Effect of HBV suppression on liver related outcomes

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HIV and hepatitis chronic infection: impact on morbidity and mortality
Temporal trends in morbidity and mortality

- Incidence of AIDS-defining events and associated mortality
- Liver related morbidity and mortality

Liver disease = 3rd cause of death in HIV- patients, but decreasing in more recent studies

Mortavic: causes of death in HIV-infected adults

- 20-25% of cirrhosis due to HBV
Multicenter cohort + meta-analysis of 12,382 patients, either HIV+ or HIV/HBV

36% excess risk of dying (all cause) if HBs pos. compared to HBs neg., but data collected on a long period (some before use of cART)

Nikolopoulos G, Clin Infect Dis 2009
MACS cohort: (337HBs+ - 343 HCV+) of whom 452 HIV+ ➔ 6728 person-years of F/U, 293 deaths

⇒ RR=2.2 [1.1 – 4.5] of dying of liver-related cause when HBs pos.

⇒ No difference between HCV and HBV regarding all cause deaths

Fadale-Nwulia, Clin Infect Dis 2012
Predictors of liver outcomes in HIV-HBV patients
In a large cohort of HBV patients (n=3342) with long-term follow-up (39,016 p.y for cirrhosis and 53,551 p.y for HCC): What do we learn from HBV-monoinfected patients?

Table 4. Regression coefficients and integer risk scores of baseline hepatitis B virus predictors estimated from the derivation set

- Age (each 5-year increment)
- Male
- Ref:
  - Age
  - Male

HBsAg
  - Positive: positive level B or B+C
  - Negative: negative level C

HBcAg
  - Positive: any level B or B+C
  - Negative: negative level C

Anti-HBc
  - Positive: any level B or B+C
  - Negative: negative level C

ALT (U/L)
  - Reference: 0–44
  - 1–44
  - >44

Family history of hepatocellular carcinoma
  - Yes
  - No

Presence of HBV DNA/HBV Ag
  - Negative
  - >10^4 any type
  - >10^5 any type
  - >10^6 any type
  - >10^7 any type

Levels of ALT (U/L)
  - Reference:
  - 0–44
  - 1–44
  - >44

Risk score

P value

0.001
0.001
0.001
Risk modelling for liver cirrhosis

Risk modelling for HCC

Not only HBV-DNA should be controled, but also HBsAg

Decreasing ALT level may be a good prognosis factor

HBV genotype may have an impact on liver fibrosis

Age and gender are factors that cannot be acted on

Potent antiviral treatment is a key factor in reducing the incidence of ESLD in HBV patients (both mono- and co-infected)
Short-term virological response to TDF in HIV-HBV patients

- 28 3TC-pretreated patients used for modeling of viral kinetics
- Two declining slopes
- Median time to indetectability = 272.5 days (203 – 416)

Lacombe K, et al. AIDS 2005
Mid-term virological response to TDF in HIV-HBV patients

• 102 patients (61% AgHBs +) with a median 5 years of follow-up

Figure 1. Kaplan-Meier curve for the cumulative probabilities of achieving virologic response, defined as HBV-DNA levels less than 20 IU/mL, for HBeAg-positive (n = 67) and HBeAg-negative (n = 15) HIV/HBV with patients with detectable HBV DNA at baseline (n = 82).
Long-term virological response to TDF in HIV-HBV patients

- 120 patients (63% AgHBe +) with a minimum of 1 year of TDF and up to 8 years of follow-up

![Graph showing cumulative probability of HBV-VL <60 IU/mL over the duration of TDF treatment.](image)
Decline in HBsAg and HBeAg in HIV-HBV patients treated with TDF

Maylin, et al. AIDS 2012
Hepatic flares and impact of treatment

- Frequent hepatic flares in a cohort of 308 HIV-HBV patients\(^1\): 13.4/100p.y of f.u
- Associated factors:

\[^{1}\text{Chauvel, et al. Antivir Ther 2007}\]

**High risk**: HBV-DNA > 20000 UI/mL + HIV-RNA > 10000 copies/mL + CD4 < 200/mm\(^3\)

**Low risk**: HBV-DNA < 60 UI/mL + HIV-RNA < 50 copies/mL + CD4 > 200/mm\(^3\)

→ HIV and HBV infections controled by Tx
Impact of HBV genotype

- G genotype associated with increased risk of F4 metavir stage compared to A, D and E\textsuperscript{1}

- B genotype associated with increased risk of hepatic flares, liver disease-related death compared to C\textsuperscript{2}

\textsuperscript{1}Lacombe, et al. AIDS 2005. \textsuperscript{2}Sheng, et al. CID 2012
Clinical consequences of controled HBV infection
Impact of cART on liver-related deaths, including HBV

Table 3. The adjusted IRR of cause-specific death by year longer on cART.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>IRR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause</td>
<td>0.95</td>
<td>0.92–0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AIDS</td>
<td>0.86</td>
<td>0.81–0.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-AIDS</td>
<td>0.97</td>
<td>0.95–1.00</td>
<td>0.061</td>
</tr>
<tr>
<td>NARI-death</td>
<td>0.97</td>
<td>0.90–1.05</td>
<td>0.417</td>
</tr>
<tr>
<td>LR-death</td>
<td>0.94</td>
<td>0.89–1.00</td>
<td>0.053</td>
</tr>
<tr>
<td>NADM-death</td>
<td>1.07</td>
<td>1.00–1.14</td>
<td>0.056</td>
</tr>
<tr>
<td>CVD-death</td>
<td>0.99</td>
<td>0.93–1.14</td>
<td>0.885</td>
</tr>
<tr>
<td>Violent death</td>
<td>0.90</td>
<td>0.81–1.06</td>
<td>0.027</td>
</tr>
<tr>
<td>Other death</td>
<td>1.01</td>
<td>0.94–1.09</td>
<td>0.725</td>
</tr>
<tr>
<td>Unknown death</td>
<td>0.94</td>
<td>0.86–1.01</td>
<td>0.096</td>
</tr>
</tbody>
</table>

Cl, confidence interval; CVD, cardiovascular disease; IRR, incidence rate ratio; LR, liver-related; NADM, non-AIDS-defining malignancies; NARI, non-AIDS-related infection. Models’ adjustment as in Table 2.

- Eurosida cohort: 12069 patients included in analysis

Kowalska, et al. AIDS 2012
Impact of cART on clinical outcomes in HIV-HBV patients

- 92 patients, 82% treated with FTC/TDF median f/u = 39 months

- \( I(\text{death}) \): 2.2 / 100 p.y
- \( I(\text{liver dec.}) \): 2.9 / 100 p.y

\( \Rightarrow \) Close to what is observed in HIV general population

- Liver fibrosis stability in 75% of patients

Fig. 1. Survival and liver decompensation in the HIV-hepatitis B virus coinfect ed study population.

Martin-Carbonero, et al. AIDS 2011
Focus on liver fibrosis on TDF/FTC or 3TC

Figure 2: 36-month evolution of Fibromet® score during TDF treatment

Figure 3: Transitions of Metavir fibrosis and activity score scored by liver biopsy during treatment with TDF

3a- Fibrosis score

3b- Activity score

Reversibility of cirrhosis

- 29 year-old HIV-HBV patient after 3 years of cART containing TDF+FTC¹:

  Figure 1. Regression of cirrhosis in HIV/hepatitis B virus coinfection

- in 508 HIV patients, \( \lambda(\text{cirrhosis}) \) in HBV = 1,6/100p.y, comparable to HIV mono²

End stage liver disease, and beyond
Overall survival rates after OLT in HBV-HIV patients

Approx. 20% of all OLT in HIV-patients are due to HBV

Table 1. Unadjusted and adjusted analyses of factors associated with patient survival post liver transplantation.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (vs. positive)</td>
<td>7.20 (2.06–25.19)</td>
<td>8.28 (2.26–30.33)</td>
</tr>
<tr>
<td>Not reported (vs. positive)</td>
<td>6.22 (1.76–22.07)</td>
<td>8.07 (2.34–27.82)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (vs. positive)</td>
<td>0.23 (0.07–0.79)</td>
<td>–</td>
</tr>
<tr>
<td>Unknown (vs. positive)</td>
<td>0.49 (0.20–1.20)</td>
<td>–</td>
</tr>
<tr>
<td>HIV viral load</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detectable (vs. undetectable)</td>
<td>2.23 (0.98–5.06)</td>
<td>2.89 (1.41–5.91)</td>
</tr>
<tr>
<td>Not reported (vs. undetectable)</td>
<td>1.51 (0.71–3.20)</td>
<td>1.27 (0.70–2.28)</td>
</tr>
</tbody>
</table>

Cooper, et al. 2011, AIDS
Survival rate in transplanted patients: data from France

- 13 patients (1 HDV+, 2 HCV+, 4 HCV-HDV+)
- Indication for OLT: decompensated cirrhosis (10) and HCC (3)
- Treatment after OLT: combination of TDF / 3TC + HBIg
- Overall survival rate at 32 months: 100%
  - No mitochondrial toxicity
  - Controled HBV-DNA, HDV-RNA, HIV-RNA
  - Successful treatment with PR in 1/3 HCV-RNA+

Tatteo, et al. AIDS 2009
Survival rate in transplanted patients: data from the USA

- 22 patients (2 HCV+) matched with 20 HBV mono-infected patients
- Indication for OLT: decompensated cirrhosis (19), HCC (2), fulminant (1)
- Overall survival: 85% in HIV-HBV, 100% in HBV (p=0.09)
  - 3 deaths due to causes unrelated to HBV
  - Persistent low replicating HBV-DNA in 6/7 patients with available HBV-DNA after OLT

IN CONCLUSION

- ESLD are presently predominant causes of death in HIV-infected patients, but mostly attributable to HCV.

- Determinants of liver outcomes on which one may act are of virological nature (HBV-DNA, HBsAg).

- Potent antiviral treatment (TDF + FTC/3TC) is of crucial importance for favourable liver outcomes.

- Cirrhosis might be reversible and fibrosis might decrease in patients on cART containing potent anti-HBV drugs.

- Very good survival rate after OLT.