HIV and HBV Coinfection

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University of California, Los Angeles
Objectives

• 1. Identify best practices in HBV screening and liver disease management in HIV co-infection
• 2. Optimize your approach to HBV treatment and addressing potential side effects in patients with HIV/HBV coinfection
Outline

• Epidemiology
• Clinical Course
• Diagnosis
• Treatment
Global Scope of HIV-HBV Co-infection

HBV Prevalence in HIV: 6-9% in US and Western Europe

<table>
<thead>
<tr>
<th>HIV</th>
<th>HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 million worldwide</td>
<td>400 million worldwide</td>
</tr>
<tr>
<td>1 million in the US</td>
<td>1.25 million in the US</td>
</tr>
<tr>
<td>Transmission: Perinatal/Sexual/Parenteral</td>
<td>Transmission: Perinatal/Sexual/Parenteral/Horizontal</td>
</tr>
<tr>
<td>RNA retrovirus</td>
<td>DNA hepadnavirus</td>
</tr>
<tr>
<td>Integrates in genome</td>
<td>Integrates into genome</td>
</tr>
<tr>
<td>Target: CD4 cells</td>
<td>Target: hepatocytes</td>
</tr>
<tr>
<td>Reverse transcriptase</td>
<td>Reverse Transcriptase</td>
</tr>
<tr>
<td>Nucleos(t)ide Analogues and other ARV</td>
<td>Nucleos(t)ide Analogues and immunomodulators</td>
</tr>
<tr>
<td>Mutations=Resistance</td>
<td>Mutations=Resistance</td>
</tr>
</tbody>
</table>

Outline

• Epidemiology
• Clinical Course
• Diagnosis
• Treatment
Hepatitis B Disease Progression


Perinatal Infection: 90%
Adult and Older Children Infection: 5-50%

Liver Cancer (HCC)

Cirrhosis

Liver Transplantation

Death

Liver Failure ( Decompensation)

5%-10% 

30% 

23% within 5 years

CHB: 6th leading cause of liver transplantation in the US
REVEAL Study: HBV DNA Levels and Long-term Outcomes

Viral Load at Baseline

Cumulative Incidence of HCC (%) (n=3653)

- <300 (undetectable): 1.26%
- 300-9999: 1.37%
- 10,000-99,999: 3.57%
- 100,000-999,999: 12.17%
- ≥1 million: 14.89%

Multivariate-adjusted relative risk of cirrhosis (n=3582)

- <300 (undetectable): 1.0
- 300-9999: 2.0
- 10,000-99,999: 3.6
- 100,000-999,999: 9.7
- ≥1 million: 10.6

Impact of HIV on HBV Disease Progression

• Higher rate of chronicity\textsuperscript{1,2}
  • 20 to 80\% as compared to 3-5\% in HIV -
  • risk increases with lower CD4 at time of HBV acquisition

• Higher levels of HBV replication (HBV DNA)\textsuperscript{3,4}

• Lower rate of spontaneous loss of HBeAg or HBsAg and seroconversion to anti-HBe and anti-HBs.\textsuperscript{1,4}

• Higher mortality when compared to HIV or HBV monoinfection\textsuperscript{5}

• Lower ALT levels\textsuperscript{4}

• Faster progression to cirrhosis\textsuperscript{3,6}

• Higher incidence of lamivudine resistance\textsuperscript{7}

• Increased risk of HCC, especially in immunosuppressed MSM\textsuperscript{8,9}

Long-term TDF in Pts With HBV: Reversal of Inflammation

- Open-label study of TDF in pts with chronic HBV infection (N = 585)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Outcome at 7 Yrs[^1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized ALT, % (n/N)</td>
<td></td>
</tr>
<tr>
<td>ITT*</td>
<td>57.1 (323/566)</td>
</tr>
<tr>
<td>On treatment</td>
<td>80.0 (328/410)</td>
</tr>
<tr>
<td>HBV DNA &lt; 29 IU/mL, % (n/N)</td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>70.1 (418/596)</td>
</tr>
<tr>
<td>On treatment</td>
<td>99.3 (430/433)</td>
</tr>
<tr>
<td>HBeAg loss, † % (n/N)</td>
<td>54.5 (84/154)</td>
</tr>
<tr>
<td>HBe seroconversion, † % (n/N)</td>
<td>39.6 (61/154)</td>
</tr>
<tr>
<td>HBsAg loss, † K-M % (95% CI)</td>
<td>11.8 (8.1, 16.9)</td>
</tr>
<tr>
<td>HBs seroconversion, † K-M % (95% CI)</td>
<td>9.7 (6.4, 14.6)</td>
</tr>
</tbody>
</table>

[^1]: Pts with data missing or FTC added counted as failures.

[^2]: HBeAg-positive population.

Necroinflammation improved over 5 yrs (n = 348 matched biopsies)

Knodell Necroinflammatory Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Yr 1</th>
<th>Yr 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-14</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>7-9</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>4-6</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>0-3</td>
<td>18%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Outline

• Epidemiology
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<table>
<thead>
<tr>
<th>Assay</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Protein on surface of HBV detected during acute or chronic HBV infection</td>
</tr>
</tbody>
</table>
| Anti-HBs or HBsAb                    | Indicates immunity to HBV,  
• Vaccination or immune clearance                                                                                                                                           |
| Anti-HBc (total) or HBCab (total)    | • Appears at onset of symptoms in acute hepatitis  
• Persists for life  
• Indicates exposure (previous or ongoing infection with HBV)                                                                                                     |
| Anti-HBc, IgM or HBCab, IgM          | • Presence indicates acute infection (recent infection with HBV (≤ 6 mos)  
• Negative in chronic infection  
• Occasionally occurs during severe flare of *chronic* HBV disease                                                                                      |
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>HBeAg</td>
<td>• Coproduct of nucleocapsid gene of HBV&lt;br&gt;• Acute and chronic HBV with wild-type infection&lt;br&gt;• Replicating natural variant virus&lt;br&gt;• Associated with high HBV DNA</td>
</tr>
<tr>
<td>Anti-HBe or HBeAb</td>
<td>• Produced by immune system in setting of infection clearance&lt;br&gt;• Temporary or Persistent&lt;br&gt;• Conversion to anti-HBe demonstrates&lt;br&gt;• Long-term clearance of HBV in patients or&lt;br&gt;• Emergence of precore, mixed, or core promoter mutant infection and transition to HBeAg-negative disease</td>
</tr>
</tbody>
</table>

Case 1

- 55 yo male with HIV (CD4 550, HIV VL 34,000) comes in to establish care

You obtain the following hepatitis B serology results:

- HBsAg negative, total HBcAb positive, HBsAb negative
How do you interpret this hepatitis B serologic profile?

A. He has chronic hepatitis B and you should order HBeAg, HBeAb, and HBV DNA in addition to liver function tests and chemistries.

B. He is immune to hepatitis B and needs no further testing or vaccinations.

C. He has hepatitis C infection and you should now order HCV RNA in addition to liver function tests and chemistries.

D. He has likely been exposed to hepatitis B but needs no further HBV vaccinations.

E. He has likely been exposed to hepatitis B but is unlikely to mount an immune response to an HBV booster and needs to be vaccinated for HBV.
## Serologic Screening for HBV in Co-infection

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Anti-HBs</th>
<th>Anti-HBc</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Naïve (Immunize)</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Immune (vaccine induced)</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Resolved infection (immune)</td>
</tr>
<tr>
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<td>-</td>
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<td>-</td>
<td>+</td>
<td>Acute or chronic infection (assess duration)</td>
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Isolated anti-HBc Pattern

- HBsAg neg, HBcAb pos, HBsAb neg
- Occurs in 12-19% of HIV infected patients, higher in HIV/HCV \(^{1,2,3}\)
- Represents
  - False positive
  - Window period
  - Waning immunity
  - Occult HBV viremia i.e. HBV DNA positivity without positive HBV serologies\(^4\)
- Require vaccination for HBV because of lack of anamnestic response\(^5,6\)
- At risk for HBV re-activation during periods of intense immunosuppression (very low CD4, immunosuppressant therapy with rituxan, chemotherapy)

## Serologic Screening for HBV in Co-infection

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</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Acute or chronic infection (assess duration)</td>
</tr>
</tbody>
</table>
### Indications for HBV Vaccination

- Patients without chronic HBV or without immunity to HBV (anti-HBs <10 IU/mL) (AII)
- Patients with isolated anti-HBc and with negative HBV DNA (BII)
- Early vaccination is recommended before CD4 count falls below 350 cells/mm$^3$ (AII), as low CD4 count at time of vaccination has been associated with poor responses to the vaccine

### Vaccination Schedule

- HBV vaccine IM (Engerix-B® 20 mcg/mL or Recombivax HB® 10 mcg/mL) at 0, 1, and 6 months (AII); or
- HBV vaccine IM (Engerix-B® 40 mcg/mL or Recombivax HB® 20 mcg/mL) at 0, 1, and 6 months (BI); or
- Combined HAV and HBV vaccine (Twinrix®) 1 mL IM as a 3-dose series (at 0, 1, and 6 months) or as a 4-dose series (at days 0, 7, 21 to 30, and 12 months) (AII)

- Anti-HBs should be obtained 1 month after completion of the vaccine series, anti-HBs <10 IU/mL will be considered as non-responders (BIII)

**For Vaccine Non-Responders:**
- Revaccinate with a second vaccine series (BIII)
- For patients with low CD4 count at the time of first vaccination series, some experts might delay revaccination until after a sustained increase in CD4 count with ART (CIII)

**Alternative Vaccine Dose for Non-Responders:**
- HBV vaccine IM (Engerix-B® 40 mcg/mL or Recombivax HB® 20 mcg/mL) at 0, 1, and 6 months (BI)
Case 2

- 55 yo male with HIV (CD4 550, HIV VL 34,000) comes in to establish care.

You obtain the following hepatitis B serology results:

- HBsAg positive, total HBcAb positive, HBsAb negative
#2 - How do you interpret this hepatitis B serologic profile?

A. He has chronic hepatitis B and you should order HBeAg, HBeAb, and HBV DNA in addition to liver function tests and chemistries.

B. He is immune to hepatitis B and needs no further testing or vaccinations.

C. He has hepatitis C infection and you should now order HCV RNA in addition to liver function tests and chemistries.

D. He has likely been exposed to hepatitis B but needs no further HBV vaccinations.

E. He has likely been exposed to hepatitis B but is unlikely to mount an immune response to an HBV booster and needs to be vaccinated for HBV.
# Diagnosis and Approach to Management in HIV/HBV Coinfection

<table>
<thead>
<tr>
<th>H&amp;P</th>
<th>Routine Lab Tests</th>
<th>Serology/Virology</th>
<th>Imaging/Staging Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, duration of disease, Sx/signs of cirrhosis</td>
<td>CBC incl plt</td>
<td>HBsAg, HBcAb, HBsAb</td>
<td>Abdominal ultrasound</td>
</tr>
<tr>
<td>ETOH, smoking, other SUD Renal/bone comorbidities</td>
<td>AST/ALT/tbili/alk phos/albumin/INR</td>
<td>HBeAg/HBeAb</td>
<td>Transient elastography or serum fibrosis panel (APRI, FIB-4, Fibrotest)</td>
</tr>
<tr>
<td>Metabolic risk factors</td>
<td>Chem 7 (incl Cr)</td>
<td>HBV DNA</td>
<td>Liver biopsy in select cases</td>
</tr>
<tr>
<td>Family history of HCC</td>
<td>Tests to r/o other causes of chronic liver disease</td>
<td>HAV, HCV</td>
<td></td>
</tr>
<tr>
<td>Vaccination Status</td>
<td>AFP, GGT, CD4, HIV-1 VL</td>
<td>HDV, HBV genotype?</td>
<td></td>
</tr>
</tbody>
</table>
## Classification of HBeAg Positive and Negative Chronic HBV

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>HBeAg</th>
<th>Anti-HBe</th>
<th>HBV DNA</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>+++</td>
<td>HBeAg+ High Replicative Phase (immune tolerance)</td>
</tr>
<tr>
<td>Pos</td>
<td>Neg</td>
<td>Pos</td>
<td>±</td>
<td>HBeAg negative low replicative or inactive phase</td>
</tr>
<tr>
<td>Pos</td>
<td>Neg</td>
<td>Pos</td>
<td>++</td>
<td>HBeAg negative replicative phase (HBeAg negative chronic disease)</td>
</tr>
</tbody>
</table>
HBV Classification: Genotype

• HBV genotypes related to liver disease and treatment response
  • Genotype B (vs C):
    • less liver disease progression\(^1\)
    • Better IFN response\(^2\)
  • Genotype C
    • Higher prevalence of HCC\(^3\)
  • Genotype A (vs D):
    • better IFN response\(^2\)

Outline

• Epidemiology
• Clinical Course
• Diagnosis
• Treatment
Case 2 contd

• 55 yo male with HIV (CD4 550, HIV VL 34,000).
• HBsAg+, HBcAb+, HBsAb-
• HBeAg +, HBeAb negative
• HBV DNA 7,000,000 IU/ml
• HIV genotype without mutations
• Transient elastography consistent with moderate to advanced liver disease
What treatment would you recommend?

A. No treatment as his CD4 is too high.
B. Treatment for HBV alone with entecavir 0.5 mg po qd
C. Initiate a regimen of dolutegravir/abacavir/3TC
D. Initiate a regimen of dolutegravir/TDF/FTC
E. Initiate a regimen of efavirenz/TDF/FTC
When to Initiate ART in HIV/HBV Coinfection and what ART regimen?

• Antiretroviral therapy (ART) is recommended for all HIV-infected individuals, regardless of CD4 T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection
• TDF/FTC or TDF/3TC or TAF/FTC as nucleos (t) ide backbone
• Entecavir if TDF or TAF cannot be used
  • Must be used in patients with ND HIV VL because of anti-HIV activity of entecavir
    • 1.0 mg (higher dose) in setting of lamivudine resistance
• Do not stop HBV-active therapy during ART regimen switches

2017: Therapies for Chronic Hepatitis B

- IFN
- Lamivudine (3TC)
- Adefovir
- Emtricitabine (FTC)
- Entecavir
- Pegylated IFN α2a
- Telbivudine
- Tenofovir
- Tenofovir Alafenamide

Limited data on adefovir and telbivudine in HIV/HBV, also associated with nephrotoxicity (adefovir) and myopathy/neuropathy (telbivudine)
Incidence of Lamivudine Resistance in Hepatitis B Patients

Case 2 contd

- You initiate DTG/TDF/FTC but one year later he develops mild renal insufficiency, now with a CrCl of 60 (down from 90)
- He is anxious to discontinue TDF as he has already heard about possible renal and bone side effects
- He also wants a one pill once-a-day regimen.
Which treatment would you recommend?

A.  Stop therapy and give him an ARV holiday
B.  Change regimen to dolutegravir/abacavir/lamivudine
C.  Change regimen to elvitegravir/cobicistat/TAF/FTC
D.  Continue dolutegravir/TDF/FTC
E.  Change regimen to elvitegravir/cobicistat/TAF/FTC and add entecavir 0.5 mg po qd
TAF vs TDF in Pts With HBV Infection: Efficacy

- Multicenter phase III studies in pts with chronic HBV infection (N = 1298), including pts with compensated cirrhosis

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>HBeAg-Positive Pts[^2] (N = 873)</th>
<th></th>
<th></th>
<th></th>
<th>HBeAg-Negative Pts[^3] (N = 425)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAF</td>
<td>TDF</td>
<td>P Value</td>
<td>TAF</td>
<td>TDF</td>
<td>P Value</td>
<td></td>
</tr>
<tr>
<td>HBV DNA &lt; 29 IU/mL at Wk 72[^1]</td>
<td>71.6</td>
<td>71.9</td>
<td>.78</td>
<td>92.6</td>
<td>92.1</td>
<td>.84</td>
<td></td>
</tr>
<tr>
<td>ALT normalization at Wk 48</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central laboratory criteria^[*]</td>
<td>72</td>
<td>67</td>
<td>.18</td>
<td>83</td>
<td>75</td>
<td>.076</td>
<td></td>
</tr>
<tr>
<td>AASLD laboratory criteria^[†]</td>
<td>45</td>
<td>36</td>
<td>.014</td>
<td>50</td>
<td>32</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>HBeAg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss at Wk 48</td>
<td>14</td>
<td>12</td>
<td>.47</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seroconversion at Wk 48</td>
<td>10</td>
<td>8</td>
<td>.32</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss at Wk 48</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>.52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seroconversion at Wk 48</td>
<td>&lt;1</td>
<td>0</td>
<td>.22</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

[^1]: ULN for men, ≤ 43 U/L (≤ 35 U/L if age ≥ 69 yrs); for women, ≤ 34 U/L (≤ 32 U/L if age ≥ 69 yrs).
[^*]: ULN for men, ≤ 30 U/L; for women, ≤ 19 U/L.
TAF vs TDF in Pts With HBV Infection: Safety

- Multicenter phase III studies in pts with chronic HBV infection (N = 1298), including pts with compensated cirrhosis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TAF</th>
<th>TDF</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in BMD at Wk 72, %&lt;sup&gt;[1]&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Hip</td>
<td>-0.16</td>
<td>-1.86</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>▪ Spine</td>
<td>-0.57</td>
<td>-2.37</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Median change in serum creatinine at Wk 48, mg/dL&lt;sup&gt;[2]&lt;/sup&gt;</td>
<td>0.01</td>
<td>0.02</td>
<td>.012</td>
</tr>
<tr>
<td>Median change in eGFR at Wk 48, mL/min&lt;sup&gt;[2]&lt;/sup&gt;</td>
<td>-1.2</td>
<td>-5.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Mean change in FibroTest score at Wk 48&lt;sup&gt;[3]&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ HBeAg-positive pts</td>
<td>-0.07</td>
<td>-0.04</td>
<td>.007</td>
</tr>
<tr>
<td>▪ HBeAg-negative pts</td>
<td>-0.05</td>
<td>-0.03</td>
<td>.028</td>
</tr>
</tbody>
</table>

Switching from TDF to TAF in HBV Monoinfection

GS-108 and GS-110 Switch Study Results
Continuous TAF: n=361
TDF→TAF: n=180

Chan EASL 2017
Switching from TDF to TAF in HBV Monoinfection

GS-108 and GS-110 Switch Study Results

**Median Creatinine Clearance of TDF patients with CrCl <90 at Week 96 and Week 120**

- **Week 96**
  - Median CrCl: 90 mL/min
  - Range: 50 to 113 mL/min

- **Week 120**
  - Median CrCl: 76 mL/min
  - Range: 43 to 113 mL/min

*Significant improvement in creatinine clearance in patients with CKD Stage ≥2 at Week 120 in patients who switched from TDF to TAF at Week 96*

Chan EASL 2017
TAF in HIV/HBV

- Open label, non-comparative switch study of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (E/C/F/TAF) efficacy and safety in HIV/HBV co-infected adults
- N=72
- 91.7% HIV-1 RNA <50 copies/mL, HBV DNA <29 IU/mL at week 48
- ALT levels normalized in 40% of pts
- Better renal function and reduced bone turnover with E/C/F/TAF

Monitoring on Therapy

- HBV DNA q 3 mos until ND then q 6 mos, HBeAg q6-12 mos
- ALT/AST 6 and 12 wks after initiation then q3-6 mos
- Electrolytes and Cr q 3-6 mos
- If on tenofovir: UA q 6 mos, serum phosphorus q year

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary non-response</td>
<td>HBV DNA $&lt; 1 \log_{10}$ decline at 12 weeks</td>
</tr>
<tr>
<td>Complete virologic response</td>
<td>Undetectable HBV DNA by real-time polymerase chain reaction at 24 to 48 weeks</td>
</tr>
<tr>
<td>Partial virologic response</td>
<td>$\geq 1 \log_{10}$ decline but still detectable HBV DNA at Week 24</td>
</tr>
<tr>
<td>Persistent Viremia</td>
<td>Plateau in the decline of HBV DNA and/or failure to achieve undetectable HBV DNA level after wk 96</td>
</tr>
<tr>
<td>Viral Breakthrough</td>
<td>HBV DNA by $&gt; 1$ log compared to nadir or HBV DNA 100 IU/mL with previously undetectable levels</td>
</tr>
</tbody>
</table>
HIV/HBV Management Issues

- Hepatic Flare
- Prior 3TC Resistance
- Incomplete Virologic Suppression
- Cirrhosis Management
- HCC Screening
Etiologies of ALT flares

• Immune Reconstitution
  • Occurs 6-12 weeks after ART initiation

• Cessation of anti-HBV therapy

• Emergence of Drug Resistance

• Drug-Induced Hepatotoxicity

• Other infectious causes of hepatitis
  • HAV, HDV, HCV, HEV, EBV, HSV, CMV
Hepatitis Flares in HIV-HBV coinfected patients starting HBV active HAART (TICO trial substudy)

• TICO Trial substudy:

• 36 antiretroviral naïve HIV/HBV in Thailand randomized to receive:
  - TDF vs LAM vs TDF + LAM as part of an Efavirenz-based HAART
  - 8 (22%) cases with Hepatic Flares (ALT > 5 X ULN or > 200 within 12 weeks) → 1 died from LF (3%)
  - Predictors of flares:
    • High HBV DNA
    • High ALT
    • Low CD4
  - Pathogenesis of flares: Probable Immune Restoration Disease by cytokine substudy:
    • T cell and NK activation markers ↑↑↑
    • Markers of IFNγ induction (IL-18) and activity (MCP-1) ↑↑↑

Management of ALT Flares After ART Initiation: HIV/HBV Coinfection

- In many cases, ALT will resolve even with medication continuation
- Assess for other causes of hepatitis
- Serum HBV DNA, HBeAg, HIV RNA, and CD4 may be helpful in distinguishing between IRIS, HBV resistance, and hepatotoxicity
- Biopsy may be able to distinguish between drug toxicity (eosinophils) from IRIS or immunologic flare (portal inflammation)
- Involve hepatologist early
- Discontinue ARV therapy in setting of
  - symptoms of hypersensitivity (e.g., fever, lymphadenopathy, rash)
  - Symptomatic hepatitis (i.e., nausea, vomiting, abdominal pain, or jaundice),
  - Elevations in serum aminotransferase levels >10 times the upper limit of normal

1. Stern JAIDS 2003  2. HIV OI Guidelines
Virologic Response & Resistance

• 10/82 (12%) did not achieve virologic response
  • 13% (9/67) HBeAg+
  • 7% (1/15) HBeAg-
  • 3 compliant with HIVRNA undetectable added ETV $\rightarrow$ undetectable HBVDNA after 12-27 mo
  • 4/10 LAM-R at baseline 1/4 persisted

• 4/82 (5%) breakthrough
  • 2 low adherence
  • 2 HCC (1 with rtA181V, RT L180M, rt L80I, rt M204I)

Impact of 3TC Resistance on TDF therapy

Incomplete HBV Virologic Suppression?

- DHHS and AASLD (HBV monoinfection) GL both suggest continuing therapy; no threshold for regimen change (AASLD 96 weeks suggested)
- Entecavir addition can be considered
  - 38% ND HBV DNA after entecavir intensification post TDF/FTC failure

Ratcliffe, AIDS. 2011.
HBV Management: Cirrhosis Checklist

1. Liver imaging every 6 months ± alfa fetoprotein
2. EGD every 3 years to survey for varices
3. Hepatitis A Vaccination if HAV negative
4. Annual influenza Vaccination
5. Pneumococcal Vaccination (PPSV23 and PCV13)
6. Avoidance of alcohol
7. Avoidance of NSAIDs
8. Limitation for acetaminophen 2,000 mg/day and only as needed
9. Avoidance of raw shellfish

HBV Management:
Hepatocellular carcinoma screening in HBV/HIV coinfection

• Asian men over the age of 40 years
• Asian women over the age of 50 years
• Patients with HBV and cirrhosis
• Africans and North American blacks
• Patients with a family history of HCC
HBV in HIV Infected Patients

Summary

• HBV co-infection is common in HIV patients
• HIV accelerates the progression of HBV
• Dual HBV active antiretroviral therapy (TDF/FTC, TDF/3TC, TAF/FTC) should be used to minimize HBV resistance
• Do not stop therapy for HBV during ARV regimen switches.
• Immunize patients with isolated HBcAb pattern (HBsAg neg, HBcAb positive, HBsAb negative)
• Remember cirrhosis counseling and HCC surveillance
ACTHIV 2017: A State-of-the-Science Conference for Frontline Health Professionals