HIV & Hepatitis Delta

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To which viral hepatitis applies it?

- Neglected disease
- Virus of virus
- Trojan horse
- Most severe chronic hepatitis
- No licensed treatment
- Not approved viral load test
- A vaccine could prevent it

- Hepatitis E
- Hepatitis GB
- Hepatitis D
Hepatitis Delta Virus (HDV)

- Small HDV genome: 1700-nt circular, single stranded RNA
- Defective virus that requires HBsAg (satellite virus)
- Replicates within the nucleus of infected hepatocytes
- 15 million people infected worldwide
- There is no animal reservoir – only circulates in humans
- Causes the most severe form of chronic viral hepatitis
- No FDA or EMA approved treatment
- No FDA or EMA licensed viral load test
- Diagnosis (HDV-Ab) often missed in HBsAg+ patients
- The best strategy to prevent hepatitis D is HBV vaccination
Genome size of living organisms

- **HDV**: $1.7 \times 10^3$ nt
- **Influenza**: $9.2 \times 10^3$ nt
- **HCV**: $3.2 \times 10^3$ nt
- **HIV**: $9.5 \times 10^3$ nt
- **EBV**: $2.3 \times 10^3$ nt
- **Ebola**: $9.5 \times 10^3$ nt
- **ZIKA**: $1.1 \times 10^4$ nt
- **HCV**: $1.7 \times 10^4$ nt
- **HBV**: $1.9 \times 10^5$ nt
- **E. Coli**: $4.6 \times 10^6$ nt
- **Tuberculosis**: $4.4 \times 10^6$ nt
- **Pneumococcus**: $2 \times 10^6$ nt
- **Plasmodium**: $2.3 \times 10^7$ nt
- **Humans**: $3.3 \times 10^9$ nt
Hepatitis B and D virions
HDV replication

- HDV
- HBV
- NCTP
- HBsAg
- Rolling circle replication

Cellular RNA POL II
800bp mRNA
1700bp mRNA

Hepatocyte

HDV-Ag
Small
Large

RNA
Geographic distribution - Hepatitis delta

- Amazonas
- Romania
- Mongolia
- Pakistan
- Turkey
- Taiwan
- West Africa

15 million
Delta hepatitis - Transmission

- Mainly parenteral and sex.

- Major risk groups:
  • IDUs
  • Multiple sex partners
  • Transfusions
  • Foreigners from endemic regions.
Overlapping HIV and viral hepatitis epidemics

- Hep C: 71 million
- Hep B: 240 million
- Hep D: 15 million
- HIV: 39 million

WHO. April 2017
Anti-HDV Ab in HIV-pos patients with HBsAg+ in EuroSIDA

21% (16/77)

9% (13/139)

25% (16/64)

11% (16/142)

14.5% of HBsAg+

The incidence and prevalence of delta hepatitis and HDV-related liver disease in the HIV population has dramatically declined since year 2006 (HAART):

- Broader HBV vaccination
- Decline in IDU
- Closer medical follow-up: no alcohol, early diagnosis, proper follow-up of cirrhotics, etc.

New incident HDV cases are mainly immigrants from Central-West Africa, Eastern Europe, Northern part of Latin America, and Middle East and Central Asia.
### Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>HIV monoinfection</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
<th>Hepatitis D</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>1,147</td>
<td>524</td>
<td>85</td>
<td>521</td>
<td>17</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>42.1±7.1</td>
<td>42.6±8.5</td>
<td>41.2±8.1</td>
<td>41.8±5.1</td>
<td>40.5±4.5</td>
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<tr>
<td>Male gender (%)</td>
<td>81</td>
<td>86</td>
<td>94.5</td>
<td>73.7</td>
<td>93.8</td>
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<tr>
<td>Intravenous drug use (%)</td>
<td>46.1</td>
<td>16.7</td>
<td>10.9</td>
<td>82.3</td>
<td>81.3</td>
</tr>
<tr>
<td>Mean body mass index (Kg/m²)</td>
<td>24.1±4.2</td>
<td>24.7±4.1</td>
<td>25.1±4.2</td>
<td>23.3±4.1</td>
<td>23.8±4</td>
</tr>
<tr>
<td>Alcohol intake &gt;60 g/day (%)</td>
<td>6.9</td>
<td>4.1</td>
<td>7.3</td>
<td>9.8</td>
<td>25</td>
</tr>
<tr>
<td>Baseline advanced liver fibrosis (%)</td>
<td>20.8</td>
<td>8.3</td>
<td>16.4</td>
<td>34.7</td>
<td>62.5</td>
</tr>
<tr>
<td>Mean baseline CD4 count (cells/μL)</td>
<td>566±310</td>
<td>574±323</td>
<td>698±302</td>
<td>543±291</td>
<td>476±146</td>
</tr>
<tr>
<td>Mean baseline ALT (IU/mL)</td>
<td>53.6±56.2</td>
<td>37.5±49</td>
<td>61.3±82</td>
<td>70.1±55.1</td>
<td>93.2±71</td>
</tr>
<tr>
<td>Antiretroviral therapy (%)</td>
<td>85.4</td>
<td>86.4</td>
<td>85.5</td>
<td>84.3</td>
<td>87.5</td>
</tr>
</tbody>
</table>
Time free from liver decompensation events or death in HIV+ patients

- HIV-monoinfected (n=524)
- HIV/HCV-coinfected with SVR (n=106)
- HIV/HCV spontaneous seroconverters (n=21)
- HIV/HBV-coinfected (n=85)
- HIV/HCV untreated (n=258)
- HIV/HCV non-responders (n=127)
- HIV/delta (n=17)

Patients (%)

- p=0.002
- p<0.001
- p<0.0001

Months

0 20 40 60 80 100
Hepatitis delta in the Swiss Cohort

- Anti-HDV testing of all HIV-pos with HBsAg+
  - HBsAg+: 818
  - Anti-HDV+: 15.4% (119/771)
  - Serum HDV-RNA+: 62.9% (73/116)
  - Anti-HDV+ significantly associated with:
    - IDU (61% vs 9%)
    - HCV-Ab+ (73% vs 18%)
  - Anti-HDV worsens prognosis (aHR):
    - Overall death: 2.3
    - Liver-related death: 7.7
    - HCC: 9.3

Delta in the Swiss Cohort

Therapeutic landscape for hepatitis delta

- Immunomodulators: peginterferon-α (or lambda)

- Anti-HBV agents:
  - Nucleos(t)ide analogues: tenofovir
  - Entry inhibitors: myrcludex-B
  - Gene therapy (Nucleic acid polymers): REP 2139-A

- Specific anti-HDV drugs:
  - Prenylation inhibitors: lonafarnib
  - Gene therapy (RNA interference)
  - Therapeutic vaccines

Peginterferon for HDV

• 12-48 months of pegIFNα leads to 25% undetectable plasma HDV-RNA up to 6 months after treatment discontinuation. However, relapses still occur thereafter.

• Missed opportunity with pegIFN lambda (not yet !)

• Failure of HIDIT studies to prove any benefit of combination therapy with pegIFN plus adefovir/tenofovir.
Anti-HBV Nucleos(t)ides in HIV with Delta

• 47 years-old male
• From Dagestan, East Asia
• HBsAg, HBeAg, and anti-Delta Ab (IgG) positive
• Serum HBV-DNA >9 log cop/mL
• Serum HDV-RNA 5.6 log cop/mL
• HBV-D and HDV-1
• Liver biopsy A2F2
• Treatment with pegIFN + TDF + FTC
• Clearance of serum HBsAg with seroconversion to anti-HBs, along with clearance of HBV-DNA and HDV-RNA after 10 months of therapy.
Long-term effect of TDF on hepatitis delta

- 34-year old male with advanced cirrhosis due to HDV.
- HIV-negative
- Experienced clinical improvement, normalization of liver enzymes, suppression of serum HDV-RNA and HBsAg clearance after two years of oral TDF monotherapy.
- No development of anti-HBs
- Conclusion: TDF should be tried in patients with hepatitis delta with contraindications for interferon use.

Long-term TDF in HIV patients with delta hepatitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Number of patients</th>
<th>Follow-up (years)</th>
<th>Comments</th>
<th>HDV-RNA clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyd et al. ARHR 2013</td>
<td>France</td>
<td>17</td>
<td>2.6</td>
<td>IFN added in 4</td>
<td>2</td>
</tr>
<tr>
<td>Soriano et al. AIDS 2014</td>
<td>Spain</td>
<td>19</td>
<td>4.9</td>
<td>Undetectable HBV-DNA in all</td>
<td>10</td>
</tr>
<tr>
<td>Beguelin et al. CID 2017</td>
<td>Switzerland</td>
<td>21</td>
<td>4.9</td>
<td>5 remained with detectable HBV-DNA</td>
<td>3</td>
</tr>
</tbody>
</table>
Long-term effect of TDF on hepatitis delta

- 19 individuals with hepatitis delta treated with TDF for an average of 58 months, as part of their antiretroviral combination for HIV infection.
- All experienced significant declines in serum HDV-RNA and 10 (53%) achieved undetectable viral load.
- Hepatic fibrosis as measured using elastometry, significantly improved in the subset of individuals that reached complete HDV suppression.

- Serum HBsAg became negative in 3 patients but none of them seroconverted to anti-HBs.
- We then decided to give 4 double-doses of the HBV vaccine to these three patients, but none elicited any anti-HBs response.
- Given that removal of tenofovir could be risky, we have decided to keep on TDF all our patients.

Hepatitis Delta – New therapies

- **Entry inhibitors**
  - Myrcludex B

- **Prenylate inhibitors**
  - Lonafarnib

- **Nucleic acid polymers (NAPs)**
  - REP 2139-Ca
HBV & HDV Entry Inhibitors

HBsAg

Myrcludex B (47 aa peptide)

IC$_{50}$ is 100-fold higher for myrcludex B than for biliary acids
Myrcludex B

2 mg sc/day

21 patients

Myrc

Myrc + pegIFN

pegIFN 48 weeks

pegIFN 48 weeks

pegIFN 24 weeks

pegIFN 24 weeks

pegIFN 24 weeks

24 weeks

Consistent and uniform decline (>1 log) in serum HDV-RNA but no effect on HBsAg

Lonafarnib

• Oral inhibitor of farnesyl-transferase.

• Blocks prenylation of large HDA antigen, stopping virus assembly and packaging

• Prior clinical experience in the treatment of progeria

• No selects for drug resistance
Lonafarnib

Phase 2a: 100 or 200 mg BID for 4 weeks

Nausea and diarrhea were common
No changes in serum [HBsAg]

Lonafarnib

- Recognition of dose-response
- Ritonavir increases 5-fold lonafarnib exposure
- LOWR -1 to -4 trials testing lonafarnib/ritonavir BID with dose escalation to improve GI tolerability
- PK/PD modelling predicts 99% efficacy with LNF 100 mg BID plus RTV 100 mg QD
- Synergy with peginterferon

Yurdaydin et al. EASL 2017
REP 2139-Ca

- Nucleic acid polymer (NAP).
- Intravenous administration (weekly) of oligonucleotides
- Drop in HBsAg production & HDV-RNA negativization
- Transition to subcutaneous administration in progress

Bazinet et al. EASL 2017
HDV Combination Therapy
Summary & Caveats

- All HBsAg+ pts should be tested for anti-HDV Ab. In HIV, 15% will be pos

- Serum HBV-DNA should be checked in all pts with hepatitis delta. Individuals viremic for hep B should benefit from anti-HBV nuc therapy.

- A commercial, pan-genotypic, sensitive and reproducible HDV-RNA quantitative test is needed. Roughly, >60% of anti-HDV are viremic

- TDF leads to >2 log HDV-RNA drop in 30% and clears viremia n 15%. Promising results with new specific anti-HDV drugs (i.e., entry and assembly inhibitors). Combination therapy seems the best way to move forward.

- TAF and peginterferon lambda should be on board initially.

- Whereas sustained suppression of HBV replication (functional cure) is the goal for hep B, HDV eradication would be more feasible given that there is no HDV-RNA reservoir.

- Universal HBV vaccination is the best way to prevent hepatitis delta.

- Liver transplantation is decompensated cirrhotics cures HDV.
Un abrazo