Review

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Hepatitis D virus infection: Pathophysiology, epidemiology and treatment. Report from the first international delta cure meeting 2022

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Summary

Chronic infection with hepatitis delta virus (HDV) affects between 12-20 million people worldwide and represents the most severe form of viral hepatitis, leading to accelerated liver disease progression, cirrhosis and its complications, such as end-stage-liver disease and hepatocellular carcinoma. From the discovery of HDV in 1977 by Prof. Mario Rizzetto, knowledge on the HDV life cycle and mechanisms of viral spread has expanded. However, little is still known about the natural history of the disease, host-viral interactions, and the role of the immune system in HDV persistence. Diagnosis of HDV is still challenging due to a lack of standardised assays, while accurate viral load quantification is needed to assess response and endpoints of antiviral treatment. Until recently, interferon has represented the only treatment option in patients with chronic hepatitis delta; however, it is associated with low efficacy and a high burden of side effects. The discovery of the entry inhibitor bulevirtide has represented a breakthrough in HDV treatment, by demonstrating high rates of viral suppression in phase II and III trials, results which have been confirmed in real-world settings and in patients with compensated advanced liver disease. In the meantime, other compounds (*i.e.* lonafarnib, new anti-hepatitis B virus drugs) are under development to provide alternative or combined strategies for HDV cure. The first international Delta Cure meeting was organised in Milan in October 2022 with the aim of sharing and disseminating the latest data; this review summarises key takeaway messages from state-of-the-art lectures and research data on HDV.

Keywords: Chronic hepatitis Delta; HDV; HDV RNA; cirrhosis; Entry Inhibitor; Bulevirtide; Lonafarnib; Delta Cure

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Introduction

In October 2022, the first international meeting focusing on hepatitis delta virus (HDV) infection took place in Milan. For two days, experts from the hepatology field exchanged new insights covering virology, epidemiology, pathogenesis, diagnosis, natural history, and antiviral treatment. A total of 46 abstracts were selected for poster presentation, and the aforementioned topics were explored in depth in the scientific sessions by selected experts from the field. In the following review, we not only provide an overview of the scientific content, but also summarise the open research questions that were identified during discussions at the meeting.

Epidemiology of HDV infection

Several reviews addressing the estimation of global and regional HDV prevalence rates have been published recently.[1–4] Global estimated prevalence rates differed significantly between the studies, with two studies estimating a global prevalence between 48–60 million and 62–72 million in 2018 and 2019, respectively, and the third scaling down to 12 million in 2020.[1–3] The World Health Organization currently estimates HDV prevalence to be nearly 5% of total hepatitis B surface antigen (HBsAg)-positive carriers, who account for 296 million people worldwide.[5,6] Especially in the light of newly available treatment options, having a reliable estimate of global prevalence and clinical disease burden is important. There are several explanations for these diverse numbers. Population-based studies are lacking and screening strategies differ from country to country. For example, testing of all HBsAg-positive samples for the presence of anti-HDV antibodies is recommended by EASL (the European Association for the Study of the Liver) and APASL (the Asian Pacific Association for the Study of the Liver), whereas only testing of patients at risk is recommended by AASLD (the American Association for the Study of Liver Diseases).[7–9] Furthermore, test strategies are not harmonised, HDV RNA assessment is not always performed in case of positive anti-HDV antibodies and quantification of HDV RNA is not standardised, which leads to inter- and intra-assay

variability. Finally, a lack of data from different countries causes "white spots" on the map of HDV epidemiology.

At the first international Delta Cure meeting some of these white spots were elucidated: the epidemiology topic was covered during the respective session and 13 abstracts were selected for poster presentation. HDV epidemiology was addressed from multiple directions including high- and low-prevalence regions. For example, in Pakistan, prevalence rates range from 14.9% to 60% of all HBsAg-positive samples, leading to an overall prevalence rate of 16.6%. In contrast, reports from Italy showed an anti-HDV prevalence rate of only 2.5% of all HBsAg-positive samples in a cohort of 3,417 immigrants who were diagnosed in five different first level clinical centres.[10] Based on the analysis of a healthcare reimbursement database, the HDV prevalence and incidence in the outpatient setting in Italy was analysed by Lampertico and colleagues. From 2015 until 2019, 7.5% of HBsAg-positive patients were positive for HDV and 136 patients were newly diagnosed with HDV, leading to an incidence rate of 2.4%.[11] The topic of screening strategies was covered in an abstract by Strzepka *et al.* who analysed local screening rates from a US hepatology clinic. Based on their data, local screening rates were calculated to be 56%, meaning that 44% of HBsAg-positive patients had not been tested for HDV.[12] The improvement of screening rates has been identified as one of the unmet needs in the HDV cascade of care. Based on data from a US Veterans Affairs cohort, only 8.5% of patients positive for HBsAg were tested for anti-HDV and only 8.2% of these anti-HDV-positive patients underwent subsequent HDV RNA testing.[13] A reliable identification of infected patients is not only essential for treatment initiation but also for management of potential clinical complications that might occur during chronic viral infection.

Key points

- HDV infects approximately 10-20 million people worldwide, corresponding to 5% of total HBsAg carriers; HDV screening strategies need to be improved in order to refine these estimates.
- HDV is considered the most severe form of viral hepatitis, leading to accelerated development of cirrhosis and its complications (decompensation, HCC); more data about HDV pathogenesis are needed in order to define predictors of disease progression.
- Many tools are currently available for HDV diagnosis and HDV RNA quantification: assay standardisation is crucial to correctly assess treatment response and compare data, while new biomarkers are needed to improve diagnosis and prognosis.
- Surrogate endpoints have been defined by regulatory agencies and scientific societies, in order to assess the efficacy of antiviral treatments: long-term validation is needed to correlate treatment endpoints with improved clinical outcomes and survival.
- Treatment with PegIFNα results in suboptimal off-therapy responses, coupled with a low tolerability profile. However, PegIFN has a synergistic effect with other anti-HDV drugs and could represent a good combination strategy.
- Bulevirtide, the first-in-class entry inhibitor for HDV, was conditionally approved by the European Medicines Agency in 2020 for the treatment of compensated chronic HDV infection. Phase II/III and real-world data on bulevirtide monotherapy are available.
- Bulevirtide demonstrated good efficacy in terms of virological and clinical responses both in clinical trials and real-world settings, including in patients with advanced cirrhosis and portal hypertension, coupled with an optimal safety profile.
- Other investigational drugs are under development for HDV, such as lonafarnib (currently being tested in a phase III study) and new agents aimed at HBV functional cure (currently being tested in phase II studies in HDV-infected patients).
- The main unmet needs in HDV include: extensive screening of HBsAg carriers, insight about HDV pathophysiology and predictors of fibrosis progression, HDV RNA assay standardisation, identification of predictors of viral response with current antiviral therapies, as well as individualisation and optimisation of treatment schedules.

Natural history of HDV infection

The natural course of chronic HDV infection was addressed in several abstracts. Across all abstracts, patients with HDV infection were found to have high rates of liver-related complications such as cirrhosis, decompensated cirrhosis, or hepatocellular carcinoma (HCC) at the time of diagnosis.[14–18] Long term, these patients were more likely to develop liver-related clinical endpoints (hepatic decompensation, liver transplantation, HCC, or liver-related death) than hepatitis B virus (HBV)-monoinfected patients.[19] Potential reasons for these differences were shown in the analysis by Garcia-Pras *et al.*[20] In their study, the liver transcriptome of formalin-fixed paraffin-embedded liver biopsies from viraemic and non-viraemic HDV-infected patients, HBV-monoinfected patients and healthy controls was analysed by Nanostring technology. Overall, innate immunity and liver damage-related genes were upregulated in livers of HDV viraemic patients compared to all control groups. More precisely, leukocyte chemotaxis, cytotoxicity of natural killer and T cells, and inflammasome-associated cell death were upregulated in HDV-positive *vs.* HBV-monoinfected liver samples. The extent to which these findings explain the observed clinical differences requires further investigation, but certainly these results underscore the importance of immunologic studies as part of investigations into HDV pathogenesis.

In a recently published Swedish study, long-term data on patients with HDV who presented to secondary medical centres was analysed.[21] In this real-world study involving 337 patients with anti-HDV positivity, patients with detectable HDV viraemia were shown to have a 3.8-fold increased risk of developing liver-related outcomes compared with non-viraemic patients. Long-term prognosis remained poor for patients with viraemia without cirrhosis, but was still better than previous studies from tertiary centres had suggested. After 5 and 10 years of follow-up, 82% and 64% of these patients remained free of cirrhosis or liver-related events, respectively. These findings are important as they highlight the need for markers to predict disease progression, particularly in the context of newly available antiviral treatment options. Further research is needed to reliably predict long-term clinical progression and thus identify patients in need of priority antiviral treatment.

Diagnosis of HDV: Clinical serology, virology and new biomarkers

Currently, diagnosis of HDV infection relies on detection of anti-HDV antibodies (IgG and IgM) and HDV RNA quantification. While IgG anti-HDV persists after HDV clearance, IgM anti-HDV is considered a surrogate marker of HDV-related disease activity, as IgM levels have been associated with biochemical response to IFN treatment and liver-related complications.[22,23] However, many assays for anti-HDV serology show significant variability in terms of diagnostic performance (sensitivity and specificity): this can result from the assay set-up, the type of antigen used (recombinant hepatitis delta antigen [HDAg],

Table 1. Commercial kits currently available for HDV RNA quantification.

Kit name	LOD	LLOQ	Linear range	Genotype	Certified
Robogene ® HDV RNA Quantification kit 2.0	6 IU/ml	47-83 IU/ml	5-1x10^8 IU/ml	1-8	CE
RealStar ® HDV RT-PCR	9.48 IU/ml	na	40-40x10^7 IU/ml	1-8	RUO
EurobioPlex HDV qRT-PCR EBX-004	100 IU/ml	100 IU/ml	10^2-10^8 IU/ml	1-8	CE
Bosphore ® HDV Quantification-Detection kit	45 cp/ml	100 cp/ml	10^2-10^8 cp/ml	1-8	CE
Lightmix HDV kit	10 cp/ml	10 cp/ml	10^1-10^6 cp/ml	1	RUO
DiaPro HDV RNA quantification kit	100 cp/ml	100 cp/ml	10^2-10^7 cp/ml	1-8	CE
HDV Genesig standard kit	100 cp/ml	n.a.	10^2-10^7 cp/ml	1-8	RUO

HDV, hepatitis delta virus; LOD, lower limit of detection; LLOQ, lower limit of quantification; (q)RT-PCR, (quantitative) reverse-transcription PCR; RUO, research-use only.

peptides) and interference from other materials (*i.e.* serum proteins). Gerber and colleagues summarised results from the last decade of French national quality control for the diagnosis of HDV infection, reporting concordance rates for IgM ranging from 43 to 100%.[24] Consequently, the availability of fully automated, reproducible assays with high diagnostic performance and the capability to provide quantitative results represents an unmet need in diagnostic serology for HDV. Finally, in the future, the development of easy point-of-care serological assays both for HBsAg and HDV should be prioritised to improve screening, particularly in low- and middle-income countries.

HDV virologic testing suffers from a lack of availability of commercial and automated tests, as well as a lack of standardised assays. Indeed, many laboratories use in-house kits; moreover, there are still many technical issues that impact the HDV RNA quantification process, such as sample volume, manual *vs.* automated extraction, internal control and quantification standard, reverse transcription quantitative PCR, devices used for amplification, and sequences of primers and probes. The World Health Organization international standard for HDV RNA is obtained from HDV genotype 1-positive plasma, while international standards for HDV genotypes 2-8 are currently missing. At the Delta Cure meeting, Gerber and colleagues reported a concordance rate for HDV RNA assays ranging from 45 to 100% with a significant improvement in recent years.[24]

Commercial kits currently available for HDV RNA quantification are shown in Table 1. Even when using the same kit, different methods of extraction in the same assay can lead to significant differences in terms of HDV RNA quantification: in a single-centre Italian retrospective study conducted on 229 sera from 157 patients with HDV, quantification of HDV RNA by Robogene 2.0 was significantly influenced by the extraction method, manual extraction being ~1 log more sensitive than automated extraction.[25] The need for reliable tests for quantitative HDV RNA assessment in all HDV genotypes, along with fully automated assays is crucial not only for HDV diagnosis but also for treatment monitoring in order to correctly assess all endpoints of antiviral treatment.

New HBV-derived biomarkers are currently under investigation in the context of HDV infection, especially hepatitis B core-related antigen (HBcrAg) and HBV RNA, which mirror the transcriptional activity of covalently closed circular DNA (cccDNA) in HBV monoinfection. Unlike in HBV monoinfection, where HBcrAg and HBV RNA levels are usually concordant, in HDV infection, Degasperi and colleagues reported a divergent pattern for HBcrAg and HBV RNA, with HBcrAg testing positive and HBV RNA negative in most patients.[26] Another Italian group showed that patients with HBcrAg >3 log U/ml were characterised by higher alanine aminotransferase (ALT) levels and liver stiffness, suggesting that active transcription of cccDNA is required to support effective HDV pathogenicity.[27] New HBV biomarkers have also been associated with clinical outcomes: indeed, HBcrAg levels predicted HCC risk and mortality in a retrospective Italian study with a median follow-up of 8 years,[28] while HBV RNA levels were significantly lower in HDV-infected patients with a virological response to pegylated-interferon (PegIFN) in the HIDIT-II study.[29]

Antiviral treatment of HDV infection

Endpoints of HDV therapy

The ideal endpoint of any antiviral treatment is improvement in clinical outcomes, which is preventing fibrosis progression to cirrhosis, decompensation, HCC development and liver-related deaths. However, in order to assess efficacy of antiviral treatments in the short-term and to develop new drugs, other surrogate endpoints are usually defined. In the context of HDV treatment, the US Food and Drug Administration and the joint EASL-AASLD conference for HDV treatment endpoints defined two types of treatment endpoints according to treatment strategy (long-term *vs.* finite duration) that are presented in Table 2.[30,31]

PegIFN

IFN exerts its antiviral effect via transcription of interferon-stimulated genes in the nucleus, thus inducing an “antiviral state”. In HDV infection, IFN has also been shown to suppress cell division-mediated HDV spread, through destabilisation of HDV RNA during cell division.[32,33]

Data on the efficacy of IFN in HDV infection are heterogeneous due to the limited number of studies, different treatment durations, limited number of patients included, and short follow-up. In a recent review of 13 studies including 1,078 patients, the overall virological response, defined as undetectable HDV RNA

Table 2. HDV treatment endpoints.

	Short-term (Finite) treatment	Long-term treatment
FDA[30]	HDV RNA <LLOQ and ALT normalisation*	≥2 log HDV RNA reduction + ALT normalisation
EASL-AASLD[31]	HDV RNA <LLOQ 6 months after stopping treatment, ALT normalisation and ideally HBsAg loss	≥2 log HDV RNA reduction

ALT, alanine aminotransferase; HDV, hepatitis delta virus; LLOQ, lower limit of quantification.
* Timing of assessment according to treatment strategy.

after 24 weeks off-treatment, was 31%.[34] Yet determinants of IFN response are poorly known, leading to difficulties in predicting antiviral treatment efficacy or defining stopping rules for IFN-based therapies. Moreover, low overall efficacy and IFN-related adverse events *de facto* limit or contraindicate IFN-based treatment for some patients, *e.g.* those with advanced cirrhosis. Nevertheless, due to its peculiar mechanism of action, IFN has the potential to act synergistically in combination treatments. In this line, PegIFNλ is currently under investigation: compared to IFNα, IFNλ binds to a different and unique receptor that is highly expressed on hepatocytes, with limited expression on haematopoietic and central nervous system cells; it is thus hoped that it will be associated with reduced systemic side effects. The LIMT-2 phase III trial evaluating PegIFNλ 180 μg/week for 48 weeks in patients with HDV is currently ongoing.

Bulevirtide

Bulevirtide (BLV), a first-in-class entry inhibitor of HBV-HDV, administered as subcutaneous injections, is a linear 47-amino acid chemically synthesized lipopeptide that specifically binds to Na+-taurocholate-co-transporting polypeptide (NTCP). NTCP receptor blockage results in inhibition of HDV entry into hepatocytes.

BLV: Clinical trials

In phase II clinical trials, BLV was evaluated both as a monotherapy (MYR-202, MYR-203 arm D-F, MYR 204 arm D) and in combination with PegIFN (MYR 203 arms B-C-E, MYR-204 arms B–C) with different doses (2 mg *vs.* 5 mg *vs.* 10 mg) and treatment durations (24 weeks, 48 weeks, 96 weeks).[35–37] Overall, BLV led to HDV RNA reductions both as a monotherapy and combined with PegIFN; in combination treatment, the antiviral effect was synergistic and resulted in a more pronounced HDV RNA decline.[38] The MYR-301 phase III study evaluated the safety and efficacy of BLV monotherapy – 2 mg *vs.* 10 mg for 144 weeks *vs.* 10 mg for 96 weeks (48-week delayed treatment arm) – in a total of 150 patients (43% with compensated cirrhosis). Combined response, defined as virological response (undetectable HDV RNA or ≥2 log decline *vs.* baseline) plus biochemical response (ALT normalisation) at week 48, was achieved by 45% (2 mg) and 48% (10 mg) of BLV-treated patients, respectively. Virological response rates were 71% *vs.* 76%, while ALT normalisation occurred in 51% *vs.* 56% of patients, respectively.[39]

At the Delta Cure meeting, many abstracts reported results of integrated efficacy, safety, resistance and histological analyses from phase II and III trials: Lampertico and colleagues showed comparable combined response rates in the 2 mg and 10 mg arms, which supported the European Medicines Agency's decision to approve the 2 mg dose of BLV.[40] A combined analysis of paired biopsies from patients treated in the MYR-203 and MYR-301 studies showed strong intrahepatic HDV RNA decline at week 48 in BLV-treated patients, as well as improvement of inflammation and fibrosis scores.[41,42] Resistance analysis in patients with a primary non-response to BLV (<1 log HDV RNA decline at week 24) did not identify any amino acid substitution at the interaction site with the NTCP receptor conferring resistance to BLV.[43]

Integrated safety analysis from phase II and III trials reported a dose-dependent BLV-induced bile acid increase, as NTCP also acts as a bile salt transporter. Nevertheless, bile acid elevation was asymptomatic and not associated with adverse events including pruritus, skin disorders and eosinophilia. Overall, pruritus was reported in 11% of patients; however, no clear association was seen between bile acid levels and the onset and duration of pruritus. On-treatment bile acid levels were independent from ALT values and the presence of cirrhosis.[44] Most adverse events during BLV treatment were mild or moderate in severity, rates of grade 3-4 laboratory abnormalities were similar across BLV and control groups.[45] An exploratory analysis in patients treated with BLV in the MYR-301 trial reported that BLV administration was also associated with improvements in health-related quality-of-life outcomes.[46]

BLV: Real-life studies

To date, the largest real-world studies have come from German, French and Italian experiences. The German multicentre study reported interim results on a total of 115 patients (52% with cirrhosis) treated with BLV 2 mg/day. Virological response was achieved in 58% of patients at week 24 (data available for 43 patients). Significant improvements in ALT levels and FIB-4 fibrosis score were observed. No BLV-related serious adverse events occurred, while fatigue was the most frequent adverse event reported.[47] Baseline bile acid levels, but not on-treatment increases, inversely correlated with HDV RNA decline.[48] In a small patient group with paired HVPG (hepatic venous pressure gradient) measurements, HVPG remained stable in one viral responder and increased in two patients with a partial viral response.[49]

In the multicentre ANRS French cohort, 173 patients (55% with cirrhosis) received BLV either as a monotherapy or in combination with PegIFN at the investigators' discretion (43% of total patient population). The interim analysis included 115 patients reaching treatment week 24 and 55 patients reaching treatment week 48, respectively. Rates of virological response were 39% at week 24 and 69% at week 48 (BLV monotherapy) compared to 84% and 85% (BLV + PegIFN), respectively. Biochemical response rates were 54% and 61% after 24 or 48 weeks of BLV monotherapy, compared to 35% and 39% with BLV + PegIFN. Combined response rates at week 24 and 48 were 17% and 31% with BLV monotherapy compared to 34% and 35% with BLV + PegIFN, respectively. 8% (week 24) and 17% (week 48) of patients achieved HDV RNA undetectability with BLV monotherapy, compared to 44% and 62% with BLV + PegIFN, respectively. Therefore, PegIFN also showed a synergistic effect with BLV in terms of virological response in a real-world setting; however, administration of IFN resulted in lower ALT normalisation, thus reducing biochemical and combined response rates compared to BLV monotherapy.[50]

The single-centre Italian real-world study reported long-term outcomes of 18 patients with compensated advanced cirrhosis and clinically significant portal hypertension treated with BLV 2 mg/day monotherapy for up to 72 weeks: virological, biochemical and combined response rates were 67%, 72% and 56%, respectively. Aspartate aminotransferase, gamma-glutamyltransferase and IgG levels significantly improved, together with albumin values.[51] The case report of one Italian patient is of special interest: this patient with compensated cirrhosis treated with BLV monotherapy for three years maintained HDV RNA undetectability 48 weeks after stopping treatment. Furthermore, liver stiffness decreased and stigmata of

Table 3. Key questions and open issues for chronic HDV infection.

Topic	Key questions
Epidemiology and natural history	• What are the correct global and regional prevalence rates of chronic HDV infection? • Which parameters reliably predict the clinical course of chronic HDV infection? • What routes of HDV transmission exist?
Virology and pathogenesis	• What is the immunological phenotype of chronic HDV infection? • Which immunological phenotype is associated with disease control and disease progression? Which immunological pathways are associated with disease control and disease progression? • How does the co-infection with HBV influence immune control capacities? • What functions do the HD proteins have? • What host proteins are necessary for efficient HDV replication and generation of infectious HDV particles?
Diagnosis, clinical virology and new biomarkers	• How to harmonize HDV RNA quantification? • What are reliable non-invasive tests to reliably identify patients with and without liver fibrosis or cirrhosis? • Can new virological markers be used as markers to predict clinical course and treatment response?
Antiviral treatment	• What is the desired treatment endpoint of antiviral treatment in case of persistent HBsAg? • How can HBsAg loss be achieved? • Which antiviral substance for which patient? Which treatment strategy for which patient? • Duration of bulevirtide treatment? • Long-term effects of bulevirtide treatment? • Definition of treatment response and non-response? • Combination therapy? Which combination partner? What order? • How to treat patients with decompensated liver disease? • Strategies for combination treatment (How, when, which compounds?)

HDV, hepatitis delta virus.

portal hypertension improved (platelet count normalised and pre-BLV small varices regressed). Liver biopsy at week 48 after cessation of therapy showed minimal inflammatory features but improvement in liver fibrosis and resolution of autoimmunity features reported in histology before treatment. Intrahepatic HDAg, HDV RNA, cccDNA and hepatitis B core antigen stained negative, while HBsAg stained positive in only 0.4% of the complete liver biopsy, which might resemble HDV viral cure.[52]

In conclusion, the safety and effectiveness of BLV in patients with chronic HDV has also been confirmed in real-world settings, including in patients with advanced compensated cirrhosis. Extended follow-up data are needed in order to confirm long-term virological suppression and especially clinical outcomes, such as prevention of liver-related events. More data are also needed in order to investigate predictors of viral response on- and off-treatment, define optimal treatment duration/BLV stopping rules, as well as personalised treatment strategies (BLV monotherapy *vs.* BLV + PegIFN combination).

Lonafarnib

Lonarfanib (LNF) prevents the farnesylation of the large delta antigen, thus interfering with the envelopment of the nascent HDV nucleoprotein complex by HBsAg. It is administered orally and boosted with ritonavir (RTV) in order to improve bioavailability. The phase II studies LOWR-1 and 2 investigated different doses of LNF (25 mg, 50 mg and 75 mg twice daily) with or without PegIFN.[53,54] The 50 mg dose induced the highest HDV RNA log decline at week 24 combined with acceptable gastrointestinal tolerability, with diarrhoea being the most common side effect of LNF. Long-term follow-up of patients treated in the LOWR-1 and 2 studies reported at the Delta Cure meeting showed durable biochemical response and HDV RNA undetectability in five patients, mostly occurring after an early post-treatment ALT flare.[55] A phase III study with LNF 50 mg + RTV twice daily for 48 weeks with or without PegIFN in 407 patients with HDV is currently ongoing, as is a combination study with LNF + PegIFNλ for 48 weeks. The press release on week 48 data from the LNF phase III D-LIVR study showed that 19% of patients treated with LNF + RTV + PegIFN and 10% with LNF + RTV achieved the primary endpoint (≥2 log HDV RNA decline + ALT normalisation) compared to 1.9% in the placebo arm (p <0.0001 and p = 0.004, respectively).[56]

Investigational anti-HBV agents

As one of the ideal surrogate endpoints of HDV treatment is HBsAg loss, investigational HBV agents able to achieve HBV functional cure (defined as HBsAg loss ± anti-HBs seroconversion) could also result in HDV cure. Among RNA-interfering agents, small-interfering RNAs (siRNA) are currently under investigation both in HBV-monoinfected and HDV-coinfected patients. In HBV monoinfection, the REEF-1 and 2 phase II studies showed strong on-treatment HBsAg declines following administration of the siRNA JNJ-3989. However, none of the patients were able to achieve HBsAg loss at the end of therapy.[57,58] Clinical trials investigating siRNAs for the treatment of HDV coinfection are currently ongoing.[59,60] In the B-CLEAR trial, the antisense oligonucleotide bepirovirsen (GSK3228836) administered for 12 or 24 weeks led to on-treatment rates of HBsAg loss of 20-30%.[61,62]

REP-2139 is a nucleic acid polymer that inhibits HDV replication via direct interaction with HDAg and blocks HDV release by inhibiting viral envelopment using the HBV subviral particle assembly pathway.[63,64] Administration of REP-2139 250 mg subcutaneously in combination with PegIFN 90 μg/week and tenofovir disoproxil fumarate for 48 weeks was reported in four patients with compensated cirrhosis (and without PegIFN in a patient with decompensated cirrhosis). Two patients showed HBsAg loss, which was preceded by an ALT flare in one case.[65]

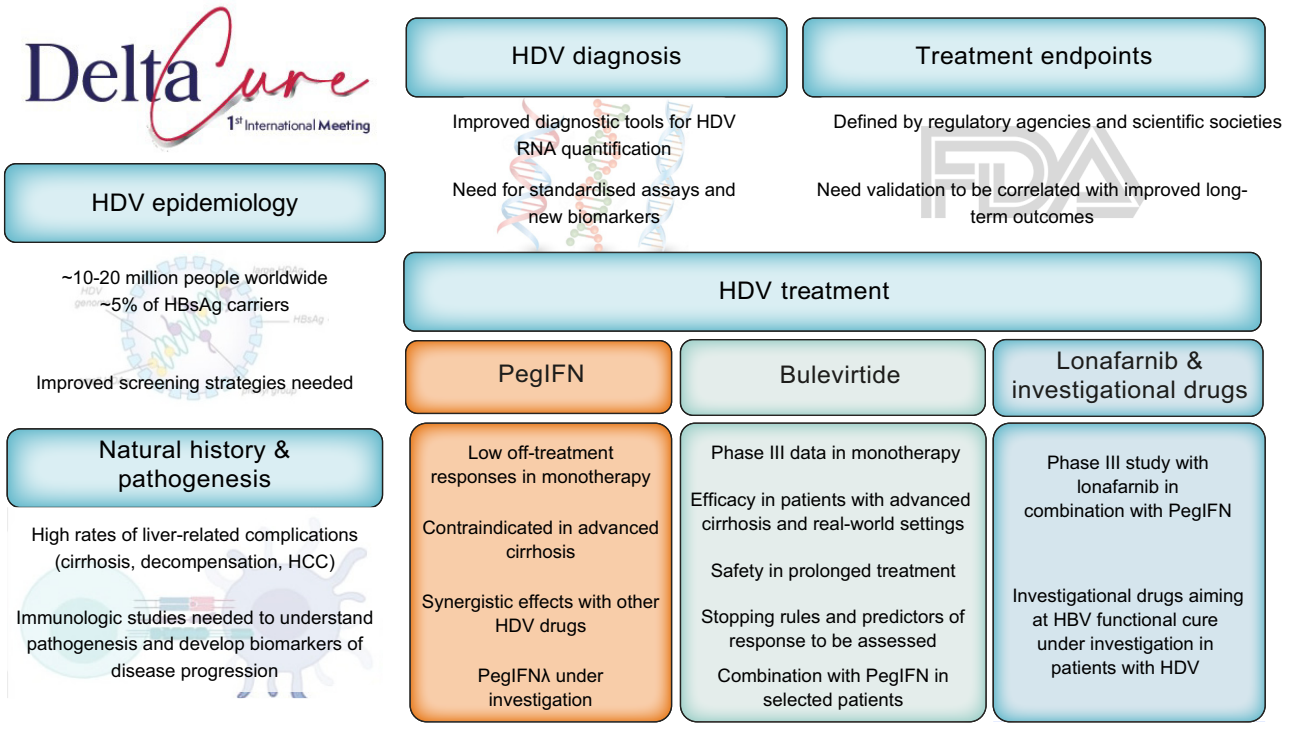

Fig. 1. Key messages from the 1st Delta Cure meeting 2022. HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus; PegIFN, pegylated interferon.

Key questions and unmet needs in HDV

Despite the impressive knowledge gained since HDV discovery in 1977, many aspects of the virus and the related disease are still poorly understood. A summary of key questions and unmet needs that emerged from the conference is presented in Table 3. Concerning HDV epidemiology, current estimates suffer from a lack of test standardisation (anti-HDV *vs.* HDV RNA), non-homogeneous screening strategies across different countries and gaps in HDV testing, especially in low- and middle-income countries. Many aspects of HDV pathophysiology and pathogenesis are still unknown, especially concerning the HDV life cycle and interaction with host cell proteins, as well as the role of the immune system in HDV chronicity and liver damage. More data are also needed to understand the natural history of HDV and predict the clinical course of chronic HDV infection in terms of development of fibrosis and liver-related complications. In this line, development of new biomarkers associated with disease progression is also needed. Another gap in current knowledge involves the lack of reliable non-invasive tests to stage liver fibrosis, as current cut-offs are derived from other viral hepatitis settings and not validated in the HDV field. Moreover, another important gap in HDV diagnosis involves the lack of standardisation of HDV RNA assays, where reliable and reproducible tests are needed in order to correctly diagnose HDV infection and assess treatment endpoints. There are also many unsolved questions related to HDV treatment: while the safety and efficacy of BLV, the first drug to be approved for HDV, has been demonstrated across the spectrum of fibrosis, including in patients with advanced fibrosis, the optimal treatment duration, as well as predictors of treatment response, have still not been defined. The ideal treatment endpoint (*i.e.* HBsAg loss) cannot currently be achieved and the reliability of surrogate treatment endpoints in terms of clinical benefits (*i.e.* improved survival and long-term outcomes) need to be prospectively confirmed. Finally, the possibility of combining different compounds in order to increase treatment efficacy is currently another unmet need in HDV therapy, as are effective strategies for more advanced patients, such as those with decompensated cirrhosis.

Conclusions and outlook

Overall, the first international meeting on hepatitis delta was a successful scientific conference that provided new insights into the epidemiology, pathophysiology, virology, and antiviral treatment of chronic HDV infection. The meeting provided room for intensive discussions between basic researchers, clinicians, and clinical scientists. Key messages emerging from the meeting are summarised in Fig. 1. In the last 40 years since HDV discovery, knowledge about HDV infection has rapidly evolved: from better understanding of the viral life cycle, new targets for antiviral therapy have emerged, with several compounds under clinical development. However, many aspects regarding the pathophysiology, immunology and natural history of HDV infection still need to be elucidated: only a better understanding of these topics will allow for improvements in treatment strategies as well as refinement of currently available therapeutic options.

Abbreviations

ALT, alanine aminotransferase; BLV, bulevirtide; cccDNA, covalently closed circular DNA; HBcrAg, hepatitis B core-related antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDAg, hepatitis delta antigen; HDV, hepatitis delta virus; IFN, interferon; LNF, lonafarnib; NTCP, Na+-taurocholate-co-transporting polypeptide; PegIFN, pegylated interferon; RTV, ritonavir; siRNA, small-interfering RNAs.

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Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

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Supplementary data

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