Drug development in HBeAg positive subpopulations

Professor Patrick Kennedy

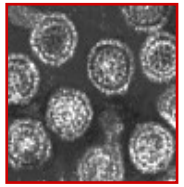
Blizard Institute,

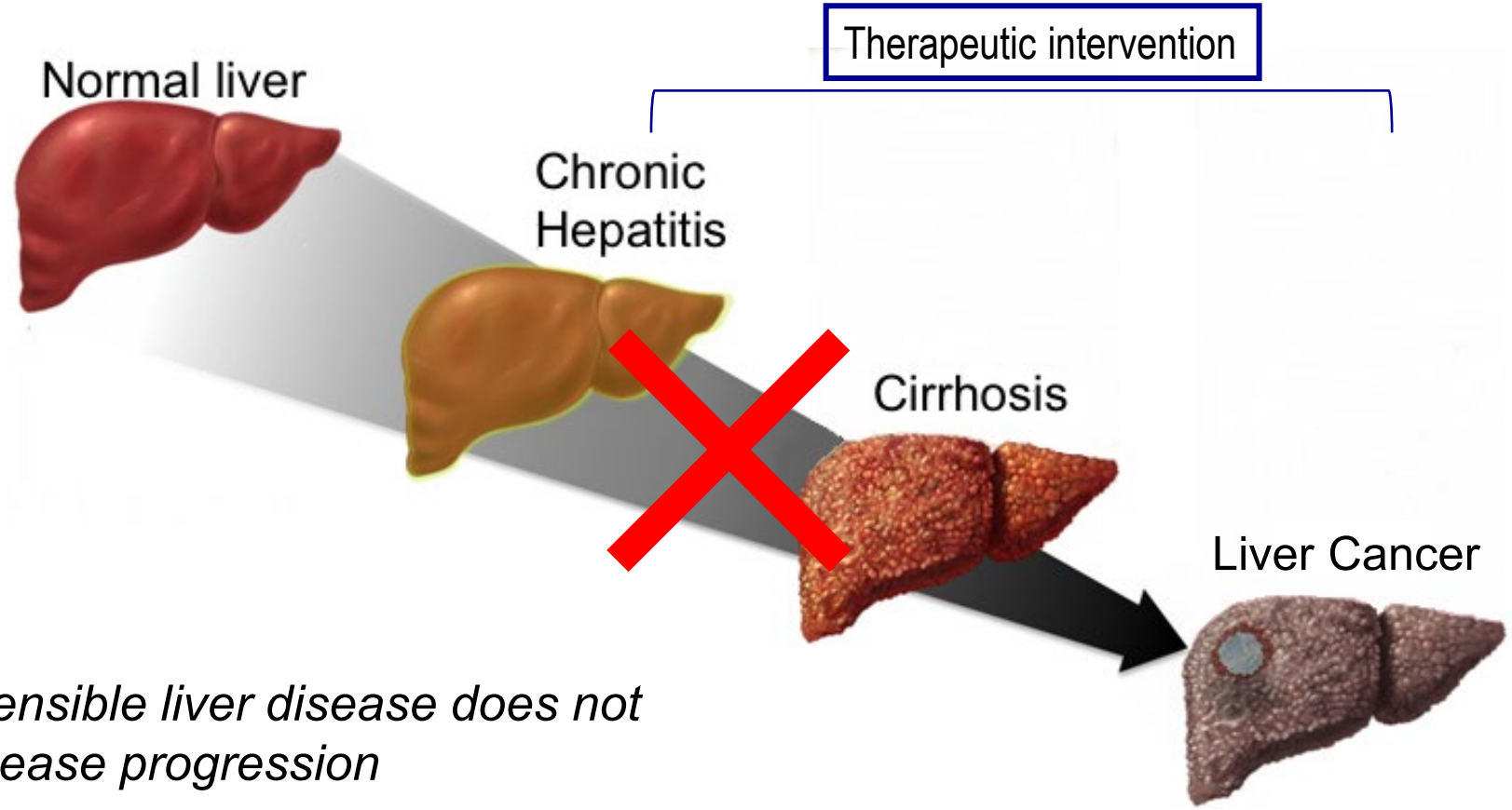
Barts and The London School of Medicine and Dentistry

Barts and The London
School of Medicine and Dentistry

November 3rd, 2022

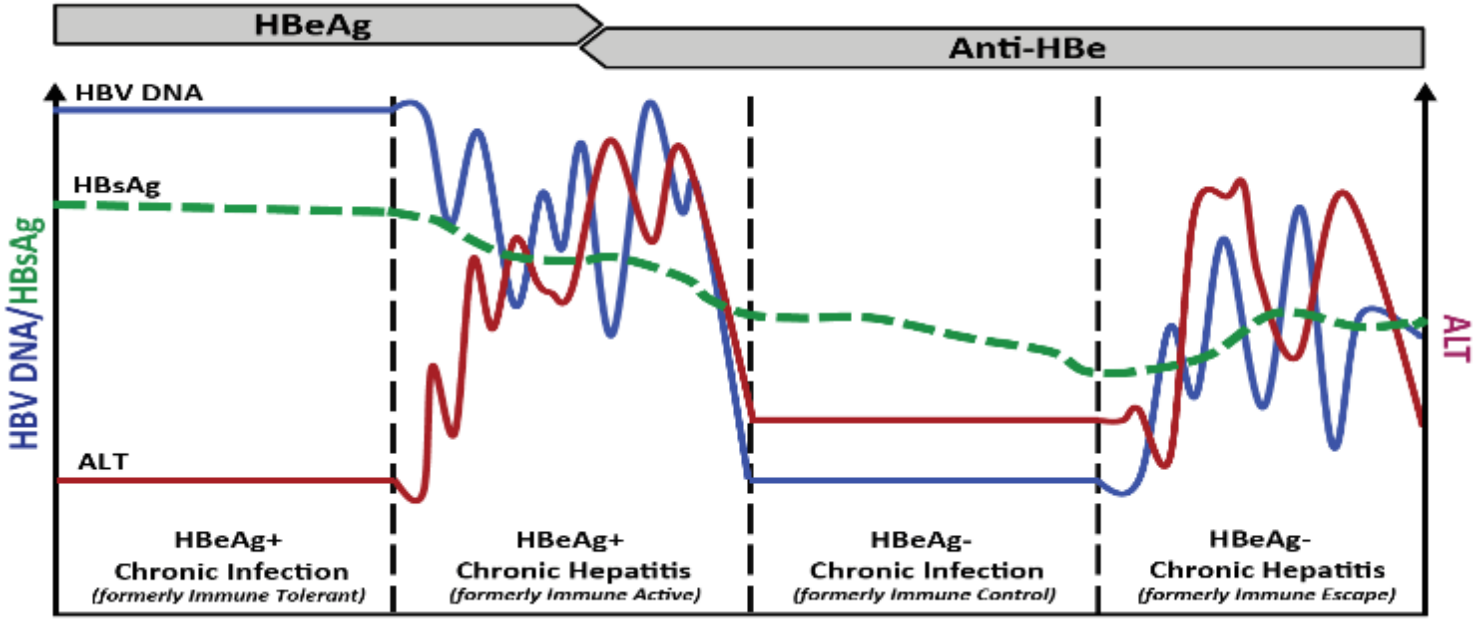
CHB is a dynamic disease





- *Lack of ostensible liver disease does not exclude disease progression*
- *Early Treatment Vs monitoring*

EASL terminology



Adapted from *Gill & Kennedy, Clin Med 2015*

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*

HBV, hepatitis B virus; HBeAg, hepatitis B 'e' antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma.
Gill US & Kennedy PTF, *Clin Med (Lond)*;2015

The clinical challenge of chronic HBV infection

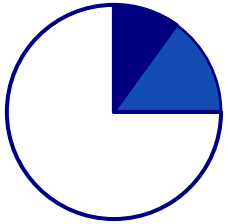
In the majority of countries, HCC accounts for 75–85% of all primary liver cancer cases[1]

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]

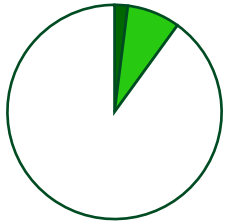
0.3–2.2%

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



10–25%

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



10%

Diagnosis made[4]

2%

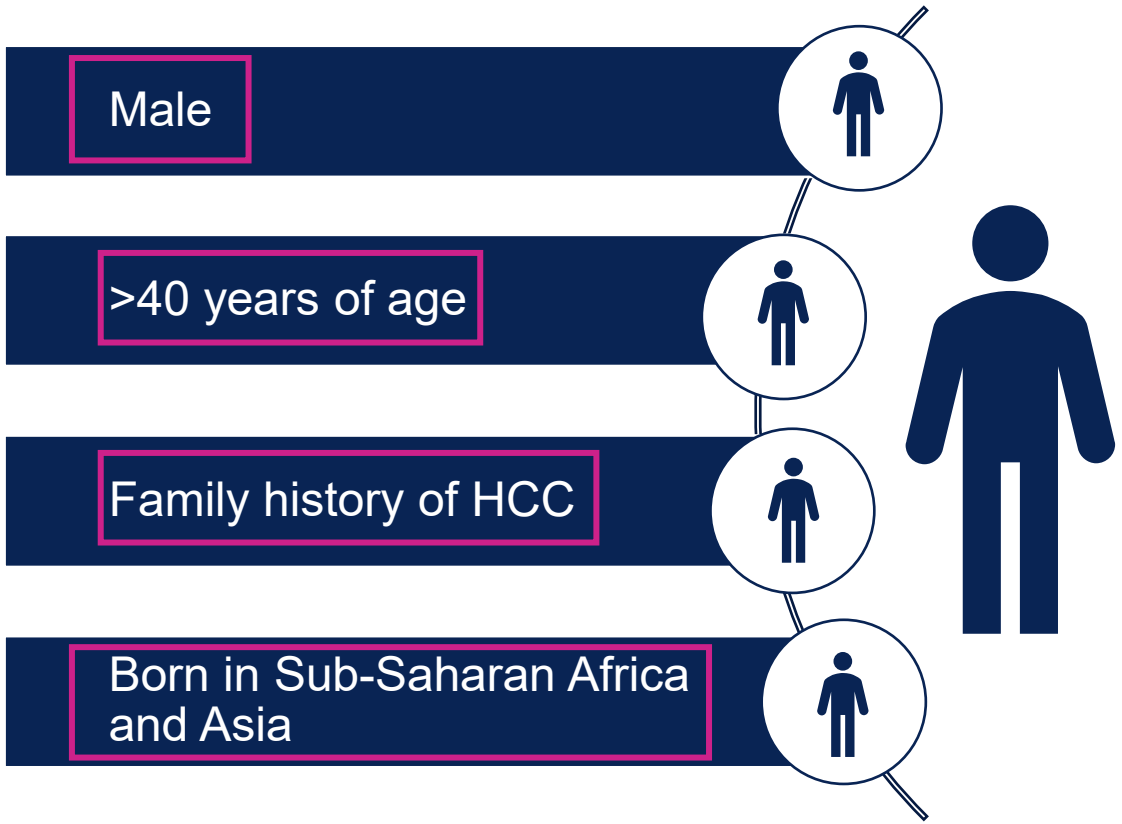
Treatment received[4]

CHB, chronic hepatitis B; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PY, person-years.

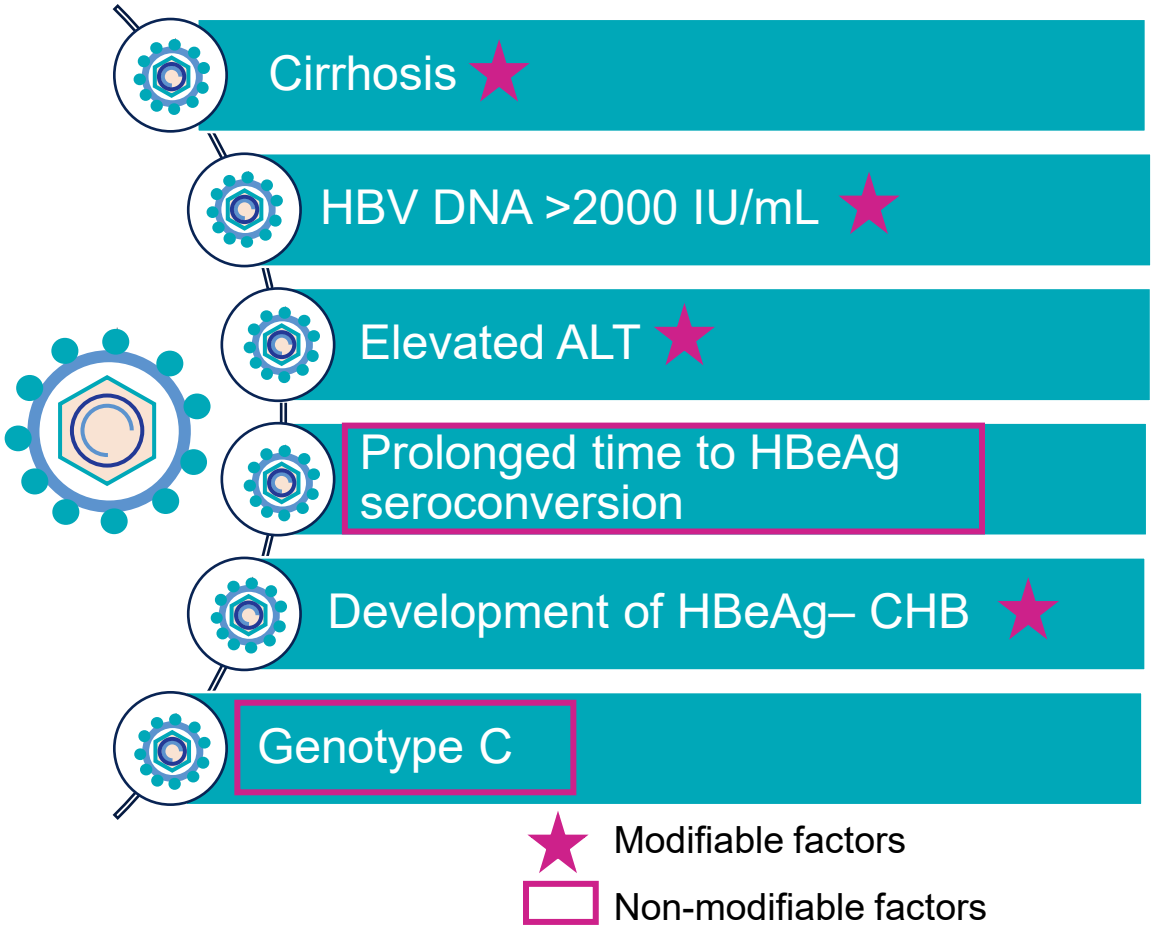
1. Sung H, et al. *CA Cancer J Clin* 2021;71:209–49; 2. El-Serag HB. *Gastroenterology* 2012;142:1264–73; 3. Balogh J, et al. *J Hepatocell Carcinoma* 2016;3:41–53;
4. Razavi-Shearer D, et al. *Lancet Gastroenterol Hepatol* 2018;3:383–403.

Untreated CHB and HCC risk

Host factors[1–8]



Viral and disease factors[1–8]



ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBeAg, hepatitis B 'e' antigen; HBV, hepatitis B virus; HCC: hepatocellular carcinoma; IU, international units.

1. Chen CJ, et al. *JAMA* 2006;295:65–73; 2. Iloeje UH, et al. *Gastroenterology* 2006;130:678–86; 3. Wong G. *J Hepatol* 2018;69:793–802; 4. Tong M, et al. *Aliment Pharmacol Ther* 2018;47:1181–200; 5. Yip CF. Presented at APASL 2018, oral presentation YIA-C-05; 6. Terrault NA, et al. *Hepatology* 2018;67:1560–99; 7. Yu MW, et al. *J Natl Cancer Inst* 2005;97:265–72; 8. Yang HI, et al. *NEJM* 2002;347:168–74.

The importance of timing HBV treatment initiation

Contents lists available at ScienceDirect

Antiviral Research

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

Reasons to consider early treatment in chronic hepatitis B patients

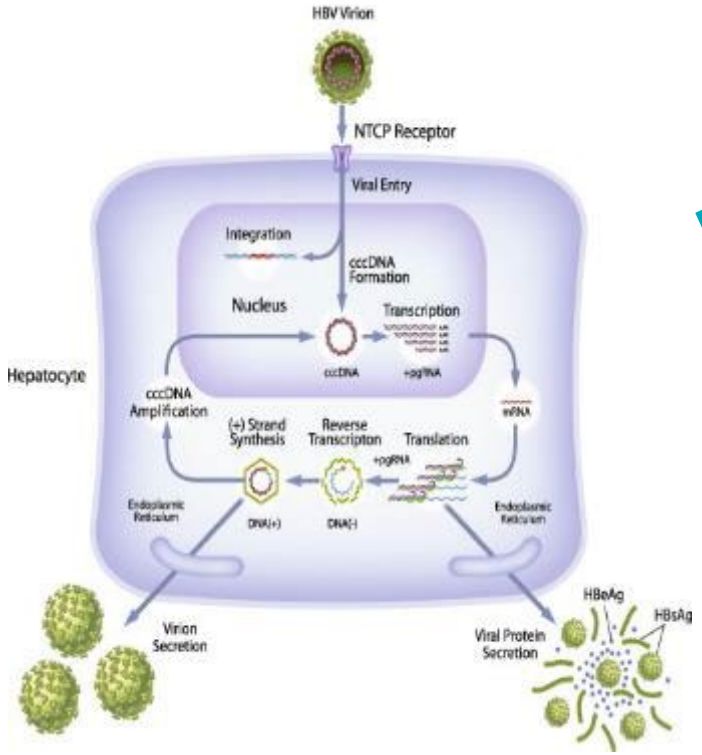
Apostolos Koffas[a], Jörg Petersen[b,**], Patrick T. Kennedy[c,*]

[a] *Gastroenterology Department, General University Hospital of Larisa, Larisa, Greece*
[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*

HBV, hepatitis B virus.
Koffas A, et al. *Antiviral Res* 2020;177:104783.

Addressing the challenge of HBV DNA integration[1–6]

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

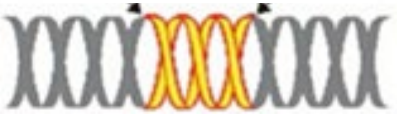


↑ **cccDNA**
pgRNA

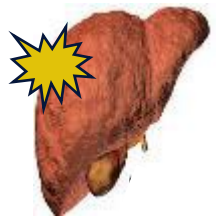
Inflammation

Cirrhosis

HBV DNA integration



HBV DNA



Hepatocellular carcinoma

cccDNA, covalently closed circular DNA; HBeAg, hepatitis B ‘e’ antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; mRNA, messenger RNA; NTCP, sodium taurocholate contransporting polypeptide; pgRNA, pregenomic RNA.

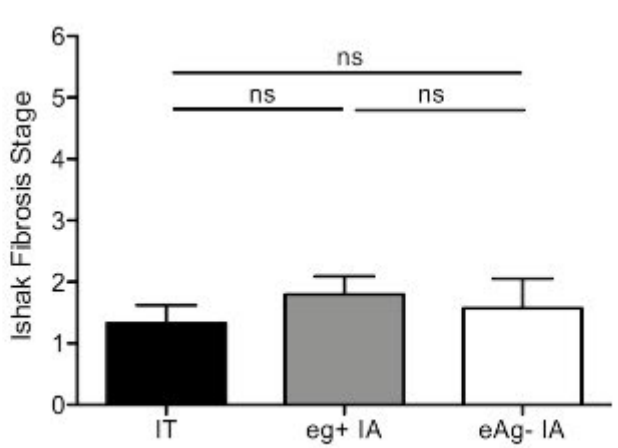
1. Liang LB, et al. *Int J Infect Dis* 2016;52:77–82; 2. Larsson SB, et al. *Liver Int* 2014;34:e238–45; 3. Jiang Z, et al. Ge*nome Res* 2013; 4. Tu T, et al. *J Virol.* 2015; 5. Zhao LH, et al. *Nat Commun* 2016;5:12992; 6. Yang R, et al. *J Cancer* 2018;9:3295–302.

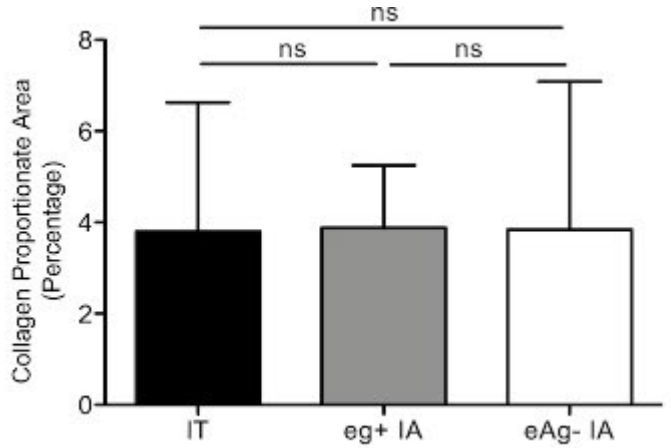
Why we should consider early treatment in ‘immune-tolerant’ CHB

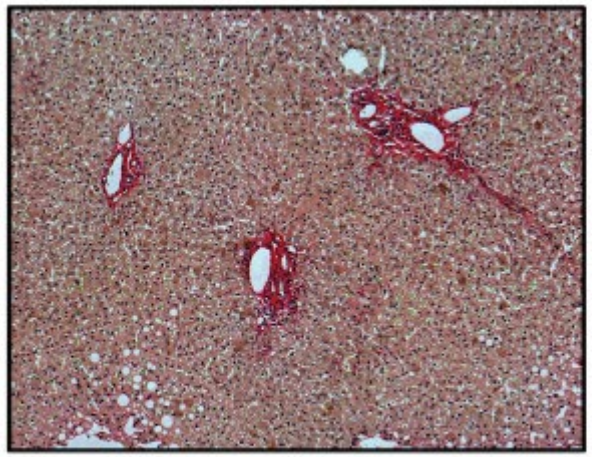
- This disease phase is not benign
- Clonal hepatocyte expansion and HBV DNA integration are observed
- Virus-specific T-cell responses are preserved
- Reduces the pool of HBV infection and risk of viral transmission in young people

CHB, chronic hepatitis B; HBV, hepatitis B virus.

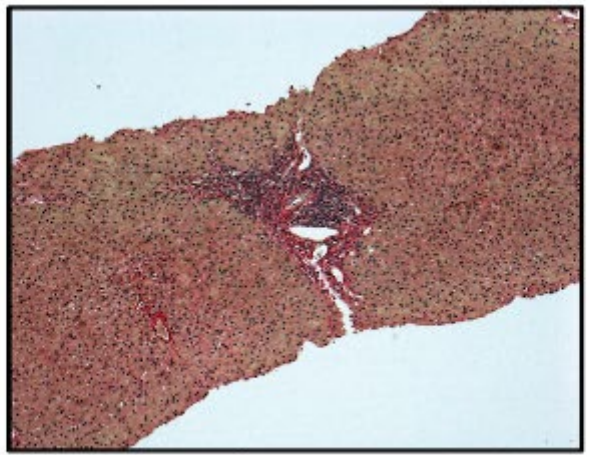
Liver damage in ‘immune-tolerant’ patients



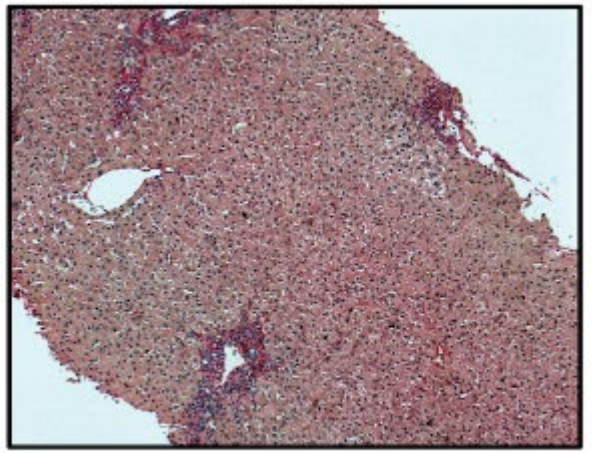




IT



HBeAg-positive IA

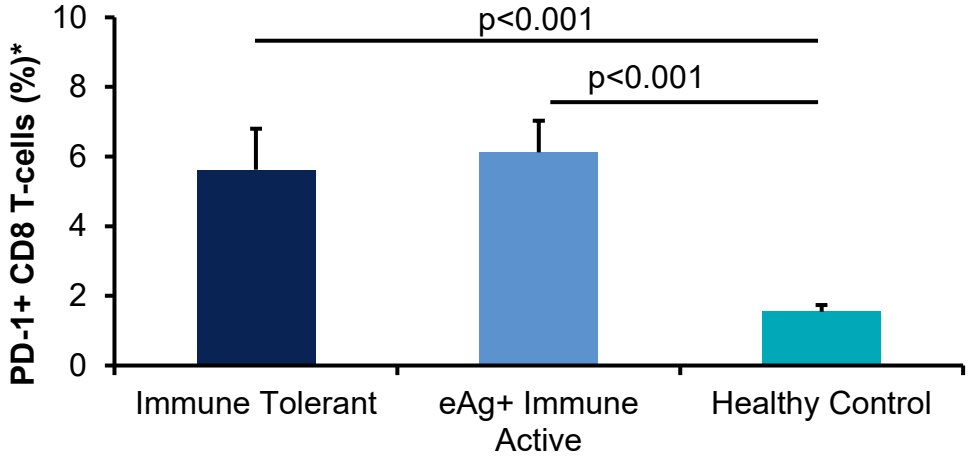


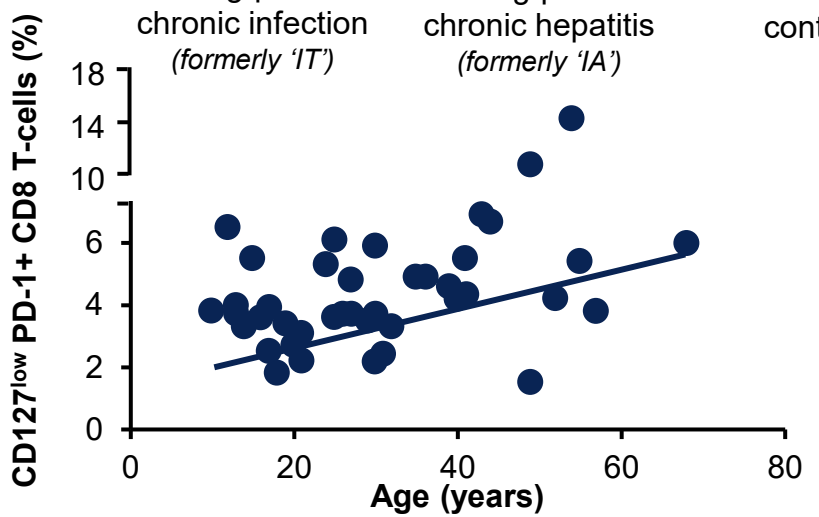
HBeAg-negative IA

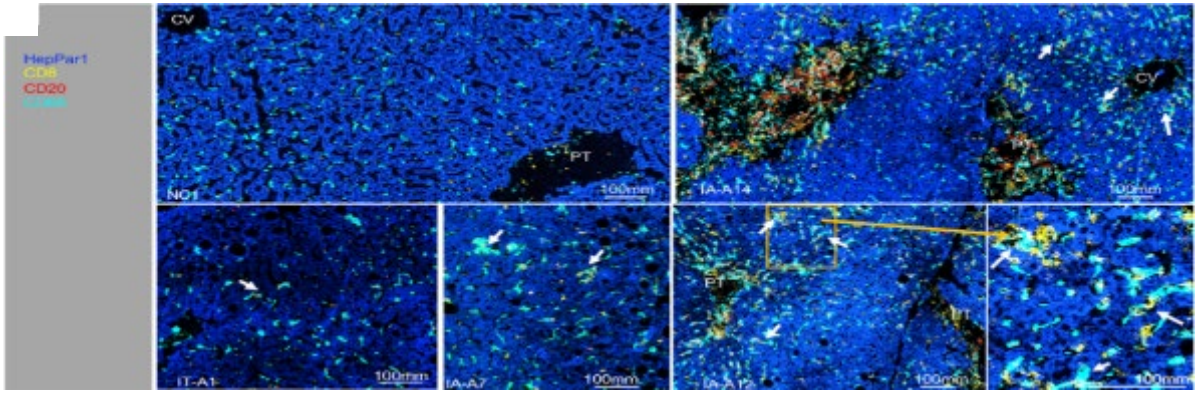
HBeAg, hepatitis B ‘e’ antigen; IA, immune active; IT, immune tolerant; ns, not significant.
Mason WS, et al. *Gastroenterology* 2016;151:986–98.

T-cell responses in HBeAg-positive chronic infection

Evidence of immune activity in the 'immune-tolerant' disease phase[1,2]







Although there is greater HLA-DR+ and CD45RO expression in IA vs IT patients, immune cells and evidence of effector function are observed in IT at similar frequencies as IA patients

Median %phenotype marker+ in immune subsets: IA vs IT

	CD4+ CD3+	CD8+ CD3+	CD20+	CD68+	CD11b+	CD57+ CD3-
%HLA ABC+ IA	99%	97%	98%	100%	94%	99%
%HLA ABC+ IT	99%	96%	98%	98%	79%	96%
%HLA DR+ IA	76%	66%	90%	96%	82%	70%
%HLA DR+ IT	58%	37%	74%	91%	87%	46%
%CD45RO+ IA	75%	74%	59%	34%	75%	25%
%CD45RO+ IT	51%	58%	10%	20%	63%	13%
%CD38+ IA	25%	23%	30%	28%	46%	56%
%CD38+ IT	22%	12%	30%	23%	32%	44%
%CD69+ IA	16%	18%	20%	6%	14%	11%
%CD69+ IT	16%	15%	20%	4%	4%	10%
%Ki67+ IA	17%	17%	22%	11%	38%	33%
%Ki67+ IT	13%	16%	24%	8%	24%	28%
%GranzB+ IA	7%	6%	9%	9%	57%	13%
%GranzB+ IT	4%	3%	1%	11%	72%	5%
%Perforin+ IA	2%	2%	2%	1%	8%	9%
%Perforin+ IT	1%	2%	0%	1%	4%	8%

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

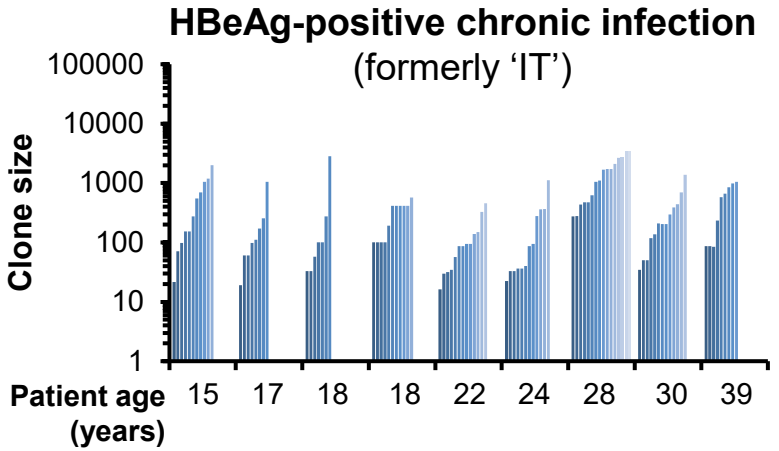
*Error bars represent 95% confidence interval.

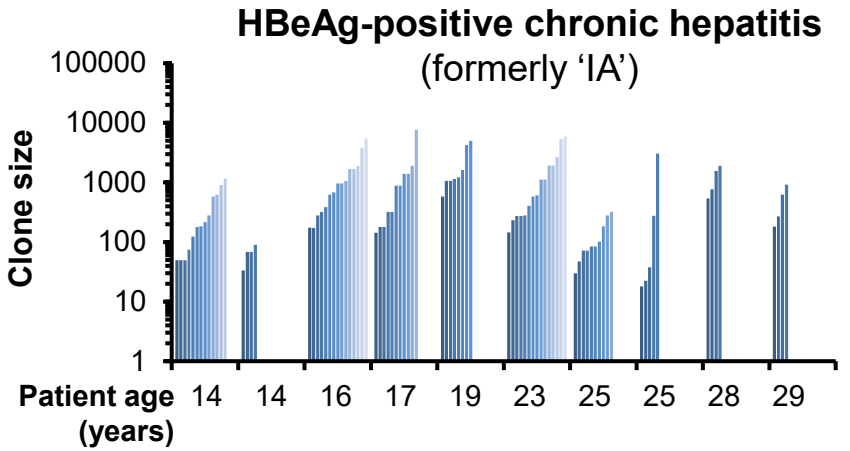
CD, cluster of differentiation; GranzB, granzyme B; HBeAg, hepatitis B 'e' antigen; HLA ABC, human leukocyte antigen class I; HLA-DR, human leukocyte antigen class II; IA, immune active; IT, immune tolerant; PD-1, programmed cell death protein 1.

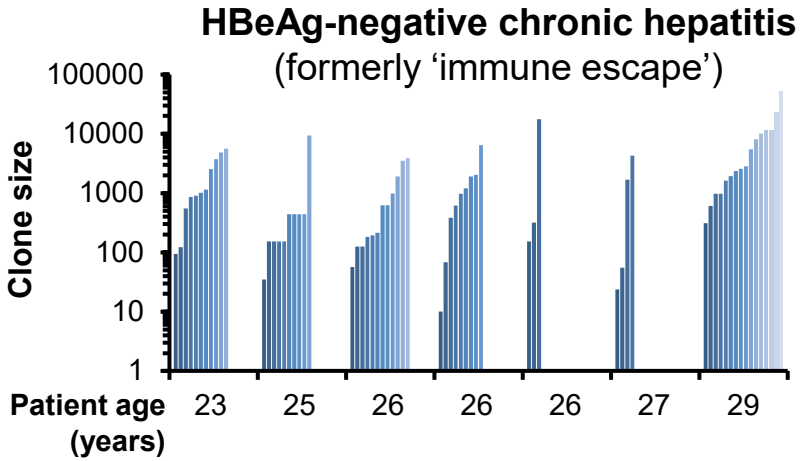
1. Kennedy P, et al. *Gastroenterology* 2012;143:637–45; 2. Traum D, et al. *JCI Insight* 2021;6:e146883.

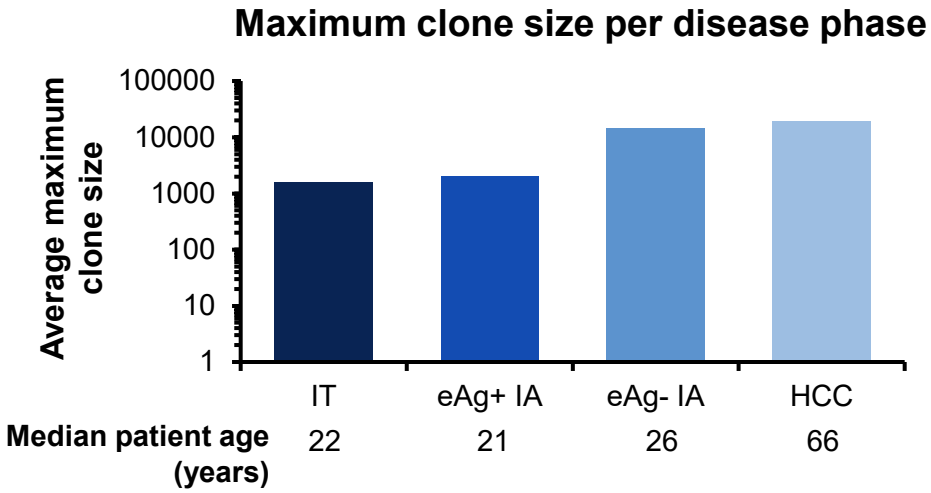
Immune activity in HBeAg-positive chronic infection

Clonal hepatocyte expansion in 'immune-tolerant' patients









(HB)eAg, (hepatitis B) 'e' antigen; HCC, hepatocellular carcinoma; IA, immune active; IT, immune tolerant.

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

Evidence of extensive transcriptionally active HBV integrations involving genetic regions crucial for cell proliferation in the setting of HBeAg positive infection

Romina Salpini[1], Luca Carioti[1], Arianna Battisti[1,2], Lorenzo Piermatteo[1], Livia Benedetti[1], Francesca Ceccherini-Silberstein[1], Upkar S. Gill[2], Valentina Svicher[1], Patrick T.F. Kennedy[2]

1. University of Rome Tor Vergata, Department of Experimental Medicine, Rome, Italy 2. Barts Liver Centre, Blizard Institute, Barts and The London SMD, QMUL, London, United Kingdom

TOR VERGATA
UNIVERSITÀ DEGLI STUDI DI ROMA

Queen Mary
University of London
Barts and The London

Study population

Liver tissues from 42 eAg+ chronically infected patients:

→ 27 with eAg+ hepatitis [eAg+CH]

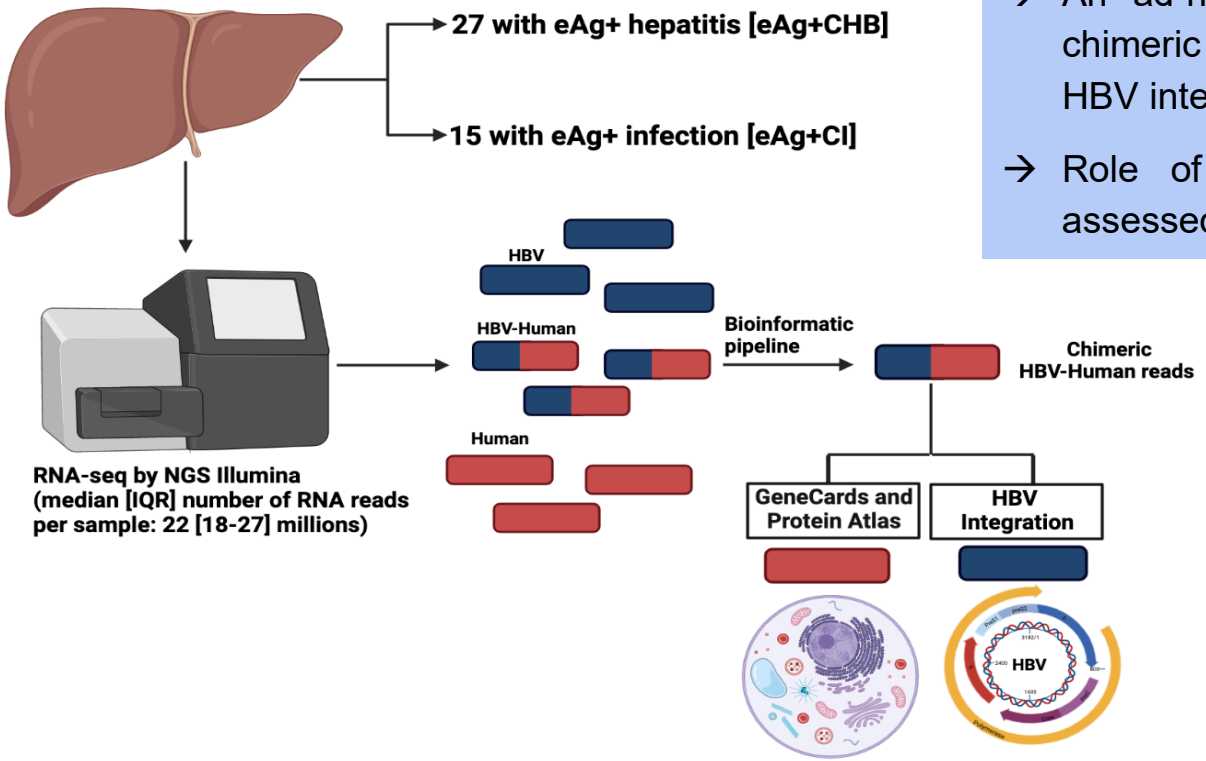
→ 15 with eAg+ infection [eAg+CI])

Experimental design

→ Total RNA-seq by NGS

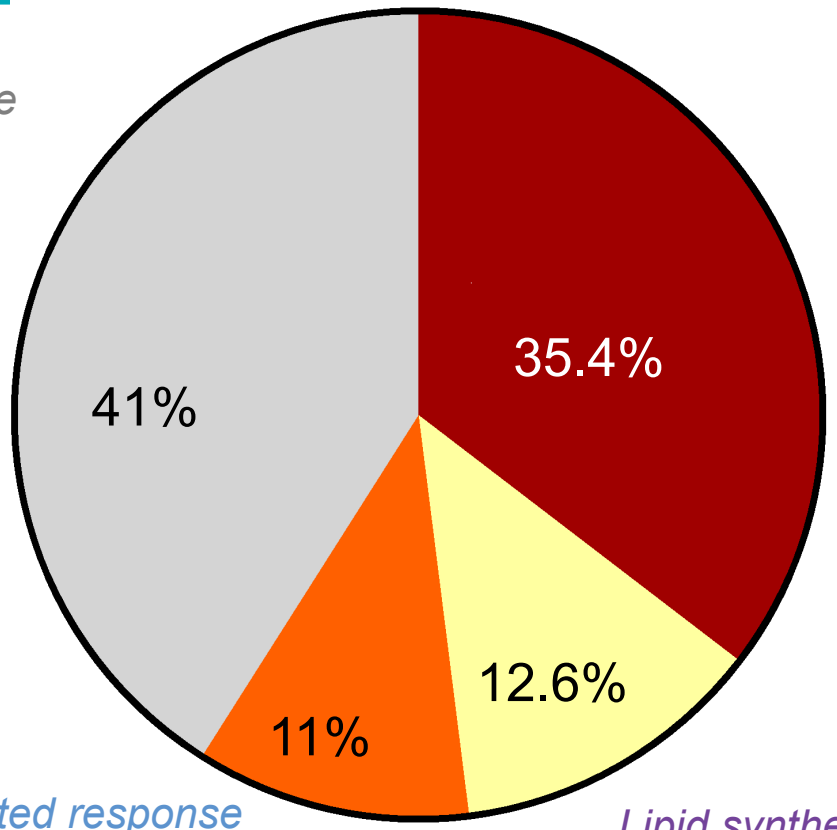
→ An ad-hoc bioinformatic pipeline to recognize chimeric HBV-human transcripts resulting from HBV integration.

→ Role of genes involved in HBV integration assessed by GeneCards and Protein Atlas.



HBV integrations result in the production of chimeric HBV-human aberrant transcripts, that involve genes regulating crucial intracellular pathways, that could confer a proliferative advantage to the hepatocytes, implying a relevant role in HBV-related pathogenic potential.

Other genes whose role needs to be better explored)



- Genes modulating cell survival/proliferation
- Genes involved in lipid metabolism pathways
- Genes involved in immune response
- Genes involved in other functions

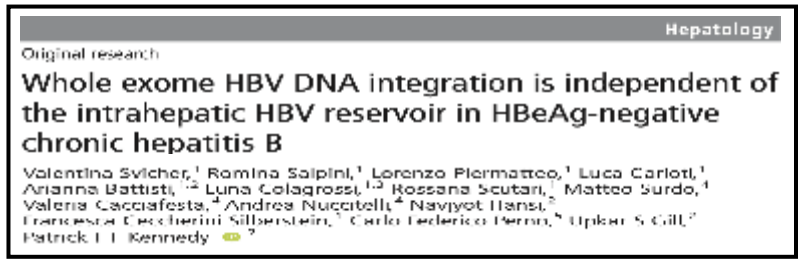
Cell cycle regulation
DNA replication and RNA transcription
Phosforilative cascade and redox status regulation
Apoptosis cascade

Lipid synthesis, transport and degradation

B-cell mediated response
T-cell mediated response
Cytokine and inflammatory pathway

High frequency of transcriptionally active HBV integrations involving crucial human genes in eAg-positive CHB, even in young patients with no or limited liver fibrosis, supporting early treatment initiation in this setting

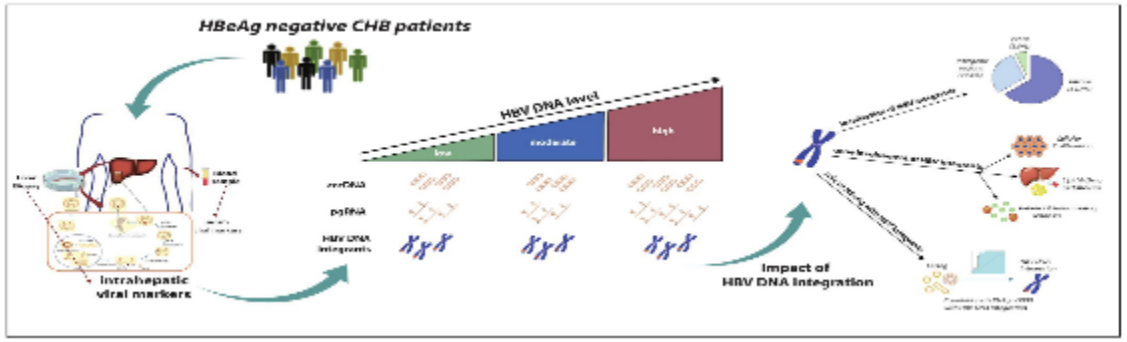
HBV DNA integration occurs across all CHB disease phases


Hepatology

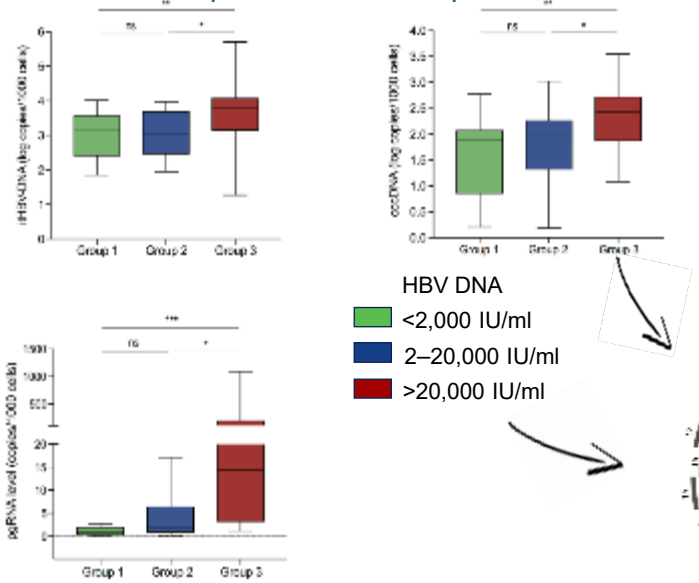
Original research

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,[1] Valeria Cacciafesta,[4] Andrea Nuccitelli,[4] Navjyot Hans,[5] Francesca Ceccherini Silberstein,[1] Carlo Federico Perno,[1,3] Upkar S Gill,[6] Patrick TF Kennedy [6,7]

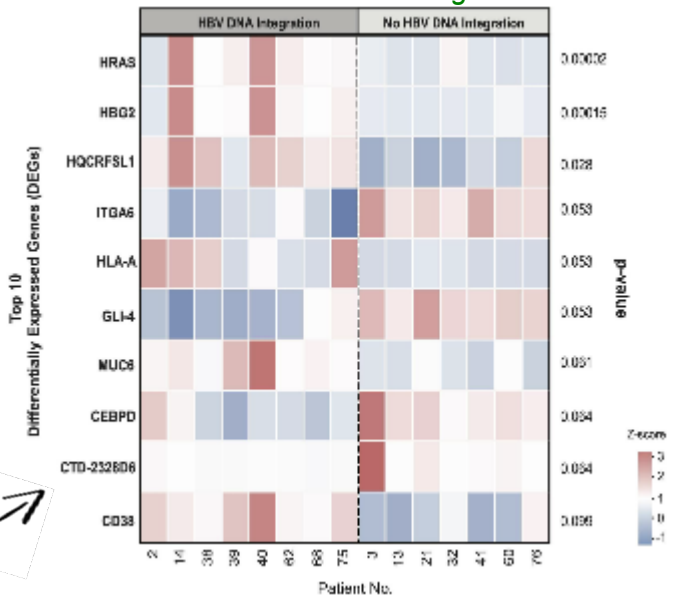


Differential expression of intrahepatic viral markers



Visualisation of HBV DNA integrations within the viral genome

Differentially expressed genes in relation to HBV DNA integration

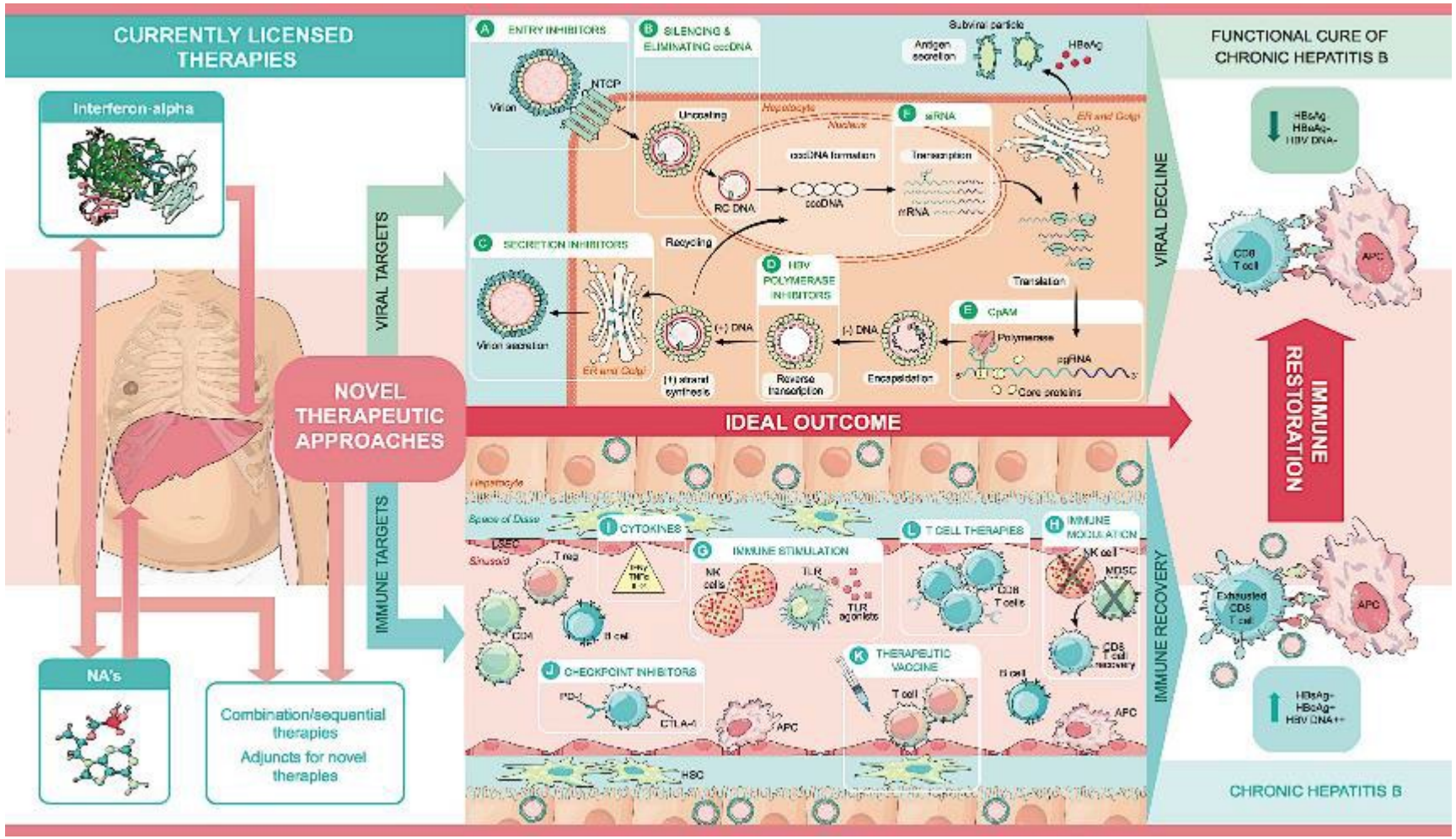


*p<0.05; **p<0.01; ***p<0.001.

cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; HBeAg, hepatitis B 'e' antigen; HBV, hepatitis B virus; IU, international units; ns, not significant; pgRNA, pregenomic RNA.

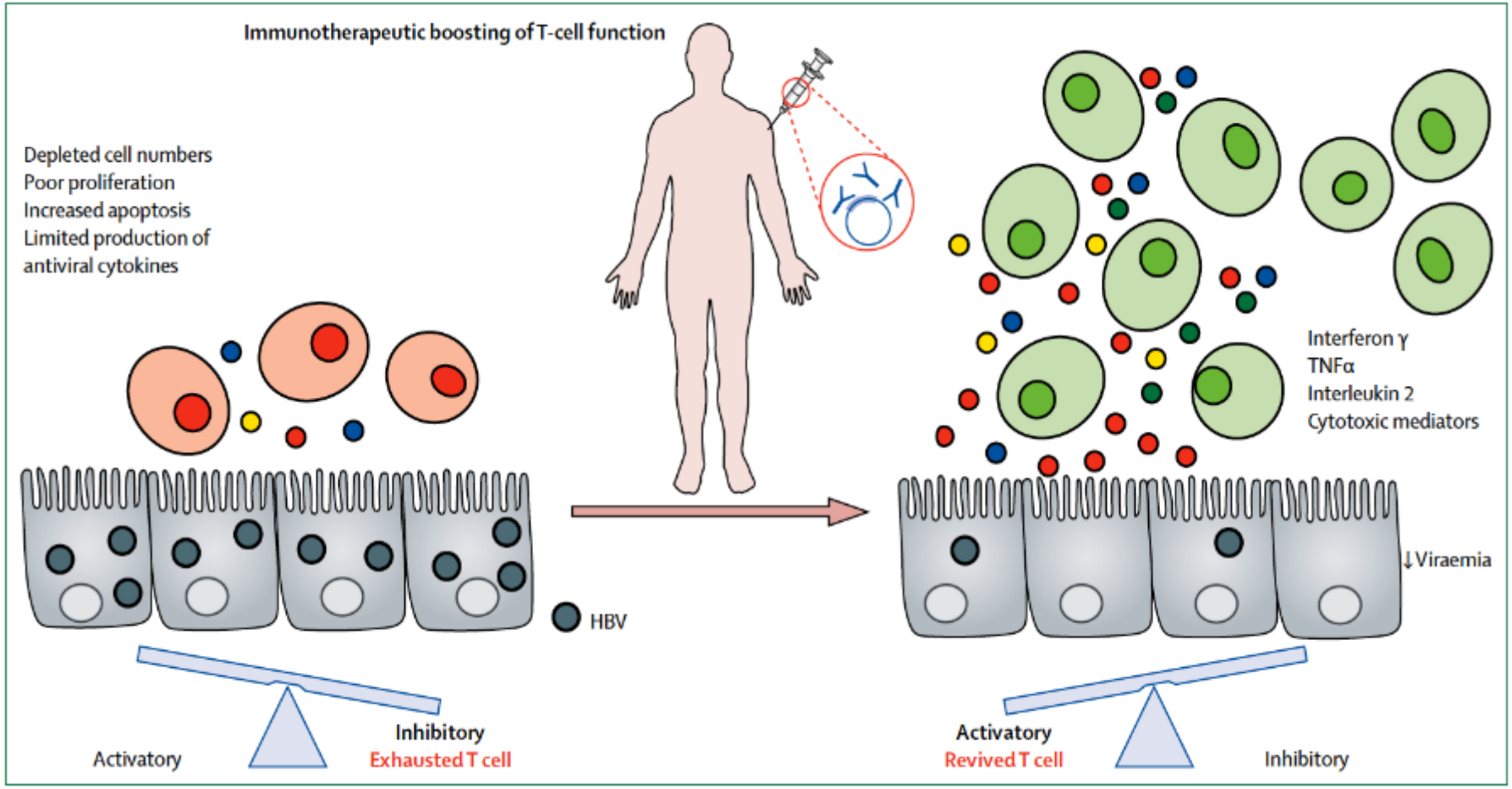
Svicher V, et al. *Gut* 2021;70:2337–48.

Data to date from the functional cure program



Gill US & Kennedy PTF *J Hepatol* 2017;67(2):412–414.

Shifting the balance of the immune response



HBV, hepatitis B virus.

Maini MK & Pallett LJ *Lancet Gastro Hep* 2018;3(3):192-202.

Clues from the early studies

- Greatest HBsAg reduction with siRNA seen in previously untreated HBeAg+ patients
- siRNA (AB-729) was associated with increased HBV-specific T cell activation and proliferation, coupled with a reduction in exhausted CD8+ T cells
- Need for more studies to better understand this virus-specific response- phenotypic & transcriptional analysis
- ? Role for next generation CAMs in HBeAg+ populations with high viral load

Early treatment: the changing treatment landscape

- **Resistance**
- **Safety**
- **Cost**
- **Lifelong treatment**

Concluding remarks

- **We should treat the HBeAg positive populations- given the evidence of HBV DNA integration and clonal hepatocyte expansion as recognised events associated with hepatocarcinogenesis**
- **Patients in the IT phase should be considered treatment candidates- there may be therapeutic gains to be made with earlier treatment**
- **Ideal combination of novel therapies remains to be defined, but data are emerging which will inform the best combination approaches in select patient groups**
- **Need for more "precision" studies to better define the effect of novel therapies in the liver- and these should be built in to clinical trial design**

CHB, chronic hepatitis B; HBV, hepatitis B virus; IT, immune tolerant; IU, international units.