Outline – Delta Hepatitis (HDV)

- Definition
- Epidemiology
- Risk factors
- Diagnosis and Natural History
- Treatment
Hepatitis Delta

- Caused by the hepatitis delta virus (HDV)
- “Satellite virus”
  - Infects only those with hepatitis B (HBV)
- Can lead to acute or chronic disease
- May be acquired simultaneously with HBV as co-infection OR may be acquired by chronically infected HBV patients as super infection
Epidemiology
HDV Worldwide Prevalence: 15 – 20 Million

• Common in Eastern Europe, Southern Europe, Mediterranean region, Middle East, West and Central Africa, East Asia, Amazon Basin
  – > 100K in US
  – > 200K in EU
  – > 2M in China

• In US, at least 4% of HBV infected patients have HDV
4.5% - 15% of HBV population coinfected with HDV

HDV Worldwide Prevalence: 15 – 20 Million

### HDV Has 8 Genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Commonly Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>North America, Europe, Middle East, North Africa</td>
</tr>
<tr>
<td>2 and 4</td>
<td>East Asia</td>
</tr>
<tr>
<td>3</td>
<td>Amazon Basin of South America</td>
</tr>
<tr>
<td>5,6,7,8</td>
<td>West and Central Africa</td>
</tr>
</tbody>
</table>
HDV Geographic Footprint Is Growing

U.S. major metro hotspots identified

Top 10 U.S. Cities in 2016
1. Chicago, Illinois
2. Berwyn, Illinois
3. Brooklyn, New York
4. Corona, New York
5. Waukegan, Illinois
6. New York, New York
7. Bronx, New York
8. Jamaica, New York
9. Lombard, New York
10. Aurora, Illinois

U.S. HDV Prevalence in 2018: ~110,000

Increased screening leads to increased HBV and HDV diagnosis

HDV: Most Rapid Progression of Viral Hepatitis

Progression to Cirrhosis

<table>
<thead>
<tr>
<th>Virus</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>10 – 20% within 20 Years</td>
</tr>
<tr>
<td>HBV</td>
<td>20% within 5 Years</td>
</tr>
<tr>
<td>HDV</td>
<td>70% within 5 – 10 Years</td>
</tr>
</tbody>
</table>

Adverse Outcomes More Common With HDV/HBV Than HBV Alone

Table 3. Associated risks of chronic hepatitis D

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Approximate relative risk increase*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis [58, 90, 110]</td>
<td>2- to 3-fold</td>
</tr>
<tr>
<td>Hepatocellular carcinoma [58, 61, 78, 90, 111–113]</td>
<td>3- to 6-fold</td>
</tr>
<tr>
<td>Liver transplantation [48]</td>
<td>2-fold</td>
</tr>
<tr>
<td>Hepatic decompensation [111]</td>
<td>2-fold</td>
</tr>
<tr>
<td>Mortality [42, 78, 90, 111]</td>
<td>2-fold</td>
</tr>
</tbody>
</table>

*Compared with hepatitis B mono-infection.
HDV Causes Most Rapid Disease Progression

At diagnosis, > 50% of HDV patients are cirrhotic

Risk Factors
Hepatitis Delta Risk Factors

- Birth to an infected mother
- Intravenous drug use
- Sex with an infected partner
- Contact with blood from or open sores of an infected person
- Needle sticks or exposures to sharp instruments
- Sharing items (razors, toothbrushes, etc.) with an infected person
- HDV endemic country of origin
- Elevated ALT despite suppressed HBV DNA
Populations at Risk For HDV Infection

- People chronically infected with HBV
- Infants born to mothers with HDV
- Sex partners of persons infected with HDV
- MSM
- Injection drug users
- Household contacts of people with HDV
- Health care and public safety workers at risk for occupational exposure to blood or blood-contaminated fluids
- Hemodialysis patients
HDV: Signs/Symptoms

- Fever
- Fatigue
- Loss of appetite
- Nausea
- Vomiting
- Abdominal Pain
- Dark urine
- Clay-colored stools
- Joint pain
- Jaundice

These signs typically appear 3-7 weeks after infection.

Prevention

- Risk factor avoidance
- Hepatitis B vaccine
- No vaccine available for HDV
Molecular Biology
HDV Structure

- Positive single stranded circular RNA genome of ~1700 nucleotides
- HDV RNA genome is ~74% of paired bases giving it a rod-like structure
- Encodes HDAg, in 2 forms
  - Small (S-HDAg)
  - Large (L-HDAg)
  - HDAg associated with HDV genome forming a ribonucleoprotein (RNP)
  - RNP is enveloped by HBsAg

Hepatitis D Virus (Delta): The Most Pathogenic Hepatitis Virus

15-C isoprenoid lipid added to small HDAg to form large HDAg (prenylation)

**HDV Requires HBsAg to Complete Virus Assembly**

- Assembly with HBsAg is mediated by large delta antigen prenylation

HDV consists of a single stranded, circular RNA genome, with an envelope made up of HBsAg.
• HDV genome encodes for a single protein, the hepatitis delta antigen.

• HDV relies on host cell machinery for replication.

• New virions can be assembled only in the presence of hepatitis B virus.
Diagnosis & Natural History
HDV: Diagnostic Tests

- HDV antibodies (IgG, IgM)
- HDV RNA
- HBsAg

Testing Algorithm

HDV Antibody

- No HDV
  - No active HDV infection (25%)
- HDV RNA
  - Active HDV infection (75%)

+ HDV RNA
HDV RNA Quantification is the Gold Standard in HDV Diagnosis and Management

- Available in Quest - a leading provider of diagnostic services
  - Over 2,200 patient service centers across the US
  - Highly targeted patient and physician outreach
  - HDV testing program for HBV-positive patients
- HDV RNA quantification
- HBV/HDV reflex testing
What are the guidelines?

Emerging consensus: All HBsAg+ patients should have a one-time test for HDV!
HBV/HDV Coinfection

- Simultaneous infection with HBV and HDV
- Usually resolves
- > 5% develop chronic disease
- **Acute Liver Failure** more common with HDV/HBV than HBV alone

WHO 2019
HDV Superinfection

- Occurs when a person already with chronic HBV acquires HDV
- Results in rapid progression to cirrhosis and liver failure
  - 15% in 1-2 years
  - 70-80% in 5-10 years
- Higher risk of HCC
  - 3-6 fold increase
- Higher risk of mortality
  - 2 fold increase


HDV Clinical Course and Outcomes

HDV: A devastating disease with no approved treatment

HIGH DISEASE BURDEN

~70% Cirrhotic\(^1\)
Within 5-10 years

LOW SURVIVAL RATE

~60% Mortality\(^2\)
Within 10 years

HIGH COST TRANSPLANTS

~$575K Cost\(^3\)
>14,000 Waiting List

25% of People on Waiting List Die Each Year Before Receiving a Liver Transplant\(^4\)

Treatment
HDV Treatment

- No FDA approved therapy for HDV
- PEG IFN alpha is only drug with any demonstrated efficacy
- 20-25% response rate and rarely achieve sustained viral clearance
- Suboptimal due to:
  - Significant side effects (including cytopenias)
  - Limited efficacy
  - High long-term relapse rates

HDV Treatment

- ~2.5 log decline in median HDV RNA at EOT
- 25% neg 24 wks post Rx in patients receiving PEG-IFN
- 0% with nucleoside analog alone (no effect on HBsAg)

HIDIT-1; Wedemeyer, et al. NEJM. 2011.
HIDIT-II: PEG IFN + Tenofovir/Placebo for HDV Infection
96 Weeks of Treatment, 24 Weeks Follow up

N=120

>50% of “24-week SVRs” relapse at 4 years: not like HCV!

Late Relapse is Common with PEG IFN alpha

- Long term f/u of HIDIT-1
- Of 16 patients that were negative for HDV RNA at 6 months after therapy ended, 9 will test positive during long term f/u

HBV Functional Cures Will Not Eradicate HDV

• Approved HBV nucleos(t)ide treatments only suppress HBV DNA
  – They do not affect HBsAg and have no effect on HDV

• Investigational HBV treatments target functional cure
  – Not expected to completely eliminate HBsAg needed by HDV
HDV Treatments in Development
# HDV Treatments in Development

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Company</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lonafarnib</td>
<td>Eiger Pharmaceuticals</td>
<td>Daily Oral</td>
</tr>
<tr>
<td>Peginterferon Lambda</td>
<td>Eiger Pharmaceuticals</td>
<td>Weekly SQ injection</td>
</tr>
<tr>
<td>Bulevirtide</td>
<td>Gilead</td>
<td>Daily SQ injection</td>
</tr>
<tr>
<td>Rep-2139</td>
<td>replicor</td>
<td>Weekly IV infusion</td>
</tr>
</tbody>
</table>
Bulevirtide (Myrcludex, Hepcludex)
A Novel HBV Entry Inhibitor

- Synthetic 47 aa lipopeptide resembling pre-S1 portion of HBsAg, binds to bile acid receptor (NTCP), blocking viral entry
- Development program evaluated BLV 2 mg or 10 mg alone, with or w/out PEG IFN and PEG IFN alone
- Targets NTCP (bile acid receptor)
- Subcutaneous dosing
- Approved in Europe mid-2020 at 2 mg dose SQ daily based on early results in ~150 patients

Secondary Endpoint
- HDV RNA < LLOD at Week 48
- ALT nl at Week 48, 72
- HDV RNA > 2 log decline and ALT nl at Week 48, 72
- HBsAg undetectable or > 1 log decline at Week 48, 72

Primary Endpoint
- HDV RNA < LLOD at 24 weeks post-tx (Week 72)

Phase 2b, Open-Label Bulevirtide / TDF Study

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Median HDV RNA Change from Baseline at Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>2mg MyrB/TDF</td>
<td>-1.75</td>
</tr>
<tr>
<td>5mg MyrB/TDF</td>
<td>-1.60</td>
</tr>
<tr>
<td>10mg MyrB/TDF</td>
<td>-2.70</td>
</tr>
<tr>
<td>TDF</td>
<td>-0.18</td>
</tr>
</tbody>
</table>

MYR301: Phase 3, Randomized, Open-label Trial of Bulevirtide Monotherapy for Patients with Chronic Hepatitis Delta

Key inclusion criteria:
- CHD with/without cirrhosis and CPT ≥7
- ALT >1x to <10x ULN
- Platelets ≥60,000/mm³
- Controlled HIV coinfection allowed

Week 0 24 48 Follow-up

- Delayed treatment (n=51)
  - BLV 10 mg sc qd

- BLV 2 mg sc qd

- BLV 10 mg sc qd

Wedemeyer H, et al. EASL 2022. #GS006
Behrendt et al. Liver International 2022, epub ahead of print
MYR301: Phase 3, Randomized, Open-label Trial of Bulevirtide Monotherapy for Patients with Chronic Hepatitis Delta

**Key efficacy outcomes at Weeks 24 and 48**

- **Combined response** defined as undetectable HDV RNA or ≥2 log IU/mL decline from baseline and ALT normaliza.

*P<0.0001 vs delayed treatment arm; Combined response defined as undetectable HDV RNA or ≥2 log IU/mL decline from baseline and ALT normaliza.

**ALT normalization at Weeks 24 and 48**

- Delayed treatment (n=51)
- BLV 2 mg (n=49)
- BLV 10 mg (n=50)

**Change from baseline in liver stiffness at Week 48**

- Delayed treatment (n=45)
- BLV 2 mg (n=48)
- BLV 10 mg (n=42)

*P<0.001; †P<0.0001 vs delayed treatment arm

Wedemeyer H, et al. EASL 2022. #GS006
Behrendt et al. Liver International 2022, epub ahead of print
### MYR301: Phase 3, Randomized, Open-label Trial of Bulevirtide Monotherapy for Patients with Chronic Hepatitis Delta

**Data are n (%)**

<table>
<thead>
<tr>
<th></th>
<th>Delayed treatment (n=51)</th>
<th>BLV 2 mg (n=49)</th>
<th>BLV 10 mg (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>39 (77)</td>
<td>40 (82)</td>
<td>44 (88)</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>3 (8)</td>
<td>5 (10)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>SAE</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TRAEs</td>
<td>0</td>
<td>24 (49)</td>
<td>36 (72)</td>
</tr>
<tr>
<td>AEs of interest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>9 (18)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>6 (12)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (2)</td>
<td>5 (10)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>ISRs</td>
<td>0</td>
<td>8 (16)</td>
<td>15 (30)</td>
</tr>
</tbody>
</table>

- No deaths
- ISRs mild to moderate in severity
- Asymptomatic total serum BA and eosinophils elevations in BLV arms
  *Injection site reactions

Wedemeyer H, et al. EASL 2022. #GS006
1 patient with recurrent viremia after stopping therapy

2 patients who remained on therapy had persistent viral suppression with normalization of ALT
Improved clinical outcomes noted (resolution of varices)

- These data may be a sign of how bulevirtide will be used…as a long-term maintenance therapy

Loglio A et al, J Hepatology 2022;76:464-469
• Nucleic acid polymers (NAPs) are oligonucleotides with broad spectrum in vitro antiviral activities
• Reported to act via entry inhibition in other viruses
• Also proposed to bind to amphipathic protein structures
• These amphipathic protein structures are common in viral proteins, but are also found in key host cell proteins
• REP 2139 inhibits secretion of HBsAg from cells
Phase 2 REP 301 Study

12 HDV pts in Moldova
- Anti-HDV/RNA +
- HBsAg > 1000
- Non-cirrhotic

- Responses mostly maintained on interferon
- 5 patients rebound with cessation of IFN (EASL 2017)
- Responses maintained to date (EASL 2018)
First-in-Class Treatments in Development for HDV

Multiple Options to Treat HDV

- **Lonafarnib**
- **PEG IFN Lambda**

**Daily Oral Therapy**

**Combination Therapy**

- **Lonafarnib / Ritonavir**
- **Lonafarnib / Ritonavir + PEG IFN Lambda**

**Weekly SQ Monotherapy**

- **PEG IFN Lambda**
Lonafarnib

- Small molecule, first-in-class, oral prenylation inhibitor
- Well-characterized through Phase 3
  - > 2,000 subjects dosed in oncology program by Merck (Schering)
  - Dose limiting toxicity is GI (class effect)
- Over 120 HDV patients dosed across international sites
- US & EU Orphan Designation, FDA Breakthrough and EMA PRIME Designation
- Broad range of lonafarnib + ritonavir doses and durations studied
- US and multiple international sites
Hepatitis D Virus (Delta): The Most Pathogenic Hepatitis Virus

Lonafarnib inhibits prenylation of 15-C isoprenoid lipid added to small HDAg to form large HDAg (*prenylation*).

LOWR: Phase 2 Lonafarnib Study

Compared to PEG-IFN-alfa-2a Alone

Peg IFN Lambda: A Better Tolerated Interferon

- A novel, first-in-class Type III interferon
- Binds to a unique receptor versus Type I interferons
  - Highly expressed on hepatocytes
  - Limited expression on hematopoietic cells and CNS cells
- Uses similar downstream signaling pathway as Type I interferons
- Studied in > 3,000 subjects across 17 clinical trials (HCV / HBV)
- Comparable antiviral activity with less of the typical IFN alfa related side effects

LIMT: Phase 2 Lambda Study

A Better Tolerated Interferon for HDV Monotherapy

Primary Endpoint:
• Evaluate Safety, Tolerability, Efficacy

Secondary Endpoint:
• Proportion of Patients with HDV RNA BLQ 24 weeks after EOT

Peginterferon Lambda Activity Through Week 48

Lambda 180 mcg has Comparable Antiviral Activity to Alfa 180 mcg with Improved Tolerability

Peginterferon Lambda: 36% Durable Virologic Response

DVR Endpoint = BLQ at 24 Weeks Post-Treatment

Etzion et al, EASL 2019, LINT Phase 2 Study; Robogene® 2.0 HDV RNA PCR assay, LLOQ = 14 IU/mL; DVR = BLQ at 24 Weeks Post-Treatment
**LIFT: Phase 2 Lambda & Lonafarnib Combination Study**

- Median Decline of HDV RNA: -3.4 Log at Week 24
- 95% of Patients Achieve > 2 Log Decline in HDV RNA at Week 24
- > 50% of Patients Achieve Undetectable or BLOQ HDV RNA at Week 24

A Better Tolerated Interferon for Combination

**On-treatment**

- Lambda 180 mcg QW
- Lonafarnib 50 mg BID
- Ritonavir 100 mg BID

**Post-treatment**

- 24 Weeks

**Follow Up**

- 24 Weeks

**N=26**

* biopsy

**Primary Endpoint:**
- ≥ 2 Log HDV RNA reduction at EOT

**Secondary Endpoint:**
- Histological Improvement (biopsy confirmed)

**Dosing**
- End of Treatment Data Q4’19

Koh C et al, AASLD 2019
Lonafarnib, Ritonavir, and Lambda Interferon for HDV: Interim End-of-Treatment Results – the LIFT Study

**Aims:**
Evaluate the safety and antiviral effects of therapy with lonafarnib (LNF), ritonavir (RTV), and lambda interferon (LMD) in patients with chronic hepatitis D

**Methods:**
Phase 2a, open-label, prospective treatment trial in 26 patients for 24 weeks, with 24 weeks of post-therapy follow-up

**Main Findings:**
At the end of therapy (19 of 26 patients), the median HDV RNA decline was 3.4 log IU/ml (p<0.0001) with 10 (53%) patients achieving undetectable or BLOQ HDV RNA in serum.

**Conclusions:**
Triple combination therapy with LNF/RTV/LMD in chronic HDV patients appears to be safe and tolerable for up to 6 months in most patients.

Koh C, et al., Abstract LO8

58% of patients achieved undetectable or BLOQ* HDV RNA by the end of therapy
Summary

• HDV is the most severe form of viral hepatitis
• HDV remains underdiagnosed
• HBV vaccination is protective against acquiring HDV
• HDV/HBV infection causes more rapid disease progression as compared to HBV monoinfection
• New therapies being developed based upon HDV life cycle
• Several HDV therapies currently in phase 2 and 3 development
  – Bulevirtide and lonafarnib
• Promising future!
The Near Future For HDV Therapy?

- Hoped for new treatments: Bulevirtide, Ionafarnib, PEG IFN lambda, nucleic acid polymers (NAPS)
- Bulevirtide approved in Europe, possibly in US soon
- Viral suppression enhanced with addition IFN alpha for bulevirtide, lonafarnib
- Issue is whether rates of sustained response will be significantly enhanced with combination therapy and whether IFN will improve this
- Maintenance therapy with a safe monotherapy not associated with resistance may be preferred by some clinicians and patients