Risk and Management of Hepatitis B Reactivation

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No Disclosures
Outline

- The problem
  - Brief background on HBV
  - Definitions of HBV reactivation
- Risk of reactivation
  - Riskfactors
    - Immuno suppressive or immunomodulating agents
    - DAA and HAART treatment
- HBV screening
  - Who to screen with what tests
- The treatment
  - The role and timing of antiviral therapy
Hepatitis B highly prevalent worldwide
Endemic in some parts of the world
Immigrants from high incidence areas carry the same risk of HBV as the population in their birth country
Over one third of HCV and a variable amount of HIV infected patients will have an occult HBV infection
Acute Hepatitis B virus infection, serologic markers

- HBsAg
- HBeAg
- anti HBe
- Total anti-HBc
- IgM anti HBc
- Anti- HBs

Symptoms

Weeks after exposition

0 4 8 12 16 20 24 28 32 36 50 100
### Chronic Hepatitis B

**Table: Phases of Chronic Hepatitis B**

<table>
<thead>
<tr>
<th>Immuno-tolerance</th>
<th>Immuno-active</th>
<th>Inactive carrier</th>
<th>Reactive phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg positive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HBeAg negative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Graph: Change in HBV DNA and ALT over time**

- **HBV DNA**
  - **HBeAg +ve chronic hepatitis**
  - **Inactive (carrier) state**
  - **HBeAg –ve active chronic hepatitis**

- **ALT**
  - **HBeAg +ve chronic hepatitis**
  - **Inactive (carrier) state**
  - **HBeAg –ve active chronic hepatitis**
Immune Control vs Clearance

- Immune control ≠ not clearance
- “Resolved HBV” a misnomer—still HBV DNA in liver

Immune Control vs Clearance
Immune Control vs Clearance

cccDNA

T cell

T cell

T cell
Immune Suppression Comes Along

- Immune control can be lost
- Immune-mediated liver damage with immune reconstitution
Hepatitis B Virus Reactivation

- Variable time interval to hepatitis flare
- Immune suppression
- HBV DNA
- ALT

- Hepatic failure
- Chronic hepatitis
- Acute hepatitis
HBV Reactivation

Definition

- Loss of HBV immune control in a patient with inactive or “resolved” HBV infection
- Abrupt reappearance or increase in viral replication with liver damage occurring during and/or following immune reconstitution

Clinically

- Range from subclinical to severe/fatal hepatitis
- Rise in HBV DNA ± return of HBeAg
- ALT increase (may be mild or very dramatic)
- May progress to liver failure/death despite antiviral therapy

RISK OF REACTIVATION
Risk Factors for HBV reactivation

- Male gender
- Younger age
- Immune suppressed state
- Failure to screen and/or vaccinate patients at risk

- HBsAG seropositivity
- HBeAG seropositivity
- Viral load: HBV DNA >2000 IU/ml & HBeAg+ or >20,000 IU/ml & HBeAG-
- Precore-core mutation

- High corticosteroid doses
- Intensity of immunesuppression
- Timing of antiviral therapy in patients at risk
Risk of Reactivation

- In the past decades more and more therapeutic agents have emerged in the field of oncology and auto immune diseases which can cause a HBV reactivation
- HBV reactivation is usually recognized late
- This results in:
  - Interruption of the therapeutic agent (70%)
  - Morbidity 1-20% (fulminant hepatitis or ALF)
  - Mortality 2.3% (0.4-20%)
Consequences of Delayed Recognition of HBV Reactivation

Hepatitis
- May be severe or even fulminant sometimes resulting in liver failure
- Occasionally may miss HBV DNA spike because HBV DNA may fall when ALT rises
  - This may lead to misdiagnosis and, ultimately, may result in subsequent flares of HBV
- By the time ALT rises . . . may be too late to bring under control

Interruption of chemotherapy
- Potential for poorer cancer-related outcome

# High Risk Agents

## Risk of reactivation >10%

<table>
<thead>
<tr>
<th>Action</th>
<th>Risk Category</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-cell suppressive therapy</strong> (Rituximab, Ofatumab)</td>
<td>HBsAg +/- anti HBc +: 30-60%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HBsAg -/ anti HBc +: &gt;10%</td>
<td></td>
</tr>
<tr>
<td><strong>Antracyclin</strong> (Doxorubicin, Epirubicin)</td>
<td>HBsAg +/- anti HBc +: 15-30%</td>
<td></td>
</tr>
<tr>
<td><strong>Corticosteroid treatment &gt; 4 weeks, high dose</strong></td>
<td>HBsAg +/- anti HBc +: &gt; 10%</td>
<td></td>
</tr>
</tbody>
</table>

* Corticosteroid treatment: Prednisolone (or equivalent) high dose > 20 mg daily
Rituximab and Ofatumab

- Monoclonal antibodies against CD20 (B-cell marker)
- Reduces B-cell numbers and antibody levels
- Increasingly used in the hematologic field
- Increased risk of HBV reactivation, including HBsAg-negative patients
- Reverse seroconversion: reappearance of HBsAg in previously HBsAg-negative patient due to loss of immune control
- Immunosuppressive effect persists long after cessation of treatment

## Rituximab Related Viral Infections in Lymphoma Patients

<table>
<thead>
<tr>
<th>Virus</th>
<th>Outcome (died/alive)</th>
<th>Frequency, n (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B virus</td>
<td>13/12</td>
<td>25 (39.1)</td>
<td>[2,11–30]</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>2/13</td>
<td>15 (23.4)</td>
<td>[4,7,36]</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>2/4</td>
<td>6 (9.4)</td>
<td>[7,36,38]</td>
</tr>
<tr>
<td>Echovirus</td>
<td>0/3</td>
<td>3 (4.7)</td>
<td>[36,39,40]</td>
</tr>
<tr>
<td>Influenza A virus</td>
<td>0/2</td>
<td>2 (3.1)</td>
<td>[36]</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>0/2</td>
<td>2 (3.1)</td>
<td>[41,42]</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>1/1</td>
<td>2 (3.1)</td>
<td>[23,31]</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>2/0</td>
<td>2 (3.1)</td>
<td>[6,43]</td>
</tr>
<tr>
<td>Cytomegalovirus and BK papovavirus</td>
<td>1/0</td>
<td>1 (1.6)</td>
<td>[44]</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>1/0</td>
<td>1 (1.6)</td>
<td>[5]</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>1/0</td>
<td>1 (1.6)</td>
<td>[22]</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>1/0</td>
<td>1 (1.6)</td>
<td>[45]</td>
</tr>
<tr>
<td>JC papovavirus</td>
<td>1/0</td>
<td>1 (1.6)</td>
<td>[7]</td>
</tr>
<tr>
<td>Varicella-zoster virus and cytomegalovirus</td>
<td>1/0</td>
<td>1 (1.6)</td>
<td>[7]</td>
</tr>
<tr>
<td>Varicella-zoster virus and JC papovavirus</td>
<td>0/1</td>
<td>1 (1.6)</td>
<td>[7]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>26/38</strong></td>
<td><strong>64 (100)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Detection 3-27 months
Rituximab (anti CD20) Increases Risk of Fulminant Hepatitis B in Occult HBV Patients

- 20% of 224 patients with occult HBV (anti-HBc +) with malignant lymphoma developed fulminant hepatitis B

### Cox proportional hazard analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab containing regimen</td>
<td>16.84</td>
<td>2.1-137.4</td>
<td>0.008</td>
</tr>
<tr>
<td>Steroid containing regimen</td>
<td>5.01</td>
<td>0.61-40.88</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Hui et al. Gastroenterology 2006
Hematologic Malignancy: The Bigger Risk

100 patients with NHL undergoing CHOP; 27 HBsAg positive

Solid tumors

- Solid tumors: highest risk in breast cancer patients
- Reactivation in 41% of HBsAg positive patients
- Anthracycline containing regimes.
- Usually reactivation occurs after the 3rd cycle of chemotherapy
- Of those who flare:
  - 35% interruption CTx
  - 35% premature termination CTx

# Intermediate Risk Agents

## Risk of reactivation 1-10%

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TNF-α inhibitors (Etanercept, Adalumimab, Infliximab)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- HBsAg +/- anti HBc +: 1-10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- HBsAg -/ anti HBc +: 1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other cytokine and integrin inhibitors (Abatacept, Ustekinumab)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- HBsAg +/- anti HBc +: 15-30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tyrosine kinase inhibitors (Imatinib, Nilotinib)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- HBsAg +/- anti HBc +: 1-10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- HBsAg -/ anti HBc +: 1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anthracyclines: Doxorubicine en Epirubicine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- HBsAg- / anti-HBc+:1-10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Corticosteroid treatment ≥ 4 weeks, low dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- HBsAg+ / anti-HBc+: 1-10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Corticosteroiden ≥ 4 weeks, intermediate/high dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- HBsAg - / anti-HBc+:1-10%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Corticosteroid treatment: Prednisolone (or equivalent) high dose > 20 mg, intermediate dose 10-20 mg, low dose < 10 mg daily
TNF α Inhibitors
Outcome in 88 Anti-HBc(+) Rheumatoid Arthritis (RA) Patients Treated with TNF-alpha Inhibitors

Tyrosine Kinase Inhibitors

- Considered intermediate risk
- Several well documented case series and case reports demonstrated HBV reactivation
- Sometimes resulting in acute liver failure and death
- Given the mechanism of action estimated reactivation rate 1-10%
- Scarce data for exact numbers
Low Risk Agents

<table>
<thead>
<tr>
<th>Risk of reactivation &lt;1%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traditional immunosuppressive agents</strong></td>
</tr>
<tr>
<td>- HBsAg +/- anti HBc +: &lt; 1%</td>
</tr>
<tr>
<td>- HBsAg -/ anti HBc +: &lt;&lt; 1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Corticosteroid treatment &lt; 1 week</th>
</tr>
</thead>
<tbody>
<tr>
<td>- HBsAg +/- anti HBc +: &lt; 1%</td>
</tr>
<tr>
<td>- HBsAg -/ anti HBc +: &lt;&lt; 1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Corticosteroid treatment ≥ 4 weeks in a low dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>- HBsAg +/- anti HBc +: &lt; 1%</td>
</tr>
</tbody>
</table>

Corticosteroid treatment: Prednisolone (or equivalent) high dose > 20 mg, intermediate dose 10-20 mg, low dose < 10 mg daily
Corticosteroids

- In the 1970’s it was demonstrated HBsAg positive patients with chronic hepatitis given steroid treatment did worse.
- A placebo controlled study demonstrated that long-term treatment with 10 mg prednisolone resulted in delay in biochemical remission, early relapse and significant increase in complications.
- Corticosteroids enhance viral replication by 2 possible mechanisms:
  - Depressed cytotoxic T-cell function
  - Direct stimulation of HBV genomic sequence
- Data show that the risk of reactivation is determined by the duration and the dose of corticosteroid that is prescribed.

50 patients with NHL who were HBsAg positive randomized to epirubicin, cyclophosphamide and etoposide (ACE) ± prednisolone (PACE)

- HBsAg Patients (%)
- HBV Reactivation: 73* (ACE), 38 (PACE)
- ALT > 10 x ULN: 13 (ACE), 44* (PACE)
- Jaundice: 4 (ACE), 28* (PACE)
- Complete Remission: 36 (ACE), 46 (PACE)
- Survival at 4 Yrs: 36 (ACE), 68 (PACE)

*P < .05

Steroid Withdrawal or Pulse Therapy

- Clinical studies have demonstrated that a marked increase in viral replication and AST often occur in prednisolon regimens starting with 30-60 mg and tapering over 4-12 weeks.

- Increases in HBV DNA levels accompanied by ALT flares have been shown to occur in 30-70% of patients with HbeAg positive chronic hepatitis B receiving a tapered regimen.

- Low dosages (<10 mg) for a period of more than a month have been shown to be associated with an intermediate risk in HbsAg positive patients.

- Scarce data on short term steroids in general and low dose in HbsAg negative patients seem very low risk < 1%.

References:
Perrillo et al. gastro 2015
HCV and HIV Infected Patients

- DAA treatment in HCV patients
- HAART treatment in HIV infected patients
DAA Treatment

- HBV-HCV co-infection is common in areas where both infections are endemic and in high risk populations.
- Can be as high as 42-67%
- In the past HBV reactivation was reported in patients with HBV-HCV co-infection treated with PEG-interferon and ribavirin.
- Recently very successful new treatment has emerged: DAA treatment.
- Data suggest an increased risk for HBV-reactivation during DAA treatment.
- Meta analysis showed a pooled HBV reactivation rate 14.1%
- FDA and PRAC have confirmed the risk

<table>
<thead>
<tr>
<th>Case Number (Reference)</th>
<th>Time to Event, d</th>
<th>Clinically Ill With HBV Reactivation</th>
<th>DAA Therapy Status</th>
<th>Hospitalized</th>
<th>HBV Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>Not stated</td>
<td>Discontinued</td>
<td>Yes</td>
<td>Tenofovir</td>
</tr>
<tr>
<td>2 (42)</td>
<td>43</td>
<td>Not stated</td>
<td>Discontinued</td>
<td>No</td>
<td>Entecavir</td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>Yes: Jaundice and increasingly elevated aminotransferase levels; the patient died; the patient refused entecavir at another hospital</td>
<td>Discontinued</td>
<td>Yes (patient died)</td>
<td>Entecavir</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>Yes: The patient died</td>
<td>Discontinued</td>
<td>Yes (patient died)</td>
<td>Entecavir</td>
</tr>
<tr>
<td>5 (29)</td>
<td>56</td>
<td>Yes: Jaundice, tender hepatomegaly, malaise, nausea, and epigastric pain</td>
<td>Discontinued</td>
<td>-</td>
<td>Tenofovir-emtricitabine</td>
</tr>
<tr>
<td>6 (29)</td>
<td>14</td>
<td>No: The patient began therapy with tenofovir at the first indication of an increase in the HBV viral load (HIV-negative and no history of organ therapy, chemotherapy, or other immunosuppression)</td>
<td>Completed</td>
<td>-</td>
<td>Tenofovir</td>
</tr>
<tr>
<td>7 (26)</td>
<td>77</td>
<td>Yes: Encephalopathy and liver transplantation</td>
<td>Discontinued</td>
<td>Yes (transplantation)</td>
<td>Tenofovir</td>
</tr>
<tr>
<td>8</td>
<td>42</td>
<td>Not stated: Minimal increase in alanine aminotransferase levels</td>
<td>Completed</td>
<td>-</td>
<td>Entecavir</td>
</tr>
<tr>
<td>9 (38)</td>
<td>56</td>
<td>Yes: Jaundice and hospitalized; also HIV co-infection</td>
<td>Completed</td>
<td>Yes</td>
<td>Tenofovir</td>
</tr>
<tr>
<td>10 (28)</td>
<td>28</td>
<td>No</td>
<td>Completed</td>
<td>-</td>
<td>No treatment</td>
</tr>
<tr>
<td>11</td>
<td>42</td>
<td>Not stated: The patient had influenza at the same time</td>
<td>Discontinued</td>
<td>-</td>
<td>No treatment</td>
</tr>
<tr>
<td>12 (43)</td>
<td>56</td>
<td>Not stated</td>
<td>Discontinued</td>
<td>Yes</td>
<td>Entecavir</td>
</tr>
<tr>
<td>13</td>
<td>70</td>
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<td>Completed</td>
<td>-</td>
<td>No treatment</td>
</tr>
<tr>
<td>14</td>
<td>64</td>
<td>Not stated</td>
<td>Completed</td>
<td>-</td>
<td>No treatment</td>
</tr>
<tr>
<td>15</td>
<td>56</td>
<td>Not stated</td>
<td>Completed</td>
<td>-</td>
<td>No treatment</td>
</tr>
<tr>
<td>16</td>
<td>57</td>
<td>Not stated</td>
<td>Completed</td>
<td>-</td>
<td>No treatment</td>
</tr>
<tr>
<td>17</td>
<td>42</td>
<td>Not stated</td>
<td>Completed</td>
<td>-</td>
<td>No treatment</td>
</tr>
<tr>
<td>18</td>
<td>56</td>
<td>Yes: Malaise and hospitalized with very elevated aminotransferase levels</td>
<td>Discontinued</td>
<td>Yes</td>
<td>No treatment</td>
</tr>
<tr>
<td>19</td>
<td>196</td>
<td>Not stated, but baseline (\alpha_1)-fetoprotein level was 5.2 (\mu g/L)</td>
<td>Completed</td>
<td>-</td>
<td>No treatment</td>
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<tr>
<td>20</td>
<td></td>
<td>Not stated</td>
<td>Completed</td>
<td>-</td>
<td>Not stated</td>
</tr>
<tr>
<td>21</td>
<td>28</td>
<td>Not stated</td>
<td>-</td>
<td>-</td>
<td>Not stated</td>
</tr>
<tr>
<td>22</td>
<td>84</td>
<td>Not stated</td>
<td>-</td>
<td>-</td>
<td>Not stated</td>
</tr>
<tr>
<td>23</td>
<td>42</td>
<td>Not stated</td>
<td>-</td>
<td>-</td>
<td>Not stated</td>
</tr>
<tr>
<td>24</td>
<td>28</td>
<td>Not stated</td>
<td>-</td>
<td>-</td>
<td>Not stated</td>
</tr>
<tr>
<td>25</td>
<td>14</td>
<td>Not stated</td>
<td>-</td>
<td>-</td>
<td>Entecavir</td>
</tr>
<tr>
<td>26</td>
<td>29</td>
<td>Not stated</td>
<td>-</td>
<td>-</td>
<td>Not stated</td>
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<tr>
<td>27</td>
<td>42</td>
<td>Not stated</td>
<td>-</td>
<td>-</td>
<td>Entecavir</td>
</tr>
<tr>
<td>28</td>
<td>77</td>
<td>Yes: Jaundice</td>
<td>-</td>
<td>-</td>
<td>Tenofovir</td>
</tr>
<tr>
<td>29 (44)</td>
<td>28</td>
<td>Yes: Weakness, poor appetite, and jaundice</td>
<td>Not stated</td>
<td>-</td>
<td>Entecavir</td>
</tr>
</tbody>
</table>
Risk of HBV Reactivation During DAA

- Mechanism of reactivation is unknown
  - DAA are not known to cause immunosuppression

- Hypothesis
  - Actively replicating HCV might produce a host immune state favorable for controlling HBV which is disrupted by DAA

HAART Treatment

- HBV-HIV co-infection is common. Prevalence varies from 0 to 89.5%
- HBV co-infection results in a 19 times higher mortality rate in HIV patients
- Reactivation of HBV during HIV treatment has been described even in anti HBs positive patients
  - Reactivation is seen:
    - After treatment adaption according to HIV mutations, to a treatment regimen without a nucleoside analog
    - Development of resistance to nucleoside analogs
    - In patients after immune reconstitution

65 year old male
- Positive anti HBs and anti HBc, HBV DNA negative
- ART treatment started
- After 4 months: HBsAg detectable, HBV DNA neg
- Switch to HAART
- HBV DNA rise
- 4 weeks later hepatitis

Manegold et al. CID 2001
SCREENING
Who Should Be Screened?

- AASLD recommends screening high-risk individuals
  - Immigrants
    - Asia, Africa, Pacific Islands, Middle East, Eastern Europe, South/Central America, Caribbean, Aboriginal
  - Children of immigrants
  - Men who have sex with men
  - HIV/HCV positive
  - History of IDU, incarceration
  - Hemodialysis patients
Who Should Be Screened (2)

- ASCO recommends screening:
  - All patients before starting anti-CD20 therapy
  - High risk individuals

- AGA recommends screening:
  - In patients at moderate or high risk for HBV reactivation
    (anticipated incidence for reactivation > 1%)
Who Should Be Screened?

- High-risk individuals
  - Immigrants
    - Asia, Africa, Pacific Islands, Middle East, Eastern Europe, South/Central America, Caribbean, Aboriginal
  - Children of immigrants
  - Men who have sex with men
  - HIV/HCV positive
  - History of IDU, incarceration
  - Hemodialysis patients

What Is Currently Being Done?

Few oncologists routinely screen all patients initiating chemotherapy for HBV

Khokhar et al. Chemotherapy. 2009; Lee et al. Curr Oncol. 2010
What Is the Cost Associated With HBV Screening?

Cost-effectiveness depends on screening strategy and population

- HBsAg testing in all patients is cost-effective in patients undergoing adjuvant chemotherapy for solid tumors
- Anti-HBc testing increases cost with no clear benefit in this study

Optimal Screening Strategy

- Screening high-risk individuals requires recognition of a high risk population
- Screening all patients is cost-effective and easiest to implement
- HBsAg should be tested in all individuals; with follow up HBV DNA
- Role of testing anti HBc is less clear recommendations are mixed
  - EASL: HBsAg and anti HBc
  - AASLD: HBsAg and anti HBc
  - CDC: HBsAg and anti HBc and anti- HBs
  - ASCO: HBsAg
- Anti HBc should always be tested before treatment with CD-20 antibodies
HCV and HIV Co-infections

- HCV patients starting DAA:
  - Patients with a history of HBV infection require clinical monitoring
  - Guidelines recommend evaluating all patients for HBV co-infection (HBsAg, anti HBs and anti HBc) before starting HCV DAA treatment

- HIV patients
  - Screen for HBsAg, anti-HBs and anti-HBc
  - Vaccinate whenever negative
  - Monitor HBV DNA load in patients with HBV positive markers
TREATMENT AND PREVENTION OF HBV REACTIVATION
Profylactic Start or Treatment of HBV Reactivation

- In 5 randomized studies the optimal timing of antiviral therapy was determined
- In total 139 cases and 137 controls
- Pooled data demonstrated a significant risk reduction for HBV reactivation with antiviral profylaxis
- Based on these data the AGA calculated
  - High risk agents: 435 reactivations prevented per 1000 patients
  - Intermediate risk agents (HBsAg positive): 44 reactivations prevented per 1000 patients
  - Low risk agents: 1 reactivation prevented per 1000 patients

Lamivudine Profylaxis Reduces Risk of HBV Reactivation

HBsAg-positive patients with lymphoma treated with high-dose chemotherapy randomized to “preemptive” vs “on-demand” lamivudine

Value of Preemptive Antivirals

- HBsAg-positive patients with NHL treated with CHOP randomized to “preemptive” vs “on-demand” lamivudine


On-demand group: start Lamivudine if ALT > 1.5 x ULN
Preemptive group: start Lamivudine on day 1 of CHOP

HBsAg Patients (%)

- HBV Reactivation and Hepatitis Flare: 48
- HBV Reactivation and ALT > 10 x ULN: 36
- HBV Reactivation and Jaundice: 20
- Death (After ChemoTx): 0

Preemptive antivirals decrease HBV reactivation

Choice of Antiviral Therapy and Monitoring

- Choice of therapy affected by HBV DNA level
  - HBV DNA < 2000 IU/mL: any therapy can be used (including lamivudine)
  - HBV DNA > 2000 IU/mL: entecavir or tenofovir
- Choice of therapy affected by duration of therapy
  - > 12 months: entecavir or tenofovir
- HBV DNA and ALT should be monitored every 3 months

Timing of Antiviral Therapy

- **When to start**
  - Ideally before or together with chemotherapy
  - Do not delay start of chemotherapy

- **When to stop**
  - If baseline HBV DNA > 2000 IU/mL: high risk of withdrawal flare
    - Continue therapy as for chronic HBV infection
  - If baseline HBV DNA < 2000 IU/mL
    - 6-12 months after end of chemotherapy
    - (12 months for CD-20 antibodies)

- Monitor for withdrawal flares with monthly HBV DNA and ALT

IN SUMMARY
- Screening for HBsAg, anti-HBc in **ALL** patients scheduled for immunotherapy or chemotherapy and DAA and HIV therapy
- HBsAg carriers should be started on an antiviral agent, irrespective of DNA status or ALT level
- Anti-HBc positive patients who will be treated with anti-CD20 should receive an antiviral agent irrespective of HBsAg
- Optimal length of treatment is at least 6-12 months after the end of treatment
High-risk (HBV reactivation > 10%)

- HBsAg positive/ anti HBc positive
- HBsAg negative/ anti HBc positive
- HBsAg positive / anti-HBc positive
- B-cel suppressive agents (Rituximab, Ofatumumab)
- Antiviral prophylaxis ≥ 12 months after completing treatment
- Anthracyclines (Doxorubicine, Epirubicine)
- Corticosteroids ≥ 4 weeks, ≥ 10 mg
- Antiviral prophylaxis ≥ 6 months after completing treatment
Intermediate risk (HBV reactivation 1-10%)

- HBsAg positive/anti HBc positive
- HBsAg negative/anti HBc positive
- TNF-α inhibitors

- Cytokine of integrin inhibitors
- Tyrosine kinase inhibitors

- HBsAg positive/anti HBc positive
- Corticosteroids ≥ 4 weeks, low dose

- HBsAg negative/anti HBc positive
- Corticosteroids ≥ 4 weeks dose ≥ 10 mg

- Anthracycline

Antiviral profylaxis ≥ 6 months after completing immunosuppressive therapy
Low risk (HBV reactivation < 1%)

- HBsAg positive/ anti-HBc positive
- HBsAg negative/ anti-HBc positive

- Traditional immuno suppressants
- Corticosteroids ≤ 1 week

- HBsAg positive / anti-HBc positive
- Corticosteroids ≥ 4 weeks, dose < 10 mg

No routine antiviral profylaxis necessary
Thank you!