HIV-HBV coinfection: contemporary issues

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An update of global prevalence of HIV-HBV coinfection: data from WHO

- Meta-analysis (2002 – 2016) conducted by WHO to inform the WHO guidelines
- 506 estimates of HBeAg prevalence from 41% of countries around the world

$$P(\text{HBsAg in HIV}) = 6.1\% \ [4.0 – 9.9] = 2.6 \text{ millions PLHIV and HBV}$$

- Greatest burden: Africa (69% of cases)
- Prevalence higher in PWID (11.8%)
- $$P(\text{HBV}) \times 1.4$$ in PLHIV compared to HIV negative individuals

Platt, J Viral Hepat 2019
Major research issues: what can be transferred from HIV and HBV mono- to co-infection?

HBV
- Novel diagnostic markers
- Novel therapeutics

HIV
- Treatment simplification
- New drug classes
Novel diagnostic markers

Issues with current HBV markers:

- HBV DNA is undetectable and serological status is the same during potent NA
- HCC is still occurring

Papatheodoridis GV et al. Hepatology, 2017
Novel diagnostic markers

Alternative HBV markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Clinical use</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV RNA</td>
<td>NA discontinuation HBeAg seroclearance</td>
</tr>
<tr>
<td>qHBcrAg</td>
<td>Differentiating states NA discontinuation HBeAg seroclearance HCC</td>
</tr>
<tr>
<td>qHBeAg</td>
<td>HBeAg seroclearance</td>
</tr>
<tr>
<td>qHBsAg</td>
<td>HBsAg seroclearance</td>
</tr>
<tr>
<td>qAnti-HBc Ab</td>
<td>HBV immune response HBeAg seroclearance</td>
</tr>
</tbody>
</table>

- Is there a marker that can be more useful clinically?

Coffin CS et al., *Gastroenterology*, 2019
Novel diagnostic markers

HIV-HBV co-infection

- Could these makers be helpful in HIV-HBV co-infection?

158 HIV-HBV co-infected patients, at initiation of TDF

<table>
<thead>
<tr>
<th></th>
<th>Difference in baseline mean levels (95%CI)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>qHBcrAg*</td>
<td>qAnti-HBc Ab**</td>
</tr>
<tr>
<td>AIDS-defining illness</td>
<td>+0.555 (+0.023, +1.088)</td>
<td>-0.523 (-1.039, -0.007)</td>
</tr>
<tr>
<td>CD4+ cells (per 100/mm³)</td>
<td>--</td>
<td>+0.198 (+0.105, +0.292)</td>
</tr>
</tbody>
</table>

*Adjusted for gender, HBV DNA, ALT, and qHBsAg.
**Adjusted for age and HBeAg-status.

Dezanet L et al, submitted
Novel diagnostic markers

HIV-HBV co-infection

- Could these makers be helpful in HIV-HBV co-infection?

96 HBeAg+, HIV-HBV co-infected patients, during TDF

<table>
<thead>
<tr>
<th></th>
<th>Predicting HBeAg-seroclearance*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M24</td>
</tr>
<tr>
<td></td>
<td>Se</td>
</tr>
<tr>
<td>qHBeAg &lt;10 PEIU/mL at M12</td>
<td>0.85</td>
</tr>
<tr>
<td>qHBcrAg &lt;7.5 log_{10} U/mL at M0</td>
<td>0.86</td>
</tr>
<tr>
<td>qAnti-HBc Ab &gt;4.1 log_{10} PEIU/mL at M0</td>
<td>0.51</td>
</tr>
</tbody>
</table>

*Estimated from time-dependent ROC.

Novel diagnostic markers

Kinetics of HBcrAg in 158 patients

HBeAg pos.

HBeAg neg.

HBsAg loss

Dezanet L et al, submitted
Novel diagnostic markers

Kinetics of anti-HBc Ab in 158 patients

Dezanet L et al, submitted
Novel diagnostic markers

Remaining questions for HIV-HBV co-infection

- HBV RNA, pgRNA, other circulating RNAs, L/M/S HBsAg quantification as novel diagnostic markers?  
  → to be assessed in a collaboration with EuroSIDA, Swiss HIV cohort and French HIV-HBV cohort (Gilead Grant)

- Are any of these markers useful in screening for HCC in HIV-HBV coinfected individuals?  
  → might be assessed with EuroSIDA and Swiss HIV cohort
Novel therapeutics: rationale from the HIV context

- Illustration from the HIV-HBV coinfection: Meta-analysis of 23 papers including cohorts and clinical trials, n=516 on TDF

Small proportion of patients with detectable HBV-DNA depiste > 5 years of TDF

Price H et al., PLoS One 2013
Novel therapeutics: rationale from the HIV context

- Replenishment of cccDNA pool from infected hepatocytes despite viral suppression

Novel therapeutics

Direct antiviral agents + immunomodulatory agents

Fanning, Nature Rev 2019
### Novel therapeutics

#### Drugs in clinical development for HBV

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Class</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAAs</td>
<td>Core protein inhibitors</td>
<td>AB-506, ABI-H0731, ABI-H2158, EDP-514, JNJ-6379, JNJ-0440, RO7049389</td>
</tr>
<tr>
<td></td>
<td>siRNA, antisense RNA</td>
<td>AB-729, DCR-HBVS, GSK/IONIS-HBV-LRx, IONIS-HBVRx, JNJ-3989, RO7062931, Vir-2218</td>
</tr>
<tr>
<td></td>
<td>HBsAg secretion inhibitors</td>
<td>REP-2139, REP-2165</td>
</tr>
<tr>
<td>IAAs &amp; immuno-therapeutics</td>
<td>TLR-7 agonists</td>
<td>AL-034, RG-7854, RO7020531</td>
</tr>
<tr>
<td></td>
<td>TLR-8 agonist</td>
<td>GS-9688</td>
</tr>
<tr>
<td></td>
<td>Therapeutic vaccines</td>
<td>AIC-649, INO-1800, TG1050</td>
</tr>
<tr>
<td></td>
<td>RIG-I and NOD2 agonist</td>
<td>Inarigivir</td>
</tr>
<tr>
<td></td>
<td>Apoptosis inducer</td>
<td>APG-1387</td>
</tr>
<tr>
<td></td>
<td>FXR agonist</td>
<td>EYP-001</td>
</tr>
</tbody>
</table>

Lopatin U. *Clinic Liv Dis*. 2019
Novel therapeutics

Remaining questions for HIV-HBV co-infection

- Drug-drug interactions with antiretrovirals? → not yet considered (but is it too early?)

- Are trials available for HIV-HBV co-infected patients? NO (not yet…)
  → there seems to be considerable interest in other clinical trial networks (ACTG…)
Treatment simplification

HIV infection

GEMINI-I & II studies: Dolutegravir/lamivudine versus dolutegravir/tenofovir/emtricitabine, ART-naive

- Two-drug regimen meets non-inferiority against three-drug regimens with respect to suppressed HIV RNA

Treatment simplification

Simplification according to recommendations

**EASL recommends:**
- The preferred regimens are ETV, TDF and TAF as **monotherapies** (Evidence level I, grade of recommendation 1).
- LAM, ADV and TBV are not recommended in the treatment of CHB (Evidence level I, grade of recommendation 1).

**EACS recommends:**
- Initial ART with 3TC/DTG: **HBsAg negative**, HIV-VL <500,000 copies/mL, CD4 count >200 cells/μL
- Prior to ART simplification with a regimen without TDF/TAF, HBV status should be re-checked
- Alternative treatment for switch: DTG+RIL

EASL HBV Clinical Practice guidelines, 2017; EACS Guidelines, v10.0, November 2019
Treatment simplification

HIV-HBV co-infection

- Is dolutegravir/lamivudine going to cause problems with LAM resistance in HIV-HBV co-infection?

- Almost all HBV highly viremic patients
- Two-thirds HBeAg+
- Sexual transmission route

Treatment simplification

HIV-HBV co-infection

- Is dolutegravir/lamivudine going to cause problems with LAM resistance in HIV-HBV co-infection?

- LAM or TDF -treated patients from Côte d’Ivoire
- Low viremic
- One-quarter HBeAg+
- No LAM-R in patients with VL < $10^5$ UI/mL
- Only 2 cases of LAM-R in patients with high level persistant viremia

Low risk of LAM-resistance when HBV-DNA viral loads are low.

Boyd A et al., Antiviral Ther, 2015.
Treatment simplification

HBV mono-infection

- FINITE trial:
  - Randomised N = 44
  - Withdrew consent n = 2
  - TDF-stop n = 21
    - Week 144 TDF-restart n = 8
    - Week 144 TDF-stop n = 13
    - Week 144 TDF-continue n = 21
  - TDF-continue n = 21

- 13/21 did not restart TDF
- 4 lost HBs Ag / 3 acquired anti-HBsAb (v. 0 in other arm)
- All had a rebound in HBV-DNA but 9/13 controlled replication without restarting treatment
Treatment simplification; functional T cell restauration after TDF interruption

Rinker, J Hepatol 2018
Treatment simplification

Remaining questions for HIV-HBV co-infection

- Can treatment simplification work in HIV-HBV co-infected individuals with controlled HBV DNA replication?
  - Complete HBV Tx interruption by switching to DTG-RIL
  - Partial HBV Tx simplification by switching to DTG-3TC

- Which patients could be eligible to a simplification strategy?
New drugs class: Integrase inhibitors

HIV-HBV co-infection

- Does the use of INSTI-containing ART induce higher **seroconversion** rates in HIV-HBV co-infected patients?

72 HIV-HBV co-infected patients switching to elvitegravir/cobicistat/FTC/TAF

<table>
<thead>
<tr>
<th></th>
<th>GS-US-292-1249 Study</th>
<th>Historically with TDF-containing ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg-seroconversion</td>
<td>3.3% at week 24</td>
<td>2-3% per year</td>
</tr>
<tr>
<td>HBsAg-seroconversion</td>
<td>2.9% at week 48</td>
<td>&lt;1% per year</td>
</tr>
</tbody>
</table>

New drugs class: Integrase inhibitors

HIV-HBV co-infection

- Does the use of INSTI-containing ART induce higher seroconversion rates in HIV-HBV co-infected patients?

Table 1. Viral serologies.

<table>
<thead>
<tr>
<th></th>
<th>Prior admit</th>
<th>Re-admission</th>
<th>Discharge</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV viral load*</td>
<td>5.32 log</td>
<td>1.79 log</td>
<td>&lt; 20 copies/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>copies/mL</td>
<td>copies/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 Count</td>
<td>36 cells/mL</td>
<td>214 cells/mL</td>
<td>413 cells/mL</td>
<td></td>
</tr>
<tr>
<td>HBV Surface Ab</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV Surface Ag</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV Core Ab</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV eAg</td>
<td>Positive</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV eAb</td>
<td>Negative</td>
<td>Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV viral load*</td>
<td>7.12 log</td>
<td>5.34 log</td>
<td>2.75 log</td>
<td>&lt; 20 copies/mL</td>
</tr>
<tr>
<td></td>
<td>copies/mL</td>
<td>copies/mL</td>
<td>copies/mL</td>
<td></td>
</tr>
<tr>
<td>AST/ALT</td>
<td>39/51</td>
<td>2435/1987</td>
<td>194/214</td>
<td>37/30</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0.3</td>
<td>1.4</td>
<td>2.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>74</td>
<td>175</td>
<td>336</td>
<td>105</td>
</tr>
</tbody>
</table>

- Nigerian patient who has been put on RAL + FTC/TDF: IRIS with HBeAg clearance after treatment initiation
New drugs class: Integrase inhibitors

Remaining questions for HIV-HBV co-infection

- Does switching to an INSTI-containing ART regimen induce higher seroclearance rates?
  → Necessity to collate case series
  → Need for a exposure / non exposure design: To be possibly evaluated in the French HIV-HBV cohort (over 15 years of f/u, collected exposure to RAL, EVG, DTG (very few) and BIC since January 2019
  → other well defined cohorts?
Take home message

• New estimates of HIV-HBV coinfection prevalence: 6.1%, x1.4 in PLHIV, highest burden in Africa

• 4 main challenges in 2020:
  – Evaluating efficacy of novel biomarkers of treatment efficacy in the context HIV
  – Preparing the field for the use of innovative drugs for functional cure: PLHIV and HBV should not be left behind!
  – Treatment simplification: time to rethink treatment paradigm in HIV-HBV coinfection?
  – Impact of INSTI: new drug of choice with regards to HBV clearance?