Hepatitis delta in HIV patients in Europe

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Hepatitis D

- HDV is a small RNA (1.7 Kb) defective agent that only replicates in the presence of HBsAg.
- Two clinical forms: co-infection and super-infection.
- Hepatitis delta is the most aggressive viral hepatitis.
- 15-20 million people infected worldwide (~5% of chronic HBV).
- Endemic in the Middle East, Amazonian region, Central Asia, Central Africa & Mediterranean basin
- Transmitted mainly parenterally (IDU outbreaks) and sexually.
- Given that HDV use human host enzymes for replication, no specific antivirals have been developed so far. Interferon provides benefit in less than a quarter of patients.
Objectives

• Investigation of delta hepatitis in EuroSIDA:
  
  ➢ Prevalence and correlates of HDV infection
  
  ➢ Impact on survival
EuroSIDA

Large prospective cohort with over **16,597** patients from 33 European countries, Israel and Argentina.

- Demographics
- CD4 counts & viral loads
- Start/stop dates of all drugs
- AIDS defining illnesses & deaths
- Non-AIDS malignancies
Study population

• All individuals with available plasma samples recruited in EuroSIDA until 2006.

• Clinical follow-up extended up to March 2011.

# Delta virologic sub-study in EuroSIDA

<table>
<thead>
<tr>
<th>Virus</th>
<th>Markers</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>HBsAg</td>
<td>EIA</td>
</tr>
<tr>
<td></td>
<td>HBV-DNA</td>
<td>bDNA (LLD 600 IU/ml)</td>
</tr>
<tr>
<td></td>
<td>HBV genotypes</td>
<td>LiPA</td>
</tr>
<tr>
<td>HDV</td>
<td>HBV Ab</td>
<td>EIA</td>
</tr>
<tr>
<td></td>
<td>HDV-RNA</td>
<td>q-PCR (LLD 10 IU/ml)*</td>
</tr>
<tr>
<td>HCV</td>
<td>HCV Ab</td>
<td>EIA</td>
</tr>
<tr>
<td></td>
<td>HCV-RNA</td>
<td>real time-PCR (Roche)</td>
</tr>
</tbody>
</table>

* Le Gal et al. JCM 2005
Statistical analysis

- Chi square tests and Wilcoxon (or Kruskall-Wallis) for comparisons.

- Logistic regression for identification of factors associated with anti-HDV+.

- Multivariate Poisson regression modelling for assessing predictors of progression to clinical end points (AIDS, LRD, death).
Results

<table>
<thead>
<tr>
<th>Total no. patients</th>
<th>16,597</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg+</td>
<td>1,319 (7.9%)</td>
</tr>
</tbody>
</table>
| Anti-HDV Ab+       | 61/422 (14.5%)  
                    (95% CI: 11.1-17.8) |
| HDV-RNA+           | 31/38 (81.6%)  
                    (95% CI: 69.3-93.9%) |

Median follow-up HBsAg+ patients

90.2 months (IQR 51.1 – 135.2).
Prevalence of anti-HDV Ab in HBsAg+ patients in EuroSIDA

- **North**: 9% (13/139)
- **Central**: 21% (16/77)
- **East**: 11% (16/142)
- **South**: 25% (16/64)

Legend:
- Light blue: north
- Yellow: central
- Green: east
- Red: south
<table>
<thead>
<tr>
<th>Variable</th>
<th>All HBsAg+ patients</th>
<th>HDV Ab-positive</th>
<th>HDV Ab-negative</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>422</td>
<td>61 (14.5)</td>
<td>361 (85.5)</td>
<td></td>
</tr>
<tr>
<td>Median age (years)</td>
<td>37</td>
<td>34</td>
<td>38</td>
<td>0.0007</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>84.1</td>
<td>72.1</td>
<td>86.1</td>
<td>0.0056</td>
</tr>
<tr>
<td>White ethnicity (%)</td>
<td>357 (84.6)</td>
<td>54 (88.5)</td>
<td>303 (83.9)</td>
<td>0.36</td>
</tr>
<tr>
<td>Risk group (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MSM</td>
<td>213 (50.5)</td>
<td>7 (11.5)</td>
<td>206 (57.1)</td>
<td></td>
</tr>
<tr>
<td>IDU</td>
<td>104 (24.6)</td>
<td>44 (72.1)</td>
<td>60 (16.6)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>67 (15.9)</td>
<td>6 (9.8)</td>
<td>61 (16.9)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>38 (9.0)</td>
<td>4 (6.5)</td>
<td>34 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Median CD4 count (cells/µL)</td>
<td>285</td>
<td>281</td>
<td>294</td>
<td>0.53</td>
</tr>
<tr>
<td>Median nadir CD4 count (cells/µL)</td>
<td>142</td>
<td>143</td>
<td>141</td>
<td>0.90</td>
</tr>
<tr>
<td>Median plasma HIV-RNA (log cop/mL)</td>
<td>2.7</td>
<td>2.7</td>
<td>2.7</td>
<td>0.77</td>
</tr>
<tr>
<td>Patients on HAART (%)</td>
<td>310 (73.5)</td>
<td>41 (67.2)</td>
<td>269 (74.5)</td>
<td>0.23</td>
</tr>
<tr>
<td>Patients on 3TC, TDF or FTC (%)</td>
<td>299 (70.9)</td>
<td>41 (67.2)</td>
<td>258 (71.5)</td>
<td>0.50</td>
</tr>
<tr>
<td>HCV-Ab positive (%)</td>
<td>119 (28.2)</td>
<td>43 (70.5)</td>
<td>76 (21.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum HBV-DNA positive (%)</td>
<td>61</td>
<td>59</td>
<td>63</td>
<td>0.54</td>
</tr>
<tr>
<td>Median HBV-DNA (IU/mL)</td>
<td>19,346</td>
<td>949</td>
<td>24,522</td>
<td>0.003</td>
</tr>
<tr>
<td>Serum HBV-DNA &gt;10^7 IU/ml (%)</td>
<td>17</td>
<td>11</td>
<td>20</td>
<td>0.11</td>
</tr>
<tr>
<td>HBV genotypes (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>D</td>
<td>39</td>
<td>50</td>
<td>12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>A</td>
<td>56</td>
<td>27</td>
<td>78</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Predictors of serum HBV-DNA levels
Multivariate regression model

- Female gender: p-value 0.5
- Non-white ethnicity: p-value 0.2
- Age (per 10 years): p-value 0.2
- Baseline CD4 count (per 100 cells/µL): p-value 0.9
- CD4 nadir (per 100 cells/µL): p-value 0.4
- Plasma HIV-RNA (log copies/mL): p-value 0.2
- Use of anti-HBV drugs: p-value 0.3
- Anti-HDV+: p-value 0.001
- Anti-HCV+: p-value 0.8
- HBV genotype A: p-value 0.03

Estimate (β; 95% CI): -0.7 (-1, 0) for Anti-HDV+; -0.5 (-1, 0) for HBV genotype A.
Progression to AIDS or death
(91 events; 3233 PYFU)

- **Anti-HDV Ab**: 2.2 (p-value < 0.01)
- **CD4 count (per 100 cells/µl)**: 0.7 (p-value < 0.01)
- **CD4 nadir (per 100 cells/µl)**: 1.3 (p-value 0.21)
- **Plasma HIV-RNA (per 1 log cop/ml)**: 1.3 (p-value < 0.01)
- **Antiretroviral therapy**: 0.5 (p-value 0.43)
- **Male gender**: 1.7 (p-value 0.04)
- **Age (per 10 years)**: 2.2 (p-value < 0.01)
- **White ethnicity**: 0.5 (p-value 0.61)
- **Anti-HCV Ab**: 0.5 (p-value 0.65)
- **HBV genotypes: A vs. D**: 0.43 (p-value 0.43)
  - **Others vs. D**: 0.94 (p-value 0.94)
  - **Unknown vs. D**: 0.84 (p-value 0.84)
Progression to AIDS
(31 events; 3069 PYFU)

- Anti-HDV Ab
  - p-value: 0.37

- CD4 count (per 100 cells/µl)
  - Adjusted incidence rate ratio: 0.5
  - p-value: <0.01

- CD4 nadir (per 100 cells/µl)
  - p-value: 0.28

- Plasma HIV-RNA (per 1 log cop/ml)
  - Adjusted incidence rate ratio: 1.4
  - p-value: 0.03

- Antiretroviral therapy
  - p-value: 0.99

- Male gender
  - p-value: 0.87

- Age (per 10 years)
  - p-value: 0.42

- White ethnicity
  - p-value: 0.86

- Anti-HCV Ab
  - p-value: 0.64

- HBV genotypes: A vs. D
  - p-value: 0.49

- Others vs. D
  - p-value: 0.91

- Unknown vs. D
  - p-value: 0.39
Progression to death
(76 events; 3355 PYFU)

- Anti-HDV Ab
- CD4 count (per 100 cells/µl)
- CD4 nadir (per 100 cells/µl)
- Plasma HIV-RNA (per 1 log cop/ml)
- Antiretroviral therapy
- Male gender
- Age (per 10 years)
- White ethnicity
- Anti-HCV Ab
- HBV genotypes: A vs. D
  - Others vs. D
  - Unknown vs. D

Adjusted incidence rate ratio (95% CI)

- Adjusted incidence rate ratio: 0.5, 0.13, 0.38, 0.43, 0.70, 0.87
Progression to LRD
(21 events; 3382 PYFU)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted incidence rate ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HDV Ab</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CD4 count (per 100 cells/µl)</td>
<td>4.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CD4 nadir (per 100 cells/µl)</td>
<td>0.3</td>
<td>0.10</td>
</tr>
<tr>
<td>Plasma HIV-RNA (per 1 log cop/ml)</td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>Antiretroviral therapy</td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>2.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>White ethnicity</td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>Anti-HCV Ab</td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>HBV genotypes: A vs. D</td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Others vs. D</td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Unknown vs. D</td>
<td></td>
<td>0.57</td>
</tr>
</tbody>
</table>
Limitations

• Assessment of HDV markers in only a fraction of HBsAg+ patients (422/1319; 32%). However, the delta population (n=61) is the largest characterized virologically so far in HIV patients.

• Lack information on HBeAg status. It was not recorded and could have driven the association found between HBV genotypes and serum HDV-RNA.
Conclusions

• The overall prevalence of anti-HDV in chronic HBsAg+/HIV carriers in EuroSIDA is **14.5%**.

• Most anti-HDV patients exhibit detectable HDV viremia.

• Viral interference between HBV and HDV is manifested in all but HBV genotype D carriers, in whom overt co-replication of both viruses occurs, which might result in enhanced liver damage.

• We report for the first time that Delta hepatitis increases the risk of liver-related deaths and overall mortality in HIV patients.
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