BEST OF EASL

Current and future approaches for the treatment of HBV

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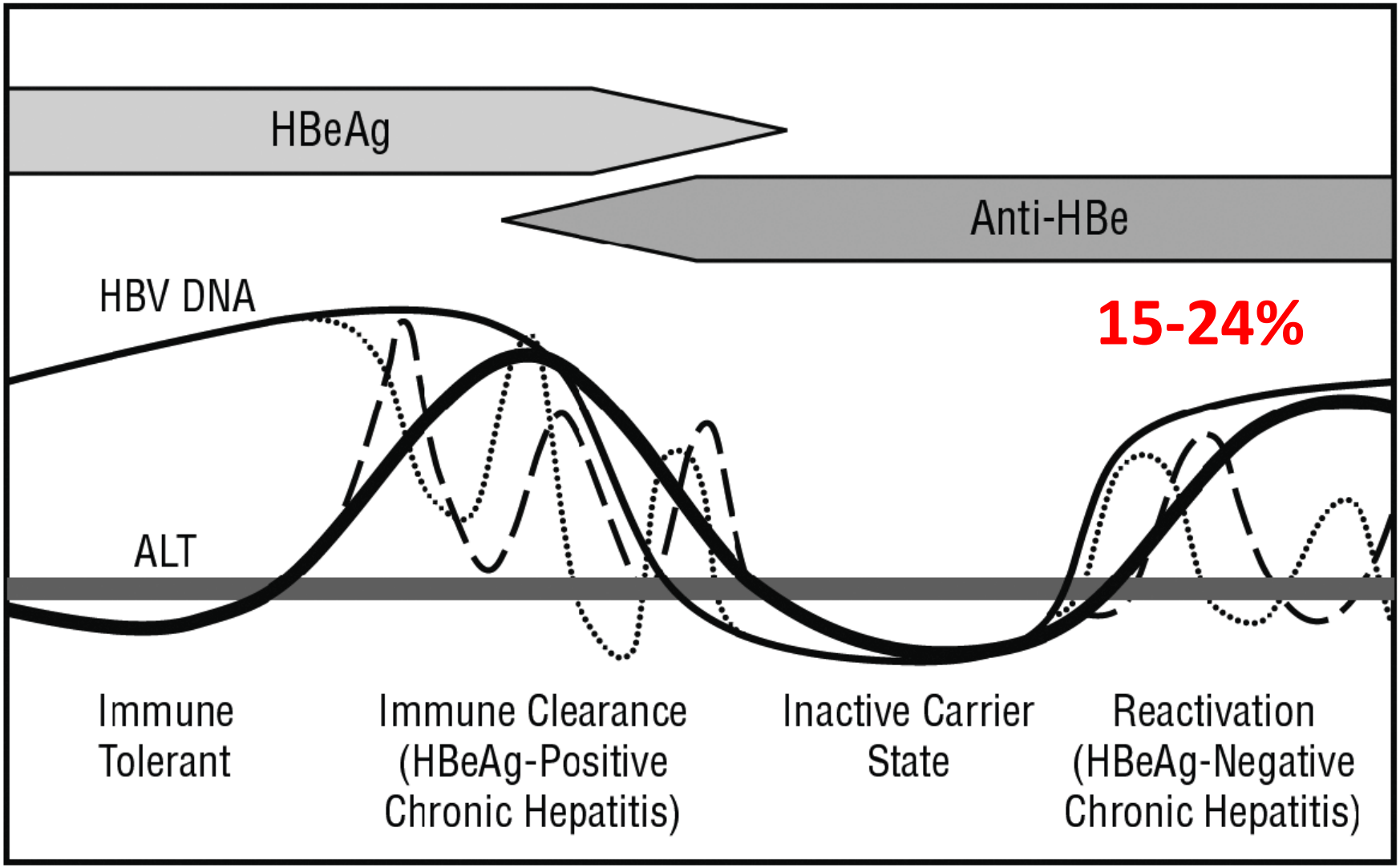
Natural history of HBV infection



WONG and LOK, Arch Intern Med 2006;166:9-12

HSU *et al,* Hepatology 2002;35:1522-7; FATTOVICH *et al,* Hepatology 1986;6:167-72

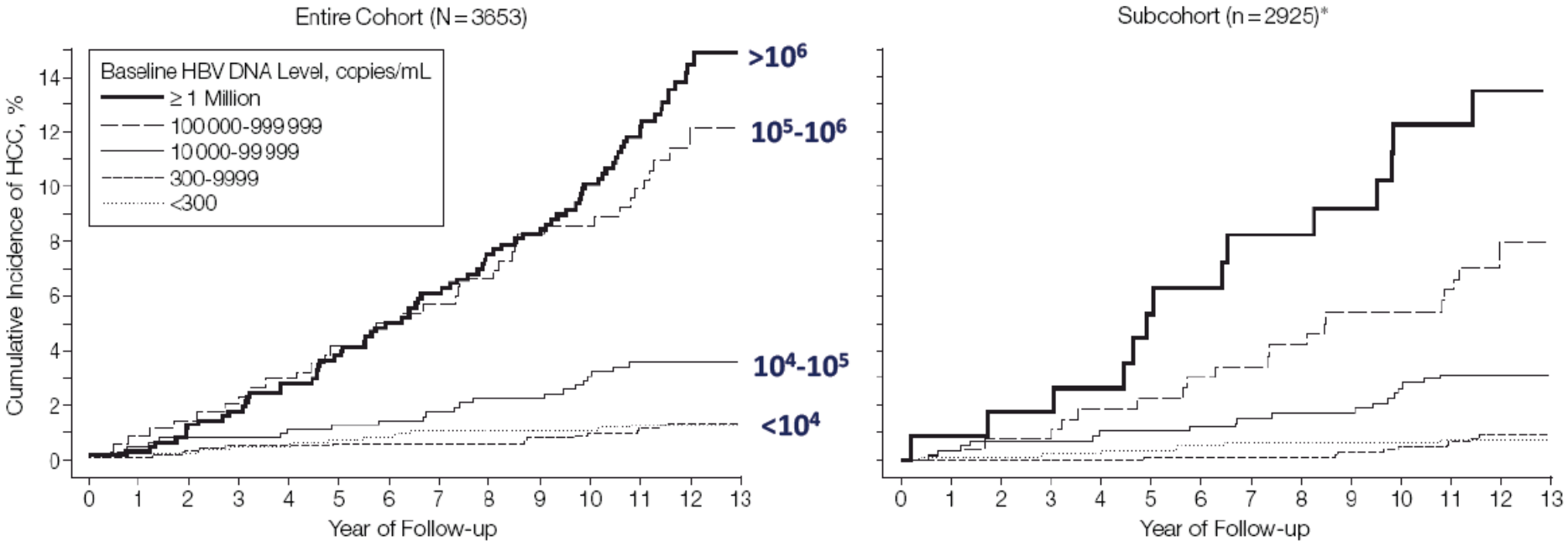
What are the endpoints of therapy in chronic hepatitis B?

- To decrease the viral load, the number of infected cells and the associated inflammation, in order to prevent liver disease progression to cirrhosis and HCC, and death
- Ideally, to eradicate HBsAg, i.e. to achieve a sterilizing cure (infrequent)
- More realistically, to reach a serological profile comparable to that of an inactive carrier:
  - In HBeAg+: seroconversion to anti-HBe
  - In anti-HBe+: persistent abatement of viral load

EASL Clinical Practice Guidelines, *J Hepatol* 2012;57:167-185

Cumulative incidence of HCC according to HBV DNA
A prospective study (REVEAL-HBV Study)

(n=3653; mean FU 11.4 years; 41,779 person-years)



*Subgroup of patients with HBeAg-, normal ALT, no cirrhosis at enrolment (n=2925)

CHEN *et al,* JAMA 2006;295:65-73

Whom to treat, in 2016

Patients in the immunoactive phase

- HBeAg+, VL > 2,000 UI/mL, elevated ALT
- HBeAg-, VL > 2,000 UI/mL, elevated ALT (but fluctuating!)

Inactive carriers (HBeAg-, VL < 2,000 UI/mL, persistently normal ALT)

- In case of immune-suppressive therapy, to prevent viral reactivation

Immune tolerant patients (HBeAg+, VL > 6 log UI/mL, normal ALT)

- If family history of cirrhosis or HCC (Other criteria? In case of sudden VL reduction? If ALT levels in the upper range of normality? All of them?)

Pregnant women

- If VL > 6 log UI/mL, during the last trimester of pregnancy, to prevent transmission to the newborn (together with HBIG and vaccine)

EASL Clinical Practice Guidelines 2012; AASLD guidelines 2015
HUANG *et al,* JAMA 2014; PERRILLO *et al,* JAMA 2015; CHAN *et al,* Gastroenterology 2014
CHEN *et al,* Hepatology 2015; BROWN *et al,* 2016; VISVANATHAN *et al,* Gut 2016

Two classes of drugs

INTERFERON

Immunomodulating
and antiviral effect
(rarely leads to HBsAg loss)

Treatment duration is finite

Safety issues
Many contraindications

ANALOGUES

Only antiviral effect

Lead to suppression of HBV,
very rarely to eradication

Require administration for life
(risk of relapse at treatment
cessation)

Virological and biochemical response rates to current HBV treatments

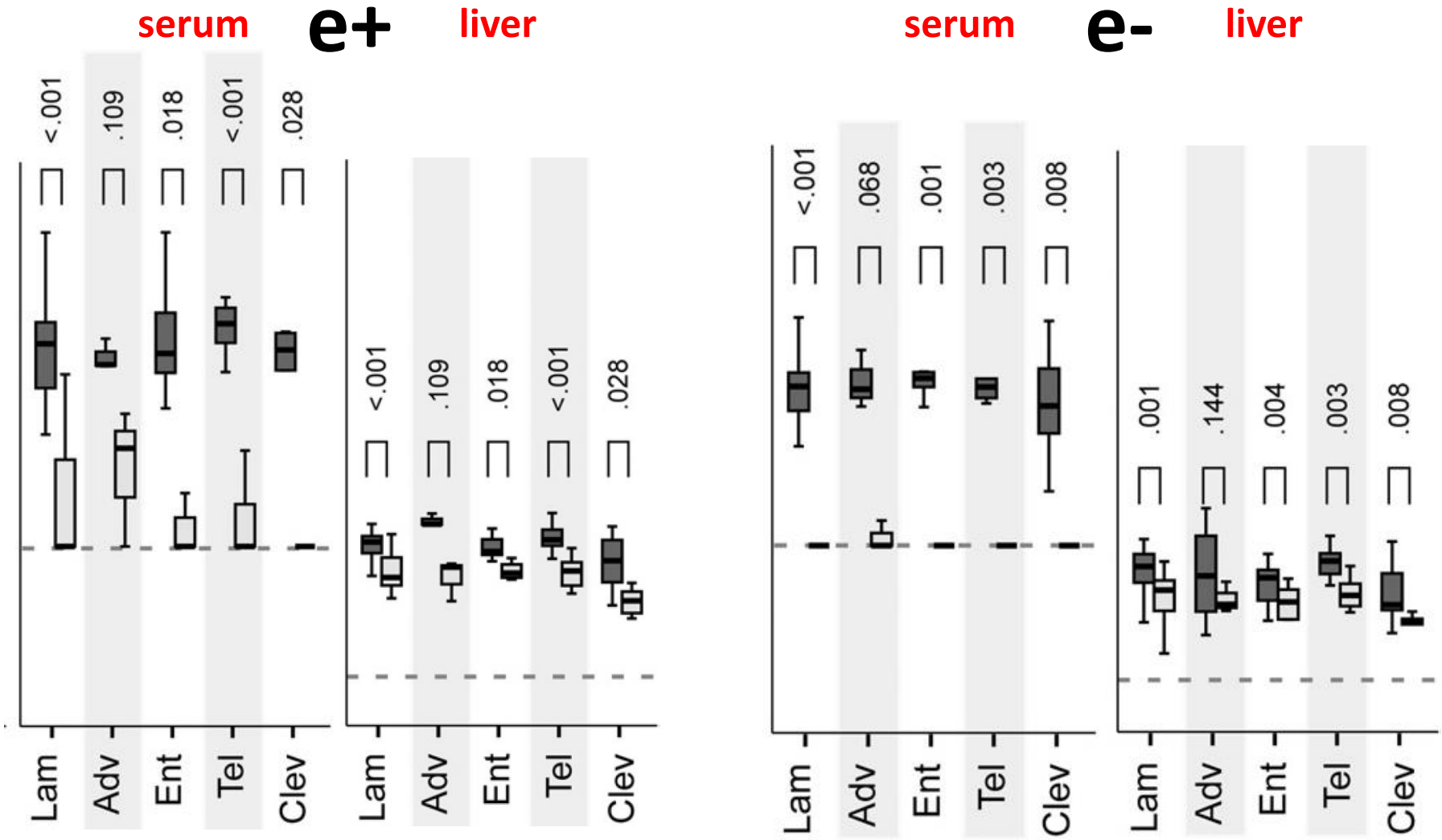
	Entecavir[1,2]	Tenofovir[3]	PEG-IFN α-2a[4,5]
HBeAg positive	n = 354	n = 176	n = 271
HBV DNA undetectable	67%	76%	25%[a]
HBeAg seroconversion	21%	21%	27%
ALT normalisation	68%	68%	39%
HBsAg loss	2%	3.2%	2.9%[b]
HBeAg negative	n = 325	n = 250	n = 177
HBV DNA undetectable	90%	93%	63%[a]
ALT normalisation	78%	76%	38%
HBsAg loss	0.3%	0%	0.6%[b]

Results at 48 weeks; [a]HBV DNA < 400 copies/mL; [b]At 72 weeks

1. CHANG et al, N Engl J Med 2006;354:1001–10; 2. LAI et al, N Engl J Med 2006;354:1011-20
3. MARCELLIN et al, N Engl J Med 2008;359:2442–55; 4. LAU et al, N Engl J Med 2005;352:2682-95
5. MARCELLIN et al, N Engl J Med 2004;351:1206–17

A 1-year treatment with NUCs leads to a modest decrease of intrahepatic cccDNA

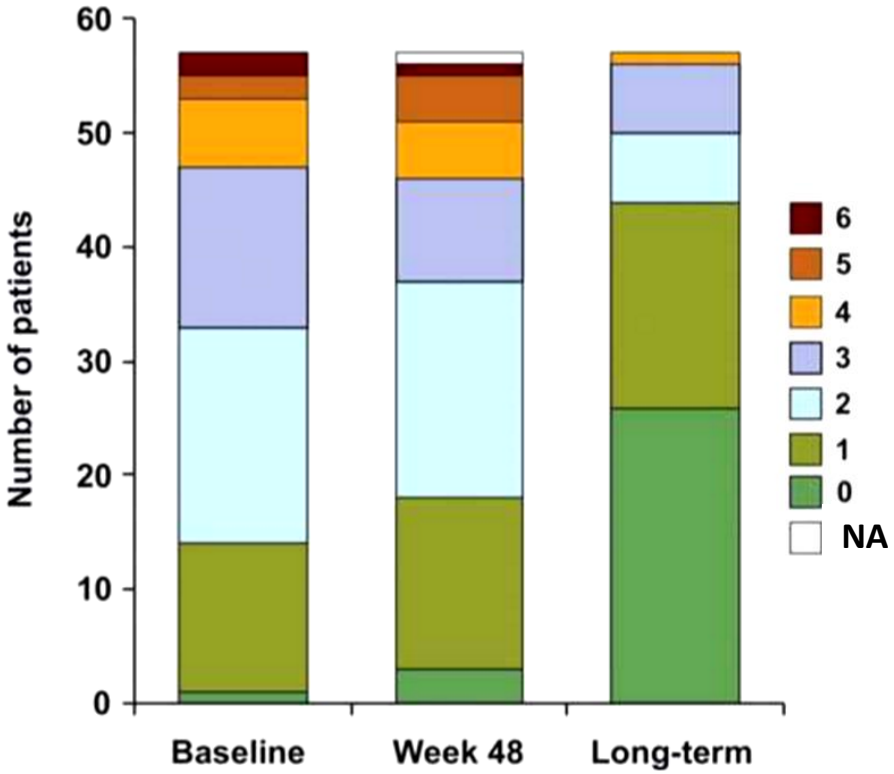
(only 5/117 or 4% had undetectable cccDNA)



WONG *et al,* Clin Gastroenterol Hepatol 2013;11:1004-10

Long-term NUC therapy and fibrosis improvement

ETV, n=57, median FU 280 weeks

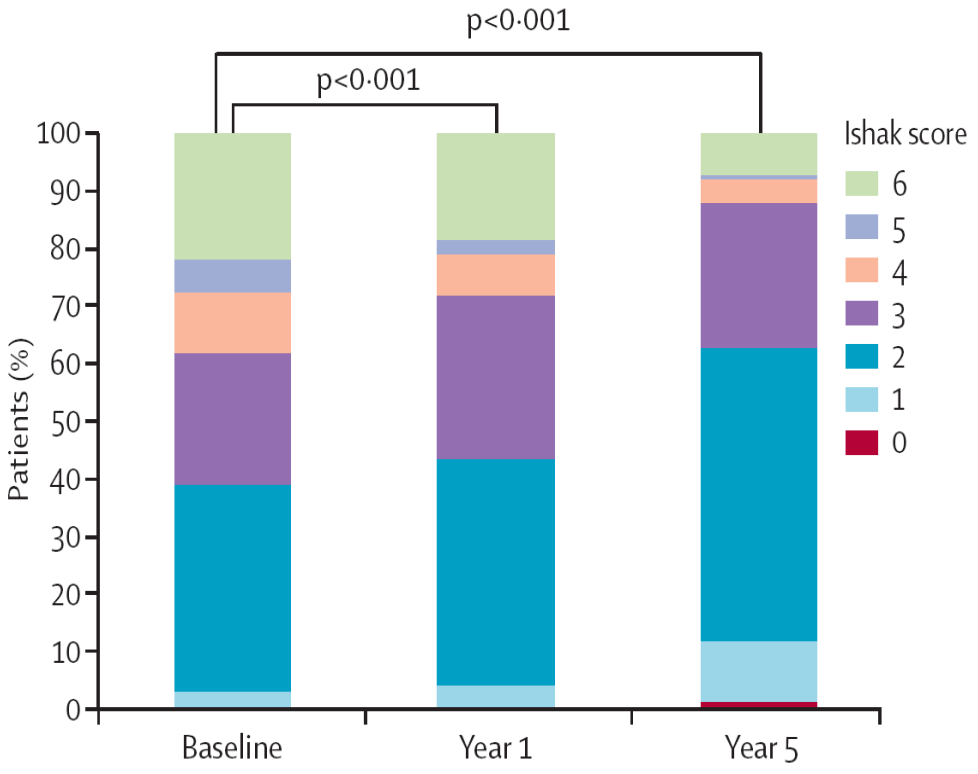


CHANG *et al,* Hepatology 2010;52:886–93

TDF, n=348

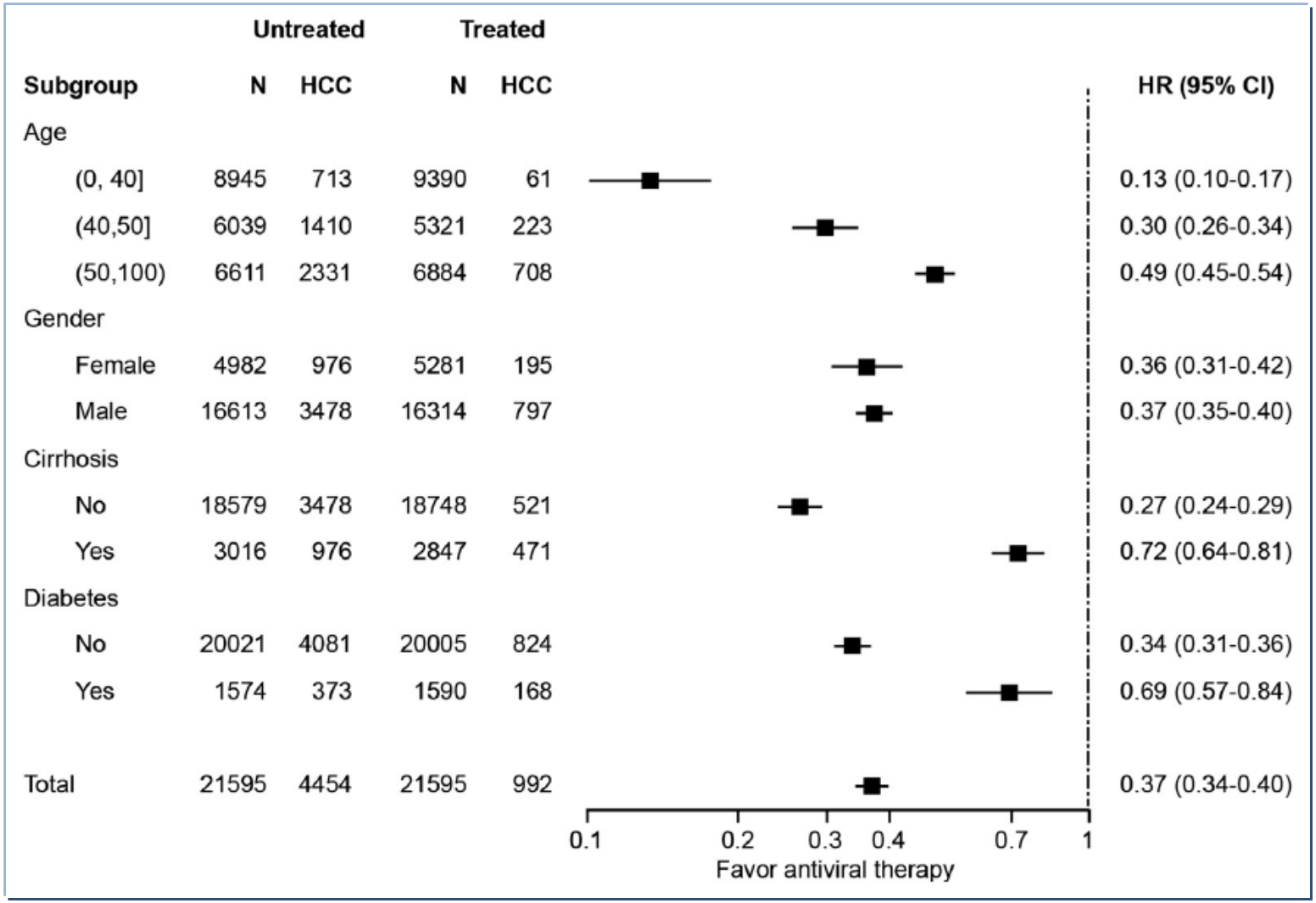
Cirrhosis regression: 71/96 (74%)

Progression to cirrhosis of non-cirrhotics : 3/252 (1,2%)



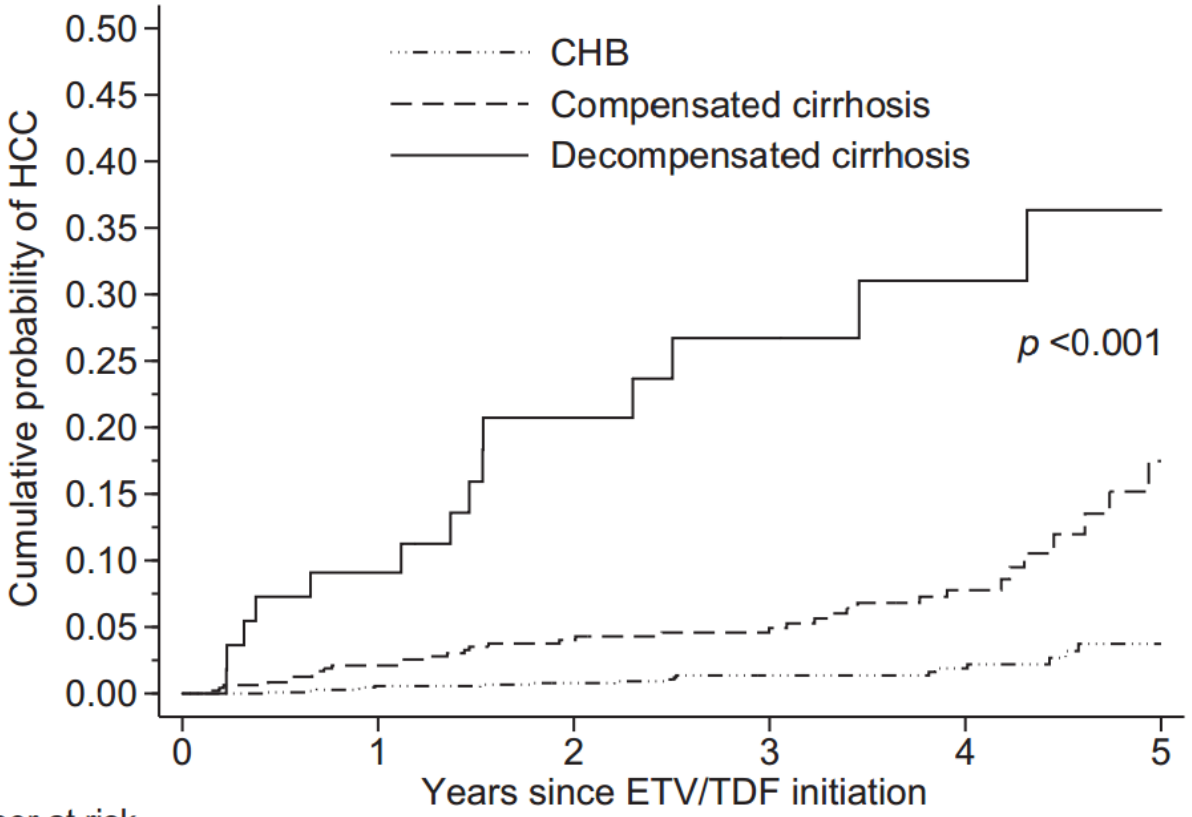
MARCELLIN *et al,* Lancet 2013;381:468-475

Propensity-score study of HCC prevention by NUC treatment of chronic hepatitis B: a stratified sub-analysis



WU *et al*, Gastroenterology 2014;147:143-51

Cumulative incidence of HCC in 1666 chronic hepatitis B patients treated with entecavir and/or tenofovir, by liver disease severity



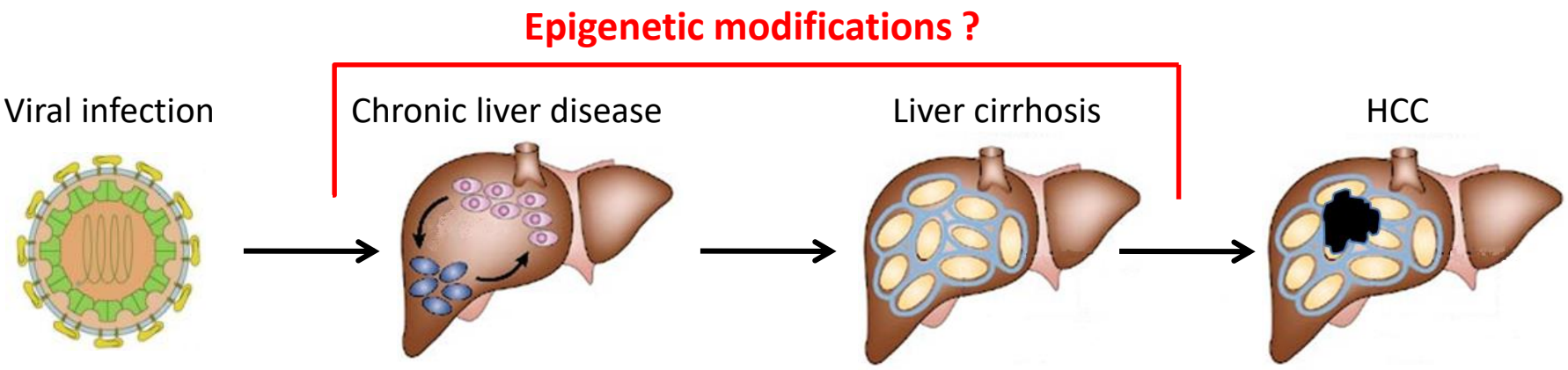
Number at risk

CHB	1085	1041	78	566	327	124
Comp. cirrhosis	476	443	355	280	168	33
Decomp. cirrhosis	55	46	31	21	14	5

PAPATHEODORIS *et al,* J Hepatol 2015;62:363-70

Prevention of HCC by NUC treatment in advanced HBV-related liver disease is suboptimal

- Reversal of cirrhosis is not universal
- Persistence of additional causes of liver disease (metabolic syndrome, surreptitious alcohol drinking)
- Pre-existing somatic mutations due to long-standing exposure to carcinogens (aflatoxin)
- **Persistence of integrated HBV DNA at sensitive sites**
- **Epigenetic changes (miR602, TFIIH, miR148a…)**



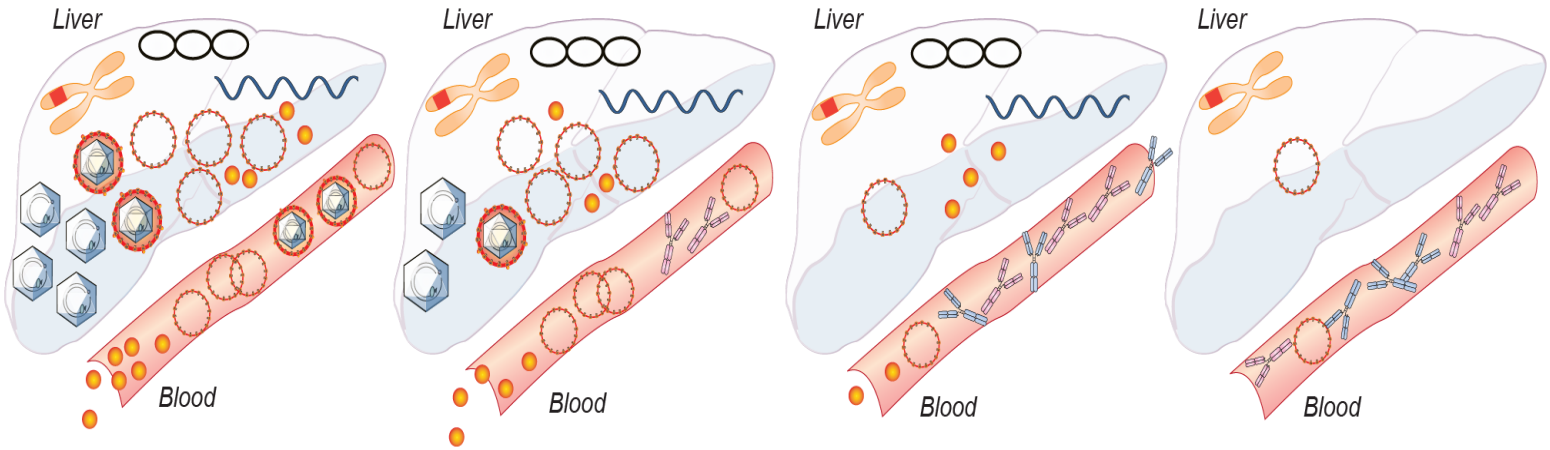
(adapted from FARAZI & DEPINHO, Nat Rev Cancer 2006)

Main limitations of current treatments

- **Limited access to care**
- **Not all patients are treated**, especially during the immuno-active phase (minimal hepatitis or non-inflammatory phase are beyond current guidelines)
- **IFN-α is poorly tolerated and has a low response rate**
- **Nucleos(t)ide analogues must be given for life**, potentially leading to the emergence of RAS (especially in case of use of low barrier to resistance drugs in resource poor countries) and safety issues
- **The cccDNA decline rate is very slow** (partly due to continous replenishment of the pool due to incomplete viral suppression)
- **HBsAg clearance is rare** (although the most desirable endpoint) with potential, continuing effects on adaptive immune response
- **The risk of HCC is not eliminated**, despite viral «response»

MASON and ZOULIM, Gut 2012; GISH et al, Lancet Infect Dis 2014; AASLD/APASL/EASL guidelines
PAPATHEODORIDIS et al, J Viral Hepat 2016; REVILL et al, Nature Reviews Gastroenterol Hepatol 2016
BUTI *et al,* Dig Dis Sci 2015; YUEN *et al,* Gastroenterology 2008; LOK *et al,* Hepatology 2016
WERLE *et al,* Gastroenterology 2004; MARCELLIN *et al,* AASLD 2014; BOYD *et al,* EASL 2016

With current technologies, a sterilizing HBV cure is unlikely



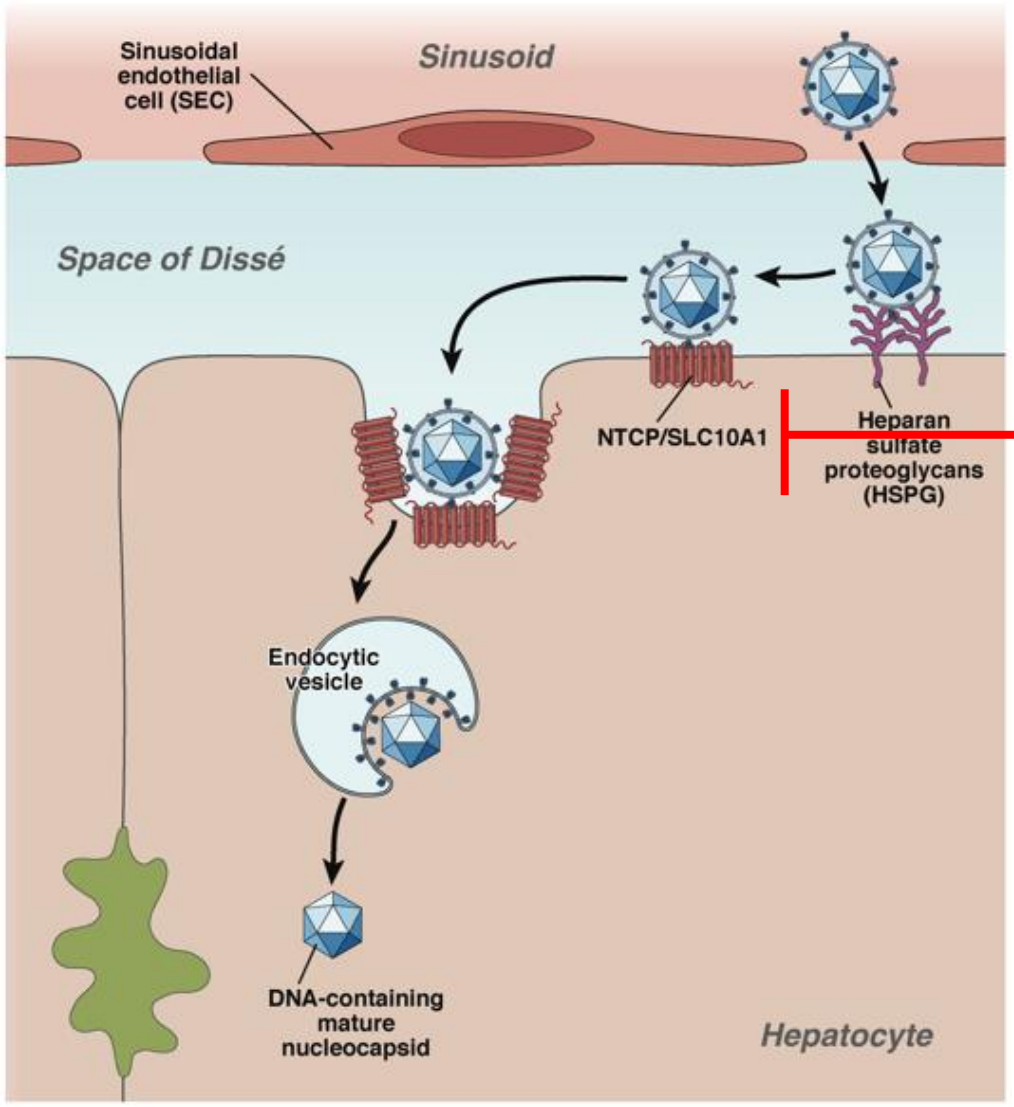
cccDNA is eliminated
(but HBV DNA persists integrated)

Antiviral therapy can be stopped
Low risk of spontaneous reactivation
cccDNA is inactivated

DURANTEL and ZOULIM, J Hepatol 2016
ZEISEL *et al,* Gut 2015; REVILL *et al,* Nature Reviews Gastroenterol Hepatol 2016

What about the future?

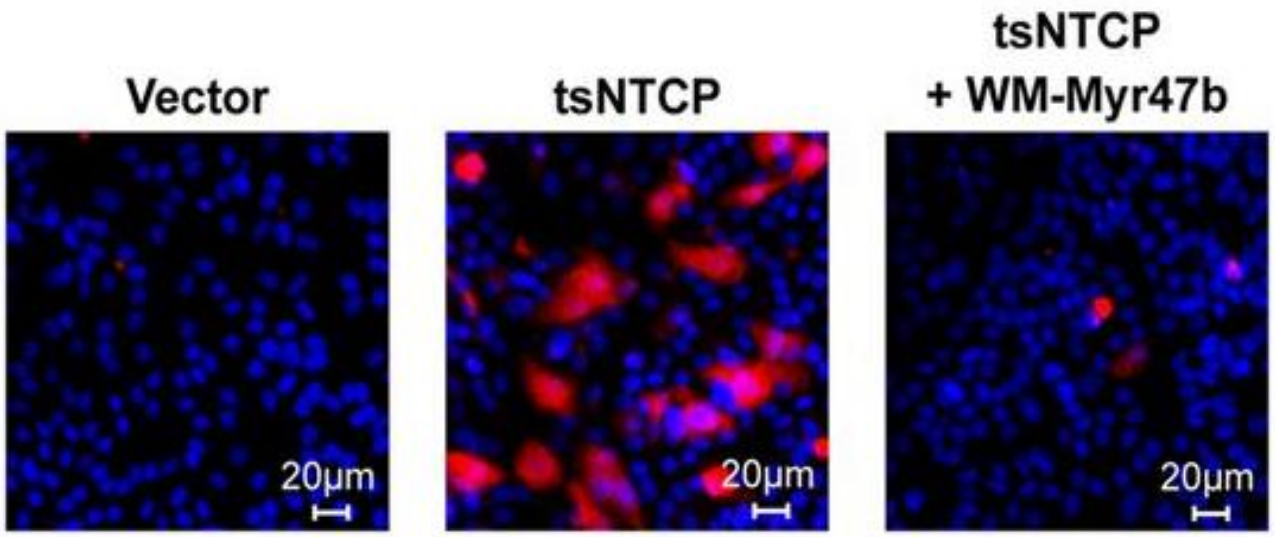
Target #1 : viral entry



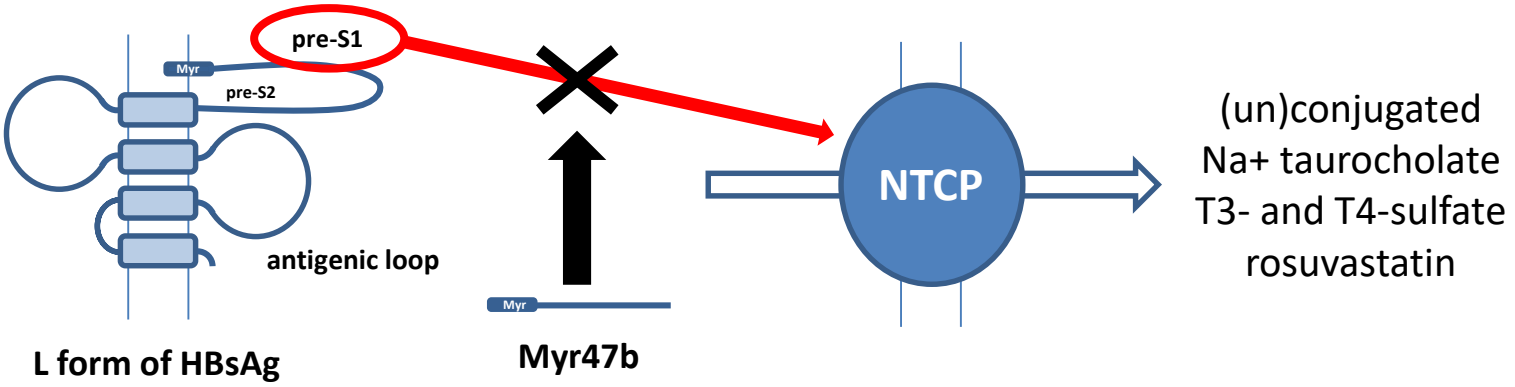
Entry inhibitors
Myrcludex
(pre-S1 peptide)

YAN *et al,* eLife 2012; URBAN *et al,* Gastroenterology 2014

NTCP expression supports WMHBV infection of HepG2 cells



ZHONG *et al,* J Virol 2013;87:7176-7184



Target #2 : the viral minichromosome (cccDNA)

cccDNA degradation

- IFNα or Lymphotoxin-β-induced, core-mediated activation of cytidine deaminase APOBEC3A/B

LUCIFORA *et al,* Science 2014

cccDNA deletions

- CRISPR/Cas9

SEEGER *et al,* Mol Ther Nucleic Acids 2014

cccDNA transcription suppression

- *Via* inhibition of p300/CBP histone acetyltransferase

BELLONI *et al,* Proc Natl Acad Sci USA 2009

TROPBERGER *et al,* Proc Natl Acad Sci USA 2015

- *Via* increased binding of transcriptional repressors to IFN-stimulated RE

BELLONI *et al,* J Clin Invest 2012

- Blocking Smc5/6 degradation

DECORSIERE *et al,* Nature 2016

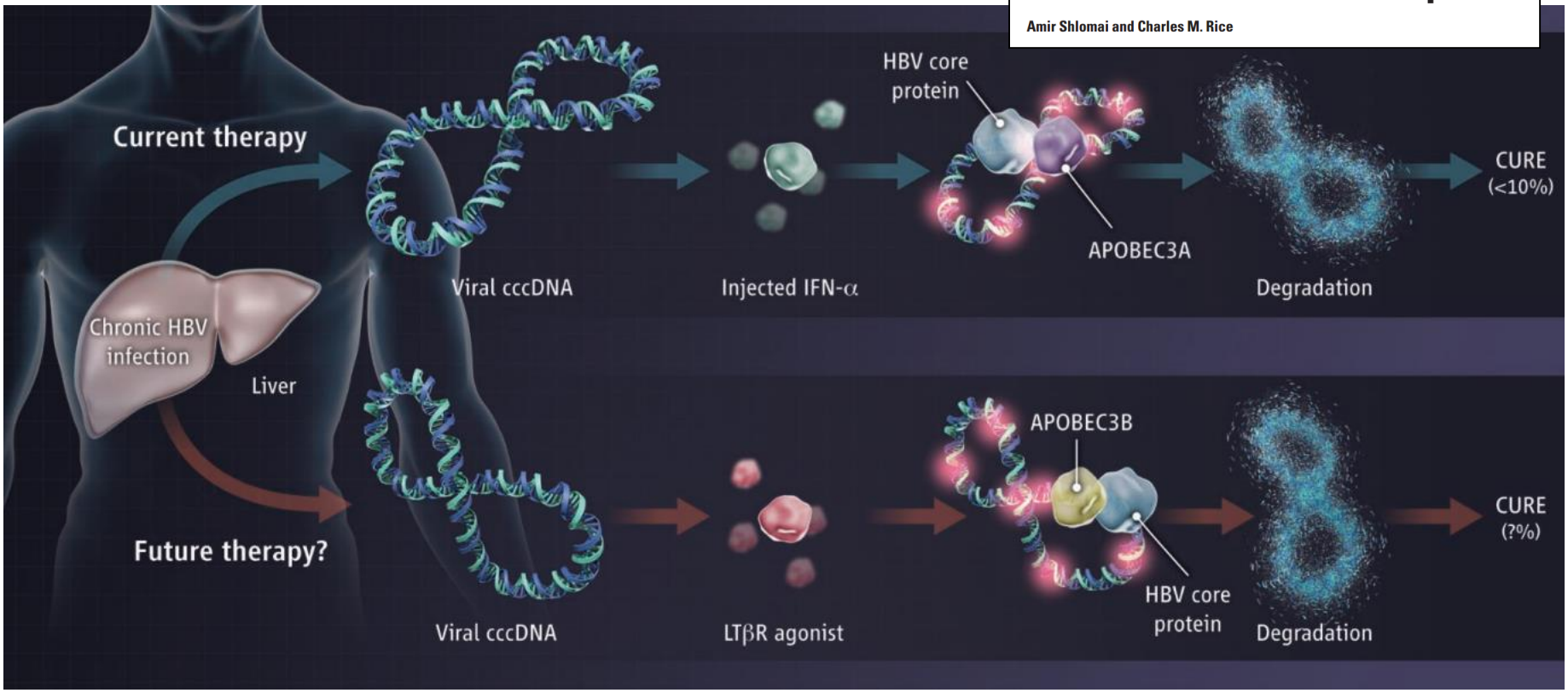
Specific and Nonhepatotoxic Degradation of Nuclear Hepatitis B Virus cccDNA

Julie Lucifora,[1,2]* Yuchen Xia,[1]* Florian Reisinger,[1] Ke Zhang,[1] Daniela Stadler,[1] Xiaoming Cheng,[1] Martin F. Sprinzl,[1,3] Herwig Koppensteiner,[1] Zuzanna Makowska,[4] Tassilo Volz,[5] Caroline Remouchamps,[6] Wen-Min Chou,[1] Wolfgang E. Thasler,[7] Norbert Hüser,[8] David Durantel,[9] T. Jake Liang,[10] Carsten Münk,[11] Markus H. Heim,[4] Jeffrey L. Browning,[12] Emmanuel Dejardin,[6] Maura Dandri,[2,5] Michael Schindler,[1] Mathias Heikenwalder,[1]†‡ Ulrike Protzer[1,2]†‡

VIROLOGY

Getting Rid of a Persistent Troublemaker to Cure Hepatitis

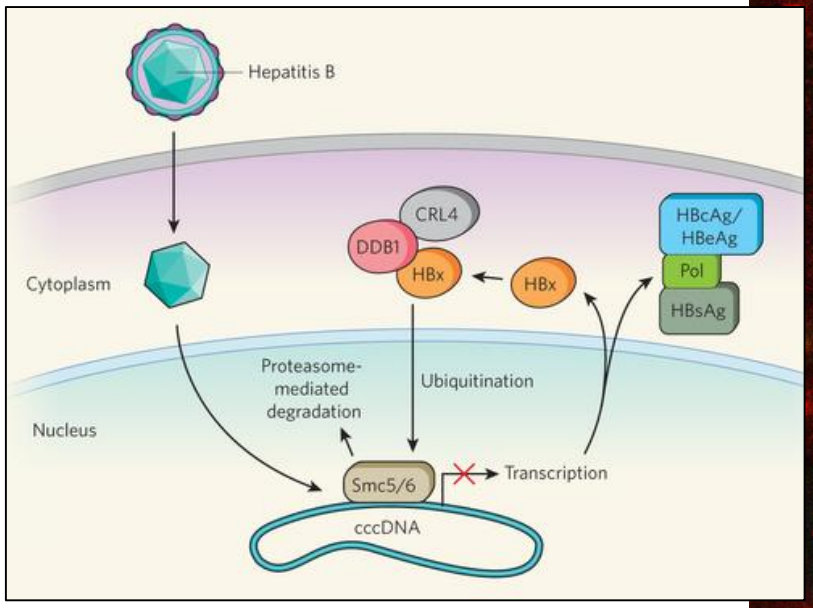
Amir Shlomai and Charles M. Rice

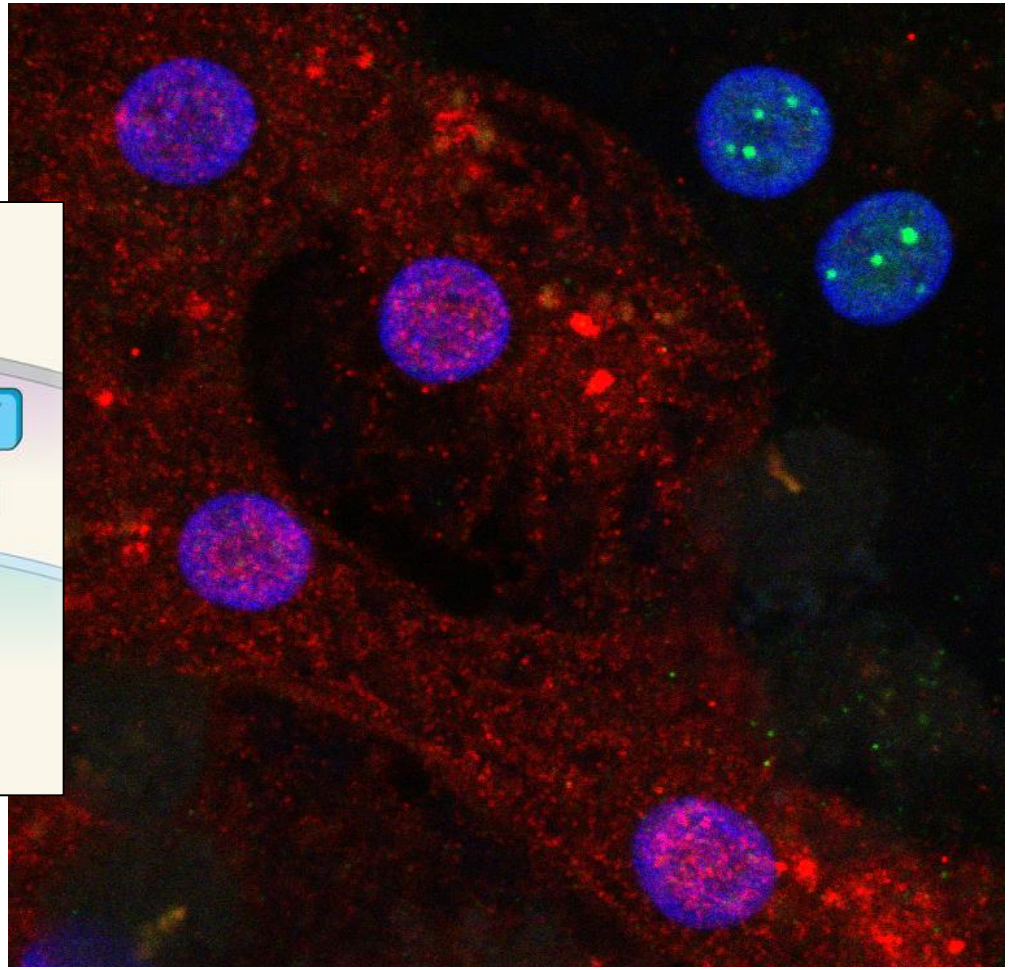


LUCIFORA *et al,* Science 2014;343:1221-8; SHLOMAI & RICE, Science 2014;343:1212-3

The HBV X protein promotes the Smc5/6 degradation in PHH by hijacking the cellular DDB1-containing E3 ubiquitin ligase

➔ **release of the Smc5/6 transcription inhibition of episomal DNA templates**





HBcAg **Smc5/6** **Nuclei**

DECORSIERE *et al,* Nature 2016;531:386-9; LIANG, Nature 2016;531:313-4

Target #3 : the viral envelope

Strategies under study:

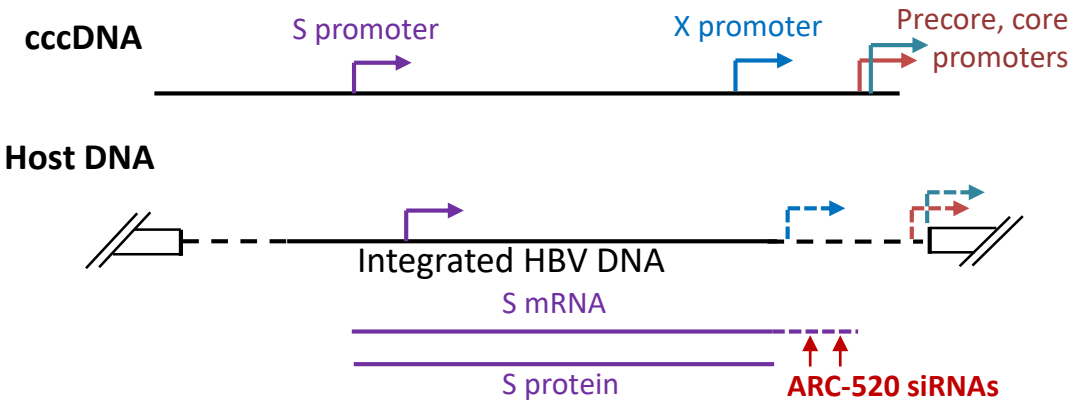
- RNA interference (siRNA)
- Nucleic acid polymers (NAPs)

Goals:

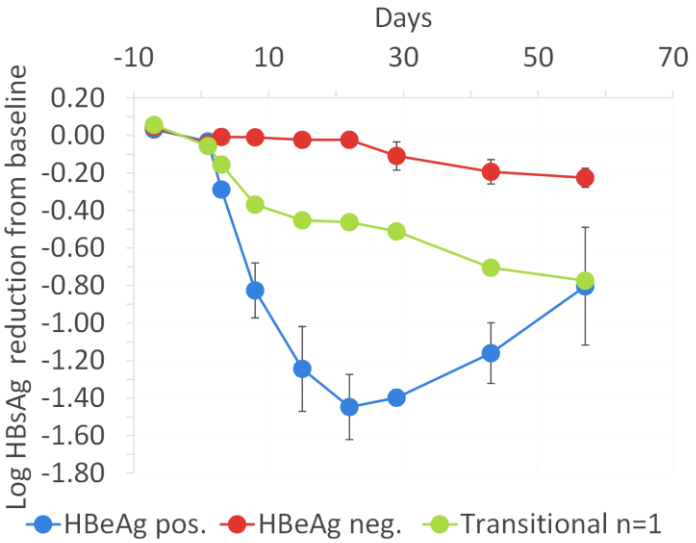
- To inhibit virion production
- To restore the antiviral activity of exhausted T cells

ARC-520 (anti-HBs siRNA) induces a profound and durable knockdown of viral antigens and DNA in a phase II study

Impact of integrated sequences on siRNA efficacy



HBsAg reduction in therapy naive patients with a single 4 mg/Kg dose



Challenges:

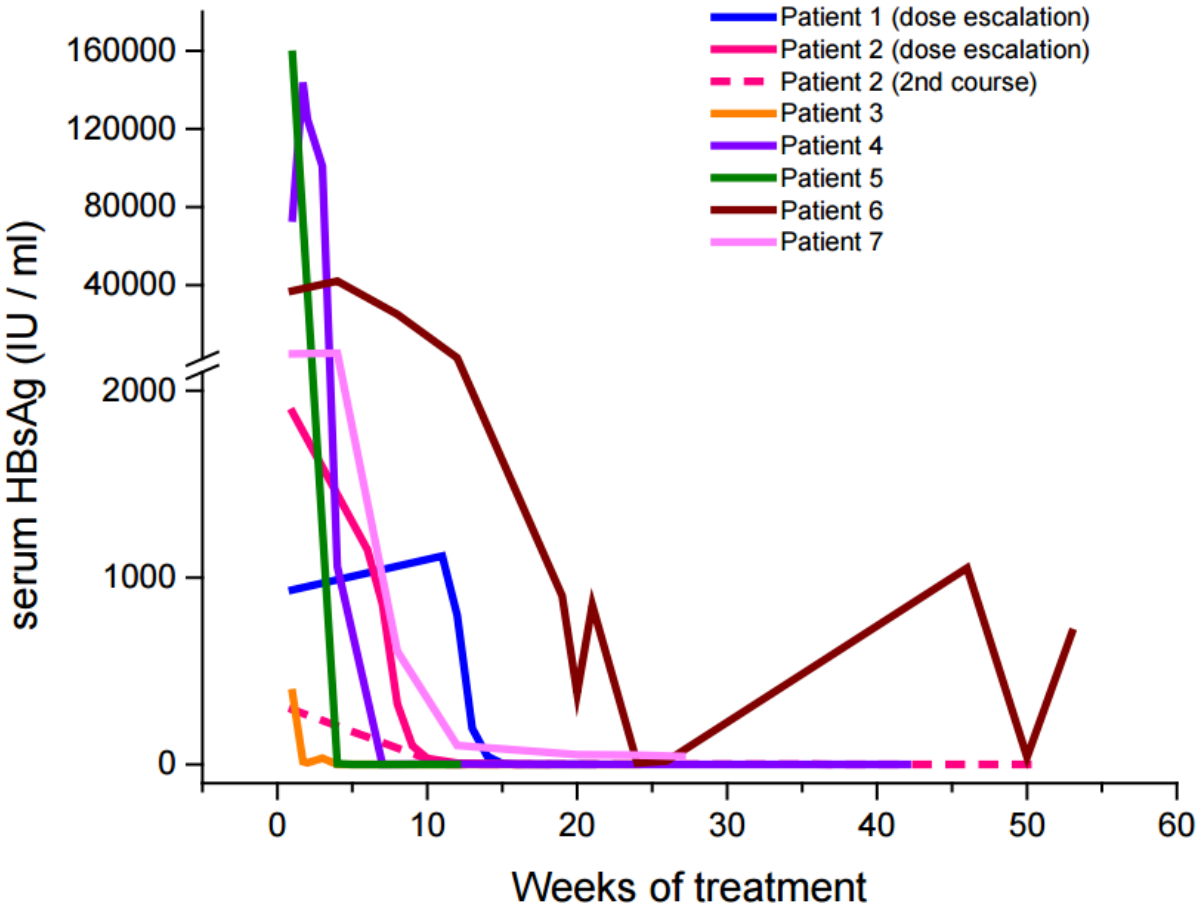
- HBV sequence diversity (10 genotypes, 7.5% heterogeneity)
- Uptake by appropriate cell type (liposomes, cholesterol conjugation)
- Endosomal escape (cationic lipids, melitin-like peptide)
- Avoid innate immune response (complex lipids, chemical modifications)
- IV administration!

Arrowhead Research CORPORATION

YUEN *et al,* AASLD 2015, abstract #LB-9

REP-2139 (Nucleic Acid Polymer) 500 mg IV qW monotherapy

(REP 101 study, n=7)



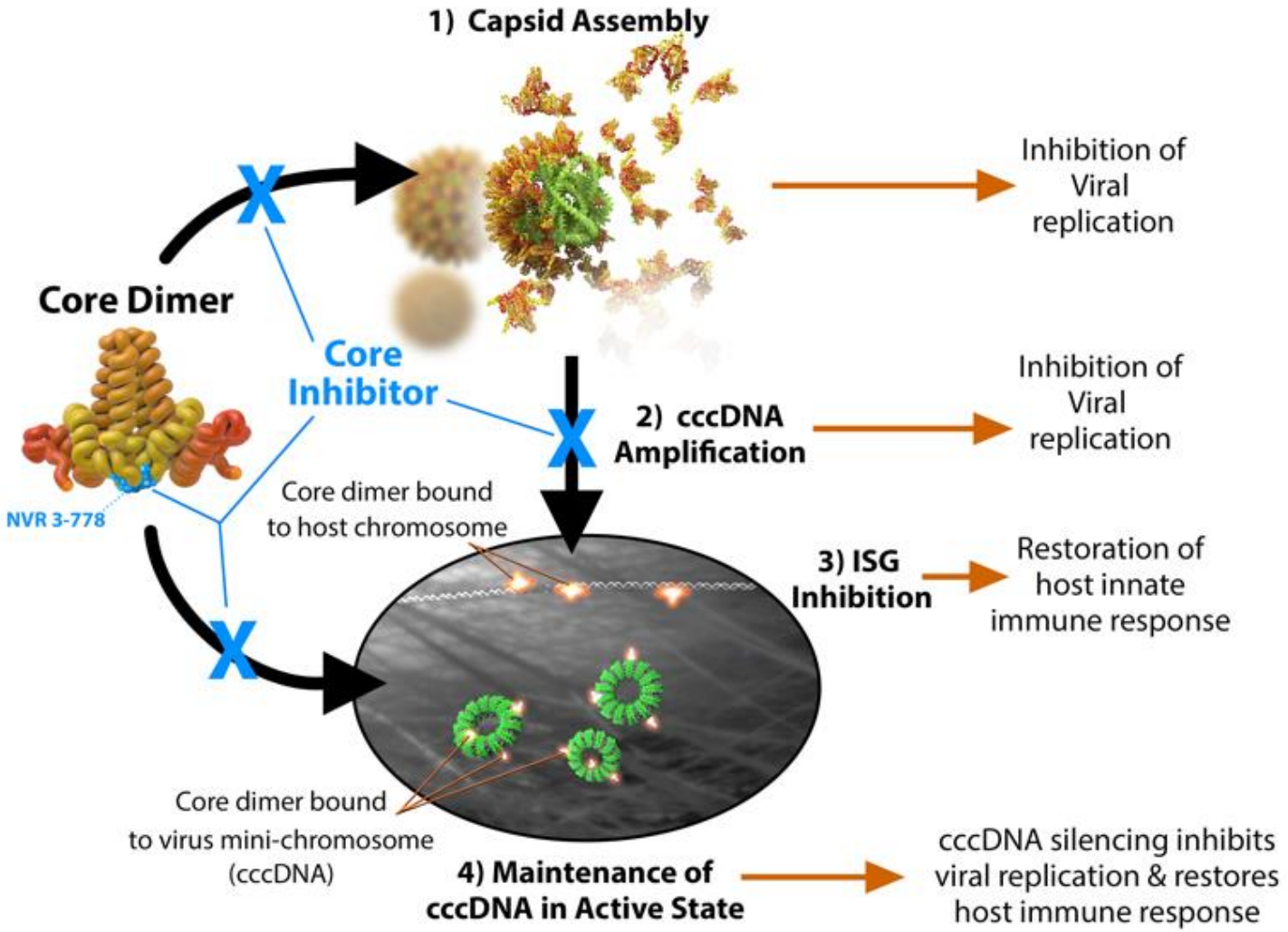
Anti-HBs seroconversion observed in patients treated with REP-2139 + Zadaxin

Phase II study in hepatitis B started in October 2015 in Moldova

replicor

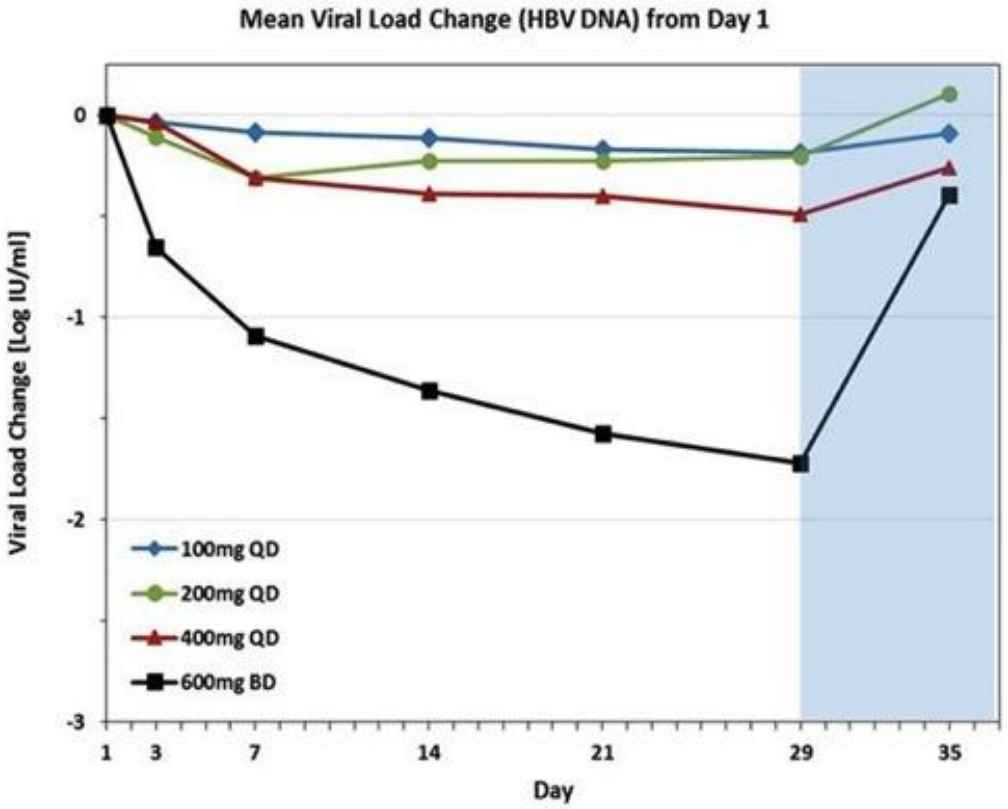
AL-MAHTAB *et al*, 2015

Target #4 : the viral capsid

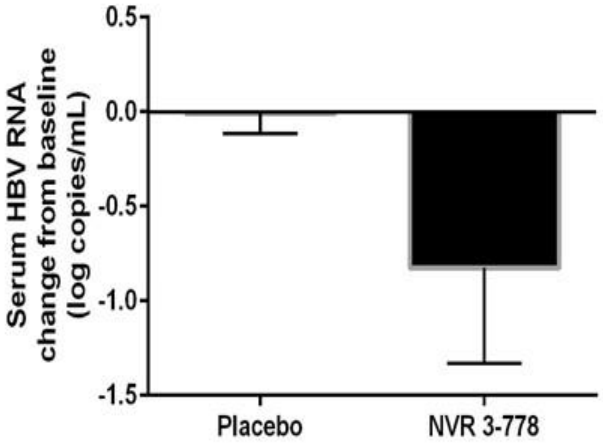


(from FLORES O, Novira Therapeutics, presented at HepDart 2015)

NVR 3-778 targets the N-terminal assembly domain of HBV core, leads to defective core particles and reduces serum HBV DNA and RNA



Cohort I: 600 mg BID
serum HBV RNA change from baseline



novira THERAPEUTICS

YUEN *et al,* AASLD 2015, abstract #LB-10
KLUMPP K *et al,* Proc Natl Acad Sci USA 2015;112:15196-201

Target #5 : the host immune system

- HBV persists with **virus-specific and global T-cell dysfunction** mediated by multiple regulatory mechanisms, but without distinct T-cell–based immune signatures for clinical phenotypes

PARK *et al*, Gastroenterology 2015

- Children and young adults with chronic hepatitis B have a Th1-cell cytokine profile and a **partial profile of T-cell exhaustion**
- Young patients with CHB have more HBV-specific T cells with the ability to proliferate and produce cytokines than adult patients with CHB
- HBV infection in younger patients is *not associated* with an immune profile of T-cell tolerance

KENNEDY *et al*, Gastroenterology 2012

- HBV exposure *in utero* induces a robust Th1-polarized response in the newborn (« trained immunity »)

HONG *et al*, Nature Comm 2015

Immune checkpoint inhibitors may restore pre-existing immune responses: the example of anti-PD-1

- Blockade of PD-1 increases responses of liver HBV-specific T cells

FISICARO *et al,* Gastroenterology 2012

- Blockade of PD-1 with BMS-936558 (Medarex-1106, nivolumab), a fully human anti-PD-1 monoclonal IgG4 in a single, ascending dose, phase I trial in ***hepatitis C*** led to significant HCV RNA reductions (one patient aviremic one year after dosing)

GARDINER *et al,* PLoS One 2013

Conclusions

Current treatments for HBV:

- Allow suppression of viral replication in most patients who have access to potent NUCs
- Must be prolonged for life, with limited effects on HBsAg and cccDNA
- Do not eliminate completely the risk of complications

Future treatments for HBV:

- Will allow reaching a functional / complete cure (a sterilizing cure is unrealistic with current technologies)
- Ideally, should be short-term
- May require a paradigm shift, e.g. targeting host gatekeepers (innate and adaptive responses)