Management of Hepatitis B & C in Resource Limited Settings

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Presented at the 6th International Workshop on HIV & Hepatitis Co-infection, 31 May – 2 June 2010, Tel Aviv, Israel
Outline

• How prevalent is HBV and HCV in RLS?
• Why is it important to treat HBV and HCV in RLS?
• What current management modalities?
• In RLS, does HBV impact HIV disease or early response to HAART?
• Conclusions

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HIV prevalence: UNAIDS 2006

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HIV-HBV co-infection affects 4 million people

90% (36 million) of HIV-infected persons have HBV marker
One in six HIV-infected persons in developing countries has CH-B

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HBV Epidemiology

- 300–400 million infected worldwide
- HIV 5–30+% depending upon cohort, country
- Africa
  - Uganda 73% (n=64)
  - Tanzania 9% (n=66), Malawi 16.9% (n=279)
- Nigeria
  - HIV pop 16.7% (Jos, Nigeria)
  - Gen pop/blood donors 9.7%, 21%, 25%, 10% (Jos),
  - HIV prevalence 4.6% (3 million individuals)
- Thailand
  - HIV pop 8.7%
  - Gen pop 3%

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HIV negatively affects natural history of chronic hepatitis B

- Increased risk of CH-B (up to 6x ↑)
- ↓HBeAg clearance
- ↑ HBV DNA
- Loss of anti-HBs+
- ↑HCC with ↓CD4 count
- Increased cirrhosis/liver mortality
  - ALT not higher

5293 men (326 CH-B) followed 10.5 years

Thio et al, Lancet 2002

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Goals of Hepatitis B Treatment

- Prevention of long-term negative clinical outcomes (e.g., cirrhosis, HCC, death) by durable suppression of HBV DNA
- Primary treatment endpoint
  - Sustained decrease in serum HBV DNA level to low or undetectable
- Secondary treatment endpoints (RLS)
  - Decrease or normalize serum ALT
  - Improve liver histology
  - Induce HBeAg loss or seroconversion
  - Induce HBsAg loss or seroconversion

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## Approach to HBV treatment in HIV-infected patient

<table>
<thead>
<tr>
<th>Virus needing treatment</th>
<th>Considerations</th>
<th>Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>PEG-IFN or adefovir or early HAART</td>
<td>LMV/FTC/TDF/ETV without anti-HIV regimen</td>
</tr>
<tr>
<td>HIV or HIV/HBV</td>
<td>TDF+ FTC/LMV ETV with full HAART</td>
<td>LMV/FTC/TDF/ETV without anti-HIV regimen</td>
</tr>
<tr>
<td>Naive</td>
<td>TDF+ FTC/LMV ETV with full HAART</td>
<td>LMV/FTC/TDF/ETV without anti-HIV regimen</td>
</tr>
<tr>
<td>Prior LMV</td>
<td>TDF + FTC/LMV TDF+ ETV with HAART</td>
<td>LMV/FTC/TDF/ETV without anti-HIV regimen</td>
</tr>
</tbody>
</table>

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Management of co-infected patients in RLS – What is different?

• Need for modification of recommendations to account for limited availability of anti-HBV agents and diagnostics

• Of the 7 agents used for treatment in High income countries:
  – 3TC widely available
  – TDF & Adefovir limited availability
  – TDF increasingly more available because of expanding ART programs

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Management of HBV mono and HIV co-infected patients in RLS

- **PHC/Clinic 1st**: HBsAg and Liver enzymes before initiation of HAART

- **District level -2nd**: Assessmt for liver disease and complications. Routine monitoring of Liver enzymes once or twice during the first 6 months & when CD4 or HIV RNA is assayed

- Presence of HBeAg & repeatedly elevated enzymes suggests active disease and need for anti-HBV therapy (District/regional centres)

- Detection of HBV DNA is helpful but this is unlikely to be available – Regional centres

- Presence of HBeAg adds further weight (May also not be available in many programs)

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New WHO ART guidelines (2009)

‘Everyone with hepatitis B virus (HBV) co-infection that needs treatment, should start treatment with a regimen based on tenofovir and either 3TC or FTC, regardless of CD4 T-cell count’
TDF/LMV or FTC efficacious as HBV therapy in HIV-HBV co-infection in Thailand

- 36 HIV/HBV Thai subjects in RCT
- No difference in HBV DNA decline or HBeAg SC at 48 wks
- Drug-resistant HBV in 2 subjects in LMV group

Matthews et al, Hepatol 2008

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Maintainance therapy

- Unless HBeAg seroconversion occurs, once 3TC or TDF started as part of HAART, continue indefinitely

- If co-infected patients switched to 2nd line HAART, discontinue anti-HBV only if HBeAg seroconversion for 6 mths

- Premature discontinuation may lead to acute hepatitis (17%); also caused by 3TC resistance
Lamivudine-Resistance develops more rapidly in HIV-coinfection

- Emergence of resistance is clinically evident with elevation in ALT/AST
- In US, 90% of coinfected persons with h/o LAM use

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Monitoring HBV on therapy

• On therapy:
  – Serum ALT- check every 6 months
  – HBV DNA- every 6 months

• Off therapy
  – Monitor HBV DNA and ALT with change in HIV status

• HCC: monitor with imaging, α-feto protein or Lx Biopsy
  – cirrhotics
  – API: > 40y or family history

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Hepatitis B Virus Co-infection Impacts Baseline HIV Parameters and HAART-related Hepatotoxicity Risk in an HIV-infected Nigerian Cohort.

- John Idoko¹, Seema Meloni², Mohammed Muazu¹, Claudia Hawkins³, Bitrus Bidang¹, Nimzing Gwamzi¹, Phyllis Kanki², Robert Murphy³. Ernest Ekong⁴, Chloe Thio⁵

¹Jos University Teaching Hospital, Plateau State, Nigeria, ²Harvard School of Public Health, Boston, MA, USA, ³Northwestern University, Chicago, IL, USA, ⁴Military Reference Hospital, Lagos, Nigeria, ⁵Johns Hopkins Medical Institutions, Baltimore, MD, USA.

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HBV Co-infection Impacts Baseline HIV Parameters and HAART-related Hepatotoxicity

- 1968 subjects tested
- 229 (16.7%) HBsAg+
- Compared to HIV monoinfection, the HBV/HIV group had:
  - Lower CD4: 99 vs 132 (p<0.0001)
  - Higher HIV RNA: 91529 vs 53278 (p<0.0001)
  - Less CD4 increase on HAART: 220 vs 247 (p=0.02)
  - Higher ALT: 42.9 vs 31.7 (p=0.01)
  - More hepatotoxicity: 4.3% vs 0.4% (p=0.007)
Table 2: HIV RNA <200 copies/ml at 3 and 6 months

<table>
<thead>
<tr>
<th></th>
<th>HIV/HBV</th>
<th>HIV/HBeAg+</th>
<th>HIV/HBeAg-</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months (%)</td>
<td>65</td>
<td>67</td>
<td>60</td>
<td>68</td>
</tr>
<tr>
<td>6 months (%)</td>
<td>74</td>
<td>76</td>
<td>75</td>
<td>76</td>
</tr>
</tbody>
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Figure 3: Median baseline CD4 cell count stratified by HIV and HBV status

![Bar graph showing median baseline CD4 cell count stratified by HIV and HBV status.]

Table 3: CD4 cell count at 6 months

<table>
<thead>
<tr>
<th></th>
<th>HIV/HBV</th>
<th>HIV</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (cells/mm³)</td>
<td>222</td>
<td>247</td>
<td>0.01</td>
</tr>
<tr>
<td>&gt;50 cell/mm³ (%)</td>
<td>75</td>
<td>73</td>
<td>NS</td>
</tr>
</tbody>
</table>

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Effect of HBV DNA Levels on HIV Infection and Response to ART in a HIV/HBV Co-infected Nigerian Cohort

John Idoko\textsuperscript{1}, Seema Meloni\textsuperscript{2}, Mohammed Muazu\textsuperscript{1}, Claudia Hawkins\textsuperscript{3}, Bitrus Bidang\textsuperscript{1}, Nimzing Gwamzi\textsuperscript{1}, Phyllis Kanki\textsuperscript{2}, Robert Murphy\textsuperscript{3}, Ernest Ekong\textsuperscript{4}, Chloe Thio\textsuperscript{5}

\textsuperscript{1}Jos University Teaching Hospital, Plateau State, Nigeria, \textsuperscript{2}Harvard School of Public Health, Boston, MA, USA, \textsuperscript{3}Northwestern University, Chicago, IL, USA, \textsuperscript{4}Military Reference Hospital, Lagos, Nigeria, \textsuperscript{5}Johns Hopkins Medical Institutions, Baltimore, MD, USA

Presented at the 6\textsuperscript{th} International Workshop on HIV & Hepatitis Co-infection, 31 May – 2 June 2010, Tel Aviv, Israel
HBV associated with lower CD4 count in HIV+ Nigerian PEPFAR cohort

<table>
<thead>
<tr>
<th></th>
<th>HBV DNA (IU/ml)</th>
<th>HBeAg status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;20,000</td>
<td>≥20,000</td>
</tr>
<tr>
<td>Median CD4+ T-cell count (cells/mL)</td>
<td>129</td>
<td>85</td>
</tr>
<tr>
<td>Median HIV RNA (log cp/mL)</td>
<td>4.99</td>
<td>4.97</td>
</tr>
<tr>
<td>Median ALT (IU/mL)</td>
<td>20</td>
<td>29</td>
</tr>
</tbody>
</table>

In multivariate analysis, high HBV DNA and HBeAg+ status independently associated with lower CD4 counts

Idoko et al, CID 2010

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HBeAg positive subjects have slower LMV-based HAART response

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio for HIV RNA ≤ 400 cp/ml at 24 weeks</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg neg</td>
<td>1.27</td>
<td>0.81-1.98</td>
<td>0.30</td>
</tr>
<tr>
<td>HBeAg pos</td>
<td>0.54</td>
<td>0.31-0.92</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline HIV RNA</td>
<td><em>per 1 log increase</em></td>
<td>0.66-0.91</td>
<td>0.002</td>
</tr>
</tbody>
</table>

By 48 weeks, no difference in HIV RNA suppression

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HIV/HCV Coinfection in RLS

- Dearth of data on HIV/HCV coinfection
- HIV accelerates HCV disease
- HCV infection influence on HIV
  - ARV-associated hepatotoxicity
  - Response to ARV therapy
  - Natural history of HIV disease
  - Extrahepatic manifestations

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HIV/HCV Infection in Jos Nigeria

- 1968 patients tested
- 271 (13.8%) HCV/HIV coinfected
  - Monoinfection (Nigeria-2%, 4.5%, 6%)
- HCV/HIV coinfected vs monoinfected patients had:
  - No difference in baseline HIV RNA or CD4
  - Older: 38 vs 34 yrs (p<0.0001)
  - Higher increase in ALT at 6 months: 41.5 vs 30.6 (p<0.003)
  - More hepatotoxicity: 2.0% vs 0.3% (P<0.05)


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Risk Factors for Progressive Fibrosis and Cirrhosis

- Longer duration of infection
- Alcohol excess (>50 gm/day)
- Persistently elevated ALT levels
- Age >40 years at time of infection
- Male gender
- Coinfections: HBV, HIV, Schistosomiasis
- High BMI, obesity
- Organ transplantation

Poynard T, Lancet 1997 349:825-32
Benhamou J, Hepatology 1999 30:1054-8
Kamal S, Hepatology 2006;43:771-779
Asselah T, Gut 2006, 55:123-130

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Treatment Goals

- **Viral eradication**
  - Sustained loss of HCV RNA in serum (6 mos post-Rx)

- **Prevention of disease progression**
  - Normalization of liver enzymes
  - Improved quality of life
  - Improved liver histology
  - Decreased cirrhosis
  - Decreased HCC
  - Improved survival

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HCV Treatment and Status of HIV Disease

• **Advanced and uncontrolled HIV Disease**
  – Little justification for HCV treatment

• **Stable HIV disease not requiring ARVs**
  – Candidate for HCV treatment with close monitoring
  – ACTG Study 5184

• **Stable HIV disease on ARVs**
  – Good candidate (particularly if CD4>200 cells/uL)
  – Increased toxicity with ZDV and ddl
  – Potential decreased HIV activity with ZDV, d4T

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Management of HCV HIV

- Diagnosis & clinical evaluation
- Is HCV active viral infection
- Monitoring
- Treatment
  - Pegylated interferon
  - Ribavirin
  - Alcohol, substance use, psychiatric illness
- Diagnosis of End stage liver disease
- Liver transplant (Not available)
- Palliative mgt – (cirrhosis, HCC)

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Conclusion

• In RLS, the high prevalence of HIV and HBV has given rise to high burden of co-infection

• Management of HBV, HCV and coinfection with HIV is handicapped by the availability of drugs and diagnostics

• Among HIV-infected Nigerian individuals, HBV coinfection, especially among those with high levels of HBV replication, was associated with lower CD4+ T cell counts at ART initiation

• Patients with HBeAg-positive status had a slower virological response to ART, compared with HBeAg negative patients.

• Further work is needed to understand the effects of HBV on CD4+ T cells and immune response to HAART

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