HBV-TAG

2021 CONFERENCE

BLAZING SADDLES: EXPANDING TREATMENT CRITERIA

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Professor of Translational Hepatology

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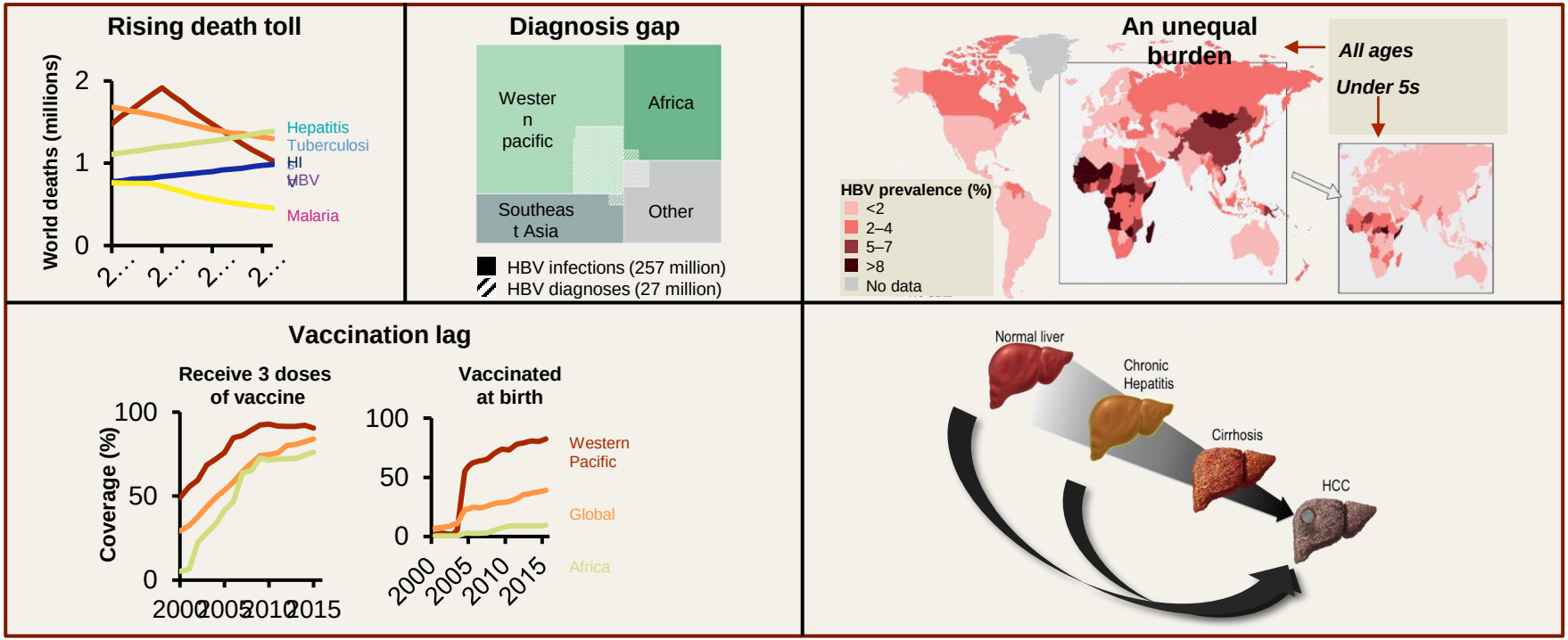
Chronic hepatitis B – the challenge



Graber-Stiehl I. The silent epidemic killing more people than HIV, malaria or TB. Nature News 2018. Available at: https://www.nature.com/articles/d41586-018-07592-7 (accessed February 2021)

HCC: hepatocellular carcinoma

The global impact of HCC

In the majority of countries, HCC accounts for 75–85% of all primary liver cancer cases[1]

Liver cancer =

6th most common type of cancer worldwide[1]

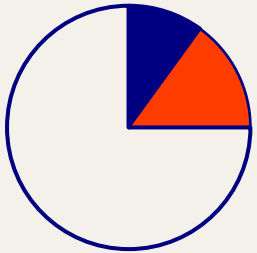
3rd most common cause of cancer-related death[1]

>800k deaths/year[1]

HBV infection accounts for the majority of liver cancer deaths worldwide (~56%)[1]

0.3–2.2%

incidence rate per 100 PY of HCC in CHB patients without and with compensated cirrhosis[2]



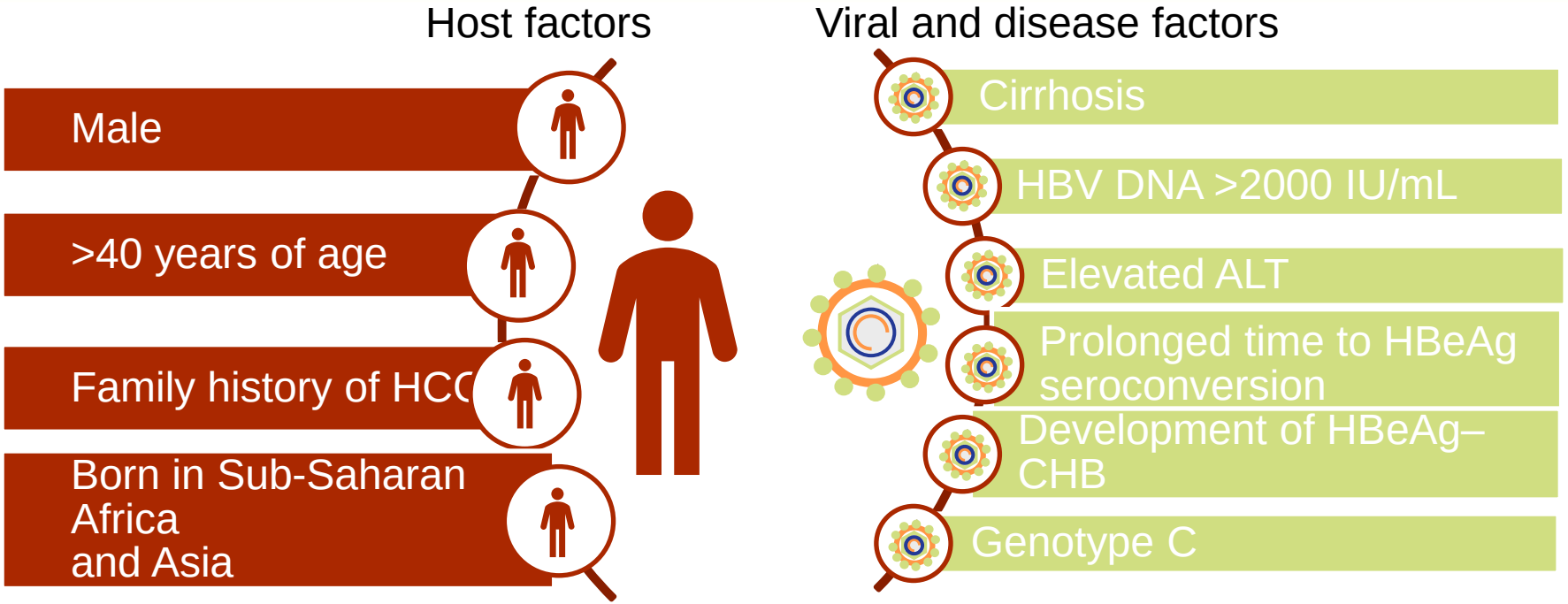
10–25%

lifetime risk of HCC in patients infected with HBV[3]

1. Sung H, et al. CA Cancer J Clin 2021;doi: 10.3322/caac.21660;
2. El-Serag HB. Gastroenterology 2012;142:1264–73;
3. Balogh J, et al. J Hepatocell Carcinoma 2016;3:41–53

PY: person-years

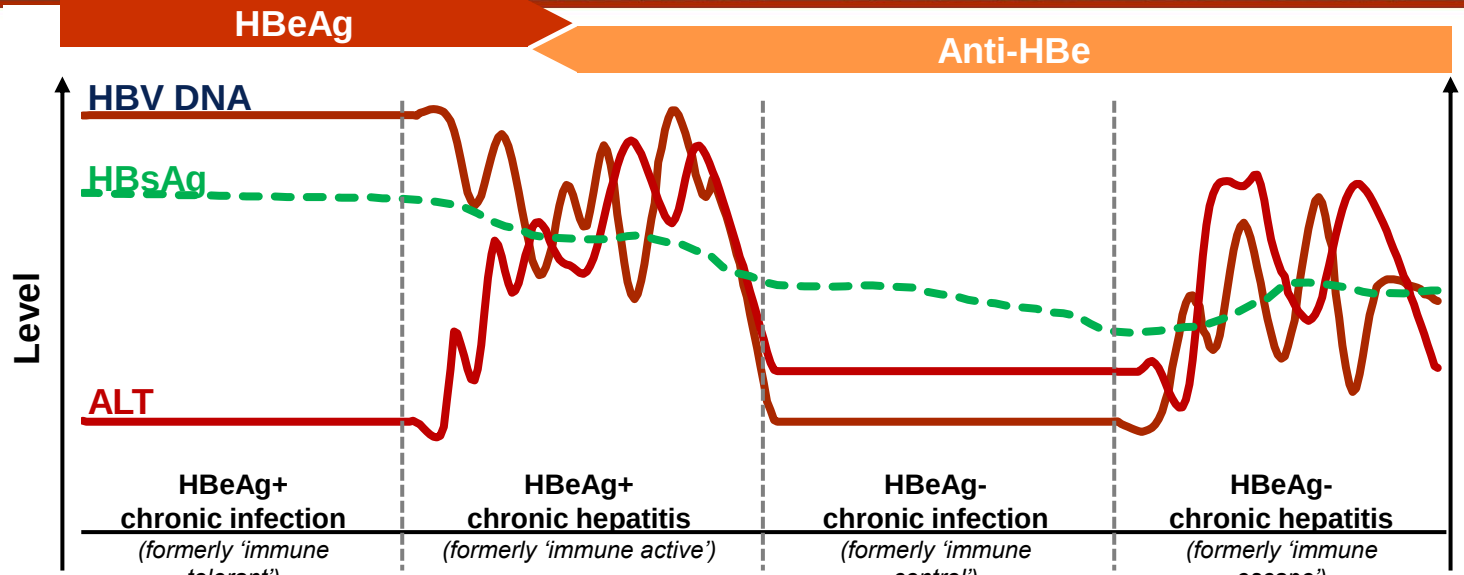
Untreated CHB and HCC Risk



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; HBeAg: hepatitis B ‘e’ antigen

Natural history and disease phase of CHB



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*

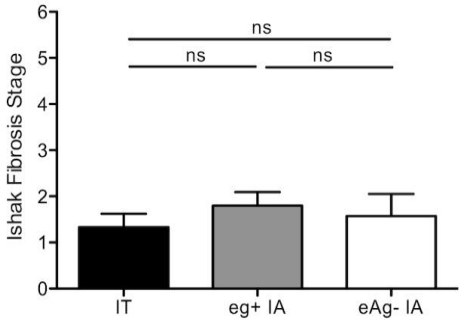
Adapted from Gill U and Kennedy P. Clin Med 2015;15:191–6; EASL. J Hepatol 2017;67:370–98

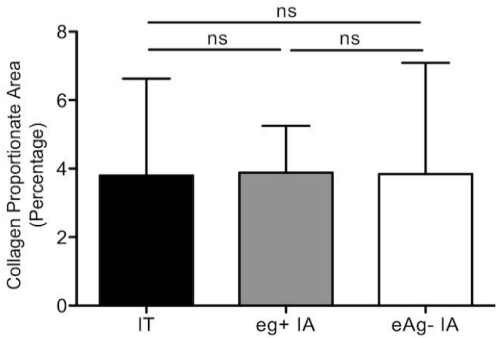
Anti-HBe: hepatitis B 'e' antibody; HBsAg: hepatitis B surface antigen

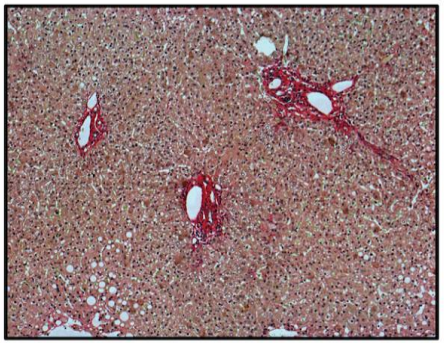
Why we should consider treating “immune tolerant” CHB

- This disease phase is **not** benign
- *Clonal hepatocyte expansion & HBV DNA integration are observed*
- Virus-specific T cell responses are preserved
- Reduce the pool of HBV infection and risk of viral transmission in young people

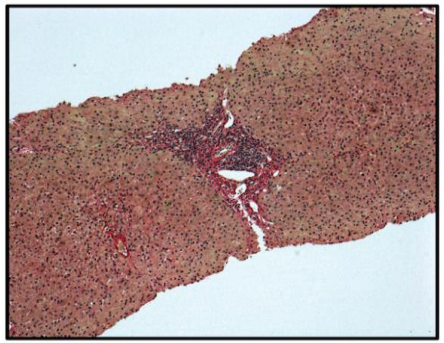
Liver damage in ‘immune tolerant’ patients



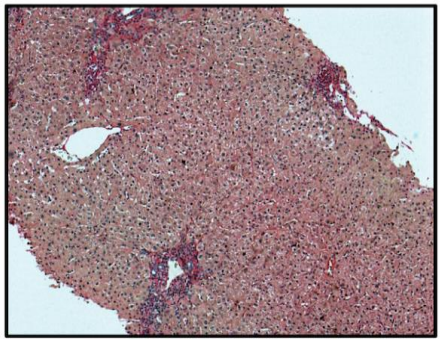




Immune Tolerant



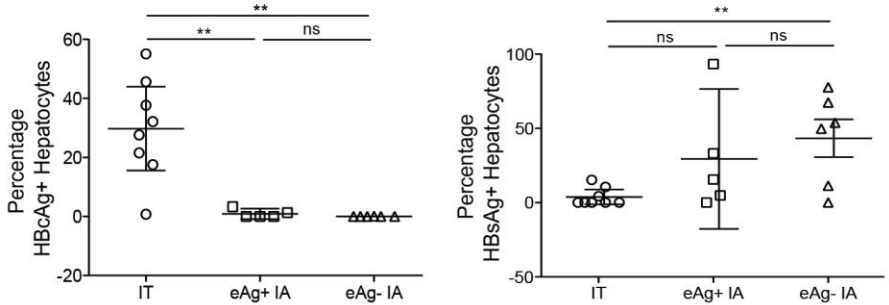
HBeAg+ Immune Active

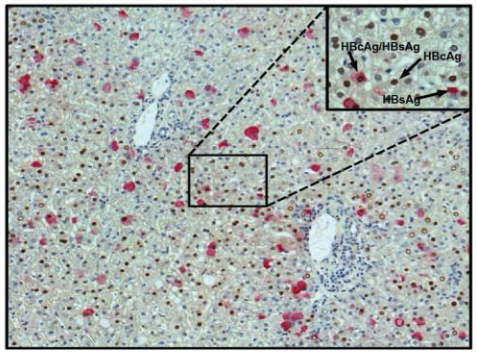


HBeAg- Immune Active

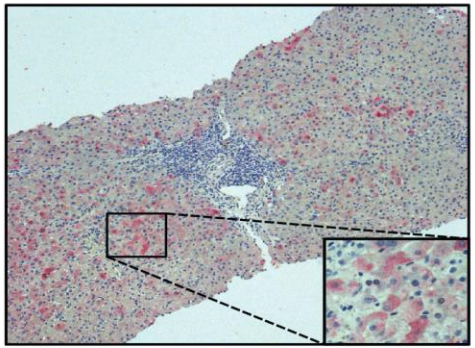
Mason et al., Gastroenterology 2016

Nuclear core positive hepatocytes differentiate ‘immune tolerant’ disease

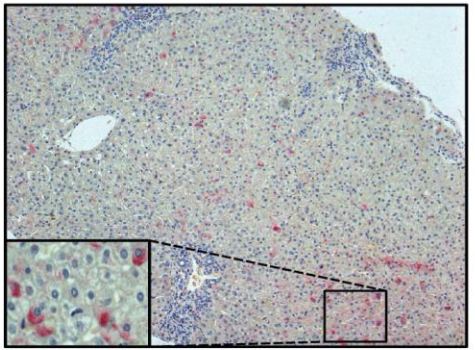




Immune Tolerant



HBeAg+ Immune Active

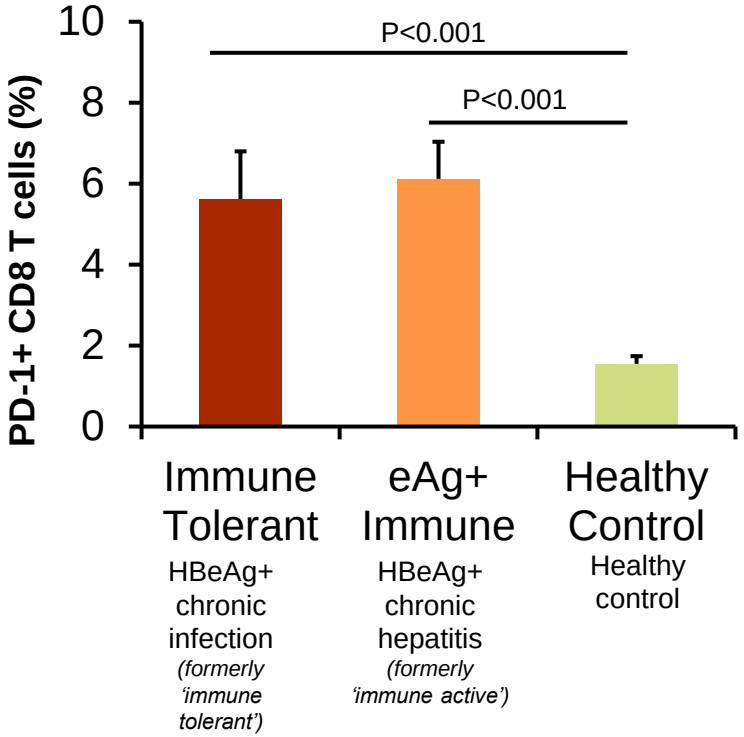


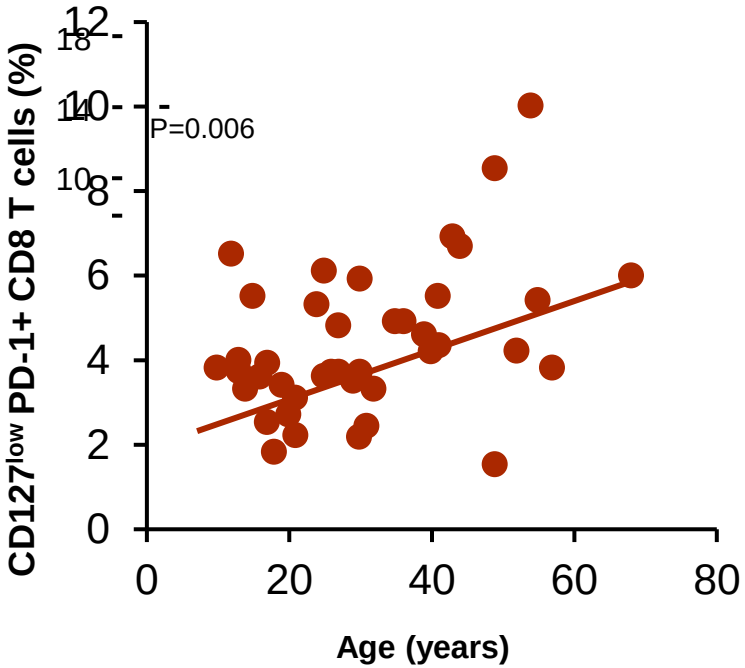
HBeAg- Immune Active

Mason et al., Gastroenterology 2016

T-cell responses in HBeAg+ chronic infection

Evidence of immune activity in the ‘immune-tolerant’ disease phase

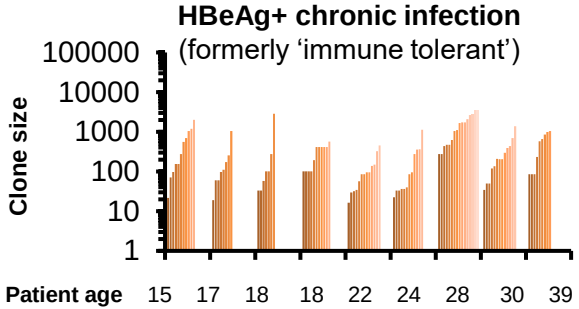


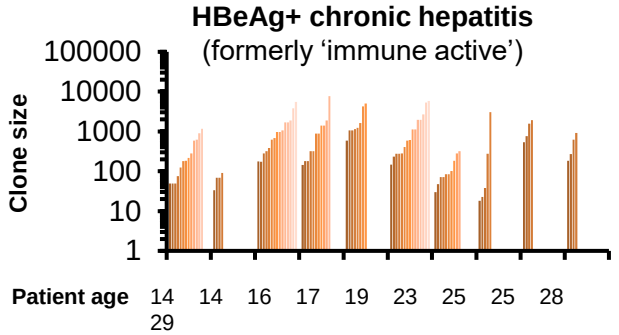


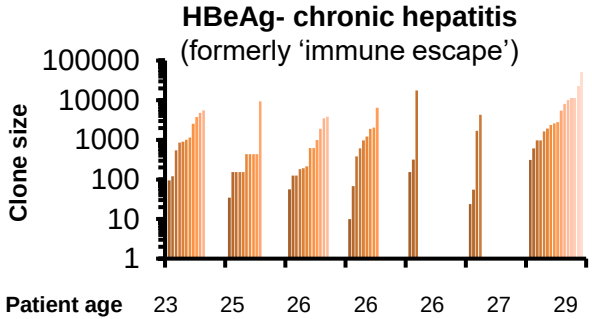
Kennedy P, et al. Gastroenterology 2012;143:637–45

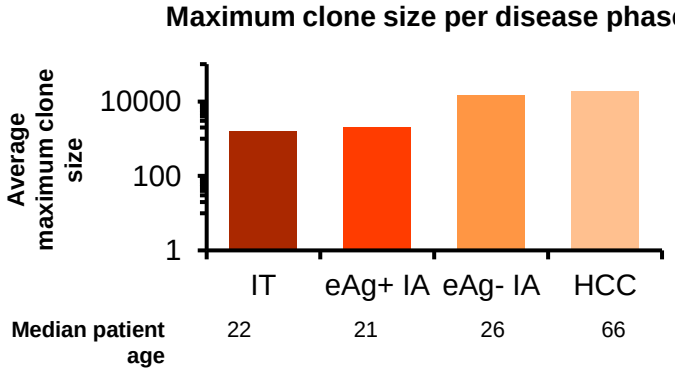
Immune activity in HBeAg+ chronic infection

Clonal hepatocyte expansion in 'immune-tolerant' patients









Mason WS, et al. Gastroenterology 2016;151:986–98

IA: immune-active; IT: immune-tolerant

Frequency of HBV DNA integration

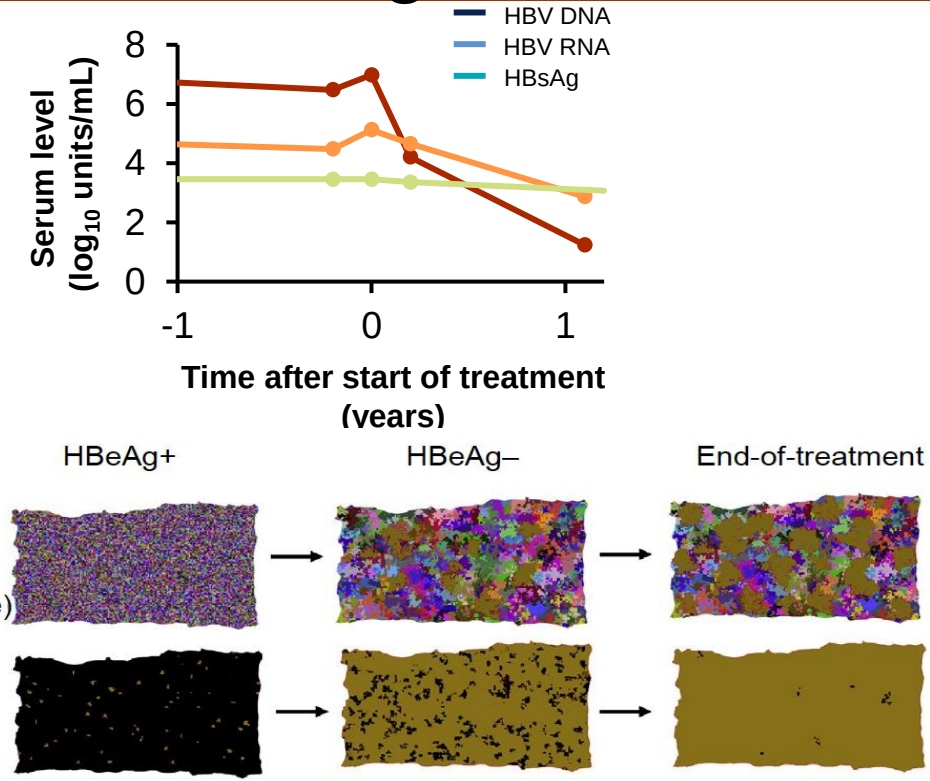
(Determined by end point dilution followed by inverse nested PCR)

Patient group	Frequency of total integrations per liver	Minimum frequency of distinct integrations per liver
Immune Tolerant HBeAg(+)	$1.3x10^9$	$\sim 7x10^6$
Immune active HBeAg(+)	$2x10^9$	$\sim 6x10^6$
Immune active HBeAg(-)	$5.6x10^9$	$\sim 5x10^6$

- Significant levels of integration across ALL disease phases tested
- With a liver size of $5x10^{11}$ hepatocytes, enough integration to mutate essentially every gene at least once
- HBV integration is a random event into human genome

Mason et al., Gastroenterology 2016

Impact of earlier treatment on HBV DNA integration



Lindh M, et al. Curr Opin Virol 2018;30:24–31

cccDNA: covalently closed circular DNA

The importance of early HBV treatment

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Reasons to consider early treatment in chronic hepatitis B patients

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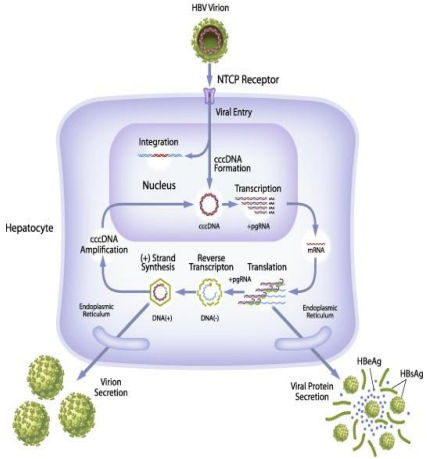
[b] *IFI-Institute for Interdisciplinary Medicine/MVZ-Hamburg at the Asklepios Klinik St Georg, University of Hamburg, Hamburg, Germany*
[c] *Barts Liver Centre, Blizard Institute, Barts and the London School of Medicine and Dentistry, London, UK*

Check for updates

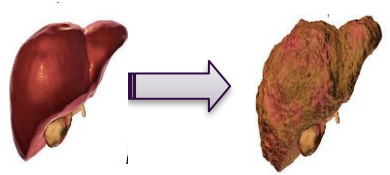
Koffas A, et al. Antiviral Res 2020; 177:104783

HBV DNA integration- the next challenge

- A large, transcriptionally active intrahepatic HBV reservoir increases risk of liver inflammation & disease progression
- Integration is known to contribute to HBV-driven tumourigenesis

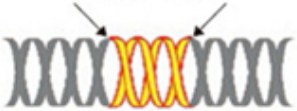


cccDNA
pgRNA

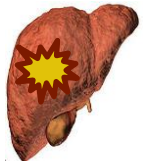


Inflammation **Cirrhosis**

HBV DNA integration



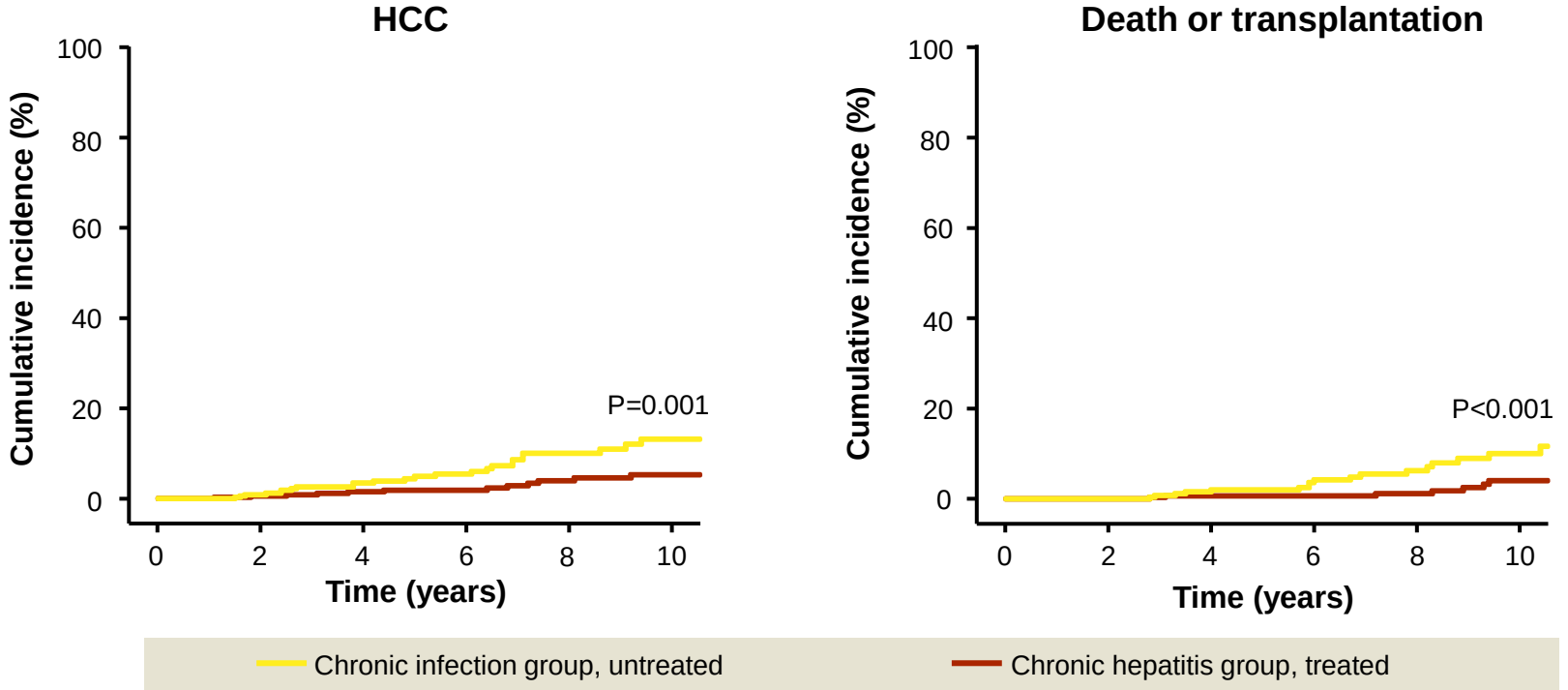
HBV DNA



Hepatocellular Carcinoma HCC

Liang LB, IJID 2016
Larsson SB wt al., Liver Int. 2014
Jiang Z et al., Genome Res. 2013
Tu T. et al., J Virol. 2015
Zhao LH et al., Nat Comm, 2016
Yang et al., J Cancer. 2018

Early HBV treatment improves outcomes

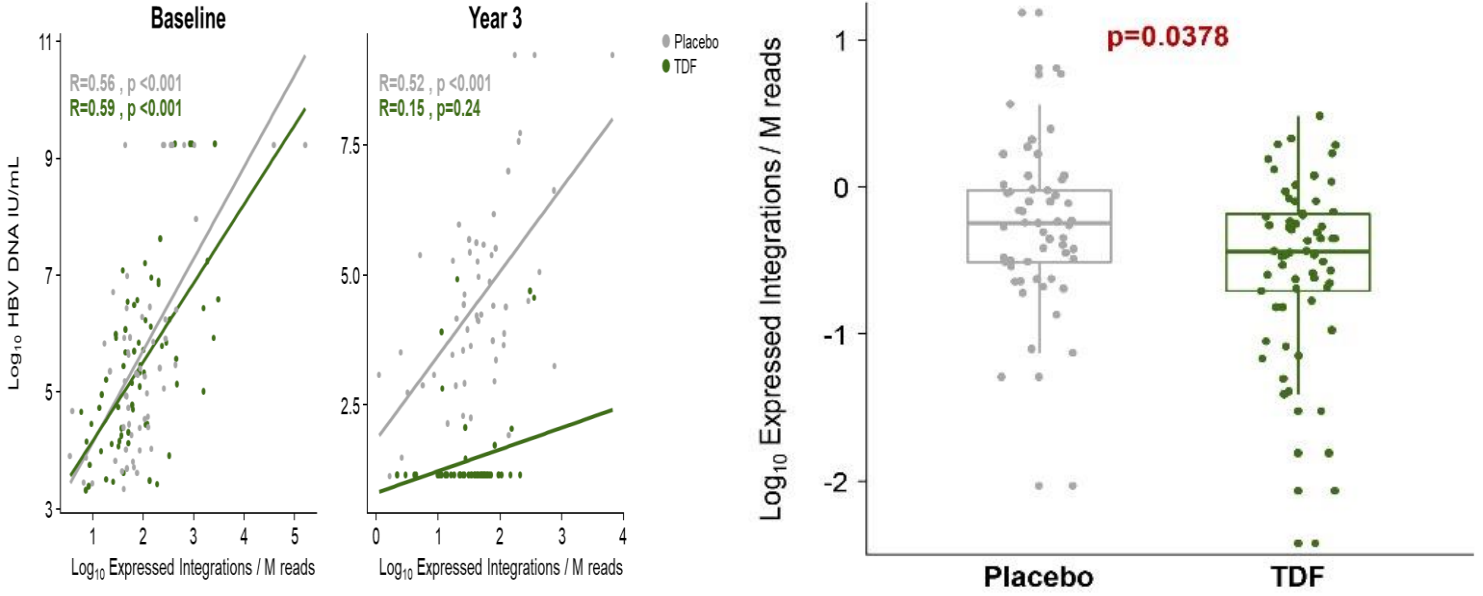


Historical cohort study of patients in tertiary hospital in Korea from 2000 to 2013.
413 untreated IT-phase patients with normal ALT levels and 1497 IA-phase patients treated with nucleos(t)ide analogues

Kim GA, et al. Gut 2018;67:945–52

TDF reduces the number of transcriptionally active viral integrations in chronic hepatitis B infection

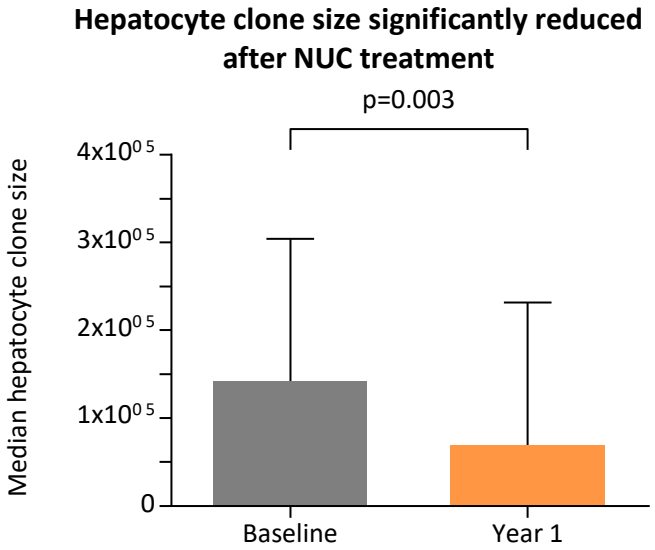
TDF mediated HBV DNA suppression: reduction of iMr at year 3



Hsu Y-C, et al. AASLD 2020

NUC therapy reduces clone size & downstream effects of HBV DNA integration

NUCs reduce transcriptional dysregulation of human genes & genetic pathways



- Gene mapping of the HBV integration events using RNA sequencing
- HBV integration frequently involves genes involved in cell proliferation antiviral and inflammatory responses
- Dysregulated protein coding genes, some of which are cancer related- underlining biological importance of these integrations
- NUCs can reduce viral genomic perturbation & downstream effects of integration

Chow N, et al. AASLD 2020

Svicher V, et al. Gut 2020;doi: 10.1136/gutjnl-2020-323300; Hsu Y-C, et al. AASLD 2020

HBV DNA integration across all CHB disease phases

Hepatology

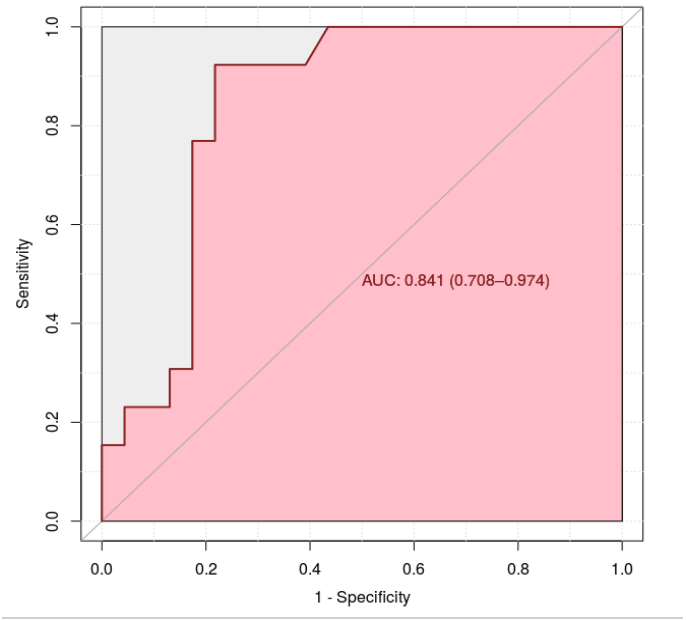
Original research

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 Kennedy [2]

Svicher V, et al. Gut 2020;doi: 10.1136/gutjnl-2020-323300

Correlation of serological markers with HBV DNA integration



Area under receiver operating characteristics (AUROC) curve of HBsAg levels and occurrence of HBV integration (area under curve [AUC] = 0.841; threshold: 5,000 IU/ml).

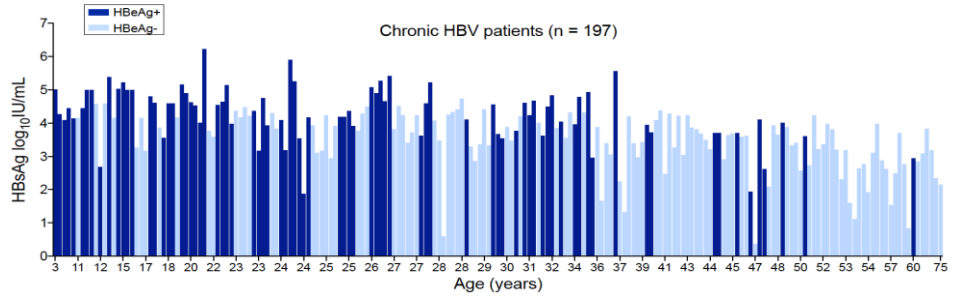
By AUROC, HBsAg >5,000 IU/ml identifies HBV integration with the best diagnostic accuracy (83.5%)

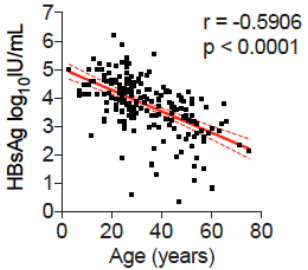
Negative Predictive Value	94.7%
Positive Predictive Value	70.6%

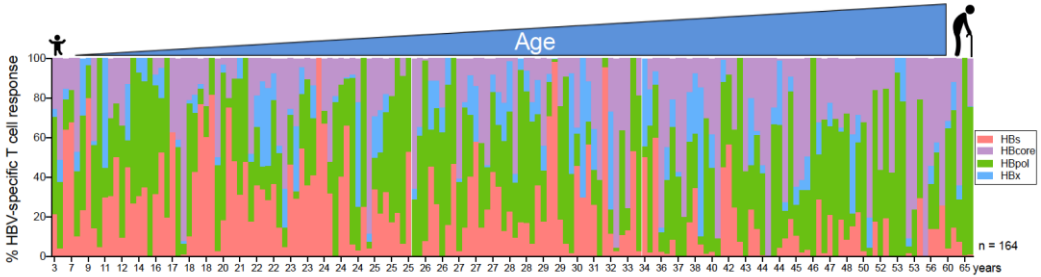
Sensitivity	**92.3%**
Specificity	**78.3%**

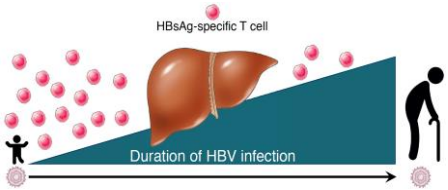
Effects of HBsAg on immune cells

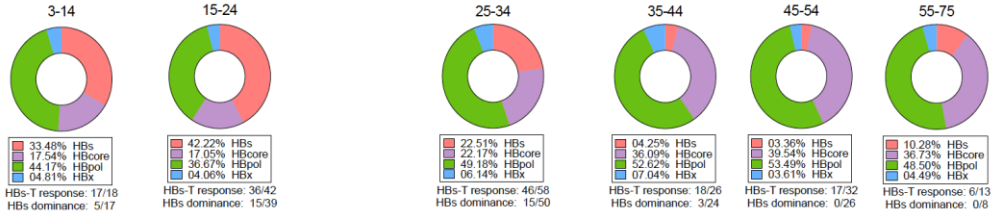
- HBV specific T cells analysed in a large patient cohort
- HBs-specific T cells reduce based on duration of infection, rather than HBsAg quantity











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

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

Concluding Remarks

- Our understanding of the IT and other quiescent phases of CHB has evolved in recent years
- *Clonal hepatocyte expansion, HBV DNA integration & events associated with hepatocarcinogenesis*
- *The IT phase may provide an ideal immunological window of opportunity for novel HBV therapies*
- Compelling case to broaden treatment criteria & to include IT patients in the functional cure program