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

Brian McMahon, Alaska Native Tribal Health Consortium, Anchorage, AK
Shaun Shadaker, CDC, Atlanta, GA

CHIPO Coalition Call

March 15, 2021

Disclosures

- Authors have nothing to disclose

- Project funded through a CDC-Foundation grant from Gilead Sciences; Gilead Sciences will provide tenofovir disoproxil fumarate (TDF) for patients who meet World Health Organization (WHO) treatment eligibility

- *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

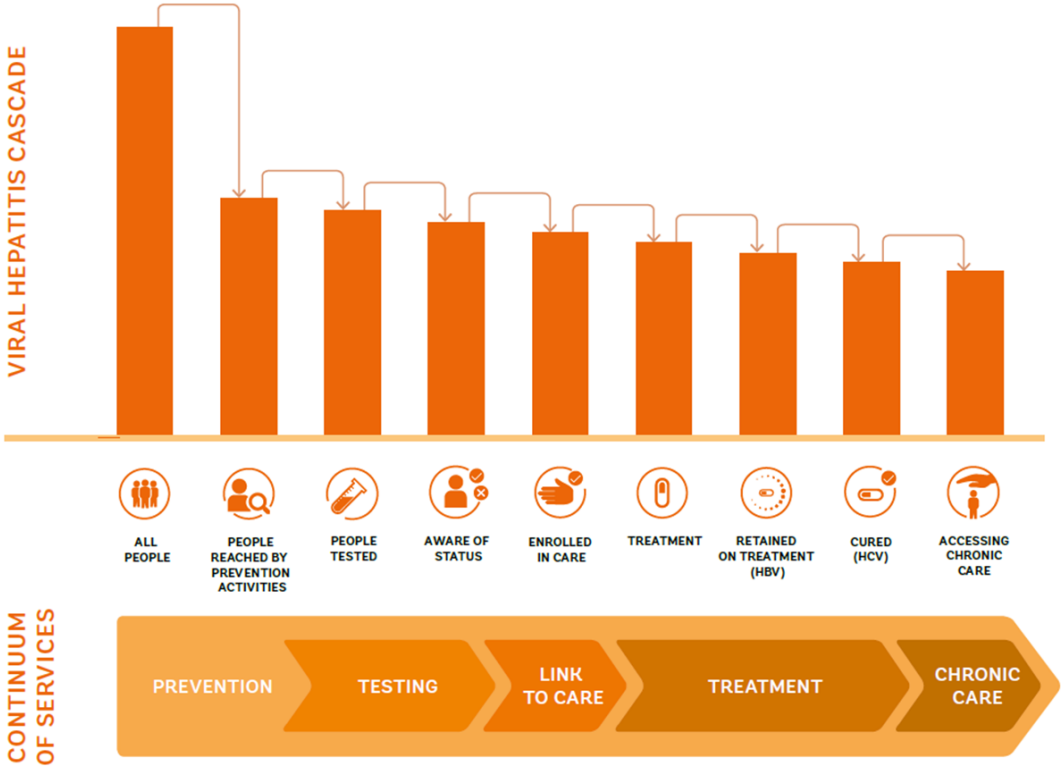
WHO Response to Hepatitis B

- 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

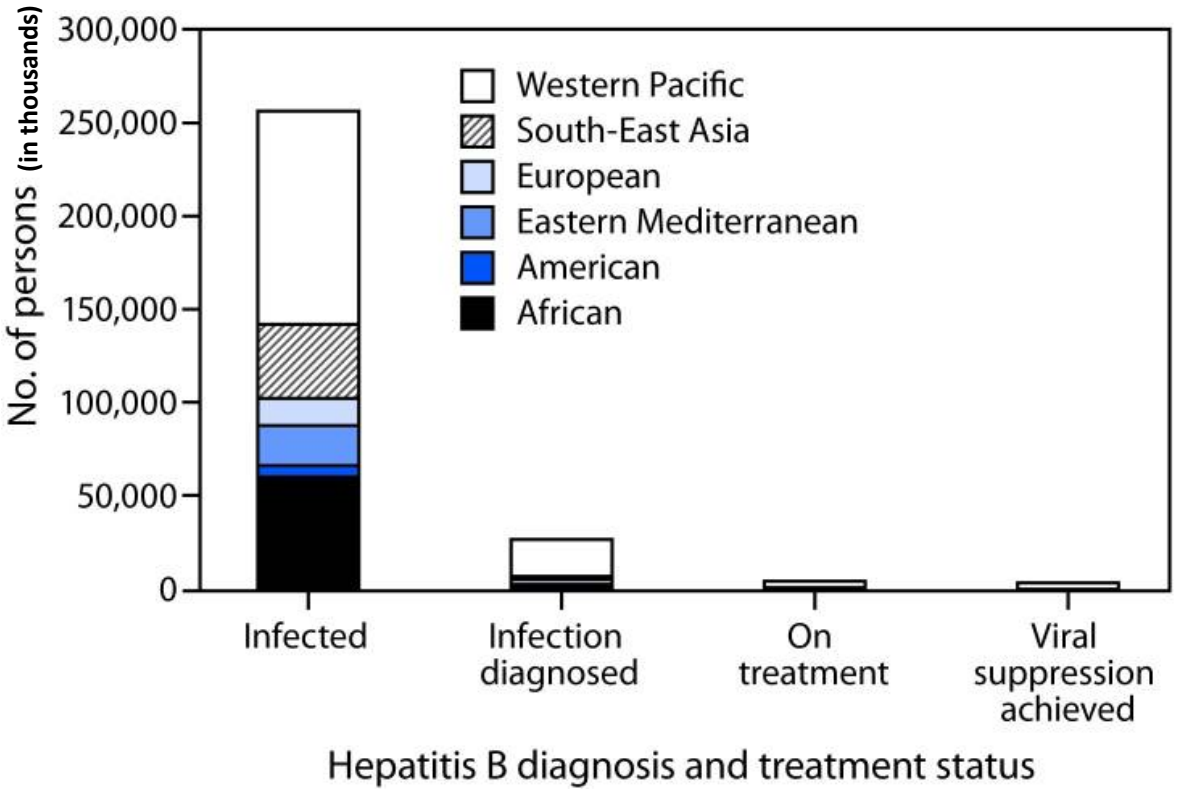
Source: https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-b

WHO's Cascade of viral hepatitis prevention, diagnosis, care, and treatment, 2016



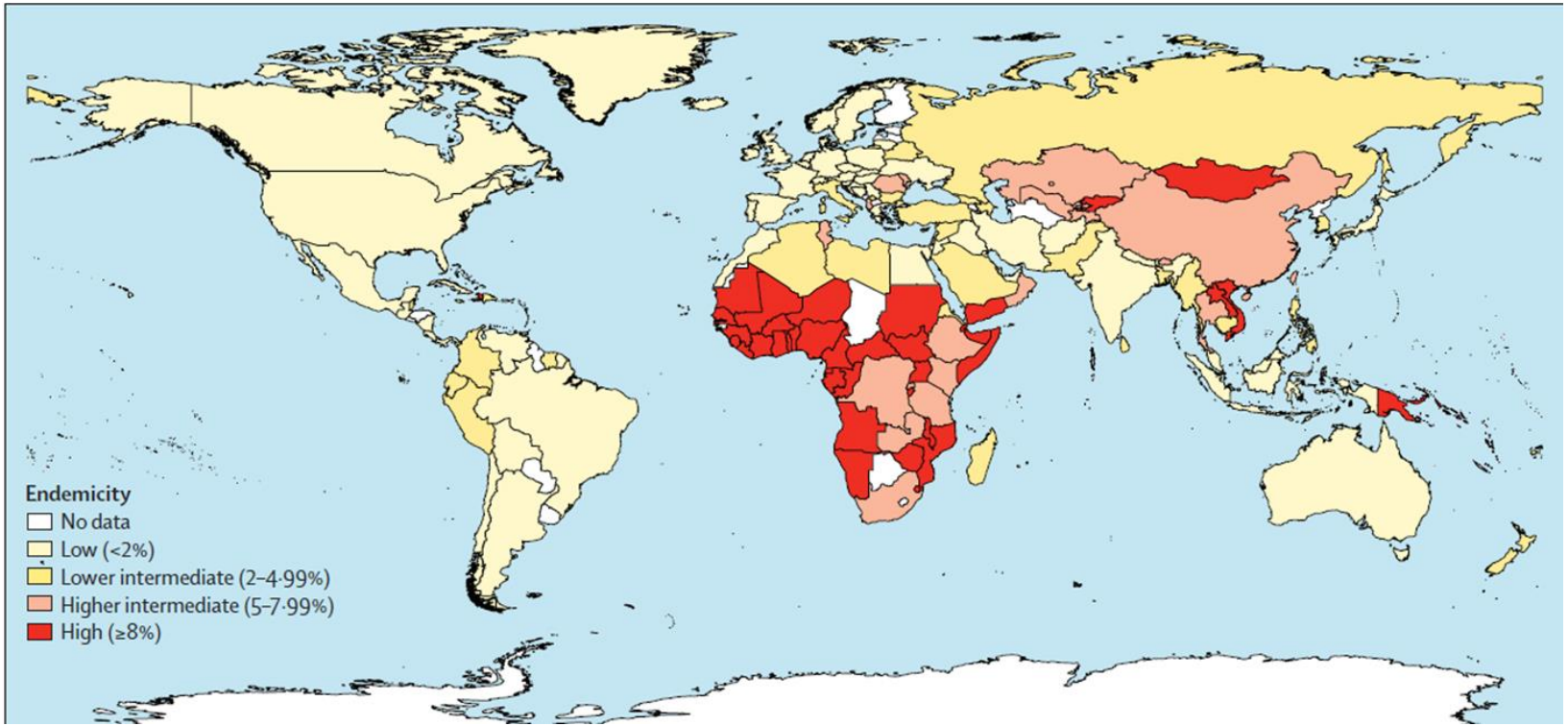
Source: Global health sector strategy on viral hepatitis 2016–2021. Geneva, World Health Organization; 2016 *(16)*.

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



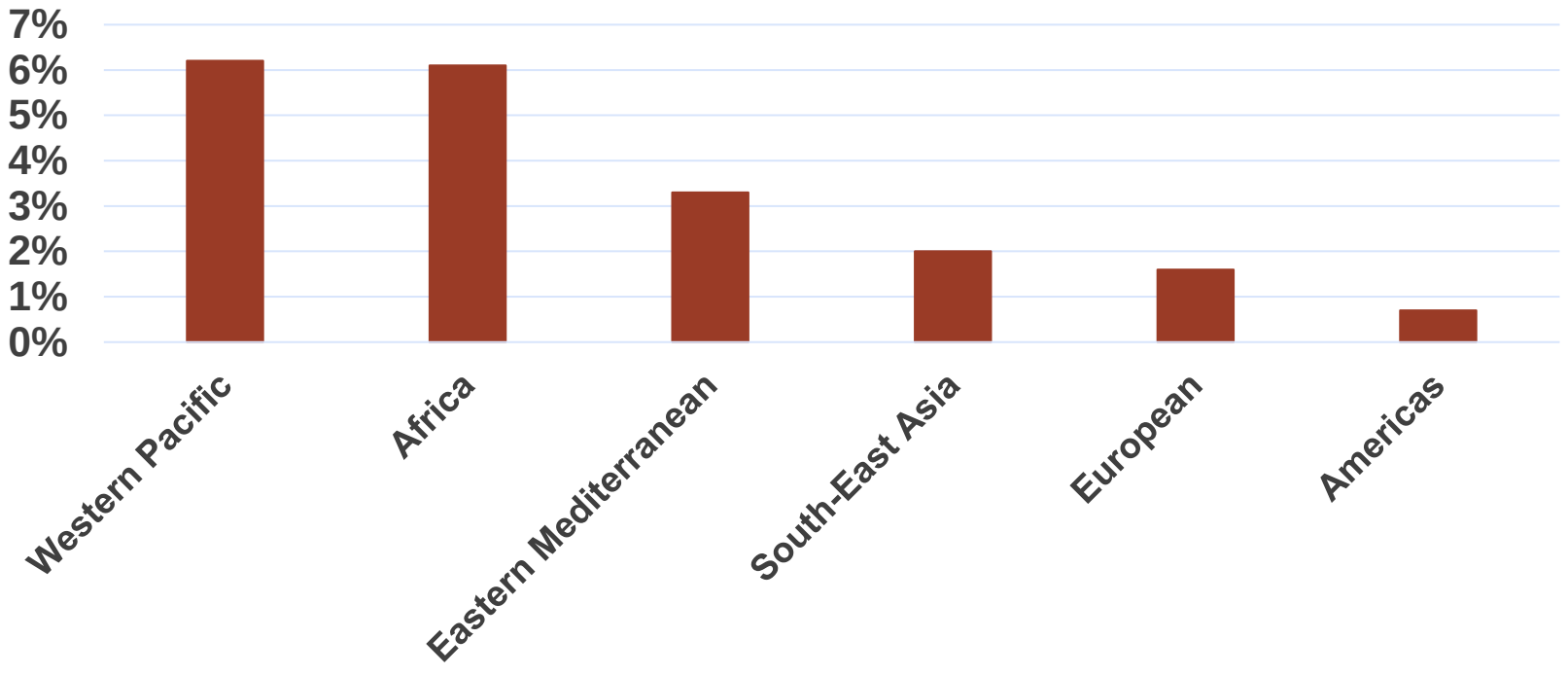
Source: Hutin et al.MMWR.2018

Global Hepatitis B Virus Surface Antigen Prevalence in Adults, 1957–2013



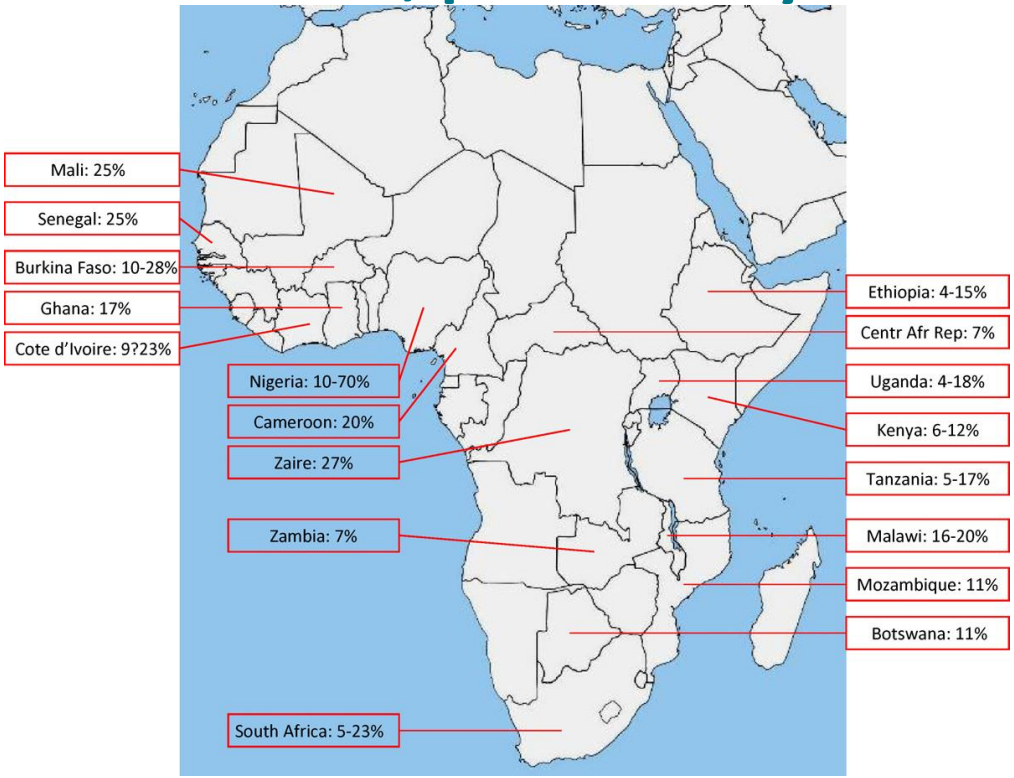
Source: Schweitzer A et al.Lancet.2015

Hepatitis B Prevalence by WHO Region



Source: Hepatitis B Prevalence by WHO Region

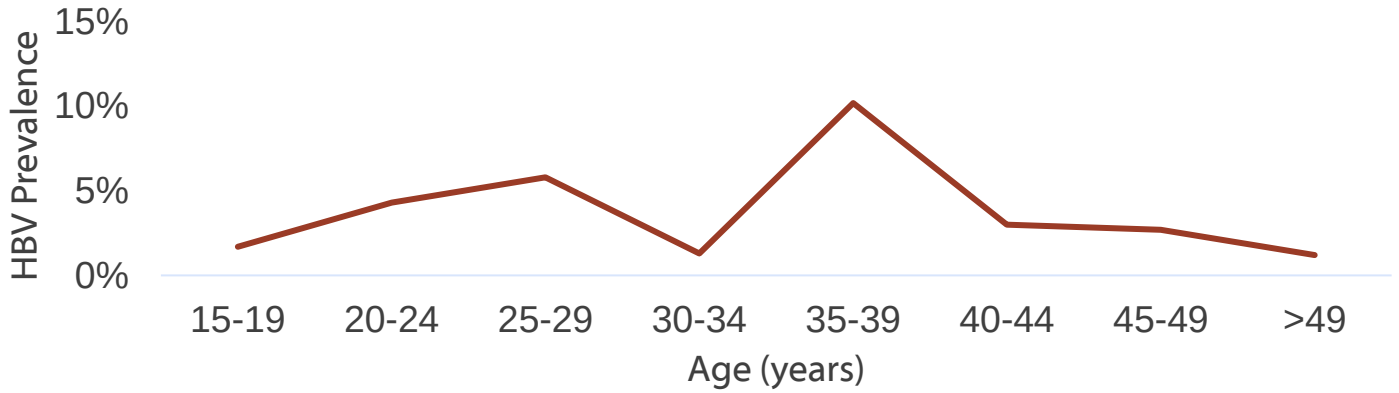
HBsAg Prevalence Rates in sub-Saharan African HIV-Infected Individuals, per Country



Source: Barth et al. International Journal of Infectious Diseases.2012

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%**



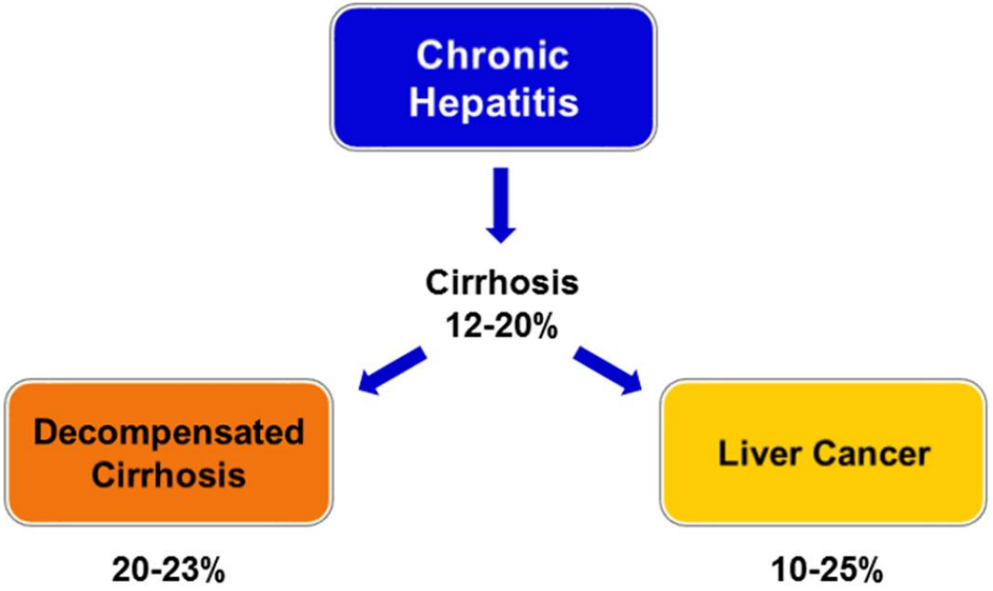
Source: THIS 2016-2017

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

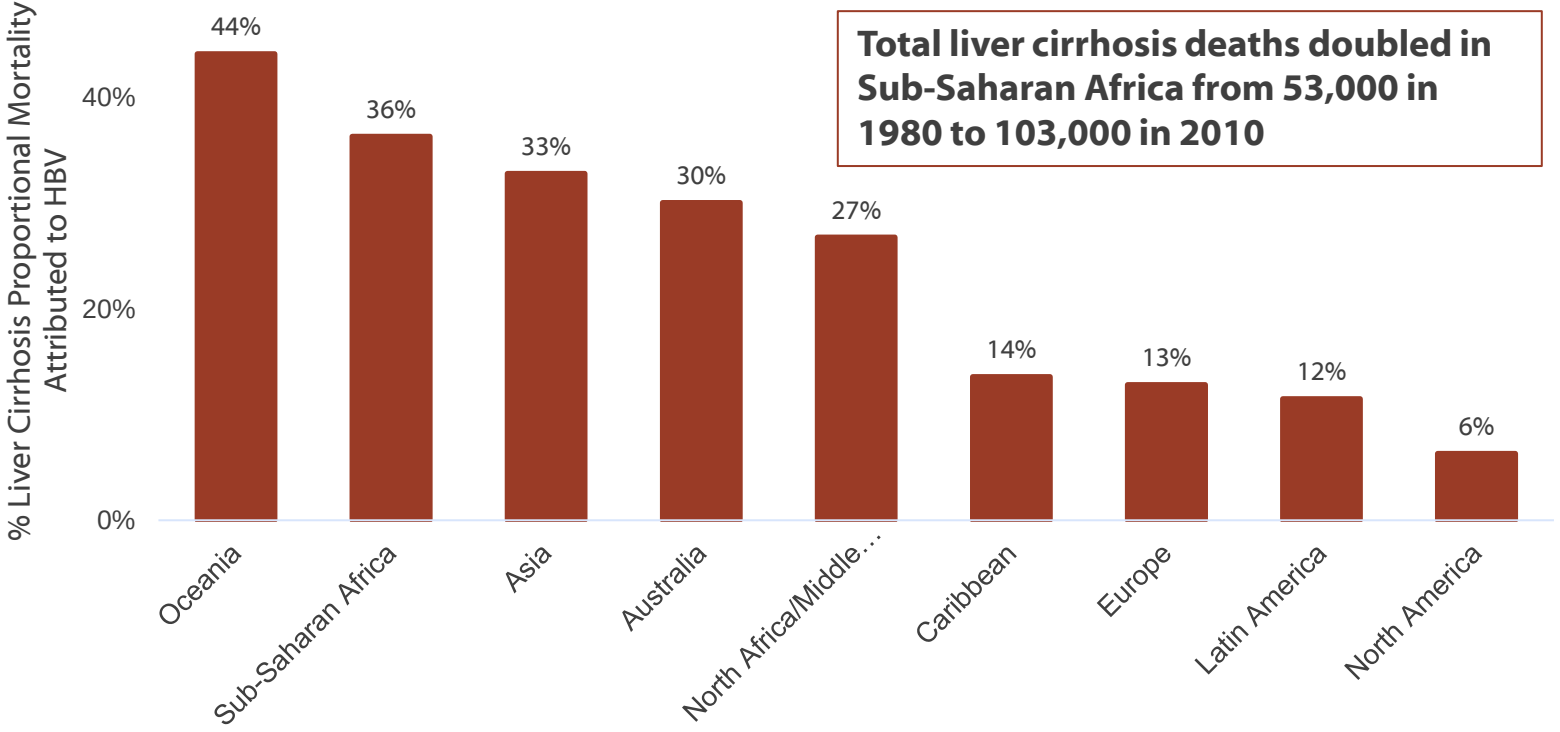
Source: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b; Lok & McMahon.Hepatology.2009

Five-Year Complication Rate in Chronic HBV Infection



Fattovich G, et al, *Hepatology*. 1995 Jan;21(1):77-82;
Fattovich G, et al. *Gut*. 1991 Mar;32(3):294-8;
Liaw YF, ET AL. *Hepatology*. 1988 May-Jun;8(3):493-6. 1988;
Liaw YF, ET AL. *LIVER*. 1989 Aug;9(4):235-41.

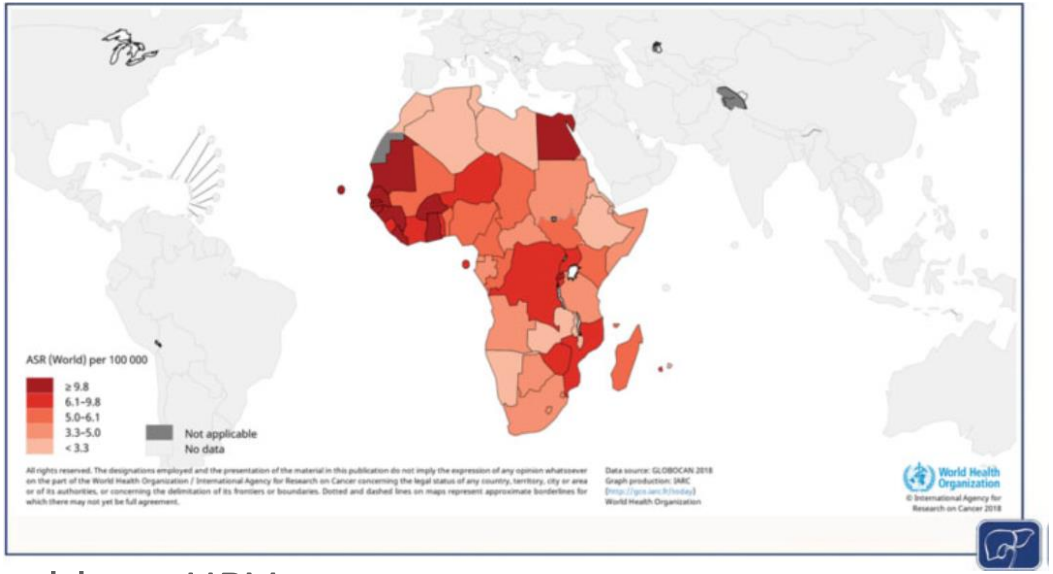
Model of Estimated Liver Cirrhosis Mortality Attributed to HBV By Region, 2010



Source: Mokdad et al. BMC Medicine. 2014

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



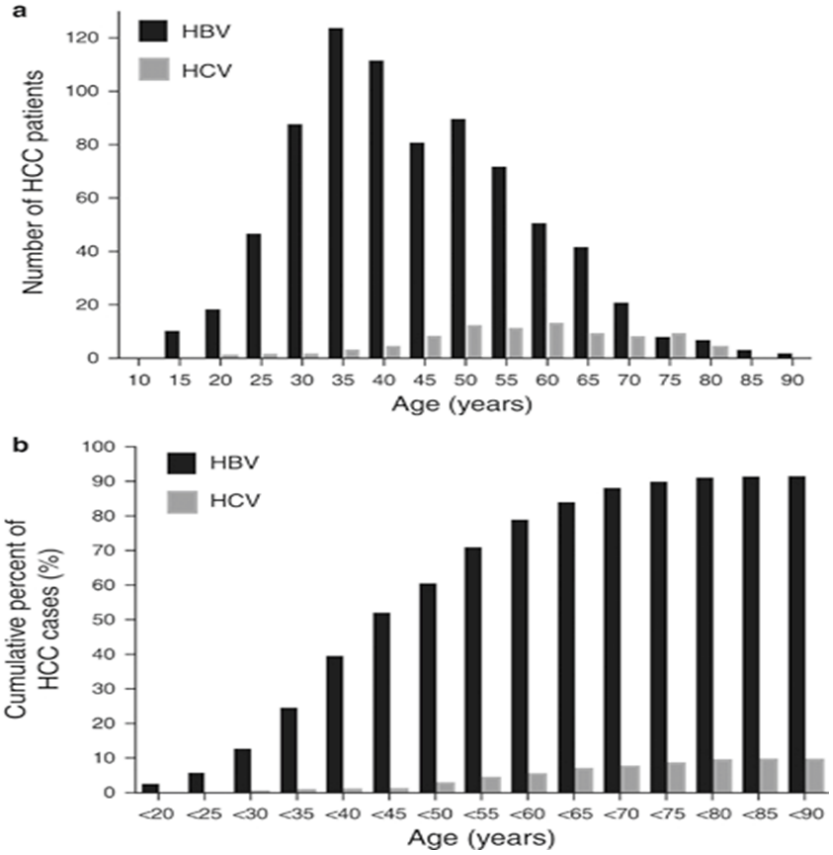
- 55% attributable to HBV
- Born in Africa associated with early development of liver cancer

Source: Okeke et al.Semin Liver Dis.2019

HBV-Induced Hepatocellular Carcinoma Occurs 10 Years Earlier in Life in Africa

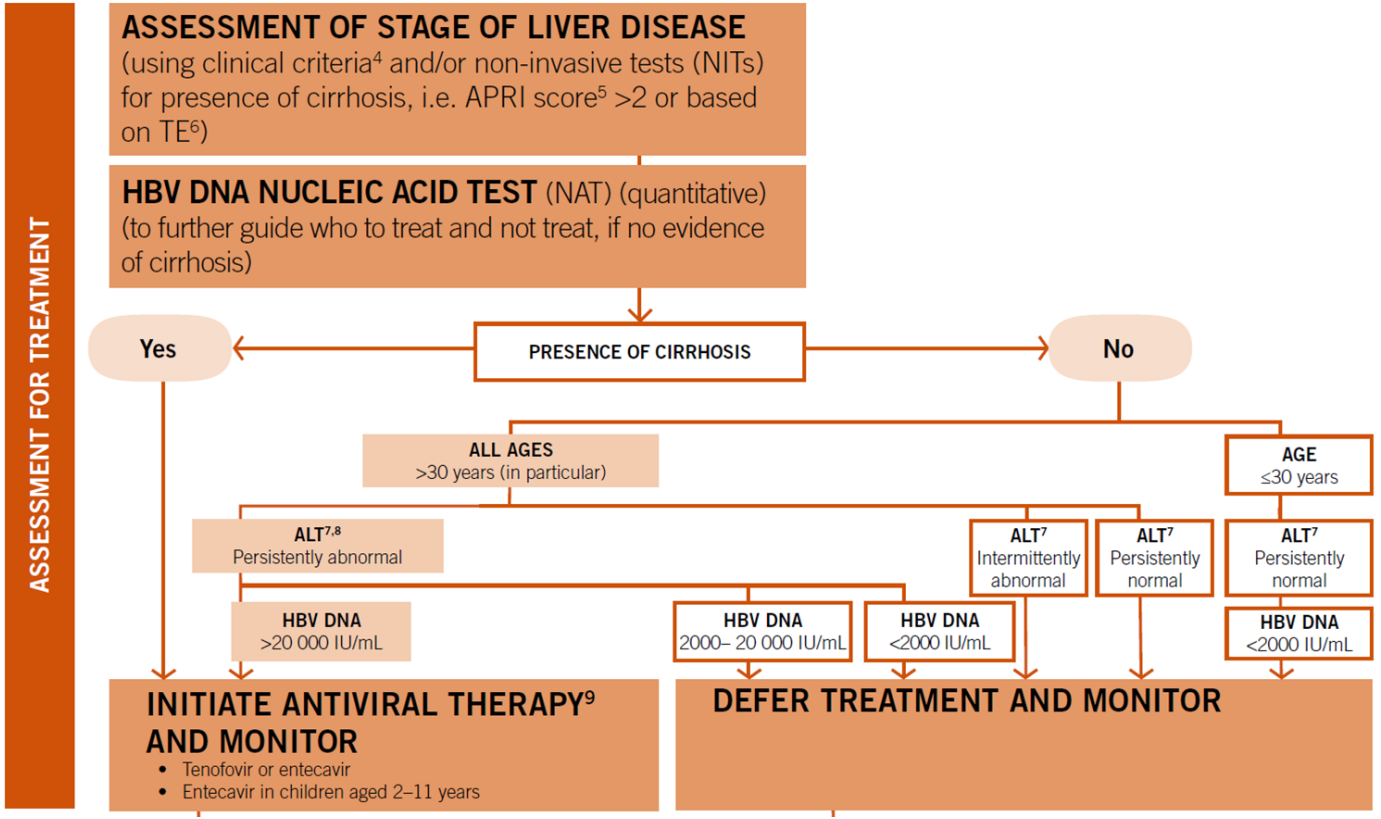
- 1552 patients with hepatocellular carcinoma (HCC) from 14 centers in Nigeria, Ghana, Uganda, Malawi, Ivory Coast and Tanzania

- 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



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

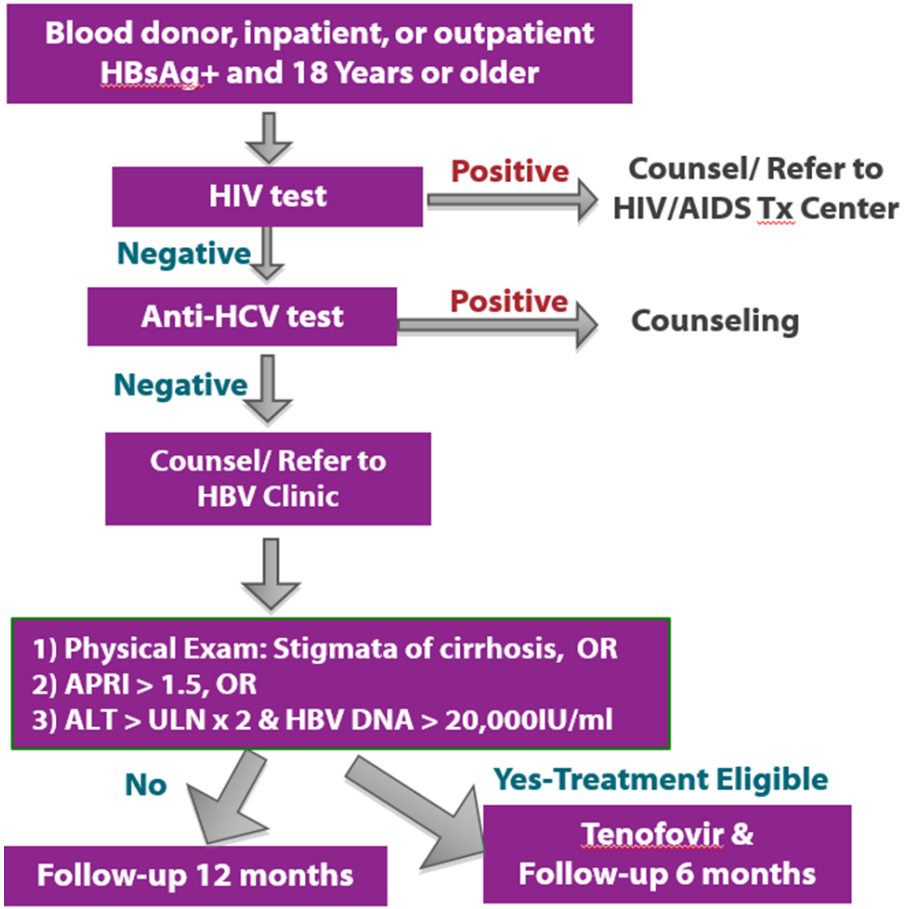
Methods

- 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

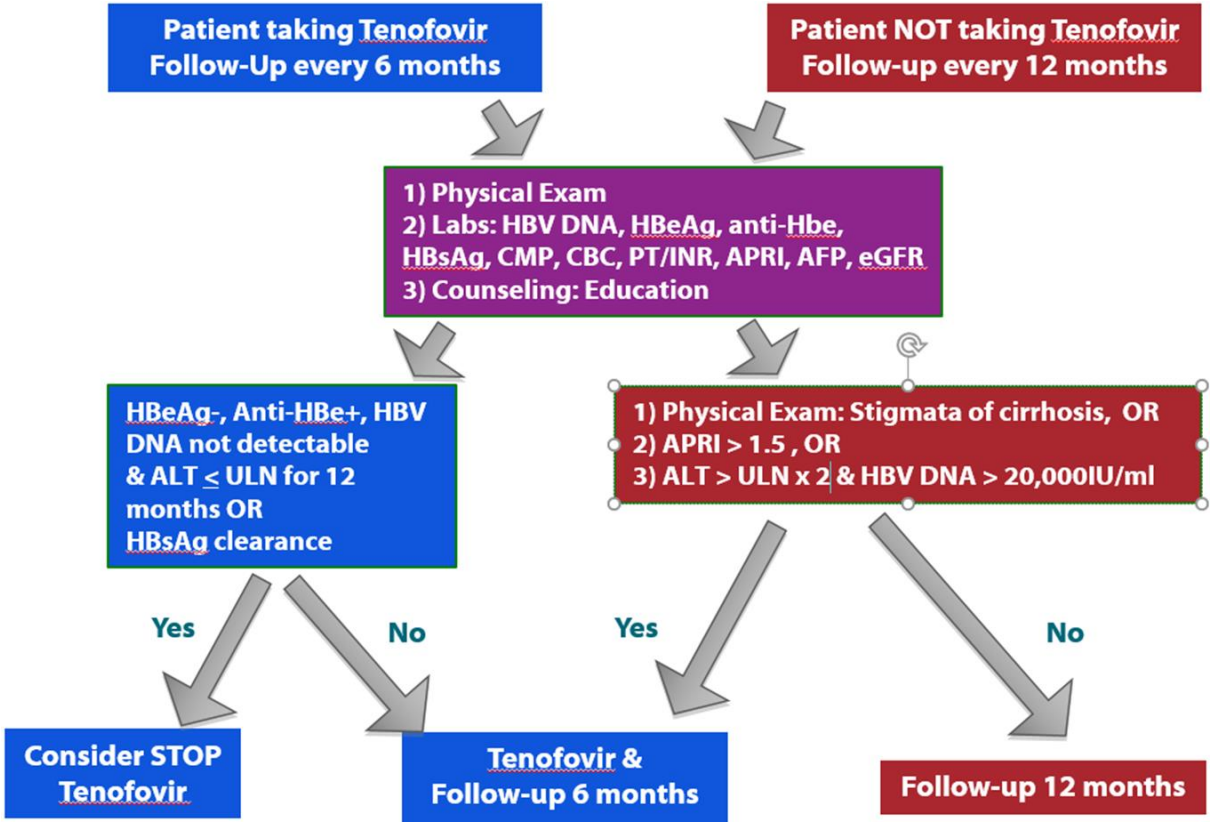
Hepatitis B Treatment Eligibility

- 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



Follow-Up


Patient taking Tenofovir
Follow-Up every 6 months
Patient NOT taking Tenofovir
Follow-up every 12 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
1) Physical Exam: Stigmata of cirrhosis, OR
2) APRI > 1.5 , OR
3) ALT > ULN x 2 & HBV DNA > 20,000IU/ml
Yes
No
Yes
No
Consider STOP Tenofovir
Tenofovir & Follow-up 6 months
Follow-up 12 months

Data Analysis

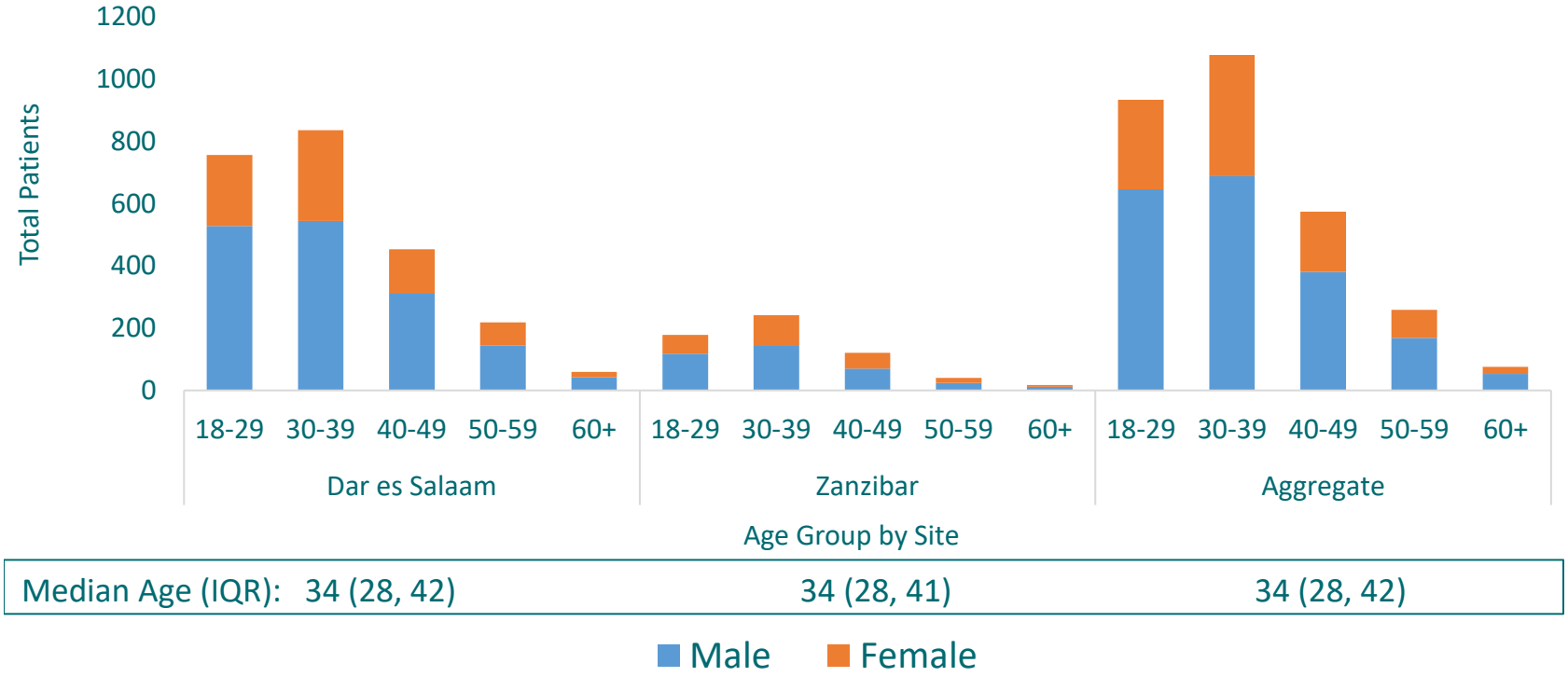
- Raw data is transmitted quarterly to CDC for cleaning, processing and analysis from Dar es Salaam and Zanzibar
- Results reported from January 2017 – December 2020, stratified by program site
- Analysis conducted in SAS version 9.4

Preliminary Results

Summary of Recruitment for HBV Program in Tanzania, 2017–2020

	Dar es Salaam Muhimbili	Zanzibar Mnazi Mmoja	Total
Invited	2,962	613	3,575
Anti-HCV+	24	5	29
HIV+	16	0	16
Anti-HCV/HIV +	1	0	1
Refused/Opted out	635	12	647
Enrolled	2,326	601	2,927

Age and Sex Distribution among 2,921* Enrolled Patients 2017–2020

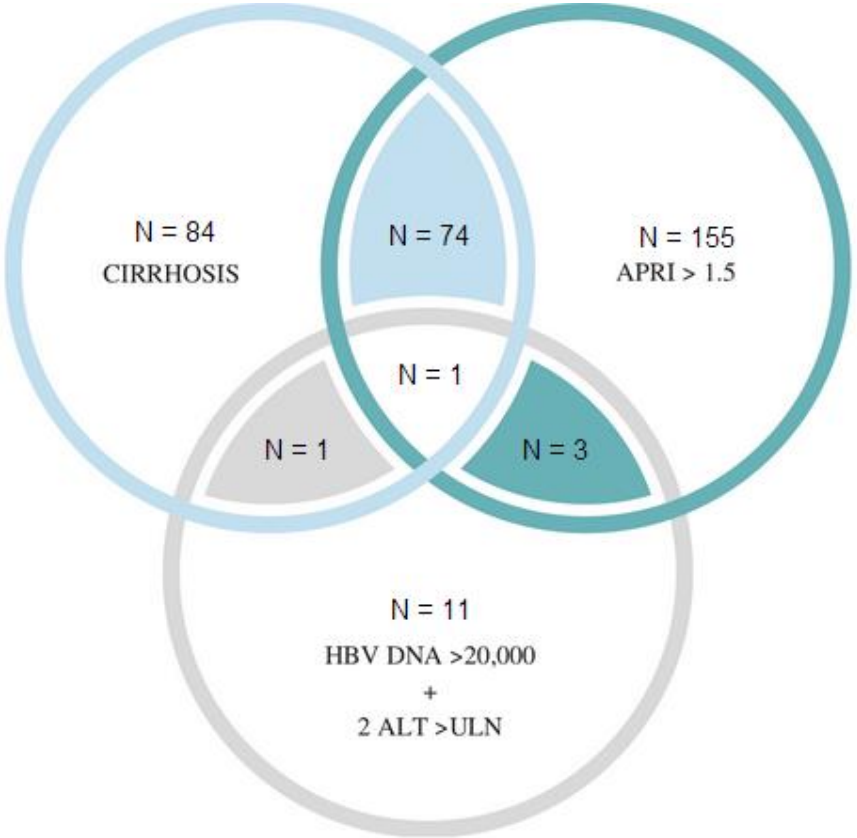


* 6 Patients had missing or invalid age/sex data

Summary of Treatment Eligibility Ascertainment

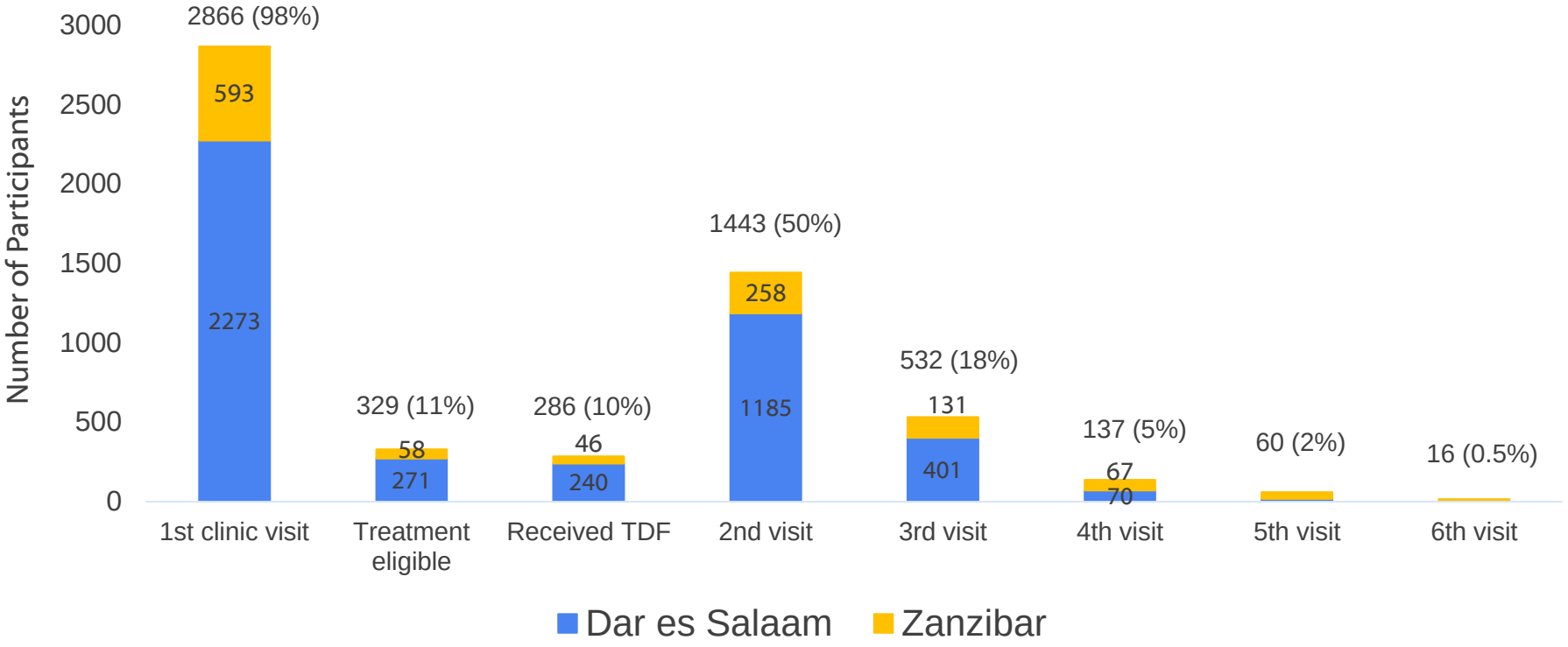
	Dar es Salaam Muhimbili	Zanzibar Mnazi Mmoja	Total
Treatment Eligible	271	58	329
Liver Cirrhosis	120 (44%)	40 (69%)	160 (49%)
APRI >1.5	197 (73%)	36 (62%)	233 (71%)
HBV DNA >20,000 + ALT (>2xULN) + Age >30 yr	10 (4%)	6 (10%)	16 (5%)

Summary of Treatment Eligibility Ascertainment

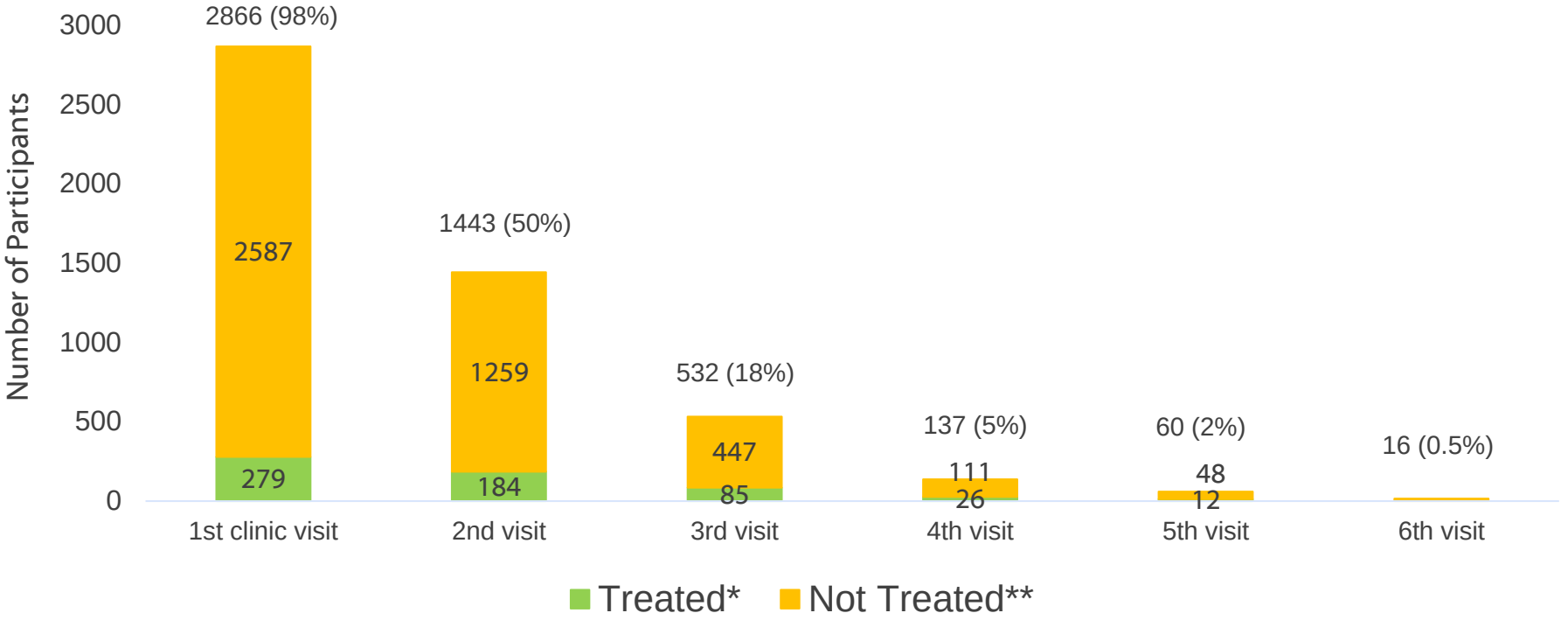


APRI	47%
Cirrhosis	26%
APRI & Cirrhosis	22%
HBV DNA	3%
APRI + HBV DNA	1%
Cirrhosis + HBV DNA	<1%
APRI + Cirrhosis + DNA	<1%

Care Continuum for 2,927 Enrolled Patients by Location, 2017–2020



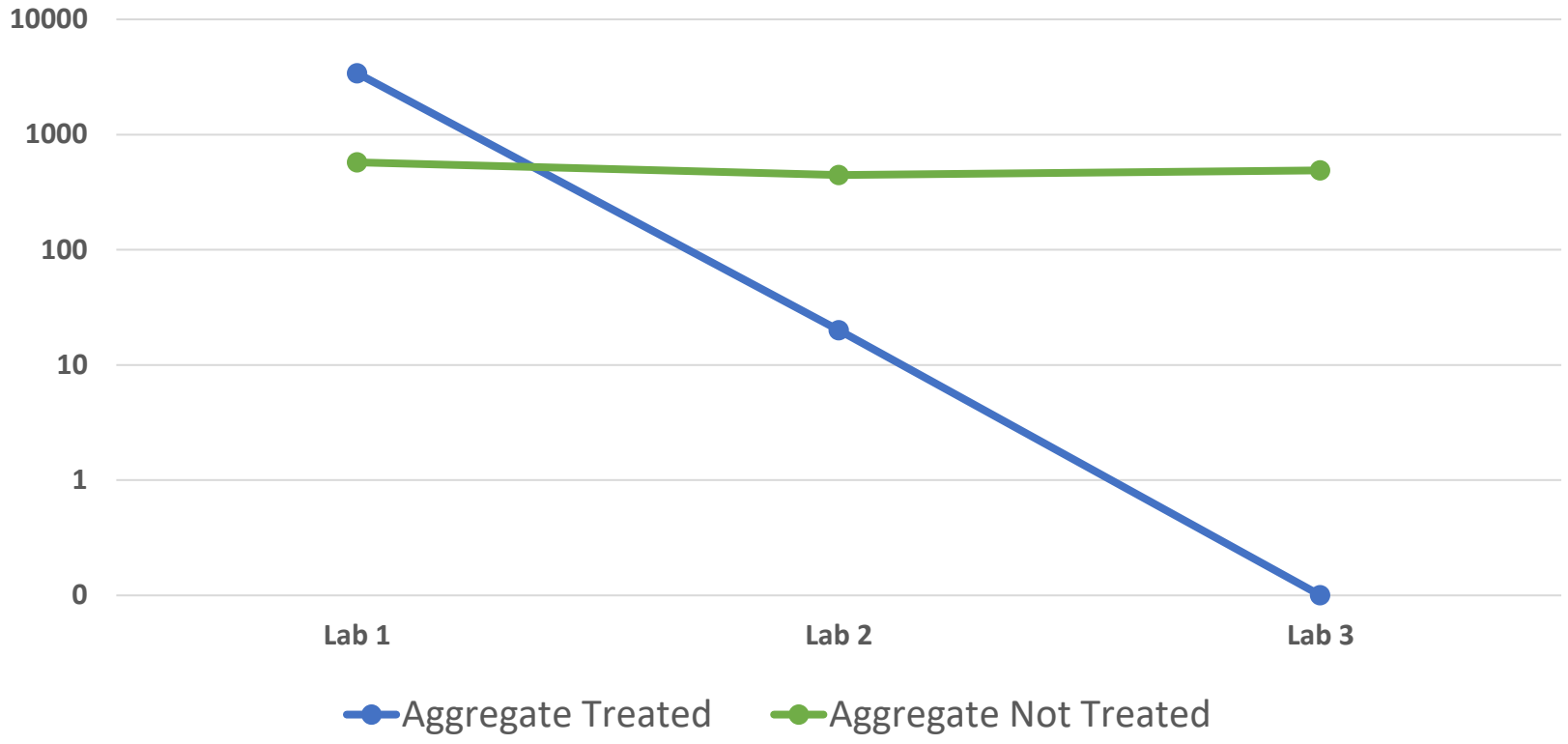
Care Continuum for Patients with Chronic HBV by Treatment Status, 2017–2020



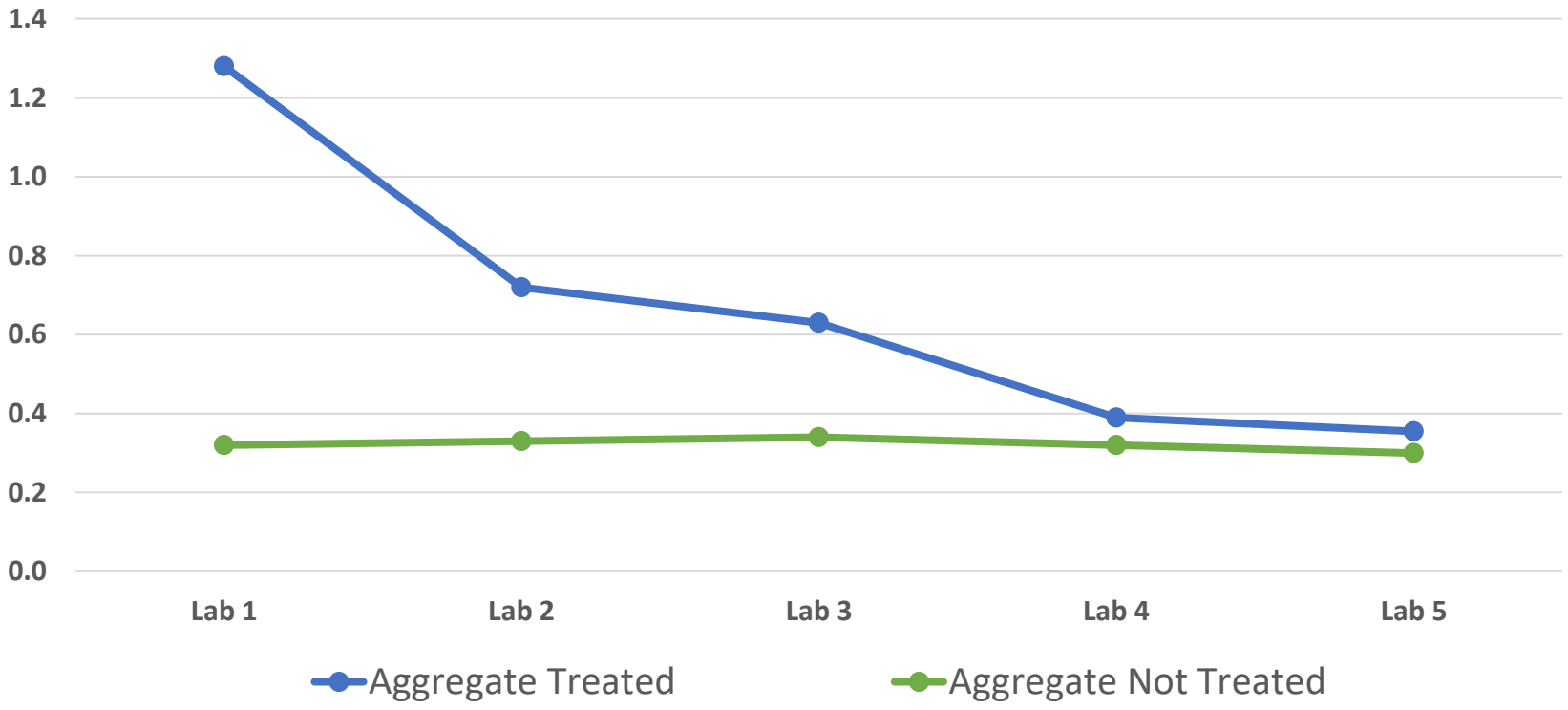
* Includes patients who died or discontinued treatment

** Includes treatment ineligible and eligible but not treated

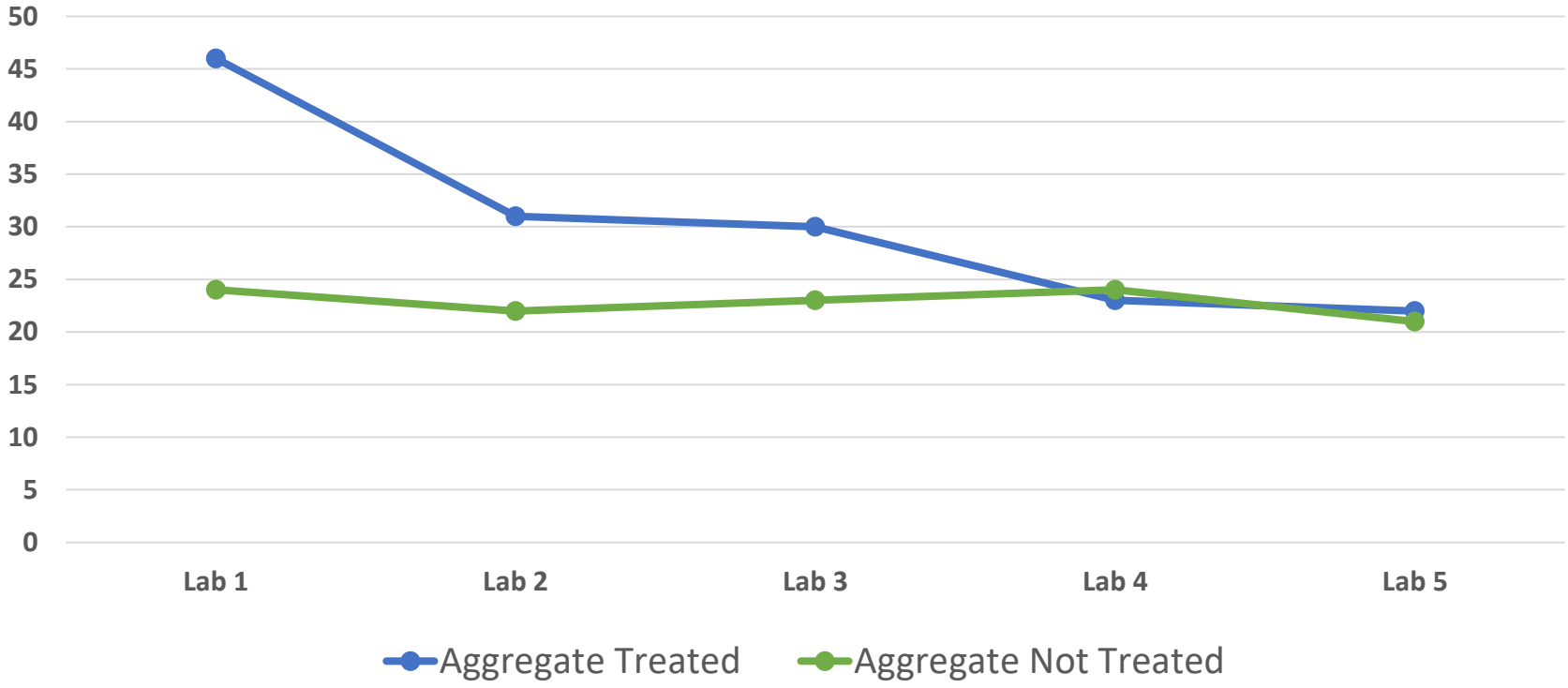
Interim Proximal Disease Outcomes – Median HBV DNA per Visit (Log Scale)



Interim Proximal Disease Outcomes – Median APRI Score per Visit



Interim Proximal Disease Outcomes – Median ALT Score per Visit



Summary of Morbidity and Mortality among 2,927 Enrolled Persons, 2017–2020

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

*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

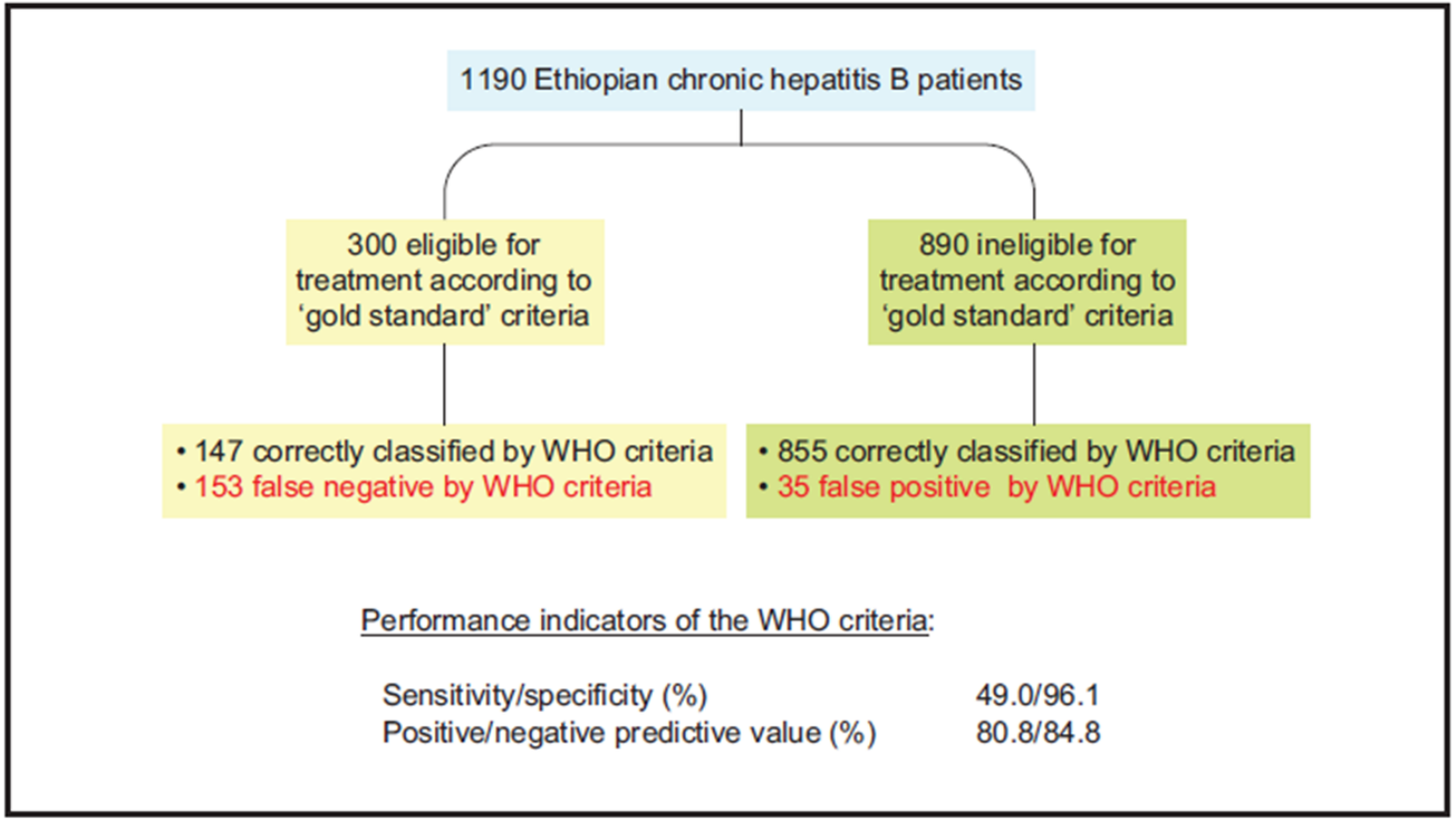
CDC-Atlanta: Aaron Harris, Paige Armstrong, Geoff Beckett, Noele Nelson, Nancy Glass

CDC-Foundation: Catherine Zilber, Brian Graaf

Tanzania: Program staff and participants

Extra Slides

Are WHO guidelines missing treatment eligible patients?



Source: Aberra et al. J Hepatol.2019

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.