EASL Guidelines on Hepatitis D Virus

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EASL Clinical Practice Guidelines on hepatitis delta virus

Clinical Practice Guidelines

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European Association for the Study of the Liver*

Summary

Hepatitis D virus (HDV) is a defective virus that requires the hepatitis B virus to complete its life cycle and cause liver damage in humans. HDV is responsible for rare acute and chronic liver diseases and is considered the most aggressive hepatitis virus. Acute infection can cause acute liver failure, while persistent infection typically causes a severe form of chronic hepatitis which is associated with rapid and frequent progression to cirrhosis and its end-stage complications, hepatic decompensation and hepatocellular carcinoma. Major diagnostic and therapeutic innovations prompted the EASL Governing Board to commission specific Clinical Practice Guidelines on the identification, virologic and clinical characterisation, prognostic assessment, and appropriate clinical and therapeutic management of HDV-infected individuals.

Introduction

Hepatitis D or delta virus (HDV) is a defective virus, as its life cycle depends on the hepatitis B virus (HBV), from which HDV borrows all three HBV envelope proteins (HBV surface antigen [HBsAg]) to both enter and egress from the hepatocyte and sustain its productive infection.[1] HDV has a negative-sense single-stranded RNA genome of about 1,700 nucleotides. Recent proposals suggest classification into the *Deltavirus* genus of the Kolmioviridae family, part of the Ribozyviria realm.[2] Within the infected cell nucleus, HDV utilises the host RNA polymerase II to replicate via double rolling circle RNA synthesis. Newly synthesised, multimeric linear RNAs undergo autocatalytic cleavage and the resulting monomers are circularised via host cell-mediated ligation[3] (Fig. 1). HDV replication is independent of HBV, with both *in vitro* and *in vivo* studies demonstrating that HDV may persist during liver regeneration by transmission of HDV RNA through cell division, even in the absence of HBV.[4] Interestingly, several HDV-like viruses have recently been identified in different animal species (birds, fish, amphibians, snakes and invertebrates) without any association with a Hepadnavirus infection, suggesting that HDV has a long evolutionary history, and the HDV-HBV association may be specific to humans.[5,6]

HDV encodes a single structural protein (hepatitis D or Delta antigen, HDAg), expressed in two isoforms that are identical except for an additional 19 residues located at the C terminus of the large form (L-HDAg), though they have distinct biological functions. While the small protein (S-HDAg) is required for viral replication, L-HDAg, which results from an editing event induced on the antigenomic RNA by the host's adenine deaminase,[7] shuts down viral replication, promoting the packaging of mature virions; this is facilitated by an isoprenoid prosthetic side chain covalently bound to its C-terminus by a host cell farnesyltransferase[8] (Fig. 1). The two HDAg proteins bind to the HDV RNA genome to form a ribonucleoprotein which is then surrounded by an envelope containing all three HBsAg isoforms.[9] Due to its structure, HDV binds to the same cell receptor as HBV, *i.e.* sodium taurocholate cotransporting polypeptide (NTCP), via interaction with the pre-S1 domain of the L-HBsAg isoform, thus mediating HDV entry into hepatocytes.[10]

The unique features of HDV, such as the tight and mandatory interplay with HBV on the one hand and the ability to persist in the absence of the helper virus on the other, explain why it is so difficult to clear HDV infection. Furthermore, HDV RNA acts as a ribozyme and self cleaves to replicate; it does not encode any protein with enzymatic activity and borrows the enzymes required for replication from the infected cell: this poses an additional challenge to the identification of HDV-specific targets for antivirals.

HDV can infect susceptible hosts via coinfection with HBV, or by superinfecting chronic HBV carriers. HBV/HDV coinfection, which may result in the clearance of both viruses, usually leads to acute hepatitis, with a wide clinical spectrum ranging from asymptomatic/mild hepatitis to acute liver failure. Severe cases of acute hepatitis are more frequent in HBV/HDV coinfection than in primary HBV monoinfection.[11] HDV superinfection of an HBsAg-positive individual – as a rule – leads to persistence of HDV resulting in chronic hepatitis D (CHD), which is associated with a worse clinical outcome than HBV monoinfection, with more rapid and more frequent progression to cirrhosis.[12] Studies conducted in Italy in the late '80s re-

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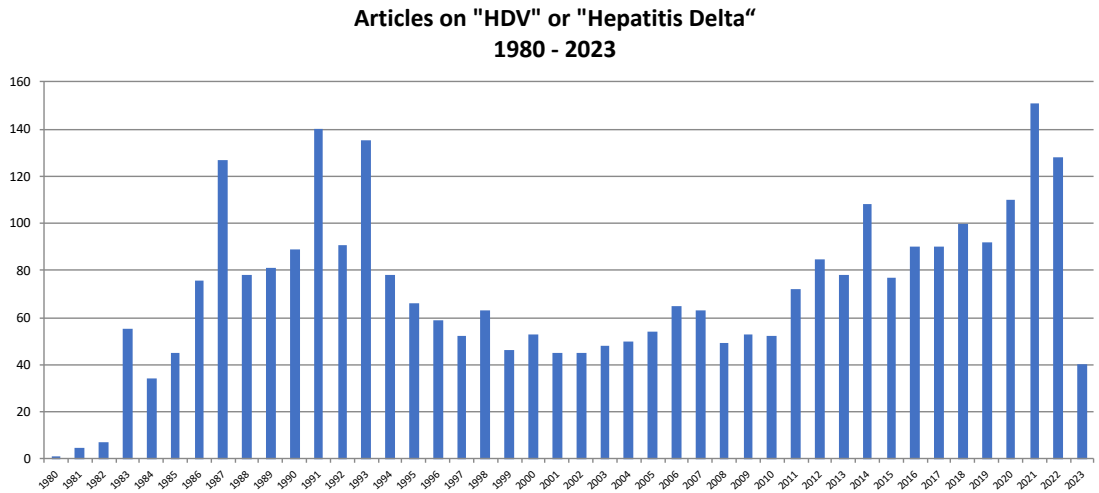
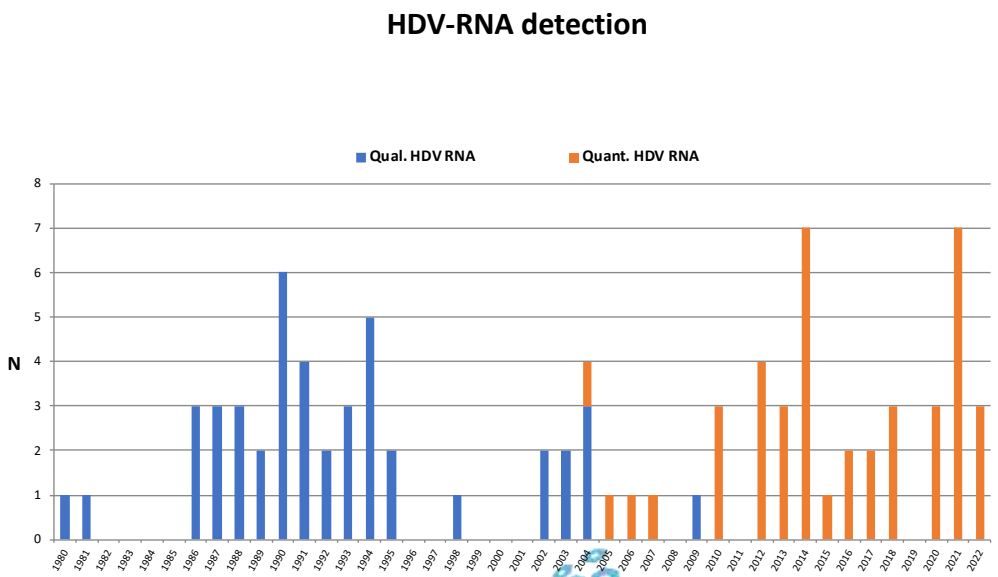
Aims of the HDV CPG :

- ✓ Since the **complexity of the clinical management** of patients with CHD has **increased** significantly in recent years and in view of the **newly available knowledge** and **therapeutic perspectives**, the EASL commissioned the first International Clinical Practice Guidelines on Hepatitis Delta Virus
- ✓ **The HDV CPG are intended for clinicians who may deal with the management and care of patients with HDV infection.**
- ✓ Therefore, as first step the main topics for clinical management were identified and then the key questions (PICO) were formulated

Critical issues to be addressed in development of HDV CPG:

- ✓ Chronic Hepatitis D is a rare, orphan disease (ORPHA:402823) and a limited number of large prospective studies are available. Furthermore, for many topics the data are scarce and the quality of evidence low
- ✓ During the more than 40 years of the HDV tale 2 major waves of papers were published, with substantial implementation of diagnostic tools overtime
- ✓ Thus, there was the need to reconciliate old and new findings to meet the PICO (*P- Patient, Problem or Population; I - Intervention; C – Comparison, Control or Comparator; O - Outcome*) methodology
- ✓ Finally, in the near future updates will be required, particularly when post-treatment folllow up data from phase III randomised-controlled trials will be available





Topics and PICO questions

Screening

- How and which HBsAg-positive individuals should be screened for HDV infection?

Diagnosis and patients' stratification

- Which diagnostic test should be used to diagnose ongoing HDV infection?
- Which HBV markers should be tested in patients with acute or chronic HDV?
- When should invasive (liver biopsy) and non-invasive tests (NITs) be used in the clinical management of patients with hepatitis D?

Clinical aspects, natural history and cofactors

- Which factors should be considered to identify patients with CHD who are at higher risk of liver disease progression?
- How and when should HCC surveillance be performed in patients with CHD?

Patient monitoring and selection for treatment

- How should untreated patients with CHD be monitored?
- Which patients with CHD should be considered for antiviral treatment?

Therapeutic approaches

- Which patients with CHD can be treated with PegIFNa ?
- Which patients with CHD can be treated with BLV?
- When should NAs be used in patients with CHD?
- Which is the best prophylactic strategy for prevention of post-transplant hepatitis D recurrence?

Treatment endpoints

- Which parameters should be monitored during and after antiviral treatment?

How and which HBsAg-positive individuals should be screened for HDV infection?

Recommendations

- Screening for anti-HDV antibodies should be performed with a validated assay at least once in all HBsAg-positive individuals **(LoE 3, strong recommendation, strong consensus).**

- Re-testing for anti-HDV antibodies should be performed in HBsAg-positive individuals whenever clinically indicated (*e.g.*, in case of aminotransferase flares, or acute decompensation of chronic liver disease) **(LoE 3, strong recommendation, strong consensus)**, and may be performed yearly in those remaining at risk of infection **(LoE 5, weak recommendation, strong consensus).**

Which diagnostic test should be used to diagnose ongoing HDV infection?

Recommendation

- HDV RNA should be tested in all anti-HDV-positive individuals using a standardised and sensitive reverse-transcription PCR assay to diagnose active HDV infection **(LoE 2, strong recommendation, strong consensus).**

✓In HDV-infected patients, **persistence of HDV replication** is associated with the **worst prognosis**, with the converse applying with HDV RNA clearance.

✓Preliminary reports suggest that **viral load** correlates with **disease activity and progression**; however, further studies with standardized assays are required to confirm these findings and define the prognostic role of quantitative HDV RNA monitoring in untreated patients.

✓**HDV RNA serum levels may fluctuate overtime**, **becoming temporarily undetectable**; therefore, the definition of status of HDV infection cannot be based on a single determination and requires repeated tests (at least 2) 3 to 6 months apart.

✓Recent studies showed that the HDV viral load declines overtime in a significant proportion of patients, mainly cirrhotic, and this may be associated with reduction of transaminases levels.

✓Therefore, serum **HDV RNA re-testing is required** not only **to exclude a temporary undetectability** when characterizing a newly diagnosed HDV infection, but also in case of persistent remission of disease activity to show a possible clearance of serum HDV RNA

When should invasive (liver biopsy) and non-invasive tests (NITs) be used in the clinical management of patients with hepatitis D?

Statement

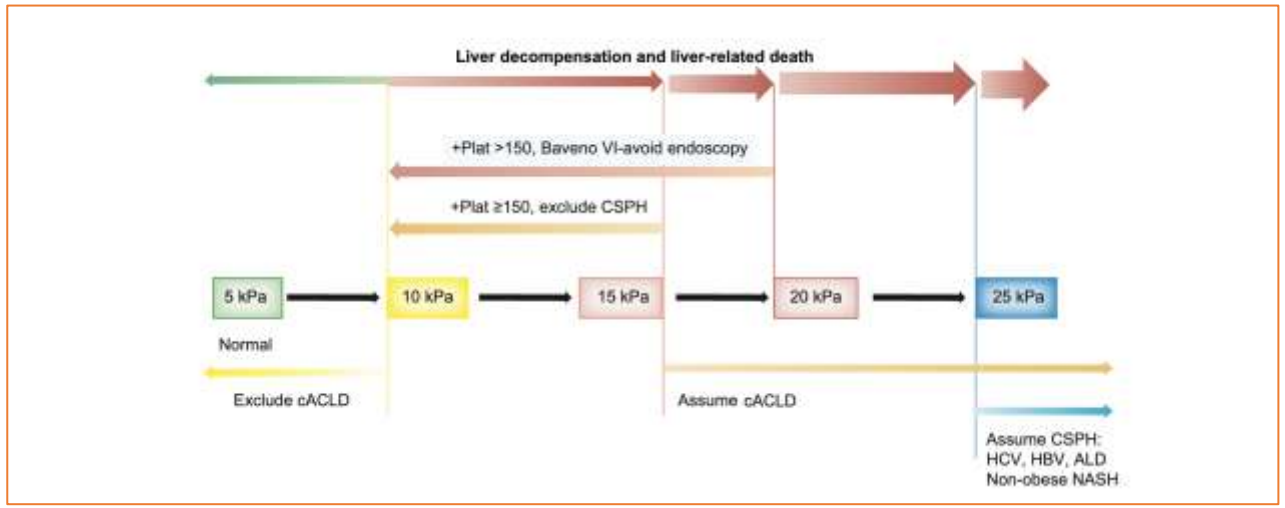
- Fully published data on the use of NITs in patients with CHD are currently limited and the correlation with liver histology is missing in a significant proportion of cases **(LoE 4, strong consensus).**

Recommendations

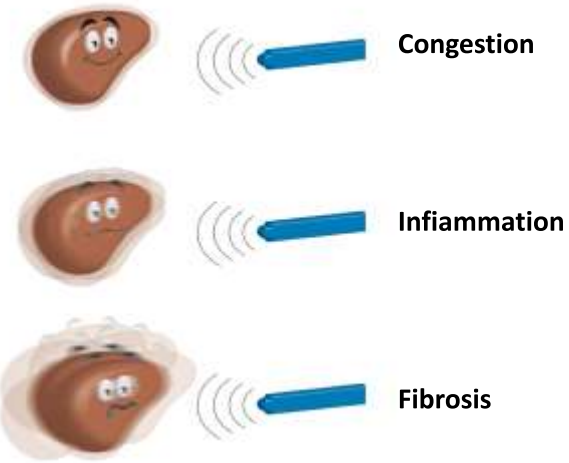
- Liver biopsy is recommended whenever it may contribute to the patient's management or for grading and staging liver disease when clinical signs or indirect evidence (by imaging techniques) of cirrhosis are absent **(LoE 3, strong recommendation, consensus).**

- NITs may be used to assess advanced liver disease, but specific cut-off values are not well established **(LoE 5, weak recommendation, strong consensus).**

- In the setting of CHD, NITs have not been consistently validated in large multicenter studies
- In **combined scores** that use **indirect markers of liver inflammation** (ALT) or **techniques** (TE and SWE) that are **influenced** not only by fibrosis, but **also by inflammation and congestion**, may **overestimate fibrosis** because of the significant impact of hepatic inflammation that characterizes a substantial proportion of CHD patients.
- **Thresholds** ranging from **12 to 14 kPa** had been proposed to predict cirrhosis with sensitivity 77.8-78% and specificity of 82.5-86%
- As the influence of necro-inflammation on stiffness values declines with the increase of fibrosis, **it's reasonable to use in CHD the TE thresholds proposed by Baveno VII** in order **to identify** patients with compensated advanced chronic liver disease (**cACLD**) and with clinically significant portal hypertension (**CSPH**).



Elastometry of the Liver:
3 vectors condition the liver stiffness



Baveno VII, J Hepatol 2022

Factors influencing the outcome of HDV infection and disease

Absent/Mild liver disease

Liver cirrhosis/ Liver related events

Factors associated to benign course

- ✓ HDV genotype 2 and 5
- ✓ Virologic response to IFNa treatment
- ✓ ↓ necroinflammation (AST/ALT)

Factors associated to progression

- ✓ HDV genotype 1 or 3
- ✓ Persistent HDV viremia/higher viral load (?)
- ✓ HBV replication/HBV genotype (?)
- ✓ Coinfection (HIV/HCV)
- ✓ Older age
- ✓ Male sex
- ✓ Origin (?)
- ✓ ↑ necroinflammation (AST/ALT)
- ✓ ↑GGT/ ↓ PCHE
- ✓ DM/Obesity
- ✓ Alcohol

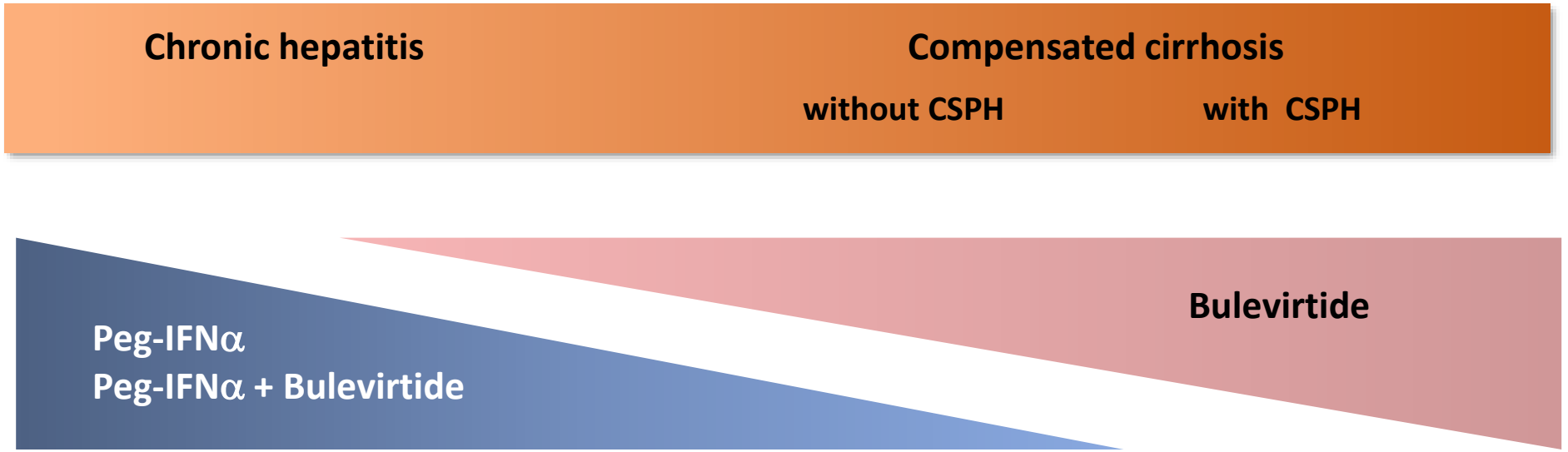
4. Patient monitoring and selection for treatment

Which patients with CHD should be considered for antiviral treatment?

Recommendations

- All patients with CHD should be considered for antiviral treatment **(LoE 3, strong recommendation, consensus).**
- Patients with decompensated cirrhosis should be evaluated for liver transplantation **(LoE 3, strong recommendation, strong consensus).**
- Patients with HCC may be considered for antiviral treatment on an individualised basis **(LoE 5, weak recommendation, strong consensus).**

Treatment of Chronic Hepatitis Delta



Finite treatment

To cure the infection/disease

Prolonged treatment

To control the infection/disease

Additional factors influencing the treatment schedule

- ✓ Phase of HBV infection (HBeAg/anti-HBe status; HBV-DNA and HBsAg levels)
- ✓ IFNa contraindiciation, tolerability
- ✓ Patient's will and compliance to treatment

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Panel

Maurizia R. Brunetto (*Chair)*
Kosh Agarwal, Tarik Asselah,
Patrizia Farci, Liana Gheorghe,
Francesco Negro,George Papatheodoridis,
Heiner Wedemeyer, Cihan Yurdaydin,
Maria Buti (EASL Governing Board representative)
Gabriele Ricco (*Secretary*)

Delphi Panel members

Mario Rizzetto, Manuel Rodriguez, Marko Korenjak, Fulya Gunsar, Emmanuel Gordien, Armand Abergel, Anna Lok, Antonina Smedile, Sabela Lens, Maria Speranta Iacob, Marinela Debu, Soo Aleman, Pietro Lampertico, Olympia Anastasiou, Katja Deterding, Christine Stern, Melanie Deutsch, Ioannis Goulis, Grazia Niro, Dulce Alfaiate, Marieta Simonova, Gulnara Agayeva, Onur Keskin, Gökhan Kabaçam, Markus Cornberg, Nancy Reau, Ulus S. Akarca, Norah Terrault, Saees Hamid.

EASL Governing Board

Which patients with CHD can be treated with PegIFNα?

Statement

- IFNα has been used since the ‘90s for the treatment of CHD. Mono- and multicentre studies have been conducted with IFNα, with only two randomised phase II studies published. Nevertheless, long-term data on clinical benefit and safety are available **(LoE 2, strong consensus).**

Recommendations

- All patients with CHD and compensated liver disease, irrespective of whether they have cirrhosis or not, should be considered for treatment with PegIFNα **(LoE 2, strong recommendation, consensus).**
- PegIFNα for 48 weeks should be the preferred treatment schedule **(LoE 3, strong recommendation, consensus).**
- Personalised treatment durations may be considered based on HDV RNA and HBsAg kinetics and treatment tolerability **(LoE 3, weak recommendation, strong consensus).**

Which patients with CHD can be treated with BLV?

Statement

- Despite the lack of data on long-term efficacy and safety, or on the optimal duration of BLV treatment, preliminary results from phase II studies (with BLV given as monotherapy or in combination with pegIFNα), on-treatment data from a phase III trial of BLV monotherapy and real-life studies suggest consideration of BLV as a treatment option for CHD whenever available **(LoE 3, consensus).**

Recommendations

- All patients with CHD and compensated liver disease should be considered for treatment with BLV **(LoE 3, strong recommendation, consensus).**
- The optimal dose and duration of treatment have not yet been defined **(LoE 5, consensus).** Until further data become available, long-term treatment with BLV, 2 mg once daily, may be considered **(LoE 5, weak recommendation, consensus).**
- The combination of pegIFNα and BLV may be considered in patients without pegIFNα intolerance or contraindications **(LoE 5, weak recommendation, consensus).**