HEPATITIS COINFECTIONS

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Disclosures  
(Activity w/i 12 months)

• Research Support (to institution):
  – Roche, Schering, SciClone, Vertex, GSK, HGS, Gilead, BMS

• Advisory Board/Consulation:
  – BMS, SciClone, Vertex, Merck, Valeant, Anadys
  – DSMB- Tibotec
  – End Point Adjudication- Pfizer
Learning Objectives

• Upon completion of this activity you will be able to:
  • Recognize the need for screening and managing of viral hepatitis in those with HIV in your practice.
  • Develop a management plan for HBV/HIV coinfection in your practice.

• This presentation will include the discussion of off-label uses.
WHY DISCUSS HCV/HIV COINFECTION?

• People living with HIV are increasing in number
• Liver disease is an IMPORTANT outcome that ID caregivers are often ill-prepared to evaluate and manage
• Gastroenterologists are frequently uncomfortable with HIV management and with HIV-infected patients
Causes of Death in Coinfection
French Mortality 2000 Cohort

Among patients with markers of HBV or HCV infection

Salmon-Ceron et al., J HEPATOL 2005
## HCV/HIV Effect on Health Utilization in A5001

<table>
<thead>
<tr>
<th></th>
<th>HCV/HIV rate* (95% CI)</th>
<th>HIV rate* (95% CI)</th>
<th>Adjusted rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nights in hospital</strong></td>
<td>14.2 (13.4–14.9)</td>
<td>5.8 (5.6–5.9)</td>
<td>2.5 (1.7–3.6)</td>
</tr>
<tr>
<td><strong>Emergency department visits</strong></td>
<td>6.3 (5.8–6.8)</td>
<td>3.4 (3.2–3.5)</td>
<td>1.5 (1.2–2.0)</td>
</tr>
<tr>
<td><strong>Disability days</strong></td>
<td>112.5 (110.3–114.7)</td>
<td>67.6 (67.0–68.2)</td>
<td>1.6 (1.2–2.2)</td>
</tr>
</tbody>
</table>

Linus et. al. CROI 2009 Oral #102
ETIOLOGIES OF LIVER INJURY

- HCV or HBV
- Steatosis
- Mitochondrial Injury
- Immune Reactivation
- Alcohol
- Or other Drugs
- HIV
- ART

GUT TRANSLOCATION?
WHO SHOULD BE TESTED?

HIV-infected patients should be tested routinely for evidence of chronic HCV infection

Initial testing for HCV should be performed using the most sensitive immunoassays licensed for detection of antibody to HCV (anti-HCV)

USPHS GUIDELINES, MMWR, 2009
Updated ALT Ranges

Newly calculated healthy limits are indicated in each panel. A) Male participants. B) Female participants. To convert the alanine aminotransferase thresholds to nkat/L, multiply by 16,667.

Rapid Progression of Liver Disease in HIV/HCV-Coinfected Patients

- Prospective study of fibrosis progression in 67 coinfected patients
- 2 biopsies; median time between biopsies was 2.84 years

>25% of patients with mild fibrosis on initial biopsy had ≥2 stage progression in fibrosis score

Patients With Mild Fibrosis (≤F1) on First Biopsy

Sulkowski M et al. AIDS, 2007
TREATMENT & MANAGEMENT PRINCIPLES
HCV TREATMENT
Standard of Care 2010

Confirm HCV Present
Determine VL and Genotype
Evaluate Histology
Evaluate Contraindications to Rx

Genotype 1 or 4
Peg IFN alfa 2a or 2b + Ribavirin for 48 wks
EVR Evaluation → Early d/c
SVR 40-45%

Genotype 2 or 3
Peg IFN alfa 2a or 2b + ribavirin 800 mg/qd for 24 wks
SVR 70-85%

Pooled SVR 50-55%
TREATMENT RECOMMENDATIONS in HIV

- PegIFN + Ribavirin is the recommended treatment (A1)
  - Genotype 1 SVR 14-29%
  - Genotype 2, 3 SVR 43-73%
- Many experts recommend weight-based ribavirin (A2) despite PARADIGM trial
- 48 Weeks of Therapy in All Patients (A1)
- Acute HCV should be treated with same regimen for >24 weeks (B3)

USPHS GUIDELINES, MMWR, 2009
Issues Limiting Treatment of HCV

- Inexperience using agents
- Liver Disease too Advanced
- Psychiatric complications
- Anemia
- Neutropenia
- Weight loss
- Drug Interactions
NEW TREATMENTS FOR HCV
Superiority should be required for first approval of small molecules

Combination small molecule trials may be appropriate after Phase 2b evaluation of individual agents

Prior to NDA studies must be initiated in special populations
- HCV/HIV coinfection
- Decompensated Liver Disease
- Pediatric populations

Appropriate representation of high prevalence minority groups is essential

Sherman et. al, HEPATOLOGY, 2007
SUMMARY OF NEW TREATMENTS

- Many targets for directed HCV therapy are available
- Some agents show promise, but development is slow and should not delay treatment in individual patients now
  - New Agent Approval - ?2011
- Expect need for Pegylated Interferon and ribavirin for the foreseeable future
HBV/HIV Disease Burden

Worldwide Prevalence of Chronic Hepatitis B and HIV

- **HIV**
  - 50 million

- **HBV**
  - 350 million

- **4-8 million** HBV/HIV coinfected
Increased Liver Mortality in HIV/HBV Coinfected Men: MACS

- 5293 men (326 HBsAg+ baseline) followed 10.5 years

HBV/HIV: Deciding Who to Treat

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents; MMWR 2009

- **HBsAg+**
  - HBeAg Pos
    - HBV DNA >20,000 IU
      - ALT NL
        - Consider LBx
      - ALT >NL
        - Inflammation/Fibrosis
    - ALT >NL
      - Consider LBx
  - Cirrhotic
    - HBV DNA >2000 IU
      - ALT NL
        - Inflammation/Fibrosis
      - ALT >NL
        - TREAT
  - HBeAg Neg
    - ALT >NL
      - TREAT
    - ALT NL
      - Consider LBx

Inflammation/Fibrosis
## Agent Comparison

<table>
<thead>
<tr>
<th>AGENT</th>
<th>EFFICACY</th>
<th>RESISTANCE</th>
<th>COST</th>
<th>Level A/B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>+++</td>
<td>++++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Adefovir</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Entecavir</td>
<td>++++</td>
<td>++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Telbivudine</td>
<td>++++</td>
<td>++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>++++</td>
<td>+</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>PegIFN</td>
<td>++++</td>
<td>+</td>
<td>++</td>
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*Level A/B*
HBV Mutation

• Arises due to the relatively low fidelity of the HBV polymerase

• Mutation rate of approximately $3 \times 10^{-4}$
  (Park et al., *Eur J Biochem*, 2004)

• 10-fold higher than most DNA viruses
HBV Polymerase Key Mutations

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Terminal Protein</th>
<th>Spacer</th>
<th>Polymerase or Reverse Transcriptase</th>
<th>RNase H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domain</td>
<td>(rt1) A</td>
<td>B</td>
<td>C</td>
<td>D (rt244)</td>
</tr>
<tr>
<td></td>
<td>183</td>
<td>349</td>
<td>692</td>
<td>845</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lamivudine</th>
<th>L80V/I</th>
<th>V173L</th>
<th>M204V/I/S</th>
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<tbody>
<tr>
<td></td>
<td>L180M</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L169T, A181T</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T184S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adefovir</td>
<td>A181T/V</td>
<td>V214A</td>
<td>N236T/N238D</td>
</tr>
<tr>
<td></td>
<td>V84M, S85A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entecavir</td>
<td>S184G</td>
<td>S202I</td>
<td>M250V</td>
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<tr>
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<td>L169T, V173L,</td>
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<td></td>
<td>L180M, M204V</td>
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<tr>
<td>Tenofovir</td>
<td>A194T</td>
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<tr>
<td></td>
<td>V214A, Q215S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telbivudine</td>
<td></td>
<td>M204I</td>
<td></td>
</tr>
<tr>
<td>Telbivudine and lamivudine</td>
<td>L180M</td>
<td>M204V</td>
<td></td>
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</tbody>
</table>

Consequences of Sequential MonoTherapy

- Flares in Infected Individuals
- Development of Multidrug Resistant HBV
- Transmission of Resistant Virus
- Development of Compensatory Mutations Affecting Vaccine and Adaptive Immunity
## Co-Inhibition of HIV

<table>
<thead>
<tr>
<th>AGENT</th>
<th>STRONG</th>
<th>WEAK</th>
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<tbody>
<tr>
<td>Lamivudine</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tenofovir/Emtricitibine</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Emtricitibine</td>
<td>X</td>
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<tr>
<td>Adefovir</td>
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<tr>
<td>Entecavir</td>
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<td>X</td>
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<tr>
<td>Telbivudine</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>PegIFN</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Conserved Pol Domains
HIV and HBV

Bartholomeusz et al., Antiviral Therapy, 2004
Sequential therapy for HBV has the potential to lead to widespread multidrug resistance with clinical and public health consequences.

Under certain conditions, all NA HBV agents MAY inhibit HIV replication and permit selection of HIV drug resistant populations.
All patients with HIV should be screened for HBV and evaluated for treatment candidacy

Treatment goal is complete suppression of HBV viral replication

To prevent development widespread multidrug resistance, two agents with non-overlapping HBV resistance profiles should be considered whenever possible

In patients with existing drug resistance, addition of a new agent with a different resistance profile rather than sequential therapy is preferred

Careful evaluation of ART in the setting of HBV is indicated in both initial and subsequent patient encounters

In most circumstances, the decision to treat HBV should be linked with the decision to treat HIV
...and miles to go before we sleep.

paraphrased from Robert Frost- 1923