Hepatitis Delta in Sub-Saharan Africa

With expert speaker:
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Hepatitis D Virus in Sub-saharan Africa

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Webinar, June 6, 2019
Outline

- Introduction
- Epidemiology
- Ethiopian Experience
- Challenges
- Future perspectives
- Summary
Hepatitis D Virus

• Defective virus
• 35 nm diameter consisting 
  small delta Ag surrounded by 
  outer coat of HBsAg
• Very small genome - ssRNA, negative sense (1,700 nucleotides)

Wang et al.; 1986 - Ryu et al.; 1993
Replication of HDV

Hughes et al., Lancet 2011; 378;9785, 73-85.
Replication of HBV

Ganem & Prince, NEJM 2004
Modes of Transmission

• Requires presence of HBsAg

• Similar modes of transmission to HBV

• Vertical transmission of HDV - rare

• Infection during early childhood

• Sexual transmission

• Percutaneous exposure, scarification

• Special risk groups:- IV drug users, Dialysis, HIV +, Hemophilia

• Blood transfusion, unsterile syringes …
Hepatitis D Virus

• Immune mediated liver injury
  ∗ Superinfection in a patient with CHB
  ∗ Coinfection
HBV-HDV coinfection
Typical serological course

CDC
HBV-HDV coinfection
Typical serological course

- Clinically indistinguishable from acute HBV
- Usually acute and self-limited
- HDV and HBV clearance
- High frequency of acute liver failure (in IDUs)

CDC
HBV-HDV Super-infection
Typical serologic course

Jaundice
Symptoms
HDV RNA
HBsAg
IgM anti-HDV
Total anti-HDV
ALT
Time after Exposure

CDC
HBV-HDV Super-infection

Typical serologic course

- Severe hepatitis in previously diagnosed HBsAg-carrier or a known CHB: Exacerbation
- HDV becomes chronic almost in 90%

CDC
Natural history of HCV

Acute Hepatitis C
- Spontaneous Clearance (75-80%)

Chronic Hepatitis C
- Cirrhosis
  - Annual risk
    - Liver Failure (4-5%)
    - HCC (1-3%)
    - Death (3-4%)
  - 5-10% (20 yrs)
Natural history of HBV

- HBsAg e-ve infection
  - 70%

- Chronic Infection
  - 30%

- Chronic Hepatitis B

- Liver Failure
  - Cirrhosis
  - HCC
  - 40%
Natural history of HDV

Co-infection
- Fulminant: 2-10%
- Recovery: 60-80%
  - 10-30%

Super-infection
- Chronic Infection: 70%
  - Liver Failure, Cirrhosis, HCC
- 60-90%
• Responsible for most severe and difficult to treat hepatitis
 • Severe/fulminant acute hepatitis
 • Rapid progression to cirrhosis and HCC
 • Annual rate of cirrhosis (4%), HCC (2.8%)

* Screen for HDV in all carriers once when initiating and when worsening
Viral Dominance

**Typical**
- HBV DNA suppressed
- High HDV RNA
- ALT elevated
- Advanced fibrosis
- HBeAg-ve, HBeAb+

**Atypical**
- HBV DNA high
- ALT levels fluctuate
- Progressive
- HCC
Epidemiology

Geographic Distribution of HDV Infection

HDV Prevalence
- High
- Intermediate
- Low
- Very Low
- No Data

Taiwan
Pacific Islands

CDC

20
• 15-20 million worldwide infection

• Large geographic variations

• High - Eastern Europe, the Middle East, Central Asia, northern South America and certain countries in sub-Saharan Africa

• Scarcity of data from Africa

• Potentially major problem considering the data on HBV
Prevalence of Anti-HDV antibodies in Africa

Central Africa:
- Gen. Pop: 25.64%(12.09-42)
- HCC:37.77%(12.13-67.54)

West Africa:
- Gen. Pop: 7.33% (3.55-12.20)
- HCC:9.57%(2.31-20.43)

East and South Africa:
- Gen.Pop: 0.05%(0.00-1.78)

Pooled overall seroprevalence of hepatitis D virus was 8.39%

Anti-HDV in CLD Vs Asymptomatic OR 5.24 (95% CI 2.74–10.01; p<0.0001)
HDV genotype distribution in Sub-Saharan Africa
Outcomes

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>HDV genotype 1:46</td>
<td>29</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>HDV genotype 2:72</td>
<td>55</td>
<td>49</td>
<td>27</td>
</tr>
</tbody>
</table>
Outcomes

Genotype 1 HDV in acute hepatitis
- Increased risk of fulminant failure

Genotype 1 HDV in chronic hepatitis
- Rapid progression to cirrhosis
- Risk of HCC 3X higher
- Mortality 2X higher

Su et al. Gastroenterol 2006
Guidelines

WHO response
WHO does not have specific recommendation on hepatitis D.

APASL, 2015
- Less common

AASLD, 2018
- Testing at risk
- Periodic retesting
- HBV DNA low, high ALT
- Uncertainty
- Anti-HDV — HDV RNA,
  - HBV DNA
- Peg IFN-alpha 12 months

EASL, 2017
- Treatment in persistent HDV replication (PEG-IFN)
- HDV RNA level
- RX >/ 1 year
Persons born in regions with reported high HDV endemicity*
   Africa (West Africa, horn of Africa)
   Asia (Central and Northern Asia, Vietnam, Mongolia, Pakistan, Japan, Taiwan)
   Pacific Islands (Kiribati, Nauru)
   Middle East (all countries)
   Eastern Europe (Eastern Mediterranean regions, Turkey)
   South America (Amazonian basin)
   Other (Greenland)
Persons who have ever injected drugs
Men who have sex with men
Individuals infected with HCV or HIV
Persons with multiple sexual partners or any history of sexually transmitted disease
Individuals with elevated ALT or AST with low or undetectable HBV DNA
Ethiopia

- East Africa

- The current population of Ethiopia is \textbf{109,907,625} as of Monday, June 3, 2019, based on the latest United Nations estimates.

- Estimated HBV prevalence 10%
Previous Studies

• 2.7% among patients with viral Hepatitis
  Gebreselassie L et. al IARC Sci Publ. 1984

• 5.8% of military recruits with chronic HBV infection

• Hospital based study (249 cases) from 1986-90; 24% anti-HDV positive in cirrhotic patients
  CLD in Ethiopia: Identification of common causes. E. Tsega
• A treatment program at St. Paul’s Hospital MMC

• Advanced analysis from 1267 patients
• HDV serology - ELISA
• HBV viral load
• HDV RNA detection
• HDV genotype

Centre national de référence des hépatites B, C et Delta,
Hôpitaux Universitaires de Paris-Seine- Saint- Denis, Bobigny, France

• Fibroscan - Echosens 402
Baseline characteristics in HDV RNA-positive vs HDV RNA-negative patients, Ethiopia

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HDV RNA-negative (n = 1255) n (%)</th>
<th>HDV RNA-positive (n = 12) n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male (740) (59.0)</td>
<td>8 (66.7)</td>
<td>.771</td>
</tr>
<tr>
<td></td>
<td>Female (515) (41.0)</td>
<td>4 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Age group (y)</td>
<td>18-25 (271) (21.6)</td>
<td>3 (25.0)</td>
<td>.223</td>
</tr>
<tr>
<td></td>
<td>26-35 (532) (42.4)</td>
<td>3 (25.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>36-45 (280) (22.3)</td>
<td>2 (16.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;45 (172) (13.7)</td>
<td>4 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>Married (766) (61.0)</td>
<td>10 (83.3)</td>
<td>.143</td>
</tr>
<tr>
<td></td>
<td>Single/divorced/widowed (489)</td>
<td>2 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td>Civil servant (312) (24.9)</td>
<td>3 (25.0)</td>
<td>.163</td>
</tr>
<tr>
<td></td>
<td>Private (555) (44.2)</td>
<td>2 (16.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Housewife (134) (10.7)</td>
<td>2 (16.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other (254) (20.2)</td>
<td>5 (41.7)</td>
<td></td>
</tr>
<tr>
<td>Address</td>
<td>Addis Ababa (852) (67.9)</td>
<td>2 (16.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oromia (196) (15.6)</td>
<td>1 (8.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SNNPR (60) (4.8)</td>
<td>1 (8.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amhara (70) (5.6)</td>
<td>4 (33.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tigray (39) (3.1)</td>
<td>1 (8.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Afar (13) (1.0)</td>
<td>3 (25.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other (25) (2.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

- Alcohol abuse
  - Yes (44) (3.5) vs. No (1211) (96.5): P = 1.000

- Fasting TE value (kPa)*
  - ≤7.9: 923 (75.3) vs. 4 (36.4): P = 0.923
  - 8.0-11.7: 102 (8.3) vs. 2 (18.2): P = 0.192
  - >11.7: 201 (16.4) vs. 5 (45.5): P = 0.192

- ALT (U/L)
  - ≤40: 1011 (80.6) vs. 8 (66.7): P = 0.192
  - 41-80: 179 (14.3) vs. 2 (16.7): P = 0.192
  - >80: 65 (5.2) vs. 2 (16.7): P = 0.192

- HBV viral load (IU/mL)
  - <2000: 702 (56.5) vs. 6 (50.0): P = 0.717
  - 2000-20 000: 250 (20.1) vs. 2 (16.7): P = 0.717
  - ≥20 000: 290 (23.3) vs. 4 (33.3): P = 0.717

- HCV serostatus:
  - Positive (27) (2.5) vs. 1 (9.1): P = 0.249
  - Negative (1057) (87.5) vs. 10 (90.9): P = 0.249
HDV Prevalence

• 25 samples - positive or indeterminate for HDV antibodies with the Diasorin assay,

• 19 were confirmed positive with the Dia. Pro assay

• Overall HDV prevalence of 1.5% (19 of 1267).

• Using a sensitive HDV RNA RT-PCR assay, 0.9%

• 2/3 rd has active infection
Association with Liver Injury

- ALT levels 40 U/L (IQR 29-57) compared to 25 U/L (IQR 18-36), $P = 0.031$

- Median fibroscan
  
  $10.7 \text{ kPa} \ [\text{IQR 6.8-36.8}] \ vs \ 5.8 \text{ kPa} \ [\text{IQR 4.6-7.9}], \ P = .014$
Association with Mortality

Mortality was significantly associated with active HDV infection at univariable analysis (crude odds ratio 5.3; 95% confidence interval 1.1-24.7; P = .035).
HDV genotypes

• All HDV-infected strains belonged to genotype 1

• These strains clustered together (2 clusters considering R0 sequences and one for full-length genome sequence) and with ancient previously described HDV-1 sequences from Somalia and Ethiopia, and together with sequences from Central and Eastern Africa

• The strains also shared the Serine 202 African marker in the HDV-1 L-HDAg
Phylogenetic trees - using R0 / whole-genome sequences

At least two studies show clade homogeneity (Clade I)

Phylogenetic trees of Ethiopian strains, using (A) R0 or (B) whole-genome sequences.

Sub-Summary

- HDV prevalence was 1.5% - 2/3rd active infection
- Associated with raised ALT, fibroscan values
- Though small sample size, it is associated with high mortality
- Screen for HDV at initiating treatment for HDV and during worsening
Acknowledgement
EthNoHep Group

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Centre for Imported and Tropical Diseases, Oslo University Hospital, Ullevål, Oslo, Norway

• Asgeir Johannessen
## Case-control study to assess the impact of HDV

<table>
<thead>
<tr>
<th>Viral Marker</th>
<th>Blood donors</th>
<th>Patient controls (free from liver diseases)</th>
<th>CLD</th>
<th>HCC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDV-Ab</td>
<td>03/98 (3.1%)</td>
<td>04/82 (4.9%)</td>
<td>13/63 (20.6%)</td>
<td>11/49 (22.4%)</td>
<td>31 Anti-HDV +</td>
</tr>
</tbody>
</table>

- Among 180 HBsAg positive Healthy controls 7 (7/180) positive for anti HDV antibody (3.8%)

- Among 112 HBsAg positive CLD patients 24 (24/112) positive for anti HDV antibody (21.4%)

Unpublished data, Ongoing, 2019
Patient/client specific clinical and virological characteristics of those with HDV full genome sequenced (n = 6)

<table>
<thead>
<tr>
<th>Study groups</th>
<th>Lab. Code</th>
<th>Age/sex</th>
<th>Virological characteristics</th>
<th>Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV co-infected</td>
<td>ETH3790</td>
<td>34/M</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td></td>
<td>ETH2170</td>
<td>36/F</td>
<td>Pos</td>
<td>Pos</td>
</tr>
<tr>
<td></td>
<td>ETH2280</td>
<td>33/M</td>
<td>Neg</td>
<td>Pos</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLD patients</th>
<th>Lab. Code</th>
<th>Age/sex</th>
<th>Virological characteristics</th>
<th>Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ETH4060</td>
<td>60/M</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td>ETH4100</td>
<td>33/M</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td>ETH6220</td>
<td>51/F</td>
<td>Neg</td>
<td>Pos</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood donors</th>
<th>Lab. Code</th>
<th>Age/sex</th>
<th>Virological characteristics</th>
<th>Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ETH2056</td>
<td>47/M</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>Blood Donors</td>
<td>HIV co-infection</td>
<td>CLD</td>
<td>HIV YM(1)DD</td>
<td>Total</td>
</tr>
<tr>
<td>---------------------</td>
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<td>---------------</td>
</tr>
<tr>
<td>Anti-HDAg</td>
<td>3.2%</td>
<td>8%</td>
<td>12.7%</td>
<td>None</td>
</tr>
<tr>
<td>HDV Viremia rate</td>
<td>33.3%</td>
<td>30.0%</td>
<td>23.1%</td>
<td>321 patients</td>
</tr>
</tbody>
</table>

- All were genotype 1
- serine at amino acid position 202

How HDV dominance impaired?
- Immune escape HBsAg mutations Q164A and sE164D
- Concomitant rtV173L
- HBV drug resistant mutations (rtM204V/I)

- More than 80% anti-HDV Ab positive high HBV DNA
- Certain amino acid sequences in the C-terminal domain of the surface protein are essential for assembly of HDV particles
- HBV drug resistant mutations (rtM204V/I) 29.3% in HIV infected

Kenya

- Anti-HDV 31% in health individuals - Northern Kenya
- Around 1% (2/202) in the southern part of Kenya

Treatment

• No effective cure
• Peg. Interferon - 25% viral clearance
• Frequent relapse - SVR is replaced with MVR
• FHF - Liver transplant
• LT - Best outcome
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Clinical Trial phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lonafarnib</td>
<td>Prenylation Inhibitor</td>
<td>III</td>
</tr>
<tr>
<td>Myrcludex B (Bulevirtide)</td>
<td>Entry Inhibitor</td>
<td>III</td>
</tr>
<tr>
<td>Lambda (PEG INT)</td>
<td>Immune response stimulator</td>
<td>II</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>NTCP inhibitor</td>
<td>II</td>
</tr>
<tr>
<td>Additional 4 drugs in Pre-clinical trial</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drug Watch chart updated March 2019.
Hepatitis in Sub-saharan Africa

• Prevalence of HBV 8-10% in most countries
(100 million HBV in Africa; 5 million HDV infection)

• Generalized epidemic - Not confined to specific segment or high risk groups

• Biological and molecular tests are unacceptably expensive in SSA and sent abroad

• HBV patients get free drug only if they have HIV infection

• Left with following natural course of the disease - many end up in Hospitalization
Hepatitis in Sub-saharan Africa: Challenges

- Epidemiology Data
- Prevention

Awareness - Campaigns, civil society: extremely low

Birth dose vaccine, HBIG: <10% in SSA

No birth dose vaccine under national program; HBIG not available

- HBsAg: 35 USD
- HBIG: >100 USD

HBV vaccination prevents from HDV infection
Hepatitis in Sub-Saharan Africa

- **Diagnosis**
  - HDAg(IgM): 80 USD
  - HDV RNA: 202 USD

- Biological and molecular tests are unacceptably expensive in SSA and sent abroad.
Hepatitis in Sub-Saharan Africa

Drug Therapy

Accessibility

Only 1% chronic carriers are able to access treatment

HBV patients get free drug only if they have HIV infection

HDV is more worse
One year cost of PEG interferon is around 15,600 USD
Hepatitis in Sub-saharan Africa

Chronic lack of funding of viral hepatitis programs

- Care during hospitalization
- Decompenstion management, Liver Transplant
- Cancer Management
- Hospice care is not widely available

Many end up in Hospitalization - affect entire family emotionally and financially
Health care system

- Out-of-pocket payment for health services
- Most laboratories do not have advanced investigation set-ups
- Proper protection means for health professionals- Vaccination, Personal protections (Gloves,..) , Sterilizing materials
- Lack of political will and commitment in Viral Hepatitis
- Lack of programs by the MOH -
Needs/Opportunities for improvement

• Awareness campaigns

• Availability of literature, websites for health care providers- Hepatitis B foundation, Hepatitis Delta network

• Some improvement on data from African studies

• Many lessons should be drawn from HIV

• Training on HDV tests for African professionals

• Involvement in Research

• Strengthening HBV birth-dose, HBIG
Recommendations

• Universal protection of health care workers - Hospital safety

• Vaccinate for hepatitis at birth instead of starting at six weeks

• Drug availability - Pharmaceuticals

• Collaboration:- Clinicians, associations, advocate to government

• Unacceptable global inequalities - Scientific and Medical collaboration from developed countries

• Across SSA, hepatitis does not receive the attention that HIV did in 2000 from NGO and civil society - NGO, Civil Society involvement

• Governments:- Prioritization of the health agenda - Safety for Health workers the environment, prioritizing lab reagents and drugs
Conclusion

• HDV is overlooked - not routinely reported, underestimated

• Clade homogeneity in the Ethiopian studies - 1

• Severe form of viral hepatitis with rapid progression to HCC

• More data is needed from the Eastern Africa to - support from HDIN

• Current therapy - Interferon, emerging oral therapies

• Prevention;

• Super;- Educate to reduce risk behaviors

• Coinfection;- Pre or post-exposure prophylaxis (HBIG and/or HB vaccine)
“Countries must invest in programs that keep people healthy & out of hospitals. Prevention is not only better than cure - it’s cheaper”

WHO Director #WHA72
THANK YOU

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Q & A

Please submit questions in the chat box!
Thank you for joining! This presentation will be uploaded to Youtube and emailed to you shortly.

For more information visit:
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