Surveillance and management of hepatitis B carriers in the primary care setting

Man-Fung Yuen, JP

MD, PhD, DSc

Chair Professor of Gastroenterology and Hepatology

Li Shu Fan Endowed Professor of Internal Medicine

Chief of Division of Gastroenterology and Hepatology,

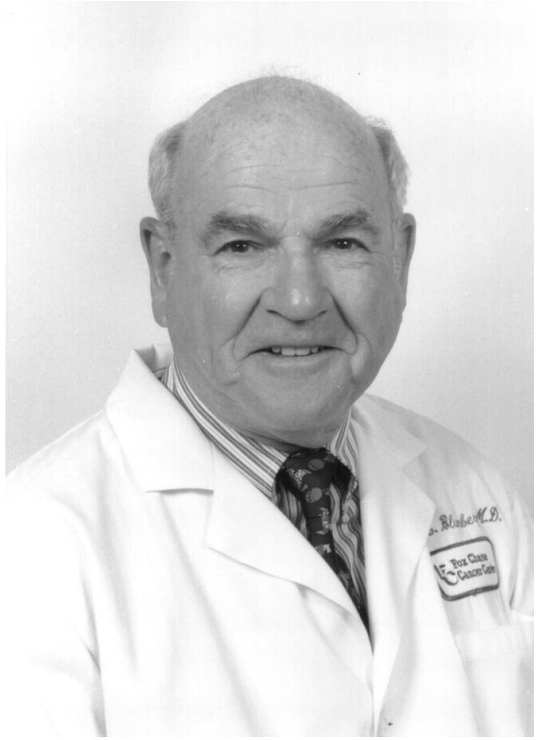
Department of Medicine, School of Clinical Medicine,

The University of Hong Kong, Hong Kong

HKU Med School of Clinical Medicine
Department of Medicine
香港大學內科學系

Discovery of HBV in humans by Baruch Samuel Blumberg (1925 – 2011)

Nobel Prize Winner in Physiology or Medicine 1976

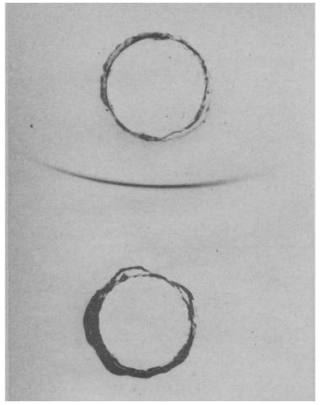


JAMA. 1965 Feb 15;191:541-6.

A "NEW" ANTIGEN IN LEUKEMIA SERA.

BLUMBERG BS, ALTER HJ, VISNICH S.

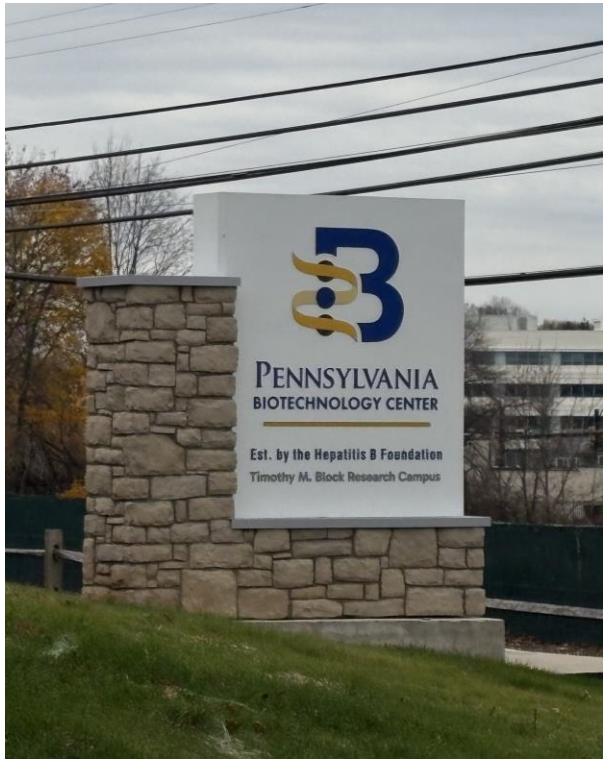
PMID: 14239025 [PubMed - indexed for MEDLINE]

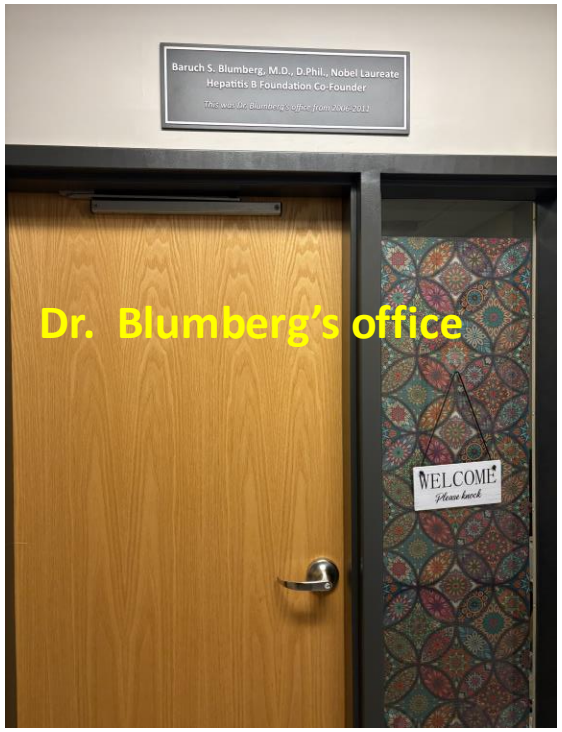


Detection of Australian Antigen by double immunodiffusion in an agarose gel between samples of a leukaemic and a haemophilic patient

Hepatitis B surface antigen (HBsAg)

Hepatitis B Foundation – Baruch S. Blumberg Institute





Dr. Blumberg's office

2025 – 6 decades of discovery & global research on HBV

My HKU HBV research started in 1995
(30 years – halfway through the 6 decades)

https://www.youtube.com/watch?v=NQcwqoV7E1Y

Hepatitis B infection – global disease

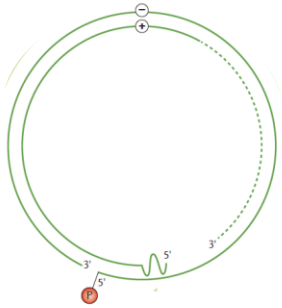
In 2022, 254 million people are living with chronic hepatitis B in the world,
1.2 million new infections each year &
1.1 million deaths due to liver cancer and cirrhosis

World Health Organisation. Hepatitis B fact sheet. 2024.
Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b

Hepatitis B Virus: compact genomic structure

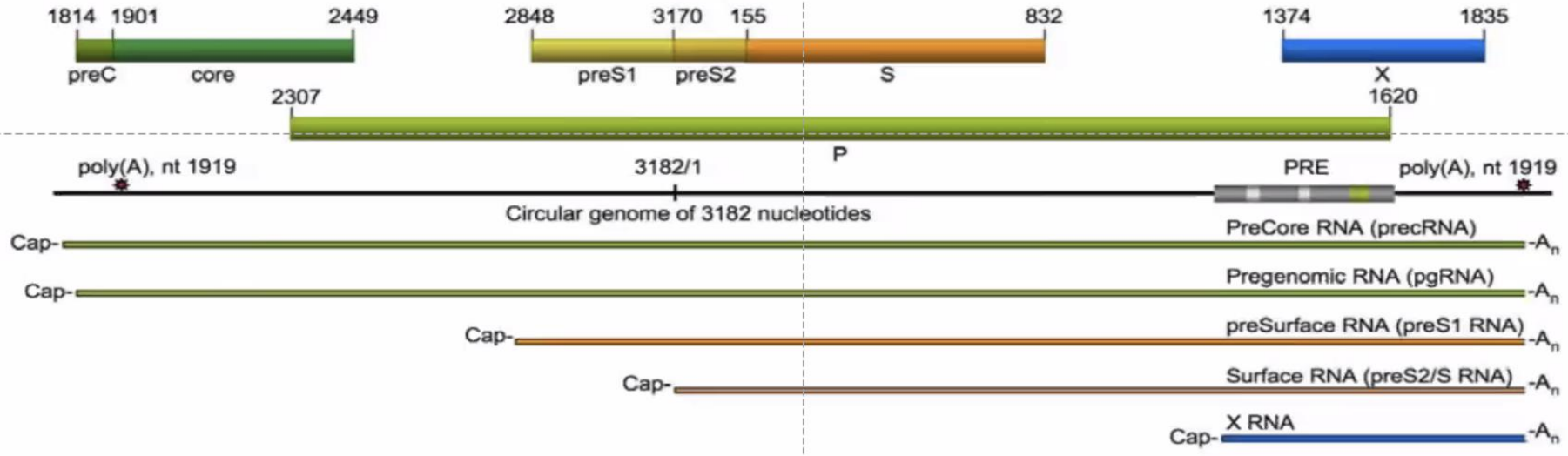
Viral genomic structure

- Relaxed circular DNA (3.2 KB)
- 4 overlapping reading frame



Yuen MF et al., Nat Rev Dis Primers. 2018;4:18035

Viral transcripts from HBV genome



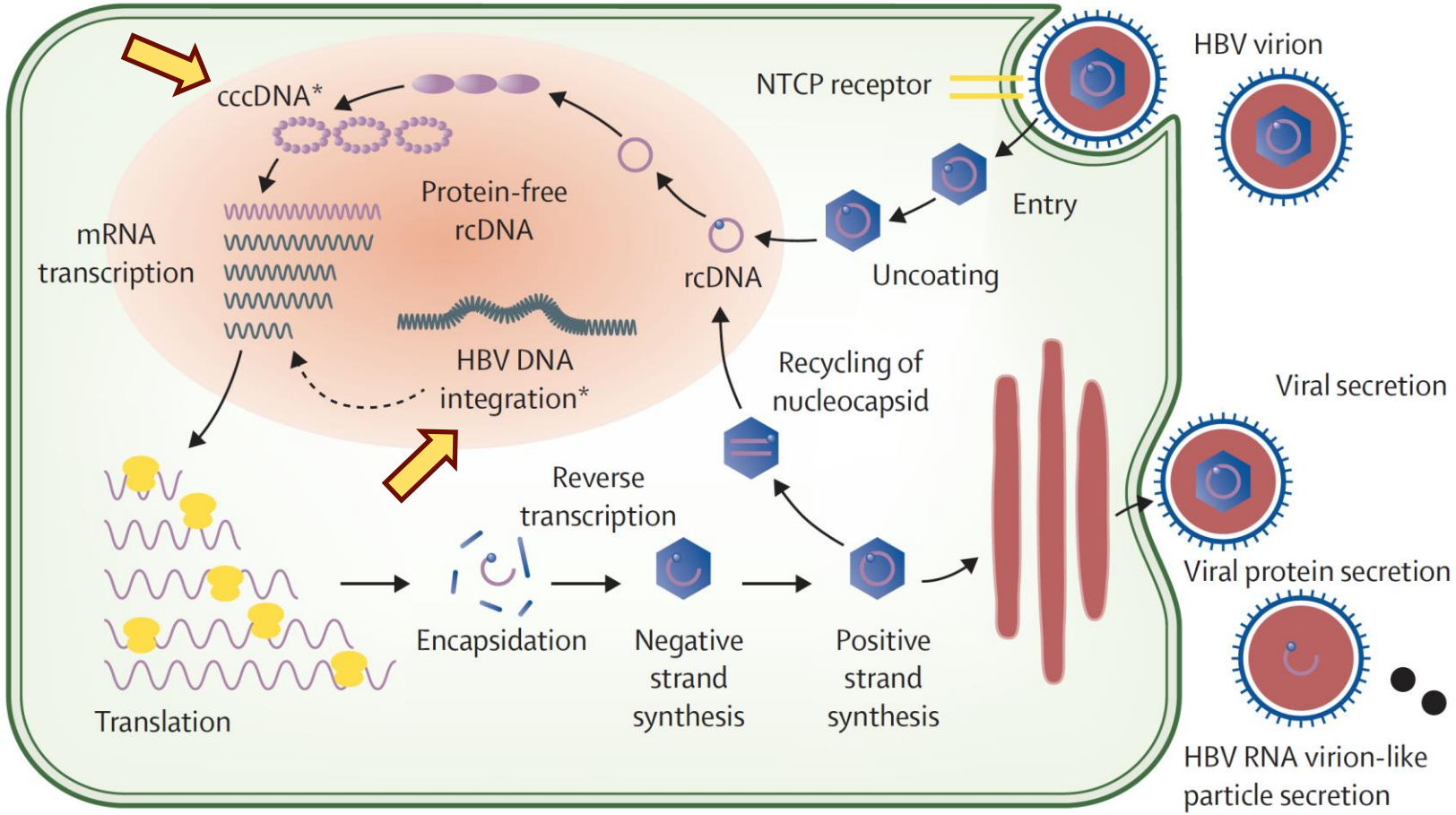
HBeAg (HBcrAg)

pgRNA, HBV DNA, HBcAg (HBcrAg)

HBsAg

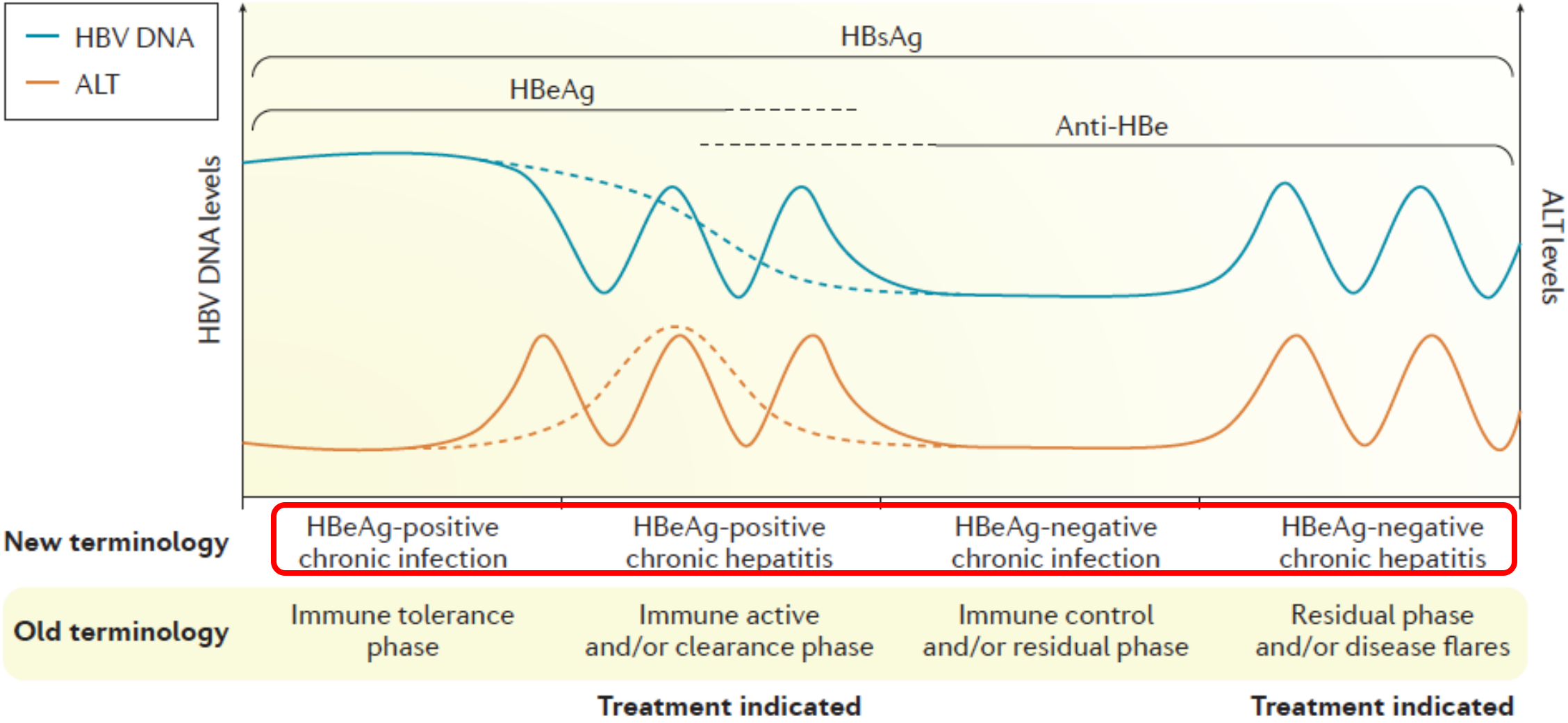
Sommer G, Heise T. Front Biosci 2008;13:5533-47

Hepatitis B Virus: complex life cycle



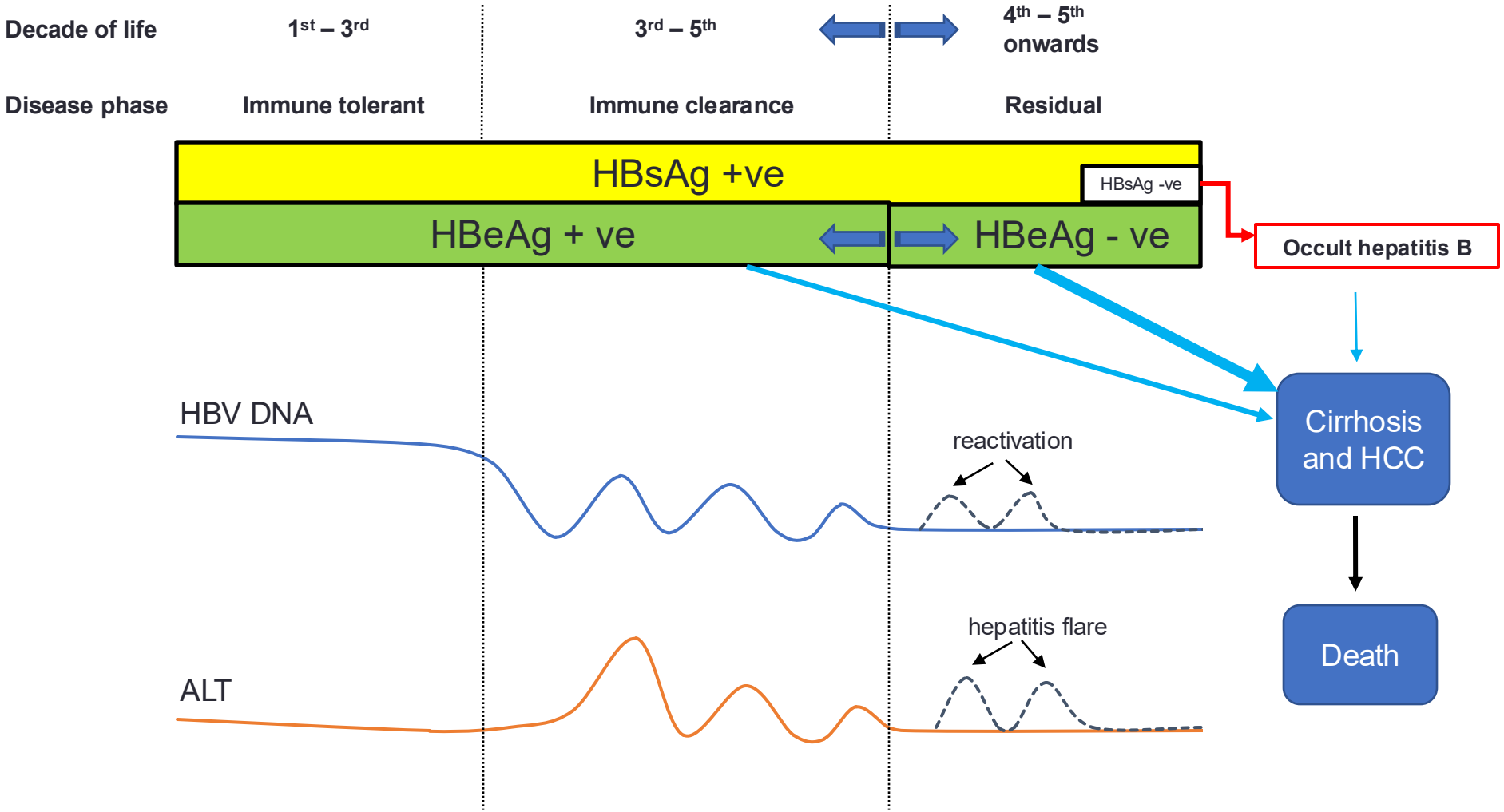
Seto WK, Lo YR, Pawlotsky JM, Yuen MF. The Lancet 2018;10161:2313-24

Different disease phases categorized by HBeAg, HBV DNA and ALT



Yuen MF., et al. Nat Rev Dis Primers 2018;4:18035

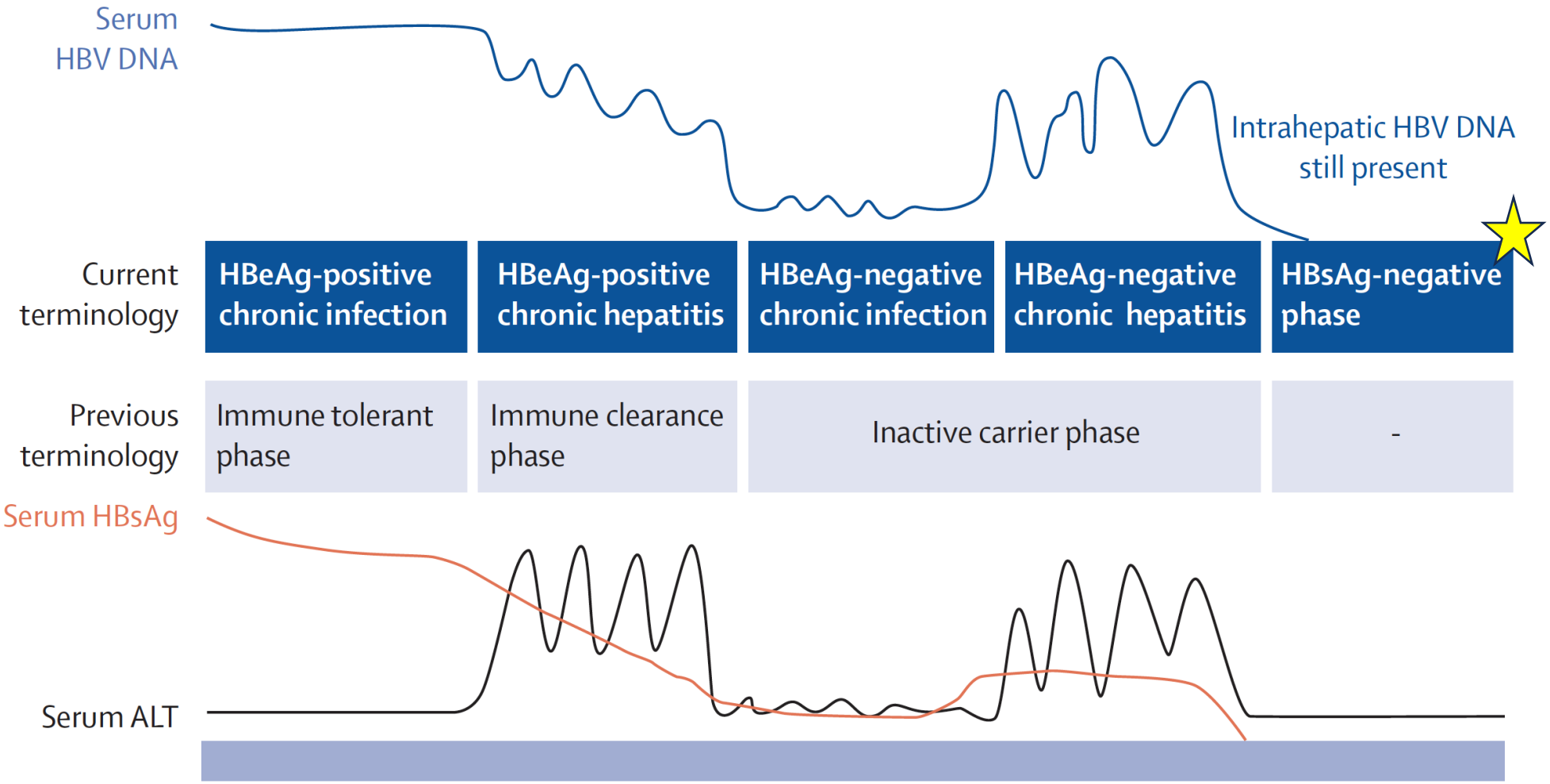
HBsAg seroclearance: last phase of chronic hepatitis B infection



Modified from Yuen MF, occult hepatitis B infection, Hepatitis B Virus and Liver Disease

Chronic Hepatitis B Infection: disease phase update

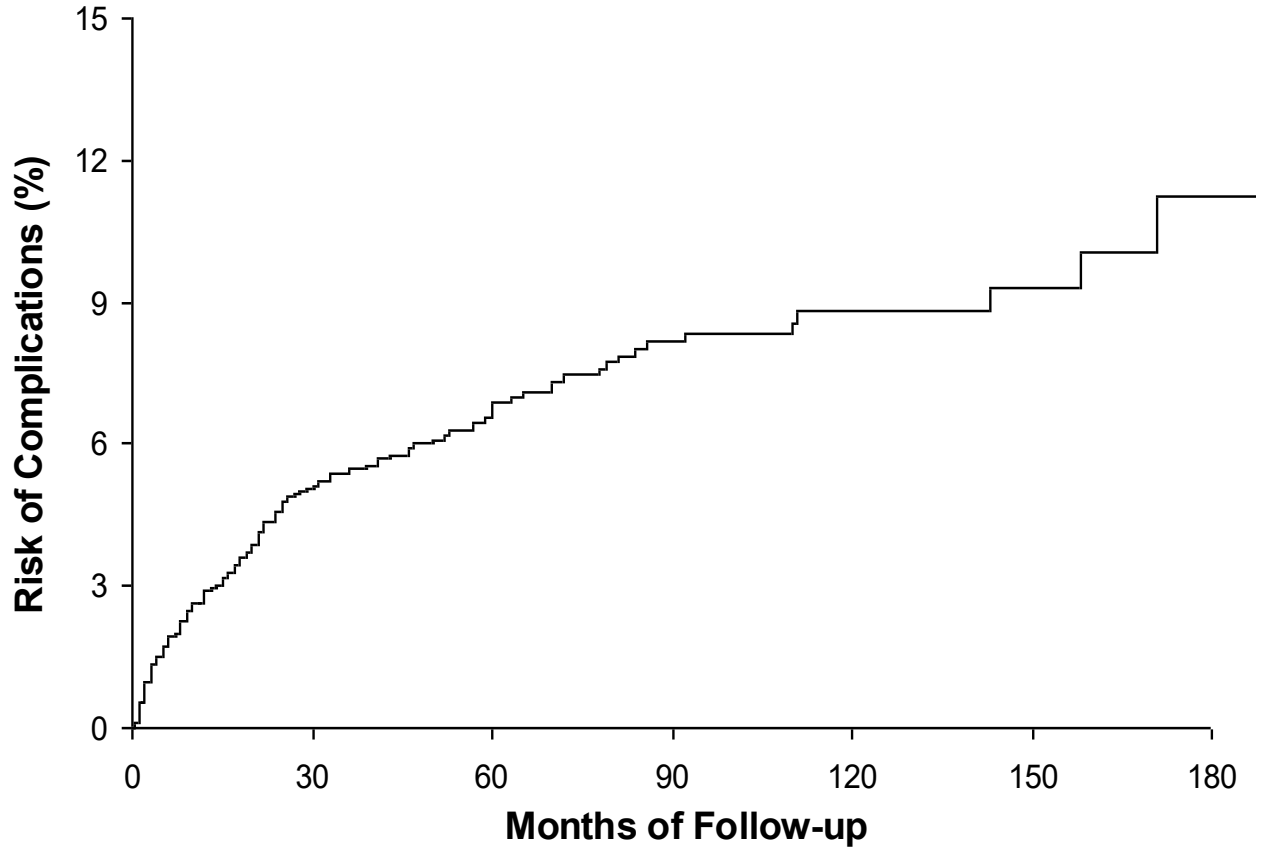
HBsAg seroclearance



Seto WK… Yuen MF. The Lancet 2018;10161:2313-24

HBeAg seroconversion and disease complications

Development of disease complications



Number of Patients	3233	1562	921	579	300	152	39

- 3,233 Chinese patients with chronic hepatitis B
- Median age of HBeAg seroconversion
  - 35 year
- 170 patients developed HCC or cirrhotic complications

Yuen MF, et al. Gut 2005;54(11):1610-1614

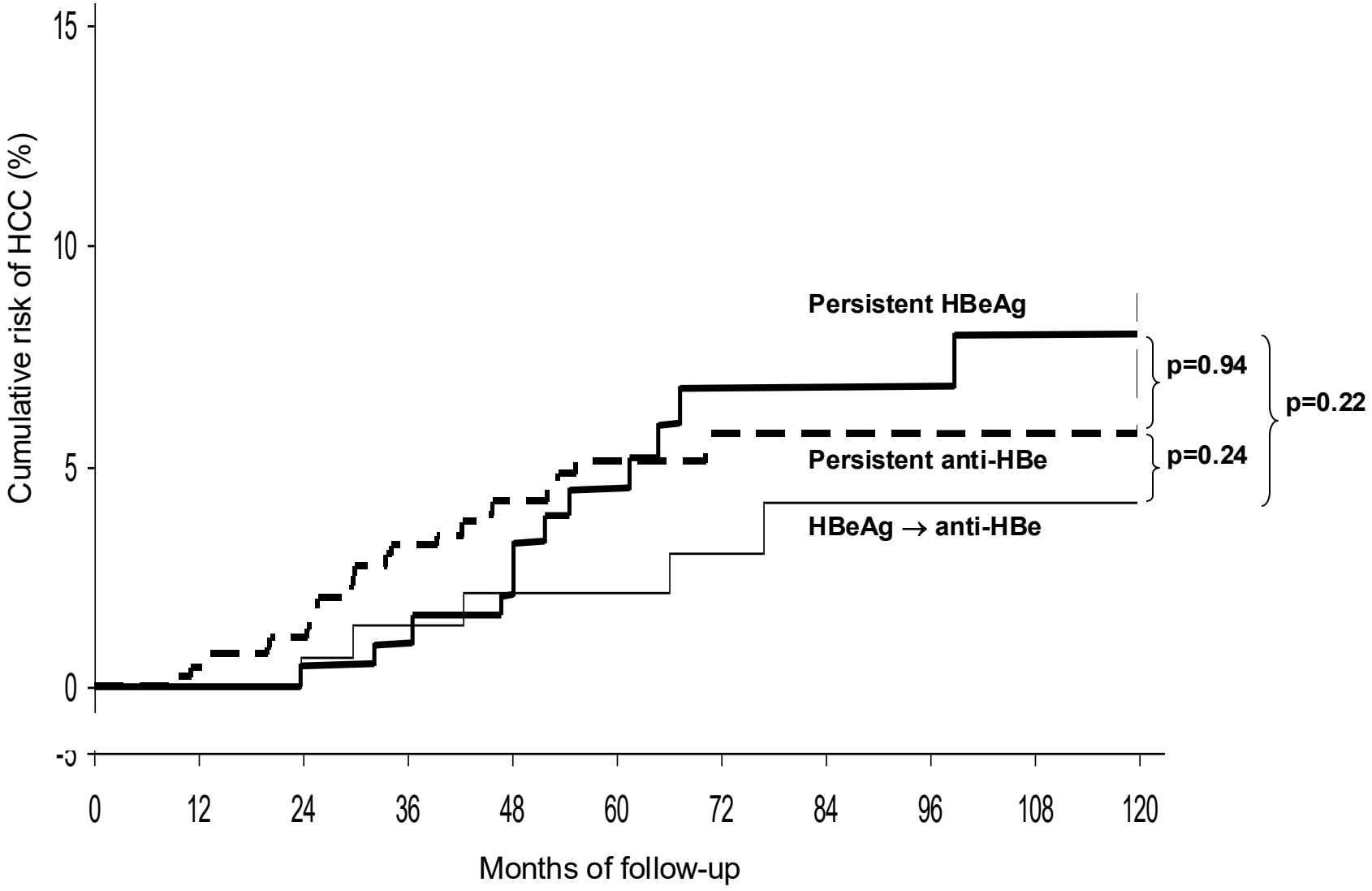
Age of development of disease complications

- Development of cirrhosis complications and HCC
  - 3,233 Chinese patients
  - Mean follow-up 46.9 months

	Median age in yrs	% anti-HBe
HBeAg seroconversion	35	-
All complications	57.2	73.5%
Ascites	57.7	68.8%
SBP	60.0	76.7%
Varices	54.3	76.3%
Encephalopathy	58.5	65.0%
HCC	59.0	81.1%

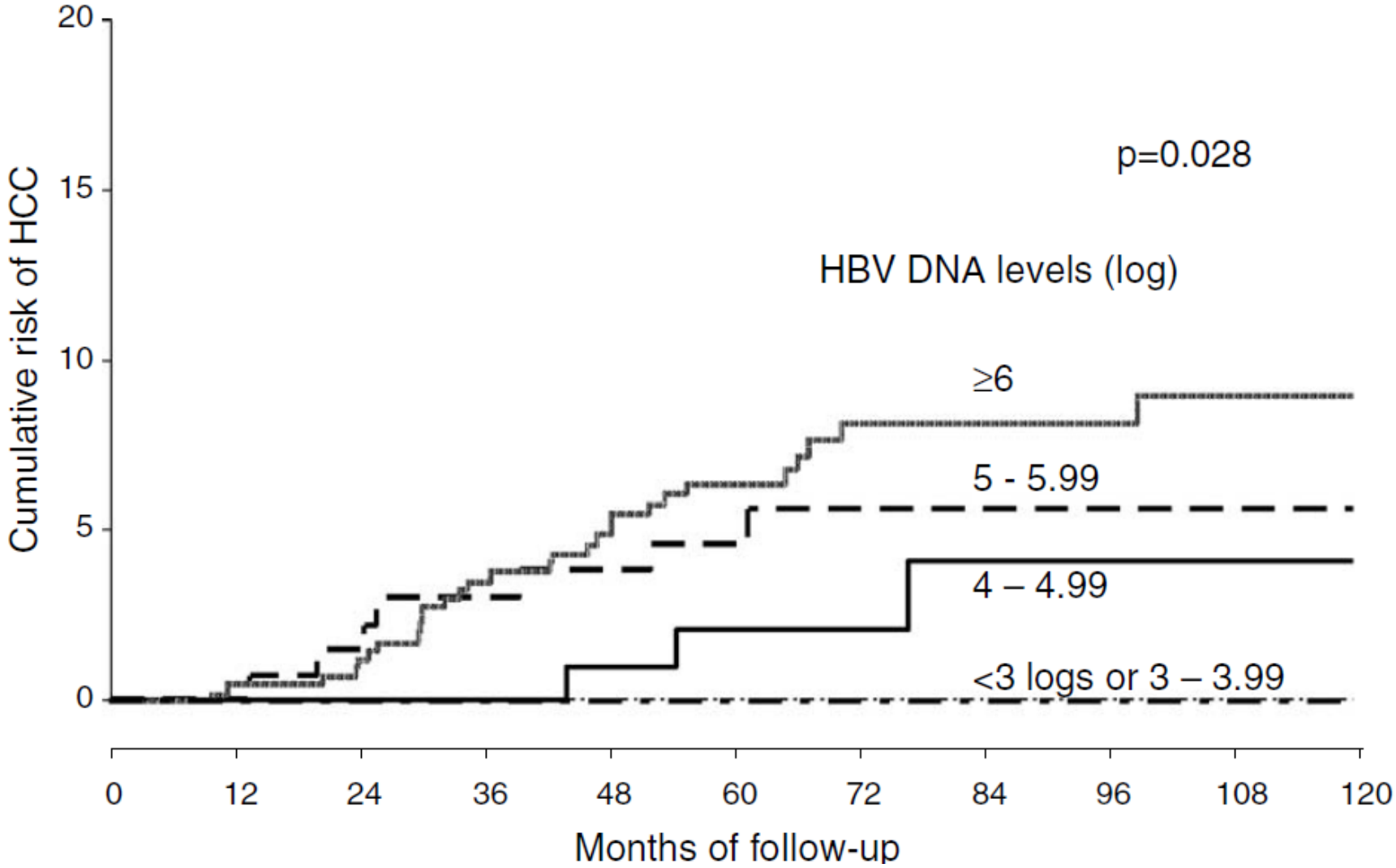
Yuen MF, et al. Gut 2005;54(11):1610-1614

HBeAg/ anti-HBe status and HCC development



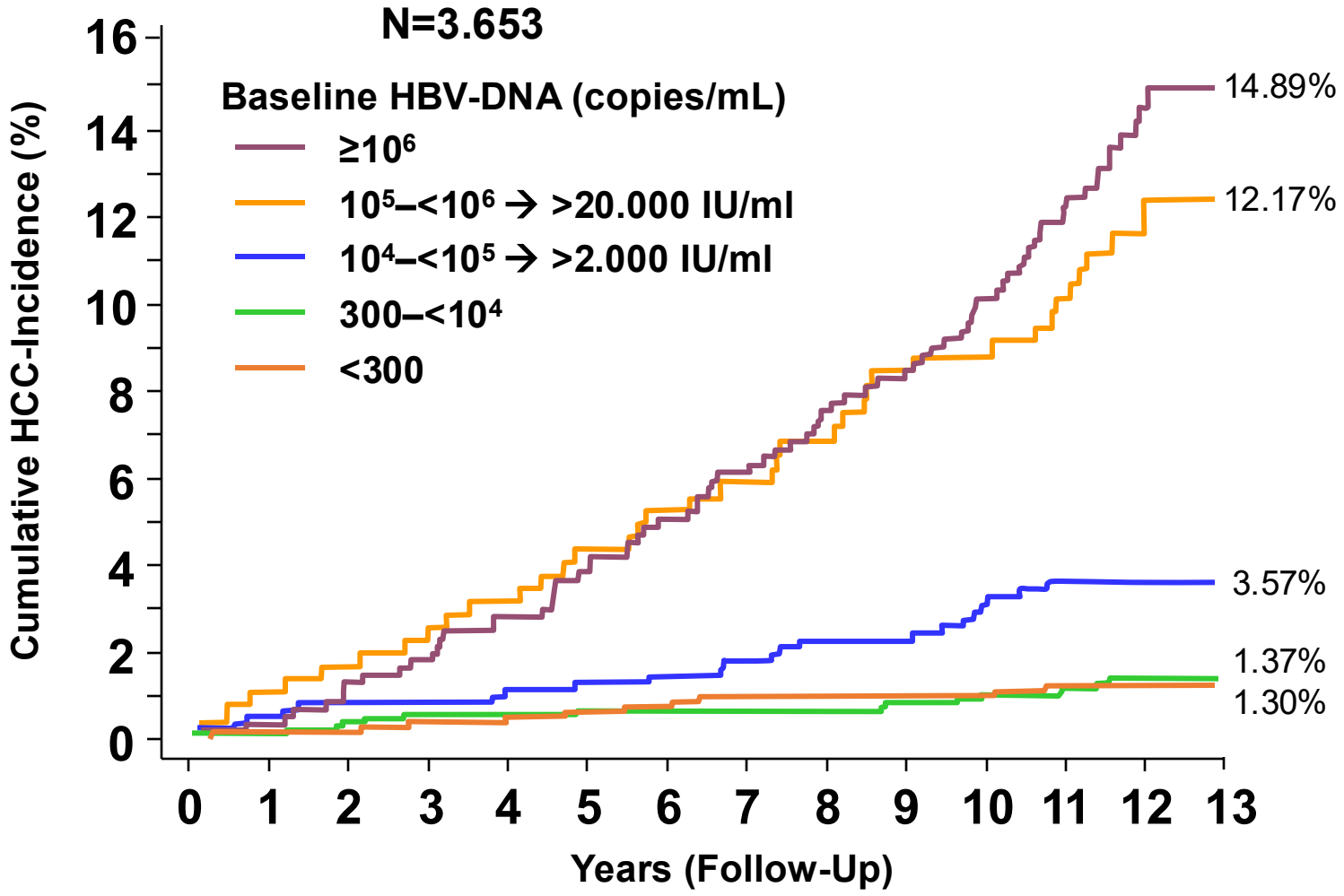
Yuen MF et al., J Hepatol 2009;50:80-8

HBV DNA and HCC development



Yuen MF et al., J Hepatol 2009;50:80-8

HBV DNA and HCC development in HBeAg -ve patients with normal/low ALT levels



Patient characteristics

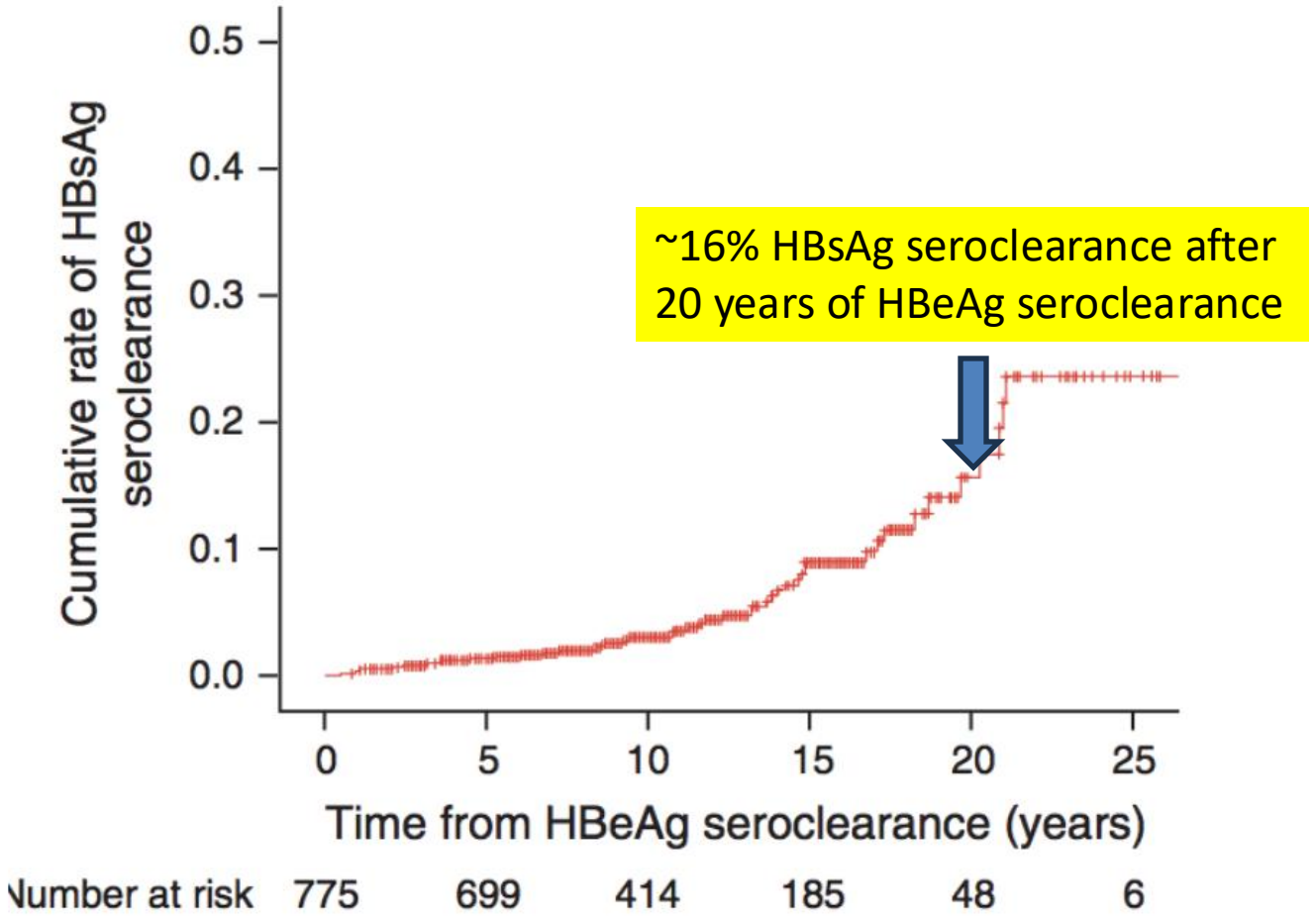
1) HBeAg –ve 85%

2) ALT < 45 U/L 94%

3) Cirrhosis 2%

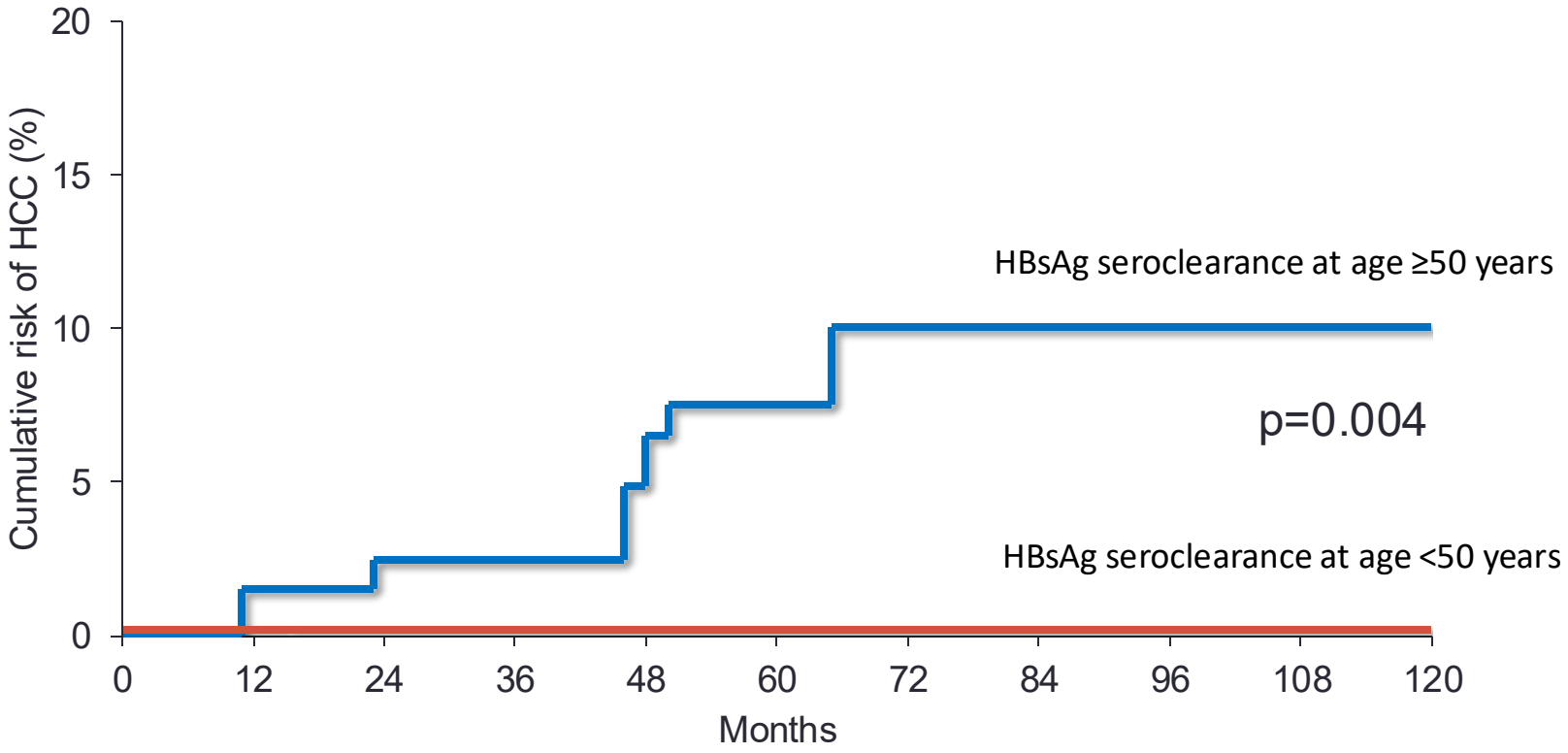
Chen et al. JAMA. 2006;295(1):65-73.

Cumulative rate of HBsAg seroclearance after HBeAg seroclearance



Fung J… Yuen MF. Am J Gastro 2014;109(11):1764-70

Clinical significance of HBsAg seroclearance: reduce HCC risk if achieved in younger age

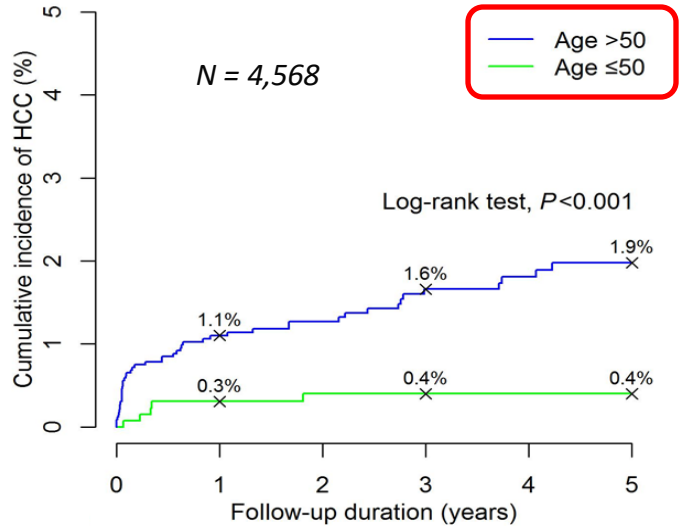


Significant liver fibrosis

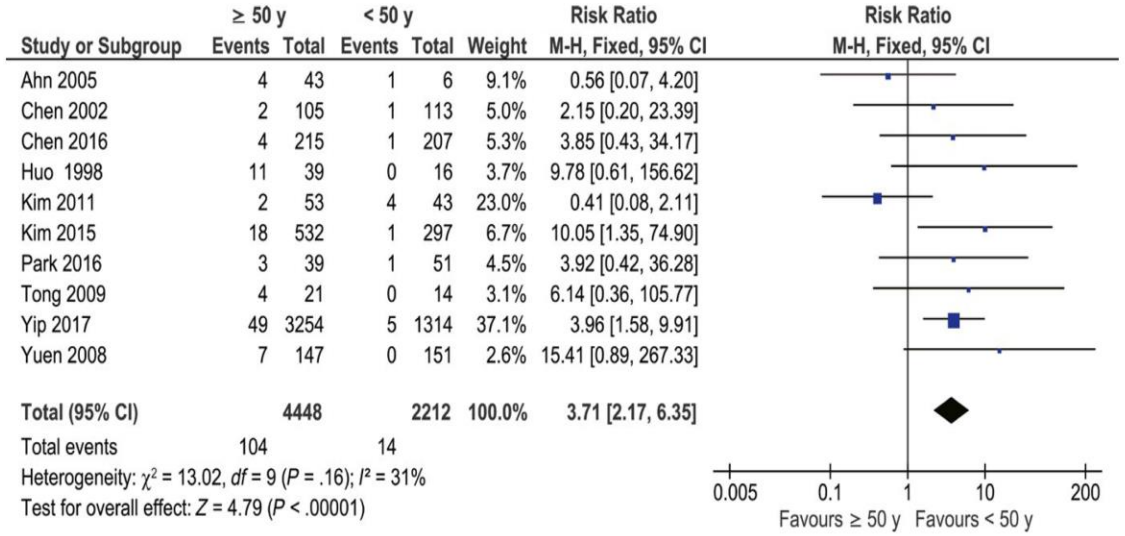
7.9% (HBsAg seroclearance < 50 years old) vs 29.5% (HBsAg seroclearance ≥ 50 years old (p=0.001)

Yuen MF. et al. Gastroenterology 2008;135:1192-1199.

All subsequent studies confirmed HBsAg seroclearance leading to HCC risk reduction



Yip TC et al. J Hepatology 2017;67:902-908



Meta-analysis 12 studies n=6,660

HCC occurrence
< 50 years 14/ 2212 (0.63%) vs. ≥ 50 years: 104/ 4448 (2.34%)

Kuang XJ et al. J Viral Hepat 2018;25:1026-37

N = 629 Characteristics	Multivariate analysis		
	HR	95% CI	p Value
Age of HBsAg seroclearance ≥50	12.14	1.61–91.68	0.02
Male	8.96	1.17–68.80	0.04
Cirrhosis	10.80	4.25–27.43	<0.001

Kim GA et al. J Hepatol 2015;62(5):1092-9

Treatment aim and strategy for HBV infection

Aim: reduce infection and liver related morbidity and mortality

Treatment for existing hepatitis B patients

1) Chronic suppression of virus replication
2) Achieve HBsAg seroclearance (functional cure)

Yuen MF et al. Nat Rev Dis Primers 2018;4:18035.

The new treatment paradigm is to continue CHB treatment until HBsAg seroclearance is achieved for both HBeAg-positive and HBeAg-negative CHB patients.

Yuen MF, et al. J Clin Gastroenterol 2016;50:286–294.

Treatment guidelines from major Liver Associations and organizations

Guideline	HBeAg+			HBeAg-		
	HBV DNA (IU/mL)	ALT (U/L)	Liver disease	HBV DNA (IU/mL)	ALT (U/L)	Liver disease
EASL 2017	≥2000	>ULN[a]	Moderate liver **NECROINFLAMMATION** or fibrosis Irrespective of fibrosis	≥2000	>ULN[a]	Moderate liver **NECROINFLAMMATION** or fibrosis Irrespective of fibrosis
AASLD 2018	>20,000	≥2 x ULN[b]	Significant **HISTOLOGICAL** disease	≥2000	≥2 x ULN[b]	Significant **HISTOLOGICAL** disease
APASL 2016	≥20,000	≥2 x ULN[a]	Moderate to severe **INFLAMMATION** or significant fibrosis	≥2000	≥2 x ULN[a]	Moderate to severe **INFLAMMATION** or significant fibrosis
WHO 2024	≥2000[c,d]	>ULN[d]	Significant fibrosis (≥F2) or cirrhosis[d]	≥2000[c,d]	>ULN[d]	Significant fibrosis (≥F2) or cirrhosis[d]
China 2022	Positive[e]	>ULN[f,g]	No requirement	Positive[e]	>ULN[f,g]	No requirement
		≤ULN[f,g]	Significant **INFLAMMATION** or significant fibrosis		≤ULN[f,g]	Significant **INFLAMMATION** or significant fibrosis

[a]ALT ULN: 40 U/L; [b]ALT ULN: 35 U/L for males and 25 U/L for females
[c] in the absence of access to HBV DNA assays, treat if persistently abnormal ALT alone (two ALT > ULN in 6-12 month period)
[d] treat if have co-infection (HIV, HCV, HDV), family history of liver cancer or cirrhosis, immune suppression, comorbidities (eg, DM, or MAFLD), or extrahepatic manifestation (e.g. glomerulonephritis) regardless of APRI, HBV DNA, or ALT levels)
[e] Recommend the lower limit of quantification (LLoQ) to be ≤10-20 IU/mL
[f] Recommend lowering ALT cut-off value. Application of an ALT cut-off value of 30 U/L for men and 19 U/L for women to Chinese CHB patients requires further investigation
[g] Treat if ALT ≤ULN and family history of HBV-related cirrhosis or HCC, or >30 YEARS of age or marked inflammation/ fibrosis or HBV-related extrahepatic manifestations. Treat if ALT >ULN and excluded other causes of ALT elevation

EASL. *J Hepatol*. 2017;67:370-98; Terrault NA, et al. *Hepatology*. 2018;67:1560-99; Sarin SK, et al. *Hepatol Int* .2016;10:1-98; World Health Organization. *Guidelines for the Prevention, Diagnosis, Care and Treatment for People with Chronic Hepatitis B Infection*. 29 Mar. 2024, https://www.who.int/publications/i/item/9789240090903. Accessed April 2024. Chinese Society of Hepatology and Infectious Disease (2022), *J Clin Transl Hepatol*. 2023. doi: 10.14218/JCTH.2023.00320.

WHO algorithm for treatment of people with CHB infection

PATIENT CENTERED APPROACH TO TREATMENT

There may be individual circumstances in which there are reasons to consider treatment. A patient-centered 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

Consider treatment for individuals concerned about infectivity, transmission, associated stigma, the risk of oncogenicity, progressive liver fibrosis, and who have a strong motivation for treatment

TREAT ALL ADULTS AND ADOLESCENTS (≥ 12 years of age)

(including pregnant women and girls and non-pregnant women of reproductive age)

1. SIGNIFICANT FIBROSIS (≥F2) or CIRRHOSIS (F4) (regardless of HBV DNA or ALT levels)
   - Clinical criteria for cirrhosis[a]
   - Non-invasive tests: APRI >0.5 or transient elastography >7 kPa (adults)[b]

or

2. HBV DNA >2000 IU/mL and ALT level >ULN[c]

or

3. PRESENCE OF ANY of the following (regardless of APRI score, HBV DNA, or ALT level)
   - Coinfection (eg, HIV, HDV, HCV)
   - Family history of liver cancer or cirrhosis
   - Immune suppression
   - Comorbidities (eg, diabetes, metabolic dysfunction-associated steatotic liver disease)
   - Extrahepatic manifestations (eg, glomerulonephritis or vasculitis)

or *In absence of access to HBV DNA assay*

4. PERSISTENTLY ABNORMAL ALT LEVELS ALONE[c,d]

[a] Non-invasive tests including APRI and transient elastography have not yet been validated for children and adolescents.
[b] Clinical features of decompensated cirrhosis: portal hypertension (ascites, variceal hemorrhage and hepatic encephalopathy), coagulopathy or liver insufficiency (jaundice). Other clinical features of advanced liver disease and cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema and edema.
[c] ULN for ALT defined as <30 U/L for men and boys and <19 U/L for women and girls. Persistently normal or abnormal may be defined as two ALT values below or above the ULN at unspecified intervals during a 6- to 12-month period. ALT levels fluctuate with CHB and require longitudinal monitoring to determine the trend.
[d] Raised ALT may normalize in pregnancy and is therefore not a good marker for deciding about long-term treatment in pregnancy. Pregnant women should be reassessed after delivery.

World Health Organization. *Guidelines for the Prevention, Diagnosis, Care and Treatment for People with Chronic Hepatitis B Infection*. 29 Mar. 2024, https://www.who.int/publications/i/item/9789240090903. Accessed April 2024.

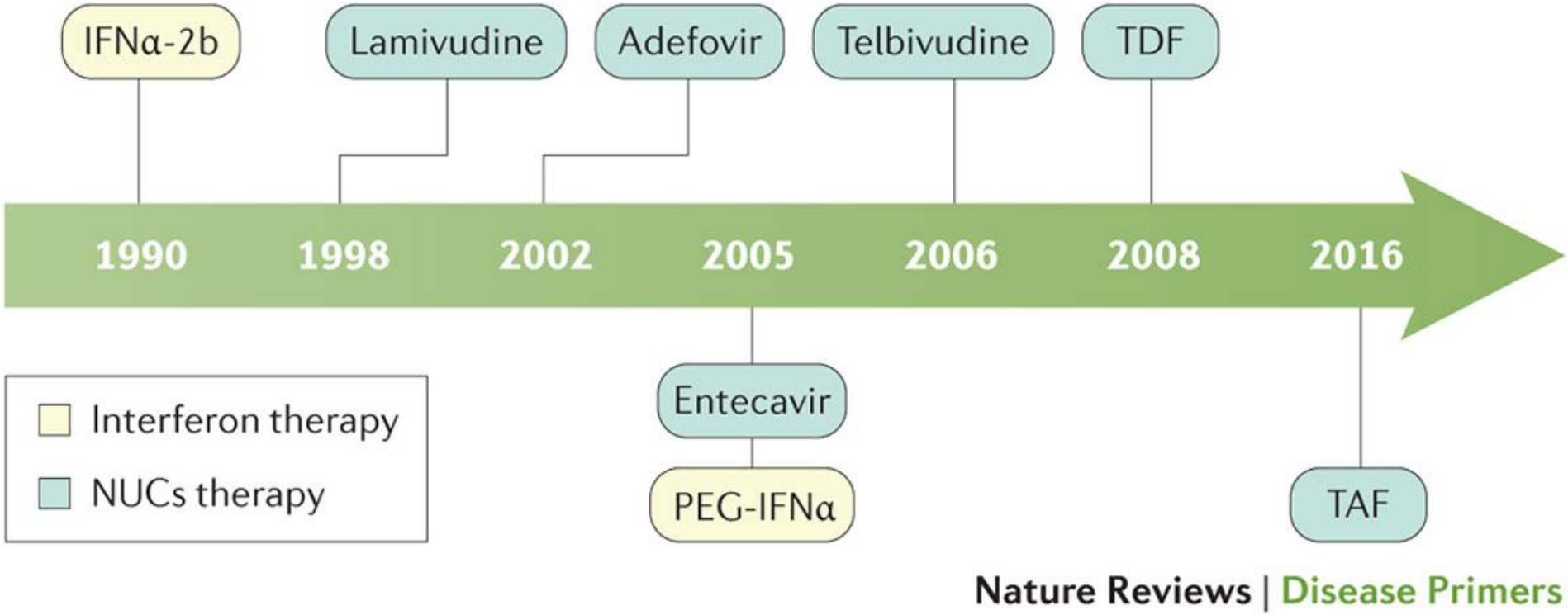
Summary of treatment recommendations from different working groups/ panels/ societies

	North American Expert Panel[1]	East Asia Expert Opinion[2]	US Expert Panel[3]	Hepatitis B Primary Care Working Group[4]	Chinese Hepatology and ID Societies[5]	Test and Treat All[6]
All HBsAg+						Treat
Non-cirrhotic						
HBV DNA <2000 IU/mL, normal ALT*	Consider treating (significant histological disease)				Treat if qualify under certain conditions†	Treat
HBV DNA <2000 IU/mL, elevated ALT*					Treat	Treat
HBV DNA ≥2000 IU/mL, normal ALT*	Treat if qualify under certain conditions‡	Treat if qualify under certain conditions§	Treat if >30 years		Treat if qualify under certain conditions¶	Treat
HBV DNA ≥2000 IU/mL, elevated ALT*	Treat	Treat	Treat	Treat	Treat	Treat
Cirrhotic	Treat	Treat	Treat	Treat	Treat	Treat
HIV/HBV coinfected	Treat	Treat	Treat	Treat	Treat	Treat

1. Martin P, et al. Clin Gastroenterol Hepatol 2022;20:1766–75; 2. Kao JH, et al. Aliment Pharmacol Ther 2020;52:1540–50; 3. Dieterich D, et al. Gastro Hep Adv 2023;2:209–18; 4. Hepatitis B Primary Care Work Group. Available at: https://www.hepatitisb.uw.edu/page/primary-care-workgroup/guidance (accessed July 2023); 5. Chinese Hepatology and ID Societies guidelines. Chin J Hepatol 2022;30:1309–31; 6. Razavi H, et al. J Hepatol 2023;78:S888-9.

*ALT threshold limits: Refs 1, 2 and 5, ALT 30 U/L for males and 19 U/L for females; Ref 4, ALT 35 U/L for males and 25 U/L for females; †Treat if: family history of cirrhosis or HCC, age >30, liver histopathology showing significant hepatic inflammation (≥G2) or fibrosis (≥S2), or HBV-related extrahepatic manifestations; ‡For HBeAg- patients, treat if: fibrosis; for HBeAg+ patients, consider treating based on: risk factors for developing HCC, patient's age, lifestyle and desire to undergo treatment; §Treat if: ≥F2 fibrosis, ≥A2 necroinflammation; consider treatment if: first-degree family history of cirrhosis or HCC, extrahepatic manifestations, age >40 years; ¶Treat if: family history of cirrhosis or HCC, age >30, liver histopathology showing significant hepatic inflammation (≥G2) or fibrosis (≥S2), or HBV-related extrahepatic manifestations. Please see glossary for abbreviations.

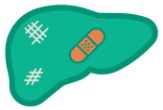
Existing treatment agents for chronic HBV infection: Peg-IFN & nucleos(t)ide analogs



Yuen MF et al., Nat Rev Dis Primers. 2018;4:18035

Summary of preferred CHB therapies



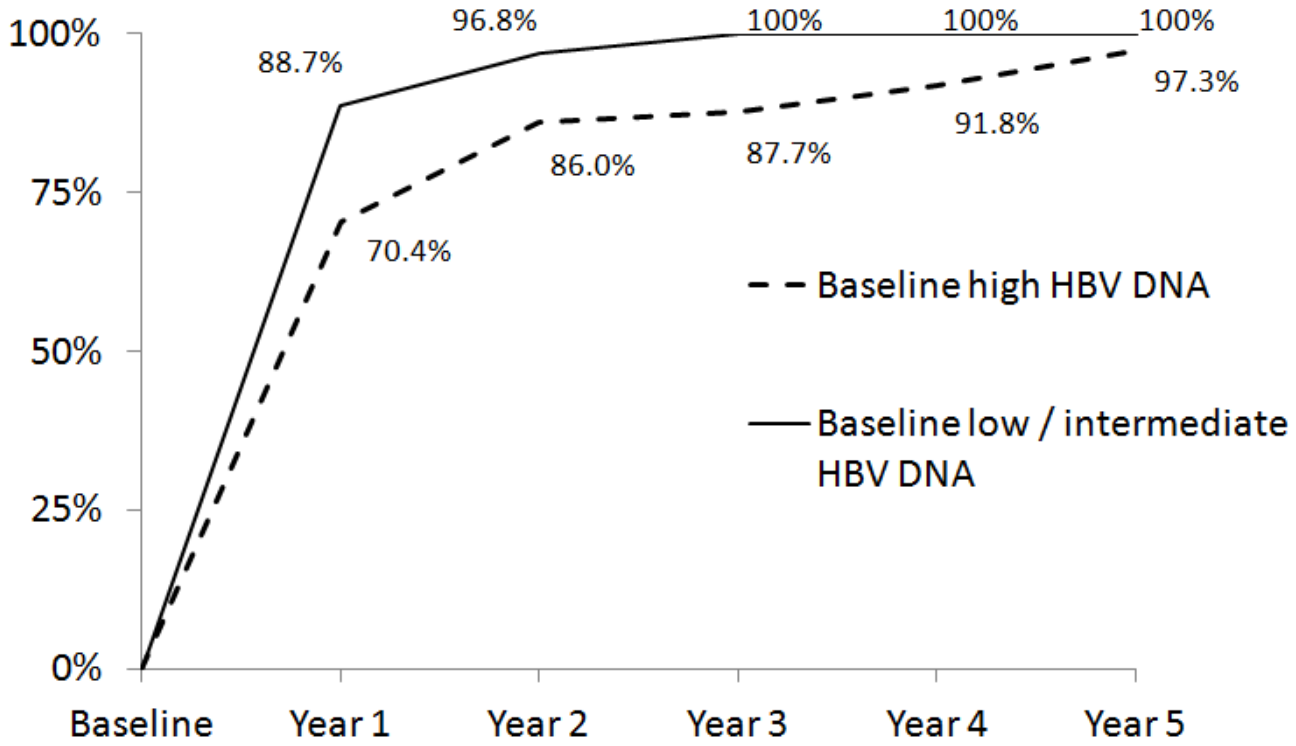


Guideline	HBeAg+ or HBeAg- Without cirrhosis	Compensated cirrhosis	Decompensated cirrhosis	Age >60 years	Renal/bone disease
EASL 2017	**TAF, TDF, ETV,** or Peg-IFN	**TAF, TDF, ETV**; Peg-IFN may be used in selected patients with compensated cirrhosis	**TDF or ETV**	**TAF or ETV**	**TAF or ETV**
AASLD 2018	**TAF, TDF, ETV,** or Peg-IFN	**TAF, TDF, ETV**	**TDF or ETV***		**TAF or ETV**
APASL 2015	**TDF, ETV** or Peg-IFN	**TDF or ETV;** Peg-IFN for well-compensated disease	**TDF or ETV**		
WHO 2024	**TDF or ETV** or TDF + 3TC or TDF + FTC (if no access to TDF monotherapy)	**TDF or ETV**	**TDF or ETV**		**TAF or ETV**
China 2022	**TAF, TDF, ETV, TMF** or Peg-IFN	**TAF, TDF, ETV** or Peg-IFN	**ETV, TDF, or TAF** (considered if necessary)		**TAF or ETV**

*TAF or ETV should be considered in patients with decompensated cirrhosis who have renal dysfunction and/or bone disease

EASL. *J Hepatol*. 2017;67:370–98; Terrault NA, et al. *Hepatology*. 2018;67:1560–99; Sarin SK, et al. *Hepatol Int* .2016;10:1–98; World Health Organization. *Guidelines for the Prevention, Diagnosis, Care and Treatment for People with Chronic Hepatitis B Infection*. 29 Mar. 2024, https://www.who.int/publications/i/item/9789240090903. Accessed April 2024. Chinese Society of Hepatology and Infectious Disease (2022), *J Clin Transl Hepatol*. 2023. doi: 10.14218/JCTH.2023.00320.

All patients had undetectable HBV DNA after 5 years of NUS treatment



		Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients	High baseline HBV DNA		71	61	56	56	52
	Low / intermediate baseline HBV DNA		151	127	117	114	104

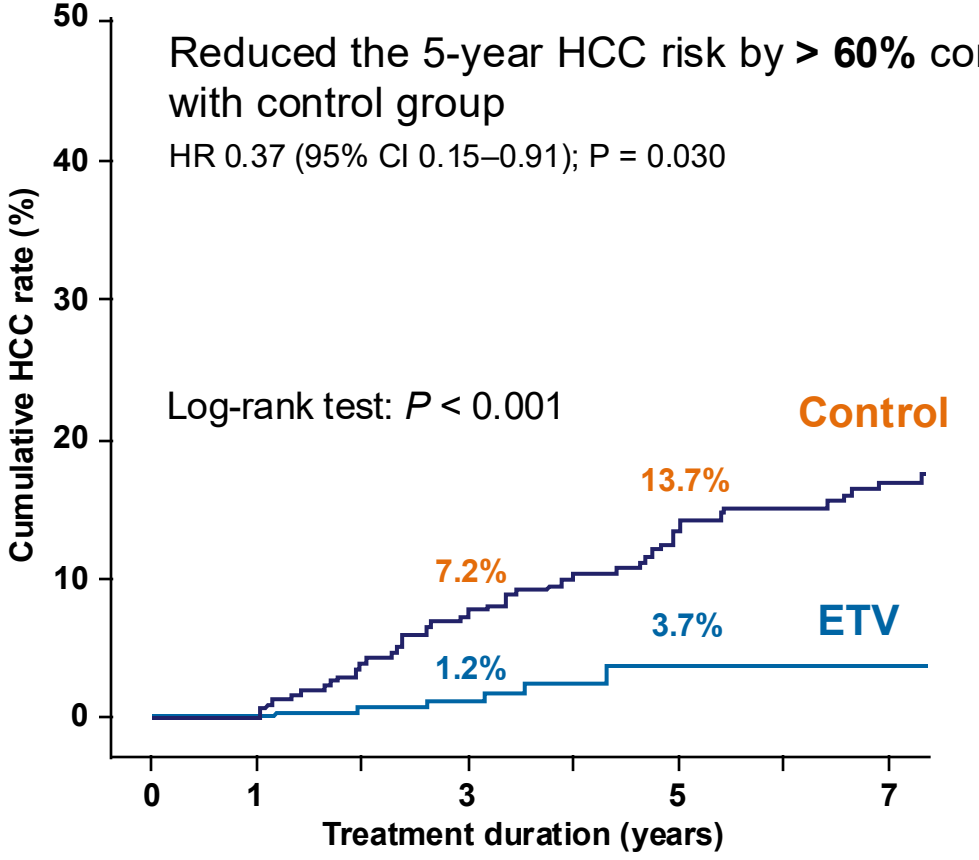
Cumulative rates estimated by the Kaplan-Meier Method (p=0.006)
High HBV DNA defined as HBV DNA ≥7.3 log IU/mL

Seto WK… Yuen MF. J Gastroenterol Hepatol 2014;29:1028-34

NUC treatment reduces HCC incidence (cohort studies)

Reduced the 5-year HCC risk by **> 60%** compared with control group

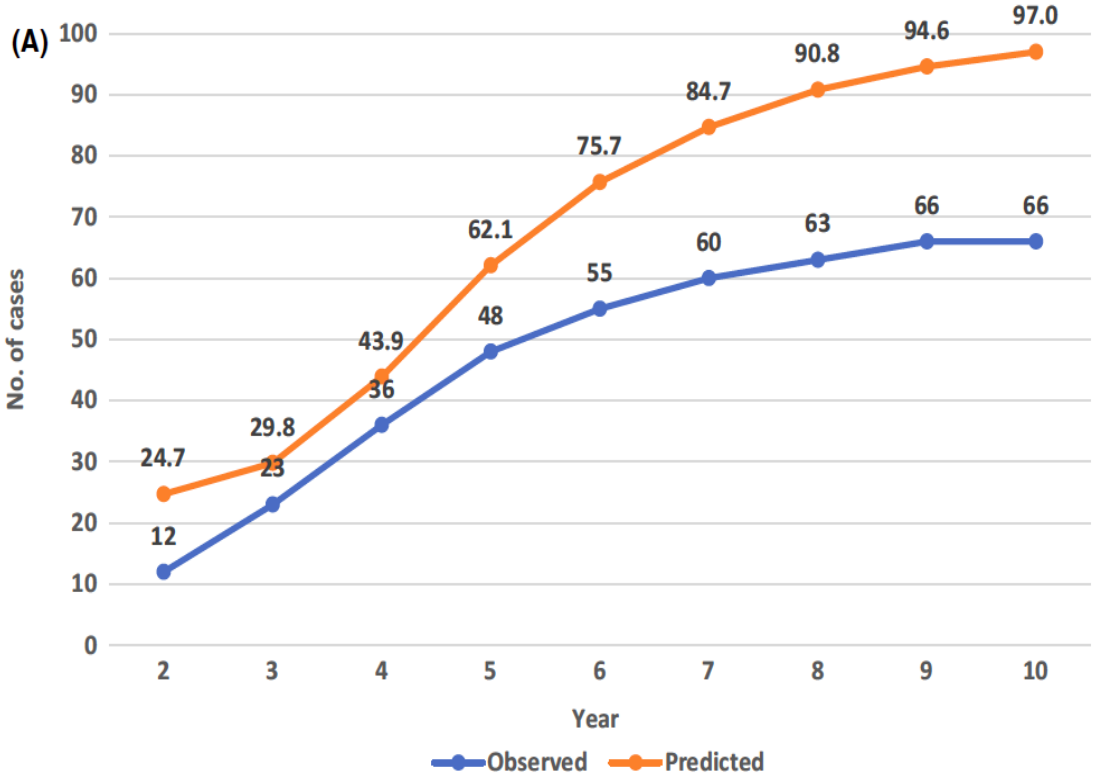
HR 0.37 (95% CI 0.15–0.91); P = 0.030



Hosaka T, et al. Hepatology 2013;58:98–107.

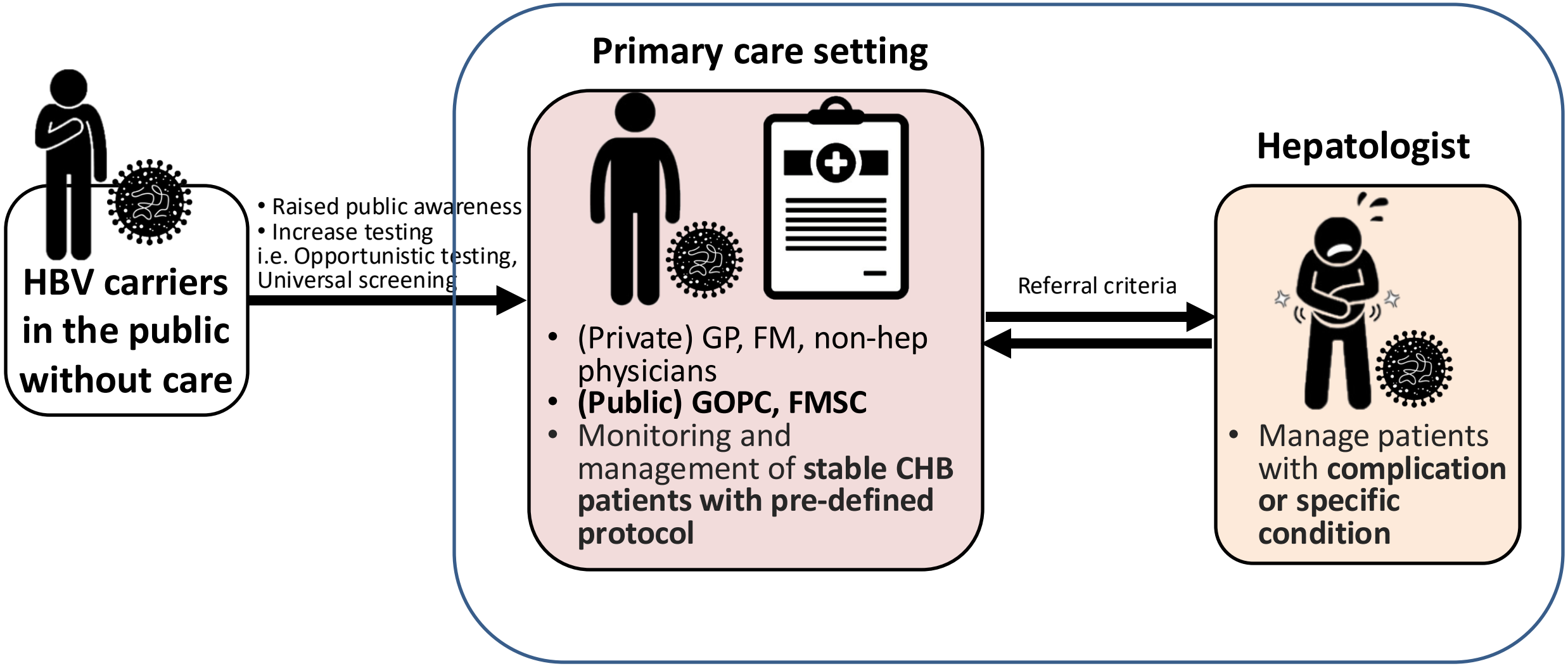
Reduced the standardized incidence ratios (SIR): a ratio of observed over predicted HCC cases at yearly interval

Reduction of 10-year HCC risk by **> 32%** compared to predicted incidence



Ko KL... Yuen MF. J Viral Hepat 2020;27(4):397-406.

Management of chronic HBV patients in primary care setting



Discussion on guidance on management of chronic hepatitis B (CHB) in primary care setting

- Majority of stable CHB patients can be initially assessed and subsequently managed in primary care setting
- Developing locally applicable guidance on management of CHB patients
- Defining criterial for referral between hepatology and primary care setting

Discussion on guidance on management of chronic hepatitis B (CHB) in primary care setting

- Focused on key areas to facilitate management in primary care setting
  - General management of CHB patients
  - Define subgroup of CHB patients requiring hepatology care
  - Criteria for referral to specialist care
  - Criteria for downloading cases from hepatology to primary care

General management of CHB patients

- Initial assessment
  - Clinical
  - Blood test
    - LFT, RFT, CBC, AFP, (APRI & FIB-4 scores)
    - HBsAg, HBeAg, HBV DNA
- Subsequent monitoring
  - Refer hepatologists if special population or criteria met
  - Follow up for stable CHB patients

Indication for HBV antiviral treatment

- CHB patients with advanced fibrosis (LSM > 7), cirrhosis, decompensated liver disease or HCC, and detectable HBV DNA
- Elevated ALT above ULN and HBV DNA > 2,000 IU/mL
- Pre-emptive treatment for patient on anti-cancer chemotherapy or immunosuppressive therapy at risk of hepatitis B reactivation, or
- Transplant patient with hepatitis B infection, or
- Pregnant women with HBV DNA >200,000 IU/mL for peripartum prophylaxis, or
- In addition, anti-viral treatment can be considered in patients at increased risk of complication e.g. family history of cirrhosis or HCC, patients over age of 40 with persistent high HBV DNA level, comorbidities such as diabetes or metabolic dysfunction-associated steatotic liver disease
- Personalised assessment and shared decision-making are key to ensuring a person-centred approach to treatment initiation, balancing individual preferences with the need for strict adherence to long-term treatment.

Non-invasive assessment of liver fibrosis/ cirrhosis

AST-to-platelet ratio index (APRI)

$$\text{APRI} = \frac{\frac{\text{AST level (U/L)}}{\text{AST (ULN)(U/L)}}}{\text{Platelet count } (10^9/\text{L})} \; x \; 100$$

- > 0.5 indicative of significant fibrosis
- > 1.0 indicative of cirrhosis

- Further evaluation e.g. transient elastography, magnetic resonance elastography (MRE)

Fibrosis-4 index (FIB-4)

$$\text{FIB–4} = \frac{\text{Age (years) x AST level (U/L)}}{\text{Platelet count } (10^9/\text{L}) \text{ x } \sqrt{\text{ALT (U/L)}}}$$

- > 3.25 indicative of advanced fibrosis
- 1.45 – 3.25 indeterminant

- Further evaluation e.g. transient elastography, magnetic resonance elastography (MRE)

Non-invasive assessment of liver fibrosis/ cirrhosis

Transient elastography – liver stiffness

- > 8 indicative of advanced fibrosis
- > 11 indicative of cirrhosis

- Repeat in 2-3 years interval depending on clinical situations

Monitoring for stable CHB patients

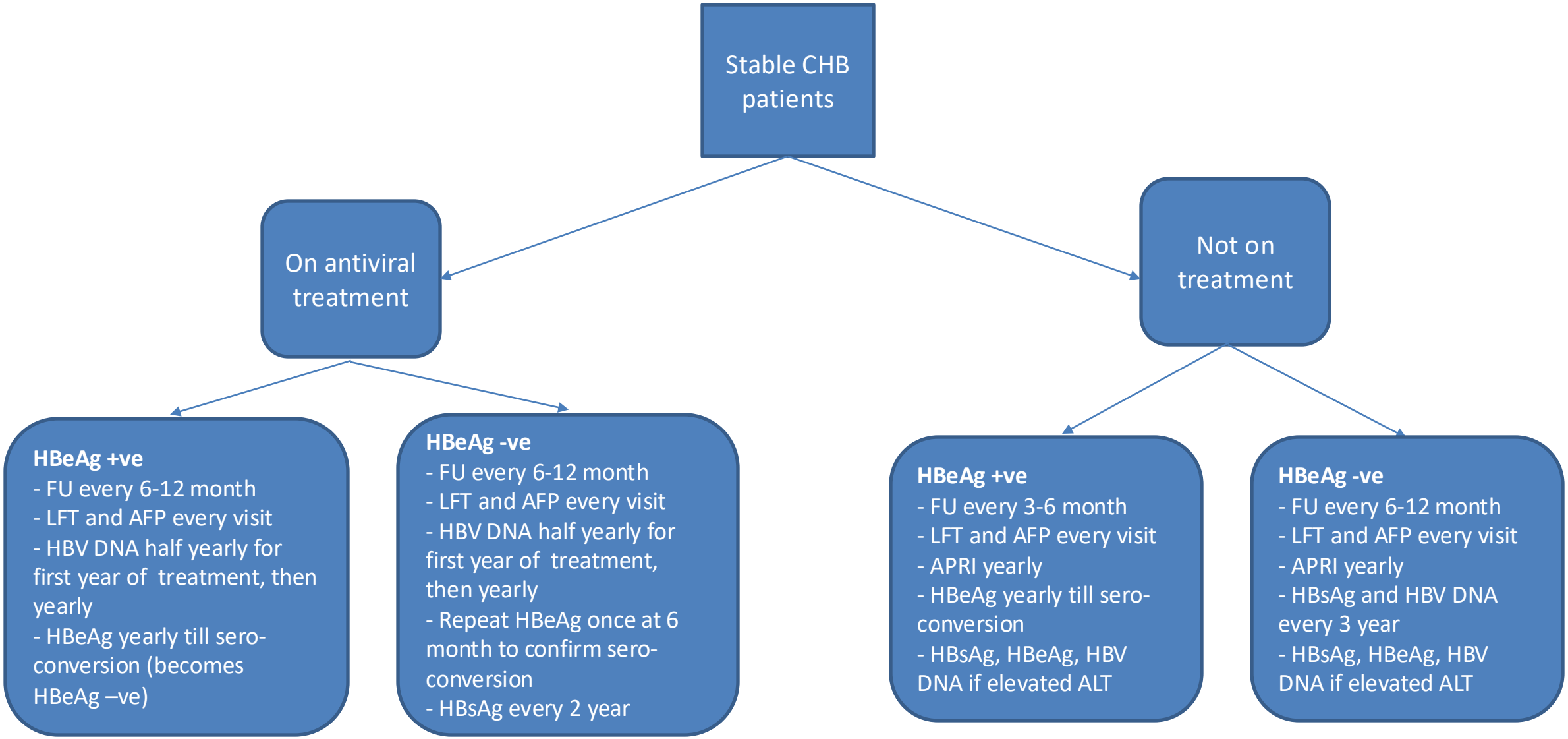
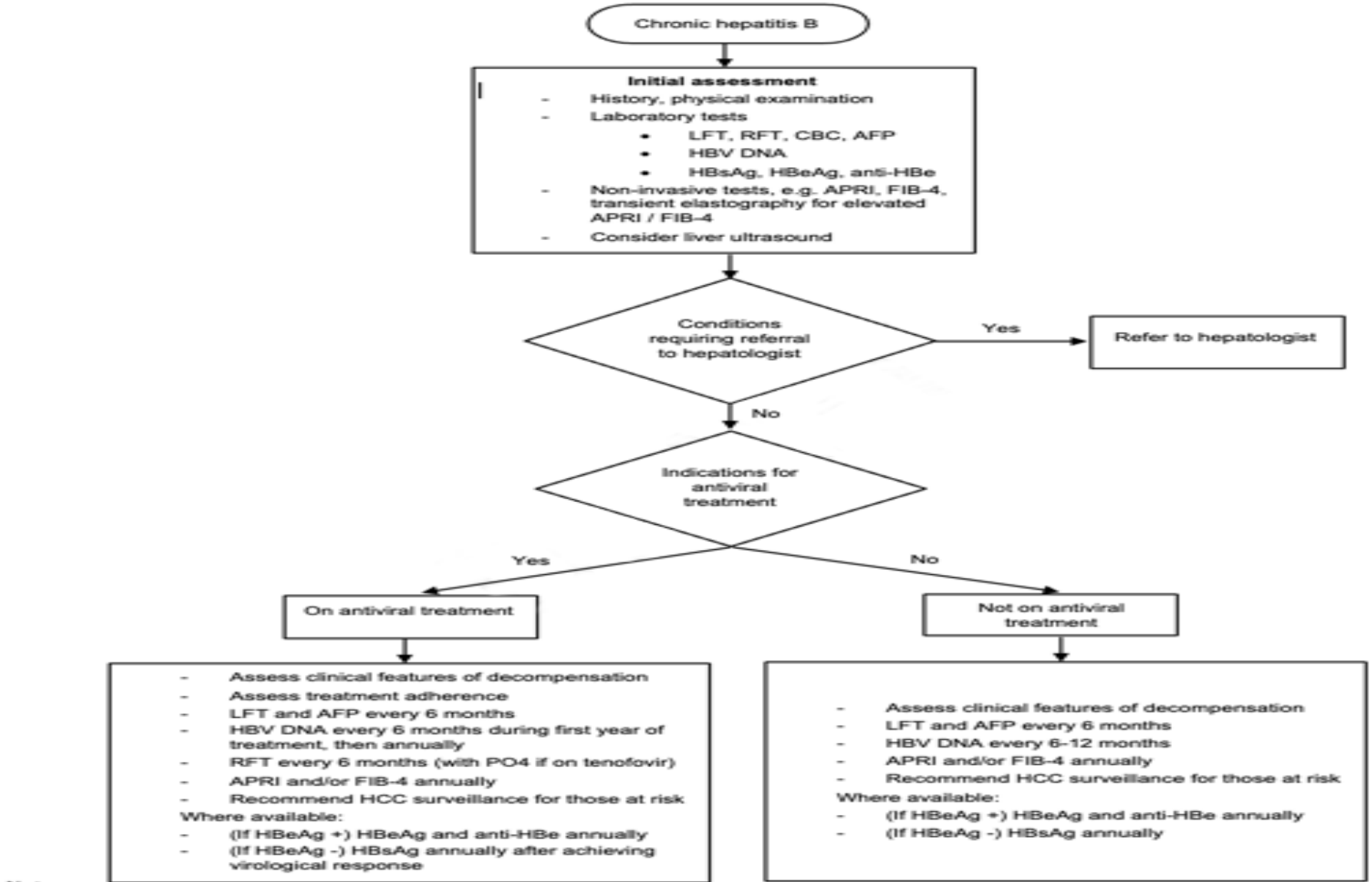


Figure 2 Algorithm for management of individuals with CHB in primary care settings



Note:

- More frequent monitoring may be required at treatment initiation, in those with abnormal ALT and/or HBV DNA >2000 IU/ml but not yet on treatment, or where treatment adherence is a concern.
- The suggested frequency of monitoring serves as a general reference. Clinicians may adapt their approach based on individual patients' needs, patient acceptance, and resource availability.

HCC surveillance in chronic hepatitis B

HCC surveillance is recommended for people with CHB who have the following risk factors:

- People with cirrhosis (high priority)
- People with a family history of HCC (high priority)
- Males over 40 years of age
- Females over 50 years of age

Criteria for referral

- From primary care setting to hepatology
  - Persistent unexplained elevated blood test
    - Low viral load (HBV DNA < 2000 IU/mL) or
    - After starting anti-viral and HBV DNA downward trend
  - Acute hepatitis
    - ALT > 5x ULN regardless of etiology, or
    - Deranged in bilirubin and clotting profile in parallel with rise in ALT, or
    - Urgent referral if symptoms and signs of acute liver failure (hepatic encephalopathy, jaundice) or INR > 1.8
  - Virologic breakthrough while on antiviral treatment
    - > 1 log (10-fold) increase in serum HBV DNA from baseline after initial response after compliance confirmed
  - Abnormal AFP
    - Persistent AFP > 20 despite normal ALT and liver imaging

Subgroup of patients requiring hepatology care

- Development of complication
  - HCC
  - Cirrhosis
- Concurrent liver condition
  - Liver diseases e.g. Autoimmune hepatitis, primary biliary cholangitis
  - Significant liver lesion identified on imaging
- Special population
  - Co-infection with HCV or HIV
  - < 18 year-old
  - Pregnant women
  - Patient on immunosuppressive treatment
  - Renal replacement therapy

Conclusions

- Chronic hepatitis B (CHB) is a global and regional important disease
- CHB is a life-long infection with significant proportion of patients developing long-term complications of cirrhosis and hepatocellular carcinoma
- Disease natural history and treatment options are well established
- International and regional treatment recommendations for CHB are available
- Treatment is safe; nucleotide analogs are widely available and associated with decreased rates of HCC, cirrhosis, liver related and all cause mortality.
- Screening to identify CHB carriers and regular surveillance for disease complications e.g. HCC/ cirrhosis are required
- Use of different hepatitis B related investigations and imaging can identify low- and high-risk patients and monitor disease progress
- Primary care involvement of managing low-risk patients is vital and possible if treatment indications and managements are clearly defined and referral system is in place

Thank you