Hepatitis B in Africa: Epidemiology, Pathophysiology and Challenges

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Outline

• Introduction

• Preamble

• Transmission pattern for HBV in Uganda
  ❖ Sexual
  ❖ Needle stick/sharing sharps
  ❖ Blood transfusion

• Natural history of HBV infection

• The consequences of infection

• Elimination challenges

• Summary
Preamble Sub Saharan Africa (SSA)

- SSA comprises 48 LMIC
- Total population 936.1 million
- GDP is 1.6 trillion US dollars, Health expenditure 6.5% of GDP
- Has 3% of global healthcare workforce
- >50% of liver related mortality associated with HBV or HCV

World Bank 2015
Globally

- Global health problem
- Worldwide 2 billion exposed to hepatitis B
  - 240 million have current infection
- 10th leading cause of death
  - (1 million annually)
  - From liver cancer, liver cirrhosis or liver failure

Uganda: 10% chronic infection, overall exposure- 52.3%

Population with exposure and infection

Transmission of HBV Is Proportional to HBV DNA Level

Horizontal Transmission
Higher DNA, higher risk

- Contaminated needles
- Sexual
- Healthcare worker
- Transfusion
- Hemodialysis

Vertical Transmission

Mother
> $10^{6-8}$ IU/mL

Infant

*Perinatal*

Common in regions with HBsAg prevalence of > 2%

No clear risk factors in 20% to 30% of patients

Sexual transmission does occur

- 438 participants of RHSP
- 14% HIV infected
- 181 (41%) exposed to HBV (HBcAb pos)
- 21 (5%) HBsAg pos

Lara et al; 2011; J Med Virol;83:796-800
Increasing exposure with age

Lara et al; 2011; J Med Virol;83:796-800
So....

- Risk of transmission increased with increasing age and number of sexual partners as well as HIV and syphilis

- Sexual transmission does occur

Lara et al; 2011; J Med Virol; 83:796-800
Sharps and sexual transmission possible

- 182 medical students screened for HBsAg and HBcAb
- Students from preclinical (yr 1&2) and clinical years (yr 3-5) in 2001 included
- Overall: 11% HBsAg+, 65.9% HBcAb+
- No stat difference in HBsAg in the 2 groups
- Exposure rose sharply from preclinical to clinical

Pido et al, 2005; Afr Health Sci;5:93-98
Exposure versus infection

Pido et al, 2005; Afr Health Sci;5:93-98
Risk factors for exposure and infection

- Sexual relationship
- Accidental needle-stick injuries
Safety of Donor blood in Uganda

• Donor blood screened for HBsAg, Anti-HCV, anti-HIV and syphilis

• Blood should there be safe from transfusion related infections

• Effect of occult Hepatitis B not known
Occult HBV infection

• Defined as detectable HBV virus in person HBsAg-

• Usually HBcAb +
Occult HBV (OBI) exists in patients in Mulago

- 314 sera from patients admitted in the emergency room
- Tested for HBsAg, HBcAb, HBV DNA and mutations in those with OBI
- HBsAg+ 8%
- HBsAg-/HBVDNA detected (OBI) in 94 (30%)
- Patients HBsAg+ significantly higher median VL of 3344 IU/mL
- Median viral load of OBI was 837 IU/mL
- 19/94 (20%) OBI had viral loads >10,000 IU/mL
- Surface-gene mutations were present in 48% of patients with OBI

Implication

With current testing methods at the UBTS it is possible HBV is being transmitted via blood transfusion

Natural history

Exposure

Resolve (immune):
- Age
- Immunity

Persist (Chronic):
- Age
- Immunity
Age-dependent risk of becoming a carrier of HBV

% of patients who become chronic carriers

- Birth
- 1-6 Months
- 7-12 Months
- 1-4 Years
- Adults

Age at HBV infection

WHO HBV treatment guideline 2015
Natural Progression of CHB

15%–40% of CHB patients may experience disease progression.

10%–15% in 5 yr

30% Cirrhosis

5%–10%

Liver Cancer

23% in 5 yr

Liver Failure

30%

Chronic Infection

Liver Transplantation

Death

Acute flare

Hepatocellular Carcinoma in Africa
Primary Liver Cancer Incidence and Mortality

Number of New Cases and Deaths in Thousands, Worldwide, 1985

NEW CASES
- Males: 214
- Females: 101

DEATHS
- Males: 212
- Females: 100

Int J Cancer, 1993; 55: 891-903
HBV induces HCC in the young

- African Liver Cancer Consortium

- Data from 14 centers across Africa
  - Nigeria-6 (n=387)
  - Ghana-3 (n=560)
  - Uganda-1 (n=98)
  - Malawi-1 (n=227)
  - Ivory coast-1 (n=152)
  - Sudan-1 (n=108)
  - Tanzania-1 (n=20)

- Total 1552 analyzed

Yang JD et al, 2015; Am J Gastroenterol
HCC in HBV occur at young age

• Median age 45 (35–57), 72% patients were male

• 766 (49%) had HBV, 74 (5%) HCV, 18 (1%) had HCC from HBV/HCV, 694 (45%) other/unknown etiologies

• The median age (IQR; Range) in HBV, HCV, HBV/HCV, and other/unknown etiologies were 42 (34–55), 55 (46–65; 18–80), 43 (32–54; 22–95), and 47 (35–60; 8–86), respectively (P <0.001)

• The most frequent age range at HCC diagnosis was 32.5–37.5 years for HBV

Yang JD et al, 2015; Am J Gastroenterol
Clinical Characteristics, Management and Outcomes of Patients with Hepatocellular Carcinoma in Africa: A Multi-Country Observational Study from the Africa Liver Cancer Consortium

Yang JD et al, 2017, Lancet Gastro hepatol
Method

• Clinical information was abstracted on consecutive HCC patients diagnosed between August 2006 and April 2016

• The Cox proportional Hazards model was used to identify factors affecting survival.

Yang JD et al, 2017, Lancet Gastro hepatol
Methods

• 2,566 HCC patients at 21 tertiary referral centers in 9 African countries
  • Egypt -2
  • Ghana -4
  • Nigeria -9
  • Ivory Coast, Cameroon, Sudan, Ethiopia, Tanzania, Uganda -1

Yang JD et al, 2017, Lancet Gastro hepatol
## Baseline information

<table>
<thead>
<tr>
<th></th>
<th>Egypt (N=1,251)</th>
<th>Other African Countries (N=1,315)</th>
<th>Total (N=2,566)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>58 (8)</td>
<td>47 (15)</td>
<td>52 (13)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>972 (77%)</td>
<td>905 (69%)</td>
<td>1877 (73%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Liver cirrhosis</strong></td>
<td>1247 (99.7%)</td>
<td>601 (66%)</td>
<td>1848 (86%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HBV</td>
<td>16 (1%)</td>
<td>597 (45%)</td>
<td>613 (24%)</td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>1054 (84%)</td>
<td>63 (5%)</td>
<td>1117 (43%)</td>
<td></td>
</tr>
<tr>
<td>HBV/HCV co-infection</td>
<td>29 (2%)</td>
<td>35 (3%)</td>
<td>64 (2%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>0 (0%)</td>
<td>196 (15%)</td>
<td>196 (8%)</td>
<td></td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>152 (12%)</td>
<td>424 (32%)</td>
<td>576 (22%)</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFP, median [IQR]</td>
<td>47 [10-359]</td>
<td>139 [6.5-1011]</td>
<td>58 [10-520]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Tumor characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multinodular tumor</td>
<td>575 (46%)</td>
<td>566 (84%)</td>
<td>1141 (59%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Size of largest tumor (cm)</td>
<td>5 +/- 3</td>
<td>8 +/- 4</td>
<td>6 4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Ascites</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>None</td>
<td>925 (74%)</td>
<td>290 (33%)</td>
<td>1215 (57%)</td>
<td></td>
</tr>
<tr>
<td>Mild-Moderate</td>
<td>313 (25%)</td>
<td>493 (56%)</td>
<td>809 (38%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>9 (1%)</td>
<td>92 (11%)</td>
<td>101 (5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatic encephalopathy</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>None</td>
<td>1201 (96%)</td>
<td>642 (76%)</td>
<td>1843 (88%)</td>
<td></td>
</tr>
<tr>
<td>Mild-Moderate</td>
<td>39 (3%)</td>
<td>171 (20%)</td>
<td>210 (10%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>11 (1%)</td>
<td>35 (4%)</td>
<td>46 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

Yang JD et al, 2017, Lancet Gastro hepatol
# Treatment of African HCC patients

<table>
<thead>
<tr>
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<th>Egypt (N=1,251)</th>
<th>Other Countries (N=1,315)</th>
<th>Total (N=2,566)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment</td>
<td>956 (76%)</td>
<td>43 (3%)</td>
<td>999 (39%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Curative treatment</td>
<td>442 (35%)</td>
<td>8 (0.6%)</td>
<td>450 (18%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Transplant</td>
<td>10 (0.8%)</td>
<td>0 (0%)</td>
<td>10 (0.5%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Resection</td>
<td>26 (2%)</td>
<td>8 (0.6%)</td>
<td>34 (1%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Local ablation</td>
<td>406 (32%)</td>
<td>1 (0.1%)*</td>
<td>407 (16%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TACE</td>
<td>567 (45%)</td>
<td>5 (0.4%)</td>
<td>572 (22%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>65 (5%)</td>
<td>13 (1%)</td>
<td>78 (3%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Other systemic treatment</td>
<td>0 (0%)</td>
<td>20 (2%)</td>
<td>20 (0.8%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Yang JD et al, 2017, Lancet Gastro hepatol
Survival data

- Follow up and survival information were available for 48% of HCC patients in Egypt and 44% of patients in Other African Countries.

- Median survival was longer in Egypt than in Other African Countries (10.9 vs. 2.5 months; $P<0.01$).

Yang JD et al, 2017, Lancet Gastro hepatol
Study conclusion

• HBV leading cause of HCC in African countries except Egypt

• HCC develops at a younger age group

• Occurs at advanced age

• Survival is dismal

Yang JD et al, 2017, Lancet Gastro hepatol
Vision: “A world where viral hepatitis transmission is halted and everyone living with viral hepatitis has access to safe, affordable and effective prevention, care and treatment services”

Goal: Eliminate viral hepatitis as a major public health threat by 2030.

Elimination:
- Cut new cases by 90%
- Cut numbers of people dying from hepatitis by 65%
## WHO Hepatitis global coverage targets

<table>
<thead>
<tr>
<th>Intervention</th>
<th>2030</th>
<th>2020</th>
<th>Baseline 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. HBV vaccination</td>
<td>90%</td>
<td>90%</td>
<td>82%</td>
</tr>
<tr>
<td>2. HBV birthdose</td>
<td>90%</td>
<td>50%</td>
<td>38%</td>
</tr>
<tr>
<td>3. Safe injection</td>
<td>90%</td>
<td>50%</td>
<td>5%</td>
</tr>
<tr>
<td>4. Harm reduction</td>
<td>300</td>
<td>200</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>(75% coverage)</td>
<td>(50% coverage)</td>
<td></td>
</tr>
<tr>
<td>5. HBV Treatment</td>
<td>80%</td>
<td></td>
<td>&lt;1%</td>
</tr>
<tr>
<td>6. HCV Treatment</td>
<td>80%</td>
<td>8 million treated</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5m HBV, 3m HCV)</td>
<td></td>
</tr>
</tbody>
</table>

www.who.int
Elimination in SSA possible but several barriers exist

• Non-existent PMTCT
• No 3rd trimester antiviral prophylaxis when required
• No BD in most countries and inadequate coverage of vaccination schedules
• Poor diagnostics and linkage to care
• Inadequate blood safety programs
• Inadequate implementation of standard precautions for infection control, unsafe injection and harm reduction practices
Barriers to elimination in SSA

• Social stigma associated with viral hepatitis

• In some countries limited political will to support these programs
Three-dose hepatitis B vaccine coverage: Major progress, but AFR, EMR and EUR < 85%

Source: WHO UNICEF joint reporting form
Hepatitis B birth dose coverage lowest in African Region

Source: WHO UNICEF joint reporting form
Treatment: Who to treat

- Evidence of compensated or decompensated cirrhosis (Physical or APRI score >2 in adults)
  - Regardless of ALT levels, HBeAg status or VL levels
- >30 years with PAALT levels, VL >20,000 IU/mL
  - Even without evidence of cirrhosis
- HIV/HBV co-infected patients
Medications for CHB

- Recommended drugs: TDF and Entecavir

- Entecavir for children aged 2–11 years
  - Lamivudine, adefovir or telbivudine not recommended due to resistance

- In HBV/HIV-coinfection, adolescents and children aged 3 years or older, tenofovir + lamivudine (or emtricitabine) + efavirenz

- Interferon for highly selected patients

WHO HBV guideline 2015
Summary of HBV in Africa

- Chronic HBV is of a profound public health importance
- Frequent co-infection with HIV
  - Accelerates progression to cirrhosis and HCC
- Poor screening and management strategies
Summary

• Accurate epidemiological data on liver-related mortality in sub-Saharan Africa are lacking
• Multiple fronts should be adopted to fight HBV
• Increase HBV vaccination
  - Introduce birth dose
• Stop transfusion related transmission
  - For every 1000 units transfused in sub-Saharan Africa, 4.3 transmit HBV and 2.5 transmit HCV
• Stop reuse of needles in healthcare settings
  - WHO report from 2000 estimated that between 13 and 23% of needles in healthcare settings in sub-Saharan Africa were reused

WHO HBV guideline 2015
Summary

• HIV programmes should perform universal screening for HBsAg
  - Co-infected patients offered TDF based ART

• TDF monotherapy should be made available for mono-infected patients

• Massive testing for HBV should be introduced

• Sensitization of health care workers and general population should be done
Thank You