HBV: trattare tutti i viremici?

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Treatment decision making

- mortality
- morbility
- progression rate

Available drugs:
- efficacy
- side effects

Factors influencing the criteria to treat a subject with a viral infection

Virus
- *Biology*
- *Direct pathogenicity*
- *heterogeneity*

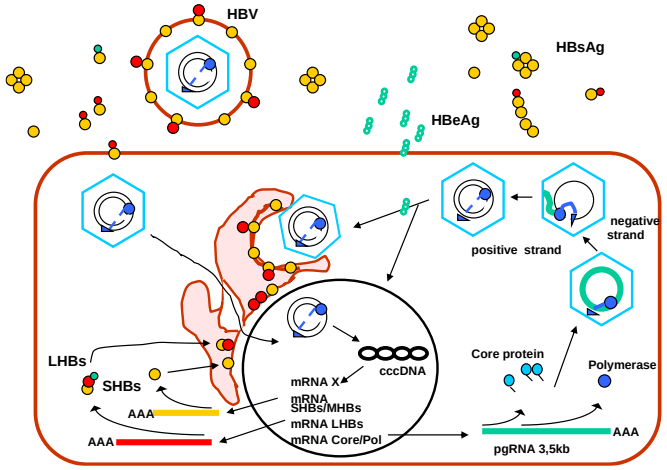
Treatment
- *Efficacy*
- *Mode of action*
- *Route of administration*
- *Treatment duration*
- *Side effects*

❖ **Socio-economical condition of the geographical area**
❖ **Health care system**

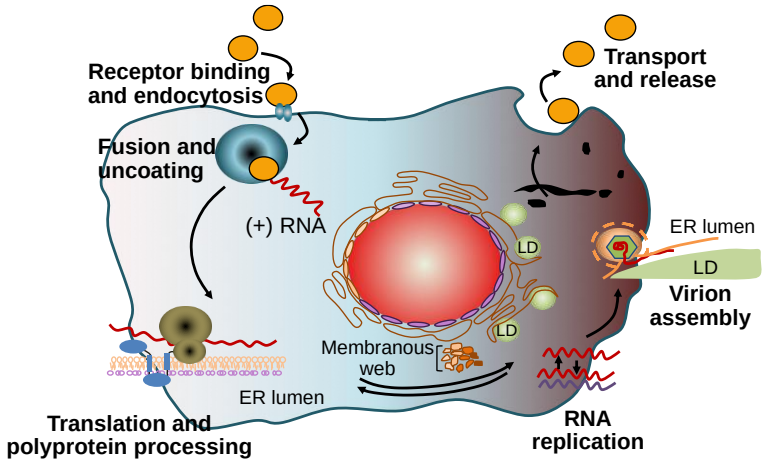
Virus-host interaction

Disease
- *Caused? Associated? Absent?*
- *Factors associated with outcome*
- *Severity*
- *Mortality*

HBV

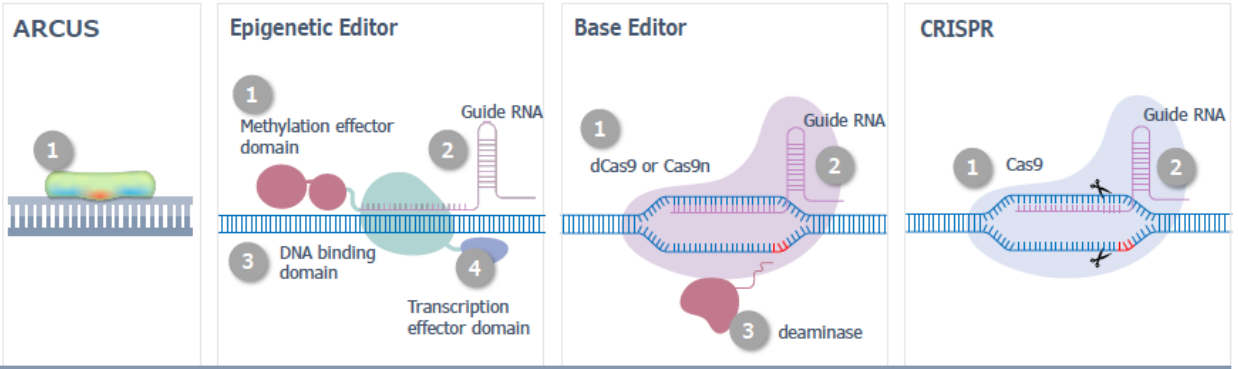


HCV



DNA	Genome	RNA
high	Mutation rate	very High
yes	Viral genetic archieving	no
one	Drug target	multiple
no cccDNA	Viral clearance	yes

Gene Editors Include Components to Identify the Target Site and Make a Cut
Epigenome Editors Include a Methylation Effector



	ARCUS	Epigenetic Editor[1]	Base Editor[2]	CRISPR Editor[3]
Intended Edit Result	Eliminate cccDNA, integrated DNA	Silences cccDNA and integrated DNA via methylation	Mutates and inactivates cccDNA and integrated DNA	Creates cccDNA indels or excises portion of DNA with multiple guides
Cut type	Cut resulting in double stranded break with 3′ overhangs	Methylation (No Cut)	Single Stranded Nick	Cut resulting in double stranded break with blunt ends
Kilobases (kb)	~1 kilobase	~7 kilobases	4.8-5.4 kilobases	3.2-4.1 kilobases
# of Components	1 component	≥3 components (based on number of gRNAs)	≥3 components (based on number of gRNAs)	≥2 components (based on number of gRNAs)

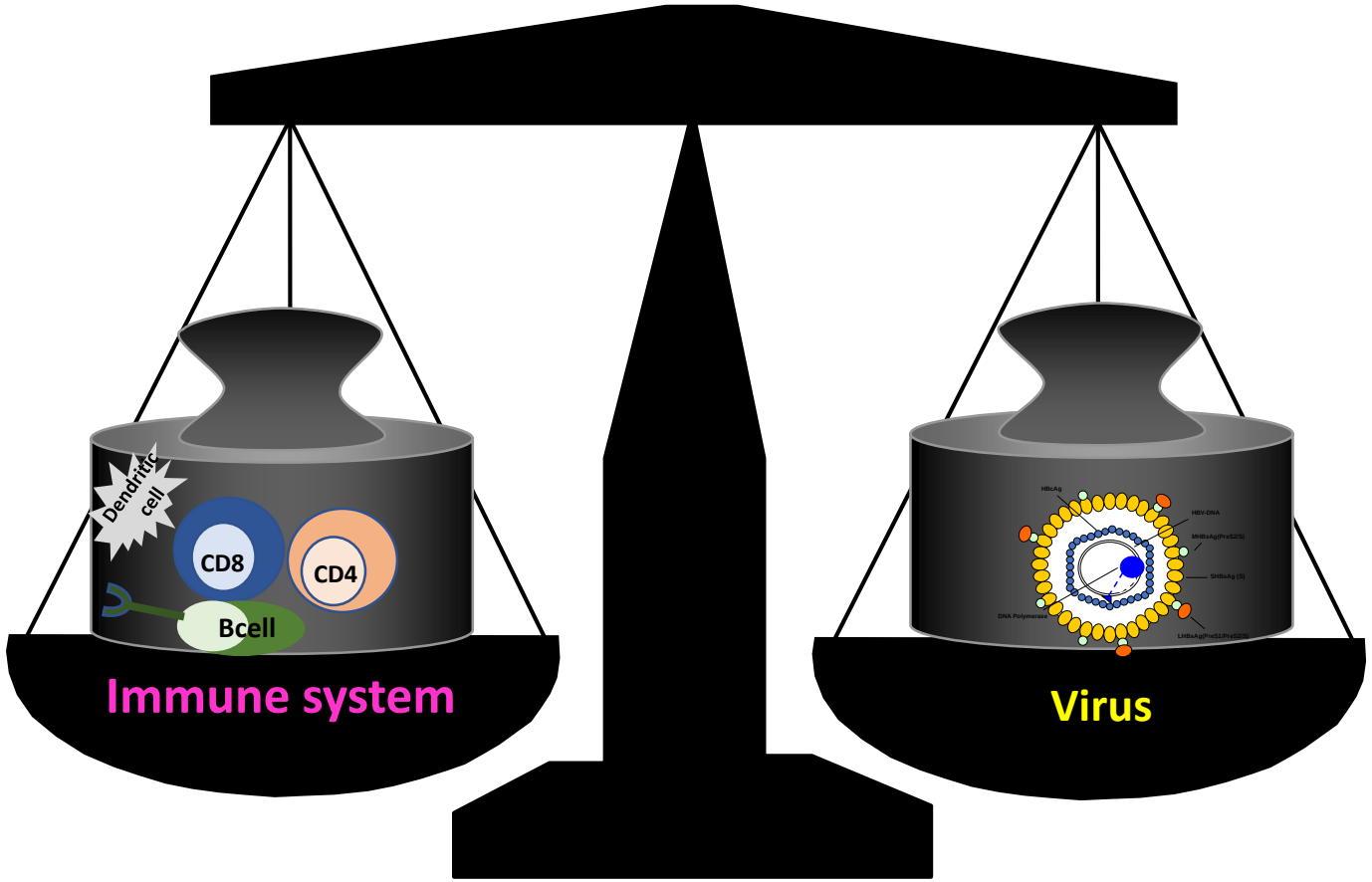
Critical issues to overcome

- Optimize the delivery to target sequences within cccDNA
- Guide RNA (gRNA) should target both cccDNA and intDNA
- Possible mismatches of gRNA with unconserved HBV sequences
- Repair of cut cccDNA → recovery of transcritional activity
- Cutting integrated HBVDNA could cause chromosomal translocation?

- No on-target effect (translocation or oncogenic)
- No off-target effect
- No germline editing
- Long term safety

Adapted from Zoulim F, HBV Forum 2024

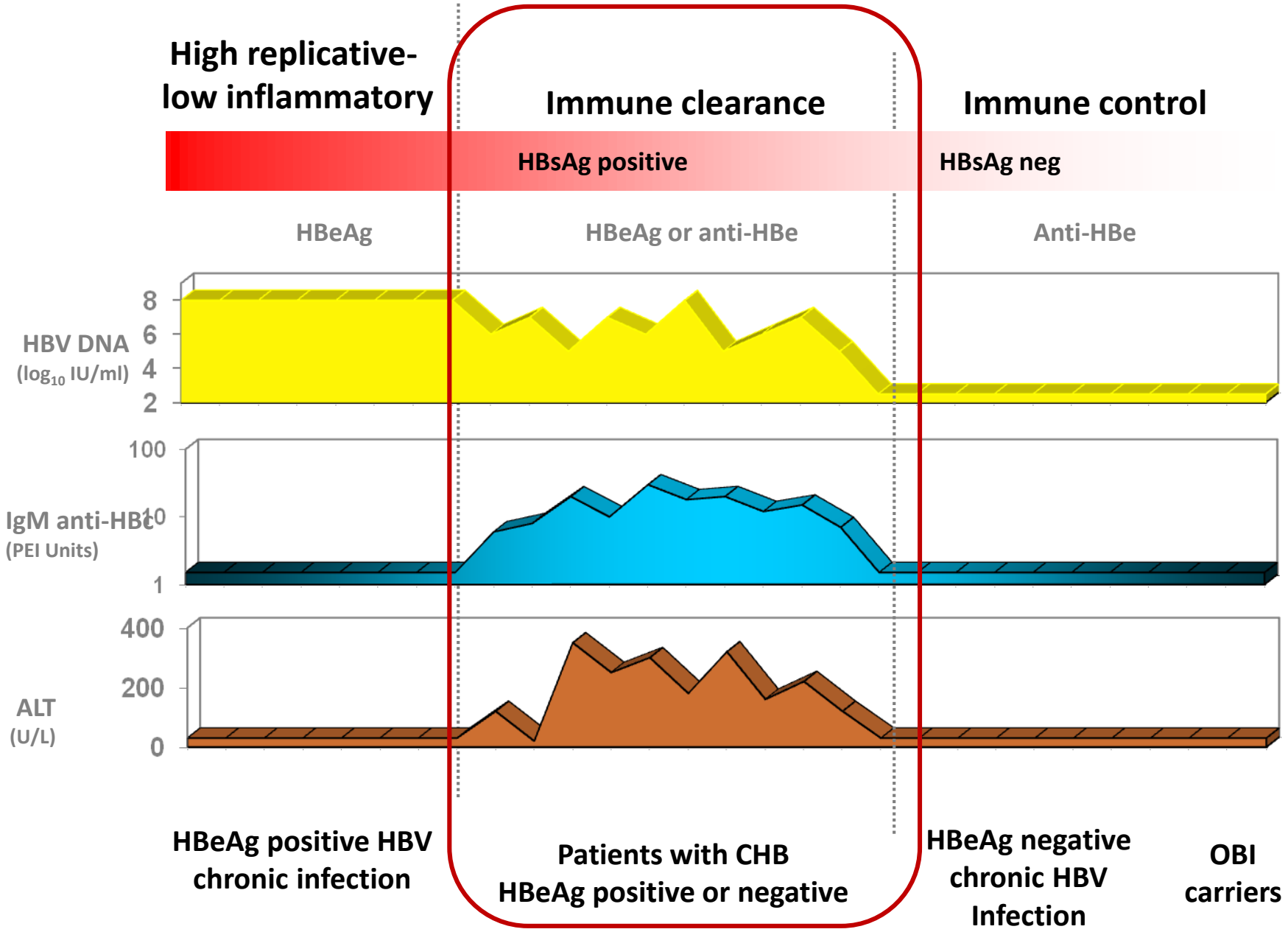
Outcome of hepatitis B virus infection and liver disease



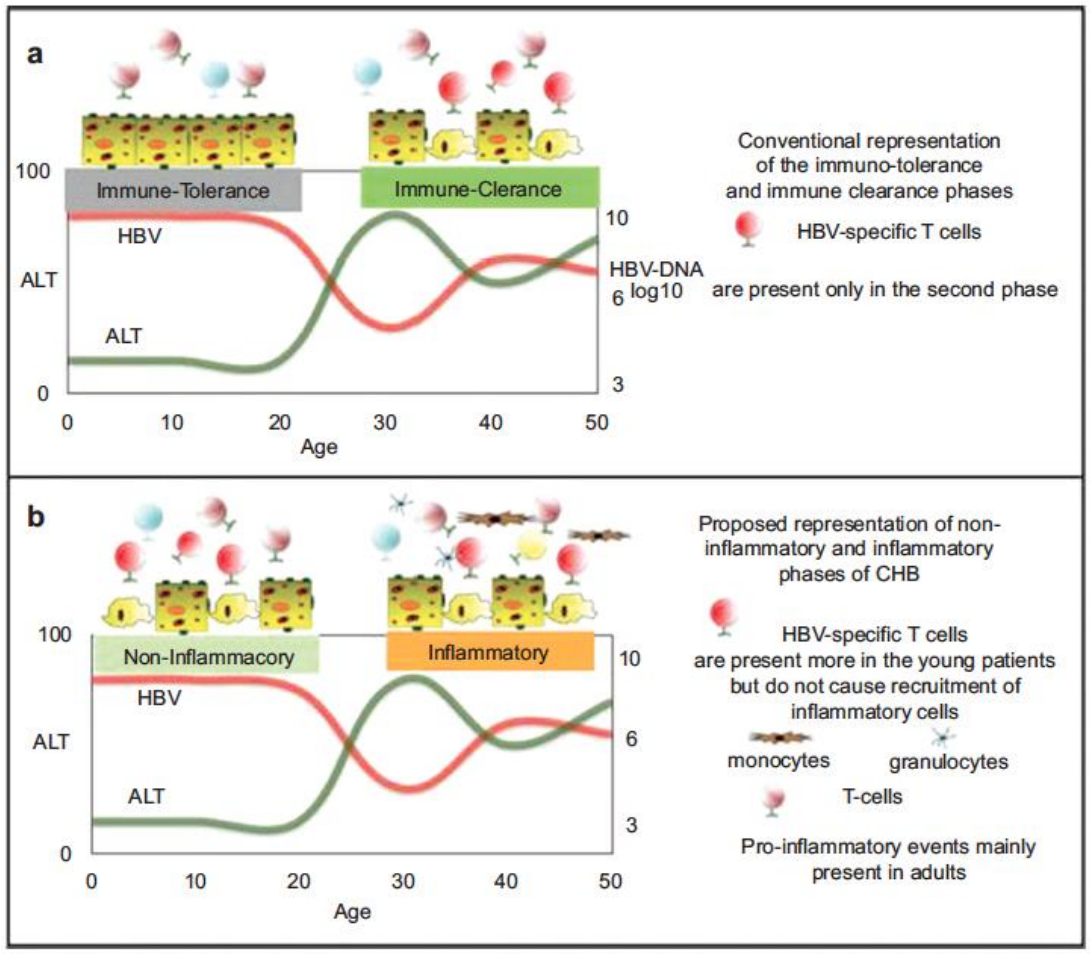
A coordinated humoral and cellular immune response may control HBV infection, allowing its persistence without liver damage

The unique HBV biology in the contest of liver physiology, allows the virus to replicate without liver damage

Natural history of Chronic Hepatitis B Virus Infection



The immune tolerant phase of chronic HBV infection: new perspectives on an old concept



A change in TLR-mediated immune response during life could explain the findings:

• anti-inflammatory cytokines (IL-10) production prevails in children as compared to adults.

• pro-inflammatory cytokines (IL-1-beta, TNF-α) increase during early life until they reach the state of chronic low grade systemic inflammation (inflammaging) that is characteristic of eldery.

• T-cell response shifts from a Th2/Treg type response in newborns to a more Th1 response in children/adults with a progressive increase of effector T-cell pools, more sensitive to cytokines-mediated activation

- **Adolescents** with chronic HBV infection **do not show any tolerogenic T-cell features**; they could mount a normal Th1 T-cell response and harbour HBV-specific T cells.
- These **HBV-specific T cell** were **quantitatively and functionally superior** to those found in HBV infected adults in the "immune-clearance phase".

Kennedy PT et al, Gastroenterology 2012;Bertoletti A et al, Cellular & Molecular Immunology 2014

The immune tolerant phase of chronic HBV infection: new perspectives on an old concept

Should more data support the proposed thinking, some practical consequences might arise:

- if **young CHB patients** exhibit a **more conserved HBV-specific immune response**, than that observed in adult patients, but do not trigger a full blown pro-inflammatory reaction; **therapy designed to boost HBV specific immunity** (vaccine therapy, check points inhibitors) **is more likely to be successful** and indeed less damaging in young patients.

- we should start to consider and evaluate CHB in adults as an inflammatory rather than a viral induced disease.

- The efficacy of therapy based on suppressing platelet function in blocking the development of HCC in HBV transgenic mice represents the first step towards this analysis.

Kennedy PT et al, Gastroenterology 2012; Bertoletti A et al, Cellular & Molecular Immunology 2014

Entecavir and Peg-IFN in Adults with HBeAg pos immune-tolerant chronic HBV infection

- **28** HBeAg pos, HBV-DNA >10^7 IU/ml and ALT < 1.5 ULN
- 27 were Asians, median age 37.2 (22.2-61.2) years
- ETV 0.5 mg/die for 8 weeks followed by combination of ETV + Peg-IFN for 40 weeks

	EOT	EOF
	Number (%)	Number (%)
Endpoints	0	0
HBsAg loss	0	0
HBeAg loss	**1 (4)**	**1 (4)**
HBeAg seroconversion	**1 (4)**	**1 (4)**
HBV-DNA < 20 IU/ml	**5 (18)**	**0**
HBV-DNA < 1000 IU/ml	**26 (93)**	**0**
ALT < 1 x ULN	**11 (39)**	**13 (46)**
ALT < 1.5 ULN	**16 (57)**	**21 (46)**
Primary endpoints		
HBeAg loss/HBV-DNA < 1000 IU/ml	**1 (4)**	**0**

- 70% of pts had had 2 x ALT elevation when Peg-IFN was added
- 30% had 5x ALT elevation

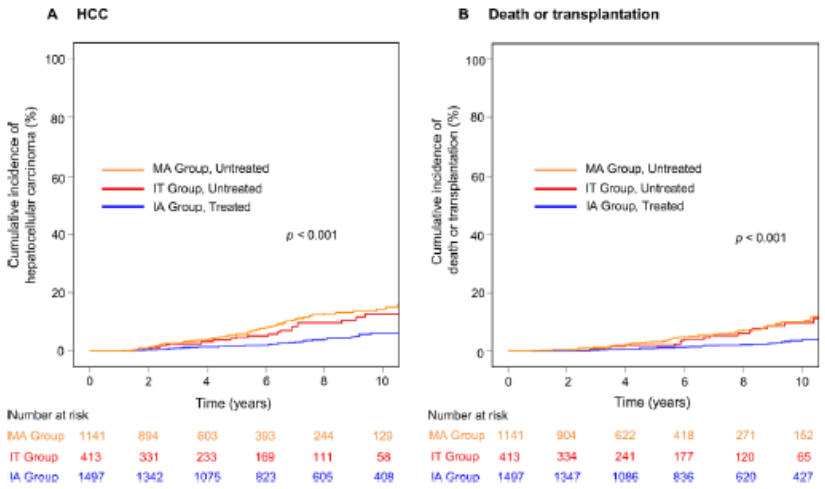
A lead in strategy of 8 weeks of ETV followed by combination therapy with Peg-IFN had limited efficacy in adults IT phase and cannot be recommended

Feld JJ et al Hepatology 2019

High risk of HCC and death in patients with immune-tolerant-phase chronic hepatitis B

4535 HBeAg positive carriers with HBV-DNA > 20000 IU/ml

	Immune tolerant (IT)	**Immune Active (IA)**	**Midly Acitive (MA)**
	464 with ALT <1xULN	2724 with ALT >2 ULN	1347 ALT 1-2xULN
1 y fu	51 → IA	1227 no NUC	206 → IA
	413	**1497**	**1141**
During 6.3 y median fu	24 HCC 18 death/LT	54 HCC 34 death/LT	83 HCC 52 death/LT



Factors predictors of clinical events

- ✓ **Older age** (HR 1.07), **male sex** (HR 2.3), **lower HBV-DNA levels** (HR 0.62) and **lower PLTS levels** (HR 0.99)
- ✓ Baseline **HBV-DNA serum levels** were **comparable** between IT and IA (8.0 vs 7.7 log IU/ml, p=0.20)

Kim G.A et al Gut 2017

Extremely low risk of hepatocellular carcinoma development in patients with chronic hepatitis B in immune-tolerant phase

946 IT Carriers (HBeAg pos, HBV-DNA >20 000 IU/mL and ALT ≤40 IU/L) enrolled between 1989 and 2017

- Mean age 36.7 years, 429 men, 517 women
- Mean ALT 24.6 U/l, mean HBV-DNA levels were 8.50 $\log_{10}$ IU/mL
- 476 (**50.3%**) patients **remained in IT** phase throughout the study period (**median: 63.6 months**).

- The cumulative **incidence** rate of **phase change** was **70.7%** at **10 years**
- The cumulative i**ncidence** of **HCC** was **1.7%** at **10 years**
- Multivariate analyses revealed that **HBV-DNA level >10^7 IU/mL** was associated independently with a **reduced risk of phase change** (hazard ratio [HR] = 0.734, *P* = 0.008), whereas a **high ALT level**, above 34 IU/L for men and 30 IU/L for women, was associated independently with a **greater risk of phase change** (HR = 1.885, *P* < 0.001).

The **criterion of HBV-DNA level > 10^7 IU/mL** may be useful to define **immune-tolerant phase**.
In addition, an **extremely low risk of HCC** development was observed in patients with **CHB in immune-tolerant phase.**

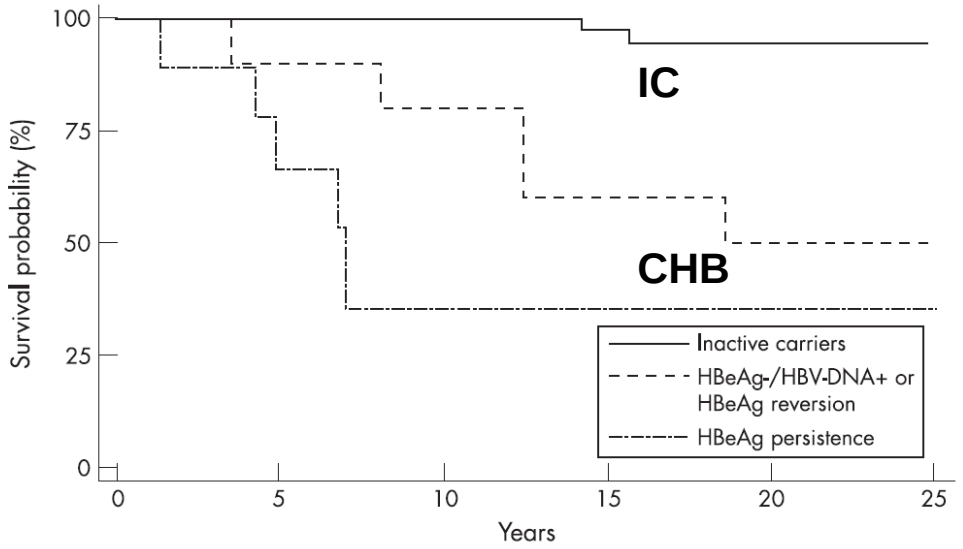
Lee HW et al, PP&T 2020

HBeAg negative infection: clinical outcome

Long-term outcome of chronic hepatitis B in Caucasian patients: mortality after 25 years.

Fattovich et al, Gut. 2008;57(1):84-90.

- 40 IC: 2 (5%) liver related death (HCC → 2 of 7 patients with cirrhosis at the time of HBeAg→ anti-HBs seroconversion**)**

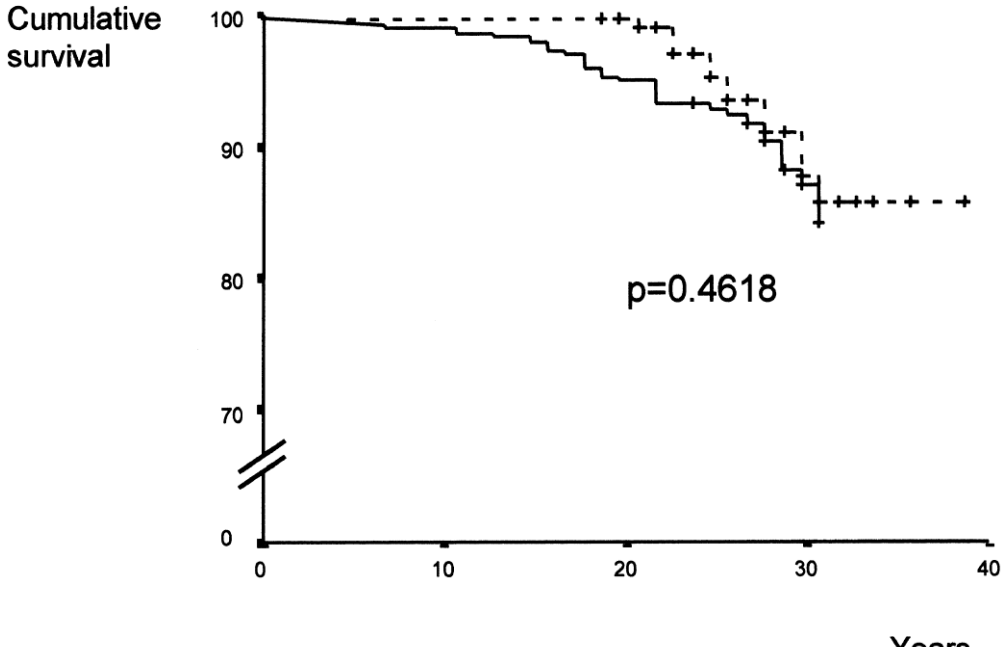


Patients at risk						
Inactive carriers	40	40	39	37	34	28
HBeAg-/HBV-DNA+ or HBeAg reversion	10	9	8	6	5	3
HBeAg persistence	9	6	6	6	2	1

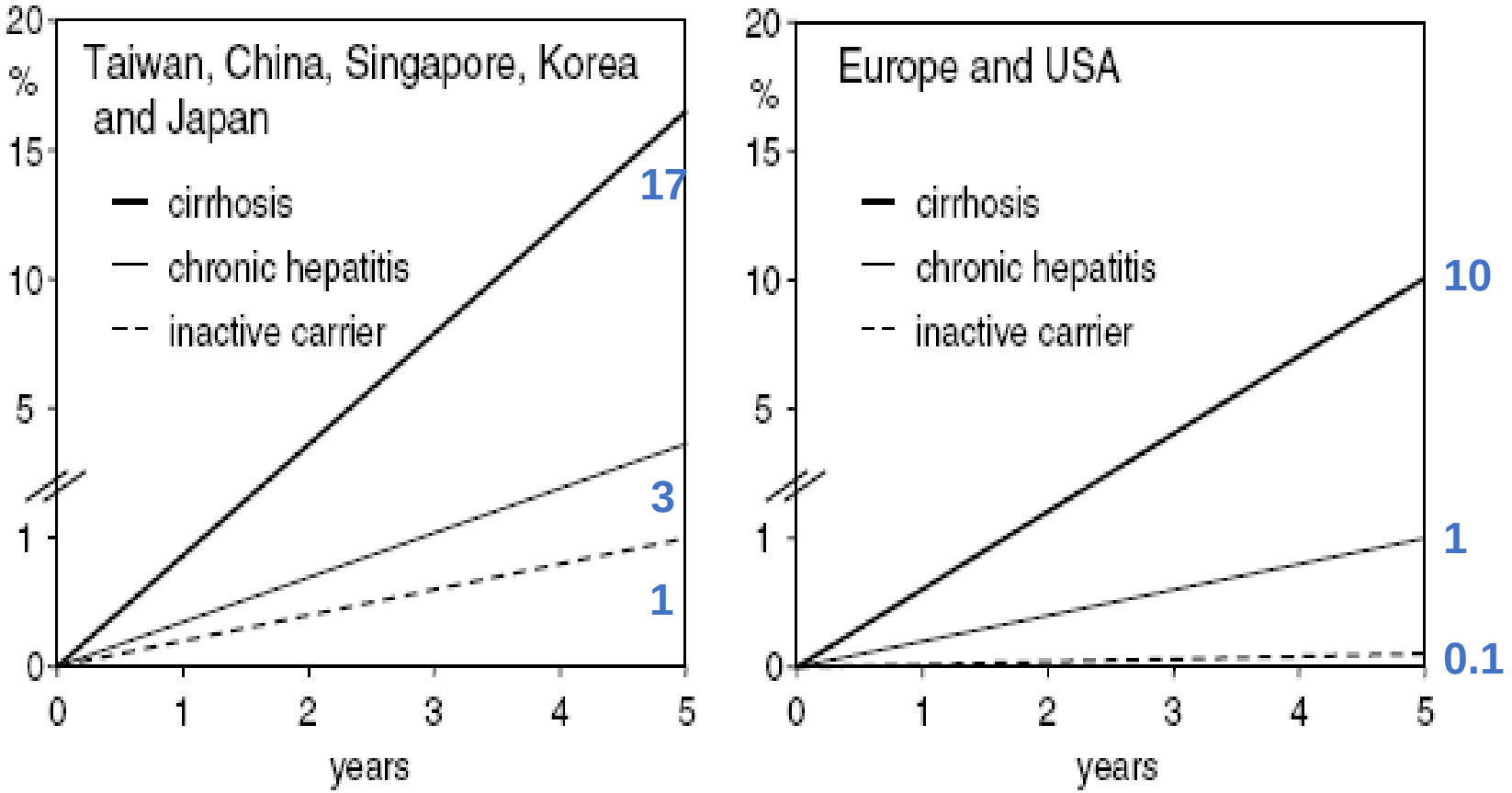
Natural history of chronic HBV carriers in northern Italy: Morbidity and mortality after 30 years

Manno et al, Gastroenterology 2004;127(3):756-763

- 296 blood donors excluded from donation because of serum HBsAg detection and 157 HBV-negative blood donors as control population.
- Liver related death in 3 HBsAg carriers (2 HCC, 1 Alcoholic cirrhosis) and 1 Control (HCC); high alcohol intake in all died patients.



Cumulative 5 year incidence of HCC in pts with CHB infection according to geografical area and clinical status

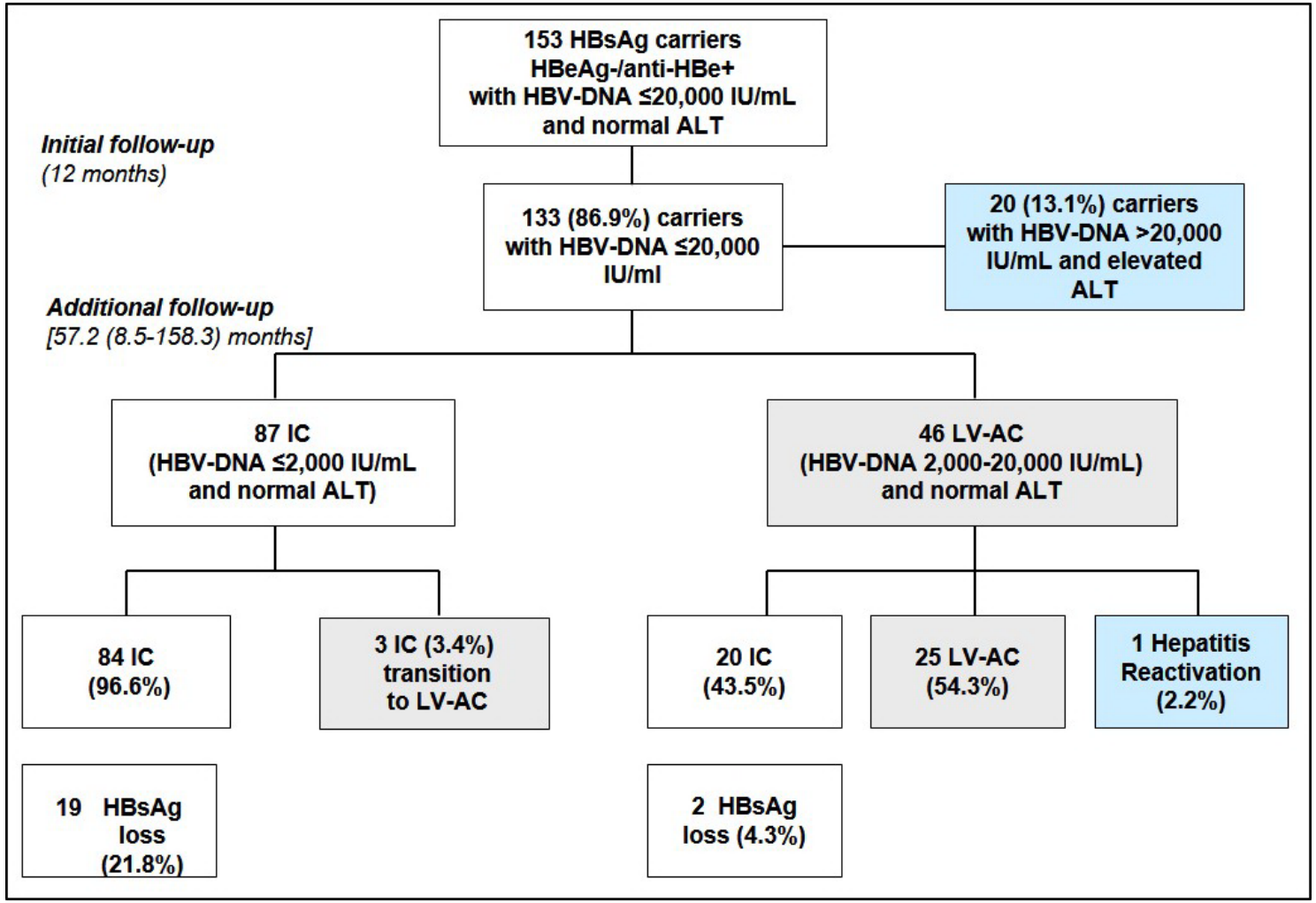


What about the influence of HBV genotype, mode of infection, environmental factor, accuracy in the stratification of the HBsAg carriers?

Fattovich G, J Hep 2008

Long-term outcome of inactive and active, low viraemic HBeAg-neg-Hepatitis B virus infection: Benign course towards HBsAg clearance

HBV infection outcome during the overall follow up of HBeAg-negative/HBsAg carriers with HBV-DNA ≤20 000 IU/mL and normal ALT at presentation



Oliveri F & Surace L etl, Liver Internl 2017

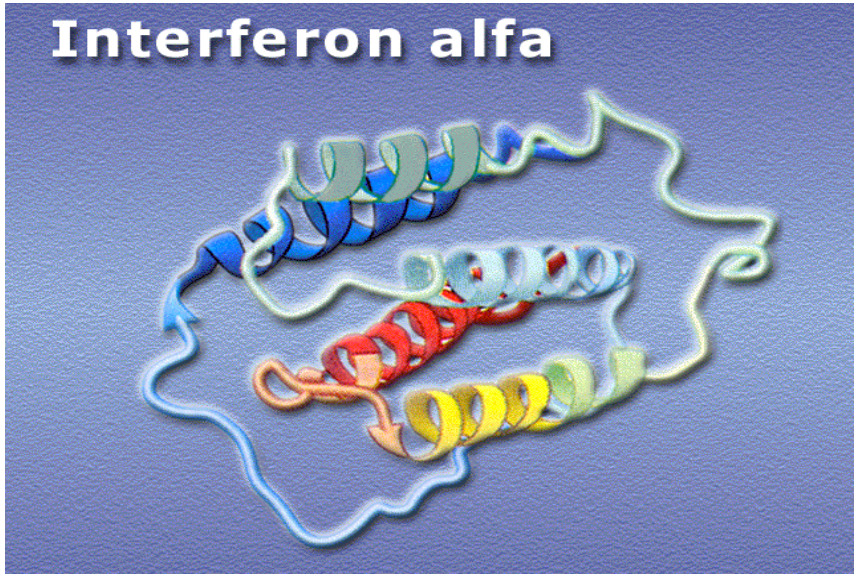
Virologic end points of antiviral therapy in CHB

Pharmacological suppression

HBeAg negative Infection

Functional cure

Clearance of the infection



Antiviral activity
Immunomodulatory activity
Antiproliferative activity

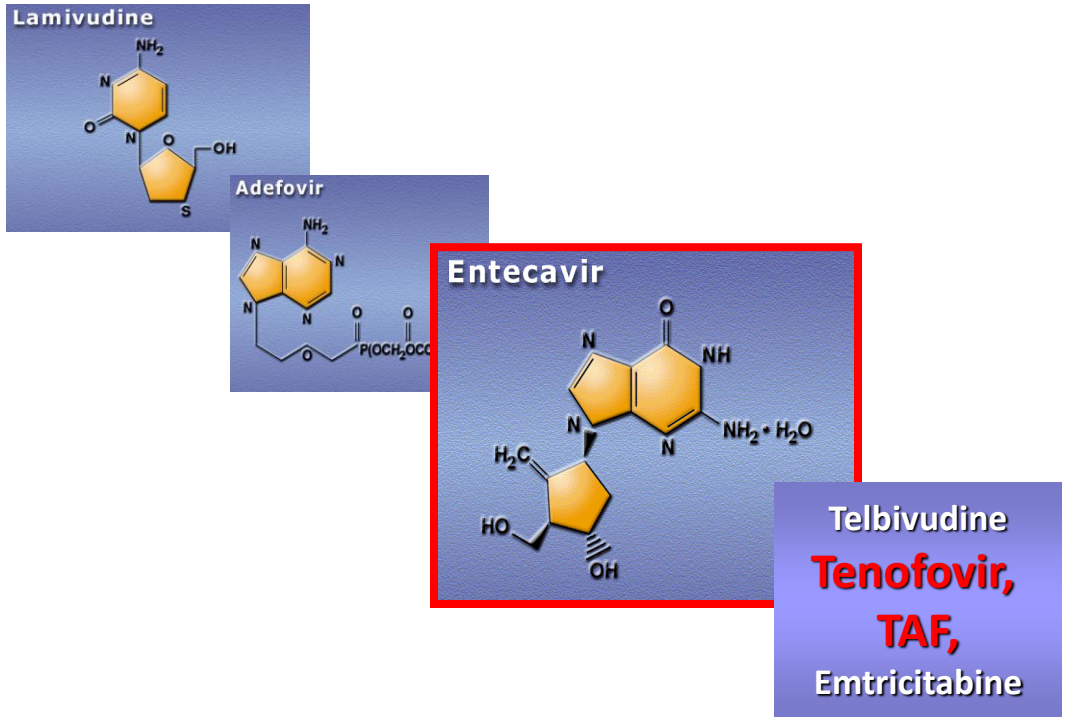
Peg-IFNα in CHB
180 µg/week sc for 1 year

Finite treatment

HBeAg pos. *CHB:* HBeAg/anti-HBe seroc. at 1 y post treatment **35-48%,** HBsAg loss 3-7% 6 months after EOT

HBeAg neg. *CHB:* HBV-DNA < 2000 IU/ml, n ALT at 5 y **25%**, **12%** HBsAg loss

Antiviral activity
competitive inhibition of the RT activity of HBV polymerase



ETV	TDF	TAF
0.5 mg/die	245 mg/die	25 mg/die

Long term treatment

- HBV-DNA undetectable after 3 y treatment in **>90%** of cases; HBeAg/anti-HBe seroc. **29-31%** after 3-4 y
- **HBsAg loss** in **3 to 10%** of **HBeAg positive** patients after 5 y treatment and **<1%/year** in **HBeAg negative** patients; 19.7% (0-39.4%) and 4.8% (0-19.6%) in HBeAg neg and positive CHB after NUC discontinuation

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection☆

Indications for treatment:Recommendations

- All patients with HBeAg-positive or -negative chronic hepatitis B, defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis, should be treated (Evidence level I, grade of recommendation 1).
- Patients with compensated or decompensated cirrhosis need treatment, with any detectable HBV DNA level and regardless of ALT levels (Evidence level I, grade of recommendation 1).
- Patients with HBV DNA >20,000 IU/ml and ALT >2xULN should start treatment regardless of the degree of fibrosis (Evidence level II-2, grade of recommendation 1).
- Patients with HBeAg-positive chronic HBV infection, defined by persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years regardless of the severity of liver histological lesions (Evidence level III, grade of recommendation 2).
- Patients with HBeAg-positive or HBeAg-negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations can be treated even if typical treatment indications are not fulfilled (Evidence level III, grade of recommendation 2).

Patients with **HBeAg-positive chronic HBV infection** who are **younger than 30 years and do not fulfill any of the above treatment indications should be followed at least every 3–6 months** (Evidence level II-2, grade of recommendation 1).

J Hepatol 2017;67:370–398

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

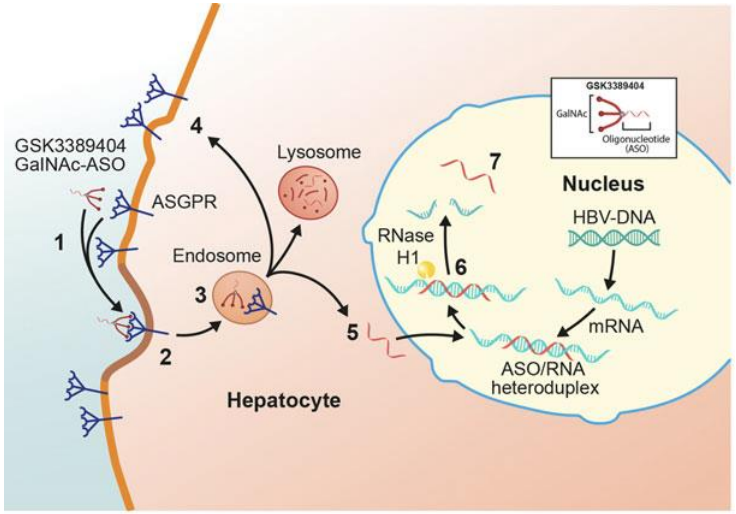
*«The preferred primary endpoint for phase II/III trials evaluating finite treatments for chronic hepatitis B (CHB) is a **"functional" cure**, defined as **sustained HBsAg loss** and **HBV DNA less than the lower limit of quantitation** (LLOQ) **24 weeks off-treatment**»*

Why to move from virological suppression to HBV functional cure?

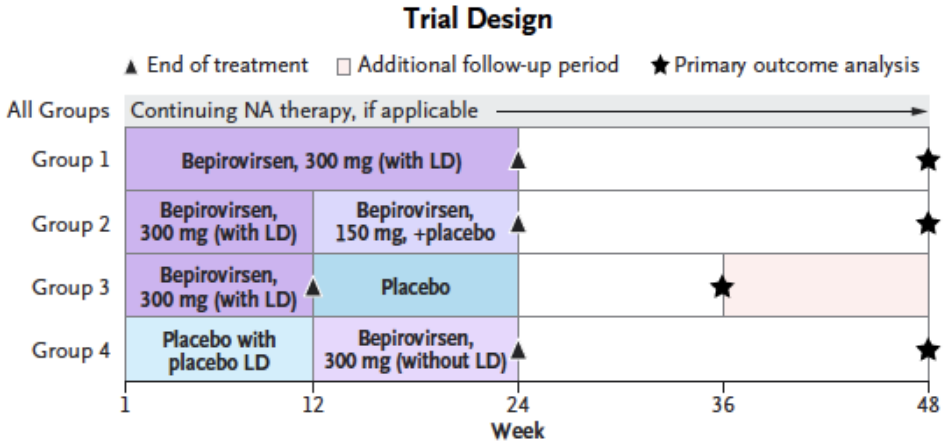
- ✓ HBsAg loss implies a profound suppression of HBV replication and integrated viral genomes
- ✓ HBsAg loss is considered to be the most relevant surrogate end point because it is associated with sustained off-treatment improvement of clinical outcomes Lok AS et al Hepatology 2017
- ✓ HBsAg loss has been shown to have an additional clinical benefit (lower rates of HCC and hepatic decompensation) over HBV DNA suppression alone, particularly in patients with cirrhosis Yip TC ET AL J Hep 2019 and J Hep 2023
- ✓ HBsAg seroclearance is easy to measure with standardized and widely available assays
- ✓ HBsAg seroclearance is associated with removal of the stigma

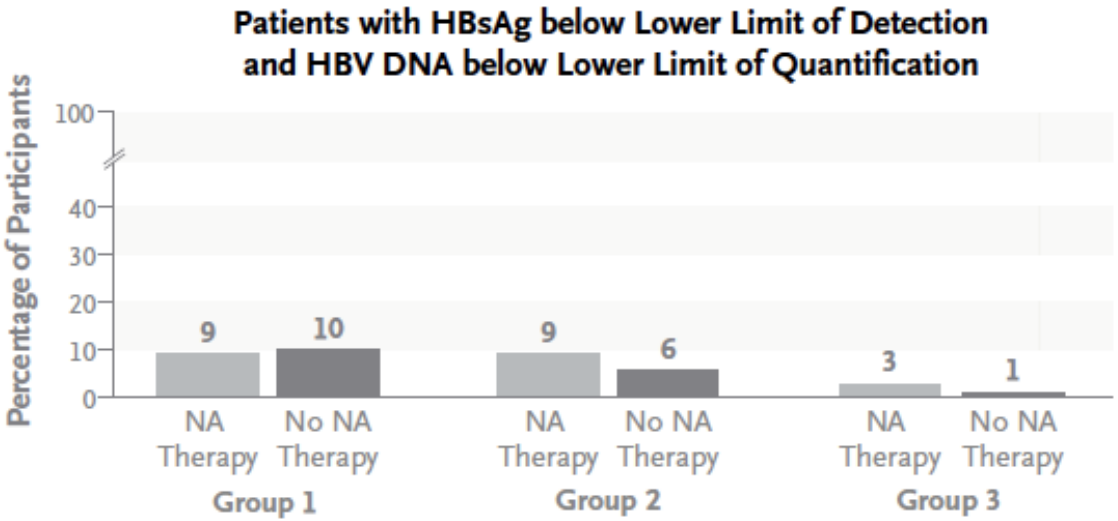
Ghany MG et al Hepatology 2023

Efficacy and safety of Bepirovirsen in CHB



- Antisense oligonucleotide targeting all HBV mRNA and pregenomic RNA
- It is conjugated with N-Acetil galactosamine, therefore binds to Asialoglycoprotein receptor
- Possible immunostimulatory activity through TLR-8

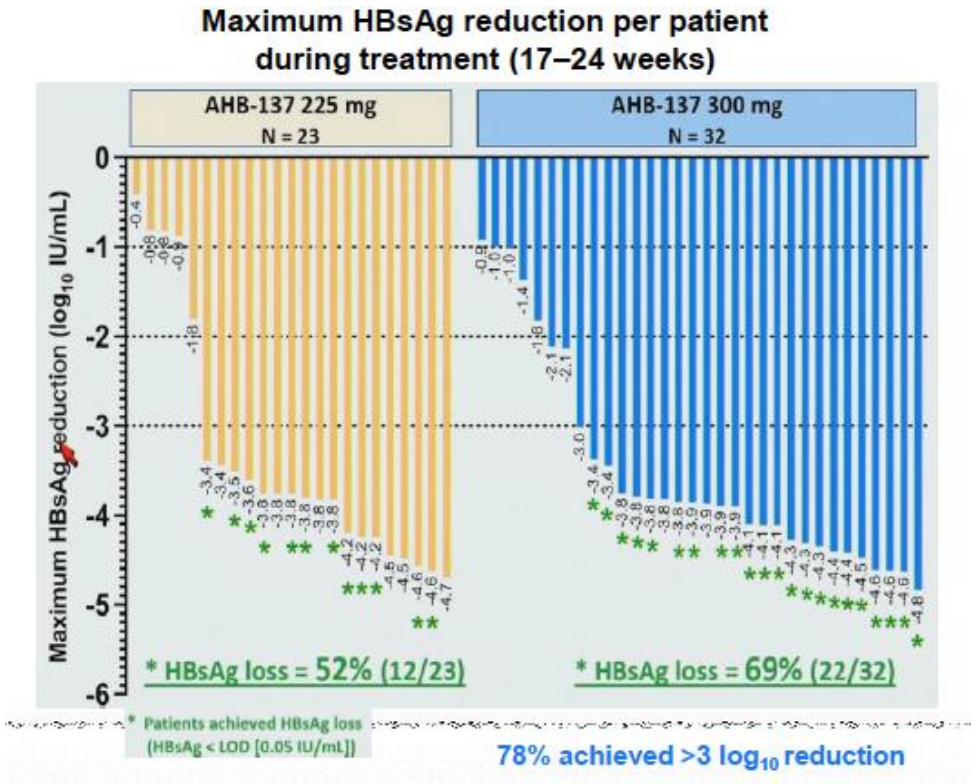




- ✓ 70% of the patients were HBeAg negative
- ✓ The **rate of HBsAg loss** was influenced by baseline HBsAg: **20% among pts with BL HBsAg levels < 3 log** vs 6% among those with levels > 3 log
- ✓ HBsAg BL levels of **3000 IU/ml** could be a predictor of response

Han K et al Clin Pharm Drug Deveolp 2019; Yuen M-F, NEJM 2022

AHB-137 (ASO) Phase 2-a open label trial in HBeAg neg CHB on NUC

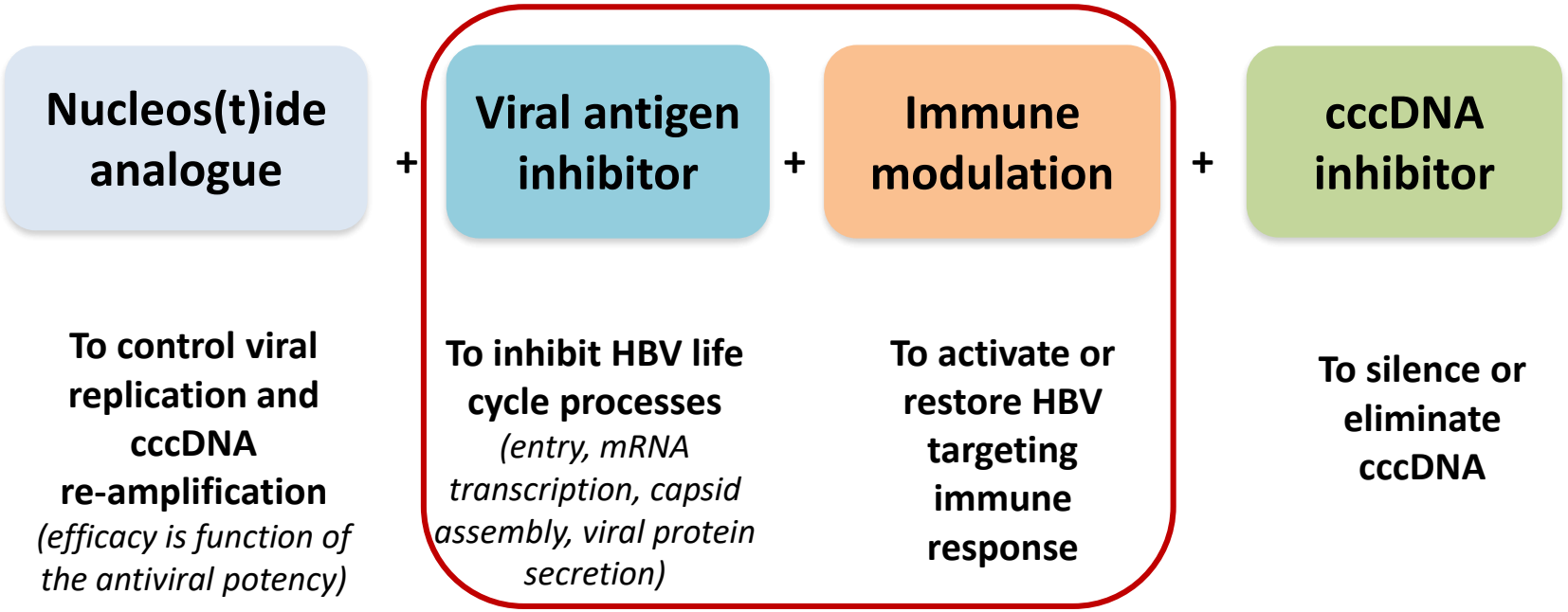


HBsAg reduction	225 mg	300 mg
≥ 1 $\log_{10}$	83%	94%
≥ 3 $\log_{10}$	78%	78%
HBsAg loss	52%	69%

- ✓ 78% of the patients achieved > 3 log HBsAg decline during 17-24 weeks of treatment
- ✓ HBsAg loss occurred in the majority of cases within 8-12 weeks
- ✓ 45% of the patients developed anti-HBs by 24 weeks in the 300 mg group

Ding Y et al, AASLD 2024

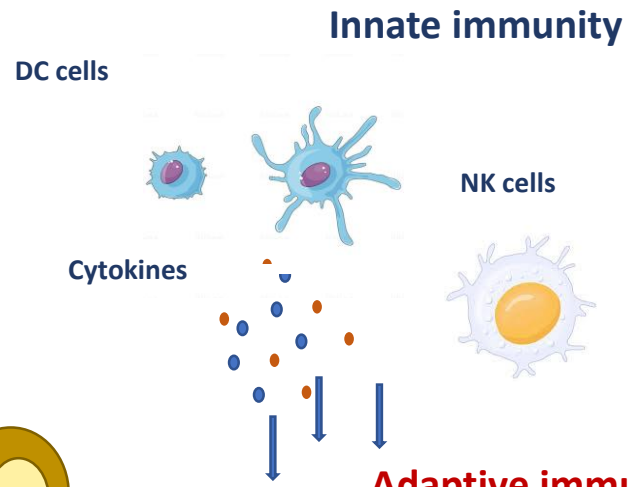
Treatment combination to cure HBV infection and disease



Functional cure

Modified from Seto WK And Yuen MF. Clinical Liver Disease 2016;8,4, 83-88

To restore a competent Immune response



GenHevac-B, Engerix-B, NASVAC
HB-110, JNJ-64300535, TG1040
VRON-0200, VBI-2601
VTP-300 (ChAdOx-HBV)
AIC649

Therapeutic vaccines

Metabolic regulation

IDO1
Arginase

Check point inhibitors

Anti-PD1 (Nivolumab, Cemiplimab)
Anti-PD-L1 (ASC22)
PDL1-LNA

ImmTAV molecules

- Immune mobilizing monoclonal T Cell receptors against virus molecules represent a therapeutic strategy combining an affinity-enhanced T Cell receptor with an anti-CD3 T Cell-activating moiety.
- The bispecific fusion protein redirects T cells to specifically lyse infected cells expressing the target virus-derived peptides presented by human leukocyte antigen (HLA).

Monoclonal antibodies

Anti-HBs
VIR-3434
GC1102

Tipping points:

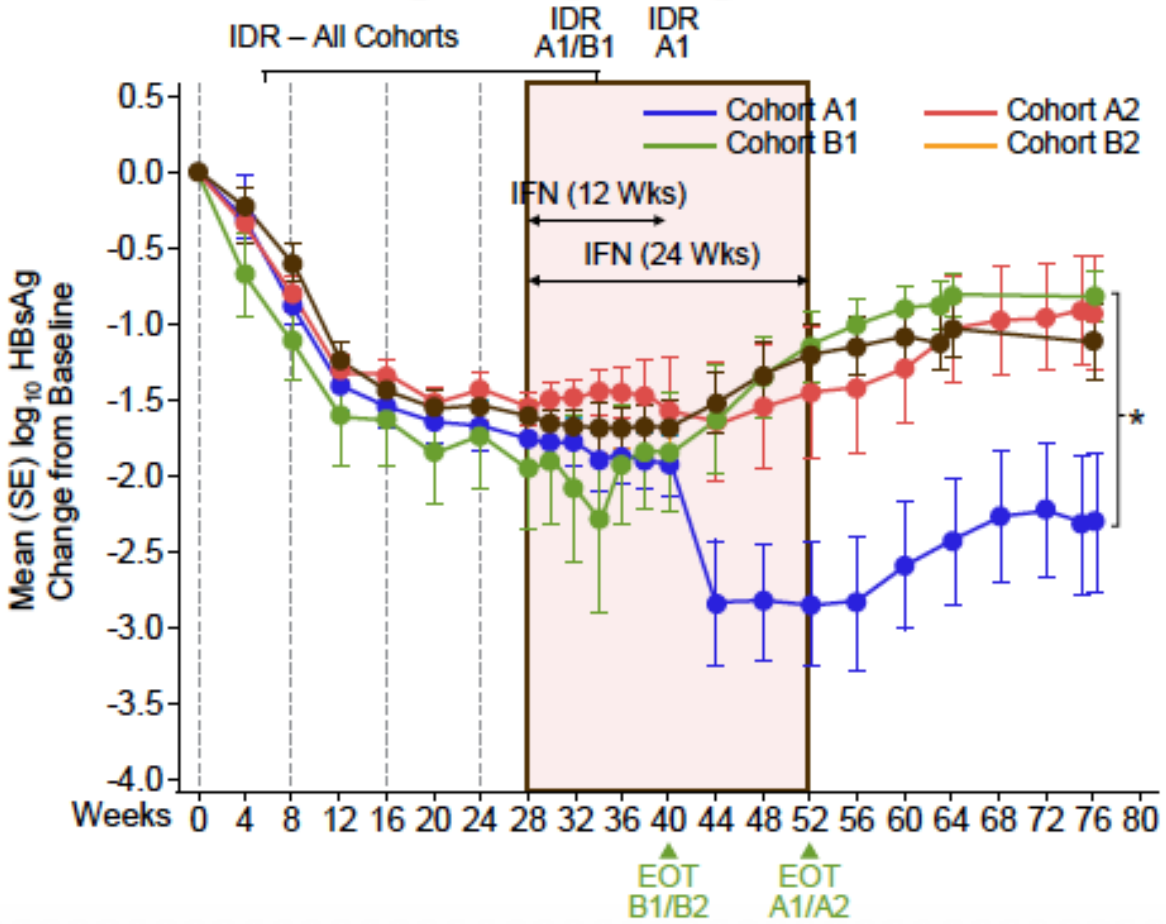
- To avoid unspecific boosting of innate immunity
- To tailor the HBV specific immunity limiting the killing of infected hepatocytes
- To define the right timing for the treatment (combination or sequential treatment?)
- One fits all approch is unlikely

Fergusson JR et al Hepatology 20202; Lim SG et al Nature Reviews Gastro&Hep 2023

IMPROVE-I study
Imdusiran (siRNA AB-729) in combination with pegIFN-alfa-2a in NUC suppressed HBeAg-negative CHB

IHEP HBV

Mean Log HBsAg Change from Baseline



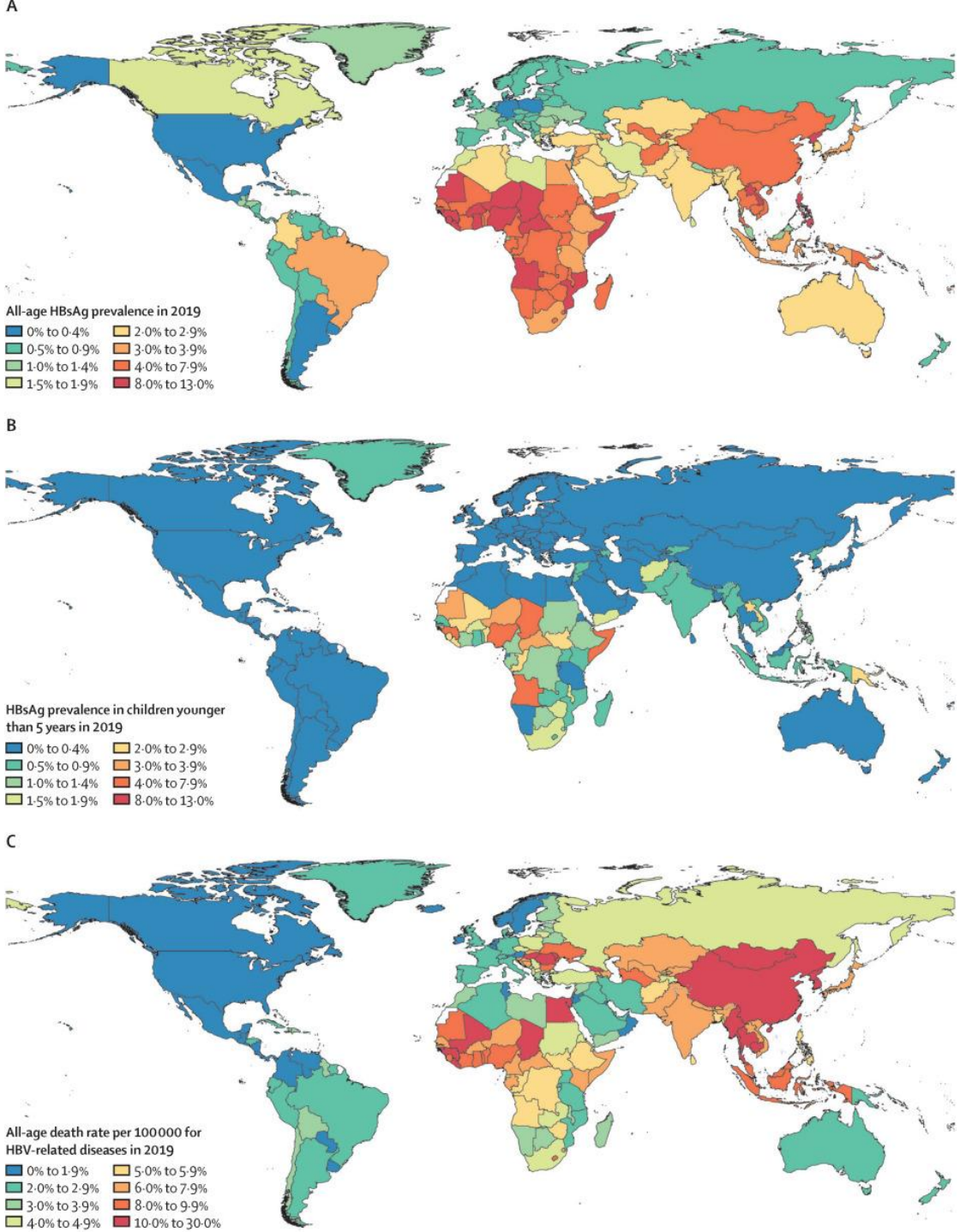
Rate of HBsAg loss at defined timepoints

	Cohort A1: IDR x 6 + NUC + IFN x 24W (n=12)	Cohort A2: IDR x 4 + NUC + IFN x 24W (n=13)	Cohort B1: IDR x 5 + NUC + IFN x 12W (n=8)	Cohort B2: IDR x 4 + NUC + IFN x 12W (n=10)
Any time	6 (50)	3 (23)	2 (25)	0
EOT <0.05	4 (33)	3 (23)	0	0
EOT <0.005	4 (33)	2 (15)	0	0
EOFU <0.05	4 (33)	2 (15)	0	0
EOFU <0.005	2 (17)	2 (15)	0	0
Discontinuation	9 (75)	3 (23)	4 (50)	5 (50)
Data are n (%)				

- Higher rates of HBsAg loss with 24 wks IFN vs 12 wks IFN
- Sustained HBsAg loss associated with anti-HBs (40–1000)
- **Sustained HBsAg loss only if baseline HBsAg <1000 IU/mL**

Sequential siRNA and pegIFN (12-24 wk) in NUC suppressed

Yuen MF, EASL2024



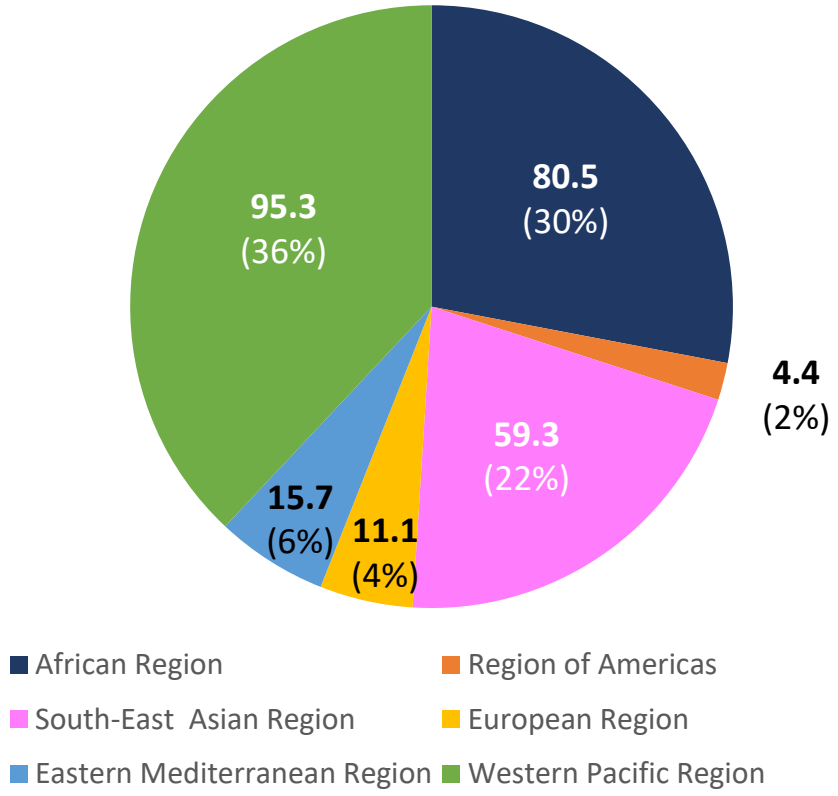
Global, regional, and national burden of hepatitis B, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019

- ✓ The prevalence of chronic HBV infection declined over time, particularly in children younger than 5 years, since the introduction of hepatitis B vaccination.
- ✓HBV-related death rates also decreased, but HBV-related death counts increased as a result of population growth, ageing, and cohort effects.
- ✓By 2019, many countries had met the interim seroprevalence target for children younger than 5 years, but **few countries** had **met** the **WHO-GHSS** interim targets for **deaths** and **new cases.**
- ✓Progress according to all indicators must be accelerated to meet 2030 targets, and there are **marked disparities in burden and progress across the world**. HBV interventions, such as **vaccination, testing, and treatment, must be strategically supported and scaled up to achieve elimination.**

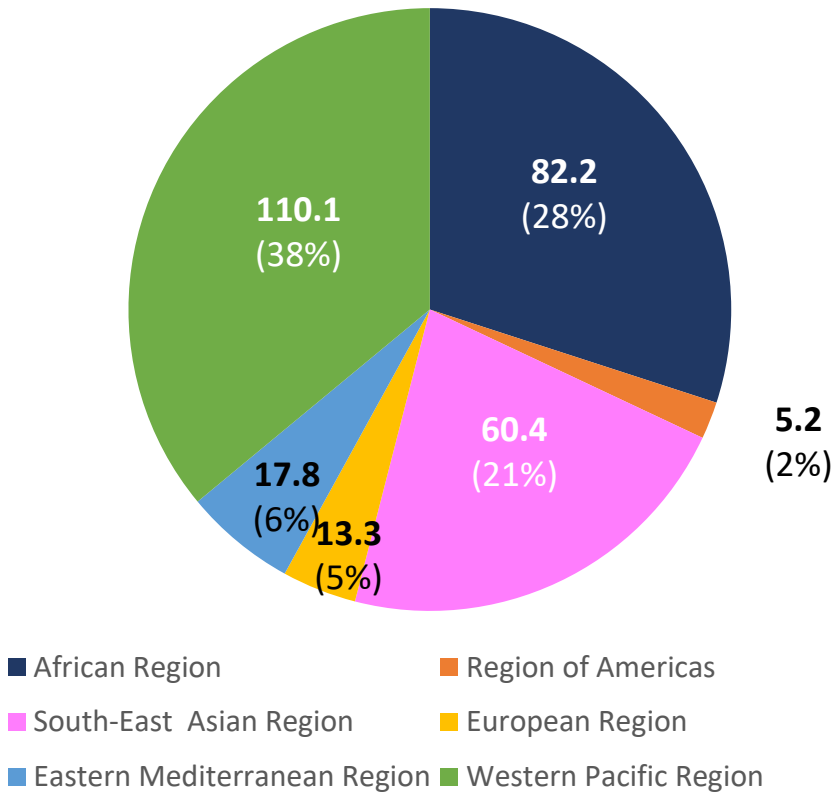
GBD 2019 Hepatitis B Collaborators* , Lancet Gastro&Hep2022

Distribution of people living with hepatitis B who are undiagnosed and untreated by WHO region

Proportion and number (in millions) of people living with hepatitis B who are undiagnosed, by WHO region

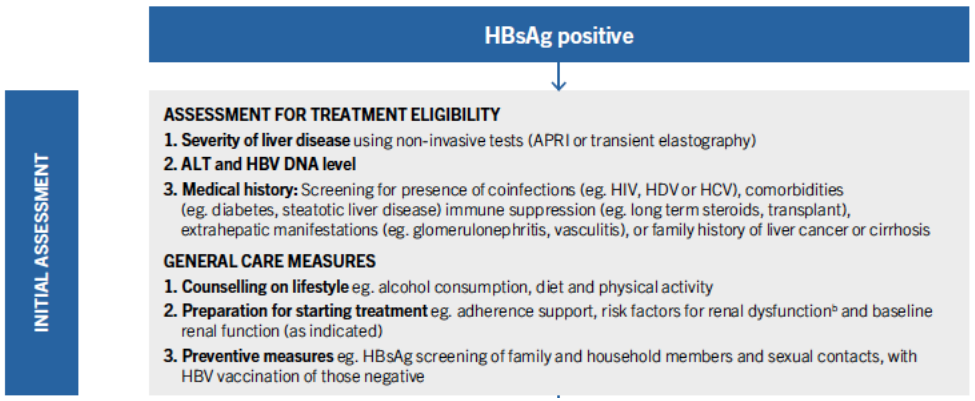


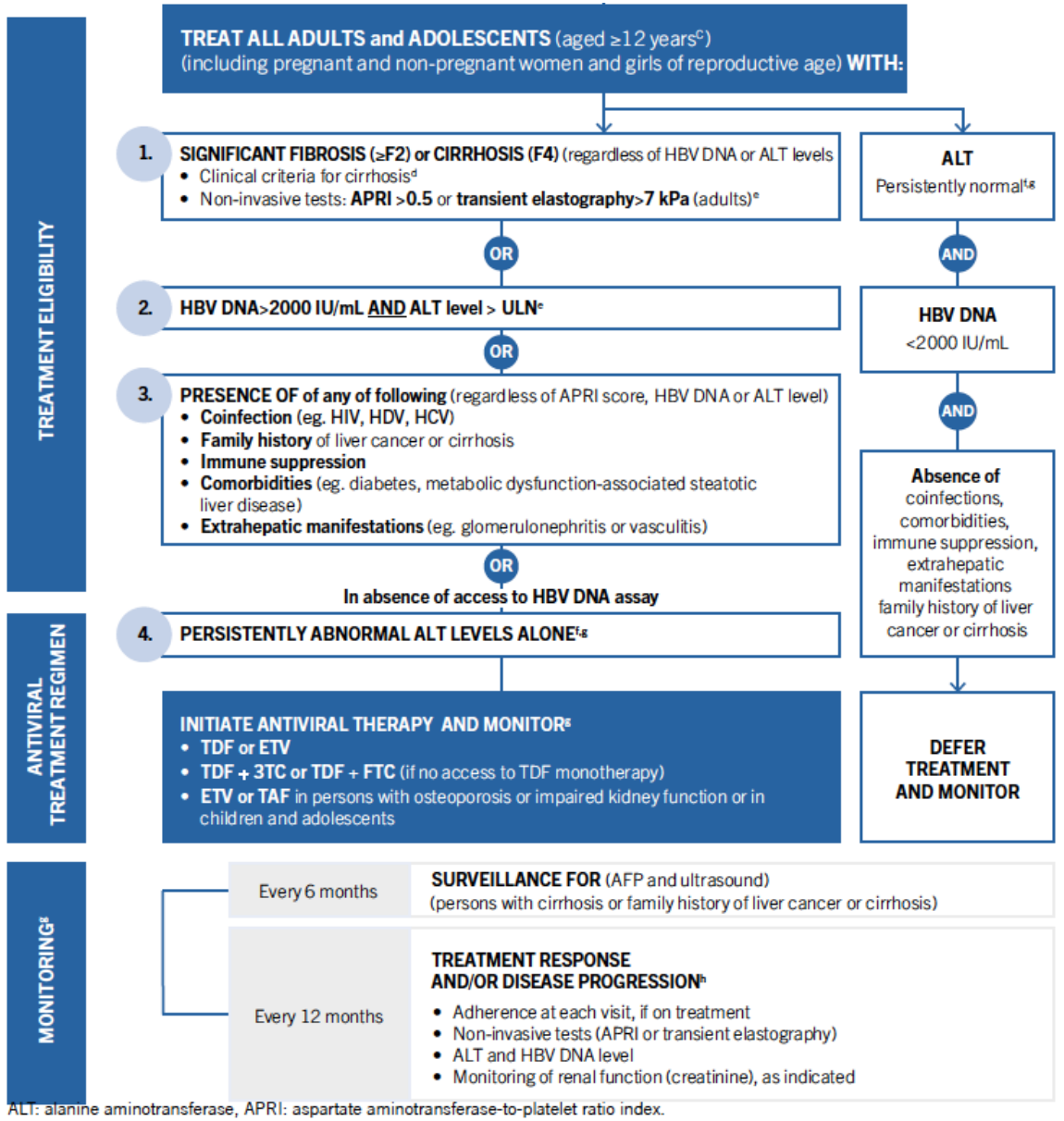
Proportion and number (in millions) of people living with hepatitis B who are untreated, by WHO region



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

- The objective of the 2024 guidelines is to provide expanded and **simplified treatment criteria** for adults but now also for adolescents; **expanded eligibility for antiviral prophylaxis for pregnant women to prevent mother-to-child transmission of HBV**…..
- The guidelines are addressed primarily to **clinicians** as well as **national hepatitis programme managers** …, especially in **low- and middle-income countries**….. Their Implementation should be informed by **local context**, including hepatitis B epidemiology and prevalence of other comorbidities, availability of resources, the organization and capacity of the health system and anticipated cost–effectiveness.





ALT: alanine aminotransferase, APRI: aspartate aminotransferase-to-platelet ratio index.

WHO, March 2024

Extensor of the Guidelines
(WHO; International/Regional Scientific Association)

Aims of the Guidelines

Socio-economical conditions

Health care system

Sustainability for the health care system of the diagnostic flow

Sustainability for the health care system of the treatment

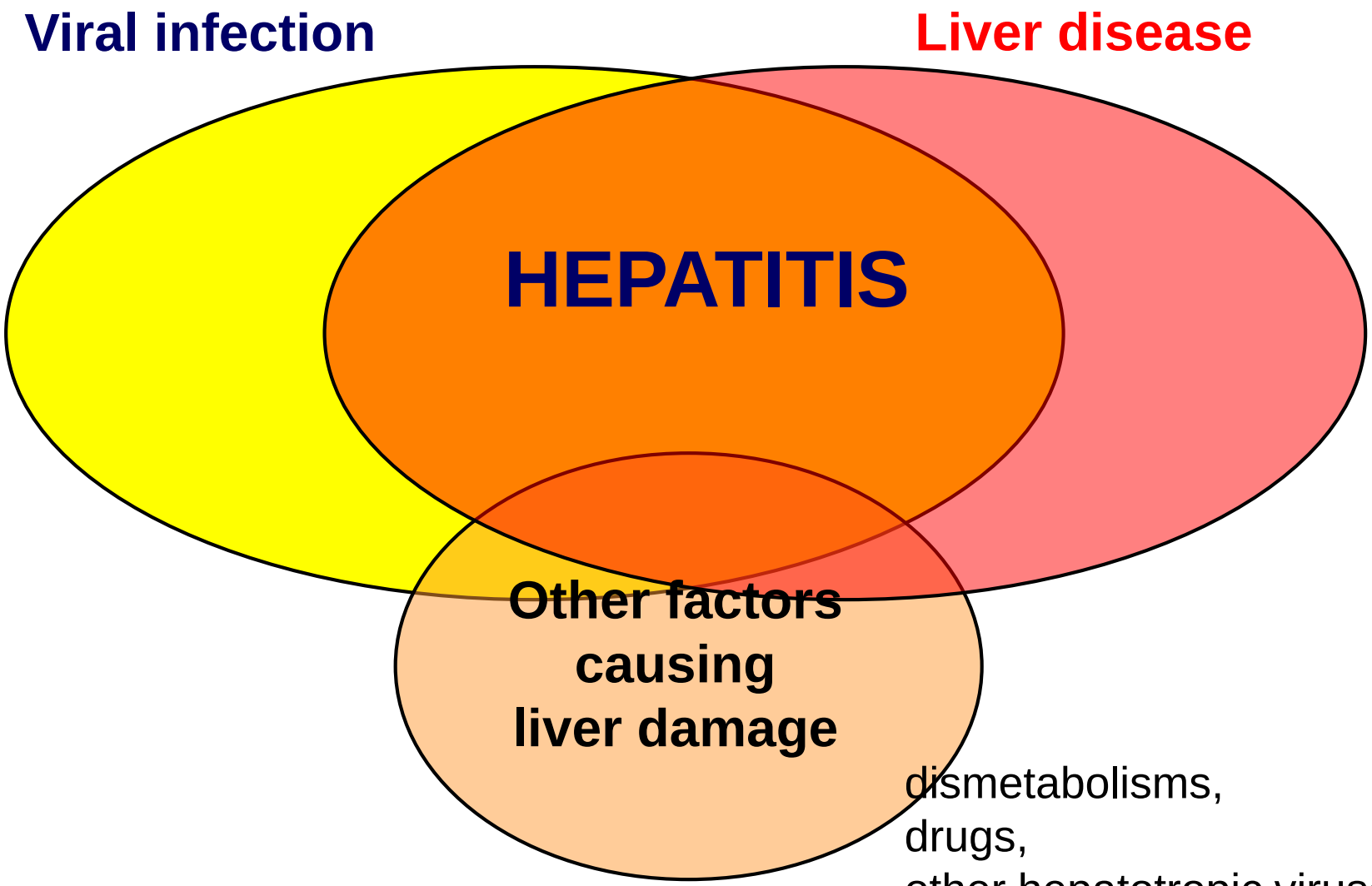
Cost for the health care system of disease complications

Epidemiology (infection/disease)

Natural History (infection/disease)

Impact of the intervention on mortality/morbidity

Identification of virus induced liver disease



Precision medicine: what is it?

The goal of precision medicine is to target the right treatment(s) to the right patient at the right time, by taking into account differences in their individual disease, general health, genes, environment, and lifestyle.

Current Medicine

One Treatment Fits All

Cancer patients with eg. colon cancer

Therapy

Future Medicine

More Personalised Diagnostics

Cancer patients with eg. colon cancer

Blood, DNA, Urine and Tissue Analysis

Therapy tailored to different cancer profiles

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Clinical Practice Guidelines

EASL JOURNAL OF HEPATOLOGY

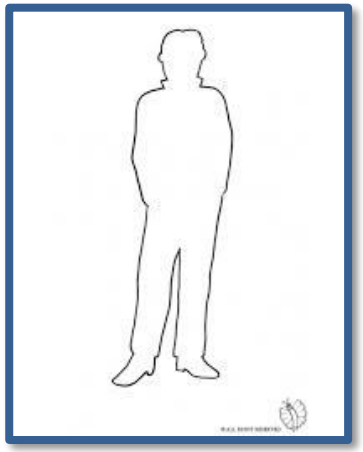
EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection☆

European Association for the Study of the Liver*

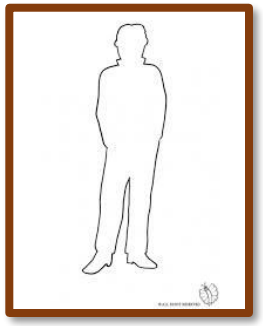
- The objective of this manuscript is **to update the recommendations for the optimal management of HBV infection**.
- In order to keep the manuscript and particularly the reference list within a reasonable length, only references published after 2012 have been considered**, since the readers can find the older supportive references in the 2012 EASL HBV CPGs**.
- **The CPGs do not fully address prevention including vaccination**.
- In addition, despite increasing knowledge, areas of uncertainty still exist and therefore clinicians, patients and public health authorities must **continue to make choices based on the evolving evidence**

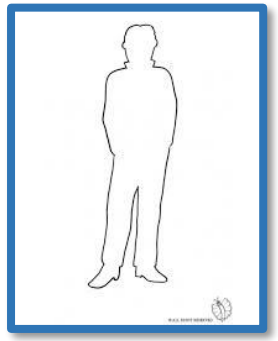
HBV infection in Humans

Infection with early spontaneous HBsAg clearance



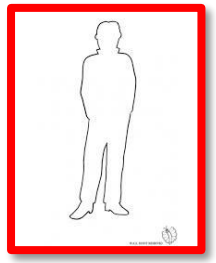
Infection and progression to chronicity





Immune control of the HBV chronic infection *(anti-HBe positivity and HBV-DNA persistently < 2000 IU/ml)*

HBeAg negative Infection (60%)



Persistence of HBV replication and liver disease

Chronic hepatitis B

316 million people with chronic HBV infection (Lancet GE 2022)