Breaking boundaries – new guidance for Hepatitis B management

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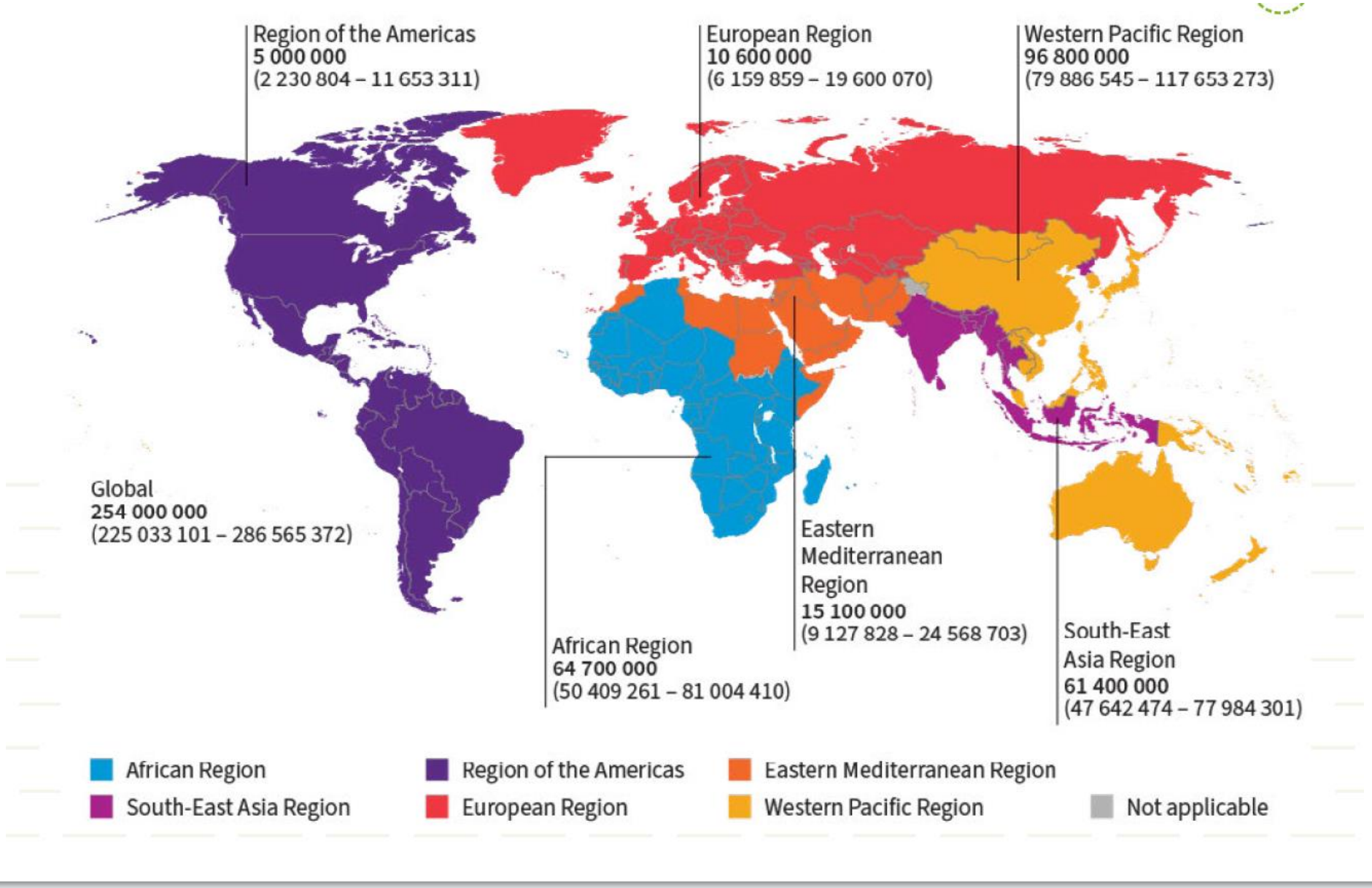
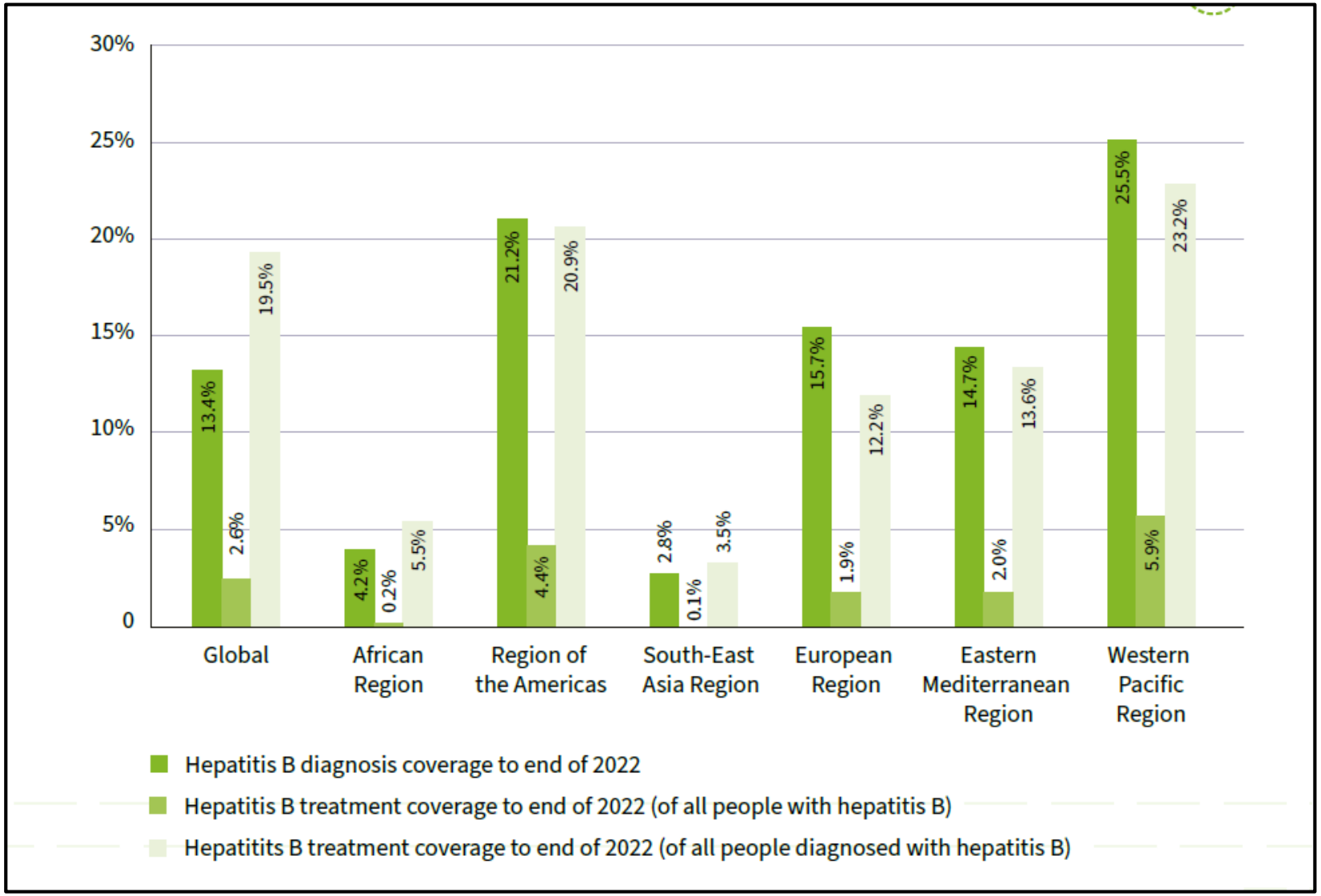
ELIMINATE ~~HEPATITIS~~

Prevalent cases of chronic hepatitis B by WHO region, 2022



In 2022, 13% of 254 million people with chronic HBV were diagnosed with 3% treated



WHO Global Hepatitis Report, 2024

Coverage of hepatitis B testing and treatment by WHO region, 2022

WHO region	Total number of hepatitis B infections (all ages) in 2022	Number of people with hepatitis B infection diagnosed, end 2022	Number of people receiving hepatitis B treatment, end 2022	Diagnosis coverage, end 2022 (%)	Treatment coverage among all people with hepatitis B, end 2022 (%)	Treatment coverage among all people diagnosed, end 2022 (%)
African Region	64 700 000	2 700 000	150 000	4.2%	0.2%	5.5%
Region of the Americas	5 000 000	1 100 000	220 000	21.2%	4.4%	20.9%
South-East Asia Region	61 400 000	1 800 000	60 000	2.8%	0.1%	3.5%
European Region*	10 600 000	1 700 000	200 000	15.7%	1.9%	12.2%
Eastern Mediterranean Region	15 100 000	2 300 000	300 000	14.7%	2.0%	13.6%
Western Pacific Region	96 800 000	24 700 000	5 720 000	25.5%	5.9%	23.2%
Global	254 000 000	34 100 000	6 650 000	13.4%	2.6%	19.5%

Source: Global Hepatitis Reporting System, WHO.

WHO Global Hepatitis Report, 2024

Mr. LZ

38 y.o man

- First time blood donor
- HBsAg positive, NAT positive
- HIV negative, Hep C negative
- Married with 2 children – age 10 & 6
- Non-smoker, minimal social alcohol
- Examination – normal liver span, normal clinical findings
- BMI 32

Results

TBr	14
CBr	6
Alb	39
ALP	110
GGT <50	52
ALT <40	42
AST <40	47
WCC	6,9
Platelets	187
Hb	14,8
INR	1,1
Cholesterol	6,2
TG	2,4
HBA1C	6,4%
AFP	7,7 (0-7)

HIV – negative

Hep A total Ab – positive

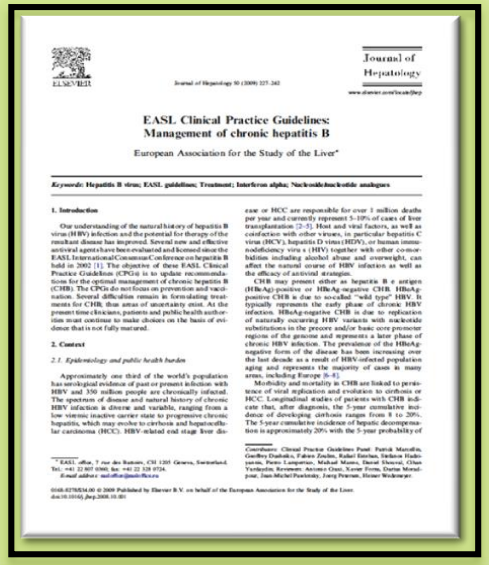
Hep C – negative

Hep BsAg–positive
Hep B eAg - negative
Hep B viral load - 1745 IU/ml

Ultrasound abdomen

Increased echogenicity of liver, normal span
Spleen, Gallbladder all normal
PV – patent
No HCC
No ascites

Multi-society HBV treatment guidance



EASL Clinical Practice Guidelines: Management of chronic hepatitis B

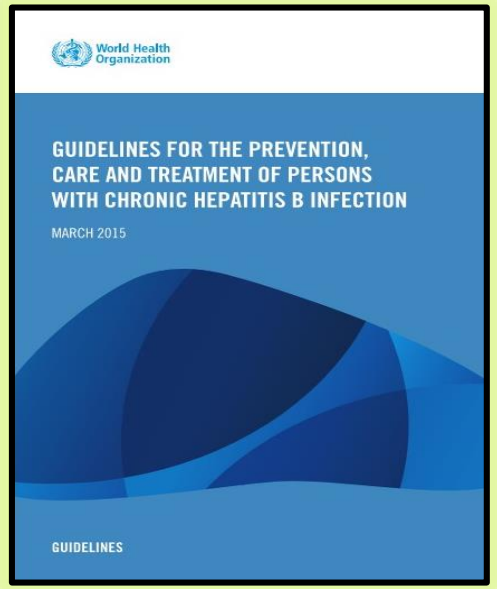
European Association for the Study of the Liver*

Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update

- Many iterations
- Aim of care – improve QO
  - improve outcome by preventing progression to cirrhosis, end-stage liver disease, HCC

AASLD PRACTICE GUIDELINES

Chronic Hepatitis B: Update 2009



World Health Organization

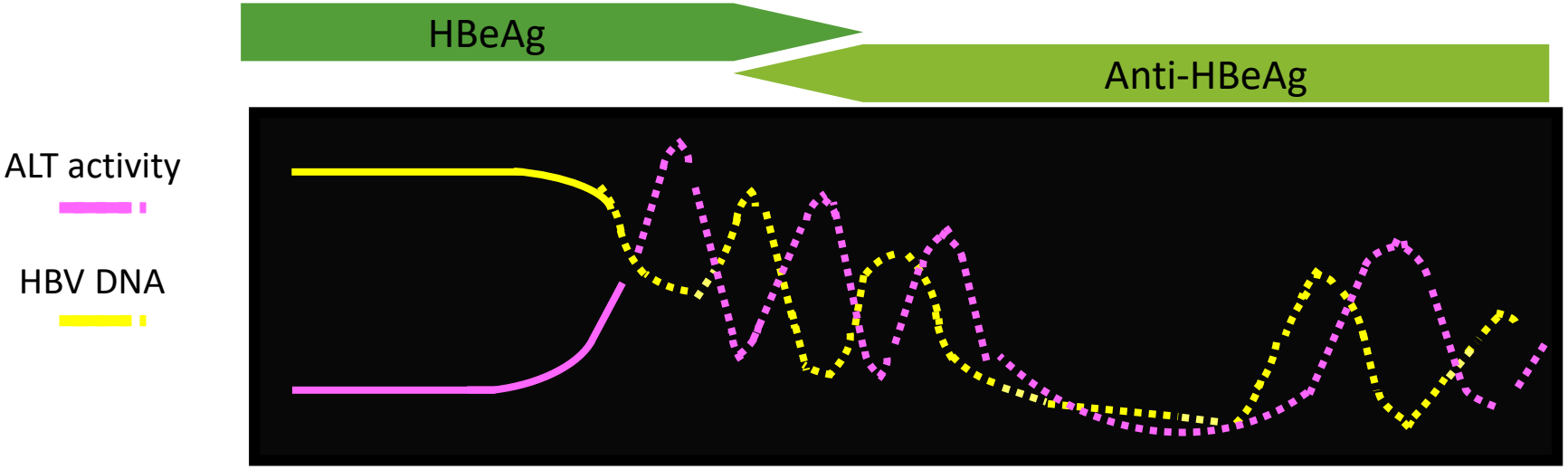
GUIDELINES FOR THE PREVENTION, CARE AND TREATMENT OF PERSONS WITH CHRONIC HEPATITIS B INFECTION

MARCH 2015

GUIDELINES

Phases of chronic HBV infection

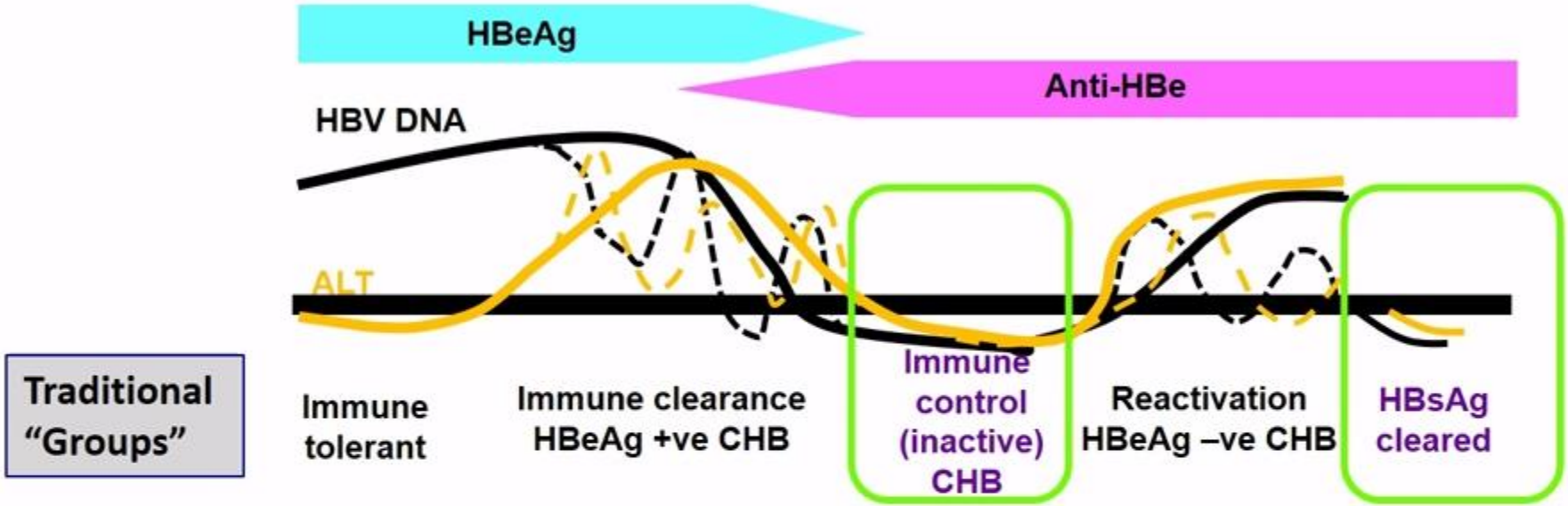
Natural history dynamic and complex. Phases have variable duration and are not necessarily sequential

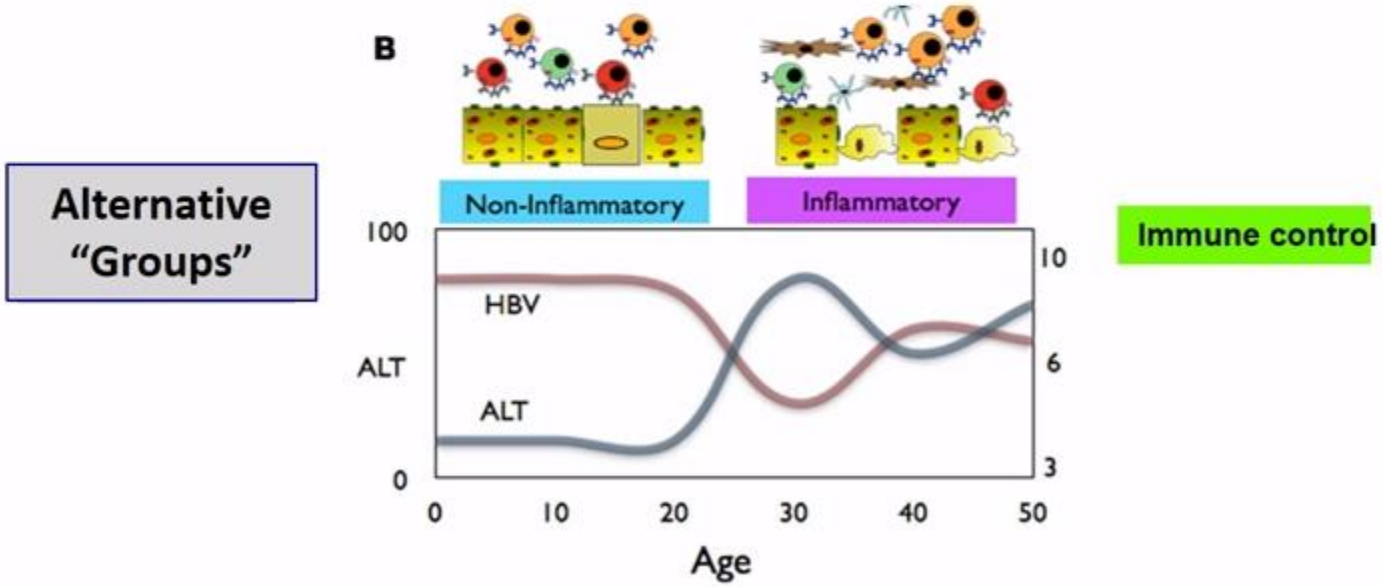


Phase	Immune Tolerant	Immune Active	Immune Control	Immune Escape/Reactive
Liver	Minimal inflammation and fibrosis	Chronic active inflammation	Mild hepatitis and minimal fibrosis	Active inflammation and progressive fibrosis

Yim HJ, et al. Hepatology. 2006;43:S173-S181.

New perspectives





Natural history of chronic HBV and treatment Indications

Parameter	HBeAg Positive		HBeAg Negative		Resolved HBV Infection
	Chronic *Infection*	Chronic *Hepatitis*	Chronic *Infection*	Chronic *Hepatitis*	
Old terminology	Immune tolerant	Immune active/clearance HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis/Immune reactive	HBsAg negative, anti-HBc positive
HBsAg	High	High/intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	> 10^7 IU/mL	10^4 to 10^7 IU/mL	< 2000 IU/mL*	> 2000 IU/mL	Undetectable
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe	None
Disease progression	Low	**Moderate to high**	Low	**Moderate to high**	None (HCC)
Treatment	Not indicated‡	**Indicated**	Not indicated	**Indicated**	Not indicated§

*HBV DNA levels up to 20,000 IU/mL can occur without signs of chronic hepatitis. †Persistently or intermittently. ‡Treatment is indicated in some patients. §Prophylaxis for select cases.

EASL. J Hepatol. 2017;67:370.

Summary - management of chronic HBV without cirrhosis

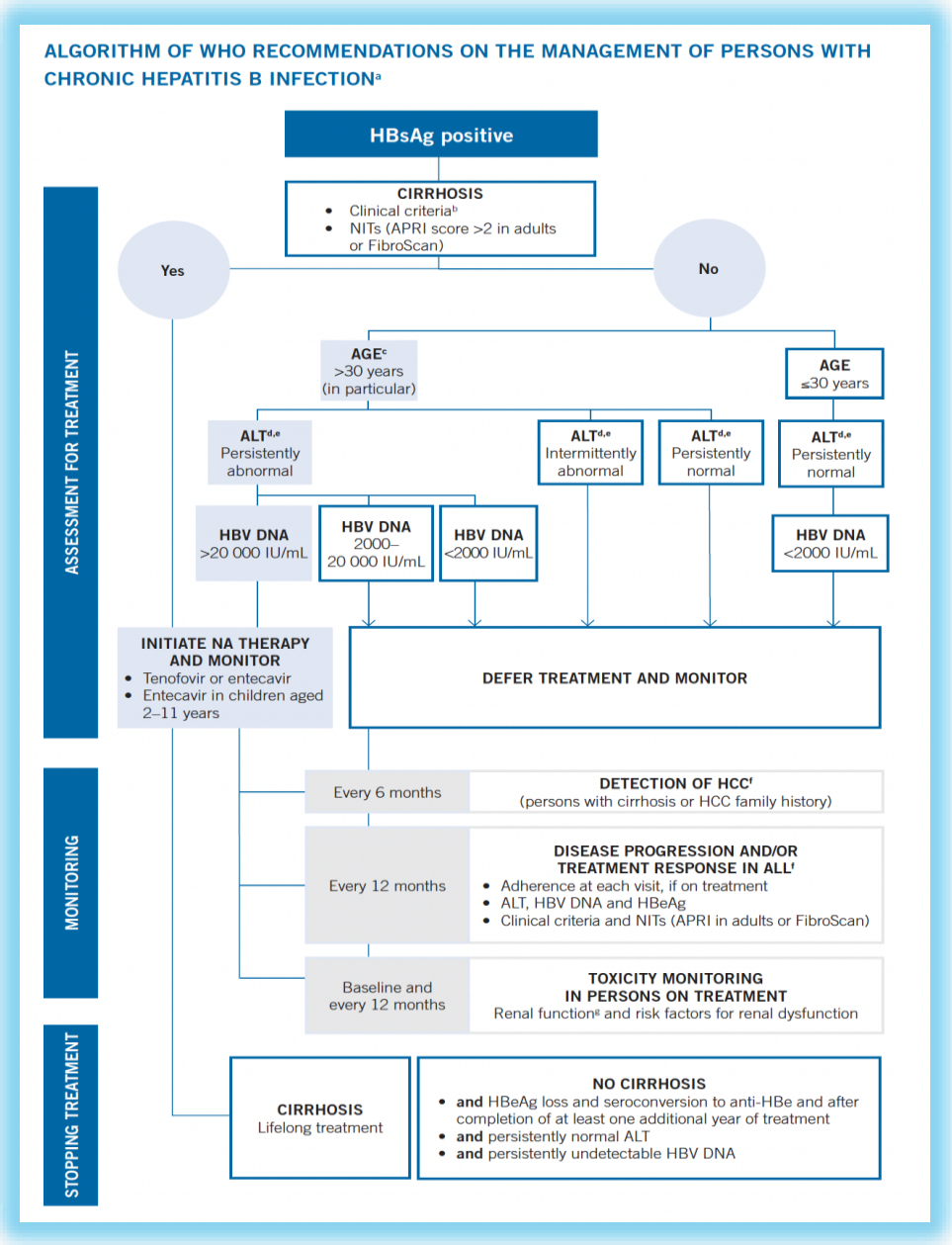
Threshold for Treatment	APASL[1] (2015)	EASL[2] (2017)	AASLD[4] (2018)
HBV DNA, IU/mL			
▪ HBeAg positive	> 20,000	> 2000	> 20,000
▪ HBeAg negative	> 2000	> 2000	≥ 2000
ALT	> 2 x ULN	> ULN	≥ 2 x ULN
▪ ULN for males	40 IU/mL	40 IU/L	35 U/L
▪ ULN for females	40 IU/mL	40 IU/L	25 U/L

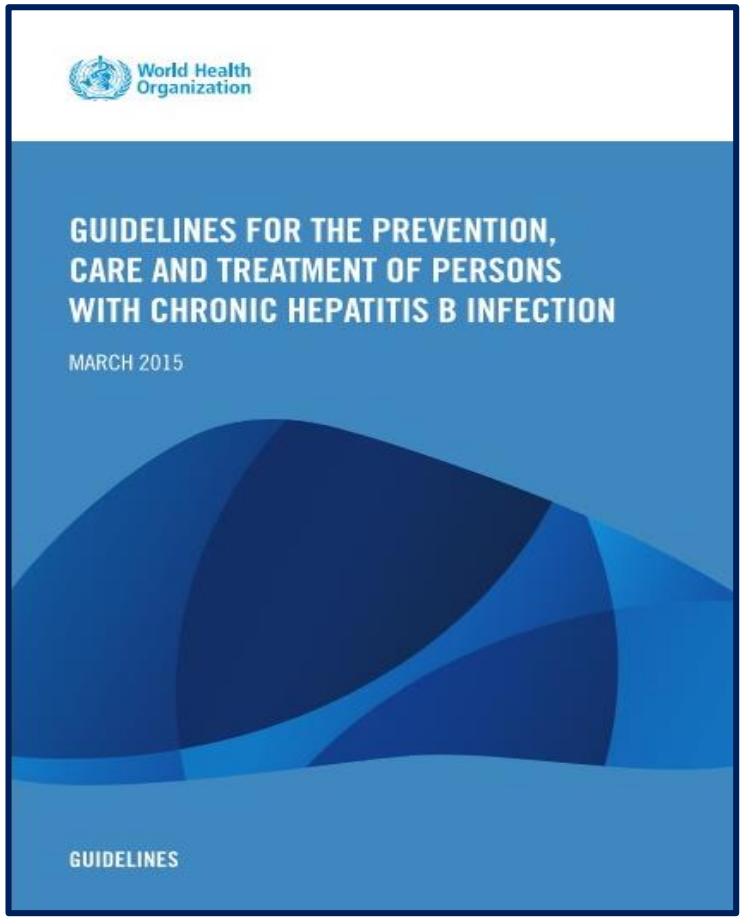
1. Sarin. Hepatol Int. 2016;10:1. 2. EASL. J Hepatol. 2017;67:370. 3. Martin. Clin Gastroenterol Hepatol. 2015;13:2071. 4. Terrault. Hepatology. 2018;67:1560.

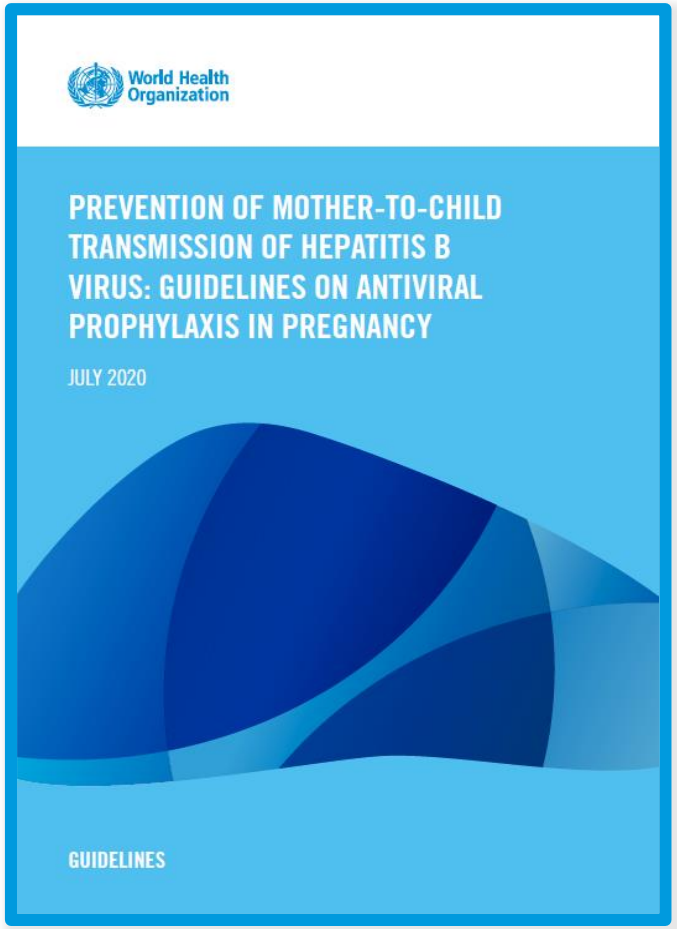
Association Guidelines for Preventing HBV MTCT

EASL	2017	TDF LAM, LdT	Second trimester of pregnancy	HBV DNA >$2x10^5$ IU/mL, HBsAg levels > 4 logs IU/mL
AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES	2018	TDF LAM, LdT	28-32 weeks of gestation	HBV DNA >2×10^5 IU/mL.
APASL	2015	TDF, LdT	28-32 weeks of gestation	HBV DNA >$10^{6–7}$ IU/mL

HBV Guideline Recommendations (2015) and PMTCT (2020)







Perspectives

- **ALT > ULN but < 2 x ULN** requires consideration of liver disease severity by biopsy or noninvasive testing
  - Other factors to consider: age, family history of HCC or cirrhosis, previous treatment history, extrahepatic manifestations
- Low-level viremia (HBV DNA < 2000 IU/mL) and **compensated cirrhosis** should be treated, regardless of ALT
- **Decompensated cirrhosis** and HBsAg positive must be treated, regardless of HBV DNA, HBeAg status, or ALT
- **Immune-tolerant adults >40 yrs of age** (ie, normal ALT, HBV DNA > 1 million IU/mL, and liver biopsy showing significant necroinflammation or fibrosis) should be treated

Terrault. Hepatology. 2018;67:1560.

Civil society

“At the World Health Assembly in 2016, WHO made a historic commitment to eliminate viral hepatitis by 2030. However, with only 7 years left, most countries are not on track to reach this target and over a million people continue to lose their lives to hepatitis each year. Egypt has shown that hepatitis elimination is possible, but a substantial scale up in the response is required if more countries are to reach this milestone.”

Danjuma Adda; Jessica Hicks; Cary James, Alexandra Smith

Vol 9, Issue 4, P281-282, April 2024

“Viral hepatitis: time for action”

“WHA calls for a treat all approach for hepatitis B in the Lancet”

World Hepatitis Alliance

THE LANCET
Gastroenterology & Hepatology

The need for updated WHO HBV guidelines?

- Still major gaps in testing and treatment uptake
- Guidelines complex
- Regional differences in demographics + epidemiology
- Emerging evidence
- Access challenges

✓ Expanded and simplified treatment criteria

✓ Progressive simplification

✓ High birth rate and high % of population<20yrs (25% of all HBsAg+ve in SSA)
✓ Liver cancers at younger age in SSA
✓ 75% HBsAg+ve HBV DNA <2000 IU/mL in SSA

✓ Ongoing HBV DNA integration – oncogenicity
✓ Significant rate of ongoing new infections through MTCT in SSA
✓ More cohort data now available from SSA

✓ Limited access to HBV DNA in LMIC
✓ Low uptake of Hep BD in SSA

Focus of WHO Guidelines

Feature	WHO Guidelines	Other Guidelines
Settings	• Low- and middle-income countries • Generalised/concentrated epidemic settings	• High-income countries
Target audience	• National Program Managers	• Treating clinicians
Approach	• The "public health approach" • Simplified and standardized approaches • Preferred regimens	• Individualized treatment • Multiple treatment options
Formulating recommendations: Evidence-based approach	• GRADE - Feasibility, equity, end-user acceptability, resource use considered	• Variable use of evidence-based framework
Guidelines Committee representation	• 50% LMICs, programme managers, civil society	• Clinicians and researchers HICs

? Need for global harmonization of Guidance?

Key aspects of new HBV guidance - 2024

- Non-invasive fibrosis assessment
- Simplifying diagnosis
- Simplifying service delivery
- Who to treat?
- How to treat - first-line treatment?
- PMTCT

Non-invasive Assessment of liver disease

- **Evidence of significant fibrosis (≥F2)** should be based on **an APRI score of >0.5** or **transient elastography value of >7.0 kPa**

- Cirrhosis **(F4)** should be based on clinical criteria (varices, ascites etc)

  OR an **APRI score of >1.0**

  OR Transient elastography value of >12.5 kPa.

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	+++

Testing for HBV – HBsAg, HBV DNA

New recommendations:

HBsAg TESTING

Use a single quality assured serological in vitro diagnostic test
Laboratory-based immunoassay or
Rapid diagnostic test (RDT)) that meets minimum performance standards
Diagnostic accuracy of POC assays review (15 studies): high sensitivity (96–98%) and specificity (98–99%)

Table 2.1 Nomenclature and biomarkers characteristic of the different phases of hepatitis B

Nomenclature		HBeAg-positive infection	HBeAg-positive disease	HBeAg-negative infection	HBeAg-negative disease	Grey zone	Occult hepatitis B
Other terms		Immune tolerant	Immune (re)active	Inactive carrier state	Immune-active or HBeAg-negative disease	Indeterminate	None
Serology	HBsAg	Positive	Positive	Positive	Positive	Positive	Negative
	Quantitative HBsAg	3.5–4.5 log10 IU/mL	3.5–4.5 log10 IU/mL	2.5–3.5 log10 IU/mL	2–3 log10 IU/mL	2–3 log10 IU/mL	Negative
	HBeAg	Positive	Positive	Negative	Negative	Negative	Negative
	Anti-HBe	Negative	Negative	Positive	Positive	Positive	May be positive
	HBV DNA	Typically $>10^7$ IU/mL	Typically $>10^5$ to 10^7 IU/mL	$<10^5$ IU/mL	Typically 10^3 to 10^5 IU/mL	3.3 log10 (2000 IU/mL) to 4.3 log10 (20 000 IU/mL)	Low at detection limit
Biochemistry	ALT	Around ULN	Raised	Around ULN	Raised	Fluctuate around ULN	Around ULN
Histology	Liver biopsy	Minimal necroinflammation or fibrosis	Moderate or severe necroinflammation and varying degrees of fibrosis	Minimal necroinflammation and fibrosis	Moderate to severe necroinflammation or fibrosis	Minimal or low necroinflammation	Usually minimal or low necroinflammation Fibrosis can be present
cccDNA[a]	(Assumed)	Relatively high copy number per cell	Relatively high copy number per cell	Low copy number or transcriptional activity	Lower copy number but transcriptional activity	Low number and transcription variable	Data uncertain
Integrated HBV DNA	Usually assumed	Present	Present	Present and account for majority of HBsAg	Present and account for majority of HBsAg	Present	Present
HBcrAg	Measured	High levels	High levels	Low or undetected	Lower levels	May be detected	Data not available
HBV RNA	Measured	High levels	High levels	Low or undetected	Lower levels	May be detected	Data not available

Point-of-care (POC) HBV DNA :

POC HBV DNA nucleic acid testing (NAT) assays may be used as an **alternative approach** to laboratory-based HBV DNA testing for eligibility and monitoring

Reflex HBV DNA testing:

Reflex testing of HBsAg positive may be used as an additional strategy to promote linkage to care and treatment. Either l**aboratory-based** reflex HBV DNA testing or **clinic-based reflex** testing in a health-care facility through immediate sample collection following a positive HBsAg rapid diagnostic test (RDT)

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*

20-25% of HBsAg +ve

2.

3.

4.

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:

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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 males and 19 U/L for females). For adolescents, this should be based on ALT>ULN on at least two occasions in a 6- to 12-month period

20-35% of HBsAg +ve

3.

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OR

20-35% of HBsAg +ve

3. **Presence of coinfections** (such as HIV, hepatitis D or hepatitis C); **family history of liver ca** rosis; **immune suppression; comorbidities (**such as metabolic-associated steatotic liver disease**); or extrahepatic manifestations**, *regardless of the APRI score or HBV DNA or ALT levels*

5-8% of HBsAg +ve

4.

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[c]), *regardless of HBV DNA or ALT levels*

20-25% of HBsAg +ve

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OR

20-35% of HBsAg +ve

3. **Presence of coinfections** (such as HIV, hepatitis D or hepatitis C); **family history of liver ca… …sis; immune suppression; comorbidities (**such as metabolic-associated steatotic liver disease**); or extrahepatic manifestations**, *regardless of the APRI score or HBV DNA or ALT levels*

OR

5-8% of HBsAg +ve

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.*

20% of HBsAg +ve

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).

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)

World Health Organization

Preventing HBV MTCT of HBV using antiviral prophylaxis

Updated recommendation

If 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

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

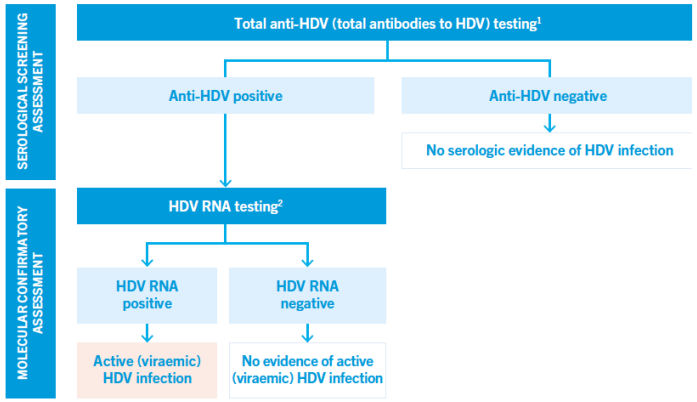
CAN BE BASED ON A RDT

HDV testing

New recommendations

Universal testing approach

- Serological testing for anti-HDV antibodies may be performed **for all individuals** who are HBsAg positive
- Serological assay to detect total anti-HDV
- Reflex testing

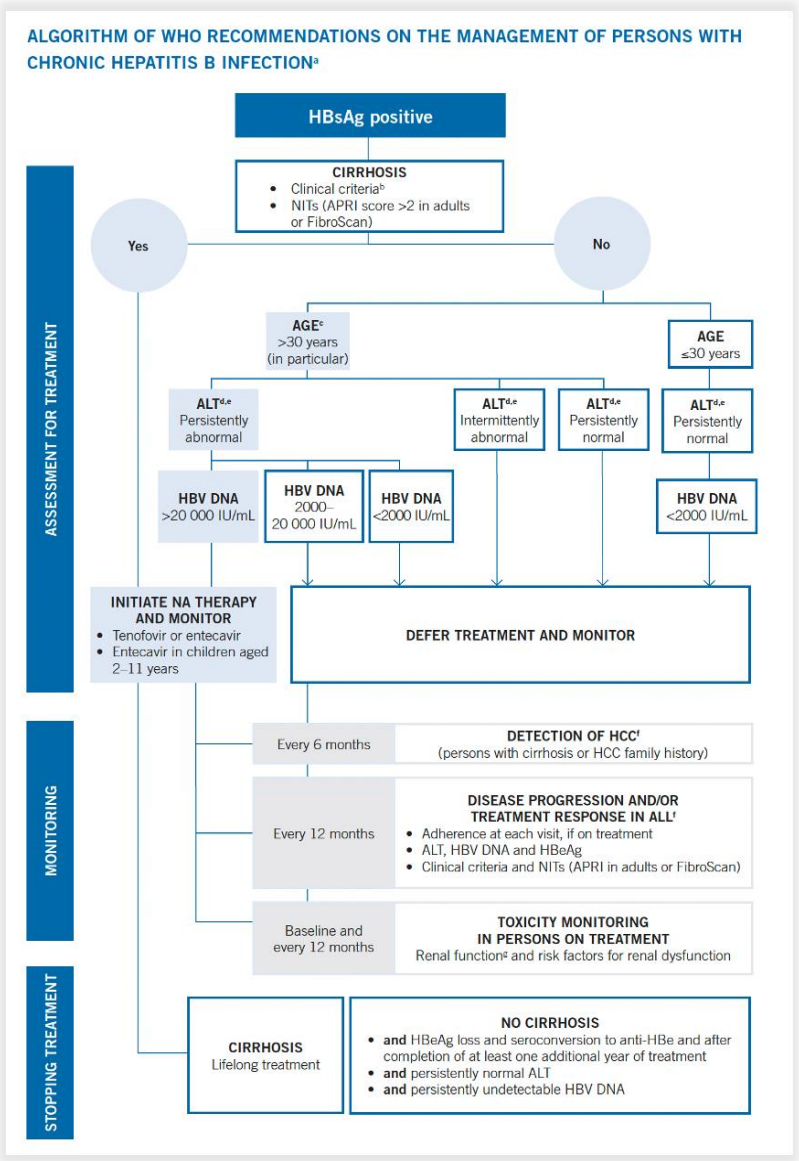


Priority population testing approach

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:

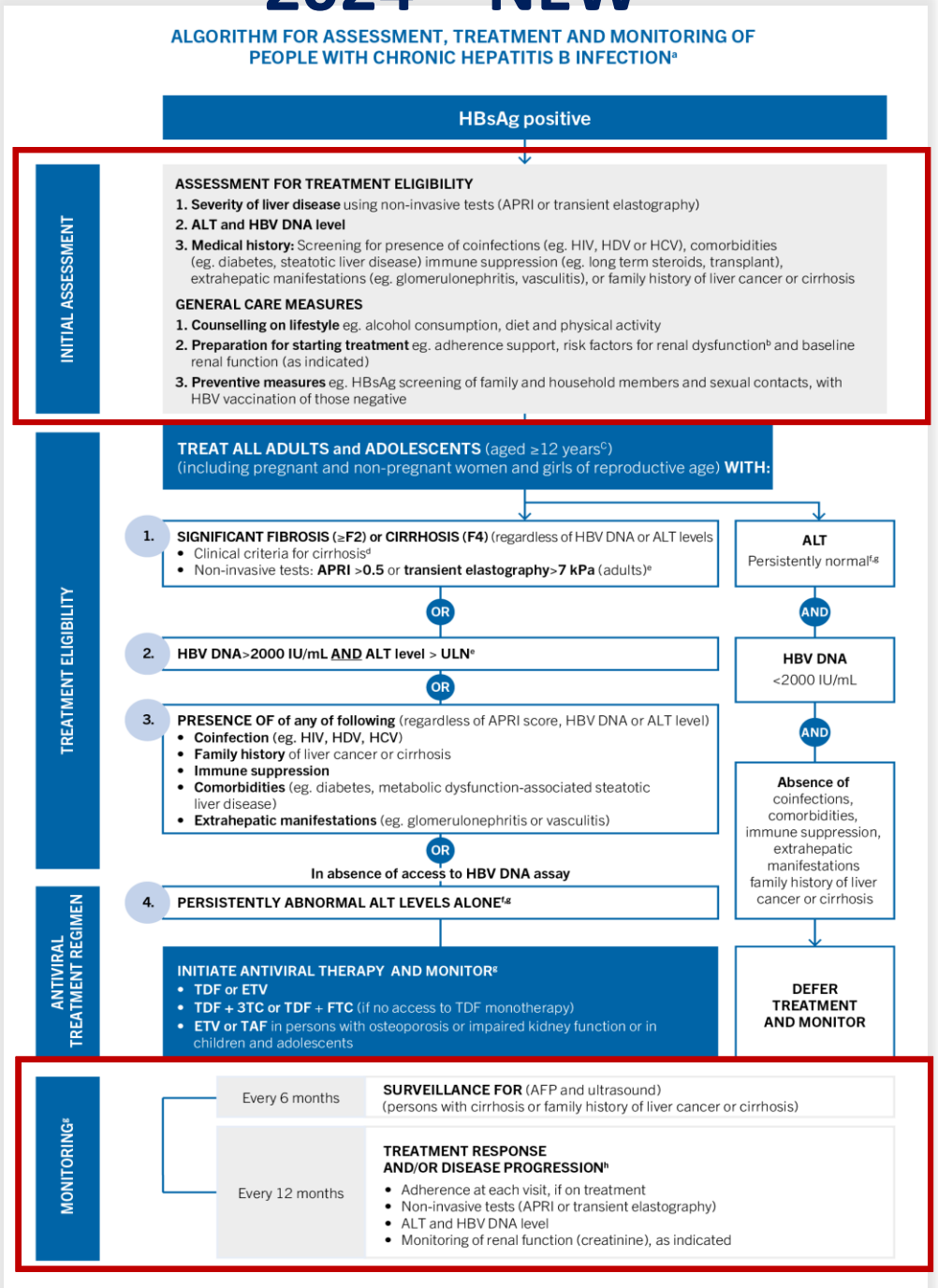
- people born in **HDV-endemic** countries, regions and areas;
- people with **advanced liver disease**, those receiving HepB treatment; and those with features suggesting HDV infection (such as low HBV DNA with high ALT levels); and
- people considered to have **increased risk** of HDV infection (haemodialysis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

2015



Expansion of care to capture ~50% of those HBsAg positive

2024 – NEW



Mr. LZ

38 y.o man

- First time blood donor
- HBsAg positive, NAT positive
- HIV negative, Hep C negative
- Married with 2 children – age 10 & 6
- Non-smoker, minimal social alcohol
- BMI 32 – US: **“Increased echogenicity of liver”**
- ALT 42 (>30)
- VL <2000

Hep BsAg-positive
Hep B eAg - negative
Hep B viral load - 1745 IU/ml

TBr	14
CBr	6
Alb	39
ALP	110
GGT <50	52
ALT <40	42
AST <40	47
WCC	6,9
Platelets	187
Hb	14,8
INR	1,1
Cholesterol	6,2
TG	2,4
HBA1C	6,4%
AFP	7,7 (0-7)

Mr LZ - ? liver disease assessment

- **APRI score: 0.6**
- **Fibroscan: 7.8 kPa CAP Score: 302 db**

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*

Presence of coinfections (such as HIV, hepatitis D or hepatitis C); **family history of liver cancer or** cirrhosis; **immune suppression; comorbidities (**such as metabolic-associated steatotic liver disease**); or extrahepatic manifestations**, *regardless of the APRI score or HBV DNA or ALT levels*

Mr LZ

Management

Start TDF 300mg daily

Address weight, lifestyle, diet, ? Statin?

6 monthly surveillance for HCC: AFP and Ultrasound liver

Wife to screen – vaccinate or manage if required

Scenarios showing window of action for 2024–2026 in scaling up viral hepatitis treatment and differences in infections, mortality, cancer cases and lives saved, 2015–2050