HIV/HBV co-infection
Les Liaisons Dangereuses

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Inatoa madoa doa yote!!

BEFORE

AFTER

OMO PROGRESS

1kg
Liver Related Mortality
in HIV Infected Patients in HAART Era

Liver Related Mortality (%)

Brescia, Italy¹
Boston, USA²
Madrid, Spain³
Germivic, France⁴

Prevalence of HBV: Global Estimates

HBsAg Prevalence
- High (≥8%)
- Intermediate (2% to 8%)
- Low (<2%)

<table>
<thead>
<tr>
<th>Country</th>
<th>HBsAG +ve, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taiwan</td>
<td>10.0–13.8</td>
</tr>
<tr>
<td>Vietnam</td>
<td>5.7–10.0</td>
</tr>
<tr>
<td>China</td>
<td>5.3–12.0</td>
</tr>
<tr>
<td>Africa</td>
<td>5.0–19.0</td>
</tr>
<tr>
<td>Philippines</td>
<td>5.0–16.0</td>
</tr>
<tr>
<td>Thailand</td>
<td>4.6–8.0</td>
</tr>
<tr>
<td>Japan</td>
<td>4.4–13.0</td>
</tr>
<tr>
<td>Indonesia</td>
<td>4.0</td>
</tr>
<tr>
<td>South Korea</td>
<td>2.6–5.1</td>
</tr>
<tr>
<td>India</td>
<td>2.4–4.7</td>
</tr>
<tr>
<td>Russia</td>
<td>1.4–8.0</td>
</tr>
<tr>
<td>US</td>
<td>0.2–0.5</td>
</tr>
</tbody>
</table>

HBV/HIV co-infection - Prevalence

Australia (anti-HBc)
MACS (HBsAg)
RFH (HBsAg)
N.Europe
C.Europe
S.Europe
E.Europe

EUROSIDA (HBsAg)
Global HIV/HBV

Thio, C. Hepatology 2009; 49(5): s138
AKUH - HIV and viral hep co-infection study
Reena Shah et al, AIDS 2008

- HIV POSITIVE CONSECUTIVE PATIENTS
- CONSENT OBTAINED
- QUESTIONNAIRE FILLED RE-RISKS
- BLOOD OBTAINED FOR FBC LFTs CD4 VL HBsAg HCV-ab

- HBsAg +ve : HBV VL, HBeAg
- HCV - Viral load
- Started on ARVs if required
Total Recruited - 378

- HIV ONLY 351 93%
- HIV/HBV 23 6%
- HIV/HCV 4 1%
HIV and hep B/C coinfection

Local scenario: 378 HIV-infected in- and outpatients

- 93% no coinfection
- 6% hep B
- 1% hep C
Patients with HIV/HBV Co-infection
HIV ONLY VERSUS HIV/HBV

- NO DIFFERENCE IN THE 2 GROUPS IN TERMS OF:
  - VIRAL LOAD P=0.25
  - CD4 COUNTS P=0.405
  - LFTS P=0.212
Comparing only HIV infection and HBV co-infection by the risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>only HIV</th>
<th>HBV co-infection</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Circumcision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>215 (61.43%)</td>
<td>13 (56.52%)</td>
<td>0.640</td>
</tr>
<tr>
<td>yes</td>
<td>135 (38.57%)</td>
<td>10 (43.48%)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary</td>
<td>31 (9.54%)</td>
<td>0 (0.00%)</td>
<td>0.343</td>
</tr>
<tr>
<td>secondary</td>
<td>105 (32.31%)</td>
<td>6 (31.58%)</td>
<td></td>
</tr>
<tr>
<td>tertiary</td>
<td>189 (58.15%)</td>
<td>13 (68.42%)</td>
<td></td>
</tr>
<tr>
<td>HepB_vaccination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>286 (81.71%)</td>
<td>23 (100.00%)</td>
<td><strong>0.024</strong></td>
</tr>
<tr>
<td>yes</td>
<td>64 (18.29%)</td>
<td>0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td>Transfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>293 (83.95%)</td>
<td>20 (86.96%)</td>
<td>0.703</td>
</tr>
<tr>
<td>Yes</td>
<td>56 (16.05%)</td>
<td>3 (13.04%)</td>
<td></td>
</tr>
</tbody>
</table>
HBsAg+ve  23

- HBeAg +ve  17% (4)
- HBeAg-ve  83% (19) (p = 0.0018)

- 70% of HBsAg patients used ARVs: 16
ARVs USED BY PATIENTS HIV/HBV CO INFECTION

- CBV/NVP: 4%
- CBV/STO: 40%
- TRU/STO: 26%
- Other: 30%
Clinical disease and HBV/HIV co-infection
HIV/HBV Co-infection: Increased risk of ESLD due to HBV

HBV Replication

Geographical distribution of HBV genotypes A to H

- North Europe & USA - A
- Mediterranean basin - D
- Africa E & D A
- Far East B & C

Rare types:
- F - Latin America
- G - France, USA
- H - Mexico, Latin America
Natural history of HBV infection - where does co-infection fit in?

- **Early Childhood**: > 95% Immune Tolerance
- **Immune Tolerance**
- **Inactive Carrier**
- **HCC**
- **HBeAg+ Chronic Hepatitis B**
- **Adulthood**: < 5%
  - HIV/HBV: Increased likelihood
  - HIV/HBV: Increased VL
  - Lower ALT
  - Increased Fibrosis

HBeAg- Chronic Hepatitis B

HIV/HBV: Reduced seroconversion

**HIV/HBV**
- Higher Viral loads

## Phases of chronic HBV

### Patient Populations in Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Marker</th>
<th>Immune Tolerant (Type 1)</th>
<th>Immune Active (Type 2)</th>
<th>Inactive HBsAg Carrier (Type 3)</th>
<th>HBeAg neg. CHB (Precore/Core Promoter Mutant) (Type 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HBeAg</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ALT</td>
<td>Normal</td>
<td>↑</td>
<td>Normal</td>
<td>↑</td>
</tr>
<tr>
<td>HBV DNA (IU/mL)</td>
<td>&gt; 2x10^4</td>
<td>&gt; 2x10^4</td>
<td>&lt; 2x10^2</td>
<td>&gt; 2x10^3</td>
</tr>
<tr>
<td>Inflammation on Histology</td>
<td>Normal/Mild</td>
<td>Active</td>
<td>Normal</td>
<td>Active</td>
</tr>
</tbody>
</table>
African Patients
RFH HIV/HBV cohort (n=79)

- 35% female
- Median age 42yrs
- More likely eAg -ve disease (OR 2.7 p=0.048)
- More likely advanced liver disease (F3/4) (OR 7.3 p=0.002)
- Similar HBV DNA levels (median = 5.74 x 10⁶ c/ml)
- Similar response to TDF+FTC (85% < 200 IU/l at max F/U)

Armenis et al, 5th International HIV/Hepatitis Workshop 2009
When do we need to Rx HBV?

• Everybody with detectable HBV DNA?

• Based on HBV DNA levels?

• Those with evidence of significant liver disease?
  - Based on abnormal ALTs?
  - Histological activity on a liver biopsy?
  - Other tests?
Level of HBV DNA (PCR-assays) at entry & progression to cirrhosis in a population-based cohort study

3582 HBsAg untreated asian carriers
mean follow-up 11 yrs > 365 patients newly diagnosed with cirrhosis

All Participants
(n = 3582)

HBeAg(-), Normal ALT
(n = 2923)

* Adjusted for age, sex, cigarette smoking, and alcohol consumption.

HBV-DNA viral load (> 10^4 cp/ml) strongest predictor of progression to cirrhosis independent of ALT and HBeAg status

Illoeje UH, Gastroenterology 2006; 130: 678-686
How do we stage liver disease in HIV/HBV co-infected patients?

• Liver enzyme testing (ALT/AST) - unreliable

• Liver biopsies - prohibitively expensive and need access to an experienced histopathologist

• 'Non-invasive' tests
  - Serum markers - combined to work out a probability index
  - Elastometry
Why not liver enzyme testing?

• Lower ALT/AST in HIV/HBV co-infected patients BUT more advanced hepatic fibrosis

• Possible explanations
  - Direct fibrogetic effect of HBV
  - HIV directly stimulates stallete cells
  - Systemic immune activation as a result of HIV - hepatic fibrosis
HIV infection increases stellate cell activation

Fold change qRT-PCR

mock  HIV IIIB  gp120

Tuyama et al. CROI Boston 2008

Collagen I  α-SMA (smooth muscle actin)
Immune activation and liver disease

Cirrhosis
HCV
Alcohol

Altered portal vein circulation

HIV -> GIT CD4+ T-cell depletion

Hepatic fibrosis
HSC activation

IL-1
TNF-α
IFN-α
IL-12

Microbial translocation

LPS

Immune activation

Mathurin et al., Hepatology 2000; 32:1008-1017; Paik et al., Hepatology 2003; 37:1043-1055; Balagopal et al., Gastroenterology 2008; 135:226-233..
Practical ‘non-invasive’ tests

- **Biochemical markers**
  - \( \text{APRI} = \frac{\text{AST}(/ULN)}{\text{PLATELET}(109/l)} \times 100 \)
  - \( \text{FIB-4} = (\text{age (yrs)}) \times \frac{\text{AST}(\text{IU/})}{\text{Platelets (109/l)}} \times \frac{\text{ALT} (\text{IU/l})}{\text{1/2}} \)
Elastography

The probe induces an elastic wave through the liver.

The velocity of the wave is evaluated in a location from 2.5 to 6.5 cm below the surface.

Exploded volume

2.5 cm

1 cm Ø

4 cm

Liver biopsy: 1/50,000 of the liver
FibroScan®: 1/500 of the liver
Elastography in HIV/HCV co-infected patients

Source: J Acquir Immune Defic Syndr © 2006 Lippincott Williams & Wilkins

JAIDS 2006; 41: 175-9
Treatment of HBV

• **AIMS**
  - Halt/slow progression to cirrhosis
  - Prevent HCC

• **END POINTS:**
  - Normalization of serum ALT
  - Negative or low HBV DNA level
  - Loss of HBeAg + - appearance of anti-HBe
  - Improvement in liver histology
  - Loss of HBsAg +/- appearance of HBsAb
What does Rx aim to achieve?

HBeAg- Chronic Hepatitis B

Immune Tolerance

Inactive Carrier
eAb+, sAg+ HBV DNA undetectable

HBeAg+ Chronic Hepatitis B

Viral Clearance
e-Ab seroconversion
S-Ab seronversion
Anti-HBV Therapies

Immune modulators

IFN-alpha
Pegylated-Interferon-alpha

Polymerase Inhibitors

Lamivudine
Adefovir
Entacavir
Telbivudine
Tenofovir
Emtricitabine
Treatment of HBV/HIV: key issues

- TDF/FTC works
- What choices if HAART is not indicated
- What is the impact of lamivudine 'monotherapy'
Similar (more potent) anti-HBV Activity of Tenofovir compared to Adefovir in Co-infected Patients

- ACTG A5127: HBV/HIV-1 co-infected pts
  - HBV DNA 100,000
  - Stable antiretroviral therapy; HIV-1 RNA 10,000
- Reduction in HBV DNA with tenofovir non-inferior to adefovir

**TDF+FTC - RFH experience over 4 years**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline (n=59)</th>
<th>4-8 months (n=55)</th>
<th>Maximal follow up (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median HBV DNA (copies/ml)</td>
<td>4.6 x 10^6</td>
<td>215</td>
<td>25</td>
</tr>
<tr>
<td>(copies/ml)</td>
<td>25-6.4 x 10^6</td>
<td>25-1.12 x 10^7</td>
<td>25- 8.9 x 10^5</td>
</tr>
<tr>
<td>IQR</td>
<td>25-6.4 x 10^6</td>
<td>25-1.12 x 10^7</td>
<td>25- 8.9 x 10^5</td>
</tr>
<tr>
<td>HBV DNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10^2</td>
<td>6 (10%)</td>
<td>25 (45%)</td>
<td>53 (78%)</td>
</tr>
<tr>
<td>10^2-10^3</td>
<td>10 (17%)</td>
<td>14 (25%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>10^3-10^4</td>
<td>7 (12%)</td>
<td>6 (11%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>10^4-10^5</td>
<td>0 (0%)</td>
<td>4 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>10^5-10^6</td>
<td>2 (3%)</td>
<td>3 (5%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>&gt;10^7</td>
<td>34 (58%)</td>
<td>3 (5%)</td>
<td>2 (3%)</td>
</tr>
</tbody>
</table>

Rodger et al. AP&T 2009 (in press)
Treatment Algorithm:
Patients with Compensated Liver Disease and No indication for HIV therapy (CD4 count > 350/µl)

- No treatment
- Monitor every 6–12 months
- Monitor ALT every 3-12 months
- Consider biopsy and treat if disease present***

HIV/HBV*

HBV DNA <2,000 IU/mL**

- No treatment
- Monitor every 6–12 months

HBV DNA ≥2,000 IU/mL

ALT Normal

- Monitor ALT every 3-12 months
- Consider biopsy and treat if disease present***

ALT Elevated

- PEG IFN**** (favorable response factors are: HBeAg+ - HBV Genotype A – elevated ALT and low HBV-DNA)
- Telbivudine (if HBV-DNA ist still detectable at week 24 add adefovir to minimize resistance development risk)
- Adefovir and telbivudine de novo therapy
- Early HAART initiation including Tenofovir+3TC/FTC

HBV DNA <2,000 IU/mL**

Response to Interferon-α in HIV-HBV coinfected patients

* Randomized trial
Can immune control really be restored and maintained in HIV+ patients?

Wursthorn K et al. Antiviral Therapy 2006;11:647-52.
Telbuvidine - ?anti-HIV activity

No *in vitro* activity against 8 wild-type HIV-1, 2 drug resistant HIV-1 isolates

E Low, *et al.* CROI 2009;P813a

C Avila, *et al.* CROI 2009;P813b
HIV/HBV Co-infection

CD4 >500 or No indication of HAART

- HBV Rx Indicated\(^b\)
  - a) PegIFN if Genotype A, high ALT, low HBV DNA
  - b) Early HAART including TDF + FTC/3TC\(^e\)

- No HBV Rx indicated\(^b\)
  - Monitor Closely

CD4 < 500 or Symptomatic HIV or Cirrhosis\(^a\)

- Lamivudine experienced
  - Add or substitute one NRTI with TDF\(^d\)

- Lamivudine Naive
  - HAART Including TDF+3TC or FTC\(^c\)
Incidence of HBV Resistance in Patients Treated with LAM in HBV infection vs HIV/HBV coinfection

Impact of lamivudine resistance on progression of liver disease

 Patients with severe fibrosis or cirrhosis

- Placebo (n = 215)
- YMDDm (n = 209) (49%)
- Wild-Type (n = 221)

Liaw, N Engl J Med. 2004
Envelope/Polymerase Mutations and Antigen/Antibody Binding Capacity in HBV/HIV Co-infected Subjects with LAM Resistance

TWO Important consequences

a) Vaccine escape HBV
b) Detection escape HBV

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Ag–Ab binding [IC$_{50}$ (µg/ml)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild type</td>
<td>Wild type</td>
</tr>
<tr>
<td>HBIG escape</td>
<td></td>
</tr>
<tr>
<td>sG145R</td>
<td>rtW153G</td>
</tr>
<tr>
<td>Anti-viral drug resistant</td>
<td></td>
</tr>
<tr>
<td>sE164D</td>
<td>rtV173L</td>
</tr>
<tr>
<td>sW196S</td>
<td>rtM204I</td>
</tr>
<tr>
<td>sI195M</td>
<td>rtM204V</td>
</tr>
<tr>
<td>sM198I</td>
<td>rtV207I</td>
</tr>
<tr>
<td>sE164D/I195M</td>
<td>rtV173/rtL180/rtM204V</td>
</tr>
</tbody>
</table>

Case Study

- Patient MN
- 40 years, nurse, HIV positive
- ARVs (CBV/stocrin) since 2002, adherent
- HIV VL<50 since 2003
- Admitted with hepatic failure to ICU
- Died within 24 hours despite supportive measures
Results:

- CD4 550, VL<50
- Hep A negative
- HBsAg +ve, HBV DNA >1,000,000 c/ml
- eAg negative
- Liver enzymes greater that 4 times normal
- INR 3
- Albumin 22
ARV Rollout
AZT/d4T+LAM+NNRTI
?Global Impact
Unequal Burden?
Even the best are only human..........................