Hepatitis B Infection

Who need to therapy in HBV infection

Seyed Moayed Alavian M.D.

Professor of Gastroenterology and Hepatology

Chairman of Iranian Association for Study of Liver Diseases

E mail: alavian@thc.ir

Current Recommendations

Progress Toward Eliminating HBV

WHO HBV Elimination Targets

- Goal: **eliminate viral hepatitis** as a public health threat by 2030[1]
- 90% reduction in new chronic viral hepatitis infections
- 65% reduction in mortality related to viral hepatitis

Updated Recommendations	
CDC 2022	**HBV screening** with 3-test panel (HBsAg, anti-HBs, and total anti-HBc) at least once during adults' lifetime[2]
ACIP 2022	All adults aged 19-59 yr should receive **HBV vaccine**[3,4] ▪ Should vaccinate if aged ≥60 yr with risk factors (eg, sexual or household contacts of people who are HBsAg+, previously diagnosed with diabetes, HIV, or chronic liver disease) ▪ May vaccinate if aged ≥60 yr without risk factors

1. who.int/health-topics/hepatitis/elimination-of-hepatitis-by-2030. 2. Conners. MMWR Recomm Rep. 2023;72:1.
3. Murthy. MMWR Morb Mortal Wkly Rep. 2022;71:229. 4. cdc.gov/vaccines/schedules/hcp/imz/adult-schedule-notes.html#note-hepb.

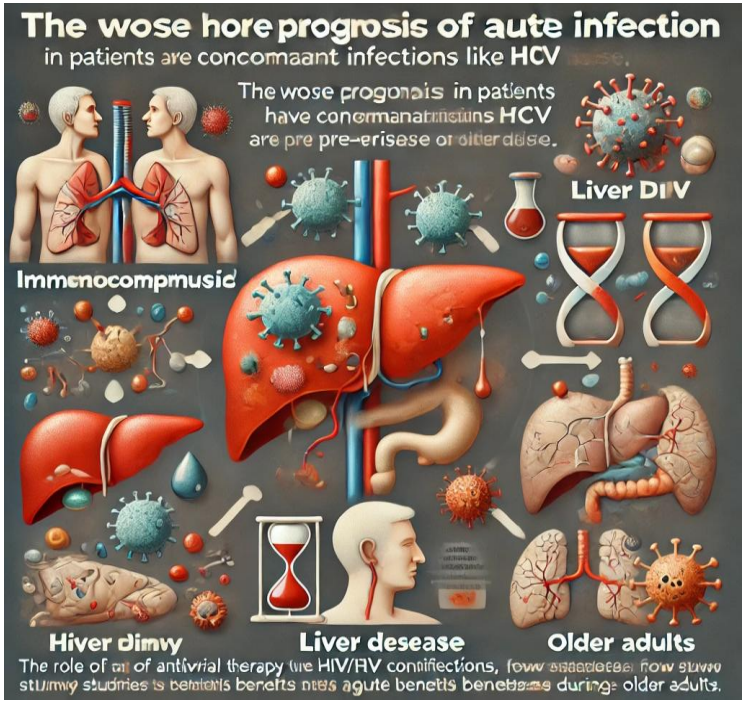
Acute HBV Infection

- The diagnosis of acute hepatitis B is based upon the detection of HBsAg and IgM anti-HBc.
- However, IgM anti-HBc can also be seen during severe exacerbation of chronic HBV.
- Treatment of acute HBV depends upon the clinical setting.
- For most patients, treatment is mainly supportive.
- The likelihood of liver failure from acute HBV is less than 1%.
- In immunocompetent adults, the likelihood of progression to chronic HBV infection is less than 5%.

The prognosis with acute infection is relatively worse in patients who

- are i**mmunocompromised**,
- have concomitant infection with **HCV or HIV**,
- have **pre-existing liver disease**, or
- are **older adults**

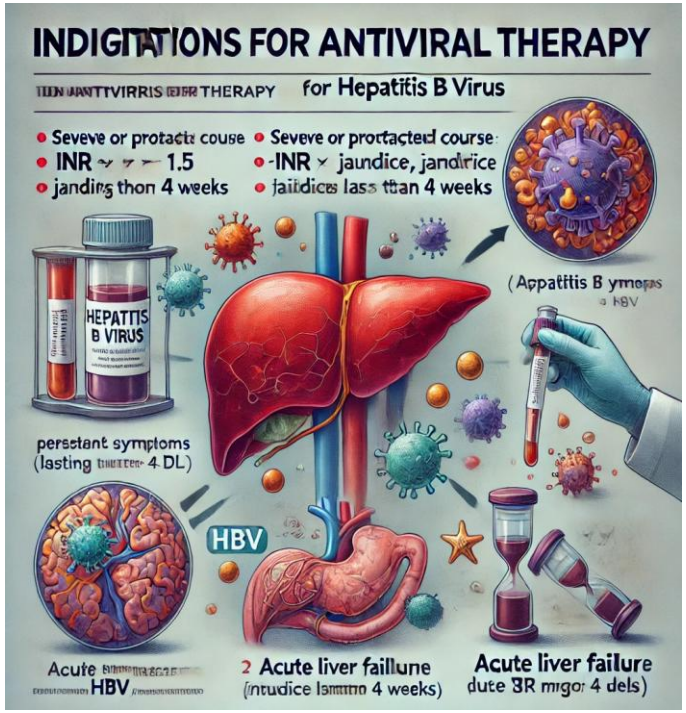
- But the role of antiviral therapy for such patients remains unsettled since few studies have addressed its benefits during acute infection.



- Indications for antiviral therapy
- Severe or a protracted course

(eg, those who develop a coagulopathy [INR >1.5], those with persistent symptoms or marked jaundice [bilirubin >3 mg/dL] for more than 4 weeks after presentation) .

- Acute liver failure due to HBV

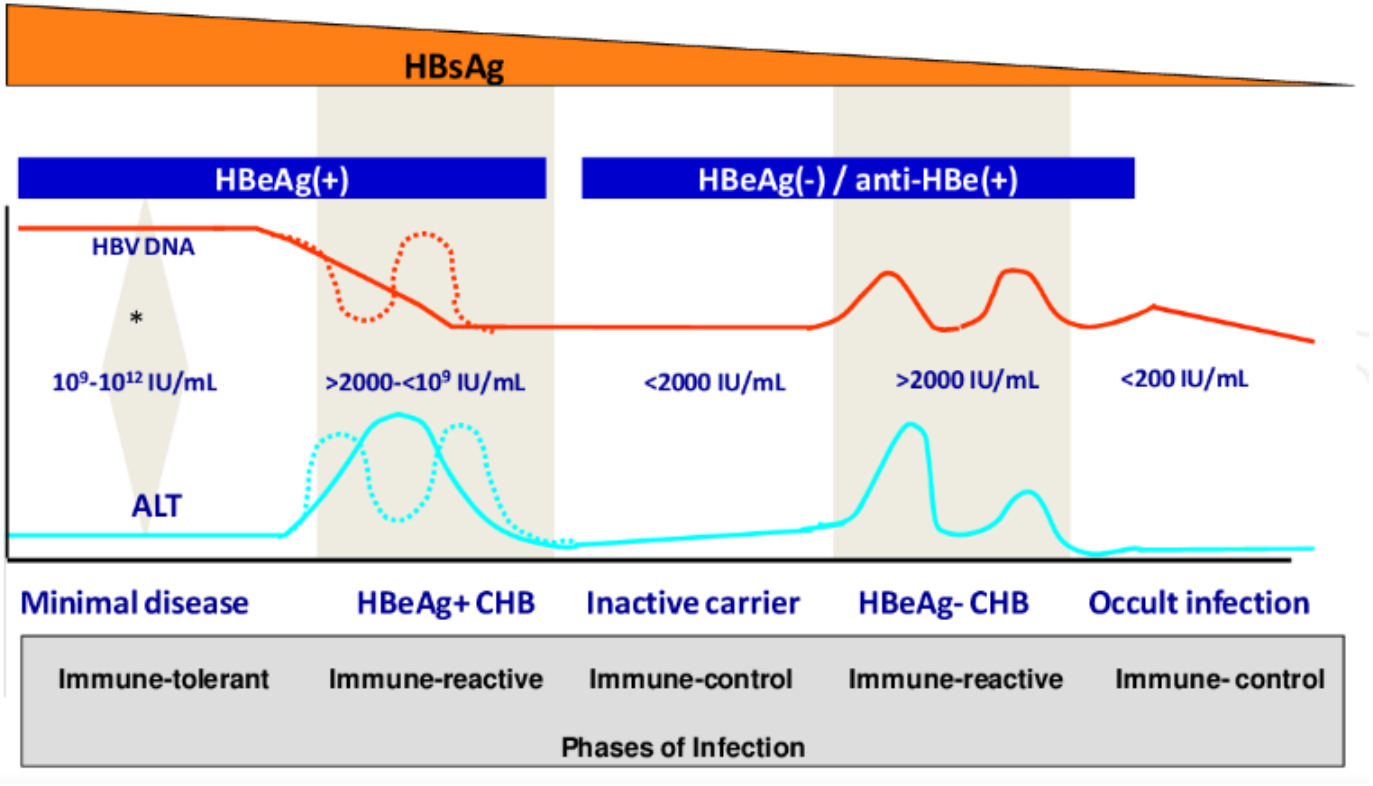


- Interferon should be avoided because of the risk of infection and further increase in hepatic necroinflammation.
- Entecavir or tenofovir are preferred.

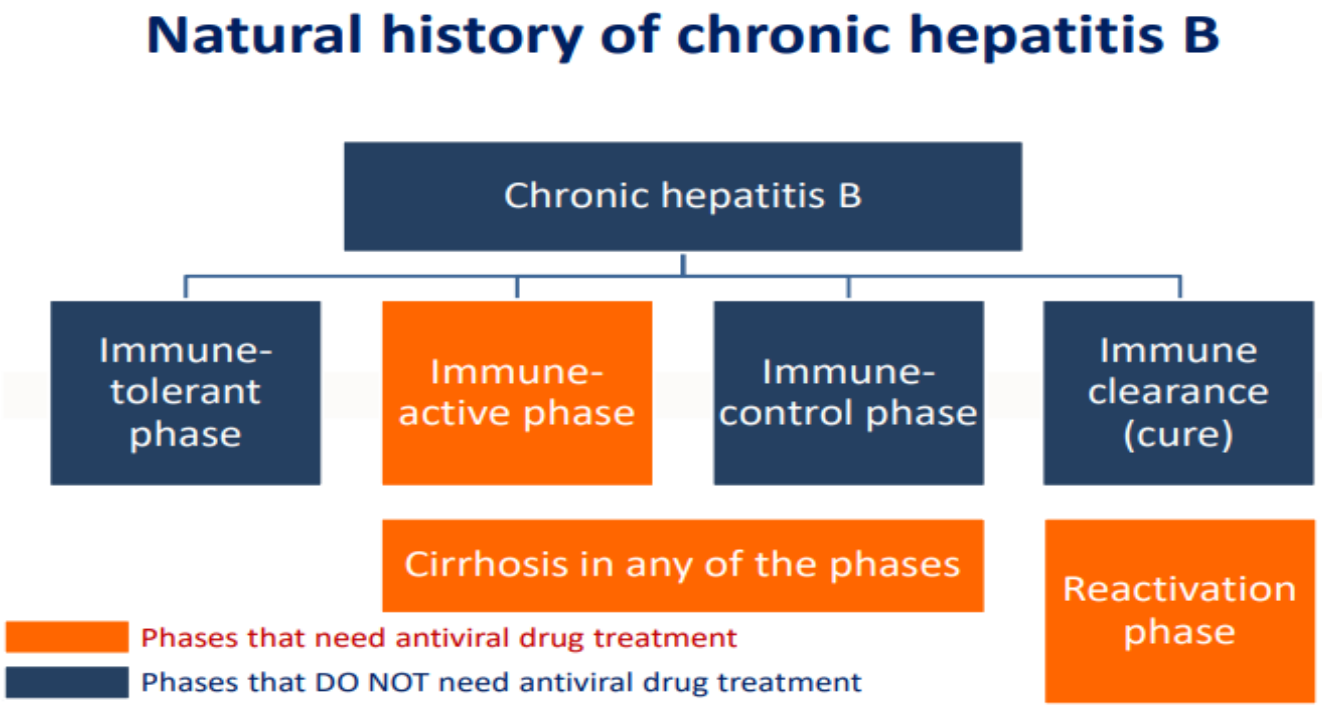
- Treatment can be stopped after confirmation (2 consecutive tests 12 weeks apart) that the patient has cleared HBsAg.

Chronic HBV Infection

Natural history of chronic HBV infection

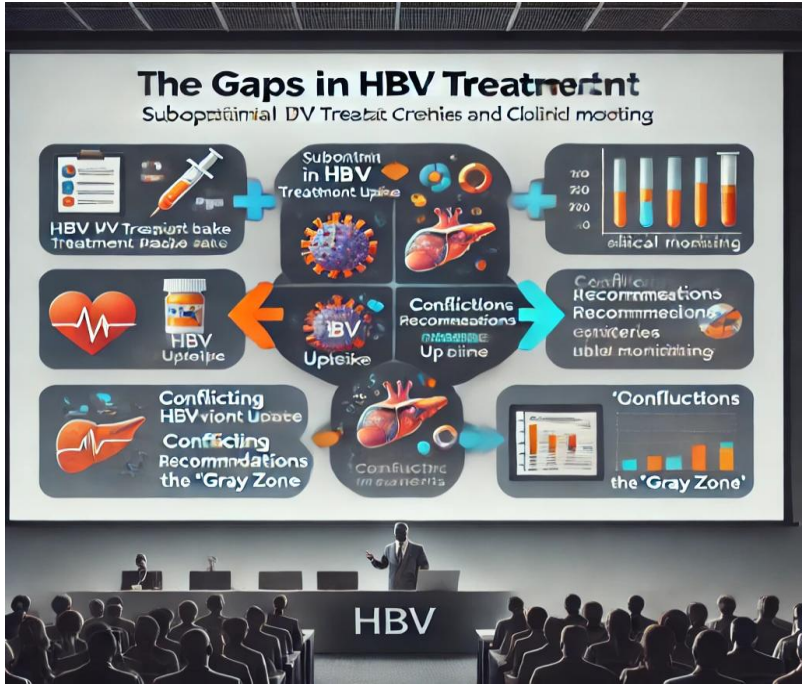


Who to treat?


Natural history of chronic hepatitis B
Chronic hepatitis B
Immune-tolerant phase
Immune-active phase
Immune-control phase
Immune clearance (cure)
Cirrhosis in any of the phases
Reactivation phase
Phases that need antiviral drug treatment
Phases that DO NOT need antiviral drug treatment

Gaps in HBV Treatment

- Suboptimal HBV treatment uptake
  - **Complexity** of treatment criteria and clinical monitoring
  - Conflicting recommendations between guidelines
  - Confusion on how to manage patients in the **“gray zone**



Need for a more simplified approach to treating HBV

HBV Guidelines: Treatment Indications

Criteria	AASLD[1] 2018	APASL[2] 2016		EASL[3] 2017
HBeAg Positive				
HBV DNA, IU/mL	>20,000	>20,000	>20,000	>2000
ALT	≥2x ULN	>2x ULN	>2x ULN	> ULN
Liver biopsy				≥ moderate necroinflammation ± fibrosis
HBeAg Negative				
HBV DNA, IU/mL	>2000	>2000	>20,000	>2000
ALT	≥2x ULN	>2x ULN	>2x ULN	> ULN
Liver biopsy				≥ moderate necroinflammation ± fibrosis

- **Normal ALT (AASLD):** ≤35 U/L (men); ≤25 U/L (women)
- **Normal ALT (APASL and EASL):** <40 U/L

1. Terrault. Hepatology. 2018;67:1560. 2. Sarin. Hepatol Int. 2016;10:1. 3. EASL. J Hepatol. 2017;67:370.

AASLD Guidance: Additional People to Treat

Treat those with:

- Low-level viremia (HBV DNA <2000 IU/mL) and **compensated cirrhosis**, regardless of ALT level
- **Decompensated cirrhosis** who are HBsAg+, despite HBV DNA or ALT level and HBeAg status

Consider treating those with:

- Additional factors for persons with ALT <2x ULN and HBV DNA under threshold: age, **family history of HCC or cirrhosis**, treatment history, **extrahepatic manifestations present**, and cirrhosis present
- Select group of immune-tolerant adults **(aged >40 yr) with normal ALT level** but **elevated HBV DNA** (1,000,000 IU/mL) and a liver biopsy indicating **significant necroinflammation or fibrosis**

If treatment is not indicated, **actively monitor**, as candidacy may change with disease progression

Terrault. Hepatology. 2016;63:261. Terrault. Hepatology. 2018;67:1560.

CHB Extrahepatic Manifestations and Family History of Liver Cancer

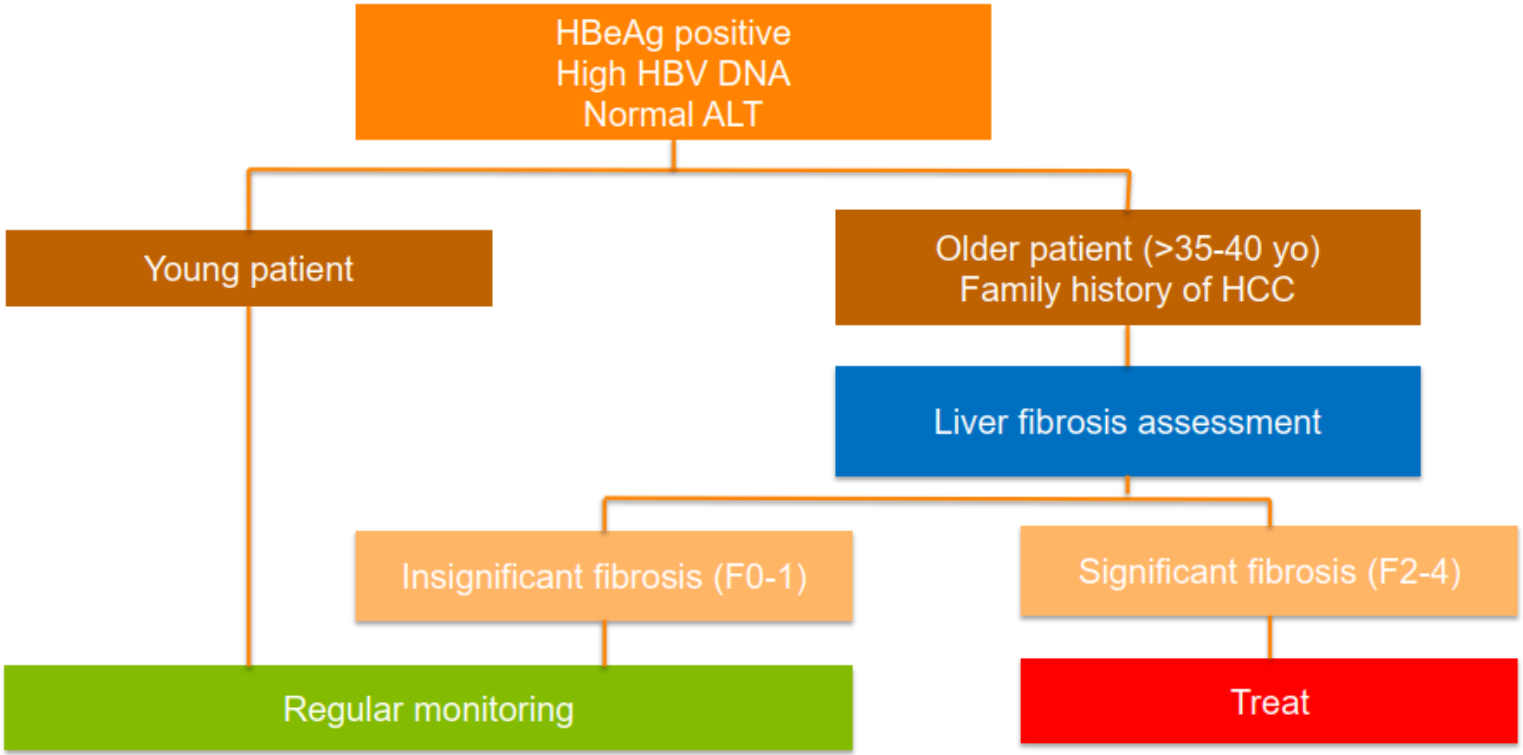
Extrahepatic Manifestations

- Vasculitis
- Skin manifestations (eg, purpura)
- Polyarteritis nodosa
- Arthralgias
- Peripheral neuropathy
- Glomerulonephritis

Family History of Liver Cancer

- Family history of liver cancer increases HCC risk, independent of hepatitis
- HCC risk >70-fold if family history of liver cancer **and** hepatitis B/C serum markers compared with no family history or hepatitis

EASL. J Hepatol. 2017;67:370. Mazzaro. J Clin Med. 2022;11:6247. Turati. Hepatology. 2012;55:1416.



© 2015 AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES WWW.AASLD.ORG

or

In the absence of access to an HBV DNA assay:
4. 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.[e]
(adults and adolescents: conditional recommendation, very-low-certainty evidence)
[a]

Patients in the Indeterminate Phase or “Gray Zone”

HCC Risk in Patients With Indeterminate-Phase CHB

- Retrospective study of adults with untreated CHB and no cirrhosis (N = 3366) in United States and Taiwan
  - Clinical phase informed by 2018 AASLD guidelines
- 38.7% (n = 1303) in indeterminate HBV phase at baseline (not confirmed in inactive, active, or tolerant phase)
- At 10-yr follow-up:
  - **52.7% remained indeterminate**
  - 21.7% transitioned to immune active
  - 24.1% transitioned to inactive

14x higher HCC risk in those who remained persistently indeterminate CHB vs inactive CHB **(18x for persons ≥45 yr of age)**

Huang. Clin Gastroenterol Hepatol. 2022;20:1803.

Antiviral Therapy Reduced HCC Risk by 70% in Patients With CHB in Indeterminate Phase

- 855 patients without advanced fibrosis at 14 international centers
- Inverse probability of treatment weighting used to balance treated (n = 394) and untreated (n = 425) patients

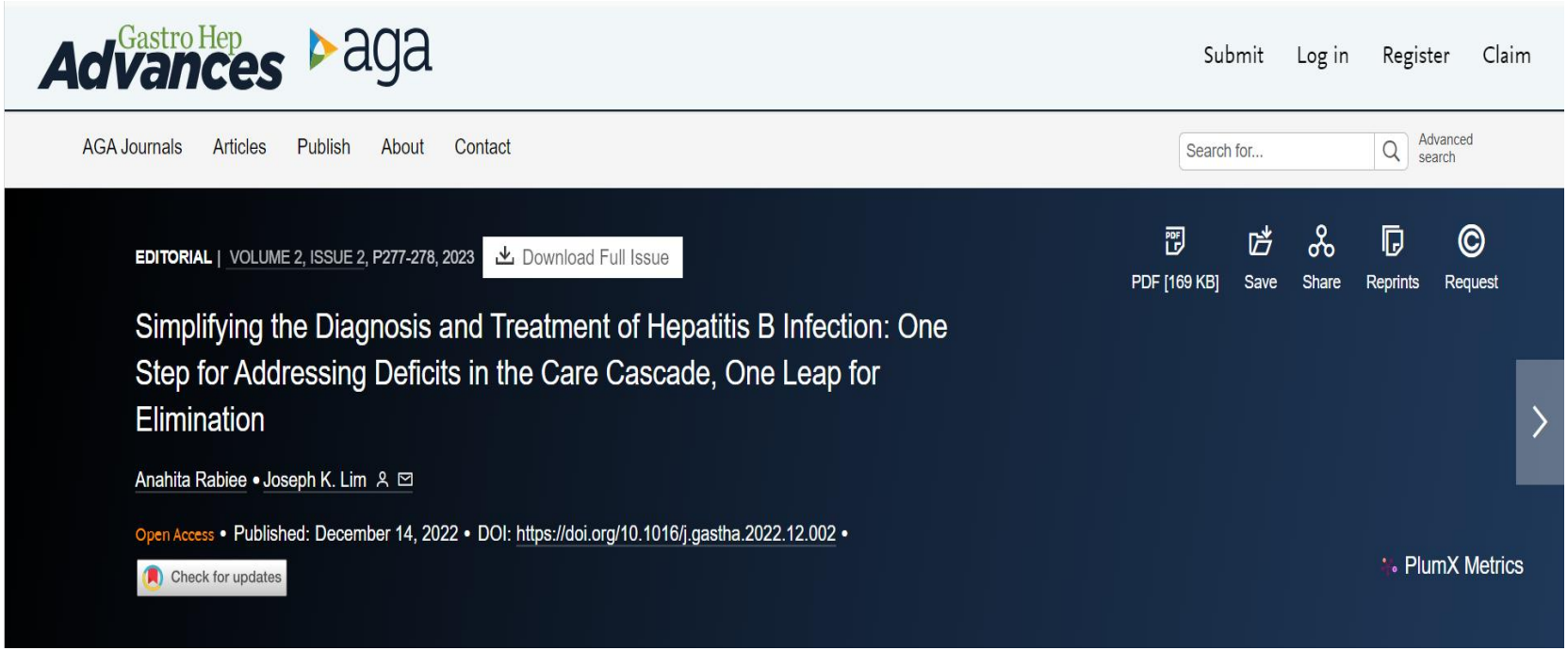
Cumulative Incidence of HCC

%	5 Yr	10 Yr	15 Yr
Untreated	3	15	19
Treated	3	4	9

Higher HCC incidence observed in subgroup analyses for:
males, >35 yr of age, HBeAg+, HBV DNA >1000 IU/mL

Huang. Hepatology. 2023;78:1558.
See also accompanying editorial by Lok and Dusheiko. Hepatology. 2023;78:1332.

Closing the Treatment Gap



Simplified Approach Hepatitis B Algorithm for Treatment of Chronic Hepatitis B

Age, Yr	HBV DNA, IU/mL	ALT, U/L
≥30	>2000	Any ALT level
<30	>2000	> ULN (females: > 19U/L, males: >30 U/L)

Irrespective of ALT levels, treat all patients with CHB with cirrhosis and detectable HBV DNA levels

World Health Organization

Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection

March 2024

Who to treat among people with CHB

New recommendations – who to treat

Treatment is recommended for all adults and adolescents (aged ≥12 years) with CHB (including pregnant women and girls and non-pregnant 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 (or an APRI score of >1 or transient elastography value of >12.5 kPas), regardless of HBV DNA or ALT levels.

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

or

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 recommendation, high-certainty evidence [HBV DNA >20 000 IU/mL] and lowcertainty evidence [HBV DNA 2000–20 000,]; adolescents: conditional recommendation, low-certainty evidence)

or

3- Presence of coinfections (such as HIV, hepatitis D or hepatitis C); family history of liver cancer or cirrhosis; immune suppression (such as long-term steroids, solid organ or stem cell transplant); comorbidities (such as diabetes or metabolic dysfunction—associated steatotic liver disease); or extrahepatic manifestations (such as glomerulonephritis or vasculitis), regardless of the APRI score or HBV DNA or ALT levels.

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

or

In the absence of access to an HBV DNA assay:

4. 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 recommendation, very-low-certainty evidence)

The four new recommended options for meeting treatment eligibility will substantially expand treatment access to most individuals testing positive for HBsAg.
There may also be individual circumstances in which, although individuals may not meet any of the four options for treatment eligibility, there are specific individual concerns regarding i**nfectivity**, **transmission**, **associated stigma**, the **risk of oncogenicity** and progressive liver fibrosis and a strong individual motivation
to consider treatment, despite the lack of direct evidence.

In such cases, a **patient-centred approach** with discussion between individuals and their health-care provider will be key in helping them make informed decisions about whether to begin treatment or not. This should consider the uncertainties resulting from lack of direct evidence for treatment benefit and low risk of transmission for those with HBV DNA <2000 IU/mL, overall lower benefit-to-risk ratio, the
financial implications associated with long-term treatment and importance of sustained treatment adherence.

Key Take-home Points

- **Treatment is recommended for all adults with CHB with:**

- 1. Evidence of significant fibrosis (≥F2) based on an APRI score of >0.5 or transient elastography value of >7 kPa
- 2. HBV DNA >2000 IU/mL and an ALT level above the upper limit of normal (ULN) (30 U/L for men and 19 U/L for women).
- 3. Presence of coinfections (such as HIV, HDV or HCV);
- Family history of HCC or cirrhosis;
- Immune suppression;
- Comorbidities (such as diabetes or MASLD); or
- Extrahepatic manifestations
- 4. Persistently abnormal ALT levels