HBsAg Loss and Transaminase Flares: Therapeutic Implications for Functional Cure of HBV

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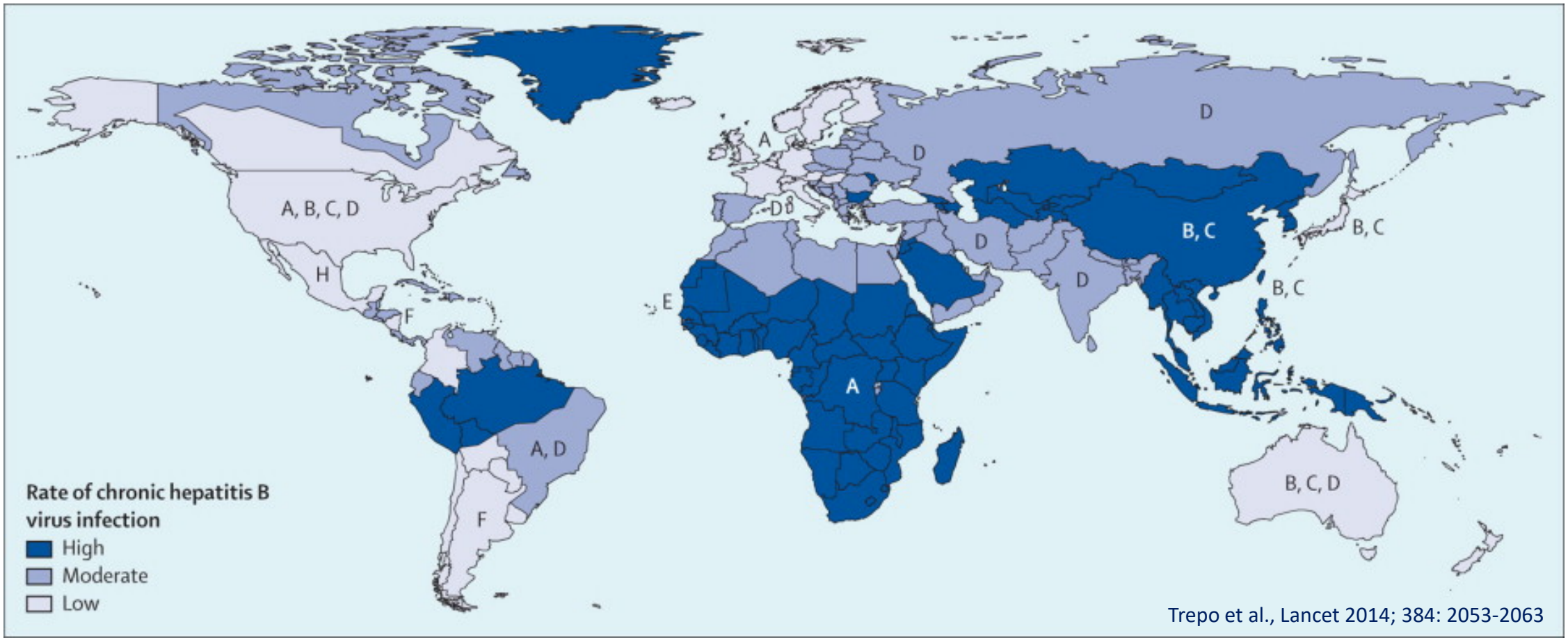
Disclosures

Employee and shareholder, Replicor Inc.

Global burden of chronic hepatitis B infection (CHB)

272 million patients have HBV worldwide - 926,000 deaths annually and increasing[1]

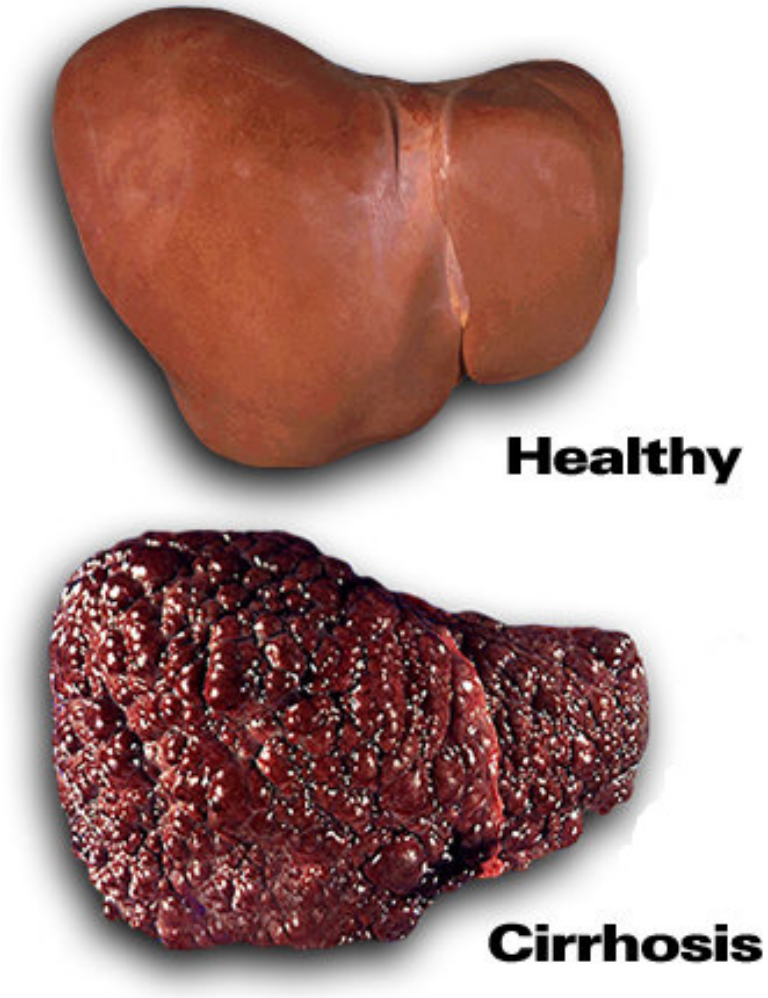


Trepo et al., Lancet 2014; 384: 2053-2063

True prevalence is higher! CHB can be asymptomatic for years…community based testing is lacking

1. Polaris observatory HepDart 2021

Why treat chronic HBV infection?



Chronic hepatitis

↓

Inflammation, altered liver function

↓

Scarring

↓

Cirrhosis

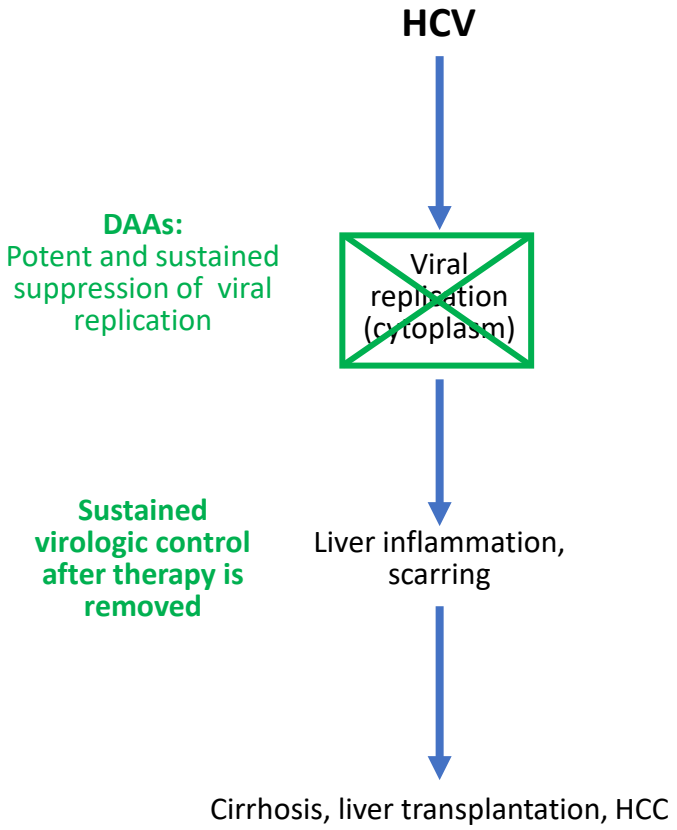
↓

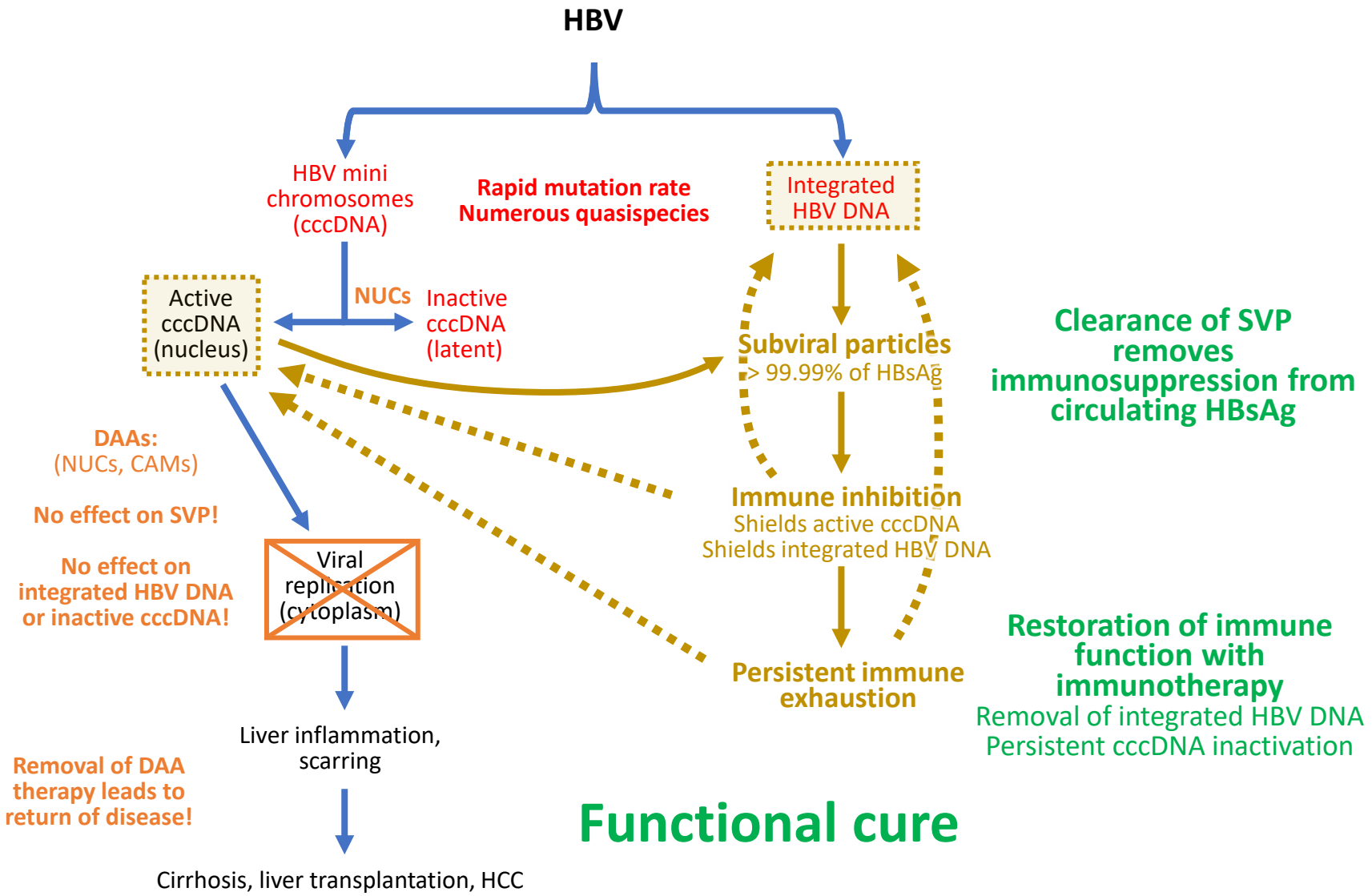
Liver decompensation or liver cancer

↓

Death

Lessons learned from HCV to not apply to HBV!





Production of SVP drives chronicity of HBV infection

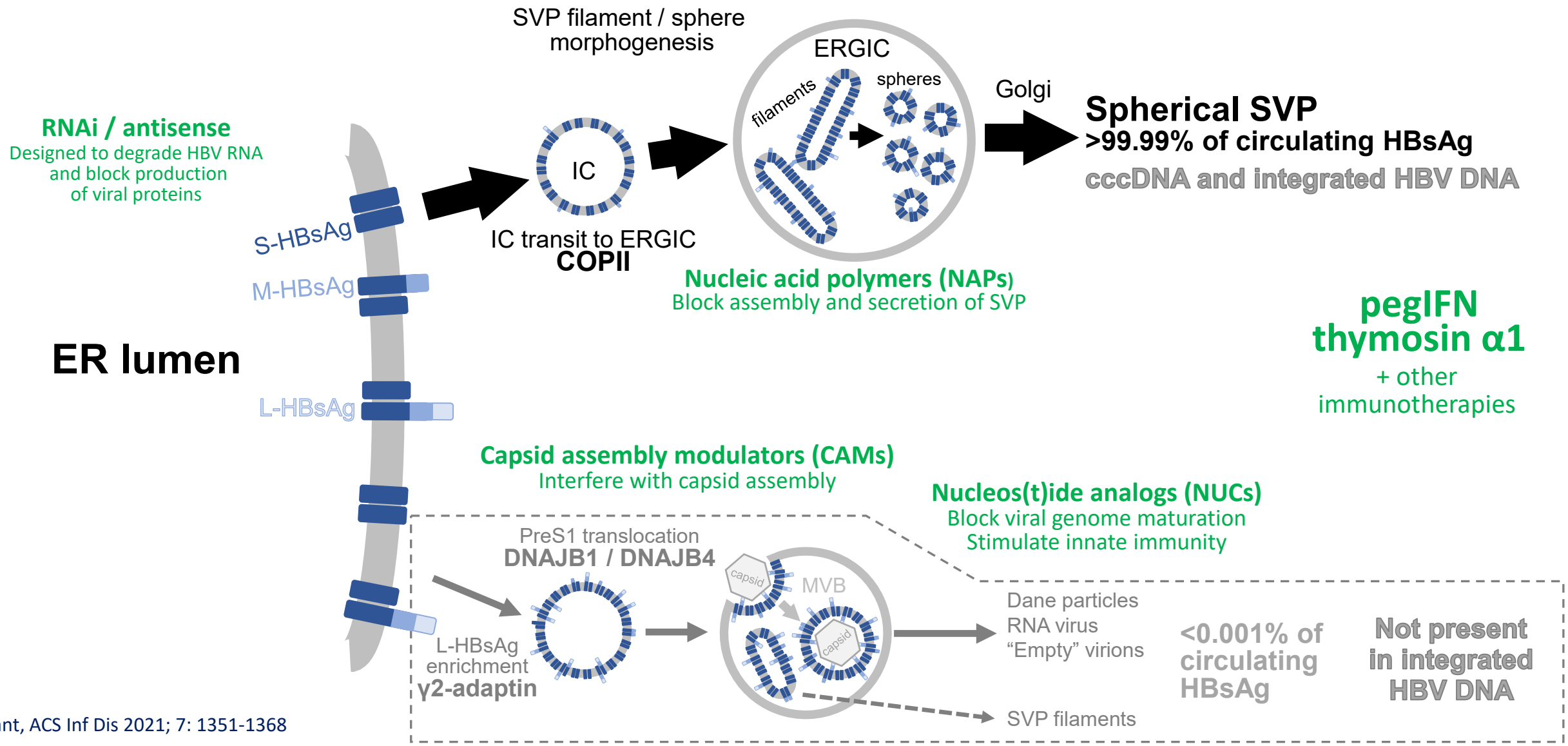
Immunoinhibitory properties of SVP (HBsAg)

Immune function	Target of inhibition	Effect observed
Innate SVP block inactivation of cccDNA	TLR function	*In vitro, in vivo*
	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
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 for therapeutic vaccination to achieve its full potential

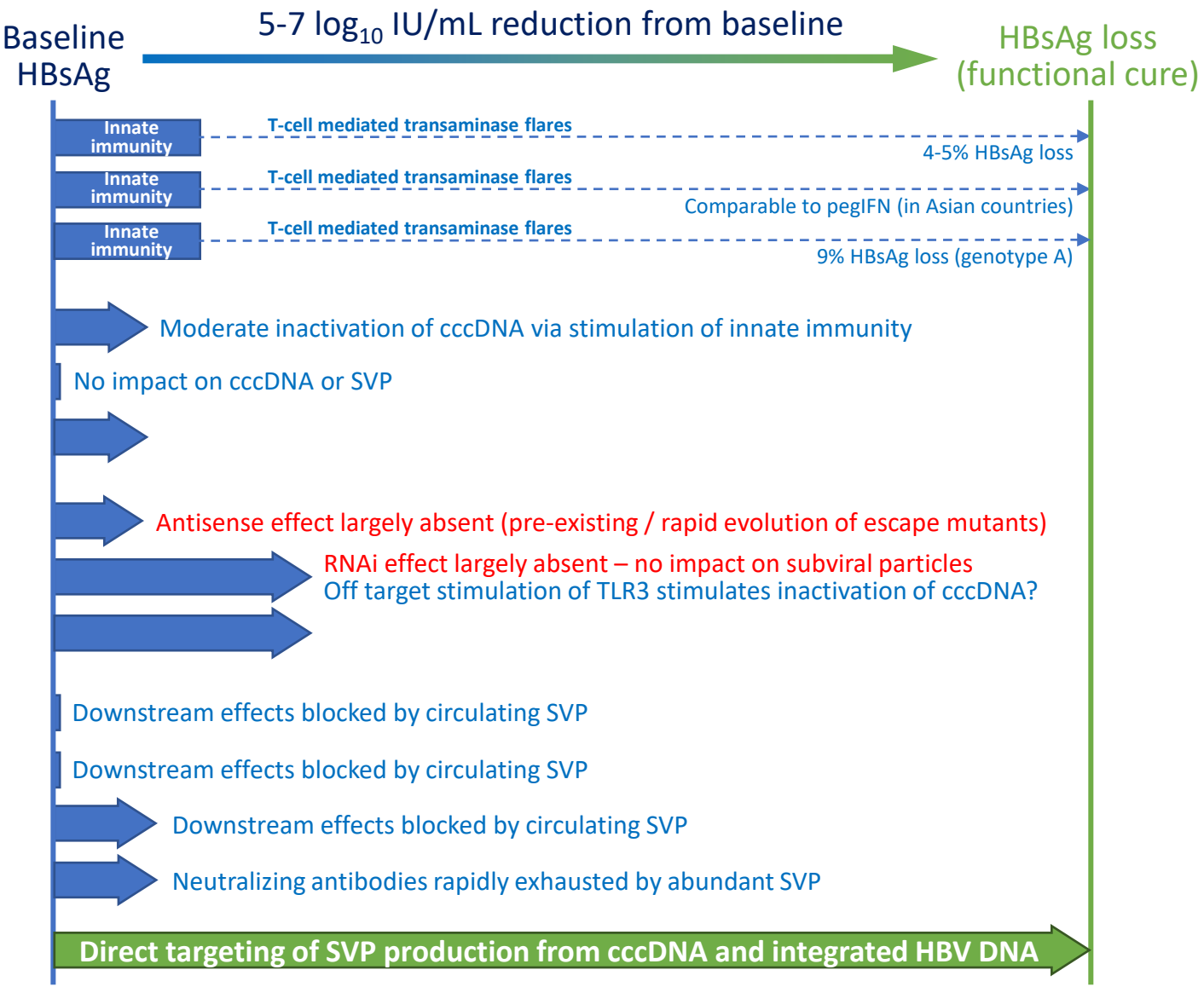
Impact of investigational approaches on SVP



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

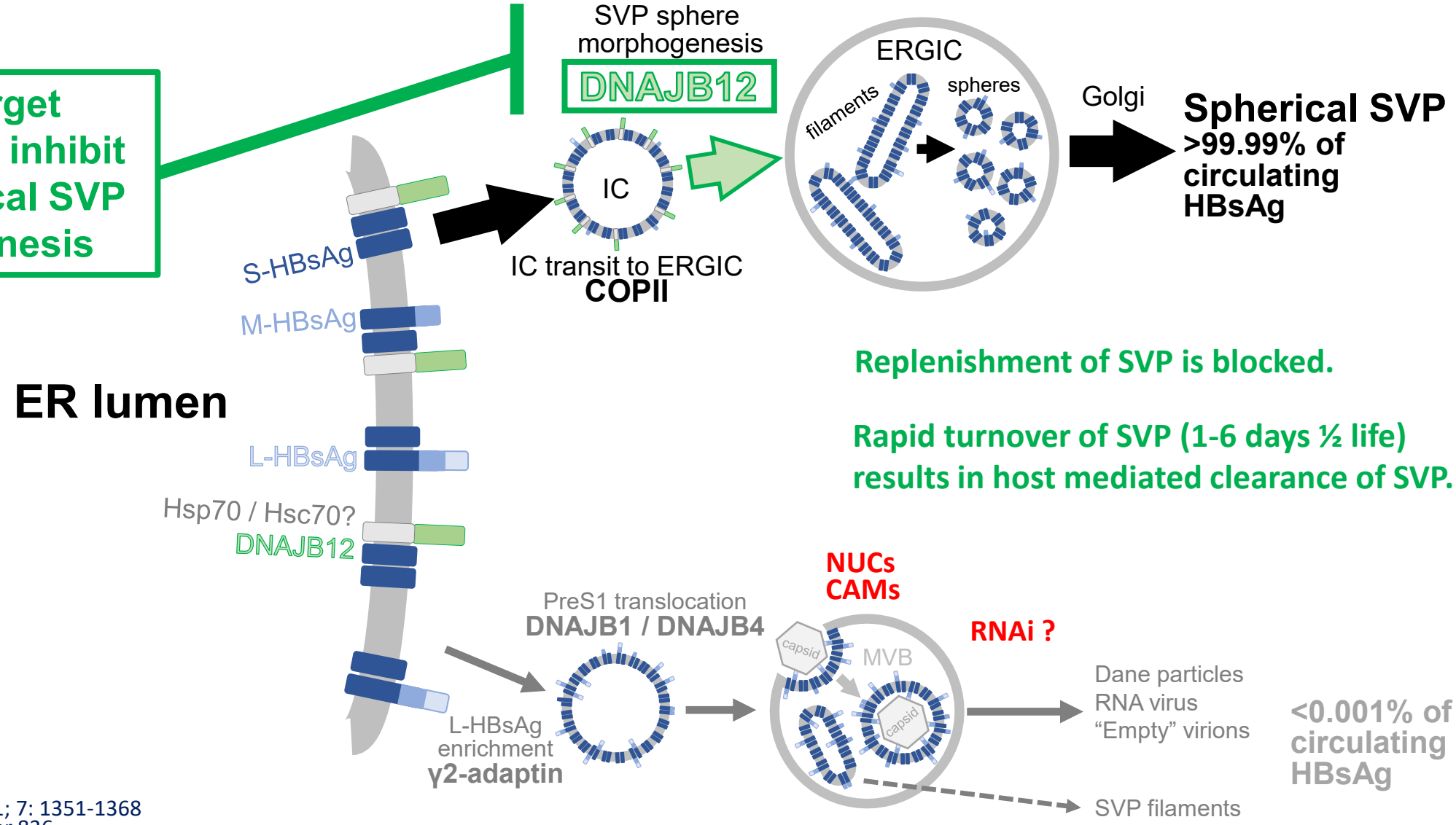
HBsAg loss – a critical milestone for functional cure of HBV

Antiviral agent	Mechanism of action
pegIFN	Stimulate innate immunity T-cell agonist
Thymosin alpha 1	T-cell agonist Stimulate innate immunity
pegIFN + NUCs	
NUCs (incl. ASPINs)	Inhibit HBV RT Stimulate innate immunity
CAMs	Misdirect capsid formation
NUCs + CAMs	
Antisense	*Degrade HBV mRNA* (TLR9 agonist – bepirovirisen)
RNAi	*Degrade HBV mRNA* TLR3 agonist (all dsRNA)
NUCs + CAMs + RNAi	
Therapeutic vaccines	Stimulate B- and T-cell immunity
TLR 7/8 agonists	Stimulate innate immunity
PD-1 antagonists	Inhibit immune checkpoint blockade
Recombinant anti-HBs	Sequester HBsAg
NAPs	Inhibit assembly / secretion of SVP



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

NAPs target DNAJB12 to inhibit HBV spherical SVP morphogenesis



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

Transaminase flares:
A key step in establishing functional cure

Transaminase flares are driven by hepatocyte death

ALT / AST: hepatocytes throughout the liver
GGT: hepatocytes lining the sinusoidal epithelium

Non-viral hepatitis (i.e. NASH): generalized loss of functional hepatocytes -> **reduced liver function (↑bilirubin, ↓albumin, ↑INR)**

Acute viral hepatitis: loss of functional hepatocytes with spread of infection -> **reduced liver function**

Chronic viral hepatitis: liver function acclimates and is maintained in steady state with chronic infection

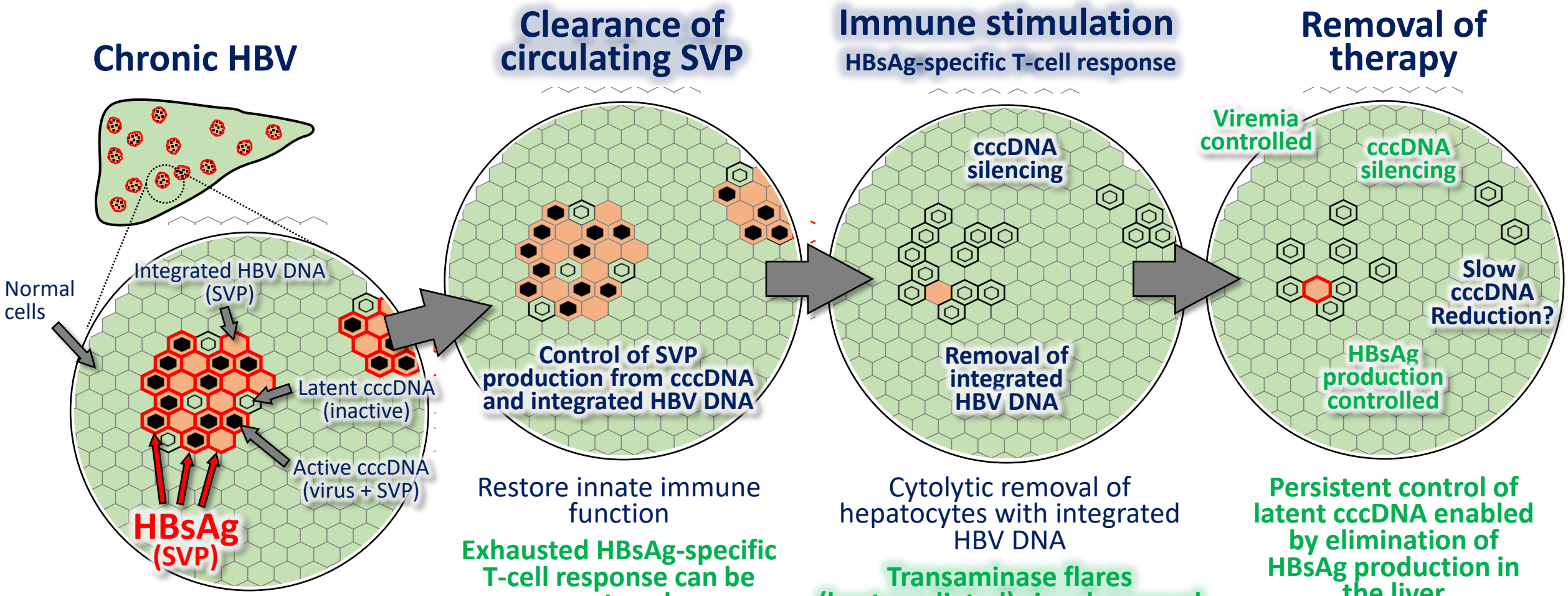
- **flares signal immune mediated clearance of infected (non-functional) hepatocytes**
- **no change in liver function**
- **when viremia is suppressed, flares are always associated with improved virologic status**

NUCs: HBeAg seroconversion, reduction of circulating HBsAg
pegIFN: SVP clearance, HBsAg seroconversion, functional cure

T-cell mediated clearance of infected hepatocytes is crucial to achieve functional cure

Vaillant, ACS Viruses 2021; 13: 745

The path to functional cure



Vaillant, ACS Viruses 2021; 13: 745

Immune restoration: essential to achieve functional cure

Integrated HBV DNA / SVP cycle prevents functional cure

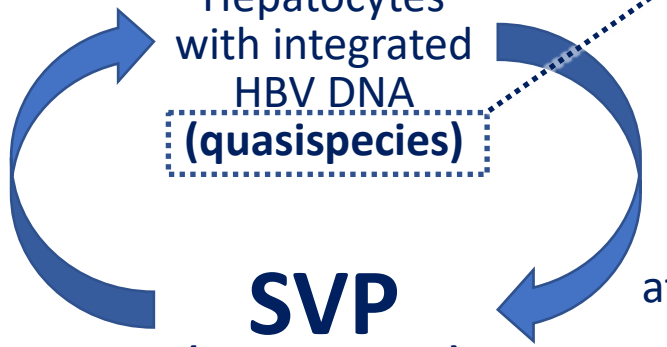
T-cell mediated clearance of integrated HBV DNA is essential

pegIFN, thymosin α1, PD-1 antagonists
endogenous polyclonal T-cell mediated cytolytic clearance
(transaminase flares)
Efficacy and tolerability issues
in monotherapy

Polyclonal T-cell response required!

HBsAg specific T-cell response required

Therapeutic vaccines??



Hepatocytes with integrated HBV DNA **(quasispecies)**

SVPs "shield" integrated HBV DNA from clearance and cccDNA from inactivation

No production of virus or antigens other than HBsAg

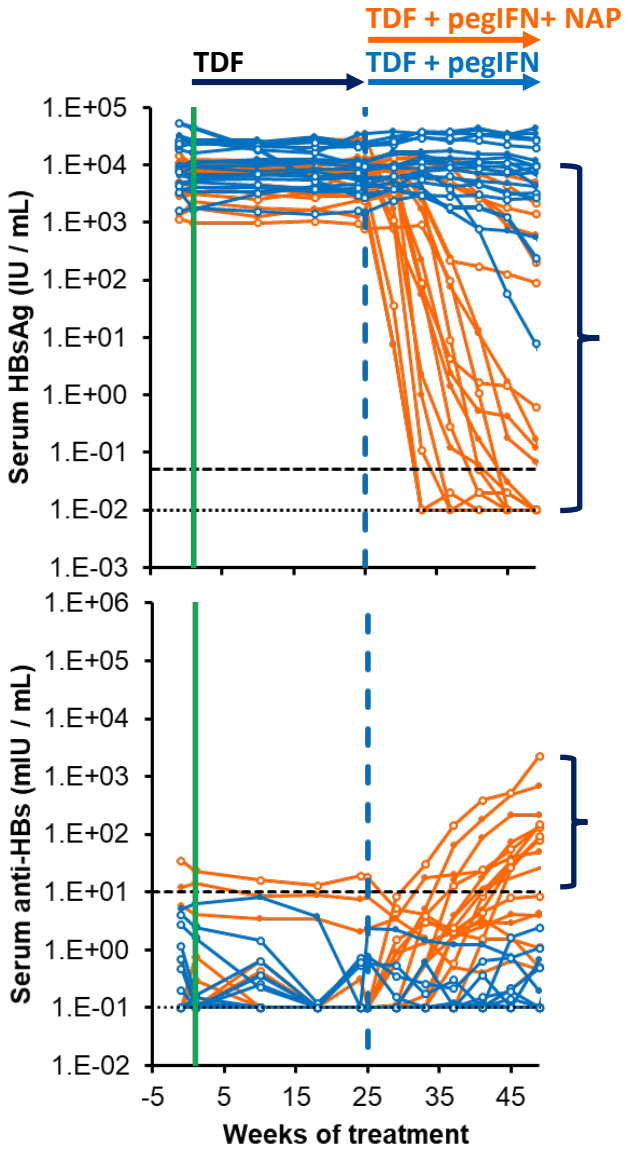
HBsAg production not affected by innate immunity

SVP
(quasispecies)

NAPs (REP 2139-Mg)
clearance of SVP
No immunostimulatory properties

TLR7 (vesatolimod/JNJ-4964/RG7854)
TLR8 (selgantolimod)
TLR9 (bepirovirisen)
TLR3 (all RNAi)
No impact on SVP production

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

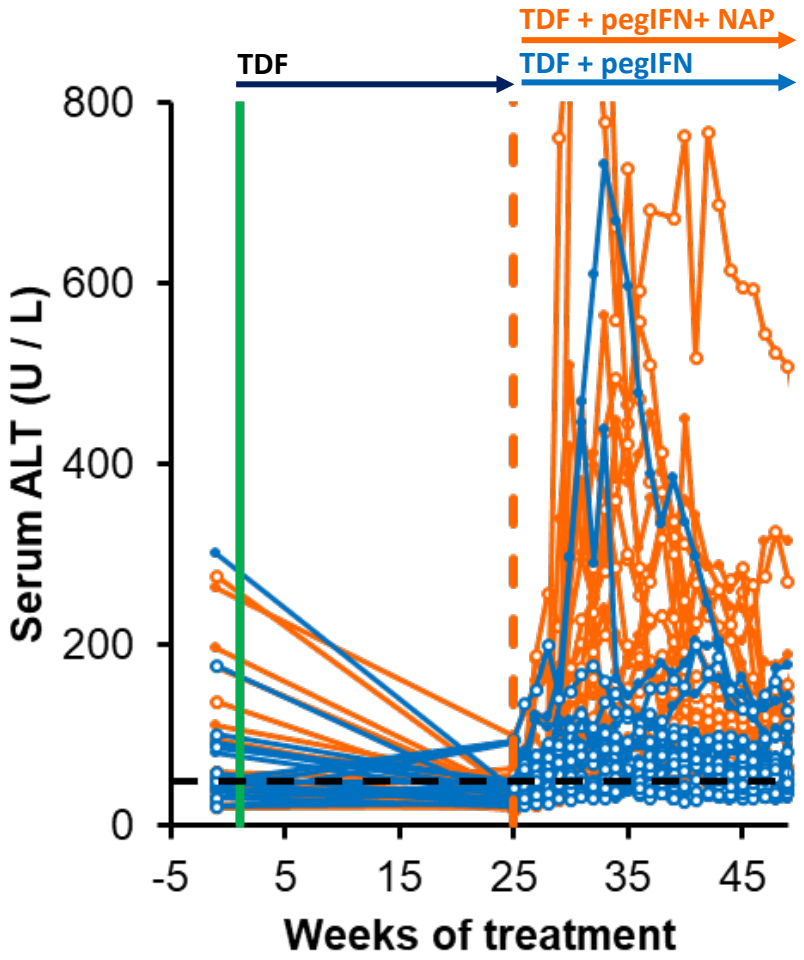
NAP monotherapy:
REP 2055 = REP 2139
Up to 7 $\log_{10}$ HBsAg reduction at 12 weeks
HBsAg seroconversion
Low rates of HBV functional cure

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:
NAPs dramatically improve response to TDF + pegIFN



Dramatic increase in host mediated transaminase flares[1]

- occur in 95% of participants[2]
- no alteration in liver function / asymptomatic[2]
- 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:
Outcomes after removal of all therapy

Completed treatment and 24-48 weeks of follow-up		36
Clinical response	Normal ALT	89%
	Normal liver median stiffness	56%
HBsAg response	< 1000 IU/mL	72%
	< 1 IU/ml	50%
	≤ LLOQ (0.05 IU/mL)	42%
	Seroconversion	53%
HBV DNA response	≤ 2000 IU/mL	78%
	Target not detected (TND)	47%
Virologic response	Partial cure (Inactive HBV) (HBV DNA ≤ 2000 IU/mL, normal ALT)	39%
	Functional cure (HBsAg < LLOQ, HBV DNA TND, normal ALT)	39%
	Clinical benefit, no therapy required (low risk of progression, reduced risk of HCC)	**78%**

→ **Reversal of liver inflammation / fibrosis**

All with:
- **HBsAg < 0.005 IU/mL (ARCHITECT® NEXT)**
- **No HBsAg immunocomplexes**
- **HBV RNA target not detected**
- **HBcrAg < LLOQ**

Efficient silencing of cccDNA

Removal of integrated HBV DNA

Bazinet et al., Gastroenterol. 2020; 158: 2180-2194
Bazinet et al., Hepatol Comm 2021, 5: 1873-1887

The Ideal Therapeutic Vaccine for Chronic HBV

Selection of antigen

- HBcAg, HBeAg, HBx, pol are not productive (only target cells with active cccDNA)
- HBsAg drives recognition of hepatocytes harbouring active cccDNA or integrated HBV DNA

Emulation of HBsAg presentation in SVP to optimize antigenic response

- Include all three HBsAg isoforms (small, medium and large)
- HBsAg co-presentation with lipids and other mammalian factors (i.e. HDL)

Include multiple HBsAg subtypes

- Stimulate a broad polyclonal response
- Numerous HBsAg quasispecies are present in cccDNA and integrated HBV DNA

Adjuvanted to stimulate CD4+ / CD8+ T-cell response

- Encourage cytolytic clearance of integrated HBV DNA

VBI-2601 / BRII-179: an advanced therapeutic vaccine

Based on Sci-B-Vac™ (Prehebviro™) developed by Dr. Daniel Shouval

J Viral Hepat 1996; 3:37-42

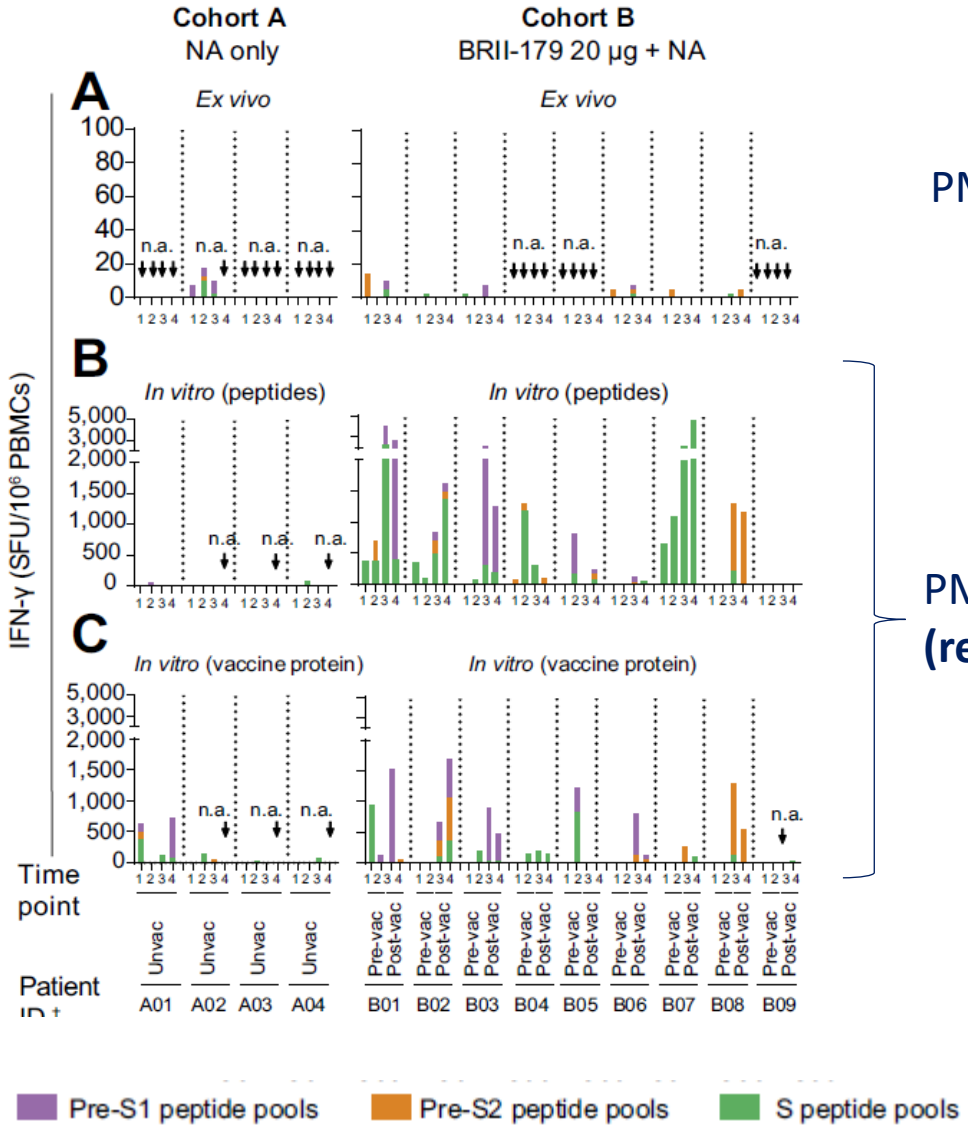
Expression of small, medium and large isoforms of HBsAg in CHO cells to produce SVP closely mimicing human SVP

Checklist for other therapeutic vaccines	**GS-4774**	**VVX001**	**VTP-300**	**JNJ 64300535**	**HepTCell**
Selection of antigen (HBsAg)	**YES**	**YES**	**YES**	**NO**	**?**
Presentation of antigen (SVP)	**NO**	**NO**	**YES**	**NO**	**NO**
Multiple HBsAg subtypes	**NO**	**NO**	**NO**	**NO**	**?**
Adjuvanted for T-cell stimulation	**YES**	**YES**	**YES**	**YES**	**YES**

VBI-2601 checklist for therapeutic vaccine:

Selection of antigen (HBsAg)	**YES**
Presentation of antigen (SVP)	**YES**
Multiple HBsAg subtypes	**NO = but lets see what happens in chronic HBV**
Adjuvanted for T-cell stimulation	**YES**

VBI-2601 (BRII-179): HBsAg specific T-cell response

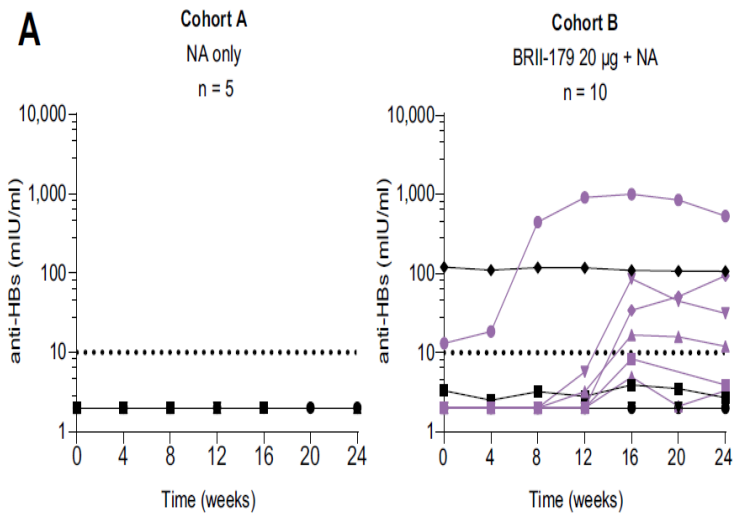


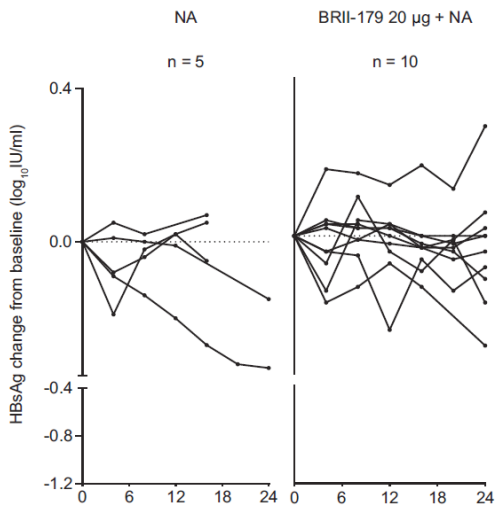
PMBC bathed in endogenous SVP

PMBC cultured *in vitro* for 9-10 days
(recovery from SVP immunosuppression)

Ma et al., JHEP Reports 2021; 3: 100361

VBI-2601 (BRII-179): Virologic response





Substantial HBsAg seroconversion

No significant impact on HBsAg (SVP)
Single HBsAg subtype?

No transaminase flares

Could synergistic effects be observed if SVP were cleared?

Ma et al., JHEP Reports 2021; 3: 100361

Summary

Chronic HBV infection (HBsAg) creates immunological impairment

Targeting of HBV subviral particles (SVP) is essential for effective HBsAg clearance

- Required to restore immune function
- Not targeted by NUCs, CAMs, RNAi or antisense
- Efficiently targeted by NAPs

Immunotherapy is required to restore control of HBV infection (functional cure)

- **But can only occur with SVP clearance!**
- TLR agonism not productive (does not affect HBsAg production from integrated HBV DNA)
- Restoration of HBsAg specific T-cell function is critical (ensures clearance of integrated HBV DNA)
- Effectiveness of existing approaches (pegIFN / thymosin α1) is driven by T-cell agonism
- Therapeutic vaccines must focus on stimulating HBsAg specific T-cell function
  - Will a single HBsAg species be sufficient? (numerous HBsAg quasispecies are present)
  - Critical readout for activity will be transaminase flares, not anti-HBs production (indicate T-cell mediated clearance of infection in the liver)