ACG International Webinar Series:
What's new in the treatment of hepatitis delta (HDV)?
Hosted by the Pakistan Society for the Study of Liver Diseases (PSSLD)

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What's new in the treatment of hepatitis delta (HDV)?

Nancy Reau, MD, FACP
Professor of Medicine
Richard B. Capps Chair of Hepatology
Chief, Section of Hepatology
Associate Director, Solid Organ Transplantation
Rush University Medical Center
**Agenda**

- Epidemiology of HDV
- Screening and Diagnosis
- Treatment – current and future

**Brief Review of hepatitis delta**

**CAUSE**
Infection with HDV
Requires HBV: coinfection or superinfection

**TRANSMISSION**
Via direct contact with bodily fluids
Routes of transmission: contaminated needles or transfusion, sexual transmission, mother-to-baby

**SYMPTOMS**
Often asymptomatic
No particular symptoms relate specifically to HDV

**COURSE OF INFECTION**
Acute or chronic
*Acute*: occurs suddenly, may cause severe symptoms, resolves within 6 months. However, can lead to acute liver failure
*Chronic*: long-term consequence of infection associated with high risk for liver disease

**CONSEQUENCES OF INFECTION**
Increased risk for cirrhosis and HCC than HBV alone
The most severe form of chronic viral hepatitis, due to more rapid progression to liver-related death and HCC than the other viruses
HDV Is the Most Severe Form of Viral Hepatitis

**HEPATITIS A**
- No, but can cause fatal fulminant hepatitis in a very small proportion

**HEPATITIS B**
- Adults: 5%
- Children: 90%
- 20%-30% (lifetime)

**HEPATITIS C**
- 15%-30% (20 years)

**HEPATITIS D**
- 76%
- Cirrhosis within 5 years; HCC within 10 years

**HEPATITIS E**
- Can occur rarely in immunosuppressed individuals
- No, as virus does not result in chronic infection

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Increased Risk for Long-term Consequences of Viral Hepatitis in Patients With HDV/HBV Coinfection vs HBV Monoinfection

- Risk for long-term consequence in patients with HBV monoinfection
- Risk for long-term consequence in patients with HDV/HBV coinfection

Disease progression in chronic HBV is not linear, and HCC can develop in the absence of cirrhosis.

1 Epidemiology of HDV

Approximately 4.5-13% of HBsAg-positive carriers are co-infected with HDV

Estimated number of individuals infected with HDV globally
- Based on analysis of prevalence in 6 WHO regions (95 countries): 12 million (8.7-18.7 million)
- Based on meta-analysis of published data (83 countries): 48-60 million

Prevalence rate (%)
- >20
- 0
- No data available

Estimated number of individuals with HDV in selected countries

An estimated 48-60 million people are infected with HDV worldwide.

- USA: 127,000
- Japan: 61,000
- France: 31,000
- Germany: 32,000
- Italy: 49,000
- Spain: 68,000
- UK: 43,000
- China: 10,300,000

Numbers shown are patient numbers, i.e., prevalence of HDV in HBsAg-positive patients. HBsAg: hepatitis B surface antigen; HDV: hepatitis delta virus.

Risk of developing HDV vs general population or HBsAg-positive population without HDV. HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HDV: hepatitis delta virus; HIV: human immunodeficiency virus.

Groups at high risk of HDV (in order of greatest risk):

- Migrants from endemic countries
- People who inject drugs
- Commercial sex workers
- Men who have sex with men
- HCV-infected individuals
- Cirrhosis patients
- Hemodialysis recipients
- HIV-infected individuals
- HCC patients

Additional factors contributing to increased HDV prevalence:

- Migrants from endemic countries
- No HBV vaccination
- Mother to baby

Risk of developing HDV vs general population or HBsAg-positive population without HDV. HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HDV: hepatitis delta virus; HIV: human immunodeficiency virus.
Clinical course of hepatitis delta

HDV exposure → Acute HDV → 51.9% → Spontaneous clearance

Virus persists → Chronic disease → 76.5%

Fibrosis → Cirrhosis → HCC development can occur independently of cirrhosis in some individuals

HCC → Death

29.7% in 3.1 years

5.6% in 5.4 years

HDV/HBV vs HBV monoinfection: more rapid progression to cirrhosis and HCC

Meet Lin

• 27 yo woman newly diagnosed with HBV after her brother was found to have hepatitis B and family screening recommended.
  - No symptoms
  - ALT 17 IU/ml
  - PLTs 182
  - HBsAg positive
  - HBV DNA detectable but not quantifiable

- Should you screen Lin for HDV?
2 Screening and Diagnosis of HDV

The HDV Patient Journey in the United States

**MOST COMMON**

New HBV patient visit

- Not screened for HDV

Established HBV patient

- Managed for HBV

Increase in LFT ± symptoms and suppression of HBV DNA* triggers HDV test

Diagnosed with HDV

- Anti-HDV positive
- HDV RNA positive

**LESS COMMON**

Patient risk factors prompt HDV screen

- Endemic region, PWID, MSM
- STD history per multiple sexual partners, coinfected with HIV or HCV, elevated ALT with low HBV DNA

Not screened for HDV

- Patient screened for HDV due to risk factors

HCP screens all HBV for HDV

- HDV-positive

**In the United States, the patient’s journey from screening through monitoring reveals many opportunities to improve the HDV cascade of care**

HCP=healthcare provider; LFT=liver function test; MSM=men who have sex with men; STD=sexually transmitted disease.

*Starts treatment or HDV dominance

Internal data: Gilead Sciences, Inc.
All patient with HBsAg should be tested for HDV

Co-morbidities, including alcoholic, autoimmune, metabolic liver disease with steatosis or steatohepatitis and other causes of chronic liver disease should be systematically excluded including co-infections with hepatitis D virus (HDV), hepatitis C virus (HCV) and HIV.

**EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection**

European Association for the Study of the Liver

Simultaneous coinfection with HBV and HDV → Usually results in spontaneous clearance of both viruses

HDV superinfection in an HBV carrier → Usually results in persistent viral replication

HDV superinfection in an HBV carrier → May occasionally result in HDV RNA clearance after many years

ALT=alanine aminotransferase; HBV=hepatitis B virus; HDV=hepatitis delta virus; IgG=immunoglobulin G; IgM=immunoglobulin M; RNA=ribonucleic acid.
Testing Recommendations for HDV

WHOM TO TEST?

AASLD (2018)
- HBsAg+ patients with HDV risk factors
- Low/undetectable HBV DNA and high ALT

EASL (2017)
- All patients infected with HBV

APASL (2016)
- Patients with chronic HBV and chronic liver disease

WHO (2015)
- NO RECOMMENDATION

HOW TO TEST?

- Anti-HDV
- HDV RNA

Despite guidelines being in place, a large proportion of HBsAg+ individuals remains untested for HDV. New strategies and education on reflex testing should be considered.
### Diagnosis of Different Stages of HDV Infection\(^1\)-\(^4\)

<table>
<thead>
<tr>
<th>Diagnostic Marker</th>
<th>Acute HDV/HBV Coinfection</th>
<th>Acute HDV Superinfection</th>
<th>Chronic HDV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anti-HBc, IgM</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Serum HDAg (by EIA/RIA)</td>
<td>Early and short-lived, and frequently missed</td>
<td>Early and transient, and frequently missed</td>
<td>Transient and may not be detected</td>
</tr>
<tr>
<td>Serum HDV RNA (by RT-PCR)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anti-HDV, total</td>
<td>Late, low titer</td>
<td>Rapidly increasing titer</td>
<td>High titer</td>
</tr>
<tr>
<td>Anti-HDV, IgM</td>
<td>+</td>
<td>Rapidly increasing and persistent titer</td>
<td>Variable titers, usually high titers</td>
</tr>
</tbody>
</table>

**Note:** HDV genotyping is not done routinely in clinical practice.

EIA = enzyme immunoassay; HBc = hepatitis B core; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HDAg = hepatitis delta antigen; HDV = hepatitis delta virus; IgM = immunoglobulin M; RIA = radioimmunoassay; RNA = ribonucleic acid; RT-PCR = reverse transcription polymerase chain reaction.


### Algorithm for the Evaluation of HDV

1. **HBsAg (+) patients**
   - **Anti-HDV**: 
     - **HDV RNA**: 
       - **ALT**: 
         - **Normal**: Previous HDV infection
         - **Elevated**: Check for other etiologies of elevated ALT besides HBV infection
   - Standard of care management of HBV

2. **Standard of care management of HBV**
   - **ALT**: 
     - **Assessment of fibrosis**
       - Liver biopsy
       - FibroScan®
       - Serum fibrosis markers
Diagnosis of HDV Requires Testing for HDV Antibodies and HDV RNA

Anti-HDV total
- First-line screening test
- Generally available globally
- Limited availability in developing countries

HDV RNA
- Assessed by NAT/RT-PCR
- Qualitative and quantitative
- Confirmatory test for active infection
- Availability and accessibility
- Potential for false-negatives
- High cost-burden


Anti-HCV Reflex to HCV RNA: Impact on Testing

HCV RNA reflex testing of anti-HCV positive patients in Barcelona, Spain, 2015-2018
Analysis of diagnostic tests performed by a central laboratory before and after implementing a reflex testing protocol

Percentage of anti-HCV positive patients screened for HCV RNA

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Traditional</th>
<th>Reflex</th>
</tr>
</thead>
<tbody>
<tr>
<td>52.3%</td>
<td>2719/5195</td>
<td>91.3%</td>
</tr>
</tbody>
</table>

Implementation of viral load reflex testing significantly increases the diagnostic effectiveness and allows for the identification of underdiagnosed cases

Algorithm for the Evaluation of HDV

HBsAg (+) patients → Anti-HDV

- Standard of care management of HBV

+ HDV RNA → ALT

Normal
- Previous HDV infection

Elevated
- Check for other etiologies of elevated ALT besides HBV infection

Assessment of fibrosis
- Liver biopsy
- FibroScan®
- Serum fibrosis markers

HBV serology

HDV serology

<table>
<thead>
<tr>
<th>Condition</th>
<th>HBsAg</th>
<th>Anti-HBc IgM</th>
<th>Anti-HBc IgG</th>
<th>HDV DNA</th>
<th>HDAg</th>
<th>Anti-HDV IgM</th>
<th>Anti-HDV IgG</th>
<th>HDV RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute HBV/HDV co-infection</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acute HBV/HDV superinfection</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chronic HBV/HDV infection</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Resolved HBV and HDV</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

HBV and HDV serology markers can indicate the stage of infection

HBV and HDV serology markers can indicate the stage of infection


Barriers to HDV screening

Diagnostic challenges

1. HDV antibody tests are not widely available and can be inconclusive
2. Lack of routine screening of patients with HBsAg
3. Lack of standardization of HDV RNA tests (although newer assays are better standardized)

Education challenges

1. Limited and conflicting guidance on HDV screening (national and international guidelines)
2. Limited HCP education/awareness of HDV
3. Reduced motivation to screen due to no approved treatment options until recently

Lack of screening

Meet Lin

- Lin is tested for anti-HDV and it is positive → HDV PCR positive
- What do you do next?
More Rapid Progression With HDV/HBV Coinfection vs HBV Monoinfection: A Study From 1987

Retrospective Italian cohort (N=146) of HBsAg-positive patients; 18/146 (12%) tested positive for anti-HDV and were followed for 1 to 15 years

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of HBsAg carriers</th>
<th>Anti-HDV positive (n=13)</th>
<th>Anti-HDV negative (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPH</td>
<td>Normal liver</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>CAH</td>
<td>CPH</td>
<td>—</td>
<td>0%</td>
</tr>
<tr>
<td>CAH</td>
<td>Normal liver</td>
<td>—</td>
<td>18 - 31%</td>
</tr>
<tr>
<td>Unchanged</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPH</td>
<td>CPH</td>
<td>—</td>
<td>6</td>
</tr>
<tr>
<td>CAH</td>
<td>CAH</td>
<td>—</td>
<td>14 - 39%</td>
</tr>
<tr>
<td>Active cirrhosis</td>
<td>Active cirrhosis</td>
<td>—</td>
<td>11</td>
</tr>
<tr>
<td>Deteriorated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPH</td>
<td>CAH</td>
<td>—</td>
<td>77%</td>
</tr>
<tr>
<td>CAH</td>
<td>Active cirrhosis</td>
<td>10 - 30%</td>
<td></td>
</tr>
</tbody>
</table>

Progression to cirrhosis was significantly higher in anti-HDV positive patients than in patients without antibody to HDV (P<0.001)
• PEG-INF is currently the only approved HDV therapy
• HBV anti-viral therapy is used when HBV DNA is detected or to decrease the risk of HBV flare during HDV treatment
• New therapies late in development (and approved in some places)

Journal of Hepatology 2017 vol. 67 j 370–398

PegIFNa and HDV

• On-treatment virologic response rates 17-47%.
• 25% HDV RNA negative 24 weeks after treatment cessation
• Late relapses beyond week 24 > 50% of responders
  – Monitor all HDV patients as long as HBsAg detectable
  – HBsAg loss in approximately 10% of PegIFNa patients
• Neither NAs nor ribavirin showed significant effects on HDV RNA levels in patients with HDV infection.

Journal of Hepatology 2017 vol. 67 j 370–398
Ten-year follow-up of long-term peginterferon-α treatment for chronic delta hepatitis

- **Background:** HDV/HBV coinfection is the most severe form of viral hepatitis with limited treatment opportunities. Off-label therapy with PEG-IFNα for 1–2 years was so far the only option, however with sub-optimal responses.

- **Aims:** To evaluate long-term treatment responses during PEG-IFNα therapy (up to 5 years) in CHD patients.

- **Methods:** 13 patients were involved. Mean treatment duration: 75 months [2–397]; extension past 5 years in 5 cases; FU duration: 104 months [2–211]. Classification by virologic response: negative serum HDV RNA (LLD 100 GE/mL). Record of long-term survival and liver-related outcomes.

**Responders and outcomes**

**Virologic response: sustained**

<table>
<thead>
<tr>
<th>Year</th>
<th>Responders (n=7)</th>
<th>Non-responders (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 3</td>
<td>2 virologic responders</td>
<td>3 virologic responders</td>
</tr>
<tr>
<td>Year 5</td>
<td>3 virologic responders</td>
<td>3 virologic responders</td>
</tr>
<tr>
<td>Year 10</td>
<td>1 virologic responders</td>
<td>1 virologic responders</td>
</tr>
<tr>
<td>Year 12</td>
<td>0 virologic responders</td>
<td>0 virologic responders</td>
</tr>
</tbody>
</table>

**Liver-related outcome:**

- 0 (0)
- 2 (3)

**Death:**

- 1 (14)
- 5 (83)

Data are n [%], unrelated to liver disease.

**Cumulative virologic response:**

- 7/13 patients responded at last follow-up;
- 4 lost HBsAg;
- 2/13 patients responded past 5 years of treatment;
- Only responders had normalized transaminases at follow-up.

Kim GE, et al. AASLD TLMX2020. #1028

- **Extended peg-IFNα therapy results in sustained negativation of HDV RNA after 2 years of treatment and even after drug cessation.** Response was associated with HBsAg loss in 31% of patients.

- **Treatment response was associated with clinical improvement.**

- **Patients with HBsAg loss did not require retreatment; HBsAg seroconversion as marker for functional cure of CHD.**

- **Prolonged IFN-based regimes are probably not reasonable in light of the availability of more specific and more efficient drugs with less side effects. Monotherapy, or short-term IFN-combination provoking functional cure is more appropriate.**
Final results of a multicenter, open-label Phase 2 clinical trial (MYR203) to assess safety and efficacy of bulevirtide (myrcludex B) with pegIFN-α2a in patients with chronic HBV/HDV co-infection

**Primary endpoint:**

Undetectable HDV RNA at Week 72

<table>
<thead>
<tr>
<th>Week 48</th>
<th>Week 72</th>
</tr>
</thead>
<tbody>
<tr>
<td>[** Asterisk **]</td>
<td>[** Asterisk **]</td>
</tr>
<tr>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>13.3</td>
<td>26.7</td>
</tr>
<tr>
<td>9/15</td>
<td>4/15</td>
</tr>
<tr>
<td>6/15</td>
<td>4/15</td>
</tr>
<tr>
<td>2/15</td>
<td>0</td>
</tr>
</tbody>
</table>

Two-tailed Fisher’s Test *p=0.0209; **p=0.0022

![HDV RNA levels (log)](image)

**Median serum HDV RNA log reduction**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 48</th>
<th>Week 72</th>
</tr>
</thead>
<tbody>
<tr>
<td>pegIFN-α</td>
<td>-1.30</td>
<td>-0.26</td>
</tr>
<tr>
<td>MyrB 2 mg + pegIFN-α</td>
<td>-4.81</td>
<td>-4.04</td>
</tr>
<tr>
<td>MyrB 5 mg + pegIFN-α</td>
<td>-5.59</td>
<td>-1.48</td>
</tr>
<tr>
<td>MyrB 2 mg</td>
<td>-2.84</td>
<td>-1.08</td>
</tr>
</tbody>
</table>

Wedemeyer H, et al. EASL 2019, Vienna, Austria. #GS-13

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**Safety and efficacy of 2 mg bulevirtide in patients with chronic HBV/HDV co-infection: First real-world results**

<table>
<thead>
<tr>
<th>BLV 2 mg n=77</th>
<th>BLV 2 mg + pegIFN n=68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>41.6±11.8</td>
</tr>
<tr>
<td>Male</td>
<td>54 (70)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>48 (62.3)</td>
</tr>
<tr>
<td>Liver stiffness, kPa</td>
<td>15.4±11.0</td>
</tr>
<tr>
<td>FIB-4</td>
<td>3.03±2.6</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>69.3±35.7</td>
</tr>
<tr>
<td>Median HDV RNA log10 IU/mL (IQR)</td>
<td>6.26 (1.3)</td>
</tr>
<tr>
<td>Undetectable HBV DNA, n/N (%)</td>
<td>49/72 (68.1)</td>
</tr>
<tr>
<td>HBeAg positive</td>
<td>9 (7.5)</td>
</tr>
<tr>
<td>Current NUC use</td>
<td>64 (83.1)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>14 (18.2)</td>
</tr>
</tbody>
</table>

Data are mean ±SD or n (%) unless otherwise stated

De Ledinghen V, et al. AASLD 2021. #O21
Safety and efficacy of 2 mg biveirtide in patients with chronic HBV/HDV co-infection: First real-world results

De Ledinghen V, et al. AASLD 2021. #O21

Real World Effectiveness of BLV 2mg in HDV Patients with Advanced Cirrhosis

Prospective, single center, real-world study of BLV 2 mg monotherapy

Characteristics | n=18
---|---
Age, years*  | 48 (29-77)
Male, n (%)  | 12 (67)
Caucasian, n (%) | 18 (100)
HDV GT 1, n (%)  | 18 (100)
Compensated cirrhosis, n (%)  | 18 (100)
Child-Pugh A6, n (%)  | 4 (28)
CSPH features, n (%)  | 17 (94)
Esophageal varices, n (%)  | 14 (78)
Fibroscan, kPa*  | 16.4 (7.8-57.8)
Platelets, 10^3/mmcc  | 70 (37-227)
Active HCC, n (%)  | 2 (11)
Current TDF or ETV, n (%)  | 18 (100)
Previous IFN, %  | 12 (67)
ALT, U/L  | 106 (32-222)
HDV RNA, log IU/mL*  | 4.9 (3.3-3.6)

Virologic Response

Undetectable HDV RNA or ≥2 Log10 IU/mL decrease from BL

Normal ALT

Combined Response

Undetectable HDV RNA or ≥2 Log10 IU/mL decrease from BL and Normal ALT

Safety Profile

No adverse events, No injection site reactions, No BLV discontinuations
No new safety signals

Real world effectiveness of BLV monotherapy in patients with clinically significant portal hypertension. BLV 2mg was well tolerated, including in patients with advanced cirrhosis, active HCC and with platelets <60,000/mmcc**.

CSPH: clinically significant portal hypertension.

Virologic response: HDV RNA undetectable or ≥2 log IU/mL decline from baseline. Combined response: HDV RNA undetectable or ≥2 log IU/mL decline and ALT normalization from baseline.

CSPH features: "**33% of patients had platelets <60,000/mmcc.

Loglio A, et al. AASLD 2021. LPSN
A Phase 2 study of peginterferon lambda, lonafarnib, and ritonavir for 24 weeks: End-of-study results from the LIFT HDV study

**Baseline characteristic**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>17 (65)</td>
</tr>
<tr>
<td>Age, years, median (IQR)</td>
<td>40 (36, 46)</td>
</tr>
<tr>
<td>Race: Asian / White / Black, %</td>
<td>54, 31, 15</td>
</tr>
<tr>
<td>ALT, U/L, mean</td>
<td>64</td>
</tr>
<tr>
<td>AST, U/L, mean</td>
<td>47</td>
</tr>
<tr>
<td>HBV DNA, IU/mL, mean</td>
<td>&lt;20</td>
</tr>
<tr>
<td>HDV RNA, Log IU/mL, mean</td>
<td>4.74</td>
</tr>
<tr>
<td>VCTE, KPA, median</td>
<td>11.8</td>
</tr>
<tr>
<td>Ishak fibrosis score, mean (range)</td>
<td>3 (2–4)</td>
</tr>
</tbody>
</table>

**Treatment response at 12 and 24 weeks**

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Mean change in Log HDV RNA (IU/mL)</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 weeks</td>
<td>3.36</td>
<td>(2.86–3.85)</td>
</tr>
<tr>
<td>24 weeks</td>
<td>3.23</td>
<td>(2.94–4.49)</td>
</tr>
</tbody>
</table>

**Safety**

- Most common AEs
  - Diarrhea – 100%
  - Nausea – 69%
  - GERD – 65%
  - Abdominal bloating – 63%
  - Anorexia – 46%
  - Fatigue – 42%
  - Weight loss – 31%
  - Anemia – 23%
  - Hyperbilirubinemia – 19%

- 2 dose reductions
  (1 x anemia, 1 x hyperbilirubinemia)

- 5 discontinuations
  (4 x hyperbilirubinemia, 1 x ascites)

**End of study: ALT changes from baseline**

<table>
<thead>
<tr>
<th>Median (IQR)</th>
<th>Undetectable or BLOQ (n=5)</th>
<th>Remaining cohort (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT at baseline</td>
<td>64.7 (46, 125.3)</td>
<td>58.2 (44.7, 84.7)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Change in ALT</td>
<td>-43.7 (–91.3, –26)</td>
<td>-2.17 (–17.2, 41.8)</td>
<td>0.0151</td>
</tr>
</tbody>
</table>

**ALT at baseline**

- Undetectable or BLOQ (n=5): 64.7 (46, 125.3)
- Remaining cohort (n=20): 58.2 (44.7, 84.7)

**Change in ALT**

- Undetectable or BLOQ (n=5): -43.7 (–91.3, –26)
- Remaining cohort (n=20): -2.17 (–17.2, 41.8)
A Phase 2 study of peginterferon lambda, lonafarnib, and ritonavir for 24 weeks: End-of-study results from the LIFT HDV study

At 24 weeks of treatment (EOT)
- 77% >2 Log decline in HDV RNA
- 50% HDV RNA undetectable/BLOQ
- 23% HDV RNA undetectable/BLOQ 5 of 22 pts
- Discontinuation rate 19%

End of study results from LIMIT HDV study: 36% durable virologic response at 24 weeks post-treatment with pegIFN-lambda monotherapy in patients with chronic HDV infection

- 48-week treatment and 24-week f/u of pegIFN-lambda monotherapy in HDV/HBV coinfected patients
  - SC QW 120 µg (n=19)
  - SC QW 180 µg (n=14)
- Sites:
  - Pakistan (15)
  - Israel (14)
  - New Zealand (4)
- Compensated disease ULN ALT – <10 ALT ULN
- BL median HDV RNA 4.1log10
  - 6 below 4log_{10}
  - 8 above 4log_{10}
  - 120 µg arm showed significantly lower responses

Etzion O, et al. EASL 2019, Vienna, Austria. #PS-052
### End of study results from LIMIT HDV study: 36% durable virologic response at 24 weeks post-treatment with pegIFN-lambda monotherapy in patients with chronic HDV infection

**Durable virologic response (defined as serum HDV RNA below 14 IU/mL in 36% (5/14) in 180 µg arm vs 28% HDIF; DVR 50% in patients with <4 log₁₀**

<table>
<thead>
<tr>
<th>Durable virologic response (DVR) demonstrated</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVR = 36% BLOQ at 24 weeks post-treatment with lambda 180 µg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 48</th>
<th>End of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td></td>
</tr>
<tr>
<td>Lambda 120 µg</td>
<td>36</td>
</tr>
<tr>
<td>Lambda 180 µg</td>
<td>50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 72</th>
<th>End of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td></td>
</tr>
<tr>
<td>Lambda 120 µg</td>
<td>36</td>
</tr>
<tr>
<td>Lambda 180 µg</td>
<td>36</td>
</tr>
</tbody>
</table>

**Adverse events: predominantly Grade 1**

- IFN lambda (180 µg) shows antiviral activity in HDV-infected patients
- Possible alternative for combination instead of IFNs
- Post-treatment durability observed
- BL HDV RNA levels low, when compared to HDFT study
- No comparative arm with IFNαs with the new advances methods of detection
- Liver specific side effects of IFN lambda (bilirubin) observed

### Ongoing analysis of functional control / cure of HBV and HDV infection following REP 2139-Ca and pegIFNα-2a therapy in patients with chronic HBV / HDV co-infection: 3-year follow-up results from the REP 301-LTF study

- 12 Caucasian REP 301 chronic HBV/HDV patients were enrolled in REP 301-LTF trial
- 11 patients were followed to evaluate long-term efficacy and safety of combination therapy with REP 2139-Ca and pegIFN (15 weeks)

<table>
<thead>
<tr>
<th>REP 2139-Ca</th>
<th>PegIFN</th>
<th>f/u 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15</td>
<td>30</td>
</tr>
</tbody>
</table>

### 3–3.5 year response, n (%) | N=11

<table>
<thead>
<tr>
<th>Clinical</th>
<th>ALT normalization</th>
<th>8 (73)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal or declining LMS</td>
<td>7 (64)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>&lt;0.05 IU/mL</th>
<th>5 (42)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seroconversion</td>
<td>4 (36)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HDV RNA</th>
<th>Undetectable, n (%)</th>
<th>N=7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>&lt;0.05 IU/mL</th>
<th>4 (57)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive with HBV DNA ≤2000 IU/mL</td>
<td>3 (43)</td>
</tr>
</tbody>
</table>

**LMS, liver median stiffness**

- Functional cure of HBV tends to sustain in most patients for 3–3.5 years after stopping REP 2139 and pegIFN combination in this pilot study
- A controlled study with more patients is needed to confirm the benefit of this combination treatment strategy

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*Bazinet M, et al. AASLD 2019, Boston, USA. #705*
Effect of IFN response on cell division-mediated HDV spread and HDV persistence in combination with antivirals abrogating de novo infection

Zhang Z, et al. EASL 2021. #OS-1742

Effect of IFN treatment

High MOI (1 IU/cell)

Low MOI (1/64 IU/cell)

Zhang Z, et al. EASL 2021. #OS-1742
Effect of IFN response on cell division-mediated HDV spread and HDV persistence in combination with antivirals abrogating de novo infection

Drug combination targeting both spreading pathways act synergistically
- INF likely to remain an important treatment for HDV
- INF more effective if HDV load low- but may not be clinically relevant

Zhang Z, et al. EASL 2021. #OS-1742

Hepatitis delta: Conclusions

- 9-60 million people infected with HDV globally
- Defective RNA virus, requiring HBV for infection
- 4.5-13% of HBV carriers co-infected with HDV
- Most severe form of viral hepatitis
- Increased risk of cirrhosis/HCC and higher mortality vs HBV
- Progression to cirrhosis within 5 years and to HCC within 10 years
- Eight HDV genotypes
- Until recently, no approved therapeutic options
Take-home Points

- HBsAg positive individuals should be screened for HDV with anti-HDV or HDV-Ag
- Anti-HDV positive patients should have HDV PCR testing
- HDV PCR positive individuals are at high risk for clinical complications and should be considered for treatment and liver cancer surveillance

ACG International Webinar Series:
What’s new in the treatment of hepatitis delta (HDV)?
Hosted by the Pakistan Society for the Study of Liver Diseases (PSSLD)

Speaker:
Nancy S. Reau, MD, FACP

Moderator:
Zaigham Abbas, MBBS, FACP

QUESTIONS?