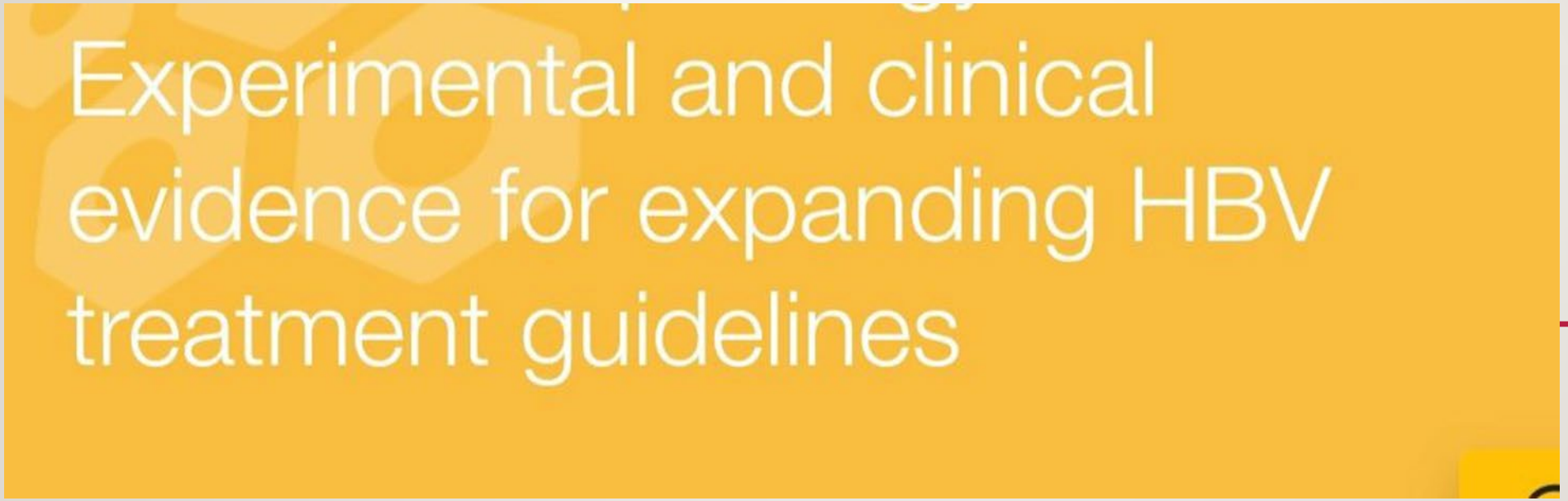


DR.EBTISAM BOUSHI

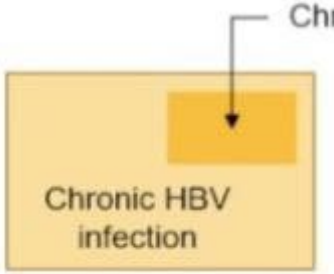
THE GENERAL ASSEMBLY OF DAMASCUS HOSPITAL

Current Guidelines

Current Hepatitis B Guidelines

EASL	EASL HBV guidelines: 2017, update in process, Delphi process finalized June 4th
AASLD	AASLD HBV guidelines: 2018, update announced
APASL	APASL HBV guidelines: 2016, update specific sections
China	Chinese HBV guidelines: 2022
World Health Organization	WHO HBV guidelines: update launched 30 March 2024

Chronic HBV infection: Who should be treated?



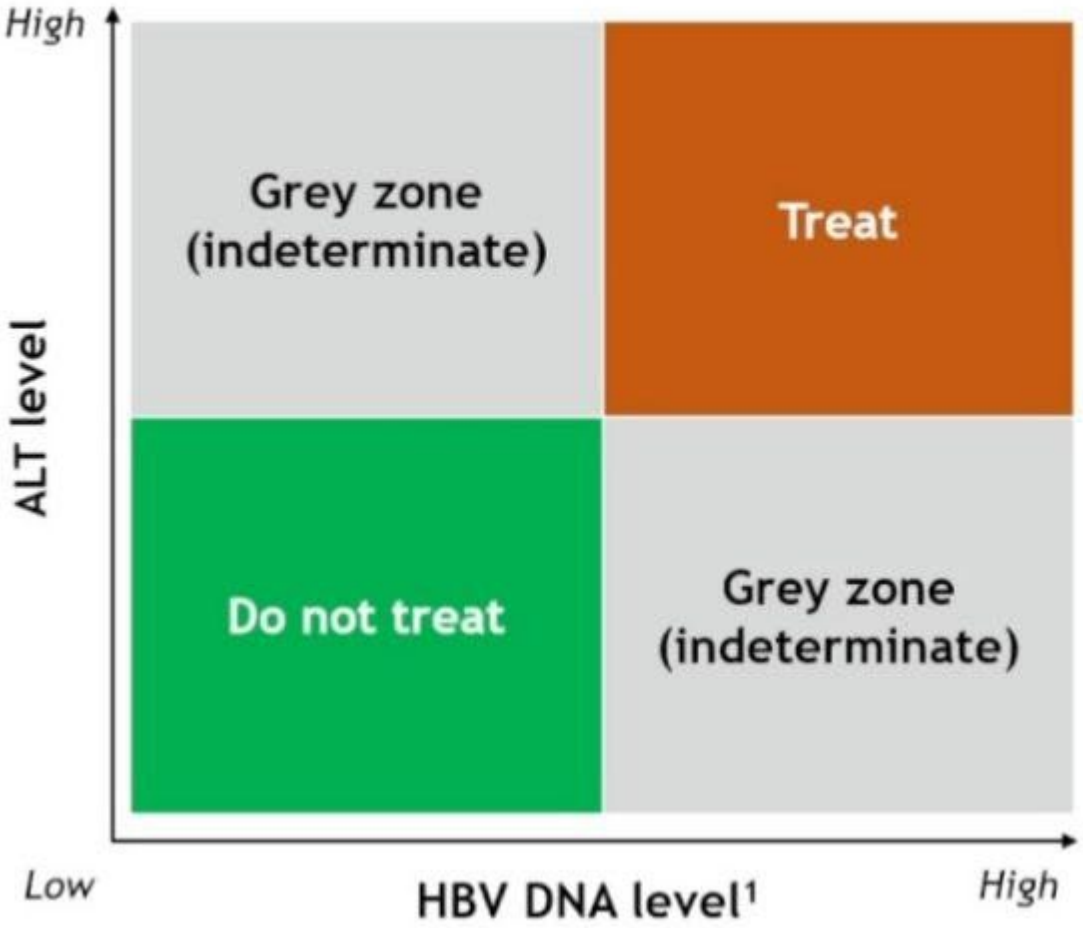
Strong consensus among guidelines

	HBeAg positive		HBeAg negative	
	Chronic HBV infection	**Chronic hepatitis B**	**Chronic HBV infection**	**Chronic hepatitis B**
HBsAg	High	High/ intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	$>10^7$ IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL
ALT	Normal	Elevated	Normal	Elevated†
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg-negative chronic hepatitis

When to initiate CHB treatments in non-cirrhotic patients?

	AASLD 2018[1]	EASL 2017[2]	APASL 2016[3]
HBV DNA (IU/ml)	>20,000 (HBeAg+) >2000 (HBeAg-)	>2000	>20,000 (HBeAg+) >2000 (HBeAg-)
ALT (ULN)	≥2 × ULN • M: 35 U/l • F: 25 U/l	>1 × ULN • ~40 U/l	>2 × ULN • 40 U/l
	<2 × ULN • Age >40 years • Family history of HCC or cirrhosis • ≥F2 (fibrosis) or ≥A3 (inflammation)	≤1 × ULN • Age >30 years • Family history of HCC or cirrhosis • ≥F2 or ≥A2	1–2 × ULN • Age >35 years • Family history of HCC or cirrhosis • ≥F2 (fibrosis) or ≥A2 (inflammation)

The „grey zone“



30–50%
of patients may fall into a
grey zone (indeterminate phase)[1]

- Specific eligibility criteria vary between guidelines[2–6]
- Viraemic patients are not always eligible for therapy[2,4,6]

The concept of antiviral therapy

Most of the current literature focuses on the immune active phases of chronic HBV infection; decision-making in other commonly encountered and challenging clinical settings depends on indirect evidence.

Lok et al. ***Hepatology.*** 2016 Jan;63(1):284-306.

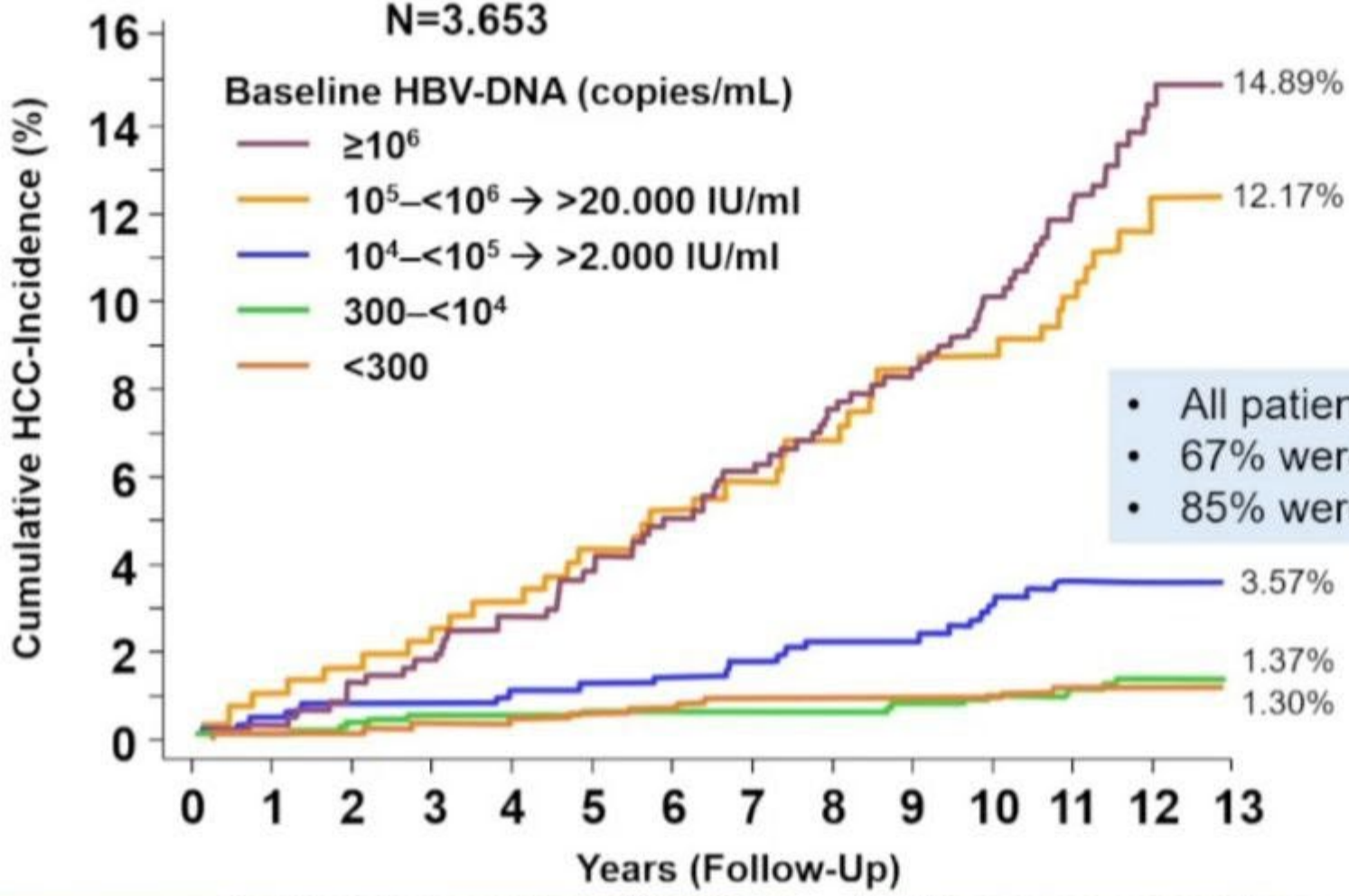
Viral suppression

Improved survival

Fibrosis regression / cirrhosis prevention

HCC risk reduction

Why so complicated: HBV DNA is an important marker for disease progression?!

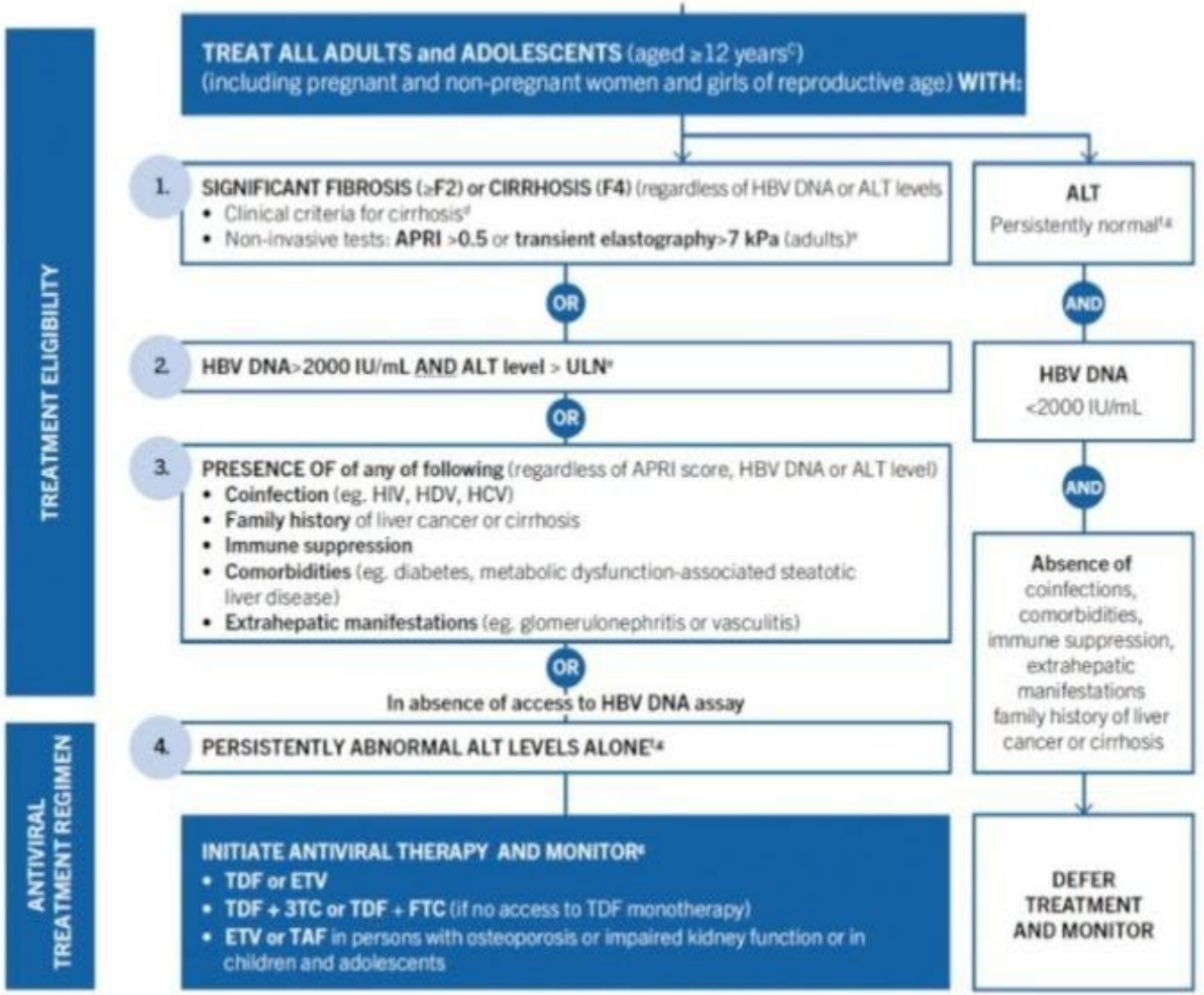


HBeAg+ infection?

- All patients were older than 30 years
- 67% were even older than 40 years
- 85% were HBeAg negative

Chen et al. ***JAMA***. 2006 Jan 4;295(1):65-73.

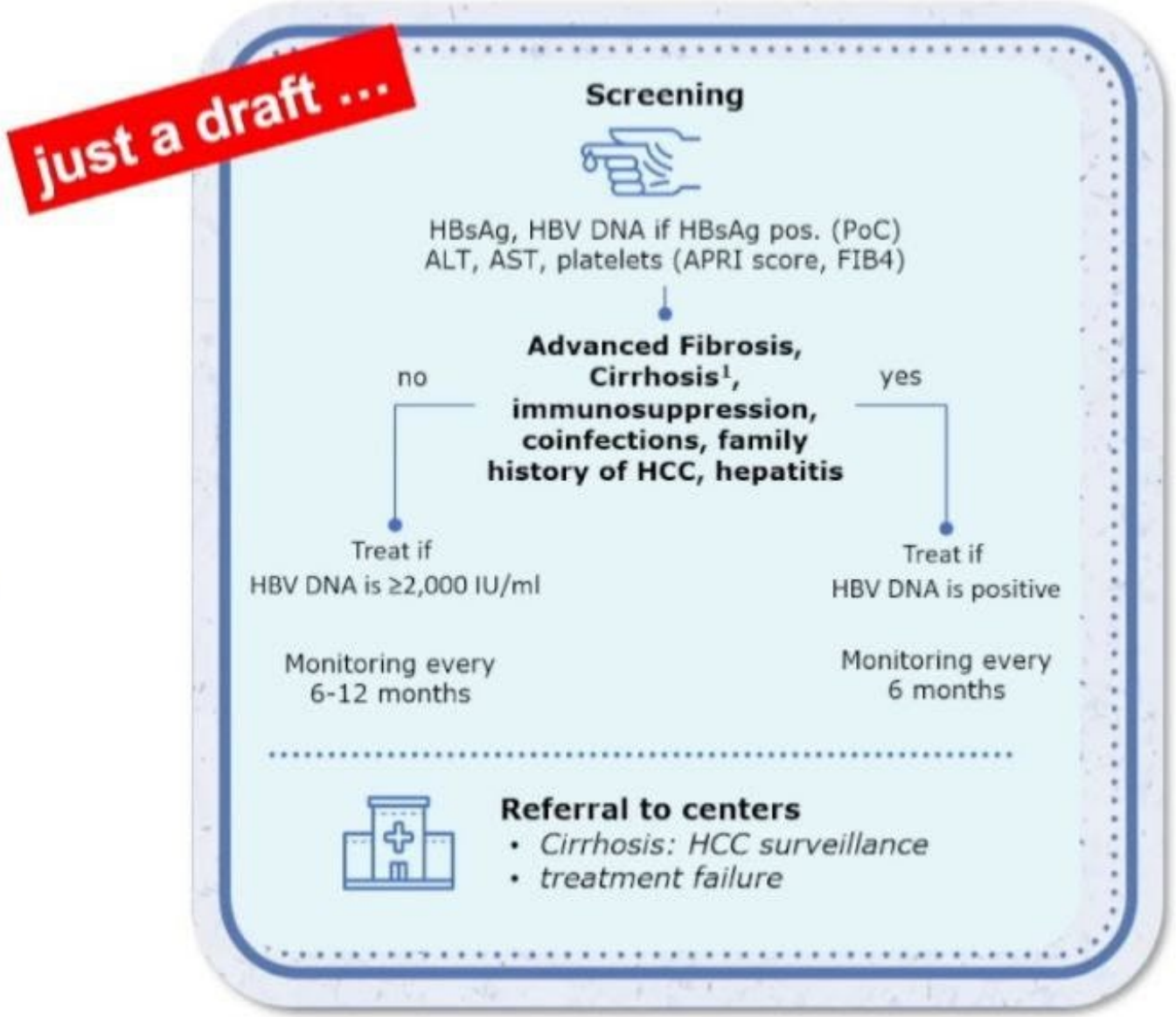
Treatment extension and simplification: WHO guidelines



World Health Organization

Guideline on a beer mat for HBV –

Are we really ready yet?



Should we treat all individuals (without cirrhosis) whose HBV DNA is ≥ 2,000 IU/mL or even positive)?

GHS 2023, Paris

PRO

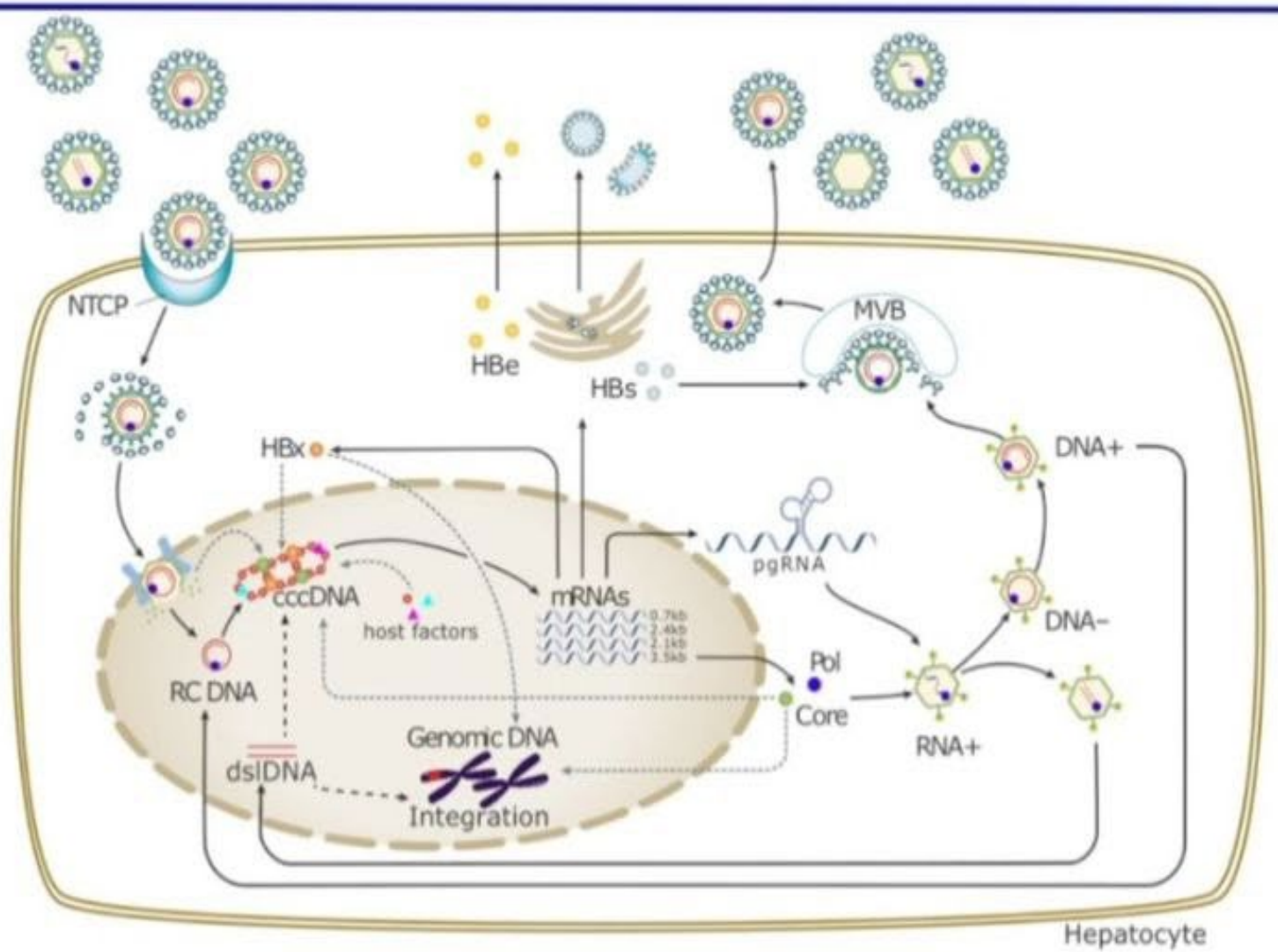
- NUCs prevent cirrhosis and HCC
- NUCs are safe
- NUCs are generic
- **That makes it simple**

CONTRA

- Not cost effective for all patient cohorts?
- Adherence to treatment may be a challenge?

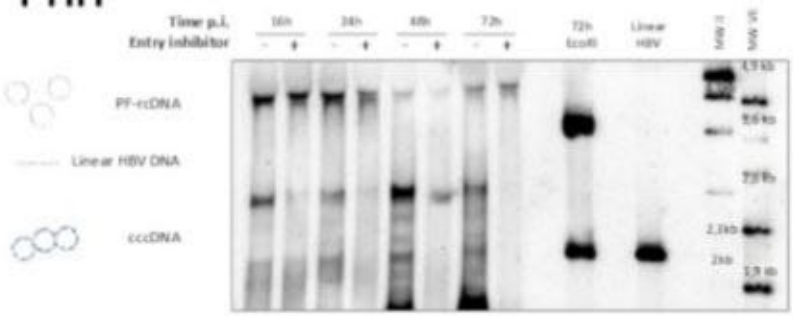
Virological science evidence regarding expanding the treatment guidelines

Persistent forms of HBV genome in hepatocytes

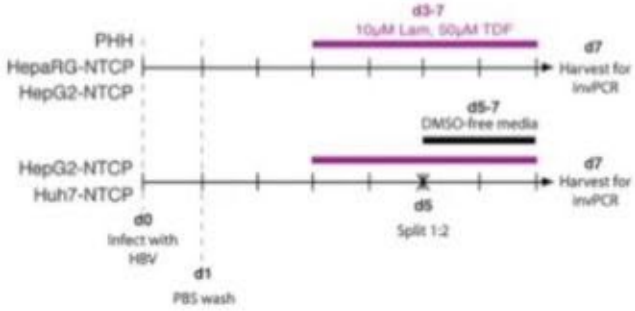


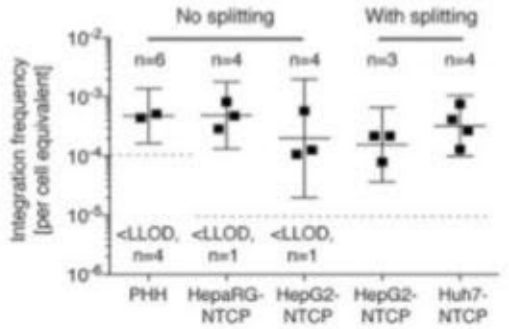
cccDNA formation and HBV integration occur early after hepatocyte infection

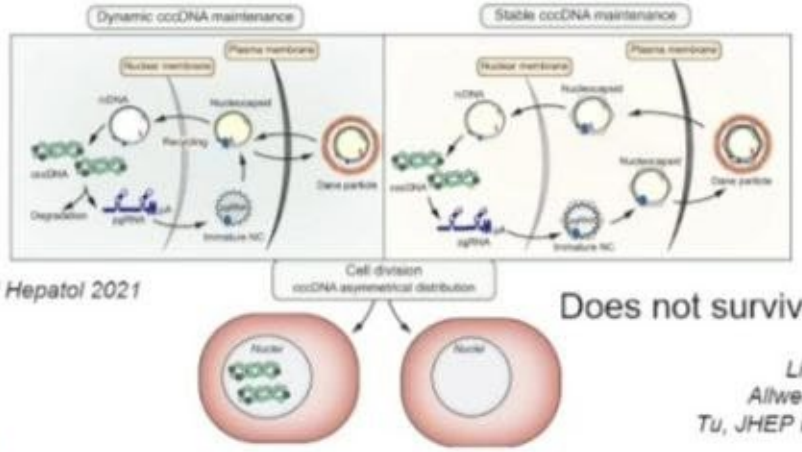
PHH



Locatelli, CMGH 2022
Ko, J Hepatol 2018
Luo, J Virol 2017



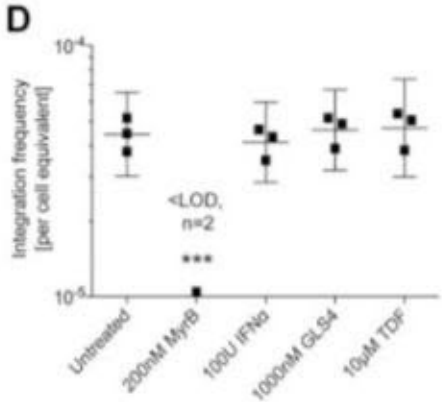




Martinez, J Hepatol 2021

Does not survive mitosis

Li, J Virol 2017
Allweiss, Gut 2018
Tu, JHEP Reports 2022



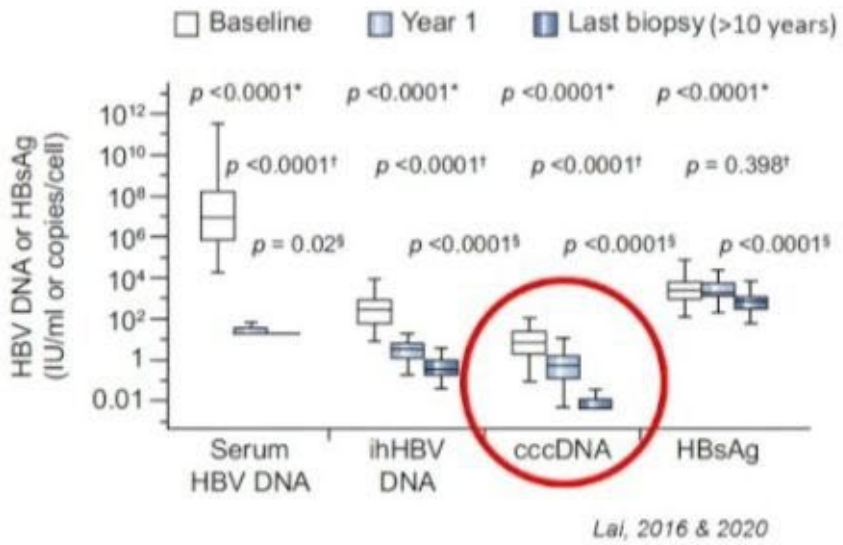
HBV DNA integrations occur <72h post-infection

stable through cell mitosis

Integration can be prevented by inhibiting HBV entry

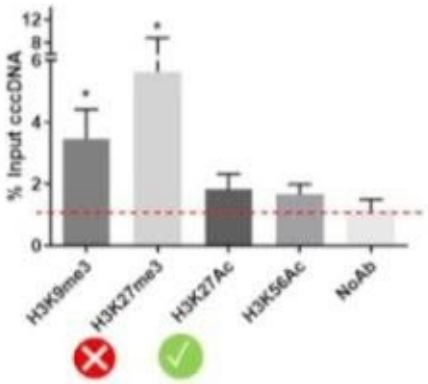
Tu et al J Virol 2018

NUCs effect on cccDNA…



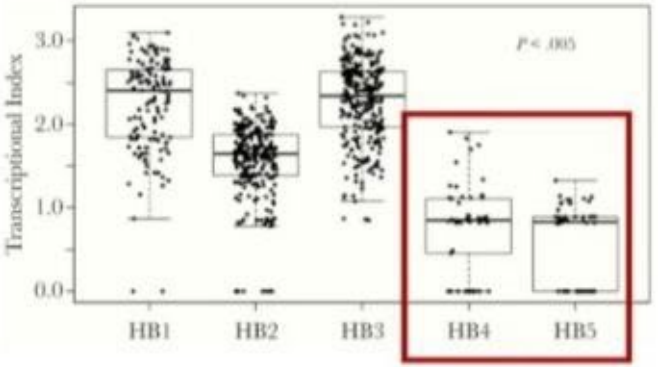
Lai, 2016 & 2020

cccDNA ChIP qPCR



Lebossé, Sci Rep 2020

cccDNA transcriptional index



Balagopal, J Infect Dis 2020
Balagopal, JCI Insight 2020

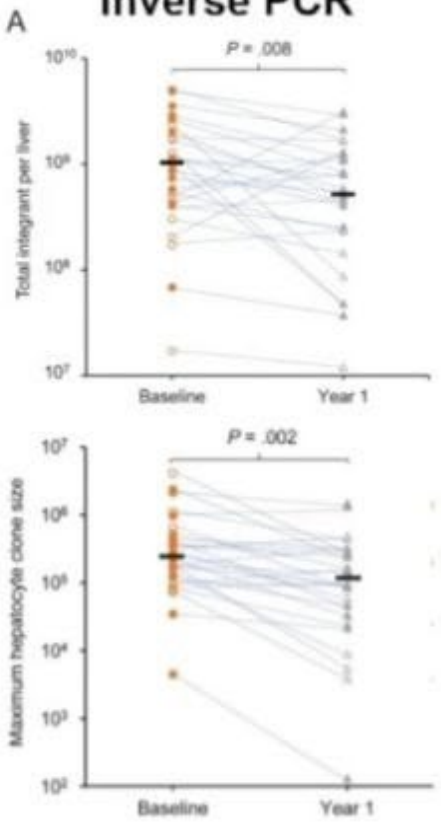
Decrease in cccDNA pool, but no complete clearance
(incomplete blockade of intrahepatic HBV replication?)

Werle-Lapostolle, Gastroenterology 2004
Boyd, 2016
Lai 2016 & 2020
Lebossé, Sci Rep 2020

Decrease in cccDNA transcriptional activity?
(unknown mechanism so far)

…NUCs effect on HBV integration

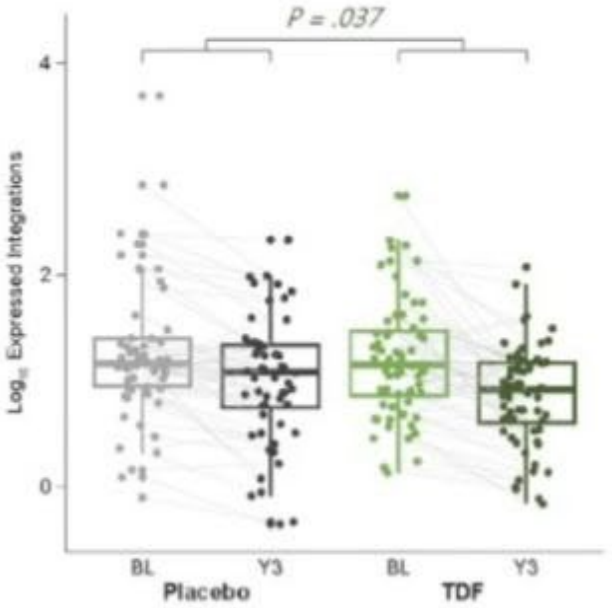
Inverse PCR



Longitudinal biopsies from 28 pts before/after 1 year NUCs

Chow, CID 2022

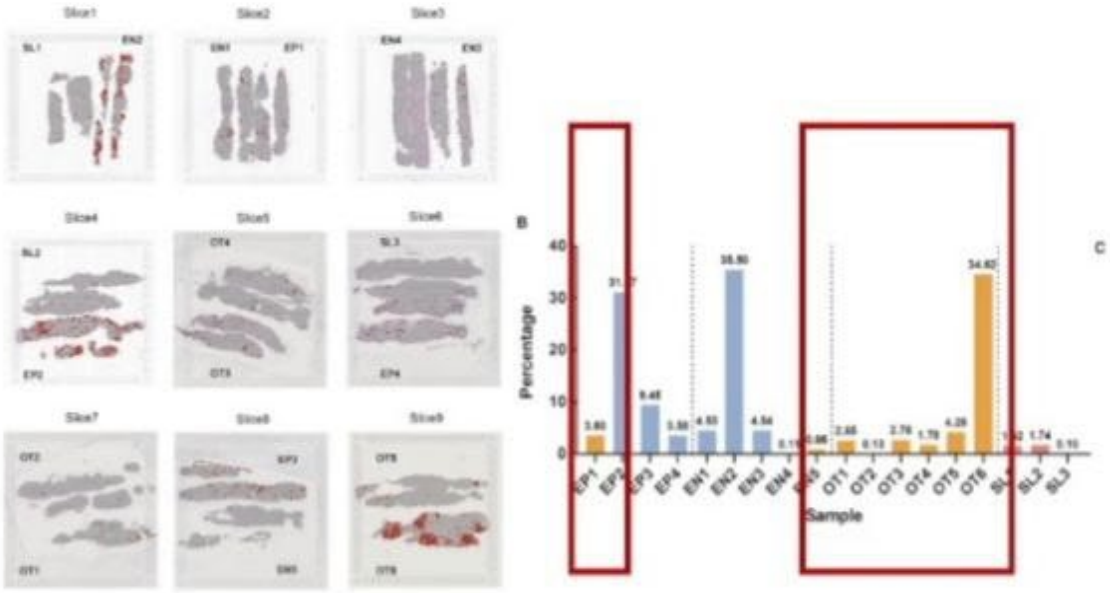
RNA- Sequencing



Longitudinal placebo controlled study on 119 CHB patients before/after 3 years NUCs (TORCH-B)

Hsu, Gastroenterology 2022

Spatial transcriptomics



Cross-sectional study on 18 CHB patients (untreated, NUC-treated, HBsAg loss)

Yu, Gut 2024

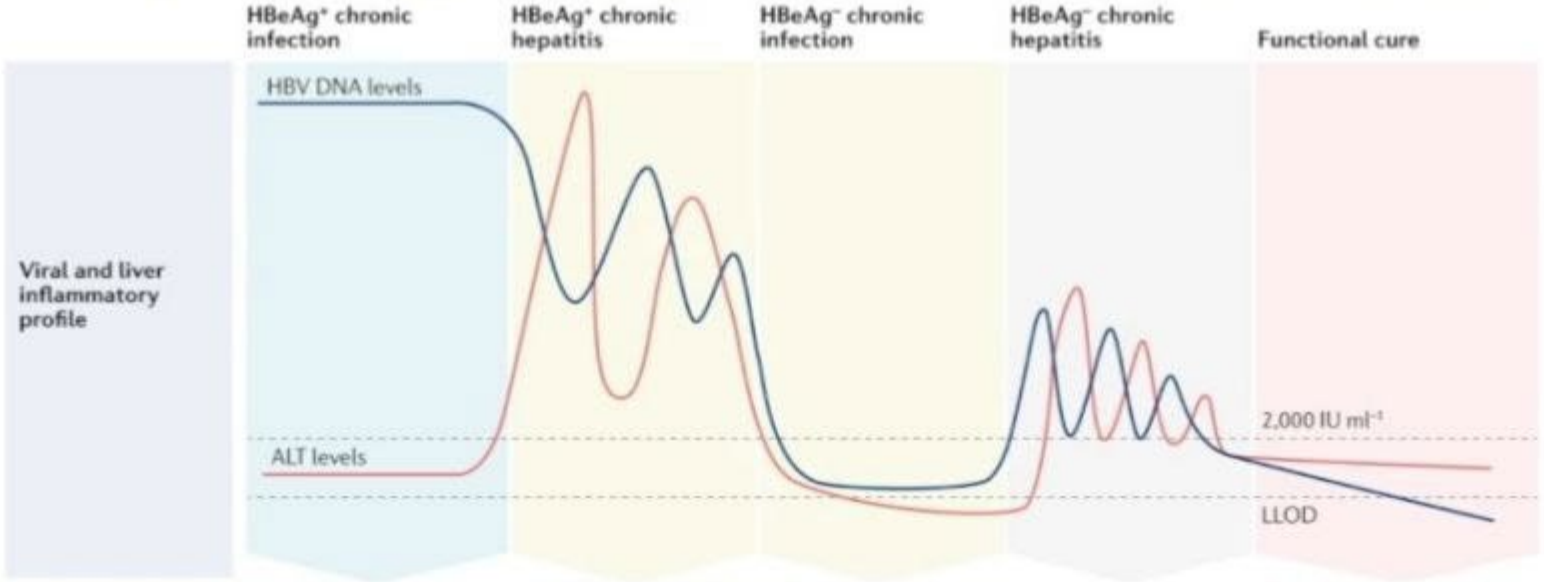
Decrease in integration burden and hepatocytes clonal expansion

INTEGRATION IS FOUND ACROSS ALL CHB PHASES (AND IN ACUTE INFECTIONS)

- New therapeutic (curative!) strategies are needed
- CAMs with "'secondary" mechanisms of action
- Genome and epigenome editing
- How to predict the evolution of HBV integration?
- How to timely monitor the effect of new therapeutic strategies on HBV reservoir (cccDNA &

Immunological evidence for expanding the treatment guidelines

We are currently treating HBV patients with chronic active hepatitis

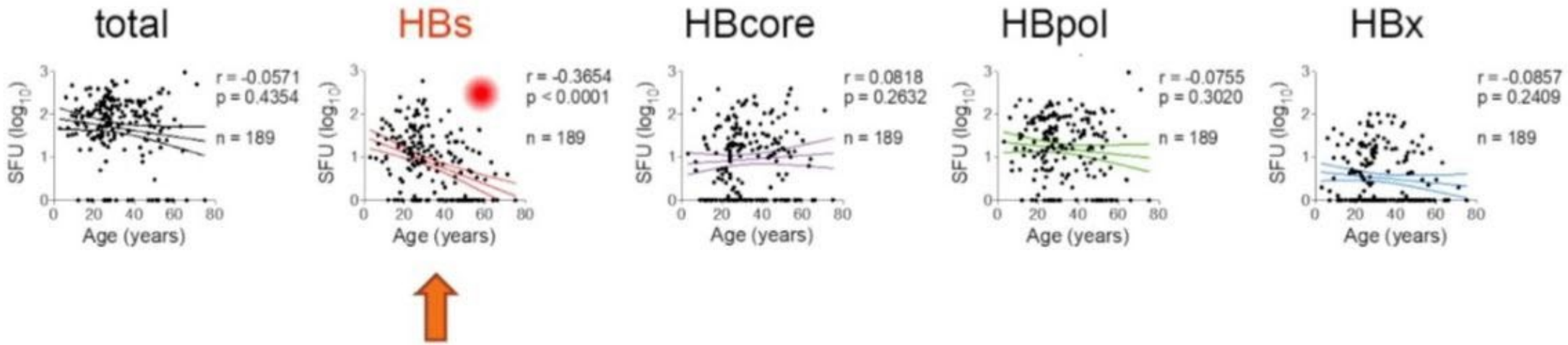


	HBeAg⁺ chronic infection	HBeAg⁺ chronic hepatitis	HBeAg⁻ chronic infection	HBeAg⁻ chronic hepatitis	Functional cure
Serum HBsAg	+++++	++++	+	++	–
cccDNA	+++++	+++++	++	+++	+
Fibrosis	Minimal fibrosis	Variable degree of fibrosis (progressing)	Variable degree of fibrosis (progressing)	Moderate to severe fibrosis (resolving)	Variable fibrosis (sequelae of previous phases)
Liver inflammatory infiltrate	Absent	High	Absent/moderate	Moderate	Absent
Profile of adaptive immunity	T cells • HBs –/+ • HBc –/+ • HBp –/+	T cells • HBs –/– • HBc –/+ • HBp –/+	T cells • HBs –/– • HBc –/+ • HBp –/+	T cells • HBs –/– • HBc –/+ • HBp –/+	T cells • HBs –/– • HBc –/+ • HBp –/+
	B cells • HBs –/– • HBc +	B cells • HBs –/– • HBc + +	B cells • HBs –/– • HBc + +	B cells • HBs –/– • HBc +	B cells • HBs + • HBc +

Fanning GC. et al, Nat Rev Drug Discov, 2019

Does it make immunologically sense to exclude young patients with HBeAg-positive infection (immune-tolerant) from treatment?

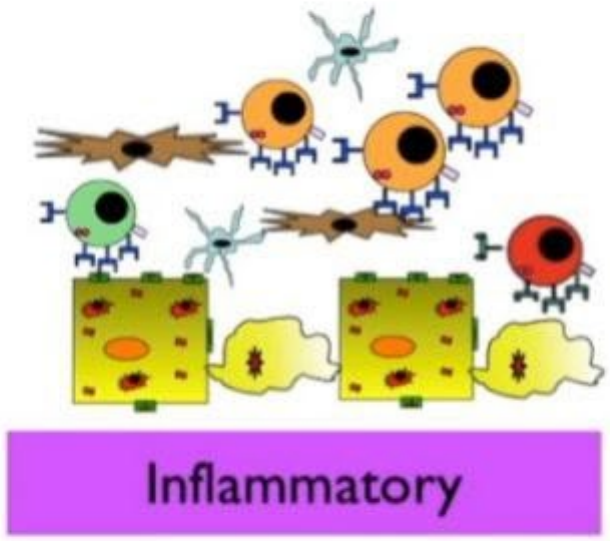
Reduction of HBsAg-specific T cells with age



HBs-specific T cells are reduced with age/ duration of HBsAg exposure

Le Bert N. et al, Gastroenterology, 2020

Intrahepatic inflammation can reduce T cell function



Increased levels of arginase

Increased frequency of Tregs

- Reduced T cells function

DOES IT MAKE SENSE TO EXCLUDE YOUNG PATIENTS WITH HBEAG-POSITIVE INFECTION FROM TREATMENT?

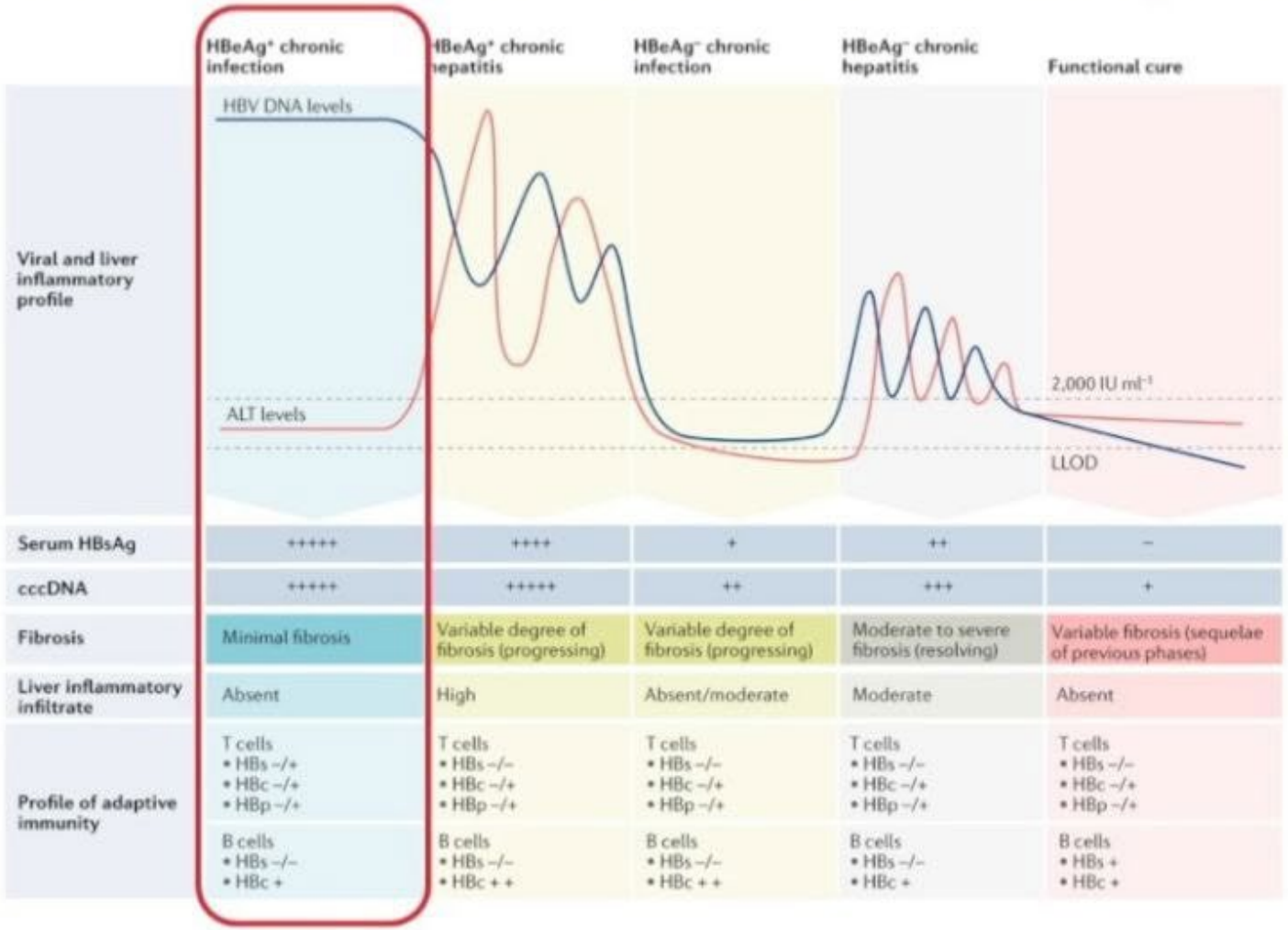
From an immunological point of view, there is no evidence to exclude them:

- Similar HBV-specific B cell response
- Similar, or even better HBV-specific T cell response
- Fibrosis impairs antigen recognition by intravascular CD8 T cells
- Inflammation reduces the functionality of T cells

Who could benefit most from immune-boosting strategies?

Younger patients

In the absence of inflammation



	HBeAg⁺ chronic infection	HBeAg⁺ chronic hepatitis	HBeAg⁻ chronic infection	HBeAg⁻ chronic hepatitis	Functional cure
Viral and liver inflammatory profile					
Serum HBsAg	+++++	++++	+	++	–
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Fibrosis	Minimal fibrosis	Variable degree of fibrosis (progressing)	Variable degree of fibrosis (progressing)	Moderate to severe fibrosis (resolving)	Variable fibrosis (sequelae of previous phases)
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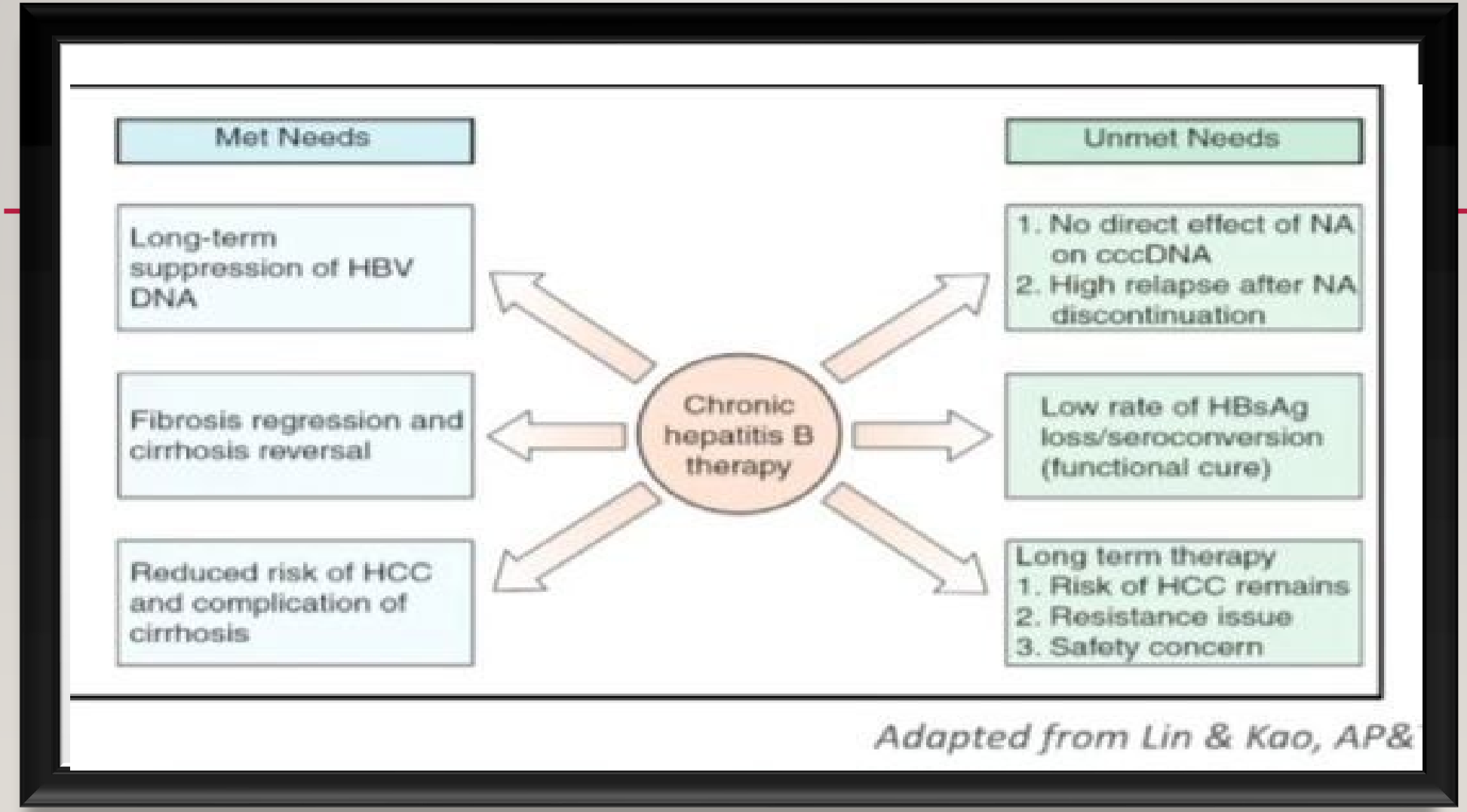
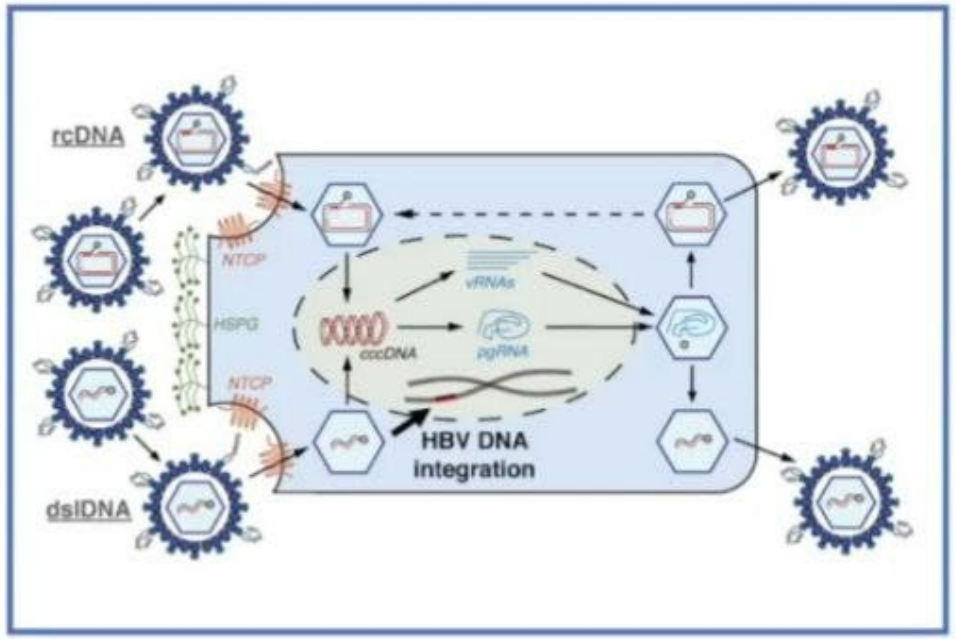
Profile of adaptive immunity	T cells • HBs –/+ • HBc –/+ • HBp –/+	T cells • HBs –/– • HBc –/+ • HBp –/+	T cells • HBs –/– • HBc –/+ • HBp –/+	T cells • HBs –/– • HBc –/+ • HBp –/+	T cells • HBs –/– • HBc –/+ • HBp –/+
	B cells • HBs –/– • HBc +	B cells • HBs –/– • HBc + +	B cells • HBs –/– • HBc + +	B cells • HBs –/– • HBc +	B cells • HBs + • HBc +

CLINICAL EVIDENCE FOR EXPANDING THE TREATMENT GUIDELINES


Met Needs
Long-term suppression of HBV DNA
Fibrosis regression and cirrhosis reversal
Reduced risk of HCC and complication of cirrhosis
Chronic hepatitis B therapy
Unmet Needs
1. No direct effect of NA on cccDNA
2. High relapse after NA discontinuation
Low rate of HBsAg loss/seroconversion (functional cure)
Long term therapy
1. Risk of HCC remains
2. Resistance issue
3. Safety concern
Adapted from Lin & Kao, AP&

There is accumulating evidence that HBV integration plays a role in HBV-related hepatocarcinogenesis



cccDNA[2–3]
pgRNA[4]

Inflammation

Cirrhosis

HBV DNA integration[5–6]

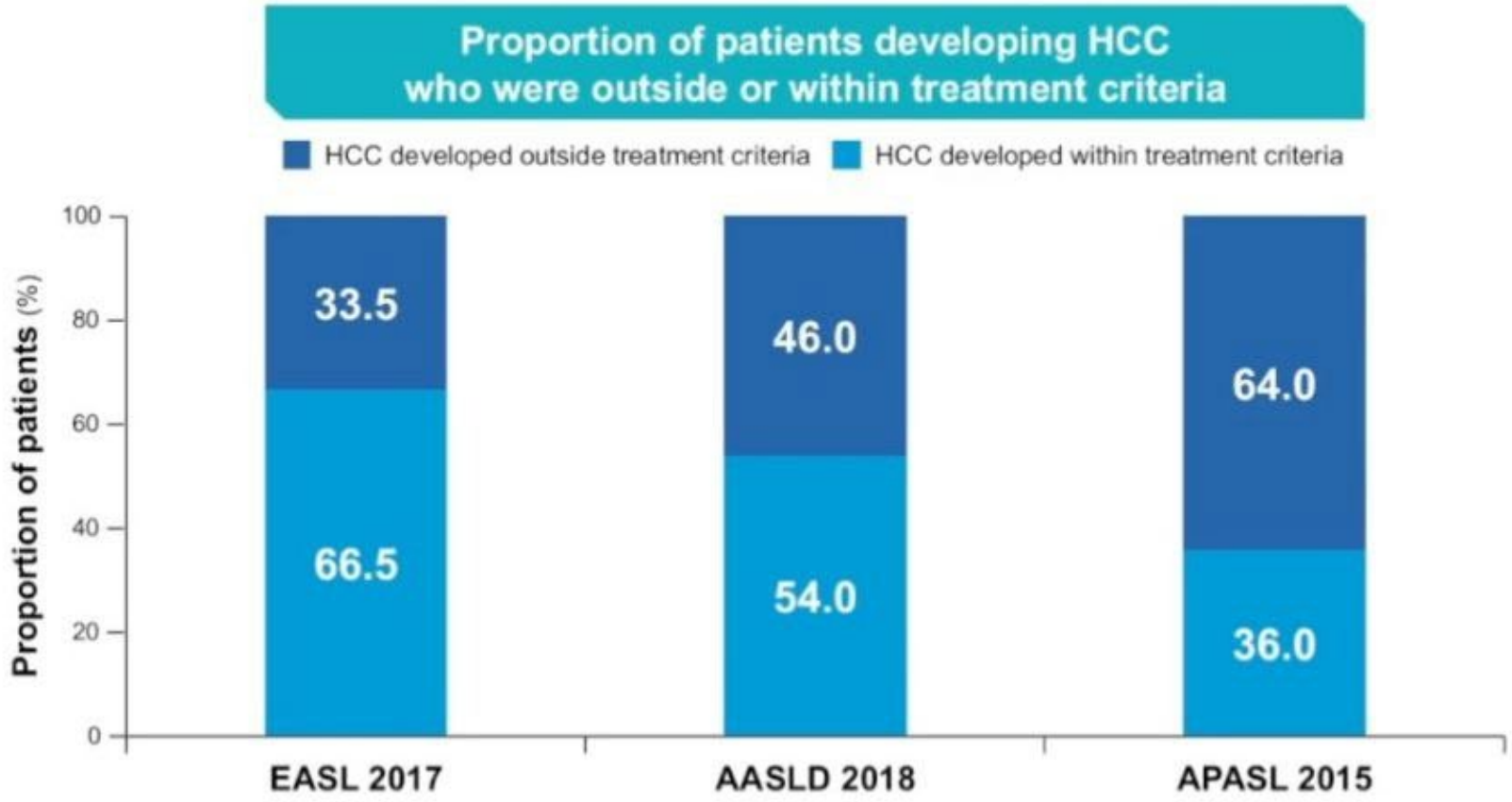
HCC

Intrahepatic HBV transcriptional activity is associated with liver inflammation and disease progression and HBV DNA integration further contributes to hepatocarcinogenesis[2–6]

1. Budzinska MA, et al. Genes (Basel) 2018;9:365; 2. Liang L-B, et al. Int J Infect Dis 2016;52:77–82; 3. Larsson SB, et al. Liver Int 2014;34:e238–45; 4. Ding W-B, et al. Hepatology 2021;74:1480–95; 5. Tu T, et al. J Viral Hepat 2015;22:737–53; 6. Zhao LH, et al. Nat Commun 2016;7:12992.

- dslDNA: double-stranded linear DNA;
- rcDNA: relaxed circular DNA.

CHB patients develop HCC outside current international treatment criteria



P-value not reported.

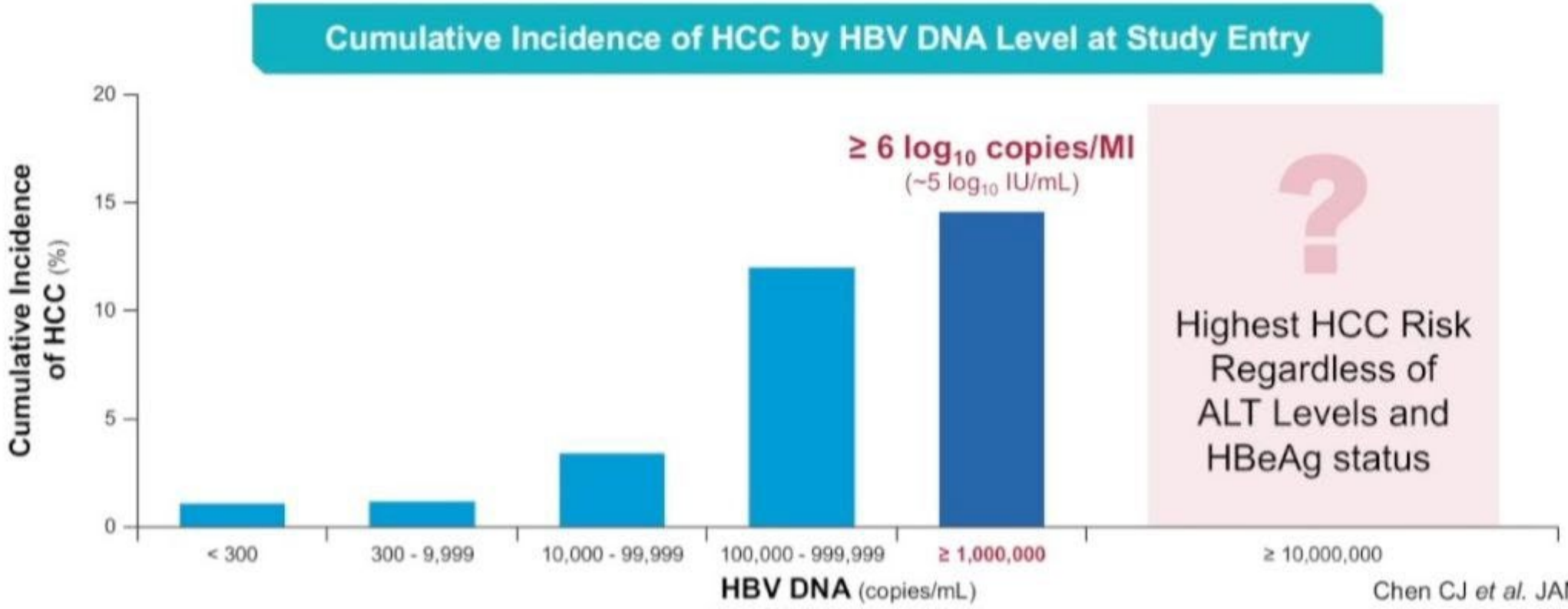
EASL, European Association for the Study of the Liver; **APASL,** Asian Pacific Association for the Study of the Liver.

Adapted from Sinn *et al.* J Viral Hepat 2019;26:1465–1472

Association between Viral Load and HCC Risk in CHB

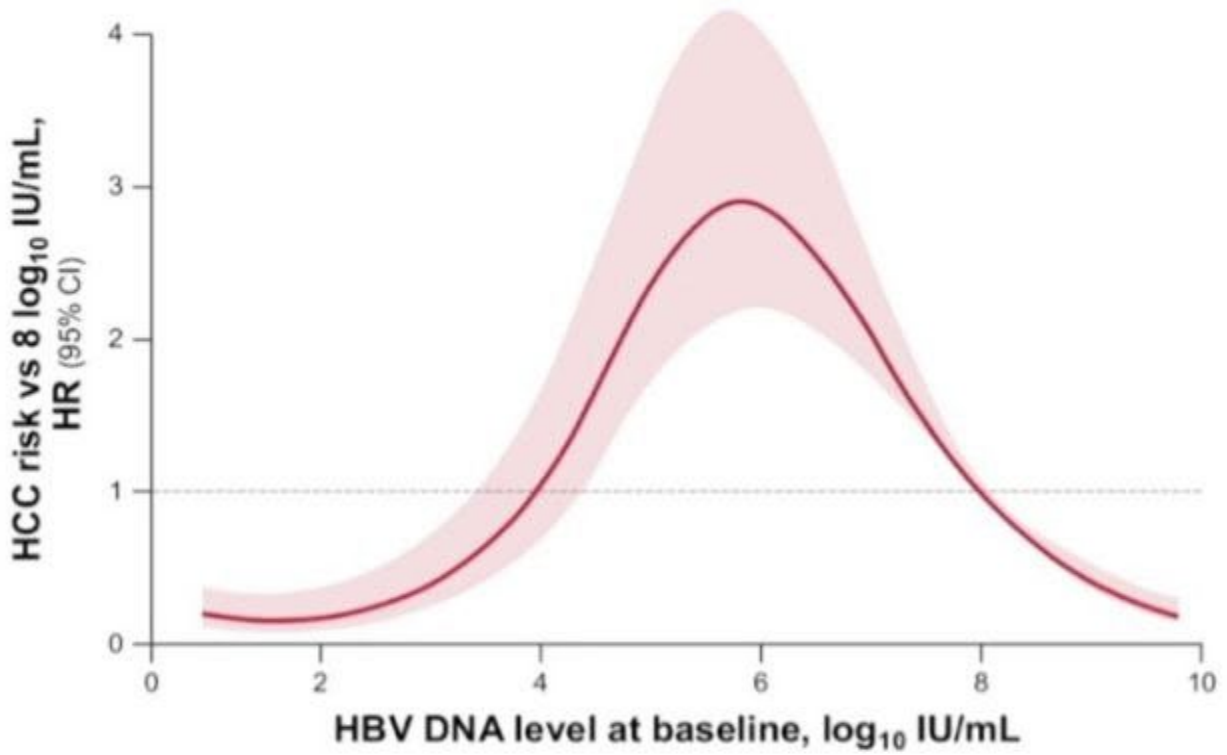
REVEAL-HBV Study

- A population-based, long-term prospective study on 3,653 previously untreated, non-cirrhotic CHB patients enrolled in Taiwan between 1991–1992: **85% were HBeAg-negative**



Chen CJ *et al.* JAMA 2006;295:65–73

Non-Linear Parabolic Association between HBV DNA Levels and HCC Risk

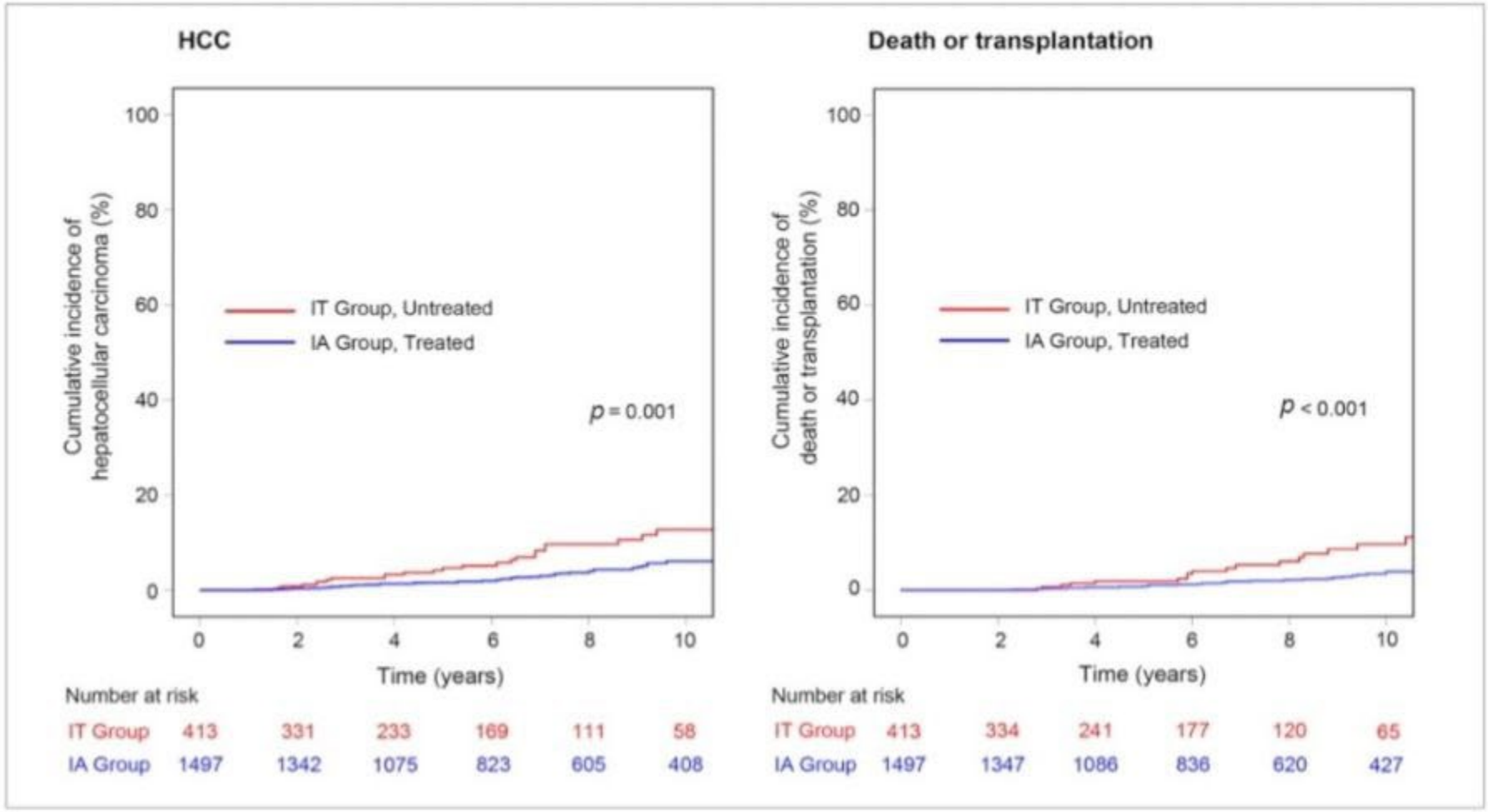


Definition of IT Phase CHB by Guidelines

Guidelines	HBV DNA	ALT	Tx
APASL 2016	>2 x 7 $\log_{10}$ IU/mL	normal	No
EASL 2017	>7 $\log_{10}$ IU/mL	normal	No (may consider Tx if age >30)
AASLD 2018	>6 $\log_{10}$ IU/mL	Normal or mildly elevated	No

Highest risk of HCC with HBV DNA level around 6 $\log_{10}$ IU/mL

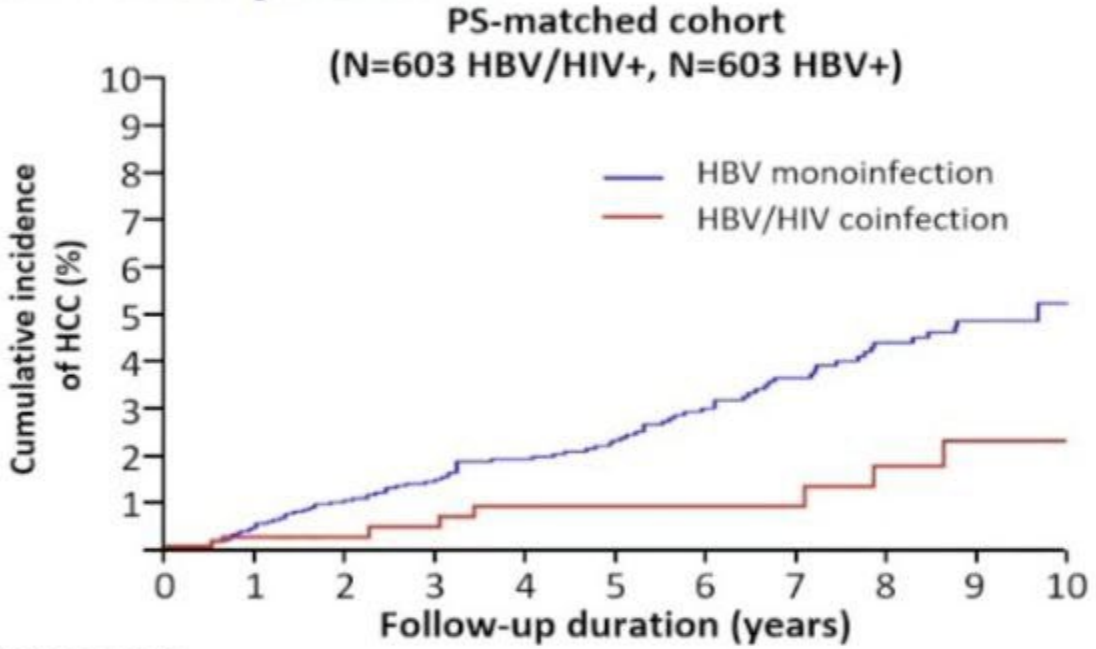
Earlier treatment improves disease outcomes



Kim et al., Gut 2018

HIV/HBV co-infected patients have a lower risk of HCC compared with treated HBV mono-infected patients

- HIV/HBV and HBV mono-infected patients from Hong Kong from 2000 to 2017*
  - Primary outcome was HCC
- Patients were PS-matched in a 1:5 ratio
- Patient characteristics
  - 85% were male
  - Mean (±SD) age was 42±12 years
  - 4.5% had cirrhosis at baseline
- Weighted Fine–Gray model showed that HIV infection was associated with a lower risk of HCC
  - Subdistribution hazard ratio: 0.39 (95% CI, 0.16–0.94, p=0.036)



Number at risk

HBV	603	558	486	427	379	325	275	228	188	153	116
HBV/HIV	603	560	494	446	396	353	298	263	214	183	161

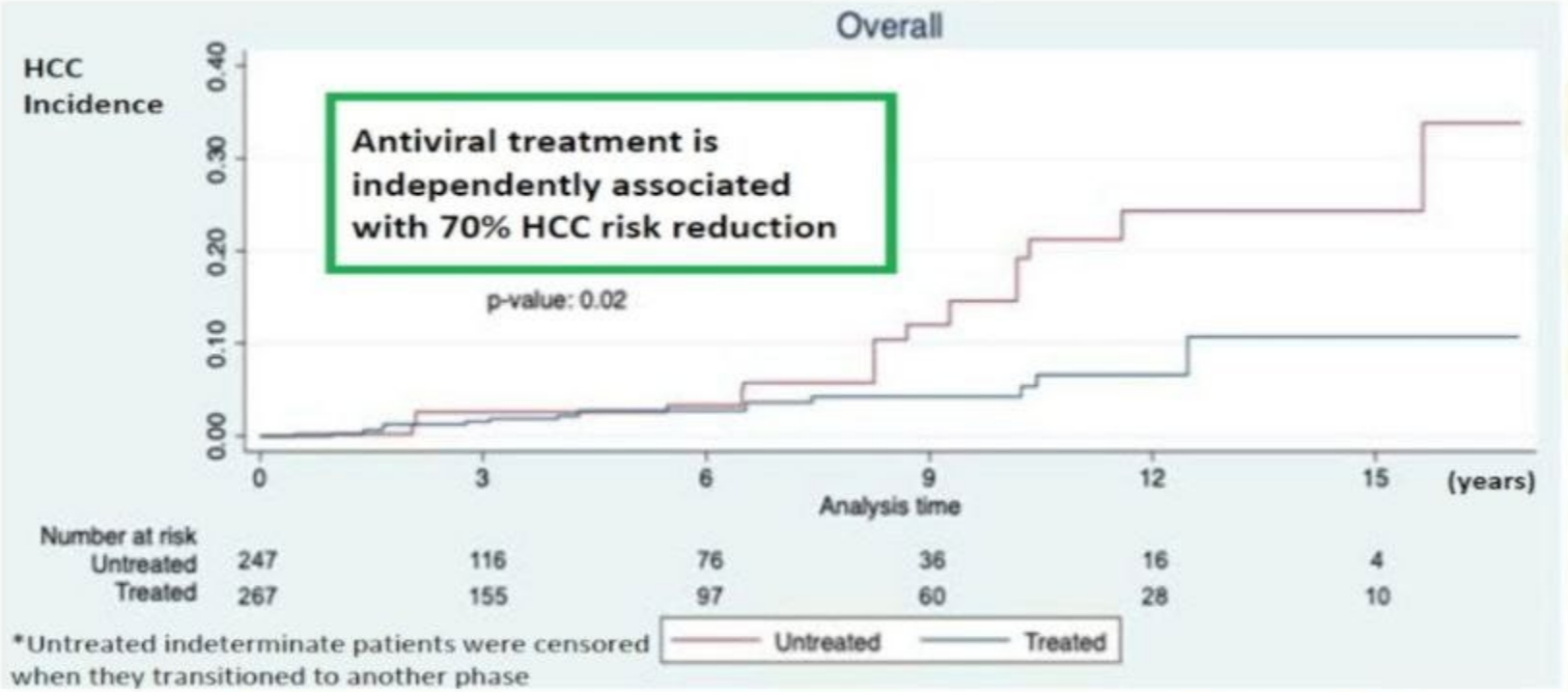
HIV/HBV patients start antiviral treatment immediately compared with HBV mono-infected patients

Adapted from Lui G, et al. Open Forum Infectious Diseases 2019;6:S188.

*Patients were excluded if they had HCV, had HCC diagnosed within 6 months, had a follow up of <6 months; HIV: human immunodeficiency virus; PS: propensity score; SD: standard deviation.

Grey Zone Patients Untreated vs Treated

- **REAL-B study, N=855 patients**
  - 21% HBeAg+
  - Mean VL 4.4 log IU/mL
  - FIB-4 >3/25 excluded
- **Mean follow-up 6.2 years**
- **Retrospective cohort from 14 sites in Europe/Asia in indeterminate phase**

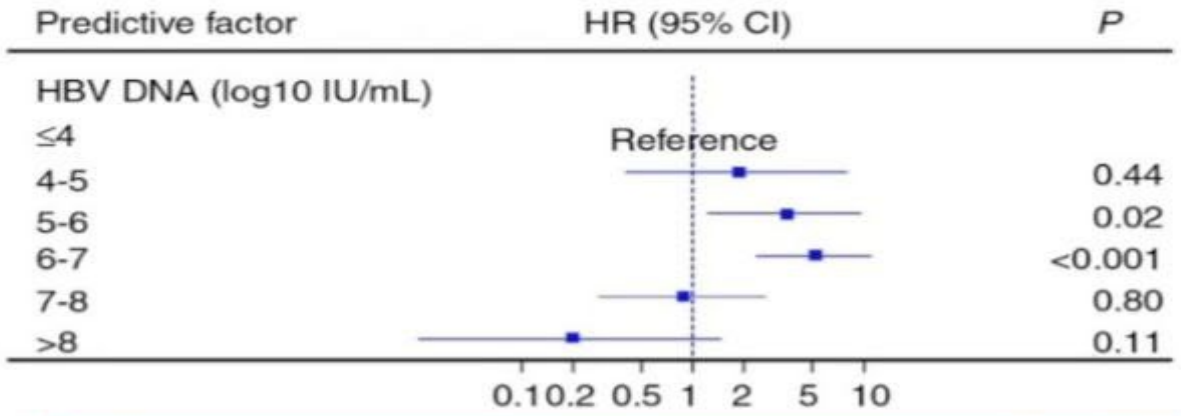


10 years: **4% treated vs 11% untreated**
HR 0.30 (95% CI; 0.1-0.6, p=0.001)

Huang D, Hepatology 2023, in press.

HBV Viral Load and FIB-4 can more Accurately Define Immune Tolerant Phase

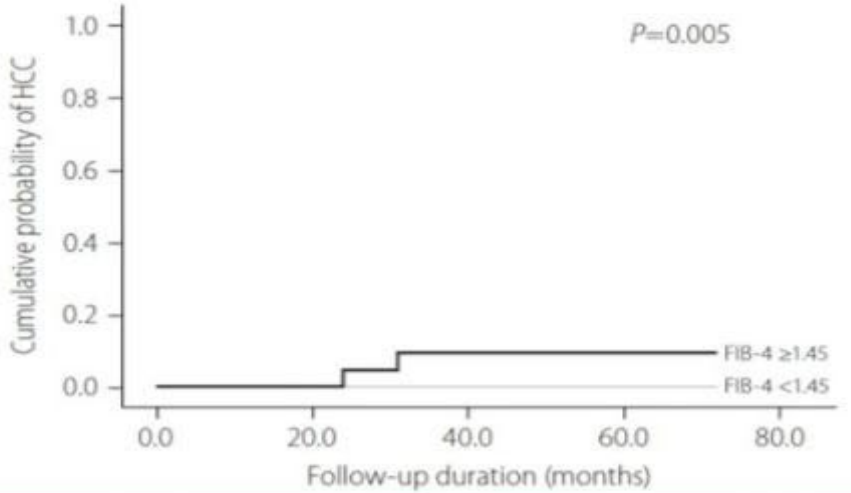
Korean Population (N = 6949)
N=2081 HBeAg-positive (including IT)
N=4868 HBeAg-negative
Age <40 years



HBV DNA levels ≥7 log associated with no significant increased risk of HCC

Kim G-A, APT 2020 Jun;51(11):1169-1179

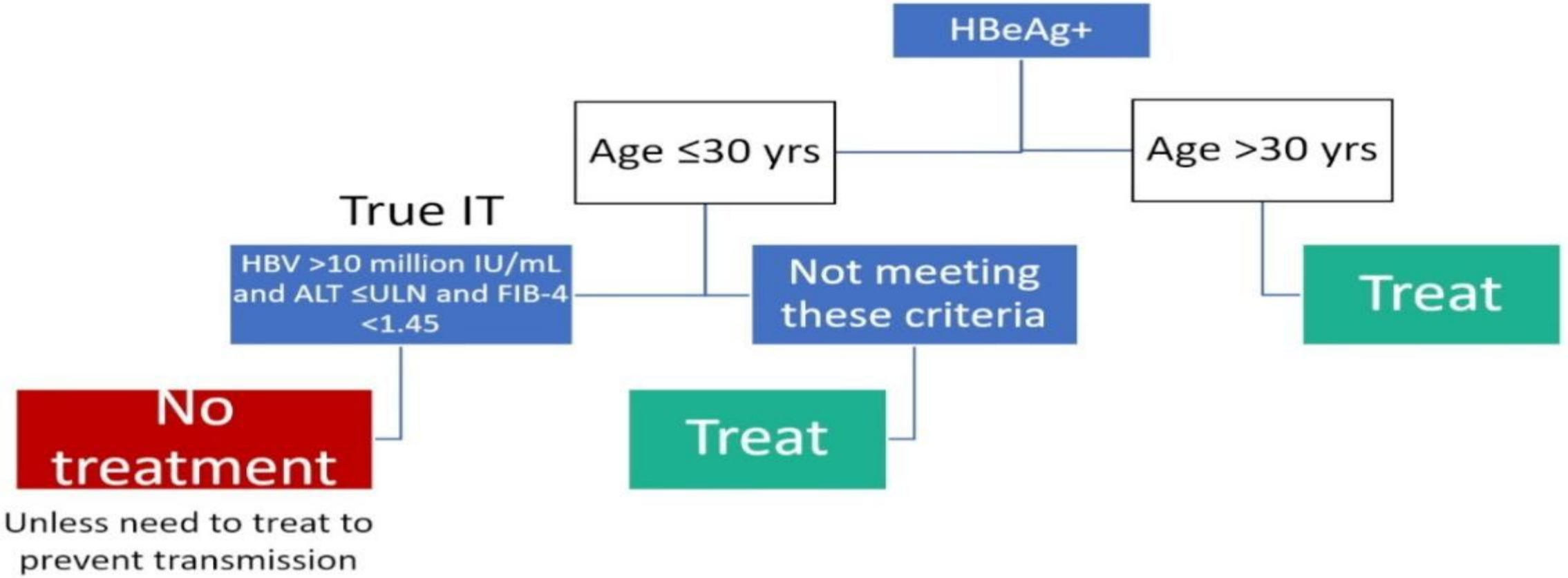
Korean Cohort



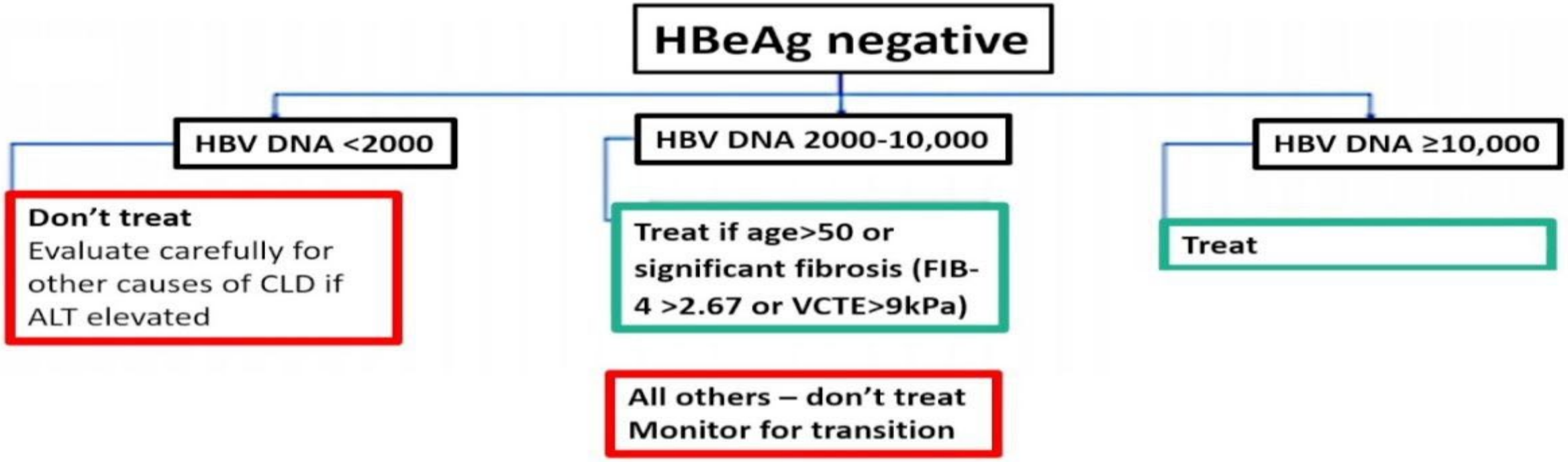
Risk of HCC was negligible in the IT-group stringently defined by a low FIB-4 index

Jeon M-Y, Clin Mol Hepatol 2021;27:295-304

Treatment Candidates: HBeAg-Positive



Treatment Candidates: HBeAg-Negative



CONCLUSIONS

- This is the time *to expand treatment guidelines for CHB patients*
- NA treatment has been shown to reduce the extent of HBV DNA integration and clonal expansion of hepatocytes
- Expanding treatment criteria will reduce the number of cases of HCC and the complications of CHB
- Early treatment is cost effective and should be employed as a bridge to Functional Cure

THANK YOU FOR YOUR ATTENTION!