How New WHO Guidance Can Transform Hepatitis B in Sub-Saharan Africa

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How new WHO Guidelines can transform Hepatitis B in sub-Saharan Africa

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Overview

- Global hepatitis B elimination response
- Challenges and gaps in Sub-Saharan Africa
- Evidence-based WHO HBV guidelines can transform the landscape
- Next Steps
Worldwide, an estimated 296 million people are chronic carriers of HBsAg

1.5M
# of new HBV infections/year

820k
# deaths/year from HBV liver cirrhosis & Cancer

12M
Anti-HDV prevalence

https://iris.who.int/bitstream/handle/10665/360348/9789240053779-eng.pdf?sequence=1
Global commitment to hepatitis elimination by 2030 (2015 WHA)
Ambitious goals and targets to reduce incidence and mortality using a Public Health approach

Absolute elimination targets defined and measurable

HBV incidence: HBsAg in children ≤5 <0.1%

Combined HBV & HCV mortality <6/100,000 population

Fig. 23. Hepatitis B incidence and mortality trends from new actions implemented under the strategy versus no new actions, 2020-2030

*95% reduction in HBV incidence and 65% reduction in mortality by 2030, compared with the 2015 baseline

Implications of elimination

From 1.5 million new infections (in 2020) to 170,000 infections (by 2030)
From 820,000 deaths (in 2020) to under 310,000 deaths (by 2030)

https://www.who.int/publications-detail-redirect/9789240027077
https://iris.wpro.who.int/bitstream/handle/10665/360348/9789240053779-eng.pdf?sequence=1
Achievements and gaps during the first global strategy (GHSS 2016-2021) implementation period-WHO Global progress report 2021

Huge gaps & regional disparity in diagnosis and treatment
Globally, only 10% of 296 M with HBV diagnosed despite 2030 target of 90%

In Nigeria, 14M infected, < 2% on Rx Vs USA-1.6 M infected, >20% on Rx

Scaling-up the hepatitis B responses has the potential to save over 8 million lives by 2030

2021 WHO Global progress report-
https://www.who.int/publications-detail-redirect/9789240027077
Sub-Saharan Africa has a disproportionately high-burden of hepatitis B infection - 82 million people

Natural history of HBV poorly characterized
- Limited contribution to global clinical trials
- Circulating genotypes (A1, D, E) less studied

Factors influence HBV responses and propensity for HCC
- Host genetic and immunologic factors
- Cultural and environmental factors
- Aflatoxins, iron, co-infections - HIV, HDV, malaria, TB, others

Resource limited setting
- Health systems – inadequate infrastructure, poorly resourced
- Access to diagnostic and treatment therapies
- Human Development Index

Inadequate data and surveillance
- Limited surveillance

Ref:
Sonderup M, Viruses 2022, 14, 82.https://doi.org/10.3390/v14010082
Mitchel T, et al. JHEP Reports 2023 vol. 5 j 100623

* 2021 WHO Global progress report
**Life expectancy at birth, years of schooling, GNI per capita)
4.3 million children (<5 years) have chronic hepatitis B – despite global success of vaccination

70% of all new global infections in sub-Saharan Africa

2030 elimination is unachievable without interrupting perinatal infections in Africa

Major gaps in HBV vaccination interventions in regions of greatest prevalence


https://iris.who.int/bitstream/handle/10665/360348/9789240053779-eng.pdf?sequence=1
Maternal HBsAg testing and treatment (if eligible), in addition to childhood vaccination is needed to achieve 2030 elimination target.

Results

- **22 243** (66.8%) of 33 309 pregnant women screened
- **3901** (17.5%) were HBsAg positive
- **2004** (51.4%) of 3901 children who were born to HBsAg-positive mothers received the Hep B BD

**Study: Cameroon (ANRS 12303)**

**Methodology**

- Single-centre, longitudinal observational
- Whole-genome sequencing to confirm MTCT

Despite receiving timely HepB–BD vaccination, 5.6% of children had breakthrough infection with HBV

Findings

- Indeterminate phenotype (grey zone)- 42.1%

- Multiple lab and viral load tests required for treatment eligibility –
  - Use of international guidelines & complexity limits treatment eligibility

- HIV coformulations of TDF with lamivudine or emtricitabine used for HBV mono-infected patients

- Poor access to HBV DNA testing
Younger age and lower HBV DNA viral loads in Africans with HBV related cirrhosis and cancers

Method:
Prospective cohort

Findings:
• Advanced disease
• Hepatitis Delta (10%)
• Low HBV DNA viraemia & occult HBV infections common
• Median survival of 11.3 months for decompensated cirrhosis (and 2.5 months for HCC*)

Individuals chronically infected with hepatitis B have a 25% to 40% lifetime risk of developing liver cancer

*Lin et al, 2022; Frontiers in Oncology
Guidelines can transform care and improve patient outcomes in countries with the highest burden.

Can guide transformation and access.

Distinctive features of WHO Guidelines:

- For low and middle income, as well as high income countries
- For programme managers, policy makers in MOH and clinicians
- Public health approach

Guidelines are the primary resource for development of national guidelines and SOPs.
Why the need for updated WHO HBV guidelines?

- Guidelines complex
  - Progressive simplification
- Emerging evidence
  - HBV genome integration, oncogenicity, ccc DNA
  - Significant rate of ongoing new chronic infections (MTCT): sub-Saharan Africa
  - Epidemiological shifts: regional, demographics
- Access challenges
  - Limited access to HBV DNA in LMIC, including SSA

Lancet Gastroenterol Hepatol 2022; 7: 796–829
Sonderup M, Viruses 2022, 14, 82.https://doi.org/10.3390/v14010082
Population Pyramid: Gambia & China, 2023
Commissioned reviews, modelling and surveys provided a key evidence base for the WHO HBV Guidelines update

**15 Systematic reviews**

1. Use of non-invasive tests
   - University College London

2a/2b. Who to treat
   - Natural history and treatment effectiveness according to VL and ALT
   - Institut Pasteur

3. MTCT rate
   - Imperial College, University of Liverpool

4. TAF and dual therapy (TDF/XTC)
   - University of Liverpool

5a/5b. POC HBV DNA (diagnostic performance and clinical impact)
   - University of North Carolina

6. Reflex HBV DNA viral load
   - University of North Carolina

7a/7b and 8. Delta testing: Who to test and how to test; Delta reflex testing
   - WHO and University of North Carolina

9. Simplified service delivery (HIV) (adherence, retention, refill and visit frequency)
   - Washington University in St. Louis

10 and 11. Simplified service delivery (models of care)
   - University of Liverpool/All India Institute/Harvard

**Landscaping, access and costs**

1. HBV diagnostics
   - CHAI

2. Delta serology and molecular tests
   - CHAI

3. TAF and dual therapy
   - CHAI

**Acceptability, values and preferences**

4 surveys and 3 literature reviews

1. Health care worker – survey
   - ICE-HBV

2. Paediatricians – survey
   - PENTA

3. MOH Programme managers – survey
   - WHO

4. Community – survey
   - HepB Foundation/WHa

5. Community – Literature review Africa
   - University of Ghana

6. Community – Literature review Asia
   - University of Melbourne

7. Community
   - Hep B Foundations

**Modelling**

1. Proportion eligible and impact of expanded treatment eligibility
   - CDA

2. Antiviral prophylaxis for all HBsAg mothers
   - Imperial College

3. Numbers needed to treat – viral load threshold
   - Institut Pasteur
Summary of new Hepatitis B Guidelines across the cascade of prevention, diagnosis, treatment & care - WHO hepatitis B guidelines 2024

- Non invasive fibrosis assessment
- Who to treat
- First-line treatment
- PMTCT
- Simplifying diagnosis
- Simplifying service delivery

29 Recommendations
14 New (including updated)
Who to treat

Treatment is recommended for all **adults and adolescents (aged ≥12 years)** with CHB (including pregnant women and girls and women of reproductive age) with:

1. **Evidence of significant fibrosis** (≥F2) based on an **APRI score of >0.5 or transient elastography value of >7 kPa** or evidence of cirrhosis (F4) (based on clinical criteria (an APRI score of >1 or transient elastography value of >12.5 kPa), **regardless of HBV DNA or ALT levels**. *(Adults: Strong/Mod, Adolescents Strong/Low)*

2. **HBV DNA >2000 IU/mL** and an **ALT level above the upper limit of normal** (ULN) (30 U/L for men and boys and 19 U/L for women and girls). For adolescents, this should be based on ALT>ULN on at least two occasions in a 6- to 12-month period. *(Adults: Strong/high; HBV DNA >20000 IU/mL & Low [HBV DNA 2000–20 000]; Adolescents: Conditional/Low)*

3. **Presence of coinfections** (such as HIV, hepatitis D or hepatitis C); **family history of liver cancer** cirrhosis; **immune suppression; comorbidities (such as diabetes)**; or **extrahepatic manifestations**, **regardless of the APRI score or HBV DNA or ALT levels**. *(Adults: Strong/Mod; Adolescents: Conditional/Low)*

4. **In the absence of access to an HBV DNA assay**:
   Persistently abnormal ALT levels (defined as two ALT values above the ULN at unspecified intervals during a 6- to 12-month period), **regardless of APRI score**. *(Adults and adolescents: Conditional/very Low)*

Monitor annually with HBV DNA, ALT and APRI score, with ongoing adherence support and retention in care.
Summary of rationale and balance of benefits and harm for treatment eligibility options

- 2 systematic reviews to inform recommendations on who to treat among people with CHB infection.
- Overall, evidence indicates much higher progression for people with HBV DNA >2000 IU/mL or ALT>ULN versus people with HBV DNA <2000 IU/mL or normal ALT.
- Evidence also indicates that the benefits of antiviral therapy will be greater in this group.
What to use for treatment
First line antiviral therapy

Updated recommendation
Tenofovir disoproxil fumarate (TDF) or entecavir (ETV) are recommended as preferred regimens
Or
TDF + lamivudine (3TC) and TDF + emtricitabine (FTC) as alternative regimens (where TDF monotherapy is not available)

Rationale
• Systematic review comparing TDF monotherapy with dual therapy showed comparable outcomes in terms of DNA suppression and normalization of ALT levels.
• Use of dual therapy allows synergies with HIV programmes and may support expansion of treatment programmes in countries with limited availability of TDF monotherapy esp. in LMIC/SSA

World Health Organization
Preventing mother to child transmission of HBV using antiviral prophylaxis

Updated 2024 recommendation

In settings where HBV DNA or HBeAg testing is available,
* Prophylaxis with TDF is recommended for all HBV-positive (HBsAg-positive) pregnant women with HBV DNA ≥200 000 IU/mL or positive HBeAg
  (strong recommendation, moderate-certainty evidence)

New 2024 recommendation

In settings where neither HBV DNA nor HBeAg testing is available,
* Prophylaxis with TDF for all HBV-positive (HBsAg-positive) pregnant women may be considered
  (conditional recommendation, low-certainty evidence)

Rationale: HBV DNA or HBeAg Available
- TDF prophylaxis for HBsAg-positive pregnant women with high HBV DNA viraemia or positive HBeAg supported by most clinical trials

Not available
- Modelling analysis suggested that prophylaxis all strategy would have great impact with about 4.9 million (95% CI: 4.7 million–5.1 million) neonatal infections averted.

*Preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent MTCT of HBV. All interventions should be given in addition to at least three doses of hepatitis B vaccination for all infants, including a timely birth dose.
Diagnostics - DNA Testing

**Point-of-care (POC) HBV DNA assays:**
POC HBV DNA nucleic acid testing (NAT) assays may be used as an alternative approach to laboratory-based HBV DNA testing to assess HBV DNA level for treatment eligibility and to monitor treatment response.
*(conditional recommendation, low-certainty evidence)*

**Reflex HBV DNA**
Reflex testing for those testing positive on HBsAg may be used as an additional strategy to promote linkage to care and treatment.
- This can be achieved through either laboratory-based reflex HBV DNA testing using a sample already held in the laboratory or clinic-based reflex testing in a health-care facility through immediate sample collection following a positive HBsAg rapid diagnostic test (RDT).
*(conditional recommendation, low-certainty evidence)*

**Rationale**
To promote linkage to care and treatment initiation.

Based on a WHO-commissioned systematic review of eight studies on the impact of reflex HBV viral load testing versus standard non-reflex approaches on DNA level testing rates, initiation of treatment and turnaround times.
Diagnostics - Hepatitis Delta (HDV)Testing

**Universal testing approach**
Serological testing for anti-HDV antibodies may be performed for all individuals who are HBsAg positive, as the preferred approach to scale up access to HDV diagnosis and linkage to care. *(conditional recommendation, very-low-certainty evidence)*

**In settings in which a universal anti-HDV antibody testing approach is not feasible because laboratory capacity or other resources are limited**, testing for anti-HDV may be given priority in specific populations of HBsAg-positive individuals, including the following:

- people born in HDV-endemic countries, regions, and areas;
- people with advanced liver disease, those receiving hepB treatment and those with features suggesting HDV infection (such as low HBV DNA with high ALT levels); and
- people considered to have increased risk of HDV infection, including haemodialysis recipients, people living with HCV or HIV, people who inject drugs, sex workers, and gay men, and other men who have sex with men. *(conditional recommendation, very-low-certainty evidence)*

**Rationale**
Observational data in several countries highlight the marked increase in case finding with the adoption of a universal testing approach.
Public health strategies to guide scale-up of the HBV response approach

1. Linkage to testing, care, treatment and prevention

2. Long term adherence to antiviral treatment

3. Retention in care

4. Integration of hepatitis testing, care and treatment with other services

5. Simplified service delivery: Decentralization, Task sharing
Differentiated care

6. Community engagement

Incorporating lessons learned from HIV, Covid 19 and HCV epidemics
Summary of new Hepatitis B Guidelines across the cascade of prevention, diagnosis, treatment & care - WHO hepatitis B guidelines 2024

• Who to treat
  • Expanding criteria for treatment (lower APRI score >0.5 and HBV DNA threshold >2000 IU/ml)
  • Expanding treatment for adolescents (including some immune tolerant)

• First-line treatment
  • TDF or Entecavir (preferred), TDF/3TC or TDF/FTC (alternative), TAF (specific age groups/ clinical situations)

• PMTCT
  • Expanding criteria for use of antiviral prophylaxis to all HBsAg positive pregnant women, where no access to HBV DNA testing

• Simplifying diagnosis
  • Use of PoC HBV DNA viral load and reflex viral load testing
  • Delta virus testing – Who to test and how to test and reflex testing

• Simplifying service delivery
  • Good practice principles for promoting adherence and retention in care
  • Decentralisation, integration and task-sharing

Expanded eligibility for treatment:
• Four options that will capture (at least 50%) of all HBsAg-positive people versus about 8–15% previously
• Options for those without access to HBV DNA testing,
• Treat everyone with early stage of fibrosis and cirrhosis will capture an estimated 20–25% of all HBsAg-positive people.
• All four recommendations on who to treat now apply to all (adults and adolescents aged ≥12 years)
• 4.9 million (95% CI: 4.7 million–5.1 million) neonatal infections averted
Implications of the new WHO guidelines for hepatitis elimination by 2030 - potentially transformative

**HBV elimination targets**

- 90% (prevention); 90% (testing); 80% (treatment)

- From 1.5 million new infections (in 2020) to **170,000** infections (by 2030)
- From **820,000** deaths (in 2020) to under **310,000** deaths (by 2030)

**From guidelines to policy and practice**

- Implementation consideration: include advocacy, resources, surveillance, community etc

*95% reduction in HBV incidence and 65% reduction in mortality by 2030, compared with the 2015 baseline*
## Next steps

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I</strong></td>
<td>Full guidelines, policy brief, web annex's and policy brief online March 30-APASL 2024</td>
</tr>
<tr>
<td><strong>II</strong></td>
<td>Adoption of the recommendations informed by local context* and implementation considerations</td>
</tr>
<tr>
<td><strong>III</strong></td>
<td>Addressing research gaps</td>
</tr>
<tr>
<td><strong>IV</strong></td>
<td>Technical and resource support to countries to scale up testing and programmes</td>
</tr>
<tr>
<td><strong>V</strong></td>
<td>Strengthening data systems for reporting</td>
</tr>
<tr>
<td><strong>VI</strong></td>
<td>Fostering government commitment and allocation of domestic resources, collaboration and partnership</td>
</tr>
</tbody>
</table>

*Local context including national HBV epidemiology, health systems and laboratory capacity, supply systems for drugs and other commodities, availability of financial resources, the organization and capacity of the health system and the anticipated cost–effectiveness of the various interventions*
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