Optimal management of special populations with chronic hepatitis B

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Disclosures

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• Research grants: Gilead, Regulus, Bristol Myer Squibb, MSD
Outline

• Introduction
  Brief background of HBV
• Special HBV sub-population
  co-infections (HBV/HIV, HBV/HCV, HBV/HDV)
  HBV in pregnancy and prevention of perinatal transmission
  HBV in the setting of immunosuppression
HBVirus

• Blumberg, 1965
• DNA/hepadnaviruses
• Acute – chronic infection
• Route of transmission: parenteral, sexual contacts, perinatal
• Public Health problem worldwide: >500,000 deaths annually
Once HBV, always HBV
Natural history

Infection vs hepatitis

HBeAg(+)  HBeAg(-)/anti-HBe(+)  HBeAg(-)XHB  HBeAg(+)XHB  HBV DNA υρού  ALT

Phase V or “occult hepatitis B”: HBsAg neg, anti-HBcAg pos
Goal of therapy
• To improve survival and preventing disease progression

End points
• HBsAg loss and long term viral suppression
co-infections
HBV/HIV coinfection

• Frequently seen, due to shared routes of transmission
• Coinfection typically acquired in adolescence or adulthood
• Approximately 7-10% of HIV(+) patients in Europe and America (up to 20-30% in high-endemicity areas)
• Slower HBeAg clearance and higher HBV-DNA levels after acute infection compared to HBV monoinfected patients
• Accelerated fibrosis progression with increased risk of cirrhosis and HCC (x4)

Konopnicki, AIDS, 2005; Hoffmann, Lancet Infect Dis, 2007
Liver damage in HIV (+) individuals

- Viral hepatitis
- NASH-metabolic syndrome
- Alcohol
- Drug related hepatotoxicity
## HIV infection and liver related mortality

<table>
<thead>
<tr>
<th>Period</th>
<th>Total number of deaths</th>
<th>Liver related deaths n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999 - 2008</td>
<td>453 / 11593</td>
<td>46 (10%)</td>
</tr>
<tr>
<td>1999 – 2008</td>
<td>2482 / 33308</td>
<td>341 (13.7%)</td>
</tr>
<tr>
<td>2005 – 2009</td>
<td>459 / 2053</td>
<td>80 (17.8%)</td>
</tr>
<tr>
<td>1998 – 2008</td>
<td>116 / 1253</td>
<td>21 (18.1%)</td>
</tr>
</tbody>
</table>

Puoti Sem Liver Dis, 2012

Liver-related mortality: 1999-2000 (n=255) vs 2009-2011 (n=548): 16% vs 9%

Weber R et al, 2012
All HBV patients should be screened for HIV infection before NAs initiation

➢ All HIV-positive patients with HBV co-infection should start antiretroviral therapy (ART) irrespective of CD4 cell count (evidence level: II-2, recommendation grade: 1)

➢ HIV/HBV coinfected patients should be treated with a TDF-or TAF-based ART regimen (evidence level: I for TDF, II-1 for TAF, recommendation grade: 1)

TDF and TAF have strong antiviral activity against HIV
At present, limited data exists on the use of TAF in HIV/HBV coinfected patients
Stopping TDF- or TAF-containing ART should be avoided because of the high risk of severe hepatic flares and decompensation
Drug toxicity (renal, bone, liver) should be closely monitored during ART.
ETV represents an alternative anti-HBV treatment without strong activity against HIV

EASL CPG, 2017
EACS
GUIDELINES
Version 9.0
October 2017
English
Screen for HIV(+) and hepatitis B co-infection

- Screen all pts with HIV for HAV, HBV, HDV
- Fibroscan helpful for staging liver damage/fibrosis
- HCC screening for all HBV cirrhotics - U/S every 6-mo
- Additional screening
  In HBV co-infected non-cirrhotics, HCC screening should be performed in those who ever had chronic hepatitis (elevated transaminases) or with risk factors for HCC (including family history of HCC, Asians, Africans)
## HBV / HCV co-infection: Prevalence

<table>
<thead>
<tr>
<th></th>
<th>HBsAg (+) / anti-HCV (+) (%)</th>
<th>Estimated prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taiwan</td>
<td>10-20 / 2,6-12</td>
<td>0,26 - 2,4</td>
</tr>
<tr>
<td>Italy</td>
<td>0,9-13,6 / 4,3-7</td>
<td>0,04 - 0,95</td>
</tr>
<tr>
<td>USA</td>
<td>0,7 -2,1 / 3</td>
<td>0,09 – 0,29</td>
</tr>
<tr>
<td>Spain</td>
<td>1,0 / 13</td>
<td>0,16</td>
</tr>
</tbody>
</table>

0,1 % – 2%
HBV / HCV co infection

- Viral interference with large spectrum of viral replication
- Imbalance between the 2 viruses
- 1yr FU : 1/3 change viral replication status
- Negative impact on liver mainly due to HCV
### HBV / HCV co-infection: Risk of HCC

Community Cohort study: 6694 pts with 10yrs FU

<table>
<thead>
<tr>
<th>Combination</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg - / antiHCV -</td>
<td>1</td>
</tr>
<tr>
<td>HBsAg + / antiHCV -</td>
<td>17,1 (8,4 - 34,8)</td>
</tr>
<tr>
<td>HBsAg - / antiHCV +</td>
<td>10,4 (4,9 - 22)</td>
</tr>
<tr>
<td>HBsAg + / anti HCV +</td>
<td>115 (32, 5- 407)</td>
</tr>
</tbody>
</table>

BMC Cancer, 2012
## HBV HCV co-infection: DAAs therapy for HCV and HBV reactivation

<table>
<thead>
<tr>
<th>Ref</th>
<th>Gender</th>
<th>Age</th>
<th>HIV coinfection</th>
<th>HCV genotype</th>
<th>Previous treatment</th>
<th>DAA regimen</th>
<th>Profile before DAAs</th>
<th>HBV DNA (IU/mL) before/after DAAs</th>
<th>ALT levels (IU/L) before/after DAAs</th>
<th>Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collins et al[21]</td>
<td>M</td>
<td>55</td>
<td>No</td>
<td>1a</td>
<td>IFN/ribavirin</td>
<td>Sofosbuvir/simeprevir</td>
<td>Inactive carrier</td>
<td>2.300/ 22 million</td>
<td>62/1.495</td>
<td>8</td>
</tr>
<tr>
<td>Collins et al[21]</td>
<td>M</td>
<td>57</td>
<td>No</td>
<td>1a</td>
<td>IFN/ribavirin</td>
<td>Sofosbuvir/simeprevir</td>
<td>Occult infection</td>
<td>20/11.255</td>
<td>Within normal limits</td>
<td>4</td>
</tr>
<tr>
<td>Ende et al[20]</td>
<td>F</td>
<td>59</td>
<td>No</td>
<td>1b</td>
<td>IFN/ribavirin</td>
<td>Sofosbuvir/simeprevir/ribavirin</td>
<td>Resolved infection</td>
<td>Undetectable/ 29 million</td>
<td>168/2.263</td>
<td>11</td>
</tr>
<tr>
<td>Takayama et al[17]</td>
<td>M</td>
<td>69</td>
<td>No</td>
<td>1b</td>
<td>No treatment</td>
<td>Daclatasvir/asunaprevir</td>
<td>Inactive carrier</td>
<td>310/10 million</td>
<td>94/237</td>
<td>6</td>
</tr>
<tr>
<td>De Monte et al[19]</td>
<td>M</td>
<td>53</td>
<td>Yes</td>
<td>4d</td>
<td>IFN/ribavirin</td>
<td>Sofosbuvir/ledipasvir</td>
<td>Resolved infection</td>
<td>Undetectable/ 960 million</td>
<td>Within normal limits /1.026</td>
<td>6</td>
</tr>
<tr>
<td>Hayashi et al[18]</td>
<td>F</td>
<td>83</td>
<td>No</td>
<td>1b</td>
<td>No treatment</td>
<td>Daclatasvir/asunaprevir</td>
<td>Unclear</td>
<td>Undetectable/ 1.000.000</td>
<td>Within normal limits/1.066</td>
<td>48</td>
</tr>
<tr>
<td>Madonna et al[22]</td>
<td>F</td>
<td>62</td>
<td>No</td>
<td>2</td>
<td>No treatment</td>
<td>Sofosbuvir/ribavirin</td>
<td>Resolved infection</td>
<td>Undetectable/ 2.080.000</td>
<td>34/1.896</td>
<td>36</td>
</tr>
</tbody>
</table>

All chronic HBV patients should be screened for HCV

SVR rates for HBV/HCV co-infected patients are comparable with those in HCV monoinfected

Treatment of HCV with DAAs may cause reactivation of HBV. Patients fulfilling the standard criteria for HBV treatment should receive NA treatment (evidence level: II, recommendation grade: 1)

HBsAg-positive patients undergoing DAA therapy should be considered for concomitant NA prophylaxis until week 12 post DAA, and monitored closely (evidence level: II-2, recommendation grade: 1)

HBsAg-negative, anti-HBc positive patients undergoing DAA should be monitored and tested for HBV reactivation in case of ALT elevation (evidence level: II, recommendation grade: 1)
HDVirus
HBV/HDV coinfection
Summary

• Epidemiology: 15-20 million infected with HDV
• HDV is often the predominant virus
• HDV takes a more severe long term disease compared to HBV
• PegIFNα is the only available agent with antiviral activity against HDV
• Virological response rates: 17-47% (mean 25%), but late relapse in >50%
• HBsAg loss in approximately 10% of treated patients during long-term follow up.
• The likelihood of long-term response can be estimated by HDV-RNA and HBsAg kinetics (weeks 12 and 24). However, no stopping rule is recommended at this stage, as the NPVs of these markers are not very strong and late responses may occur.
• There is no clear data showing that long-term therapy (96 weeks) is superior to short-term therapy (48-weeks).

All CHB patients should be screened for HDV
HBV infection and pregnancy
An important issue

• >50% of cases HBV infected individuals acquired the virus during pregnancy-delivery

• 80%-95% chronicity

• Efficient prevention
# HBV infection and pregnancy

## Antenatal course and complications with respect to HBsAg status

<table>
<thead>
<tr>
<th></th>
<th>HBsAg + ve (n=253)</th>
<th>HBsAg − ve (n=253)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy weight gain (kg)</td>
<td>11.31 ± 5.88</td>
<td>10.45 ± 4.87</td>
<td>0.089</td>
</tr>
<tr>
<td>Hb before delivery (g/dL)</td>
<td>11.52 ± 1.07</td>
<td>11.66 ± 1.08</td>
<td>0.174</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>11 (4.4%)</td>
<td>7 (2.8%)</td>
<td>0.337</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>48 (19.0%)</td>
<td>28 (11.1%)</td>
<td>0.012</td>
</tr>
<tr>
<td>IUGR</td>
<td>3 (1.2%)</td>
<td>6 (2.4%)</td>
<td>0.504</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (2.0%)</td>
<td>3 (1.2%)</td>
<td>0.724</td>
</tr>
<tr>
<td>Genital tract infection</td>
<td>34 (13.4%)</td>
<td>25 (9.9%)</td>
<td>0.213</td>
</tr>
<tr>
<td>PROM</td>
<td>35 (13.8%)</td>
<td>42 (16.6%)</td>
<td>0.386</td>
</tr>
<tr>
<td>PPROM</td>
<td>4 (1.6%)</td>
<td>7 (2.8%)</td>
<td>0.544</td>
</tr>
<tr>
<td>Antepartum haemorrhage</td>
<td>29 (11.5%)</td>
<td>14 (5.5%)</td>
<td>0.025</td>
</tr>
<tr>
<td>Placenta praevia</td>
<td>8 (3.2%)</td>
<td>2 (0.8%)</td>
<td>0.106</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>7 (2.8%)</td>
<td>1 (0.4%)</td>
<td>0.068</td>
</tr>
<tr>
<td>APH of unknown origin</td>
<td>15 (5.9%)</td>
<td>11 (4.4%)</td>
<td>0.547</td>
</tr>
<tr>
<td>Threatened preterm labour</td>
<td>30 (11.9%)</td>
<td>16 (6.3%)</td>
<td>0.030</td>
</tr>
<tr>
<td>Preterm birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37 weeks</td>
<td>31 (12.3%)</td>
<td>19 (7.5%)</td>
<td>0.074</td>
</tr>
<tr>
<td>&lt;34 weeks</td>
<td>12 (4.7%)</td>
<td>3 (1.2%)</td>
<td>0.033</td>
</tr>
<tr>
<td>&lt;32 weeks</td>
<td>6 (2.4%)</td>
<td>1 (0.4%)</td>
<td>0.122</td>
</tr>
<tr>
<td>Maternal morbidity</td>
<td>88 (34.8%)</td>
<td>48 (19.0%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Tse et al J Hepatol 2005
HBV cirrhosis in pregnant woman

• Increase rates in: prematurity, spontaneously abortions, maternal mortality

• Treated as non-pregnant

• Endoscopy does not seem to have higher rates of complications

• Large varices: cesarean
The effect of pregnancy in the course of HBV infection

MJ ter Borg al J Viral Hep  2008
Mother to child transmission

- Without prophylaxis: HBeAg (+) mothers = 70%-90%, HBeAg (-) 12%-25%
- Routes: intrauterine, perinatal, postpartrum period
- HBV DNA the main determinant

- Lamivudine, telbivudine, tenofovir can be used in the last trimester for those with HBV DNA >10^6 cp/ml
In a woman of childbearing age without advanced fibrosis who plans a pregnancy in the near future, it may prudent to delay therapy until the child is born (evidence level: II-2, recommendation grade: 1)

In pregnant women with CHB and advanced fibrosis or cirrhosis, therapy with TDF is recommended (evidence level: II-2, recommendation grade: 1)

In pregnant women already on NA therapy, TDF should be continued while ETV or other NA should be switched to TDF (evidence level: II-2, recommendation grade: 1)

Screening for HBsAg in the first trimester of pregnancy is strongly recommended (evidence level: I, recommendation grade: 1)

In all pregnant women with high HBV-DNA levels (>200,000 IU/ml) or HBsAg levels (>4log_{10} IU/ml, antiviral prophylaxis with TDF should start at week 24-28 of gestation and continue for up to 12 weeks after delivery (evidence level: I, recommendation grade: 1)

Breast feeding is not contraindicated in HBsAg-positive untreated women or on TDF-based treatment or prophylaxis (evidence level: III, recommendation grade: 2)
Immunosuppression

«Immune reconstitution»

corticosteroid chemotherapy

Consequence

• Hepatitis flare
Mild to severe decompensation

Delay in the treatment of underlying disease
Autoimmune diseases
(corticosteroids, anti-TNF)

Chemotherapy
(± monoclonal antibodies)

Transplantation for solid organ
and bone marrow

- Reumatology
- Gastroenterology
- Dermatology

.........
# HBV in the setting of immunosuppression

## Stratification by drug type and serologic profile

<table>
<thead>
<tr>
<th>Serologic profile</th>
<th>Category of risk for HBV reactivation under immunosuppression</th>
<th>Management strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg positive</td>
<td>Low risk (&lt;1%)</td>
<td>Azathioprine, methotrexate, 6-mercaptopurine, Intra-articular steroids, Any steroid dose ≤1 week</td>
</tr>
<tr>
<td></td>
<td>Moderate (1–10%)</td>
<td>Anti-TNF drugs, Cytokine or integrin inhibitors, Tyrosine kinase inhibitors, Low dose (&lt;10 mg) prednisone daily for ≥4 weeks</td>
</tr>
<tr>
<td></td>
<td>High (&gt;10%)</td>
<td>B-cell depleting drugs, Anthracycline derivatives, Moderate (10–20 mg prednisone equivalent daily) or high (&gt;20 mg daily) for ≥4 weeks</td>
</tr>
<tr>
<td>Anti-HBc positive</td>
<td>Low risk (&lt;1%)</td>
<td>Azathioprine, methotrexate, 6-mercaptopurine, Intra-articular steroids, Any steroid dose ≤1 week, Low dose (&lt;10 mg) prednisone daily for ≥4 weeks</td>
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<td></td>
<td>Moderate (1–10%)</td>
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</tr>
</tbody>
</table>

Reddy, Gastroenterology, 2015 (AGA guidelines)
Summary

• Co infections accelerate disease progression
• Pts with HBV infection should be screened for HDV, HCV and HIV (before NA therapy)
• Screen for HBV in all pregnant women
• Prophylactic TDF in pregnant with HBV DNA >200000IU/ml
• All candidates for immunosuppression/chemotherapy should be tested for HBV markers
• Stratify the risk for HBV reactivation
• Be aware also for those who are HBsAg neg but anti-HBc pos