Linkage to Care and Treatment for Persons with Chronic Hepatitis B Infection in Dar es-Salaam and Zanzibar, Tanzania

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CHIPO Coalition Call

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Disclosures

- Authors have nothing to disclose

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- The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention
Take Home Messages

▪ Hepatitis B is a vaccine-preventable disease and is treatable, yet burden of disease is high in Africa

▪ Not all patients living with chronic hepatitis B virus infection require treatment, but all require monitoring of liver enzymes, HBV viral load, and liver cancer screening

▪ Updating current guidelines may allow for testing and treatment of more individuals

▪ Hepatitis B care and treatment programs in Africa are feasible
Background
Global Burden of Chronic HBV Infection

- Prevalence: ~257 million people are living with hepatitis B virus infection

- Africa
  - WHO estimates overall prevalence of chronic hepatitis B (CHB) infection at 6.1% (95%, CI 4.6–8.5)
  - 60 million people living with CHB in Africa

Source: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
WHO Response to Hepatitis B

- 2011 Organized annual World Hepatitis Day Campaigns
- 2015 released recommendations: “Guidelines for the prevention, care and treatment of persons living with chronic hepatitis B infection”
  - Use simple non-invasive tests to assess treatment eligibility
  - Prioritize patients with advanced liver disease
  - Use of tenofovir or entecavir as first line treatment
- 2016 World Health Assembly adopted the first “Global health sector strategy on viral hepatitis, 2016–2020”
  - Strategy highlights the critical role of universal health coverage
  - Set targets aligned with Sustainable Development Goals

Source: https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-b
WHO Response to Hepatitis B

- 2017 released “Guidelines on hepatitis B and C testing”
  - Recommendations for who and how to test

- Global Hepatitis Elimination Efforts for 2030
  - Raise awareness, promote partnerships, and mobilize resources
  - Formulate evidence-based policy for data for action
  - Prevent transmission
  - Scale up screening, care, and treatment services

Source: https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-b
WHO’s Cascade of viral hepatitis prevention, diagnosis, care, and treatment, 2016

Care Cascade for Hepatitis B Treatment, by WHO Region, 2016

Source: Hutin et al. MMWR. 2018
Global Hepatitis B Virus Surface Antigen Prevalence in Adults, 1957–2013

Source: Schweitzer A et al. Lancet. 2015
Hepatitis B Prevalence by WHO Region

- Western Pacific: 6%
- Africa: 7%
- Eastern Mediterranean: 4%
- South-East Asia: 3%
- European: 2%
- Americas: 1%

Source: Hepatitis B Prevalence by WHO Region
HBsAg Prevalence Rates in sub-Saharan African HIV-Infected Individuals, per Country

Hepatitis B Prevalence in Tanzania: Results from Tanzania HIV Impact Survey (THIS 2016–2017)

- **Tanzania Mainland**: 4.2%
- **Zanzibar (Unguja)**: 3.6%
- **HIV positive**: 5.2%
- **HIV negative**: 3.4%

Source: THIS 2016-2017
Global Burden of Chronic HBV Infection

- **Mortality**
  - 15–40% develop cirrhosis, liver cancer, or liver failure in lifetime
  - ~887,000 deaths per year in 2015
  - Including liver cirrhosis and hepatocellular carcinoma

Five-Year Complication Rate in Chronic HBV Infection

- Chronic Hepatitis
  - Cirrhosis: 12-20%
    - Decompensated Cirrhosis: 20-23%
    - Liver Cancer: 10-25%

References:
© 2014 The American Association for the Study of Liver Diseases
Total liver cirrhosis deaths doubled in Sub-Saharan Africa from 53,000 in 1980 to 103,000 in 2010.
Liver Cancer is a Leading Cause of Death in Africa

Age Standardized Mortality Rates (ASR) from liver cancer across Africa in 2018 (Tanzania is 5-6.1 per 100,000 persons)

- 55% attributable to HBV
- Born in Africa associated with early development of liver cancer

Source: Okeke et al. Semin Liver Dis. 2019
HBV-Induced Hepatocellular Carcinoma Occurs 10 Years Earlier in Life in Africa

- 1552 patients with hepatocellular carcinoma (HCC) from 14 centers in Nigeria, Ghana, Uganda, Malawi, Ivory Coast and Tanzania

- Mean age 42 years for HBV; 55 years for HCV

Source: Am J Gastroenterology 2015;110:1629-31
WHO Guidelines for the Management of Chronic HBV in Low Income Countries 2015

ASSESSMENT OF STAGE OF LIVER DISEASE
(using clinical criteria and/or non-invasive tests (NITs) for presence of cirrhosis, i.e. APRI score >2 or based on TE)

HBV DNA NUCLEIC ACID TEST (NAT) (quantitative)
(to further guide who to treat and not treat, if no evidence of cirrhosis)

Assessment for Treatment

Yes

PRESENCE OF CIRRHOSIS

No

ALL AGES

>30 years (in particular)

ALT Persistently abnormal

HBV DNA >20,000 IU/mL

INITIATE ANTIVIRAL THERAPY

AND MONITOR

• Tenofovir or entecavir
• Entecavir in children aged 2–11 years

DEFER TREATMENT AND MONITOR

ALT Intermittently abnormal

HBV DNA 2000–20,000 IU/mL

ALT Persistently normal

HBV DNA <2000 IU/mL

ALT Persistently normal

HBV DNA <2000 IU/mL

ABBREVIATIONS: ALT = alanine aminotransferase; APRI = AST to Platelet Ratio Index; TE = transient elastography;
HBV Care and Treatment in Africa

- 21 million (33%) of 60 million living with CHB in Africa are eligible to receive treatment
- Only 33,700 (1%) accessing treatment

Source: Sonderup et al. J Viral Hep.2019
When to STOP Treatment

- Lifelong treatment in those with cirrhosis

- HBV DNA available
  - Criteria for >1 year:
    - HBeAg loss with appearance of anti-HBe and normal ALT
    - Not detectable HBV DNA

- HBV DNA not available
  - Loss of HBsAg
HCC Surveillance: WHO 2015 Guidelines

- Alpha fetoprotein (AFP) and Liver Ultrasound
  - Cirrhosis
  - Family history of HCC
  - Persons > 40 years if regional incidence is high
  - However, in sub-Saharan Africa, age of screening may have to be younger
Implementation of WHO Guidelines

- Training programs and materials for providers
- Developing the widespread capacity for HBV DNA testing and reliable serology tests
  - Inexpensive platforms and reagents are needed
- Establishing clinics of excellence to manage patients with HBV infections
- Instituting programs for HCC surveillance, especially in areas with the capacity to treat early tumors with resection or local ablation
Tanzania HBV Program
Tanzania HBV Demonstration Project Objectives

- To establish two clinics of excellence that will implement hepatitis B management and treatment programs following the WHO guidelines
  - Mnazi Mmoja Hospital in Stone Town, Zanzibar
  - Muhimbili Hospital in Dar es Salaam
- Implement a model HBV care and treatment program
- Evaluate feasibility and acceptability
- Evaluate the impact on proximal disease outcomes (improvements in liver enzymes and HBV DNA)
- Increase the capacity of healthcare professionals to care for patients with chronic HBV
WHO Guidelines for the Management of Chronic HBV in Low Income Countries

- WHO guidelines developed in 2015
- Two recommendations for treatment eligible:
  1. HBV DNA testing not available
     - Compensated or decompensated cirrhosis
     - AST to Platelet Ratio Index (APRI) > 2
  2. HBV DNA testing available
     - Persons >30 years with persistently elevated ALT and HBV DNA > 20,000 IU/mL
- WHO recommends TDF or ETV, (peg IFN as alternate)
  - Adherence should be monitored
Hepatitis B Testing

- National Blood Transfusion Services (NBTS)
  - Routine screening for HBsAg, anti-HCV, HIV
- Outpatient clinics
  - Pregnant women
  - Key populations (CSW, MSM, IDU)
- Inpatient clinics
  - Patients with liver disease
- Other
  - Discussing community events (not funded)

Abbreviations: CSW: commercial sex workers; MSM: men who have sex with men; IDU: injection drug use
Muhimbili National Hospital – Dar es Salaam

- Large public hospital
- Modern
  - Endoscopy
  - Ultrasound
  - HBV DNA lab capacity
- Target 1400 CHB patients
Mnazi Mmoja - Zanzibar

- Public hospital
- Lacks resources
  - No HBV DNA testing capacity
    - Send specimens to other site
  - No endoscopy
- GeneXpert™ platform available
- Ultrasound available
- Target 600 CHB patients
Methods
Project Funding

- CDC-Foundation funded project with industry grant
  - Total funding: $440,000 over 5 years (2,000 enrollees)
  - Medication provided at no-cost for those who met WHO treatment eligibility

- Additional funding was needed to support viral load testing
Methods

- Project period: Jan 2017 – Dec 2021
- HBsAg-positive and age 18 years or older
- Referred from blood banks, inpatient, outpatient clinics, and household contacts of HBsAg-positive persons
- Mono-infection
  - HIV-negative
  - HCV-negative
- 2 Clinics of Excellence Established
Hepatitis B Treatment Eligibility

- APRI > 1.5
- HBV DNA > 20,000 IU/mL & Elevated ALT > ULN x 2 & Age >30
- One or more stigmata of liver cirrhosis
  - Spider angiomata
  - Palmar erythema
  - Splenomegaly
  - Caput medusa
  - Ascites
  - Jaundice
  - Pruritis
  - Asterixis or Encephalopathy
Recruitment

Blood donor, inpatient, or outpatient HBsAg+ and 18 Years or older

HIV test

Positive → Counsel/ Refer to HIV/AIDS Tx Center

Negative → Anti-HCV test

Positive → Counseling

Negative → Counsel/ Refer to HBV Clinic

1) Physical Exam: Stigmata of cirrhosis, OR
2) APRI > 1.5, OR
3) ALT > ULN x 2 & HBV DNA > 20,000IU/ml

No → Follow-up 12 months

Yes - Treatment Eligible → Tenofovir & Follow-up 6 months
Follow-Up

**Patient taking Tenofovir**
Follow-Up every 6 months

- 1) Physical Exam
- 2) Labs: HBV DNA, HBeAg, anti-Hbe, HBsAg, CMP, CBC, PT/INR, APRI, AFP, eGFR
- 3) Counseling: Education

**HBeAg-, Anti-HBe+, HBV DNA not detectable & ALT < ULN for 12 months OR HBsAg clearance**
- Yes: Consider STOP Tenofovir
- No: Tenofovir & Follow-up 6 months

**Patient NOT taking Tenofovir**
Follow-up every 12 months

- 1) Physical Exam: Stigmata of cirrhosis, OR
  2) APRI > 1.5, OR
  3) ALT > ULN x 2 & HBV DNA > 20,000IU/ml

- Yes: Follow-up 12 months
- No: Tenofovir & Follow-up 6 months

Follow-up 12 months
Data Analysis

- Raw data is transmitted quarterly to CDC for cleaning, processing and analysis from Dar es Salaam and Zanzibar
- Results reported from January 2017 – December 2020, stratified by program site
- Analysis conducted in SAS version 9.4
Preliminary Results
## Summary of Recruitment for HBV Program in Tanzania, 2017–2020

<table>
<thead>
<tr>
<th></th>
<th>Dar es Salaam Muhimbili</th>
<th>Zanzibar Mnazi Mmoja</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invited</td>
<td>2,962</td>
<td>613</td>
<td>3,575</td>
</tr>
<tr>
<td>Anti-HCV+</td>
<td>24</td>
<td>5</td>
<td>29</td>
</tr>
<tr>
<td>HIV+</td>
<td>16</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Anti-HCV/HIV +</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Refused/Opted out</td>
<td>635</td>
<td>12</td>
<td>647</td>
</tr>
<tr>
<td>Enrolled</td>
<td>2,326</td>
<td>601</td>
<td>2,927</td>
</tr>
</tbody>
</table>
## Age and Sex Distribution among 2,921* Enrolled Patients 2017–2020

### Median Age (IQR)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dar es Salaam</th>
<th>Zanzibar</th>
<th>Aggregate</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-29</td>
<td>Male: 450</td>
<td>Female: 400</td>
<td>Male: 450</td>
</tr>
<tr>
<td>30-39</td>
<td>Male: 500</td>
<td>Female: 450</td>
<td>Male: 500</td>
</tr>
<tr>
<td>40-49</td>
<td>Male: 350</td>
<td>Female: 300</td>
<td>Male: 350</td>
</tr>
<tr>
<td>50-59</td>
<td>Male: 250</td>
<td>Female: 200</td>
<td>Male: 250</td>
</tr>
<tr>
<td>60+</td>
<td>Male: 100</td>
<td>Female: 50</td>
<td>Male: 100</td>
</tr>
</tbody>
</table>

**Total Patients**

- **Male:**
  - Dar es Salaam: 1400
  - Zanzibar: 1250
  - Aggregate: 2650

- **Female:**
  - Dar es Salaam: 1250
  - Zanzibar: 1200
  - Aggregate: 2450

**Median Age (IQR):**

- **Dar es Salaam:** 34 (28, 42)
- **Zanzibar:** 34 (28, 41)
- **Aggregate:** 34 (28, 42)

* 6 Patients had missing or invalid age/sex data
## Summary of Treatment Eligibility Ascertainment

<table>
<thead>
<tr>
<th></th>
<th>Dar es Salaam Muhimbili</th>
<th>Zanzibar Mnazi Mmoja</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Eligible</td>
<td>271</td>
<td>58</td>
<td>329</td>
</tr>
<tr>
<td>Liver Cirrhosis</td>
<td>120 (44%)</td>
<td>40 (69%)</td>
<td>160 (49%)</td>
</tr>
<tr>
<td>APRI &gt;1.5</td>
<td>197 (73%)</td>
<td>36 (62%)</td>
<td>233 (71%)</td>
</tr>
<tr>
<td>HBV DNA &gt;20,000 + ALT (&gt;2xULN) + Age &gt;30 yr</td>
<td>10 (4%)</td>
<td>6 (10%)</td>
<td>16 (5%)</td>
</tr>
</tbody>
</table>
Summary of Treatment Eligibility Ascertainment

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>APRI</td>
<td>47%</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>26%</td>
</tr>
<tr>
<td>APRI &amp; Cirrhosis</td>
<td>22%</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>3%</td>
</tr>
<tr>
<td>APRI + HBV DNA</td>
<td>1%</td>
</tr>
<tr>
<td>Cirrhosis + HBV DNA</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>APRI + Cirrhosis + DNA</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
Care Continuum for 2,927 Enrolled Patients by Location, 2017–2020

- **Dar es Salaam**
  - 1st clinic visit: 2,273 (98%)
  - Treatment eligible: 329 (11%)
  - Received TDF: 286 (10%)
  - 2nd visit: 1,185 (50%)
  - 3rd visit: 532 (18%)
  - 4th visit: 137 (5%)
  - 5th visit: 60 (2%)
  - 6th visit: 16 (0.5%)

- **Zanzibar**
  - 1st clinic visit: 593
  - Treatment eligible: 58
  - Received TDF: 46
  - 2nd visit: 258
  - 3rd visit: 131
  - 4th visit: 67
  - 5th visit: 70
  - 6th visit: 16

**Number of Participants:**
- 2866 (98%)
- 329 (11%)
- 286 (10%)
- 1443 (50%)
- 131 (5%)
- 532 (18%)
- 60 (2%)
- 16 (0.5%)
<table>
<thead>
<tr>
<th>Visit</th>
<th>Number of Participants</th>
<th>Treated*</th>
<th>Not Treated**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>2866 (98%)</td>
<td>279</td>
<td>1443 (50%)</td>
</tr>
<tr>
<td>2nd</td>
<td>1259</td>
<td>184</td>
<td>532 (18%)</td>
</tr>
<tr>
<td>3rd</td>
<td>447</td>
<td>85</td>
<td>137 (5%)</td>
</tr>
<tr>
<td>4th</td>
<td></td>
<td>26</td>
<td>60 (2%)</td>
</tr>
<tr>
<td>5th</td>
<td></td>
<td>111</td>
<td>48 (2%)</td>
</tr>
<tr>
<td>6th</td>
<td></td>
<td></td>
<td>16 (0.5%)</td>
</tr>
</tbody>
</table>

* Includes patients who died or discontinued treatment
** Includes treatment ineligible and eligible but not treated
Interim Proximal Disease Outcomes – Median HBV DNA per Visit (Log Scale)
Interim Proximal Disease Outcomes – Median APRI Score per Visit

![Graph showing median APRI score per visit for Labs 1 to 5, with aggregate treated and aggregate not treated lines.](image)
Interim Proximal Disease Outcomes – Median ALT Score per Visit

Aggregate Treated
Aggregate Not Treated
Summary of Morbidity and Mortality among 2,927 Enrolled Persons, 2017–2020

<table>
<thead>
<tr>
<th></th>
<th>Dar es Salaam Muhimbili</th>
<th>Zanzibar Mnazi Mmoja</th>
<th>Total</th>
<th>Median Age (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events from TDF</td>
<td>0</td>
<td>1*</td>
<td>1*</td>
<td></td>
</tr>
<tr>
<td>Liver Cirrhosis**</td>
<td>227</td>
<td>49</td>
<td>276 (9%)</td>
<td>36 (28, 46)</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma (HCC)**</td>
<td>38</td>
<td>2</td>
<td>40 (1%)</td>
<td>38 (33, 46)</td>
</tr>
<tr>
<td>Death</td>
<td>5</td>
<td>10</td>
<td>15 (0.5%)</td>
<td>54 (42, 59)</td>
</tr>
</tbody>
</table>

*Reported drowsiness and discontinued treatment;
** Cirrhosis noted in data, APRI >2.0, or note of stigmata;
***HCC determined by Ultrasound and/or AFP >350
Interim Findings

- Two clinics of excellence established to provide HBV care and treatment following WHO guidelines
- Successful recruitment and care on-going
- Challenges include:
  - Missing HBV DNA and liver enzyme lab data
  - High cost of HBV DNA testing
  - Adherence to antiviral treatment and follow-up appointments
  - High demand for HBV care and treatment
  - Many patients presenting with advanced liver disease
Discussion
Technical Assistance to Tanzania Partners

- Training and Education
  - The natural history of hepatitis B
  - Serologic and molecular markers for viral hepatitis
  - WHO guidelines for hepatitis B management
  - Management of patients on treatment
  - Management of patients with advanced liver disease

- Study protocol and procedures

- Logistics
  - TDF drug import license and shipment to Zanzibar
  - Specimen transport from Zanzibar to Dar es Salaam

- Data management and analysis

- Scientific presentations and publications
Ministry of Health Support

- Developed a strategic plan for viral hepatitis
  - Surveillance
  - Birth dose hepatitis B vaccination
  - Testing all pregnant women
  - Testing and hepatitis B vaccination for HCWs
  - Hepatitis B vaccination for key populations
  - Follow WHO care and treatment guidelines

- Appointed viral hepatitis lead: Dr. Azma Simba

- Viral hepatitis workgroup established
  - Included HBV and HCV on THIS
  - Regularly meet to discuss challenges, future programs, etc.
WHO Support

- WHO contemplating expansion of viral hepatitis activities
- WHO goal is to develop clinics of excellence
- Promoting viral hepatitis testing and care guidelines in country
CDC-Tanzania Support

- Scientific partner
  - Assistance with approvals through NIMR
- Logistics
  - Transport of specimens and drugs
  - Organization of meetings during annual site visits
- Coordination of communication with key stakeholders
- Liaison between DVH and Tanzanian officials
Sustainability Planning

- Expand HBV care and treatment to entire country and add locations in remote jurisdictions
  - GeneXpert™ HBV DNA platform certified by WHO in 2019
- Expand HBV program to prevent maternal to child transmission
  - Hepatitis B birth dose implementation
  - Universal HBV testing of pregnant women
- Expand HBV prevention to healthcare workers (HCW)
  - Universal HBV testing and vaccination of HCW
- Future funding sources
Next Steps

- Focus on follow up care
- Continue HBV training and education
- Monitor adherence to and side effects from TDF
- Monitor and evaluate protocol implementation
- Evaluate the feasibility and sustainability of the program
- Analyze data to evaluate the impact of the program on improvement on liver function and viral load suppression and on morbidity and mortality
Take Home Messages

- Hepatitis B is a vaccine-preventable disease and is treatable, yet burden of disease is high in Africa
- Not all patients living with chronic hepatitis B virus infection require treatment, but all require monitoring of liver enzymes, HBV viral load, and liver cancer surveillance
- Revised guidelines could allow for testing and treatment of more individuals
- Hepatitis B care and treatment programs in Africa are feasible
Thank You

CDC-Atlanta: Aaron Harris, Paige Armstrong, Geoff Beckett, Noele Nelson, Nancy Glass
CDC-Foundation: Catherine Zilber, Brian Graaf
Tanzania: Program staff and participants
Extra Slides
Are WHO guidelines missing treatment eligible patients?

1190 Ethiopian chronic hepatitis B patients

300 eligible for treatment according to ‘gold standard’ criteria
- 147 correctly classified by WHO criteria
- 153 false negative by WHO criteria

890 ineligible for treatment according to ‘gold standard’ criteria
- 855 correctly classified by WHO criteria
- 35 false positive by WHO criteria

Performance indicators of the WHO criteria:
- Sensitivity/specificity (%): 49.0/96.1
- Positive/negative predictive value (%): 80.8/84.8

Source: Aberra et al. J Hepatol. 2019