Hepatitis B Case Studies

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No conflicts of interest

This presentation is intended for educational use only, and does not in any way constitute medical consultation or advice related to any specific patient.
Case 1 – Extensive Treatment Experience

44 yo man with longstanding HIV infection, stage 2 with nadir CD4 220 and chronic hepatitis B infection. Diagnosed with both in 1996, risk factor: sex with men & women. Hx major depression.

**HIV Hx**
- Hx multiple ART regimens including d4T/3TC dual therapy in 1990s

**Chronic HBV Hx**
- eAg positive with baseline HBV level of 110 million IU/mL
- Ultrasound: Echogenic liver. In 2004, US showed early hepatofugal flow and mildly enlarged spleen
Case 1 – Extensive Treatment Experience

44 yo man with longstanding HIV infection, stage 2 with nadir CD4 220 and chronic hepatitis B infection, e-Ag positive with high baseline HBV viral level and probable cirrhosis.

• Persistent HBV viremia in $5 \log_{10} \text{IU/mL}$ range on lamivudine/adeovir (along with various antiretroviral agents) for many years
Case 1 – Extensive Treatment Experience

44 yo man with longstanding HIV infection, stage 2 with nadir CD4 220 and chronic hepatitis B infection, e-Ag positive with high baseline HBV viral level and probable cirrhosis.

- **Persistent HBV viremia** in $5 \log_{10}$ IU/mL range on lamivudine/adeovir (along with various antiretroviral agents) for many years
HBV DNA Level Associated With Increased Risk of HCC & Cirrhosis

REVEAL: Long-term follow-up of untreated HBV carriers in Taiwan

Cumulative Incidence of HCC at Year 13 Follow-up ¹ (N = 3653)

<table>
<thead>
<tr>
<th>Baseline HBV DNA (copies/mL)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 300</td>
<td>1.3</td>
</tr>
<tr>
<td>300-999</td>
<td>1.4</td>
</tr>
<tr>
<td>1000-9999</td>
<td>3.6</td>
</tr>
<tr>
<td>10,000-99,999</td>
<td>12.2</td>
</tr>
<tr>
<td>≥ 100,000</td>
<td>14.9</td>
</tr>
</tbody>
</table>

Cumulative Incidence of Cirrhosis at Year 13 Follow-up ² (N = 3582)

<table>
<thead>
<tr>
<th>Baseline HBV DNA (copies/mL)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 300</td>
<td>4.5</td>
</tr>
<tr>
<td>300-9999</td>
<td>5.9</td>
</tr>
<tr>
<td>10,000-99,999</td>
<td>9.8</td>
</tr>
<tr>
<td>100,000-999,999</td>
<td>23.5</td>
</tr>
<tr>
<td>≥ 1 million</td>
<td>36.2</td>
</tr>
</tbody>
</table>

Case 1 – Extensive Treatment Experience

44 yo man with longstanding HIV infection, stage 2 with nadir CD4 220 and chronic hepatitis B infection, e-Ag positive with high baseline HBV viral level and probable cirrhosis.

- **Persistent HBV viremia** in $5 \log_{10}$ IU/mL range on **lamivudine/adenovir** (along with various antiretroviral agents) for many years
HBV Suppression after 1 Year
HBeAg-positive Patients

- Peginterferon: 25%
- Lamivudine: 39%
- Adefovir: 21%
- Entecavir: 67%
- Telbivudine: 60%
- Tenofovir: 74%
Probability of Virologic Failure

- **Lamivudine**
  - Year 1: 24%
  - Year 2: 38%
  - Year 3: 49%
  - Year 4: 67%
  - Year 5: 70%

- **Adefovir**
  - Year 1: 0%
  - Year 2: 3%
  - Year 3: 11%
  - Year 4: 18%
  - Year 5: 29%

- **Entecavir**
  - Year 1: 0%
  - Year 2: 0.2%
  - Year 3: 1.2%

- **Telbivudine**
  - Year 1: 4%
  - Year 2: 17%

- **Tenofovir**
  - Year 1: 0%
Case 1 – Extensive Treatment Experience

44 yo man with longstanding HIV infection, stage 2 with nadir CD4 220 and chronic hepatitis B infection, e-Ag positive with high baseline HBV viral level and probable cirrhosis.

- Persistent HBV viremia in 5 log\(_10\) range on lamivudine/adeovir (& various ART) for many years until finally
- Switched to ART: Truvada, Kaletra and fosamprenavir in 2007.
- CD4 480 cells/mm\(^3\), HIV suppressed and HBV DNA at nadir 20 IU/mL
- Chemistry panel shows new Cr elevation 1.6. Serum phophate 2.5. ALT remain normal. UA: 1+ protein, 1+ glucose (normal serum glucose), no cells or casts.
- What would you do next?
### Peginterferon in HIV-HBV Coinfected Patients

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Finite treatment course</td>
<td>• Subcutaneous injection</td>
</tr>
<tr>
<td>• No drug resistance</td>
<td>• Frequent adverse effects</td>
</tr>
<tr>
<td>• Highly sustainable response*</td>
<td>• Risk of hepatitis flare</td>
</tr>
<tr>
<td>(eAg/Ab conversion)</td>
<td>• Contraindicated in advanced cirrhotics</td>
</tr>
<tr>
<td>• HBsAg clearance*</td>
<td></td>
</tr>
</tbody>
</table>

*Treatment efficacy may be limited/suboptimal in HIV-infected patients, esp. with low CD4 cell counts.

### Oral HBV-active Antiviral Agents

<table>
<thead>
<tr>
<th>Medication</th>
<th>Potency against HBV</th>
<th>Barrier to HBV Resistance</th>
<th>HIV Activity</th>
<th>Selection of HIV Resistance Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>Moderate</td>
<td>Low</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Low</td>
<td>Moderate</td>
<td>No(^a)</td>
<td>No</td>
</tr>
<tr>
<td>Entecavir</td>
<td>High</td>
<td>High</td>
<td>Partial</td>
<td>Yes</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Moderate</td>
<td>Low</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>High</td>
<td>Low</td>
<td>Partial(^b)</td>
<td>No</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>High</td>
<td>High</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

\(^a\) = anti-HIV activity at higher doses; more potent against HBV  
\(^b\) = No in vitro activity observed against HIV, but HIV RNA decline reported

http://depts.washington.edu/hepstudy/
Nucleotide Analogues: Adefovir and Tenofovir

Adefovir

Tenofovir
# HBV Polymerase Gene

**Regions of Reverse Transcriptase Gene**

- **rt1**: 1-349
- **rt344**: 692-845

**Mutations and Amino Acid Substitutions Associated with Resistance to Nucleoside Analogues**

<table>
<thead>
<tr>
<th>Gene Region</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Amino Acid Position</strong></td>
<td>80</td>
<td>169</td>
<td>173</td>
<td>180</td>
<td>181</td>
</tr>
<tr>
<td><strong>Baseline Amino Acid</strong></td>
<td>L</td>
<td>I</td>
<td>V</td>
<td>L</td>
<td>A</td>
</tr>
<tr>
<td><strong>Lamivudine Resistance</strong></td>
<td>V/I</td>
<td>L</td>
<td>M</td>
<td>T</td>
<td></td>
</tr>
<tr>
<td><strong>Adefovir Resistance</strong></td>
<td></td>
<td>T/V</td>
<td></td>
<td></td>
<td>T</td>
</tr>
<tr>
<td><strong>Entecavir Resistance</strong></td>
<td>T</td>
<td>M</td>
<td></td>
<td>S/A/I/L/F/G</td>
<td>G/I</td>
</tr>
<tr>
<td><strong>Telbivudine Resistance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>I</td>
</tr>
</tbody>
</table>
Tenofovir Alafenamide for HBV?
Case 1 – Extensive Treatment Experience

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- Persistent HBV viremia in 5 log\textsubscript{10} range on lamivudine/ adefovir (& various ART) for many years until finally

- CD4 480 cells/mm\textsuperscript{3}, HIV suppressed and HBV DNA at nadir 20 IU/mL on ART: Truvada, Kaletra and fosamprenavir in 2007.

- Chemistry panel shows new Cr elevation 1.6. Serum phophate 2.5. ALT remain normal. UA: 1+ protein, 1+ glucose.

- Tenofovir stopped. Entecavir 1.0 mg daily dose started with continued HBV suppression.

- Ultrasound in 2015: normal-sized spleen, hepatopetal flow & mildly echogenic liver
Regression of Cirrhosis in Patients on Tenofovir

Case 2 – Ongoing HBV Viremia on TDF/FTC


- 2009 – started on Truvada (TDF/FTC), abacavir, darunavir, raltegravir
- 2009-2010 – Still HBV viremic to 5-7 $\log_{10}$ IU/mL range in background of HIV suppression
Case 2 – Ongoing HBV Viremia on TDF/FTC

**Lab Trend: 'HBV DNA IU/mL (Log 10)'**

- **Entecavir**
- **L180M, M204V**
- **Tenofovir/FTC**

**ALT (IU/L)**
Case 2 – Ongoing HBV Viremia on TDF/FTC
Chronic HBV in the CNICS Cohort

1067 patients
(+)HBsAg or HBV DNA

939 patients
Treated with Tenofovir (TDF) ≥3 months

397 patients
HBV DNA measured on TDF & detectable baseline HBV DNA

### Risk Factors for Delayed HBV Suppression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC exposure</td>
<td>0.60 (0.42-0.85)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age &gt;40 yrs</td>
<td>1.08 (0.81-1.43)</td>
<td>0.62</td>
</tr>
<tr>
<td>Nadir CD4, cells/mm³ (ref: ≥500)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>350-499</td>
<td>0.58 (0.33-1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>200-249</td>
<td>0.55 (0.32-0.93)</td>
<td>0.03</td>
</tr>
<tr>
<td>&lt;200</td>
<td>0.53 (0.31-0.88)</td>
<td>0.02</td>
</tr>
<tr>
<td>HBV DNA level &gt;10,000 IU/mL</td>
<td>0.34 (0.22-0.53)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Race (ref: white)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.78 (0.56-1.08)</td>
<td>0.14</td>
</tr>
<tr>
<td>Other</td>
<td>1.21 (0.60-2.45)</td>
<td>0.61</td>
</tr>
<tr>
<td>Serum ALT &gt;80 U/L</td>
<td>1.56 (1.14-2.15)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Delayed HBV DNA Suppression on Tenofovir

Dual Therapy for HBV: TDF + ETV or FTC

• Probably not worth the cost & additional drug exposure in HBV mono-infected patients who are treatment-naive.

• Dual* therapy may be considered in patients who are:
  - Treatment-experienced esp if HBV viremic on prior therapy
  - Cirrhotic
  - HIV-co-infected (esp. if lamivudine-experienced)
  - Transplant patients

*NOTE: It remains unclear if dual therapy should be TDF/FTC vs TDF/ETV

Lok, Gastroenterol 2012;143:619.
Petersen, J Hepatol 2012;56:520.
Take Home Points

• Avoid lamivudine or emtricitabine monotherapy for your HIV-HBV co-infected patients

• Adefovir is not potent. Know the limitations of these antivirals.

• Peginterferon is not 1st-line standard of care in HIV-HBV

• HBV viral suppression can be delayed out to 2 or more years in some HIV-HBV patients.
  - Some of this may not be due to drug but to lack of immune clearance
  - Not everyone needs entecavir