New insights in management of HIV/HBV coinfected patients

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  – AbbVie, BMS, Gilead, Janssen, MSD, ViiV Healthcare

• Grant support
  – AbbVie, Gilead, MSD, ViiV Healthcare
Epidemiology of HIV/HBV co-infected individuals

Prevalence of HIV and HIV/HBV co-infection globally

Prevalence of HIV and HIV/HBV co-infection in Sub-Saharan Africa

HIV/HBV co-infection is a particular challenge in Africa

Clinical outcomes of HIV/HBV coinfection

Impact of HIV on HBV
• Reduced rates of HBV clearance $^{1,2}$
• Increased chronic liver disease $^{3,4}$
• Increase in liver-related and all-cause mortality $^{5,6}$

Impact of HBV on HIV
• Some evidences of blunted response to cART and accelerated HIV-disease $^{5,7-10}$

HIV/HBV coinfection screening

• All HIV-positive persons should be screened for HBV

• Persons who are anti-HBc positive and HBsAg negative, in particular those with elevated liver transaminases, should be screened for HBV-DNA to rule out occult HBV infection

• HDV antibodies should be screened for in all HBsAg positive persons.

### TE for staging of liver fibrosis in patients with CHB

#### Systematic review & metanalysis

<table>
<thead>
<tr>
<th>METAVIR Stage</th>
<th>LS cutoff - kPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>F ≥ 2</td>
<td>7.2</td>
</tr>
<tr>
<td>F ≥ 3</td>
<td>9.4</td>
</tr>
<tr>
<td>F4</td>
<td>12.2</td>
</tr>
</tbody>
</table>

#### EASL-ALEH CPGs

**Severe fibrosis or cirrhosis**

- Normal ALT and LS > 9 kPa
- ↑ALT (< 5xULN) and LS > 12 kPa

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2. J Hepatol 2015;63:237

**CHB**: chronic hepatitis B

27 studies with a total of 4386 patients
HBV vaccination in adults with HIV: prospective studies & RCT

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>n</th>
<th>Dose (ug)</th>
<th>Schedule</th>
<th>Response</th>
<th>Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rey et al</td>
<td>2000</td>
<td>20</td>
<td>3 x 20</td>
<td>0,1,2 mo., IM</td>
<td>55.0%</td>
<td>CD4 &gt; 500 cells/μL</td>
</tr>
<tr>
<td>Ungulkraiwit et al</td>
<td>2007</td>
<td>65</td>
<td>3 x 20</td>
<td>0,1,6 mo., IM</td>
<td>46.0%</td>
<td>Higher CD4; young age</td>
</tr>
<tr>
<td>Paitoonpong et al</td>
<td>2008</td>
<td>28</td>
<td>3 x 20</td>
<td>0,1,6 mo., IM</td>
<td>71.4%</td>
<td>Higher CD4; use of efavirenz</td>
</tr>
<tr>
<td>Irungu et al</td>
<td>2013</td>
<td>310</td>
<td>3 x 20</td>
<td>0,1-3,6 mo. IM</td>
<td>64.2%</td>
<td>CD4 &gt; 500 cells/μL; female</td>
</tr>
</tbody>
</table>

**Alternative strategies**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>n</th>
<th>Dose (ug)</th>
<th>Schedule</th>
<th>Response</th>
<th>Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fonseca et al</td>
<td>2005</td>
<td>94</td>
<td>3 x 20</td>
<td>0,1,6 mo., IM</td>
<td>34.0%</td>
<td>CD4 &gt; 500 cells/μL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>98</td>
<td>3 x 40</td>
<td></td>
<td>47.0%</td>
<td>HIV VL &lt; 10,000 copies/mL</td>
</tr>
<tr>
<td>Cornejo-Juárez</td>
<td>2006</td>
<td>39</td>
<td>3 x 10</td>
<td>0,1,6 mo., IM</td>
<td>61.5%</td>
<td>CD4 ≥ 200 cells/μL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td>3 x 40</td>
<td></td>
<td>60.0%</td>
<td></td>
</tr>
<tr>
<td>Potsch et al</td>
<td>2010</td>
<td>47</td>
<td>3 x 40</td>
<td>0,1-2,6 mo. IM</td>
<td>89.0%</td>
<td>HIV VL &lt; 80 copies/mL</td>
</tr>
<tr>
<td>Launay et al</td>
<td>2011</td>
<td>145</td>
<td>3 x 20</td>
<td>0,1,6 mo. IM</td>
<td>65.0%</td>
<td>HIV VL &lt; 80 copies/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>148</td>
<td>4 x 40</td>
<td>0,1,2,6 mo. IM</td>
<td>82.0%</td>
<td>Young age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>144</td>
<td>4 x 4</td>
<td>0,1,2,6 mo. ID</td>
<td>77.0%</td>
<td>Four-doses</td>
</tr>
</tbody>
</table>


ANRS HB03 VIHVAC-B Trial: Duration of immune response

Duration of Immune Response

Kinetics of Geometric Mean Titers of HBsAb

Launay O et al. JAMA Intern Med 2016;176:603-610
What to do with HBV-susceptible HIV-infected individuals if vaccination doesn't work?
TDF prevents HBV infections in susceptible HIV+ individuals (Amsterdam)

- 2,942 HIV+ individuals, retrospectively selected for negative HBV serology
- 871 ‘HBV-susceptible’
  - 33 HBV-infected during follow-up
- In MSM, the lowest incidence rate was found in persons using HBV-active cART containing TDF (0.14 per 100 PYFU; IRR 0.05), versus persons without HBV-active cART (incident rate 2.85)
- The significantly smallest chance of HBV infection was observed in individuals receiving HBV-active cART with TDF (log rank p<0.001)

Heuft M et al. AIDS 2014;28:999–1005
Treating HBV susceptible HIV+ individuals with 3TC or TDF prevents incident HBV infections (Tokyo)

354 HIV+ MSM, non HBV vaccinated and negative for HBsAg, HBsAb, and HBcAb at baseline

<table>
<thead>
<tr>
<th>ART</th>
<th>Observation period (PY)</th>
<th>HBV incident infection</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ART</td>
<td>446</td>
<td>30†</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>ART with 3TC or TDF*</td>
<td>1047</td>
<td>7</td>
<td>0.113 (0.049–2.61)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3TC - ART</td>
<td>814</td>
<td>7†</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TDF-ART</td>
<td>233</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Other ART</td>
<td>114</td>
<td>6†</td>
<td>0.924 (0.381–2.239)</td>
<td>.861</td>
</tr>
</tbody>
</table>

*All participants who took FTC received TDF/FTC, therefore, such treatment status was categorized into TDF-ART
†rtM204V/L mutation detected in 2 patients with no ART-other ART and 3 patients with 3TC-ART

Goals of therapy in chronic HBV infection

• Main goal
  – Improve survival and quality of life by preventing disease progression, and consequently HCC development.

• Additional goals
  – Prevention of mother to child transmission
  – Prevention of HBV reactivation
  – Prevention and treatment of HBV-associated extrahepatic manifestations.
Endpoints of therapy

• Long-term suppression of HBV DNA: main endpoint

• HBeAg loss ± anti-HBe seroconversion in HBeAg\(^+\) CHB patients
  – represents a partial immune control of the chronic HBV infection

• ALT normalization (biochemical response)
  – achieved in most patients with long-term suppression of HBV DNA

• HBsAg loss ± anti-HBs seroconversion
  – optimal endpoint, indicates profound suppression of HBV replication
Main studies for the treatment of chronic hepatitis B


**Table 3. Results of main studies for the treatment of HBsAg-positive chronic hepatitis B at 6 months following 48 or 52 weeks of pegylated interferon alfa (PegIFNα) and at 48 or 52 weeks of nucleos(t)ide analogue therapy.**

<table>
<thead>
<tr>
<th></th>
<th>PegIFNyk2a</th>
<th>PegIFNyk2b</th>
<th>Nucleoside analogues</th>
<th>Nucleotide analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>180 µg</td>
<td>100 µg</td>
<td>LAM</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBV</td>
<td>245 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ETV</td>
<td>25 mg</td>
</tr>
<tr>
<td>Anti-HBe-seroconversion</td>
<td>32%</td>
<td>29%</td>
<td>16–18%</td>
<td>12–18%</td>
</tr>
<tr>
<td>HBV DNA &lt;60–80 IU/ml</td>
<td>14%</td>
<td>7%</td>
<td>36–44%</td>
<td>13–21%</td>
</tr>
<tr>
<td>ALT normalisation</td>
<td>41%</td>
<td>32%</td>
<td>41–72%</td>
<td>48–54%</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>3%</td>
<td>7%</td>
<td>0–1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Table 4. Results of main studies for the treatment of HBsAg-negative chronic hepatitis B at 6 months following 48 weeks of pegylated interferon alfa (PegIFNα) and at 48 or 52 weeks of nucleos(t)ide analogue therapy.**

<table>
<thead>
<tr>
<th></th>
<th>PegIFNyk2a</th>
<th>PegIFNyk2b</th>
<th>Nucleoside analogues</th>
<th>Nucleotide analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>180 µg</td>
<td>100 µg</td>
<td>LAM</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBV</td>
<td>245 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ETV</td>
<td>25 mg</td>
</tr>
<tr>
<td>HBV DNA &lt;60–80 IU/ml</td>
<td>19%</td>
<td>72–73%</td>
<td>88%</td>
<td>51–63%</td>
</tr>
<tr>
<td>ALT normalisation</td>
<td>59%</td>
<td>71–79%</td>
<td>74%</td>
<td>72–77%</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>4%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Incidence of drug resistance during HBV therapy

# Treatment of HBV in HIV-infected persons

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAS-USA 2016</td>
<td>ART regimen with TDF or TAF, 3TC or FTC</td>
</tr>
<tr>
<td>DHHS 2016</td>
<td>ART regimen with TDF/FTC, TAF/FTC, or TDF plus 3TC,</td>
</tr>
<tr>
<td>EACS 2017</td>
<td>TDF-based ART regimen</td>
</tr>
<tr>
<td>EASL 2017</td>
<td>TDF- or TAF-based ART regimen</td>
</tr>
</tbody>
</table>

3. EASL HBV Guidelines 2017
4. EACS Guidelines Version 8.2, January 2017
Switch to E/C/F/TAF in HIV/HBV coinfected adults

Key inclusion criteria
- HIV/HBV+ adults on any HIV regimen
- HIV-1 RNA <50 copies/mL for >6 mo
- HBsAg+ >6 mo
- HBV DNA <9 log_{10} IU/mL

Key exclusion criteria
- Cirrhosis
- HCC
- Current/prior regimen with 3 active anti-HBV agents
- eGFR by Cockcroft-Gault ≤ 50 mL/min

Gallant J. JAIDS 2016;73:294–298
Switching to E/C/F/TAF in HIV/HBV+ Adults (N=72)

Panel A
FDA Snapshot HIV-1 RNA <50 c/mL
- Week 24: 94%
- Week 48: 92%
- Virologic Success: 94%
- Virologic Failure: 1%
- No data: 4%

Panel B
HBV DNA <29 IU/mL, M=F
- Week 24: 86%
- Week 48: 92%
- <29 IU/mL: 86%
- ≥29 IU/mL: 10%
- Missing: 4%

Gallant J. JAIDS 2016;73:294–298
Switching to E/C/F/TAF in HIV/HBV+ Adults (N=72)

Statistically significant declines in markers of bone turnover (serum CTX and P1NP) were observed.

Gallant J. JAIDS 2016;73:294–298
HCC screening in HIV/HBV coinfected patients
Predicting HCC in patients with HBV

• Predicting HCC is not straightforward.

• Difficult to create a robust and economically feasible one-size-fits-all surveillance model.

• Risk stratification models are a promising tool in identifying patients at higher risk (mREACH-B, mCU-HCC, PAGE-B)

# Recommendations on surveillance of non-cirrhotic patients with HBV

<table>
<thead>
<tr>
<th>Society</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>EASL</td>
<td>• Adults with family history of HCC (Asian or African)</td>
</tr>
<tr>
<td></td>
<td>• Adults with active viral replication (Asian or African)</td>
</tr>
<tr>
<td>AASLD</td>
<td>• Family history of HCC</td>
</tr>
<tr>
<td></td>
<td>• African/North American black</td>
</tr>
<tr>
<td></td>
<td>• Female Asian aged &gt;50 years</td>
</tr>
<tr>
<td></td>
<td>• Male Asian aged &gt;40 years</td>
</tr>
<tr>
<td>APASL</td>
<td>• No recommendations for surveillance of non-cirrhotic population</td>
</tr>
</tbody>
</table>

**EASL**, European Association for study of the liver; **AASLD**, American Association for Study of the Liver; **APASL**, Asian Pacific Association for Study of the Liver
HCC screening in HIV/HBV coinfected patients

- Liver cirrhosis
- Asian or Black ethnicity
- Family history of HCC
- NAFLD
- Replicating HBV infection

HBV Reactivation

Well-Characterized Syndrome

- Abrupt reappearance or rise of HBV DNA in previously inactive or resolved HBV infection
- Often (not always) accompanied by reappearance of disease activity
- May occur spontaneously or as a result of immunosuppression

Potential Consequences

- May lead to clinically apparent acute hepatitis
  - Can be severe
  - Can result in acute liver failure and death
- Many cases are subclinical and resolve spontaneously, or result in persistent infection
- May go undetected until
  - Advanced liver disease is present
  - Disease has been transmitted to sexual or family contacts

Reactivation of HBV in Patients With Detectable HBsAg or Anti-HBc

Clinical scenarios
- Cancer chemotherapy
- Solid organ transplantation
- Bone marrow or stem cell transplantation
- Immunosuppressive therapy for benign conditions (e.g., rheumatoid arthritis, psoriasis, and inflammatory bowel disease)

Drugs associated with HBV reactivation
- Corticosteroids
- Conventional chemotherapeutic agents
- Injectable or infused biological (e.g., anti-CD20, anti–tumor necrosis factor)

## Risk Stratification for HBV Reactivation

<table>
<thead>
<tr>
<th>Therapy</th>
<th>HBsAg-Positive</th>
<th>HBsAg-Negative, Anti-HBc-Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CD20</td>
<td>Very high(^{\dagger})</td>
<td>Moderate</td>
</tr>
<tr>
<td>Hematopoietic stem cell transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-dose corticosteroids(^{*})</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Other cytokine inhibitors (e.g., anti-CD52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination cytotoxic chemotherapy(^{\dagger}) (without corticosteroids)</td>
<td>Moderate</td>
<td>Rare</td>
</tr>
<tr>
<td>Anti-tumor necrosis factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-rejection therapy for solid organ transplant recipients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Low</td>
<td>Rare</td>
</tr>
<tr>
<td>Azathioprine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androgen deprivation therapy</td>
<td>No known effect</td>
<td>No known effect</td>
</tr>
<tr>
<td>Estrogen and progesterone blockers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{*}\) Doses of corticosteroids in excess of 20 mg of prednisone (or equivalent) have been reported to have a high risk of HBV reactivation.

\(^{\dagger}\) Examples of combinations of cytotoxic therapy that have been associated with HBV reactivation include cisplatin-based chemotherapy for squamous cell carcinoma and CHOP (cyclophosphamide [Cytoxan], hydroxydoxorubicin [Adriamycin], vincristine [Oncovin], and prednisone) for lymphoma.

\(^{\dagger\dagger}\) Although reported rates of HBV reactivation vary considerably, rough estimates of very high risk could be considered to be in excess of 20%, high in the 11%-20% range, moderate somewhere between 1% and 10%, and low less than 1%.

HBV testing and treatment during immunosuppressive therapy


*Very high risk therapies include the use of anti-CD20 or Hematopoietic Stem Cell Transplantation (see Table 3)

**Frequency of monitoring between monthly and every 3 months
### HBV reactivation during IFN-Free HCV Rx

| FDA AE data base ¹ | • HBV reactivation with DAA therapy (n=29, 5 within the US)  
| | • Anti-HBc data available in 6/29 cases; all 6 were anti-HBc+ and had reactivation  
| | • Outcomes: 3 Decompensation (2 deaths, 1LT) |
| Spanish Cohort ² Retrospective | • 341 HCV patients on DAA therapy (HBsAg+ n=5)  
| | • No clinical HBV reactivation  
| | • Virologic reactivations: 3/5 HBsAg+ patients |
| Taiwan Cohort ³ Prospective | • 93 HCV on DAA therapy (HBsAg+ n=13)  
| | • No clinical HBV reactivations or HBsAg seroconversions  
| | • Virologic reactivations: 2/13 HBsAg+ |
| LDV/SOF trials ⁴ | • 173 patients enrolled in phase 3b studies in Taiwan and Korea  
| | • 103 (60%) HBcAb+, none showed evidence of HBV reactivation. |

HBV reactivation during IFN-Free HCV Rx in an HIV/HCV-coinfected patient

- Caucasian 54-years old female with HIV/HCV co-infection
- PMH: MI, CKD stage 3, COPD. Was on DRV/r plus ETV (because of CKD)
- HCV G4, anti-HCV naïve, LS 10.5 KPa.
- HBsAg (-), HBsAb (+), HBeAb (+).
- Treated with SOF/LDV for 12 weeks (eventually achieved SVR)
- 4 weeks after DAA termination: acute hepatitis. HBsAg (+), HBeAg (+), HBeAb IgM (+), anti-HBs Ab (-), anti-HBe Ab (-). HBV DNA was 6.06 Log10 IU/ml.
- Entecavir was started with resolution of symptoms, normalization of liver enzymes, and reduction of HBV DNA and of quantitative HBV surface antigen.
Management of HBV in HCV-infected patients undergoing DAA therapy

- Patients fulfilling the standard criteria for HBV treatment should receive NA treatment.
- HBsAg-positive patients undergoing DAA therapy should be considered for concomitant NA prophylaxis until week 12 post DAA, and monitored closely.
- HBsAg-negative, anti-HBc positive patients undergoing DAA should be monitored and tested for HBV reactivation in case of ALT elevation.

Management of HIV/HBV-coinfection: A quick summary

1) Screen for HBV

2) If HBV-susceptible, vaccinate. If this doesn't work, include TDF/TAF in the ART regimen

3) If HBV coinfection, use an ART regimen based on TDF/FTC, TAF/FTC, or TDF plus 3TC.

4) Consider HBV reactivation in some clinical scenarios (chemotherapy, immunosuppression, use of biologic agents, DAA therapy against HCV), and act appropriately

5) Screen for HCC in HBV-infected individuals when indicated