HBV: prospettive terapeutiche

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hr EXCELLENCE IN RESEARCH

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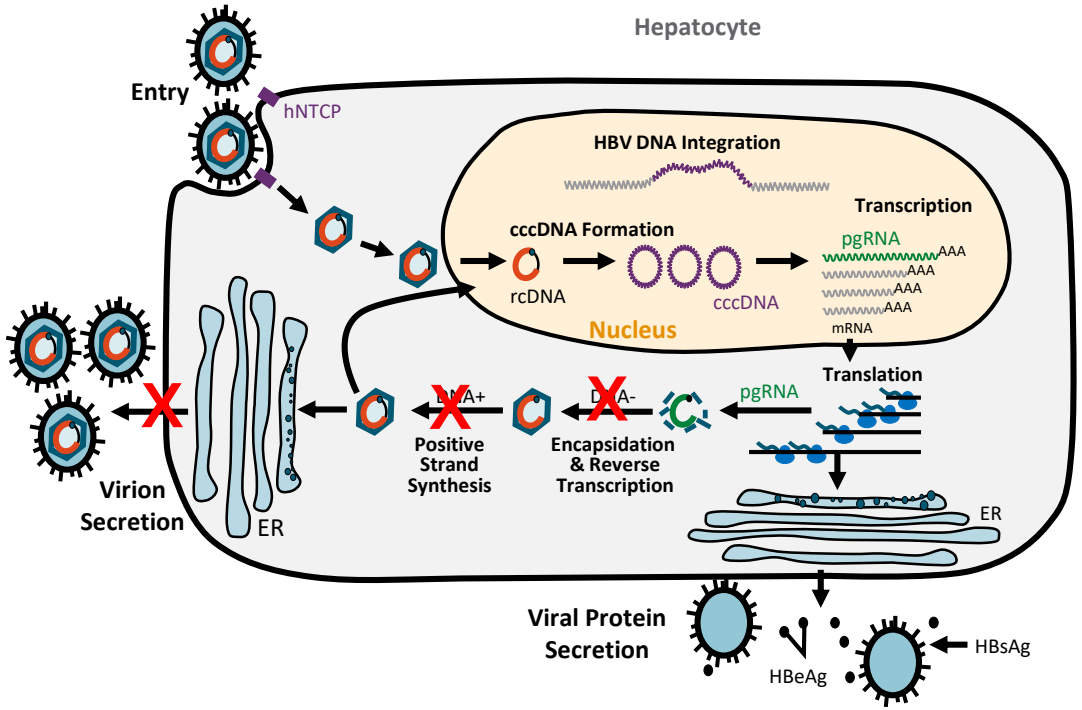
HBV Current Therapy: Suppression, but not Cure



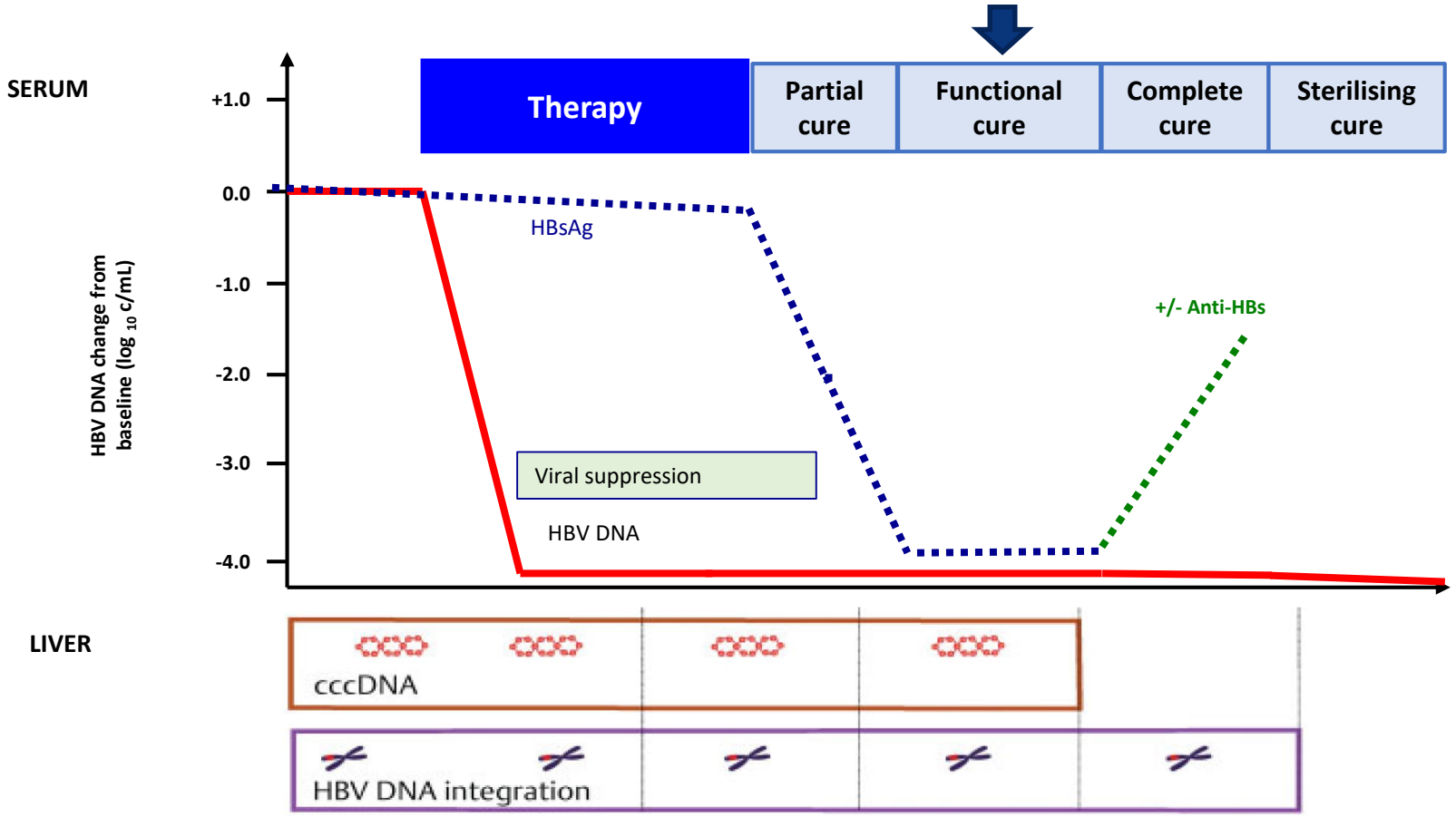
NUC monotherapy (ETV, TDF, TAF)

- **Control of HBV infection and liver disease**

- NUCs do not directly target cccDNA
- cccDNA transcription and viral antigens production are not blocked by NUCs
- HBsAg loss rates are very limited
- **Life-long therapies to maintain viral suppression**
  - Aderence, Toxicity, Resistance, Costs

Future HBV therapies: from «control» to «cure»

What do we want to achieve?



FUNCTIONAL CURE =

Sustained undetectable HBsAg and HBV DNA in serum ± anti-HBs

Testoni B et al Semin Liver Dis 2017; 37:231-242

The changing treatment paradigm in HBV

	Current	Future
Regimen	Long-term NUC monotherapy	Short term Combination therapies
Goal	Suppression of viral replication	**Functional Cure**
Primary endpoint	HBV DNA undetectable	HBsAg loss

Advantages of achieving functional cure (HBsAg loss) in HBV patients

NUC-naive (untreated) patients:

- Short-term finite therapy
- More patients will start therapy
- Treatment indication could be expanded (IT and inactive carriers?)
- Useful to reach the WHO 2030 targets

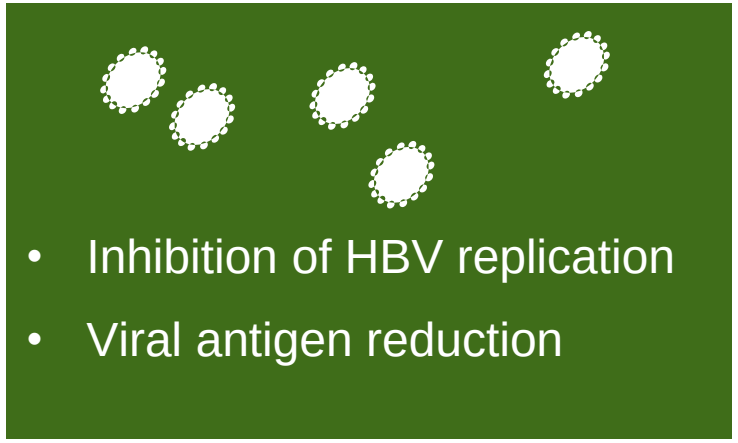
NUC-suppressed patients:

- Stop NUC safely, even in compensated cirrhotics
- Less monitoring (but not for cirrhotics)
- No safety issues and less expensive
- Reduced number of infected cells and cccDNA silencing
- Lower complications
  - HBsAg loss further reduces HCC risk compared to viral suppression without HBsAg loss and improves prognosis

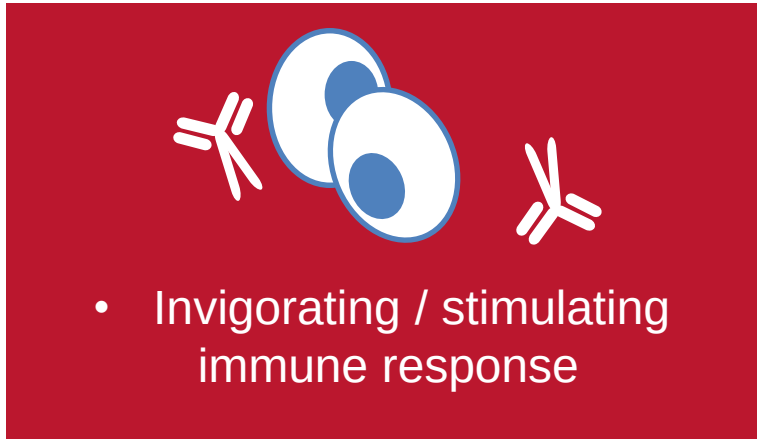
HBV Functional Cure

Two strategies

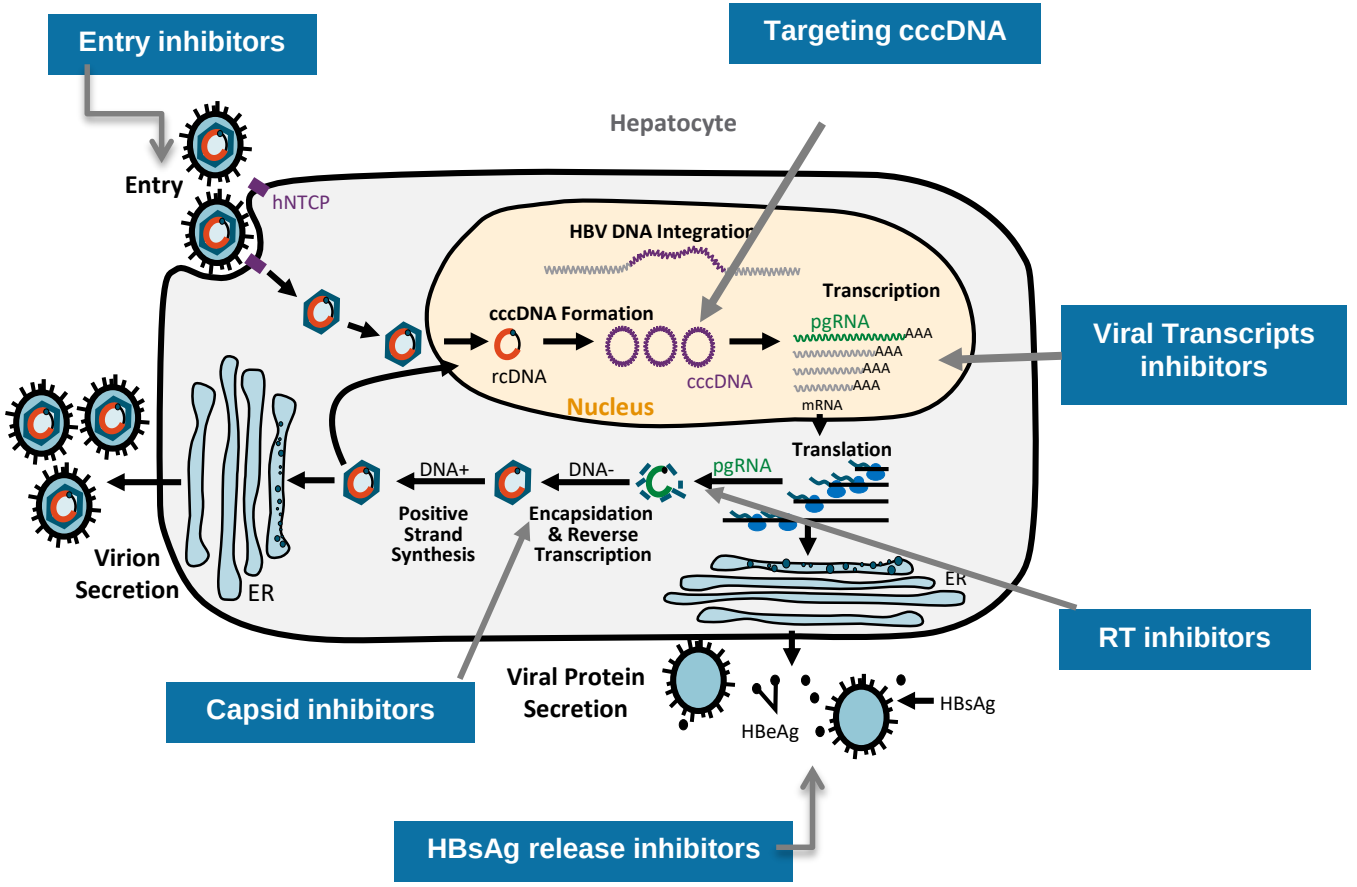
- **Interfering with the viral life cycle**



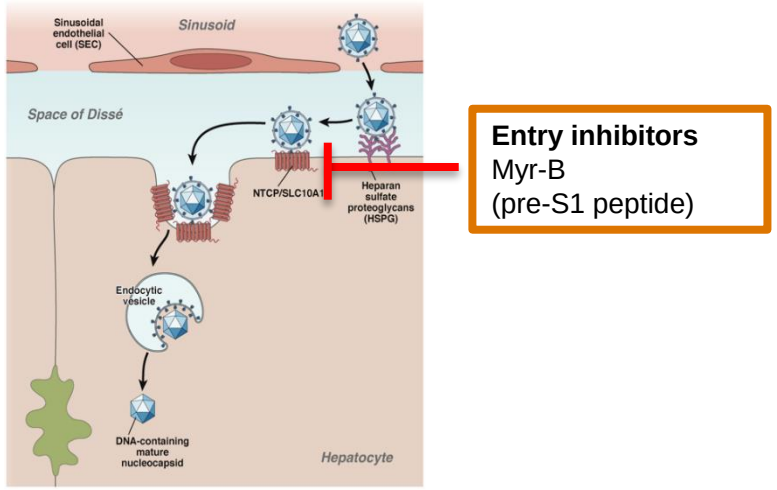
- **Modulation of antiviral immune response**



Current and future HBV virological targets for treatment and cure of CHB

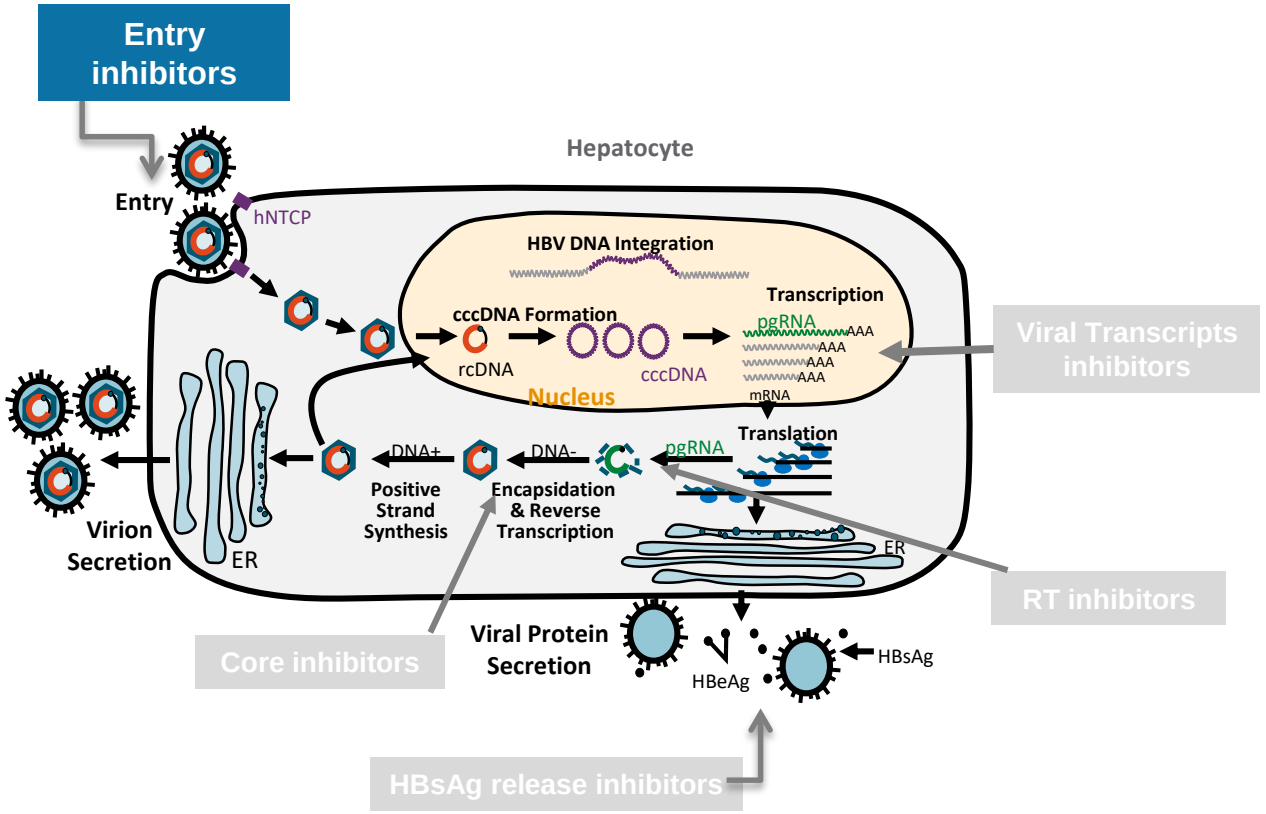


Targeting the Virus: Novel Direct-Acting Antivirals



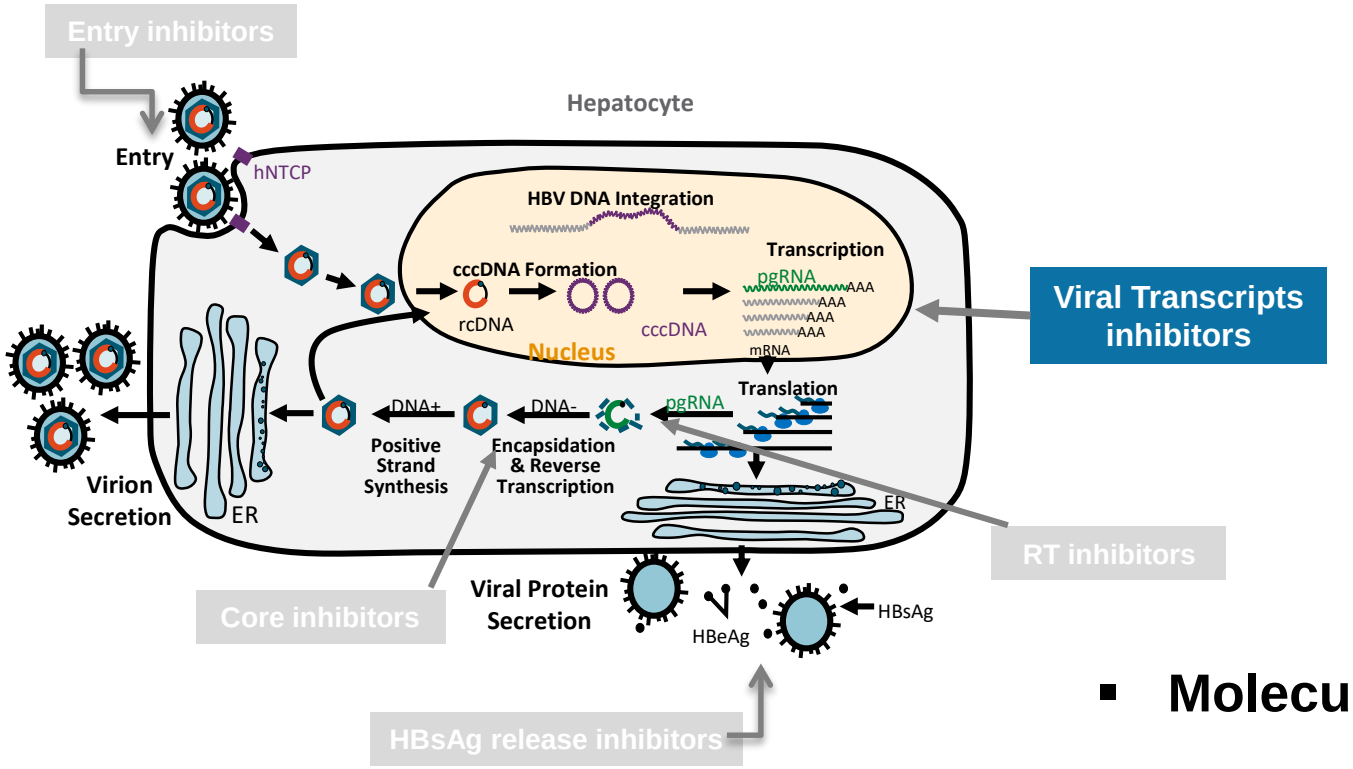
Entry inhibitors
Myr-B
(pre-S1 peptide)

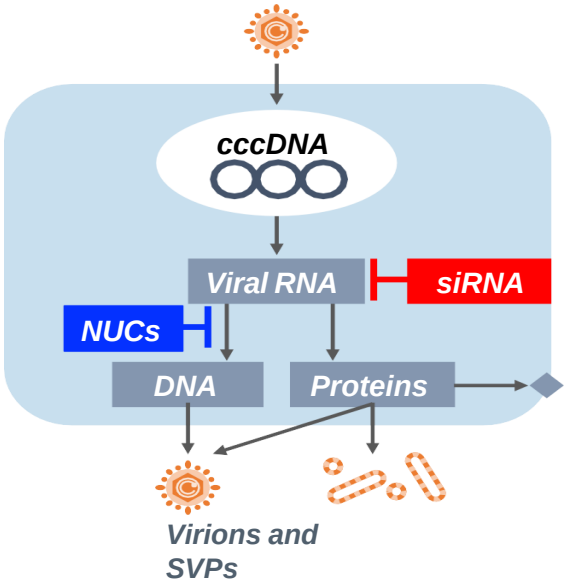
Li et al, elife 2012; Urban et al, Gastroenterology 2014



- **Molecular target**: the NTCP HBV receptor
- **MoAs**:
  Inhibits infection of new hepatocytes and HBV spreading

Targeting the Virus: Novel Direct-Acting Antivirals

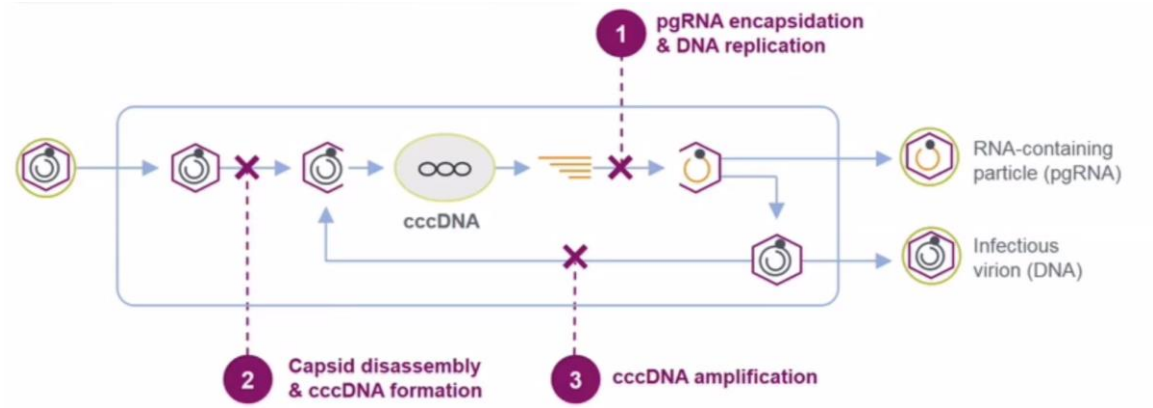


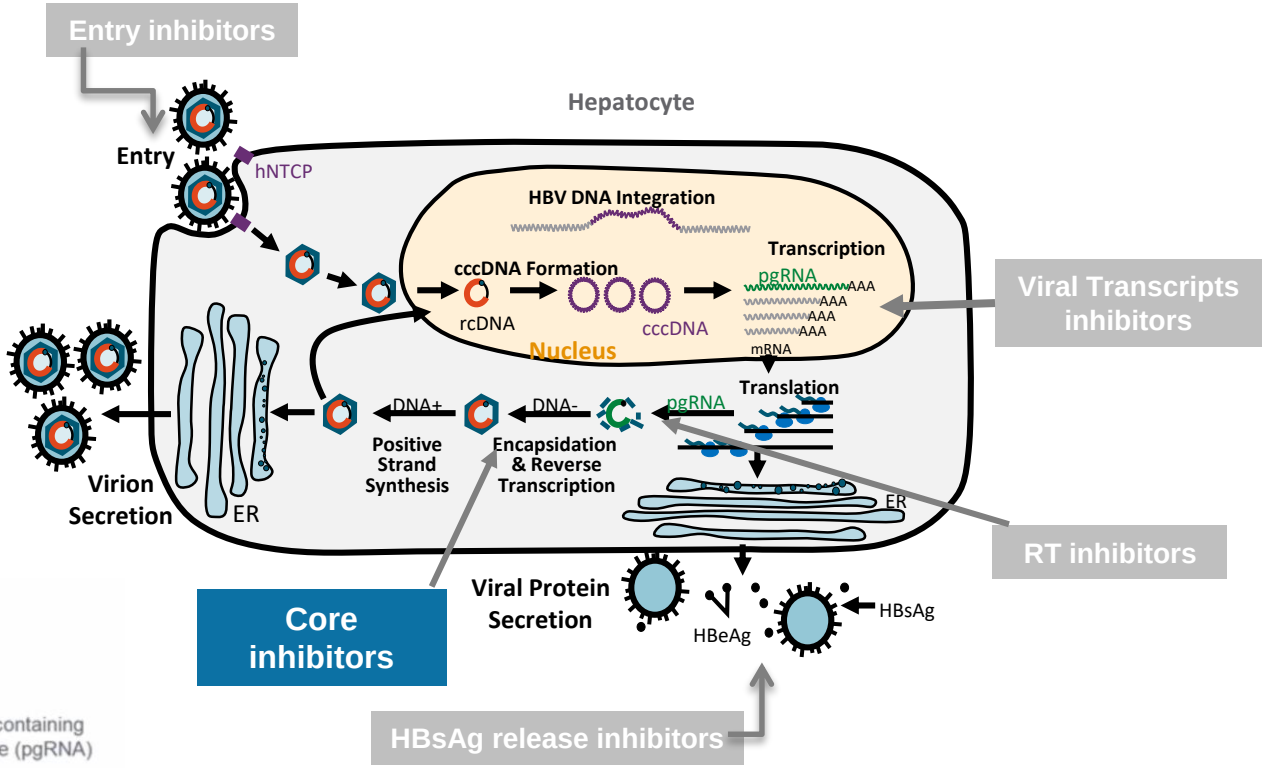


- **Molecular target:** viral RNAs
- **MoAs:**
  - Inhibition of virions and viral proteins production
  - Indirect immune modulation by reducing HBsAg/HBeAg

Targeting the Virus: Novel Direct-Acting Antivirals

- **Molecular target:** core protein assembly and pgRNA packaging
- **MoAs:**
  - Inhibition of viral replication by blocking the formation of viable RNA nucleocapsids
  - Target cccDNA replenishment (mature capsid recycling)
  - Prevention of cccDNA formation in newly infected hepatocytes

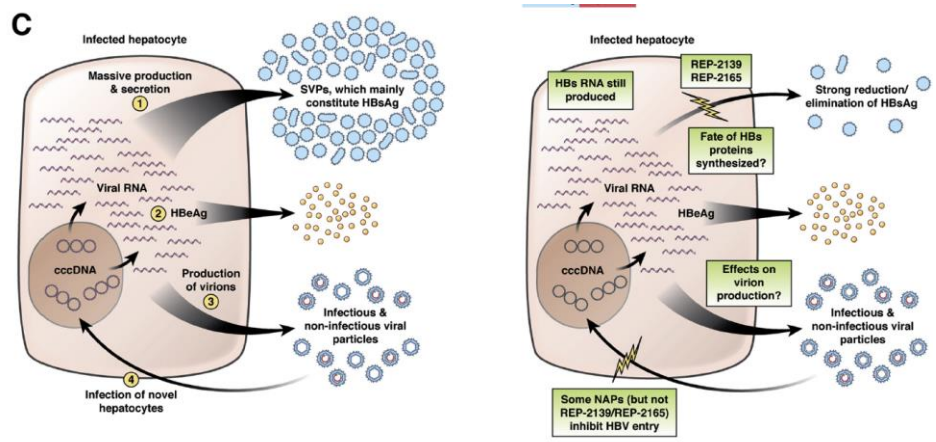


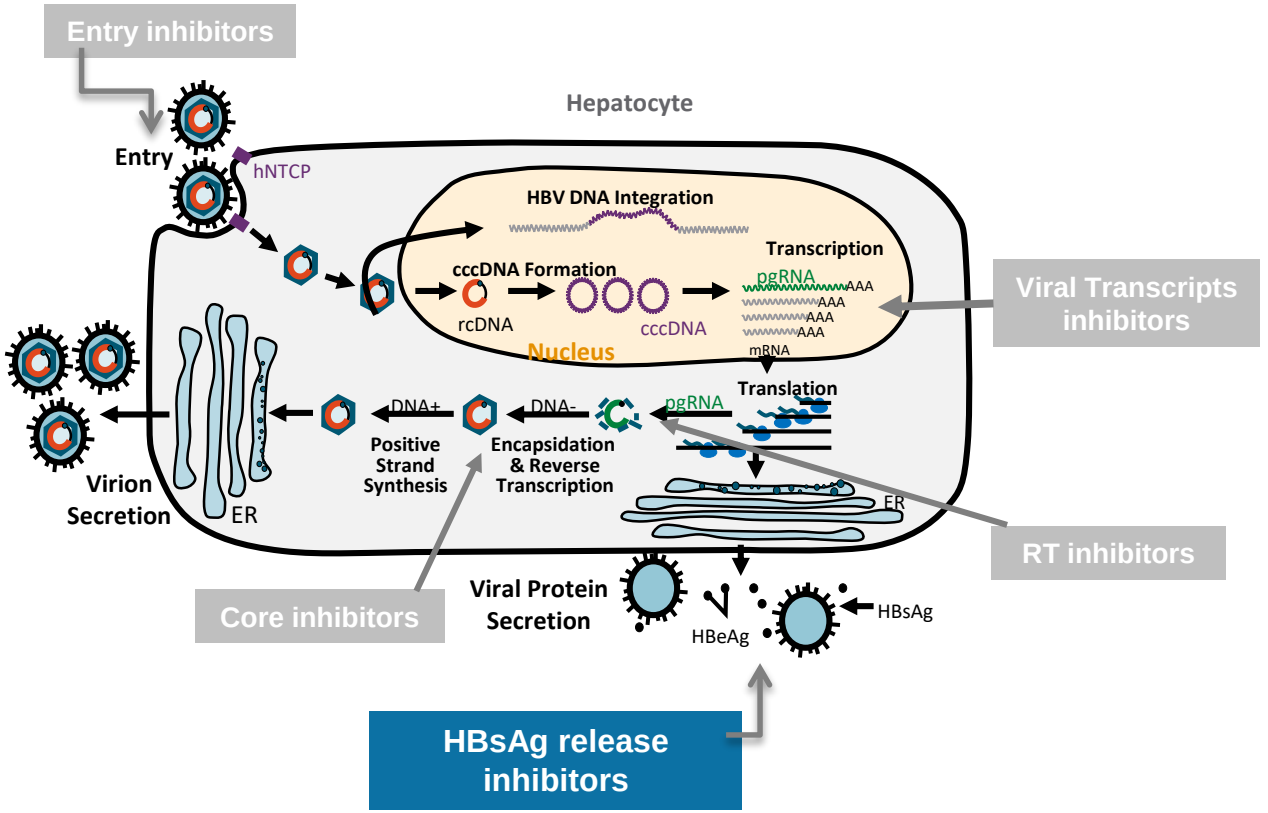


Targeting the Virus: Novel Direct-Acting Antivirals

- **Molecular target:** HBV subviral particles

- **MoAs:**
  - Inhibit assembly and secretion of HBV subviral particles. Exact mechanism of action not fully clear.
  - Indirect immune modulation by reducing HBsAg (suggested by the association of ALT flares with response)

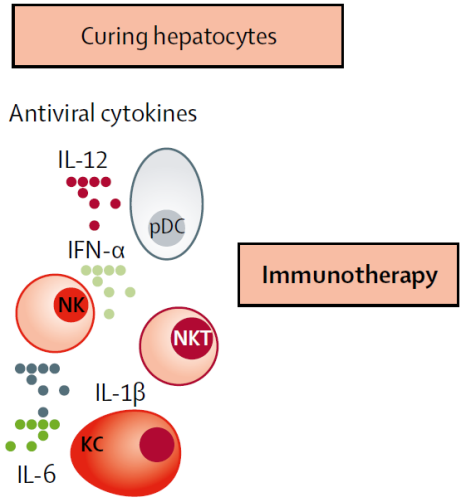




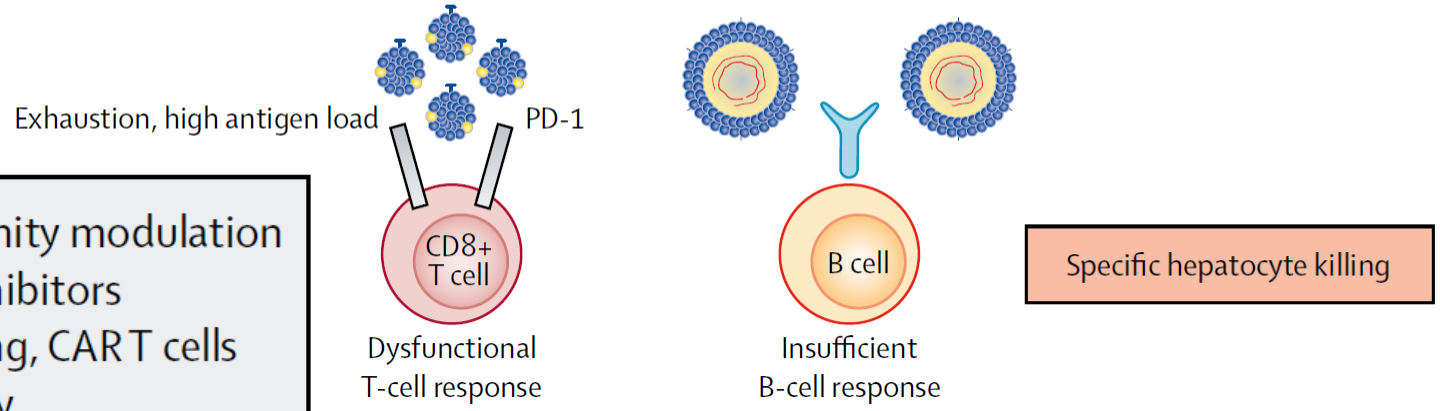
Durantel D & Asselah T. Gastroenterology 2020

Targeting Host Immune Response: Novel Immunomodulators

Innate immunity modulation
- Toll-like receptors agonists
- RIG-I agonists
- STING agonists



Adaptive immunity modulation
- Checkpoint inhibitors
- TCR engineering, CAR T cells
- Vaccine therapy



Revill PA et al. Lancet Gastroenterol Hepatol 2019

Potential Combination Therapies to Cure HBV infection

Replication inhibition ± **Antigen reduction** ± **Immune stimulation**

hNTCP

Entry inhibitors: bulevirtide

HBV polymerase

NUC: ETV, TDF, TAF

Nucleocapsids

CAM: ABI-H0731, JNJ-56136379, RO7049389

Transcription

FXR agonist: EYP001

Viral RNAs

siRNA: JNJ-3989 VIR-2218

ASO: GSK3228836

LNA: RO7062931

HBsAg release

NAPs: REP 2139 or REP 2165

Invigorate immune responses

Innate immunity

TLR7: GS9620, RO6864018, RO7020531, JNJ6479464

TLR8: GS9688

Immune check points

Anti-PD1: nivolumab

Anti-PDL1

PDL1 LNA

Oral PDL1 sm

Stimulate HBV specific B/T cells

Therapeutic Vaccines

GS4774

TG1050

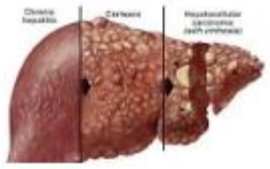
T101

SCI-B-VAC

Fanning et al. Nat Rev Drug Discov. 2019 Nov;18(11):827-844; Roca et al, Liver International 2021 in press

Heterogeneous disease and patient population

Pathobiology of HBV
Disease Phase



Disease stage

Patient history

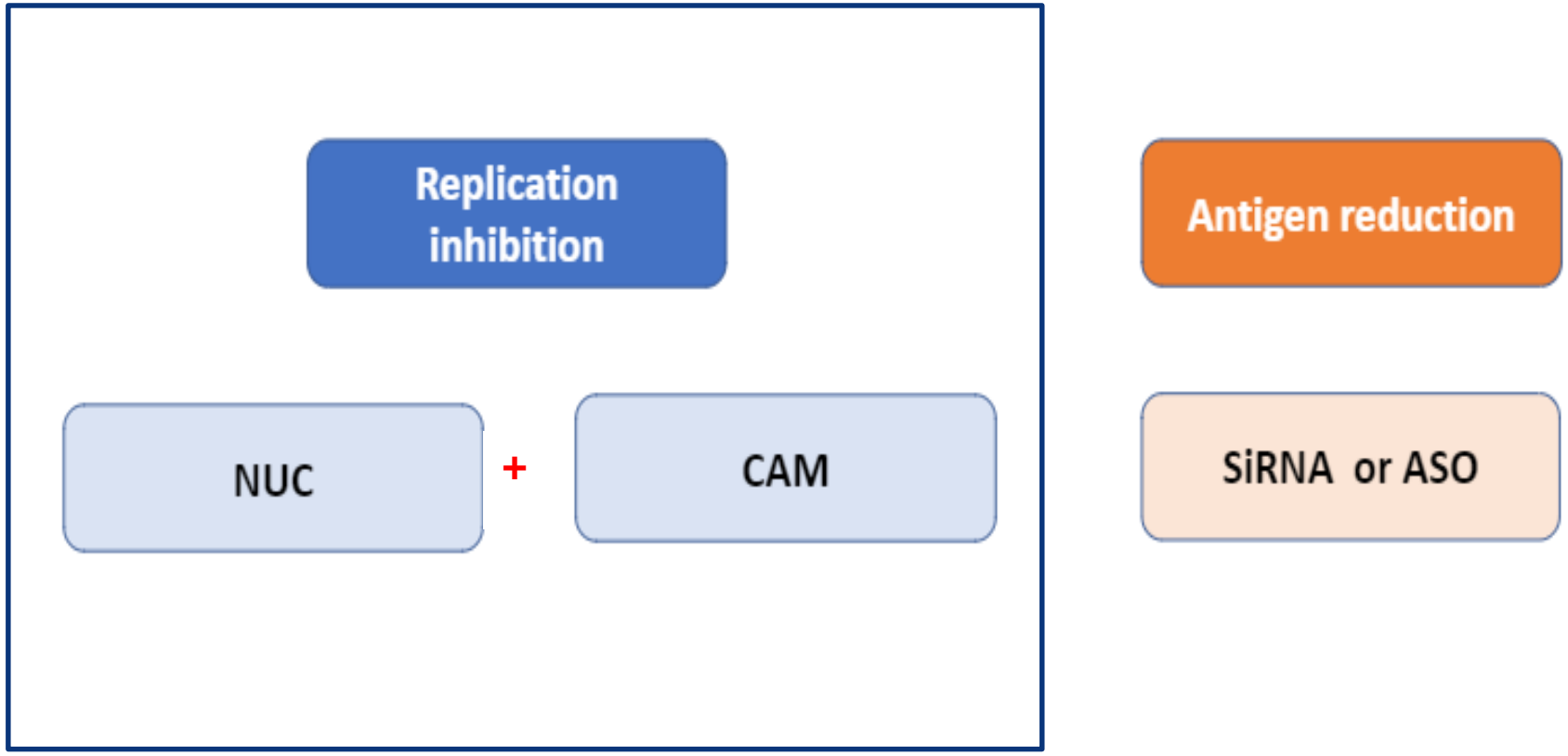
HBV
Co-infections

- **Different phases of the infection and disease: drugs with different MoA may be best suited for specific phases?**
- **Different stages of liver disease: caution for safety with advanced fibrosis**
- **Different treatment history: Tx naive patients vs IFN experienced vs NUC treated**
- **Different genotypes or mutant profiles**
  HDV

Data from Combination trials for HBV

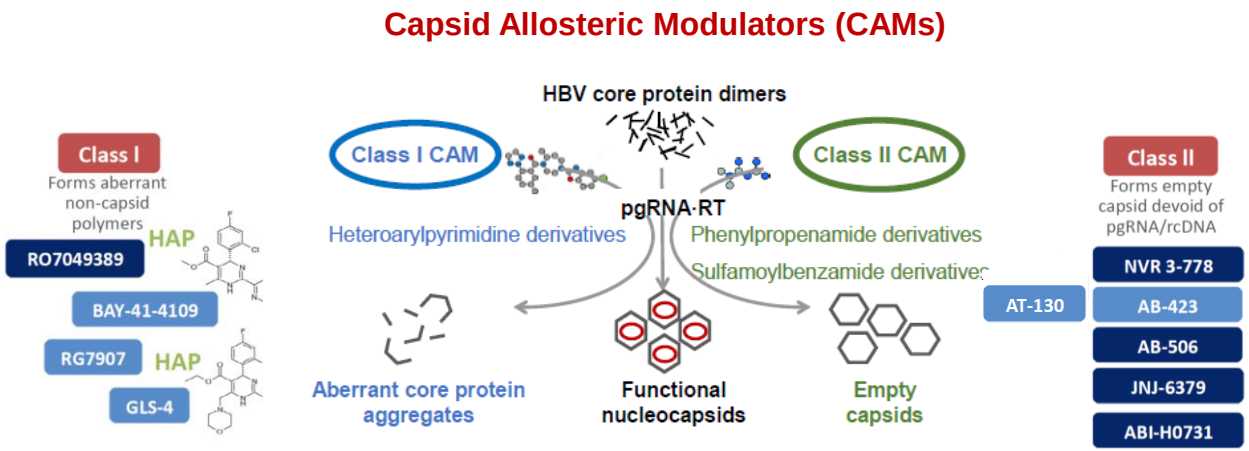
Combination of Direct Acting Antivirals

NUC+CAM



Capsid assembly inhibitors (CpAMs, CAMs)

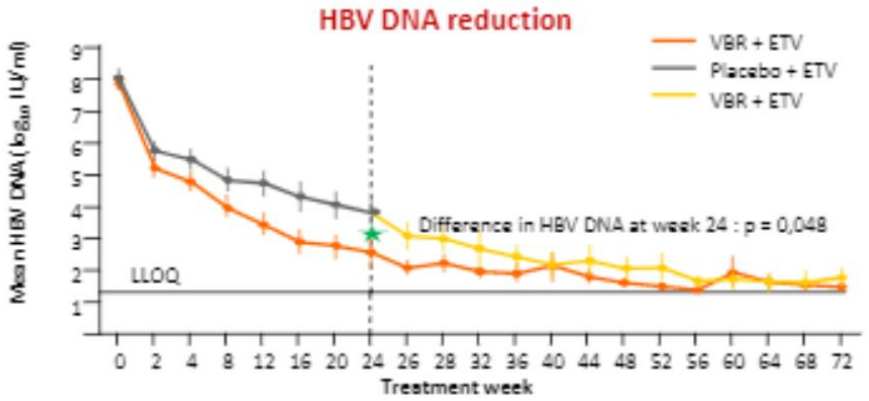
- Several compounds under development and clinical evaluation

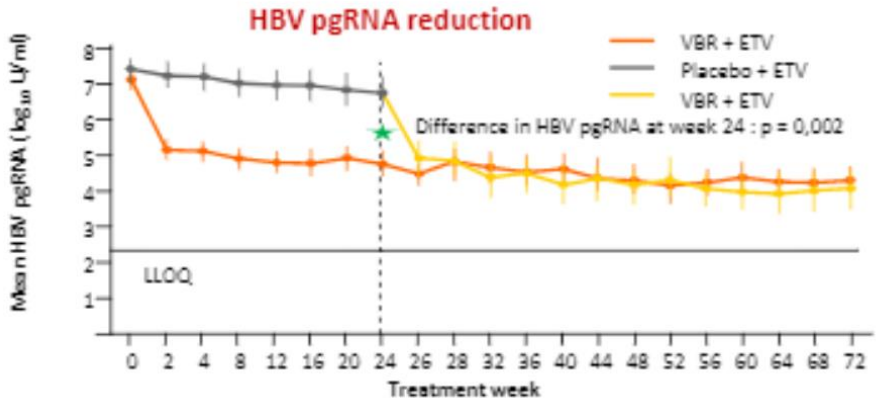


- Easy to use (once daily oral regimen)
- Decline in HBV DNA and HBV RNA (target engagement)
- No significant impact on HBsAg or HBeAg decline (so far)
- Risk for initial non-response and resistance

Core inhibitors
ABI-H0731 (Vebicorvir, core inhibitor) + NUC (phase 2 clinical studies)

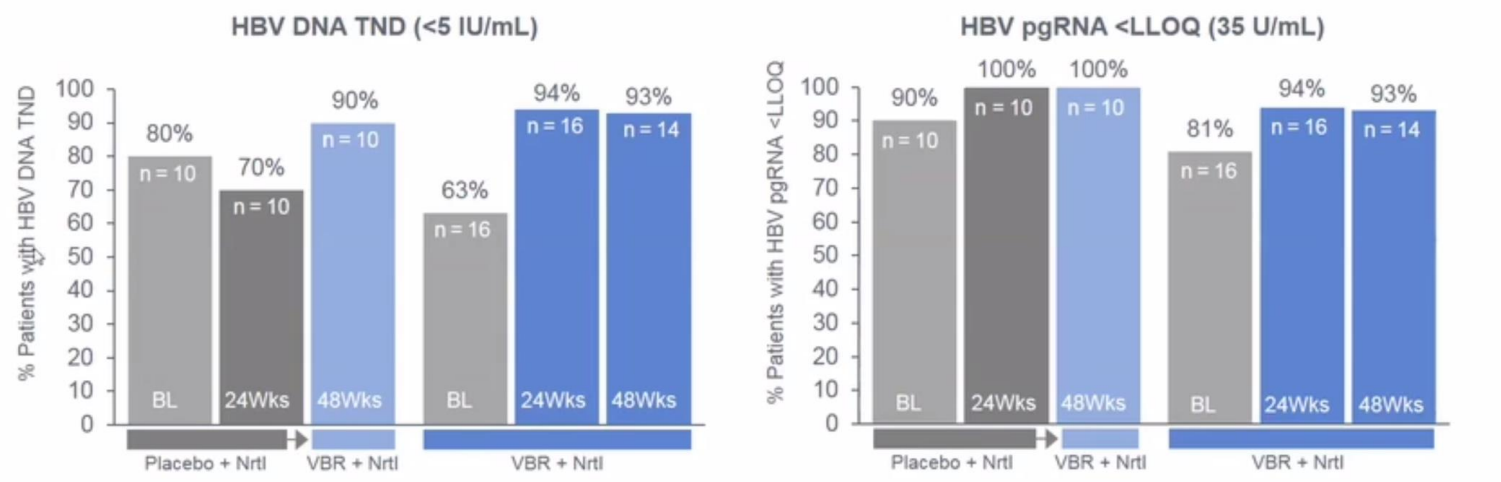
HBeAg-positive naive patients (25 pts)





NUC suppressed HBeAg-negative patients (26 pts)

Yuen MF et al EASl 2020, abs LP30



Fung S et al EASL 2020

ABI-H0731 (Vebicorvir, core inhibitor) in HBeAg positive and negative CHB

week 76 results from the 201, 202, 211 studies

Discontinuation rules for HBeAg pos and neg CHB* (study 211)

- ✓ HBV total nucleic acids (composite DNA + pgRNA) <20 IU/mL
  AND
- ✓ HBeAg negative or HBeAg ≤5 IU/mL

For at least 6 months prior to Treatment Week 76

Study 211 Interim Off-Treatment Virologic Results**

Number of patients	Discontinued treatment with VBR+NrtI	Relapsed at post-treatment Week 4	Relapsed at post-treatment Week 8	Relapsed at post-treatment Week 12	Relapsed at post-treatment Week 16	Have not relapsed*	Overall virological relapse rates
HBeAg negative	23	16	0	3	3	1	22/23 (96%)
HBeAg positive	18	17	0	0	0	1	17/18 (94%)

*These 2 patients have completed the post-treatment Week 8 visit

Sustained Virological Response (SVR): defined as off-treatment HBV DNA <20 IU/mL.

*Man-Fung Yuen et al, EASL 2020, Scott Fung et al, EASL 2020

**Assembly Bio, press conference, Nov 8th 2020

Combination of Direct Acting Antivirals
NUC + siRNAs/ASO

Replication inhibition

Antigen reduction

NUC: ETV, TDF, TAF

+

siRNA: JNJ-3989 VIR-2218
ASO: GSK3228836
LNA: RO7062931

Viral transcripts inhibitors

RNA interference/Gene silencing

- Several compounds under development and clinical evaluation

siRNAs
- JNJ-3989
- VIR-2218

ASO/LNAs*
- RO7062931
- GSK 3389404
- ISIS 505358 (GSK3228836, second generation ASO)

- Multiple platform for delivery; needs to be given IV or SC; risk of allergic reactions

- qHBsAg decline and HBV RNA reduction (target engagement)

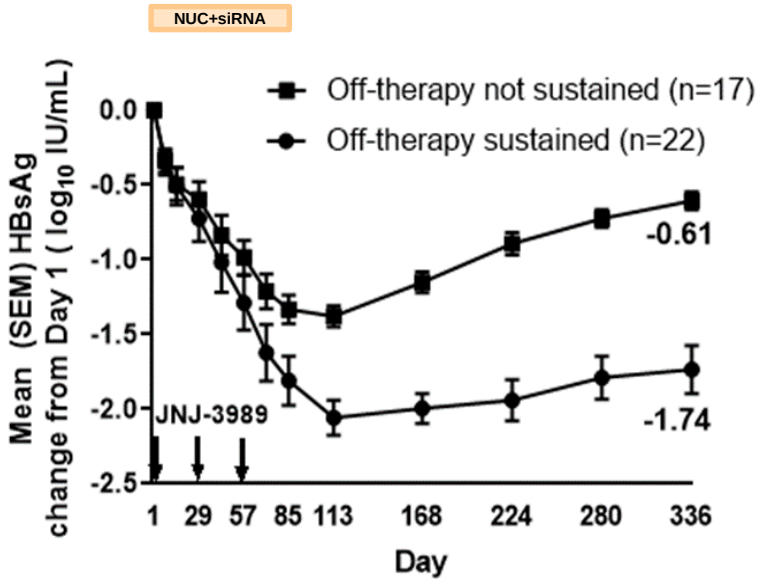
* Anti-sense Oligonucleotide (DNA) with locked nucleic acid (LNA) that resuts in RNAseH mediated degradation of HBV transcripts

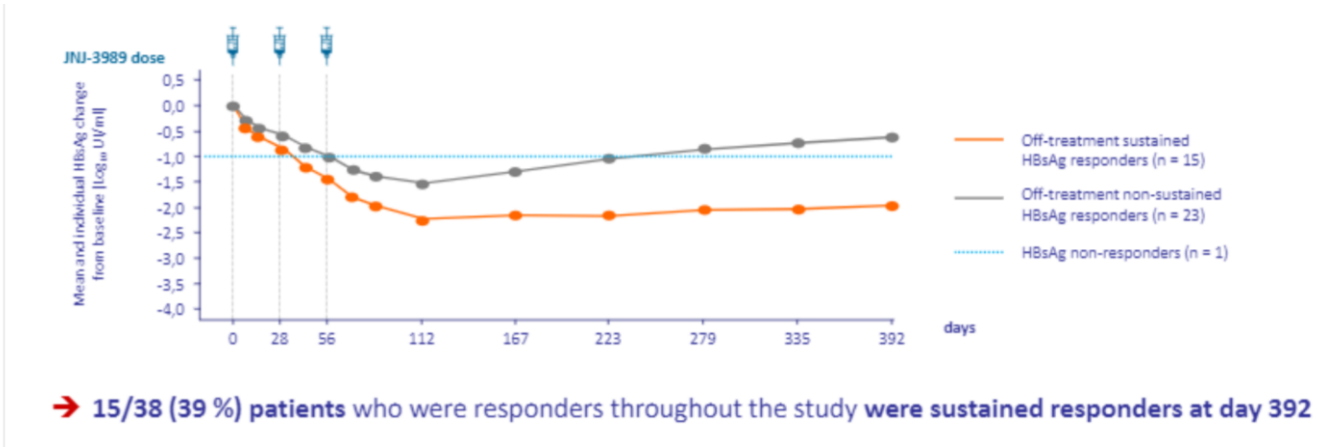
NUC + Viral transcripts inhibitors (JNJ-3989)

ARO-HBV Phase 2 study

- 40 HBeAg+ or HBeAg- patients, NUC experienced or naïve. All continued or started NUC therapy
- treated with ≥100 mg JNJ-3989 *sc* on Days 1, 27 and 57.
- 9-month follow-up data

JNJ-3989	100 mg	200 mg	300 mg	400 mg
Mean (SE) HBsAg nadir	1.72 (0.18)	1.79 (0.14)	2.04 (0.20)	1.90 (0.18)
≥1.0 log_{10} HBsAg reduction at nadir from Day 1, n (%)	**39 (98) (range 1.11–3.77)**			



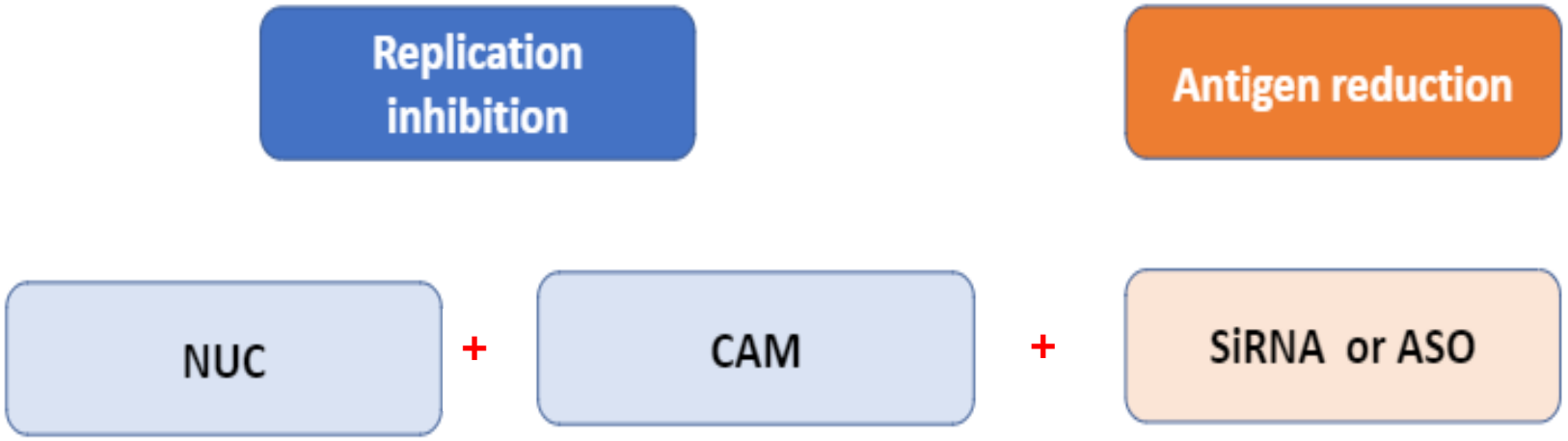


→ **15/38 (39 %) patients** who were responders throughout the study **were sustained responders at day 392**

- JNJ-3989 (100–400 mg) with NUC was **well tolerated** in patients with CHB
- A ≥1.0 log_{10} reduction in HBsAg at nadir was achieved in **98%** of patients
- A subset of patients (22/40, 56%) had **sustained HBsAg suppression** ~9 months after the last RNAi dose
  - Studies of longer term **dual therapy** (48 wks) and **triple therapy** including a CAM are underway

Gane E et al., AASLD 2019, Abs 696
Gane E et al., EASL 2020, Abs GS10

Combination of Direct Acting Antivirals
NUC + CAM + siRNA

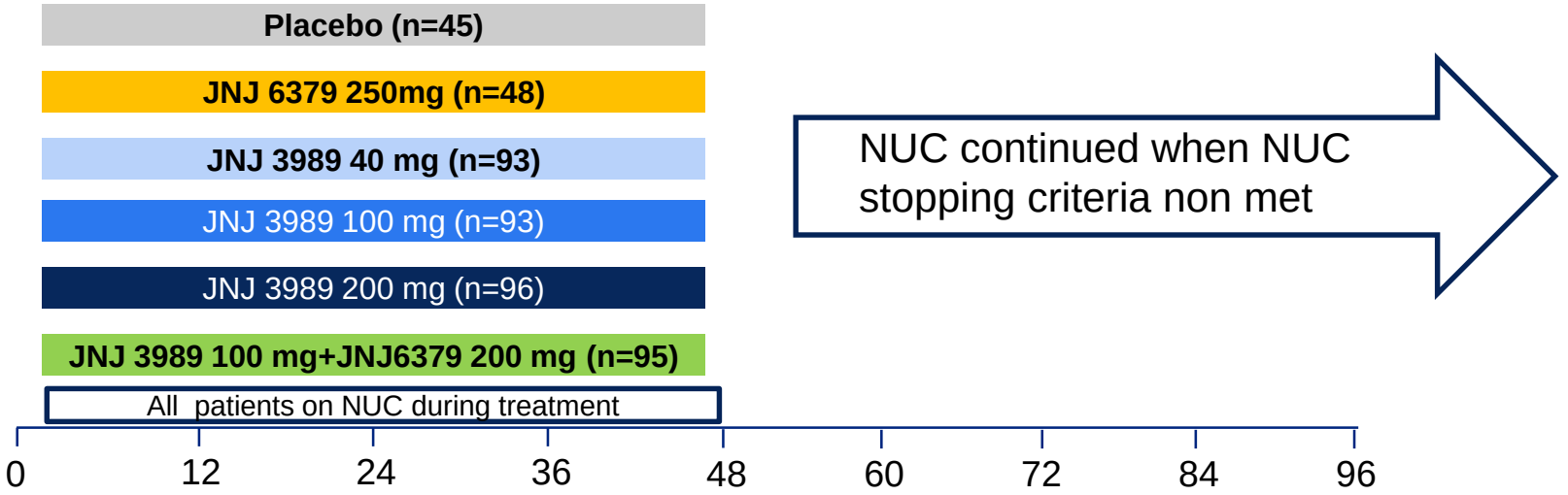


NUC + JNJ-3989 (siRNA) ± JNJ-6379 (CAM)
Phase 2b REEF-1 study

470 CHB patients randomized (2:2:2:2:1:1) to 6 arms
Monthly s.c. JNJ-3989 (40,100,200 mg) and/or 250 mg QD oral JNJ-6379 (CAM) in combination with QD oral NUC

Inclusion criteria
- Active CHB (naive or NUC suppressed)
- HBsAg > 100 IU/ml
- Non cirrhotic (Fibrosis stage F0-F2)

Stratified
- HBeAg positive or negative
- Treatment history

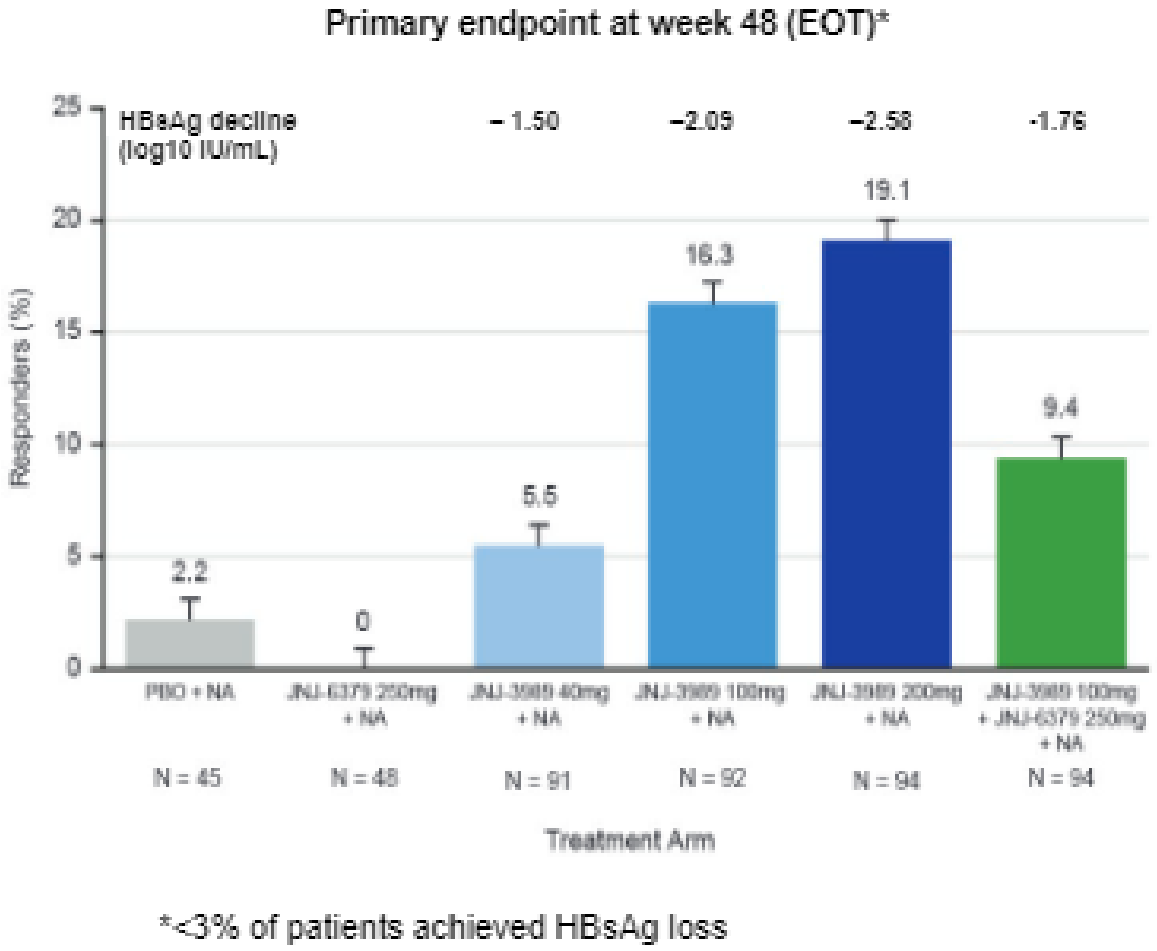


Primary end-point: proportion of patients meeting NUC stopping criteria (ALT< 3x ULN, HBV DNA< LLOQ, HBeAg negative, HBsAg <10 IU/ml at EOT

Yuen MF et al AASLD 2021, late-breaking oral presentation

NUC + JNJ-3989 (siRNA) ± JNJ-6379 (CAM)
Phase 2b REEF-1 study

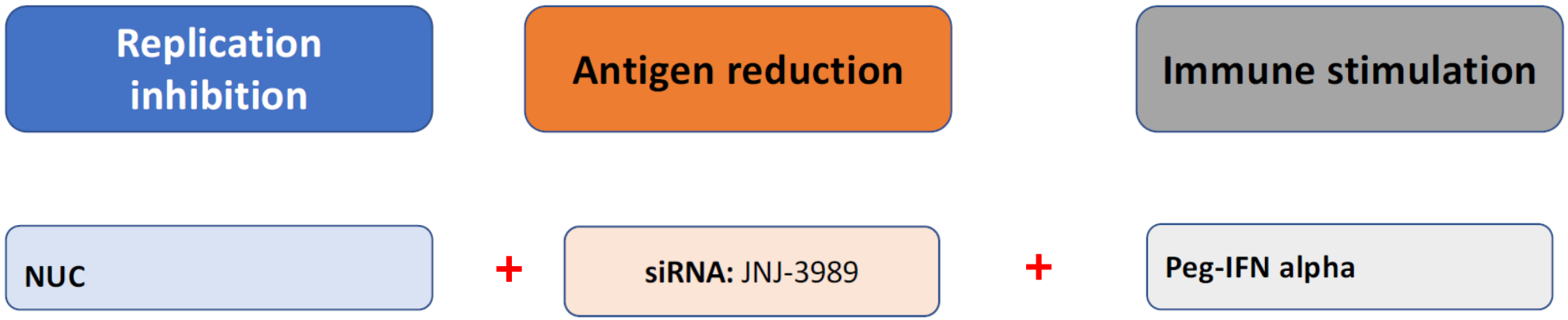
Conclusions: JNJ-3989 showed a dose dependent response with up to 19.1% meeting the primary endpoint at week 48 compared to 0% in the JNJ-6379+NA and 2.2% in the PLO+NA arm. Reduction of HBsAg levels was greatest with JNJ-3989 200 mg s.c. Q4W + NA.
All regimens were generally well tolerated and safe.



*** ALT < 3 x ULN, HBV DNA < LLOQ, HBeAg negative, and HBsAg < 10 IU/ml at EOT**

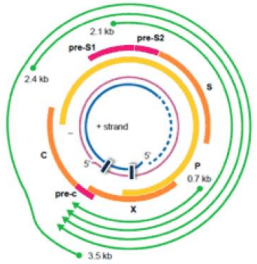
Yuen MF et al AASLD 2021, late-breaking oral presentation

Combination of Direct Acting Antivirals and Immune Modulators



NUC + VIR-2218 (siRNA) + pegIFNα2a

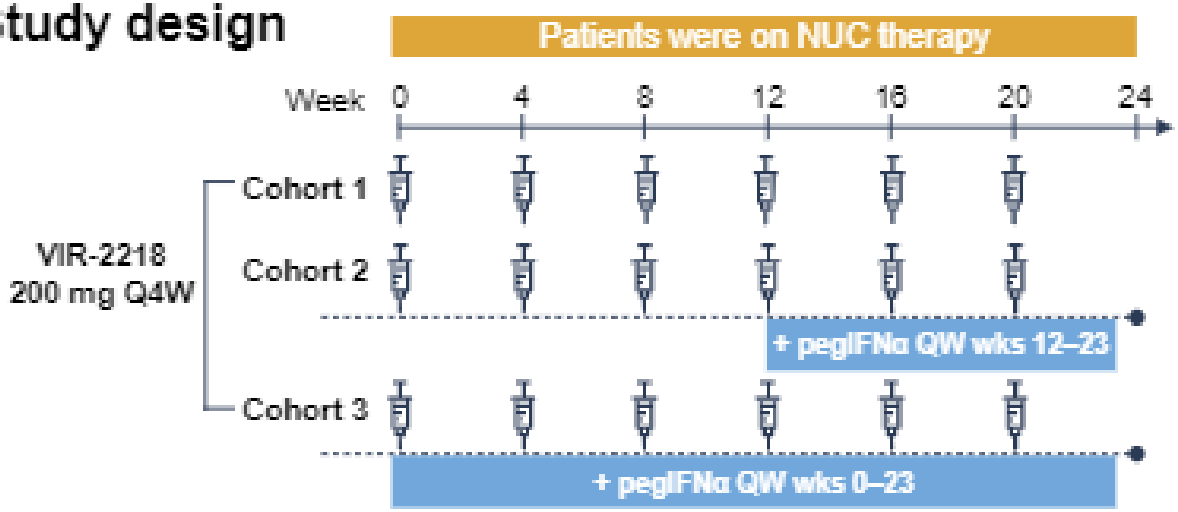
Preliminary on-treatment data from phase 2 study



VIR-2218 targets the X gene and can silence all HBV mRNAs which overlap in this region

- Phase 2 open-label study, noncirrhotic virologically suppressed CHB patients
- 48 participants have been enrolled and 22 have completed the 24-week treatment period

Study design

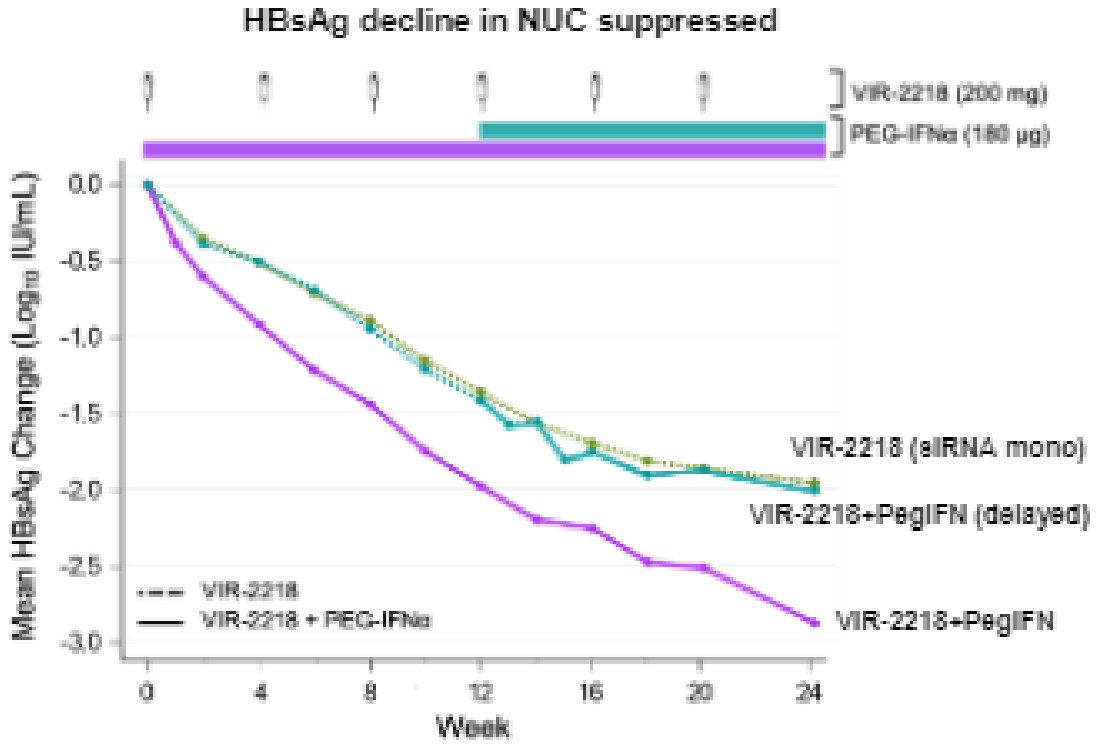


Baseline demographics	Cohort 1 (n=15)	Cohort 2 (n=15)	Cohort 3 (n=17)
HBeAg-positive, n (%)	4 (26.7)	6 (40.0)	6 (35.3)
Mean ±SD age, years	50 ±8.6	47 ±7.8	49 ±6.0
Male, n (%)	13 (86.7)	13 (86.7)	14 (82.4)
Race, n (%)			
Asian	11 (73.3)	13 (86.7)	15 (88.2)
White	0	0	1 (5.9)
Other	4 (26.7)	2 (13.3)	1 (5.9)
Mean ±SD HBsAg Log_{10} IU/mL	3.44 ±0.447	3.20 ±0.676	3.27 ±0.743
Mean ±SD ALT (U/L)	21 ±10.1	25 ±12.4	22 ±11.9
ALT >ULN	1 (6.7)	1 (6.7)	1 (5.9)

Hypothesis: Combination with pegIFN might increase HBsAg loss rates

Yuen MF et al. AASLD 2021 Abstract #26144

NUC + VIR-2218 (siRNA) +/- pegIFNα in NUC suppressed CHB patients:
Preliminary results from a phase 2 study

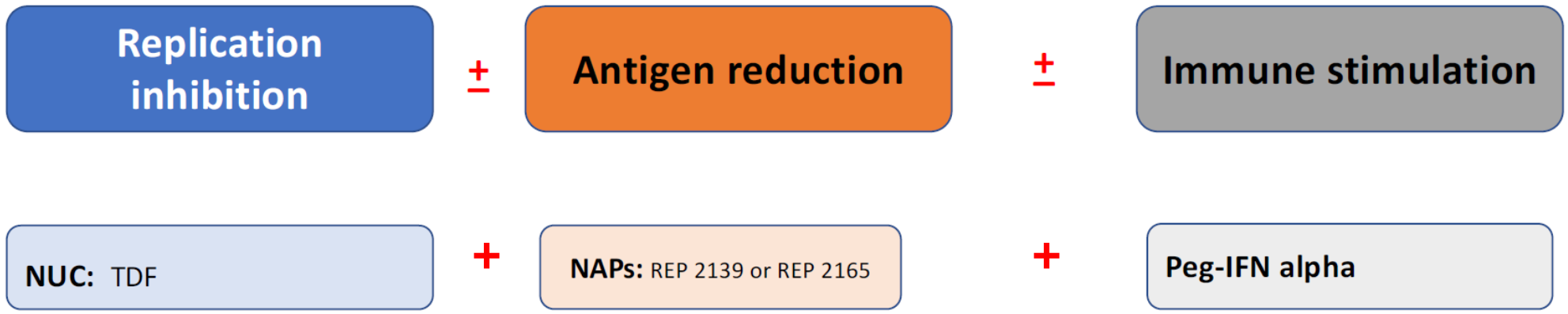


- Co-administration of VIR-2218 with pegIFNα for 24 weeks resulted in an earlier and more substantial HBsAg decline.
- **95%** (21/22) of participants receiving VIR-2218 + pegIFN concurrently for 24 weeks achieved HBsAg levels **<100 IU/ml**, with **55%** (12/22) achieving HBsAg levels **<10 IU/ml**. **Three** participants achieved **HBsAg loss** by week 24.
- Participants receiving pegIFN experienced more AEs and ALT elevations compared to treatment with VIR-2218 alone

These data support the hypothesis that the antiviral activity of VIR-2218 can be potentiated by concurrent administration of immunomodulators, such as pegIFNα.

Yuen MF et al. AASLD 2021 Abstract #26144

Combination of Direct Acting Antivirals and Immune Modulators



NAPs + TDF + PegIFNα-2a for 40 patients with HBeAg negative CHB

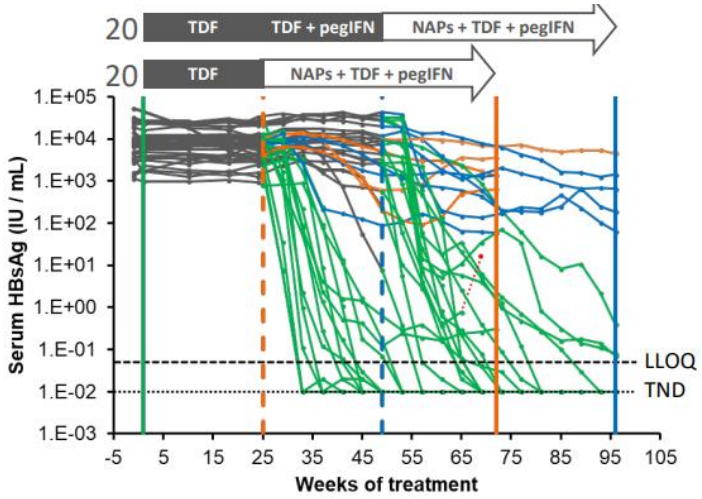
A phase II 48-week study

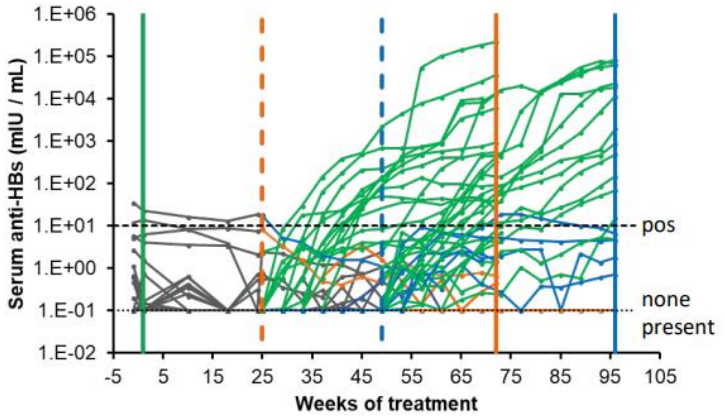
Standard of care only

HBsAg > 1 log reduction but > 1 IU/mL

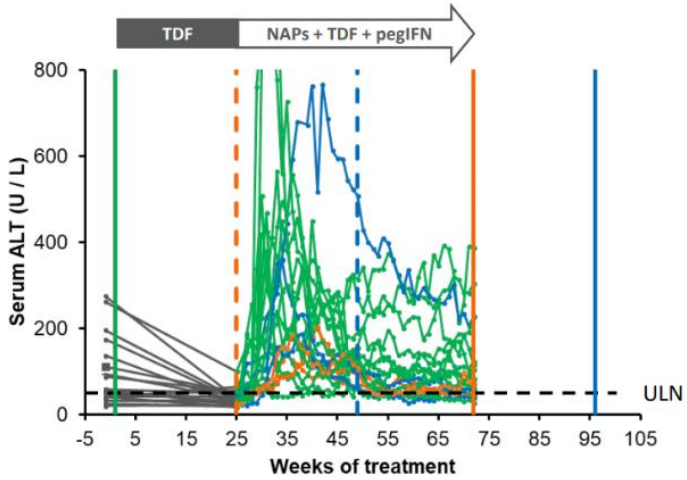
< 1 log reduction in HBsAg

HBsAg < 1 IU/mL





ALT flares



95% of pts experienced ALT flares during therapy

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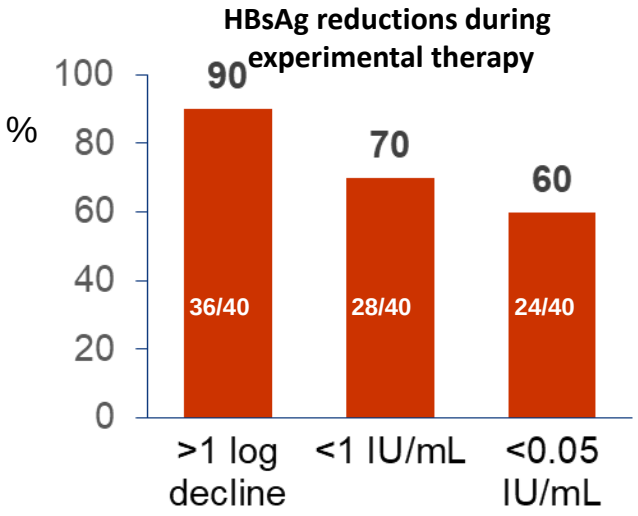
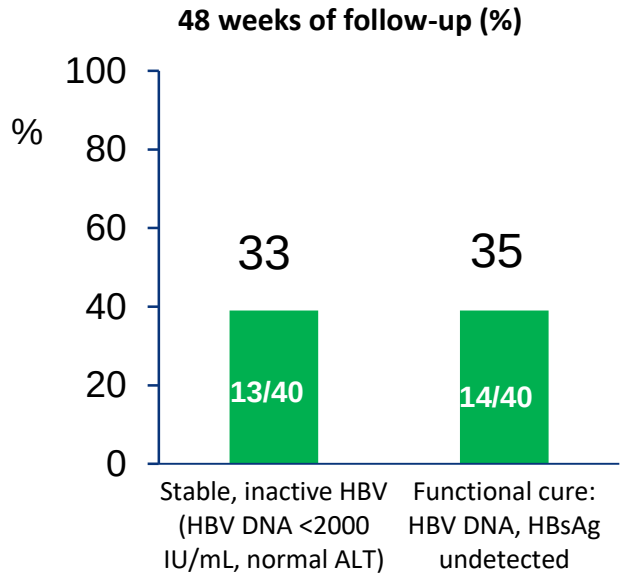
NAPs + TDF + PegIFNα-2a for patients with HBeAg negative CHB

A phase II 48-week study





Therapy	Response rates during therapy	Response rates during treatment-free follow-up
TDF pegIFN	**LOW** HBsAg loss HBsAg seroconversion	**LOW** Functional cure
TDF pegIFN **NAPs**	**HIGH** HBsAg loss HBsAg seroconversion Asymptomatic transaminase flares	**HIGH** Functional cure Normal liver function

- Marked HBsAg reduction/clearance in combination with pegIFN and TDF, with high titered anti-HBs seroconversions
- ALT flares very common: Safety in cirrhotics?
- **Clinical benefit, no therapy required: 68% of patients**

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Combination of Direct Acting Antivirals and Immune Modulators

NUC: ETV,TDF,TAF + **Immune stimulation**

Invigorate immune responses

Innate immunity

TLR7: GS9620, RO6864018, RO7020531, JNJ6479464

TLR8: GS9688

Immune check points

Anti-PD1: nivolumab

Anti-PDL1

PDL1 LNA

Oral PDL1 sm

Stimulate HBV specific B/T cells

Therapeutic Vaccines

GS4774

TG1050

T101

SCI-B-VAC

HBV: prospettive terapeutiche

Summary

- HBV functional cure: end-point of future therapies
- Many promising combination therapies are currently being evaluated in clinical trials
- New combinations involving siRNA or ASO, induce a multilog decline of HBsAg in few weeks
- The triple combination NUC-CAM-siRNA was not superior to NUC-siRNA on HBsAg decline
- Overall, HBsAg loss rates with new combination therapies are still limited