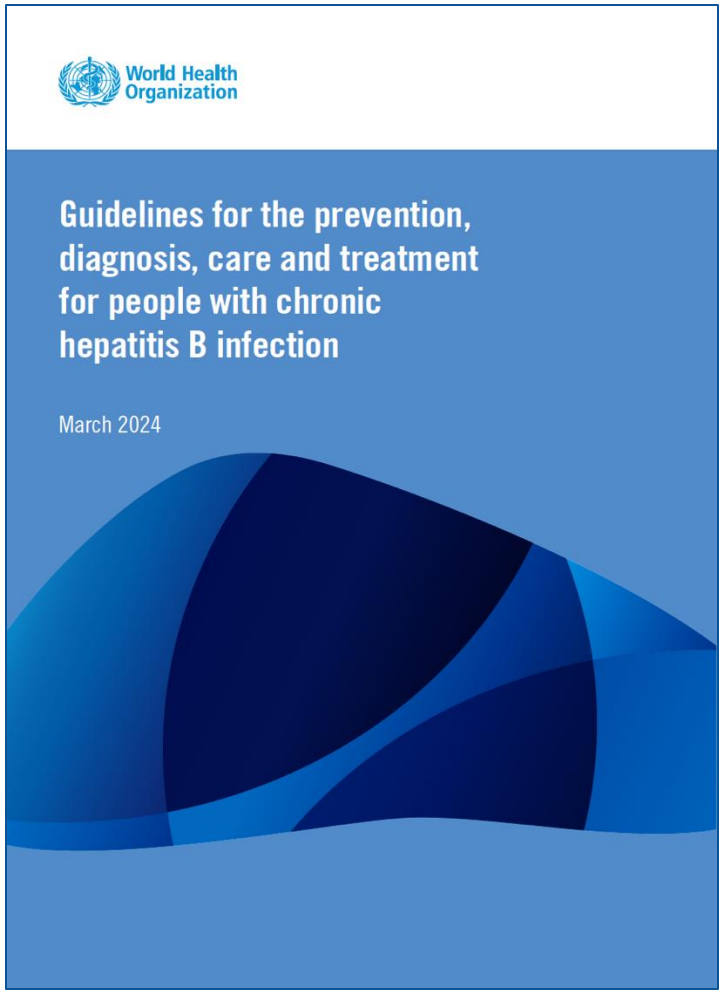
WHO 2024 Hepatitis B Guidelines

March 2024



CWN Spearman

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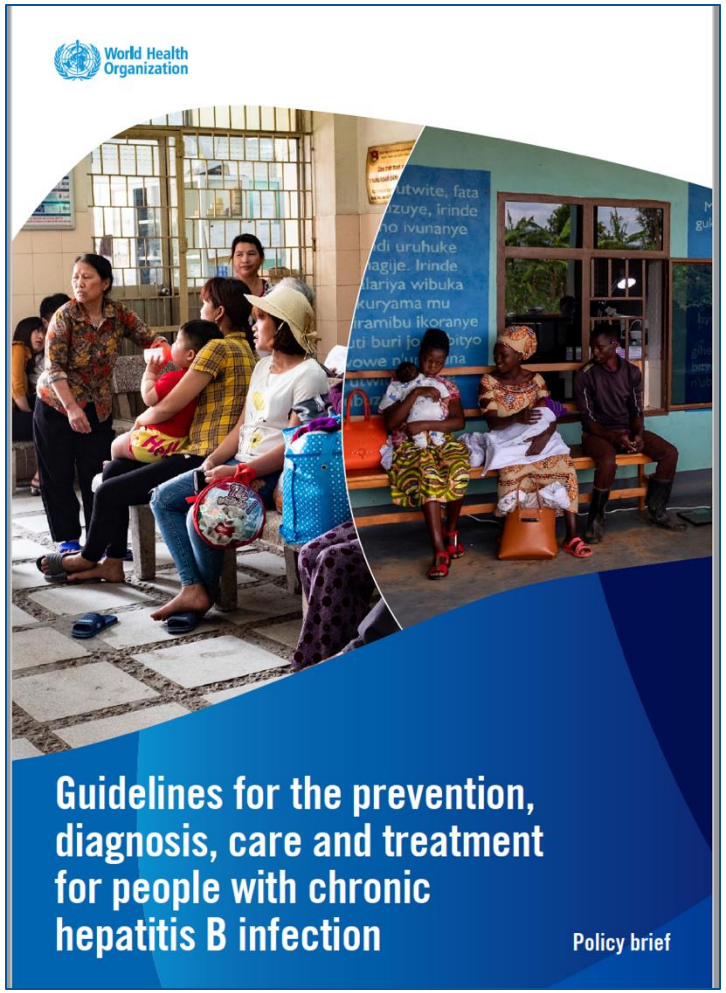


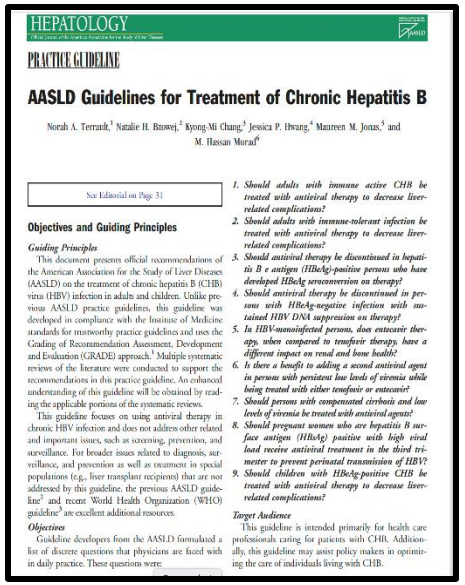
LIVER INTEREST GROUP MEETING: 26 October 2024: Johannesburg

International guidelines: HBV treatment

Journal of Hepatology

EASL Clinical Practice Guidelines: Management of chronic hepatitis B

European Association for the Study of the Liver*



HEPATOLOGY

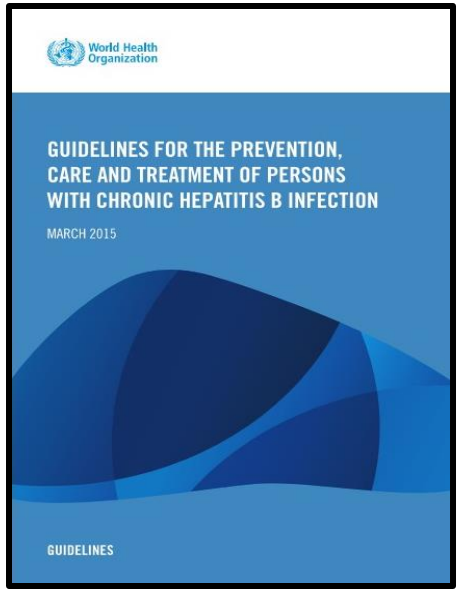
PRACTICE GUIDELINE

AASLD Guidelines for Treatment of Chronic Hepatitis B

Hepatol Int (2016) 10:1–98

GUIDELINES

Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update



World Health Organization

GUIDELINES FOR THE PREVENTION, CARE AND TREATMENT OF PERSONS WITH CHRONIC HEPATITIS B INFECTION

MARCH 2015

GUIDELINES

Generally, all guidelines

- Incorporate serum HBV DNA & ALT levels in treatment decisions
- Provide guidance on biopsy assessment of fibrosis
- Recommended treatment indications vary by the phase of chronic hepatitis B
- Other factors: Age, family history of cirrhosis & HCC

International guidelines agree: Goals of therapy

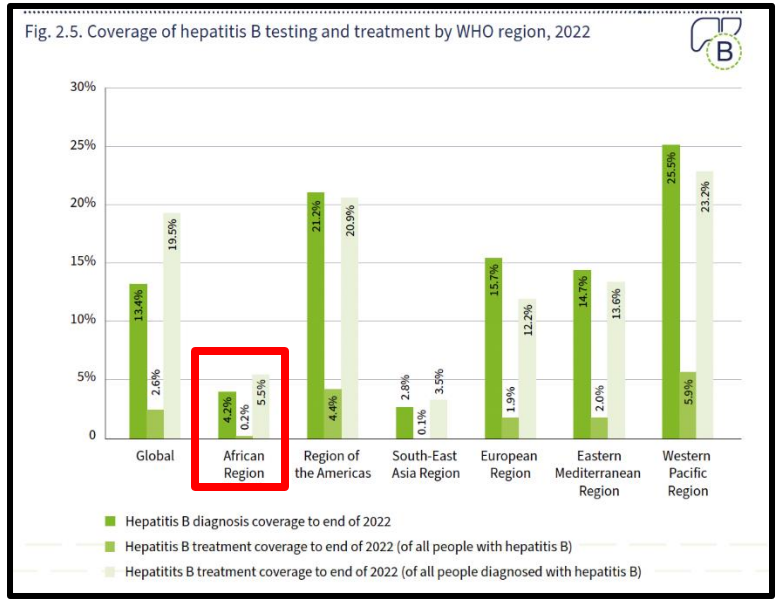
- Improve quality of life and survival by preventing progression of the disease to cirrhosis, end-stage liver disease, HCC and death

J Hepatology 2017;67:370; HEPATOLOGY 2016;63(1):262; Clinical Liver Disease 2018;12(1):33; Hepatol Int 2016;10:1

Why the need for Updated WHO HBV Guidelines?

2022: Preventative vaccines & effective antiviral therapy
Major gaps in testing and treatment uptake

- **Globally: 254 million people living with chronic HBV infection**
  - 13% diagnosed & 3% treated
- **WHO Africa: 64.7 M PLWHB:** 2.7 M diagnosed, 150 000 treated



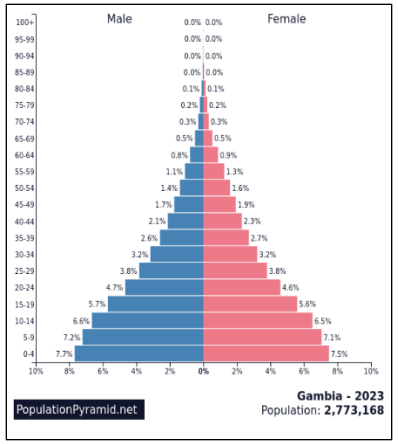
International Guidelines complex & difficult to implement in RLS

- Needed expanded and simplified treatment initiation criteria
- Decentralised and integrated service delivery models

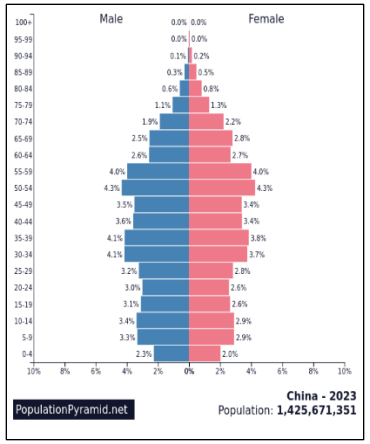
Regional differences: Demographics & epidemiology: SSA

- 25% of all HBsAg+ve in SSA <20 years
- HCC at younger age: Median age 45 yrs [IQR 35–57], multifocal
- 75% HBsAg+ve positive: HBV DNA <2000 IU/mL
  - Lack of longitudinal natural history studies

Guidelines need to be relevant to different regions



The Gambia



China

Why the need for Updated WHO HBV Guidelines?

Non-invasive Assessment of Fibrosis: WHO 2015 recommended APRI score >2

Ethiopia: WHO APRI score >2

- Missed 50% individuals eligible for treatment according to EASL criteria
- 52% patients who fulfilled WHO criteria had decompensated cirrhosis

HEPSANET
HEPATITIS B IN AFRICA COLLABORATIVE NETWORK

8 countries in SSA: 3 548 pts

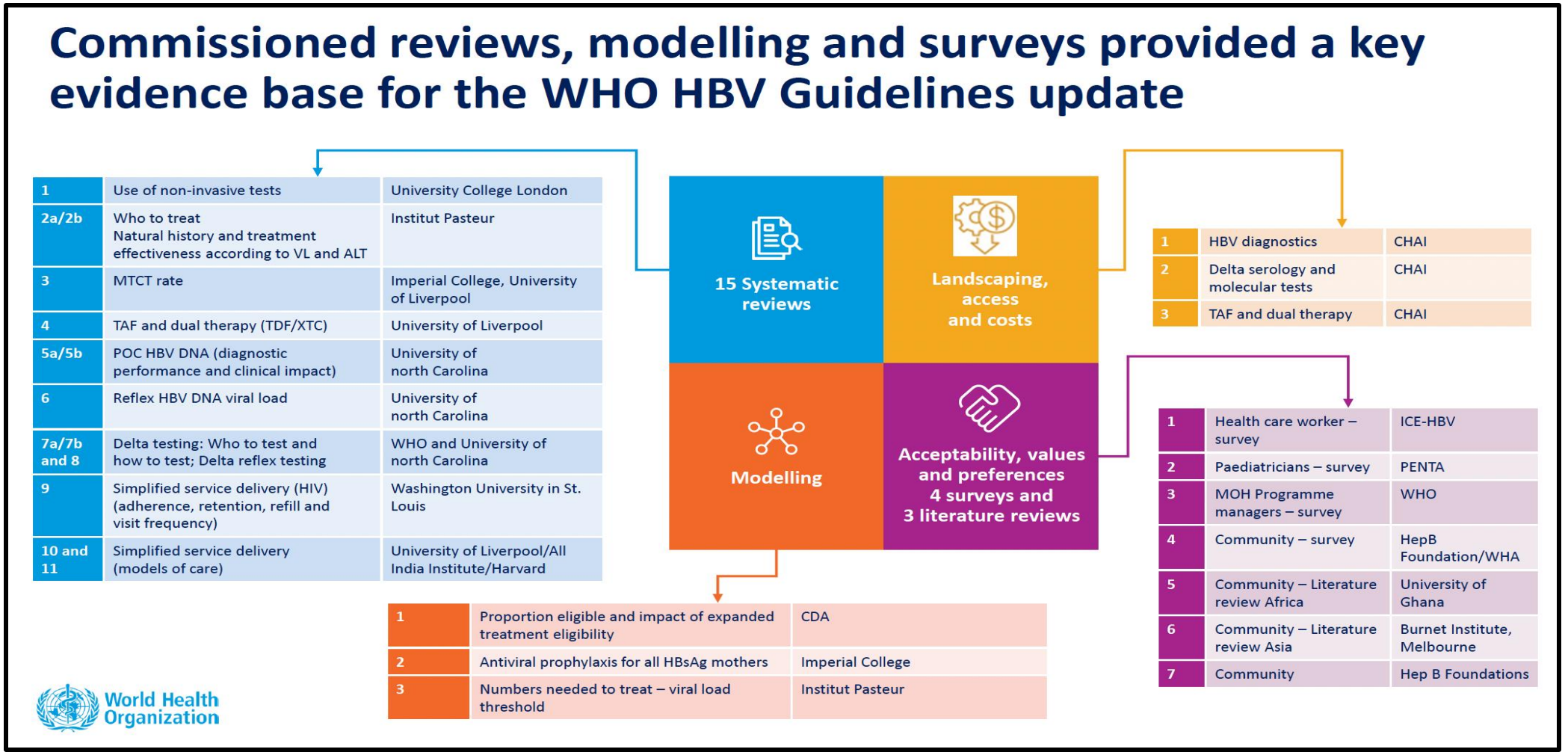
- 9% HBeAg positive
- 64.6% HBV DNA <2 000 IU/ml & 17.2% ≥ 2 000 IU/ml
- WHO APRI cirrhosis threshold >2.0: 16.5% (95% CI 12.5–20.5) sensitivity
- **Rule-in threshold for cirrhosis: 0.65**, **Rule-out: 0.36: Sens 80.6%; Spec 64.3%**

Decisions based on HBV DNA quantification: Major barrier

- Initiating treatment and appropriate follow-up
- Initiating TDF prophylaxis for prevention of HBV MTCT

J Hepatol 2019;70:1065; Nat Commun 2023;14(1):45; Lancet Gastro & Hepatology 2024;9(4):323

Updated 2024 WHO Hepatitis B Guidelines



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

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

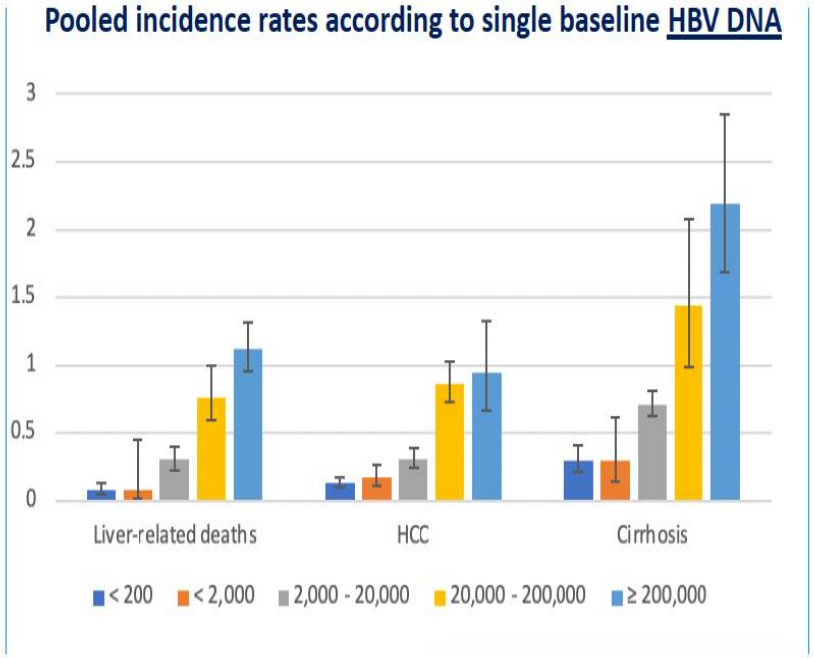
1	HBV diagnostics	CHAI
2	Delta serology and molecular tests	CHAI
3	TAF and dual therapy	CHAI

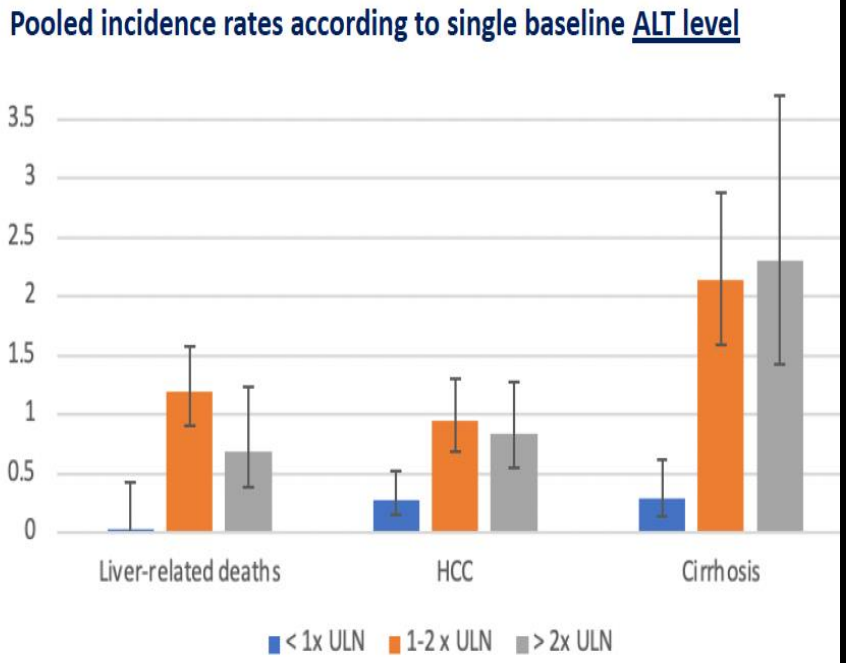
1	Health care worker – survey	ICE-HBV
2	Paediatricians – survey	PENTA
3	MOH Programme managers – survey	WHO
4	Community – survey	HepB Foundation/WHA
5	Community – Literature review Africa	University of Ghana
6	Community – Literature review Asia	Burnet Institute, Melbourne
7	Community	Hep B Foundations

15 systematic reviews, 3 modelling studies, 3 landscaping/access/cost studies; 7 acceptability/values/preferences assessments (4 surveys & 3 literature reviews)

Natural history of CHB in Adults: HBV DNA and ALT levels

WHO regions	
Western Pacific Region (WPR)	45 (65.2%)
European Region (EUR)	9 (13.0%)
Region of the Americas (AMR)	4 (5.8%)
African Region (AFR)	3 (4.3%)
Eastern Mediterranean Region (EMR)	2 (2.9%)
South East Asia Region (SEAR)	1 (2.9%)
Combination	5 (2.9%)
Year of publication	
Before 2015	28 (40.6%)
After 2015	39 (56.5%)
Unpublished	2 (2.9%)
Fibrosis stage	
F0-1	2 (2.9%)
F0-2	3 (4.3%)
F0-3	12 (17.4%)
Not reported	52 (75.4%)
Duration follow-up	
< 5 years	25 (36.2%)
≥ 5 years	44 (63.8%)





Evidence review: Western Pacific: 69 (65.2%) studies and Africa 3 (4.3%) studies

Viral Load

- Low incidence: HCC, cirrhosis & liver-related mortality in <200 & <2 000 IU/ml strata
- Dose-response increased incidence from above 2 000 to >200 000 IU/ml

ALT levels

- Low incidence: HCC, cirrhosis & liver-related mortality: <ULN strata. Higher incidence: >1-2x ULN

Efficacy of antiviral treatment: HBV DNA and ALT levels in adults

46 studies: 66% from Western Pacific region, 0 from AFRO or EMRO

- 33 RCTs and 13 observational studies
- 63% in adults and 17 (46%) in <18 yrs

Outcomes

72% reported outcomes in >20 000 IU/ml

- Only 1 RCT & 6 observational studies in <20 000 IU/ml
- 1 RCT <2 000

Viral load stratum (IU/mL)	Outcome	No. of studies	Type of studies	RR/HR	95% CI	GRADE
<2,000	HCC	1	Cohort	aHR 0.72	0.43 - 1.20	Very low
	HBsAg seroconversion	1	RCT	RR 3.72	0.30 - 45.79	Very low
		4	Cohort	RR 36.21	8.74 - 149.39	Moderate
	HBsAg loss or reduction	6	Cohort	RR 5.88	1.37-33.01	Very low
2,000 - 20,000	HCC	1	Cohort	aHR 0.45	0.14 - 1.46	Very low
20,000 - 200,000	HCC	1	Cohort	aHR 0.17	0.06 - 0.52	Low
	Worsening of fibrosis	2	RCT	RR 0.56	0.25 - 1.15	Moderate
	Improvement of fibrosis	2	RCT	RR 1.23	0.48 - 8.12	Moderate
	Worsening of necroinflammation	2	RCT	RR 0.38	0.13 - 1.01	Low
	Improvement of necroinflammation	2	RCT	RR 1.42	0.76 - 4.41	Low
	ALT normalisation	1	RCT	RR 1.49	1.13 - 1.97	Moderate
	HBeAg loss	1	RCT	RR 0.40	0.05 - 3.13	Very low
	HBsAg loss or reduction	1	RCT	RR 0.34	0.01 - 8.16	Very low
	Undetectable viral load	2	RCT	RR 6.86	2.65 - 15.15	Moderate
200,000 - 2M	HCC	1	Cohort	aHR 0.37	0.15 - 0.91	Very low
	Improvement of necroinflammation	1	RCT	RR 0.86	0.40 - 1.82	Low
	ALT normalisation	1	RCT	RR 3.64	2.43 - 5.45	Low
	HBeAg loss	1	RCT	RR 6.88	0.38 - 124.52	Very low
	HBeAg seroconversion	2	RCT	RR 17.04	3.33 - 50.23	Moderate
	Undetectable viral load	3	RCT	RR 14.02	5.25 - 31.93	Moderate

Viral Load

- Higher treatment efficacy: Higher baseline VL & ALT
- Very low to moderate quality evidence at VL<20 000 IU/ml and low to high quality at >20 000 IU/ml
- **NNT: Prevent 1 case of HCC: 210 at HBV DNA <2 000,** 59 at 2 000-20 000 and **14 at >20 000 IU/ml**

HBV DNA level	Liver-related deaths	Cirrhosis	HCC
<2000	1190	137	210
2000-20,000	182	21	59
20,000-200,000	12	7	14

Updated 2024 WHO HBV Guidelines

- **Provide 4 options for meeting treatment eligibility that will capture a much higher proportion (at least 50%) of all HBsAg-positive people versus about 8–15%**
- **New APRI criteria for staging liver disease**
- **Alternative antiviral regimens for treatment**
  - TDF or entecavir remain preferred first-line regimens
  - TDF + lamivudine (3TC) or TDF + emtricitabine (FTC) if TDF monotherapy not available
  - Tenofovir alafenamide (TAF) or Entecavir recommended for people with established osteoporosis and/or impaired kidney function
- **Expand access to antiviral prophylaxis for HBsAg positive pregnant women**
  - TDF prophylaxis: All HBsAg-positive pregnant women if lack of access to HBV DNA assays
- **Use of point-of-care HBV DNA assays**
- **Reflex Hepatitis D co-infection testing**

Recommendations: Non-invasive testing for Fibrosis

Updated recommendation:

- **APRI (aspartate aminotransferase-to-platelet ratio index)** is recommended as the **preferred non-invasive test** to assess for the **presence of significant fibrosis or cirrhosis** among adults in resource-limited settings.
- **Transient elastography (FibroScan®)** may be a preferable non-invasive test in settings where it is available and cost is not a major constraint.

(strong recommendation, moderate-certainty evidence)

New recommendation:

- **Evidence of significant fibrosis (≥F2)** should be based on **an APRI score of >0.5** or **transient elastography value of >7.0 kPa**, and **cirrhosis (F4)** should be based on clinical criteria (or an **APRI score of >1.0** or) **transient elastography value of >12.5 kPa**.

(adults: strong recommendation, moderate-certainty evidence; adolescents: strong recommendation, low-certainty evidence)

TABLE 4.1 METAVIR liver-biopsy scoring system

METAVIR stage	F0	F1	F2	F3	F4
Definition	No fibrosis	Portal fibrosis without septa	Portal fibrosis with septa	Numerous septa without cirrhosis	Cirrhosis

TABLE 4.2 Selected non-invasive tests to assess liver fibrosis

Test	Components	Requirements	Cost
APRI	AST, platelets	Simple blood tests	+
FIB-4	Age, AST, ALT, platelets	Simple blood tests	+
FibroScan®	Transient elastography	Dedicated equipment	+++

World Health Organization

Recommendations: 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 **APRI score of >0.5 or transient elastography value of >7 kPa** or evidence of **cirrhosis (F4) (based on clinical criteria or 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)* — **20-25% of HBsAg +ve**

OR

2. **HBV DNA >2000 IU/mL and an ALT level above upper limit of normal** (ULN) (**30 U/L for men and boys & 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 >20 000 IU/mL] & Low [HBV DNA 2000–20 000]; Adolescents: Conditional/Low)* — **20-35% of HBsAg +ve**

OR

3. **Presence of coinfections** (such as HIV, hepatitis D or hepatitis C); **family history of liver cancer or cirrhosis; immune suppression; comorbidities** (such as metabolic dysfunction-associated steatotic liver disease); **or extrahepatic manifestations**, *regardless of the APRI score or HBV DNA or ALT levels. (Adults: Strong/Mod; Adolescents: Conditional/Low)* — **5-8% of HBsAg +ve**

OR

4. **In the absence of access to an HBV DNA assay:**
Persistently abnormal ALT levels (defined as **two ALT values >ULN at unspecified intervals during a 6- to 12-month period**), *regardless of APRI score. (Adults and adolescents: Conditional/very Low)* — **20% of HBsAg +ve**

World Health Organization

Recommendations: First line antiviral therapies

Updated recommendation

- **Tenofovir disoproxil fumarate (TDF) or entecavir (ETV)** – are recommended as **preferred regimens** and
- **TDF + lamivudine (3TC) and TDF + emtricitabine (FTC)** as **alternative regimens** (where TDF monotherapy is not available).

(strong recommendation, moderate-certainty evidence)

New recommendation:

- **Entecavir (ETV) or tenofovir alafenamide fumarate (TAF) (if available)** is recommended for people with established osteoporosis and/or impaired kidney function and
- **For children or adolescents** for whom antiviral therapy is indicated **(ETV aged ≥ 3 years and TAF aged ≥12 years)**

(strong recommendation, moderate-certainty evidence)

Evidence-base and Rationale

- **Systematic review of 5 RCTs of TAF vs. TDF**
  - Similar outcomes for undetectable HBV DNA.
  - No differences in adverse events- TAF less decline in renal function and BMD but changes small (1-3%)
  - Limited evidence on effects on clinical outcomes.
- **Systematic review of 5 RCTs of dual therapy (TDF+FTC) vs. TDF monotherapy**
  - Similar outcomes (HBV DNA suppression, ALT normalisation, HBsAg and eAg loss, and adverse events)
- **Expanding access through dual therapy:**

  In countries with limited availability of TDF monotherapy esp. LMICs/SSA - use of dual therapy available through HIV/ART programmes may expand treatment access

World Health Organization

Recommendations: Preventing HBV Mother-to-child Transmission

Updated recommendation

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

(strong recommendation, moderate-certainty evidence)

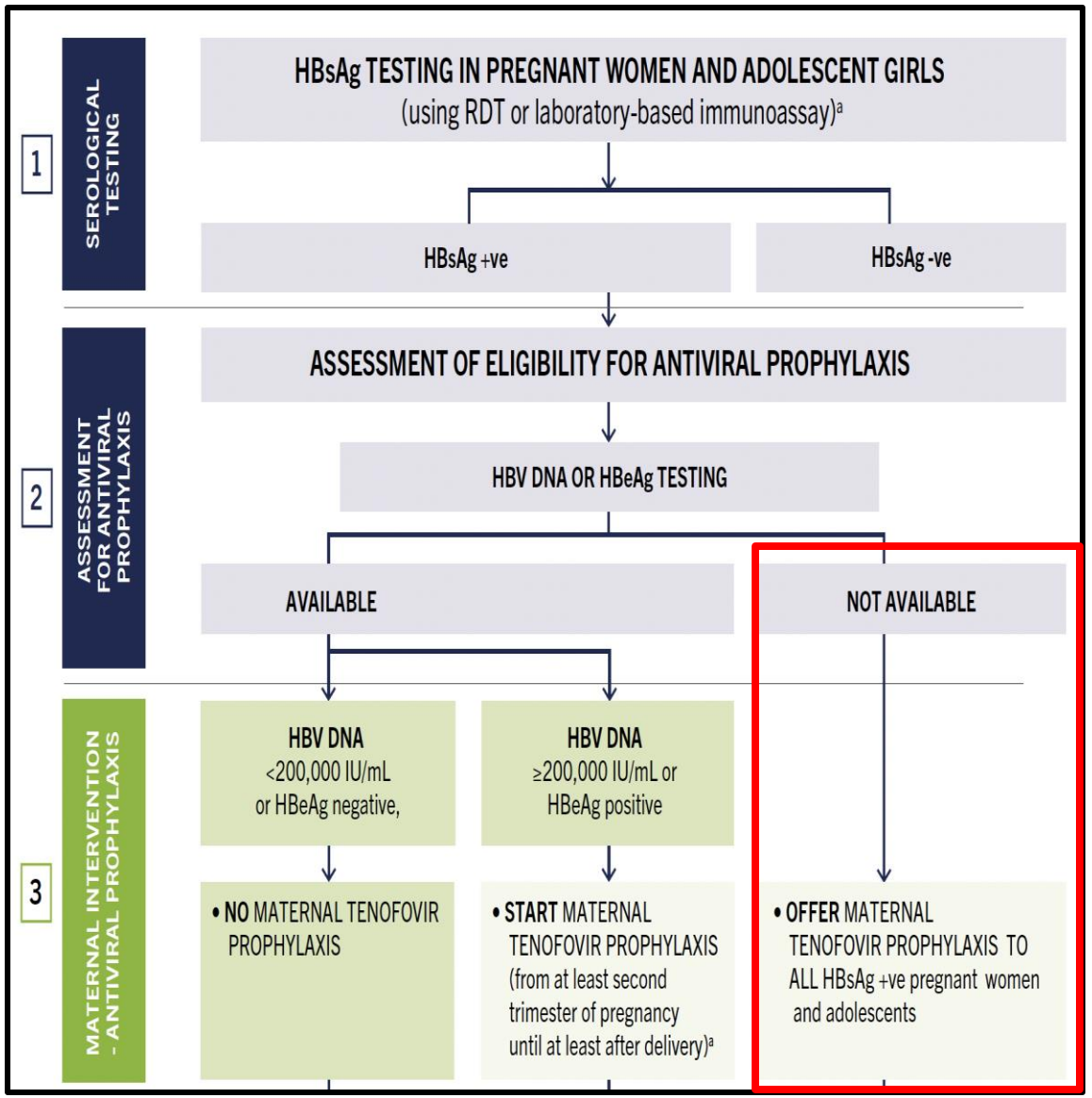
New 2024 recommendation

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)

*Preferably **from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series)**, to prevent MTCT of HBV. Can be continued if planning future pregnancies.

All interventions should be given in addition to at least three doses of hepatitis B vaccination for all infants, including a timely birth dose.



Implementation: Antiviral prophylaxis for PMTCT

Increased coverage of HepBD vaccination should be priority

- **Gavi funding:** Introducing and scaling up HB-BD vaccination: Eligible LIC countries

Universal testing for HBsAg, HIV and syphilis for pregnant women

- WHO recommends that all pregnant women routinely tested for HIV, syphilis & HBsAg during pregnancy as part of a triple MTCT elimination strategy

Increased health-care worker capacity

- Increased number of trained HCWs in antenatal clinic settings required to support expanded HepB antiviral prophylaxis and monitoring after treatment

Simplified, integrated HIV, HBV & syphilis ANC testing & treatment pathways

- Key to support implementation of HBV DNA-driven or universal hepatitis B prophylaxis

World Health Organization

Recommendations: POC & Reflex HBV 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 testing:

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)

World Health Organization

Product	Xpert HBV DNA	Truenat HBV
Manufacturer	Cepheid	Molbio
Analyser	Cepheid GeneXpert Instruments (GeneX-pert-II, GeneXpert-IV, GeneXpert-XVI Instruments)	Truelab Real Time micro PCR platform (UNO/DUO/QUATTRO / QUATTRO 4x4)
Cost	US$ 14.90 ex works per assay,[a] about US$ 17 000–70 000 per machine	US$ 12 ex works per assay[a]
Assay	Specimen type: plasma, serum Limit of detection 6 IU/mL	Specimen type: plasma, serum, whole blood Limit of detection 56 IU/mL
Regulatory approval	CE-Mark	No stringent regulatory authority approval

Three systematic reviews

- **Diagnostic accuracy of POC assays review** (15 studies): high sensitivity (96–98%) and specificity (98–99%))
- **Clinical impact review of POC assays** (7 studies) showed high uptake of testing (89% (95% CI 55–100%) and of treatment initiation (88% (95% CI 66–100%).
- **Clinical impact review of Reflex HBV DNA testing** (8 studies) showed high uptake of HBV DNA testing and treatment initiation.

Recommendation: HDV testing - Who to test?

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)

Limited access: HDV diagnostics & Rx: Africa

- High prevalence West and Central Africa
- Anti-HDV poor sensitivity: GT 5-8 & Africa GT 1
- Limited access to Bulevirtide

World Health Organization

Priority population testing approach

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:

- 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)
- People considered to have **increased risk of HDV** infection (haemodialysis recipients, people living with HCV or HIV, people who inject drugs, sex workers and men who have sex with men).

(conditional recommendation, very-low-certainty evidence)

Recommendations: HDV testing: How to test?

Diagnostic pathway

People with CHB (HBsAg positive) may be **diagnosed with hepatitis D by using a serological assay to detect total anti-HDV** followed by an **NAT to detect HDV RNA** and active (viraemic) infection among those who are anti-HDV positive.

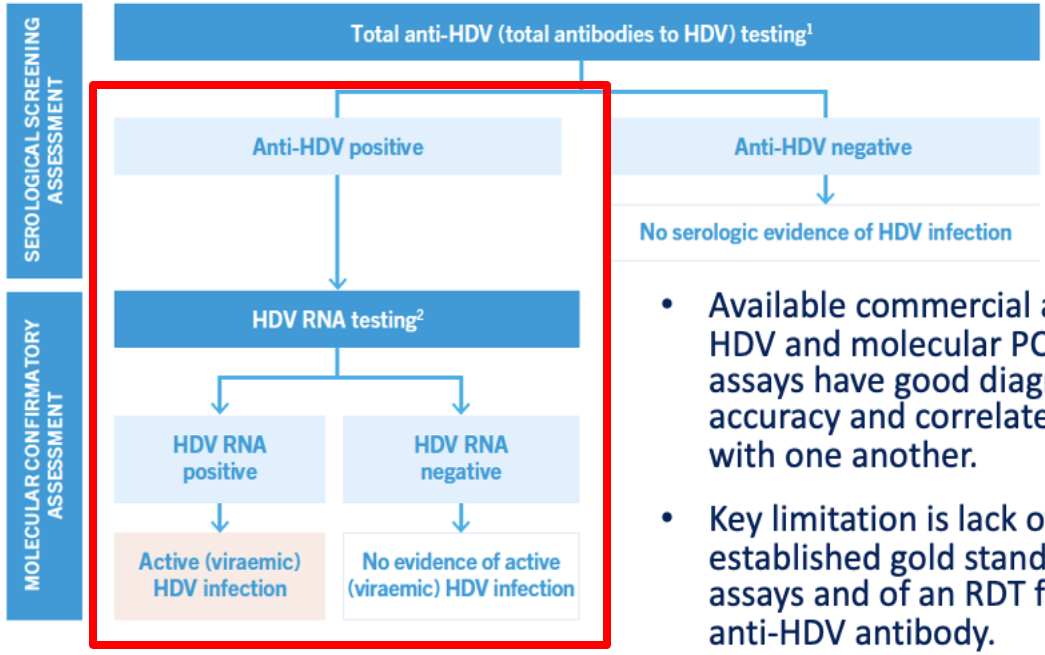
Assays should meet minimum quality, safety and performance standards.

(conditional recommendation, low-certainty evidence)

Reflex testing

Reflex testing for anti-HDV antibody testing following a **positive HBsAg test** result and also for HDV RNA testing (where available) following a positive anti-HDV antibody test result, may be used as an **additional strategy to promote diagnosis**.

(conditional recommendation, low-certainty evidence)

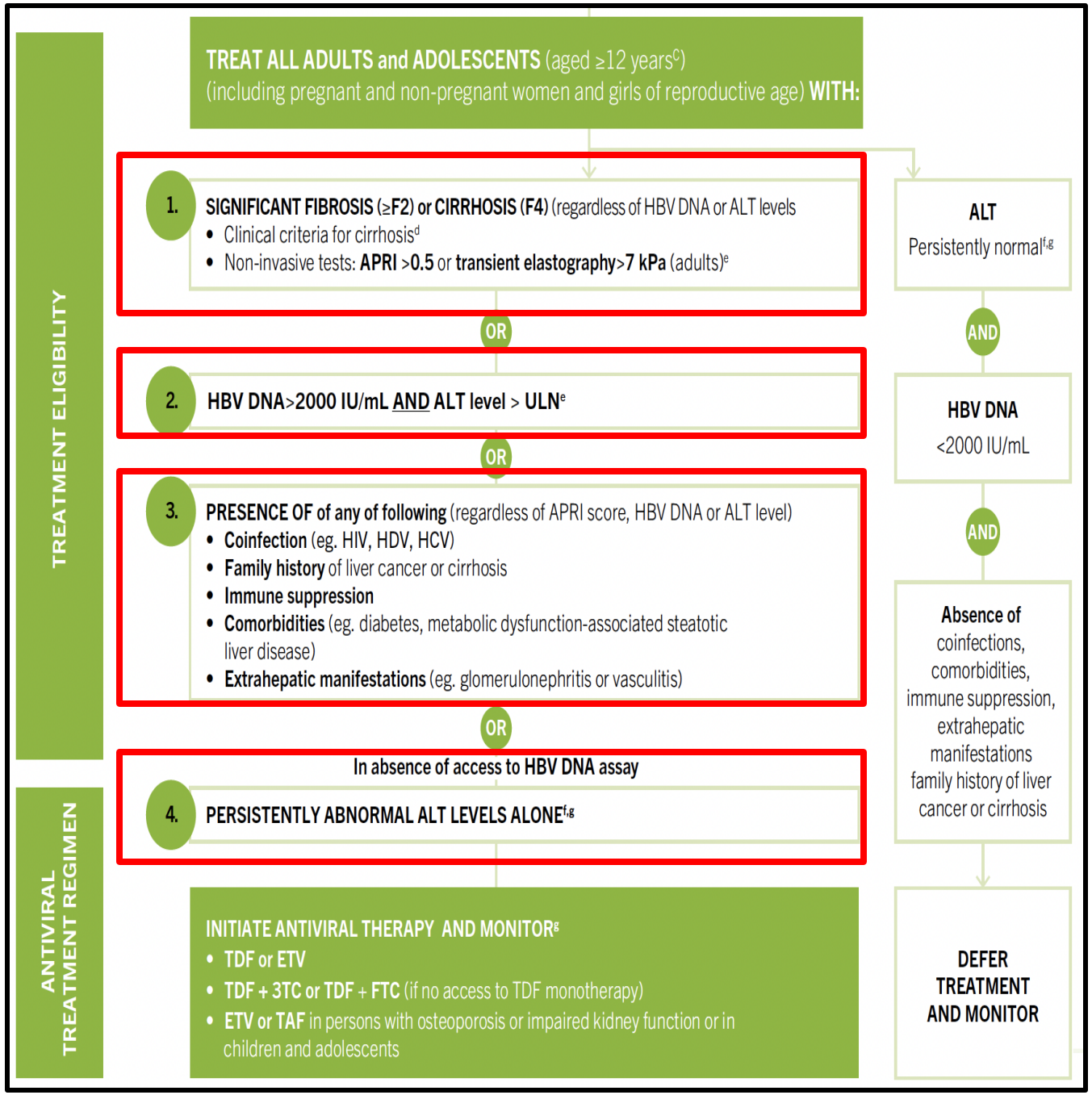


- Available commercial anti-HDV and molecular PCR assays have good diagnostic accuracy and correlate well with one another.
- Key limitation is lack of established gold standard assays and of an RDT for anti-HDV antibody.

Systematic review of reflex testing

- 11 studies of reflex anti-HDV Ab testing (3 had non-reflex comparator arm) in those HBsAg positive
- Increased uptake of serology testing (97% (95% CI: 92–100%) vs. 45% (95% CI: 0.3–98%) vs. non-reflex testing
- Very high uptake of reflex HDV RNA in those anti-HDV positive - 98% (95% CI: 77–100%) in 8 studies.

World Health Organization



WHO 2024 HBV Guidelines

Decentralise Diagnosis and Rx

Diagnostics

- POC HBsAg testing & Reflex HBV DNA
- Reflex anti-HDV and HDV RNA testing
- Clinic or Lab-based reflex testing

Diagnostic integration across programs using multi-disease testing platforms

- Existing platforms for HIV or HCV viral load or TB testing

World Health Organization

WHO 2024 Hepatitis B Guidelines: African Context

- Demystifies management of Hepatitis B
- Better addresses the epidemiology of HBV in Africa
- Addresses barriers/challenges of lack of access to HBV DNA quantification
- Enables decentralisation and integration of management
- Needs dedicated domestic funding for the viral hepatitis response
- SOLDA, GHASSA and Project ECHO: Disseminate HBV Guidelines through online webinars, workshops and iECHO clinics