Challenges with current HBV nomenclature and a call for alignment

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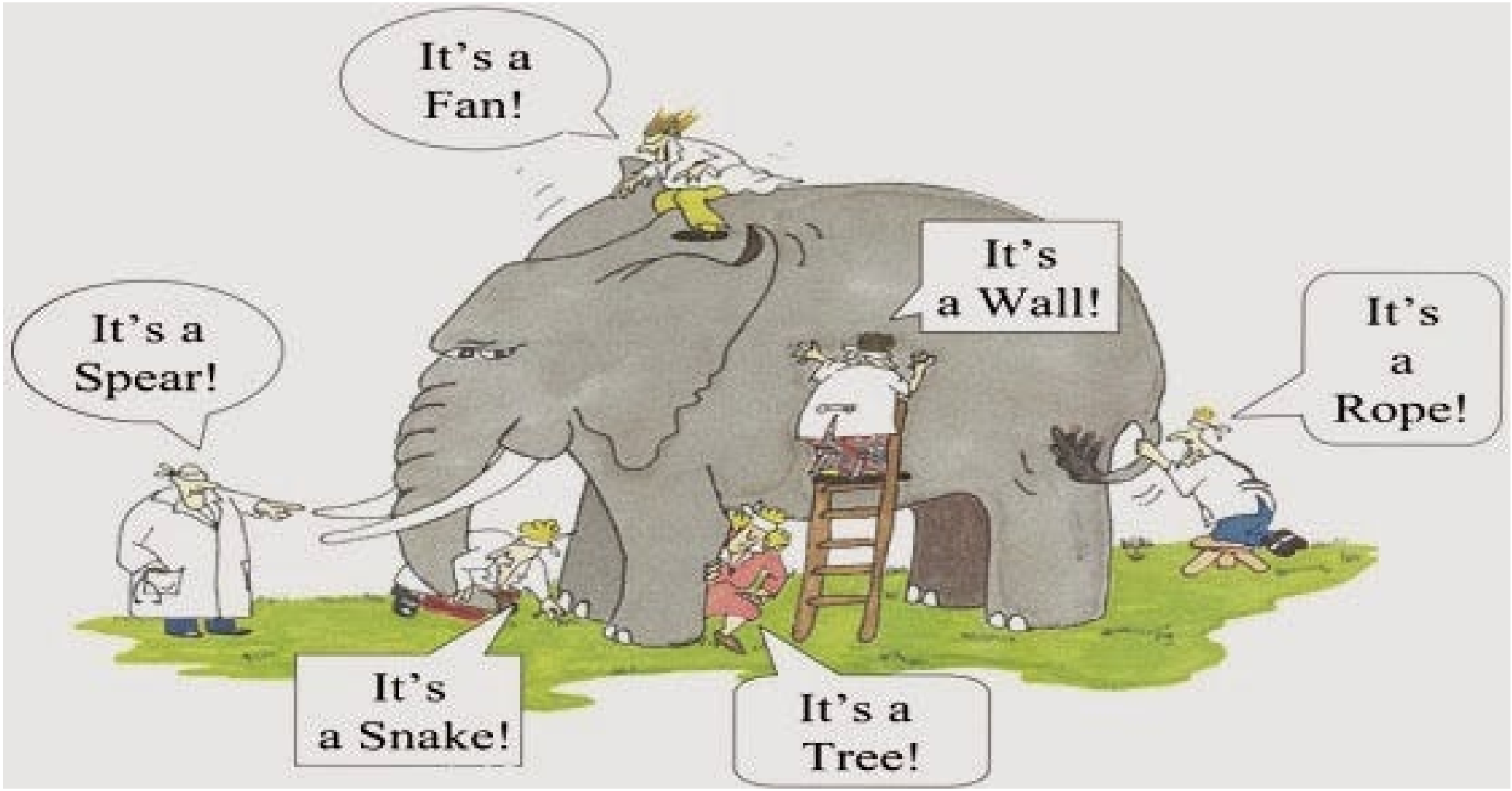
HBV Forum 13
November 14, 2024

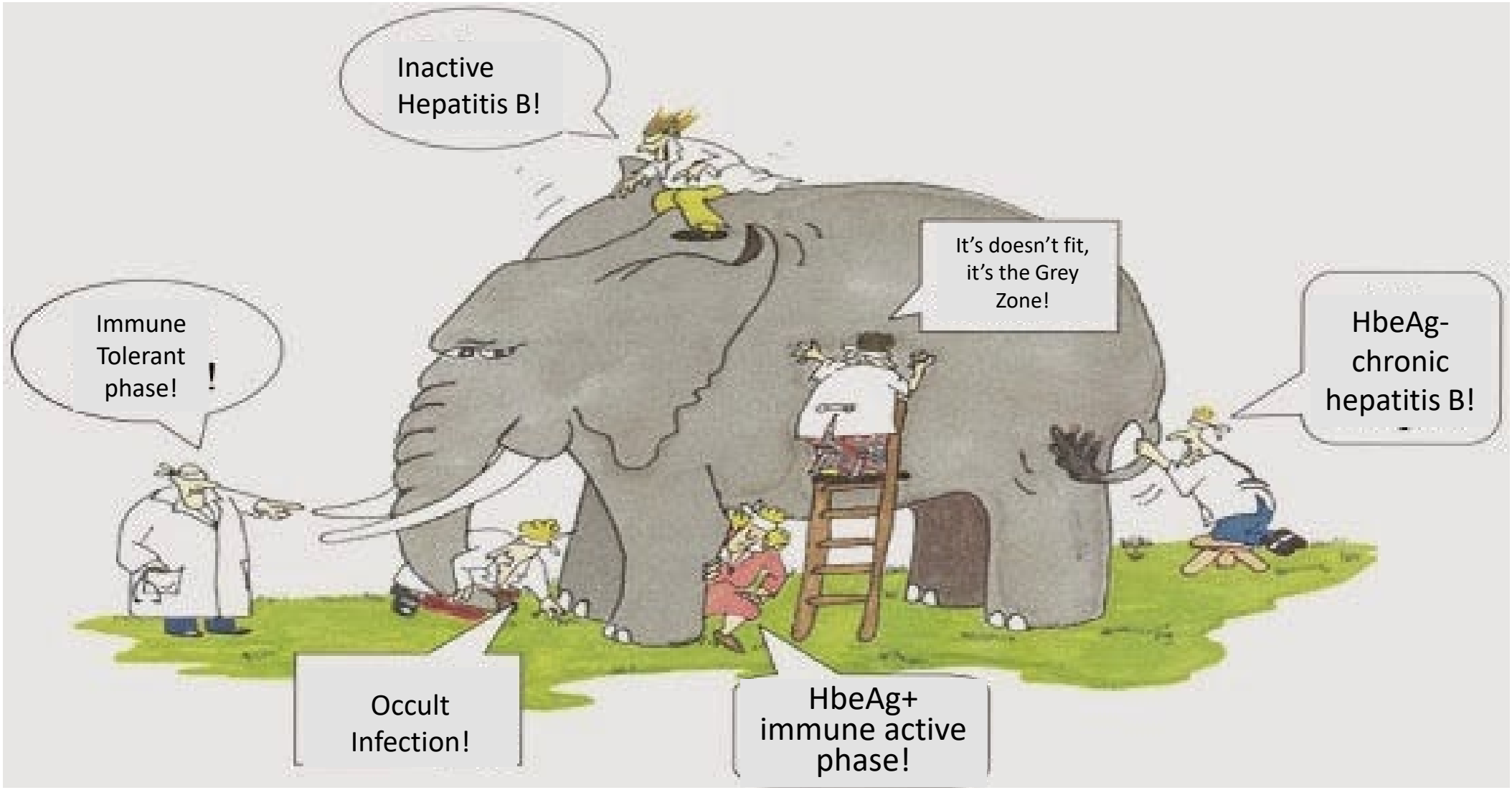
We are like the blind men and the elephant..



https://medium.com/betterism/the-blind-men-and-the-elephant-596ec8a72a7d

HBV nomenclature

Our attempt to describe a complex entity based on what we can observe



How we use HBV nomenclature

- Describe what we know of HBV and its natural course
- Identify states of the virus associated w worse outcomes

- Describe states of more activity and inflammation
- Describe states of inactivity or resolution

- Can define targets and outcomes of care & drug development

Where we are not aligned

- Names of HBV phases
  - Immune tolerant vs HBeAg+ chronic infection, hepatitis vs infection, inactive vs carrier, resolved vs occult, etc
- Definition of HBV phases
  - HBV DNA and ALT cut offs
- Normal ALT
- Treatment eligibility

We are observing the same elephant, but describing it differently
Descriptions are actually similar, just not exactly the same

Impact of non-alignment

- Lack of harmonization affects:
  - Providers
  - Researchers
  - Patients & community
  - Clinical trials
  - Regulators
  - EMRs and algorithms
- Not having clarity or consensus →
  - Perception that field is too complex and there is disagreement
  - Confusion of what is the correct approach
  - Reluctance to take on HBV care or other HBV efforts
- Harder for programs and research to be designed (more complex, more $)
- Diffused and decreased interest in the field

Now is the time to harmonize

- Urgency to reach hepatitis elimination, need to scale up HBV services & care
- Pivotal time in drug development
- Streamline approach and global applicability for
  - Studies
  - Clinical trials
  - Practice guidelines
- Need to focus limited resources in the HBV field
  - Harmonization increases reach and applicability of efforts
- Providers more likely to take on HBV care when there's clarity (& when simpler)
- Benefits the whole field & can draw more interest

Consensus → draws attention, unified voice is stronger

Current HBV Nomenclature by society (& ICD10)

WHO 2024 (Tx algorithm does not use HBeAg status	**EASL 2017**	**AASLD 2016**	**APASL 2015**	**ICD-10 coding (2015)**
HBeAg+ infection (immune tolerant)	Phase 1- **HBeAg+ Chronic HBV Infection** *Formerly:* Immune tolerant	**Immune tolerant phase**	**Immune Tolerant** HbeAg+, HBV DNA >2X10^7	B18.0 **Chronic viral hepatitis B w delta agent**
HBeAg+ disease (immune reactive)	Phase 2- **HBeAg+ Chronic hepatitis B** *Formerly:* Immune reactive HBeAg+	**HBeAg+ immune-active phase**	**Immune-reactive phase** • Immune active • Immune clearance • HBeAg+ CHB • HBeAg clearance phase	B18.1 **Chronic viral hepatitis B w/o delta agent**
HBeAg- infection (inactive carrier state)	Phase 3- **HBeAg- Chronic HBV infection** *Formerly:* Inactive carrier	**Inactive CHB phase**		B19.1 **Unspecified viral hepatitis B w/o hepatic coma**
HBeAg- disease (immune active or HBeAg- disease)	Phase 4- **HBeAg- Chronic hepatitis B** *Formerly:* HBeAg- chronic hepatitis	**HBeAg-negative immune reactivation phase**	**HBeAg+ chronic HBV infection**	B19.0 **Unspecified viral hepatitis B w/ hepatic coma**
Grey zone (indeterminate)			**HBeAg- chronic HBV infection**	
Occult hepatitis B	Phase 5- **Resolved HBV Infection** *Formerly:* HBsAg-/anti-HBc positive	Resolved CHB Infection		

Traditionally have used natural hx categories to determine when to treat

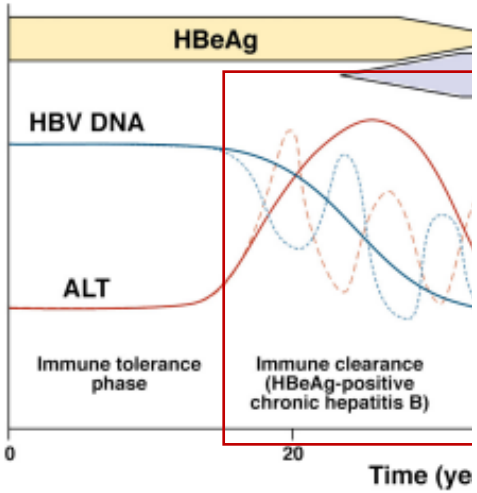
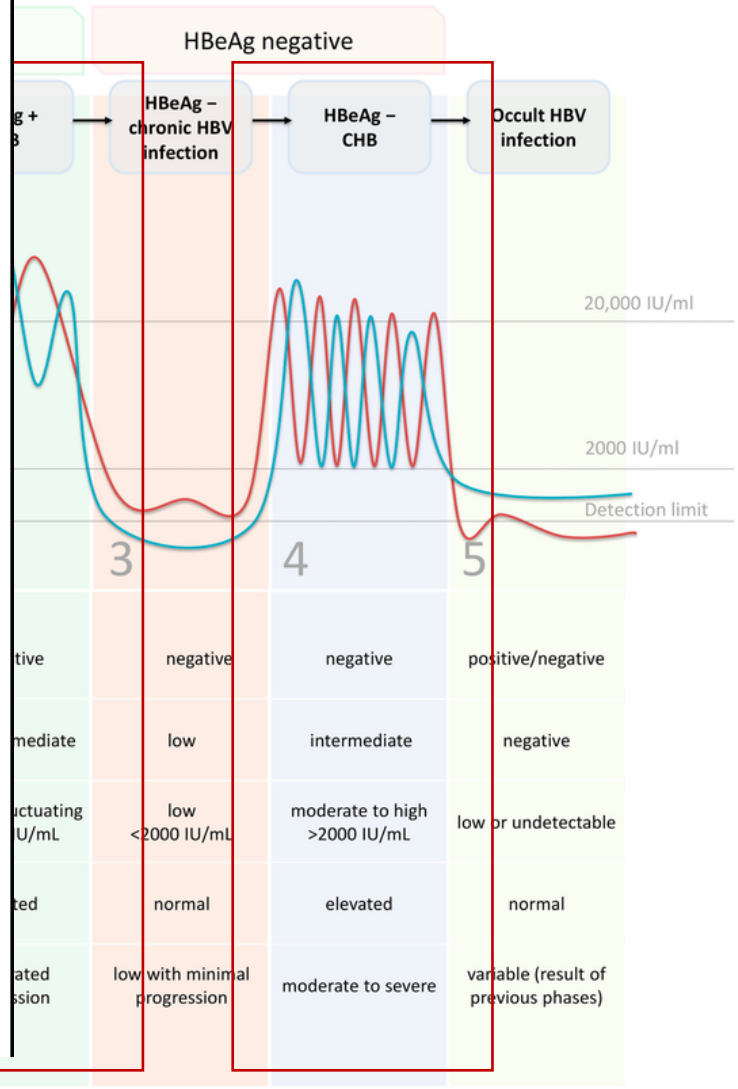
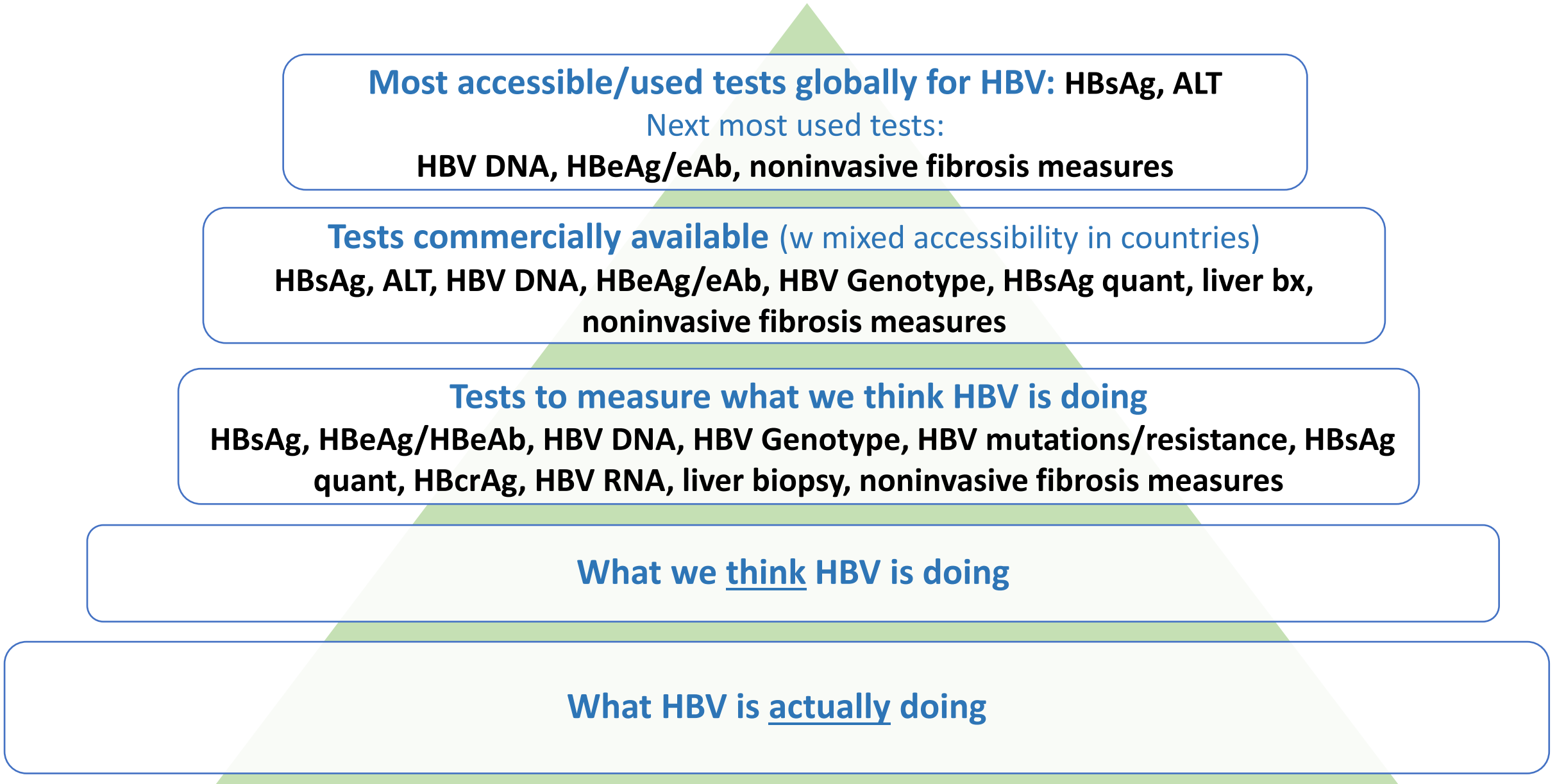


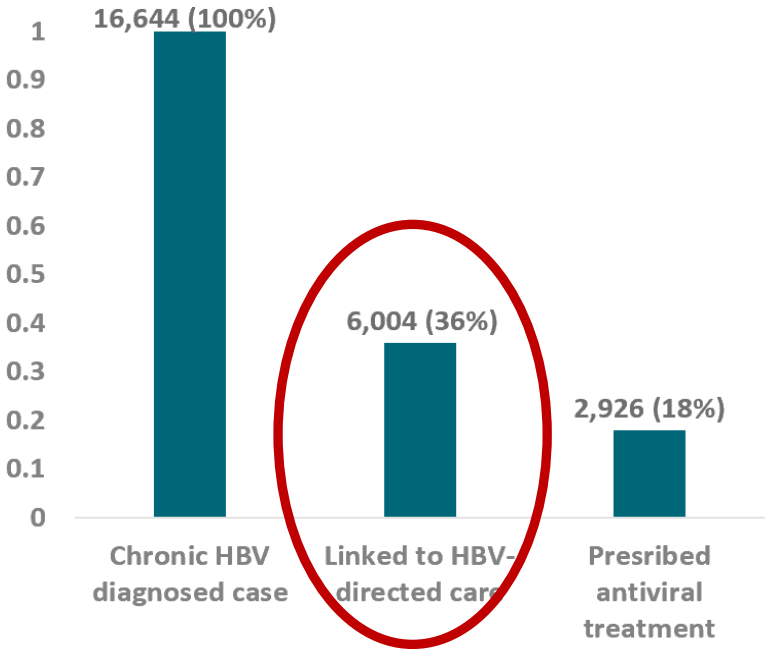
Figure 1. The natural course of chronic HBV infection consists
the presence of HBeAg, high HBV DNA levels, and persistently
immune clearance phase is characterized by the presence of
outcome of the immune clearance phase is HBeAg seroconvers
which is characterized by the absence of HBeAg and the prese
IU/mL), normal ALT levels, and no/minimal inflammation on l
absence of HBeAg, intermittent/persistently increased ALT and
with permission from Lok.[4]

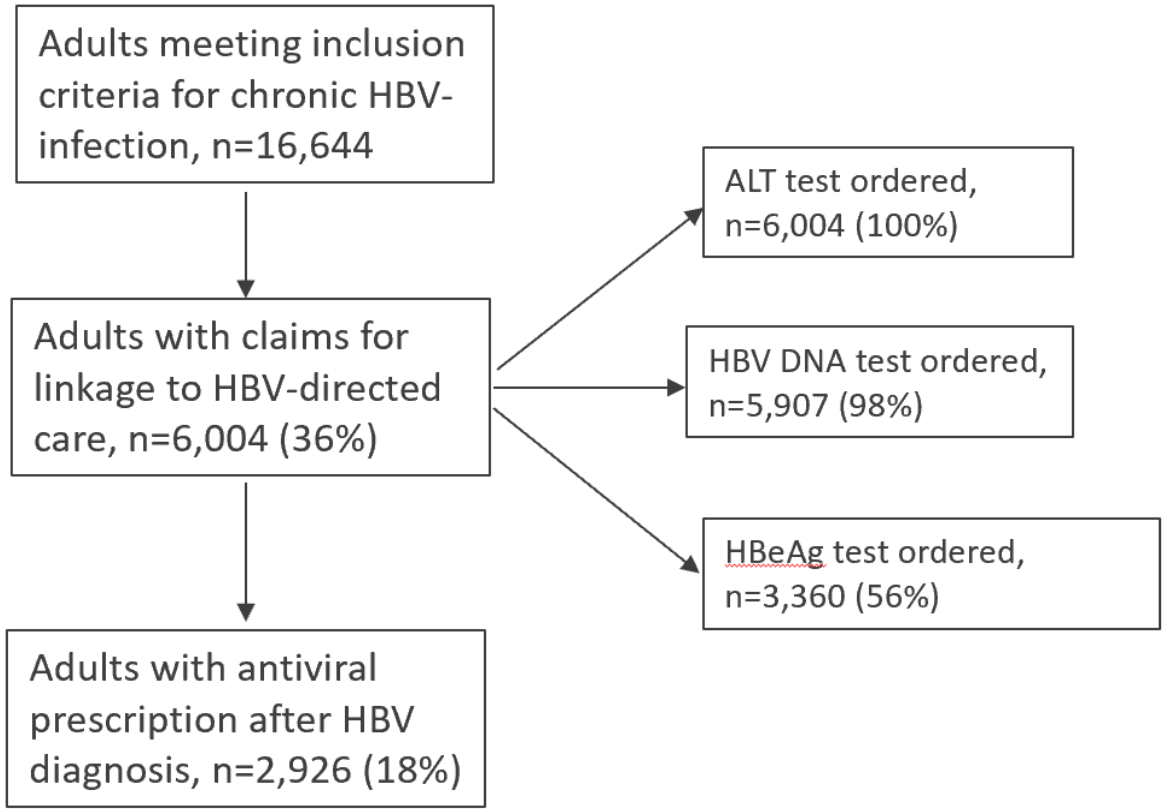


Our imperfect ascertainment of hepatitis B activity & test access



Linkage to Care and Treatment among Adults with Chronic Hepatitis B Virus Infection Using Commercial Claims Data, United States, 2008–2016





Of 16,600 w HBV, only 36% got HBV directed care.

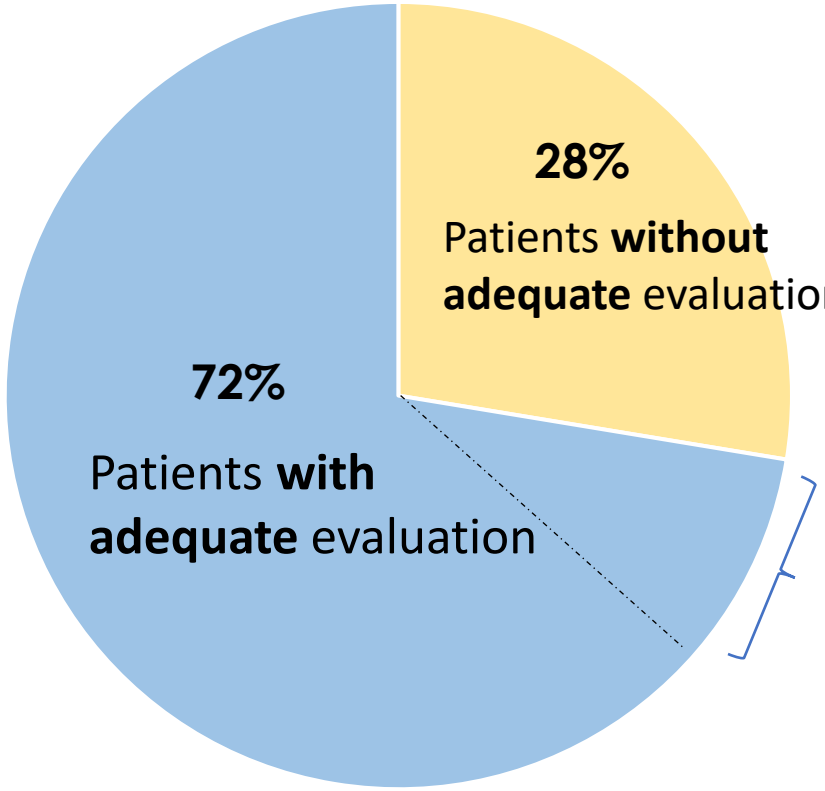
- Of those, 100% had ALT ordered, 98% had HBV DNA, 56% had HBeAg ordered

→ The more tests needed for treatment eligibility, the fewer patients get evaluated

Harris, A, et al. "Linkage to Care and Treatment among Adults with Chronic Hepatitis B Virus Infection Using Commercial Claims Data, United States, 2008–2016" The American Journal of Managed Care, August 2020, Volume 26, Issue 08

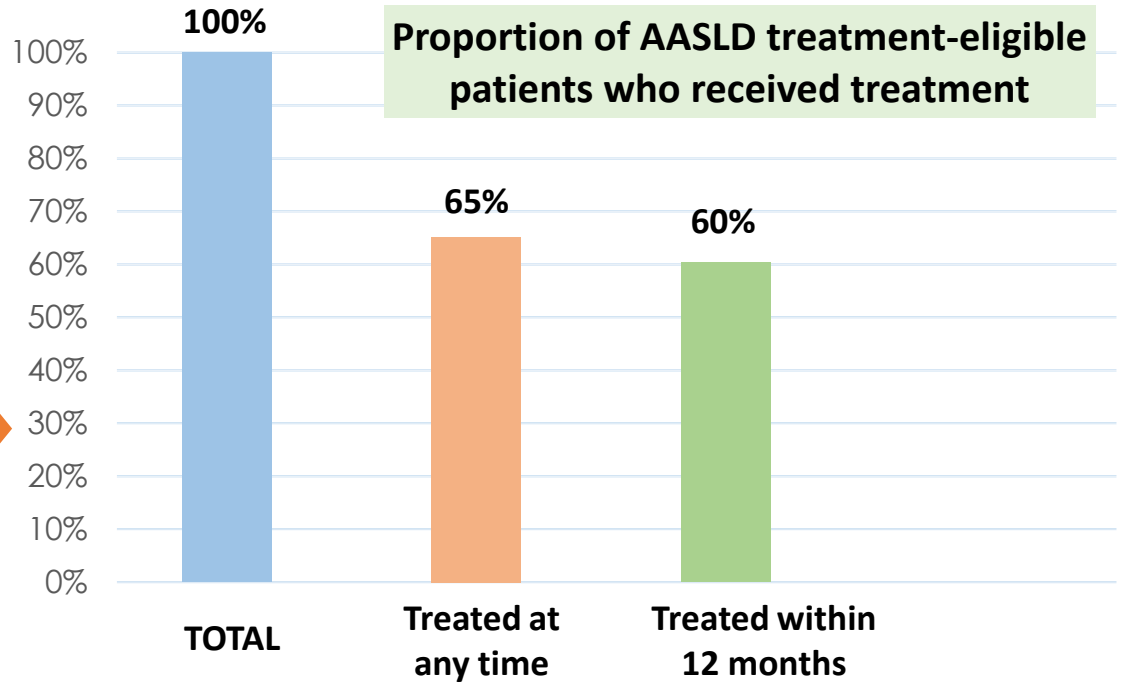
US Study: Low treatment rate among HBV patients meeting guideline criteria for antivirals

Optum Clinformatics® Data Mart Database, 2003-2019, 73 million enrollees
N=12,608 patients with confirmed chronic hepatitis B infection



Treatment-eligible patients

11% by AASLD
14% by EASL



*No significant change between 2003-2010 and 2011-2019

Mean age 46 years, 52% male
55% Asian, 18% Caucasian, 11% African American

Ye Q/Nguyen MH, J Hepatol 2021, PMID: 34474097

Issues with natural history staging for treatment eligibility

- **Real life phase determination challenging & not timely**
  - Studies of people immune tolerant show they have do have histologic activity
  - Studies show gray zone with higher risk of HCC
  - Many people with normal ALT have been shown to have fibrosis
  - Many peoples are not tested enough to catch changes and many fall out of care

- **Many patients not being treated who could benefit**
  - Waiting for signs of inflammation may not be the best approach
  - Our efforts to expand HBV treatment conflict with efforts to perfectly assess patients

Separate natural history assessment from treatment indications

Yoo JJ et al. Long-term prognosis and the need for histologic assessment of chronic hepatitis B in the serological immune-tolerant phase. Clin Mol Hepatol. 2023 Apr;29(2):482-495. PMC10121308.
Liu,et al. Presence of Liver Inflammation in Asian Patients With Chronic Hepatitis B With Normal ALT and Detectable HBV DNA in Absence of Liver Fibrosis. Hepatology Communications 6(4):p 855-866, April 2022
Mak LY, Yee LJ, Wong RJ, Ramers CB, Frenette C, Hsu YC. Hepatocellular carcinoma among patients with chronic hepatitis B in the indeterminate phase. J Viral Hepat. 2024 May 8.

Chinese HBV Guidelines 2022

Simplified algorithm- indications separate from staging & based on detectable viremia & other risk factors

Table 2. Phases of chronic HBV infection

Phases	HBeAg-positive chronic HBV infection (immune tolerance phase, chronic HBV carrier)	HBeAg-positive CHB (immune clearance phase, immune active phase)	HBeAg-negative chronic HBV infection (immune control phase, inactive HBsAg carrier)	HBeAg-negative CHB (reactivation phase)
HBsAg (IU/mL)	$>1\times10^4$	+	$<1\times10^3$	+
HBeAg	+	+	–	–
HBV DNA (IU/mL)	$>2\times10^7$	+	–	+
ALT	<ULN	Elevated (Persistently or repeatedly)	<ULN	Elevated (Persistently or repeatedly)
Liver histology	None/minimal necroinflammation and fibrosis	Obvious necroinflammation and/or fibrosis	Minimal/mild inflammation but different degrees of fibrosis	Obvious necroinflammation and/or fibrosis

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase; CHB, chronic hepatitis B; ULN, upper limit of

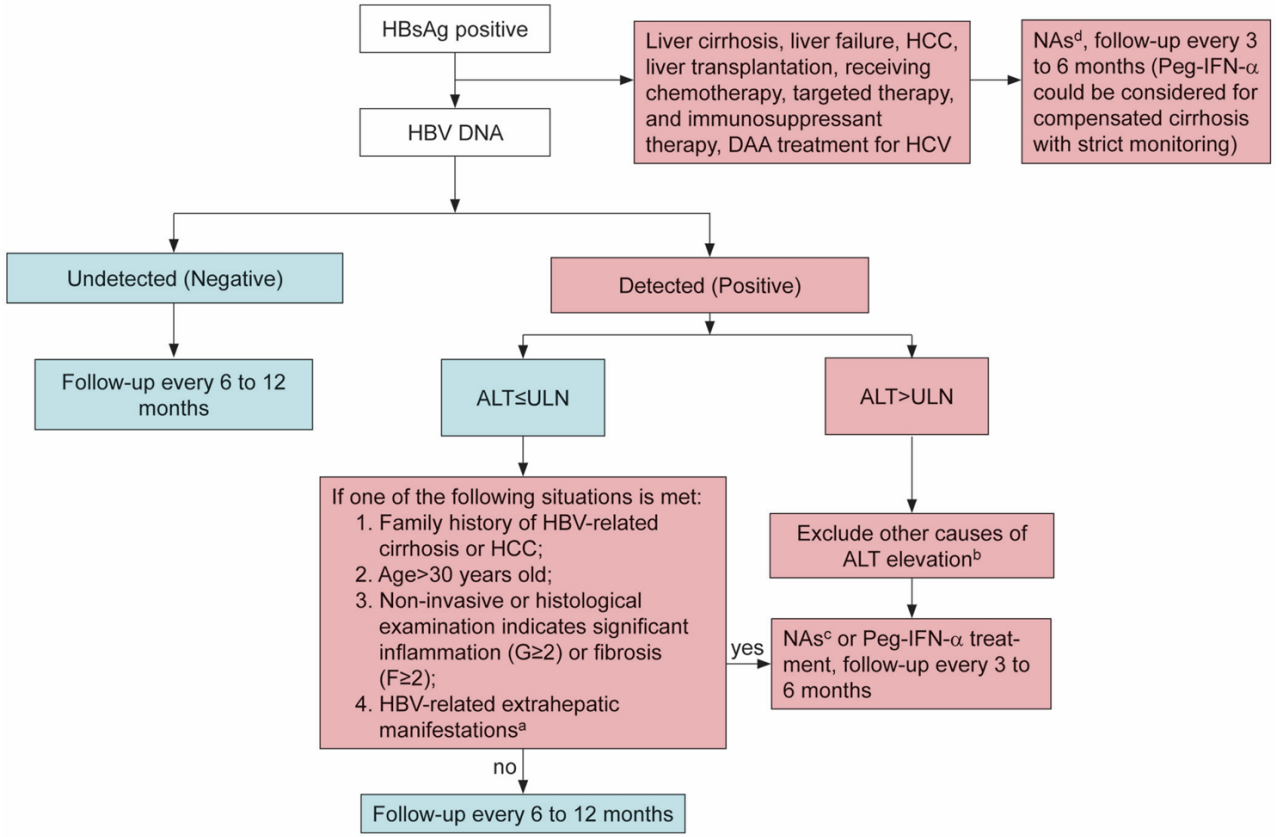


Fig. 1. Indications for antiviral therapy of chronic HBV infection. (a) HBV-related extrahepatic manifestations: glomerulonephritis, vasculitis, etc.; (b) Exclude other causes of ALT elevation: infection with other pathogens, history of taking drugs or poisons, history of alcohol consumption, lipid metabolism disorder, autoimmune disorder, liver congestion or vascular disease, genetic and metabolic liver injury, systemic disease, etc.; (c) NAs: ETV, TDF, TAF or TMF; (d) NAs: ETV, TDF or TAF. HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; DAA, direct-acting agents; Nas, nucleoside (acid) analogs; ALT, alanine aminotransferase; ULN, upper limit of normal; Peg-IFN-α, pegylated interferon alpha.

You H, Wang F, Li T, Xu X, Sun Y, Nan Y, et al. Guidelines for the Prevention and Treatment of Chronic Hepatitis B (version 2022). J Clin Transl Hepatol. 2023;11(6):1425-1442. doi: 10.14218/JCTH.2023.00320.

WHO HBV Guidelines, 2024

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[c]), *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 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 >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-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**

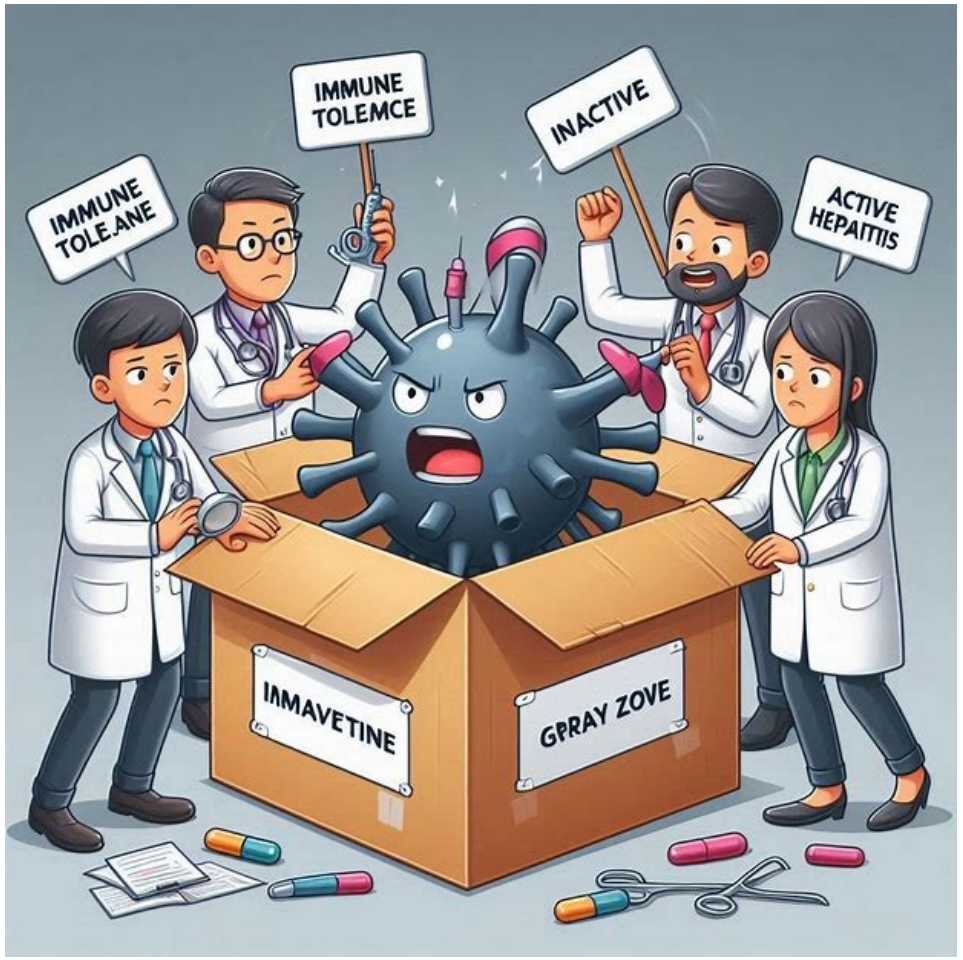
OR

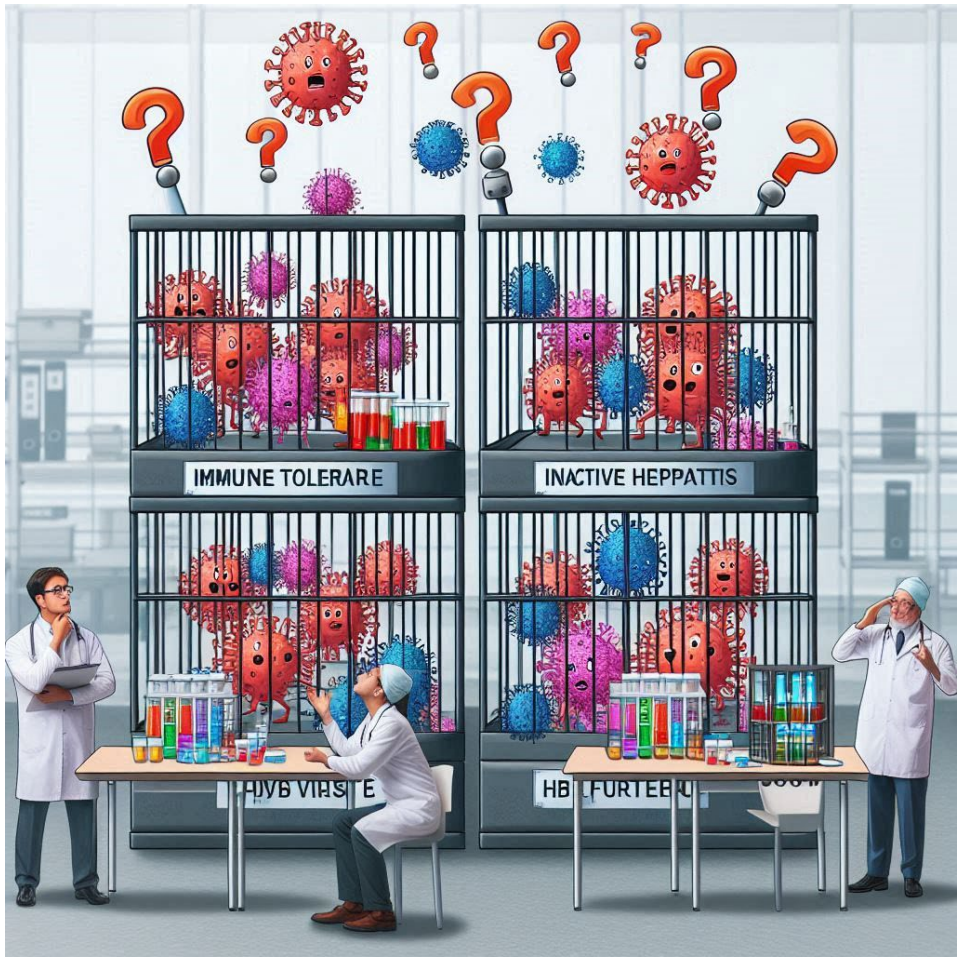
4. **In the absence of access to an HBV DNA assay:**
Persistently abnormal ALT levels (defined as two ALT values >ULN at unspecified intervals during a 6- to 12-month period), *regardless of APRI score. (Adults and adolescents: Conditional/very Low)* — **20% of HBsAg +ve**

World Health Organization

Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection (who.int) https://www.who.int/publications/i/item/978924009090

HBV doesn’t always fit into our nomenclature boxes





- Humility needed as we continue to refine our understanding
- Keep people living w HBV at the center & give them the option to be treated

Images generated by Dall-E, forgive AI mispellings