Epidemiology of Hepatitis Virus Infections in sub-Saharan Africa

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Hepatocellular Carcinoma (HCC)

• One million deaths each year, 5th most prevalent cancer worldwide and the 1st in West African males

• Hepatitis infection affects about 565 million people
  – 375 million Hepatitis B Virus (HBV)
  – 175 million Hepatitis C (HCV)
  – 15 million Hepatitis Delta (HDV)

• These viruses cause globally
  – 57% of Cirrhosis
  – 78% of Hepatocellular Carcinoma (HCC)
Global HBV prevalence rates

HBsAg Prevalence
- ≥8% = High
- 2-7% = Intermediate
- < 2% = Low
HBV Virus Particle

- HBV DNA
- Core
- Polymerase
- M-HBsAg
- S-HBsAg
- L-HBsAg
# HBV Serological Tests

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>aHBC T</th>
<th>aHBC (IgM)</th>
<th>HBeAg</th>
<th>aHBe</th>
<th>aHBs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uninfected</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Vaccinated</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Acute HBV</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Active / recovering</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Recovered</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>CHB (Rep.)</strong></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>CHB (non-Rep.)</strong></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Natural History of HBV Infection

Hepatitis B

- Immunotolerance phase
- Immunoactive phase
- Low-replicative phase
- Reactivation phase

ALT and viremia levels

HBV DNA

ALT

Time after neonatal infection (years)

0 20 30 40 50 60
Viral Load, HBeAg and risk of HCC

Likelihood of individuals with detectable HBV VL to develop HCC is 3.9 times higher than those with undetectable VL.

Yang et al 2002
## HBV Genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Geographic Area</th>
<th>Mode Transmission</th>
<th>% chronic infection</th>
<th>Median age HBe conversion</th>
<th>% Viral Load copies/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>W Europe, N America, S Africa</td>
<td>Sexual, IVDU</td>
<td>&lt;1</td>
<td>20</td>
<td>40.3 x 10E4</td>
</tr>
<tr>
<td>B</td>
<td>Asia</td>
<td>Vertical</td>
<td>1-12</td>
<td>40</td>
<td>64.3 x 10E4</td>
</tr>
<tr>
<td>C</td>
<td>Asia</td>
<td>Vertical</td>
<td>1-10</td>
<td>30</td>
<td>64.3 x 10E4</td>
</tr>
<tr>
<td>D</td>
<td>India, Middle East</td>
<td>Vertical, Sexual, Nosocomial</td>
<td>&lt;1-5</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Africa</td>
<td>Horizontal, Nosocomial</td>
<td>3-25</td>
<td>&lt;10</td>
<td>27.5 x 10E4</td>
</tr>
<tr>
<td>F</td>
<td>S America</td>
<td>Sexual, Vertical</td>
<td>1</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>
HBV Vaccine coverage

Jemal, A Cancer 2012
Horizontal Transmission in sSA

- **Prevalence pre-vaccine era**
  - <6 mo: 0-3%
  - School age: 15-35%

- Risk of the youngest child being HBsAg-positive was strongly associated with the number of HBsAg-positive elder siblings

90% - Horizontal Transmission

*Whittle et al, 1983*
In 1984, HBV prevalence was 48% (302/620) in Keneba and 80% in Manduar.

HBV transmission was largely horizontal (90%). *Whittle et al 1983*. *LANCET*
Efficacy against infection was 80% (76% to 84%). This was significantly lower in the oldest age group (65%, 56 to 73).

Whittle et al 2002. BMJ
Legacy of CHB Infections

- Despite an effective preventable vaccine, the prevalence rate in Gambia and Senegal are about 15%, with age-specific prevalence as high as 20% in 10- to 20-year olds.

- Liver Cancer is the most common in Gambian men and the 2nd in Gambian women

## Tenofovir

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>£3,094</td>
</tr>
<tr>
<td>Global Fund Generic</td>
<td>£58</td>
</tr>
</tbody>
</table>

Tenofovir was approved by the FDA in October 2001 for the treatment of HIV and in **August 2008 for the treatment of HBV**.
PRevention Of Liver Fibrosis and Cancer in Africa

WATCH Study
West African Treatment Cohort for Hepatitis B

HC4 Study
HCC Case Control study
Randomisation of Rural and Urban areas
Community Based Screening

SENSITIZATION
♀, ♂
Age > 30 years

SCREENING

Questionnaires
Virological tests
Serology
Liver Function Test
Biochemistry
Hematology

HBV Negative (-) clinic
HBV Positive (+) clinic

Treatment
5 years follow-up

Fibroscan
Ultrasound
Liver Biopsy (%)

HIV+ HCV+ Renal Failure
POC Validation – 16th ICID & 49th EASL

PERFORMANCES OF TWO RAPID TESTS OF HEPATITIS B VIRUS (HBV) INFECTION IN THE RURAL COMMUNITIES OF THE GAMBIA.

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1 Medical Research Council (MRC), The Gambia Unit, Atlantic Road, P O Box 273, Fajara, The Gambia. 2 International Agency for Research on Cancer (IARC), 150, Cours Albert Thomas, Lyon, France. 3 National Public Health Laboratory (NPFL), Kotu, Banjul, The Gambia.
WATCH Cohort

Community Based Screening from 12-2011 – 01-2014

5,980 (74%) (Eligible Population 8,170)

8.3% Prevalence (n=507)

410 HBV+

301 HBV-
Trend in HBV prevalence

Rural and Urban EA’s in The Gambia

Percentage prevalence (%)

- 18.2%
- 16.4%
- 8.3%
qPCR Assay – Important tool!

• **Purpose:**
  – To determine baseline viral load in treatment cohort
  – Monitor patients on HBV treatment
  – Assess the risk of HCC development in HBV infected patients
HBV Viral Load (log IU/ML)

Box plots of viral load by visit

1.55 log (IU/ML) after 3 months of treatment

P<0.001

H F Njai et al – 16th ICID & 49th EASL
COST - Screening Population for CHB

• Screening aims to identify asymptomatic carriers and offer early treatment to reduce the risk of cirrhosis and liver cancer

• Some screening strategies exist but feasibility & cost is often an issue limiting implementation
• Cost per person screened:
  – € 7.82

• Cost per HBV positive case detected:
  – €92.39

• Cost per person requiring treatment:
  • €1,848
PROLIFICA Milestones

- We have demonstrated the feasibility of conducting an HBV screening and treatment study, the 1st in Africa
- We have successfully implemented a key virological tool to monitor and manage HBV treatment
  - (cost £6 / sample)
- The Generic version of Tenefovir has showed effectiveness in reducing viral load
  - (cost £60 / yr)
- Legacy HBV infection is still a problem and we need to raise more awareness & implement screening programmes
Epidemiology of Hepatitis C infection in Sub Saharan Africa
HCV Virus Particle

envelope glycoproteins

core

viral RNA

envelope

approx 60 nm

Structure of Hepatitis C Virus
Hepatocellular Carcinoma (HCC)

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• Hepatitis infection affects about 565 million people
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  – 15 million Hepatitis Delta (HDV)

• These viruses cause globally
  – 57% of Cirrhosis
  – 78% of Hepatocellular Carcinoma (HCC)
• Acute hepatitis usually is asymptomatic and rarely leads to hepatic failure.

• 60–80% of infected people progress to chronic infection (Di Bisceglie, 2000).

• In industrialized countries HCV accounts for 20% cases of acute hepatitis
  • 70% cases of Chronic hepatitis,
  • 40% cases of end stage cirrhosis
  • 60% cases of hepatocellular carcinoma
  • 30% cases of liver transplant

Hepatitis C Virus Infection
Typical Serologic Course

Symptoms

anti-HCV

ALT

Titre

Normal

0 1 2 3 4 5 6 1 2 3 4

Month Years

Time after Exposure
SSA has the highest WHO estimated regional HCV prevalence: 5.3% = 32 million individuals
HIV: 23.5 million (UNAIDS 2012)

P: 3% Median prevalence: 2.2 to 13.8%
With large difference between three regions:
Central Africa: 6% (Cameroun +++13.8%)
East Africa and South Africa: 1.6%
West Africa: 2.4%

Prevalence in Central Africa

- Burundi: 11.3
- Cameroon: 13.8
- CAR: 2.4
- Chad: 4.8
- Congo: 5.5
- Dr Congo: 1.7
- Equitorial Guinea: 9.2
- Gabon: 4.1
- Rwanda: 2.8
- Sudan: 6.6
- Uganda: 6
- Central Africa Total: 6
- Blood Donors: 6
- High Risk Groups: 6
- Overall Prevalence: 25
Prevalence in West Africa

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benin</td>
<td>1.6</td>
</tr>
<tr>
<td>Burkina...</td>
<td>4.9</td>
</tr>
<tr>
<td>Gambia</td>
<td>3.3</td>
</tr>
<tr>
<td>Ghana</td>
<td>2.4</td>
</tr>
<tr>
<td>Guinea</td>
<td>1.7</td>
</tr>
<tr>
<td>Mauritania</td>
<td>1.1</td>
</tr>
<tr>
<td>Niger</td>
<td>1.8</td>
</tr>
<tr>
<td>Nigeria</td>
<td>2.1</td>
</tr>
<tr>
<td>Senegal</td>
<td>2.2</td>
</tr>
<tr>
<td>Togo</td>
<td>3.9</td>
</tr>
<tr>
<td>Blood...</td>
<td>2.4</td>
</tr>
<tr>
<td>High Risk...</td>
<td>6.0</td>
</tr>
</tbody>
</table>
Global Geographic Distribution of HCV Genotypes
Risk Factors in 3 Domains Significantly Associated With HCV Infection

- 1000 randomly selected patients questioned about risk factors in 5 domains
- 83 were anti-HCV positive; **63 had more than 1 risk factors**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history: blood transfusions, dialysis, elevated liver function tests results</td>
<td>2.92</td>
</tr>
<tr>
<td>Exposure: any blood contact</td>
<td>5.92</td>
</tr>
<tr>
<td>Work: job with high risk of HCV exposure</td>
<td>1.16</td>
</tr>
<tr>
<td>Personal history: sharing toothbrushes, receiving tattoos or piercings, acupuncture</td>
<td>1.63</td>
</tr>
<tr>
<td>Social history: illicit drug use, incarceration, past and current sexual activity</td>
<td><strong>8.15</strong> (8 fold)</td>
</tr>
</tbody>
</table>

HCV infection: risk factors

- Injection drug use: 60%
- Sexual: 15%
- Transfusion (before screening): 10%
- Other (hemodialysis; health care work; perinatal): 5%
- Unknown: 10%
HCV infection: risk factors

**Known risk**
- Transfusion or receipt of blood products before 1992
- Parenteral exposure:
  - Intravenous drug use
  - Nosocomial exposure
- Low socioeconomic strata

**Unproven or low risk**
- Perinatal transmission
- Body piercing/scarring
- Long-term haemodialysis
- Occupational exposure (e.g. healthcare worker)
- Intranasal cocaine use
- Sex with multiple partners

HCV Prevalence in different age groups
Long term impact of HCV infection

• Prospective community based cohort study in Taiwan

• Evaluation of 23,820 subjects (REVEAL-HCV) to evaluate the risk of hepatitis C virus infection on hepatic and extrahepatic deaths
  – 18 541 anti-HCV seronegatives
  – 1095 anti-HCV seropositives. 69.4% had detectable serum HCV RNA levels.

• Over an 18yr follow up, HCV patients (HCV RNA+) had significantly higher mortality from hepatic and extrahepatic diseases than anti-HCV negative patients.
Factors accelerating progression of chronic HCV infection

- Previous and concurrent alcohol consumption\(^1\)
- Male gender\(^1\)
- Other co-morbidities:
  - HIV co-infection\(^2\)
  - HBV co-infection\(^3\)
  - Obesity, hepatic steatosis
- Older age at time of infection (> 40 years)\(^1\)
Only 5% of the 170 million HCV-infected people are aware of their infection

Thomas DL, Lancet 2010;376:1441-1442
Thomas DL, AVT 2012
Innovative diagnostic tools

Rapid Testing
- Point-of-care tests
- Salivary rapid testing
  *Yaari, A J Viral Methods 2006*

Easier assessment of the infection and the liver disease
- Dry-blood spots (HCV viral load quantification/genotyping)
  *Tuaillon E Hepatology 2010*
- Portative Fibroscan (Echosens)
- Portative sonography
IN SUMMARY

• HCV is being increasingly recognized in to be a public health issue

• Insufficient large scale comprehensive data
  – Screening and access to treatment are critical
  – High time to implement programs and guidelines on Hep.C adapted to the local poor settings

• Prevalence rate ranges from 2 – 7% in cross sectional studies

• Risk factors for transmission mostly obscure

• Main genotype 1 seen, consistent with other parts of the world

• Important role of HCV RNA to identify viraemia