Hepatitis Delta Update
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
- May be acquired by chronically infected HBV patients
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
HDV Worldwide Prevalence: 15 – 20 Million

6% of HBV population coinfected with HDV
# 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

- **HDV**: 70% within 5 – 10 Years
- **HCV**: 10 – 20% within 20 Years
- **HBV**: 20% within 5 Years

**Graphical Representation**

- **Normal Liver**
- **Chronic Hepatitis**
- **Cirrhosis**
- **HCC/ESLD/Death**
- **Transplant**

**Data Sources**

HDV Causes Most Rapid Disease Progression

At diagnosis, > 50% of HDV patients are cirrhotic

Survival: HDV vs Cancer

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
How Hepatitis Delta is Not Spread

• Through food or water
• Sharing eating utensils
• Breastfeeding
• Hugging
• Kissing
• Hand holding
• Coughing or sneezing
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
Natural History of HBV and HDV Infection

Mono-infection
- Healthy liver
  - HBV infection
    - 5% Chronic HBV infection
      - 2% / year Cirrhosis
    - 95% Viral clearance
  - HDV infection
    - 5% Chronic HDV infection
      - 2% / year Cirrhosis
    - 80% HDV clearance

Co-infection
- Healthy liver
- HBV-infected liver
  - 5% Chronic HBV infection
    - 2% / year Cirrhosis
  - 95% Viral clearance
  - 5% Chronic HDV infection
    - 4% / year Cirrhosis
  - 80% HDV clearance

Super-infection
- HBV-infected liver
  - 20% HDV clearance
  - 2.8% / year Cirrhosis

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.

**HDV Clinical Course and Outcomes**

**HDV: A devastating disease with no approved treatment**

<table>
<thead>
<tr>
<th>HIGH DISEASE BURDEN</th>
<th>LOW SURVIVAL RATE</th>
<th>HIGH COST TRANSPLANTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>~70% Cirrhotic&lt;sup&gt;1&lt;/sup&gt; Within 5-10 years</td>
<td>~60% Mortality&lt;sup&gt;2&lt;/sup&gt; Within 10 years</td>
<td>~$575K Cost&lt;sup&gt;3&lt;/sup&gt; &gt;14,000 Waiting List</td>
</tr>
</tbody>
</table>

25% of People on Waiting List Die Each Year Before Receiving a Liver Transplant<sup>1</sup>

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

HDV Structure

L-HDAg

S-HDAg

Genomic RNA

HBsAg

S
L
M
HDV Requires HBsAg to Complete Virus Assembly

- Assembly with HBsAg is mediated by large delta antigen prenylation.
HDV Life Cycle

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

- 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 and HBV/HDV reflex testing

New HDV RNA Test Now Available in the United States

www.hepdconnect.org

Hepatitis Delta Connect
Thers is now a new HDV RNA test available from Quest! This test is commercially available in the U.S. and may make testing and management of patients easier for providers.
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)

Median HDV RNA Levels over Time

HIDIT-1; Wedemeyer, et al. NEJM. 2011.
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</td>
<td>Daily Oral</td>
</tr>
<tr>
<td>Peginterferon Lambda</td>
<td>EIGER</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: Entry Inhibitor Targeting NTCP

- Daily, subcutaneous injections
- Synthetic 47 amino acid, N-acylated preS1 lipopeptide
- Targets Na-taurocholate cotransporting polypeptide (NTCP)
  - On surface of hepatocytes
- Blocks receptor functions of NTCP and HBV/HDV virus entry

Bogomolov et al. J Hep 2016
**Primary Endpoint**
- HDV RNA < LLOD at 24 weeks post-tx (Week 72)

**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
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>

Phase 3 Bulevirtide Study

Across 7 Sites in Russia

- **Arm A** (n=50):
  - Week 0: NA
  - Week 48: 10mg MyrB + NA
  - Follow up (NA)

- **Arm B** (n=50):
  - Week 0: 10mg MyrB + NA
  - Week 48: 10mg MyrB + NA
  - Follow up (NA)

- **Arm C** (n=50):
  - Week 0: 2mg MyrB + NA
  - Week 48: 2mg MyrB + NA
  - Follow up (NA)

**Comparison for primary endpoint**

**Composite primary endpoint:**
HDV RNA negativation or >2log decline as well as ALT normalization
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)

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
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

On-treatment: 48 weeks
Post-treatment: 24 weeks

Lambda 120 mcg QW
Lambda 180 mcg QW

Follow-up
Follow-up

Study Complete

AASLD 2017
AASLD 2018
EASL 2019
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, LIMT 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
First-in-Class Treatments in Development for HDV

**Multiple Options to Treat HDV**

- **Lonafarnib**
  - *Daily Oral Therapy*
  - *Combination Therapy*
  - *Weekly SQ Monotherapy*
- **PEG IFN Lambda**
  - *Monotherapy*

- **Lonafarnib / Ritonavir**
- **Lonafarnib / Ritonavir + PEG IFN Lambda**
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
LIFT Treatment Response at Week 12 and 24

<table>
<thead>
<tr>
<th>Treatment Duration</th>
<th>n</th>
<th>Mean Change in log HDV RNA (IU/mL)</th>
<th>Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Weeks</td>
<td>26</td>
<td>3.36</td>
<td>(2.86-3.85)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>24 Weeks</td>
<td>22</td>
<td>3.21</td>
<td>(2.50-3.93)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*KP=<0.0001

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
  - Phase 2 – Bulevirtide and lonafarnib
  - Phase 3 - Lonafarnib