¿Cuándo asistiremos a la cura real de la Hepatitis B?

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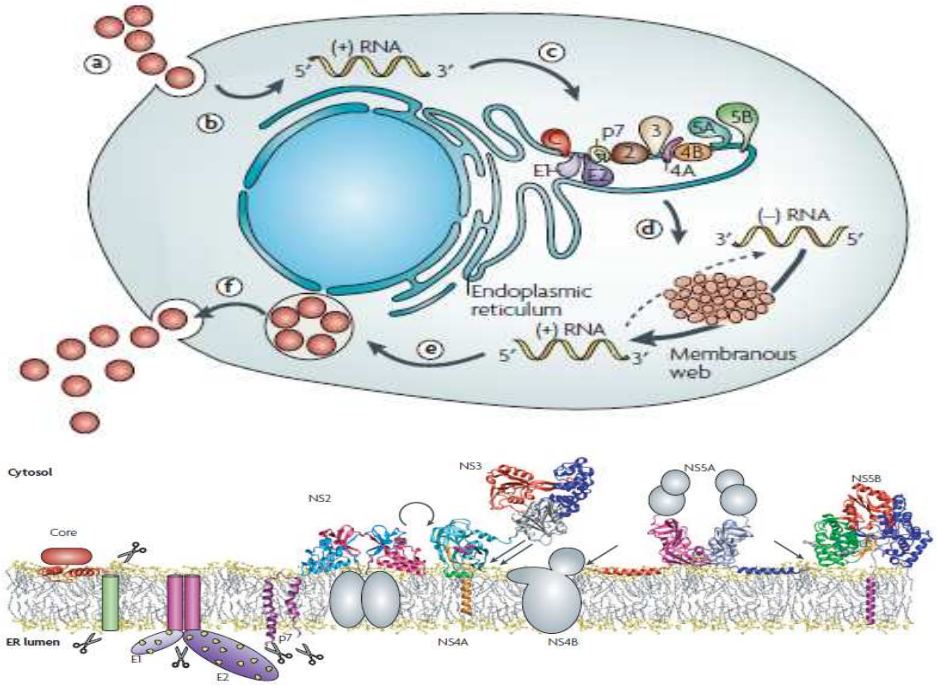
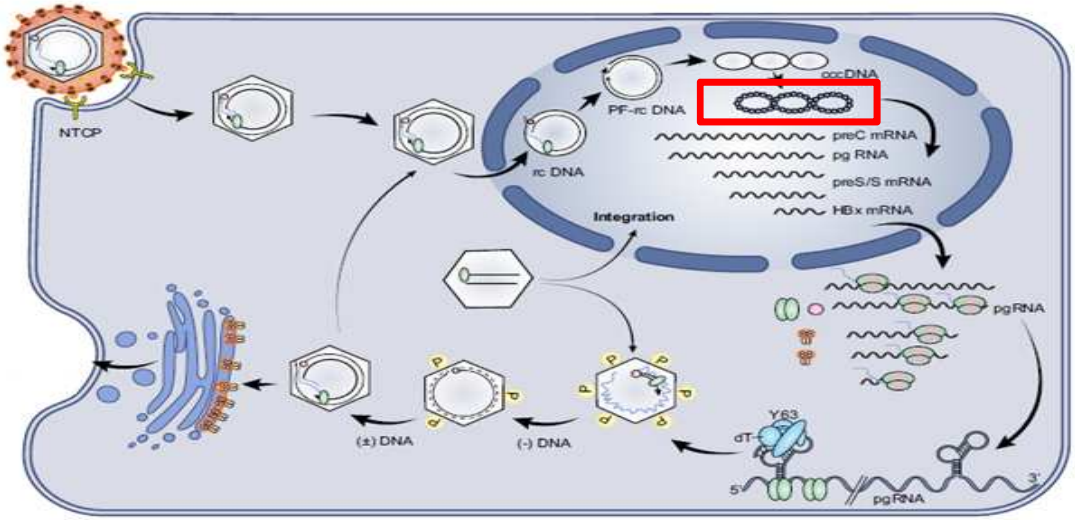
Doctora, ¿por qué él si y yo no?

Hepatitis C

Hepatitis B





Clasificación de la infección por VHB

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

	HBeAg positivo		HBeAg negativo	
	Infección crónica por VHB **HBeAg positivo**	***Hepatitis*** crónica B **HBeAg positivo**	***Infección*** crónica por VHB **HBeAg negativo**	***Hepatitis*** crónica B **HBeAg negativo**
ADN VHB	>10E7 UI/mL	10E4-10E7 UI/mL	<2000 UI/mL	>2000 UI/mL
ALT	Normal	Elevada	Normal	Normal/Elevada
Lesión hepática	Sin evidencia	Moderada/severa	Sin evidencia	Moderada/severa
Terminologia previa	Immunotolerante	Aclaramiento inmune	Portador inactivo	Hepatitis crónica B HBeAg negativo

Estrategias terapéuticas para la infección crónica por VHB

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

HBeAg positivo y HBeAg negativo	
Terapia finita	**Terapia a largo plazo**
PEG-IFNα	**Nucleos(t)ides Analogs (NA)**
• Duración limitada • Control inmunológico a largo plazo • Ausencia de resistencias	• Eficacia a largo plazo con NA de alta barrera genética • Perfil de seguridad favorable • Adecuado para un amplio grupo de pacientes

Con los tratamientos actuales un número muy reducido de pacientes alcanzarán una cura funcional

Definición

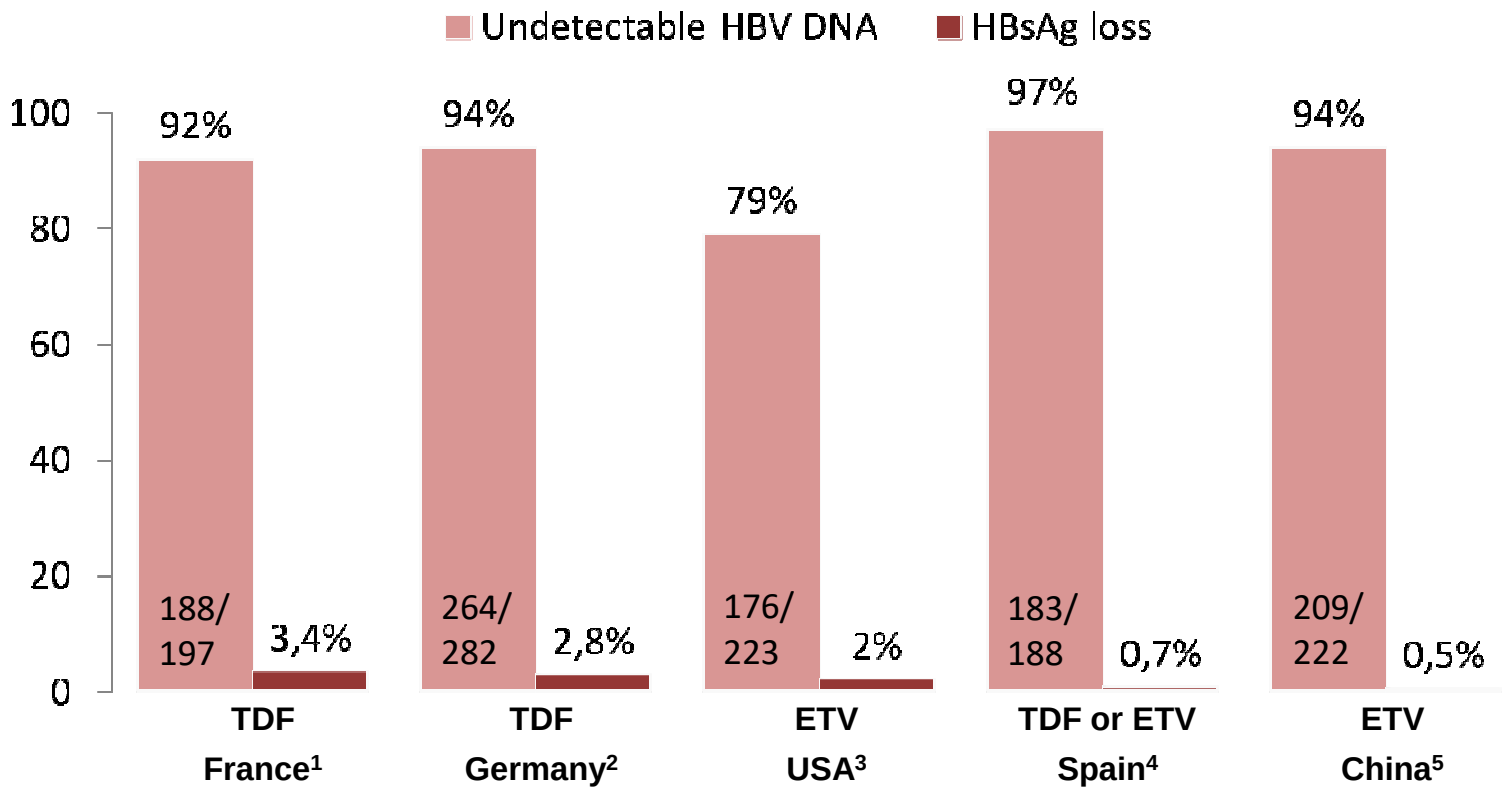
- ADN VHB indetectable
- HBsAg indetectable
- Persistencia de cccDNA

Implicaciones

- Infección resuelta de forma natural
- Riesgo de reactivación del VHB

ETV or TDF in real-world setting
HBsAg loss and virological response at year 3 of therapy

HBeAg positive and HBeAg negative



	TDF France[1]	TDF Germany[2]	ETV USA[3]	TDF or ETV Spain[4]	ETV China[5]
HBsAg loss:	3 HBeAg + 10 HBeAg -	6 HBeAg + 5 HBeAg -	5 HBeAg +* 8 HBeAg -	3 HBeAg + 1 HBeAg -	1 HBeAg +

*Data at year 5 of therapy; σ estimated data

[1]Marcellin P, *et al.* Dig Dis Sci 2016;61(10):3072-83; [2] Petersen J, *et al.* Dig Dis Sci 2016;61(10):3061-71; [3]Ahn J, *et al.* Aliment Pharmacol Ther 2016;43(1):134-44; [4]Riveiro-Barciela M, *et al.* Dig Dis Sci 2017;62(3):784-793; [5]Seto KW, *et al.* J Gastroenterol Hepatol 2014;29(5):1028-34

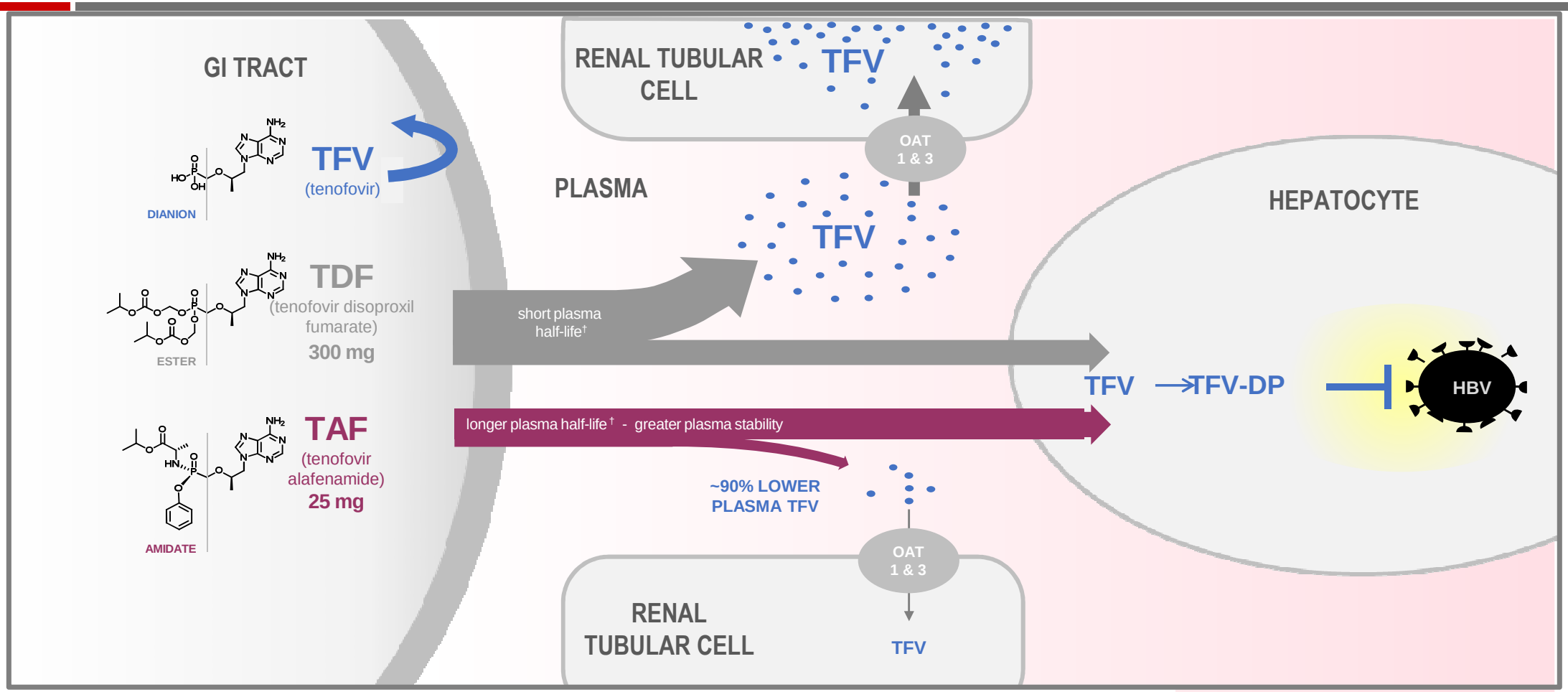
Safety of Nucleos(t)ides Analogues in real-world setting

Study	Follow-up (years)	No	NAs	AEs Discontinuation	Lactic acidosis	Renal-related events	
						TDF	ETV
USA[1]	5	658	ETV	8 (1.2%)	2 (0.3%)	-	2 (0.3%)
China[2]	5	222	ETV	0 (0%)*	0 (0%)	-	N/A
Spain[3]	4	611	TDF/ETV	0 (0%)	0 (0%)	7 (1.7%)	4 (2.1%)
USA[4]	N/A	160	TDF/ETV	0 (0%)	0 (0%)	3 (3.8%)	11 (13.8%)
Spain[5]	3	158	TDF/ETV	0 (0%)	0 (0%)	2 (2%)	2 (3%)
France[6]	3	440	TDF	23 (5%)	0 (0%)	7 (1.6%)	-
Germany[7]	3	400	TDF	11 (2.8%)	0 (0%)	5 (1.3%)	-

*2 patients discontinued therapy for ETV resistance and 1 for pregnancy

[1]Ahn J, *et al.* Aliment Pharmacol Ther 2016;43(1):134-44; [2]Seto KW, *et al.* J Gastroenterol Hepatol 2014;29(5):1028-34; [3]Riveiro-Barciela M, *et al.* Dig Dis Sci 2017;62(3):784-793; [4]Gish RG, *et al.* Clin Gastroenterol Hepatol 2012;10(8):941-6; [5]Rodríguez-Nóvoa S, *et al.* J Clin Gastroenterol 2016;50(9):779-89; [6]Marcellin P, *et al.* Dig Dis Sci 2016;61(10):3072-83; [7]Petersen J, *et al.* Dig Dis Sci 2016;61(10):3061-71

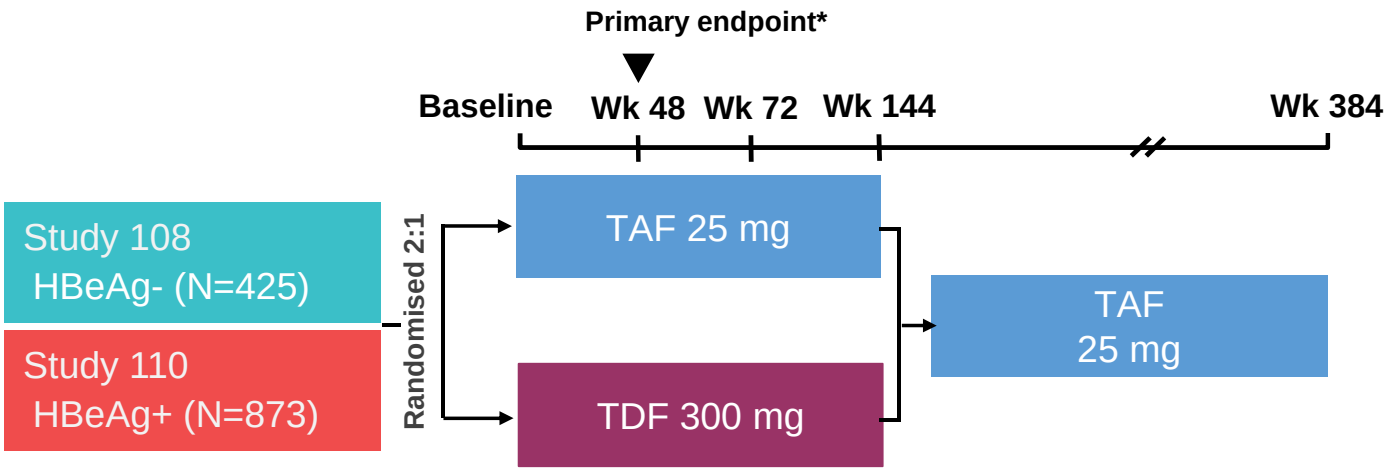
Tenofovir Alafenamide (TAF): Prodrug of Tenofovir Mechanism of the action



† $T_{1/2}$ based on *in vitro* plasma data - TDF = 0.4 minutes, TAF = 30-90 minutes.

Lee W et. *Antimicr Agents Chemo* 2005;49(5):1898-1906. Birkus G et al. *Antimicr Agents Chemo* 2007;51(2):543-550. Babusis D, et al. *Mol Pharm* 2013;10(2):459-66. Ruane P, et al. *J Acquir Immune Defic Syndr* 2013; 63:449-5. Sax P, et al. *JAIDS* 2014. 2014 Sep 1;67(1):52-8. Sax P, et al. *Lancet* 2015. Jun 27;385(9987):2606-15. Agarwal K et al. *J Hepatology* 2015; 62: 533-540; Buti M et al. Lancet G&H 2016; doi: 10.1016/S2468-1253(16)30107-8; Chan HLY et al. Lancet G&H 2016; doi: /10.1016/S2468-1253(16)30024-3

TAF HBV Phase 3 programme (Study 108 and Study 110)

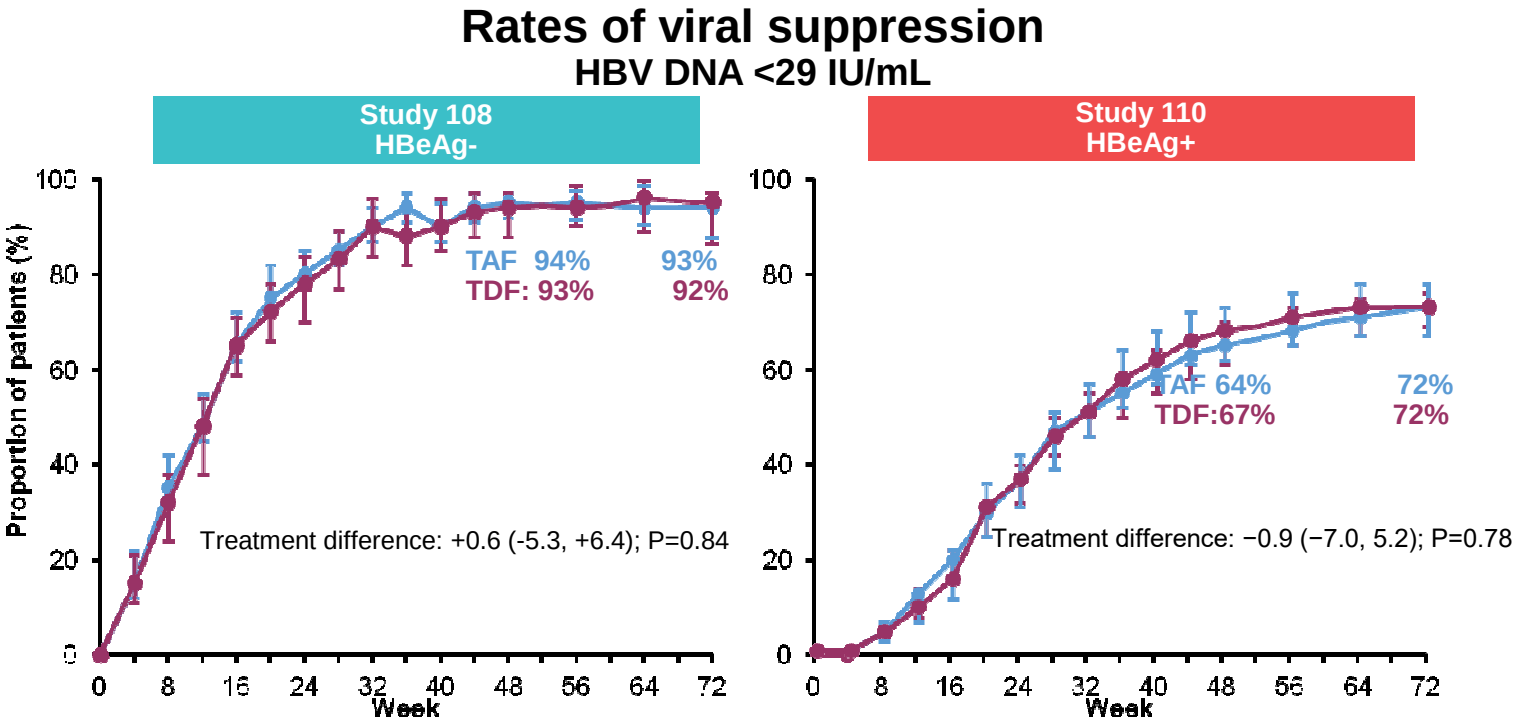


- Two Phase 3, multicentre, randomised, double-blind studies
- Inclusion criteria
  - HBV DNA ≥20,000 IU/mL, ALT >60 U/L (males), >38 U/L (females), eGFR >50 mL/min by CG
- Primary endpoint (non-inferiority margin of 10%):
  - HBV DNA <29 IU/mL at Week 48
- Key secondary endpoints
  - ALT normalisation at Week 48
  - BMD and renal parameters at Week 48

Amendment to extend double-blind to Week 144 and open-label phase to ≥Week 384 (Year 8) has recently been enacted.
The label is based on data at Week 48 and Week 72;
The licensed dose of TDF in Europe in CHB patients is 245 mg.
CG: Cockgroft–Gault

Buti M, et al. Lancet Gastroenterol Hepatol 2016;3:196–206;
Chan HLY, et al. Lancet Gastroenterol Hepatol 2016;3:185–95
https://www.clinicaltrials.gov/ct2/show/NCT01940471?term=TAF&rank=34 (Accessed February 2017)

HBV DNA suppression comparable between TAF and TDF at Week 72 (Study 108 and Study 110)

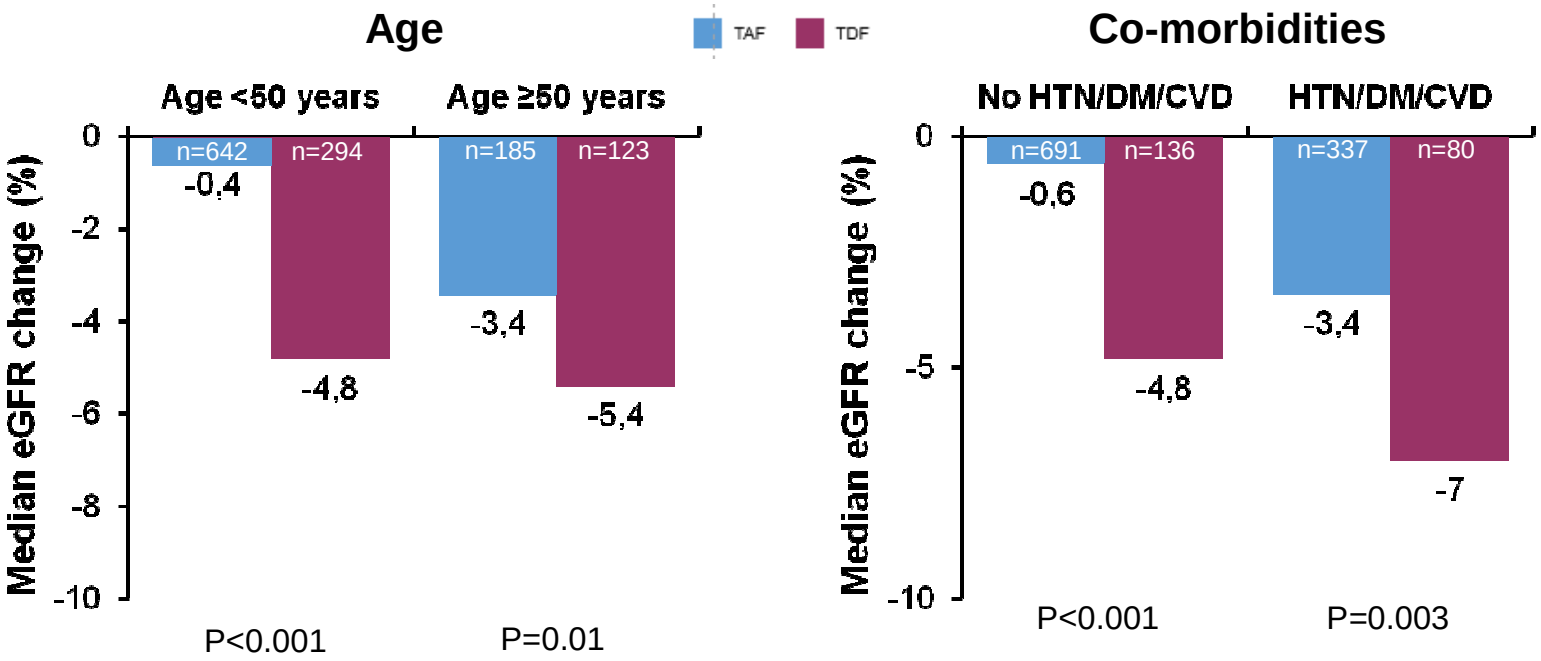


- TAF showed non-inferiority to TDF (no significant difference)
- Similar HBsAg and HBeAg loss between both arms
- No resistance detected at Week 72

Buti M, et al. Lancet Gastroenterol Hepatol 2016;3:196–206; Chan HLY, et al. Lancet Gastroenterol Hepatol 2016;3:185–95
Seto WK, et al. AASLD 2016; Oral #67

Smaller declines in $eGFR_{CG}$ and lower rates of CKD stage worsening with TAF versus TDF at Week 48 (Study 108 and Study 110)

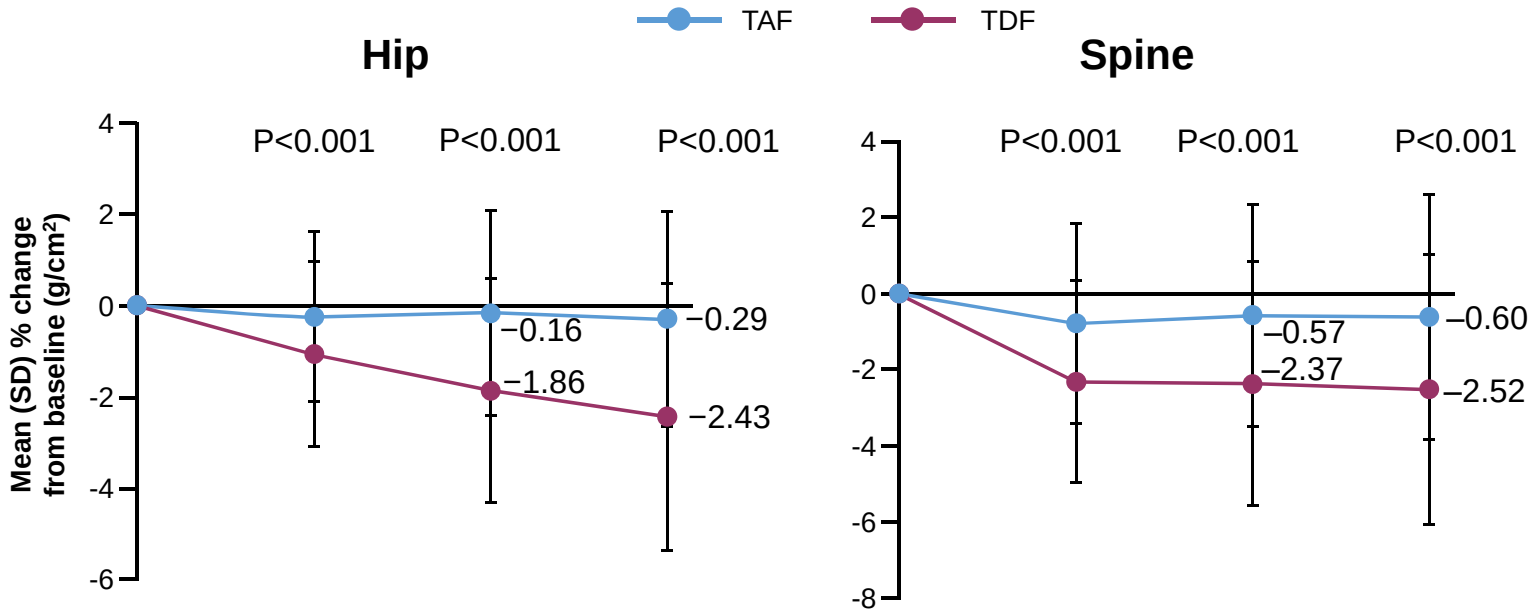
- Smaller eGFR declines with TAF versus TDF in patients ≥50 years and patients with co-morbidities (HTN/DM/CVD)



*P-values from Wilcoxon 2-sample test;
DM: diabetes mellitus; CKD: chronic kidney disease; CVD: cardiovascular disease (determined by medical history or concomitant medication); HTN: hypertension

Agarwal K, et al. AASLD 2016; Poster #1844

Significantly smaller decline in BMD with TAF versus TDF at Week 48 and at Week 72 (Study 108 and Study 110)



Week	0	24	48	72	0	24	48	72
TAF, N	851	822	807	753	856	830	814	757
TDF, N	426	405	404	373	426	410	407	374

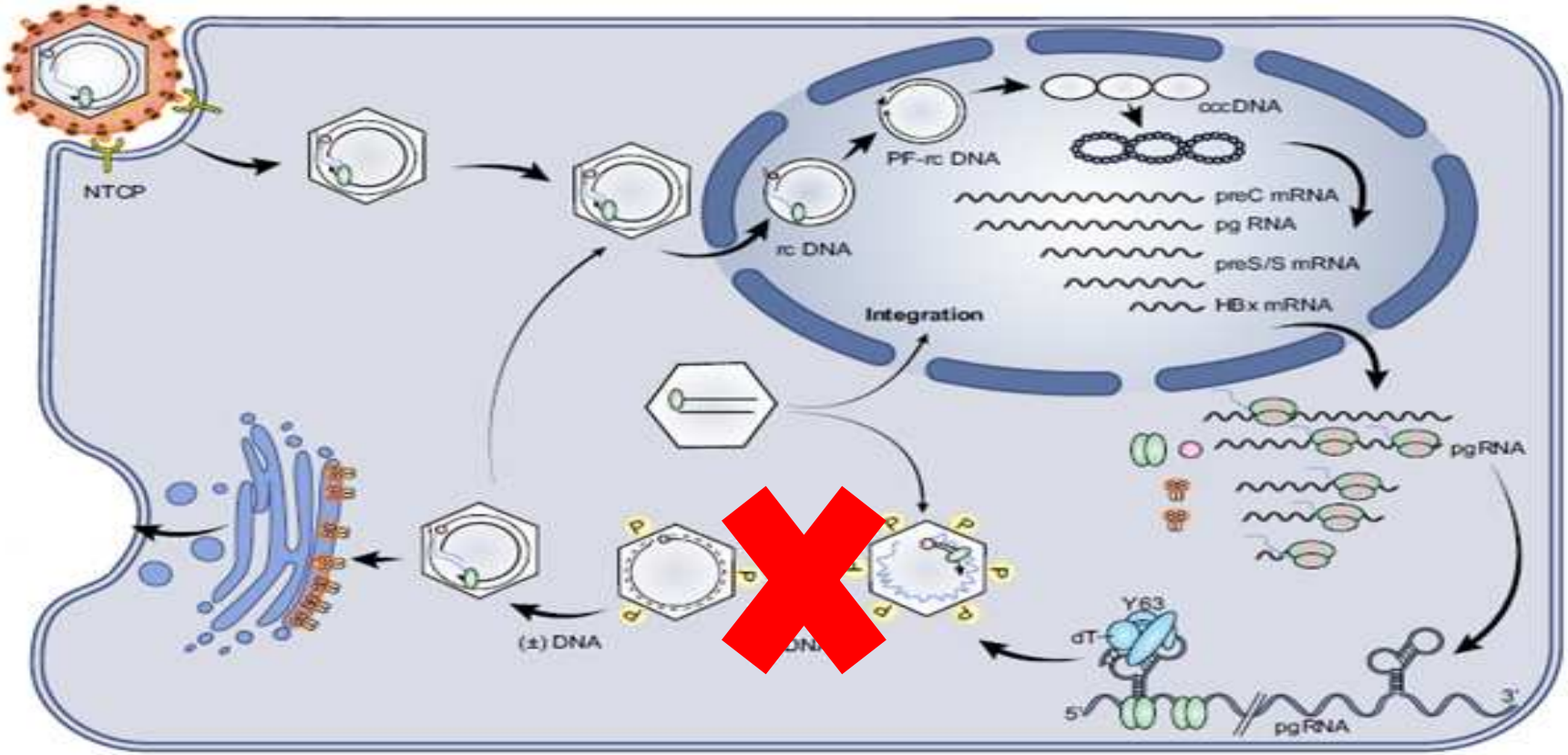
Seto WK, et al. AASLD 2016; Oral #67

P-values from the ANOVA model including treatment as a fixed effect.
ANOVA: analysis of variance

EASL Clinical Practice Guidelines on the management of HBV infection

Indications for selecting TAF or ETV over TDF
Age >60 years
Bone disease Chronic steroid use or use of other medications that worsen bone density, history of fragility fracture, osteoporosis
Renal aberration (eGFR <60 min/mL/1.73 m^2; albuminuria; low phosphate; haemodialysis) • ETV dose adjusted if eGFR <50 mL/min • No dose adjustment of TAF is required in adults or adolescents* with estimated CrCl ≥15 mL/min or in patients with CrCl <15 mL/min who are receiving haemodialysis
TAF preferred to ETV in patients with previous NA exposure

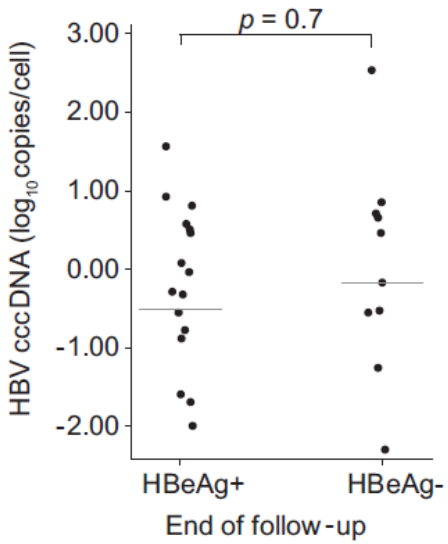
Objetivo de los análogos de nucleós(t)idos: la transcripción reversa

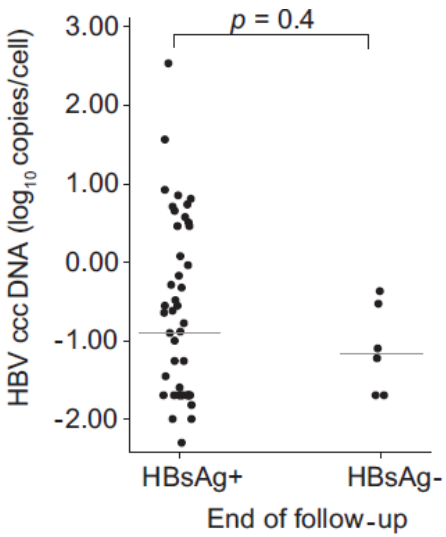


Tong S, Revill P. J Hepatol 2016;64:S4-16; Jansen L, *et al.* J Infect Dis. 2016 15;213(2):224-32

cccDNA en pacientes con supresión del ADN con TDF

60 pacientes con coinfección VIH-VHB





Intrahepatic viral loads remained detectable for all patients, even with prolonged TDF-exposure

Boyd A, *et al.* J Hepatol 2016; 65: 683-91

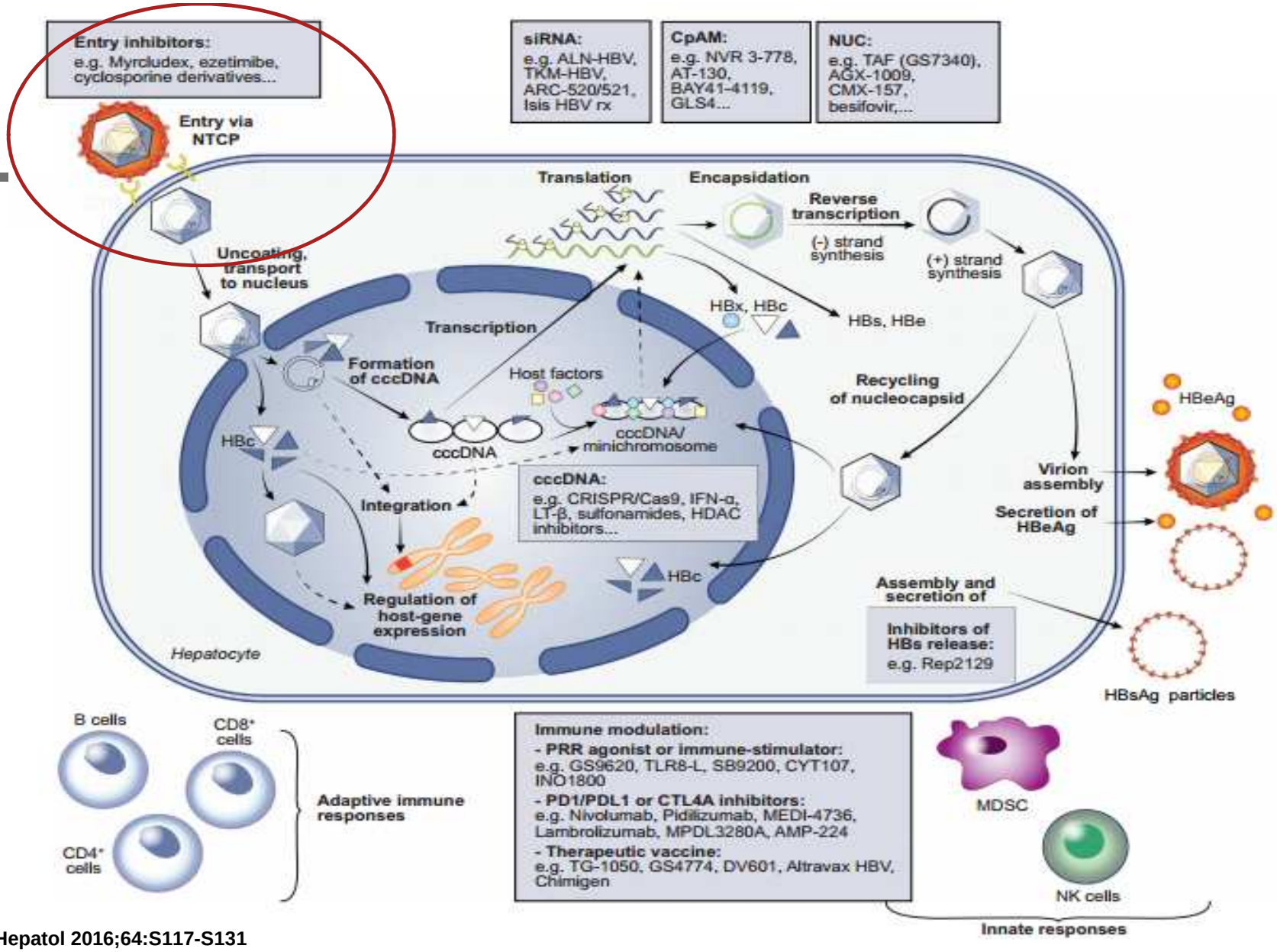
Objetivos de los nuevos tratamientos para el VHB

Cura funcional en un mayor número de pacientes

- ADN VHB y HBsAg indetectables
- cccDNA detectable

Cura completa

- ADN VHB y HBsAg indetectables
- **cccDNA indetectable**



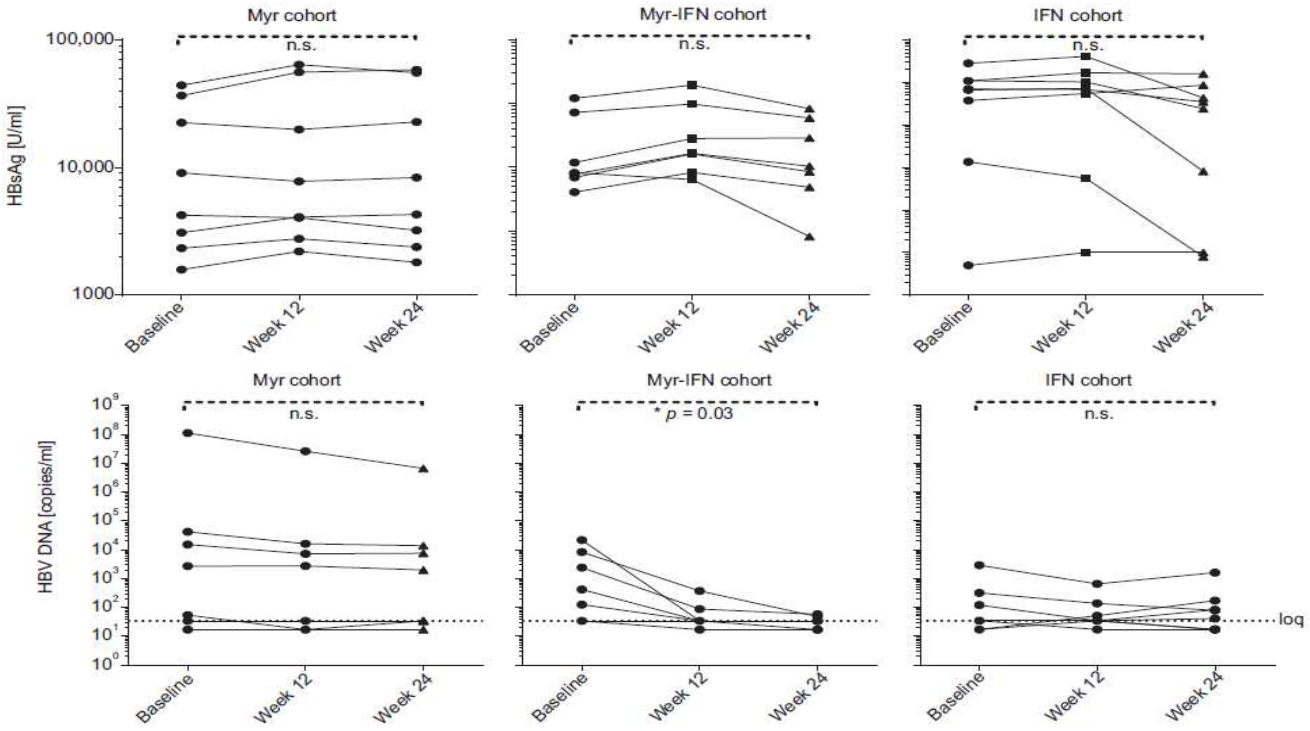
Durantel D et al. J Hepatol 2016;64:S117-S131

Entry Inhibitors: Myrcludex B (pre-S1 peptide)

Phase 2a randomized, open-label study. 24 patients with CHD were randomized (1:1:1)

- Myrcludex B
- Myrcludex B + pegIFN
- pegIFN

Primary response: HBsAg decline of > 0.5 log IU/mL at week 12



HDV

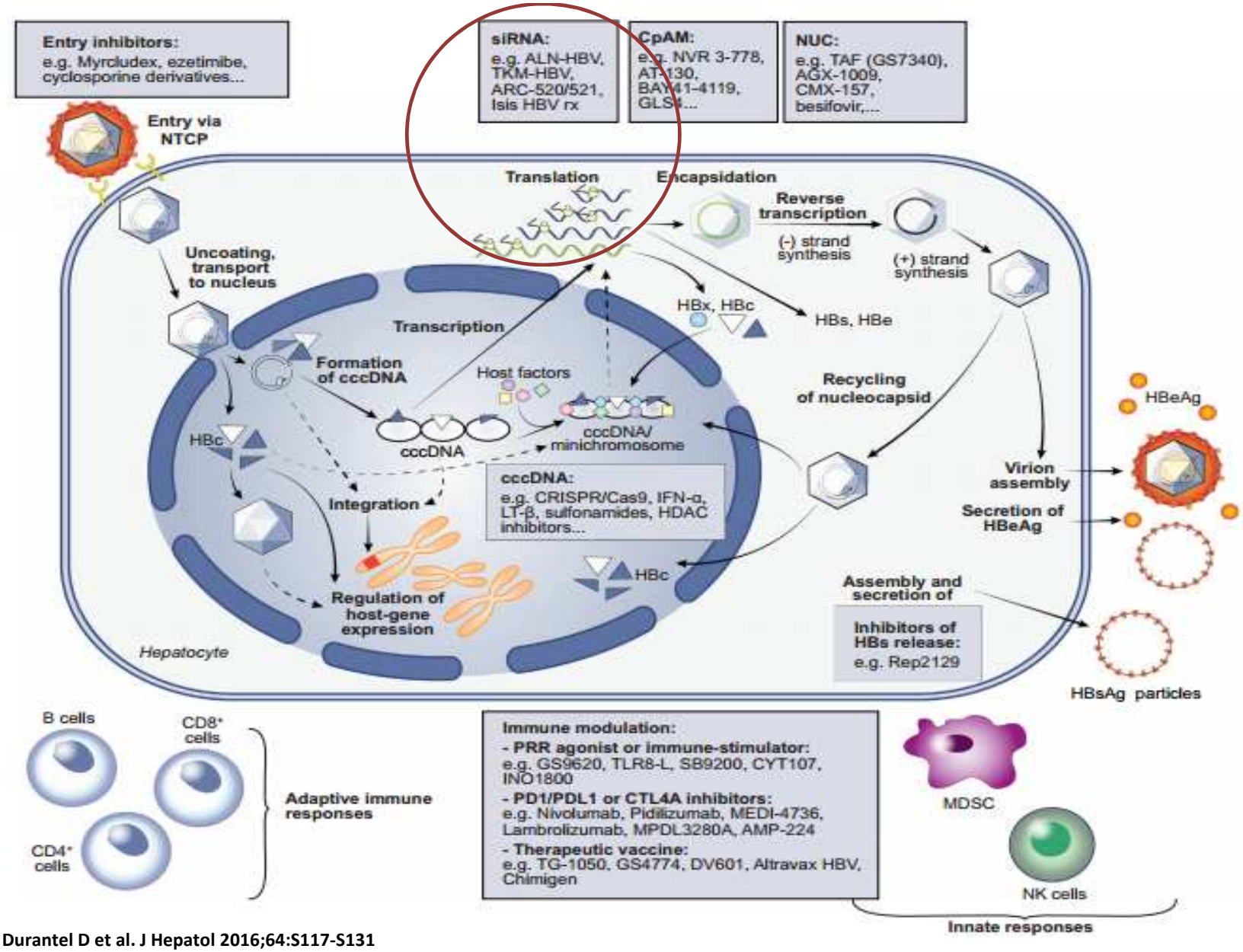
•HDV RNA declined at week 24 in all cohorts

•HDV RNA negative in 2 cases in Myr, 2 PegIFN and 5 in Myr + PegIFN

HBV

HBsAg levels remained unchanged

Bogomolov P, et al. J Hepatol 2016;65(3):490-8

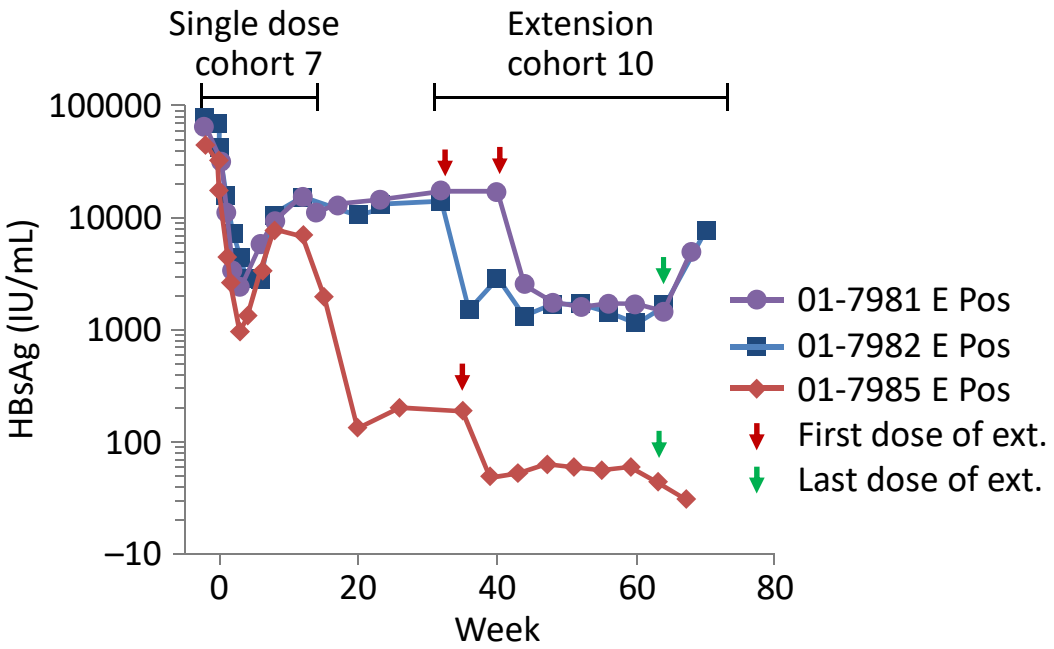


Durantel D et al. J Hepatol 2016;64:S117-S131

Terapia con RNA de interferencia

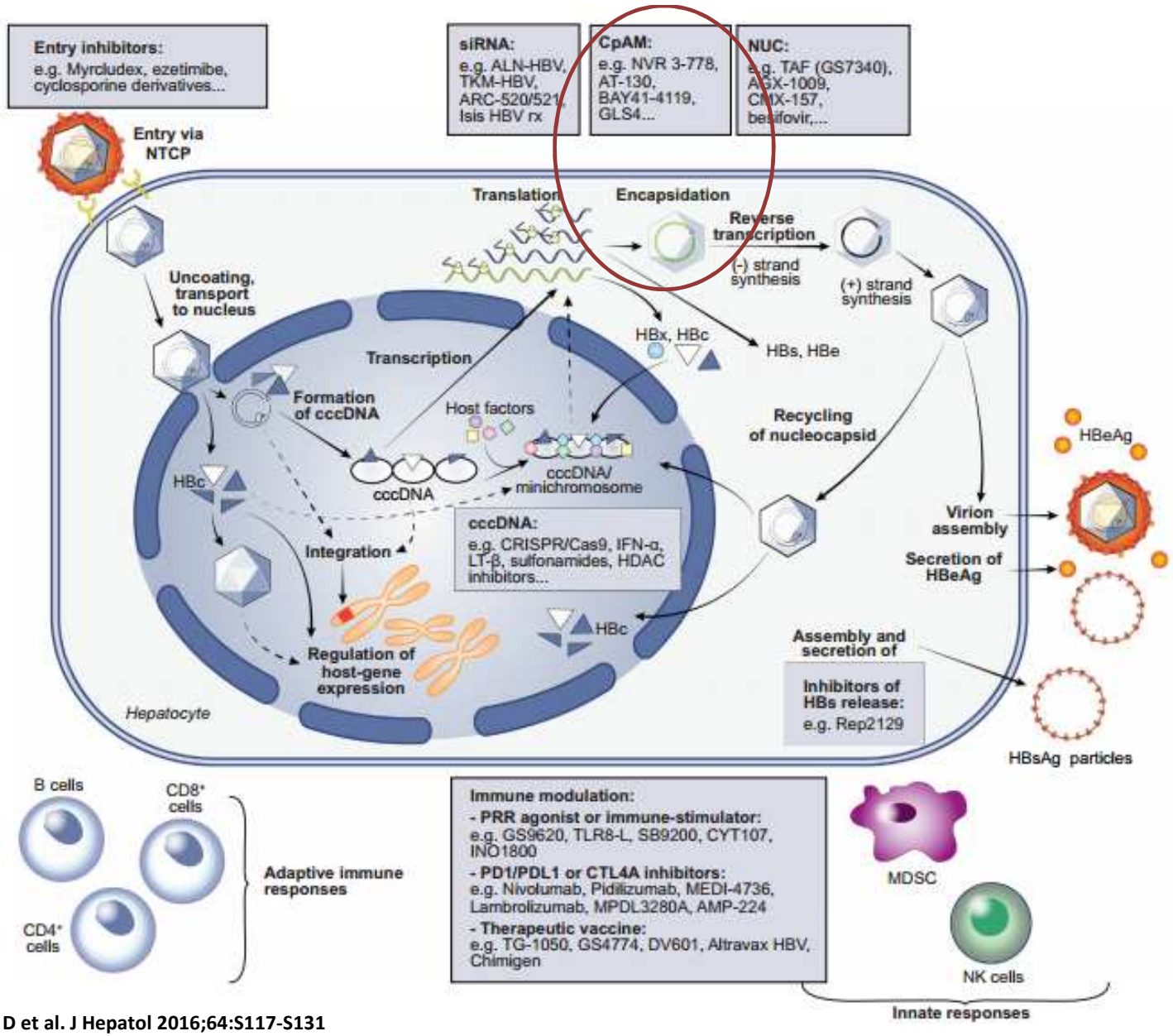
- Small non coding RNA
- Target directly HBV RNA transcripts
- Reduce HBsAg production
- Restore host-immune response
- Delivery to Hepatocytes
- Phase 2 clinical Trials
  - ARC-520: Multiple injections (Clinical Hold by FDA)
  - ARB 1416
  - **ESC-GalNAc-Conjugate** for subcutaneous administration

ARC-520 in treatment-naïve, HBeAg positive chronic HBV results in significant reductions of HBsAg



Reduction in HBeAg+ patients greater than in HBeAg– patients

Yuen ML et al EASL 2017

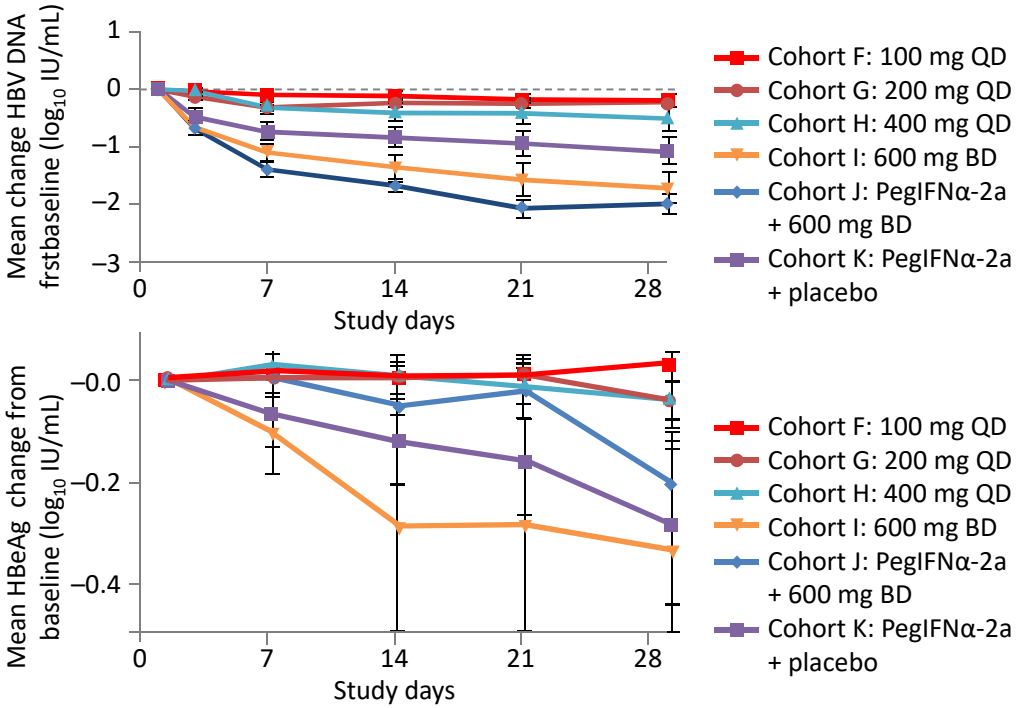


Durantel D et al. J Hepatol 2016;64:S117-S131

Inhibidores del core o cápside

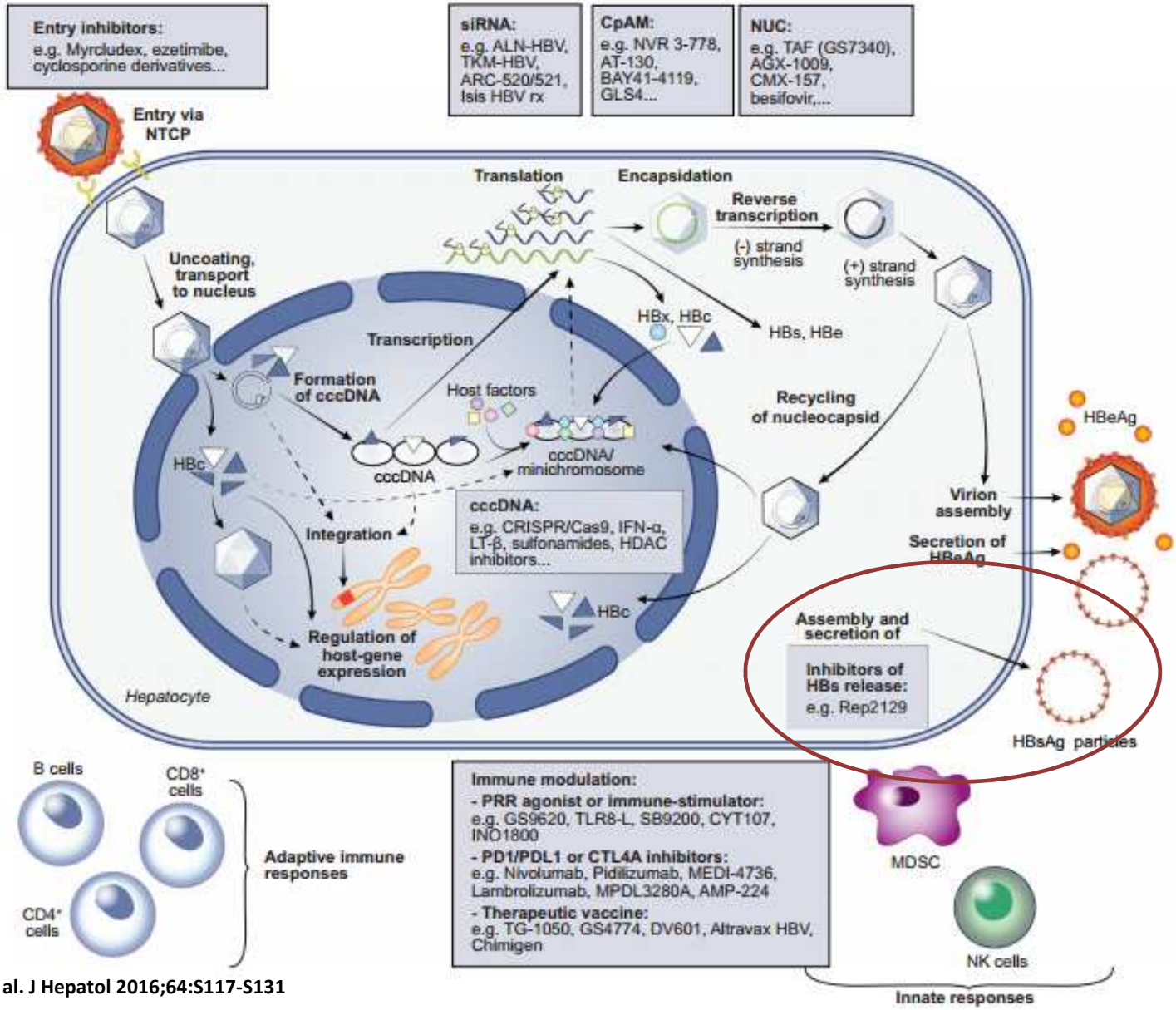
- Interfer HBV capside assembly by destabilizing core particle assembly or disrupting existing capsides

NVR 3-778 Phase 1b dose-ranging study HBeAg+ ve patients



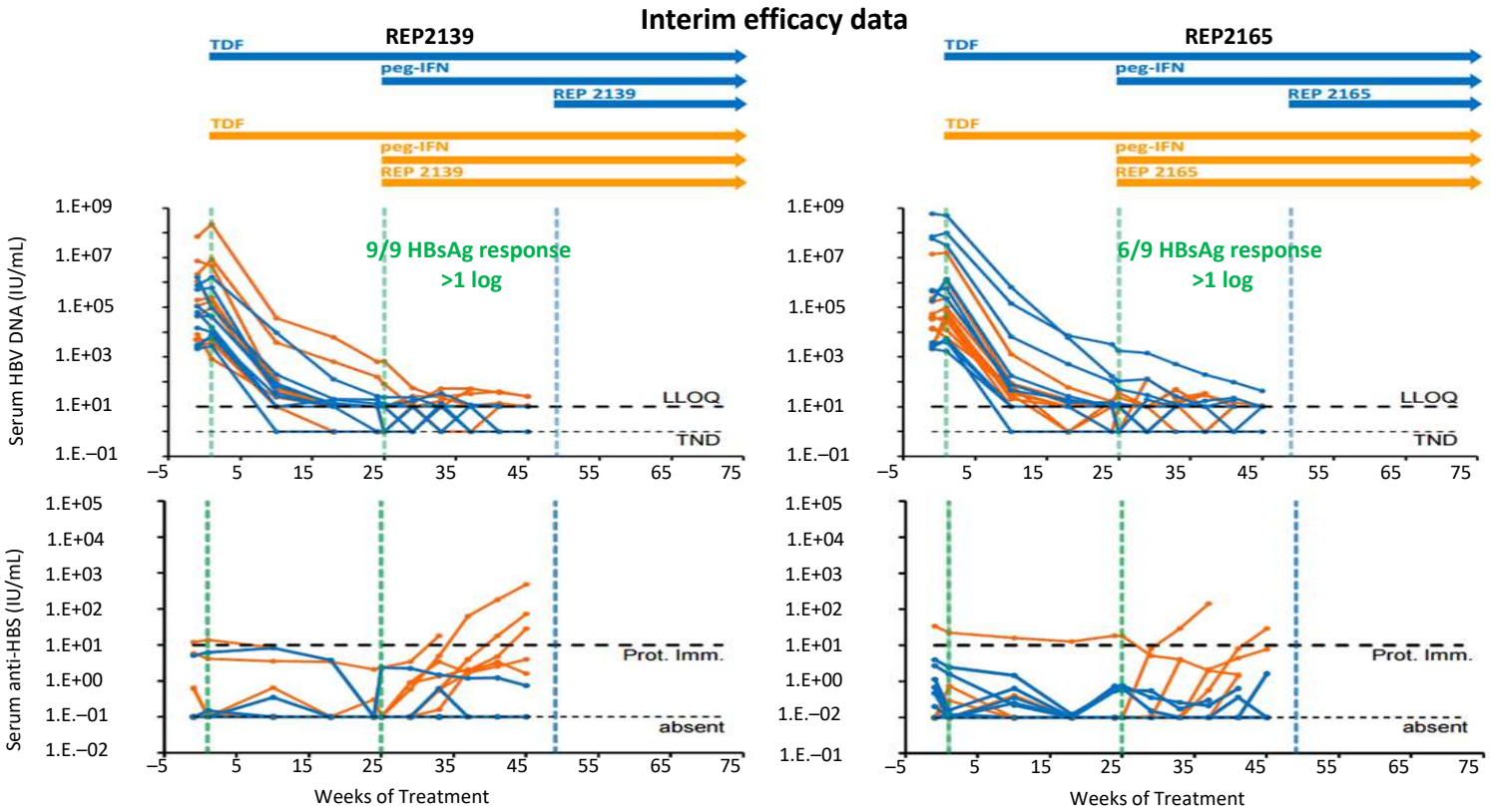
Additive effect with the NVR 3-778 +PegIFN combination on HBV DNA reduction (1.97 log IU/mL)
No changes in HBsAg levels

Yuen M-F, et al. EASL 2016, Barcelona. LBO6



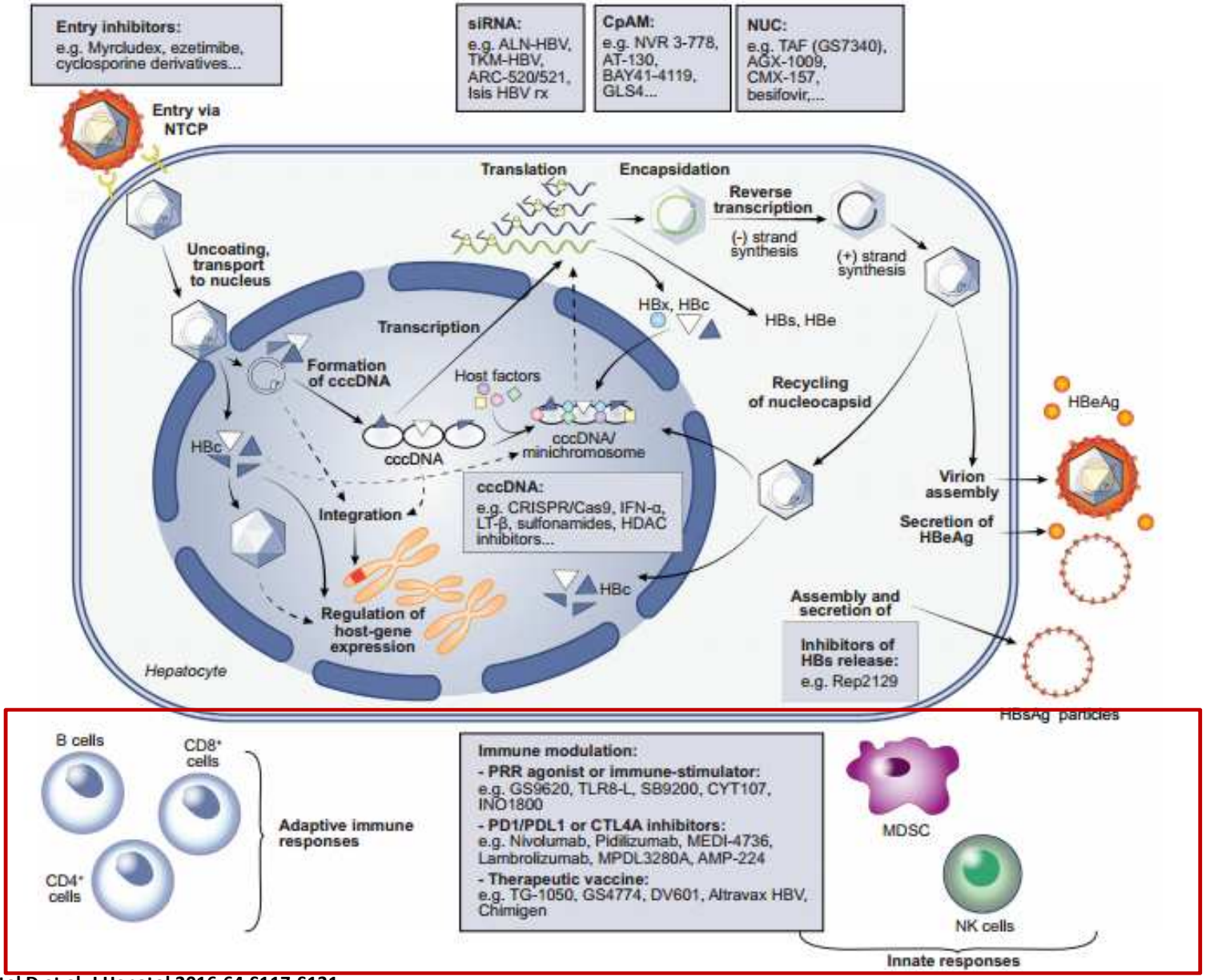
Durantel D et al. J Hepatol 2016;64:S117-S131

Efficacy of REP 2139-Mg or REP 2165-Mg combined with TDF and PegIFNα-2a in treatment-naive patients with chronic HBeAg-ve



Elevation in serum ALT correlated with HBsAg reduction (self-resolving with continued therapy)

Vaillant A, et al. AASLD 2016, Boston. #LB-7



Durantel D et al. J Hepatol 2016;64:S117-S131

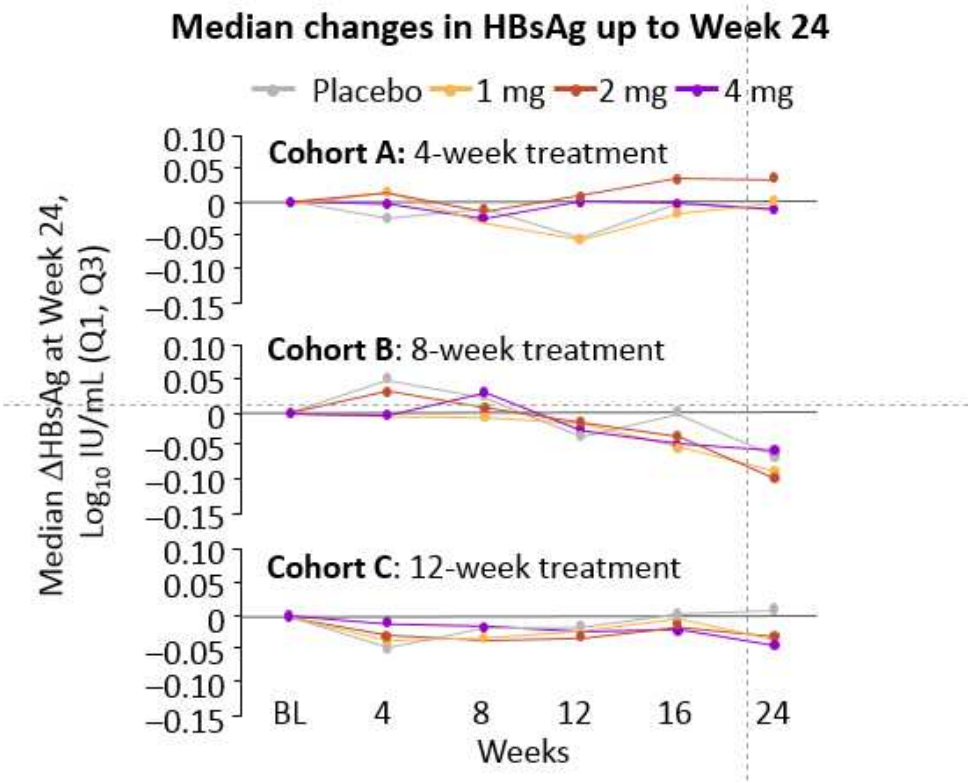
Safety and efficacy of GS-9620 (oral, TLR7 agonist) in virally suppressed patients with chronic hepatitis B

- TLR7 is a pattern-recognition receptor in the endolysosomal compartment of plasmacytoid dendritic cells and B cells
- TLR7 activation results in innate and adaptive immune stimulation

- CHB without cirrhosis
- NAs ≥1 y with HBV DNA <20 IU/mL at screening
- Once-weekly dosing

- Dose related increase in ISGs

1° Endpoint: HBsAg Decline or HBsAg loss at week 24

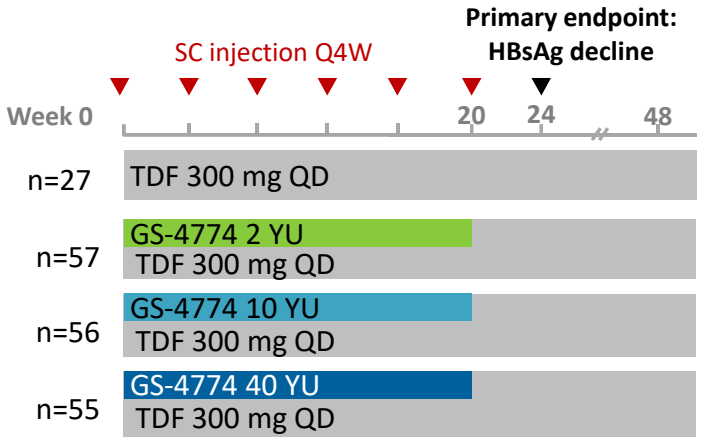


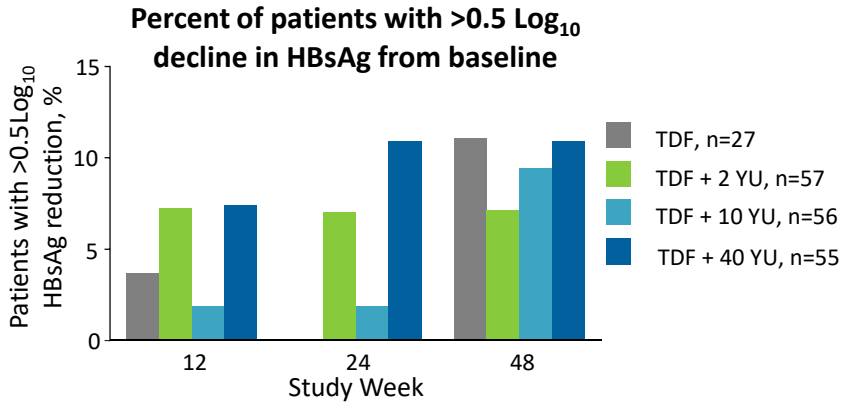
HBsAg changes were minimal in all cohorts, with no patients having greater than 0.5 log10 declines in HBsAg at Week 24 in any GS-9620 treated arms

Janssen HL, et al. AASLD 2016, Boston. #1851

Efficacy of GS-4774 combined with TDF in patients with chronic hepatitis B

- GS-4774 is a heat-inactivated, yeast-based T-cell vaccine
  - Recombinant protein containing HBV core, surface, and X proteins
- Phase 2 study

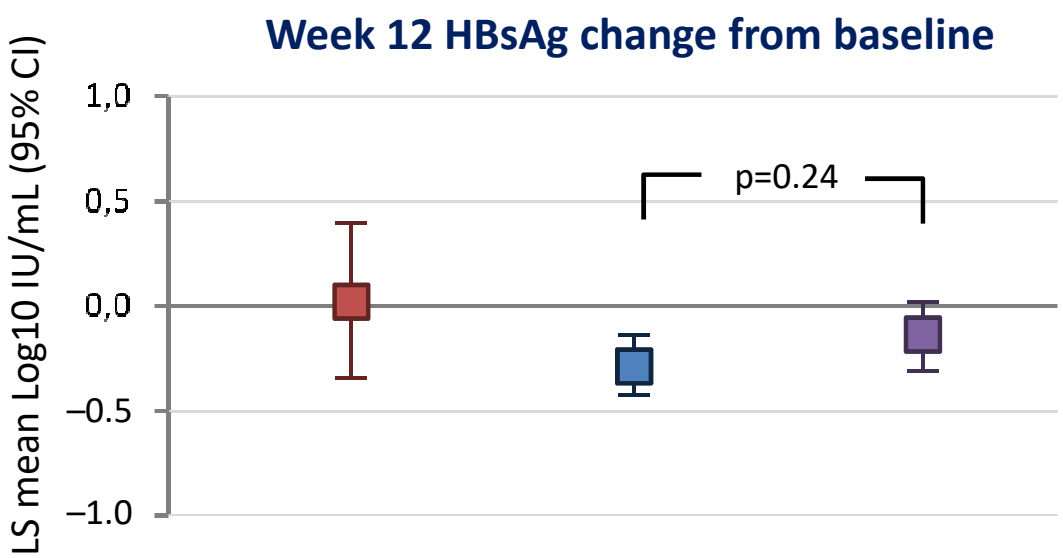


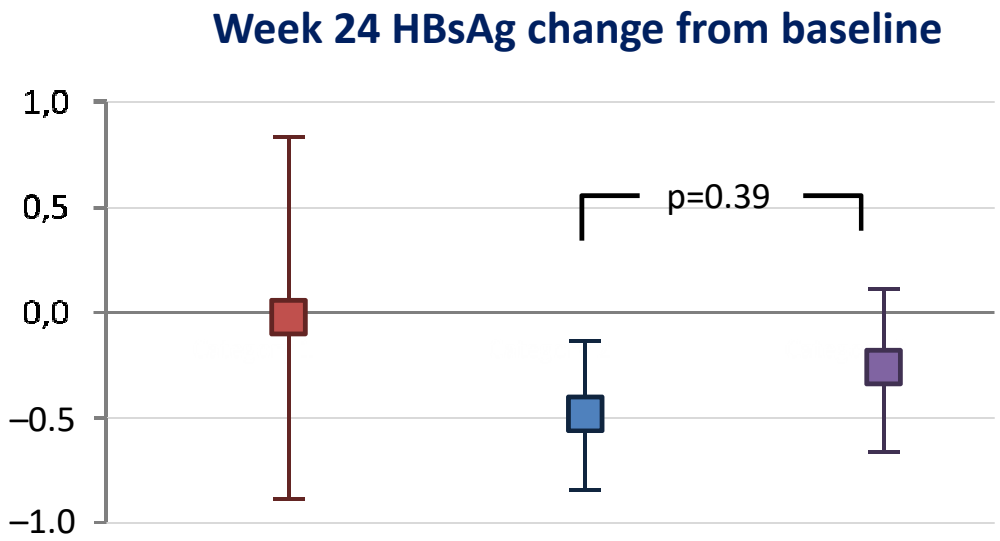


- 11 patients had >0.5 Log_{10} reductions in HBsAg at Week 24 (11 in GS-4774 groups versus 0 in TDF group) and 18 at week 48
- No patients achieved HBsAg loss by Week 48
- Higher baseline ALT, HLA DRB 15:02, and baseline HBeAg- positive status appear associated with HBsAg decline

Janssen HL, et al. AASLD 2016, Boston. #231

A phase 1 study evaluating anti-PD-1 treatment with or without GS-4774 in HBeAg-negative chronic hepatitis B patients





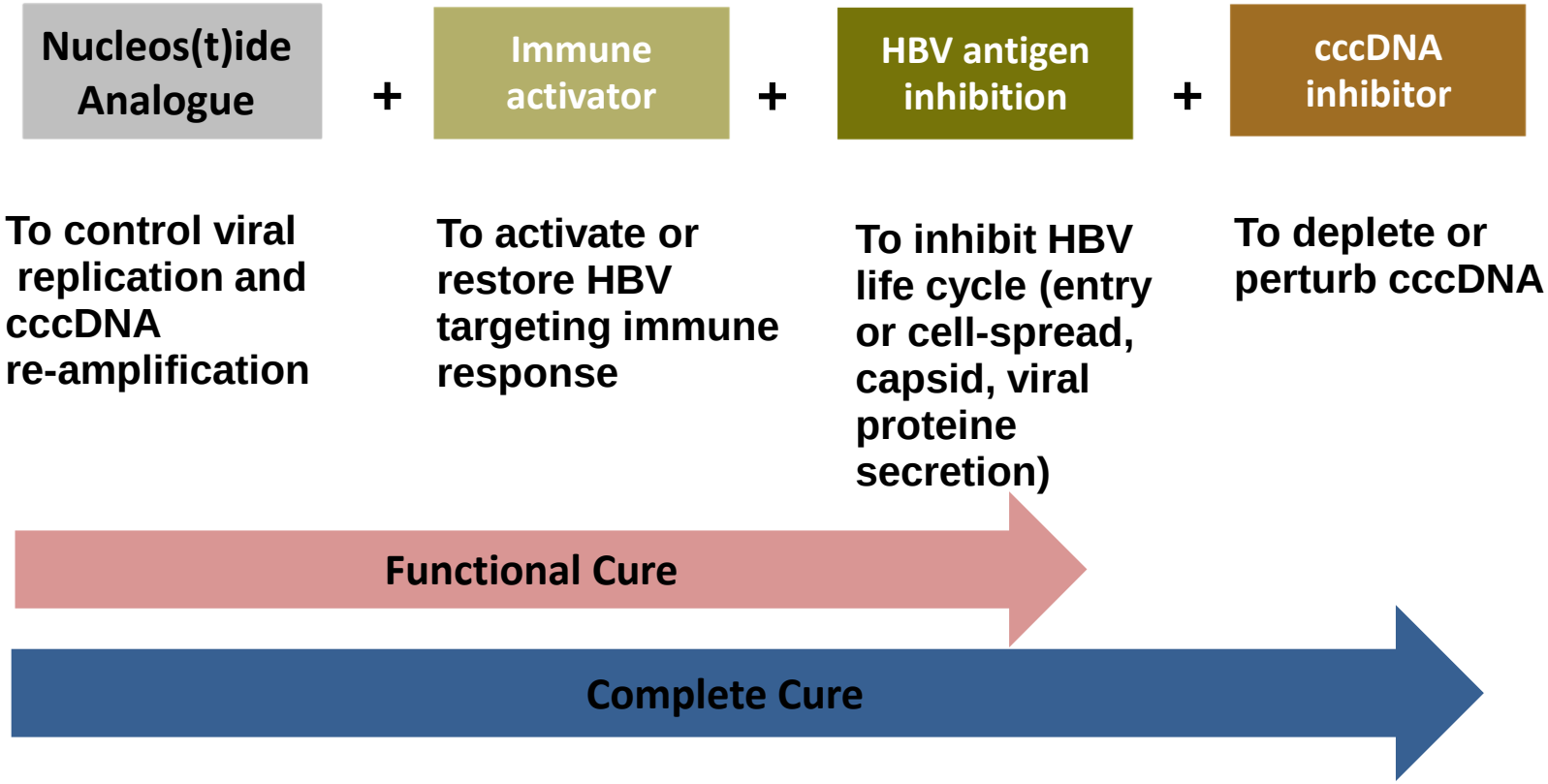
	Nivolumab 0.1 mg/kg (n=2)	Nivolumab 0.3 mg/kg (n=12)	Nivolumab 0.3 mg/kg + GS-4774 (n=10)
Mean (SD)	0.016 (0.011)	–0.30 (0.61)	–0.16 (0.20)
Median (IQR)	0.016 (0.008, 0.024)	–0.13 (–0.20, 0.06)	–0.08 (–0.21, –0.02)

Nivolumab 0.1 mg/kg (n=2)	Nivolumab 0.3 mg/kg (n=12)	Nivolumab 0.3 mg/kg + GS-4774 (n=10)
–0.049 (0.035)	–0.47 (1.26)	–0.26 (0.24)
–0.049 (0.074, 0.024)	–0.14 (–0.19, 0.05)	–0.20 (–0.39, –0.05)

- Single dose PD-1 ab ± GS-4774 well tolerated
- Modest reduction of HBsAg in all treatment arms

Gane E, et al. EASL 2017, #PS-044

An approach to curing HBV might require combination therapy



Conclusiones

- Los tratamientos actuales NO son curativos
- La supresión viral mantenida es posible pero la pérdida del HBsAg es limitada
- Los nuevos antivirales e inmunomodulares están todavía en fases iniciales de investigación
- La combinación de diferentes clases de fármacos podría tener la capacidad de curar la infección por VHB