Treatment of Hepatitis B: from the current treatment to the future

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CONFLICT OF INTEREST

I have financial relationships to disclose within the past 12 months relevant to my presentation:

Consultant and Speaker Bureau
Abbvie, BMS, Gilead, Merck/MSD, Roche

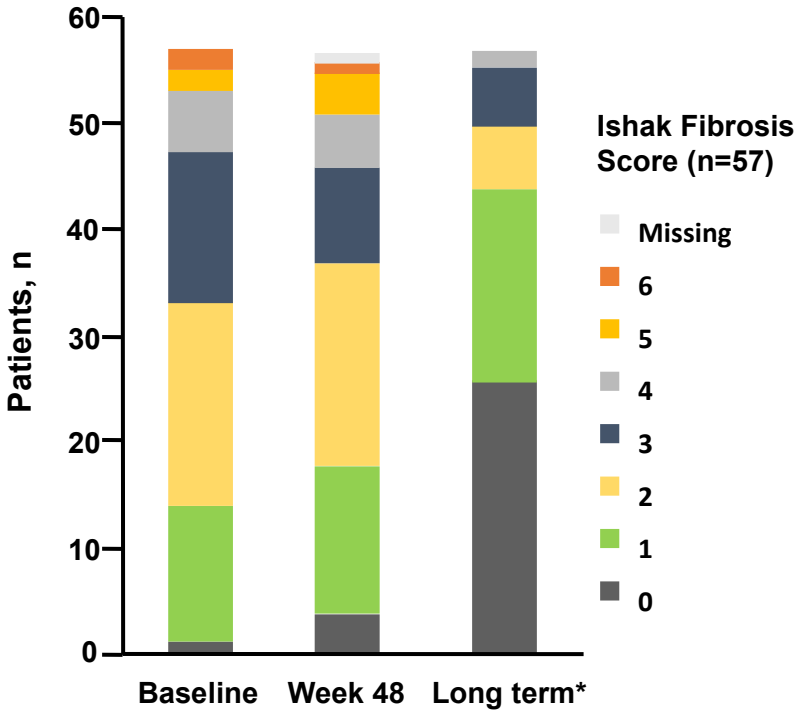
Current treatment strategies for chronic hepatitis B: main concepts and features

Features	PegIFNα	ETV, TDF, TAF
Route of administration	Subcutaneous injections	Oral
Treatment duration	48 weeks	Long-term until HBsAg loss*
Tolerability	Low	High
Long-term safety concerns	Very rarely persistence of on-treatment AEs[†]	Probably not[‡]
Contraindications	Many[§]	None[‖]
Strategy	Induction of a long-term immune control	Inhibition of viral replication
Level of viral suppression	Moderate	Universally high
Effect on HBeAg loss	Moderate[¶]	Low in first year, moderate over long term
Effect on HBsAg levels	Variable[¶]	Low**
Risk of relapse after treatment cessation	Low for those with sustained response 6–12 months after therapy	Moderate if consolidation treatment provided after HBeAg seroconversion. High for HBeAg-negative disease
Early stopping rules	Yes	No
Risk of viral resistance	No	Minimal to none[††]

*Stopping NAs after some years might be considered in selected cases; [†]Psychiatric, neurological, endocrinological; [‡]Uncertainties regarding kidney function, bone diseases for some NAs; [§]Decompensated disease, comorbidities etc.; [‖]Dose adjustments in patients with eGFR <50 ml/min are required for all NAs except for TAF (no dose recommendation for TAF in patients with CrCl <15 ml/min who are not receiving haemodialysis); [¶]Depending on baseline characteristics; **Slowly increases with treatment time in HBeAg-positive patients (a plateau in serological responses has been observed beyond treatment Year 4), usually very low in HBeAg-negative patients; [††]So far no TDF or TAF resistance development has been detected

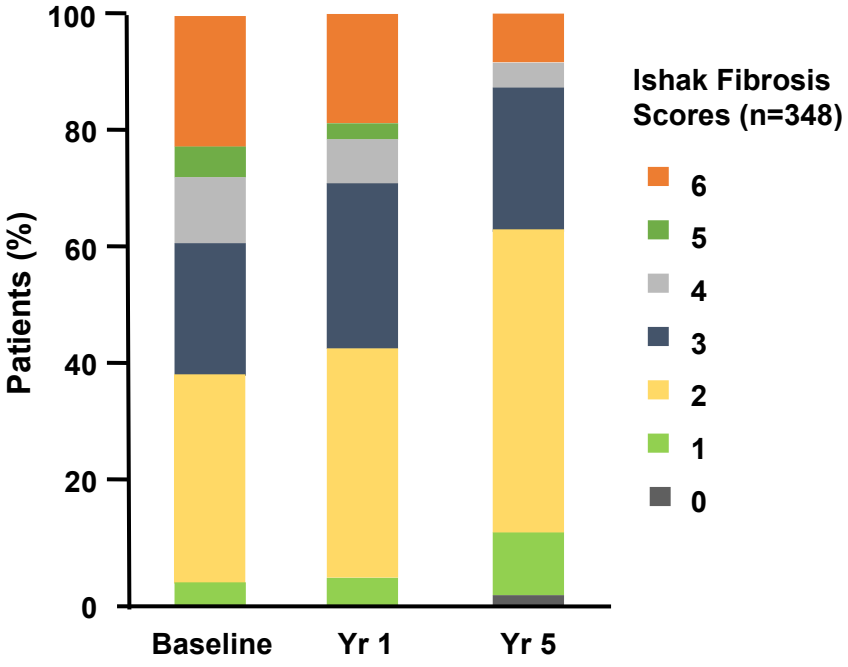
EASL CPG HBV. J Hepatol 2017;67:370–98

Long-term ETV and TDF Is Associated with Reversal of Liver Fibrosis in patients with CHB



Regression of fibrosis in 88% of pts

Reversal of cirrhosis in 4/10 pts with cirrhosis at baseline



Regression of fibrosis in 51% of pts through 5 yrs

Reversal of cirrhosis in 74% (71/96) of pts with cirrhosis at baseline

TDF: tenofovir disoproxil fumarate; ETV: entecavi* Long-term 7 years

Chang TT, et al. Hepatology 2010;52:886-893. Schiff ER, et al. Clin Gastroenterol Hepatol. 2011; 9:274-276. Marcellin P, et al. Lancet. 2013;381:468-475.

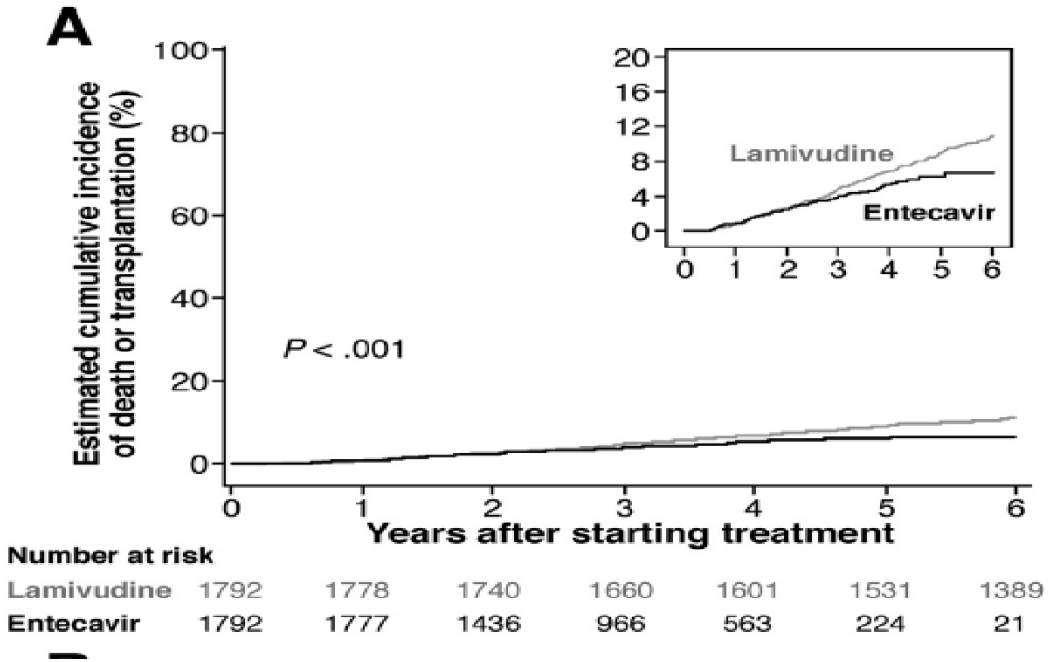
M

with chronic hepatitis B treated with entecavir vs lamivudine

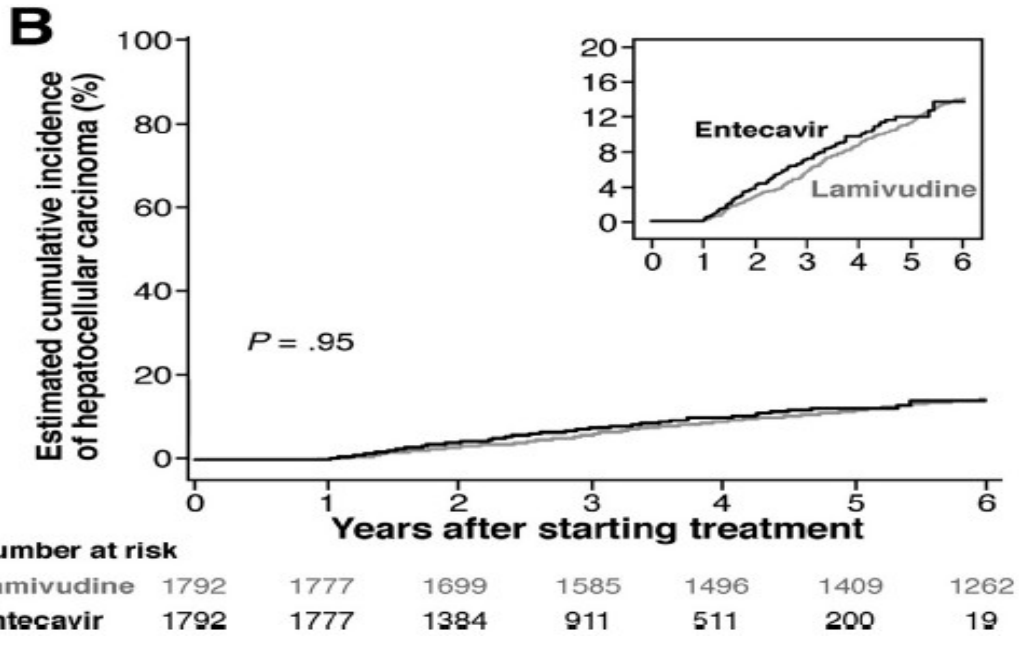
R

LAM (n=3374) between 11/1/1999 and 12/31/2011

Death or Liver Transplantation



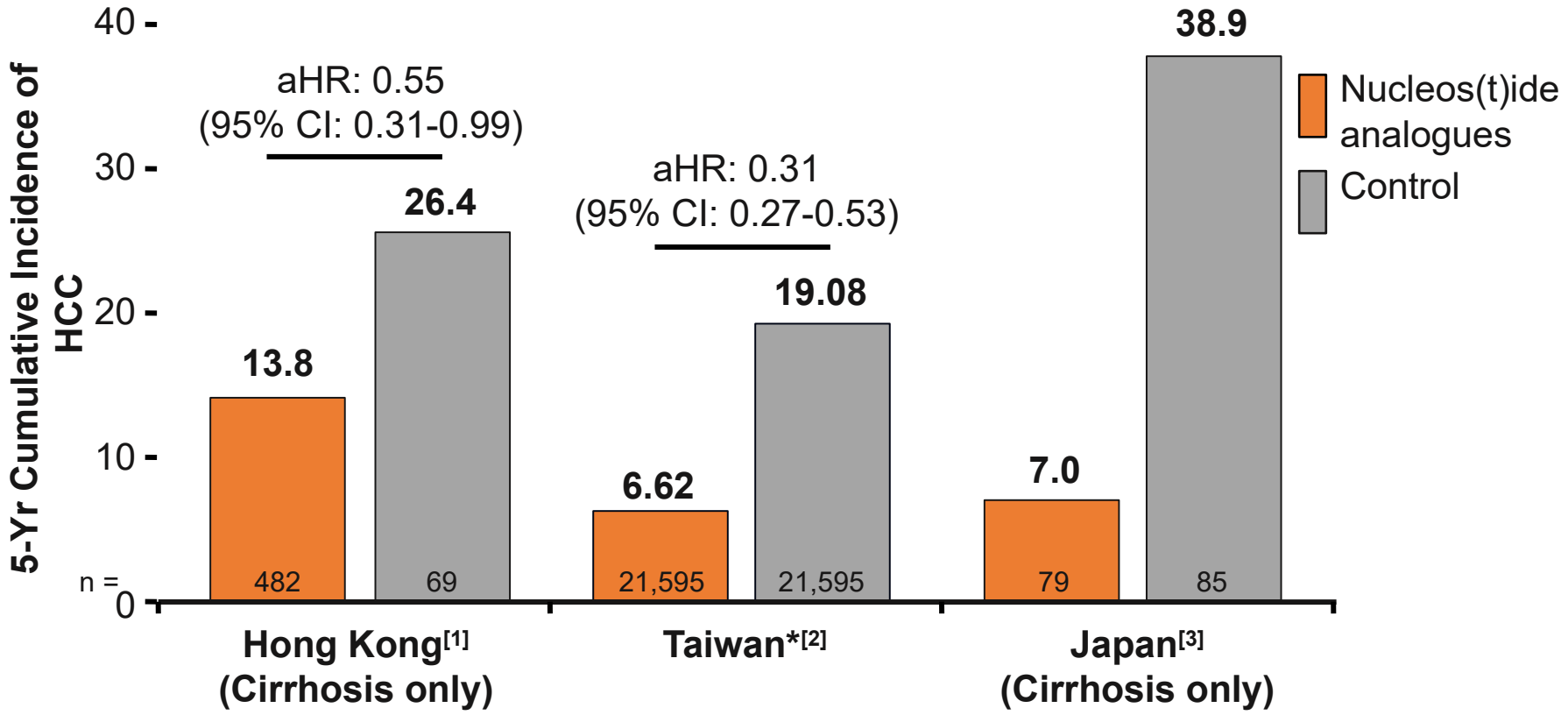
Hepatocelullar Carcinoma



ETV was associated with lower risk of death or transplantation than LAM, but no difference in HCC risk

Lim et al. *Gastroenterology* 2014;147:152-161

HCC Incidence in Pts With Chronic HBV Infection

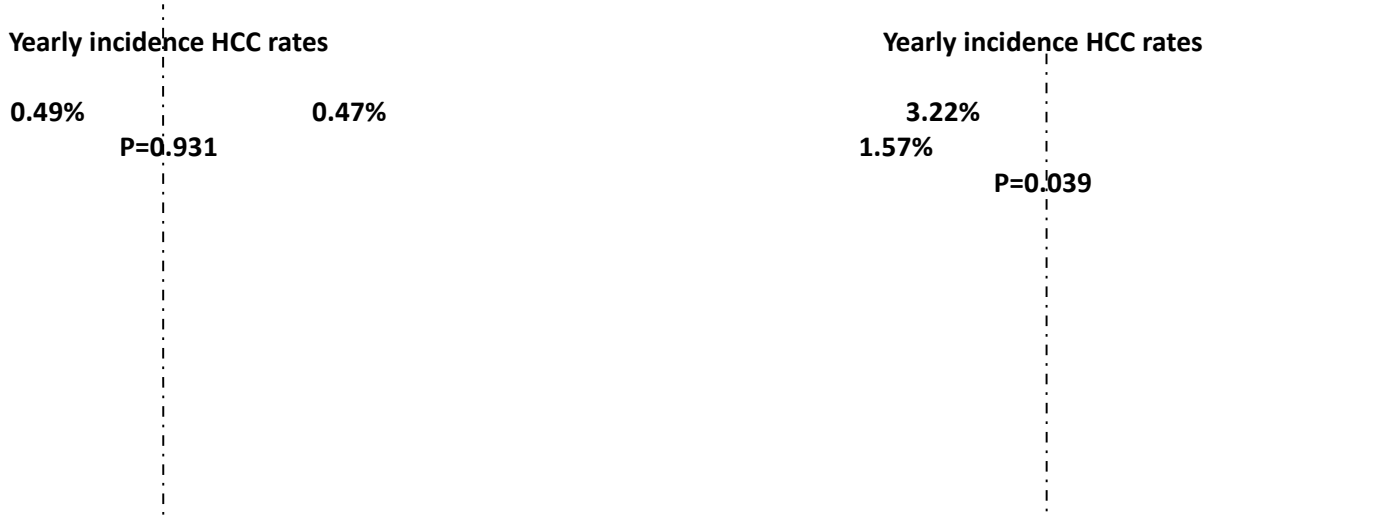


*Incidence rates include cirrhotic pts (13.6% of pts had cirrhosis at baseline) and noncirrhotic pts.

1. Wong GL, et al. Hepatology. 2013;5:1537-1547. 2. Wu CY, et al. Gastroenterology. 2014;147:143-151. 3. Hosaka T, et al. Hepatology. 2013;58:98-107.

The PAGE-B study: HCC in ETV/TDF treated pts beyond year 5

1951 patients on ETV/TDF for 72 months



- **The HCC risk decreases after the first 5 yrs of ETV/TDF therapy in patients with compensated cirrhosis at baseline but not in those with Chronic Hepatitis**
- **Older age, especially ≥50 yrs, and lower platelets represent the main risk factors for late HCC development.**

Papatheodoridis G, et al. Hepatology 2017;66:1444-1453

Safety of Nucleos(t)ide Analogues

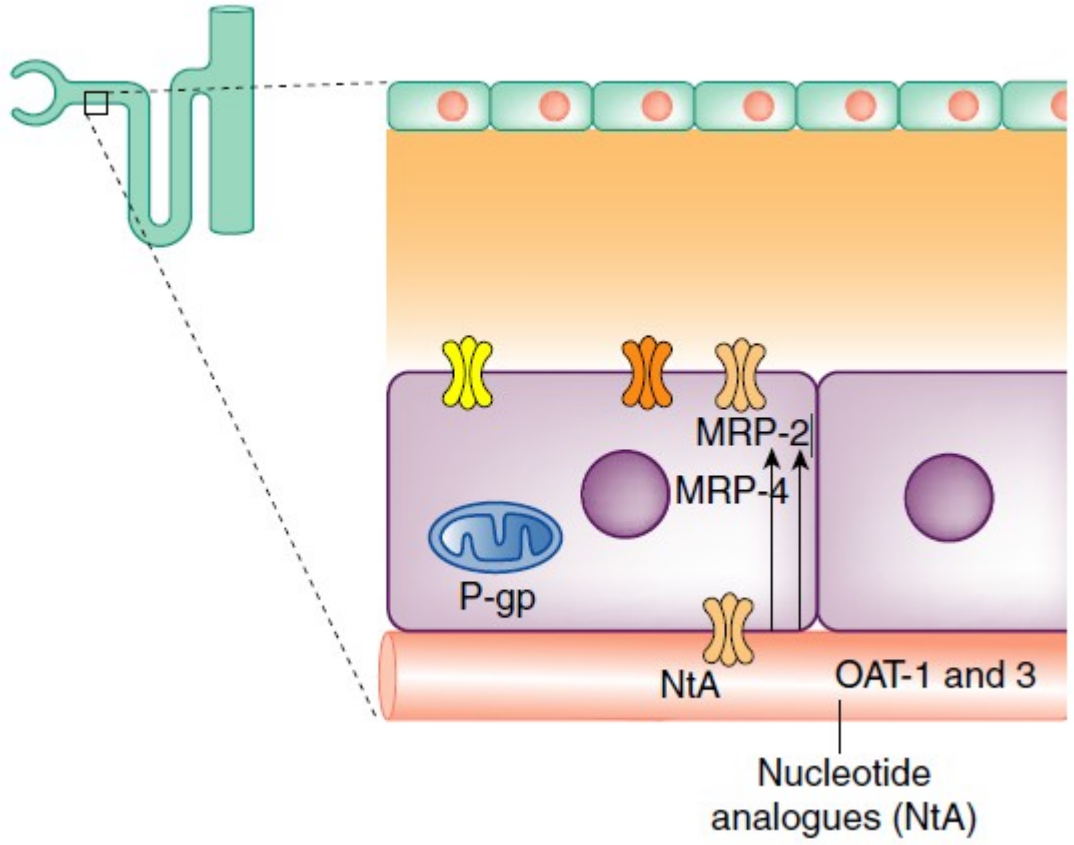
- Renal
- Bone
- Cancer
- Pregnancy

Renal Safety

Chronic HBV infection increase the risk of chronic kidney disease

All NAs are renally excreted. Need to be adjusted to GFR

ADV and TDF have been associated with a small risk of nephrotoxicity (Increase creatinine 3% vs 1% at yr 5)



Mechanisms of NA-associated Nephrotoxicity

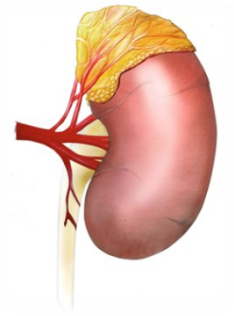
ADV and TDF are substrates of organic anion transporter (OAT)-1 and OAT-3; they are excreted by multidrug resistance protein (MRP)-4.

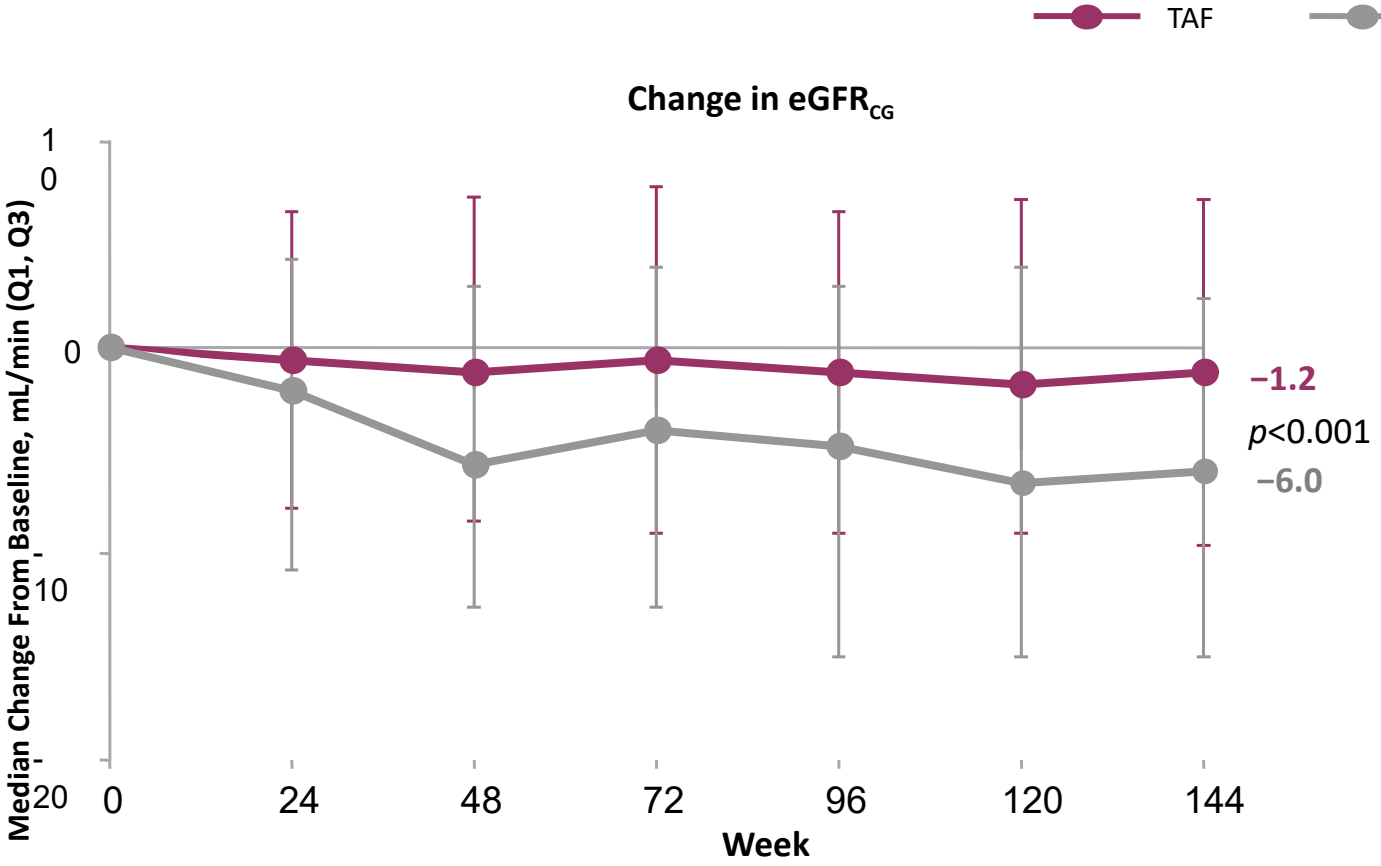
ADV and TDF would be actively transported by MRP-4 to the proximal tubule; when MRP-4 is saturated, ADV and TDF may accumulate in the intracellular environment leading to tubular damage

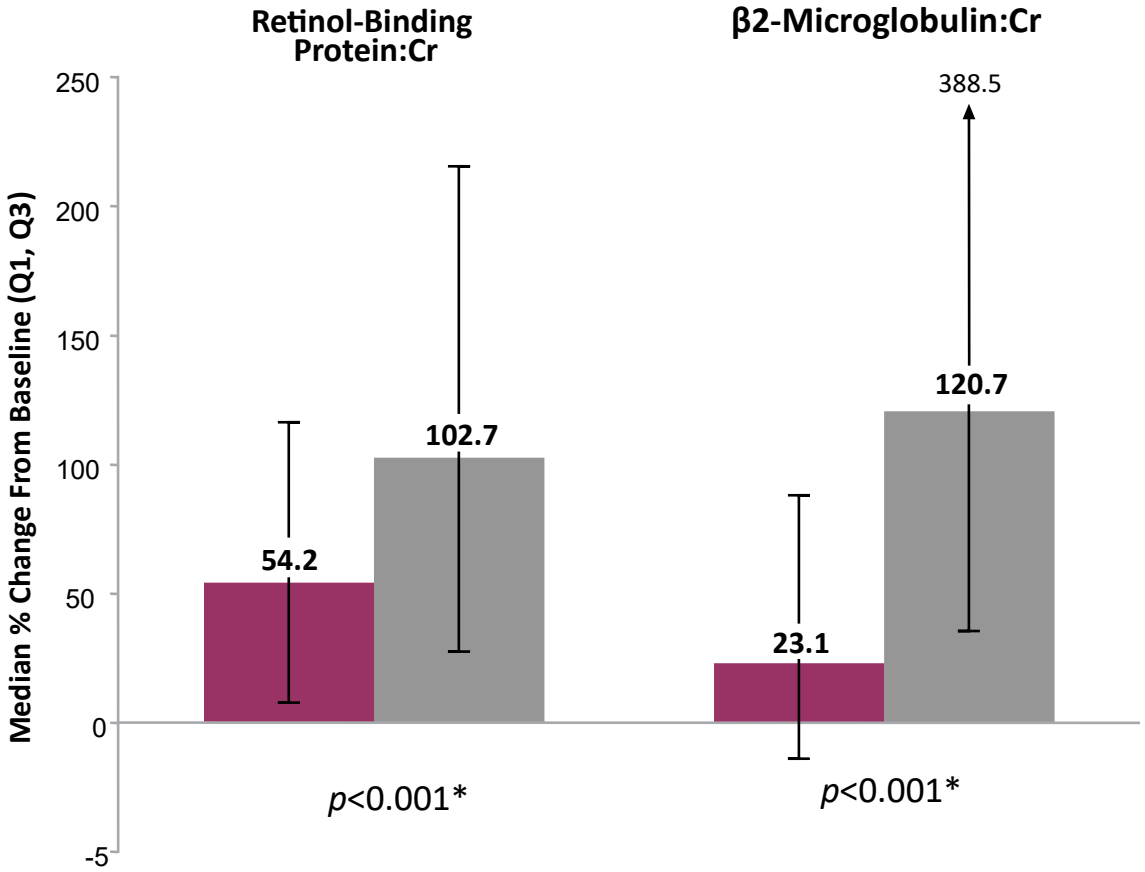
Rodriguez-Novoa S, et al. Clin Infect Dis. 2009;48:e108-e116.

Renal Safety
Change in Renal Parameters Over 144 Weeks

Study 108 and 110 Pooled Analysis: TAF vs TDF at 144 Weeks





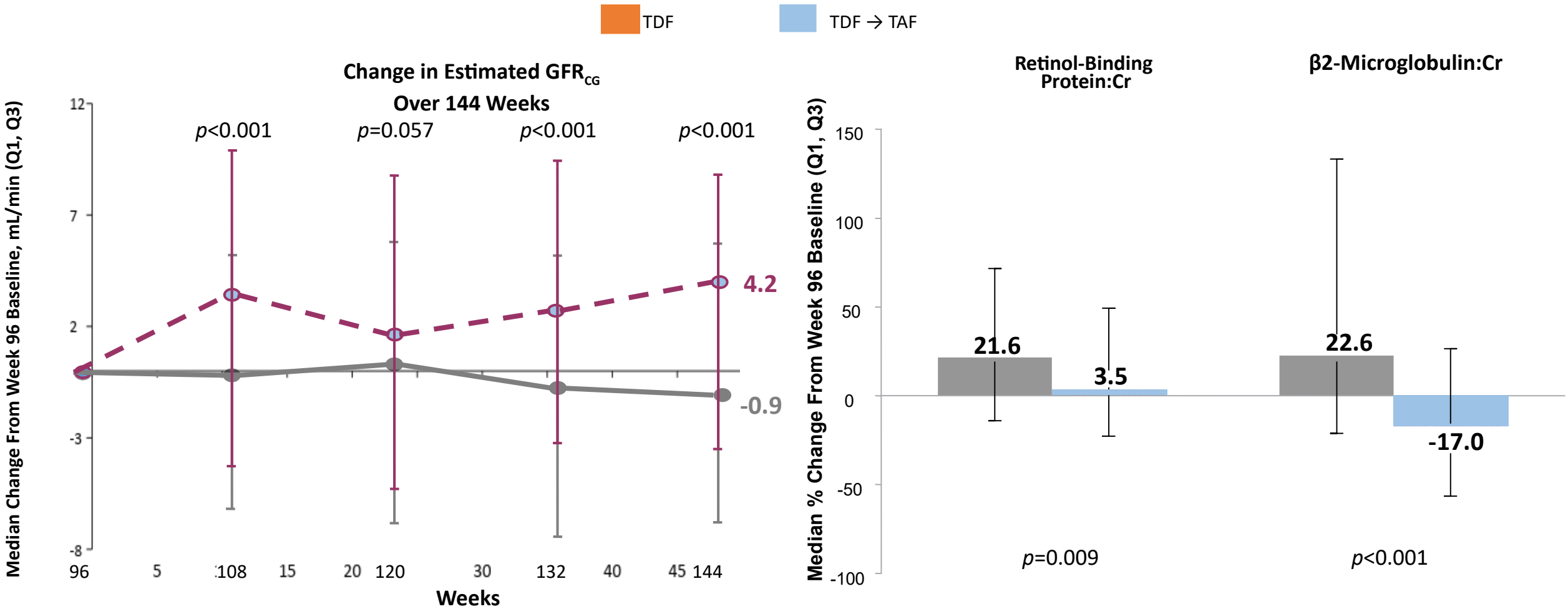


There were significantly smaller decreases in eGFR$_{CG}$ and smaller changes in proximal tubular markers with TAF compared to TDF at Week 144

*From 2-sided Wilcoxon rank-sum test

Chan, AASLD 2018, 0381

Change in Renal Parameters after switch from TDF to TAF



48 wks after switch from TDF to TAF significant improvements in eGFR$_{CG}$ and in markers of renal tubular function were observed

Seto, AASLD 2018, 0404

Bone Safety

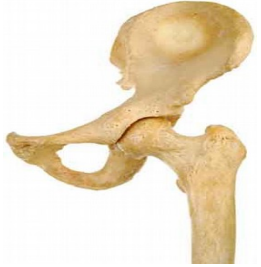
- CHB by itself also affects the skeletal system
- Vitamin D deficiency was found in 35-82% of Chinese CHB patient
- Asian patients are particularly at risk of bone problems in view of low body-mass
- Bone safety closely related with renal Aes
  - Related to nucleoside analogue effect on renal proximal tubular and phosphaturia
  - Real-life data demonstrated increased risk of hip fracture in patients received adefovir but not TDF

Rouillard S, et al.Hepatology. 2001;33: 301-307. Wong GL, et hepatitis B. Clin Gastroenterol Hepatol. 2015;13:783-790 e1. Chan HL, et al.J Hepatol. 2015;63:1086-1092

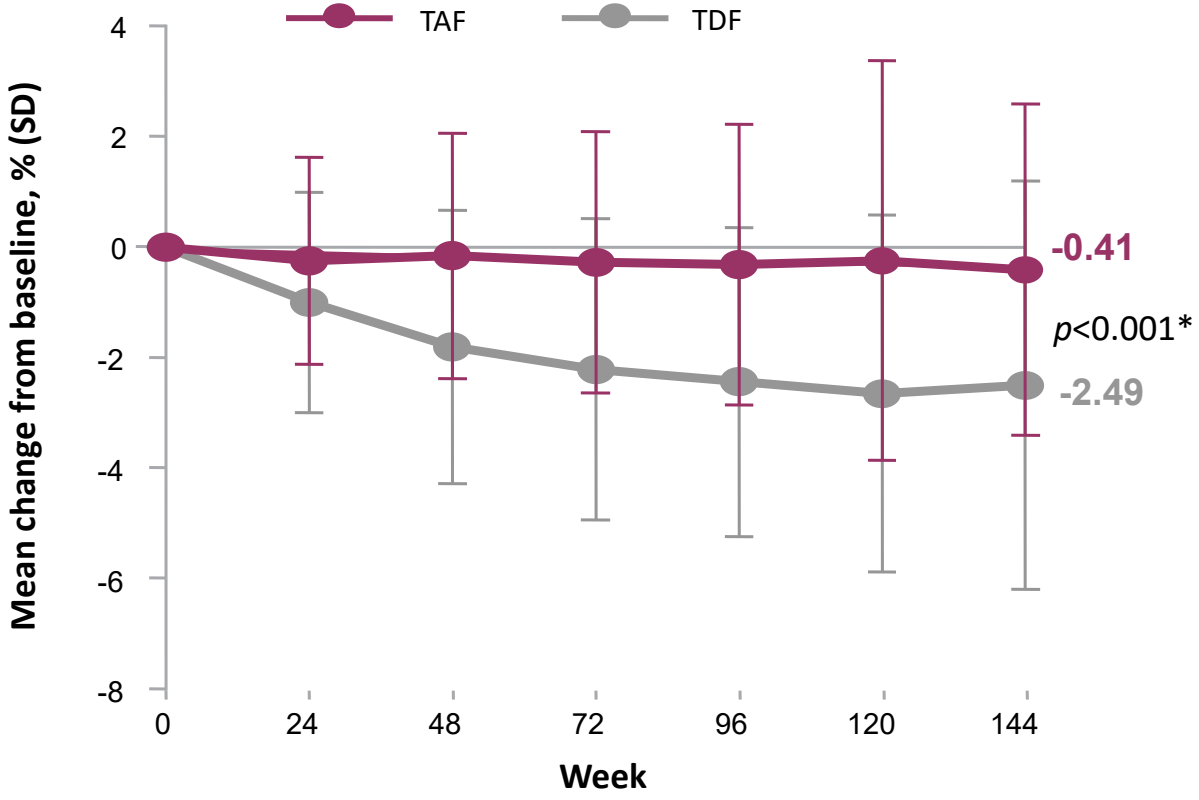
Study 108 and 110 Pooled Analysis: TAF vs TDF at 144 Weeks

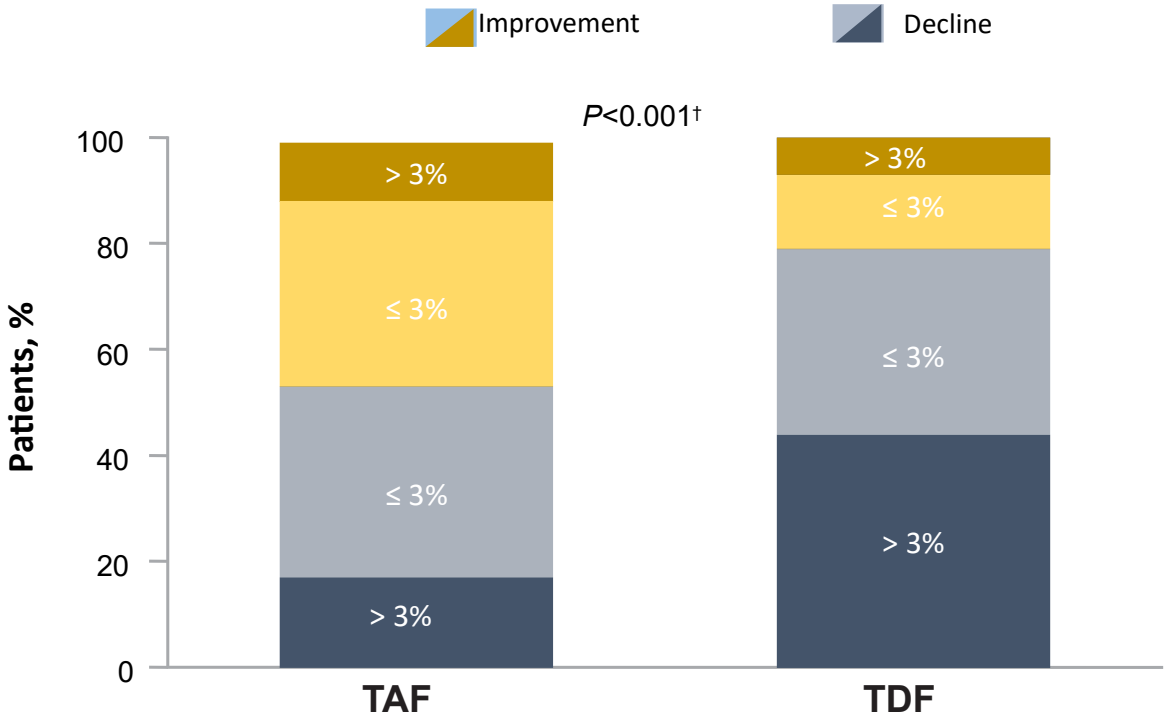
TAF vs. TDF for HBV: Bone Mineral Density

Changes in Bone Mineral Density (BMD) in Patients Over 144 Weeks



Hip





There were significantly less declines in hip BMD in patients on TAF compared to TDF

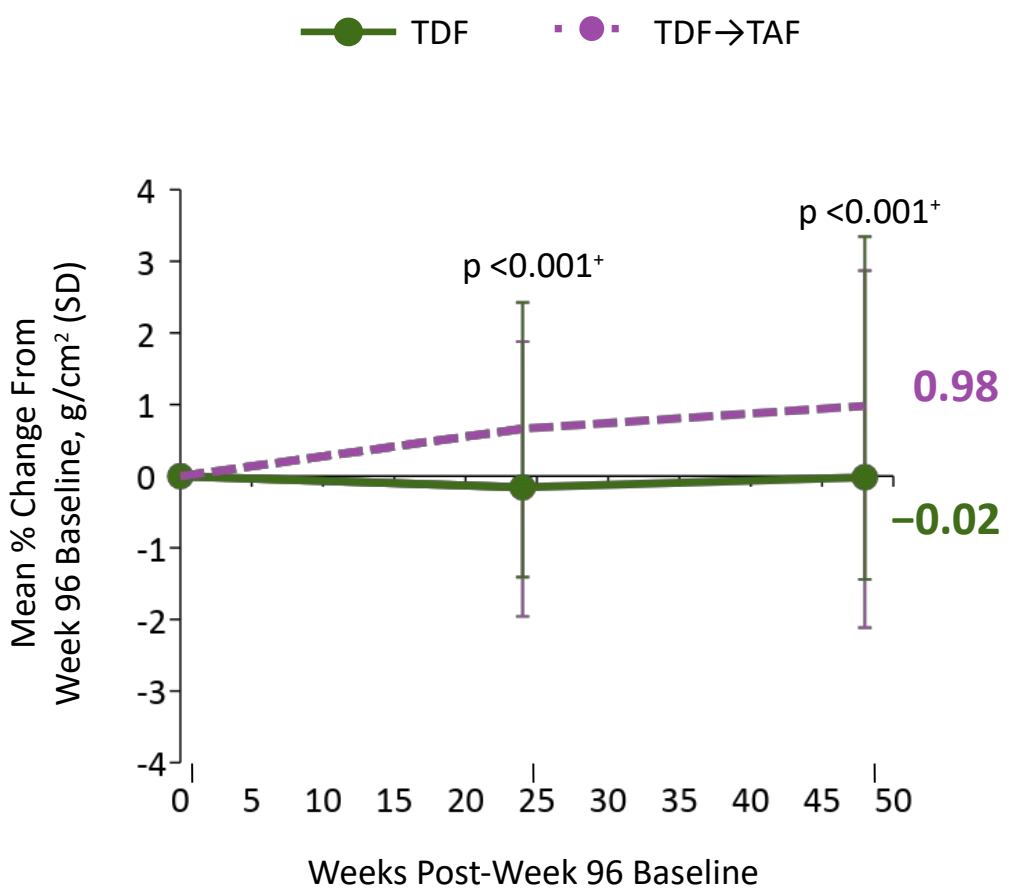
The proportion of TAF patients with hip BMD improvement was significantly higher when compared to TDF

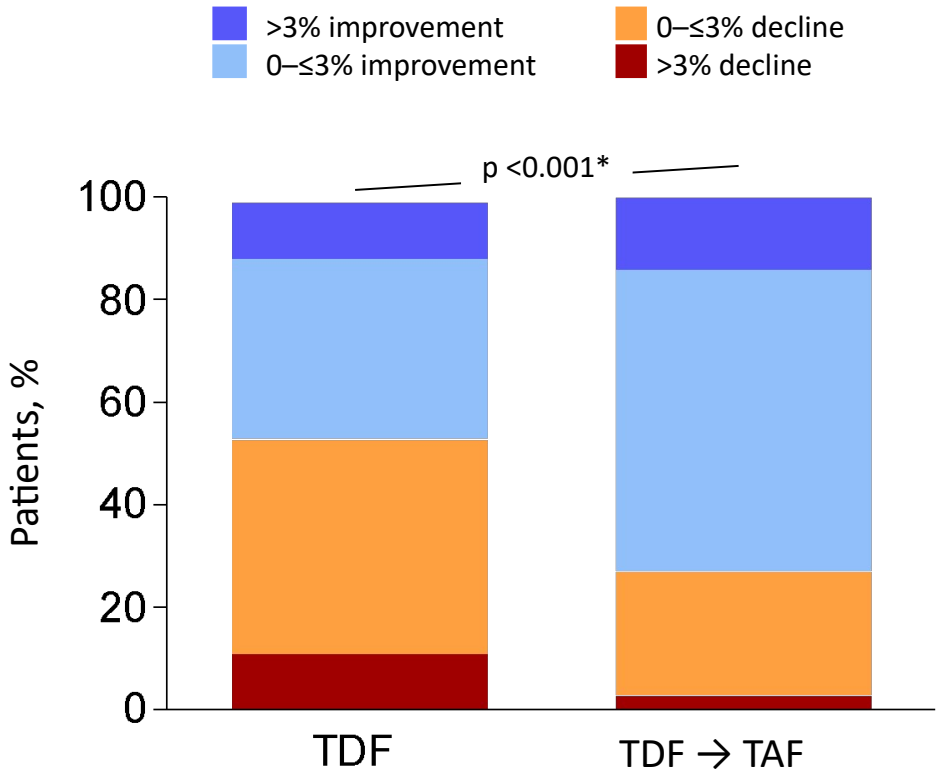
*From analysis of variance model including treatment as fixed effect

† From Cochran-Mantel-Haenszel test for ordinal data (row mean scores differ statistic was used).

Chan, AASLD 2018, 0381

Changes in Hip BMD From Week 96 Baseline to Week 144





- Greater proportions of TAF vs TDF patients showed improvements in BMD at Week 144

⁺From analysis of variance model including treatment as a fixed effect.
*From Cochran-Mantel-Haenszel test for ordinal data (row mean scores differ statistic was used).

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 alteration
(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

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

Validation of EASL 2017 Clinical Practice Guidelines for Switching HBV Patients Treated with TDF to ETV or TAF

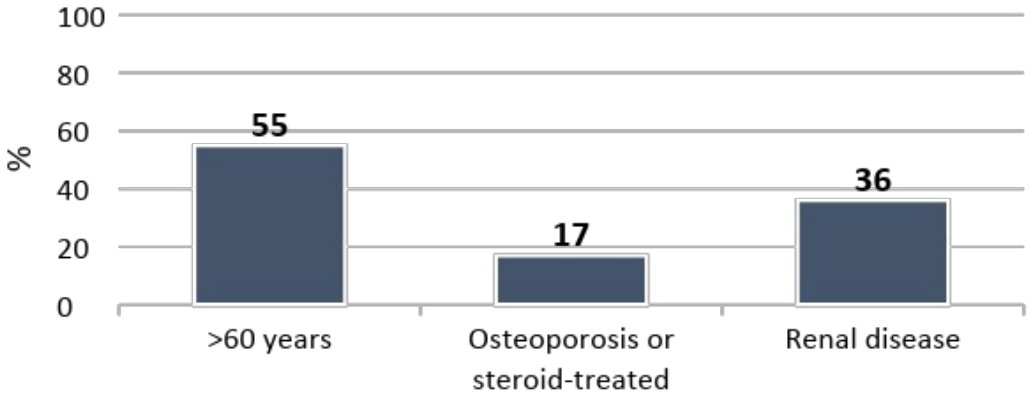
Cross-sectional study of patients treated with TDF in two EU centers that should be considered for TAF or ETV switch according to EASL Guidelines*

Patient Characteristics

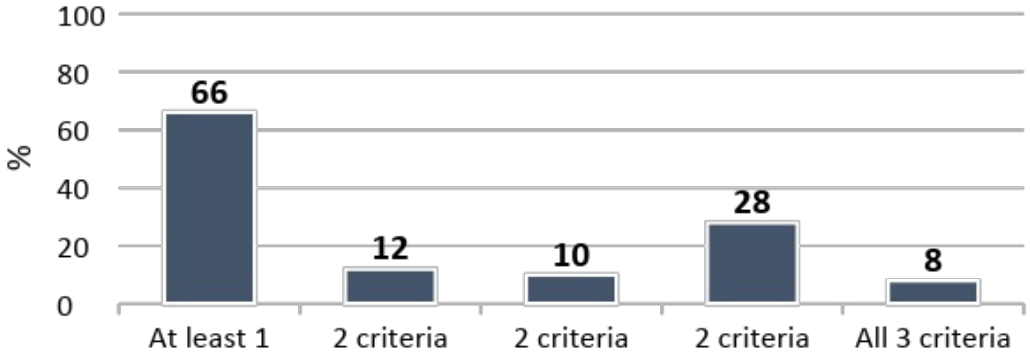
	N=565
Age, years (range)	62 (18-91)
Caucasian, %	92
HBeAg-negative, %	92
GT 3, %	77
Male, %	75
Cirrhosis, %	40
Diabetes, %	10
BMI, kg/m^2	25 (16-46)
Undetectable HBV DNA, %	95
Normal ALT, %	91
Previous LAM or ADV, %	53

A significant proportion of CHB patients on long-term TDF fulfill the EASL 2017 recommendations to switch to ETV or TAF

Characteristics According to EASL 2017 Criteria

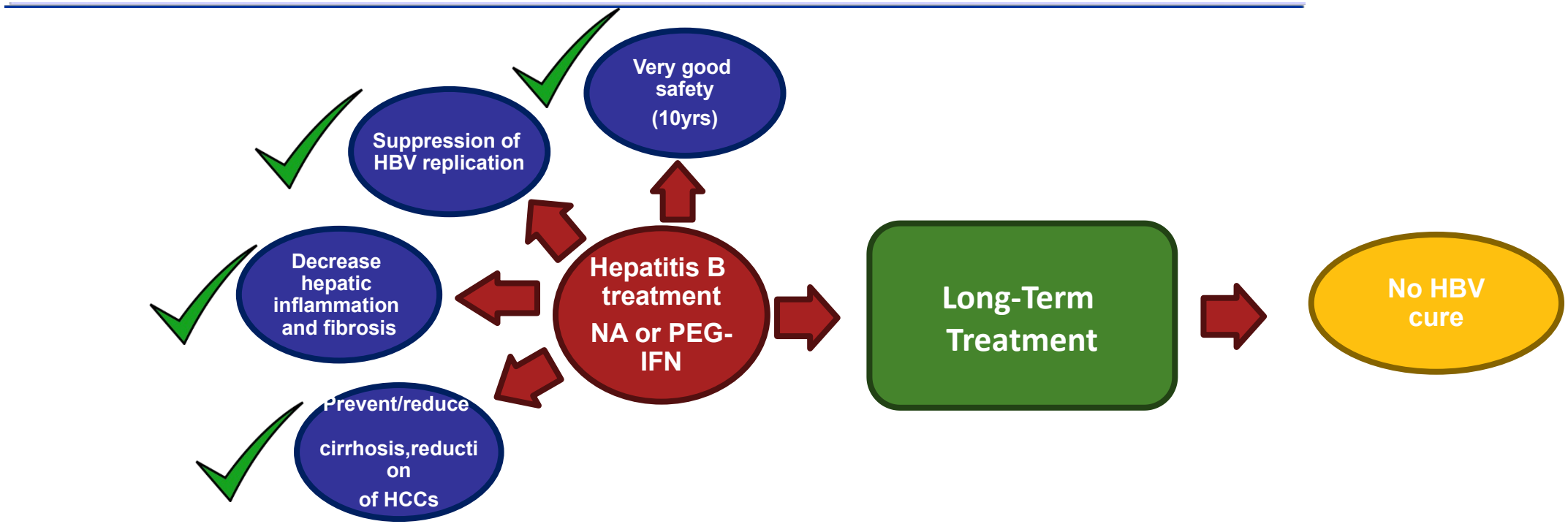


Patients with Multiple Criteria



Loglio, AASLD 2018, 269

Achievements and ongoing challenges
Hepatitis B: From a treatable disease to a curable disease ?



Liaw YF, et al. N Engl J Med 2004;351:1521–31;
Marcellin P, et al. Lancet 2013;381:468–75
Dandri M, Petersen J. Clin Infect Dis 2016;62:281-8

NAs discontinuation. EASL Recommendations

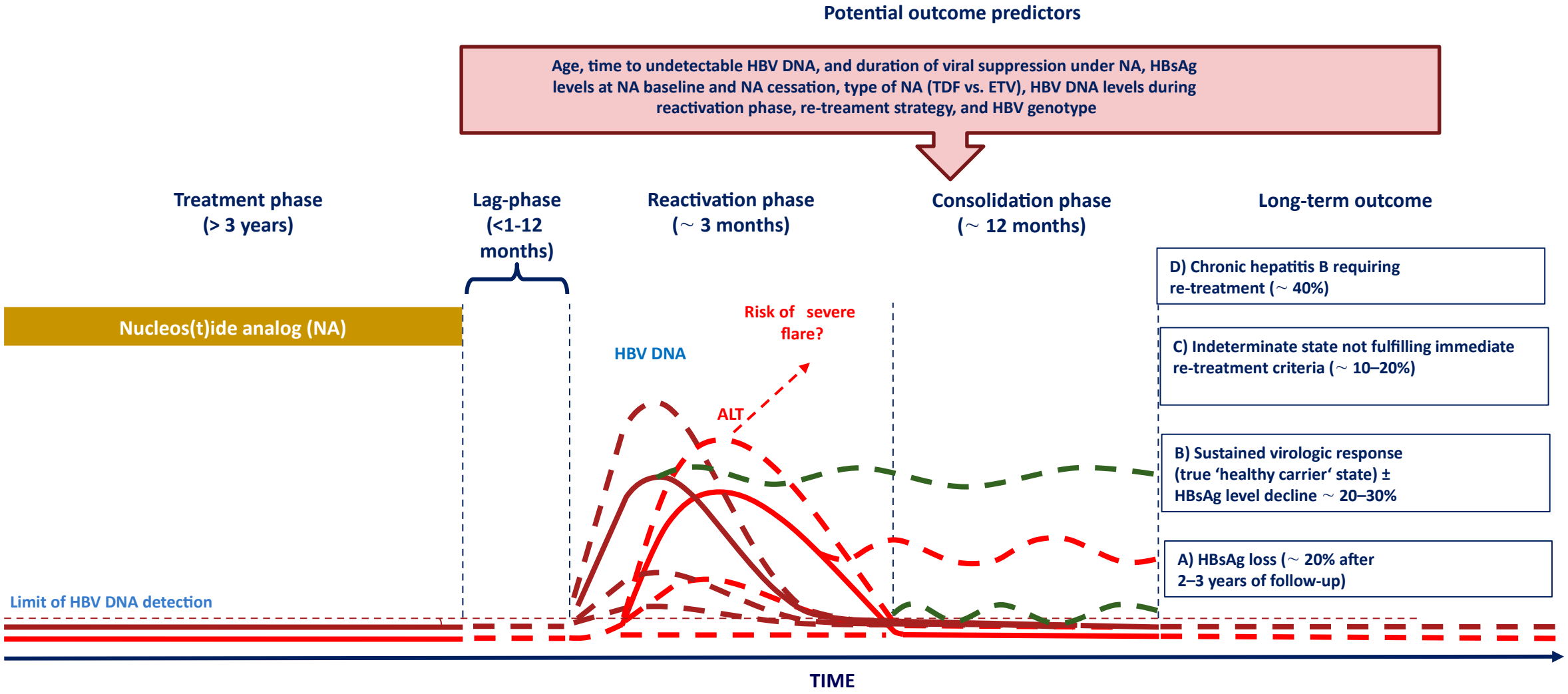
21. NAs should be discontinued after confirmed HBsAg loss, with or without anti-HBs seroconversion.
Evidence level II-2, grade of recommendation 1.

22. NAs can be discontinued in non-cirrhotic HBeAg-positive CHB patients who achieve stable HBeAg seroconversion and undetectable HBV DNA and who complete at least 12 months of consolidation therapy. Close post-NA monitoring is warranted.
Evidence level II-2, grade of recommendation 2.

23. 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 Recommendations 2017

Typical Courses in HBeAg-ve patients after stopping NAs



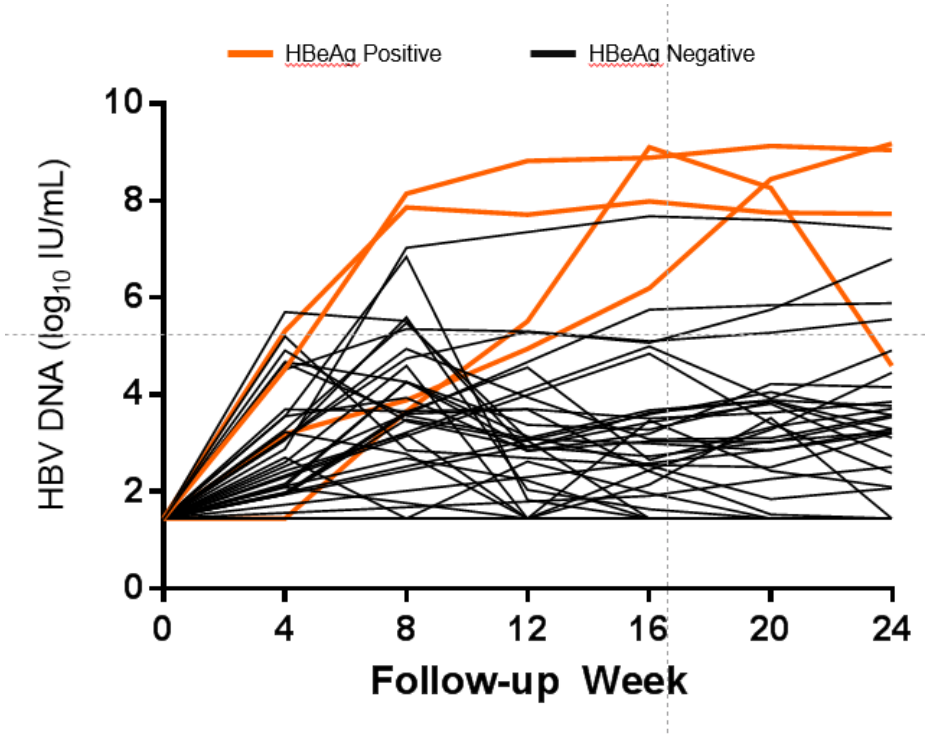
HBsAg: hepatitis B surface antigen

Lampertico P, Berg T. Hepatology 2018; 10.1002/hep.29821

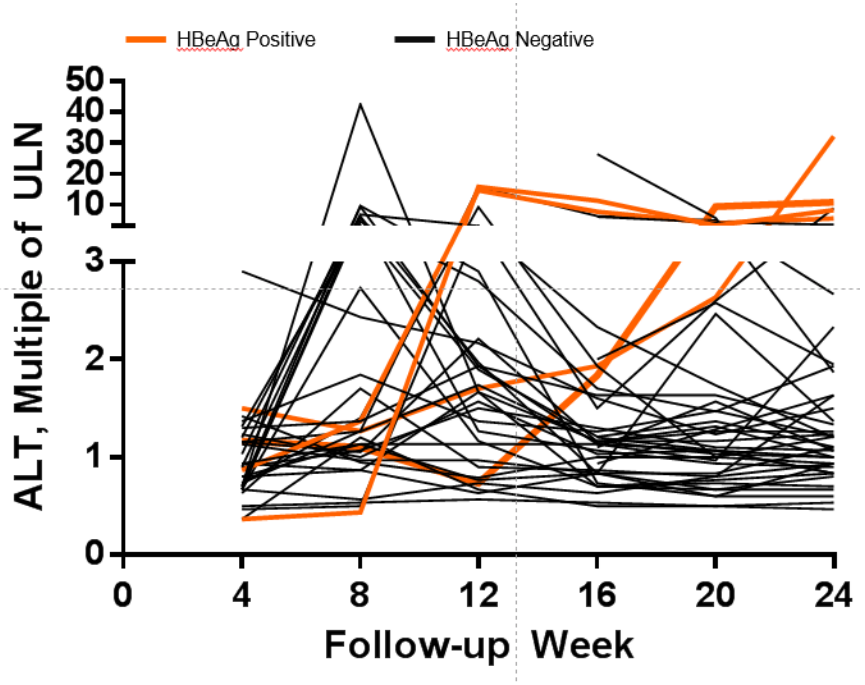
Follow of TDF study 8-10 years HBeAg+ve and HBeAg- CHB

Week 24 HBV DNA and ALT levels in Treatment Follow up Completers (N=43)

HBV DNA Profiles



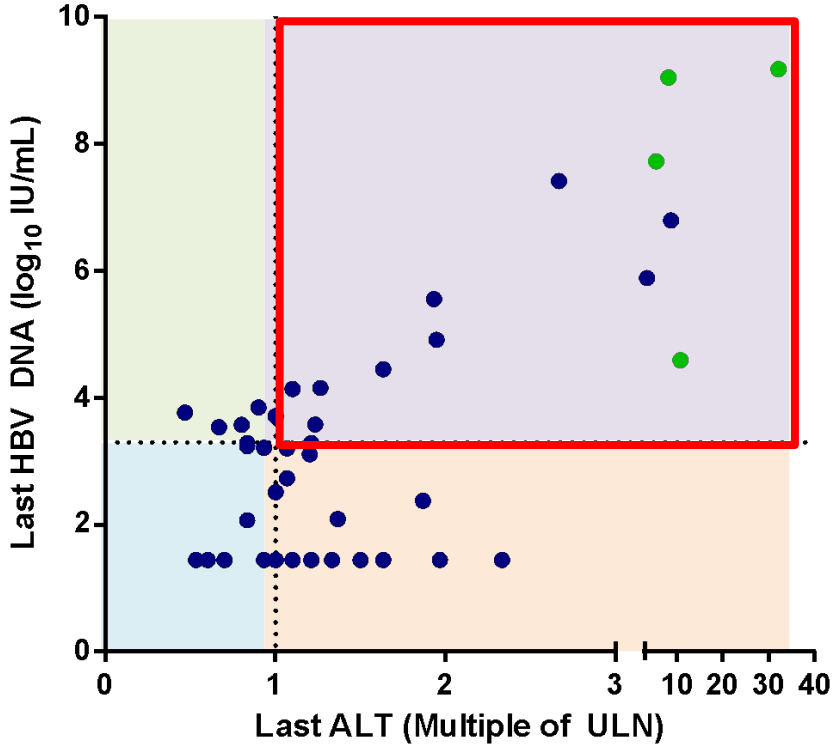
ALT Profiles



Buti M et al. AASLD 2015

Follow of TDF study 8-10 years HBeAg+ve and HBeAg- CHB

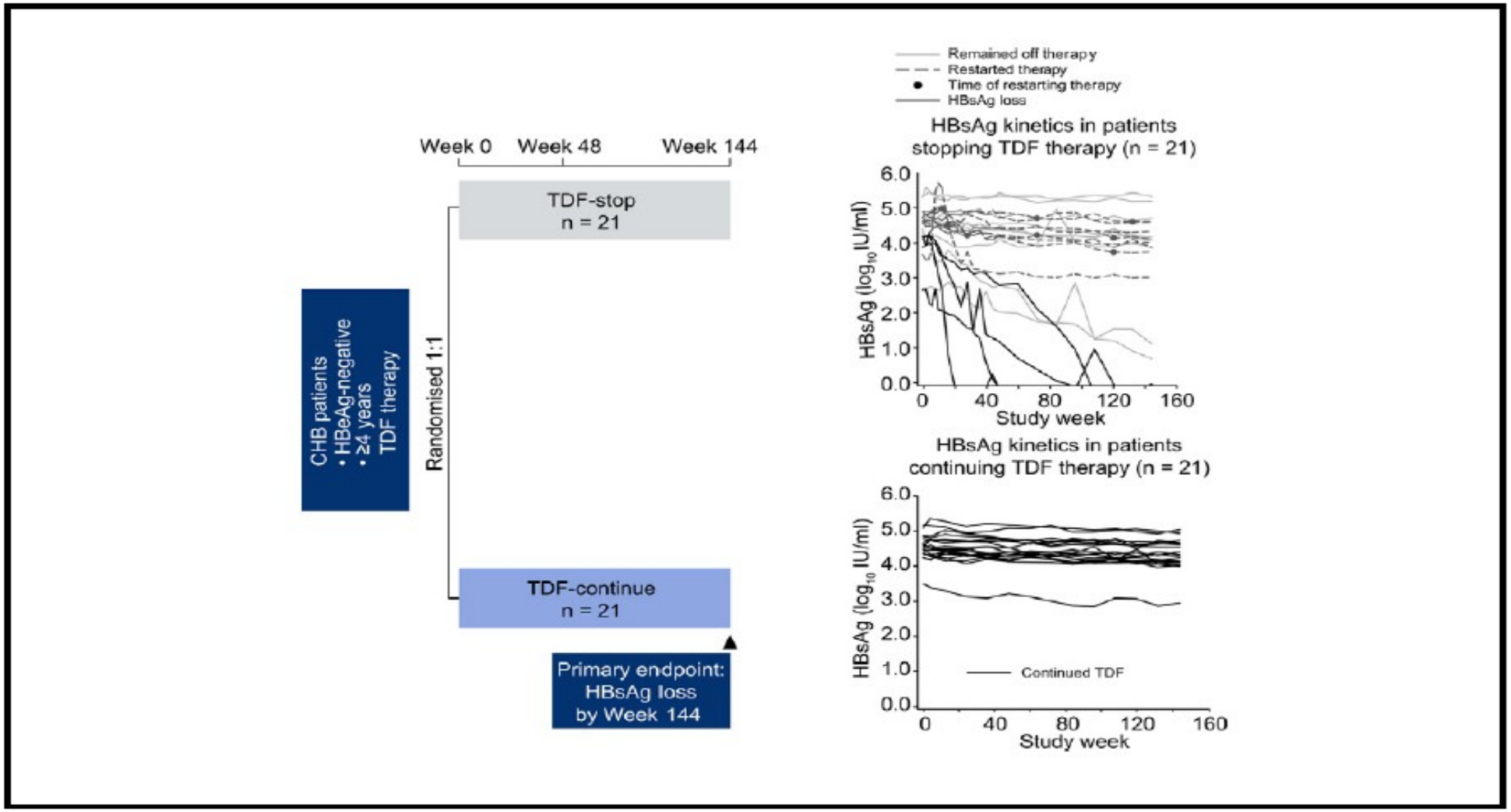
Week 24 HBV DNA and ALT levels in Treatment Follow up Completers (N=43)



N (%)	
11 (26)	HBV DNA <2000 IU/mL ALT <ULN
14 (33)	HBV DNA <2000 IU/mL ALT >ULN
5 (12)	HBV DNA >2000 IU/mL ALT <ULN
13 (30)	HBV DNA >2000 IU/mL ALT >ULN

Buti M et al AASLD 2015

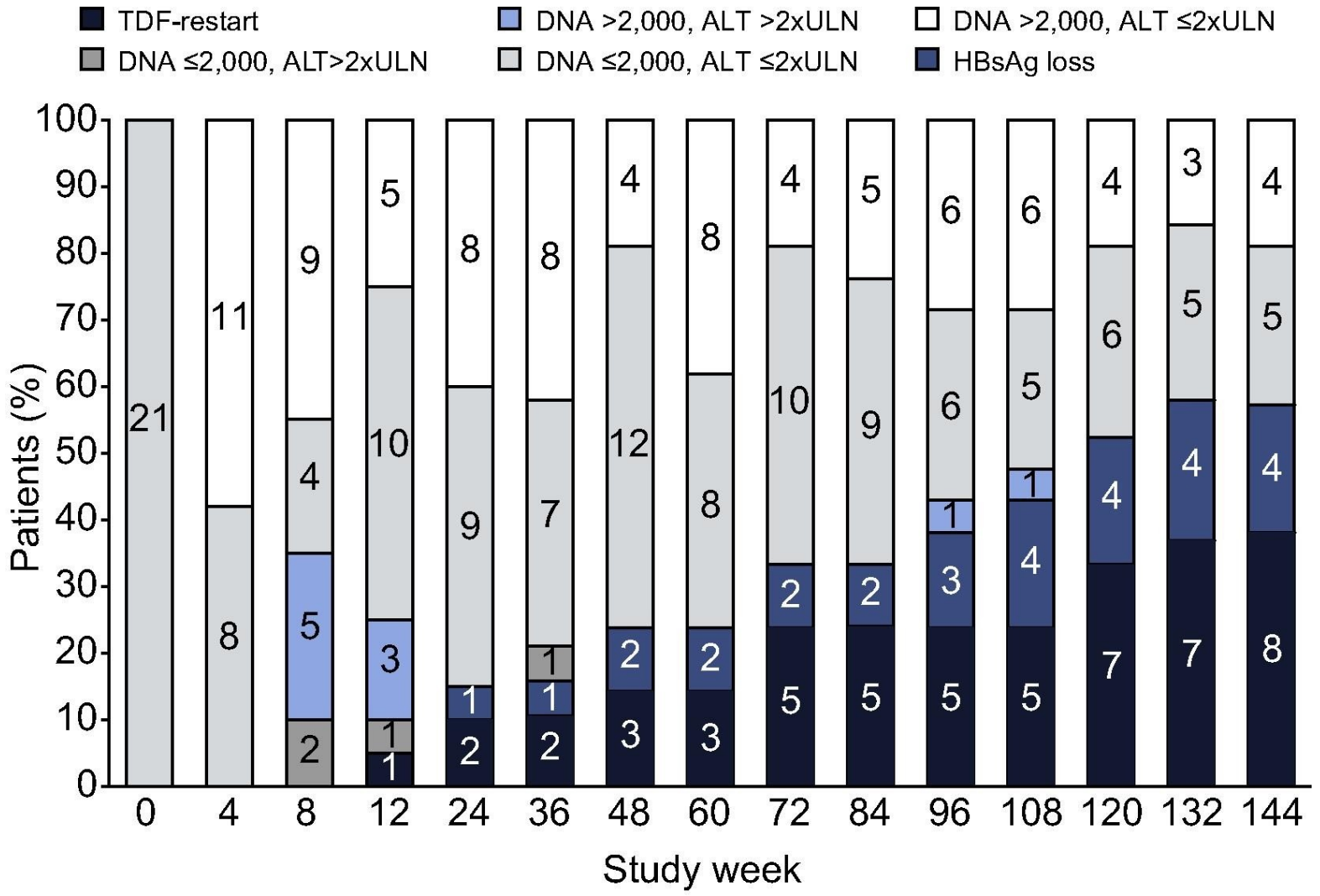
Long-term response after stopping tenofovir disoproxil fumarate in non-cirrhotic HBeAg-negative patients – FINITE study



Of the patients who stopped TDF therapy, 62% remained offt herapy to Week 144.
Four patients (19%) achieved HBsAg loss and three of them achieved HBsAg seroconversion.

Berg T et al. J Hepatol 2017

HBsAg loss after TDF Discontinuation in HBeAg negative patiens
38% HBsAg loss after 144 weeks of follow-up



Berg T J Hepatol 2017

Stopping therapy – a prospective RCT

Inclusion

HBeAg-neg with DNA neg:

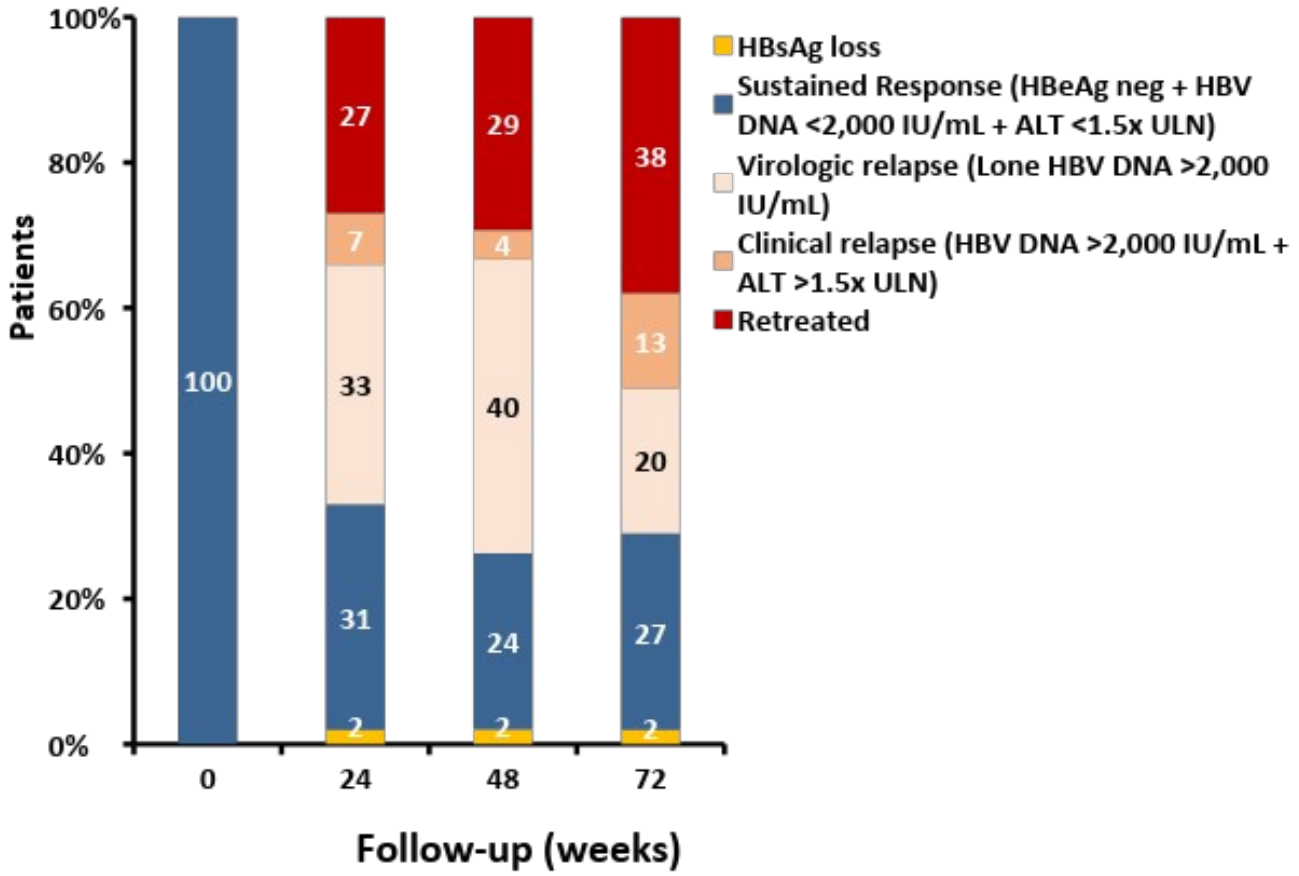
- > 3 yrs (start HBeAg-neg)
- >1 yr post HBeAg loss (start HBeAg+)

Intervention

- Randomized 2:1 stop vs continue NA
- F/u x 72 weeks

Retreatment criteria

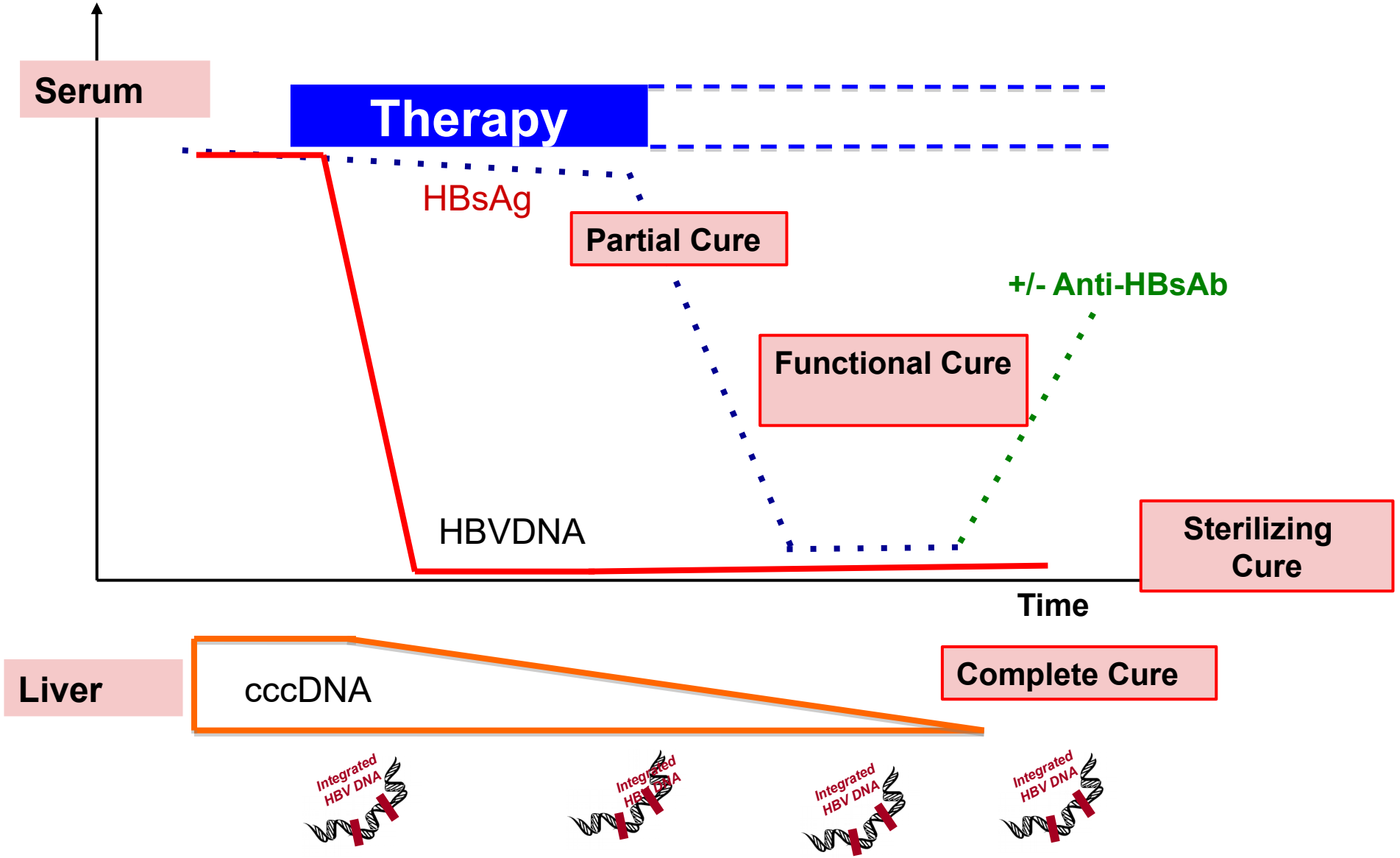
1. HBeAg seroreversion
2. HBV DNA>2000 IU/mL + ALT>5xULN x2
   or ALT >15xULN x 1
3. HBV DNA >20,000 x 2



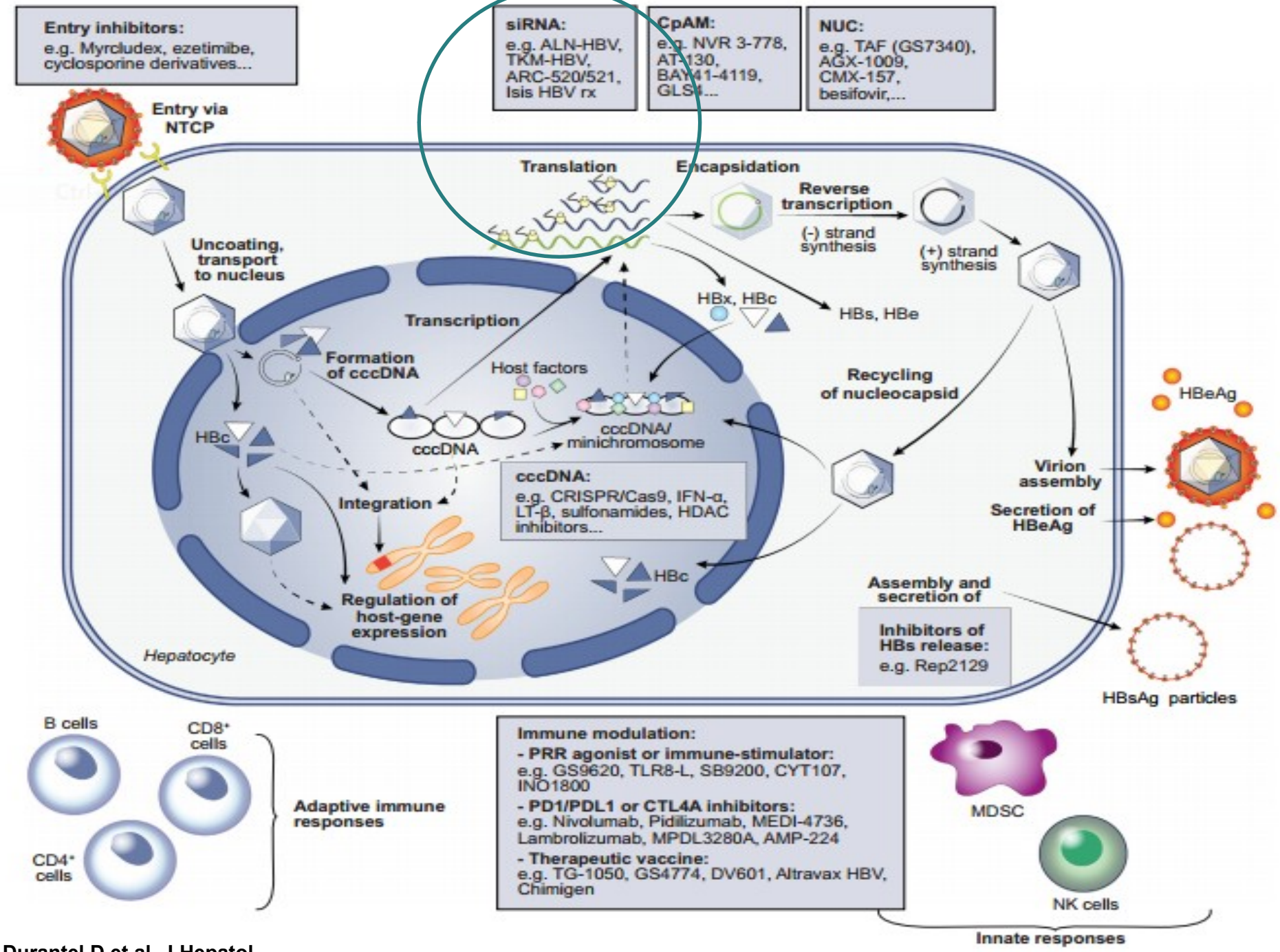
- Clinical relapse or retreatment in >50% and only ~30% with sustained off-treatment response
- Minimal effect on HBsAg levels…**not very effective approach in predominantly Asian patients**

Liem et al AASLD 2018, Abstract 268

Definition of HBV cure:what do we want to achieve ?



Lok et al, Hepatitis B Cure: From Discovery to Regulatory Approval; Hepatology / J Hepatol joint publication; 2017

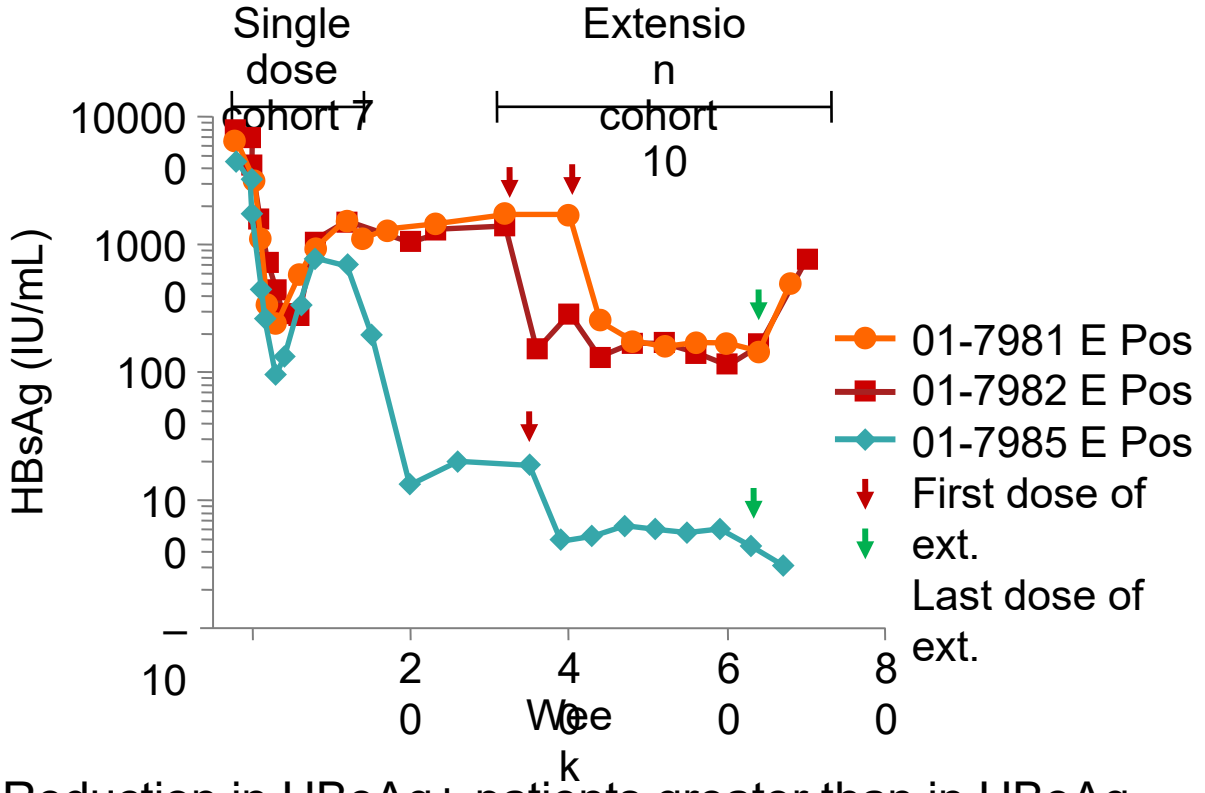


Durantel D et al. J Hepatol 2016;64:S117-S131

RNA interference Therapies

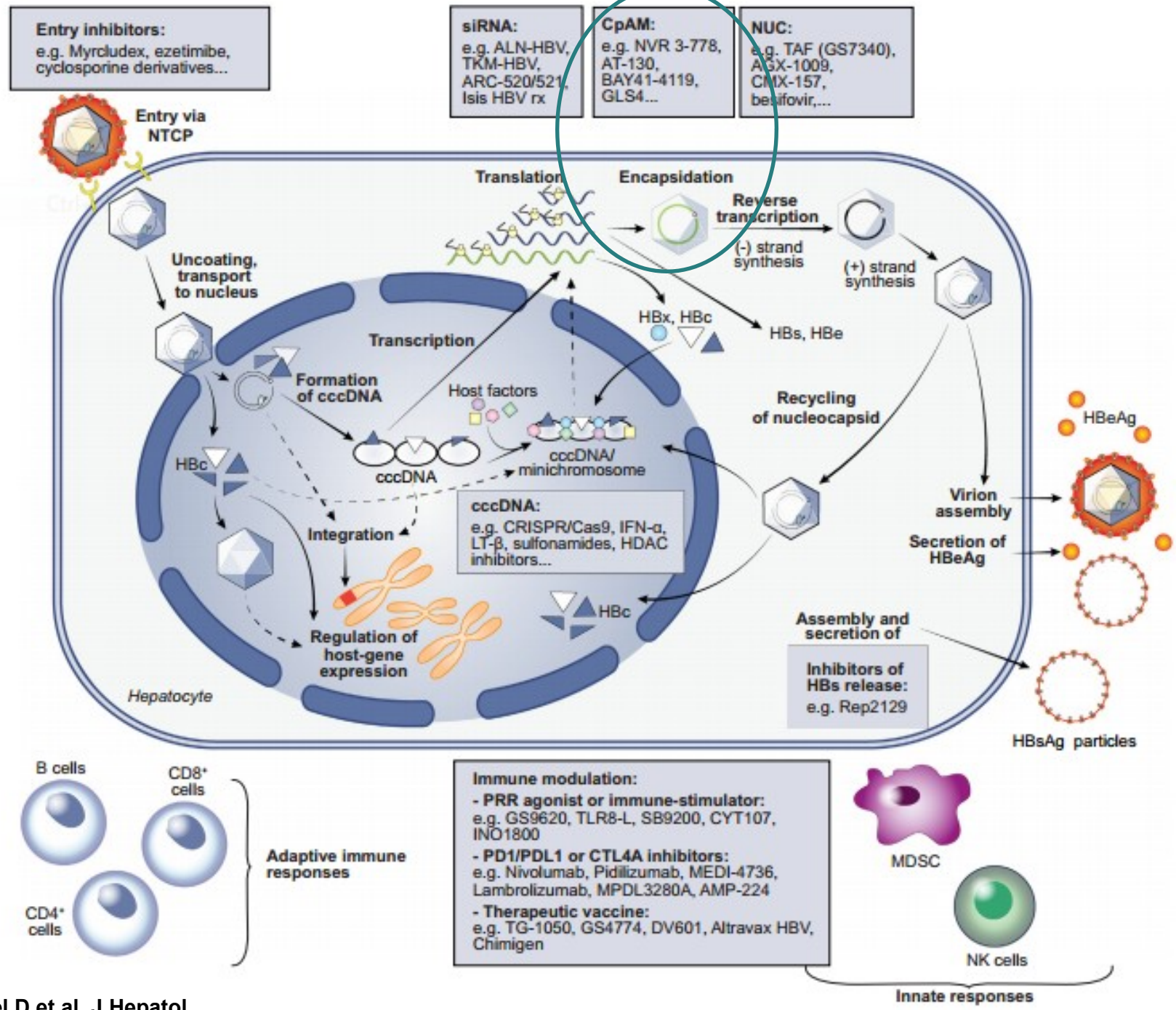
- Small non coding RNA
- Target directly HBV RNA transcripts
- Reduce HBsAg production
- Restore host-immune response
- Delivery to Hepatocytes
- Phase 2 clinical Trials
  - ARC-520: Multiple injections (Clinical Hold by FDA)
  - ARB 1416
  - **ESC-GalNAc-Conjugate** for subcutaneous administration

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



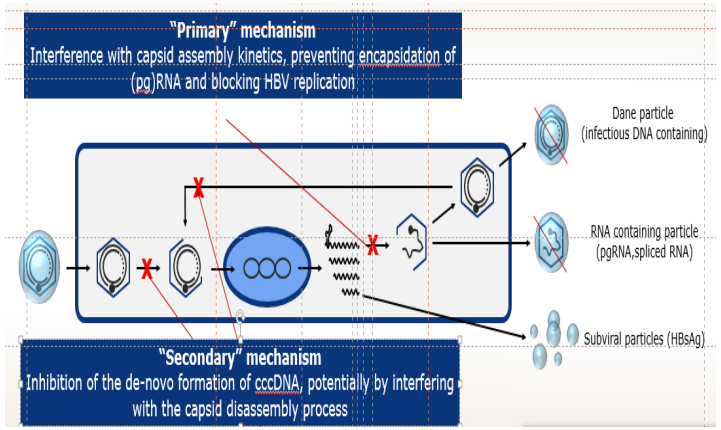
Reduction in HBeAg+ patients greater than in HBeAg– patients

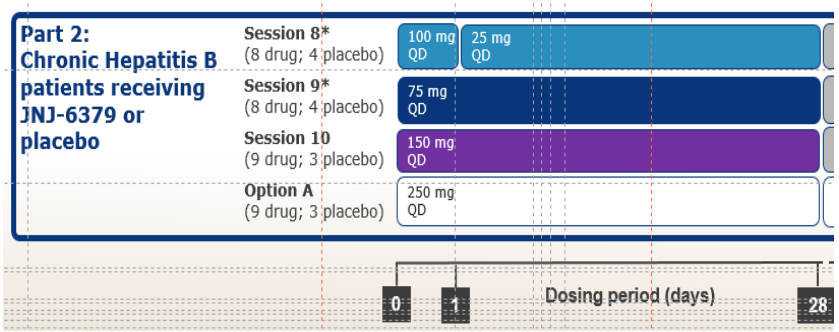
Yuen ML et al EASL



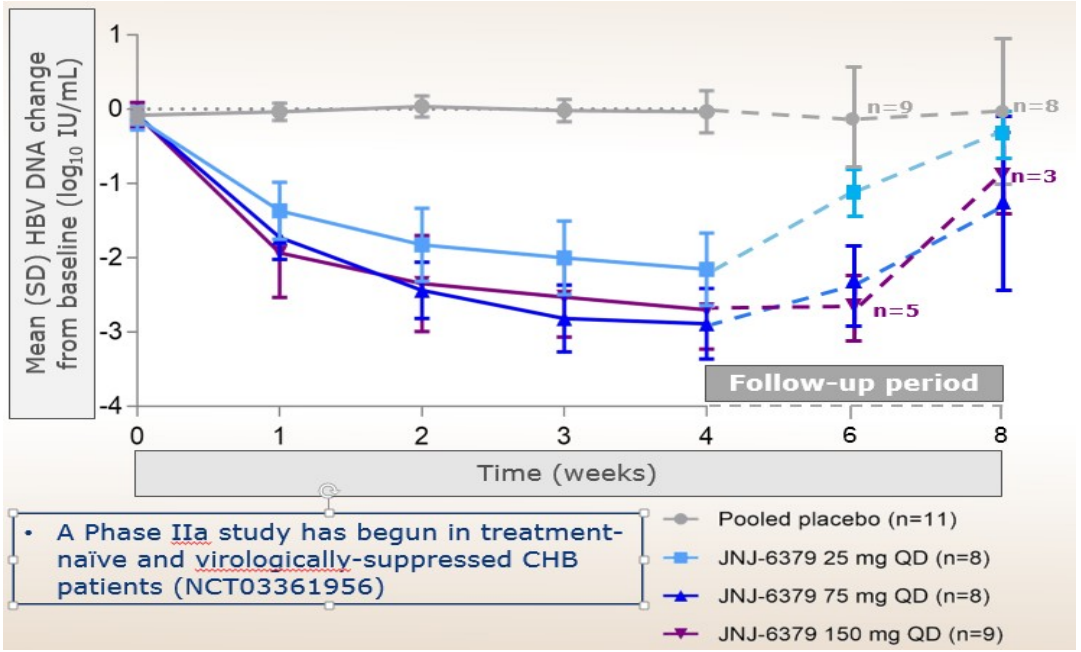
Durantel D et al. J Hepatol 2016;64:S117-S131

Safety, pharmakokinetics and antiviral activity of novel capsid assembly modulator JNJ-6379 in treatment-naive chronic hepatitis B patients without cirrhosis



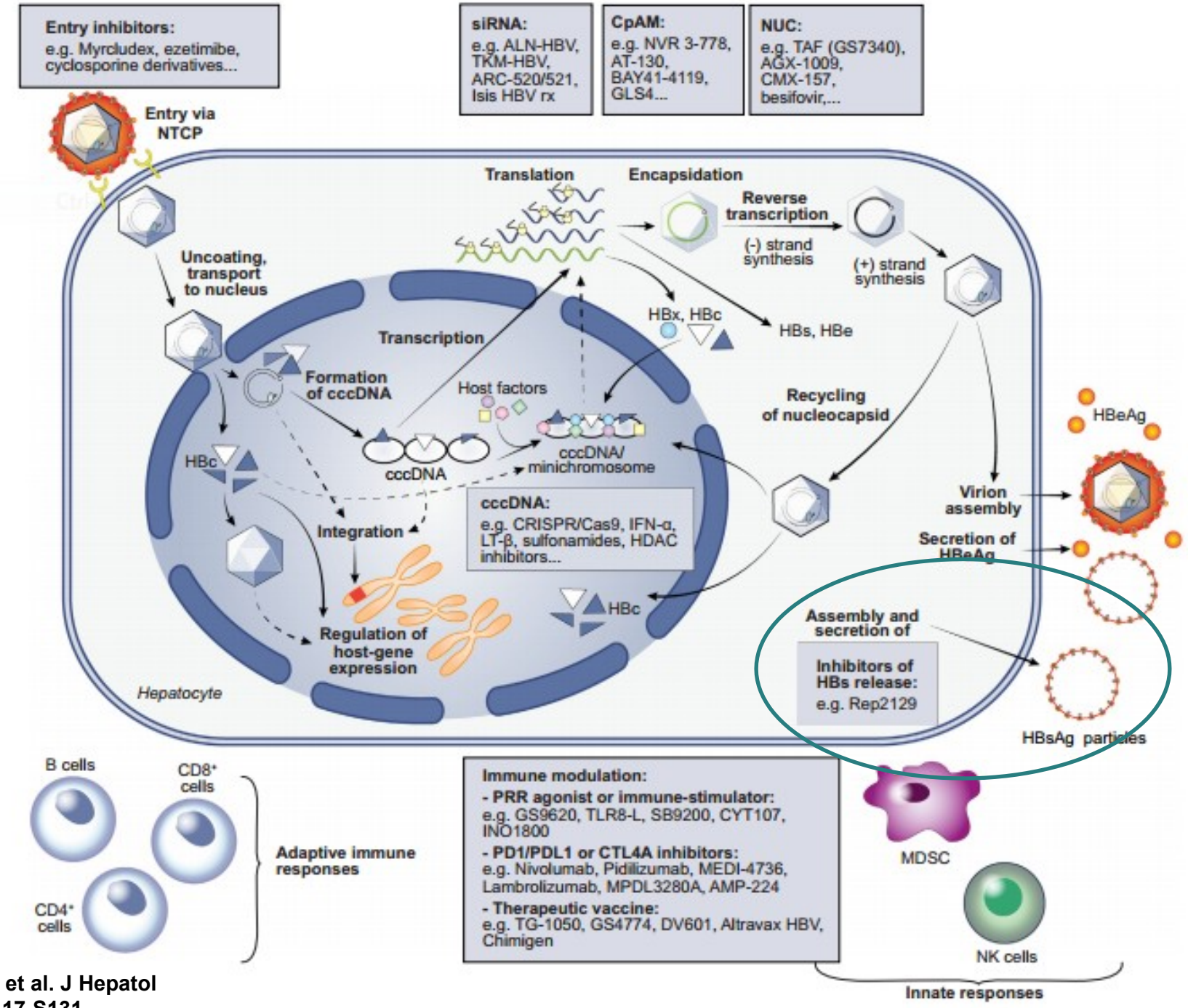


Safety profile was good



HBV DNA undetectable: 38% of cases 75 mg and 38% of 150mg
HBV RNA undetectable: 75-80% cases with same doses
No Changes in HBsAg levels

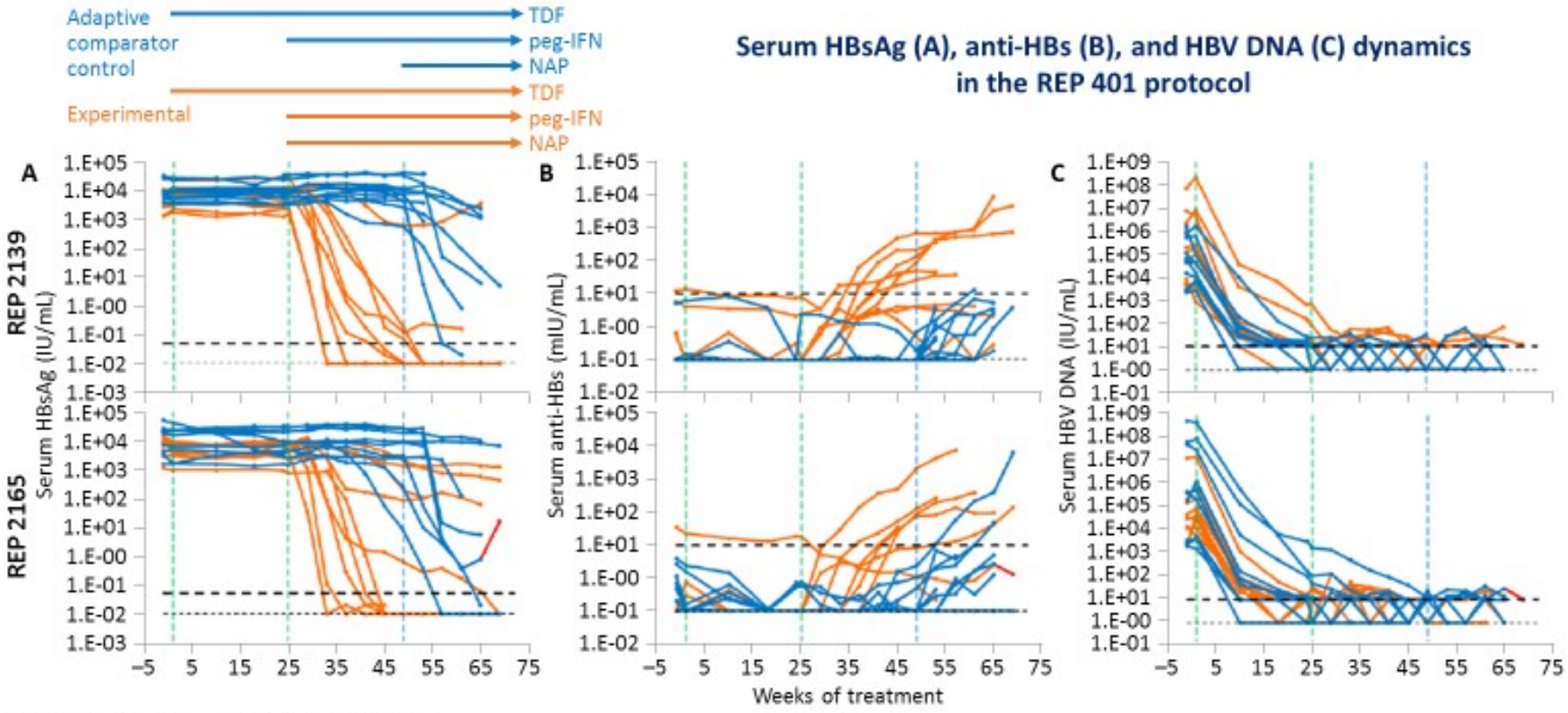
Zoulim F et al. IILC 2018; LBO-004



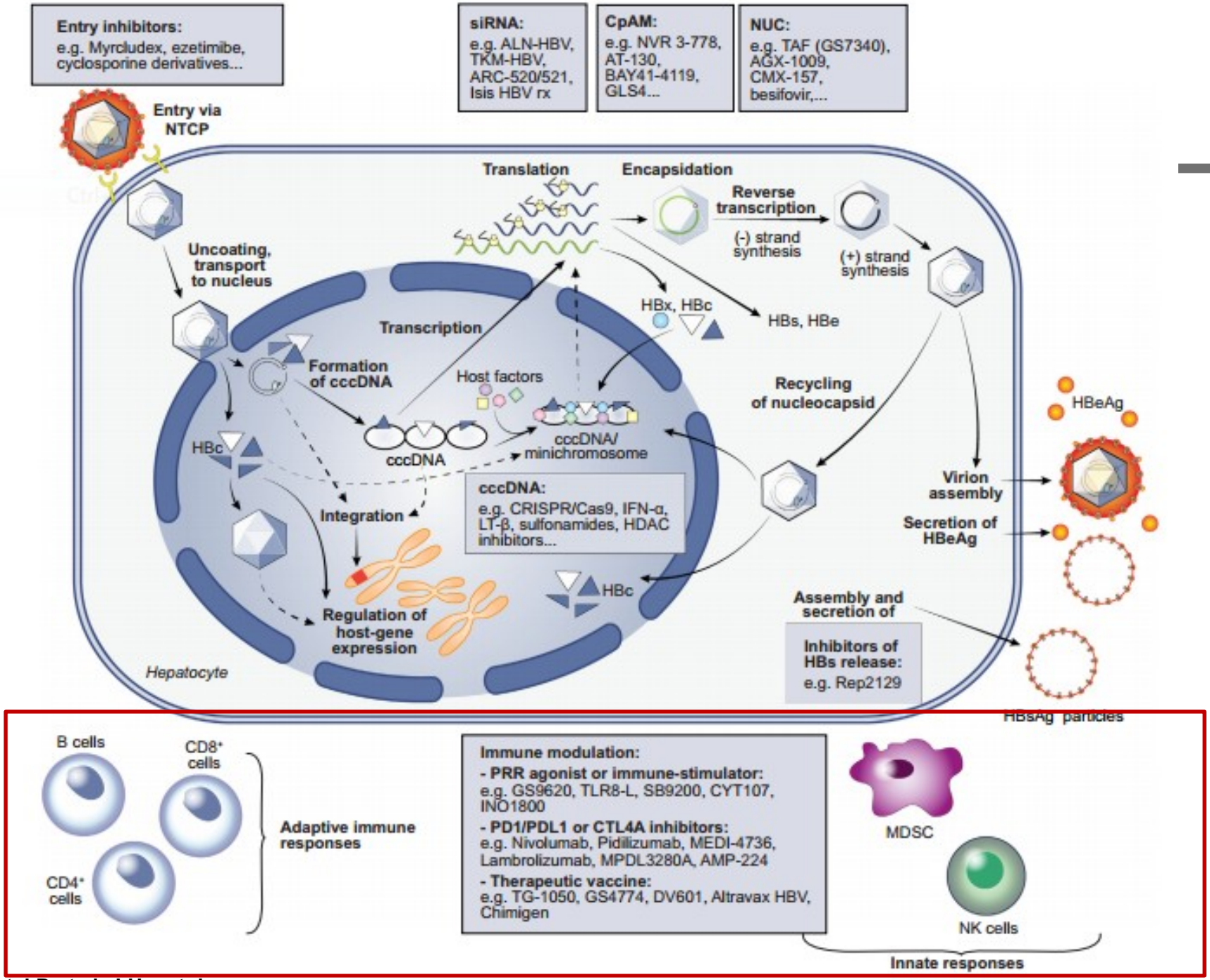
Durantel D et al. J Hepatol 2016;64:S117-S131

REP 2139 or REP 2165 in combination with TDF and PEG IFN alpha2a Treatment naïve HBeAg negative

REP 2139-Mg or REP 2165-Mg used in combination with TDF and peg-IFN alpha-2a in treatment-naive Caucasian patients with chronic HBeAg-negative HBV

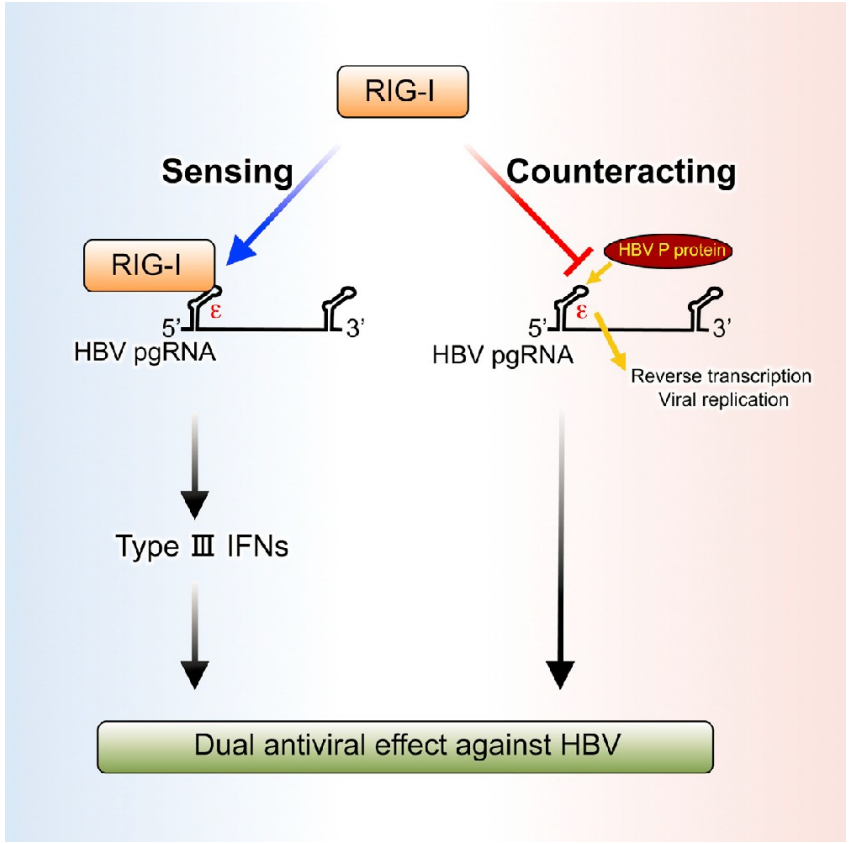


Bazinet M, et al. EASL 2017, Amsterdam. #THU-154



Durantel D et al. J Hepatol

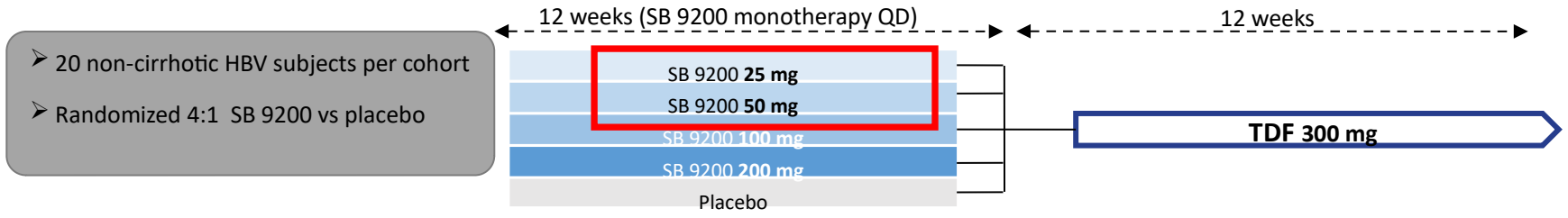
The RNA Sensor RIG-I Dually Functions as an Innate Sensor and Direct Antiviral Factor for Hepatitis B Virus



- RIG-I senses the HBV genotype A, B, and C for the induction of type III IFNs
- The 5-ε region of HBV pgRNA is a key element for the RIG-I mediated recognition
- RIG-I counteracts the interaction of HBV P with pgRNA to suppress viral replication
- Type III IFNs are predominantly induced in human hepatocytes during HBV infection

Sato et al., 2015, Cell Immunity 42, 123–132

Effects of SB9200 (Inarigivir) therapy on immune responses in patients with chronic hepatitis B



Virological markers (log10 D1 to W12)

Cohort	Study arm	HBV DNA response	HBV RNA response	HBsAg response
Cohort 1 and 2, n=38	SB9200 (n=30)	-0.66	-0.8	-0.18
	Placebo (n=8)	0.33	1.0	-0.18
Difference: SB9200 vs placebo		**1 log** HBV DNA reduction with SB9200	**1.8 log** HBV RNA reduction with SB9200	No effect

Anti-HBs Activity Biomarkers (to W12)

Cohort	Study arm	CP	'masked' anti-HBs	CP AND 'masked' anti-HBs	CP AND HBV DNA response (>0.5log)	CP AND HBV RNA response (>0.5log)	'masked' anti-HBs AND HBV DNA response
Cohort 1 and 2, n=38	SB9200 (n=30)	10 (33%)	9 (30%)	3 (30%), n=10	6 (60%), n=10	6 (67%), n=9	9 (100%), n=9
	Placebo (n=8)	1 (12%)	2 (25%)	0	0	0	0
Difference: SB9200 vs placebo		Enhanced with SB9200	No effect	Enhanced with SB9200	Enhanced with SB9200	Enhanced with SB9200	Enhanced with SB9200

Summary

- Long-term NAs can prevent development of liver cirrhosis and related complication, and reduce risk of HCC especially in cirrhotic patients

- Safety in long term therapy should be considered. TAF and ETV are recommended over TDF for patients with risk of renal and bone diseases

- NAs can be discontinued in selected non-cirrhotic patients

- New drugs are under investigation. Their efficacy and safety still need to be determined