The new treatment guidelines for CHB and CHD: are we moving towards functional cure?

Hannover Medical School, Hannover, Germany
Centre for Individualised Infection Medicine (CiiM), Hannover, Germany

Disclosures : AiCuris, AbbVie, Falk Foundation, Gilead Sciences, GSK, MSD, Novartis and Hoffmann-La Roche

Endorsed by

anrs MALADIES INFECTIEUSES ÉMERGENTES Inserm

HBV cure Task Force

ICE-HBV International Coalition to Eliminate HBV

IP-cure-B

RB-RNA

Goals / endpoints of CHB therapy

Endpoints of therapy

Recommendations

EASL™ The Home of Hepatology 2017

- The induction of long-term suppression of HBV DNA levels represents the main endpoint of all current treatment strategies (Evidence level I, grade of recommendation 1).
- The induction of HBeAg loss, with or without anti-HBe seroconversion, in HBeAg-positive CHB patients is a valuable endpoint, as it often represents a partial immune control of the chronic HBV infection (Evidence level II-1, grade of recommendation 1).
- A biochemical response defined as ALT normalisation should be considered as an additional endpoint, which is achieved in most patients with long-term suppression of HBV replication (Evidence level II-1, grade of recommendation 1).
- HBsAg loss, with or without anti-HBs seroconversion, is an optimal endpoint as it indicates profound suppression of HBV replication and viral protein expression (Evidence level II-1, grade of recommendation 1).

EASL CPG HBV. ***J Hepatol*** 2017;67:370–98

- **Functional cure**
- **HBsAg loss**

- **HBV DNA suppression**

- **HBeAg seroconversion**
- **„Inactive carrier“ status**

Recent HBV endpoint conferences

EASL/AASLD HBV endpoint conference **2019** (London)

Review

JOURNAL OF HEPATOLOGY

Guidance for design and endpoints of clinical trials in chronic hepatitis B - Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference‡

Markus Cornberg[1,2,3,*], Anna Suk-Fong Lok[4], Norah A. Terrault[5], Fabien Zoulim[6], and the 2019 EASL-AASLD HBV Treatment Endpoints Conference Faculty

AASLD/EASL HBV endpoint conference **2022** (Washington)

Received: 14 April 2023 | Accepted: 14 April 2023

DOI: 10.1097/HEP.0000000000000431

SPECIAL ARTICLE

Guidance on treatment endpoints and study design for clinical trials aiming to achieve cure in chronic hepatitis B and D: Report from the 2022 AASLD-EASL HBV-HDV Treatment Endpoints Conference

Marc G. Ghany[1] | Maria Buti[2] | Pietro Lampertico[3,4] | Hannah M. Lee[5] | on behalf of the 2022 AASLD-EASL HBV-HDV Treatment Endpoints Conference Faculty

„HBV cure“ definitions 2022

HBV DNA suppression is the basis

Table 1. Proposed definitions of HBV cure and their redefinitions.

Variable	Complete cure	Functional cure definition 2019	Functional cure definition 2022	Partial cure definition 2019	Partial cure definition 2022
HBsAg	Negative	Negative	Negative	Positive	Positive
HBsAg levels, IU/mL	Negative	<LLOQ	<LLOQ	Any	**<100**
Anti-HBs >10 IU/mL	Positive/negative	Positive/negative	Positive/negative	Negative	Negative
HBeAg/anti-HBe	Negative/positive	Negative/positive	Negative/positive	Negative/positive	Negative/positive
HBV DNA levels, IU/mL	**TND**	TND	**<LLOQ**	TND	**<LLOQ**
ALT levels	Normal	Normal	Normal	Normal	Normal
cccDNA	Absent	Present	Present	Present	Present
Integrated DNA	Absent	Present	Present	Present	Present
Clinical outcomes	Improved	Improved	Improved	Improved	Improved
Residual risk of HCC	Very low	Very low	Very low	Low	**Very low**
Durability over time	Yes	Yes	Yes	Unknown	**Yes**
Stigma for HBV	No	No	No	Yes	Yes

Note: 2022 updates to the definitions are highlighted in bold.
For all definitions, the timing of the endpoint is 24 weeks off-treatment.

2019: Cornberg, Lok, Terrault, Zoulim. ***J Hepatol***. 2020 Mar;72(3):539-557.
2022: Ghany, Buti, Lampertico, Lee. ***J Hepatol***. 2023 Nov;79(5):1254-1269.

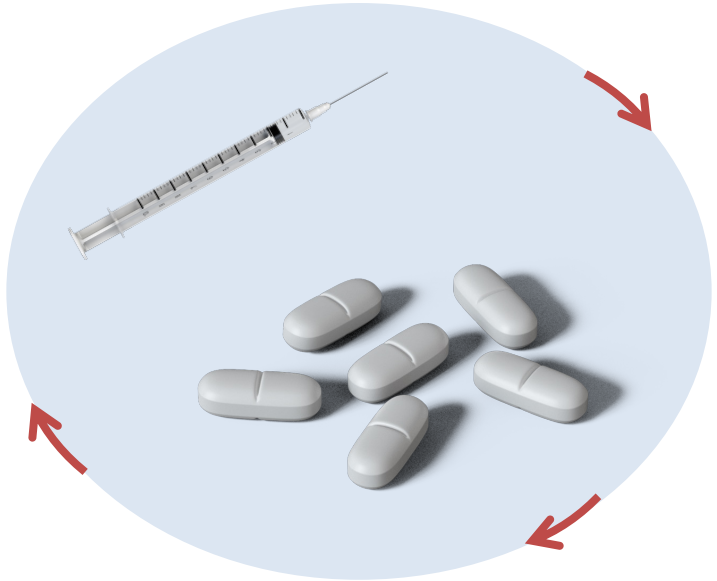
The concept of antiviral therapy

Most of the evidence exist 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

Long-term treatment in most cases HBsAg loss is rare (<0.5% per year)



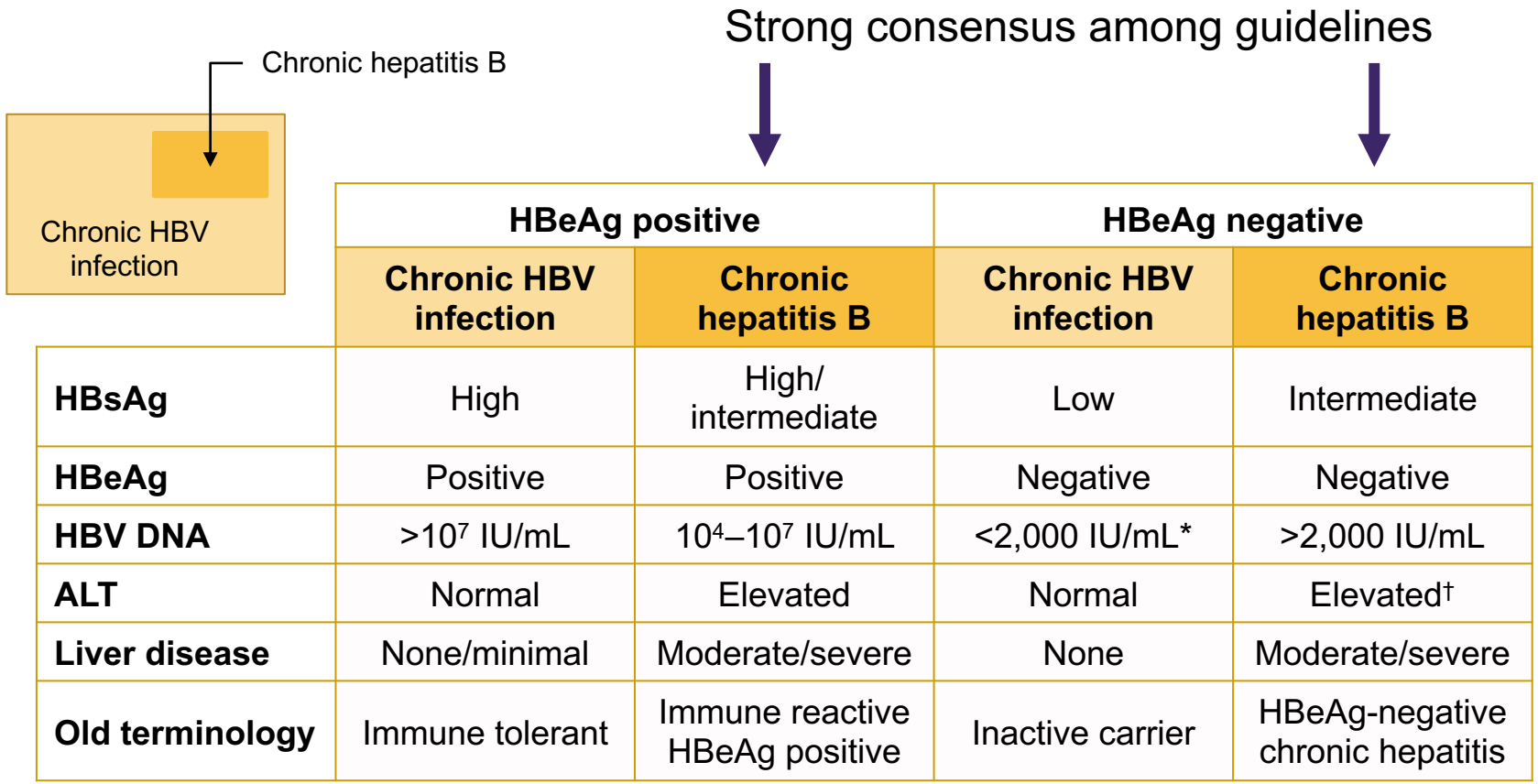
Improved survival

Fibrosis regression / cirrhosis prevention

HCC risk reduction

Marcellin et al. ***Lancet***. 2013 Feb 9;381(9865):468-75
Chang et al. ***Hepatology***. 2010 Sep;52(3):886-93
Papatheodoridis et al. ***J Hepatol.*** 2010 Aug;53(2):348-56
Hosaka et al. ***Hepatology***. 2013 Jul;58(1):98-107
Papatheodoridis et al., ***J Hepatol.*** 2014 Sep 4. pii: S0168-8278(14)00634-5
Arends et al. ***Gut.*** 2015 Aug;64(8):1289-95
Papatheodoridis et al. ***J Hepatol***. 2018 Jun;68(6):1129-1136

Chronic HBV infection: Who should be treated?

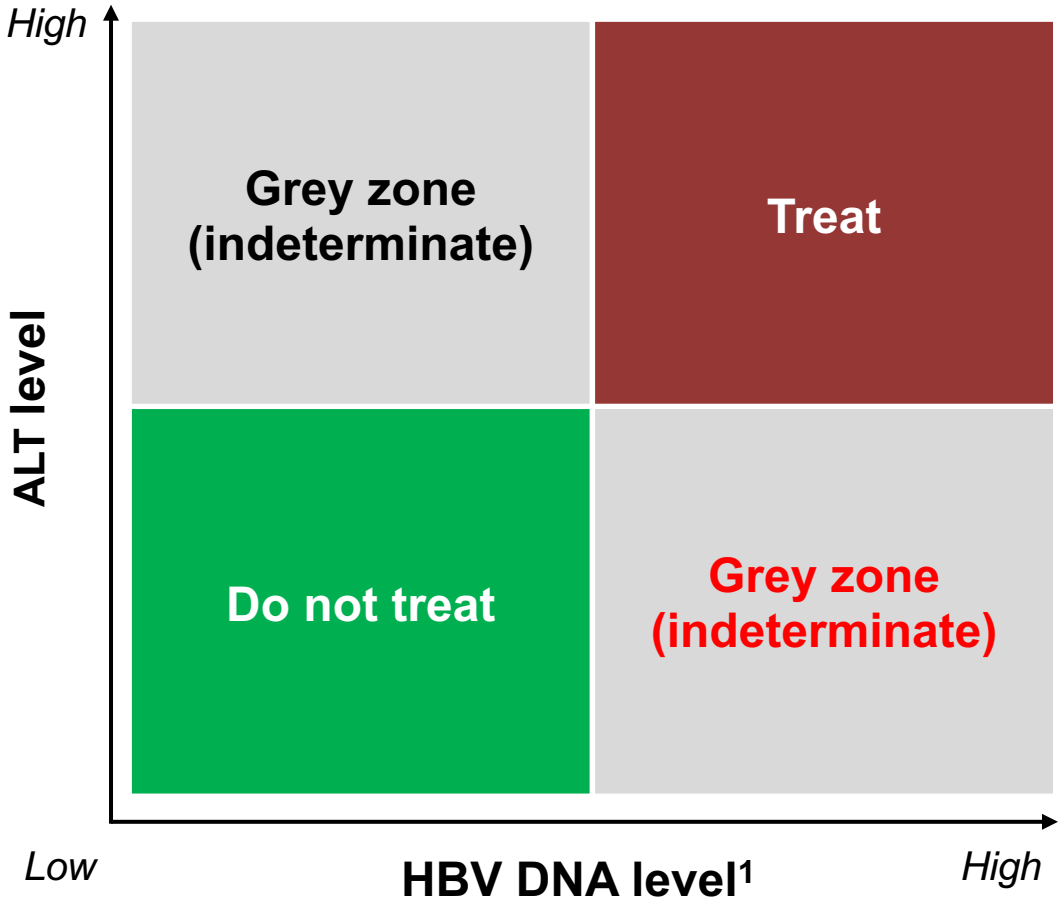


	HBeAg positive		HBeAg negative	
	Chronic HBV infection	**Chronic hepatitis B**	**Chronic HBV infection**	**Chronic hepatitis B**
HBsAg	High	High/ intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10^7 IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL
ALT	Normal	Elevated	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

*HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis;
†Persisitently or intermittently, based on traditional ULN (~40 IU/L).

EASL CPG HBV. ***J Hepatol*** 2017;67:370–98

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]

ALT, alanine transaminase; HBV, hepatitis B virus.
1. Mak LY, et al. J Viral Hepat 2024;00:1–9; 2. European Association for the Study of the Liver. J Hepatol 2017;67:370–398; 3. Lok AS, et al. Hepatology 2017;66:1296–1313; 4. Sarin SK, et al. Hepatol Int 2016;10:1–98; 5. World Health Organization. Available at: https://www.who.int/publications/i/item/9789241549059 (accessed April 2024); 6. Yuen MF, et al. Nat Rev Dis Primers 2018;4:18035.

The heterogeneity of chronic HBV infection

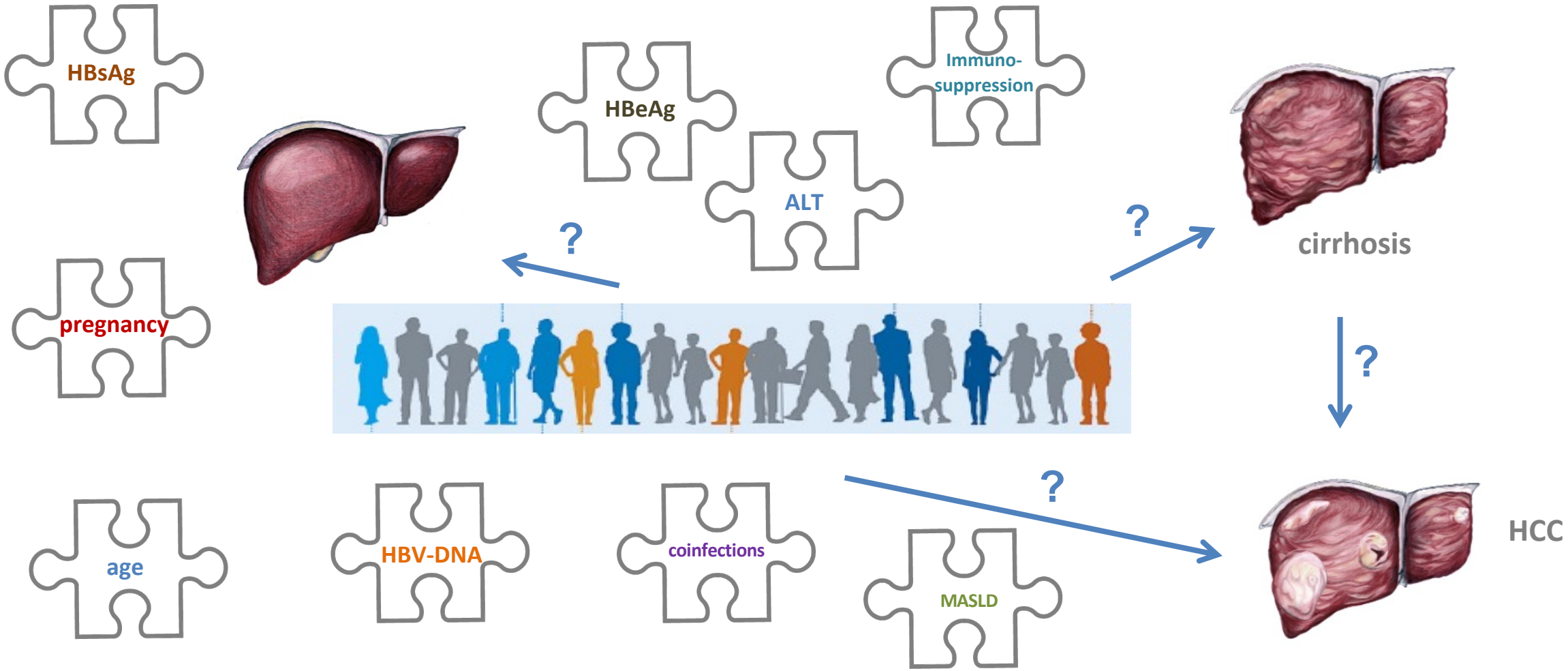
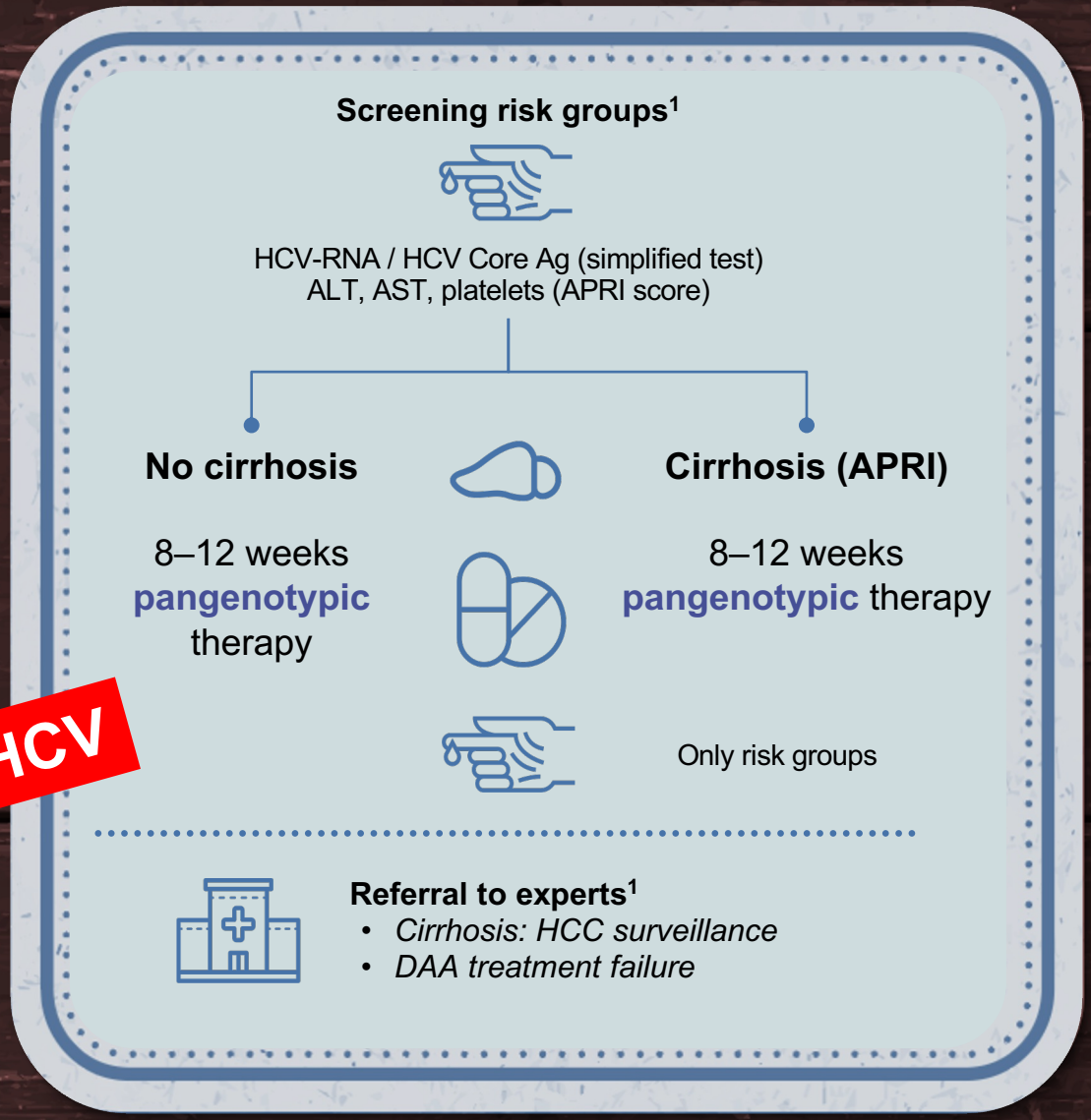


Figure modified: Bartenschlager R, Cornberg M, Pietschmann T. ***Internist*** (Berl). 2017 Jul;58(7):666-674.

Ideally, to improve linkage to treatment, we need "guidelines on a beer mat"

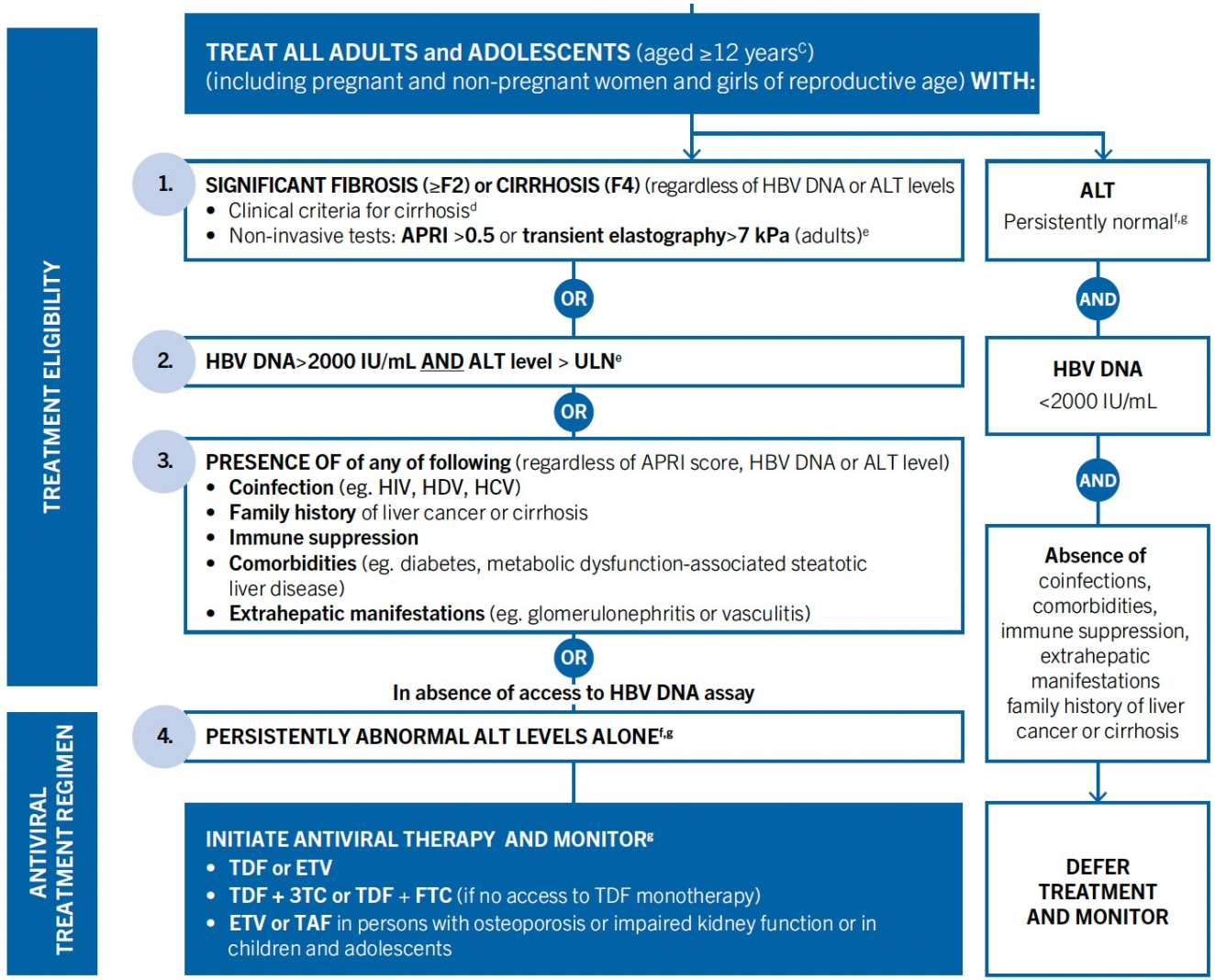
It works for HCV



Ag, antigen; ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; AST, aspartate transaminase; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma. M. Cornberg, personal communication.

1. EASL *J Hepatol* 2020;73:1170–1121.

Treatment extension and simplification: WHO guidelines



World Health Organization

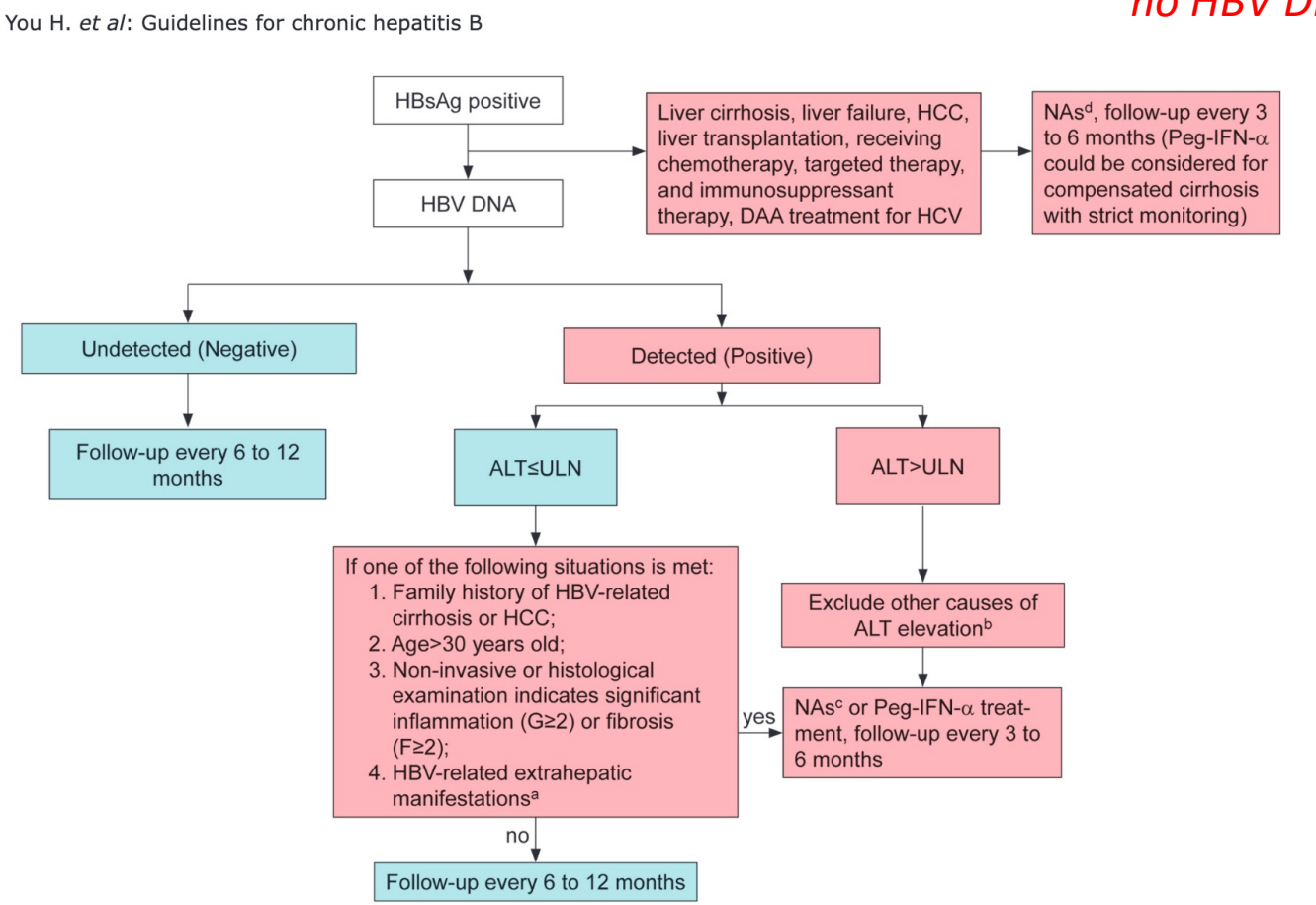
CiiM CENTRE FOR INDIVIDUALISED INFECTION MEDICINE

GHE Gastroenterologie Hepatologie Infektiologie Endokrinologie

MHH Medizinische Hochschule Hannover

Chinese Guideline

no HBV DNA cut-off of 2,000 IU/ml

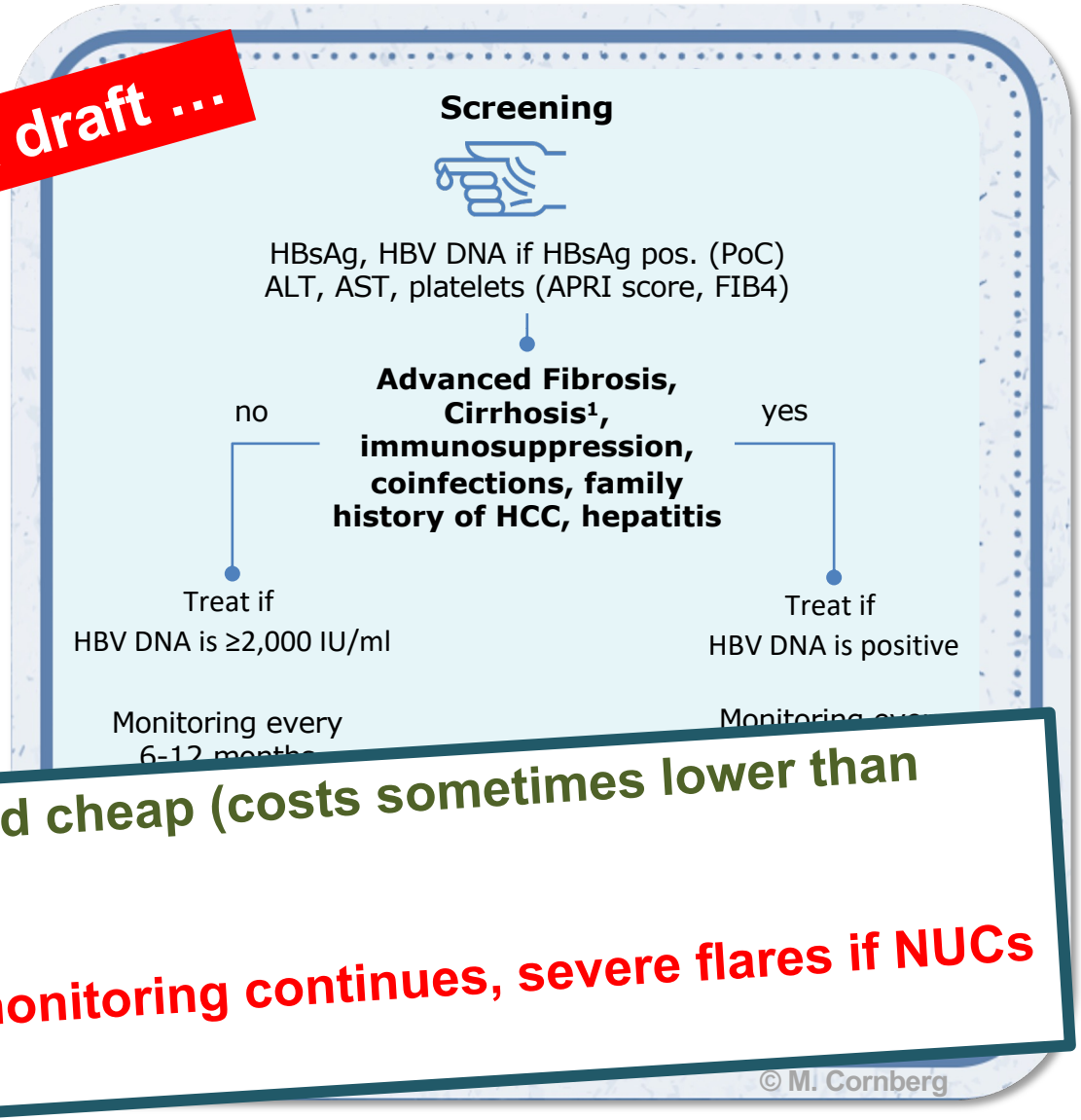


English Version: ***Journal of Clinical and Translational Hepatology*** 2023; DOI: 10.14218/JCTH.2023.00320

HBV Guideline on a beer mat

–

Are we really ready yet?



Pro: simple, NUCs are effective, safe and cheap (costs sometimes lower than tests)

Cons: long-term adherence required, monitoring continues, severe flares if NUCs are discontinued uncontrolled

„HBV cure“ definitions 2022

Thus, we want and need HBV cure!

Table 1. Proposed definitions of HBV cure and their redefinitions.

Variable	Complete cure	Functional cure definition 2019	Functional cure definition 2022	Partial cure definition 2019	Partial cure definition 2022
HBsAg	Negative	Negative	Negative	Positive	Positive
HBsAg levels, IU/mL	Negative	<LLOQ	<LLOQ	Any	**<100**
Anti-HBs >10 IU/mL	Positive/negative	Positive/negative	Positive/negative	Negative	Negative
HBeAg/anti-HBe	Negative/positive	Negative/positive	Negative/positive	Negative/positive	Negative/positive
HBV DNA levels, IU/mL	**TND**	TND	**<LLOQ**	TND	**<LLOQ**
ALT levels	Normal	Normal	Normal	Normal	Normal
cccDNA	Absent	Present	Present	Present	Present
Integrated DNA	Absent	Present	Present	Present	Present
Clinical outcomes	Improved	Improved	Improved	Improved	Improved
Residual risk of HCC	Very low	Very low	Very low	Low	**Very low**
Durability over time	Yes	Yes	Yes	Unknown	**Yes**
Stigma for HBV	No	No	No	Yes	Yes

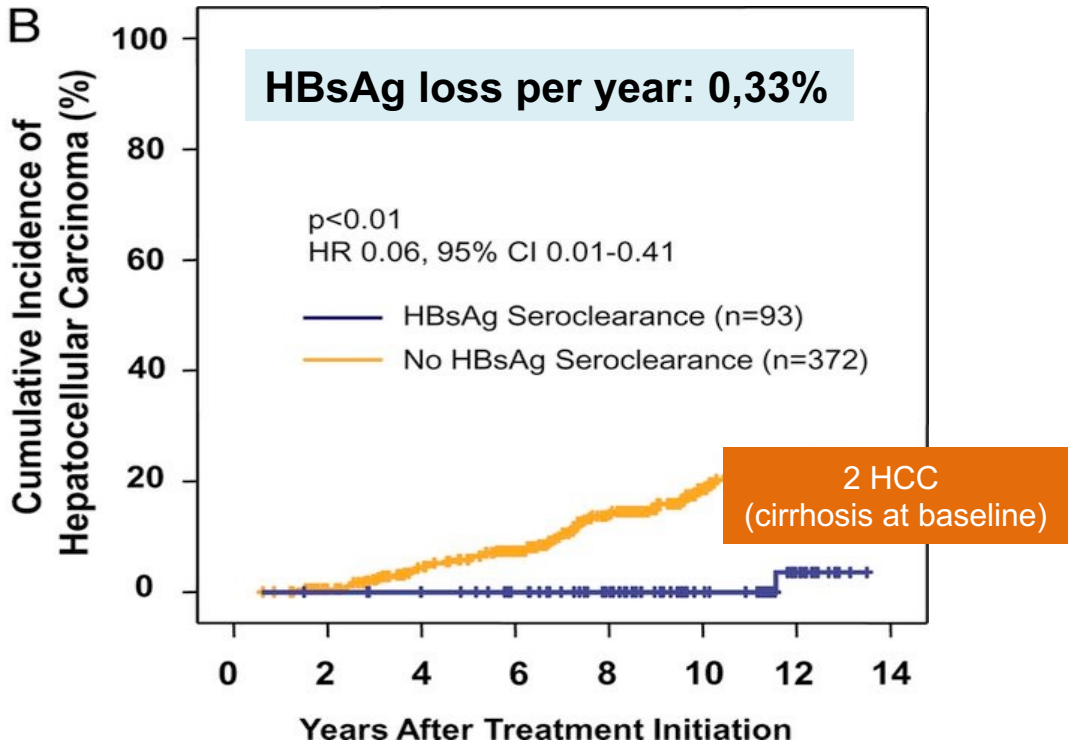
Note: 2022 updates to the definitions are highlighted in bold.
For all definitions, the timing of the endpoint is 24 weeks off-treatment.

We lack commercial and standardized assays for quantifying cccDNA and integrated HBV DNA

2019: Cornberg, Lok, Terrault, Zoulim. ***J Hepatol***. 2020 Mar;72(3):539-557.
2022: Ghany, Buti, Lampertico, Lee. ***J Hepatol***. 2023 Nov;79(5):1254-1269.

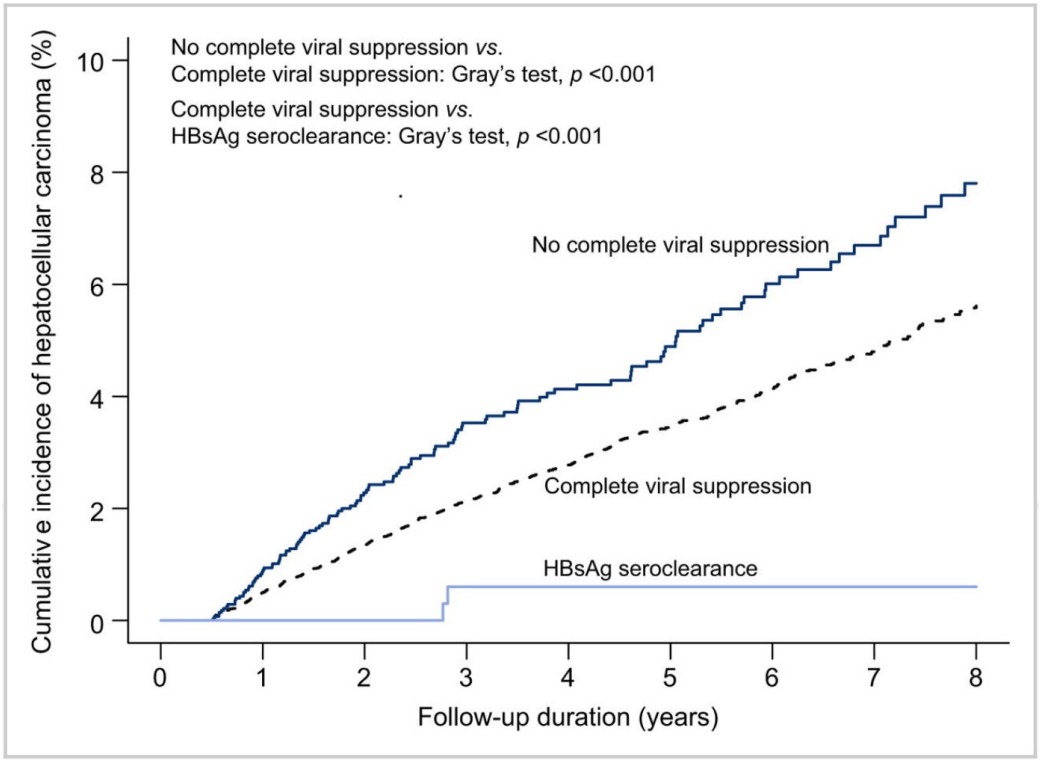
HBsAg loss - Rare but important*
HCC risk remains in patients who do not achieve HBsAg loss.

N= 5,409 treated with lamivudine or entecavir (FU 6 yrs) → N=110 with HBsAg loss



Kim et al. ***Gut***. 2014 Aug;63(8):1325-32.
*Editorial: Cornberg et al. ***Gut***. 2014 Aug;63(8):1208-9.

20,263 entecavir/TDF-treated patients with CHB
median (interquartile range) follow-up of 4.8 (2.8-7.0)
376 (2.1%) achieved HBsAg seroclearance



Yip et al. ***J Hepatol***. 2019 Mar;70(3):361-370.

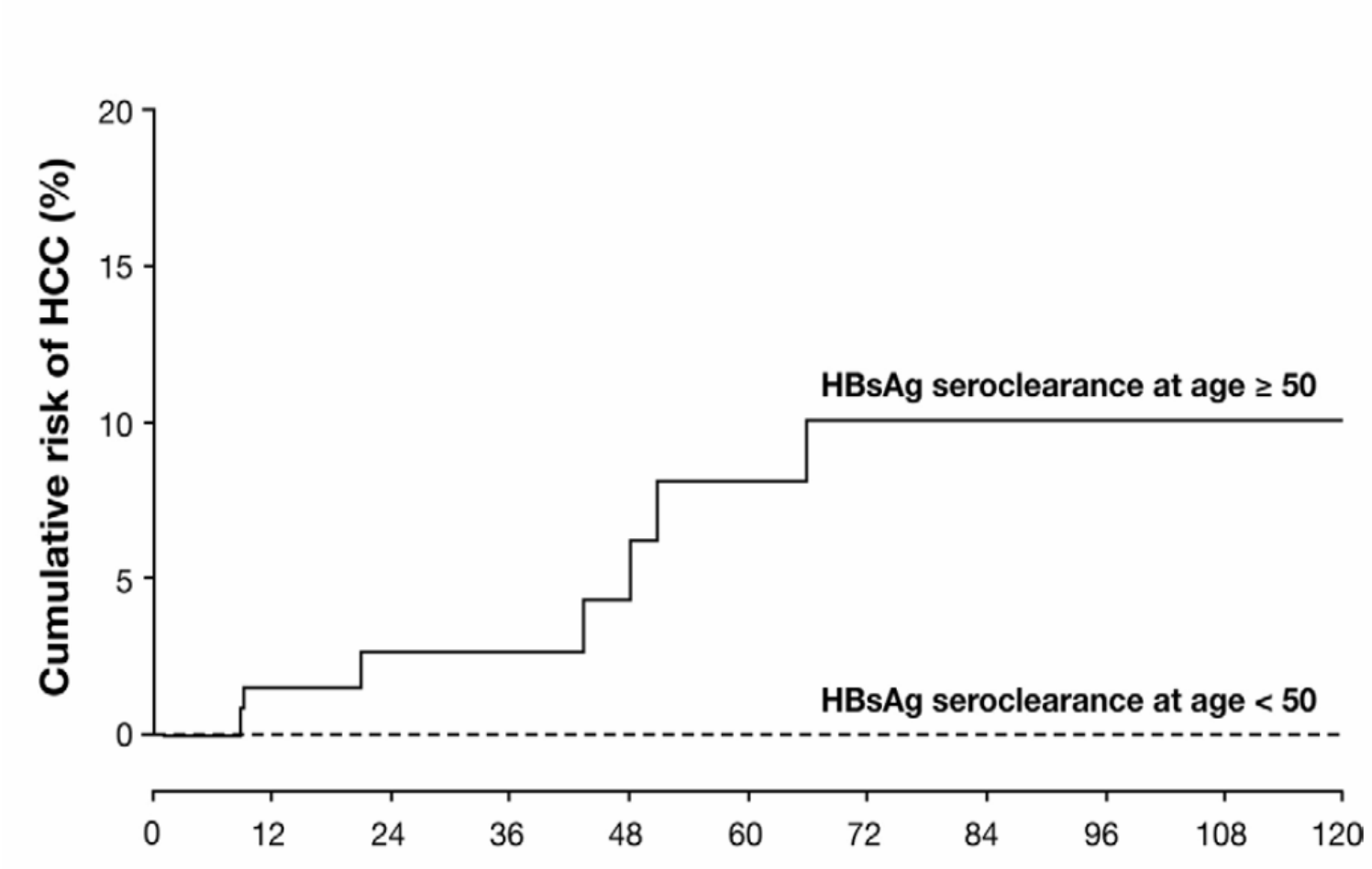
No difference in HCC incidence between patients from Alaska with and without HBsAg loss!

HCC rate / 100,000 person-years:
with HBsAg loss: **132**; without HBsAg loss: **178**
HR 0.7 (0.2-2.4); p=0.65

Characteristics	Study participants			Study participants with HCC		
	Case-patients	Control-patients	P-value[b]	Case-patients	Control-patients	P-value[b]
Total, No.	238	435		4	9	
Male sex, No. (%)	152 (64%)	267 (61%)	0.53	2 (50%)	4 (44%)	1.0
Age (years) at cohort entry,[c] Median (Q_1–Q_3)[d]	28.8 (15.9–42.2)	27.2 (14.9–38.8)	0.30	52.7 (40.2–59.6)	42.1 (32.0–48.1)	0.28

Gounder et al. ***Aliment Pharmacol Ther***. 2016 Jun;43(11):1197-207.

Ideally, HBsAg loss should be achived early



Yuen et al. ***Gastroenterology***. 2008 Oct;135(4):1192-9.

Anti-HBs is not necessarily required for the definition of functional cure

- HBsAg loss is maintained in over 90% of patients with or without anti-HBs in long-term follow-up with currently approved therapies but will need to be confirmed with therapies in development

Kim et al. ***Gut*** 2014;63:1325-1332
Alawad et al. ***Clin Gastroenterol Hepatol*** 2020;18:700-709 e703
Yip et al. ***J Hepatol*** 2017; 6;S0168-8278(17)32332-2
HBV endpoint conference 2019: Cornberg et al. ***J Hepatol*** 2020;72(3):539-557

„HBV cure“ definitions 2022

Partial cure
HBsAg <100 IU/ml as endpoint?

Table 1. Proposed definitions of HBV cure and their redefinitions.

Variable	Complete cure	Functional cure definition 2019	Functional cure definition 2022	Partial cure definition 2019	Partial cure definition 2022
HBsAg	Negative	Negative	Negative	Positive	Positive
HBsAg levels, IU/mL	Negative	<LLOQ	<LLOQ	Any	**<100**
Anti-HBs >10 IU/mL	Positive/negative	Positive/negative	Positive/negative	Negative	Negative
HBeAg/anti-HBe	Negative/positive	Negative/positive	Negative/positive	Negative/positive	Negative/positive
HBV DNA levels, IU/mL	**TND**	TND	**<LLOQ**	TND	**<LLOQ**
ALT levels	Normal	Normal	Normal	Normal	Normal
cccDNA	Absent	Present	Present	Present	Present
Integrated DNA	Absent	Present	Present	Present	Present
Clinical outcomes	Improved	Improved	Improved	Improved	Improved
Residual risk of HCC	Very low	Very low	Very low	Low	**Very low**
Durability over time	Yes	Yes	Yes	Unknown	**Yes**
Stigma for HBV	No	No	No	Yes	Yes

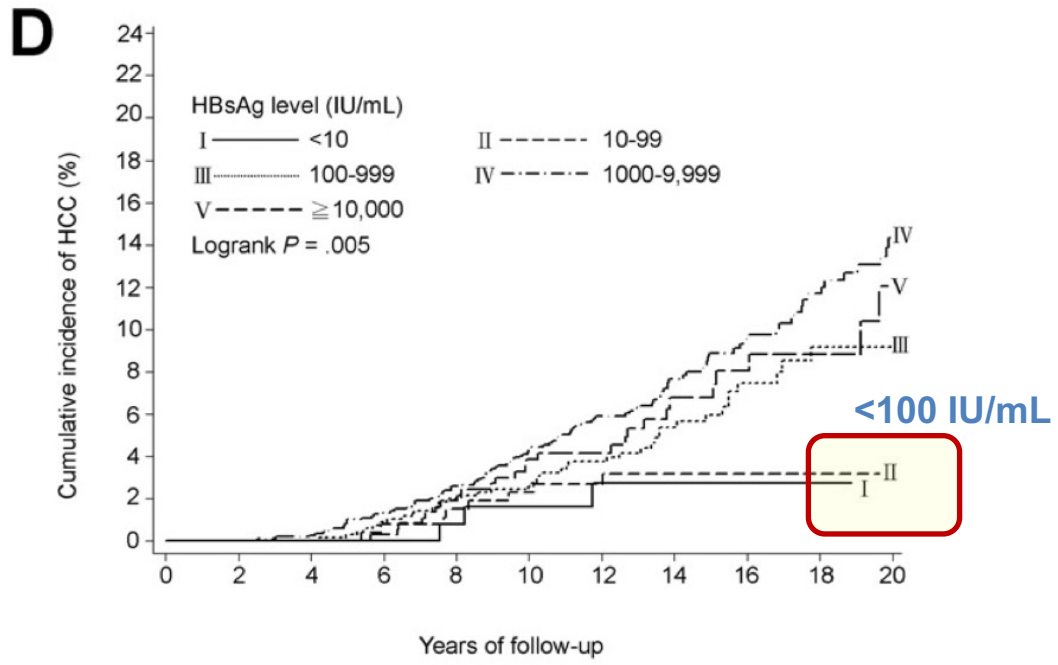
Note: 2022 updates to the definitions are highlighted in bold.
For all definitions, the timing of the endpoint is 24 weeks off-treatment.

An intermediate endpoint on the pathway to functional cure ?

Cornberg, Lok, Terrault, Zoulim. ***J Hepatol***. 2020 Mar;72(3):539-557.

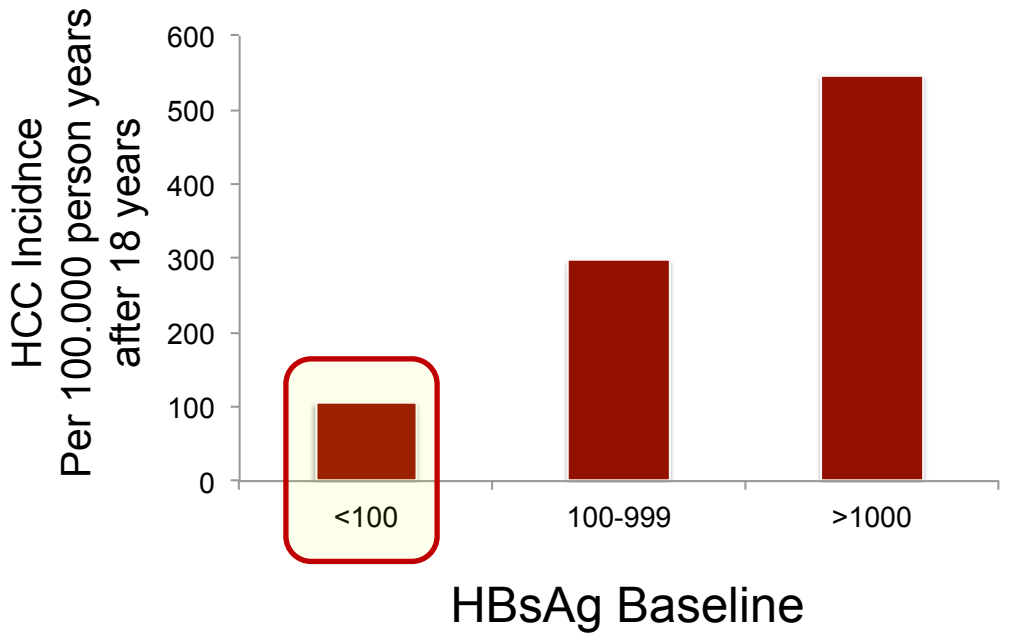
Low Levels of HBsAg (<100 IU/mL) are associated with a low risk of HCC (Asia)

ERADICATE B Study
(Hospital-based, 35% Carrier)



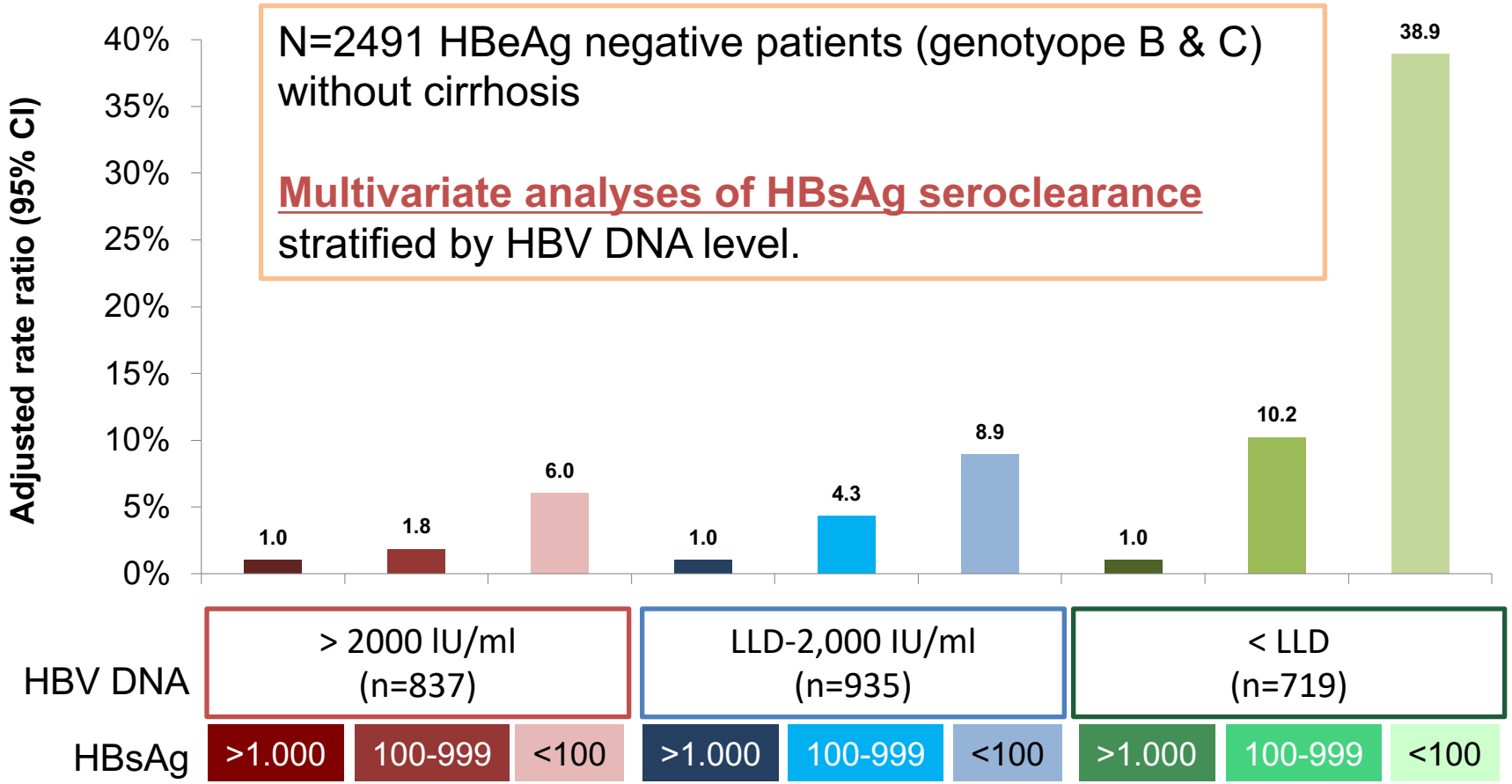
Tseng TC et al. ***Gastroenterology***. 2012 May;142(5):1140-1149

REVEAL Study
(Community-based, 56% Carrier)



Chen CJ et al. ***Hepatology*** 2011;54(Suppl):881A (AASLD 2011)

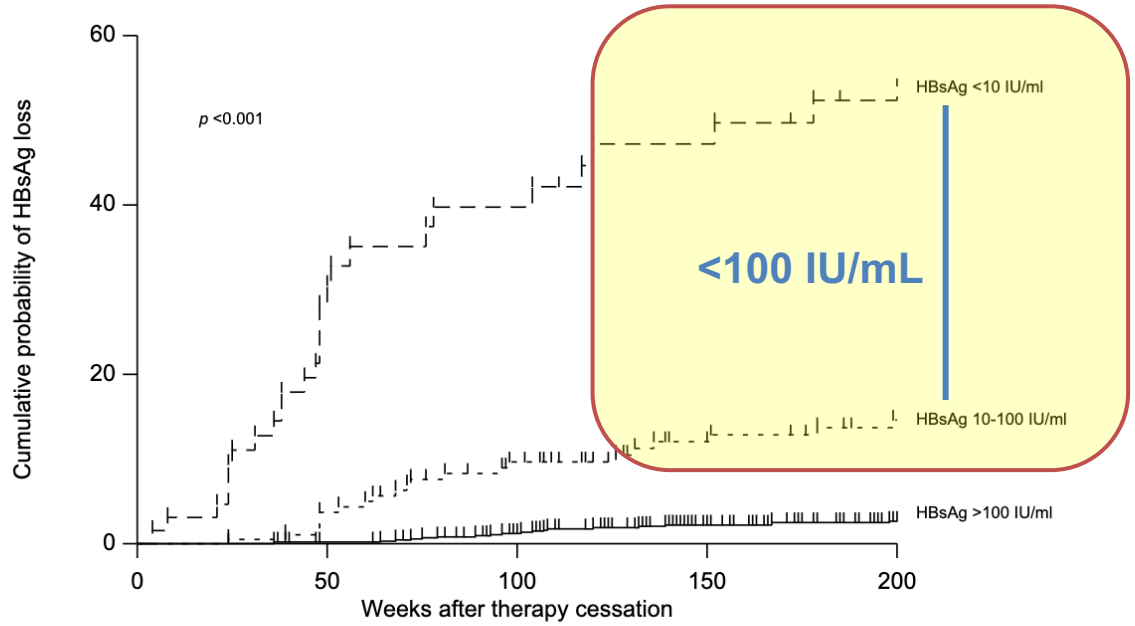
HBsAg levels (<100 IU/mL) are predictive for spontaneous HBsAg clearance



Liu J et al. ***J Hepatol*** 2013 May;58(5):853-60

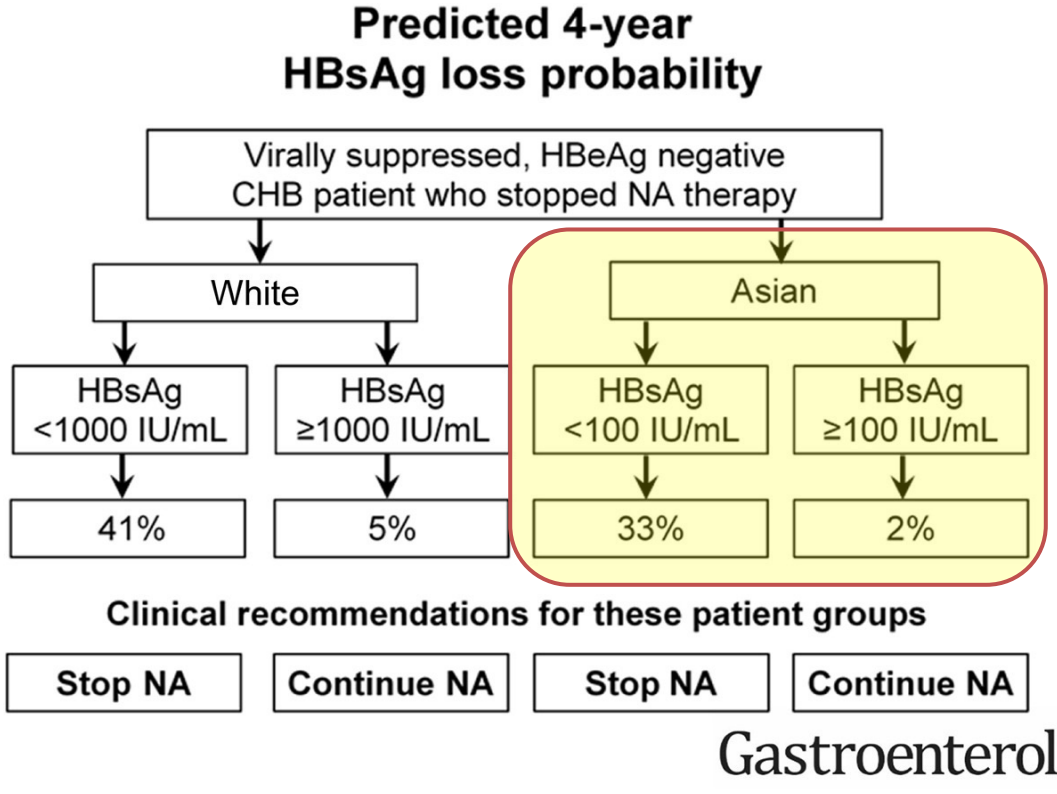
HBsAg <100 IU/mL is associated with HBsAg loss after stopping NUCs

HBsAg loss according to HBsAg after stopping NUCs



N° at risk*					
HBsAg <10	64	31	25	21	16
HBsAg 10-100	192	150	126	108	96
HBsAg >100	960	808	691	645	602

Sonneveld et al. ***J Hepatol.*** 2022 May;76(5):1042-1050.



Hirode G et al., ***Gastroenterology***. 2022 Mar;162(3):757-771.e4.

Endpoints for CHB therapy

- ***Functional cure***
- **HBsAg loss**

- This is the optimal endpoint.

- ***Partial cure***
- **HBsAg <100 IU/mL**

- An intermediate endpoint on the pathway to functional cure

- **HBV DNA suppression**

- This is the basis and yet the primary endpoint
- Guidelines will extend treatment criteria
- However long-term adherence to NUC treatment and monitoring is usually required

Goals / endpoints of CHD therapy

EASL 2023 The Home of Hepatology

Table 4. Primary endpoints for clinical trials of new anti-HDV treatments.

	Maintenance treatment	Finite treatment
FDA Developing drugs for CHD treatment (October 2019)	Surrogate endpoint likely to predict clinical benefit: ≥2 log reduction in HDV RNA and ALT normalisation (acceptable)	Undetectable HDV RNA and ALT normalisation (the timing of assessment according to treatment strategy)
EASL-AASLD HBV treatment endpoints conference (March 2019)	≥2 log reduction in HDV RNA (might suffice)	Undetectable HDV RNA at 6 months after end of treatment ALT normalisation (desired) HBsAg loss (ideal)

ALT, alanine aminotransferase; CHD, chronic hepatitis D; HBsAg, HBV surface antigen; HDV, hepatitis D virus.

EASL CPG HDV. ***J Hepatol.*** 2023 Aug;79(2):433-460.

Endpoints for CHB therapy

- ***Functional cure***
- **HBsAg loss**
- This is the optimal endpoint.

- **ALT normalization**
- This is the basis.

- ***HDV RNA suppression***
- At least >2 log decline