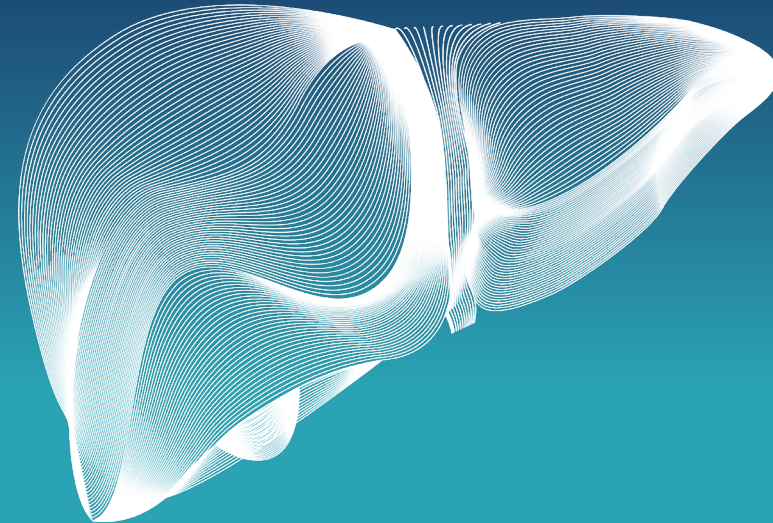
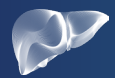


Professor Patrick Kennedy,
Professor of Translational Hepatology

*Barts Liver Centre, Immunobiology, Blizard Institute,
Barts and The London SMD,
Queen Mary University of London, UK*

What's next in hepatitis B: New Therapies, Smarter Pathways, Better Access





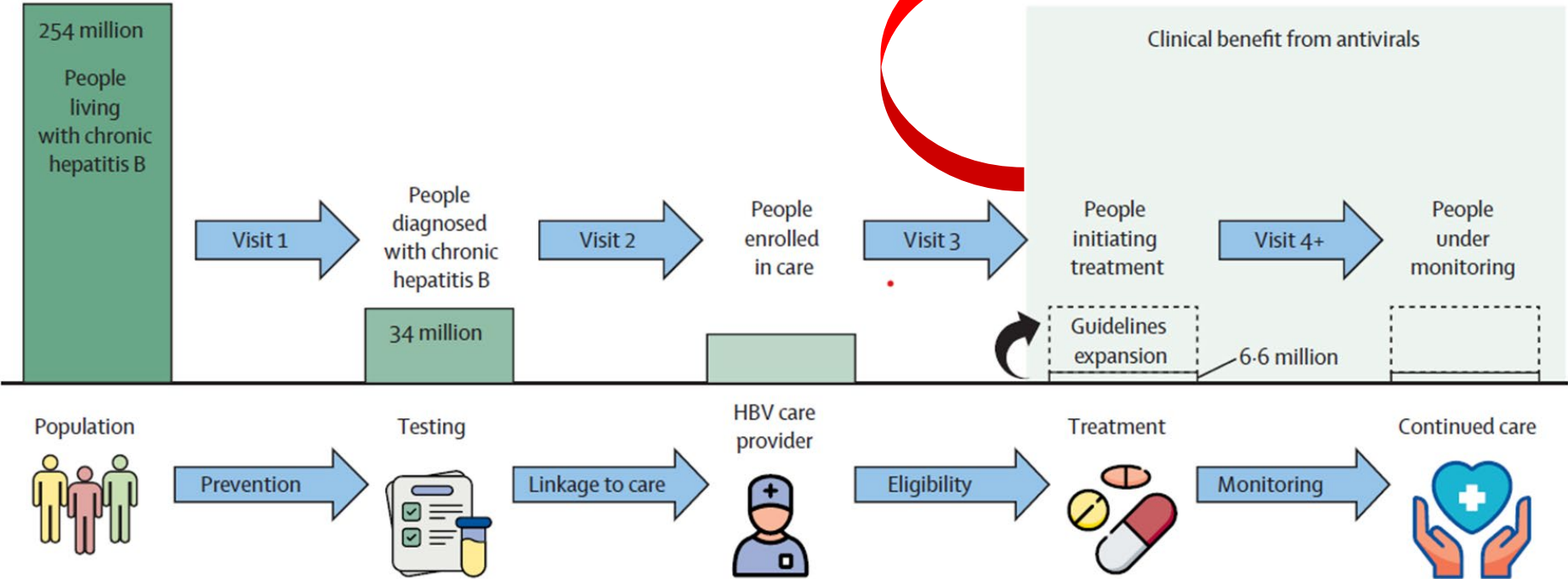
Chronic hepatitis B: The scale of the challenge

Number of global deaths and years of life lost (YLLs) in GBD 2016, and in the 2040 forecast

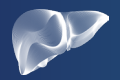
	YLLs (thousands)				Deaths (thousands)			
	2016	2040 forecast	2040 better health scenario	2040 worse health scenario	2016	2040 forecast	2040 better health scenario	2040 worse health scenario
All causes	1585 864-98 (1559 572-96- 1613 799-53)	1529 212-73 (1 315 165-66- 1 744 642-71)	1 188 899-29 (1 021 216-03- 1 357 596-47)	2 170 421-82 (1 858 433-76- 2 480 811-12)	54 698-58 (54 028-68- 55 514-89)	75 263-26 (67 310-21- 83 866-49)	62 570-88 (55 675-51- 70 026-74)	96 717-00 (86 181-44- 107 125-85)
Cirrhosis and other chronic liver diseases	37 283-07 (35 413-31- 41 442-98)	48 324-15 (43 655-69- 54 757-85)	44 158-29 (39 536-81- 50 452-38)	53 144-00 (48 394-75- 60 100-36)	1 256-85 (1 197-09- 1 376-86)	1 903-64 (1 760-57- 2 097-77)	1 787-20 (1 637-35- 1 979-96)	2 014-49 (1 881-85- 2 228-68)
Cirrhosis and other chronic liver diseases due to hepatitis B	10 846-50 (9 787-89- 12 777-41)	14 880-49 (12 899-14- 17 732-38)	14 308-72 (12 368-22- 16 964-03)	15 697-63 (13 716-23- 18 707-04)	365-57 (330-81-422-57)	582-17 (514-27-683-44)	572-65 (502-98-670-06)	593-64 (530-13-690-12)
Liver cancer	20 915-71 (20 029-12- 21 730-96)	35 487-07 (27 243-22- 49 706-06)	32 930-35 (26 712-73- 43 698-83)	37 729-38 (28 311-22- 55 428-12)	828-94 (796-16-857-96)	1 679-63 (1 311-17-2297-91)	1 602-50 (1 328-19- 2 098-20)	1 720-16 (1 315-30- 2 493-46)
Liver cancer due to hepatitis B	9 704-02 (8 495-14- 10 846-75)	15 984-92 (11 742-51- 22 690-54)	15 042-06 (11 701-98- 20 344-07)	16 334-40 (11 643-45- 24 443-45)	349-53 (301-96-391-78)	702-26 (515-29-983-42)	678-35 (529-85-899-84)	688-77 (498-29- 1 007-57)

Foreman et al., The Lancet 2018

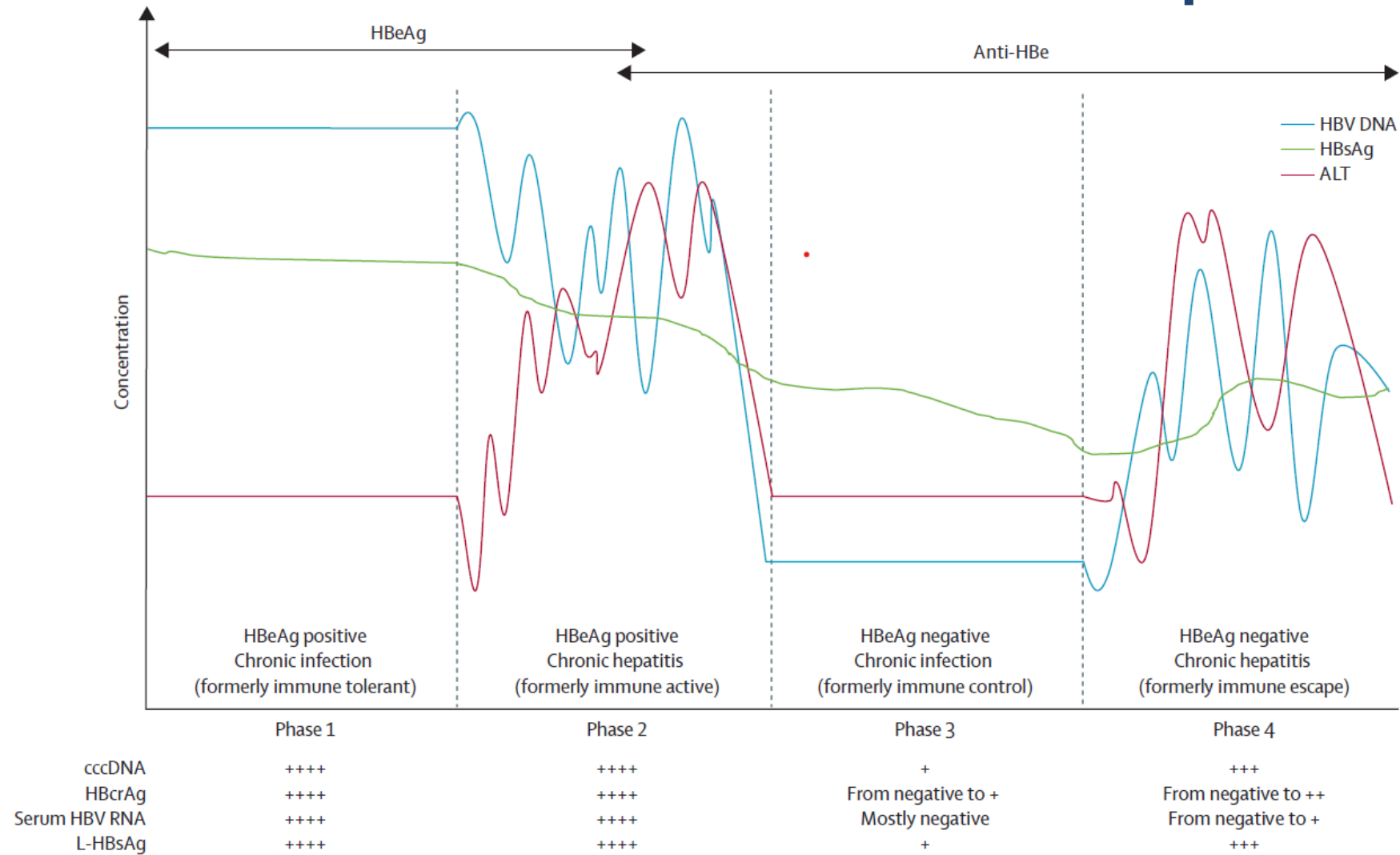
*Approximate numbers of people are shown at key steps.
Guidelines expansion refers to the existing treatment guidelines



Kennedy PT, et al., Lancet Gastro Hep 2025

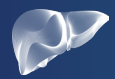


The Four Disease Phases of Chronic Hepatitis B

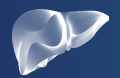


ALT = alanine aminotransferase. cccDNA = covalently closed circular DNA. HBcrAg = HBV core-related antigen.
HBV = hepatitis B virus. L-HBsAg = large HBsAg

Kennedy PT, et al., Lancet Gastro Hep 2025



HEPATITIS B VIRUS: AN ONCOGENIC VIRUS

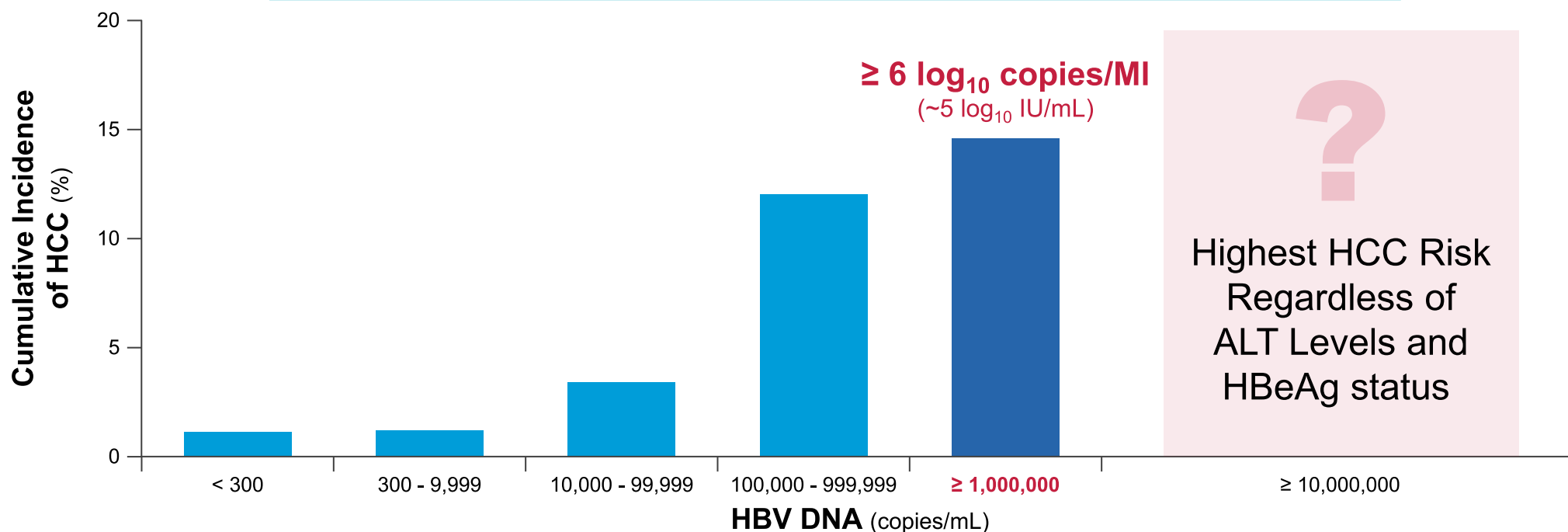


Association between Viral Load and HCC Risk in CHB

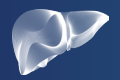
REVEAL-HBV Study

- 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**

Cumulative Incidence of HCC by HBV DNA Level at Study Entry

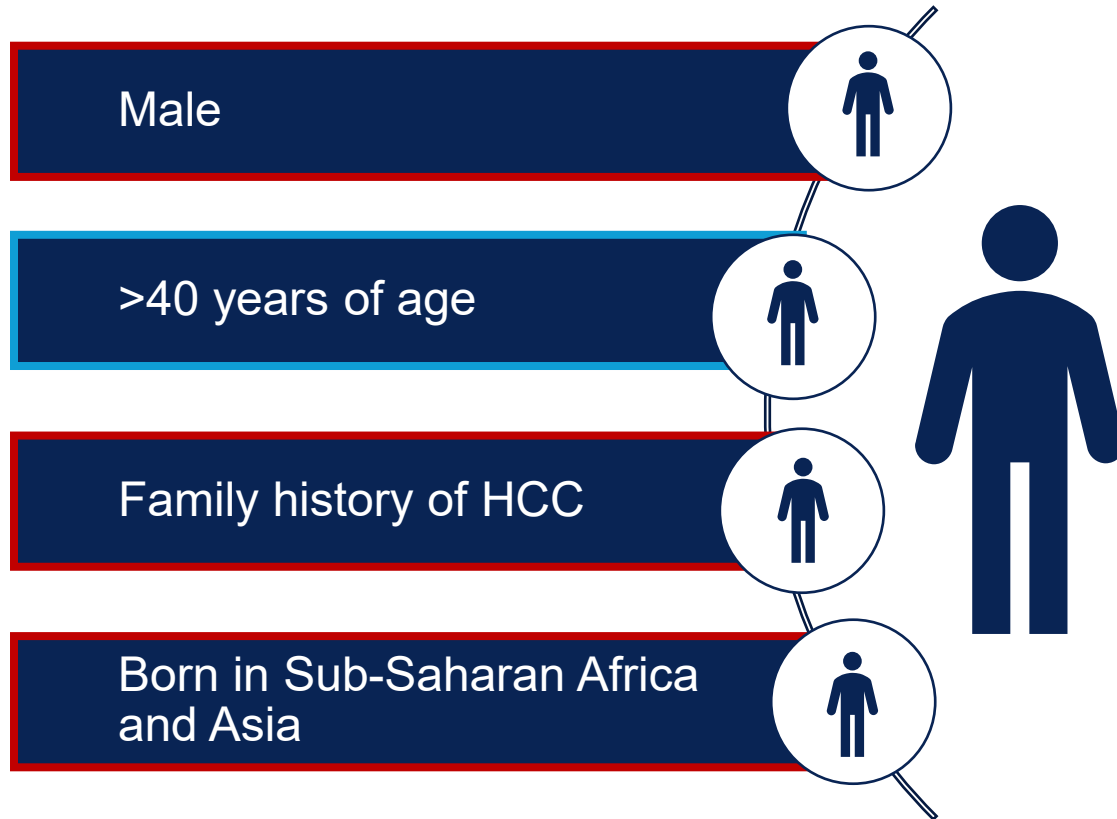


Chen CJ *et al.* JAMA 2006;295:65–73

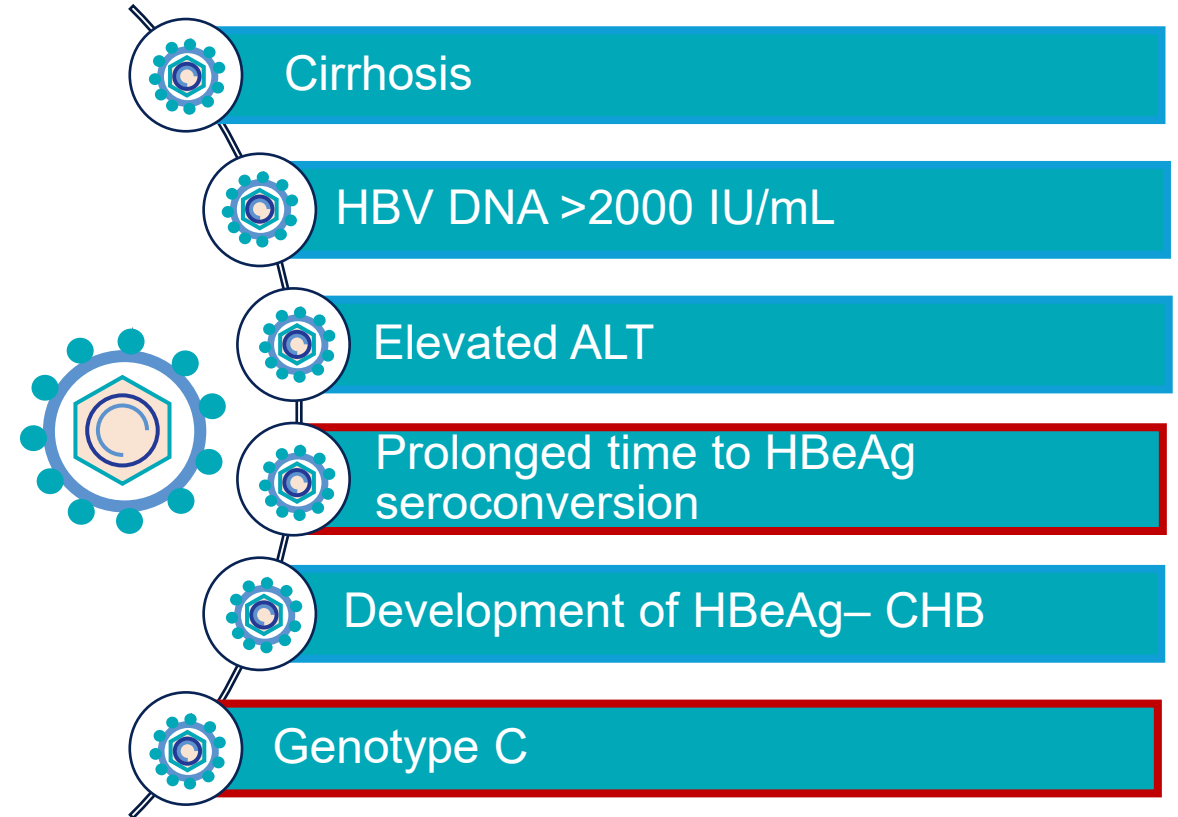


UNTREATED CHB AND HCC RISK

Host factors



Viral and disease factors

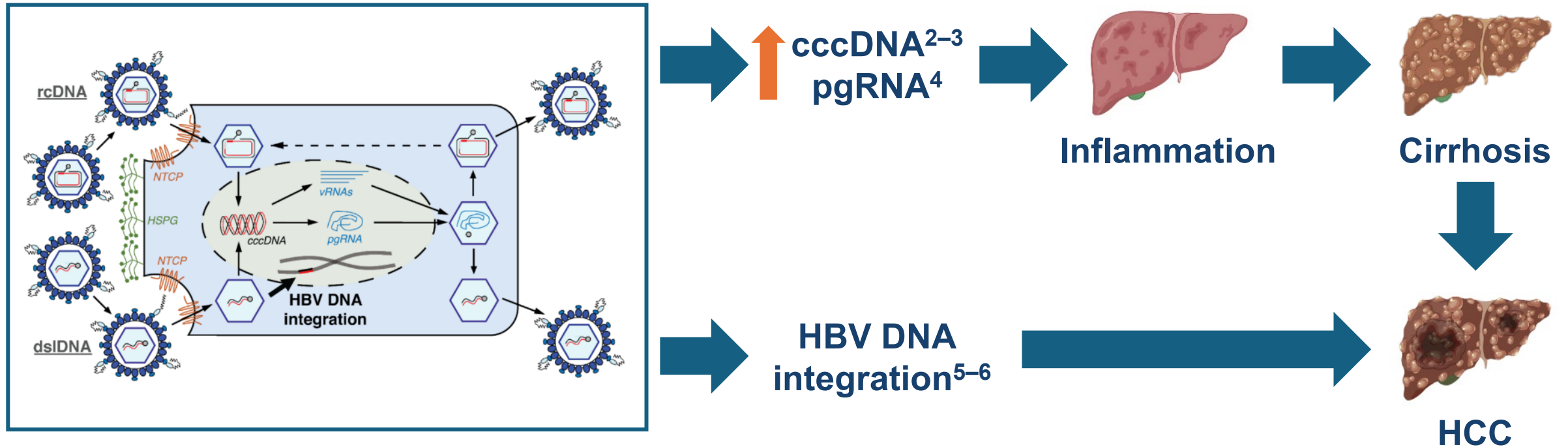


□ Modifiable factors □ Non-modifiable factors

- Chen CJ, et al. JAMA 2006;295:65–73; Iloeje UH, et al. Gastroenterology 2006;130:678–86; Wong G, J Hepatol 2018;69:793–802; Tong M, et al. Aliment Pharmacol Ther 2018;47:1181–200; Yip CF, APASL 2018; Oral YIA-C-05; Terrault NA, et al. Hepatology 2018;67:1560–99; Yu MW, et al. J Natl Cancer Inst 2005;97:265–72; Yang HI, et al. NEJM 2002;347:168–74.

- ALT: alanine aminotransferase; CHB: chronic hepatitis B;
- HBeAg: hepatitis B ‘e’ antigen; HCC: hepatocellular carcinoma.

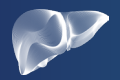
HBV integration plays a key role in HBV-related hepatocarcinogenesis



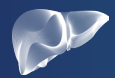
Intrahepatic HBV transcriptional activity is associated with liver inflammation and disease progression and HBV DNA integration further contributes to hepatocarcinogenesis²⁻⁶

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.

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

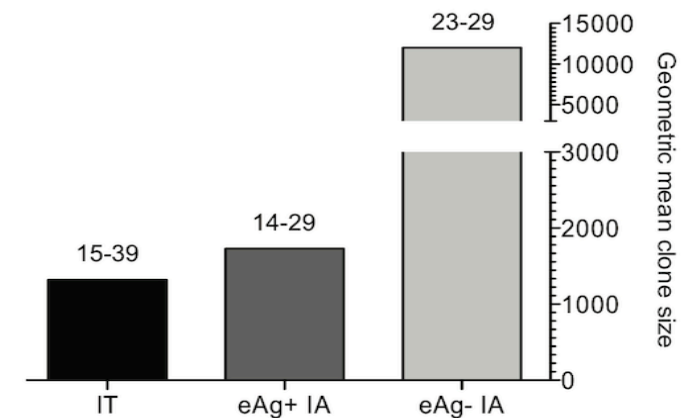
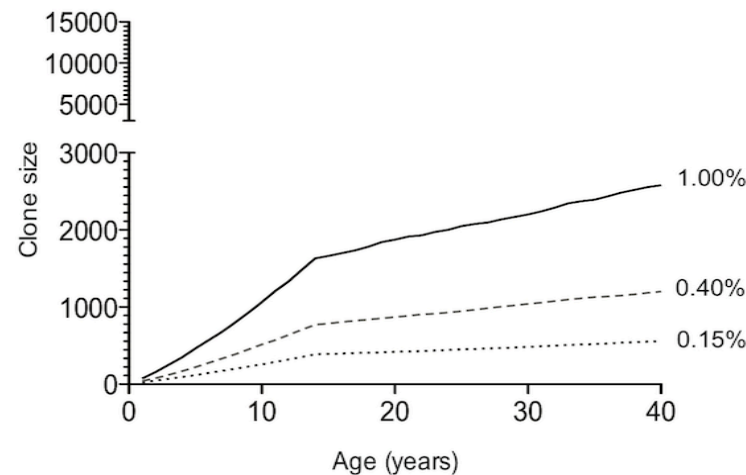
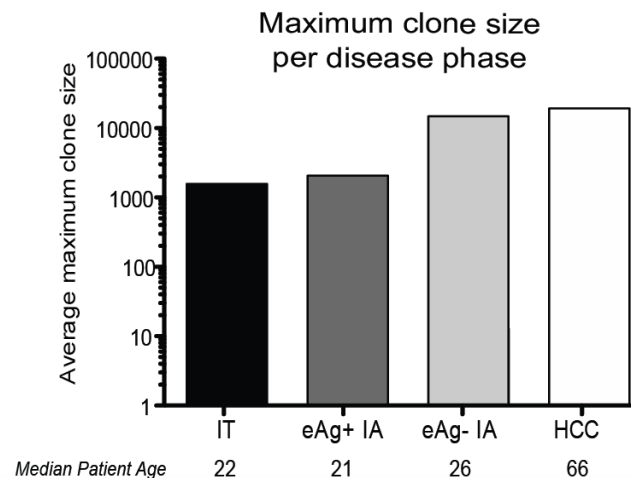
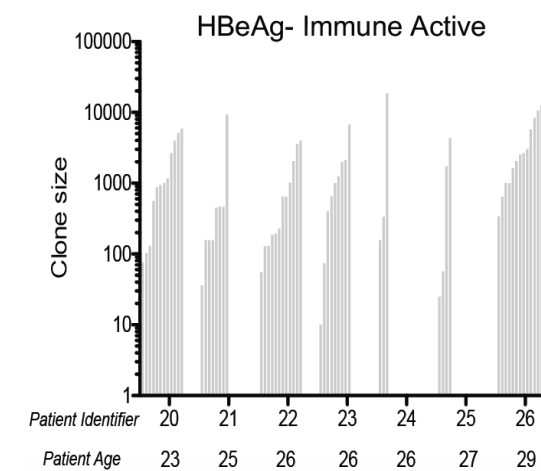
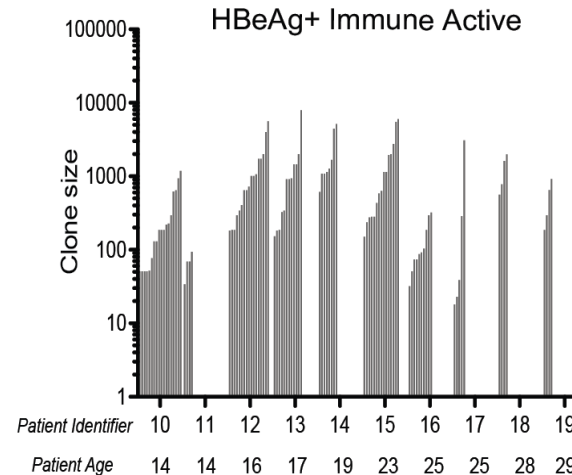
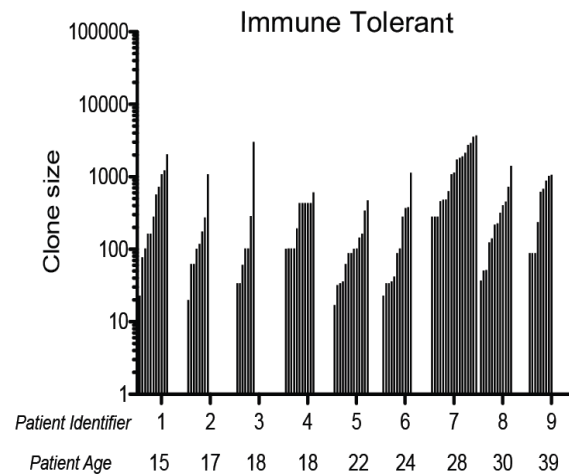


THE RATIONALE FOR EARLY TREATMENT: TO MITIGATE THE RISK OF LIVER CANCER



Events associated with Hepatocarcinogenesis

Clonal hepatocyte expansion in 'immune tolerant' patients



Mason, Gill et al., Gastroenterology 2016

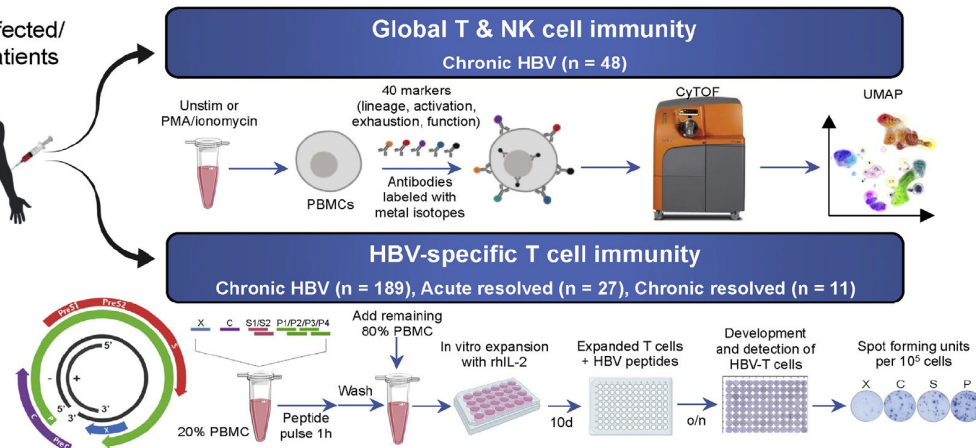
Age-related immune changes in CHB

Effects of Hepatitis B Surface Antigen on Virus-Specific and Global T Cells in Patients With Chronic Hepatitis B Virus infection

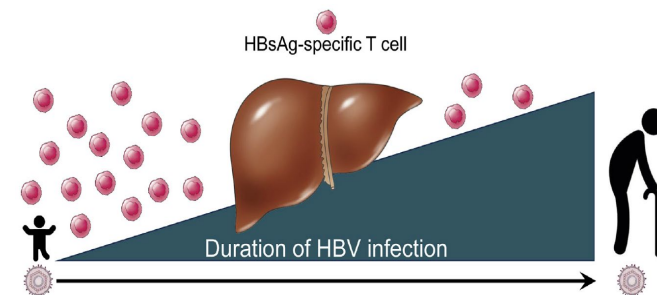
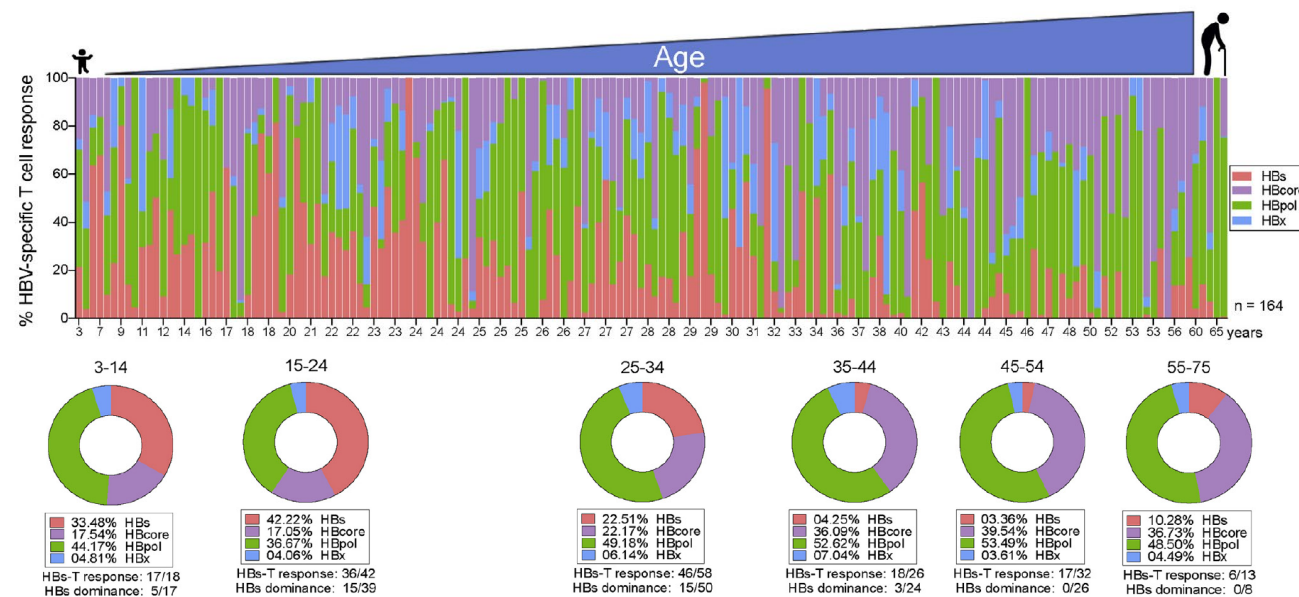
Nina Le Bert,^{1,*} Upkar S. Gill,^{2,*} Michelle Hong,^{1,*} Kamini Kunasegaran,¹ Damien Z. M. Tan,¹ Raidah Ahmad,¹ Yang Cheng,³ Charles-A. Dutertre,^{1,3} Andreas Heinecke,⁴ Laura Rivino,^{1,5} Anthony Tan,¹ Navjyot K. Hansi,² Min Zhang,⁶ Sujuan Xi,⁶ Yutian Chong,⁶ Stefan Pflanz,⁷ Evan W. Newell,³ Patrick T. F. Kennedy,^{2,§} and Antonio Bertoletti^{1,3,§}

Gastroenterology 2020;159:652–664

243 HBV-infected/
resolved patients



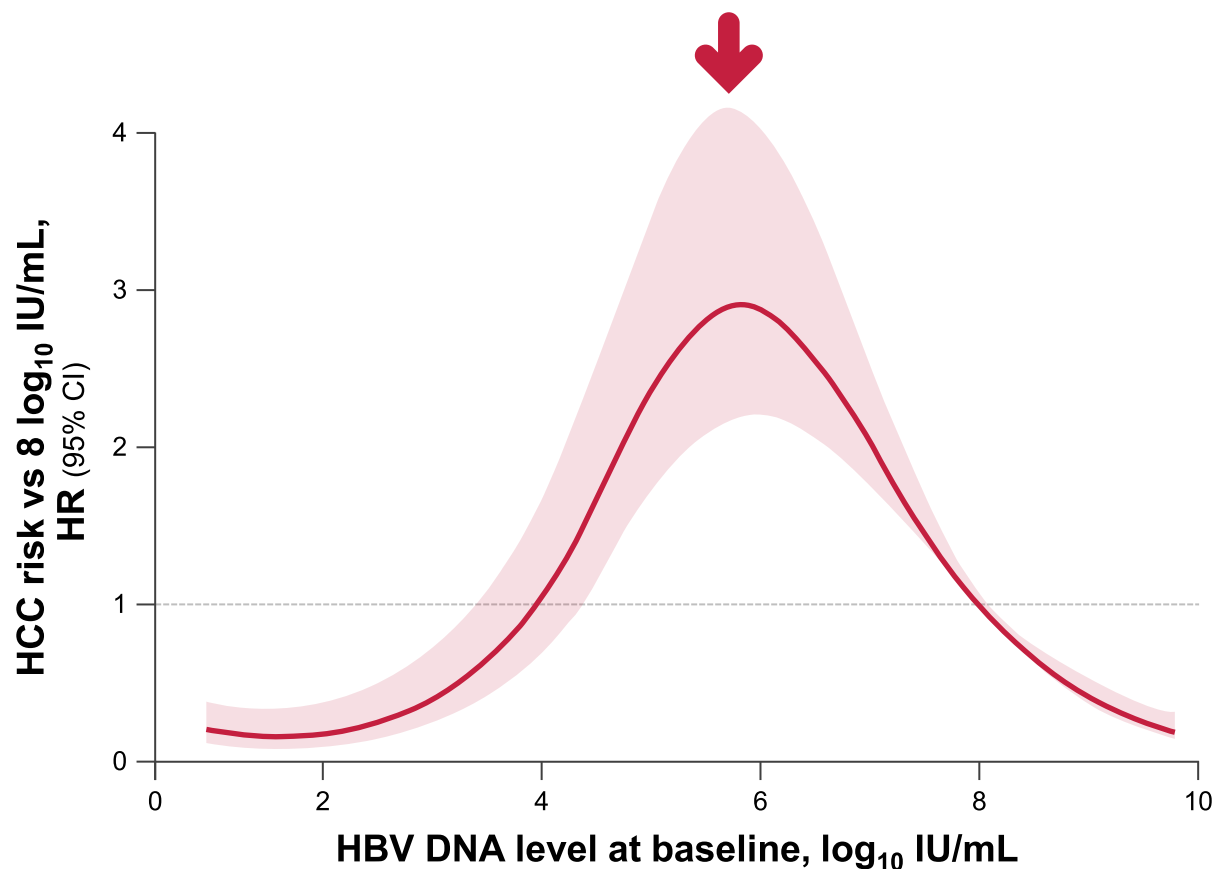
HBs-specific T cells reduce based on duration of infection, rather than HBsAg quantity



- HBV-specific T cells ↓ with age
- Earlier treatment may be beneficial for HBsAg loss`

Le Bert*, Gill*, Hong* et al., Gastroenterology 2020

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

Kim GA, Lim YS, *et al.* Aliment Pharmacol Ther. 2020;51:1169–1179.

Evidence of liver damage in immune control CHB

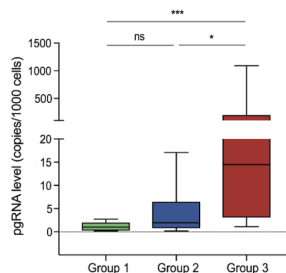
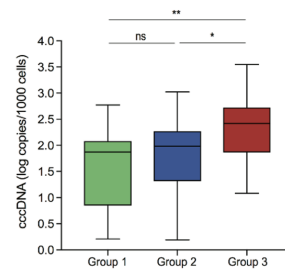
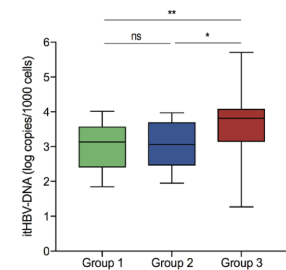
Hepatology

Original research

Whole exome HBV DNA integration is independent of the intrahepatic HBV reservoir in HBeAg-negative chronic hepatitis B

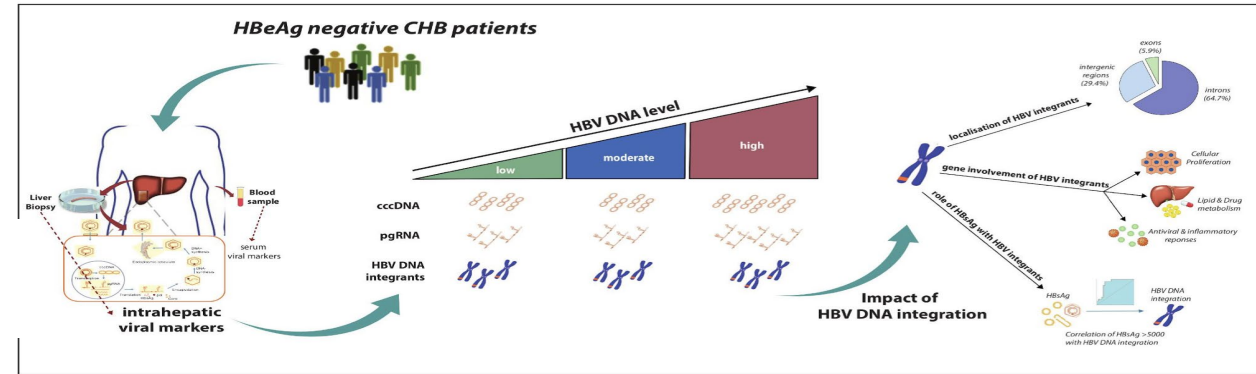
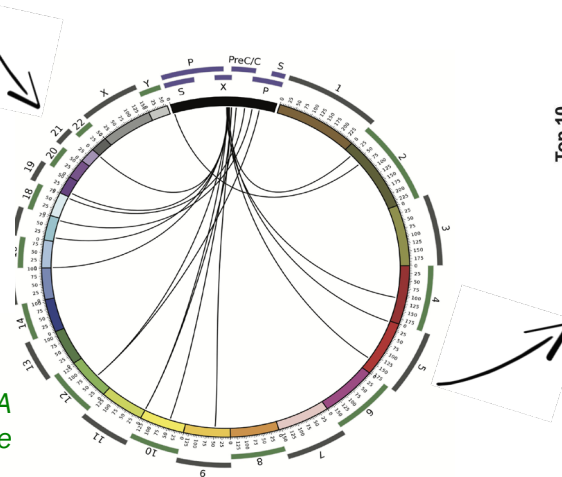
Valentina Svicher,¹ Romina Salpini,¹ Lorenzo Piermatteo,¹ Luca Carioti,¹ Arianna Battisti,^{1,2} Luna Colagrossi,^{1,3} Rossana Scutari,¹ Matteo Surdo,⁴ Valeria Cacciafesta,⁴ Andrea Nuccitelli,⁴ Navjyot Hansi,² Francesca Ceccherini Silberstein,¹ Carlo Federico Perno,⁵ Upkar S Gill,² Patrick T F Kennedy²

Differential expression of intrahepatic viral markers

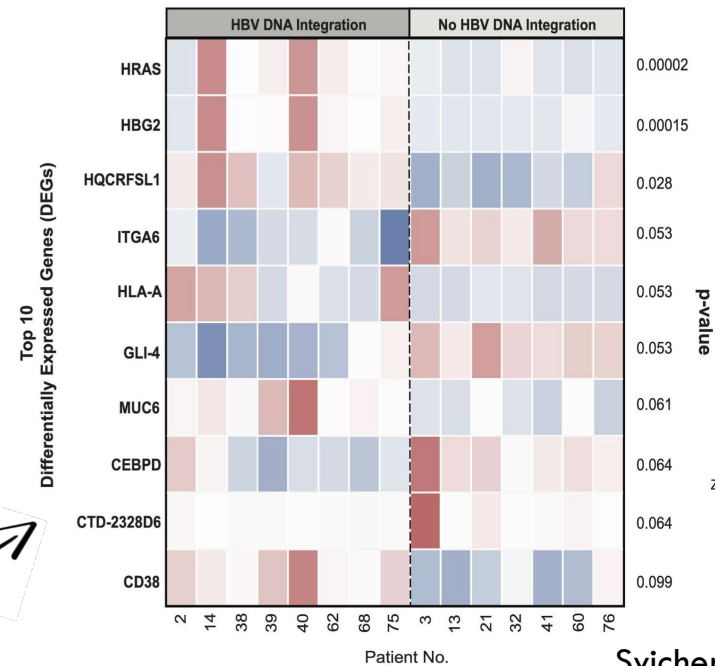


HBV DNA
■ <2,000 IU/ml
■ 2-20,000 IU/ml
■ >20,000 IU/ml

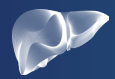
Visualisation of HBV DNA integrations within the viral genome



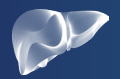
Differentially expressed genes in relation to HBV DNA integration



Svicher, Salpini et al., Gut 2020



SMARTER PATHWAYS AND BETTER ACCESS: CLINICAL PRACTICE GUIDELINES



EASL CPGs: Treatment indications

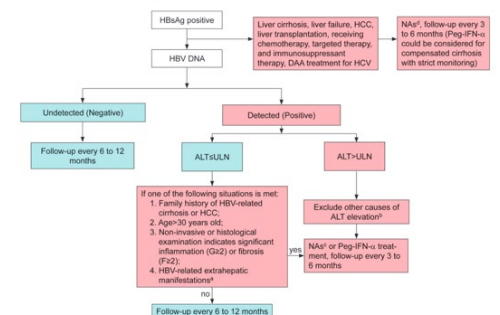
Statement

- In principle, all HBsAg-positive individuals with detectable HBV DNA are candidates for antiviral therapy. The indication for treatment is primarily based on HBV DNA and ALT levels, fibrosis stage and risk of liver disease progression and HCC (**strong consensus**).

CHRONIC HEPATITIS B GUIDELINES

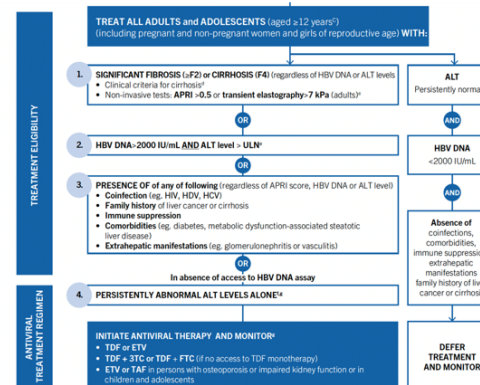
Chinese Guideline 2022/2023 (No HBV DNA cut-off of 2,000 IU/mL)

You H. et al: Guidelines for chronic hepatitis B



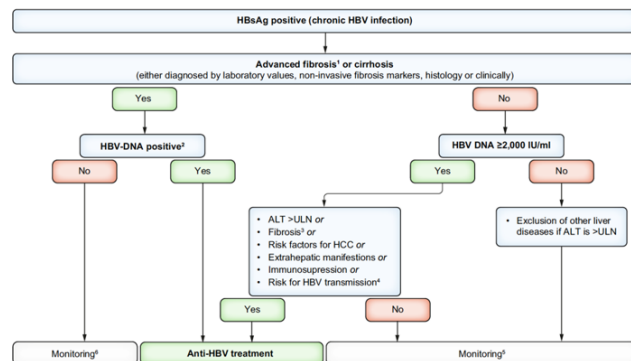
English Version: *Journal of Clinical and Translational Hepatology* 2023;
DOI: 10.14218/JCTH.2023.00320

World Health Organization WHO Guideline 2024



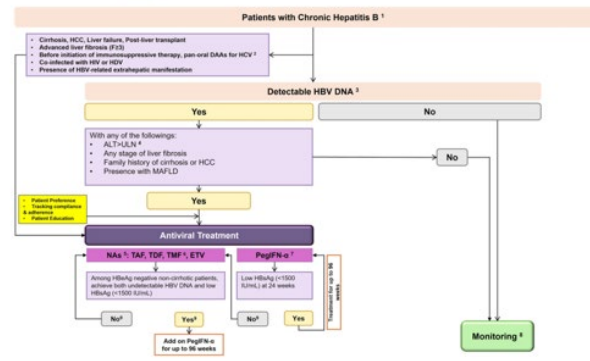
<https://www.who.int/publications/i/item/9789240090903>

EASL CPG 2025



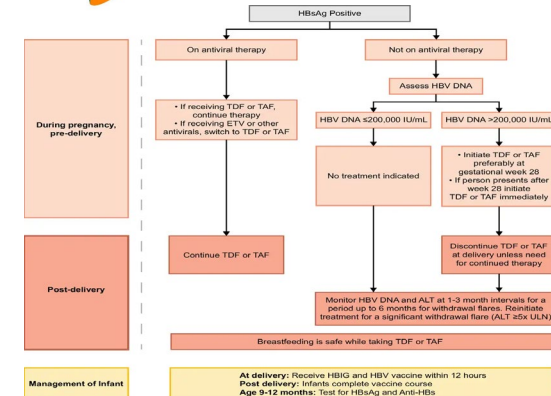
[https://www.journal-of-hepatology.eu/article/S0168-8278\(25\)00174-6](https://www.journal-of-hepatology.eu/article/S0168-8278(25)00174-6)

APASL CPG 2026

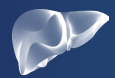


<https://link.springer.com/article/10.1007/s12072-026-11108-1>

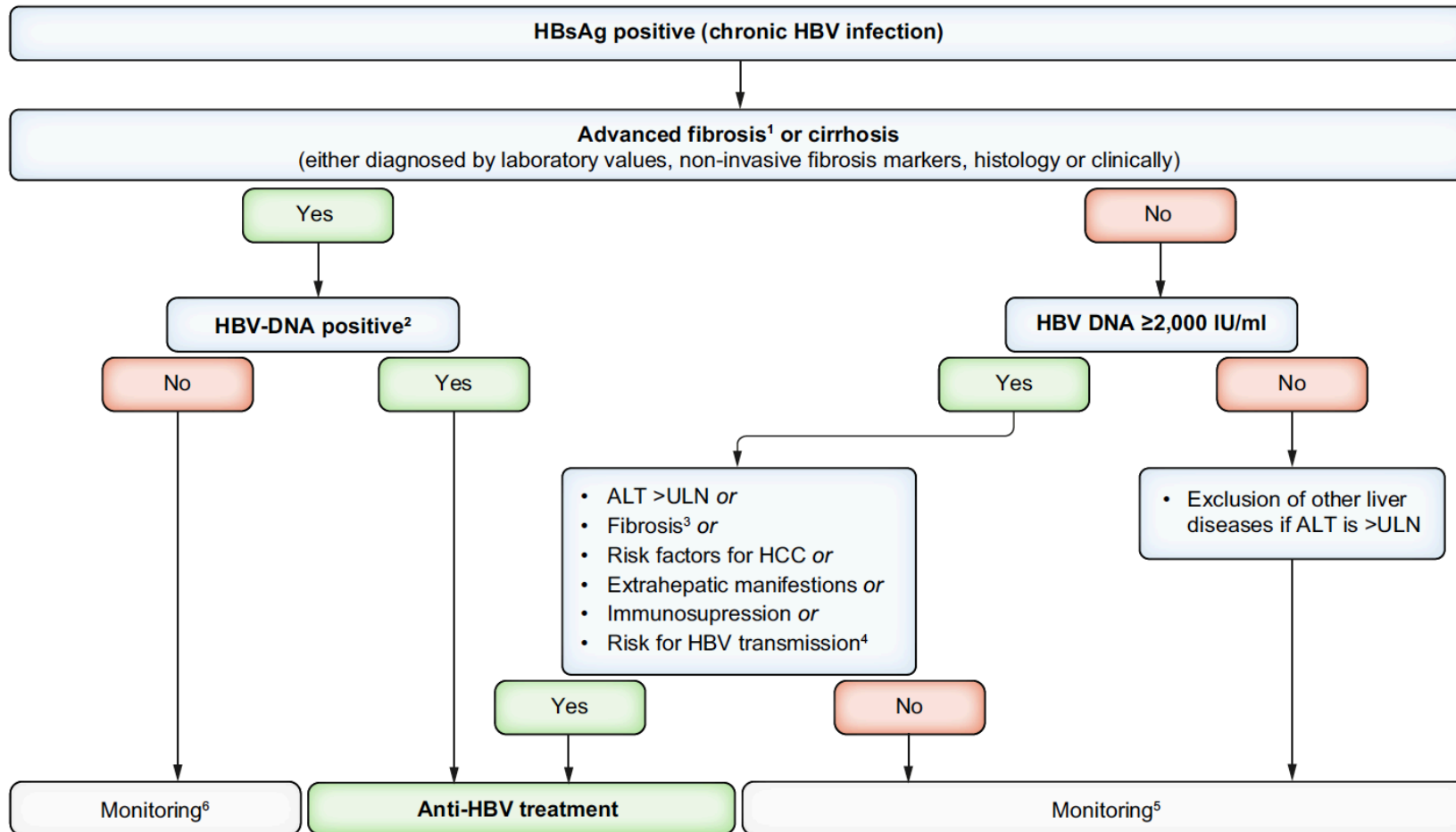
AASLD CPG 2026



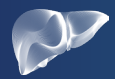
<https://journals.lww.com/hep/fulltext/10.1097/hep.0000000000001549~aasld-idsa-practice-guideline-on-treatment-of-chronic>



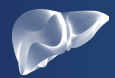
Simplified Treatment Algorithm



1. Equivalent of ISHAK F≥4 / Metavir F≥3 (non-invasive assessment is preferred, LSM >8 kPa)
2. Sensitive NAT assay (Lower limit of detection <20 U/I)
3. Equivalent of ISHAK ≥F3 / Metavir ≥F2 (non-invasive assessment is preferred, LSM ≥7 kPa)
4. The threshold values for HBV DNA vary depending on the activity and risk of transmission. Important: Tenofovir in pregnant women with HBV DNA ≥200,000 IU/ml
5. Anti-HBV treatment in HCC, HIV co-infection, extrahepatic manifestations, immunosuppression
6. Anti-HBV treatment in immunosuppression



WHATS NEXT IN HEPATITIS B: NEW THERAPIES



Efficacy and Safety of Bepirovirsen in Chronic Hepatitis B Infection

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Bepirovirsen in Chronic Hepatitis B Infection

M.-F. Yuen, S.-G. Lim, R. Plesniak, K. Tsuji, H.L.A. Janssen, C. Pojoga, A. Gadano, C.P. Popescu, T. Stepanova, T. Asselah, G. Diaconescu, H.J. Yim, J. Heo, E. Janczewska, A. Wong, N. Idriz, M. Imamura, G. Rizzardini, K. Takaguchi, P. Andreone, M. Arbune, J. Hou, S.J. Park, A. Vata, J. Cremer, R. Elston, T. Lukić, G. Quinn, L. Maynard, S. Kendrick, H. Plein, F. Campbell, M. Paff, and D. Theodore, for the B-Clear Study Group*

ABSTRACT

BACKGROUND

Bepirovirsen is an antisense oligonucleotide that targets all hepatitis B virus (HBV) messenger RNAs and acts to decrease levels of viral proteins.

METHODS

We conducted a phase 2b, randomized, investigator-unblinded trial involving participants with chronic HBV infection who were receiving or not receiving nucleoside or nucleotide analogue (NA) therapy. Participants were randomly assigned (in a 3:3:3:1 ratio) to receive weekly subcutaneous injections of bepirovirsen at a dose of 300 mg for 24 weeks (group 1), bepirovirsen at a dose of 300 mg for 12 weeks then 150 mg for 12 weeks (group 2), bepirovirsen at a dose of 300 mg for 12 weeks then placebo for 12 weeks (group 3), or placebo for 12 weeks then bepirovirsen at a dose of 300 mg for 12 weeks (group 4). Groups 1, 2, and 3 received loading doses of bepirovirsen. The composite primary outcome was a hepatitis B surface antigen (HBsAg) level below the limit of detection and an HBV DNA level below the limit of quantification maintained for 24 weeks after the planned end of bepirovirsen treatment, without newly initiated antiviral medication.

RESULTS

The intention-to-treat population comprised 457 participants (227 receiving NA therapy and 230 not receiving NA therapy). Among those receiving NA therapy, a primary-outcome event occurred in 6 participants (9%; 95% credible interval, 0 to 31) in group 1, in 6 (9%; 95% credible interval, 0 to 43) in group 2, in 2 (3%; 95% credible interval, 0 to 16) in group 3, and 0 (0%; post hoc credible interval, 0 to 8) in group 4. Among participants not receiving NA therapy, a primary-outcome event occurred in 7 participants (10%; 95% credible interval, 0 to 38), 4 (6%; 95% credible interval, 0 to 25), 1 (1%; post hoc credible interval, 0 to 6), and 0 (0%; post hoc credible interval, 0 to 8), respectively. During weeks 1 through 12, adverse events, including injection-site reactions, pyrexia, fatigue, and increased alanine aminotransferase levels, were more common with bepirovirsen (groups 1, 2, and 3) than with placebo (group 4).

CONCLUSIONS

In this phase 2b trial, bepirovirsen at a dose of 300 mg per week for 24 weeks resulted in sustained HBsAg and HBV DNA loss in 9 to 10% of participants with chronic HBV infection. Larger and longer trials are required to assess the efficacy and safety of bepirovirsen. (Funded by GSK; B-Clear ClinicalTrials.gov number, NCT04449029.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Yuen can be contacted at mfyuen@hku.hk or at Rm. 406, Professorial Block, Queen Mary Hospital, Pokfulam Rd., Hong Kong, China.

*The members of the B-Clear Study Group are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Yuen and Lim contributed equally to this article.

This article was published on November 8, 2022, at NEJM.org.

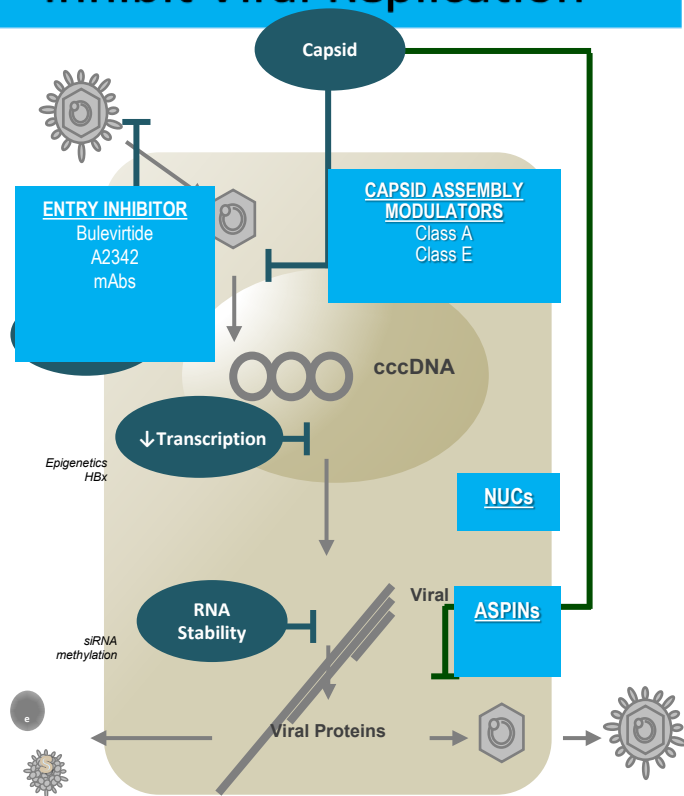
N Engl J Med 2022;387:1957-68.

DOI: 10.1056/NEJMoa2210027

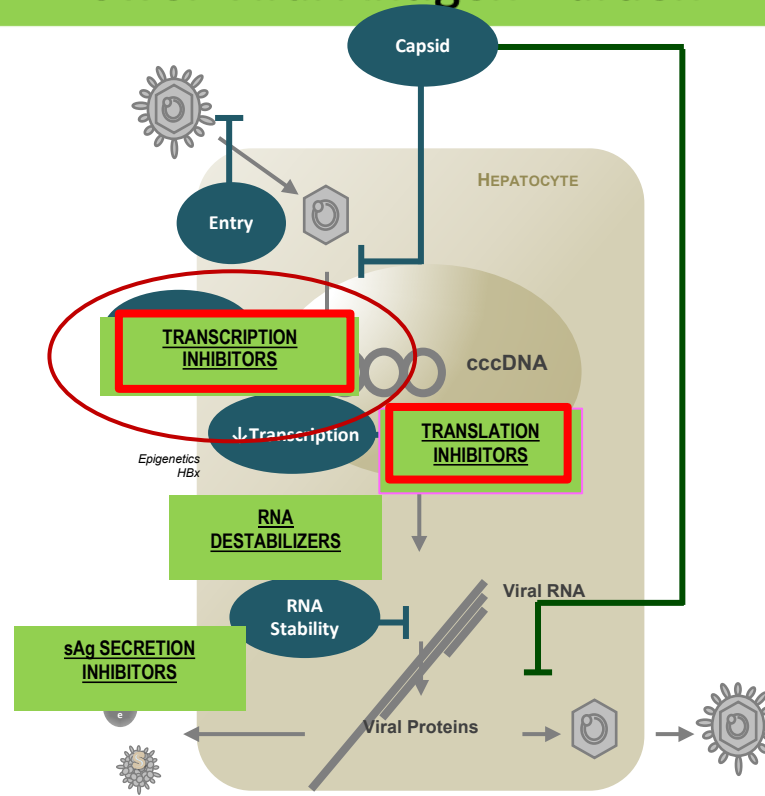
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Strategies for Functional CURE in Chronic Hepatitis B

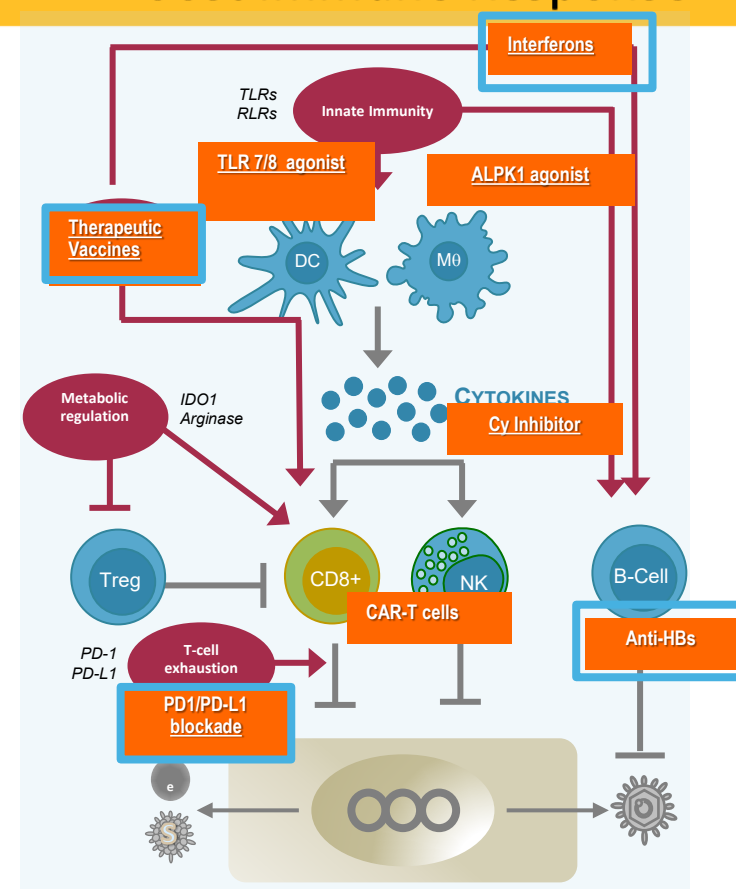
Inhibit Viral Replication



Lower Viral Antigen Burden



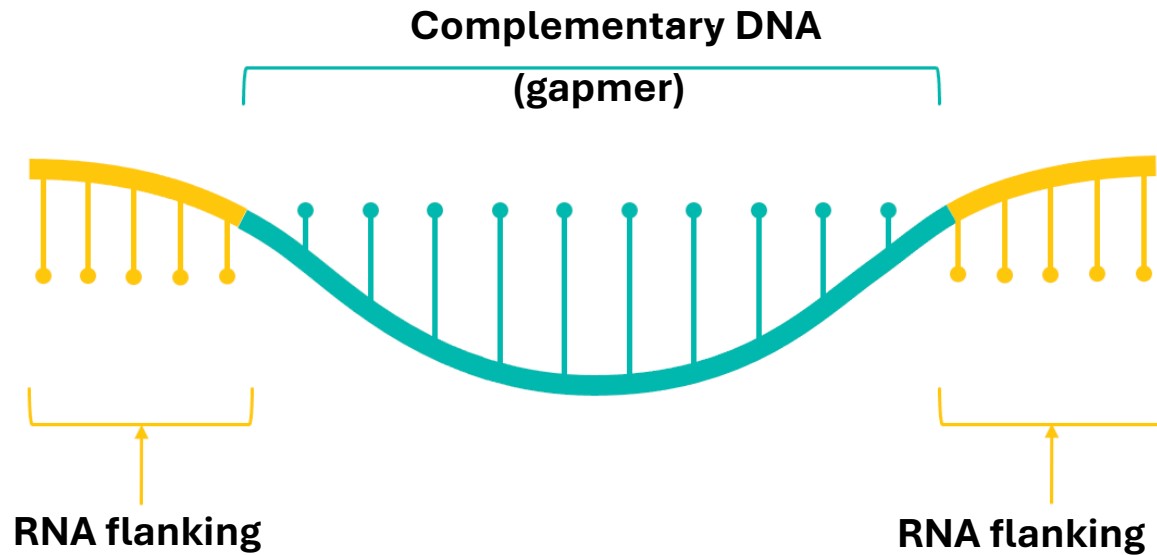
Boost Immune Response



Immunomodulatory agents

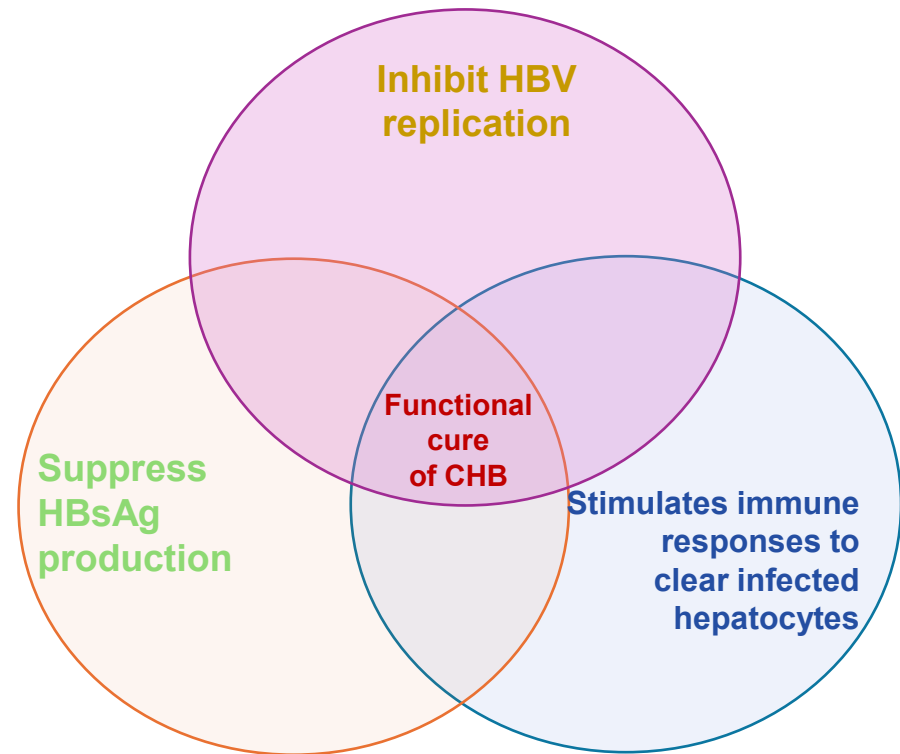
Lim SG et al, Nat Rev Gastroenterology Hepatology 2023

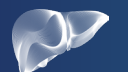
What is Bepirovirsen (Bepi) and how does it work?



- Bepirovirsen is anti-sense oligonucleotide (ASO) comprising a mix of DNA and RNA molecules
- It is delivered by injection subcutaneously weekly for 24 weeks

• How does it work?





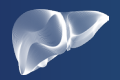
Clinically meaningful rates of functional cure in virologically suppressed patients with chronic hepatitis B infection treated with bepirovirsen: B-Well Phase 3 Trials

Professor Seng-Gee Lim, National University Health System, Singapore,
on behalf of the B-Well Study Group

- Jinlin Hou*, Seng-Gee Lim*, Maria Buti, Man-Fung Yuen, Edward Gane, Pietro Lampertico, Norah Terrault, Huy Nguyen, Hyung Joon Yim, Qing Xie, Jianmei Lin, Yunqing Qiu, Wen-Juei Jeng, Jeong Heo, Cheng-Yuan Peng, Chien-Hung Chen, Wan-Long Chuang, Yao Xie, Maria Hlebowicz, Nevin Idriz, Rajiv Mehta, Kosh Agarwal, Monica M. Gomes da Silva, Alex Franca, Roxana Cernat, Apinya Leerapun, Carla S. Coffin, Adrian Gadano, Pietro Andreone, Shigetoshi Fujiyama, Vasileios Sevastianos, Yuichiro Suzuki, Vlad Ratziu, Ghassan Riachi, Hartmut Stocker, Tien Huey Lim, Tarik Asselah, Yasuhito Tanaka, Jacinta Holmes, Xieer Liang, Jennifer Cremer, Tamara Lukić, Helene Plein, Geoff Quinn, Yu Tao, Melanie Paff, Dickens Theodore, Robert Elston, *for the B-Well Study Group*

EASL 2026
28 May 2026

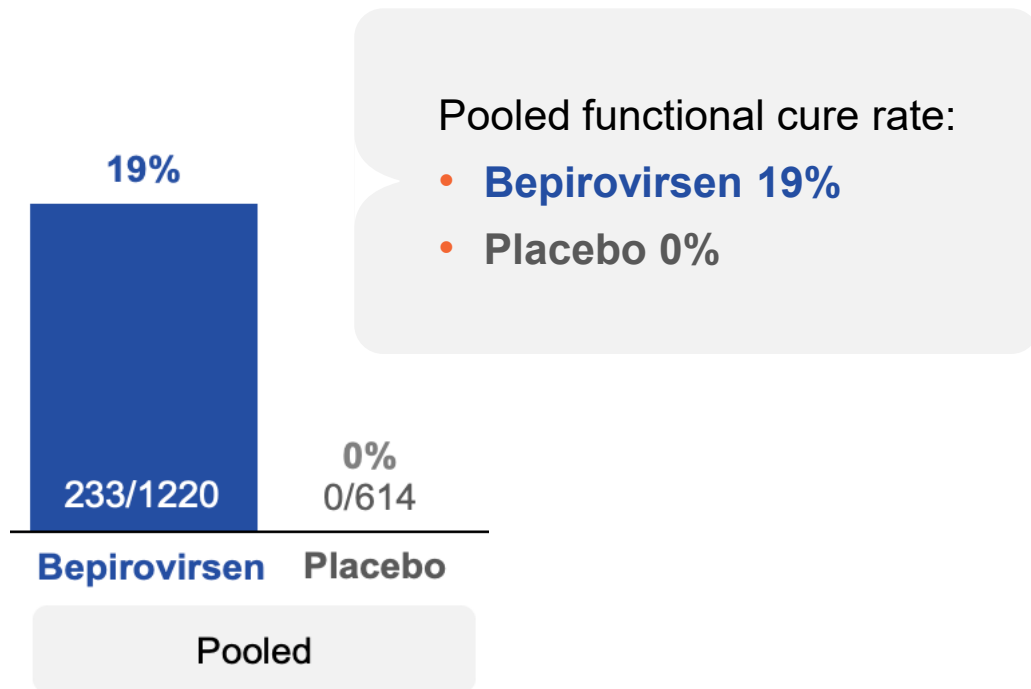
*Co-lead authors: Professors Hou and Lim contributed equally to this publication



Key Findings of Bepirovirsen treatment in phase 3 trial compared to placebo (patients taking nucleoside analogues)

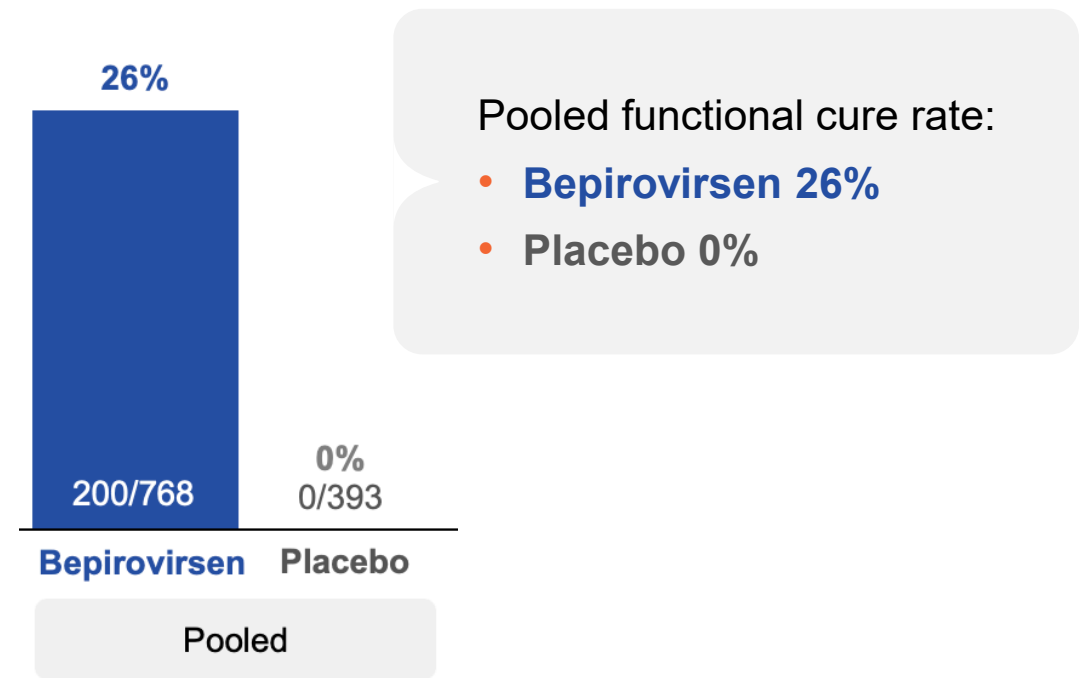
- **Primary outcome**

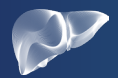
Functional cure in participants with baseline **HBsAg ≤ 3000 IU/mL**



- **Secondary outcome**

Functional cure in participants with baseline **HBsAg ≤ 1000 IU/mL**





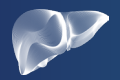
Bepirovirsen Main Side Effects

Events reported in >10% of patients

n (%)	Pooled safety population	
	Bepirovirsen N=1223 (%)	Placebo N=611 (%)
Injection site erythema	384 (31)	12 (2)
Injection site pain	277 (23)	31 (5)
Injection site pruritus	219 (18)	9 (1)
Injection site bruising	176 (14)	28 (5)
ALT increased	269 (22)	18 (3)
AST increased	183 (15)	8 (1)
Pyrexia	236 (19)	18 (3)
Platelet count decreased	180 (15)	5 (1)
Headache	168 (14)	70 (11)
Upper respiratory tract infection	147 (12)	72 (12)

SAFETY

- Stopping treatment due to side effects
 - 4/1220 patients for high ALT (liver inflammation)
 - 8/1220 due to low platelet count
- No deaths, bleeding or liver failure due to bepirovirsen treatment
- Bepirovirsen belongs to the ASO class of agents which are known to have transient side effects such as low platelet count and mild kidney effects
- In summary, Bepi is considered to have an acceptable safety profile

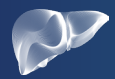


Things you need to know about Bepi treatment

- Bepirovirsen comes as an injection that is frozen/refrigerated
- Given weekly subcutaneously preferably in abdomen region
- Duration is 24 weeks of injections
- Two loading doses means the first 2 weeks needs two injections

During therapy you will need monitoring

- Platelet count
- LFT: ALT level
- Kidney function
- You need to continue oral tablets during bepirovirsen treatment and only stop when you are advised by your doctor



COMBINATION APPROACHES, NEW AGENTS AND NEW MECHANISMS TO WATCH

Peginterferon alpha-2a add-on to siRNA JNJ-73763989 in untreated patients in the HBeAg+ disease phases of chronic hepatitis B (CHB): the phase 2 REEF-IT study

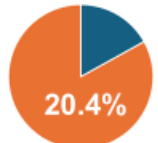
54 Participants enrolled

- ✓ HBeAg positive chronic infection/hepatitis
- ✓ Currently not treated
- ✓ Age ≥ 18 to ≤ 55 years
- ✓ ALT $< 2 \times$ ULN
- ✓ 67% were „immune-tolerant“

Treatments received

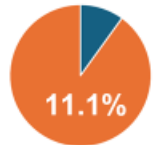
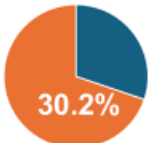
- ✓ Induction phase (36 to 52 weeks):
 - JNJ-3989 + NA for 36 to 52 weeks
 - 27/54 also received bersacpavir (2 to 32 wks)*
- ✓ IFN add-on phase (12 weeks):
 - JNJ-3989 + NA + pegIFN- α 2a
- ✓ Follow-up phase (48 weeks):
 - NA unless completion criteria were met

HBsAg loss

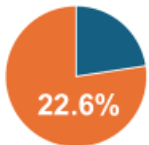


at least once

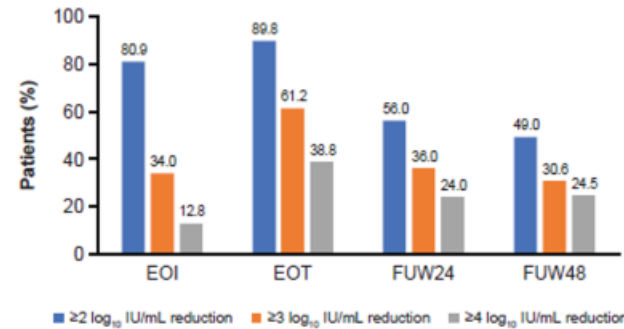
HBeAg loss



at FU W48



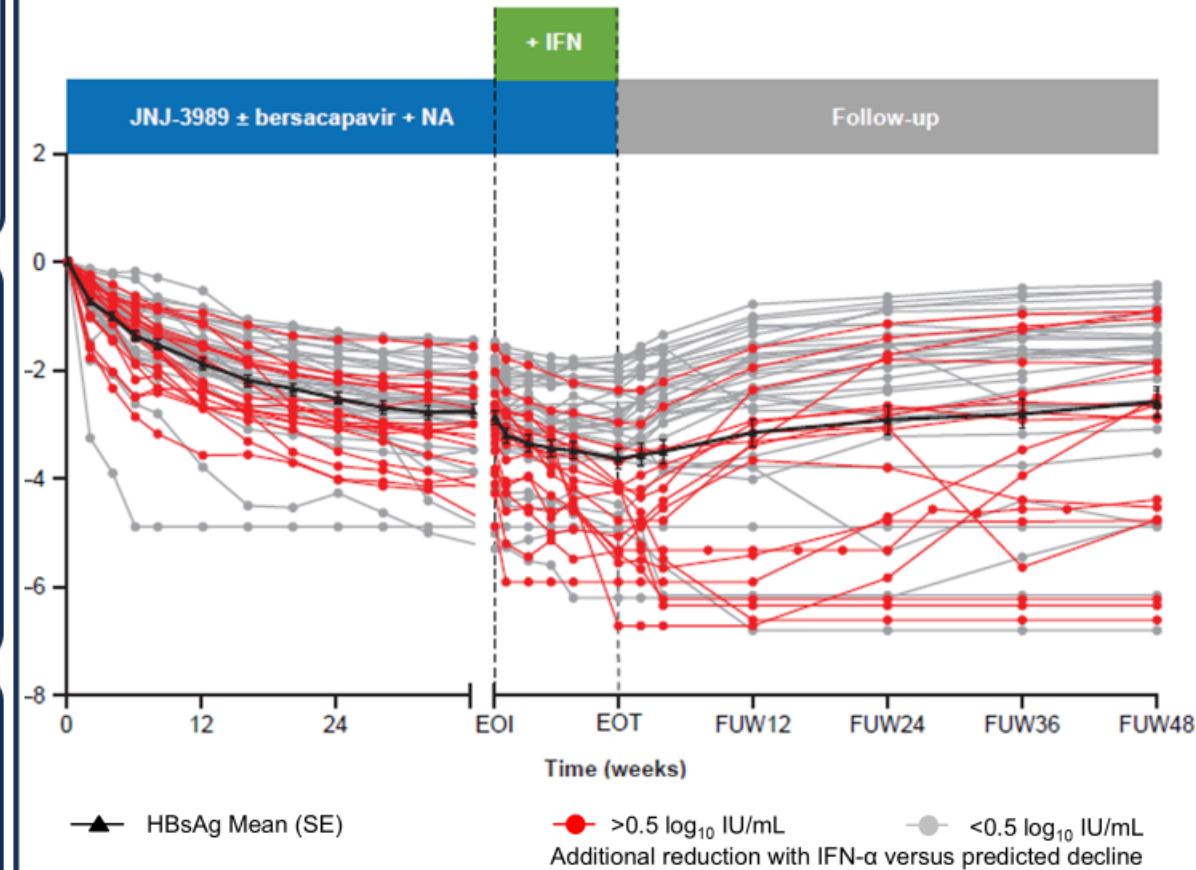
HBsAg reduction from baseline



Conclusions:

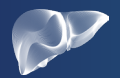
- ✓ Profound reductions of HBsAg on- and off-treatment with JNJ-3989+NA
- ✓ Further reduction by ≥ 1.0 log during IFN- α in 23.4% of participants
- ✓ No participant met the primary endpoint of functional cure at FUW24
- ✓ HBsAg loss in 20.4% with maintenance to end of study in 11.1%

HBsAg Change from Baseline ($\log_{10}$ IU/mL)



*CAM-E bersacpavir was discontinued as study intervention via protocol amendment

Patrick T Kennedy, et al. *Gut* 2025. DOI: 10.1136/gut-2025



Promising Trial data from EASL 2026



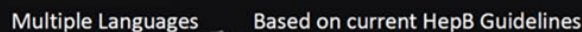
Phase 1 trial: Pevifoscorvir in HBeAg-positive treatment naïve or currently-not-treated patients with CHB for 96 weeks and then NUCs for 8 weeks. Yuen MF, et al. EASL 2026. WED-602.



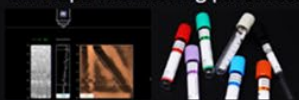
Tune-401-001: Phase 1b/2a proof of concept trial of Tune-401, a first-in-class epigenetic silencer of HBV, in patients with CHB. Gane EJ, et al. EASL 2026. LBO-003



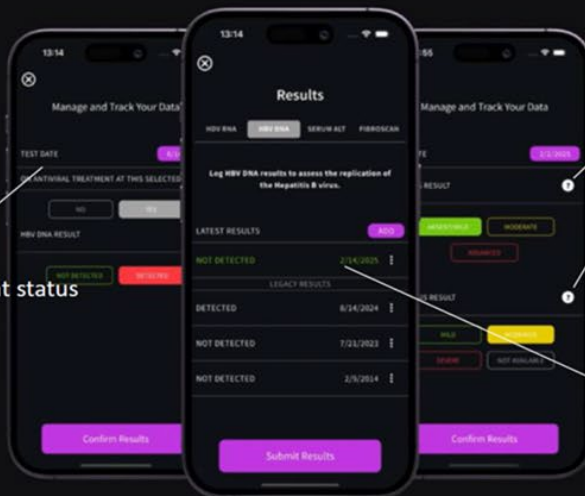
☐ **ELIMINATE B:** An ongoing Phase 1 trial assessing safety, PK, and antiviral activity of PBGENE-HBV (a first-in-class gene editor) for patients with CHB. Yuen MF, et al. EASL 2026. LBP-043.



All HepB monitoring parameters



HepB & Me



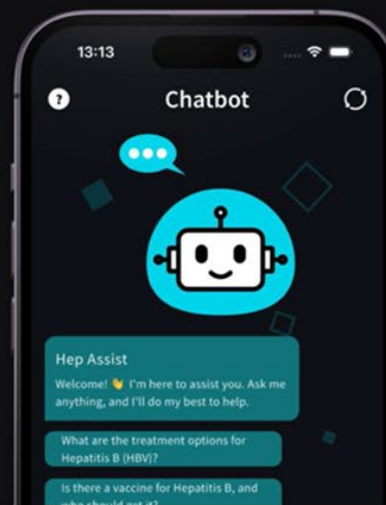
Treatment status

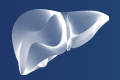
Ranges Based on HepB Guidelines

Effortless Results Entry

Keep your health records
up to date with ease.

Results History





WHATS NEXT IN CHB: TAKE HOME MESSAGES

- Functional cure is now achievable
- Can combination approaches (siRNA & ASO) increase functional cure rates- studies ongoing
- Early treatment with NAs (and as a bridge to Functional cure)
- We need to upscale scale diagnosis and access to treatment
- We need to prepare now for the initiation and management of Bepi in the clinic

