Achieving clearance of subviral particles with NAPs:

A critical milestone for HBsAg loss and functional cure

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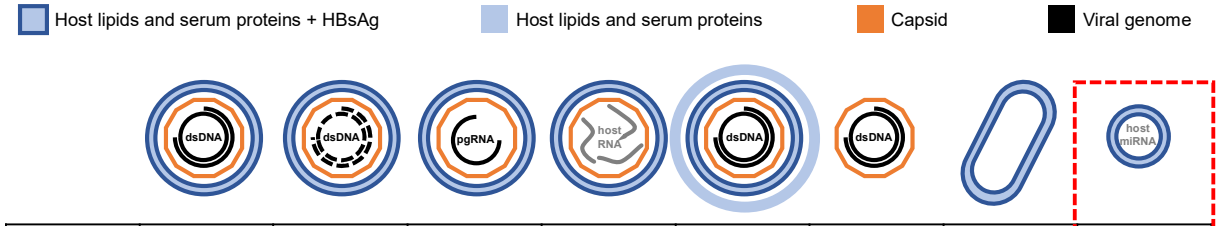
Particle production in chronic HBV infection



Particle	Dane particle	Quasispecies (mutation)	HBV RNA virion	"Empty" virions	Exosome	"Naked" capsid	SVP (filamentous)	SVP (spherical)
Ratio to Dane particle	1	0.2-0.8	0.001-1	100	unknown	unknown	10	10,000 – 100,000
Size (nM)	44				50-150	27	Ø22	22

Active cccDNA

? Integrated HBV DNA

99.99% of HBsAg is derived from subviral particles (SVP)

Vaillant, ACS Inf Dis 2021; 7: 1351-1368

Production of SVP drives chronicity of HBV infection

Immunoinhibitory properties of SVP (HBsAg)

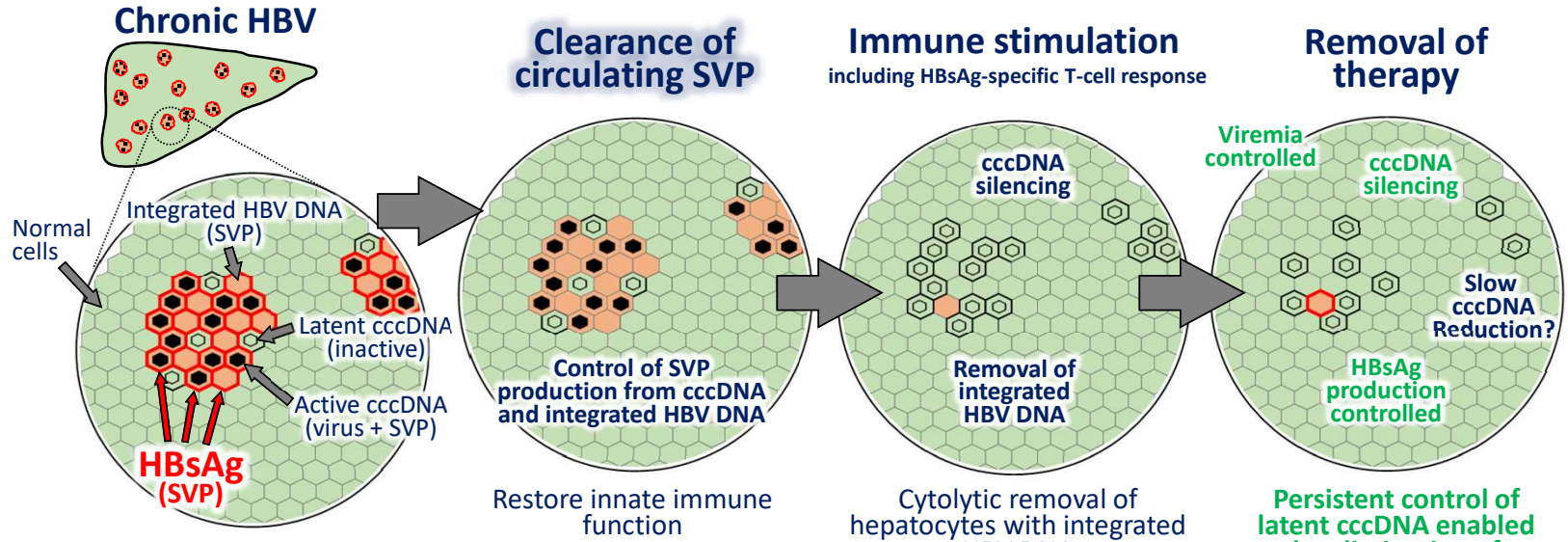
Immune function	Target of inhibition	Effect observed
Innate SVP block inactivation of cccDNA	TLR function	*In vitro, in vivo*, in humans
	Cytokine signalling	*In vitro*, in humans
	Monocyte and macrophage function	*In vitro*
	Dendritic cell function	*In vitro*
	NK cell function	*In vitro, in vivo,* in humans
	Repression of interferon response genes	In humans
Adaptive SVP inhibit clearance of integrated HBV DNA	Sequester anti-HBs	*In vitro*
	HBV specific B-cell function	In humans
	HBV specific CD4+ T-cell function	In humans
	HBV specific T-cell tolerance	*In vitro, in vivo*
	HBV specific T-cell exhaustion	*In vivo*, in humans

Vaillant, ACS Inf Dis 2021; 7: 1351-1368

SVP must be cleared from the circulation → **Allow efficient clearance of integrated HBV DNA**

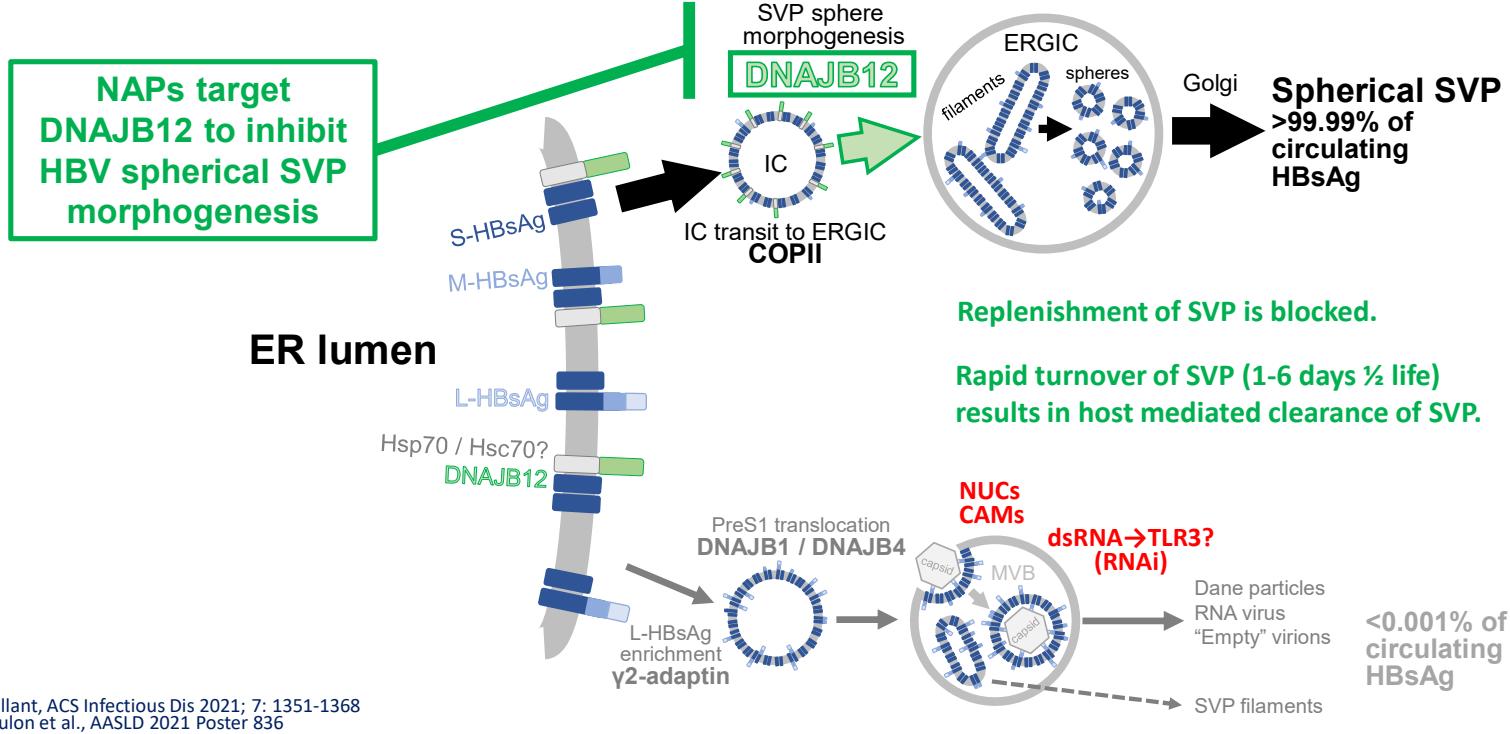
SVP must be cleared from the circulation → **Restore control over cccDNA reactivation**

The path to functional cure



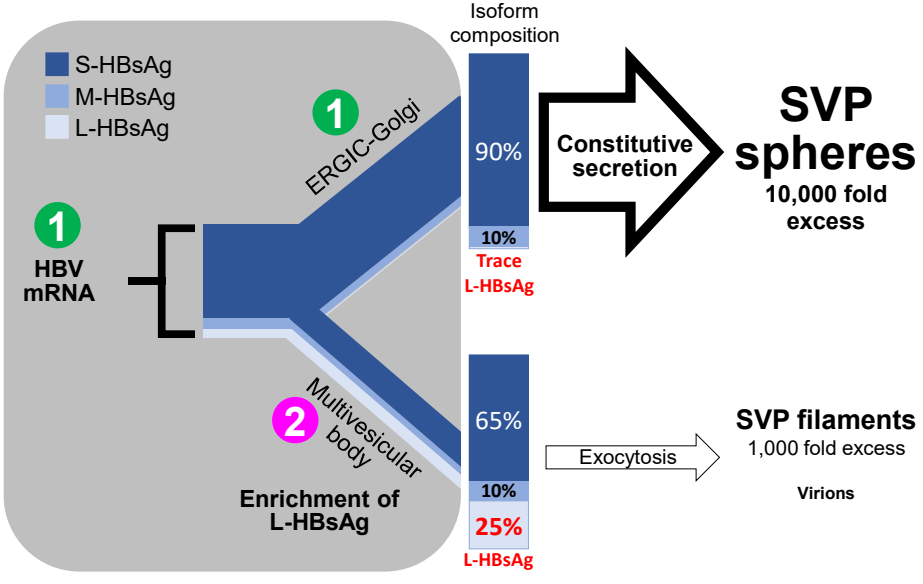
Vaillant, ACS Viruses 2021; 13: 745

Nucleic acid polymers (NAPs): a unique molecular mechanism in HBV



Vaillant, ACS Infectious Dis 2021; 7: 1351-1368
Boulon et al., AASLD 2021 Poster 836

HBsAg isoform response during therapy can identify antiviral effects



SVP turn over rapidly 99.99% of HBsAg

1 Selective decline in S-HBsAg

Signals inhibition of spherical SVP release

- HBV mRNA degradation
- Inhibition of SVP assembly

2 Selective decline in M/L-HBsAg

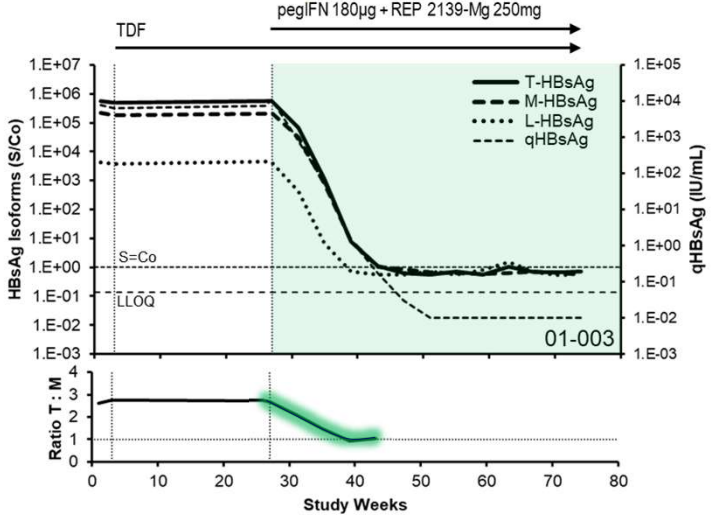
Inhibition of virion assembly?
Inhibition of exocytosis of virions / filaments?
Enhanced autophagy?

Vaillant, ACS Inf Dis 2021; 7: 1351-1368

REP 301 / 401: Validating the NAP mechanism in the clinic

Change in S-HBsAg content: change in ratio of total HBsAg (S+M+L) : preS2 (M+L) over time

HBsAg response



Strong HBsAg declines with NAPs are accompanied by selective decline of S-HBsAg

Correlation between selective S-HBsAg clearance during therapy and qHBsAg response
(all 52 participants in REP 301 + REP 401)

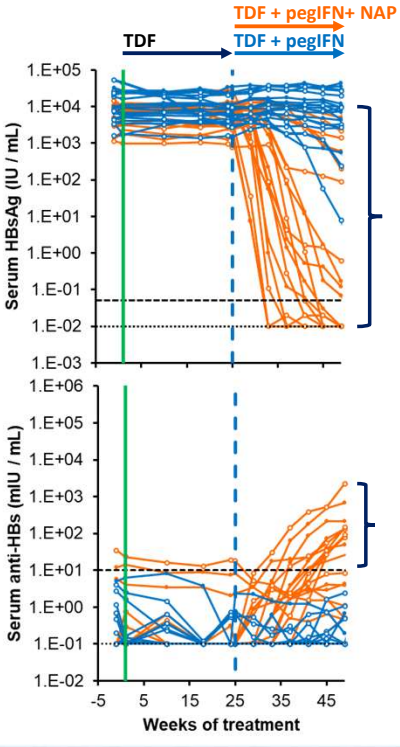
qHBsAg response during therapy (decline from baseline)	Total	Selective S-HBsAg decline	p-value
< 2 $\log_{10}$ IU/mL	10	1	< 0.01
> 2 $\log_{10}$ IU/mL	42	39	

Strong HBsAg decline with NAPs is accompanied by clearance of SVP (from cccDNA and integrated HBV DNA)

Does not occur with RNAi (AB-729)
Thi et al., J Hepatol 2021; 75: S760

Bazinet et al., Hepatology Comm 2022; April 2

REP 401 study:
NAPs dramatically improve response to TDF + pegIFN



Up to 8 log_{10} decline from baseline (to < 0.005 IU/mL)
Potent HBsAg decline

Rapid HBsAg seroconversion

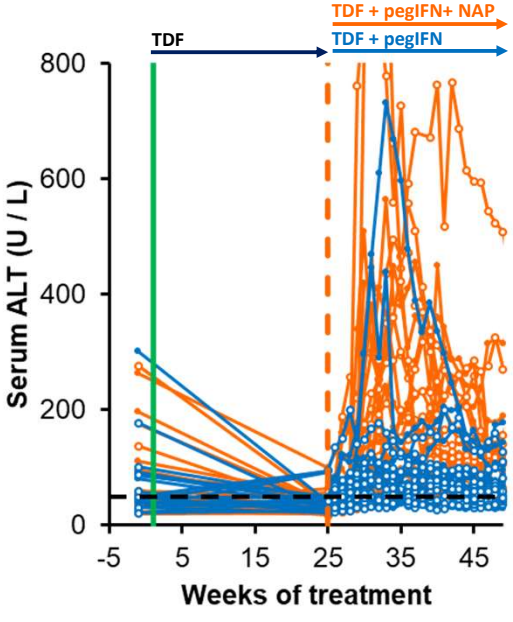
NAP monotherapy:
REP 2055 or REP 2139
Up to 7 log_{10} HBsAg reduction at 12 weeks
HBsAg seroconversion
Low rates of HBV functional cure

NAPs + TDF + pegIFN
HBsAg < 0.005 IU/mL (60%)
HBsAg seroconversion
Inactivation of cccDNA
Host mediated transaminase flares (95%)
High rates of HBV functional cure (39%)
No further therapy required in 78% of patients

GT D functional cure rate
TDF + pegIFN = 0%
(Marcellin et al, Gastroenterology 2016; 150: 134-144)
NAPs + TDF + pegIFN = 39%

Bazinet et al., Gastroenterol. 2020; 158: 2180-2194
Al-Mahtab et al., PLoS One; 2016; 11: e0156667

REP 401 study:
Host mediated transaminase flares are required for functional cure



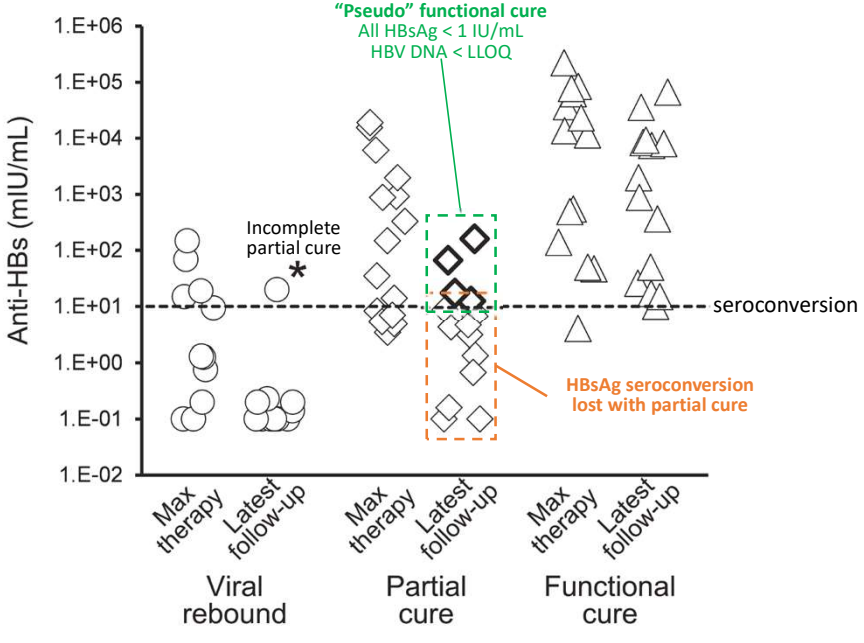
NAPs drive a dramatic increase in immunotherapy driven, host mediated transaminase flares[1]

- **occur in 95% of participants[2]**
- no alteration in liver function / asymptomatic[2]
- similar in magnitude and duration to host mediated flares observed during natural course of disease, during NUC therapy or with pegIFN monotherapy
- correlated with functional cure (when HBsAg is also < 1 IU/mL)[2]
- Signals the removal of cccDNA and integrated HBV DNA[3]

Consistent with the safe and beneficial nature of host mediated transaminase flares during therapy with approved agents, even in cirhottics[4]

1. Bazinet et al., Gastroenterol. 2020; 158: 2180-2194
2. Bazinet et al., J Viral Hep 2021; 28: 817-825
3. Bazinet et al., Hepatol Comm 2021; 28: 817-825
4. Vaillant, Viruses 2021; 131: 745

REP 401 study:
Anti-HBs response on therapy versus outcome

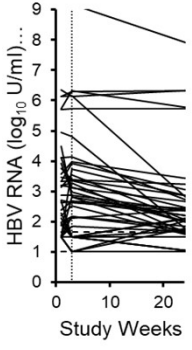


HBsAg seroconversion and anti-HBs elevation during therapy do not predict outcome

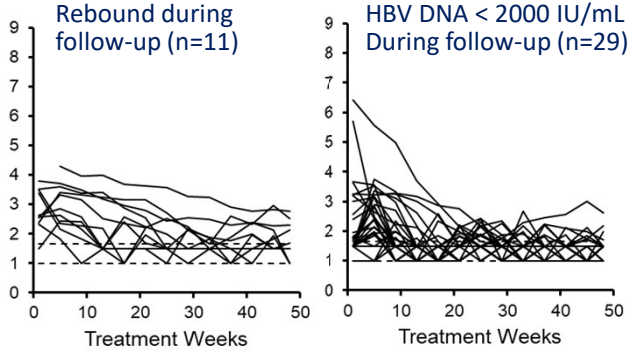
But HBsAg seroconversion persists in functional cure!

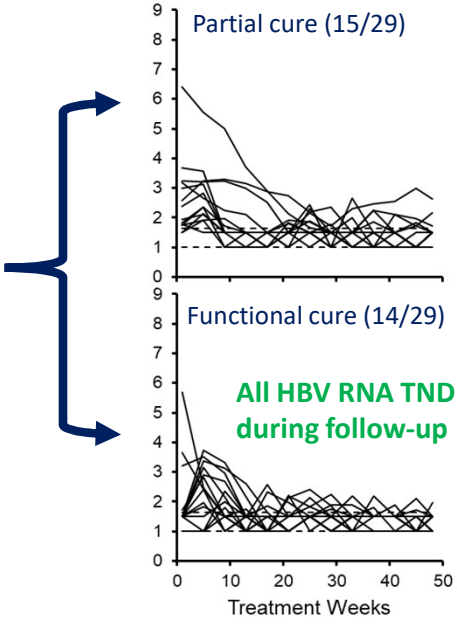
REP 401 study:
HBV RNA response on therapy versus outcome

24 weeks TDF lead-in (n=40)



48 weeks TDF + pegIFN + NAP



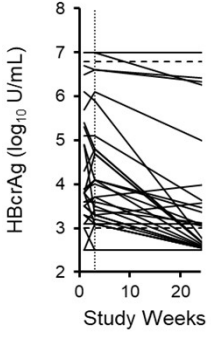


HBV RNA response does not predict clinical outcome

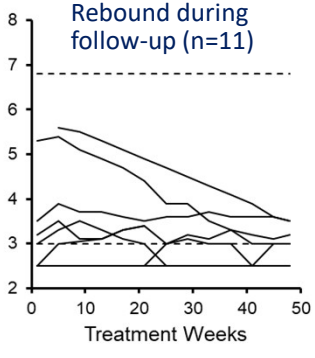
Bazinet et al., Hepatol Comm 2021, 5: 1873-1887

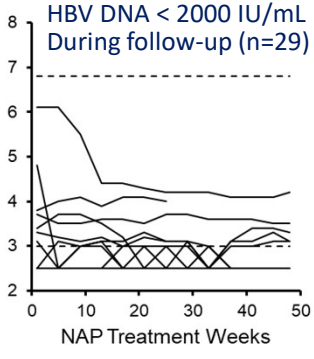
REP 401 study:
HBcrAg response on therapy versus outcome

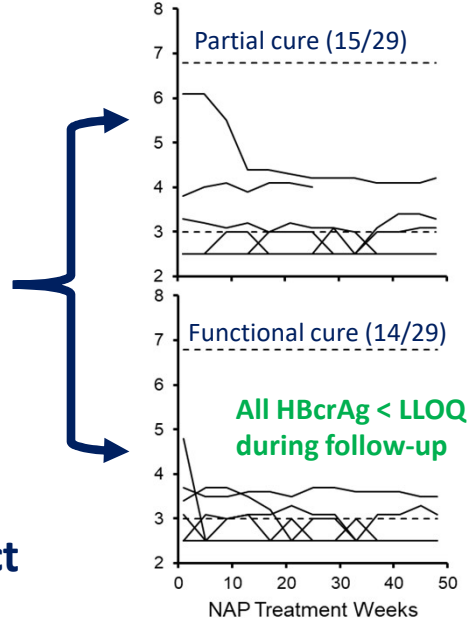
24 weeks TDF lead-in (n=40)



48 weeks TDF + pegIFN + NAP





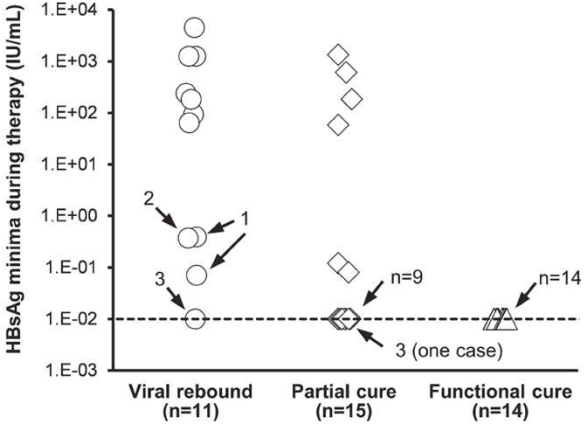


HBcrAg response does not predict clinical outcome

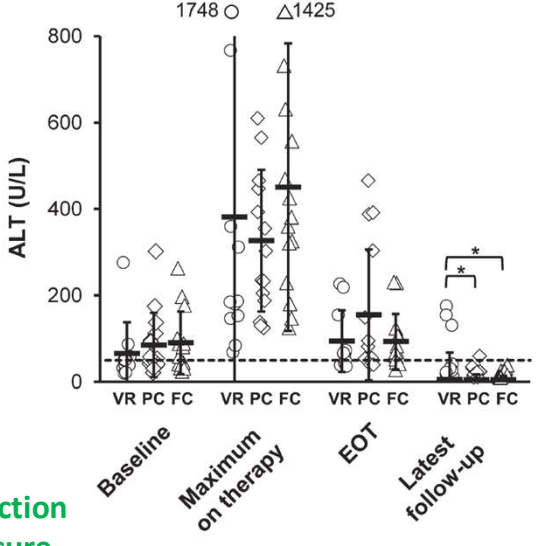
Bazinet et al., Hepatol Comm 2021, 5: 1873-1887

REP 401 study:
Extent of HBsAg clearance during transaminase flares predicts functional cure

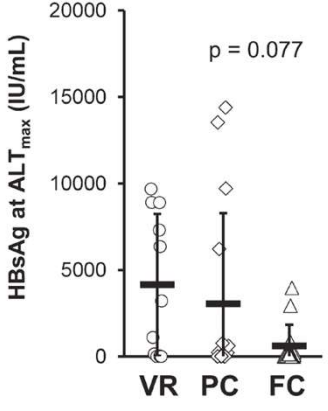
HBsAg loss is necessary but insufficient for functional cure



Transaminase flares do not predict outcome



HBsAg minima during flare predicts outcome



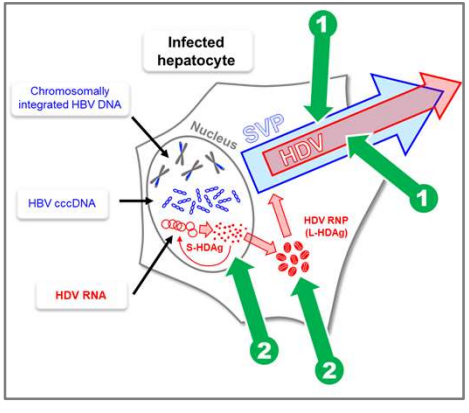
Engagement of HBsAg specific T-cell function may be essential to achieve functional cure

VR = virologic rebound
PC = partial cure
FC = functional cure

Bazinet et al., J Viral Hep 2021; 28: 817-825

Targeting HDV with nucleic acid polymers

Multiple molecular mechanisms



1 Bind HSP40 chaperone DNAJB12 (ERGIC)[1]
Inhibition of HBV SVP assembly
Inhibition of HDV RNP envelopment

2 Bind small and large isoforms of HDAg (nucleus)[2]
Inhibition of HDV RNA replication
Inhibition of HDV RNP assembly

Clinical effects during therapy[3]:

1. Clearance of HDV RNA
2. Clearance of HBsAg
3. Host (immune) mediated transaminase flares with introduction of pegIFN

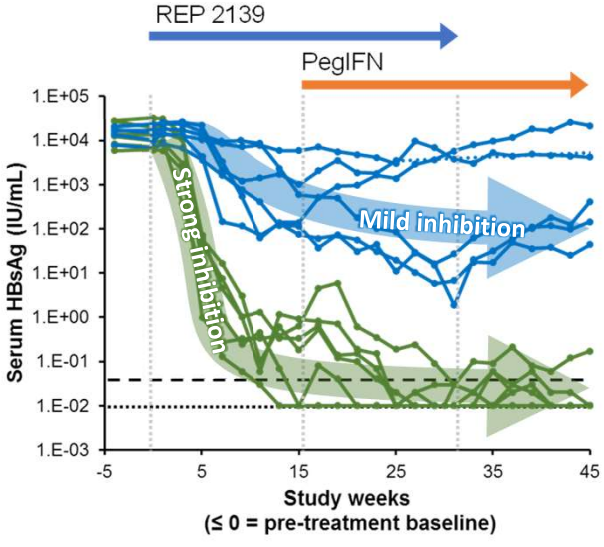
Clinical outcomes[4]:

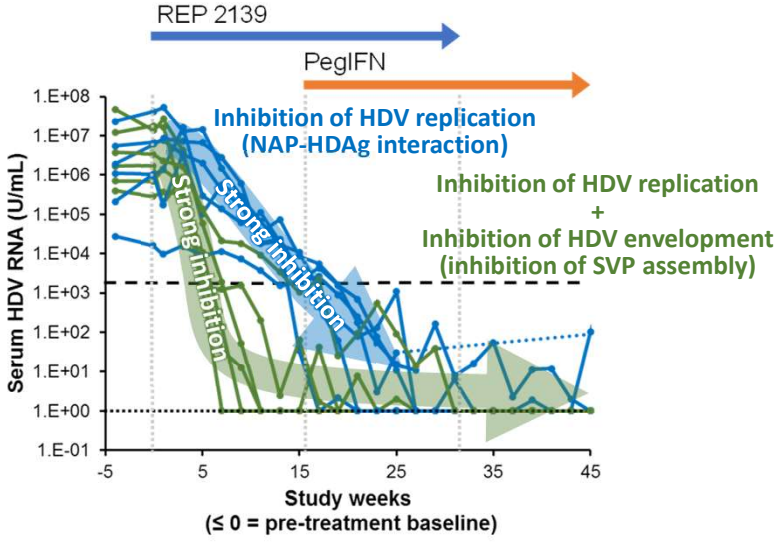
1. Normalization of liver function off therapy
2. Progressive reversal of fibrosis off therapy
3. **Functional cure of HDV: 7/11 (HDV RNA TND, normal ALT) for 3.5 years off therapy**
   ➡ **4 with functional HBV cure, 3 with partial HBV cure**

1. Boulon et al., AASLD 2020 LP-42
2. Shamur et al., Hepatology 2017; 66: 504A
3. Bazinet et al., Lancet Gastroenterol Hepatol 2017; 2: 877-889
4. Bazinet et al., Hepatol Comm. 2020; 5: 189-202

Understanding clinical responses to NAPs in HBV / HDV

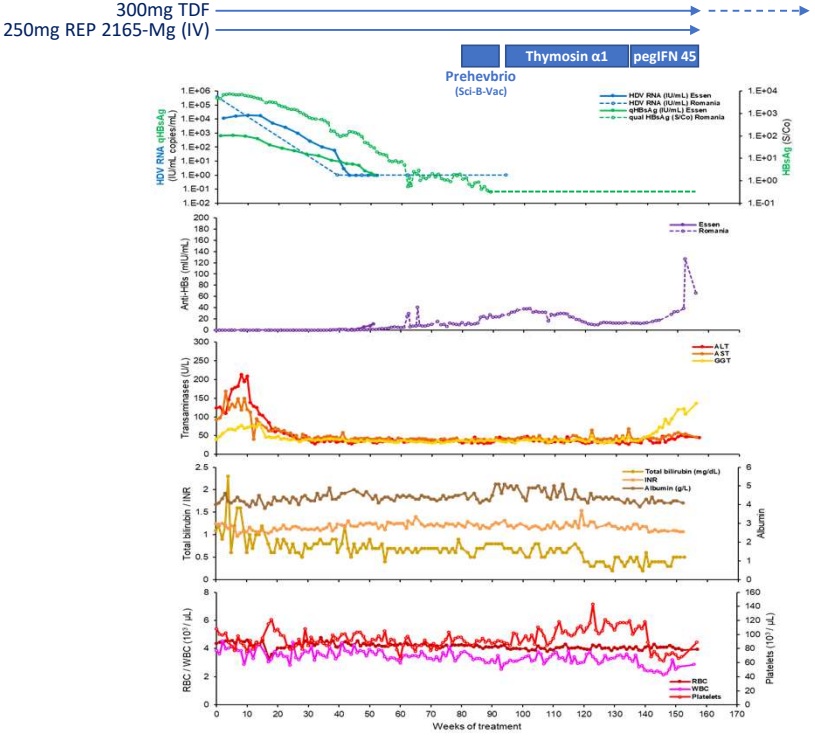
Strong HDV RNA declines with NAPs occur even when inhibition of SVP assembly is attenuated





Bazinet et al., Lancet Gastroenterol Hepatol 2017; 2: 877-889 (supplemental data)

Compassionate use of NAPs in cirrhotic HBV/HDV co-infection



Patient #1
Caucasian male, 51 years old
Chronic HBV / HDV infection
Decompensated cirrhosis (with varices)

(Adrian Streinu-Cercel, Bucharest, Romania)

Previous NUC exposure

Removal of REP 2165-Mg and pegIFN (3 months)

HDV RNA target not detected
HBsAg negative (qualitative)
Anti-HBs 24.97 mIU/mL
HBV DNA target not detected (with TDF)

ALT 31 U/L
AST 36 U/L
GGT 104 U/L
Bilirubin 13.34 µmol/L

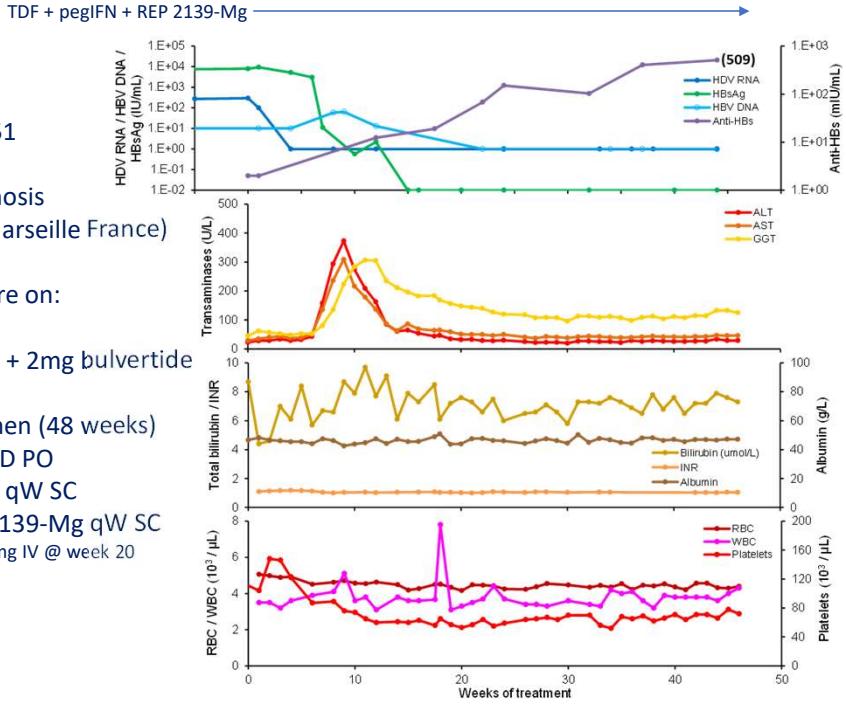
Platelets 141 x 10^3/µL (recovering)
WBC 4.31 x 10^3/µL (recovering)

Transition of REP 2139-Mg to subcutaneous administration

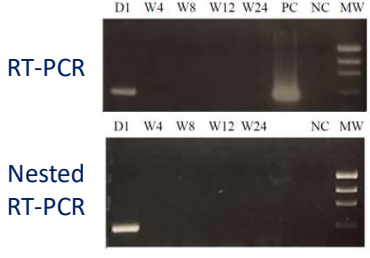
Patient #2
Senegalese male, 51
HBV / HDV (GT5)
Compensated cirrhosis
(Marc Bourlière, Marseille France)

Previous HDV failure on:
- TDF + pegIFN
- TDF + pegIFN + 2mg bulvertide

Combination regimen (48 weeks)
- 300mg TDF qD PO
- 90 µg pegIFN qW SC
- 250mg REP 2139-Mg qW SC
  transition to 125mg IV @ week 20



Pan-genotypic HDV RT-PCR
(Emmanuel-Gordien)



Removal of REP 2139-Mg and pegIFN (1 month)

HBsAg not detected (< 0.05 IU/mL)
Anti-HBs 896 mIU/mL (509 at EOT)

ALT 32, AST 49, GGT 146 U/L
T-BIL 8.2 µmol/L, ALB 48.9 g/L, INR 1.09

Platelets 117x10^3 /µL (recovering)

Other results pending…

Additional compassionate use

Patient #3
Caucasian Male, 47
Chronic HBV/HDV infection
Compensated cirrhosis (Child A5, stage 1 esophageal varices)
(Veronique Loustaud-Ratti, Limoges, France)

Previous HDV failure on:
TDF + pegIFN
TDF + pegIFN + bulvertide 2mg

Combination regimen:
300mg TDF qD PO
90 µg pegIFN qW SC
250mg REP 2139-Mg qW SC

SC administration well tolerated
8 weeks: HBsAg decline to 0.26 IU/mL (baseline 4650 IU/mL)
≤ 4 weeks: HDV RNA target not detected (baseline 5.78 $\log_{10}$ IU/mL)

Other results pending…

Patient #4
Asian Male, 54
Chronic HBV / HDV infection
Compensated cirrhosis
(Christiane Stern, Clichy, France)

Previous HDV failure on:
TDF + pegIFN
TDF + pegIFN + bulvertide 2mg
TDF + pegIFN + bulvertide 10mg

Combination regimen:
300mg TDF qD PO
90 µg pegIFN qW SC
250mg REP 2139-Mg qW SC

SC administration well tolerated

Efficacy results pending…

Summary

Subviral particles (SVP):

Key to Functional Cure

> 99.99% of circulating HBsAg
Prevent immune control and function of immunotherapy
Removal during therapy is essential for functional cure
Poorly targeted by direct acting antivirals (NUCs / CAMs / RNAi / antisense)

Integrated HBV DNA:

Bulk of SVP production in HBeAg negative infection
HBsAg specific T-cell response is required to target efficiently
Therapeutic transaminase flares signal removal of integrated HBV DNA from the liver

Key to Functional Cure

NAPs target SVP production and HDV replication

High rates of HBsAg loss and host mediated transaminase flares translate to:
High rates of functional cure of HBV (with TDF + pegIFN)
High rates of functional cure of HDV (HDV RNA TND, normal ALT with no therapy) (with pegIFN)

Successful transition of REP 2139-Mg to once weekly SC administration

SC administration appears to have improved efficacy versus IV administration
Potent activity against HBV and HDV in compensated and decompensated cirrhosis.

Expansion of compassionate use program is in progress