HBV/HIV Co-infection in sub-Saharan Africa

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HIV/HBV Co-infection

Outline of Talk

• Epidemiology of HIV and HBV
• Impact of HIV/HBV Co-infection
  - HIV on HBV
  - HBV on HIV
• Management of HIV/HBV Co-infection
• Guidelines for initiation of HAART
Global HIV and HBV Prevalence

- Globally, up to 10% of HIV-infected individuals have HBV co-infection
  - 4-6 million HIV/HBV co-infected individuals
- HBV endemic countries up to 25% HIV/HBV co-infected

Epidemiology of HIV/HBV: sub-Saharan Africa

• 70% of global 36 million people with HIV live in sSA
  - Corresponding to regions of high HBV endemicity: 8.83% seroprevalence

HIV/HBV/HCV Mortality (annual death rate) (www.worldmapper.org in Nov 2012)

• **HIV/HBV co-infections tend to outnumber HIV/HCV co-infections**
  - Chronic HBV co-infection reported in up to 36% of all HIV-positive subjects
  - Highest rates in West and Southern African cohorts
  - Reflects present low prevalence of IDU in sSA

• **Liver-related mortality 2x higher in HBV/HIV than HCV/HIV co-infection**
Epidemiology of HIV/HBV: sub-Saharan Africa

Independent transmission and acquisition of HBV and HIV

- HBV generally acquired in childhood under age of 5 years
  - Prior to HIV acquisition
- HIV infection occurs later in life, primarily via sexual route

Series from West, East and South Africa

- Chronic HBV infection over-represented in HIV patients suggesting:
  - Shared risk factors
  - Co-transmission events

Epidemiology of HIV/HBV: sub-Saharan Africa

Shared transmission routes: HBV and HIV

- HIV and HBV may share transmission routes in infants and children
  - Mother-to-child transmission
  - Lack of resources for diagnosis and management of blood-borne viruses in pregnancy and peri-partum period
- Maternal HIV infection increases mother-to-child transmission of HBV (2.5 fold in one West African study) → HIV promoting HBV replication
- Blood/blood product transfusions
  - PEPFAR, Global fund & WHO blood safety programmes
    - HBsAg screening increased from 76 to 94%
    - Laboratory processes frequently not accredited, variable
- Unsafe injection/medical and traditional scarification practices
- Sexual co-acquisition

Impact of HIV/HBV Co-infection

HIV co-infection promotes increased HBV replication and rates of HBV reactivation

- Increased MTCT of HBV
- More aggressive natural history of chronic hepatitis B

HIV impacts Maternal HBV Transmission

HIV/HBV co-infection increases risk of perinatal transmission

- Maternal HIV infection increases HBV MTCT up to 2.5 fold
  - HIV/HBV co-infected mothers are 2x more likely to be HBeAg positive
    - HBV increases risk of HBeAg seroconversion
  - 3x more likely to be HBV DNA positive
- Higher HBV DNA levels

- Essential to screen mothers for HIV and HBsAg to prevent MTCT
  - Antiviral prophylaxis - 2 agents against HBV
  - Hepatitis B Birth dose vaccine and full HBV vaccine coverage

- HBV vaccination schedules in sSA: Majority
  - 6, 10 and 14 weeks: Most mothers HBeAg negative, low HBV DNA levels
  - No Hepatitis B Birth dose vaccine
  - Full HBV vaccine coverage only 75%
SA : Impact of HIV : Maternal Transmission

Western Cape, RSA (9 355 pregnant women from antenatal clinics comparing HIV-positive and negative women) Vaccine 2013;31(47):5579

• Low HBsAg prevalence region in RSA
  - HBsAg 3.4% (53/1 543 HIV pos) v. 2.9% (44/1 546 HIV neg)

• HBeAg: 18.9% (10/53 HIV pos) v. 17.1% (7/41 HIV neg)

• HBV DNA levels were much higher in HIV positive women
  - 9.72x 10^7 IU/ml v. 1.19 x 10^6 IU/ml

• One in six HBV-infected pregnant women, irrespective of HIV status is HBeAg seropositive

• Neonates remain unprotected for first 6 weeks of life in absence of Hepatitis B birth dose vaccine

  HBV MTCT increases if HBV DNA >200 000 IU/ml
SA : Impact of HIV : Maternal Transmission


- **Retrospective cross-sectional study:** July 2011 to December 2011
- 322 study samples from discarded residual dried blood spot samples following routine infant diagnosis of HIV

10% overall HBV seroprevalence in infants <18 months

- **HIV-positive infants:** 21/161 infants HBV positive: **13.0%**; 95% CI 6.8-19.9
- **HIV-negative infants:** 12/161 HBV positive: **7.5%**; 95% CI 2.5-13.7
- Difference not statistically significant

**Concern**

- High prevalence of HBV infection in children despite HBV vaccination
- Independent of HIV status
HIV impacts on HBV vaccination

Kwazulu-Natal, South Africa

- September to December 2014
- Screened for HBsAg, anti-HBs, anti-HBc
- 183 HIV infected vs. 108 HIV uninfected children bet 5-15 years
- HBsAg positive in 2.1% vs. 0% in HIV + vs. HIV negative children
- anti-HBs response to immunization: 15.8% (HIV+) vs 61.1% (HIV-)

HIV-infected children remain at risk of HBV infection

<table>
<thead>
<tr>
<th>TABLE I. Serologic Markers of Past and/or Ongoing Infection in the HIV-Infected and Uninfected Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected</td>
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<tr>
<td>5–10 years</td>
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<tr>
<td>Ongoing infection</td>
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<td>Past infection</td>
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<tr>
<th>TABLE II. Comparison of the Immunity Against HBV in the HIV-Infected and Uninfected Cohorts According to the Age Subgroup of the Patients</th>
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<tbody>
<tr>
<td>HIV-infected</td>
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<tr>
<td>5–10 years</td>
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<tr>
<td>Presence of anti-HBs</td>
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</table>
Impact of HIV/HBV Co-infection

HIV co-infection promotes a more aggressive natural history of hepatitis B infection

- ALF in acute HBV
- Increased rates of occult HBV
- *Chronicity of newly acquired HBV infections: 3-6x*
- *Progression to fibrosis and cirrhosis: 5x faster*
- *HCC: occurs at a younger age and is more aggressive*
- Increased risk of ART hepatotoxicity
- HAART-related immune reconstitution hepatitis

MACS: Mortality of HIV/HBV co-infection: pre-ART era

5293 MSM
- HBV: 326 (6%)
- HIV/HBV: 213 (65%)
- HIV: 2346/4967 (47%)

HIV/HBV
- 17-fold higher risk of liver death compared to HBV alone

MACS: Liver-related Mortality is higher from chronic HBV than from HCV

337 men with CH-B and 343 men with CH-C at study entry into MACS

- All-cause MR similar
- Liver-related MR significantly higher in CH-B (9.6 per 1000 PYs; 95% CI, 6.9–13.2) compared to CH-C (5.0 per 1000 PYs; 95% CI, 3.0–8.4)
  - Incidence rate ratio: 2.2; \( P = .03 \)

CD4 count <200 cells/mm\(^3\)

- 16.2 fold increase in risk of liver-related death compared to CD4 count >350 cells/mm\(^3\)
Liver disease remains 2nd leading cause of death in later HAART era in HIV-infected people

D:A:D study: 33,308 participants from 1999-2008

• 15.3% with HCV (Ab or RNA+)
• 11.5% HBV (prior/active HBV infection)

2482 deaths

• 29.9% (743) AIDS-related: 4.12/1000 PY
• 13.7% (341) Liver-related: 1.89/1000 PY
• 11.6% (289) CVD-related: 1.6/1000 PY
• 11.5% (286) Non-AIDS malignancy: 1.59/1000 PY

Overall mortality declined over time

• Diabetes Mellitus: Risk factor for all specific causes of death
• CD4 counts <100 cells /ml associated with higher risk of death from all specific causes of death

AIDS 2010;24: 1537
Factors associated with liver-related death: D:A:D study

Liver-related deaths declined over time

  - 8.30/1000 PY for those with latest CD4 count <50 cells/ml
  - 0.58/1000 PY if CD4 count >500 cells/ml

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted RR</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Age, per 5 years older</td>
<td>1.16</td>
<td>1.09-1.24</td>
</tr>
<tr>
<td>IDU (MSM reference)</td>
<td>5.02</td>
<td>3.56-7.08</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.34</td>
<td>1.83-2.99</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>2.37</td>
<td>1.68-3.35</td>
</tr>
<tr>
<td>HBV</td>
<td><strong>2.37</strong></td>
<td><strong>1.74-3.22</strong></td>
</tr>
<tr>
<td>HCV</td>
<td>1.67</td>
<td>1.21-2.31</td>
</tr>
<tr>
<td>CD4 count per 50 cell/uL increase</td>
<td>0.82</td>
<td>0.79-0.85</td>
</tr>
<tr>
<td>HIV RNA &gt;5 log copies/ml</td>
<td>1.68</td>
<td>1.01-2.80</td>
</tr>
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</table>
Liver fibrosis advanced in HIV-HBV co-infection with higher HBV DNA in Nigeria

- Cross sectional study of 232 HIV+ and 93 HIV-HBV patients in Nigeria
- Transient elastography prior to HAART

HBV DNA $\geq 3.3$ log IU/ml associated with advanced fibrosis $\geq 9.3$ kPa
- Adjusted OR 6.1; 95% CI 2-18.9 $P=.002$
- HBeAg status not associated: Adjusted OR 2.7; 95% CI .8-9.3 $P=.11$

Hawkins et al, CID 2013 57(12): e189-92
Impact of HIV/HBV Co-infection
Modified Histological Activity Index (Ishak)

Necro-inflammatory activity (n=64, ART naive)

HBV mono-infected (n=32)
median 4.0 [2 – 9]
mean 4.5 ± 2.0

HBV/HIV co-infected (n=32)
median 6.0 [2 – 15]
mean 7.6 ± 4.0

p = 0.0002

CD4 count (median/mm³)
105 [2 – 843]

Sonderup et al Hepatology November 2008
Impact of HIV/HBV Co-infection

Fibrosis (n=64, ART naive)

HBV mono-infected (n=32)
- median 1 [0 – 5]
- mean 1.6 ± 1.4

HBV/HIV co-infected (n=32)
- median 3 [1 – 6]
- mean 2.7 ± 1.2

p = 0.0044

CD4 count (median/mm³)
- 105 [2 – 843]

Sonderup et al Hepatology November 2008

- ESLD associated death: % total mortality
- ESLD associated death: % HBsAg +

HBV related mortality is decreasing with the increased availability of anti-retrovirals with anti-HBV activity

Impact of HBV on HIV: SMART Study

ART re-initiation and HBV Rebound among HIV/HBV-co-infected Patients following ART Interruption in the Strategies for the Management of ART

- HIV pos individuals with CD4 count >350 cells/µL randomised to drug conservation (interrupt ART until CD4 <250 cells/µL) vs viral suppression (continued use of ART)
- 120 HIV/HBV co-infected individuals

Frequent HBV DNA rebound following ART interruption with accelerated immune def

![Graph showing cumulative percent reintitated](image)

**Multivariate Model: Predictors of ART re-initiation**

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<thead>
<tr>
<th></th>
<th>Univariate</th>
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<th>Multivariate</th>
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<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>P-value</td>
<td>Hazard ratio</td>
<td>P-value</td>
</tr>
<tr>
<td>Non-HBV/HCV</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>1.95 (1.45–2.63)</td>
<td>&lt;0.0001</td>
<td>1.71 (1.27–2.31)</td>
<td>0.0005</td>
</tr>
<tr>
<td>HCV</td>
<td>1.01 (0.87–1.18)</td>
<td>0.87</td>
<td>1.04 (0.88–1.22)</td>
<td>0.66</td>
</tr>
<tr>
<td>Prior AIDS</td>
<td>2.17 (1.91–2.45)</td>
<td>&lt;0.0001</td>
<td>1.41 (1.24–1.61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nadir CD4 count (/100 cells lower)</td>
<td>1.67 (1.60–1.75)</td>
<td>&lt;0.0001</td>
<td>1.50 (1.42–1.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline CD4 count (/100 cells lower)</td>
<td>1.20 (1.16–1.23)</td>
<td>&lt;0.0001</td>
<td>1.14 (1.11–1.18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline HIV RNA ≤400 copies/ml</td>
<td>1.18 (1.04–1.34)</td>
<td>0.011</td>
<td>1.19 (1.04–1.37)</td>
<td>0.012</td>
</tr>
<tr>
<td>Highest HIV RNA (Log10)</td>
<td>1.34 (1.25–1.44)</td>
<td>&lt;0.0001</td>
<td>1.19 (1.11–1.28)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>0.97 (0.84–1.11)</td>
<td>0.61</td>
<td>1.01 (0.88–1.16)</td>
<td>0.89</td>
</tr>
<tr>
<td>Age (/10 years)</td>
<td>1.15 (1.08–1.22)</td>
<td>&lt;0.0001</td>
<td>1.13 (1.06–1.20)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Dore et al, AIDS 2010;24:857
Impact of HBV on HIV

2352 HIV seroconverters
- Resolved HB: 474 (20%); Isolated total HBcAb: 82 (3%) and Chronic HB: 64 (3%)

Unadjusted rates (95% confidence intervals [CIs]) of clinical AIDS/death
- HB-negative: 2.43 (2.15–2.71)
- Resolved HB: 3.27 (2.71–3.84)
- Isolated HBcAb: 3.75 (2.25–5.25)
- Chronic HB: 5.41 (3.41–7.42)

Multivariable risk of clinical AIDS/death significantly higher in chronic HB group compared to HB-negative group
- HR 1.80; 95% CI, 1.20–2.69

HRs were increased but non-significant
- Resolved HB (HR 1.17; 95% CI 0.94-1.46)
- Isolated HBcAb (HR 1.14; 95% CI 0.75–1.75).

Chun et al, JID 2010;205: 185
Management of HIV/HBV Co-infection

HBV screening and Vaccination

- All newly diagnosed HIV infected individuals screened for HBV
  - HBsAg and anti-HBs
- Non-immune (HBsAg and anti-HBs negative) - Vaccinate
- Lower response to vaccination especially with low CD4 counts
- Meta-analysis (Int J STD AIDS 2013;24(2);117): 4 double dose (40ug) vaccine schedule gives higher protective anti-HBs: 0, 1, 2 & 6 months

Hepatitis A Vaccination

- Should be considered in all HIV positive patients esp MSM

Screen for Hepatitis C

- Triple HIV/HBV/HCV: DAA interaction with ART

Management of HIV/HBV Co-infection

Aetiology of abnormal liver profile: often multifactorial

- Drug-induced liver injuries
  - HAART, TB drugs, Cotrimoxazole, Fluconazole, Traditional meds, Herbal/Alternative supplements

More aggressive natural history of HBV and possibility of co-morbidities

  Lower threshold for performing liver biopsy to assess
  Differential diagnosis and the stage and grade of histologic injury

  Fibroscan & APRI: Assessment of progressive fibrosis

- Reactivation after withdrawal of therapy

- Super-infection with HCV, HAV, HDV and HEV

- Co-morbidities - Non-alcoholic fatty liver disease, alcoholic liver disease
Initiation of HAART in HBV/HIV co-infection

Goals of therapy

• Virological suppression of both HBV and HIV replication

• Reduce both AIDS and Liver-related morbidity and mortality

Choice of ARV regimen in HBV/HIV co-infected patients

• HAART regimen containing 2 agents that are also active against HBV
  ✓ Reduces the risk of resistance

WHO recommendation

• Tenofovir + lamivudine/emtricitabine + efavirenz as FDC

WHO 2016 HIV Treatment Initiation Guidelines

Treat all people with HIV regardless of CD4 cell count

It is essential to initiate treatment in the following clinical situations:

- All HBV/HIV co-infected adults with a CD4 cell count <500 cells/mm³ regardless of the stage of liver disease
- Individuals with severe chronic liver disease regardless of CD4 count
  - At greatest risk of disease progression and mortality from liver disease
  - HAART initiation may improve overall survival in cirrhotics
- All pregnant or breastfeeding women regardless of CD4 count
- All children less than 5 years of age regardless of CD4 count

3TC Naive

- ART including TDF and 3TC or FTC

3TC Experienced

- Add or substitute one NRTI & continue TDF as part of ART

WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. 2016
HIV/HBV Co-infection: Treatment Options

- Treatment of HIV without the use of tenofovir in the regimen
  - May lead to flares of hepatitis B due to ART-associated IRIS

- Treatment discontinuation, especially lamivudine, associated with
  - HBV reactivation, ALT flares and hepatic decompensation

- If ARVs need to be changed because of HIV drug resistance/toxicity
  - Tenofovir and Lamivudine or Tenofovir/Emtricitabine should be continued together with the new ARV drugs
  - Tenofovir Alafenamide (TAF) in renal toxicity

HIV/HBV Co-infection: Treatment Monitoring

Monitoring on FDC

- Recommended annual renal function assessment
- Consider annual assessment of bone function
- **Consider risk of EFV DILI presenting post-partum in women with high CD4 count**
  - Immunoallergic hepatocellular injury ➔ submassive necrosis and deaths
HIV/HBV Co-infection: Treatment

Fixed drug combination (Tenofovir, Lamivudine/Emtricitabine and EFV)

HBeAg-positive patients after 5 years of treatment: High rates of:

- HBV DNA suppression (90%)
- HBeAg loss (46%)
- HBsAg loss (12%)
- No evidence of resistance
- Reduced progression to cirrhosis
- Risk of HCC persists, but is low - ongoing surveillance required

No significant difference in response rates compared with HBV mono-infection

Number of people receiving ART and percentage of all people living with HIV receiving ART in low- and middle-income countries overall and by WHO region, 2013

**TOTAL: 11.7 MILLION**

36% [34–38%]

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Country income classification by the World Bank at the time of the 2011 Political Declaration on HIV and AIDS.

Fig. 3.3. Number and percentage of pregnant women living with HIV who received ARV drugs in low- and middle-income countries globally and by WHO region, 2013

- **Total:** 966,000
  - 67% (62–73%)

- **African Region:** 23,000 (93% [51–95%])
- **Region of the Americas:** 19,000
- **South-East Asia Region:** 2,000 (26% [18–36%])
- **European Region:** 6,000 (56% [41–77%])
- **Eastern Mediterranean Region:** 16,000 (26% [19–31%])
- **Western Pacific Region:** 901,000 (58% [62–74%])

*Country income classification by the World Bank at the time of the 2011 Political Declaration on HIV and AIDS.*

*Coverage estimates for the WHO European region are not available due to inconsistencies between programme coverage and estimated PMTCT need.*

*Sources: Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS) and 2013 UNAIDS/WHO estimates.*
Uptake of preferred first-line treatment regimen is increasing:
- FDC: Tenofovir + Lamivudine/emtricitabine + Efavirenz

ARV procurement data: WHO Global Price Reporting Mechanism
- 62% of all ARV regimens used in second half of 2013 and first quarter of 2014 contained TDF

Source: results of WHO ARV surveys from 2005 to 2013.
Protective effect of HBV-active ART against primary HBV-infection?

Does HBV-active ART protect against new HBV infection (HBV-PrEP)?

- All HBV-susceptible patients at entry: anti-HBc and anti-HBs neg (<10 IU/L)
- 2nd sample available in time for follow-up HBV serology
- n= 2,924 and MSM: n=2,280
- HBV susceptible & 2 samples available n=349

New HBV Cases (N=35)

- 1 case: woman (HBsAg negative)
- 1 case: heterosexual man (HBsAg negative)
- 33 cases MSM

- Hepatitis (ALT 2x) 7 (20.0%)
- HBsAg + 6 (17.1%)
- HBeAg + 6 (17.1%)
Kaplan Meier: HBV-free survival (MSM)

Log-rank
P = 0.004
P < 0.001

Numbers in Observation
No Treatment 107
Treatment, No TDF 86
Treatment, with TDF 189

Numbers in Observation Time (Days)
0 50 19 8
2000 67 36 16
4000 49 38 12
6000

Brinkman K, et al. 20th CROI; Atlanta, GA; 2013
Conclusions : HIV/HBV Co-infection

• sSA is the epicentre of HIV and HBV is endemic
  ✓ Increased risk of HIV/HBV co-infection

• HIV promotes HBV MTCT and promotes a more aggressive natural history of chronic hepatitis B

• WHO recommended FDC (Tenofovir, Lamivudine/Emtricitabine & EFV)
  ✓ Simplifies management of HIV/HBV co-infection regardless of immunological, virological or histological considerations
  ✓ Improves All-cause and Liver-related mortality in HBV/HIV co-infection

• Second line ART for HIV resistance
  ✓ Continue Tenofovir, Lamivudine/Emtricitabine to prevent HBV reactivation, ALT flares and potential hepatic decompensation

• HAART improves overall survival even in cirrhotics

HBV IS VACCINE PREVENTABLE
Health Disparities: sub-Saharan Africa

Burden of liver disease in sub-Saharan Africa is substantial

Challenges

• Lack of data to accurately establish disease prevalence
• Lack of access to health facilities - diagnostic and interventional
• Access and cost of medications

Apply similar programmes to HIV/AIDS to combat liver Disease in sSA
- PEPFAR
- Global Fund to Fight AIDS, TB and Malaria
→ brought medication at affordable prices to sSA