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

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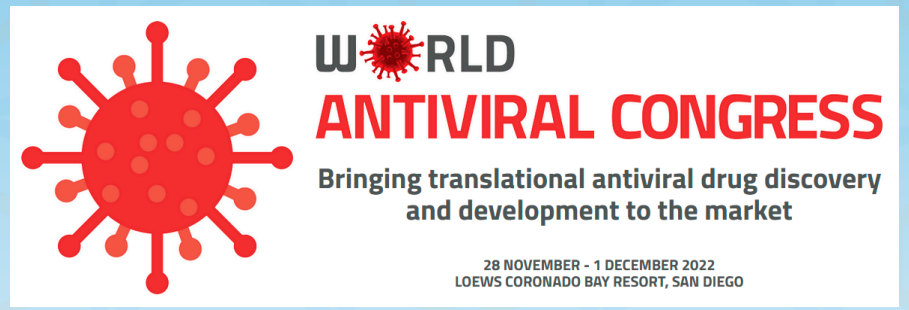
**Replicor Inc.**



# Disclosures

**Employee and shareholder, Replicor Inc.**

# Challenges in achieving functional cure of HBV

**Direct acting antivirals for HBV seems like the logical approach, but it doesn't work, many have tried.**

**Control of HCV infection with finite therapy is easily achieved with directing antivirals**

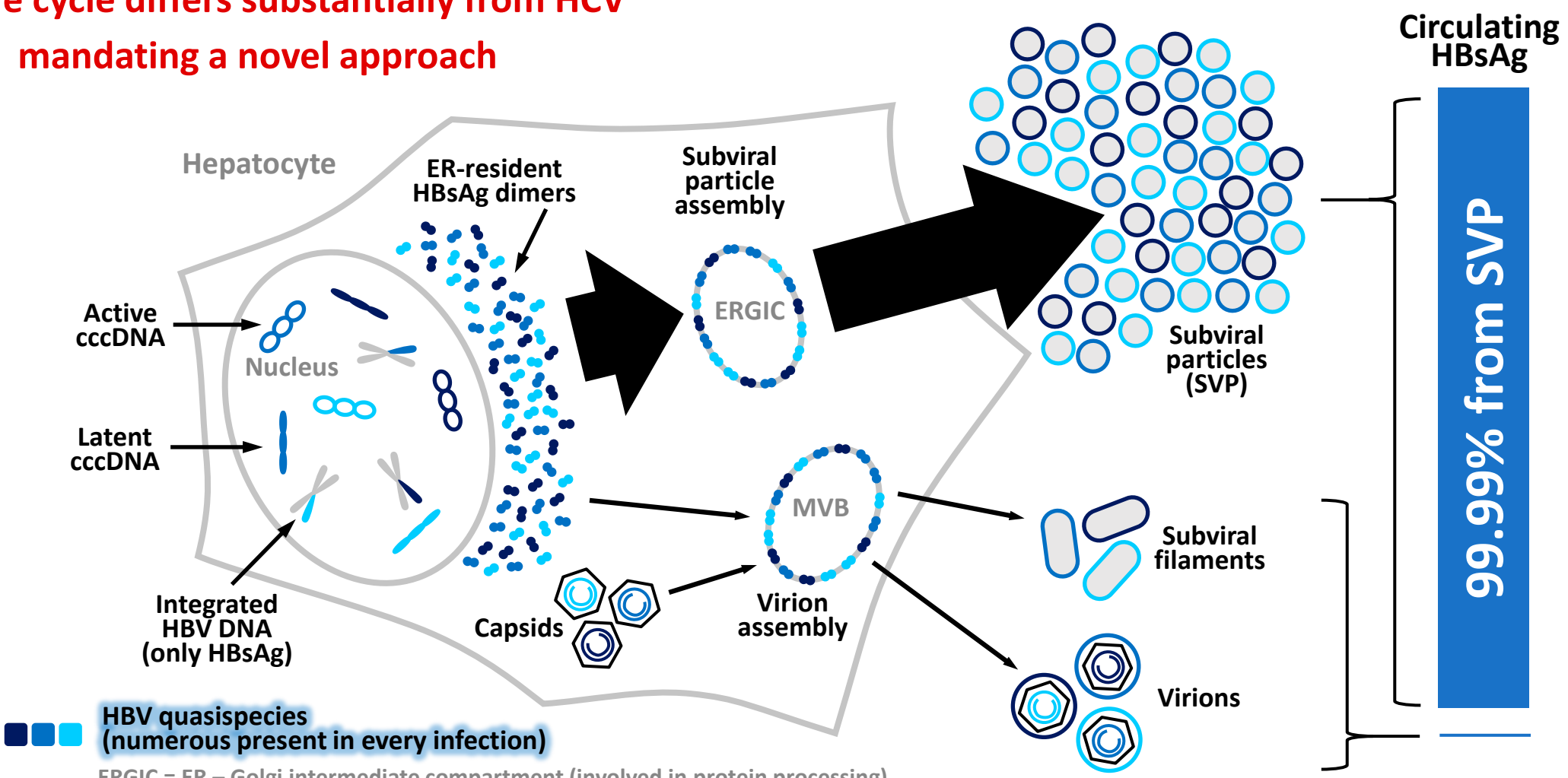
| Trade name (approved) | Drug components |
|---|---|
| SOFALDI® (Gilead, 2013): | sofosbuvir (NS5B) |
| VEIKIRA PAK® (Abbvie, 2014): | ombitasvir (NS5A) + paritaprevir (NS3/4A) + ritonavir (CYP3A) |
| HARVONI® (Gilead, 2014): | sofosbuvir (NS5B) + ledipasvir (NS5A) |
| EPCLUSA® (Gilead, 2016): | sofosbuvir (NS5B) + velpatasvir (NS5A) |
| ZAPATIER® (Merck, 2016): | grazoprevir (NS3/4A) + elbasvir (NS5A) |
| MAVYRET® (Abbvie, 2017): | glecaprevir (NS3/4A) + pibrentasvir (NS5A) |

**Control of HBV infection with finite therapy cannot be achieved with directing antivirals**

| Trade name (approved) | Drug components |
|---|---|
| Epivir HBV® (Glaxo Wellcome, 1998): | lamivudine / 3TC (HBV RT) |
| HEPASERA® (Gilead, 2002): | adefovir dipivoxil / ADV (HBV RT) |
| BARRACLUDE® (BMS, 2005): | entecavir / ETV (HBV RT) |
| Tyzeka® (Novartis, 2006): | telbivudine (HBV RT) |
| VIREAD® (Gilead, 2008): | tenofovir disoproxil fumarate / TDF (HBV RT) |
| VEMLIDY® (Gilead, 2016): | tenofovir alafenamide / TAF (HBV RT) |

# Challenges in achieving functional cure of HBV

**HBV life cycle differs substantially from HCV mandating a novel approach**




ERGIC = ER – Golgi intermediate compartment (involved in protein processing)
MVB = multivesicular body (normally involved in protein sorting)

# Challenges in achieving functional cure of HBV

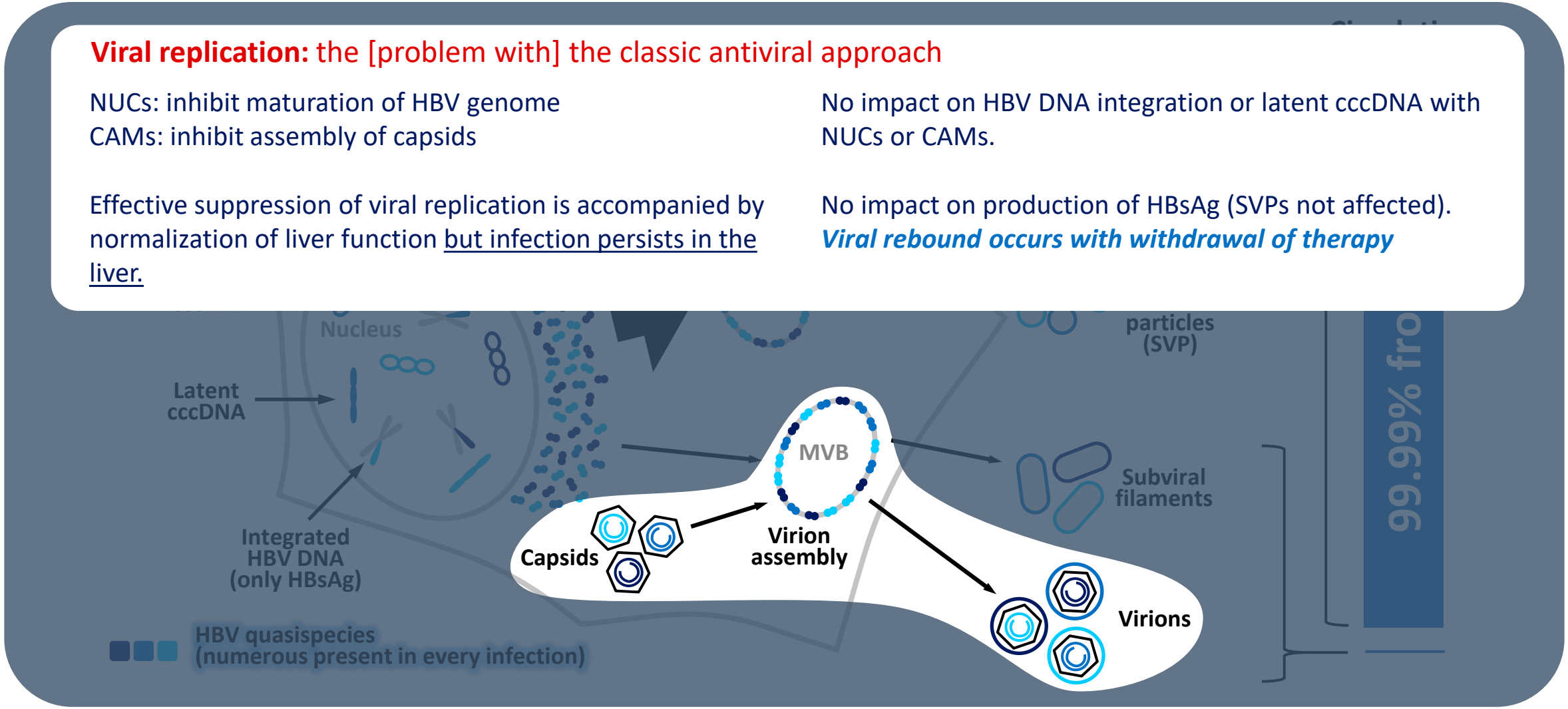
**Viral replication:** the [problem with] the classic antiviral approach

NUCs: inhibit maturation of HBV genome
CAMs: inhibit assembly of capsids

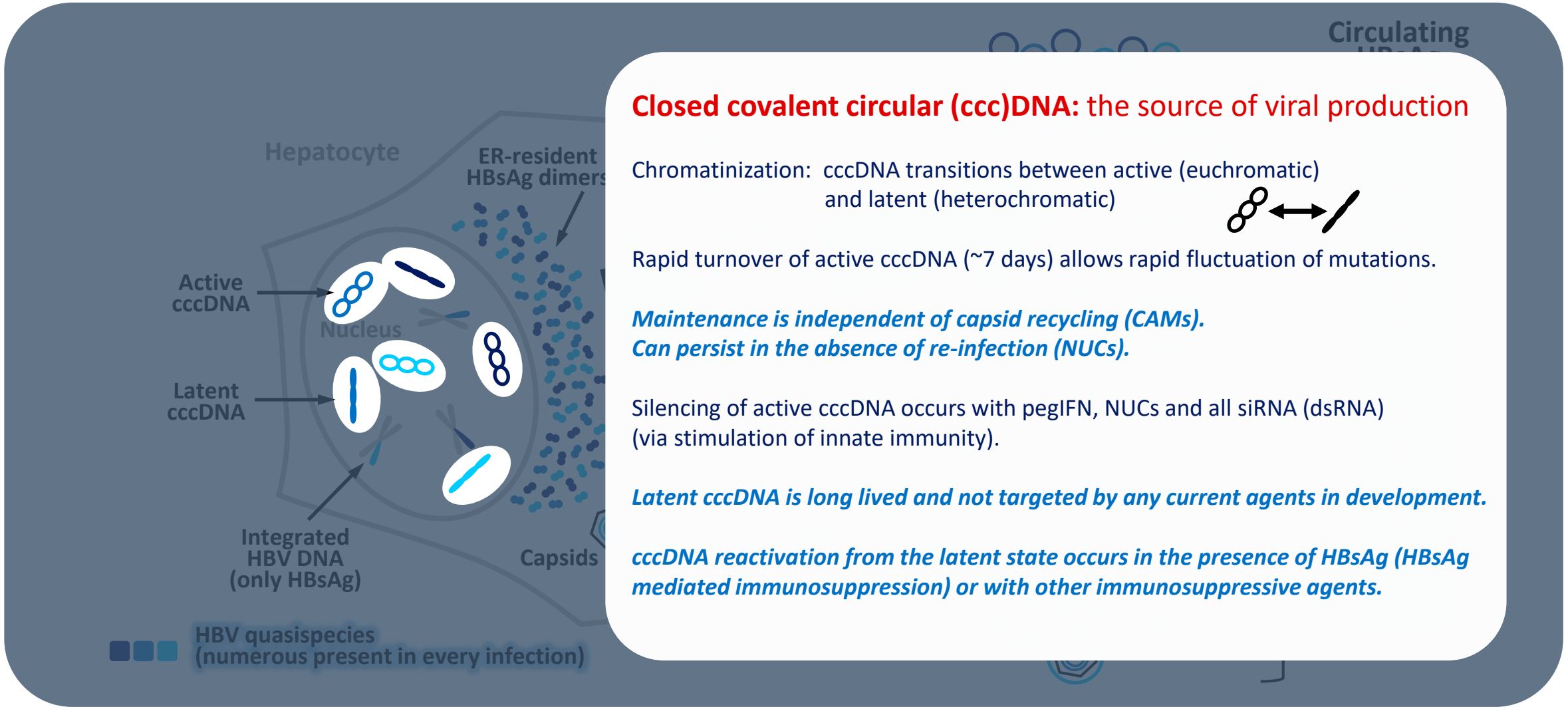
Effective suppression of viral replication is accompanied by normalization of liver function <u>but infection persists in the liver.</u>

No impact on HBV DNA integration or latent cccDNA with NUCs or CAMs.

No impact on production of HBsAg (SVPs not affected).
***Viral rebound occurs with withdrawal of therapy***



# Challenges in achieving functional cure of HBV




**Closed covalent circular (ccc)DNA:** the source of viral production

Chromatinization: cccDNA transitions between active (euchromatic) and latent (heterochromatic)

Rapid turnover of active cccDNA (~7 days) allows rapid fluctuation of mutations.

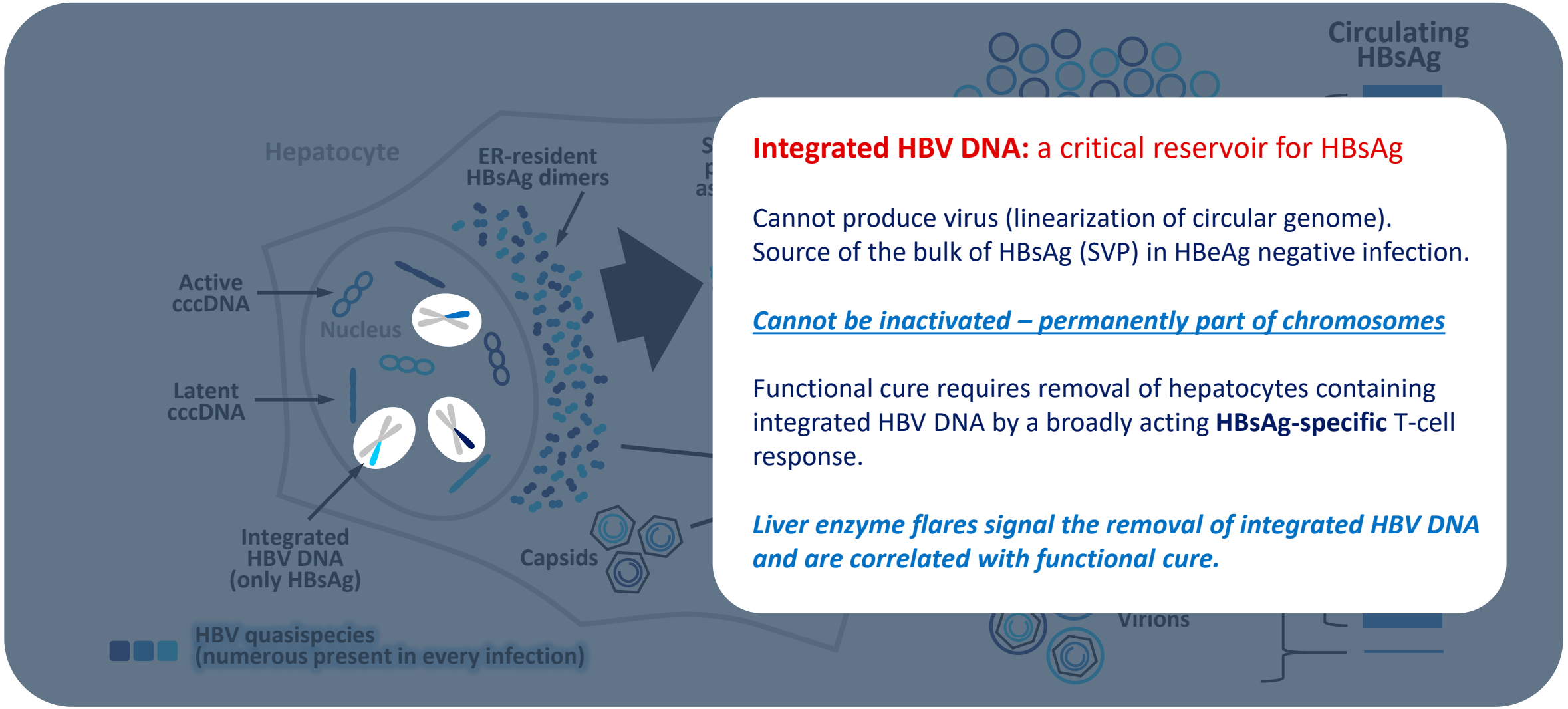
***Maintenance is independent of capsid recycling (CAMs).***
***Can persist in the absence of re-infection (NUCs).***

Silencing of active cccDNA occurs with pegIFN, NUCs and all siRNA (dsRNA) (via stimulation of innate immunity).

***Latent cccDNA is long lived and not targeted by any current agents in development.***

***cccDNA reactivation from the latent state occurs in the presence of HBsAg (HBsAg mediated immunosuppression) or with other immunosuppressive agents.***

# Challenges in achieving functional cure of HBV




**Integrated HBV DNA:** a critical reservoir for HBsAg

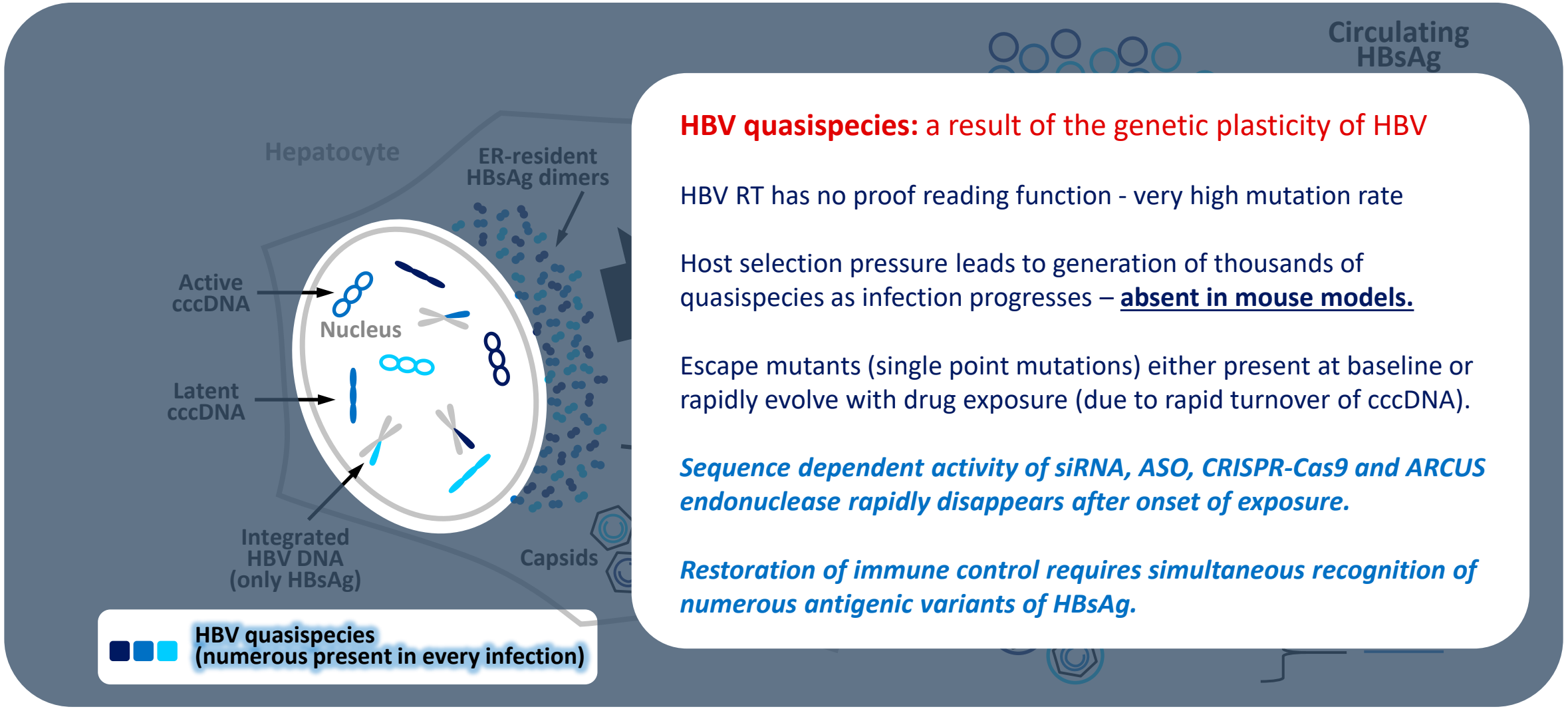
Cannot produce virus (linearization of circular genome).
Source of the bulk of HBsAg (SVP) in HBeAg negative infection.

***Cannot be inactivated – permanently part of chromosomes***

Functional cure requires removal of hepatocytes containing integrated HBV DNA by a broadly acting **HBsAg-specific** T-cell response.

***Liver enzyme flares signal the removal of integrated HBV DNA and are correlated with functional cure.***

# Challenges in achieving functional cure of HBV




**HBV quasispecies:** a result of the genetic plasticity of HBV

HBV RT has no proof reading function - very high mutation rate

Host selection pressure leads to generation of thousands of quasispecies as infection progresses – **absent in mouse models.**

Escape mutants (single point mutations) either present at baseline or rapidly evolve with drug exposure (due to rapid turnover of cccDNA).

***Sequence dependent activity of siRNA, ASO, CRISPR-Cas9 and ARCUS endonuclease rapidly disappears after onset of exposure.***

***Restoration of immune control requires simultaneous recognition of numerous antigenic variants of HBsAg.***

# Challenges in achieving functional cure of HBV

**Subviral particles:**
the driving force behind chronic HBV infection

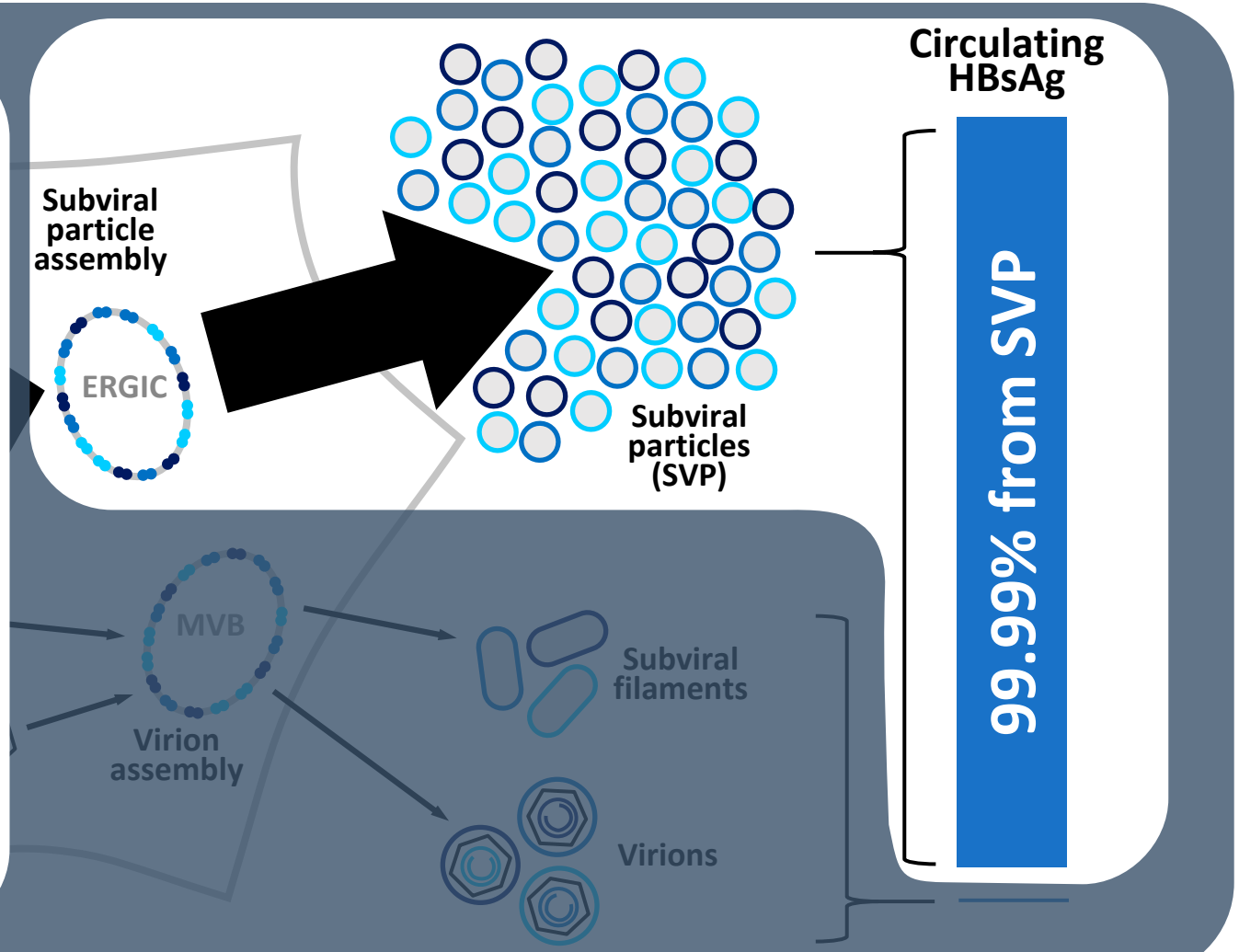
Production is independent of viral replication and cccDNA activity.

Suppresses innate and adaptive immune control of HBV infection.

HBsAg loss during therapy is the only validated marker for functional cure.

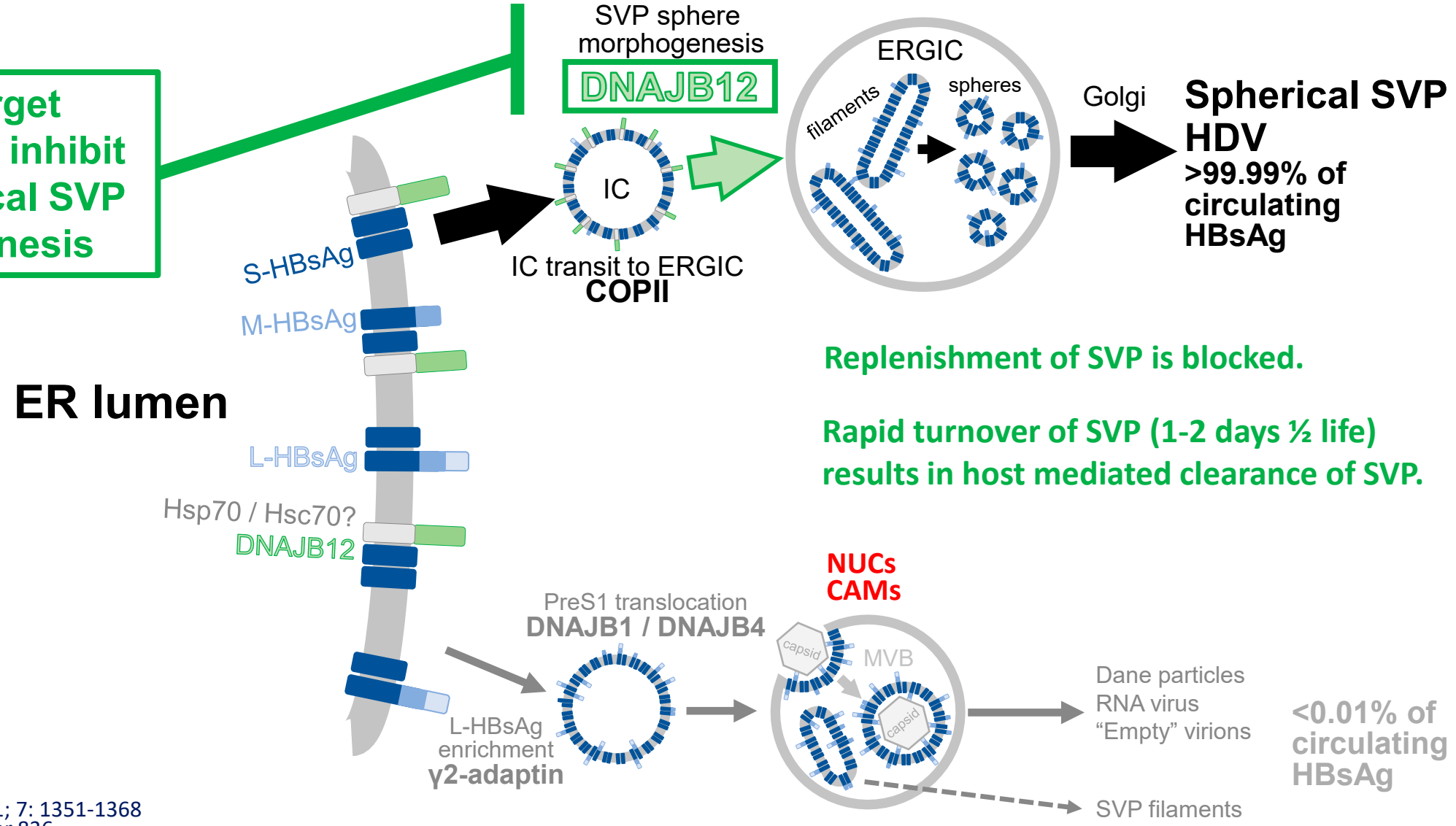
***Likelihood of HBsAg loss is correlated with the magnitude of liver enzyme flares during therapy (pegIFN, NUCs and NAPs).***

***Only NAPs directly target SVP assembly.***



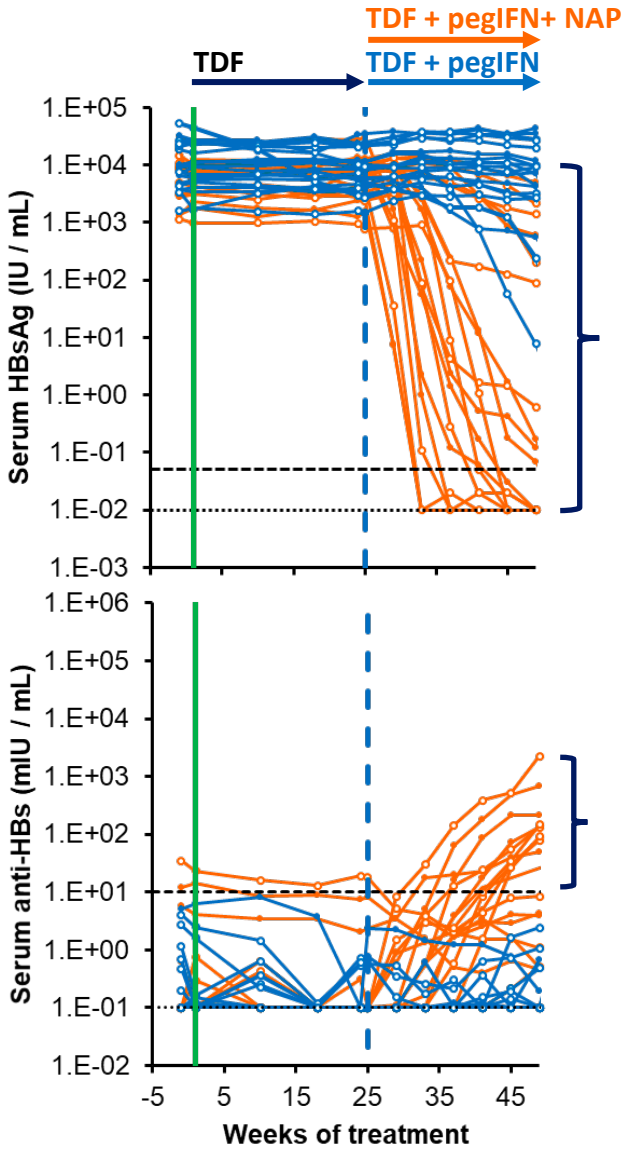
# Nucleic acid polymers (NAPs): a unique molecular mechanism in HBV

**NAPs target DNAJB12 to inhibit HBV spherical SVP morphogenesis**




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

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




Up to 7 $\log_{10}$ decline from baseline (to < 0.005 IU/mL)
**Potent HBsAg decline**

Rapid HBsAg seroconversion

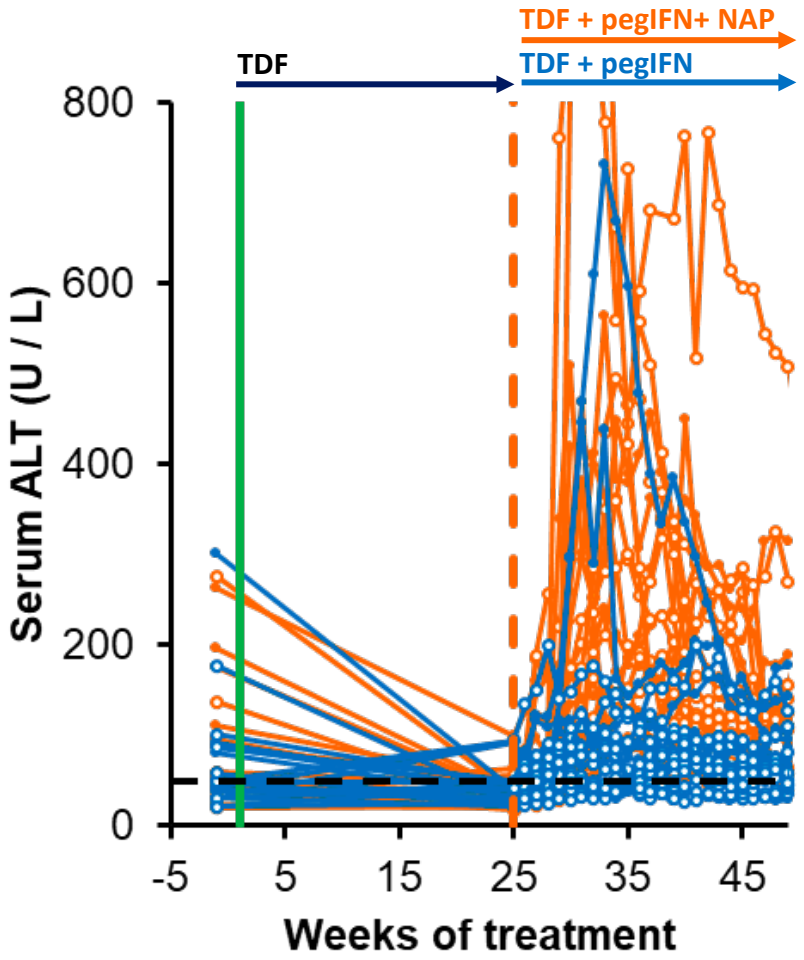
**NAP monotherapy:**
REP 2055 = REP 2139
Up to 7 $\log_{10}$ HBsAg reduction at 12 weeks
HBsAg seroconversion
**Low rates of HBV functional cure**

**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]

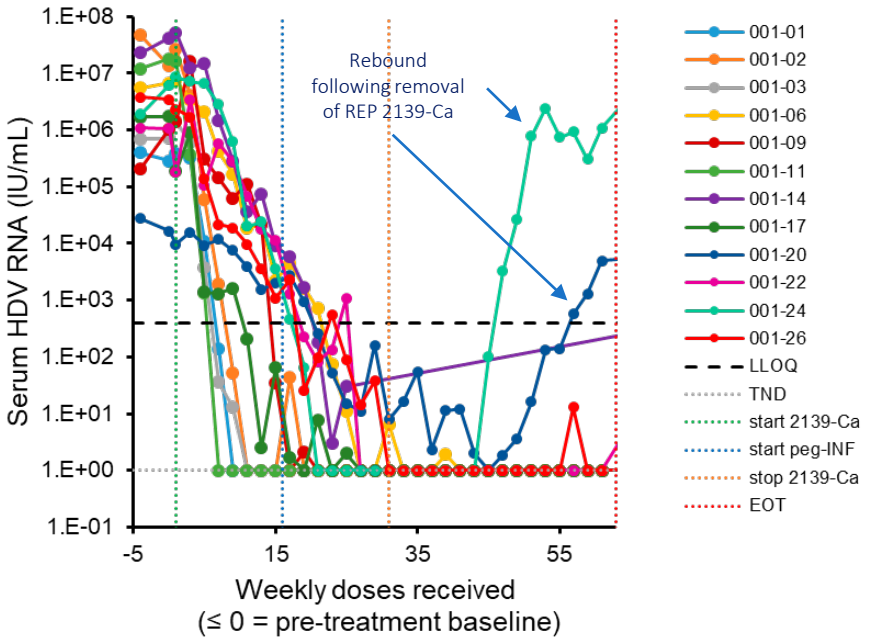
**Consistent with the safe and beneficial nature of host mediated transaminase flares during therapy with approved agents, even in cirrhotic patients[4]**


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 2139 is also effective against hepatitis delta virus (HDV)

- HDV only occurs in patients who also have hepatitis B
- This co-infection is the most aggressive form of viral hepatitis
- 70% progression to cirrhosis within 10 years
- 15-40 million patients are affected worldwide
- Opportunity for fast track approval
- Unmet medical need

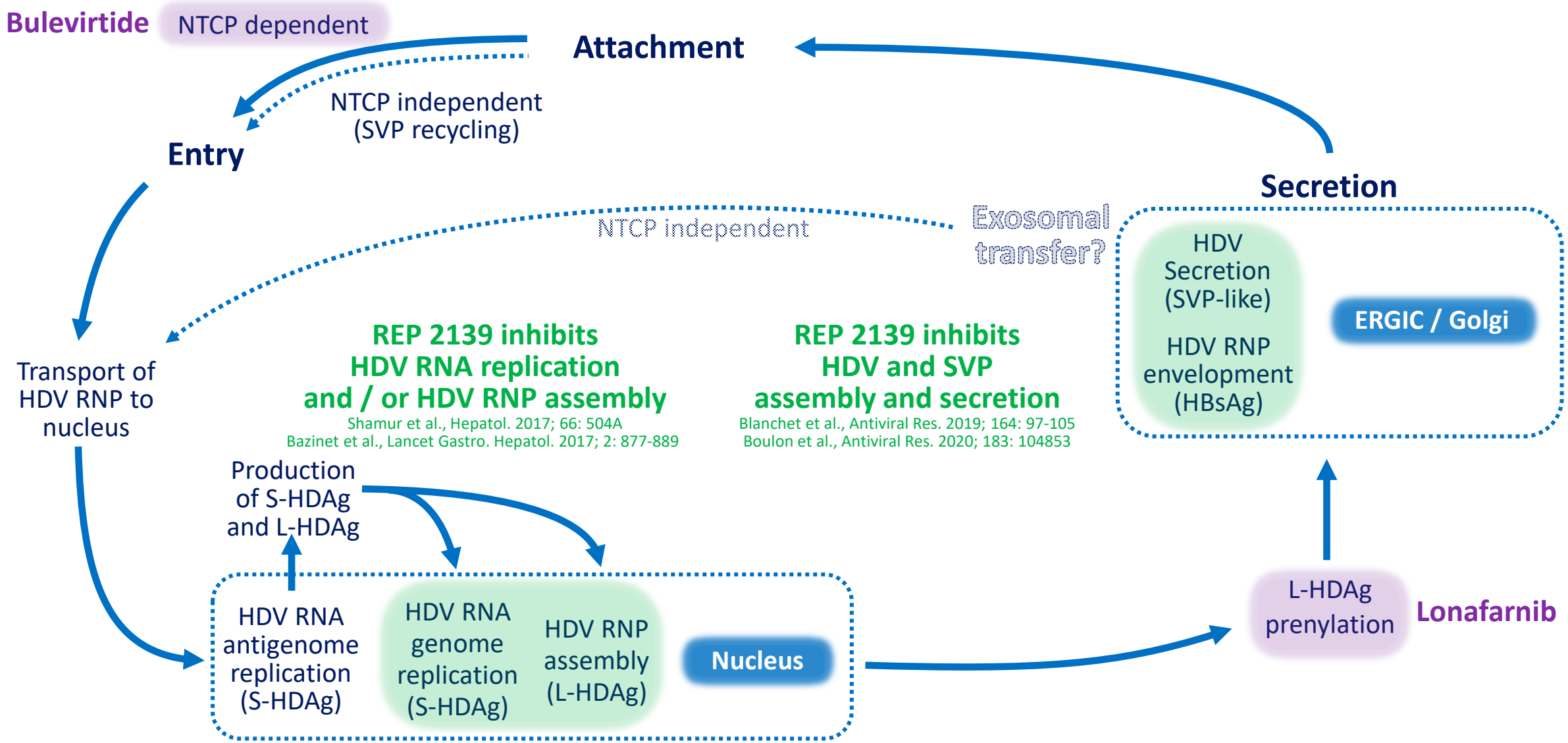
HDV RNA clearance
REP 2139-Ca + pegIFN




**7 out of 11 patients still cured of their HDV 3.5 years after withdrawal of all therapy**


Bazinet et al., Lancet Gastro Hepatol 2017; 2: 877-889
Bazinet et al., Hepatol Comm. 2020; 5: 189-202

# Targeting HDV replication with NAPs



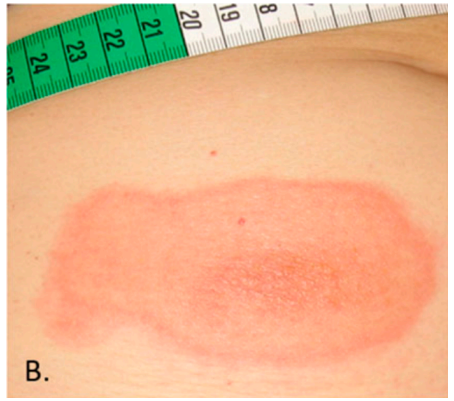
# Transition of REP 2139-Mg to subcutaneous administration

## Oligonucleotides are frequently associated with administration reactivity:

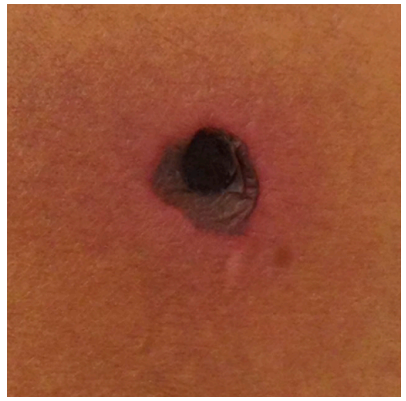
Driven by the chelation of divalent metals (magnesium, calcium and zinc).
Widely reported for all ASOs and siRNA developed / approved to date
***Occurs in up to 70% of patients*** Partridge et al., Nuc Acid Ther 2021; 31: 417-426

IV: fever, shivering, chills, headache (typically requiring supportive therapy and lengthy infusion times)
SC: induration, erythema, pain, ulceration, necrosis (lesions can exceed 10cm in diameter).

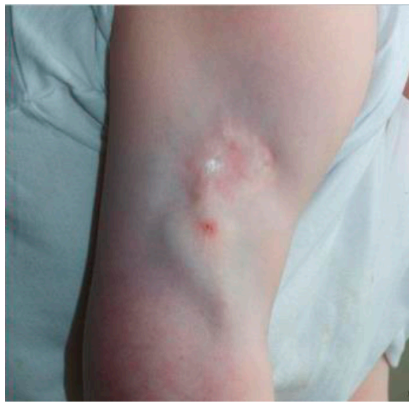
**Reported for HBV agents in development: bepirovirsen, JNJ-3989, VIR-2218, AB-729, RG6346**




Meer et al., Brit J Clin Pharmacol 2016; 82: 340-351
Induration, erythema, ulceration



Blom et al., Current Artheroscler Rep 2019; 21: 48
Necrosis



Domingos et al., Neuromusclular Disord 2018; 28: 176-177
Calcification (persistent)

# Transition of REP 2139-Mg to subcutaneous administration

## Improving administration tolerability experience with NAP formulations

Traditional formulation (normal saline, REP 2055):
*Very poor IV infusion tolerability (24h infusion, supportive therapy)*

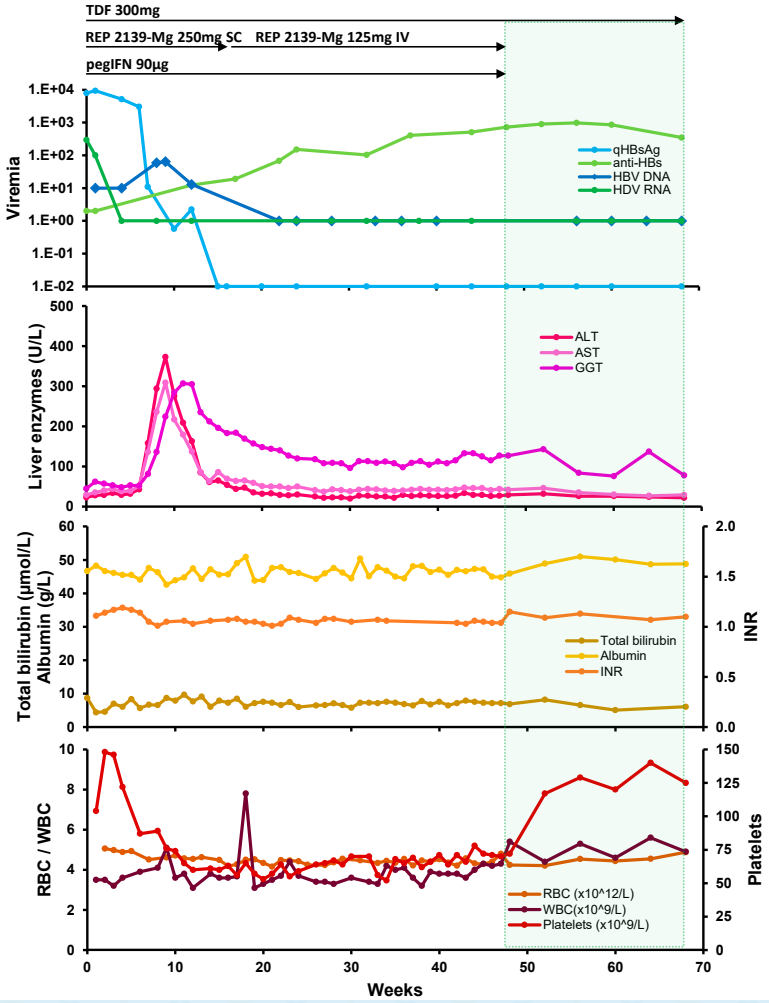
Calcium chelate complex (REP 2139-Ca)
Neutralizes chelation effects of oligonucleotides
*Substantially improved IV infusion tolerability with 2h infusion with AE mostly disappearing after 6-8 weeks.*

Magnesium chelate complex (REP 2139-Mg)
*IV infusion asymptomatic without supportive therapy with rapid infusion (1h).*

***Classic oligonucleotide ISRs are absent with SC administration of REP 2139-Mg (based on recent compassionate use data)***

# REP 2139-Mg in cirrhotic bulevirtide failure patients

**1st patient to complete therapy**
**Cirrhotic HBV / HDV (GT5),**
**Failure on pegIFN and pegIFN + BLV**




**Persistent control of HBV and HDV 5 months after withdrawal of REP 2139-Mg and pegIFN**

**Compassionate use access program: weekly SC administration of REP 2139-Mg**

**France (ANSM): cirrhotic HBV / HDV infection, bulevirtide (BLV) failure**
**8 patients enrolled, 1 completed therapy**
**TDF (qd PO 300mg)**
**low dose pegIFN (qW SC 90ug)**
**250mg REP 2139-Mg (qW SC 250mg)**

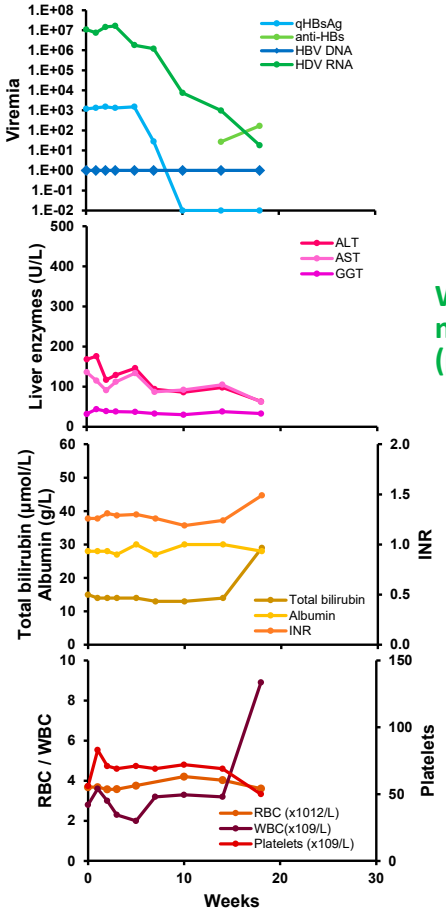
**Other countries enrolling….**

**Summary of clinical results in enrolled patients to date**

- Weekly REP 2139-Mg SC well tolerated
- Rapid HBsAg loss, HDV RNA loss and HBsAg seroconversion
- HDV genotype independent (GT1/GT5)
- Improved pegIFN tolerability in presence of REP 2139
- Reversal of varices

# REP 2139-Mg in decompensated cirrhosis

Patient 5
SC REP 2139-Mg well tolerated




**Week 4: reversal of ascites maintained with removal of diuretic (prior to antiviral response)**

Week 18: unrelated urinary and upper respiratory tract infections
- Resolved with supportive therapy
- REP 2139-Mg dosing not altered

**Compassionate use access program:**
**pegIFN and bulevirtide contraindicated**

**France (ANSM): HBV/HDV infection with decompensated cirrhosis**
**3 patients enrolled, 2 patients started therapy**
**TDF (300mg qD PO)**
**REP 2139-Mg (250mg qW SC)**

**Other countries enrolling….**

Patient 8
Awaiting liver transplant: arterial hypertension
diabetes
advanced ascites (edema in lower extremities)
HCC
fatigue

4 weeks of treatment completed: SC REP 2139-Mg well tolerated
no adverse events
reversal of ascites (and edema)
8kg water loss
loss of fatigue
antiviral results pending

# Summary

**Subviral particles (SVP):** > 99.99% of circulating HBsAg
Prevent immune control and function of immunotherapy
**Removal during therapy is essential for functional cure**

**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**

## NAPs: the only agent to directly target SVP

When used in combination with TDF and pegIFN:
**high rates of asymptomatic host-mediated transaminase flares**
**high rates of functional cure, silencing of cccDNA and removal of integrated HBV DNA**

**Successful transition of REP 2139-Mg to a convenient, once weekly SC administration**

Well tolerated
Potent antiviral response in HBV and HDV infection
Safety envelope extended to patients with cirrhosis and decompensated cirrhosis
rapid reversal of complications of advanced liver disease