present in HBV-HDV co-infection might modulate their function

VIROLOGY AND PATHOGENESIS

P55 HDV persistence can be independent from the extent of HBV reservoir and can be sustained by HBsAg production mainly derived from HBV-DNA integration

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Background and Aim:
HDV exploits HBV surface glycoproteins (L-, M- and S-HBs) for viral morphogenesis and infectivity.
Here, we investigate HBV and HDV activities and their interplay in liver biopsies from patients (pts) with chronic HDV infection (CHD) and HBV mono-infection (CHB).

Methods:
70 HBeAg-negative pts (74% NUC treated) are included: 35 with CHD and 35 with CHB. Droplet digital PCR was used to quantify intrahepatic levels of cccDNA, pgRNA, HDV-RNA and HBs transcripts deriving from cccDNA and from integrated HBV-DNA (Grudda, 2022). Ad-hoc ELISA assays were used to quantify HBs isoforms.

Results:
Pts with CHD and CHB are comparable in terms of age and NUC-treatment duration. CHD has lower serum HBV-DNA than CHB (median [IQR]: 26 [14-58] vs 4,100 [225-76,515] IU/ml, P<0.0001). CHD is characterized by higher ALT and advanced fibrosis status (median [IQR] ALT: 72 [48-119] vs 27 [21-38] U/l, P<0.001; Fibrosis score>F5 in 53.1% vs 17.1%, P=0.002).
Median (IQR) serum HDV-RNA is 6.0 (4.0-6.9) logIU/ml, positively correlated with intrahepatic HDV-RNA (Rho=0.62, P=0.006; 787 [1-7,596] copies/1000cells).
CHD presents a more restricted HBV reservoir in terms of cccDNA and pgRNA (median [IQR]: 1 (0.02-12) vs 24 (8 -93) copies/1000cells and 8 [1-147] vs 518 [57-3,894] copies/1000cells, P<0.0001 for both comparisons).
Nevertheless, both CHD and CHB are characterized by a substantial production of HBs transcripts (median [IQR]: 6,041 [323-29,446] and 12,776 [4,570-55,977]), with >99% of them deriving from integrated HBV-DNA.
By stratifying CHD pts according to cccDNA size, lower levels of HBV intrahepatic markers are observed in those with a restricted HBV reservoir (median [IQR] pgRNA and cccDNA-derived transcripts: 1.4 [0.4-25] vs 89 [6-238], P=0.005 and 0.3 [0.1-0.9] vs 41 [7-179] copies/1000cells, P=0.002 in cccDNA<1 vs cccDNA>1 copy/1000cells). Conversely, no differences are observed for intrahepatic HDV-RNA levels (median [IQR]: 782 [1-5,559] vs 1,026 [40-6,984] copies/1000cells, P=0.5). Even more, among the 35 CHD pts, 8 showed undetectable cccDNA, cccDNA-derived HBs transcripts and serum HBV-DNA. Nevertheless, these patients are characterized by a considerable amount of intrahepatic and serum HDV-RNA (median [IQR]: 5,495 [976-14,946] copies/1000cells and 6.0 [4.8-6.9] log IU/ml, respectively), as well as by the production of HBs transcripts derived from integrated HBV-DNA (median [IQR]: 3 [1 -497] copies/1000 cells) and of all the three HBs isoforms (median [IQR] ng/ml: 1,116 [123-3,987] for S-HBs, 368 [8 -1,894] for M-HBs and 1.4 [5.9-7.3] for L-HBs).

Conclusions:
Pathways sustaining HDV persistence act independently from the extent of intrahepatic HBV reservoir and are fueled by an intense production of HBs transcripts, mainly derived from integrated HBV-DNA, capable to produce all three HBs isoforms. In this light, pharmacological strategies should take into account HBsAg production from integrated HBV-DNA for achieving HDV cure.

VIROLOGY AND PATHOGENESIS

P56 Low expression of circulating liver-enriched miRNAs in anti-HDAg patients in absence of active viral replication.

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Background and Aims:
Only a limited percentage of patients with hepatitis delta virus (HDV) infection can achieve spontaneous or treatment-related control of viral replication (undetectable viral RNA). Of note, the mechanism behind this virological control is still unclear. The microRNAs (miRNAs) are small RNAs that participate in several biological processes, including the host response to viral infections. The aim of this study was to analyze the miRNA profiles of HDV-infected patients to identify potential biomarkers that differentiate virological controllers from non-controllers.

Methods:
In the explorative cohort, a plasma sample from each of 30 included HDV-infected patients (anti-HDAg positive) were analyzed: 15 controllers (with at least two consecutive samples with undetectable HDV RNA) and 15 non-controllers (persistent detectable HDV RNA). The circulating miRNAs were isolated and analyzed by microarray (Affymetrix). The differentially expressed miRNAs were identified by adjusting a linear model with empirical Bayes moderation of the variance. The most differently expressed miRNAs were validated by absolute quantification through digital PCR (QIAcuity) in a validation cohort. This latest included 48 longitudinal plasma samples from 16 untreated anti-HDAg patients (3 samples per patient). In addition, 6 plasma samples from healthy donors were also analyzed.
Patients from the validation cohort were grouped based on their HDV RNA and ALT levels in three sub-groups: patients with undetectable HDV RNA (group A), patients with detectable HDV RNA and normal ALT (B) and chronic hepatitis delta (C). Of note, in group A the first sample included was before viremia undetectability.

Results:
Considering a differential expression > 1 log2FC (raw p-value <0.05) between controllers and non-controllers, we identified 6 differently expressed miRNAs. Among them, 3 liver-enriched miRNAs (absolute log2FC >1 and average expression >1.5) formed a pattern (miR-122-5p, miR-192-5p and miR-194-5p) and were down-regulated in HDV controllers related to non-controllers (p-value <0.05). When quantifying the miRNAs in the validation cohort, we observed that all of them were generally downregulated in the longitudinal samples from the group A, even when HDV RNA was still detectable. The number of copies of the miRNAs were similar or lower than the healthy donors, especially for miRNA-194-5p, whose concentration in group A was generally lower than C group (Bonferroni-adjusted p-value <0.05).

Conclusion:
Hepatitis D patients who can control HDV replication presented a different miRNA profile characterized by down-regulated miRNA, including three liver-enriched molecules that remained low during over time. The mechanism associated with miRNAs expression and their role in HDV replication needs further studies. Study supported by the projects PI20/01692 and PI23/01065, funded by Instituto de Salud Carlos III and co-funded by European Union (ERDF, "A way to make Europe").

VIROLOGY AND PATHOGENESIS

P57 Real world patient profile for individuals with hepatitis delta virus infection treated with bulevirtide 2mg in Europe

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Background and Objectives:
Bulevirtide (BLV), a sodium taurocholate co-transporting polypeptide entry inhibitor, is the only medication approved by the European Medicines Agency (EMA) for the treatment of chronic hepatitis delta (CHD). Limited real-world data are available describing the profile of patients treated with BLV. This narrative review aims to describe the patient profile among individuals with CHD treated with BLV 2mg from published studies reporting real world experience.

Methods:
A narrative review of profiles of individuals with CHD treated with BLV 2mg for up to 48 weeks in Europe was conducted. Included research reported on virologic and biochemical outcomes of 2mg on-label BLV treatment in real world use for individuals with CHD infection. Randomized controlled trial data, protocols, and reviews were excluded.

Results:
We identified six studies that reported real world use of BLV in cohorts from Italy (n=1), Germany (n=2), France (n=2), and Austria (n=1). Individuals in these studies had a mean age of 40-50 years and were more likely to be male (44-87%). Baseline cirrhosis was common, affecting more than 50% of study populations (range: 44-78%). In studies reporting HBeAg status (n=4), positivity occurred in less than 10% of patients. Country of origin and race/ethnicity varied by study cohort. In the Italian cohort and one German cohort, included individuals were primarily Caucasian, while the other four cohorts (a second study from Germany, two from France, and one from Austria) reported a population of diverse origins including Africa, Asia, Europe, and the Middle East.

Conclusion:
Characteristics of the individuals with CHD described in studies of real-world BLV 2mg use in Europe were as follows: mean age between 40 to 50, approximately 58% had evidence of cirrhosis at treatment initiation, fewer than 10% were HBeAg positive, and country of origin and race/ethnicity was heterogeneous though two cohorts were described as predominantly Caucasian. While country specific restrictions regarding access to BLV during the study periods of the described cohorts will have influenced the patient population, it remains critical to capture CHD patient profile data to understand the trend in patients receiving CHD treatment and to ensure that all patients in need are provided the opportunity for optimal CHD management.

VIROLOGY AND PATHOGENESIS

P58 High diversity of the TCR repertoire in hepatitis delta virus patients with undetectable viral RNA

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Background:
The hepatitis delta virus (HDV) causes a chronic infection and only a limited percentage of patients can achieve spontaneous or treatment-related control of HDV replication. The function of the T cells is regulated by the activation of the T-cell receptor (TCR), whose genetic diversity is essential for inducing the immune response. Given that the interrelation between HDV infection and the immune response is still unknown, we aimed to analyze the TCR repertoire diversity in HDV patients in relation to the HDV RNA state.

Method:
PBMCs were collected from 25 HDV (anti-HDAg positive) adult patients and their CD3+ T cells were positively selected. Eight of them presented undetectable HDV RNA. A group of 27 healthy donors was used as control group. T cells' DNA was isolated and the variable (TRBV), diversity (TRBD) and joining (TRBJ) gene rearrangements (forming the CDR3 sequence) of the beta chain of the TCR were studied using next-generation sequencing (Miseq, Illumina). The nucleotide diversity (such as the number of unique clonotypes or the D50) of the CDR3, and the TRBV and TRBJ usage frequency among the HDV patients, was also determined.

Results:
HDV-patients exhibited a lower nucleotide diversity of the CDR3 compared to the control group. When considering the HDV RNA state, patients with undetectable HDV RNA showed higher diversity than those with detectable HDV RNA, but still lower than healthy donors (p-value <0.05), showing an intermediate number of CDR3 unique clonotypes. The greater diversity in the HDV RNA-undetectable group compared to the detectable was also confirmed when considering the number of TRBV-TRBJ rearrangements (56 versus 25, p= 0.0003). Additionally, these patients also presented a higher usage frequency and lower usage frequency of respectively the TRBV28 and TRBJ2 -3 than the patients with active viral replication.

Conclusion:
HDV-patients presented a lower diversity of the TCR repertoire than healthy donors, thus suggesting a kind of enrichment in some clonotypes due to the infection. The diversity of the TCR repertoire of the patients with undetectable HDV RNA was closer, but not identical, to that of the healthy donors compared to the patients with active viral replication. A more complete immune profile and a larger cohort of patients are needed to confirm these results.
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VIROLOGY AND PATHOGENESIS

P59 Dichotomy between HBcrAg and pre-genomic HBV RNA in relation to HDV RNA response in patients with chronic hepatitis delta during bulevirtide treatment

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HBsAg mediates HBV attachment to the NTCP receptor and entry into hepatocytes and is critical to the propagation of hepatitis delta virus (HDV). HBsAg originates from both covalently closed circular DNA (cccDNA) and integrated HBV DNA. Hepatitis B core-related antigen (HBcrAg) and pre-genomic HBV RNA (pgRNA) reflect cccDNA transcriptional activity. Bulevirtide (BLV) mimics a pre-S1 HBsAg protein and blocks entry to hepatocytes. While HBsAg concentrations are not affected during BLV therapy, there is limited data comparing changes in HBcrAg and pgRNA during BLV therapy. We aimed to compare levels of HBV markers (HBV DNA, HBsAg, HBcrAg & pgRNA) during BLV therapy and assess their changes in relation to HDV RNA decline and/or ALT normalisation.

Methods:
Blood samples were collected from 14 HBV/HDV co-infected patients treated with BLV (all HDV RNA positive, median age 45 yrs, 8 males, 79% compensated cirrhosis). Plasma was collected at three time points (baseline, week 12 & 24), and the following HBV/HDV biomarkers were measured: HBV DNA (Roche assay, IU/ml), HBsAg (Abbott Architect® assay, IU/ml), HBcrAg (CLEIA, Fujirebio, log10 U/ml), pgRNA (Abbott Diagnostics dualtarget real-time-PCR assay, LLoQ= 0.49 log10 U/ml), & HDV RNA (Abbott Diagnostics research use only mRealTime assay, LLoQ =5 IU/ml). Up-to-date, 10 patients have completed 24 weeks of BLV therapy.

Results:
Baseline levels of HBcrAg, HBsAg, pgRNA, HDV RNA & ALT were not predictive of a sharp HDV RNA decline (>2 log10) or ALT normalisation at week 12 and/or 24. Baseline vs treatment week 12: 1 patient (10%) achieved HDV RNA decline >2 log10 vs 4 patients (40%) with partial response (1-2 log10) and 5 patients (50%) with a slow HDV RNA decline <1 log10; 4 (40%) patients had normal ALT. There was a marked reduction in ALT (-38 IU/L, p=0.02), HDV RNA (-1.1 log10 IU/ml, p<0.01) & HBcrAg (-0.8 log10 U/ml, p<0.01), but no significant change in HBsAg (9082 vs 9434 IU/ml, p=0.8) & HBV DNA (0 vs 0 IU/ml, p=1.0). In contrast, pgRNA markedly increased (0.57 log10 U/ml, p=0.03). Baseline vs treatment week 24: 4 (40%) patients achieved >2 log10 HDV RNA decline, 5 (50%) patients had HDV RNA decline 1-2 log10 and 1 (10%) patient with a slow decline <1 log10; 5 (50%) patients had normal ALT. There was a significant reduction in ALT (-46 IU/L, p<0.01), HDV RNA (-1.83 log10 IU/ml, p<0.01) and HBcrAg (-1.1 log10U/ml, p<0.01), but HBsAg (9082 vs. 9389 IU/ml, p=0.67), HBV DNA (0 vs 0 IU/ml, p=1) and pgRNA (1.5 vs 1.58 log10U/ml, p=0.58) levels were similar.

Conclusion:
In contrast to HBsAg & HBV DNA, HBcrAg levels mirrored changes in HDV RNA during BLV therapy.
PgRNA increased in the first 12 weeks of therapy followed by a gradual decline by week 24. The lower HBcrAg and initial pgRNA increase during BLV therapy are unexplained, but could mirror relative differences in expression of HBsAg from residual cccDNA vs integrated DNA, affecting HDV propagation, as BLV is not a HDV replication/assembly inhibitor.

VIROLOGY AND PATHOGENESIS

P60 Plasma pre-S1 HBsAg levels during antiviral therapy with Bulevirtide in chronic hepatitis delta patients – any help in predicting response to therapy?

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The HBV envelope comprises LHBS, MHBS and SHBS proteins. Large HBsAg mediates HBV attachment to the NTCP receptor and entry into hepatocytes and is critical to hepatitis delta virus (HDV) propagation .Pre-S1 LHBS protein originates from both covalently closed circular DNA (cccDNA) and integrated HBV DNA. Bulevirtide (BLV) mimics a pre-S1 HBsAg protein and blocks viral entry to hepatocytes. While HBsAg concentrations are not affected during antiviral therapy with BLV, there is limited data regarding changes in plasma levels of pre-S1 HBsAg protein during BLV therapy. We aimed to measure and compare levels of pre-S1 HBsAg during BLV therapy and assess their changes in relation to HDV RNA decline and/or ALT normalisation.

Methods:
Blood samples were collected from 10 HBV/HDV co-infected patients treated with BLV (all HDV RNA positive, median age 48 years, 6 males, 90% compensated cirrhosis). Plasma was collected at three time points (baseline, week 12 & 24), and the following biomarkers were measured: total HBsAg (Abbott Architect® assay, IU/ml), pre-S1 HBsAg (Abbkine ELISA, IU/ml] & HDV RNA (Abbott Diagnostics research use only mRealTime assay, LLoQ =5 IU/ml). The proportion of pre-S1 HBsAg [%] was determined using total HBsAg concentration.

Results:
Baseline levels of total HBsAg, pre-S1 HBsAg and HDV RNA were not predictive of a sharp HDV RNA decline (>2 log10) or ALT normalisation at week 12 and/or 24. Baseline vs treatment week 12: 1 patient (10%) achieved HDV RNA decline >2 log10 vs 4 patients (40%) with partial response (1-2 log10) and 5 patients (50%) with a slow HDV RNA decline <1 log10; 4 (40%) patients had normal ALT. There was no significant change in total HBsAg (9082 vs 9434 IU/ml, p=0.8), pre-S1 HBsAg levels (55.28 vs 55.16 IU/ml, p=0.5) and proportion of total HBsAg (1.72%
vs 1.67%, p=0.65). Baseline vs treatment week 24: 4 (40%) patients achieved >2 log10 HDV RNA decline, 5 (50%) patients had HDV RNA decline 1-2 log10 and 1 (10%) patient with a slow decline <1 log10; 5 (50%) patients had normal ALT. While total HBsAg levels were similar (9082 vs. 9389 IU/ml, p=0.67), there was a significant increase in median of pre-S1 HBsAg levels to 63 IU/ml (p=0.04). Plasma pre-S1 HBsAg levels were similar irrespective of type of response to BLV therapy.

Conclusion:
While concentrations of total HBsAg did not change significantly during therapy with bulevirtide, pre-S1 HBsAg levels increased in all patients between week 12 and 24 of therapy with BLV. The meaning of changes in pre-S1 HBsAg plasma during therapy is unexplained, but bulevirtide mimics a pre-S1 HBsAg protein and blocks viral entry to hepatocytes. Pre-S1 HBsAg expression in the liver was not tested in our study. It is not clear whether this reflects the existing state of viral interference between HBV and HDV or 'upstream' action of bulevirtide and more studies assessing the role of this serological biomarker during bulevirtide treatment would be beneficial.

VIROLOGY AND PATHOGENESIS

P61 HDV co-infection and HCV eradication in persons with HIV (PWH): data from the ICONA cohort

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Background and Aims:
Direct-acting antivirals (DAA) allow to achieve sustained virological response (SVR) for HCV also in people with HIV (PWH). Few data are available about the possible role of HBV±HDV co-infections on the outcome of liver disease in PWH who obtained DAA-induced HCV eradication. The aims of this study are: to evaluate mean changes in ALT after DAA, to evaluate ALT increase >5xULN as possible HBV re-activation after HCV eradication, and to evaluate time to ALT normalization, according to HBV and HDV co-infections in HIV/HCV individuals.

Method:
Study population: all HIV/HCV co-infected individuals with available HBV/HDV serology enrolled in ICONA/HepaICONA cohorts who achieved SVR after DAA: In detail, 1. no HBV infection (HBsAg-/HBcAb-); 2. HBV co-infection (HBsAg+); 3. occult HBV infection (HBsAg- /HBcAb+); 4. HBV/HDV co-infections (HbsAg+ /HDV-RNA+).
Standard survival analyses and univariate/multivariable Cox regression models were used to estimate time to ALT normalization (ALTN: two consecutive ALT< 42 for males and <30 UI/L for females) and time to ALT>5xULN according to HBV/HDV status. Changes in ALT after DAA start according to HBV/HDV status, were evaluated with linear mixed models with random intercepts and slopes.

Results:
The analysis included 1,182 HIV/HCV individuals: 476 HBsAg-/HBcAb-, 650 HBsAg-/HBcAb+, 56 HBsAg+ (of which 6 HDV Ab+, all HDV-RNA+), with a median follow up of 4.8 years [IQR 3.4-5.9] from DAA initiation. The HDVRNA+ had significantly higher proportion of cirrhotic (50.0%), and higher liver fibrosis 14.9 kPa [10.5-72.0] assessed by transient elastography and lower nadir of CD4 count (21 cells/mmc, IQR 14-139) and all received ART regimens with anti-HBV activity (2 FTC/TAF and 4 FTC/TAF). Median CD4 count at DAA start were: 547 CD4/mmc [351-803] for HBsAg+/HDVRNA+, 529 CD4/mmc [309-793] for HBsAg+HDVAb-, 630 CD4/mmc [430-960] for HBsAg+HDVAb unknown, 693 [491-887] for HBsAg-/HBcAb- and 620 CD4/mmc [438 872] for HBsAg-/HBcAb+ (p<0.001). Figure 1 shows the proportion of PWH with ALT increase >5xUNL in relation to hepatitis status. After adjustments, PWH with HBV co-infection showed a marginally significant higher probability of ALT increase >5 ULN vs HBV-negatives (aHR 6.51, 95%CI 0.81-52.5, p=0.079) (Table 1). HBsAg positivity was associated with a lower likelihood to normalize ALT (aHR 0.64, 95%CI 0.45-0.92, p=0.015) but, when HDV co-infection was included in the model, only the quadruple infection retained significativity (aHR 0.20, 95%CI 0.05-0.82, p=0.025) (Table 2A-B). Changes in ALT after HCV eradication are shown in Figure 2.

Conclusion:
These preliminary data demonstrate that HDV replicating PWH who achieved HCV eradication show a higher probability of persistent liver necrosis, as shown by ALT elevation, thus maintaining liver damage. Treatment of HDV is mandatory in this context.

VIROLOGY AND PATHOGENESIS

P62 Role of intrahepatic HDV reservoir in potentially modulating response to bulevirtide treatment at 24 weeks.

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Hepatitis Delta Virus (HDV) is a small RNA virus that can cause a severe chronic hepatitis in patients already infected with Hepatitis B virus (HBV). HDV co-infection is a risk factor for cirrhosis and hepatocellular carcinoma (HCC) development. For a long time, there was no effective treatment for HDV hepatitis. On January 2023 bulevirtide (BLV) was approved in Italy as the first therapeutic option for HDV infection. Despite the observation of a good clinical and laboratory response, the identification of parameters to predict a more rapid and durable response to therapy remains uncertain.

The aim of this study is to analyze which parameters can be predictive of a clinical and laboratory response.
We analyzed intrahepatic and peripheral virological parameters, ALT, information on cirrhosis status from five patients of our cohort of HDV patients from Policlinico Tor Vergata of Rome, who received BLV at least for 24weeks by July 2024. Droplet digital PCR was used to quantify intrahepatic HBV and HDV markers. Combined response was defined as HDV-RNA decay >2 log and ALT normalization.
Five patients, all virologically suppressed under nucleos(t)ide analogues (NUC), received BLV for 24 weeks. Median age was 47 (45-54) years, 1 patient was Italian, 4 from Eastern-Europe. The risk of infection was sexual transmission for 4 patients, and use of injectable drugs for one.

At baseline, median (IQR) serum HDV-RNA and HBsAg were 7.5 (7.3-7.7) and 4.3 (4.2-4.3) log IU/ml, respectively.
Median ALT was 52 (43-116) U/l while Ishak score was 5 for three patients, 4 and 3 for the remaining two. Intrahepatic median (IQR) HDV-RNA was 2262 (1292-3564) copies/1000cells (Table1). Two patients received Peg-Interferon-alfa but discontinued after 2 and 4 weeks respectively for adverse effects.

Combined response was achieved in 3 patients at week 12 and in all patients at week 24 of BLV. At week 24, two patients achieved serum HDV-RNA<2 log IU/ml, while the other three had HDV-RNA>2.5 log IU/ml. Notably, a lower baseline intrahepatic HDV-RNA tended to correlate with the achievement of serum HDV-RNA<2 log IU/ml after 24 weeks of BLV-treatment (median intrahepatic HDV-RNA: 922 copies/1000cells in 2/5 patients achieving and 3564 copies/1000cells in 3/5 not achieving HDV-RNA<2 log IU/ml). Conversely, the intrahepatic HBV markers were comparable between the two groups of patients.

A limited intrahepatic HDV reservoir at baseline tended to correlate with a higher control of HDV replication after 24 weeks of BLV. The virological and clinical monitoring in longer follow-up and larger sample size is ongoing in order to corroborate this result. This can also have implication for therapeutic strategies aimed at setting up a finite course of BLV treatment.

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