Viral Hepatitis and Introducing Delta Hepatitis
Lunch and Learn Clinical Case Panel Session

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Disclosures:

Christopher Tait- None
Vinod Rustgi- Gilead, Speaker's Bureau
Hepatitis D (delta) virus (HDV) is prevalent in the chronic hepatitis B population particularly in certain high risk groups, and this prevalence is likely underestimated. Untreated chronic HDV can cause progressive liver disease and is a risk factor for HCC in untreated patients. Previously, therapeutic options were limited to interferon, but several new therapies have shown promising results in phase 2 and 3 clinical trials.
• Goals:
  • Review the basic pathophysiology and epidemiology of HDV infection
  • Review current guidelines for screening and diagnosis of acute and chronic HDV infection
  • Highlight current and emerging therapeutic options
A 42 year old male with a history of Sjogren’s syndrome and chronic hepatitis B presents as a referral for elevated liver enzymes. He is originally from Mongolia and came to the US in his 20s. Previously he had been told he has chronic hepatitis B, but was told by a previous doctor that he did not need specific therapy. His primary doctor has noticed his liver enzymes are mildly elevated. These labs are significant for an ALT 156, AST 95, Tbili 0.7, alk phos 94. Recent hepatitis B testing shows +HBsAg, +HBeAg, HBV DNA 212 IU/mL. A recent liver elastography revealed a kPA of 6, estimating F0-F1 fibrosis.

- What features of this case suggest testing for chronic hepatitis D?
- What testing is recommended for hepatitis D evaluation?
Hepatitis D Background

- Hepatitis D (delta) is a small, defective RNA virus that is dependent on HBV coinfection for infectivity.
- Genetic homology of HDV is close to plant viroids rather than hepadna viruses.
  - Perhaps evolved from tomato or cucumber mosaic viruses and then crossed over to animal kingdom.
- Types of HDV infection:
  - Coinfection with acute HBV and HDV- clinical entity indistinguishable from acute HBV. +HBcAb IgM. Subset of pts will clear both viruses.
  - Superinfection- previous chronic HBsAg carrier contracts HDV. Almost always progresses to chronic HDV infection.
  - Chronic HDV infection- chronic replication and variable progression to chronic liver disease. HBV replication is often suppressed by HDV.

HDV virion: Composed of RNA genome, single HDV encoded antigen, and lipoprotein envelope from HBsAG.

Urban et al, Hepatitis D virus in 2021: virology, immunology, and new treatment approaches for a difficult-to-treat disease, Gut 2021

Negro et al, “Diagnosis of hepatitis D infection,” UpToDate 2023
Hepatitis D Epidemiology

- Estimated 262 million chronic HBV cases worldwide.
- HDV prevalence estimates vary. Recent series estimate 4.5% of chronic HBV carriers have HDV coinfection → 12 million cases
  - Discrepancy suggests underestimation from lack of universal testing and limitations in testing materials for many countries
- Modes of transmission include perinatal, blood transmission, and sexual contact
- Endemic to certain geographic areas:
  - Mediterranean basin, Central Asia (Mongolia, Pakistan), Western and Middle Africa
- In Western countries including US, predominantly confined to high risk groups:
  - IVDU (36-50% in some series), recipients of multiple transfusions, migrants from endemic regions

Stockdale et al, Global Prevalence of Hepatitis D Infection, J Hepatology 2020

Jeng W Lok P et al, A Review of the Systemic Manifestations of HBV infection, Hepatitis D Virus, Hepatocellular Carcinoma, and Emerging Therapies, Lancet 2023
Hepatitis D Natural History

- Natural course is **variable**:
  - Acute disease: mild hepatitis to **fulminant liver failure**
  - Chronic disease: **spectrum from indolent carriage to chronic severe hepatitis** with risk of long term cirrhosis and HCC
- Severity depends on **genotype**:
  - **Genotype 1**- Predominates in Western world. Higher risk of ALF and more rapid progression to cirrhosis\(^3\).
  - **Genotype 2**- Predominant in Far East. Lower risk ALF or rapid progression to cirrhosis.
  - Less data available on 8 other genotypes described

Gish R, Diagnosis and Screening for Hepatitis D Viral infection, Hepatitis B Foundation White Paper\(^5\)
Hepatitis D Clinical Features

- Estimated **50-70%** of HBV/HDV coinfections develop **cirrhosis** within 5-10 years (3x rate of HBV monoinfection)\(^1\)
  
  **HCC risk** is increased compared with HBV monoinfection: OR 1.28-2.77\(^{1,3}\)

- While chronic hepatitis from HDV effects predominate, cases with **concurrent HBV replication** have highest rates of cirrhosis and HCC\(^3\)

- Higher association with fulminant liver failure in coinfections of **IV drug users**

- Association with **primary Sjogren’s syndrome** in chronic HDV cases\(^3\)

“Chronic HDV is the most severe form of viral hepatitis”
Robert Gist, Director, Hepatitis B foundation\(^5\)

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Urban et al, Hepatitis D virus in 2021: virology, immunology, and new treatment approaches for a difficult-to-treat disease, *Gut* 2021\(^1\)

Gish R, Diagnosis and Screening for Hepatitis D Viral infection, Hepatitis B Foundation White Paper\(^5\)
### Hepatitis D Diagnosis

#### Serologic markers in acute HBV/HDV coinfection

<table>
<thead>
<tr>
<th>Diagnostic Markers</th>
<th>Acute HBV/HDV 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- HBe IgM</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HDV RNA</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anti-HDV total antibodies (IgM + IgG)</td>
<td>Late, low titer</td>
<td>Rapidly rising</td>
<td>Higher titers</td>
</tr>
</tbody>
</table>

Negro et al, Diagnosis of hepatitis D virus infection, UpToDate 3/2023
Hepatitis D Diagnostic Testing and Screening

- Recommend **total HDV antibody** as initial test for screening or diagnosis of acute or chronic HDV, and then **HDV RNA testing** if positive (or still suspicious)
  - Antibodies may be negative/low in acute coinfection, so low threshold for RNA testing in this setting

- **Diagnostic testing** recommended in certain clinical scenarios:
  - **Acute HBV infection** - test if high risk for HDV or if unusually prolonged course
  - Acute or **worsening hepatitis** in chronic HBV patient (rule-out superinfection)

- Which patients qualify for screening controversial between guidelines:
  - EASL, Hepatitis B Foundation recommends screening **ALL** chronic hepatitis B patients for HDV
  - AASLD recommends screening only for high risk groups

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High Risk Features for HDV Coinfection (AASLD 2018)

- Persons born in regions with reported high HDV endemicity:
  - Africa (West Africa, horn of Africa)
  - Asia (Central and Northern Asia, Vietnam, Mongolia, Pakistan, Japan, Taiwan)
  - Pacific Islands (Kiribati, Nauru)
  - Middle East (all countries)
  - Eastern Europe (Eastern Mediterranean regions, Turkey)
  - South America (Amazonian basin)
  - Other (Greenland)

- Persons who have ever injected drugs
- Men who have sex with men
- Individuals infected with HCV or HIV
- Persons with multiple sexual partners or any history of sexually transmitted disease
- Individuals with elevated ALT or AST with low or undetectable HBV DNA

Terrault et al, Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018
Hepatitis D Testing

Ordering Testing
In the past, availability and accuracy of testing for hepatitis delta has been limited. However, recent advancements have given more hope for this type of testing, which is now available from several labs within the U.S. and internationally:

- **Quest Diagnostics (US)**
  - HDV Antibody, Total
  - HDV Antibody IgM
  - HDV RNA (Qualitative)
  - HDV RNA (Quantitative)
- **ARUP Laboratories (US)**
  - HDV Antibody Total
  - HDV Antibody IgM
  - HDV Antigen (ELISA)
  - HDV RNA (Quantitative)
- **BioAgilytix (US)**
  - Hepatitis D Antigen and IgM Antibody in Serum
- **Mayo Clinic Laboratories (US)**
  - HDV Antibody Total
- **Viracor (US)**
  - HDV Antibody Total
  - HDV Antibody IgM
  - HDV RNA (Qualitative)
- **Centers for Disease Control and Prevention (CDC) (US & International)**
  - HDV Antibody Total
  - HDV RNA
  - Genotyping
A 42 year old male with a history of Sjogren’s syndrome and chronic hepatitis B presents as a referral for elevated liver enzymes. He is originally from Mongolia and came to the US in his 20s. Previously he had been told he has chronic hepatitis B, but was told by a previous doctor that he did not need specific therapy. His primary doctor has noticed his liver enzymes are mildly elevated. These labs are significant for an ALT 156, AST 95, Tbi 0.7, alk phos 94. Recent hepatitis B testing shows +HBSAg, +HBEAg, HBV DNA 212 IU/mL. A recent liver elastography revealed a kPA of 6, estimating F0-F1 fibrosis.

• What features of this case suggest testing for chronic hepatitis D?
  • Migrated from endemic area (Mongolia), with ALT elevation despite low level HBV DNA. Sjogren’s syndrome also associated with chronic HDV.

• What testing is recommended for chronic hepatitis D evaluation?
  • Serum HDV total antibodies and confirmatory HDV RNA if positive.
The patient’s HDV total antibodies return with high titer, and his confirmatory HDV RNA returns elevated at 5.44 log IU/mL. His repeat liver enzymes remain elevated at ALT 144, AST 102. HBV DNA level remains low (212 IU/mL). His platelets are 263 and his INR 1.0.

- Does this patient qualify for treatment for chronic hepatitis D?
- What treatments are currently available?
- What are the goals of therapy?
- Should he receive treatment for chronic hepatitis B?
Hepatitis D Management

- **When to treat:** Recommended for chronic HDV with detectable HDV RNA and active liver disease (elevated ALT or liver biopsy with chronic hepatitis)\(^8\)
  - Asymptomatic HDV carriers (persistently normal ALT) → no therapy indicated, monitor liver enzymes Q6 months

Lok et al, Endpoints and New Options for Treatment of Chronic Hepatitis D. Hepatology 2021\(^8\)
Hepatitis D Management

• **Primary treatment goals**: suppression of HDV replication, accompanied by ALT normalization (or decrease in necroinflammatory activity on liver biopsy).
  - Usually assessed at **24 weeks** (6 months) **after** therapy. If negative HDV RNA = SVR.
  - Since SVR is low with current therapy (<30%) and relapse common, alternative endpoints are being evaluated in trials but need validation of long term clinical benefits
    - >2-log reduction (e.g. $10^5$ to $10^3$) in HDV RNA another endpoint under investigation in recent trials
  - Ideal endpoint is **HBsAg loss**, but rarely achieved with standard therapy and undetermined with new therapies so impractical

Lok et al, Endpoints and New Options for Treatment of Chronic Hepatitis D. Hepatology 2021
Hepatitis D Therapeutic Challenges

- Discovered in 1977 and recognition of need for newer therapies only recently catching up to prevalence and morbidity identified with chronic infection
- HDV virion so small it does not code its own proteins but hijacks host cell machinery and HBV proteins.
  - Subsequently, common antiviral medications including viral polymerase inhibitors used in HBV, HCV, HIV are ineffective
- Currently no approved medications that can be safely used in decompensated cirrhosis (CPB or C).
Hepatitis D Therapeutic Challenges

• Why doesn’t controlling HBV also control HDV?
  • Attempts to control chronic HDV with nucleos(t)ide analogues (NA) were unsuccessful
  • Hypothesized NA may limit HBV infectivity but HBsAg is still formed at low levels, which is all HDV requires for infectivity
Hepatitis D Therapy

• Only currently available for treatment for chronic hepatitis D in US is off-label interferon alfa (IFN-α).
  • PEG-IFN 2α (180 mcg weekly for 48 weeks subcutaneously) the only guideline recommended therapy\textsuperscript{9,10}
  • Mechanism incompletely understood. Likely augments cell-mediated antiviral effects.
  • Use limited, contraindicated with autoimmune disease stigmata, advanced/decompensated liver disease (Child’s Pugh B or C), neuropsychiatric disorders. Cautious use in elderly.
  • Wide range of adverse effects (fatigue, headache, nausea, abdominal pain, diarrhea)
  • Reported SVR rates generally low (25-30%) and late relapses are common\textsuperscript{1,8}

Lok et al, Endpoints and New Options for Treatment of Chronic Hepatitis D. Hepatology 2021\textsuperscript{8}
Several medications (some when adding to IFN or NA) have shown efficacy in phase 2 clinical trials and are being evaluated in phase 3 trials:

- **Bulevirtide** - entry inhibitor, blocks binding of HBsAg enveloped particles to NTCP entry receptor
  - Daily injection. Can cause bile acid increase. Safety in cirrhosis TBD.
- **Lonafarnib** - farnesyl-transferase inhibitor, blocks farnesylation of HDAg which is required for virion assembly.
  - Significant GI side effects, can be minimized when given with ritonavir
  - **Ritonavir** - protease inhibitor (CYP3A4 inhibitor) used in combination to boost drug levels (similar to use with HIV medications).
- **REP 2139** - HBsAg secretion inhibitor. Nucleic acid polymer (NAP) blocks assembly/release of subviral HBsAg particles and reduces HBsAg needed for HDV particle assembly

Lok et al, Endpoints and New Options for Treatment of Chronic Hepatitis D. Hepatology 2021
**Completed Phase II Clinical Trials**

<table>
<thead>
<tr>
<th>Treatment strategies</th>
<th>No of patients</th>
<th>HDV RNA levels (log IU/mL)</th>
<th>Duration of therapy (weeks)</th>
<th>Virological response</th>
<th>HDV RNA &lt; LLQ or &gt;2 log IU/mL decline or &lt; LLQ</th>
<th>HDV RNA decline (mean or median log IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PegIFNα 180 μg QW*</td>
<td>15</td>
<td>5.44</td>
<td>48</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BV 2 mg every day</td>
<td></td>
<td>6.39</td>
<td>48</td>
<td>13%</td>
<td>13.3%</td>
<td>-1.29</td>
</tr>
<tr>
<td>BV 10 mg every day</td>
<td>15</td>
<td>5.6</td>
<td>48</td>
<td>32%</td>
<td>40%</td>
<td>-2.64</td>
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<tr>
<td>BV 2 mg every day</td>
<td>15</td>
<td>5.48</td>
<td>48</td>
<td>67%</td>
<td>80%</td>
<td>-5.21</td>
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<tr>
<td>BV 10 mg every day</td>
<td>15</td>
<td>5.9</td>
<td>48</td>
<td>66%</td>
<td>86.7%</td>
<td>-6.09</td>
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<tr>
<td>LNF 50 mg two times per day + RTV 100 mg two times per day</td>
<td>12</td>
<td>-</td>
<td>24</td>
<td>42%</td>
<td>29%</td>
<td>-1.66</td>
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<tr>
<td>LNF 50 mg two times per day + PegIFNα 180 μg QW**</td>
<td>4</td>
<td>-</td>
<td>24</td>
<td>50%</td>
<td>89%</td>
<td>-3.71</td>
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<tr>
<td>PegIFNα 180 μg QW**</td>
<td>14</td>
<td>3.86</td>
<td>48</td>
<td>-</td>
<td>36%</td>
<td>-2.72</td>
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<tr>
<td>LNF 50 mg two times per day + PegIFNα 180 μg QW**</td>
<td>26</td>
<td>4.74</td>
<td>24</td>
<td>27%</td>
<td>19%</td>
<td>-3.4</td>
</tr>
</tbody>
</table>

* MY020 study, HDV RNA assay LLQ: 10 IU/mL.
1 L03W4 study, RoboGene assay, LLQ: 140 IU/mL.
2 L03W4 study, RoboGene assay, LLQ: 14 IU/mL.
3 L03W4 study, Quest Diagnostics Assay, HDV RNA LLQ: <40 IU/mL or >14 log IU/mL. *data not published or not presented.
BV: buleviride; HDV: hepatitis D virus; LNF: lonafarnib; pegIFNα: pegylated interferon-α; RTV: ritonavir.

Urban et al, Hepatitis D virus in 2021: virology, immunology, and new treatment approaches for a difficult-to-treat disease, Gut 2021
**Hepatitis D Therapies: What’s To Come**

- Promising phase II data for combination therapies of bulevirtide + IFN and lonafarnib + ritonavir +/- IFN.
- Optimal dosing strategies and safety outcomes need validation in larger trials. Several phase III trials currently underway.
- Bulevirtide (**Hepcludex**) 2 mg subcutaneously once daily approved by European Medicines Agencies (EMA) in July 2020.
  - MYR 203 trial: Less efficacious as monotherapy at 2 mg than 10 mg, but more efficacious at 2 mg when combined with IFN\(^{11}\) (per authors, unclear exactly why).
  - FDA denied bulevirtide approval 11/2022 citing "manufacturing and distribution concerns," Gilead likely to resubmit so approval is pending.

Hepatitis D Therapies: What’s To Come

• Question remains of best long term therapeutic approach:
  • **Finite therapy**: BLV or LNF +/- pegIFN? with goal of undetectable HDV RNA, HBsAG Ag loss?
  • **Long term maintenance therapy**: BLV or LNF monotherapy?
    • Will depend on longer term clinical data yet to come
• Combinations of direct acting HDV medications with medications that decrease HBsAg levels will need to be evaluated

Other Management Considerations

- **Chronic hepatitis B management:** If HBV-DNA levels are elevated, concurrent therapy with NA using preferred drugs (entecavir, TDF, or TAF) is indicated (AASLD)\(^7\)
  - Monitoring of HBV DNA every 3-6 months is recommended on therapy
- **Advanced liver disease:** currently no safe therapies for HDV in advanced cirrhosis (CPB or CPB).
  - Closely monitor and treat decompensating features and refer for transplant based on MELD
- **Post transplant:** HDV reinfection can happen with/without HBV reinfection. Main perioperative goal is preventing HBV reinfection with HBIG and NAs
- Chronic liver disease patients or patients at risk for chronic hepatitis: recommended **HBV vaccination** which is preventive of HDV infection
Chronic Hepatitis B Management Algorithm
AASLD 2018 Hepatitis B Management Guidelines

**A**

- **HBsAg-positive**
  - **ALT <ULN**
    - HBV DNA >20,000 IU/mL
  - **ALT >ULN but <2XULN**
    - HBV DNA >20,000 IU/mL
    - Note: HBV DNA 2000-20,000 IU/mL may represent seroconversion, so monitor every 1-3 months and if persists for >6 months, treat
  - **ALT ≥2XULN**
    - HBV DNA >20,000 IU/mL

**Recommendations:**
- **Treat**
  - Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBsAg every 6-12 months.
  - Exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If other causes of ALT >ULN excluded and elevation persists, treat, especially if age >40.

**B**

- **HBsAg-positive**
  - **ALT <ULN**
    - HBV DNA ≥2000 IU/mL
  - **ALT >ULN but <2XULN**
    - HBV DNA ≥2000 IU/mL
    - HBV DNA <2000 IU/mL
  - **ALT ≥2XULN**
    - HBV DNA ≥2000 IU/mL
    - HBV DNA <2000 IU/mL

**Recommendations:**
- **Treat**
  - Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBsAg annually.
  - If ALT <ULN, monitor ALT and HBV DNA every 3 months for 1 year, then every 6 months.
  - If ALT elevated, exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If persistent ALT >ULN with HBV DNA ≥2000 IU/mL, treat, especially if age >40.

*The upper limit of normal for ALT in healthy adults is reported to be 19 to 35 IU/L, for males age 18 to 25 years, and 19 to 35 IU/L for females. An upper limit of normal for ALT of 35 IU/L for males and 30 IU/L for females is recommended to guide management decisions.*
The patient’s HDV total antibodies return with high titer, and his confirmatory HDV RNA returns elevated at 5.44 log IU/mL. His repeat liver enzymes remain elevated at ALT 144, AST 102. HBV DNA level remains low (212 IU/mL). His platelets are 263 and his INR 1.0.

- **Does this patient qualify for treatment for chronic hepatitis D?**
  Yes- his ALT is elevated and HDV RNA detectable.

- **What treatments are currently available?**
  Currently, PEG-IFN2α is the only approved therapy available in the US. He should receive weekly injections for 48 weeks (1 year).

- **What are the goals of therapy?**
  Undetectable HDV RNA at 24 weeks post therapy with normalization of ALT

- **Should he receive treatment for chronic hepatitis B?**
  No, his current HBV DNA level does not meet threshold for treatment. His HDV, ALT, and HBeAg status should be monitored Q3-6 months on therapy, and HBV treatment with NA initiated if meets usual treatment criteria
References


5. Gish R, Diagnosis and Screening for Hepatitis D Viral Infection, Hepatitis B Foundation White Paper,


Questions?