HIV-HBV coinfection: Issues with treatment in 2018

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Global epidemiology

- Same routes of transmission:
  - 90% of HIV-infected patients with markers of prior HBV infection + 5-15% w/ chronic infection\(^1\)
  - HIV (33M) + HBV (400M) = 2-4M HIV-HBV\(^2\)
  - in Europe, \(P(\text{HIV-HBV}) = 7.1\%\)\(^3\)

- Routes of transmission and age at transmission differ:
  - Zones with low HBV endemicity (<2%)
    - Europe, North America
    - IDU, sex
    - \(P(\text{HIV-HBV}) = 5 – 10\%\)
  - Zones with high HBV prevalence (>8%)
    - Africa, Asia
    - perinatal, young age (injections, scarification)
    - \(p(\text{HIV-HBV}) = 15\%\)

HBV treatment guidelines

All persons with HBV/HIV co-infection should receive ART that includes tenofovir (unless history of tenofovir intolerance)

- Maintain Tenofovir in patients undergoing immunosuppressive therapy in all patients with AntiHBc Ab (prevention of HBV reactivation)
- Tenofovir should not be stopped in patients with cirrhosis

Treatment uptake in Europe

- 953 HIV-HBV patients included in Eurosida and followed after 2002
- Increase in TDF use from 4% in 2002 to 75% in 2015
- Disparities in the use of TDF between West and East parts of Europe (2005: 42% v. 7%; 2015: 63% v. 76%)

No association with a decreased risk of liver-associated event: incidence rate ratio (IRR) = 0.64 (95% CI 0.35, 1.18) between those on TDF and those without TDF

Peters L. et al. Antivir Ther 2018
What to expect from treatment?

• Control of HBV replication
• Path to HBV eradication (at least in each infected individual if not globally: « functional cure »)?
• Safety and tolerability on the long term
• Positive impact on morbi-mortality
Therapeutic goals

1st: Undetectable HBV DNA

- Meta-analysis on 23 papers including cohorts and clinical trials, n=516

A small % continues to have detectable HBV-DNA after extended therapy = residual viremia

Price H et al., PLoS One 2013
Consequences of residual viremia

Patients undergoing TDF-containing ART (French Hiv Hbv Cohort) 

(N=111)

Undetectable HBV-VL (<60 IU/mL) at end of follow-up  
(n=96)

Detectable HBV-VL (≥60 IU/mL) at end of follow-up  
(n=15)

Stabilized virological response  
(n=86)

Transient persistent viremia  
(n=10)

Low-level persistent viremia  
60-2000 IU/mL  
(n=11)

High-level persistent viremia  
>2000 IU/mL  
(n=4)
1. Strong association with previous severe immuno-suppression and persistent viremia

<table>
<thead>
<tr>
<th>PV group</th>
<th>Nadir CD4+ cell count</th>
<th>CD4+ cell count</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>At baseline</td>
<td>End of follow-up</td>
<td></td>
</tr>
<tr>
<td>VR</td>
<td>238 (136-321)</td>
<td>400 (324-576)</td>
<td>520 (405-675)</td>
<td></td>
</tr>
<tr>
<td>Transient</td>
<td>54 (30-179)</td>
<td>185 (86-532)</td>
<td>448 (285-589)</td>
<td></td>
</tr>
<tr>
<td>Low-level</td>
<td>89 (8-216)</td>
<td>430 (219-576)</td>
<td>349 (288-586)</td>
<td></td>
</tr>
<tr>
<td>High-level</td>
<td>254 (125-355)</td>
<td>474 (332-501)</td>
<td>367 (276-607)</td>
<td></td>
</tr>
</tbody>
</table>

Non adherence: no TDF in plasma
2. Seroclearance and seroconversion only occurs among those with stabilized virological response

<table>
<thead>
<tr>
<th>SR, n (%)</th>
<th>Stabilized-VR</th>
<th>Persistent viremia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Transient</td>
</tr>
<tr>
<td>HBeAg loss*</td>
<td>20 (37.0)</td>
<td>0</td>
</tr>
<tr>
<td>HBeAg seroconversion*</td>
<td>5 (9.3)</td>
<td>0</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>4 (4.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Among HBeAg-positive patients.

However, no clinical impact demonstrated so far

Boyd et al., Hepatology, 2014
Therapeutic goals

2nd: Hbe/HBs seroconversion = “functional cure”

HBeAg-loss (HBeAg+)

Incident rate = 6.5/100 p•y

HBsAg-loss (overall)

Incident rate = 0.7/100 p•y

Co-infected patients undergoing TDF-containing ART from the French Hiv-Hbv Cohort (n=111)

Boyd A et al., Liver Int 2015
Seroclearance and seroconversion rates (per year) during treatment with TDF: comparison to HBV monoinfection

<table>
<thead>
<tr>
<th></th>
<th>HBV</th>
<th>HIV-HBV</th>
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<tbody>
<tr>
<td>HBeAg-seroclearance*</td>
<td>9.9%-10.5%</td>
<td>4.8-7.7%</td>
</tr>
<tr>
<td>HBeAg-seroconversion*</td>
<td>9.2%</td>
<td>1.0-3.8%</td>
</tr>
<tr>
<td>HBsAg-seroclearance</td>
<td>0-0.5%</td>
<td>0.6%-1.6%</td>
</tr>
<tr>
<td>HBsAg-seroconversion</td>
<td>0-0.5%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

*Among HBeAg-positive patients only.

Therapeutic goals

2\textsuperscript{nd} : Hbe/HBs seroconversion = “functional cure”: why is it no achievable?

- Most patients exhibit little change in on-treatment qHBsAg

- Profiles of fast decline = HBsAg seroclearance
Of 308 patients in total cohort, 9/14 (64.3%) with HBsAg-loss achieved HBsAg-seroconversion

- Maximal rate of antibody production = 0.57-1.93 y\(^{-1}\) from a Gompertz growth model
- Much slower than acute infection (0.96-1.32 m\(^{-1}\)) or post-vaccination (0.94 d\(^{-1}\))
Therapeutic goals

2nd: HBe/HBs seroconversion = “functional cure”: why is it no achievable? The key answer

- All patients had detectable ccc-DNA replication even after 36 months
- Modeling suggests no plateau in ccc-DNA viral load

HBeAg+
ccc-DNA half-life = 1.3 months

HBeAg-
ccc-DNA half-life = 13.6 months

Reconstructed history of TDF-treatment in co-infected patients with ccc-DNA and total IH-DNA quantification

Boyd A et al., J Hepatol, 2016
Therapeutic goals

3rd: Safety on the long term: renal impact of TDF

Renal function becomes more impaired during TDF-containing ART, yet not severely (172 with eGFR measures)

Boyd A et al., Antivir Ther 2017

At the end of follow-up:
- 36/114 (31.6%) with normal baseline function had renal dysfunction
- 13/172 (7.6%) had moderate renal impairment
Risk-factors towards **mild/moderate renal impairment** (co-infected patients with normal baseline function, $n=114$)

<table>
<thead>
<tr>
<th></th>
<th>HR (95%CI)</th>
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<tbody>
<tr>
<td></td>
<td>Univariable</td>
<td>Multivariable</td>
</tr>
<tr>
<td>Baseline age (/year)</td>
<td><strong>1.04 (1.00-1.08)</strong></td>
<td><strong>1.05 (1.01-1.10)</strong></td>
</tr>
<tr>
<td>Female gender</td>
<td>1.00 (0.49-2.02)</td>
<td>2.01 (0.66-6.11)</td>
</tr>
<tr>
<td>African origin</td>
<td>0.79 (0.42-1.49)</td>
<td>0.79 (0.29-2.14)</td>
</tr>
<tr>
<td>AIDS-defining illness</td>
<td><strong>1.72 (1.07-2.77)</strong></td>
<td><strong>1.68 (1.05-2.69)</strong></td>
</tr>
<tr>
<td>HBV DNA VL&lt;60</td>
<td><strong>0.53 (0.29-0.94)</strong></td>
<td><strong>0.41 (0.23-0.76)</strong></td>
</tr>
<tr>
<td>Baseline cirrhosis</td>
<td><strong>1.56 (0.95-2.58)</strong></td>
<td>--</td>
</tr>
</tbody>
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Boyd A et al., Antivir Ther 2017
EACS guidelines in case of renal impairment

• Document the origin of renal impairment (iatrogenic, glomerular/tubular dysfunction)
• If tubular dysfunction confirmed, switch to a less nephrotoxic drug (TAF?)
• If TDF or TAF are contraindicated, switch to entecavir (combined to fully potent cART) if no previous exposure to 3TC
• If entecavir cannot be used, use TAF, give treatment every 2/3 days, and closely monitor renal function: seek advice from specialist

Liver fibrosis is mostly stable during long-term therapy with TDF (168 patients with non-invasive measures)

Boyd A et al., JIAS 2017
Risk-factors for transitioning between none/moderate liver fibrosis and severe fibrosis/cirrhosis in co-infected patients (multivariable analysis)

<table>
<thead>
<tr>
<th></th>
<th>HR (95%CI)</th>
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<tbody>
<tr>
<td></td>
<td>F0-F1-F2→F3-F4</td>
</tr>
<tr>
<td>Baseline age (/year)</td>
<td>1.06 (1.02-1.09)</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.17 (0.07-0.44)</td>
</tr>
<tr>
<td>CD4+ ≥350/mm³</td>
<td>1.03 (0.61-1.76)</td>
</tr>
<tr>
<td>Pi-use</td>
<td>1.88 (1.14-3.10)</td>
</tr>
<tr>
<td></td>
<td>F3-F4→F0-F1-F2</td>
</tr>
<tr>
<td>Baseline age (/year)</td>
<td>0.94 (0.90-0.98)</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.72 (0.27-1.92)</td>
</tr>
<tr>
<td>CD4+ ≥350/mm³</td>
<td>2.12 (1.41-3.95)</td>
</tr>
<tr>
<td>Pi-use</td>
<td>0.92 (0.55-1.55)</td>
</tr>
</tbody>
</table>

Boyd A et al., JIAS 2017
Controversy: HCC / ESLD during treatment

Data from the D:A:D collaboration among HIV-HBV co-infected patients, risk of HCC/ESLD with various antiretroviral agents

<table>
<thead>
<tr>
<th></th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Cumulative TDF-use (/ 5 years)</td>
<td>1.52 (1.14, 2.02)</td>
</tr>
</tbody>
</table>

- **Indication bias**? TDF preferred during active infection, those not at risk may be less prone to be treated with TDF-containing cART (see Peters L, et al.)

- Risk of HCC/ESLD is **not eliminated** with TDF-use

**Therapeutic goals**

4th: impact on morbidity and mortality

Collaborative analysis within UK-CHIC cohort:
25 486 HIV+ patients between 2004 and 2012

All-causes and liver-related mortality are significantly associated with HBV (and in a less extent to HCV) coinfection

Thornton, et al. AIDS 2017
Therapeutic goals

4th: impact on morbidity and mortality

Sub-analysis of 1 clinical trial in Côte d’Ivoire (Temprano):
2052 patients with 5 year-F/U

Despite early introduction of cART, higher rate of death in HIV-HBV coinfected patients with HBV-DNA > 2000UI/mL at cART initiation

Kouame, et al. CID 2018
Therapeutic goals

4th: impact on morbidity and mortality

Data from the MACS cohort, US, all men followed for HIV and HBV mono- or co-infection

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Liver-related mortality (per 1000 p•y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984-2010 HBV</td>
<td>2.9</td>
</tr>
<tr>
<td>1984-1996</td>
<td>13.1</td>
</tr>
<tr>
<td>1997-2001 HIV-HBV</td>
<td>24.4</td>
</tr>
<tr>
<td>2002-2010</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Falade-Nwulia O et al., CID, 2012
Therapeutic goals

4th: impact on morbidity and mortality

Analysis of risk factors for HBV progression: French Hospital Database, 48,189 HBV+ patients

- Liver-related risk factors:
  - Co-infection with HDV
  - Co-infection with HCV
  - Alcohol use disorders
  - Diabetes
  - Other causes of cirrhosis

- Non-liver-related risk factors:
  - Co-infection with HIV
  - AIDS in 2008-2013
  - Former AIDS (before 2008)
  - No AIDS recorded otherwise
  - CKD at cohort inception
  - Kidney transplant recipient
  - On dialysis
  - CKD otherwise
  - Cancer other than HCC
  - Cardiovascular disease
  - Respiratory disease

When HIV is well controlled, the risk of liver disease is decreased compared to other factors

Mallet V, et al. J Hepatol 2017
EACS Guidelines for screening of ESLD

• In patients without cirrhosis, liver ultrasound and fibrosis evaluation should be offered every year

• In patients with cirrhosis, liver ultrasound should be performed every 6 months, with gastroscopy every 2-3 years, and more often in case of oesaphagal varices

• Referral to liver specialist should be considered so the patient may be assessed for transplantation

In summary

• The prevalence of HIV-HBV coinfection Europe is around 7% in Europe but data are old and may be different in 2018 (call for update)

• Tenofovir (disoproxil, alafenamide, generics) is the cornerstone of cART in HIV-HBV coinfected patients whatever the level of CD4 and HBV-DNA

• Despite a moderate impact on fibrosis progression and the risk of renal impairment, maintaining therapy is essential to contain liver morbidity and mortality

• Given that the risk of HCC and ESLD is not abrogated by treatment, screening for liver complications should be performed annually (and every 6 months in cirrhotic patients)

• HIV-HBV patients should fully take part to trials evaluating the efficacy and safety of new HBV drugs, given that they are the most clinically impacted by chronic infection