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COMPETING INTEREST OF FINANCIAL VALUE > £1,000

<table>
<thead>
<tr>
<th>Statement</th>
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<tbody>
<tr>
<td>None</td>
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</tbody>
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Date: December 2015
Hepatitis Delta (HDV) in HIV Infection

Dr Kate Childs
NIHR Doctoral Research Fellow
Institute of Liver Studies
King’s College Hospital
Dec 2014
Hepatitis Delta – the last challenge in the viral hepatitides

- The basics of delta replication
- Prevalence of delta in HIV infected individuals
- Clinical course of delta in HIV
- Current treatments
- Future treatments
Why is Hepatitis Delta important?

- Considered to cause the most severe form of chronic viral hepatitis in humans.
- Easily overlooked
- High prevalence rates in some groups with HIV infection
- No efficacious treatment for HDV
HDV is a defective virus which is dependant on HBV

- HDV-RNA
  - Highly paired – rod like structure
  - No enzymes but Ribozymes
  - Only encodes S-HDAd

- HBsAg

- HDAd
  - 2 forms: S-HDAd and L-HDAd
  - S-HDAd: ↑ replication
  - L-HDAd: ↑ assembly (↓ replication)

Calle Serrano, Manns & Wedemeyer, Seminars in Liver Disease 2012
# Hepatitis Delta requires HBV SAg

<table>
<thead>
<tr>
<th>Clinical course</th>
<th>Virological outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-infection with HBV HDV</td>
<td>May get fulminant acute hepatitis</td>
</tr>
<tr>
<td>Superinfection with HDV</td>
<td>Mild hepatitis</td>
</tr>
</tbody>
</table>
Prevalence of Hepatitis Delta

www.hepatitis-delta.org
Overall Prevalence of HDV in HIV/HBV in Europe is 14.5%
Transmission

- Blood borne and highly contagious, tiny inoculum required for infection
- Different mode of transmission predominate in different areas.
- Parenteral exposure: IVDU, Blood products etc
- Infection within families in areas of high endemnicity
- Sexual transmission

Ponzetto JID 1987
Taiwan: Increasing incidence HDV amongst HIV/HBV positive MSM

Higher rate elevated RPR in incident delta cases

Chang et al CID 2014
Hepatitis delta takes a more severe long-term course than HBV monoinfection.
Compared to HIV/HBV, patients with HDV IgG had 6 fold increase in liver related death

Adjusted odds ratio death any cause 5.41 (1.39-23.8) p=0.02
aOR liver related death 6.49 (1.16-6.8) p=0.03
HDV antibody positive increases risk of liver decompensation or death in HIV positive patients
## Diagnostic tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Relevance of test</th>
<th>Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDV IgG</td>
<td>Present in all exposed or infected with HDV</td>
<td>First screening test and should be tested in all pts with HBV SAg + (BHIVA, BVHG, EASL guidelines)</td>
</tr>
<tr>
<td>HDV IgM</td>
<td>Positive in acute infection but also persists in high proportion of chronic infections</td>
<td>An indicator of disease activity</td>
</tr>
<tr>
<td>HDV RNA (quantitative and qualitative)</td>
<td>Present in active infection.</td>
<td>My get false negatives due to sequence variation. Useful in monitoring treatment response. No correlation with stage of liver disease.</td>
</tr>
<tr>
<td>Quant HBV SAg level</td>
<td>HBV SAg clearance is ultimate aim of delta treatment</td>
<td>HBV SAg levels are associated with HDV RNA levels and can be monitored during treatment</td>
</tr>
</tbody>
</table>
Presence of anti-HDV IgM predicts clinical course better than HDV RNA level

Cumulative event free survival

IgM status
- negative
- medium
- high
- positive

Heiner Wedemeyer: Hepatitis Delta

Wranke et al. PlosOne 2014
Viral Interactions between HBV/HCV/HDV

- HDV suppresses HBV replication
- In triple infection with HBV HCV

**Graph:**

- Median HBV-DNA (IU/mL)
  - Negative Anti HDV (EIA): 27400 IU/mL
  - Positive Anti HDV (EIA): 79 IU/mL

**Legend:**

- HDV
- HBV
- HCV

**Statistical Test:**

- $P < 0.001$ log rank test

Notes:

- Heidrich JVH 2009
- Jardi Hepatol 2001
Delta is the dominant virus in HIV/HBV/HDV and HIV/HBV/HCV/HCV

**aOR of undetectable**
- HBV
- HCV
- HDV

Boyd Hepatitis Viral Interactions in HIV infection 2009 J Viral Hep
57% of HIV/HBV develop lamivudine resistance compared to 0 of HIV/HBV/HDV

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV-HBV-HDV coinfected (n = 26)</th>
<th>HIV-HBV coinfected (n = 78)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype B(^a)</td>
<td>12 (92.3)</td>
<td>50 (79.4)</td>
<td>.28</td>
</tr>
<tr>
<td>Genotype C(^a)</td>
<td>1 (7.7)</td>
<td>13 (20.6)</td>
<td></td>
</tr>
<tr>
<td>HBV load at baseline(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median log(_{10}) copies/mL (range)</td>
<td>4.04 (2.76–9.80)</td>
<td>5.75 (2.01–10.01)</td>
<td>.07</td>
</tr>
<tr>
<td>&gt;5 log(_{10}) copies/mL</td>
<td>5 (38.5)</td>
<td>31 (54.4)</td>
<td>.06</td>
</tr>
<tr>
<td>Viral hepatitis markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg positive at baseline</td>
<td>5 (19.2)</td>
<td>25 (32.1)</td>
<td>.32</td>
</tr>
<tr>
<td>Anti-HBe positive at end of study</td>
<td>1 (3.8)</td>
<td>5 (6.4)</td>
<td>.53</td>
</tr>
<tr>
<td>HBsAg clearance at end of study</td>
<td>7 (26.9)</td>
<td>6 (7.7)</td>
<td>.02</td>
</tr>
<tr>
<td>New HCV infection</td>
<td>2 (7.7)</td>
<td>3 (3.8)</td>
<td>.59</td>
</tr>
<tr>
<td>Genotypic resistance to lamivudine(^c)</td>
<td></td>
<td></td>
<td>.003</td>
</tr>
<tr>
<td>Any</td>
<td>0</td>
<td>20 (57.1)</td>
<td></td>
</tr>
<tr>
<td>HBV load of 3–6 log(_{10}) copies/mL</td>
<td>0</td>
<td>12 (34.3)</td>
<td>.04</td>
</tr>
<tr>
<td>HBV load &gt;6 log(_{10}) copies/mL</td>
<td>0</td>
<td>8 (22.8)</td>
<td>.19</td>
</tr>
</tbody>
</table>
Treatment of Hepatitis Delta
IFNa to treat HDV-Infection

**PEG-Interferon alpha**

- 48-96 weeks HDV RNA SVR 17-47%
  
  Erhardt Liver International 2006
  Niro et al., Hepatology 2006
  Castelnau et al., Hepatology 2006
  Ormeci et al., Hepatogastroenterology 2011
  Karaca C et al., Antiviral Therapy 2013
The Hep-Net/International Delta Hepatitis Intervention Trial (HIDIT-1)

- PEG-IFNa-2a (180 µg oiw)
- Adefovir dipivoxil 10 mg daily

- Placebo

- Screening: N=91
- TW0: N=32*
- TW24: N=29
- TW48: N=30
- F24: N=91

Wedemeyer, Yurdaydin et al. NEJM 2011
Treatment of Hepatitis Delta with PEG-IFNa-2a: ~25% Sustained HDV RNA clearance

**Figure 1.** Virologic Response to Treatment as Determined by Serum Level of HDV RNA, According to Treatment Group.
PEG-IFNa-2a – Adefovir combination resulted in a more pronounced HBsAg suppression
The Hep-Net-International Delta-Hepatitis Intervention Trial 2: HIDIT-2

96 weeks

PEG-Interferon alpha-2a 180µg oiw + Placebo

Follow-up

N=61

5 years FU

PEG-Interferon alpha-2a 180µg oiw + Tenofovir disoproxilfumarat 245mg daily

Follow-up

N=59

Primary efficacy endpoint: HDV RNA negativity Week 96

Stratification:
Country
Previous therapy
Gender
HDV RNA response until week 120 (Intent-to-treat analysis)

- **% of patients HDV RNA negative**
  - **Treatment**
  - **FU**
  - **p=0.10**

- **Week 96**
  - PEG-IFNa-2a + Tenofovir: 47%
  - PEG-IFNa-2a + Placebo: 33%

- **Relapse**
  - 11/25 (44%)
  - 8/20 (40%)

- **HDV RNA Clearance after Therapy**
  - Neg post Tx 1 patient
  - Neg post Tx 3 patients

- **Weeks 12, 24, and 48**
  - HDV RNA response
  - (Intent-to-treat analysis)

- **Week 120**
  - 24 w post Tx
**HBsAg response until week 120**

(Intent-to-treat analysis)

% of patients with HBsAg-decline >0.5 Log10 IU/ml

- **HBsAg loss**: 4/59 patients (6.7%)
- **HBsAg loss**: 3/61 patients (4.9%)

---

Wedemeyer, Yurdaydin et al. EASL 2014
HIDIT-1: Long term follow up shows late relapses after initial response

Long Term Virological Response

Late Relapse
Lessons from HIDIT

No benefit to addition of tenofovir to pegylated interferon for treatment of Hepatitis Delta

Undetectable HDV RNA 24 weeks post treatment ≠ ‘SVR’ in Hepatitis Delta

Is the only valid endpoint for Delta treatment HBV SAg seroconversion?
Emerging evidence that long term nucleotides in HIV/HBV leads to decrease in HDV RNA

Fig. 1. Evolution of main virological markers over time.
Excellent Transplant Outcomes in Hepatitis Delta

n = 19,335 patients, global log-rank p < 0.001

Patient survival

Years after liver transplantation

Patient survival (%)

Years

Burra et al J Hepat 2013
Future HBV therapies = potential future therapies for delta

Immunomodulation
- Toll-like receptors agonists, e.g. GS-9620
- Anti-PD-1 mAb, e.g. BMS-936559
- CYT107
- GI13000
- Vaccine therapy

Entry inhibitors (HBV/HDV)
- Lipopeptides, e.g. Myrcludex-B

RNA interference, (siRNA) e.g. ARC-520

Inhibition of HBsAg release, e.g. REP 9AC

Polymerase inhibitors
- Nucleoside analogues, e.g. TAF, amadoxovir, MIV-210
- Non-nucleoside, e.g. LB80380

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Targeting cccDNA
- HAPs
- Chromatin-modifying enzymes

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Inhibition of Nucleocapsid Assembly, e.g. Bay 41-4109, NVR 3-778

Inhibition of Prenylation (HDV)
- Lonafarnib

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Prenylation inhibitors

ClinicalTrials.gov: NCT01495585
NIDDK: „Lonafarnib for Chronic Hepatitis D“

Summary

- Hepatitis delta has emerged as the most challenging of all the viral hepatitides
- Aggressive course liver disease
- No efficacious treatments
- Co-infection with HIV common and similar severe clinical course
It’s not all bad news……

- Several new treatments undergoing evaluation
- Excellent results in transplant

- Don’t forget to test for delta
Thank you for your attention

Acknowledgements:

Professor Heiner Wedemeyer,

Dr Kosh Agarwal, Dr Chris Taylor, Dr Ivana Carey
Event-free survival and follow-up week 24 response

Heidrich et al., Hepatology 2014
Hepatitis delta Ab positivity increased risk of death and liver related death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Progression to death</th>
<th>Progression to AIDS</th>
<th>Progression to AIDS or death</th>
<th>Progression to LRD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR</td>
<td>95% CI</td>
<td>P</td>
<td>IRR</td>
</tr>
<tr>
<td>Anti-HDV-positive vs. Negative</td>
<td>2.2346</td>
<td>1.664</td>
<td>4.2814</td>
<td>0.0154</td>
</tr>
<tr>
<td>HBV genotypes: A vs. D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others vs. D</td>
<td>1.3567</td>
<td>0.2845</td>
<td>6.4698</td>
<td>0.7019</td>
</tr>
<tr>
<td>Unknown vs. D</td>
<td>1.1091</td>
<td>0.3255</td>
<td>3.7791</td>
<td>0.8685</td>
</tr>
<tr>
<td>Geographical region: south vs. north</td>
<td>0.9011</td>
<td>0.4672</td>
<td>1.7379</td>
<td>0.756</td>
</tr>
<tr>
<td>West vs. north</td>
<td>0.5784</td>
<td>0.3172</td>
<td>1.055</td>
<td>0.0742</td>
</tr>
<tr>
<td>East vs. north</td>
<td>0.5843</td>
<td>0.236</td>
<td>1.4471</td>
<td>0.2456</td>
</tr>
</tbody>
</table>

95% CI, 95% confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis delta virus; IRR, incidence rate ratio.

Soriano 2011
Can we see the bigger picture?
FIVE NATIONS CONFERENCE
on
HIV and Hepatitis
8–9 December 2014
Queen Elizabeth II Conference Centre
LONDON