Current options for advances in therapy
(*including adding interferon...*)

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Hannover Medical School
Dept. of Gastroenterology, Hepatology, Infectious Diseases & Endocrinology
Delta Cure
2nd international meeting
October 5 – 6, 2023
Hannover, Germany

Chairs: Heiner Wedemeyer and Pietro Lampertico
Conflicts of Interest

Honoraria for consulting or speaking (last 5 years):
Abbott, AbbVie, Abivax, Bayer, Biotest, BMS, BTG, Eiger, Enanta, Esei, Falk Foundation, Gilead, JJ/Janssen-Cilag, MSD, MyrGmbH, Norgine, Novartis, Roche, Roche Diagnostics, Siemens, Transgene, Vaccitec, Vir

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Ankara University
Cihan Yurdaydin
EASL Clinical Practice Guidelines on hepatitis delta virus

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Francesco Negro, George Papatheodoris,
Heiner Wedemeyer, Cihan Yurdagel,
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Mario Rizzetto, Manuel Rodriguez, Marko Korenjak, Fulya Gunbas,
Emmanuel Gordien, Armand Abergel, Anna Lok, Antonina Smedile,
Sabela Lens, Maria Speranta Iacob, Marinela Mubu, Soo Aleman, Pietro
Lampertico, Olympia Anastasiou, Katja Deterding, Christine Stern,
Melanie Deutsch, Ioannis Gouli, Grazia Niro, Dulce Alfaia, Marieta
Simonova, Gulnara Agayeva, Onur Keskin, Gökhan Kabacaç, Markus
Cornberg, Nancy Reau, Ulus S. Akarca, Norah Terrault, Saees Hamid.

J Hepatol, July 2023
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).
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).
EASL Clinical Practice Guidelines on hepatitis delta virus

European Association for the Study of the Liver

Factors associated with a benign course
- HDV genotype 2 and 5 (?)
- Virologic response to IFN treatment
- ↓ Necro-inflammation (AST/ALT)

Factors associated with progression
- HDV genotype 1 or 3 (?)
- Persistent HDV viremia/higher viral load (?)
- HBV replication/HBV genotype (?)
- Coinfection (HBV/HCV)
- Older age
- Male sex
- Origin (?)
- ↓ Necro-inflammation (AST/ALT)
- ↑ GSTI/GCPCHE
- Diabetes mellitus/obesity
- Alcohol
EASL Clinical Practice Guidelines on hepatitis delta virus

European Association for the Study of the Liver

- Chronic hepatitis
- Compensated cirrhosis
  - without CSPH
  - with CSPH

- PegIFNa
- PegIFNa + bulevirtide

Finite treatment
- To cure the infection/disease

Prolonged treatment
- To control the infection/disease
Antiviral Therapy of Chronic Hepatitis D Virus Infection - Addendum to the S3 Guideline
"Prophylaxis, Diagnosis and Therapy of Hepatitis B Virus Infection" of the German Society
for Gastroenterology, Digestive and Metabolic Diseases (DGVS)
May 2023 - AWMF Register Number: 021-11

Authors/steering committee group
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Addendum-HDV_englisch_20.06.23.pdf (dgvs.de)
Not all HDV patients have a severe course of disease
HDV viremia correlates with long-term outcome: Swiss HIV cohort

Anti-HDV+ vs. anti-HDV(-)

HDV-RNA+ vs. HDV-RNA(-)
Natural history of HDV infection in Sweden

Event-free survival

Kamal, ..., Wedemeyer, Aleman, Hepatology 2020
Liver stiffness good for diagnosis of cirrhosis?

Cut-off of > 15.2 kpa correctly identified cirrhosis in 91% of patients
HDV infection in persons living with HIV in Europe (EuroSIDA and SHCS)

Death and liver-related death

HCC

Beguelin et al., Liver International 2023 epub Jan 10
TDF or ETV only
Poor outcome of hepatitis D with NUC-Treatment only

Scheller, …. Deterding. Medicine 2021 Jul 16;100(28):e26571
PEG-IFNa-2a
Treatment of Hepatitis Delta with PEG-IFNa-2a:
~25% HDV RNA suppression

Wedemeyer, Yurdaydin et al. NEJM 2011
No cure of HDV: 
Very late relapses after early virological responses!

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<th>ID</th>
<th>HDV RNA EOT</th>
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</tbody>
</table>

Individual virologic results for all patients who reached HDV RNA negativity at week 72:

*X indicates no data available (HDV RNA). HBsAg negative results are marked in blue and retreatment of the patients with interferon is marked in red.*

PEG-IFNα-2a plus TDF / Placebo for 96 weeks does not prevent relapse

PEG-IFNa-2a:
Factors associated with response to treatment
## PEG-IFNα-2a treatment of hepatitis D: response factors

<table>
<thead>
<tr>
<th>Marker</th>
<th>Role in HBV/HCV [13-15]</th>
<th>Potential role in HDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis present</td>
<td>HBV: not associated with lower treatment response</td>
<td>Not associated with lower treatment response, some studies even show an association to improved treatment response [52]</td>
</tr>
<tr>
<td></td>
<td>HCV: negative response factor</td>
<td></td>
</tr>
<tr>
<td>IL28B genotype</td>
<td>HBV: currently not recommended</td>
<td>No strong evidence, currently not recommended [70]</td>
</tr>
<tr>
<td></td>
<td>HCV: strong association to treatment response</td>
<td></td>
</tr>
<tr>
<td>Viral genotype</td>
<td>HBV: genotype A and B associated with better response than C and D</td>
<td>Genotype 5 is associated with better response to interferon treatment [71,72]</td>
</tr>
<tr>
<td></td>
<td>HCV: genotype 2, 3, 5 and 6 associated with better response than 1 and 4</td>
<td></td>
</tr>
<tr>
<td>Viral load before treatment</td>
<td>HBV: low viral load as predictor of treatment response</td>
<td>Low HDV RNA load associated with treatment response [52]</td>
</tr>
<tr>
<td></td>
<td>HCV: In some cases, shortened treatment duration possible for patients with lower viral load</td>
<td></td>
</tr>
<tr>
<td>Viral load during treatment</td>
<td>Stopping rules based on viral load are well established for both chronic HBV and chronic HCV infection</td>
<td>No clear stopping rules established, but low chances of off treatment response if no HDV RNA decline until treatment week 24 [73-75]. More detailed information in Table 3</td>
</tr>
<tr>
<td>Viral dominance patterns</td>
<td>NA</td>
<td>HDV dominance (HDV RNA &gt; HBV DNA) associated with lower HDV RNA response [77]</td>
</tr>
<tr>
<td>NK cell function</td>
<td>NA</td>
<td>High frequency of CD56(dim) NK cells at baseline associated with IFNα treatment outcome [31]</td>
</tr>
</tbody>
</table>
Low HDV viremia during treatment is associated with post-treatment relapse

HBV DNA increase during PEG-IFNa treatment despite TDF therapy
Loss of infected cells

HBcAg Levels Are Associated With Virological Response to Treatment With Interferon in Patients With Hepatitis Delta

Sandmann et al. Hepatol Commun 2022; 6(3):480-495
Bulevirtide
Bulevirtide (Myrcludex B) to Treat Hepatitis D

4.1 Therapeutic indications
Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease.

4.2 Posology and method of administration
Treatment should be initiated only by a physician experienced in the treatment of patients with HDV infection.
Bulevirtide (Myrcludex B)

- Myrcludex B specifically binds to NTCP at the basolateral membrane of differentiated hepatocytes.
- Myrcludex B shows strong inhibitory potential for HBV and HDV infection ($IC_{50}$ ca 80 pM in PHH).
- It exclusively targets parenchymal liver cells.

Urban et al., Gastroenterology 2014;147:48-64
MYR202: HDV RNA decline

Week 24  FU-Week 24
A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D

Baseline bile acid levels but not bile acid increases during bulevirtide treatment of hepatitis D are associated with HDV RNA decline

Katja Deterding, Cheng-Jian Xu, Kerstin Port, Benjamin Maasoumy, Markus Cornberg, Heiner Wedemeyer
Lonafarnib: phase 3 trial ongoing (press release Dec 2022)

- **48 weeks**
  - n=175: LNF + RTV
  - n=125: LNF + RTV pegIFNα-2a
  - n=50: pegIFNα-2a
  - n=50: Placebo

- **24 weeks**
  - Follow up
Lonafarnib: phase 3 trial ongoing
(press release Dec 2022 & EASL Presentation June 2023)

Virological Response: 
≥ 2 Log Decline in HDV RNA

Biochemical Response: 
ALT Normalization

https://ir.eigerbio.com/static-files/9bf8edda-112c-44c1-a746-d8ede5f2897f
Lonafarnib: phase 3 trial ongoing
(press release Dec 2022 & EASL Presentation June 2023)
D-LIVR study: Composite endpoint (Virological and biochemical response) at EOT and Post-treatment follow-up

**RANDOMIZED POPULATION, N=338**

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients, %</th>
<th>(N/N)</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>2.6%</td>
<td>(1/39)</td>
</tr>
<tr>
<td>LNF + RTV</td>
<td>11.5%</td>
<td>(17/148)</td>
</tr>
<tr>
<td>LNF + RTV + pegIFNα</td>
<td>21.8%</td>
<td>(24/110)</td>
</tr>
<tr>
<td>pegIFNα</td>
<td>9.8%</td>
<td>(1/41)</td>
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<tr>
<td>LNF + RTV + pegIFNα</td>
<td>26.4%</td>
<td>(29/110)</td>
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</table>

*p<0.0001

*PTWK24 responders may be different from responders at EOTWK48

HDV RNA undetectability rates off-therapy?

modified from Etzion O et al, EASL 2023
Nucleic Acid Polymers
Nucleic Acid Polymers for HDV Infection
Rep-3129: Blocking Particle Release

HBsAg

HDV RNA

Nucleic Acid Polymers Against HDV

Additional case reports presented during recent meetings (EASL, AASLD, APASL)
siRNAs against HBV
REEF-D: Change in HBsAg and HDV RNA Over Time

- Treatment with JNJ-3989 led to robust reductions in HBsAg and HDV RNA
- The antiviral activity criteria to start Part 2 of the study were met

SE, standard error.

*HDV RNA ≥2 log_{10} IU/mL decline from baseline or undetectable in combination with normal ALT at Week 48. †Data in the immediate active arm are available for 17 patients up to Week 12, and for 14, 11, and 9 patients at Weeks 24, 36, and 48, respectively, due to early JNJ-3989 treatment discontinuation. ‡8 JNJ-3989–treated patients with ≥0.5 log_{10} reduction from baseline in HBsAg and HDV RNA, and 4 of those with ≥1 log_{10} reduction in HDV RNA.
REEF-D: Individual ALT Levels Over Time by Baseline HBsAg Level

Available data beyond Week 48 are included. F, follow-up.

*Confirmed (2 consecutive visits) ALT ≥3 × ULN and ≥2 × nadir.

- 12/17 patients in the immediate active treatment arm experienced ALT elevations† (starting mainly between weeks 8 and 20) leading to treatment discontinuation
- PEG-IFNa is still the standard treatment of hepatitis D for most patients world-wide

- Bulevirtide approved by EMA
  - virological and biochemical responses in most patients
  - how long to treat? Decompensated cirrhosis?
  - Combination with PEG-IFNa?

- Additional new treatments in clinical development
  (PEG-IFN lambda, Lonafarnib, NAPs, siRNAs against HBV)

- Personalized management approach for individual patients with chronic hepatitis D required!
Hepatitis D