UNIVERSITÄT LEIPZIG
Medizinische Fakultät

2024 16 PARIS HEPATOLOGY CONFERENCE

Universitätsklinikum Leipzig
Medizin ist unsere Berufung.

TRANSPLANTATIONSZENTRUM

UNIVERSITÄRES LEBERTUMORZENTRUM LEIPZIG

30 JAHRE TRANSPLANTATIONS ZENTRUM LEIPZIG

Controversy:
Treat everyone with detectable HBV DNA?
NO!

Thomas Berg

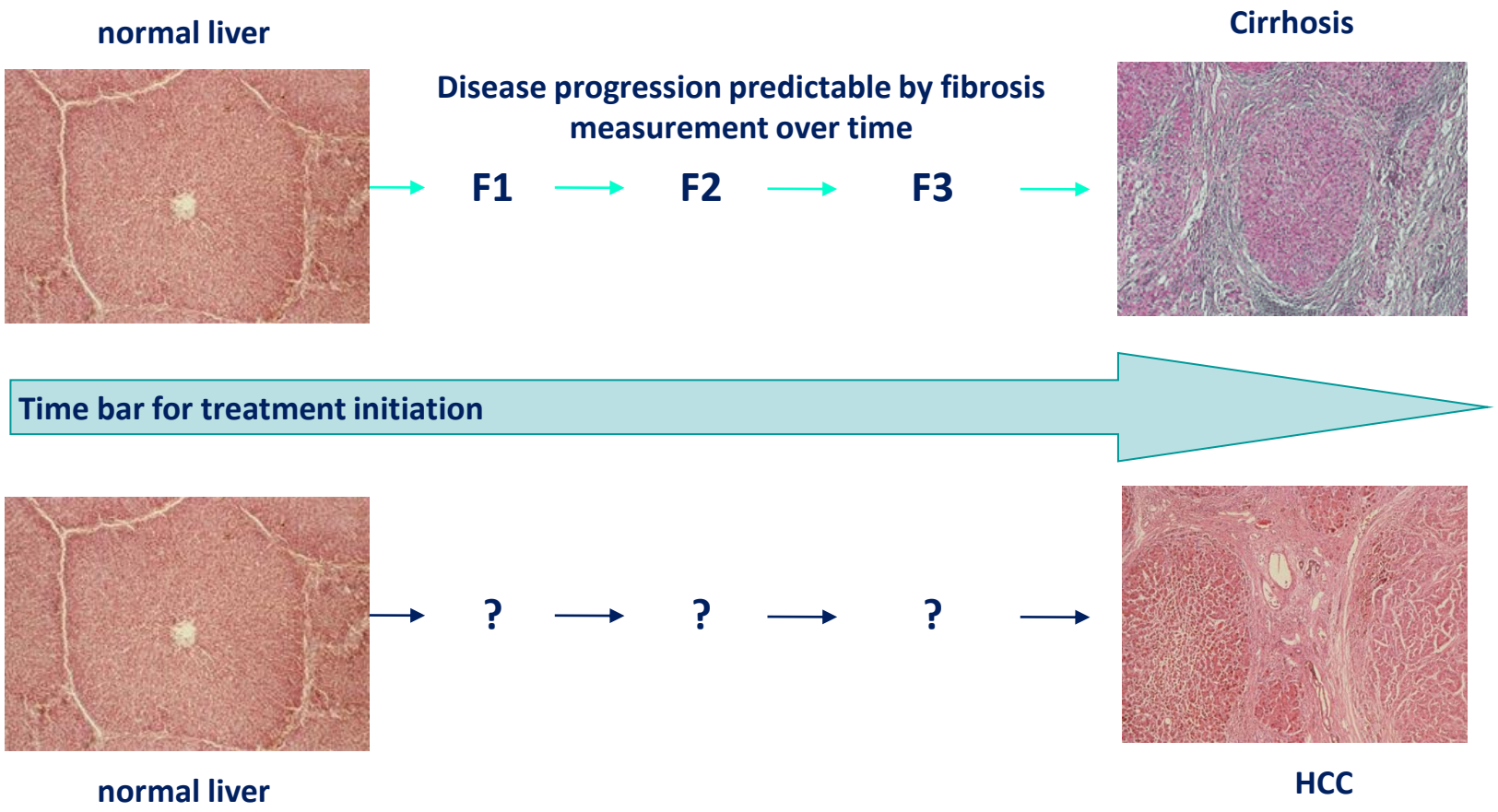
Division of Hepatology

Department of Medicine II

LEIPZIG UNIVERSITY MEDICAL CENTER

The HBV journey

HBV infection = A fibrotic liver disease



HBV infection = An oncogenic disease

Goals of therapy in chronic HBV infection

Global Consensus:

- **The main goal of therapy for patients with chronic HBV infection is to improve survival and quality of life by preventing disease progression, and consequently HCC development**

EASL HBV Clinical Practice Guideline J Hepatol 2017; 67: 370
AASLD Terrault NA et al. Hepatology 2018;67: 1560
APASL Sarin SK et al. Hepatol Int 2015

Current recommendations for treatment initiation

Global consensus:

- Individual patterns of HBV DNA and ALT levels to guide treatment indication, taking into account HBeAg and cirrhosis status
- ALT > 2 x ULN and HBV DNA > 2,000/20,000 IU/mL: start treatment
- If cirrhosis, treat irrespective of ALT levels

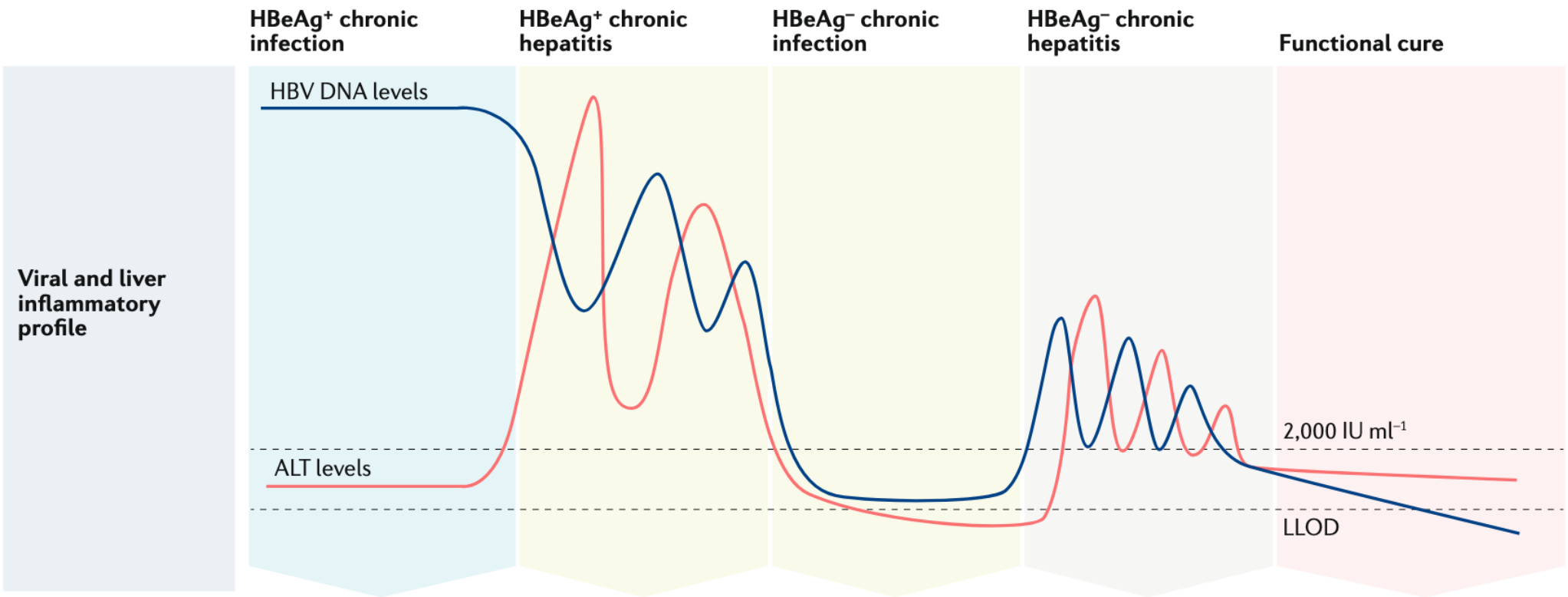
No global consensus:

Definition of normal ALT, as well as ALT/HBV DNA cut-offs to indicate tx

HBeAg positive HBV infection

EASL HBV Clinical Practice Guideline J Hepatol 2017; 67: 370
AASLD Terrault NA et al. Hepatology 2018;67: 1560
APASL Sarin SK et al. Hepatol Int 2015

Who ist best candidate for antviral treatment
Current approaches concentrate on inflammation and fibrosis progression



	HBeAg+ chronic infection	HBeAg+ chronic hepatitis	HBeAg− chronic infection	HBeAg− chronic hepatitis	Functional cure
Serum HBsAg	Monitor	Treatment	Monitor	Treatment/Monitor	-
cccDNA	+++++	+++++	++	+++	+
Fibrosis	Minimal fibrosis	Variable degree of fibrosis (progressing)	Variable degree of fibrosis (progressing)	Moderate to severe fibrosis (resolving)	Variable fibrosis (sequelae of previous phases)
Liver inflammatory infiltrate	Absent	High	Absent/moderate	Moderate	Absent

Figure: *Nat Rev Drug Discov*. 2019 Nov;18(11):827-844

Who is best candidate for antviral treatment

Should we also treat patients with low-level viremia?

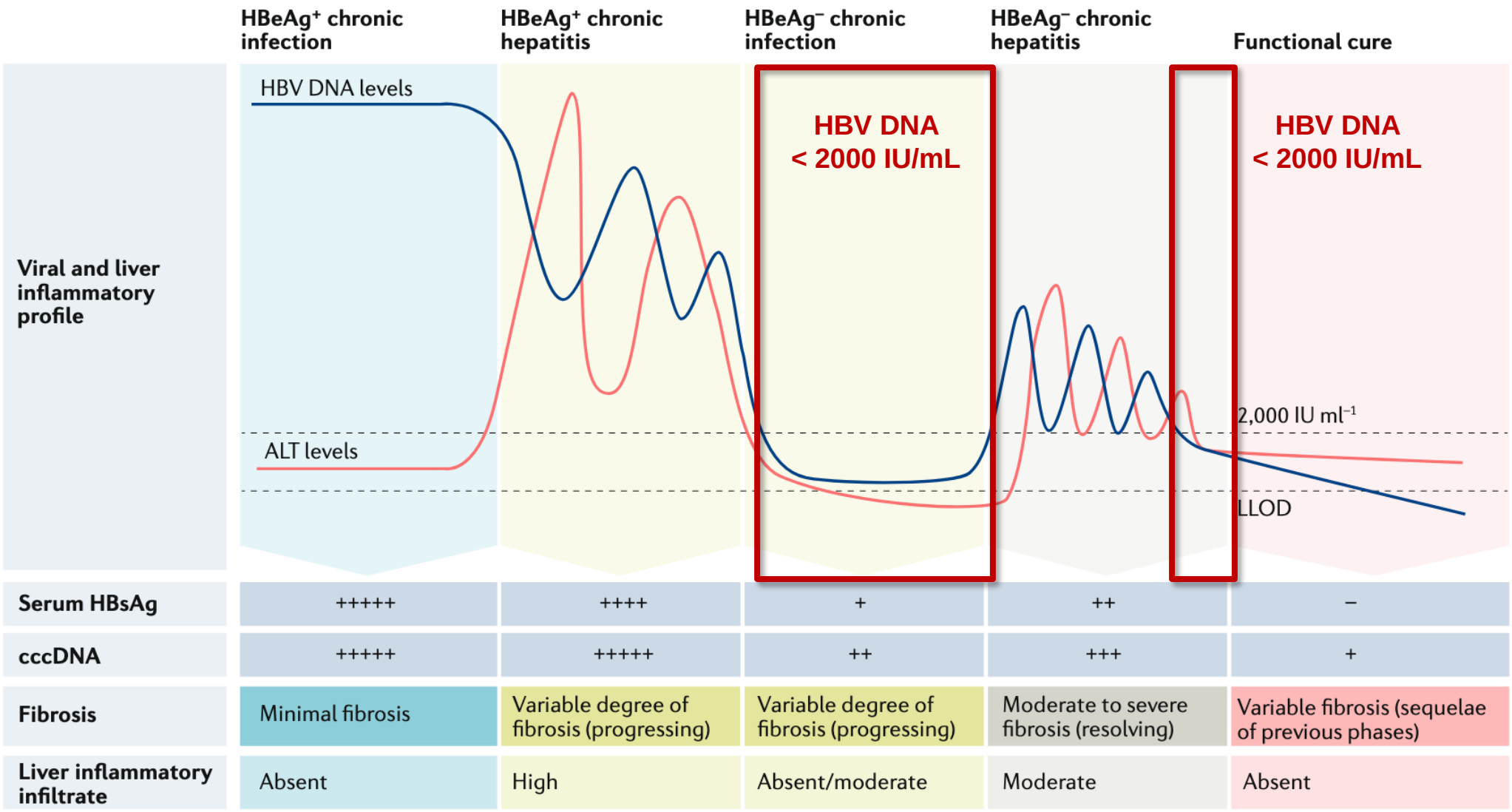
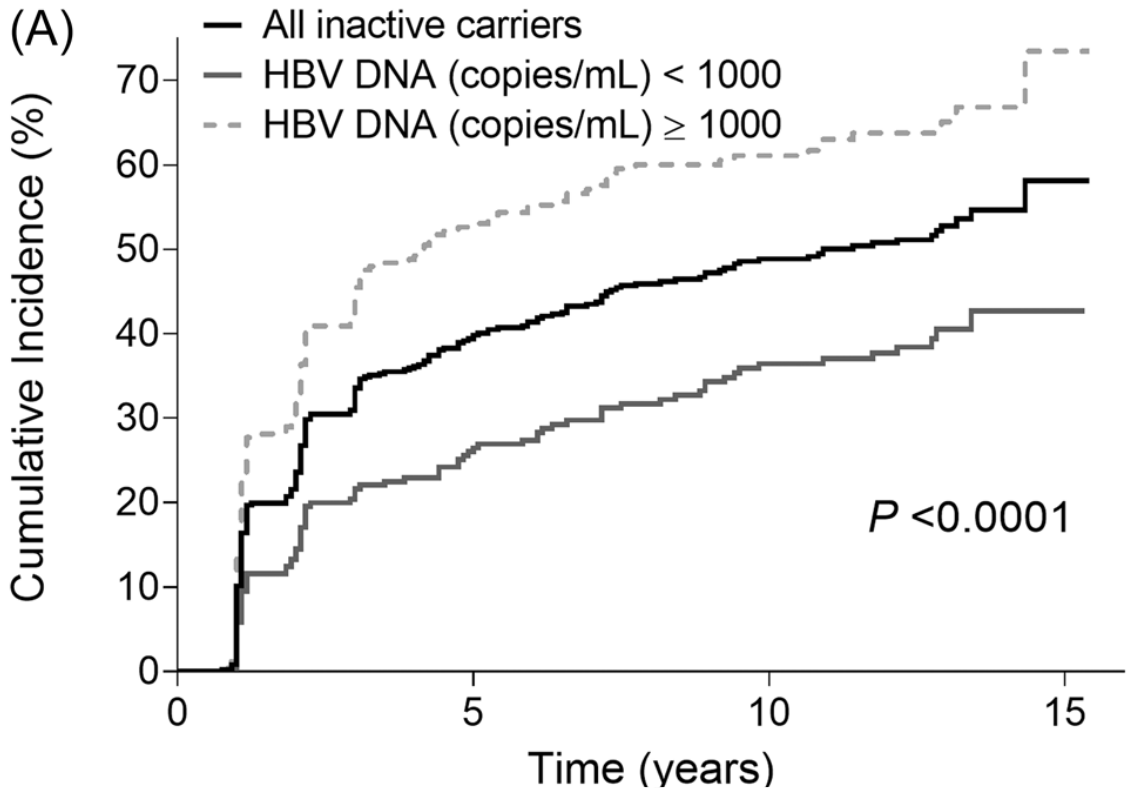


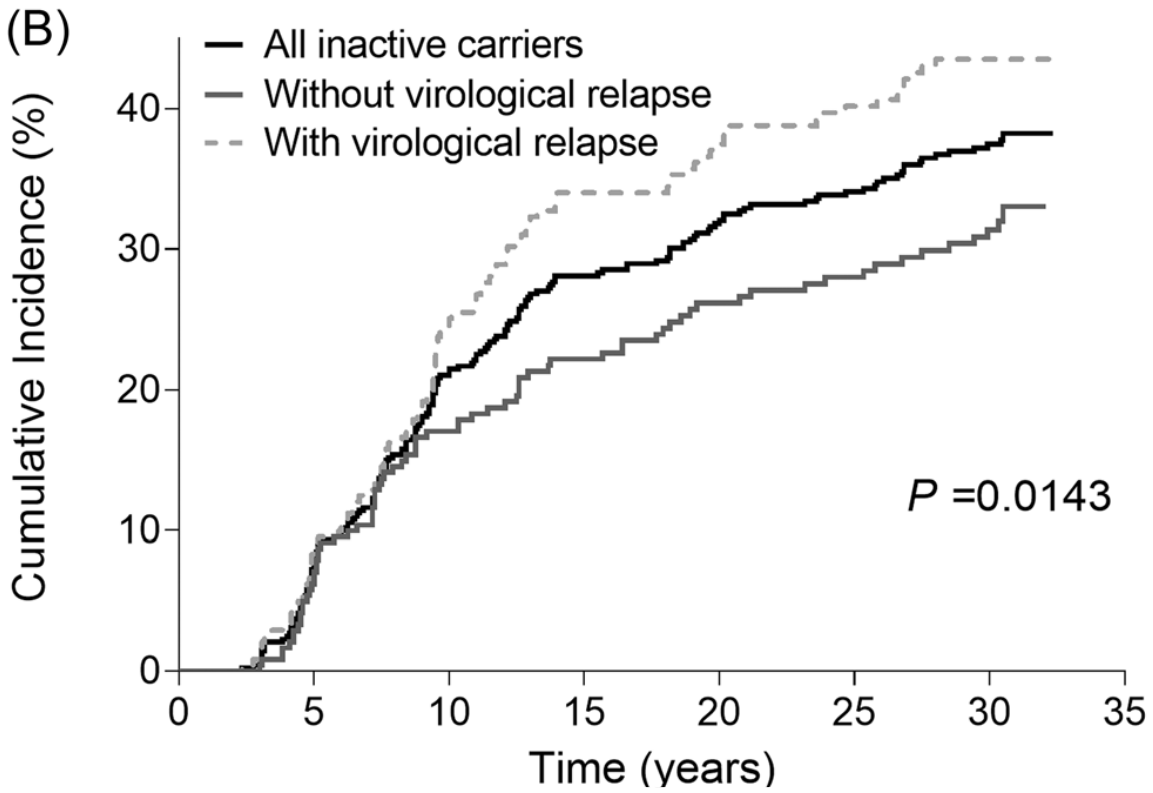
Figure: *Nat Rev Drug Discov*. 2019 Nov;18(11):827-844

Cumulative incidence of HBV reactivation in HBeAg-negative HBV infection („inactive carriers“; N=438)

Virological relapse, stratified by baseline HBV DNA

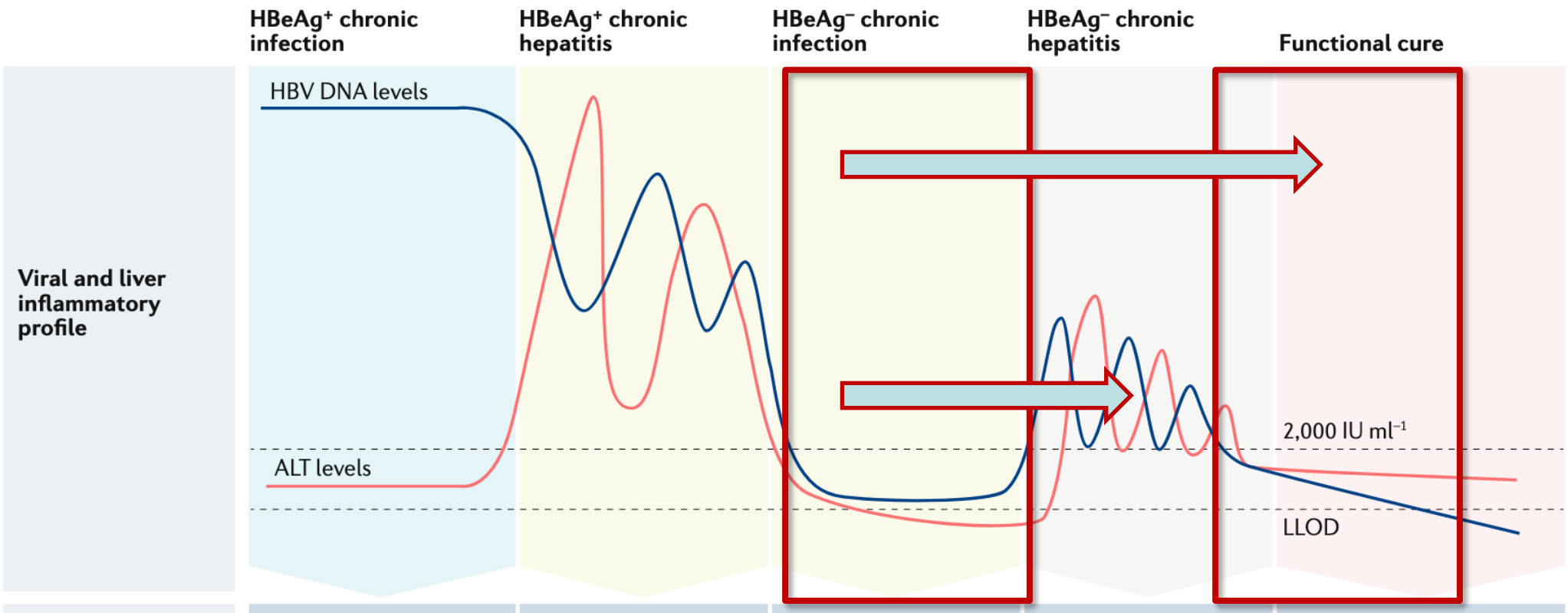


Biochemical relapse, with and without virological relapse



Wu W-J et al. J Med Virol. 2023;95:e29138

How to predict phase transition and how to define the true “inactive carrier”?



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Serum HBsAg	+++++	++++	+	++	–
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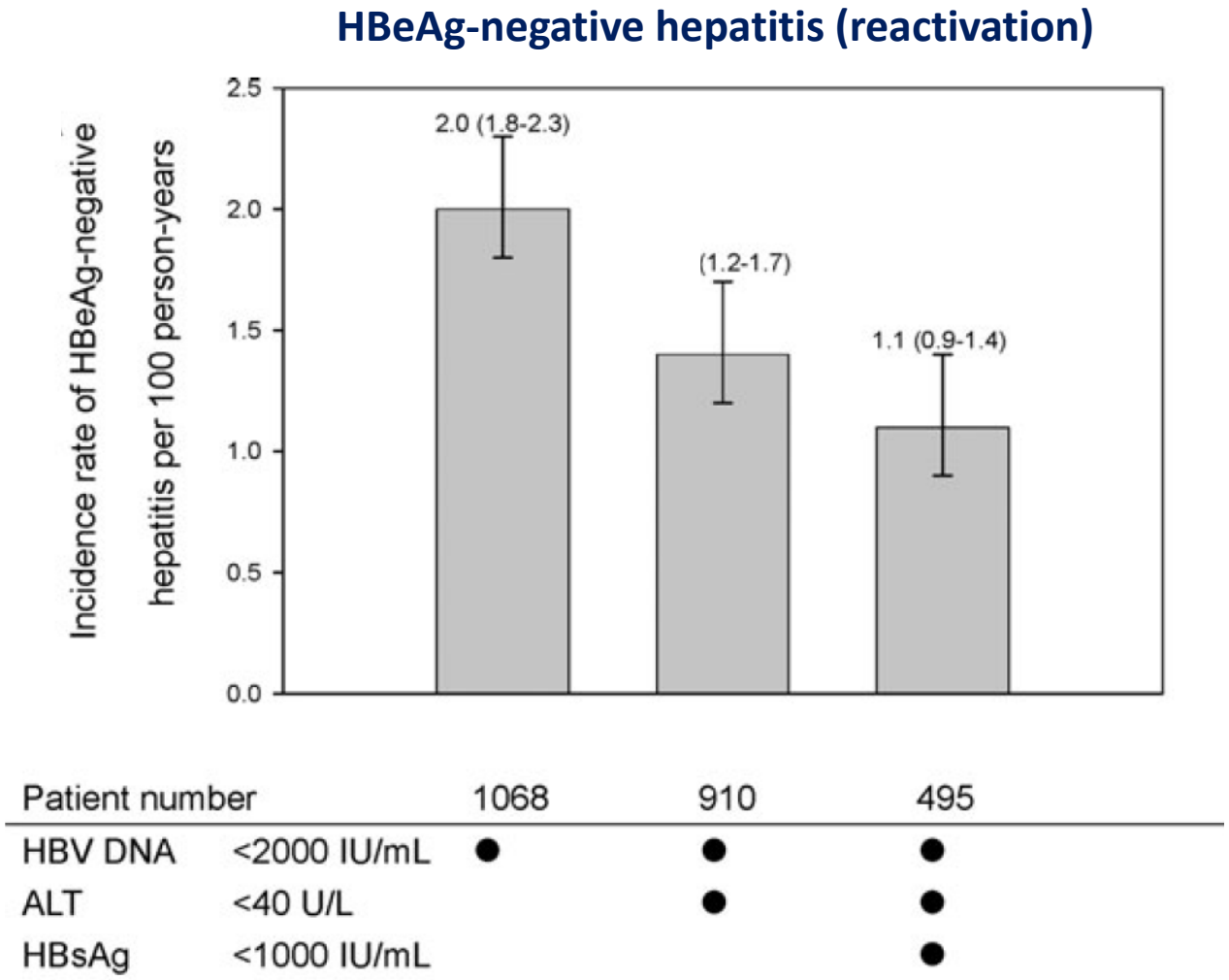
Liver inflammatory infiltrate	Absent	High	Absent/moderate	Moderate	Absent

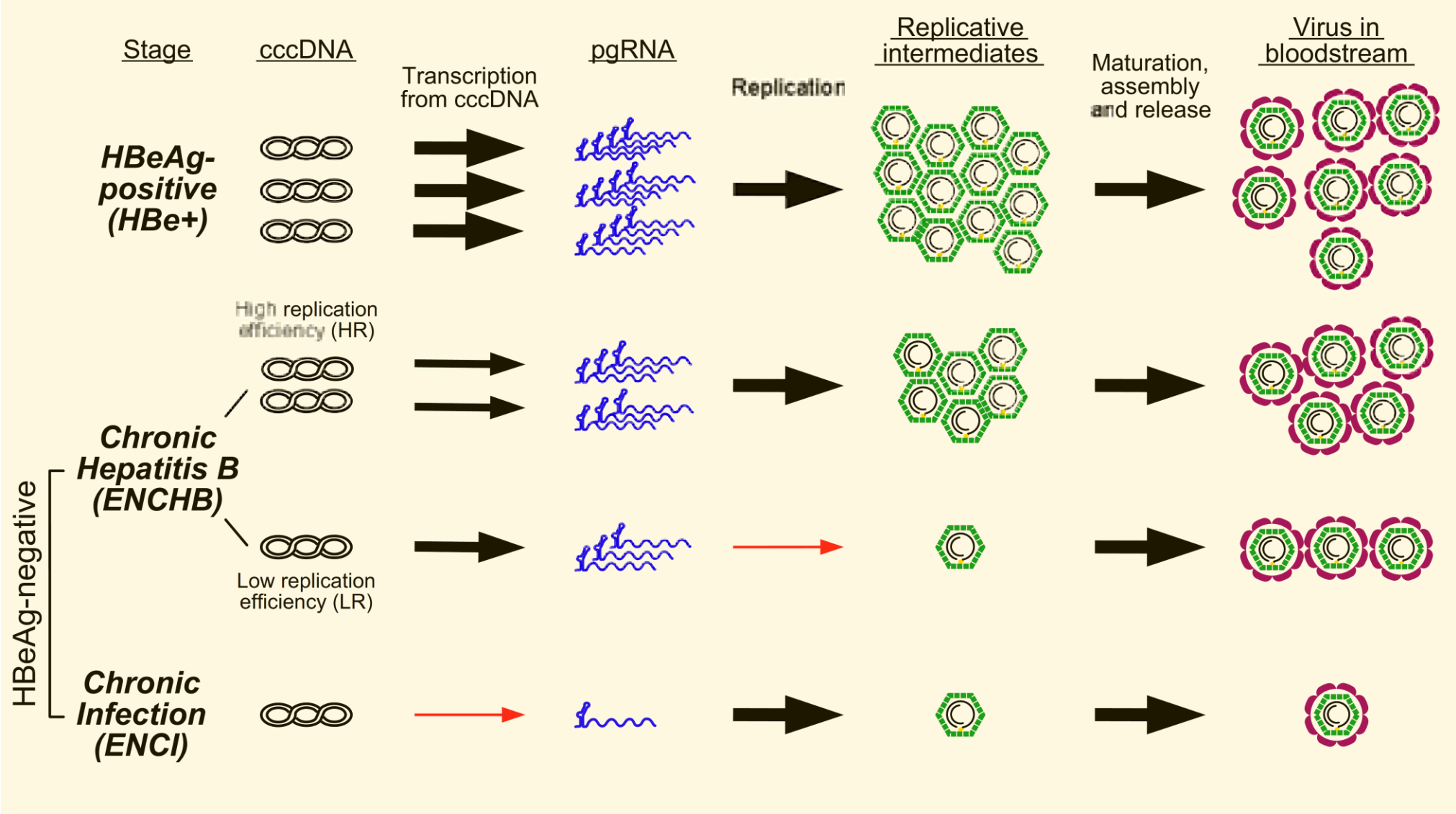
Figure: *Nat Rev Drug Discov*. 2019 Nov;18(11):827-844

Risk of hepatitis reactivation in patients with low baseline HBV DNA (< 2000 IU/mL) – HBsAg levels matter



Tseng TC et al. *Hepatology 2013;57:441-450*

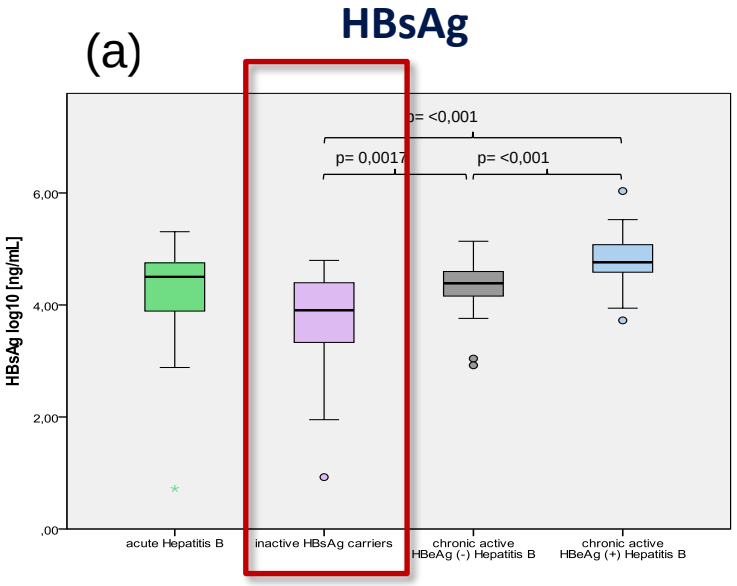
Intrahepatic virological profiles of chronic hepatitis B phases

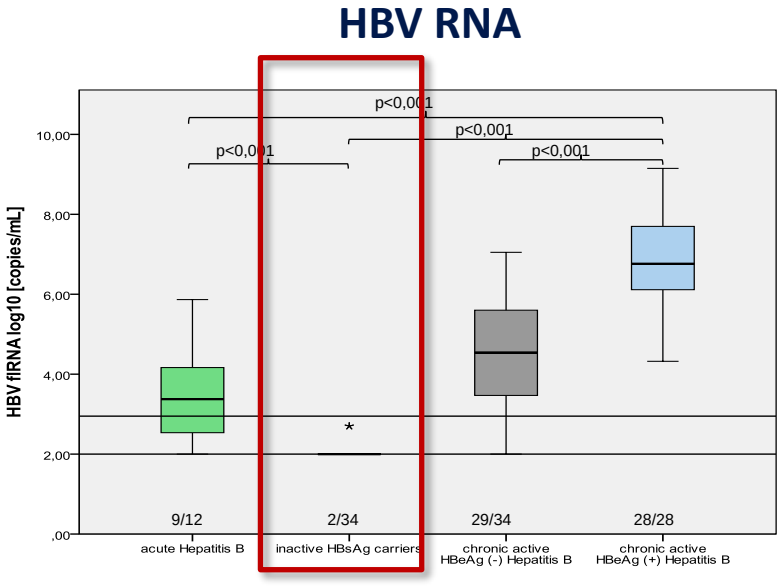


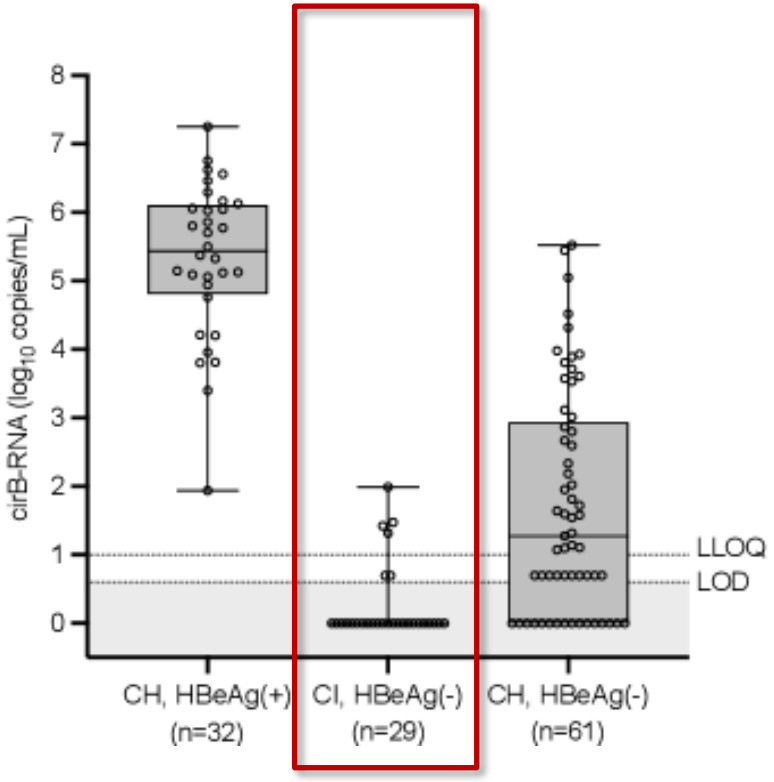
ENCHB = HBeAg-negative chronic hepatitis B; ENCI = HBeAg-negative chronic infection (carrier)

Suslov A et al. J Hepatol 2021; 74: 794-800

Quantitative serum HBV RNA levels at different phases of chronic HBV infection





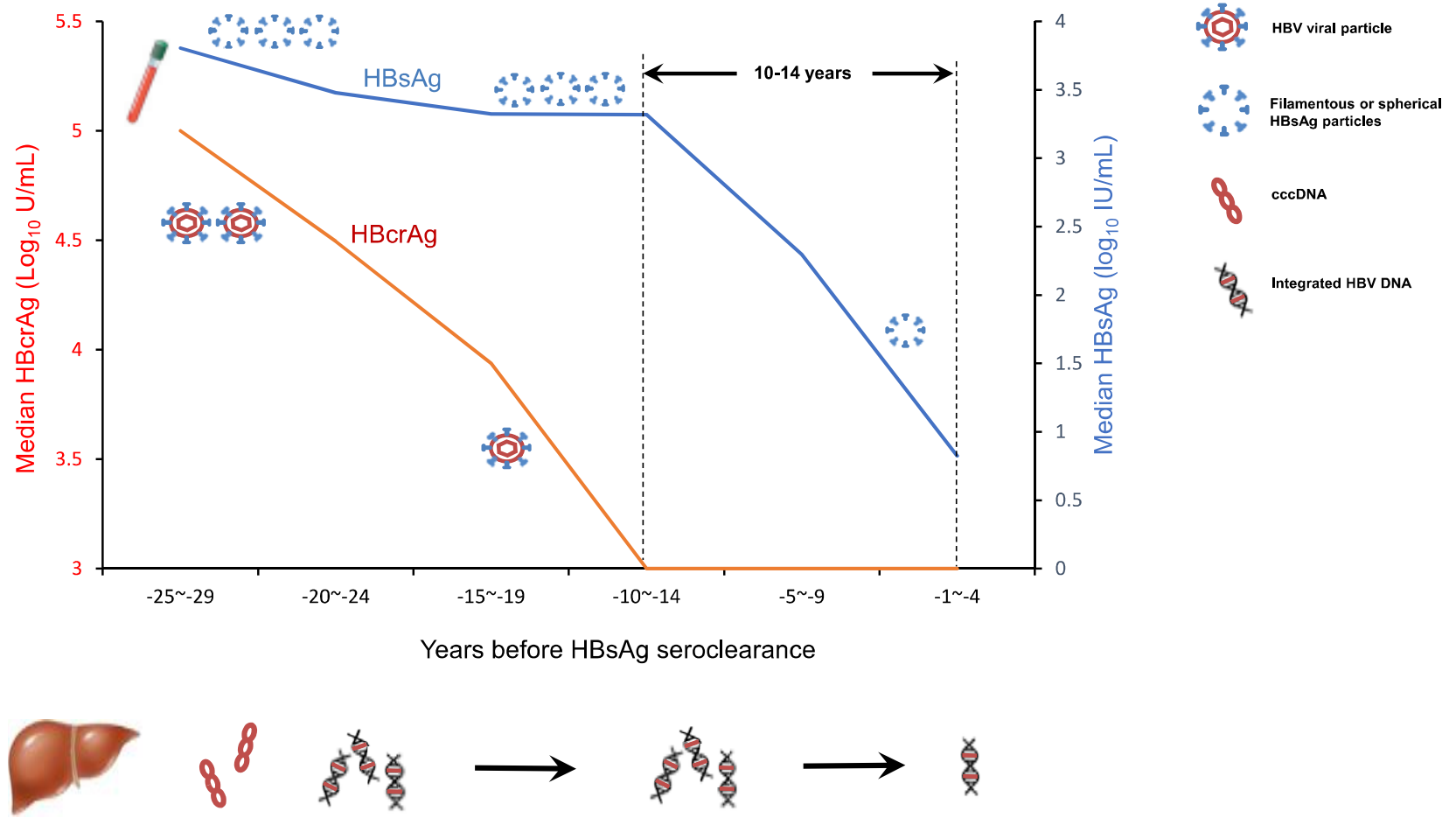


„True“ inactive carriers

Krauel et al. (2016) 32nd annual Meeting of the German Association of the Study of the Liver, GASL

Testoni B et al. Gut 2023 Oct 25:gutjnl-2023-330644

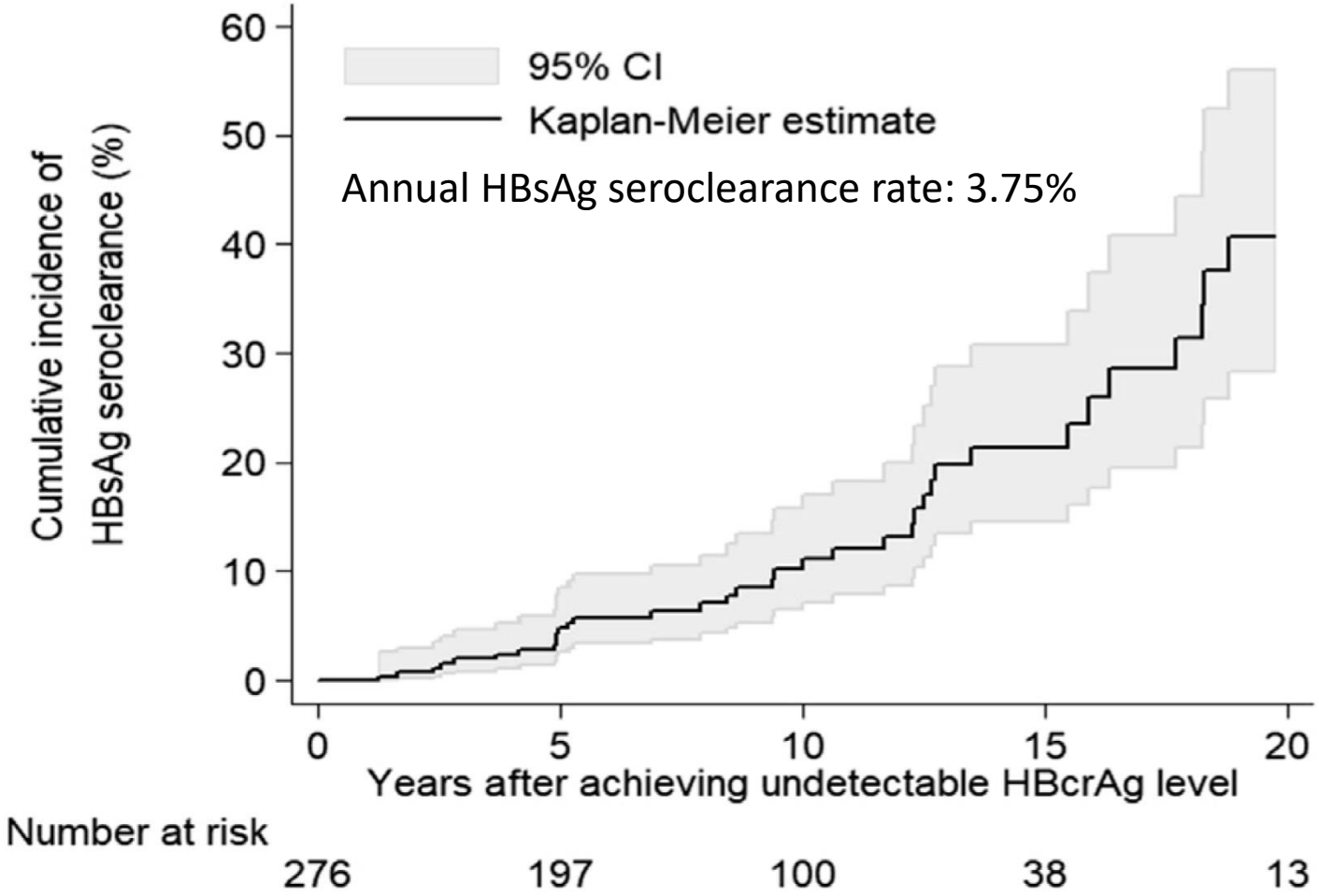
Low HBcrAg Levels Correlate with Higher Spontaneous HBsAg Seroclearance in Chronic Hepatitis B With High HBsAg Levels



High HBsAg levels > 1,000 IU/mL

Tseng T-C *et al*. Gastroenterology 2023;164:669–679

Cumulative incidence of spontaneous HBsAg seroclearance in patients with high HBsAg levels after achieving undetectable HBcrAg levels



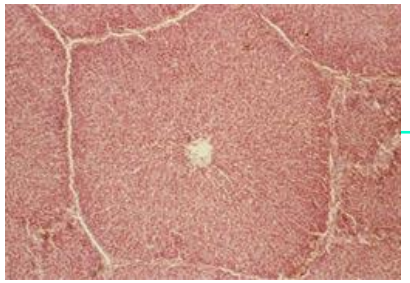
High HBsAg levels > 1,000 IU/mL

Tseng T-C *et al*. Gastroenterology 2023;164:669–679

The HBV journey

HBV infection = A fibrotic liver disease

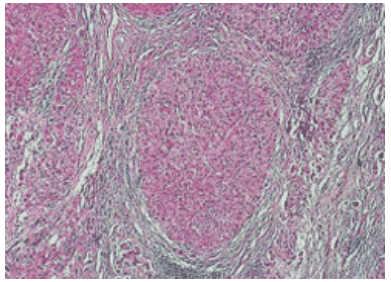
normal liver



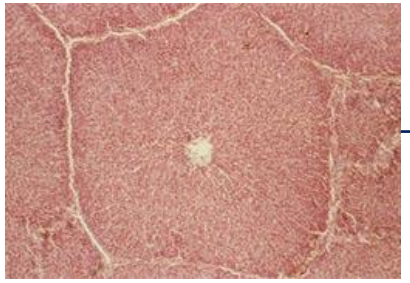
Disease progression predictable by fibrosis measurement over time

F1 → F2 → F3 →

Cirrhosis

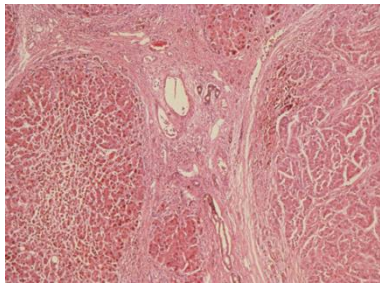


Time bar for treatment initiation



normal liver

? → ? → ? →



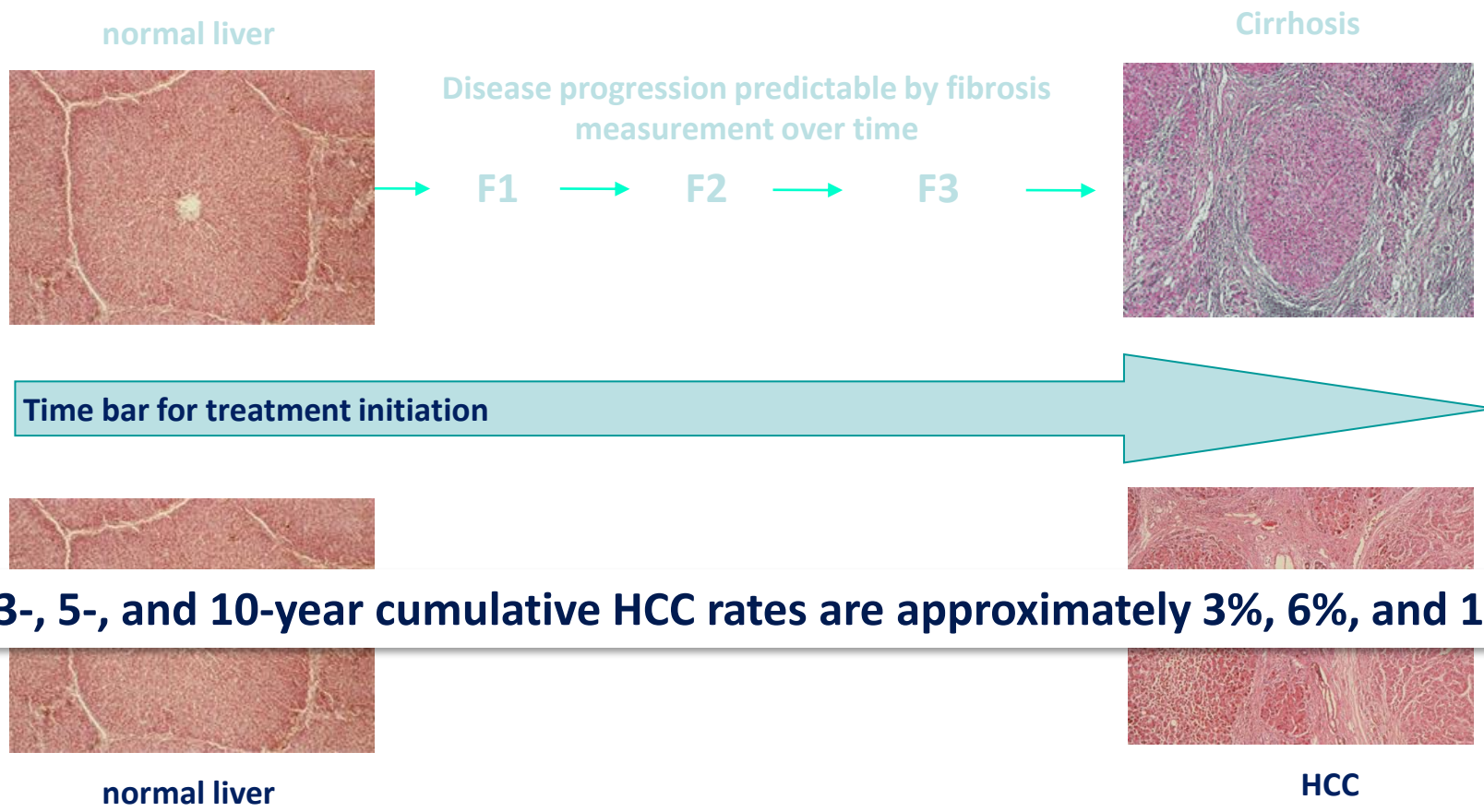
HCC

HBV infection = An oncogenic disease

*Paptheodoridis G et al. JHEP Reports 2021; 3: 100290

The HBV journey

HBV infection = A fibrotic liver disease

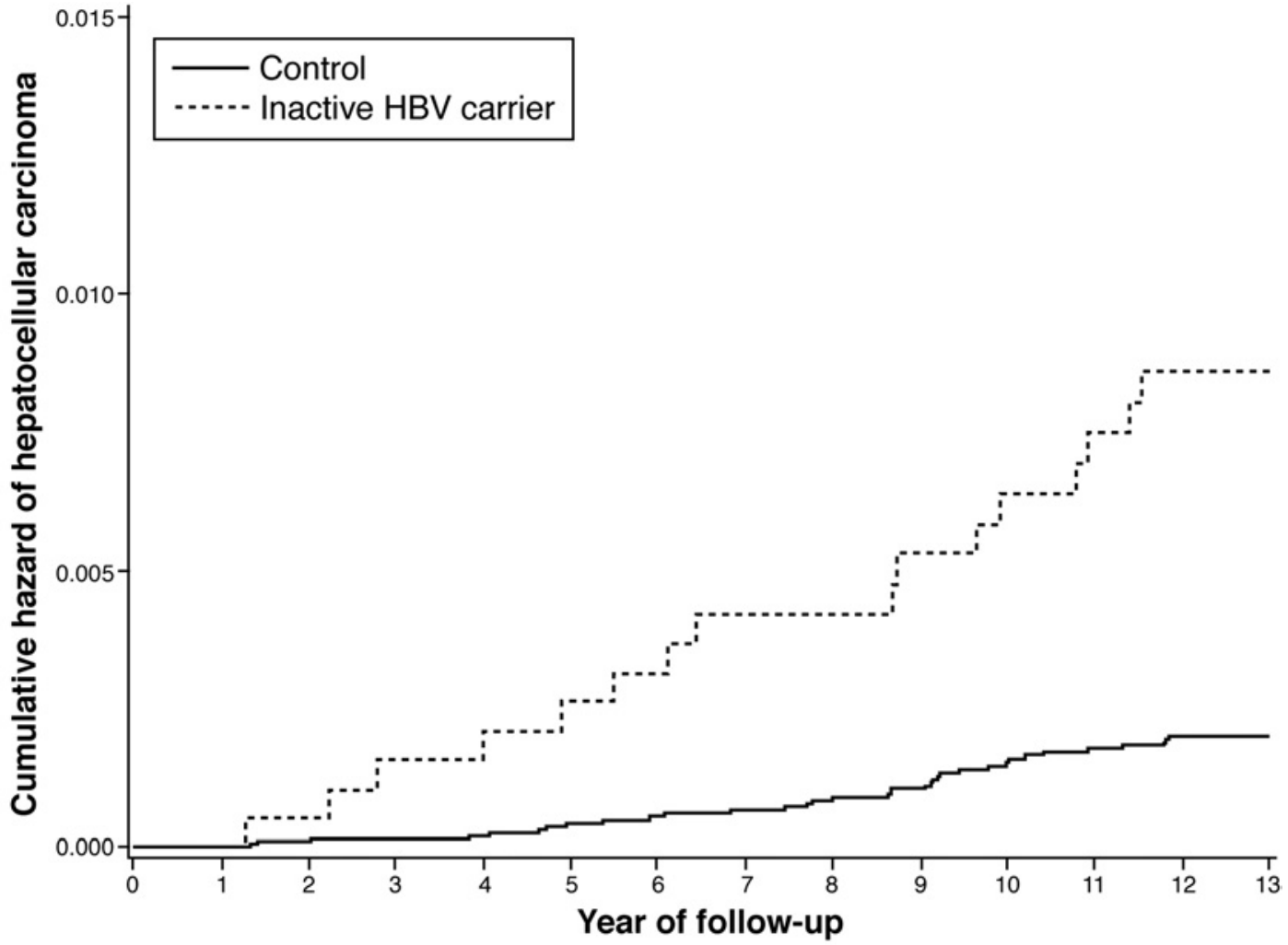


The on-treatment 3-, 5-, and 10-year cumulative HCC rates are approximately 3%, 6%, and 10%, respectively*

HBV infection = An oncogenic disease

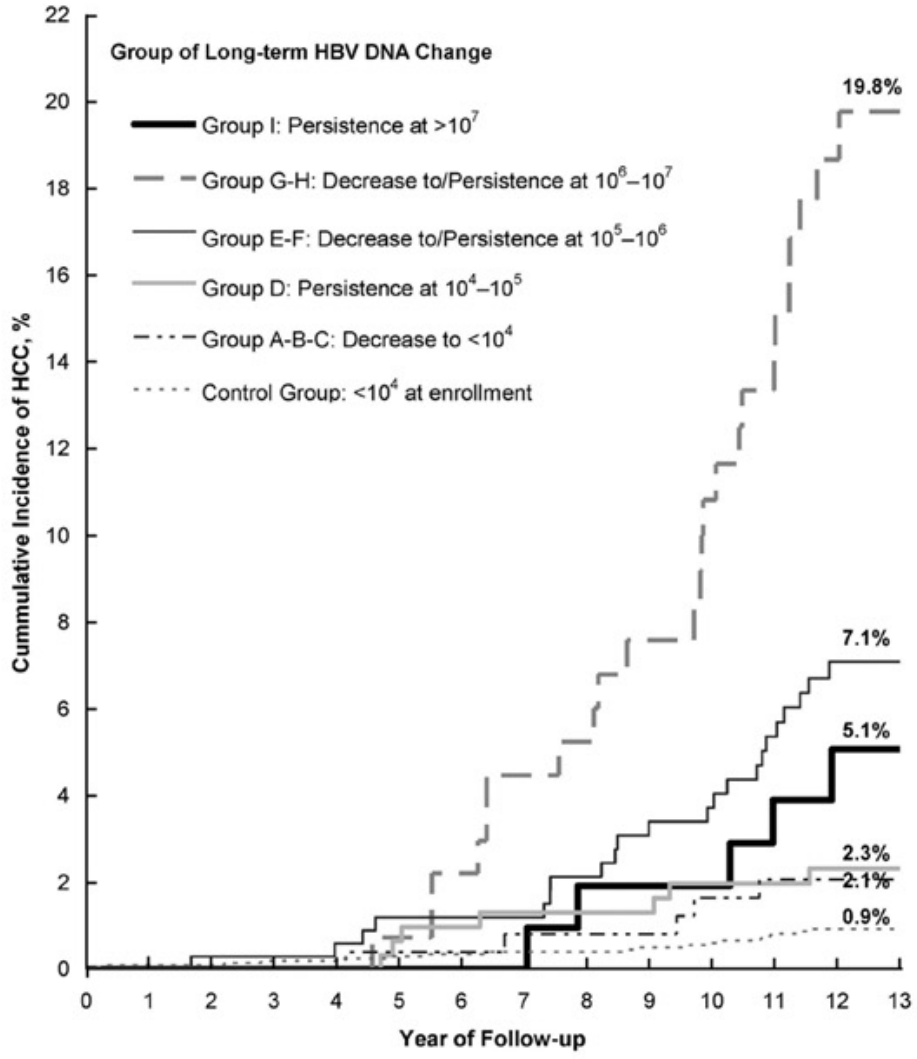
*Paptheodoridis G et al. JHEP Reports 2021; 3: 100290

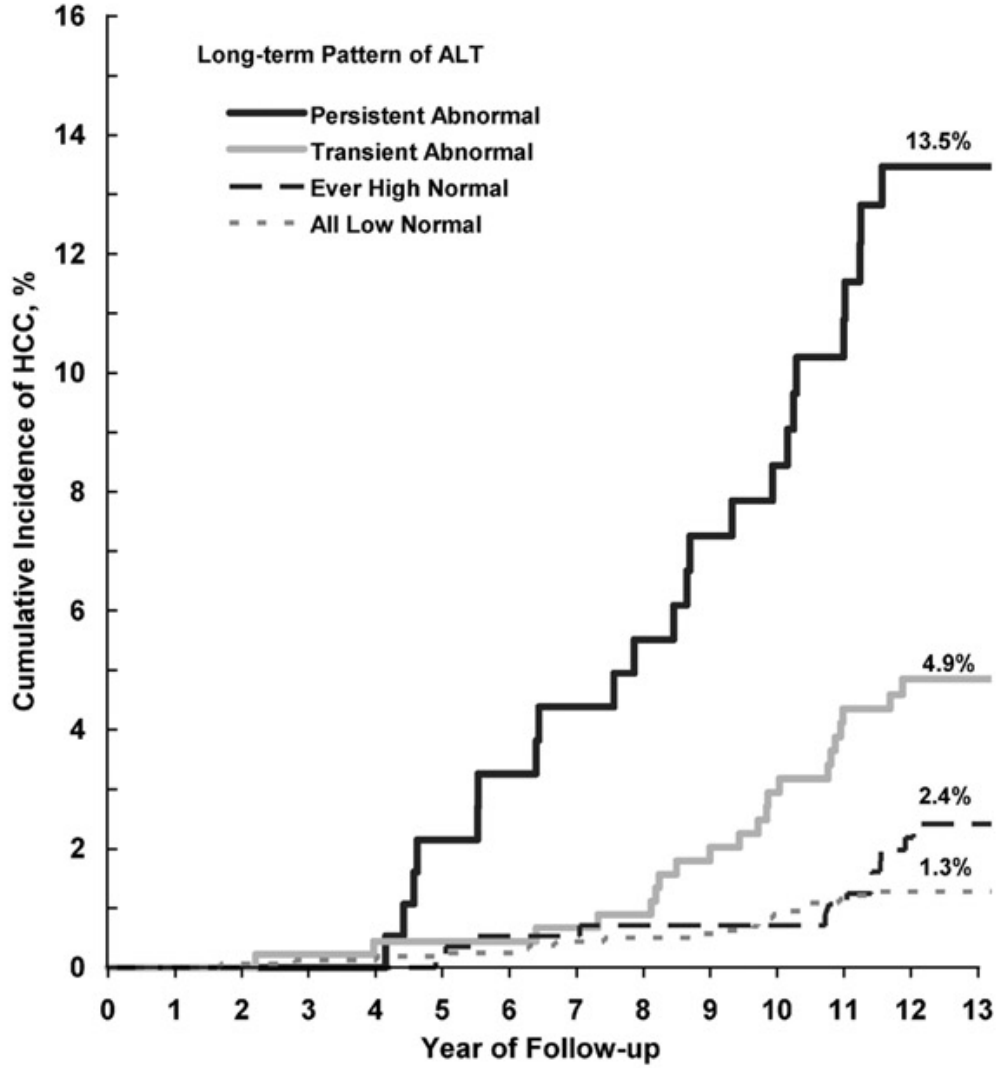
Carriers of Inactive Hepatitis B Are Still at Risk for HCC (THE REVEAL HBV Study Group)



Chen J-D et al. GASTROENTEROLOGY 2010;138:1747–1754

Changes in Serum Levels of HBV DNA and ALT Determine HCC Risk (THE REVEAL STUDY GROUP)





Chen C-F et al GASTROENTEROLOGY 2011;141:1240–1248

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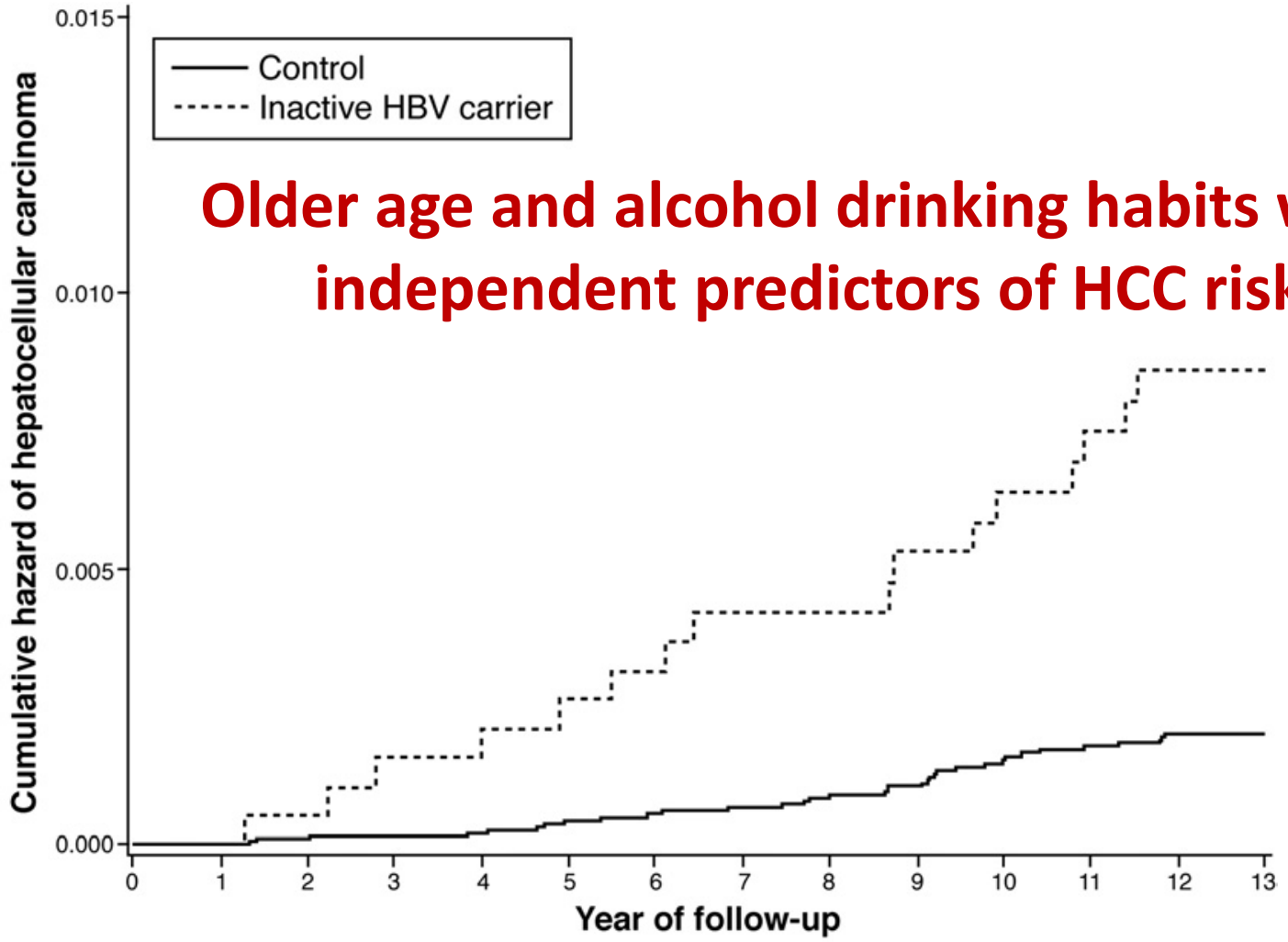
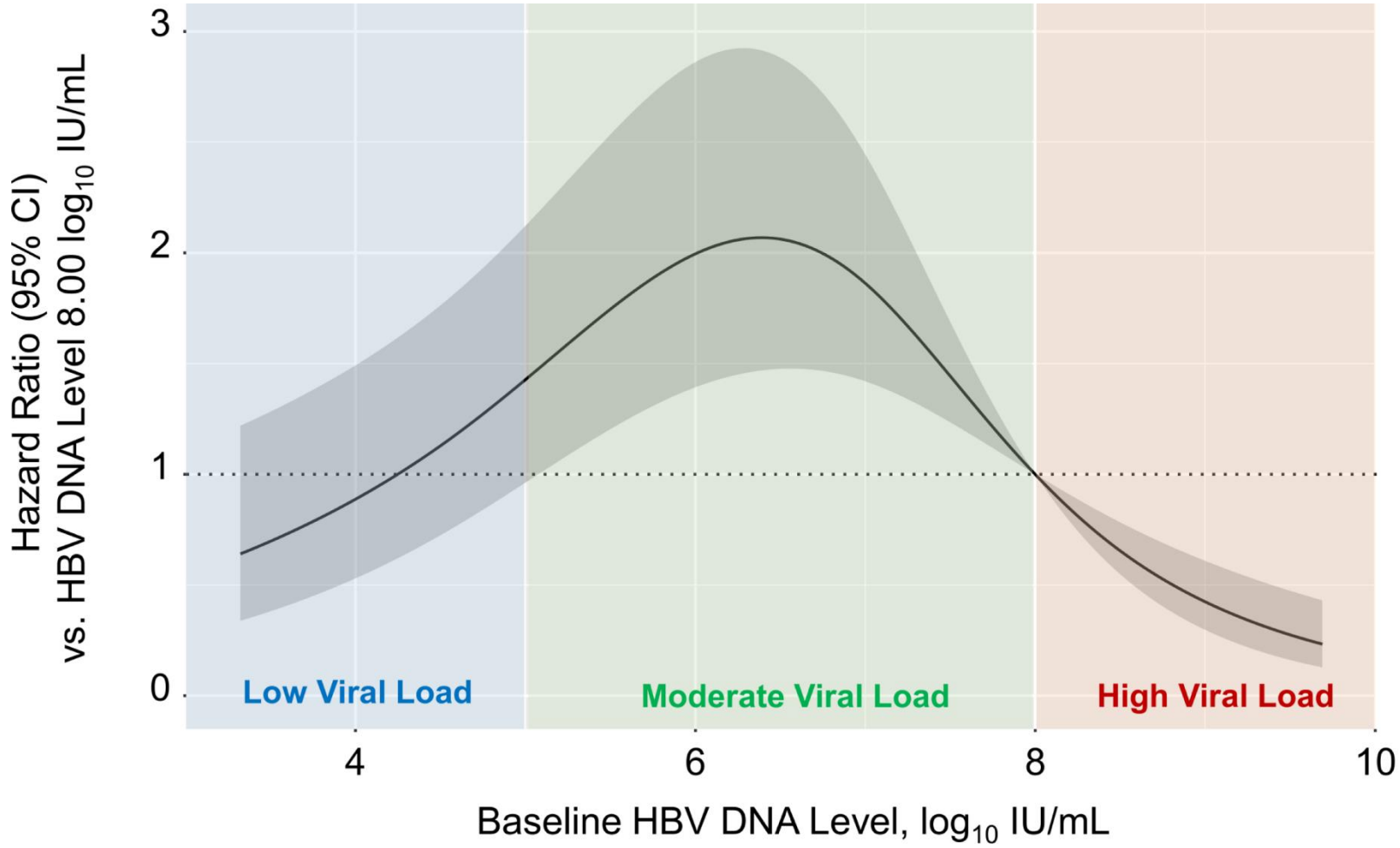


Older age and alcohol drinking habits were independent predictors of HCC risk

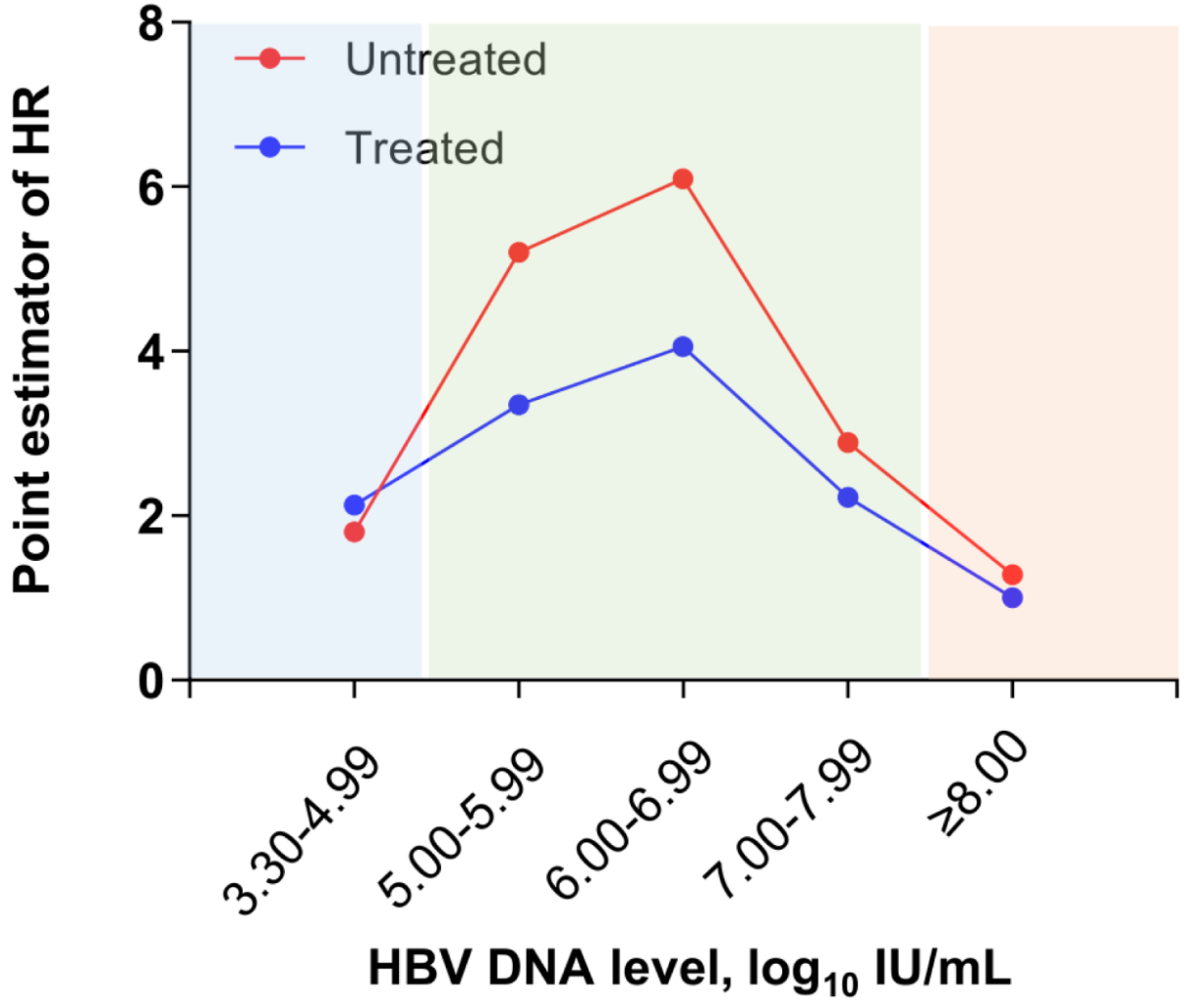
Chen J-D et al. GASTROENTEROLOGY 2010;138:1747–1754

Hazard ratios for the risk of HCC development under NA therapy depending on baseline HBV DNA levels



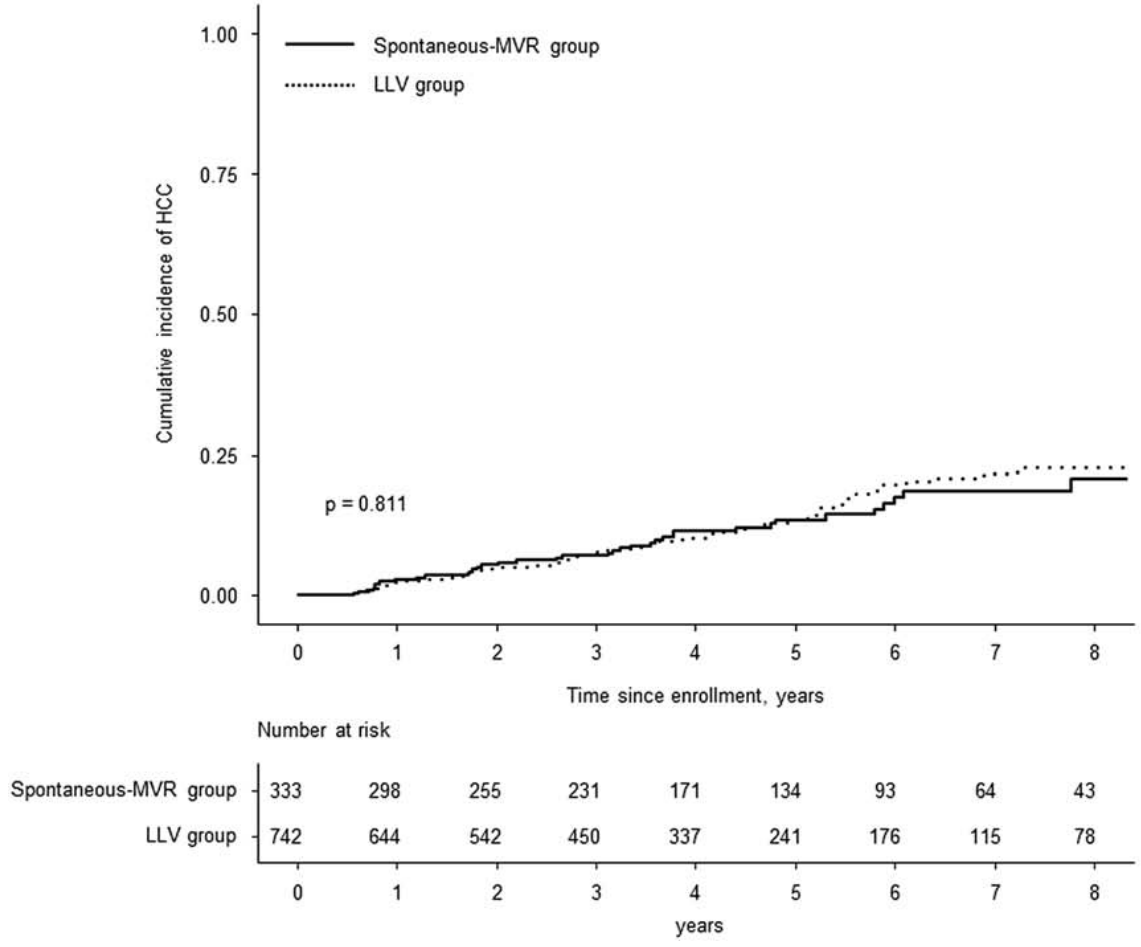
Choi W-M et al. Gut 2023; Oct 9:gutjnl-2023-330225

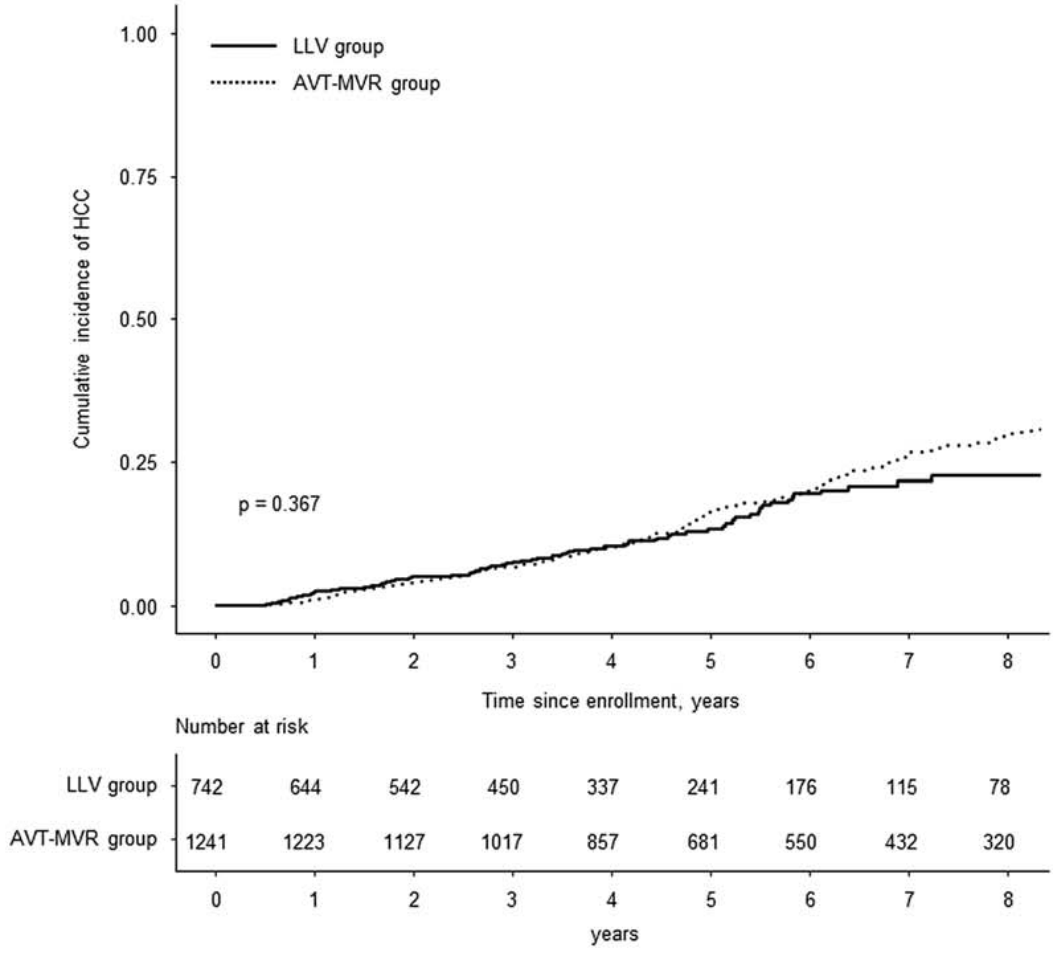
HCC Incidence in treated and untreated patients stratified according to baseline HBV-DNA



Choi W-M et al. Gut 2023; Oct 9:gutjnl-2023-330225

Cumulative incidence of HCC in compensated HBV cirrhosis
Low-level viremia versus undetectable HBV DNA
(spontaneously or treatment-induced)





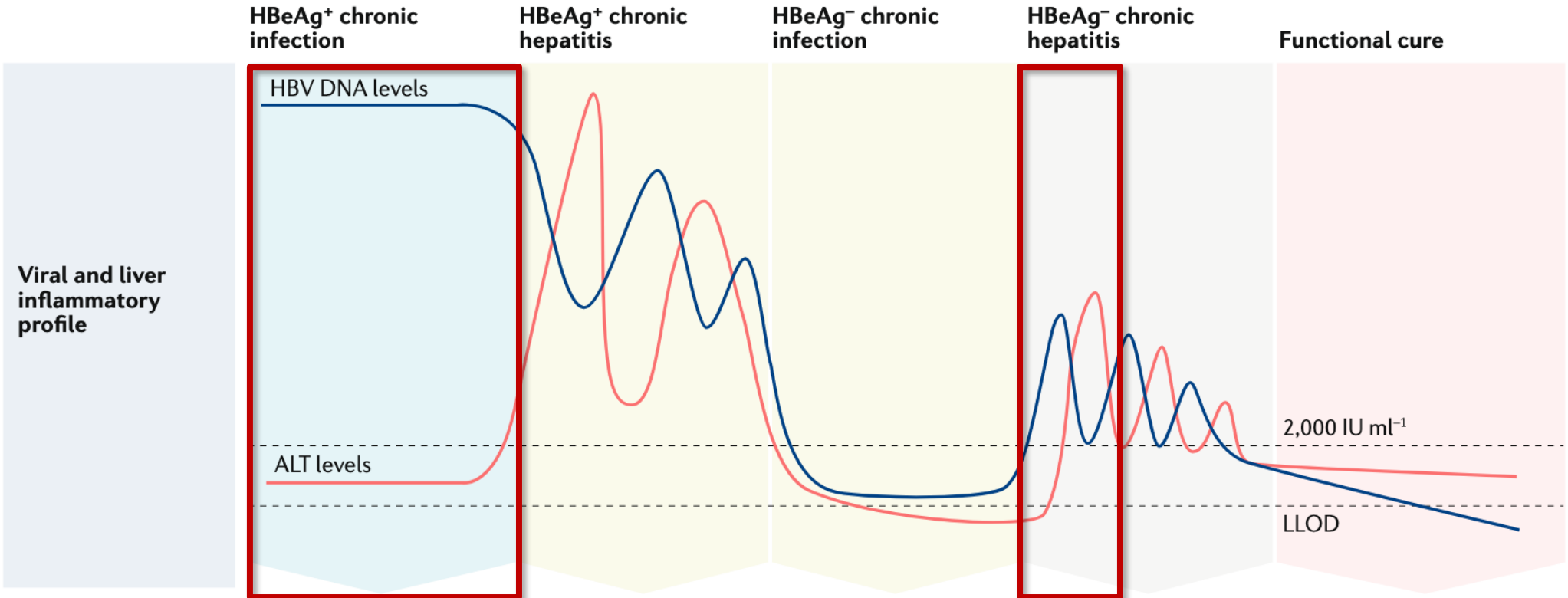
Huang DQ et al. Hepatology 2023; 77: 1746 | DOI: 10.1097/HEP.0000000000000037

Multivariable Cox-regression analyses to find the independent prognostic factors of HCC development in cirrhosis

	Univariable		Multivariable[a]	
Variables	***p***	***p***	**Adjusted HR**	**95% CI**
Male	< 0.001	< 0.001	1.85	1.43–2.38
Diabetes	0.002	0.005	1.42	1.11–1.81
Positive HBeAg	0.286	0.189	1.20	0.91–1.59
FIB-4 index	< 0.001	< 0.001	1.08	1.06–1.11
Albumin ≤ 3.5 g/dL	< 0.001	0.046	1.37	1.01–1.86
eGFR, mL/min/1.73 m^2	0.415	0.653	1.00	1.00–1.01
Patients groups	0.422	0.625		
LLV group	—	—	1	Reference
Spontaneous-MVR group	0.762	0.387	0.83	0.55–1.26
AVT-MVR group	0.332	0.975	1.00	0.75–1.32

Huang DQ et al. Hepatology 2023; 77: 1746 | DOI: 10.1097/HEP.0000000000000037

In order to prevent HCC development sufficiently – start early in the phases of HBV infection when viremia is still high



	HBeAg+ chronic infection	HBeAg+ chronic hepatitis	HBeAg− chronic infection	HBeAg− chronic hepatitis	Functional cure
Serum HBsAg	+++++	++++	+	++	–
cccDNA	+++++	+++++	++	+++	+
Fibrosis	Minimal fibrosis	Variable degree of fibrosis (progressing)	Variable degree of fibrosis (progressing)	Moderate to severe fibrosis (resolving)	Variable fibrosis (sequelae of previous phases)
Liver inflammatory infiltrate	Absent	High	Absent/moderate	Moderate	Absent

Figure: *Nat Rev Drug Discov*. 2019 Nov;18(11):827-844

Treating patients with low-level viremia does not affect clinical endpoints

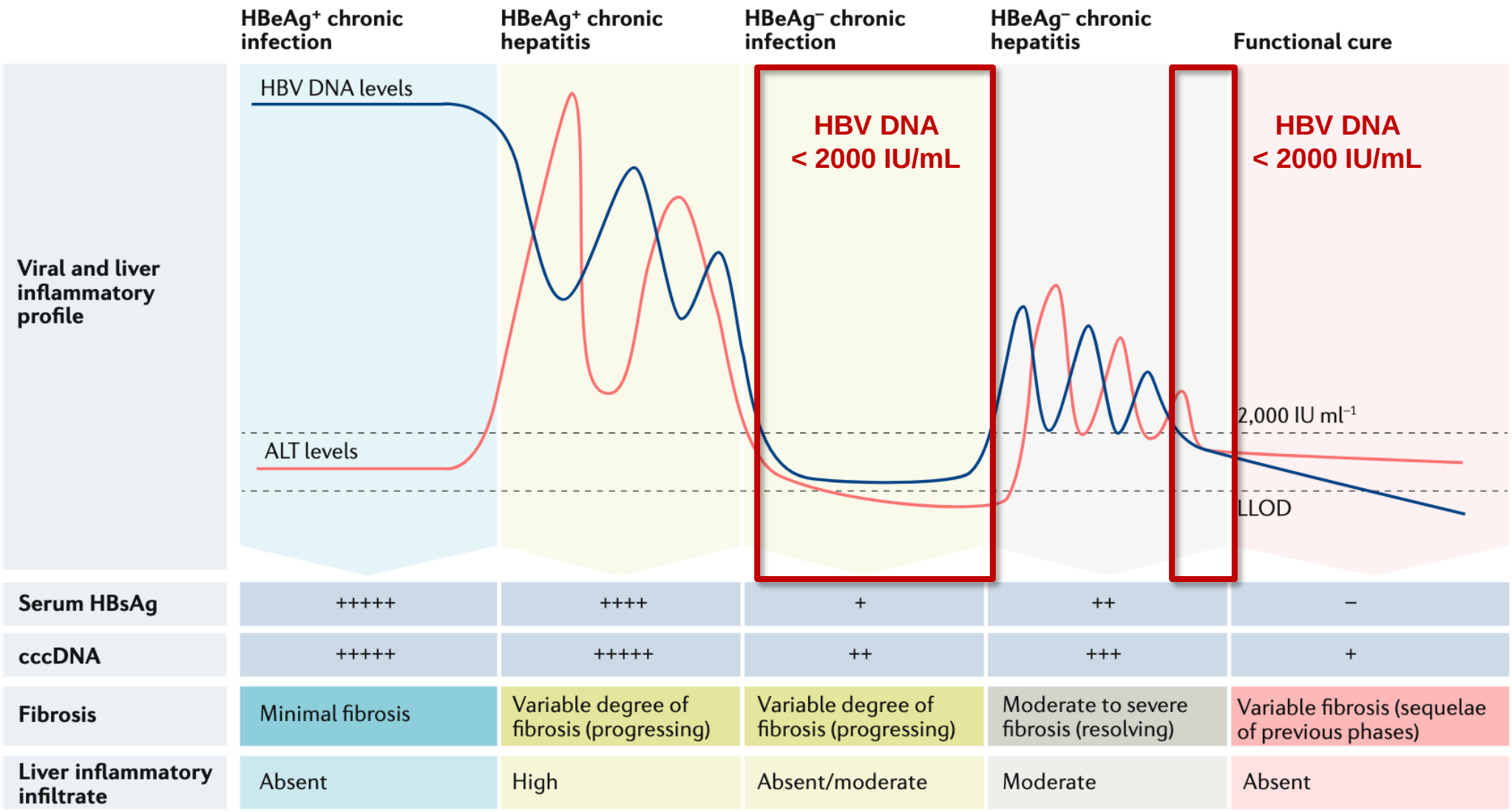
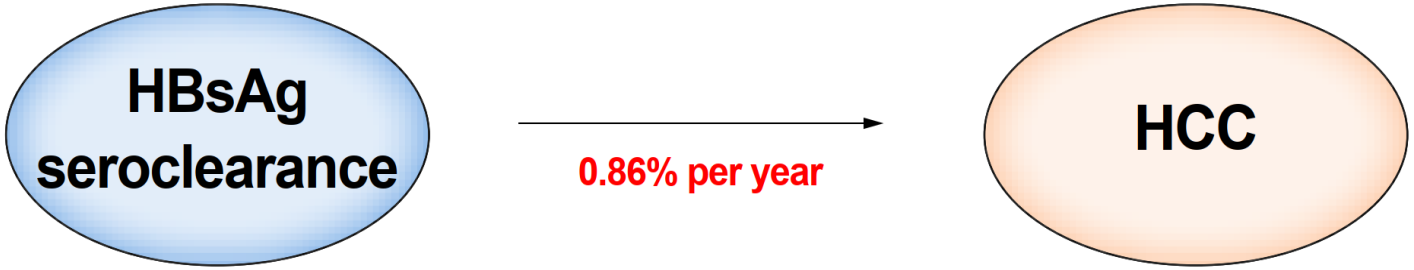
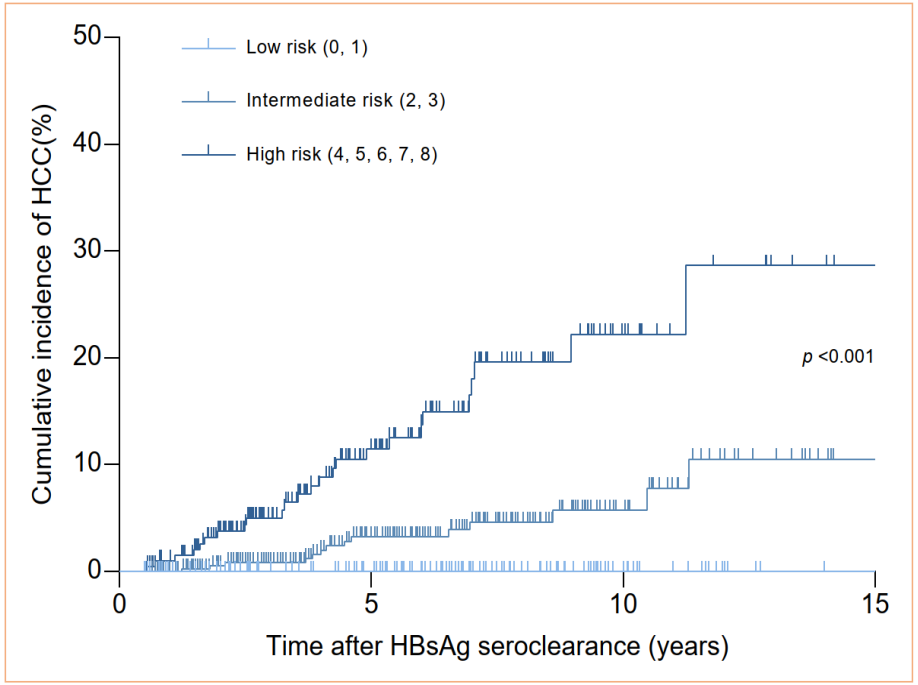


Figure: *Nat Rev Drug Discov*. 2019 Nov;18(11):827-844

A risk prediction model for HCC development after HBsAg seroclearance



	Risk score
Age (10-year increment)	
<40	0
≥40, <50	1
≥50, <60	2
≥60	3
Cirrhosis	
No	0
Yes	2
Family history of HCC	
No	0
Yes	1
More than moderate drinking	
No	0
Yes	2



N=831 patients with HBsAg loss could be followed and included in the analysis

Yang H et al. J Hepatol 2022;77(3):632-641

Do not treat everyone with detectable HBV DNA
Summary and Conclusion

- A bona fide ”inactive carrier" state exists in chronic HBV infection, with HBV DNA levels below 2,000 IU/mL deemed insufficient to warrant therapeutic intervention

- Upon validation through subsequent evaluations, the risk of fibrotic disease progression is negligible, while the probability of HBsAg seroclearance over the long-term is considerable

Do not treat everyone with detectable HBV DNA
Summary and Conclusion

- New HBV biomarkers reflecting cccDNA transcriptional activity might be helpful to better define HBeAg-negative HBV infection (“inactive carrriers”) not at need for therapy

- The oncogenic potential during this low-replicative phase is depends upon the individual's preceding infection history and remains unaltered by treating low-level viremia (even in cirrhosis…?)

Long-term NA treatment is not without any risk…

Setting & Patients

Electronic healthcare database in Hong Kong managed by the Hospital Authority

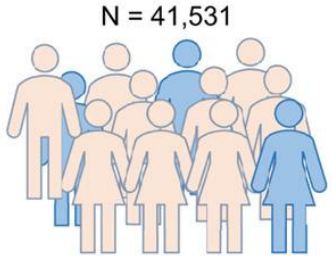
Coverage of ≈80 % of population

Electronic healthcare database

Systematic data retrieval

Study population and primary endpoint

N = 41,531

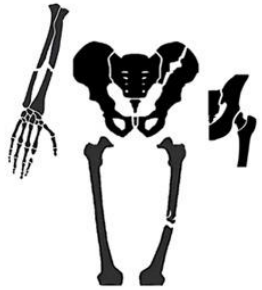


ETV

TDF

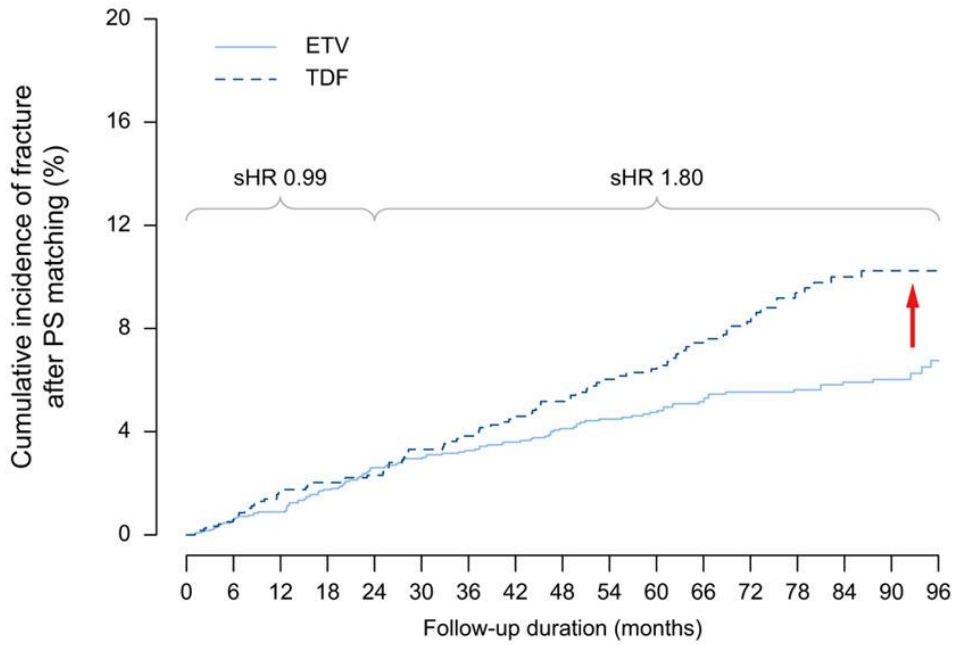
Patients with chronic hepatitis B (CHB) aged ≥60 years between January 2005 and December 2022 receiving ETV or TDF

Propensity score matching



Incident bone fracture

Results



Conclusion:
Fracture risk increased after TDF treatment for ≥24 months in elderly patients with CHB.

Selection of nucleos(t)ide analogues should be individualised based on age and comorbidities.

Yip T C-F et al. J Hepatol 2024; 80: 553