MÁSTER EN HEPATOLOGÍA

UAM Universidad Autónoma de Madrid

Universidad de Alcalá

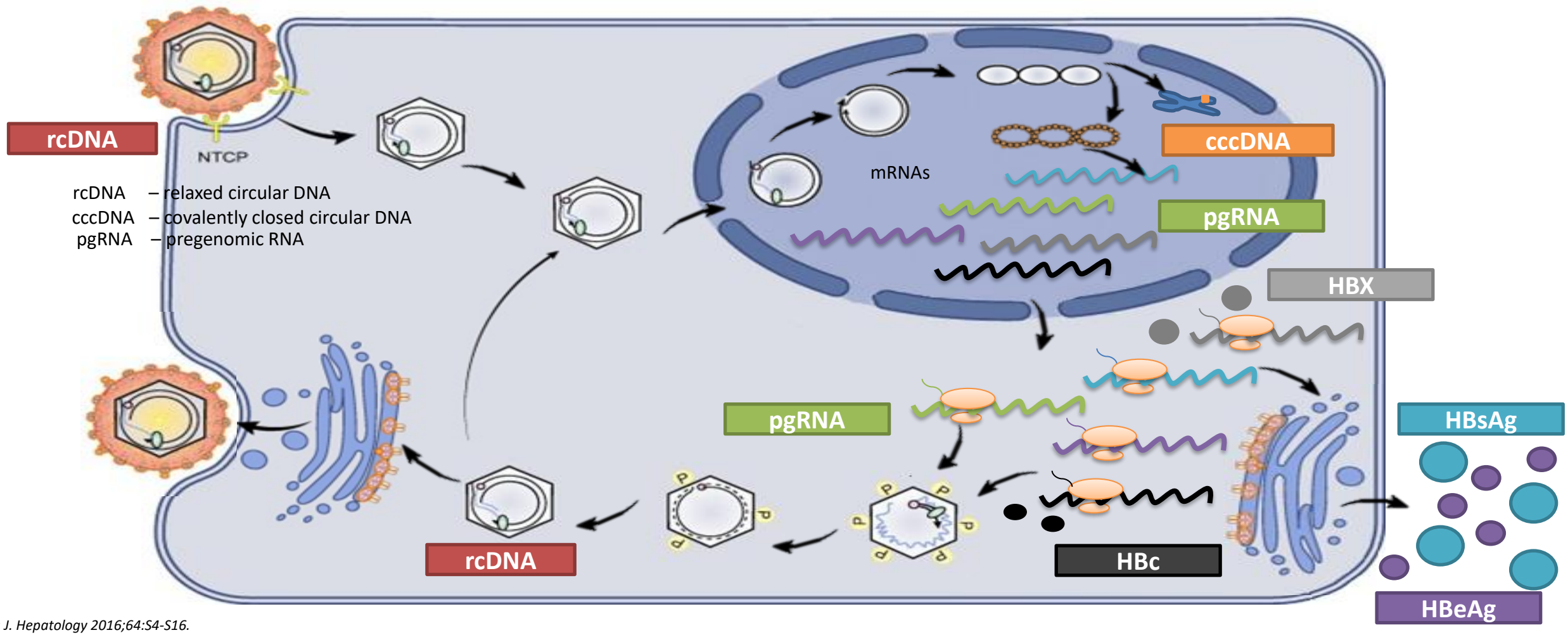
Asignatura: Hepatitis Virales

“Nuevas opciones terapéuticas en Hepatitis B”

Sabela Lens

Hospital Clínic de Barcelona, IDIBAPS, Universidad de BARCELONA, CIBERehd

Ciclo de vida Virus Hepatitis B



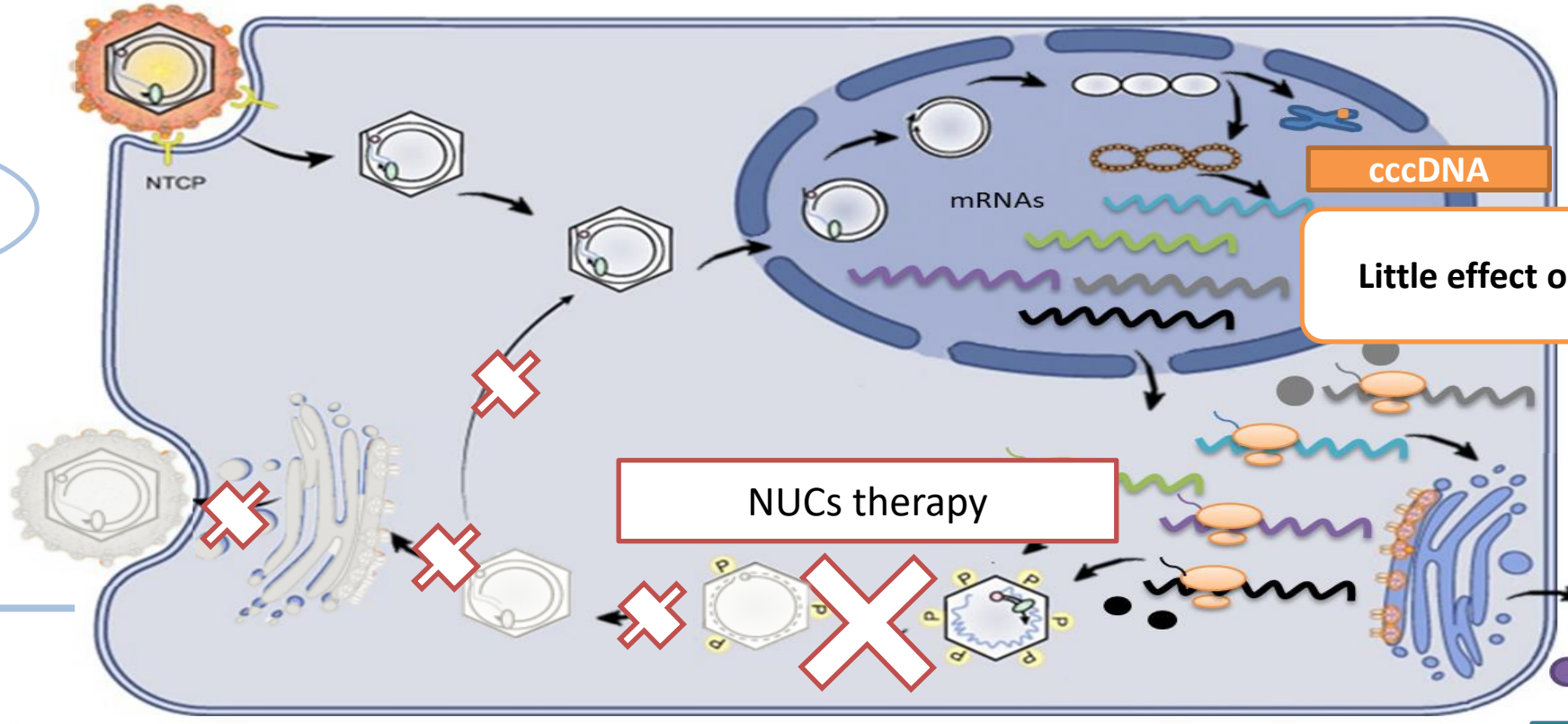
From: J. Hepatology 2016;64:S4-S16.

Ciclo de vida Virus Hepatitis B

Reduced cccDNA replenishment

Reduced virion secretion

Effective suppression of hepatitis B virus

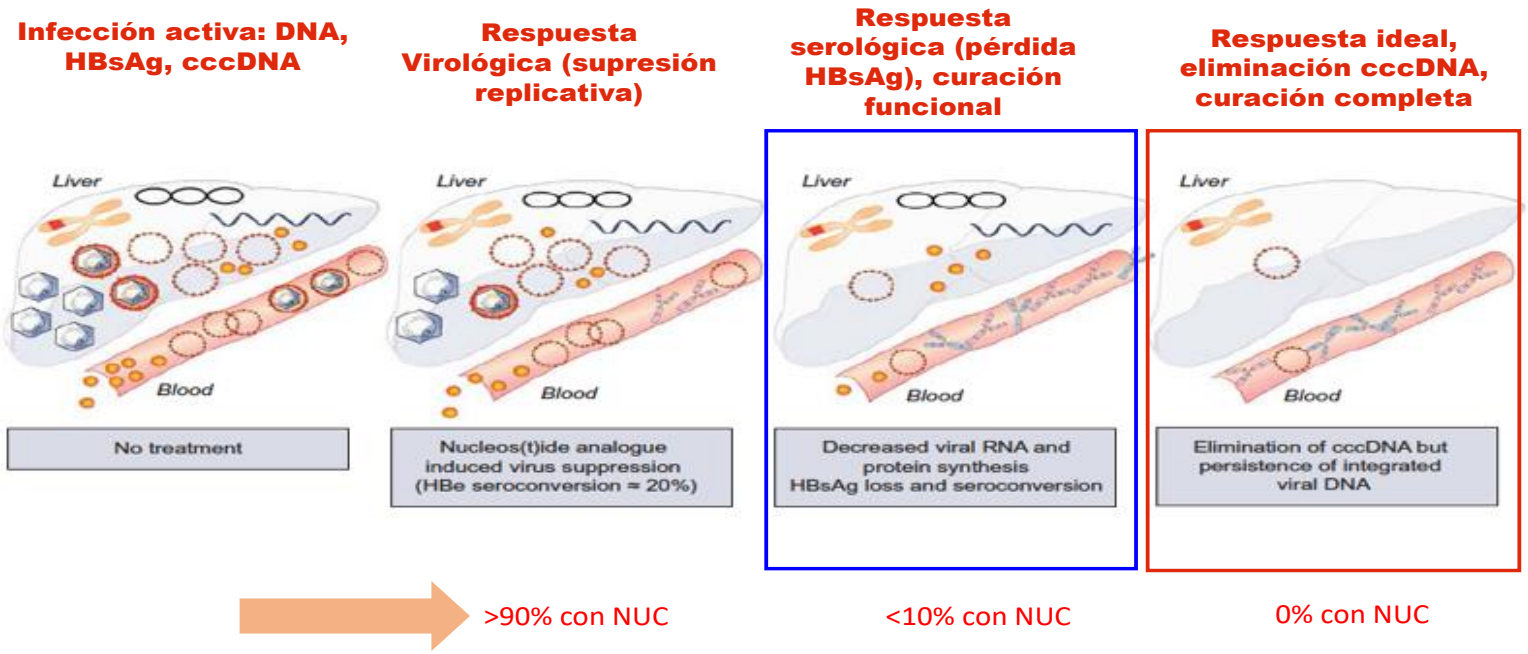


Treatment duration = indefinite

HBsAg loss (functional cure) is a rare event

Concepto de respuesta virológica y curación en Hepatitis B

Curación funcional: HBsAg- (con o sin anti-HBs) con DNA-VHB indetectable



Cornberg M et al. J Hepatology 2020
Figura adaptada de Durantel D and Zoulim F. J Hepatol, 2016

¿Cómo podemos alcanzar mayor tasa de curación funcional?

Interferón pegilado + Análogos Nucleós(t)idos (ANs)

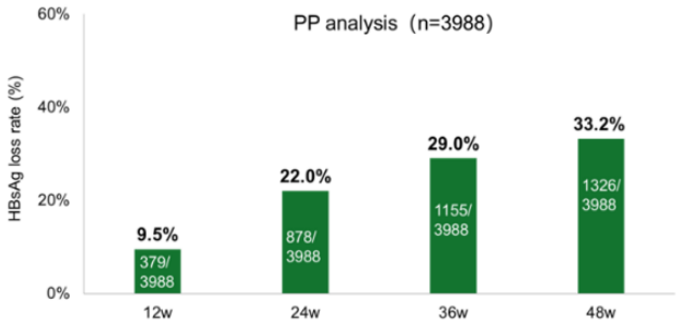
Everest Project
Multicentre real-world study in China (NCT04035837)
Focused on functional cure of CHB

Patients with CHB recruited since 2018
(NA therapy >1 year; HBV DNA <100 IU/mL; HBeAg negative, HBsAg ≤1500 IU/mL)

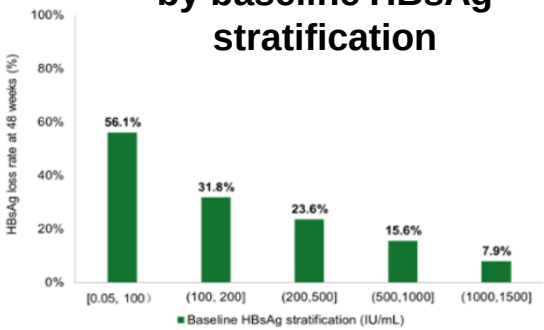
"Add-on" or "switch to" pegIFNα for 48–96 wks
(as decided by doctor and patient)

Analysis of data from patients completing 48 weeks' treatment
(mITT: n=5648; PP: n=3988)

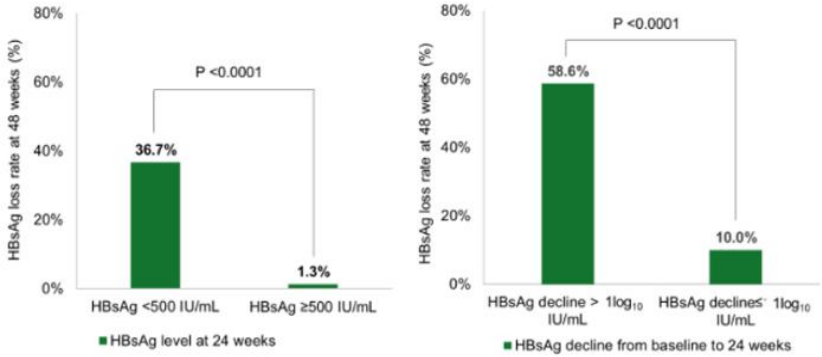
HBsAg loss rate (PP analysis)



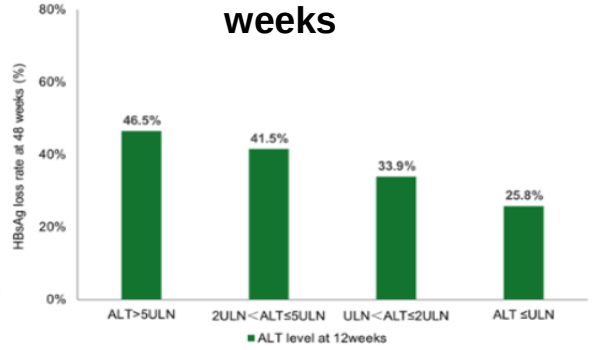
HBsAg loss rate at 48 weeks by baseline HBsAg stratification



HBsAg level or decline range at 24 weeks



ALT level at 12 weeks predicting HBsAg loss at 48 weeks

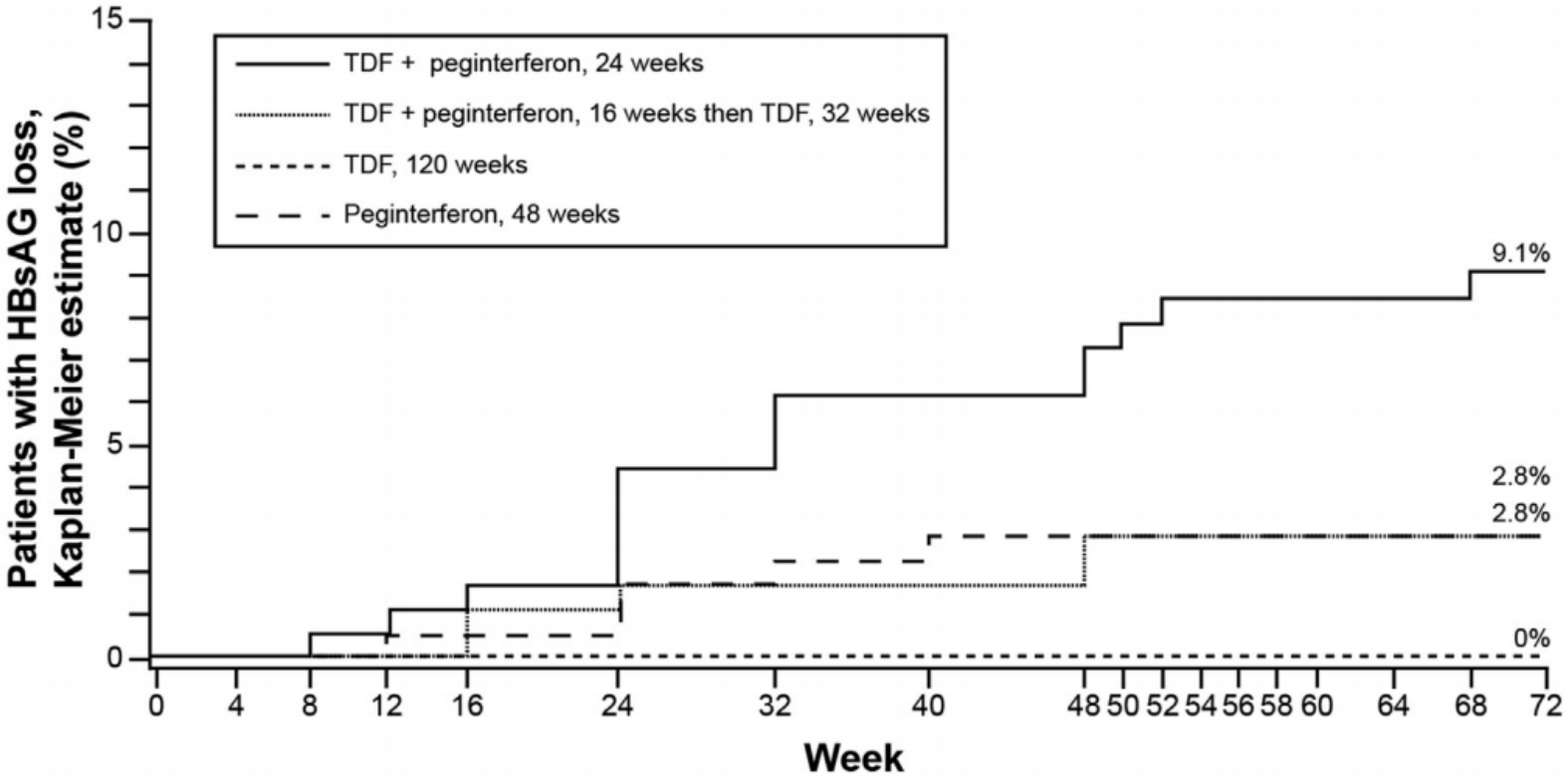


Lower HBsAg at baseline, lower HBsAg at 24 weeks, a rapid decline of HBsAg, and ALT elevations at 12 weeks are predictors for functional cure at 48 weeks

Xie C, et al. ILC 2022; SAT369

Interferón pegilado + Análogos Nucleós(t)idos (ANs)

n=740 → A: TDF+PegIFN x 24s vs (B) TDF+PegIFN x 16s + TDF 32s vs (C) TDF x24s vs (D) PegIFN x 48s

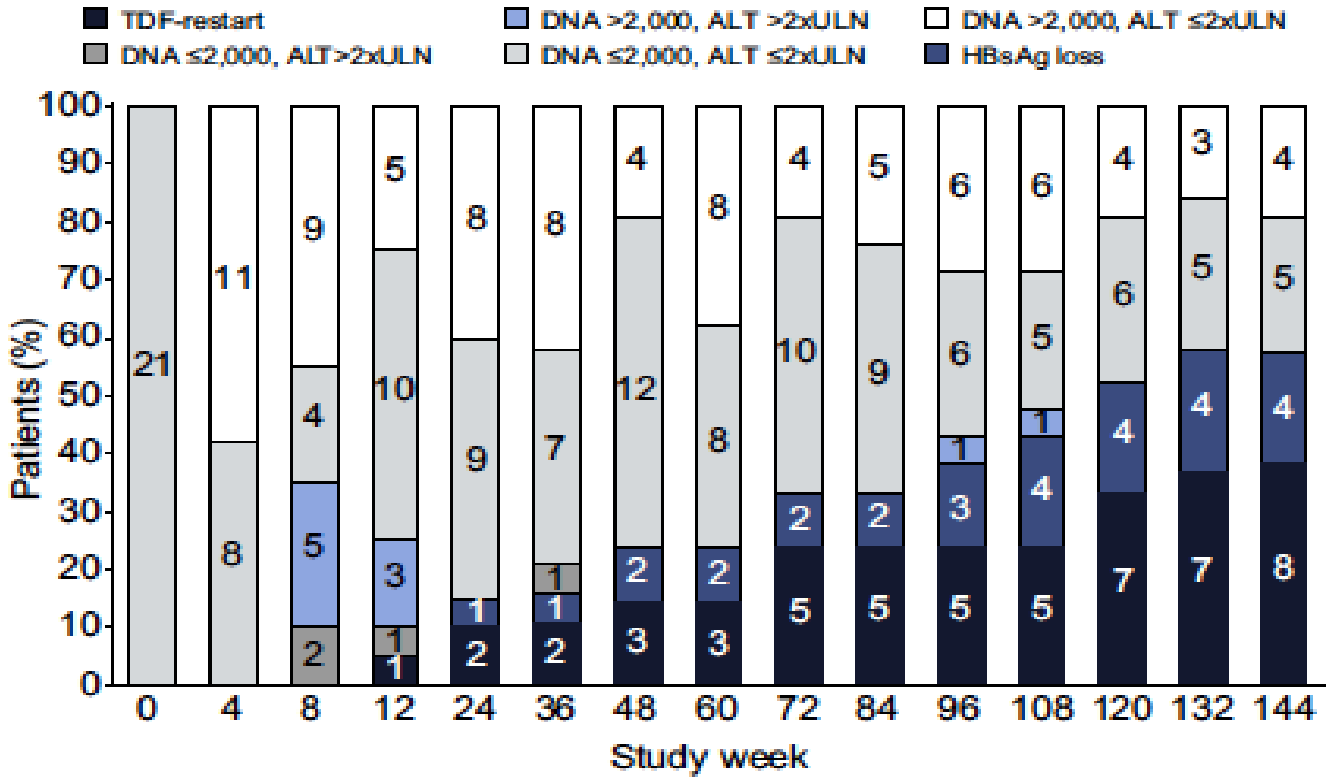


Marcellin et al, Gastroenterology 2016

Suspensión tratamiento antiviral ANs

Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved long-term (3 years) virological suppression under NA(s) may be considered if close post-NA monitoring can be guaranteed (Evidence level II-2, grade of recommendation 2).

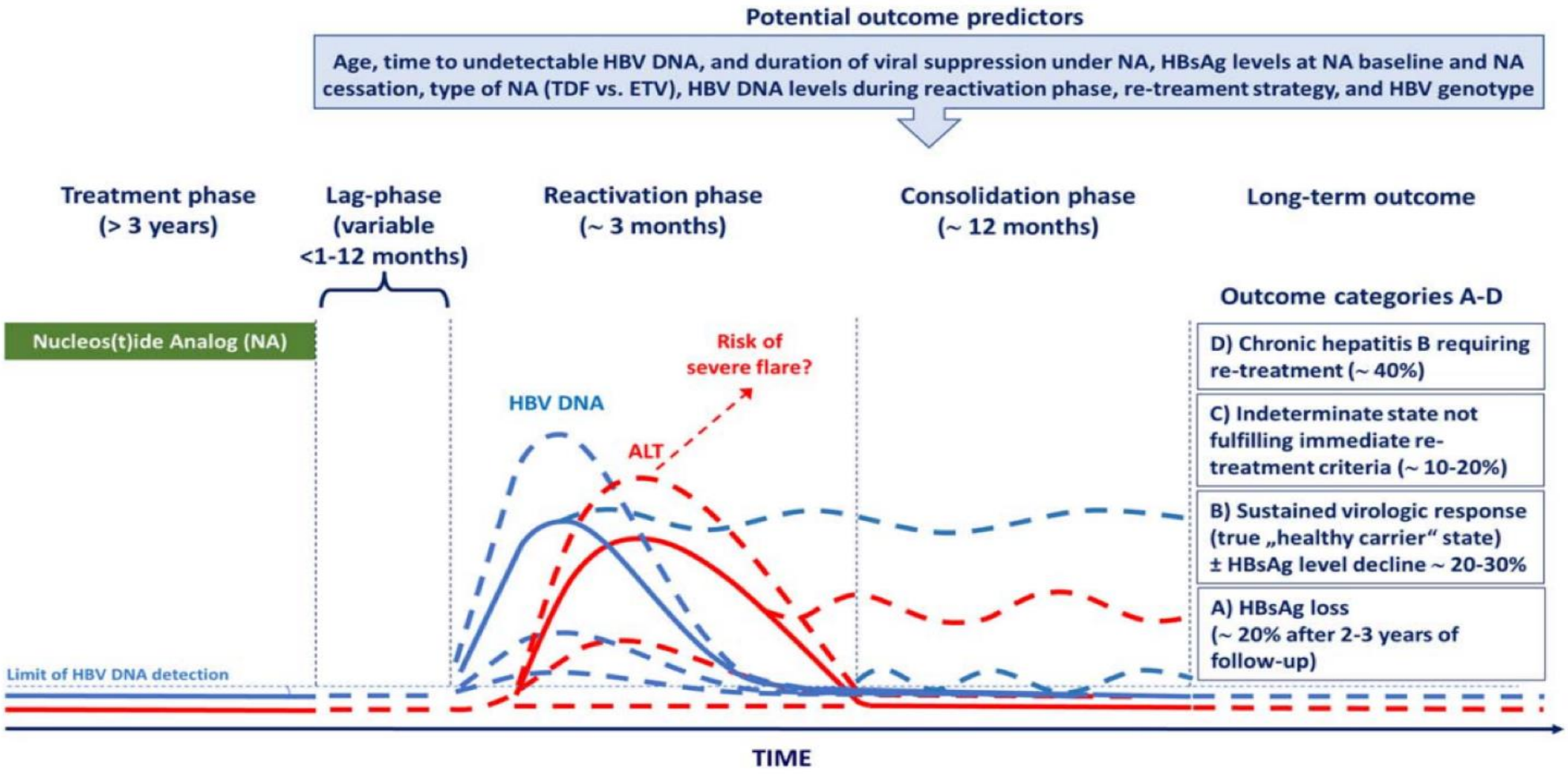
EASL clinical guidelines, J Hepatol 2017



N=21
3 years FU
62% off-therapy
19% HBsAg loss

Berg et al, J Hepatol 2017

Suspensión tratamiento AN

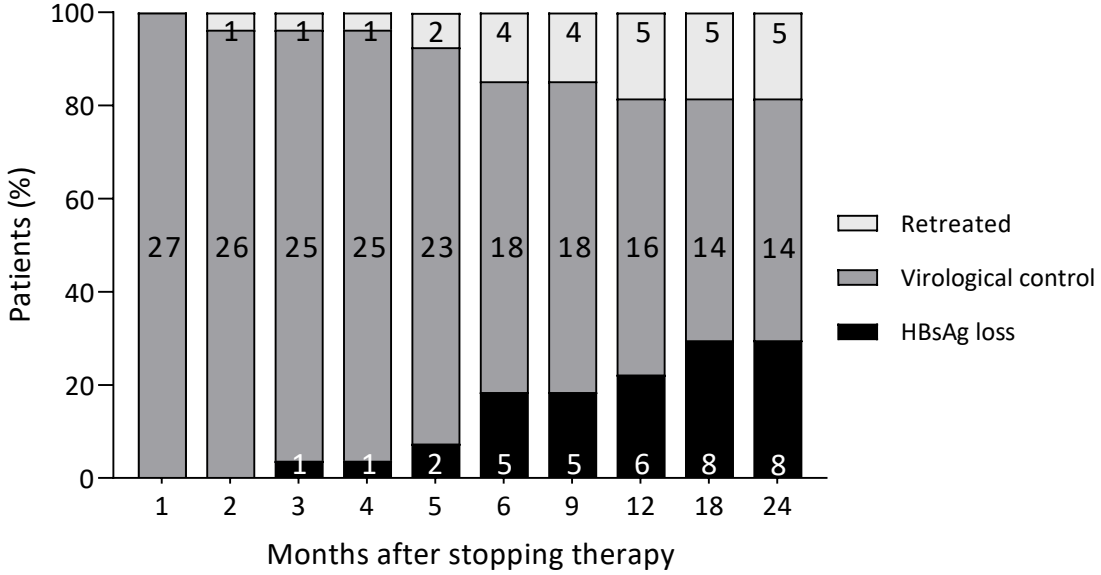


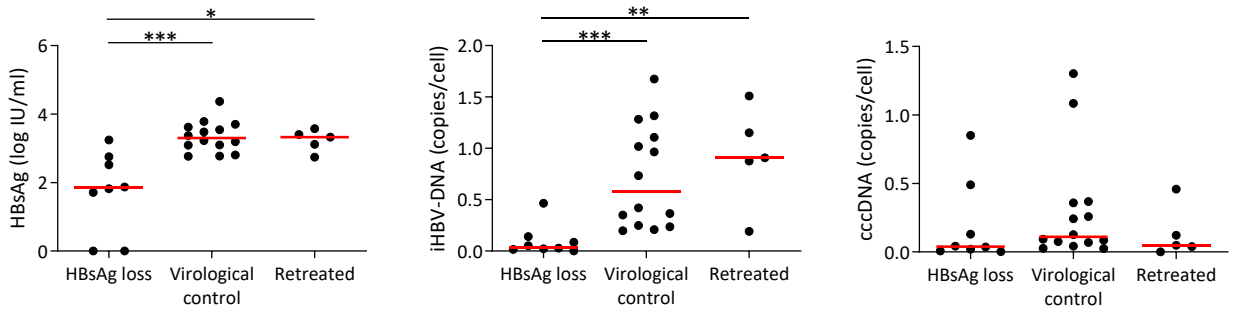
LAMPERTICO AND BERG HEPATOLOGY, 2018

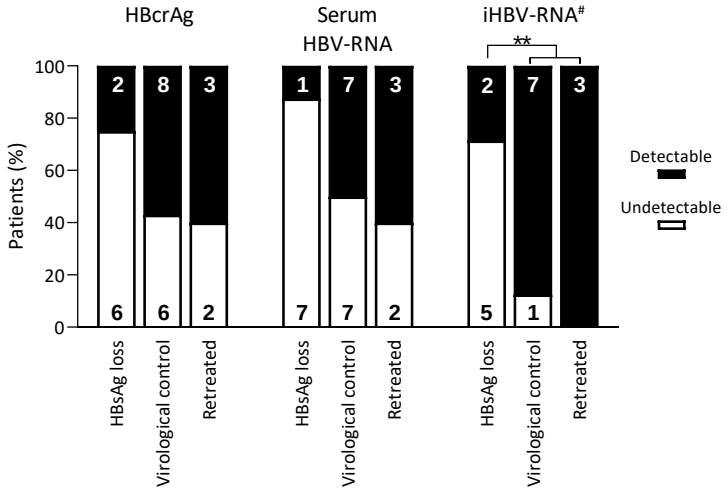
Suspensión tratamiento AN: predictores de respuesta

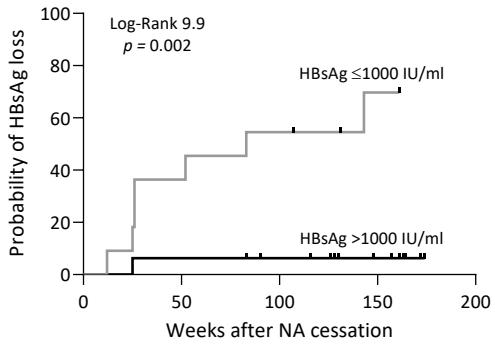
Estudio unicéntrico prospectivo:

27 pacientes HBeAg-negativo, sin CH, tto AN >3 años







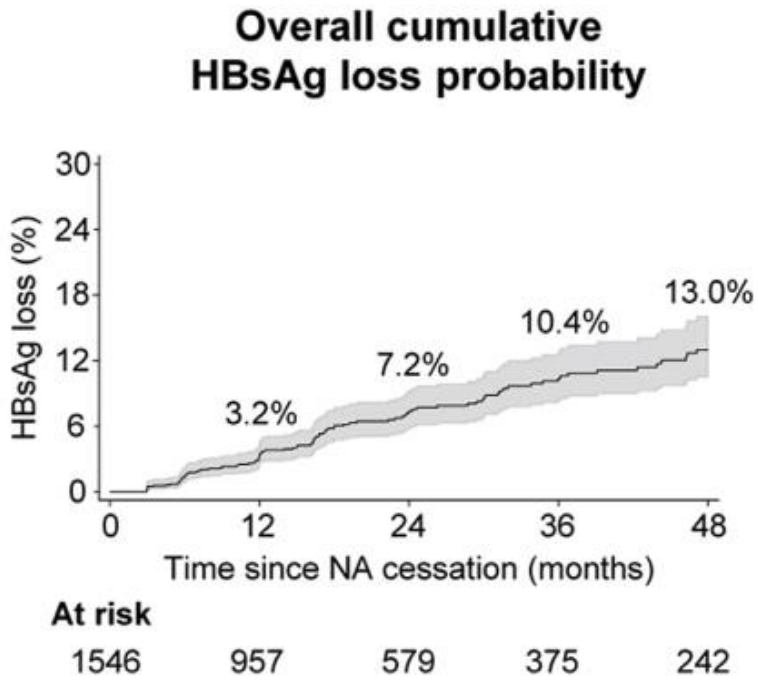


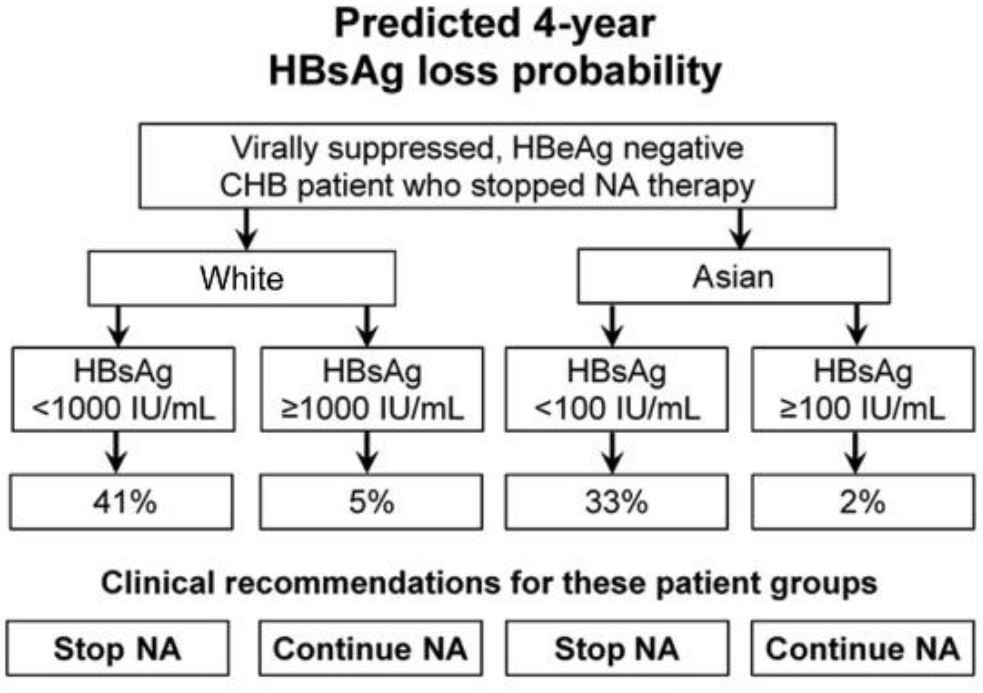
Se	Sp	PPV	NPV	LR+	LR-
88%	79%	64%	94%	4.16	0.16

García-López M and Lens S et al. J Hepatology 2021

Suspensión tratamiento AN: predictores de respuesta

REACT-B Study: 13 Centers North America, Asia, Europe. n=1552 HBeAg-neg CHB patients → n=114 HBsAg loss



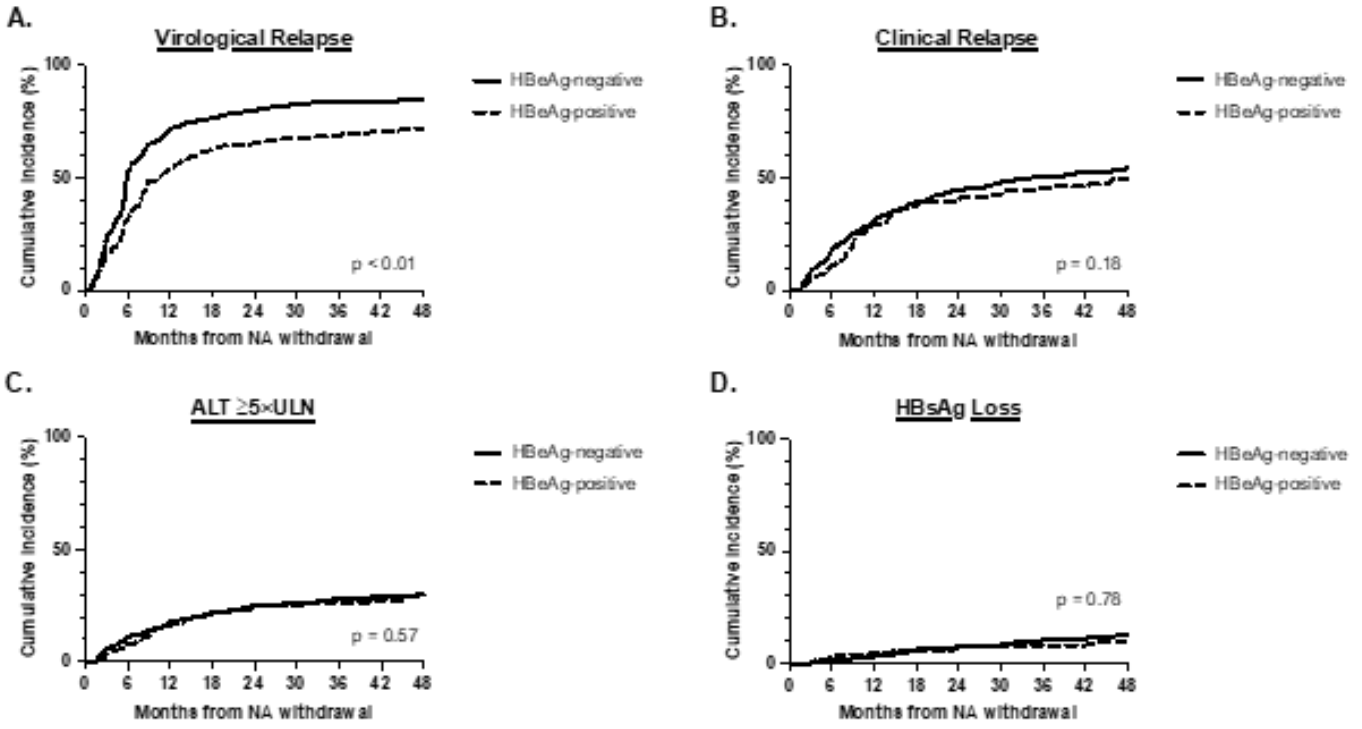


Hirode et al, Gastroenterology 2021

Suspensión tratamiento AN: impacto de HBeAg pre-tratamiento

CHB patients (N = 1360)

- From centres across North America, Europe and Asia
- At NA discontinuation all were:
  - Non-cirrhotic
  - HBeAg negative

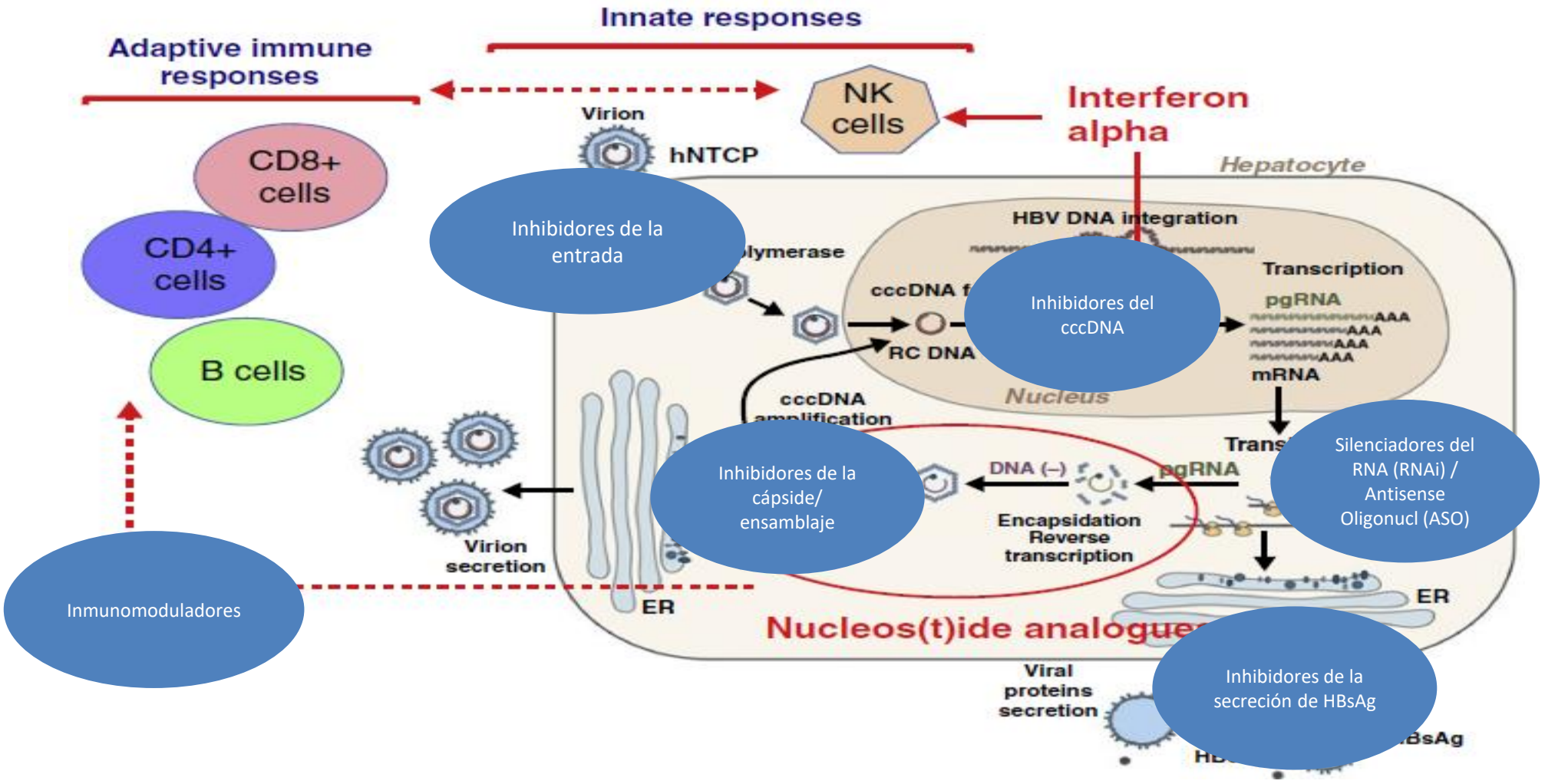


- CHB patients who were HBeAg negative vs positive at SOT experienced higher rates of virological relapse
- Off-therapy ALT elevations and HBsAg loss were not associated with HBeAg status at SOT

Choi SJH, et al. ILC 2022; SAT415

¿Cómo actúan los nuevos tratamientos contra VHB?

Nuevas dianas terapéuticas



Adapted from Zoulim et al, Curr Opin Virology 2016; Durantel & Zoulim F, J Hepatol 2016

Guía práctica de los ensayos clínicos en Hepatitis B

Endpoint del estudio:

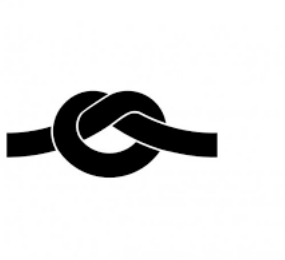
Diseño del estudio:

Criterios de inclusión:

Fármaco del estudio:

Guía práctica de los ensayos clínicos en Hepatitis B

Endpoint del estudio:
- Curación funcional
- Control Virológico
- Cambios en biomarcadores



Diseño del estudio:
- Monoterapia o combinación
- Pbo / Peg IFN / ANs / suspensión ANs
- Terapia secuencial
- Duración / seguimiento

Criterios de inclusión:
- Hepatitis crónica
- Naïve o tratados con ANs
- HBeAg + o –
- qHBsAg
- DNA-VHB o ALT
- Cirrosis

Fármaco del estudio:
- Vía administración
- Seguridad

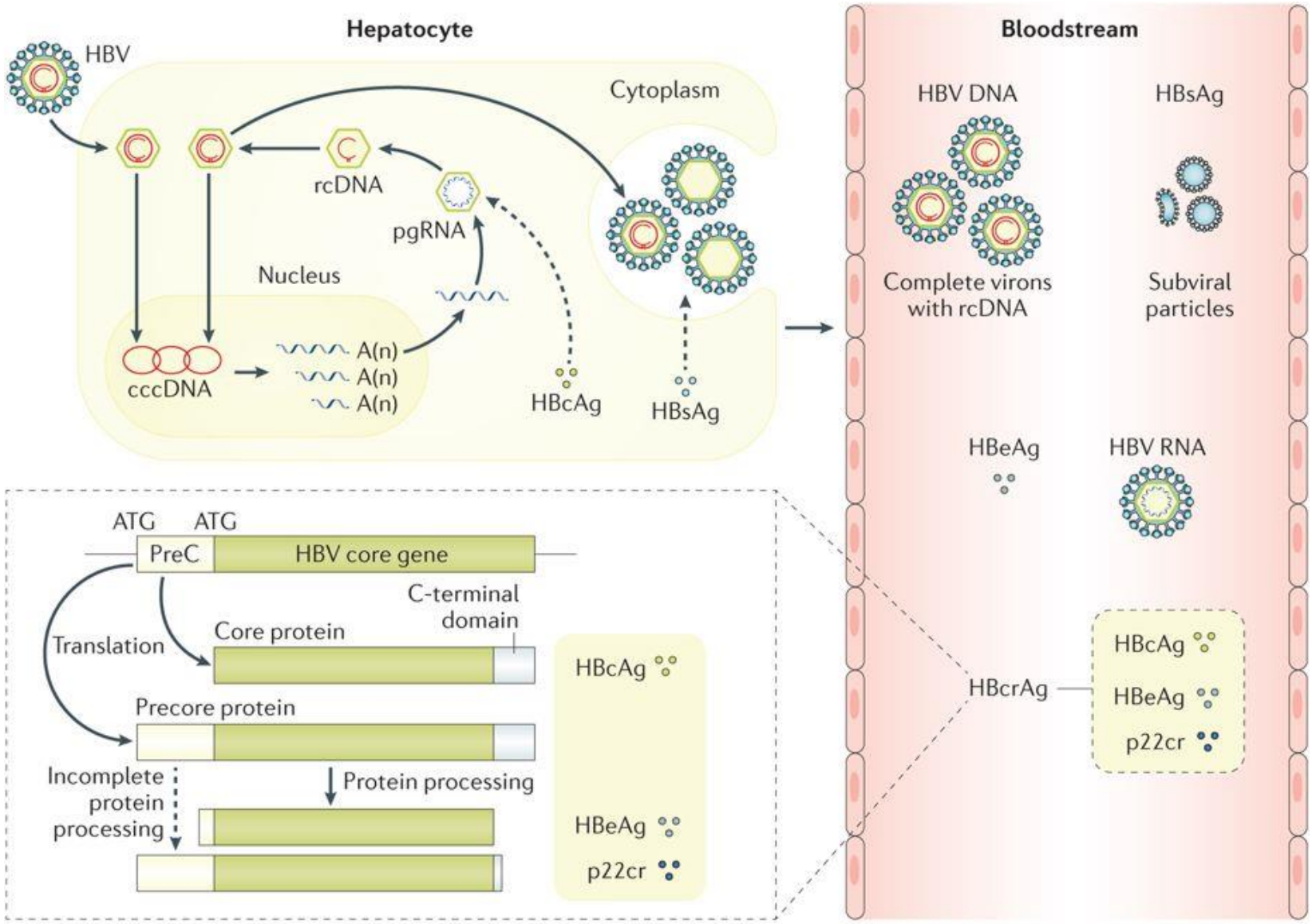
Cornberg et al J Hepatology 2020

Biomarcadores VHB

Antígenos:
HBsAg
HBeAg
HBcrAg

Fragm Virus:
DNA-VHB
RNA-VHB

Anticuerpos:
Anti-HBs
Anti-HBe
Anti-HBc

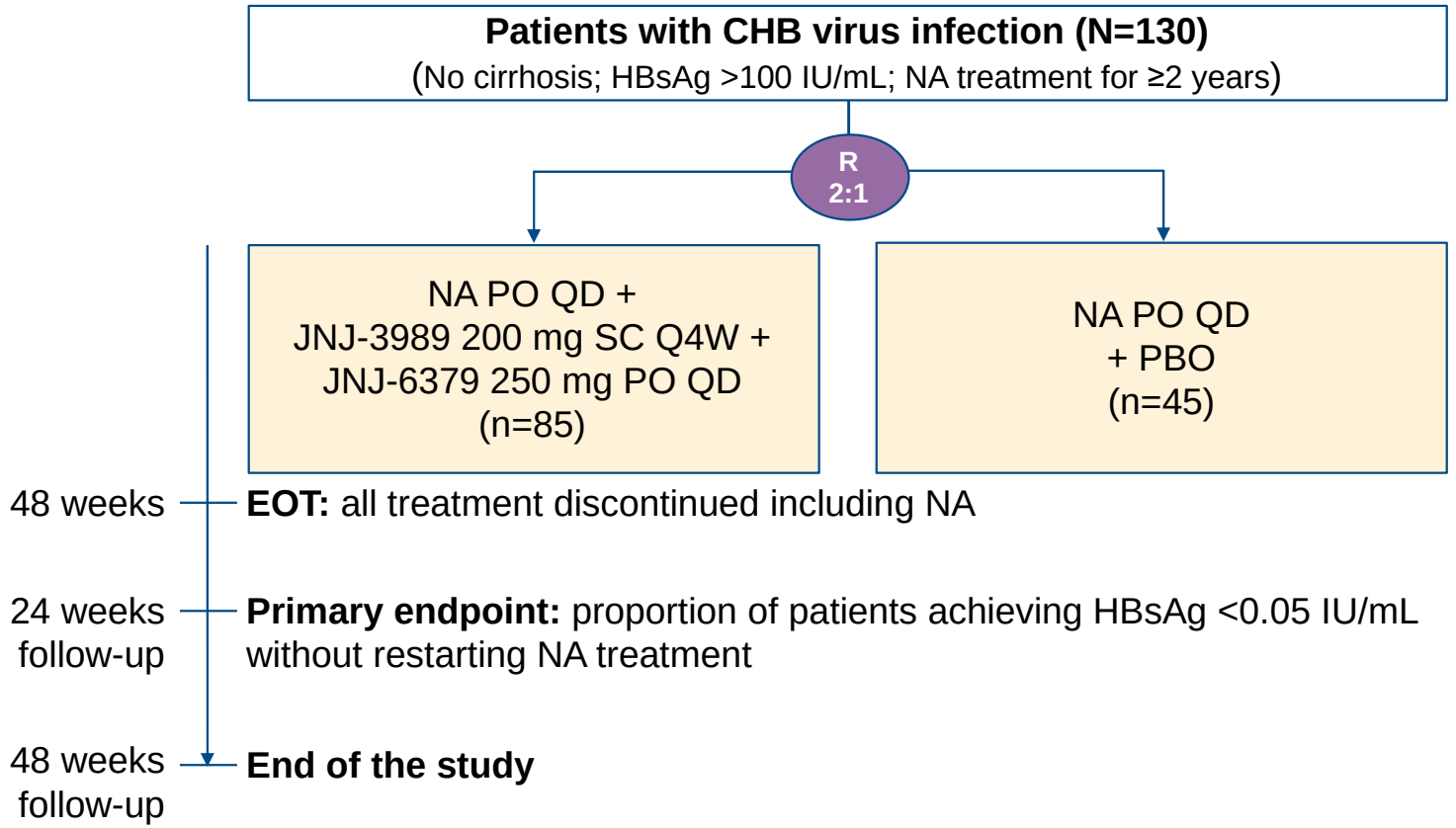


Nature Reviews | Disease Primers

Capsid Assembly Modulators (CAM) + small interfering RNA (siRNA)

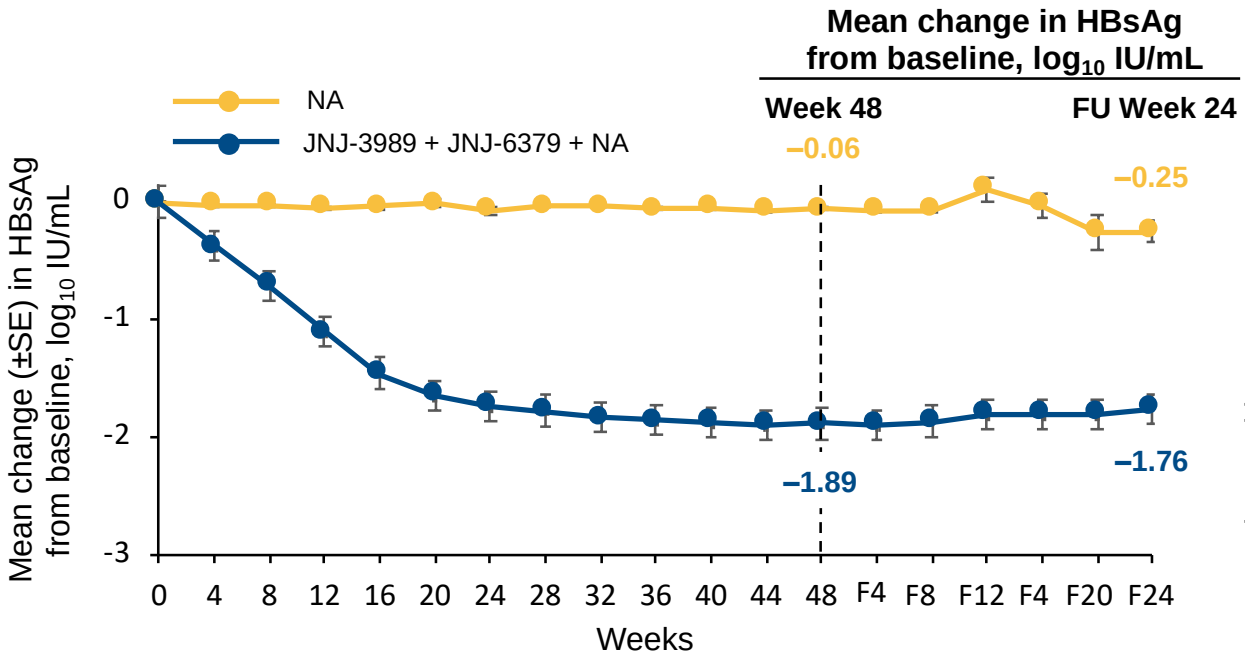
BACKGROUND & AIMS

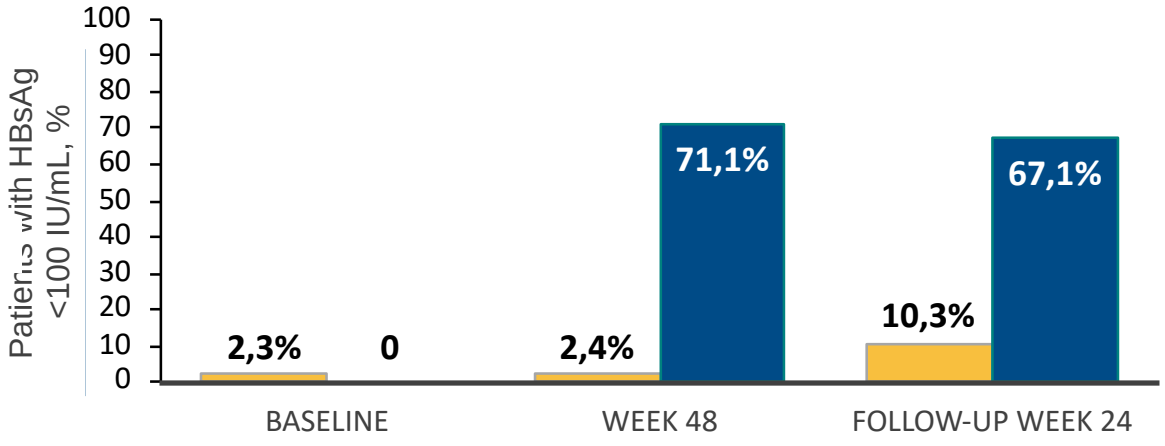
- JNJ-3989 is an siRNA designed to target all HBV RNAs, thus reducing synthesis of all HBV proteins
- JNJ-6379 is a CAM-N that inhibits viral replication by inducing the formation of empty viral particles
- **AIM:** The REEF-2 study* (NCT04129554) assessed the efficacy and safety of 48 weeks of the combination JNJ-3989, JNJ-6379, and NA in HBeAg-negative VS† CHB patients



Lim SG, et al. ILC 2022; SAT452

Capsid Assembly Modulators (CAM) + small interfering RNA (siRNA)





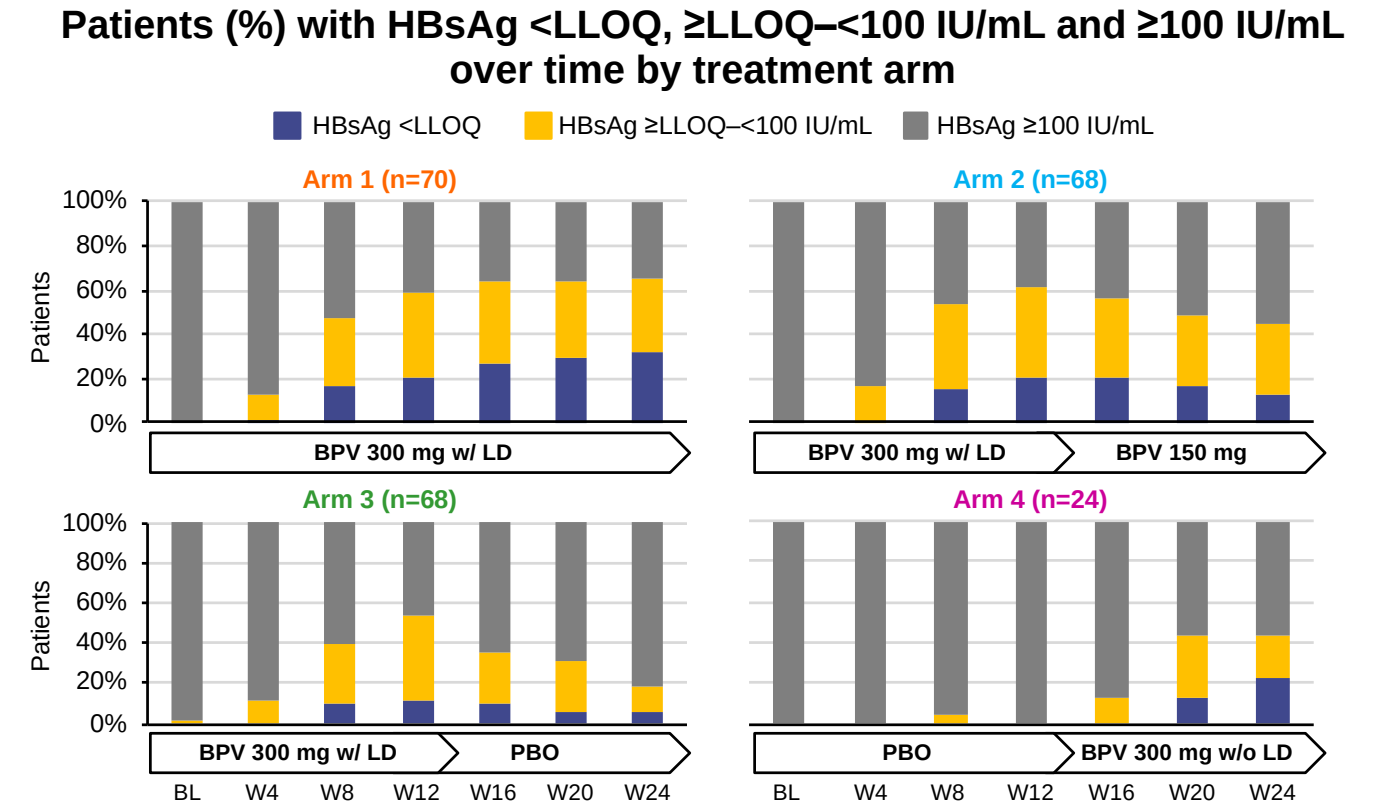
- In VS and HBeAg-negative CHB patients, 48-week treatment with JNJ-3989 + JNJ-6379 + NA or NA alone did not lead to HBsAg seroclearance 24 weeks after stopping all treatment
- JNJ-3989 + JNJ-6379 + NA showed greater reduction in HBsAg over 48 weeks vs NA alone and was generally well tolerated and safe

Lim SG, et al. ILC 2022; SAT452

Antisense oligonucleotide (ASO)

Study	Bepirovirsen GSK3228836	Phase 2
Design	Bepirovirsen GSK3228836 150-300 mg	
Patients	Naïve n=230 Treated n=227	HBeAg+/-
Endpoint	Patients achieving HBsAg <LLOQ and HBV DNA <LLOQ sustained for 24 weeks without rescue medication after planned BPV EOT	

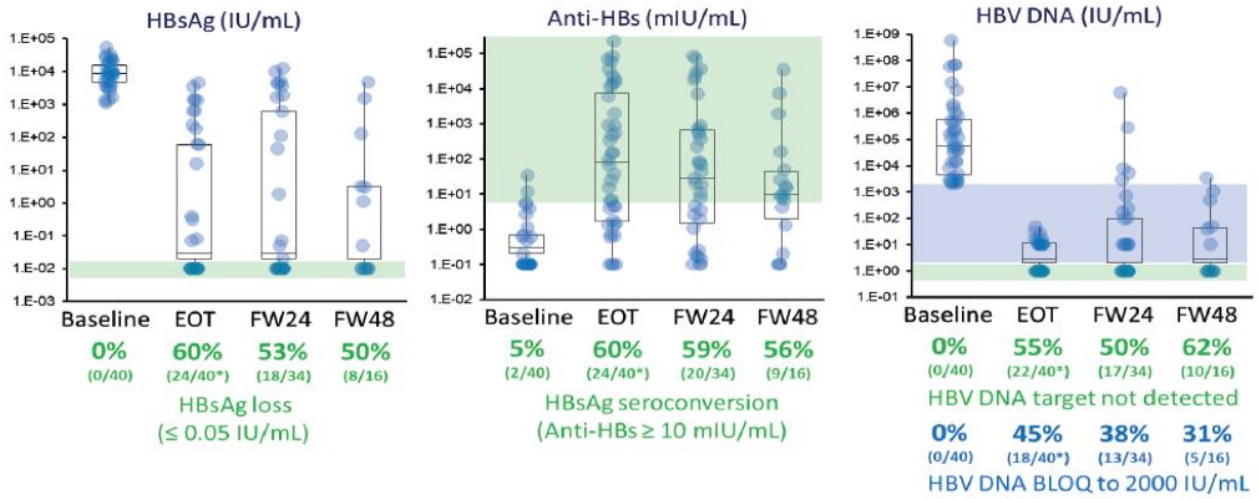
- 24 weeks' 300mg BPV resulted in HBsAg <LLOQ and HBV DNA <LLOQ in 29% of patients at EOT;
- Higher in the low baseline qHBsAg
- Safety was good

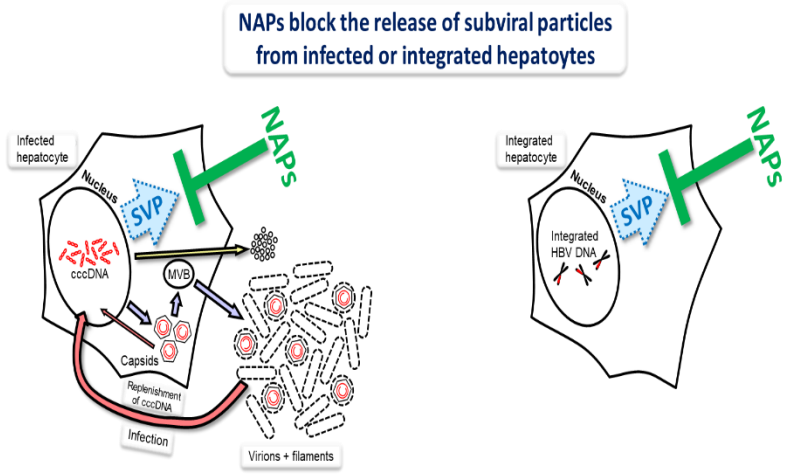


Lim SG, et al. ILC 2022; SAT452

Nucleic acid polymers (NAPs)

Study	REP 2139 o REP 2165 (i.v weekly)	Phase 2
Design	24 wk TDF →REP 2139 or REP 2165 +TDF + Peg-IFN alfa 48 wk vs TDF+ Peg-IFN	
Patients	Naïve+treated	HBeAg-
Endpoint	Primary: Safety and Efficacy at end of treatment Secondary: HBsAg negativization / changes and virologic control at end of treatment and 24-48 wk FU	



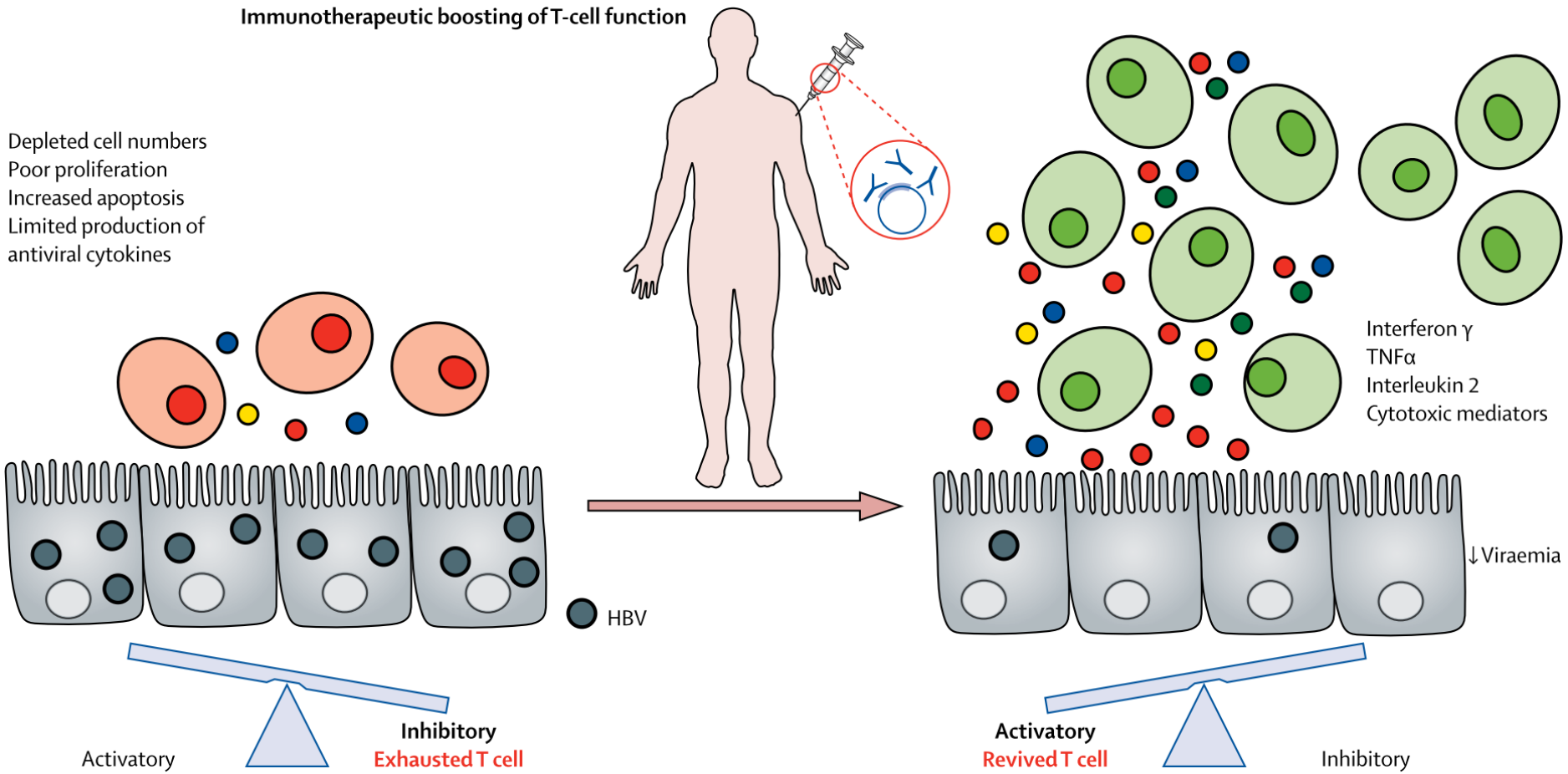


EOT HBsAg (n=40):
>1 log from BL n=36 (90%)
< 1 IU/mL n=27 (67%)
< 0.05 IU/mL n=24 (60%)

24-48 wk FU (n=36)
Functional cure n=14/36 (38%)

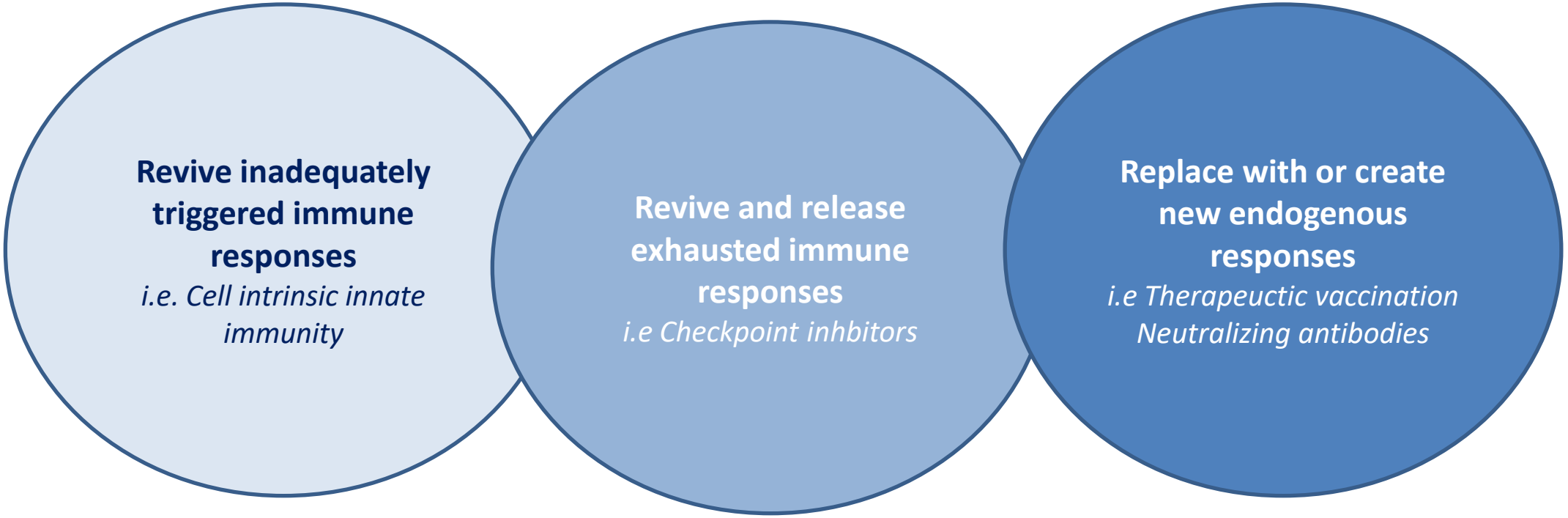
Bazinet et al Lancet 2017 and Gastroenterology 2020

Inmunomoduladores



Maini, Pallett, et al. Lancet 2018

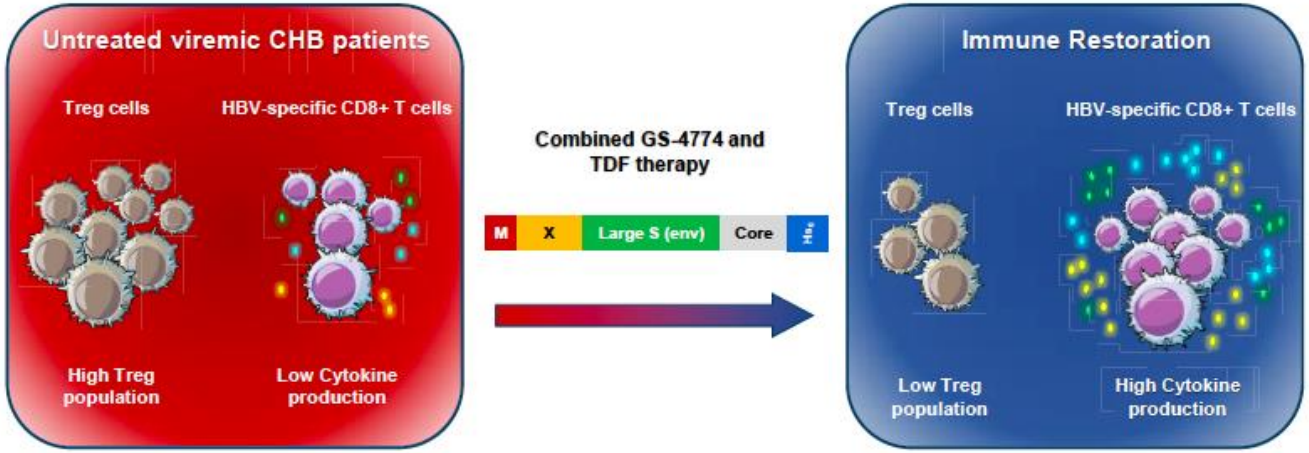
Inmunomoduladores

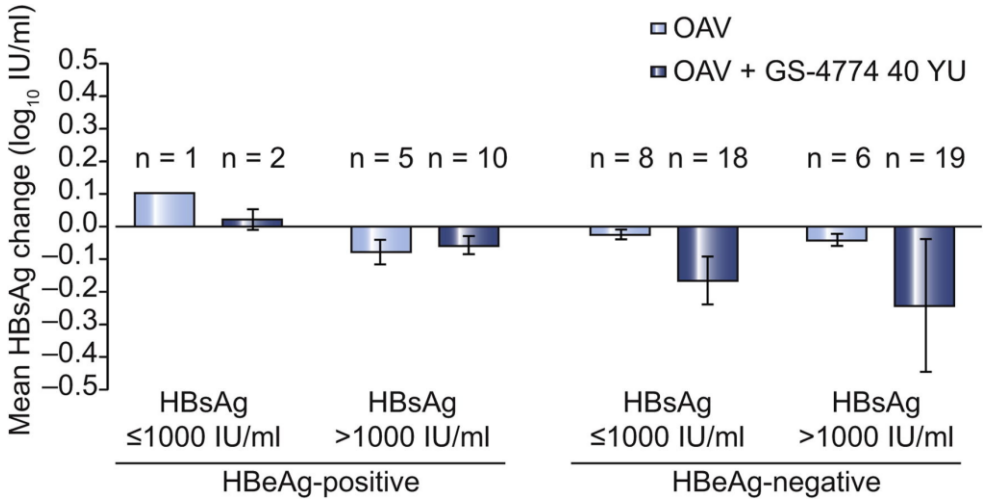


Vacunas terapéuticas

Gastroenterology 2019;157:227–241

Combined GS-4774 and Tenofovir Therapy Can Improve HBV-Specific T-Cell Responses in Patients With Chronic Hepatitis

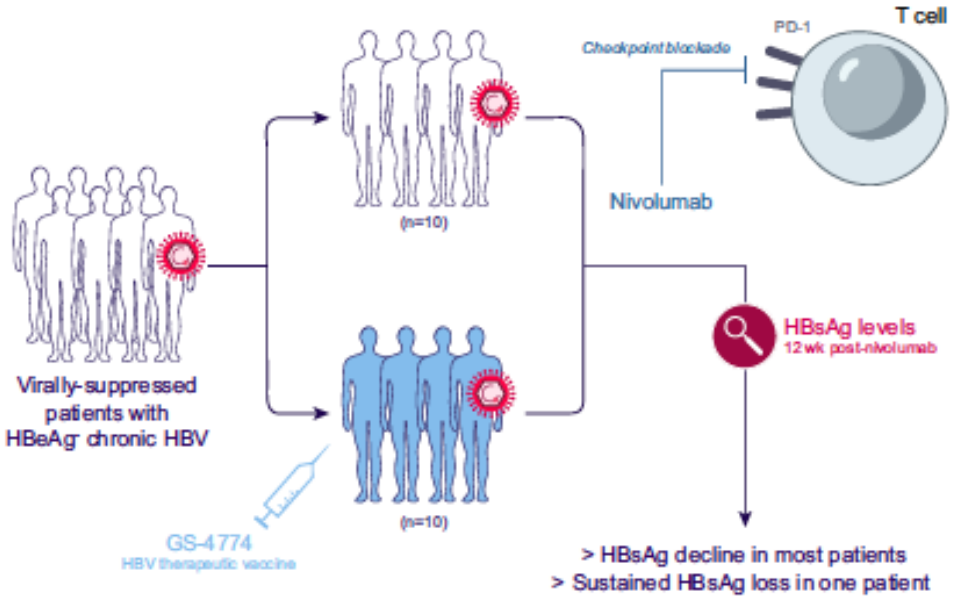


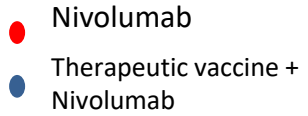


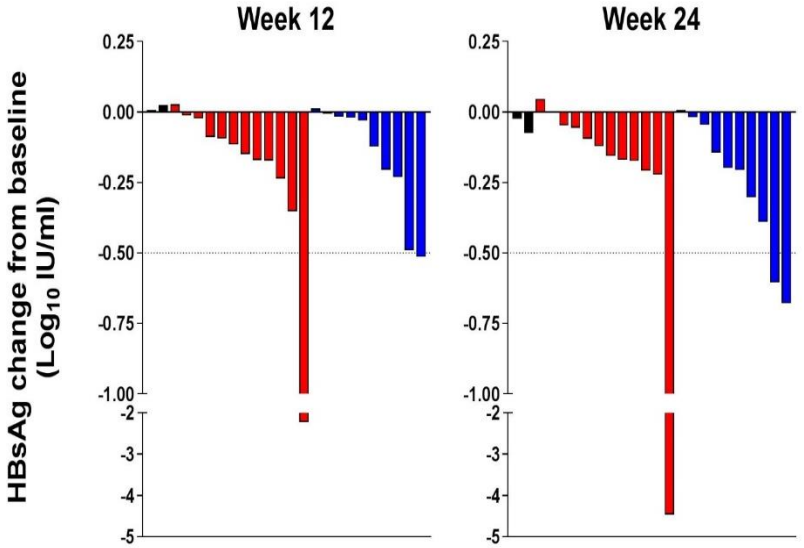
Lok et al. J Hepatology 2016
Boni et al. Gastroenterology 2019

Anti-PD1 / checkpoint inhibitors

Study	Anti-PD1 MAb Nivolumab	Phase 1b
Design	Nivolumab 0.1-0.3 mg/kg monotherapy (n=10) vs + Nivolumab + GS-4774 (n=10)	
Patients	HBeAg- treated with NA	
Endpoint	↓log_{10}HBsAg 12 weeks	







Gane et al J Hepatol. 2019 Nov;71(5):900-907.

Vacunas terapéuticas

TherVacB Home Project Team Patients Media Center Intranet

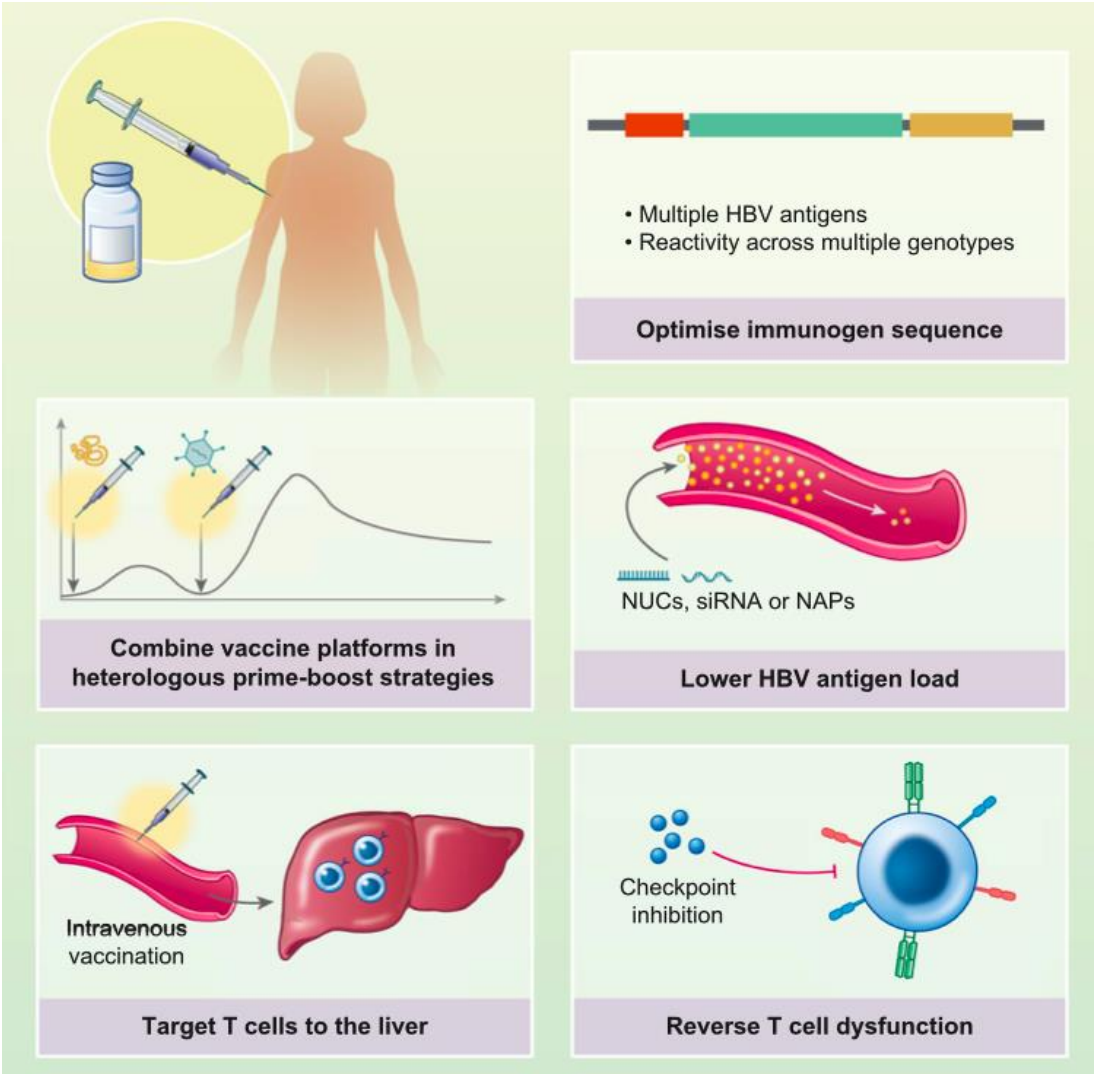
OUR APPROACH

Cutting-edge therapeutic vaccination technology - made in the EU

vaccines MDPI

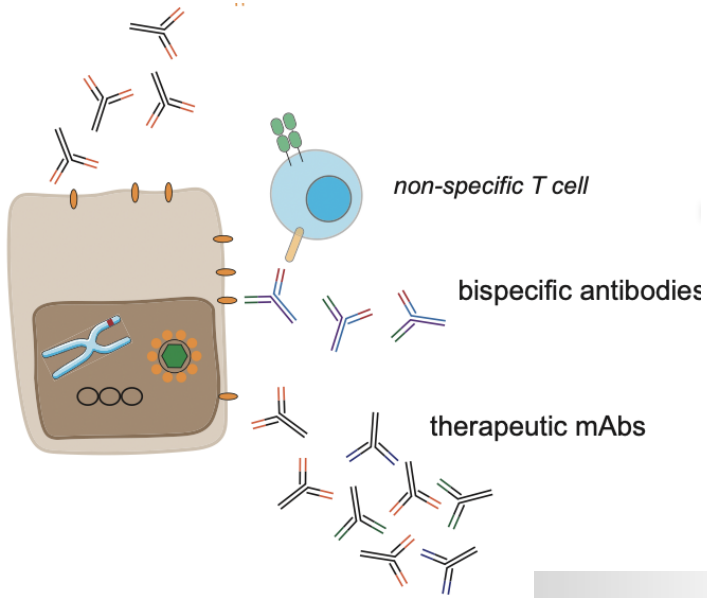
Article

The Design and Development of a Multi-HBV Antigen Encoded in Chimpanzee Adenoviral and Modified Vaccinia Ankara Viral Vectors; A Novel Therapeutic Vaccine Strategy against HBV



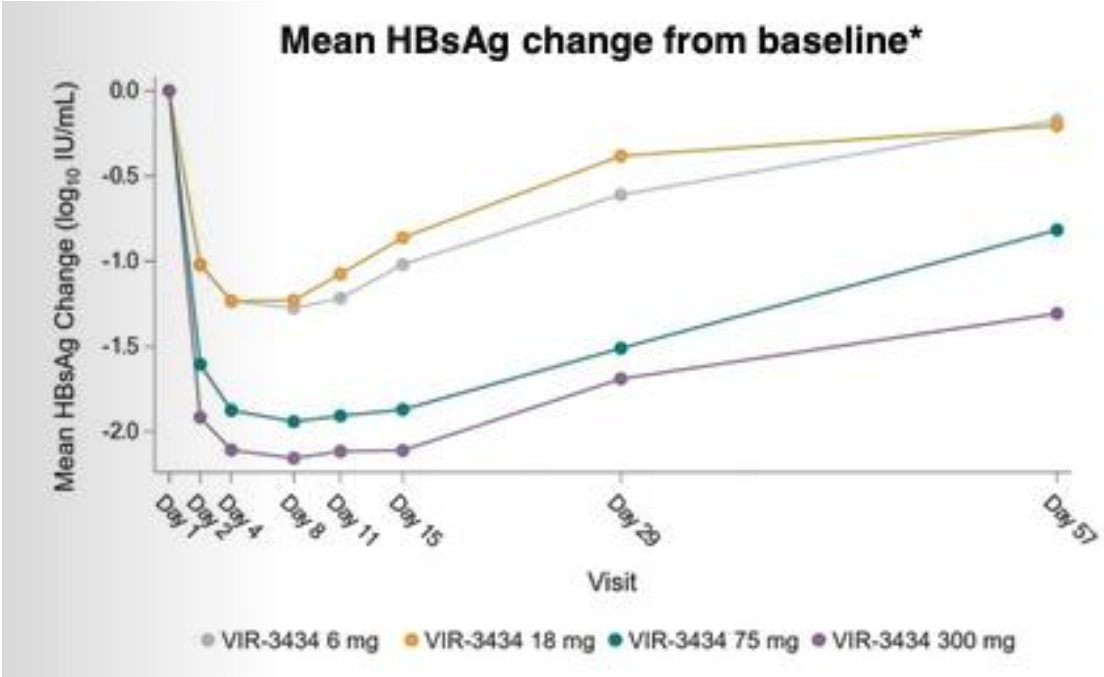
Cargill and Barnes, Clin Exp Immunology 2021

Anticuerpos monoclonales



VIR-3434 is **Fc-engineered human mAB** targeting the conserved antigenic loop of HBsAg

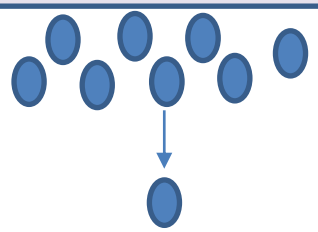
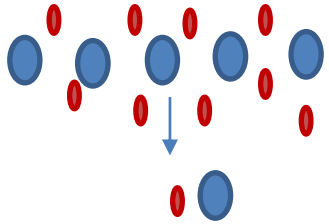
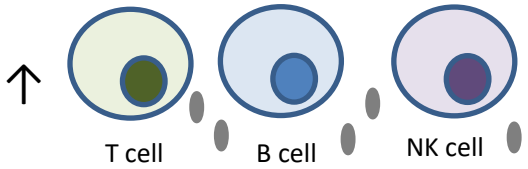
- Inhibits HBV entry into hepatocytes
- Enhanced immunological activity (T cells)
- Clearance of HBsAg and delivery to cendritic cells



Phase I trial
Single dose, n=24
HBeAg-neg, under NAs, qHBsAg < 3000 IU/mL

Argwal K et al. ILC 2022

¿Cuál es la mejor estrategia?

mecanismo	Supresión VHB	↓ carga antigénica	Inmunomoduladores
			
actual	AN	PegIFN	PegIFN
	CpAM/CAM	siRNA	Agonistas TLR
	siRNA Inh entrada Inh cccDNA	NAPs Inhib cccDNA	Checkpoint inhib Vacuna terapéutica

‘Take-home messages’

- Los tratamientos actuales (IFN y particularmente NA) pueden **controlar** la replicación del VHB y disminuir (pero no eliminar) el riesgo de complicaciones asociadas con el VHB (principalmente HCC). La **curación funcional** (pérdida de HBsAg), sin embargo, es poco frecuente.

- Los nuevos tratamientos ya están en desarrollo clínico, aunque con resultados diversos (algunos muy prometedores, incluso en el campo de la coinfección VHB/VHD). El objetivo es lograr la curación funcional del virus con un tratamiento **finito** y **sin efectos secundarios** y, probablemente con terapias en **combinación**.

- Los nuevos **biomarcadores** serológicos (HBsAg, HBcrAg, RNA-VHB) son las nuevas dianas para la evaluación de la eficacia de estas terapias.

PI15/00151
PI16/00111
PI18/00079
IFI18/00006

Viral Hepatitis Unit
Liver Unit
Hospital Clínic
Barcelona

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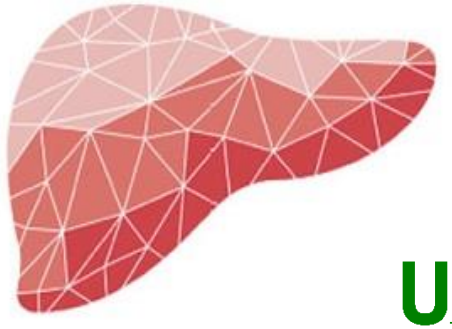

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