Impact of antiretroviral therapy on HBV-related liver disease

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Outline

• Background - Liver disease prior to ART
• ART and HBV virological outcomes
• ART and HBV liver disease outcomes
• Can we cure HBV?
• Summary

Worldwide HBsAg and HIV prevalence, 2006

UNAIDS 2006
HIV increases liver mortality from CHB prior to HAART

- 5293 men (326 HBsAg+ baseline) followed 10.5 years
- RR of liver death 17.7 in coinfected vs. only HBsAg+

Liver-related mortality is higher from HBV than from HCV in the MACS

- 337 men with CHB and 343 with CHC at study entry in MACS
- Outcome: liver-related mortality (LRM) expressed as rate/1000 PYs

Multivariate analysis of LRM in HIV-coinfected

<table>
<thead>
<tr>
<th></th>
<th>IRR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis status (HCV ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>2.0</td>
<td>1.0-1.9</td>
<td>0.047</td>
</tr>
<tr>
<td>Age/10 year increase</td>
<td>1.6</td>
<td>1.1-2.3</td>
<td>0.009</td>
</tr>
<tr>
<td>Most recent CD4 count (&gt;350 ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200-350</td>
<td>7.1</td>
<td>2.4-20.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;200</td>
<td>16.3</td>
<td>6.2-42.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAART</td>
<td>0.7</td>
<td>0.3-1.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Also adjusted for alcohol, recruitment period, race
Liver fibrosis advanced in HIV-HBV co-infection with higher HBV DNA in Nigeria

- Cross sectional study of 232 HIV+ and 93 HIV-HBV patients in Nigeria
- Transient elastography prior to HAART

HBV DNA >4000 IU/ml in HIV-HBV co-infected Nigerian subjects prior to HIV therapy

ART AND HBV VIROLOGICAL OUTCOMES
**Meta-analysis of TDF response in 550 HIV-HBV co-infected subjects**

![Graph showing TDF response over time for HIV-HBV co-infected subjects with HBeAg positive and negative.](image)


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**Treatment response in 165 HIV-HBV co-infected subjects with median 2.8 yrs treatment**

![Bar graph showing proportion of participants with undetectable HBV DNA by regimen.](image)

Matthews et al CID 2013 56(9):e87-94

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**Factors associated with detectable HBV DNA in those with HIV RNA < 400 cp/ml**

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 yrs)</td>
<td>0.90</td>
<td>0.48, 1.69</td>
<td>0.74</td>
</tr>
<tr>
<td>HBeAg positive</td>
<td>12.06</td>
<td>3.73, 38.98</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;95% adherent</td>
<td>2.52</td>
<td>1.16, 5.48</td>
<td>0.02</td>
</tr>
<tr>
<td>HAART &lt;2 yrs</td>
<td>2.64</td>
<td>1.06, 6.54</td>
<td>0.04</td>
</tr>
<tr>
<td>CD4 &lt; 200 cells/mm³</td>
<td>2.47</td>
<td>1.06, 5.73</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Matthews et al CID 2013 56(9):e87-94
Response to TDF in multinational ACTG studies: 5175 and 5208

HBsAg kinetics in 104 HIV-HBV subjects on TDF-based ART

66 HBeAg+
- Baseline sAg 4.6 log IU/ml
- 2.2 log decline yr 6
- 5 HBsAg loss

38 HBeAg-
- Baseline sAg 2.8 log IU/ml
- 0.6 log decline yr 6
- 3 HBsAg loss


ART AND HBV LIVER DISEASE
Incidence of cirrhosis in HIV-HBV on TDF-based HAART is low

- 508 Spanish HIV-hepatitis non-cirrhotic patients
- Two TEs 2.6 ± 1.0 yrs apart
- 54 (10.6%) developed cirrhosis
- 1/24 (4.2%) with HBV

Multivariable analysis for risk of developing cirrhosis adjusted for baseline factors including TE

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-HCV with SVR</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HIV-HCV</td>
<td>3.73</td>
<td>0.04</td>
</tr>
<tr>
<td>HIV-HBV</td>
<td>0.69</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Tuma et al, AVT 2010 15:881-6

Liver decompensation-free survival in 79 HIV-HBV co-infected subjects

- 97% on HBV-active ART
- 45.7% HBeAg+
- Median f/u 35 months
- 11 (15%) cirrhosis baseline
- 8 (10%) with liver decompensation
  - 7 cirrhosis baseline

Martin-Carbonero et al, AIDS 2011; 25:73-79

Liver disease progression by TE

- 71/79 with two TE over median time of 40.1 mos
- Median TE scores stable
- Proportion with no or mild fibrosis increased from 47.8% to 64.7%
- 6 (8.4%) with increase in fibrosis stage
- Limitation: no control group

Martin-Carbonero et al, AIDS 2011; 25:73-79
Fibrosis progression in 184 French HIV-HBV patients on TDF

- Fibrosis measured by Fibrometer every 12 mos
- Median 1u 29.5 mos
- 115 (63%) <F4 prior to TDF
- 12 (10.4%) with incident F4 (4.5/100 PYs) after median of 11.2 months

![](chart1.png)

Change in mean Fibrometer during TDF treatment

![](chart2.png)

Factors associated with increase in Fibrometer to F3-F4

<table>
<thead>
<tr>
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<th>HR</th>
<th>95% CI</th>
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<tr>
<td>HCV serology positive</td>
<td>3.6</td>
<td>1.3-9.8</td>
</tr>
<tr>
<td>Age &gt;40.6 yrs</td>
<td>2.9</td>
<td>1.0-5.1</td>
</tr>
<tr>
<td>&gt;4 glasses alcohol/day</td>
<td>3.1</td>
<td>1.4-6.9</td>
</tr>
<tr>
<td>AIDS defining event</td>
<td>2.5</td>
<td>1.1-5.6</td>
</tr>
<tr>
<td>GGT flare &gt;50 IU/ml</td>
<td>2.6</td>
<td>1.2-5.7</td>
</tr>
<tr>
<td>CD4 &gt;350 cells/mm³</td>
<td>0.3</td>
<td>0.2-0.7</td>
</tr>
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</table>

Boyd et al, AVT 2010 15:963
Prevalence of elastography-defined liver fibrosis (>9.3 kPa) and cirrhosis (≥12.3 kPa) among Ugandans

APRI improves with HAART in HIV-hepatitis co-infected

CXCL10 elevated in HIV-HBV co-infected patients on ART

- Thai HIV-HBV co-infected subjects vs HBV monoinfected or uninfected
- Prior to ART: LPS, sCD14, CXCL10, CCL2 higher in co-infected
- With ART: CXCL10 declined but remained elevated
- In vitro, LPS and IFN-γ synergistically increased CXCL10
- In other studies, CXCL10 associated with hepatic flares (Crane et al, JID 2009; 199:974–81)

Crane et al, JID spub March 2014
CAN WE CURE HBV?

Types of HBV cure

• Functional cure (akin to SVR in HCV)
  – Maintain undetectable HBV DNA off therapy
  – Ideally anti-HBs+
• Eradication (complete) cure
  – Eliminate cccDNA

Barriers to cure

• cccDNA
  – Stable intranuclear form that is transcription template
  – Not substantially affected by current anti-virals (1 log reduction)
  – Difficult to eradicate even with natural recovery
• Functional cure is possible
  – anti-HBs in 5% on long-term anti-virals
Drug targets in HBV replication cycle

Virological approaches

- Block entry-
  - Myrcludex B
- Silence cccDNA
- Endonucleases to cleave cccDNA
- HBV capsid inhibitor - destabilizes capsid assembly
- siRNA targeted to viral mRNA
  - Li et al. Cell Biochem Biophys 2014 Feb;  
  - Wooddell et al. Mol Ther 2013 21:973
- RNase H inhibitors
- Sirtuin 1 inhibitors

Myrcludex B inhibits HBV replication in early but not chronic HBV in humanized mice

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Immunological approaches

- TLR7 agonist
  - Leads to development of anti-HBs in woodchuck model (Menne et al., J Hepatol 2011)
  - In chimps, prolonged suppression of HBV DNA (Lanford et al., Gastro 2013 144: 1508)
- PD-1 blockade
- Therapeutic vaccine
- Adoptive transfer of genetically modified T cells that express receptor directed against HBV surface proteins (Youse et al., Gastro 2013 144: 1508)
- Nanoparticles with HBV-CpG induce IFN-α thru TLR9 dependent pathway
- LTβR agonist (Ludhess Science 2014 Feb)

Summary

- Virological response from ART
  - HBV DNA
  - HBsAg
  - High level of adherence
- Decreased fibrosis progression
  - Not universal
- Substantial progress but risk is not zero. Need cure
- Several potential virological or immunological approaches
- Data on immune response during recovery from natural infection needed

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