Delta Hepatitis:
An Overview & Update

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Disclosures

• Gilead, Abbvie-Advisory role
Outline – Delta Hepatitis (HDV)

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

- Caused by the hepatitis delta virus (HDV)
- “Satellite virus”
  - Infests 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>
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<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

<table>
<thead>
<tr>
<th>Virus</th>
<th>Progression Rate</th>
</tr>
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<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>

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
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
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 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

- 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?

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection
European Association for the Study of the Liver

Other causes of chronic liver disease should be systematically excluded including co-infections with hepatitis D virus (HDV), hepatitis C virus (HCV) and HIV.

Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance
Norah A. Terrault,1,2 Aima S.F. Lok,2 Brian J. McMahon,3 Krung-Mi Chung,4 Jessica P. Hoang,5 Maureen M. Jonas,4 Robert S. Brown Jr.,6 Ninette H. Dawson7 and John B. Wang8

The AASLD 2016 HBV Guidelines recommend testing of HBsAg-positive persons at risk for HDV, including those with HIV infection, persons who inject drugs, men who have sex with men, and immigrants from areas of high HDV endemicity.
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

Chronic HBV infection

5%

2% / year

Cirrhosis

2% / year

Co-infection

Healthy liver

HDV

Chronic HDV infection

5%

95%

Viral clearance

Cirrhosis

2% / year

Super-infection

HBV-infected liver

HDV

Chronic HDV infection

80%

20%

HDV clearance

Cirrhosis

4% / year

2.8% / year

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>
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<tbody>
<tr>
<td>~70% Cirrhotic¹</td>
<td>~60% Mortality²</td>
<td>~$575K Cost³</td>
</tr>
<tr>
<td>Within 5-10 years</td>
<td>Within 10 years</td>
<td>&gt;14,000 Waiting List</td>
</tr>
</tbody>
</table>

25% of People on Waiting List Die Each Year Before Receiving a Liver Transplant¹

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)

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

Entry Inhibitors (bulevirtide)

Attachment and entry

Nucleic Acid Polymers (REP 2139)

Transport to Nucleus

Assembly

Replication

Prenylation Inhibitors (ionafarnib)

Peginterferon Lambda

HDV genome

small delta antigen

large delta antigen

HBV surface antigen

large HDAg

Prenylated LHDAg

HDV genome

small HDAg

large HDAg

prenylated HDAg

prenylated LHDAg

prenylated HDAG

prenylated LHDAG
## HDV Treatments in Development

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Company</th>
<th>Stage of Development</th>
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<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 3 Bulevirtide Study

Across 7 Sites in Russia

Arm A (n=50)
- Week 0: NA
- Week 48: 10mg MyrB + NA
- Week 144: follow up (NA)

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

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

**Study Design:**

- **On-treatment:**
  - 48 weeks

- **Post-treatment:**
  - 24 weeks

**Study Timeline:**

- Lambda 120 mcg QW
- Lambda 180 mcg QW

**Conferences:**

- 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

Week 48 End of Treatment
- BLQ: 5/14 (36%)
- ALT Normalization: 2/14 (14%)

Week 72 End of Follow-up
- BLQ: 5/14 (36%)

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

A Better Tolerated Interferon for Combination

N=26

On-treatment

Post-treatment

Primary Endpoint:

• ≥ 2 Log HDV RNA reduction at EOT

Secondary Endpoint:

• Histological Improvement (biopsy confirmed)

Follow Up

• Dosing
• End of Treatment Data Q4’19

- 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

Lonafarnib / Ritonavir

- PEG IFN Lambda

PEG IFN Lambda

- Weekly SQ Monotherapy
- Monotherapy
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>
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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!