Compassionate use of subcutaneous REP 2139-Mg in cirrhotic HBV / HDV coinfection

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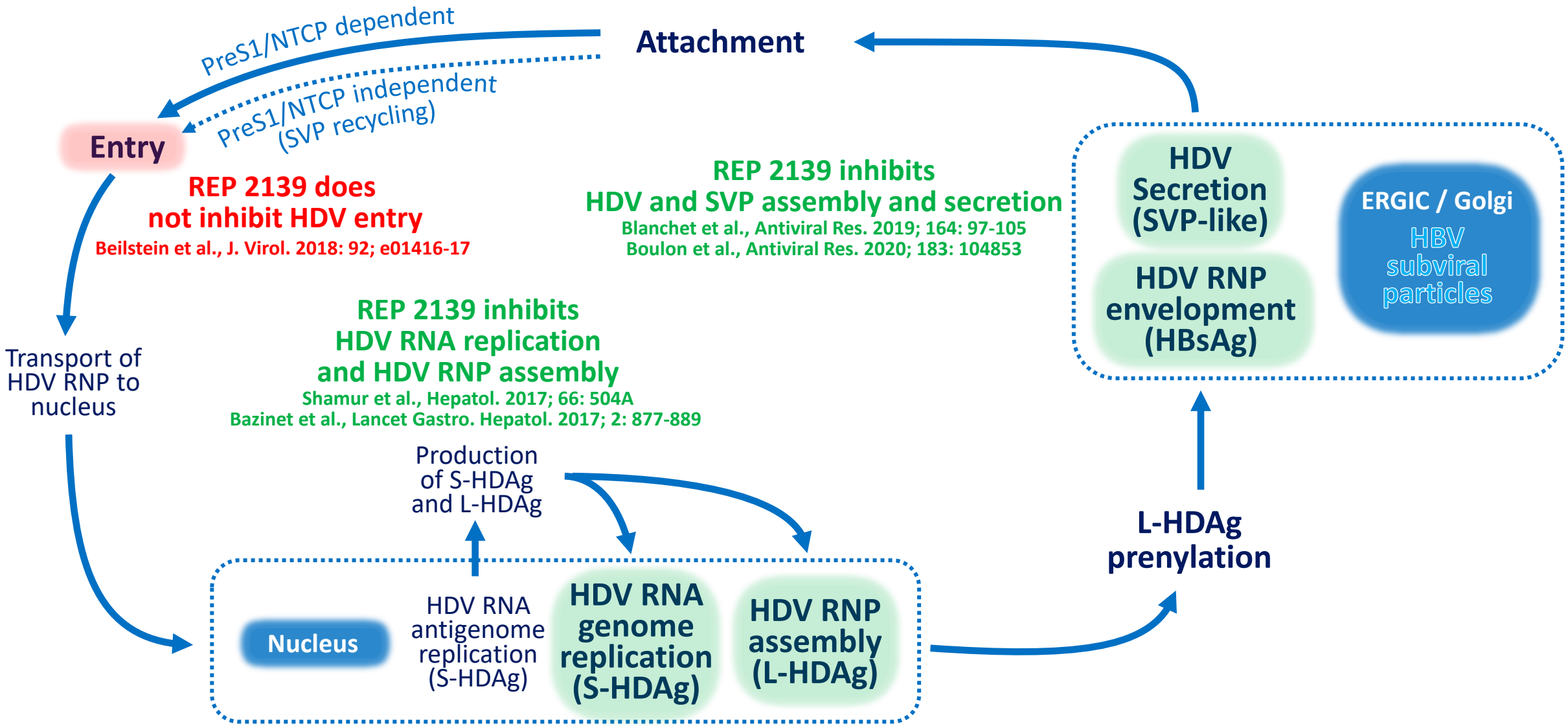
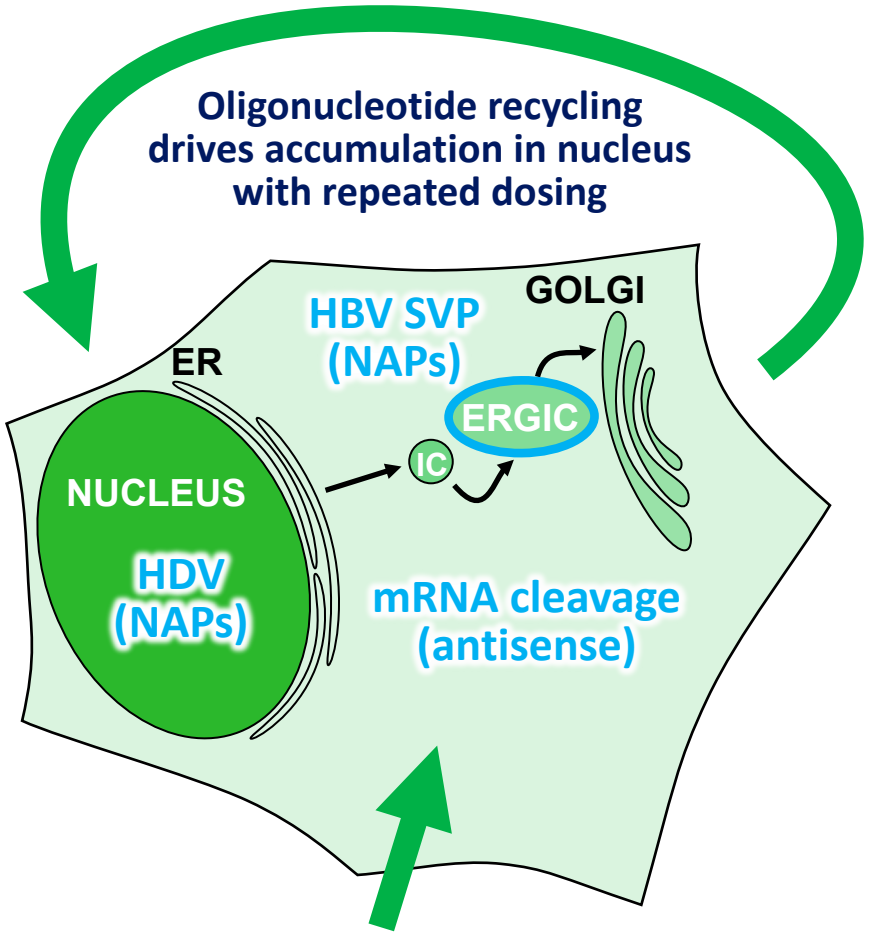
Hepatitis Delta International Network

Targeting HDV replication with NAPs



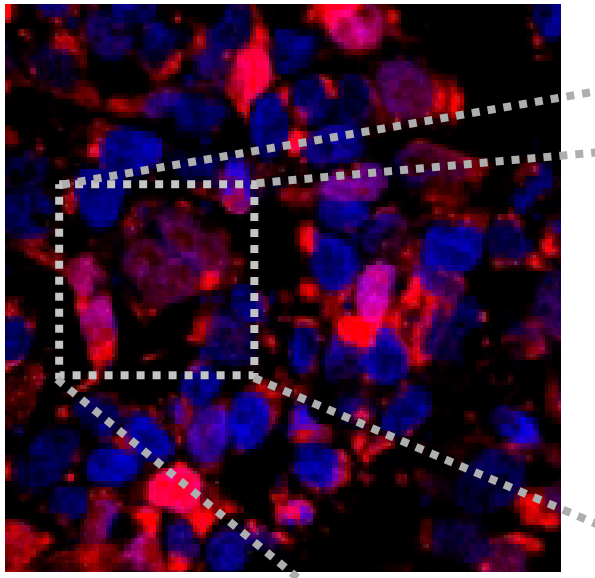
Intracellular accumulation of phosphorothioate oligonucleotides drives NAP antiviral activity



NAP trafficking in HepG2.2.15 cells

Nuclei

CY3-REP 2139 (single dose)



Blanchet et al., Antiviral Res. 2019; 164: 97-105

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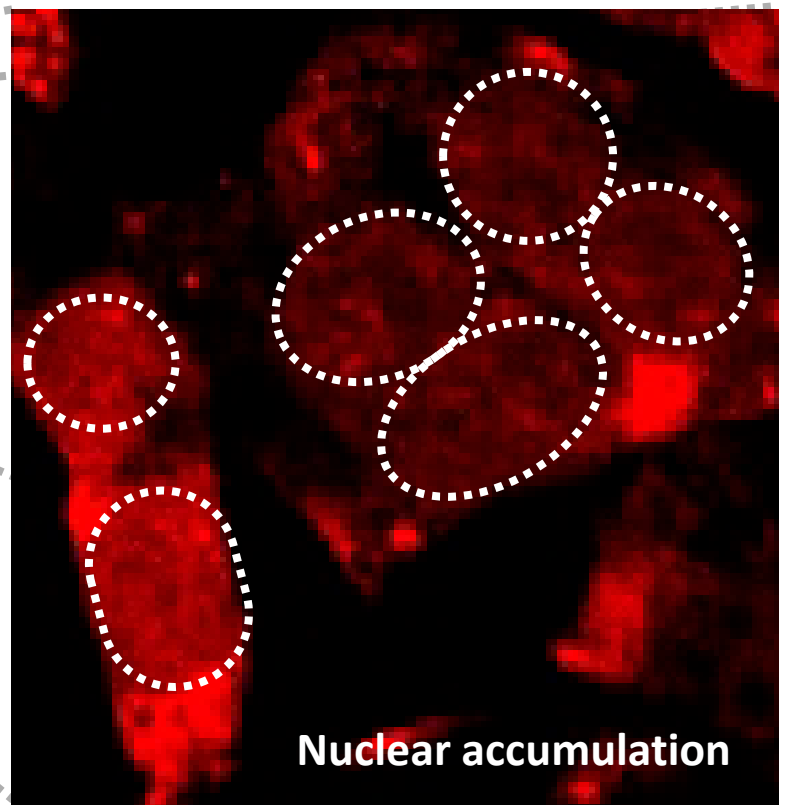
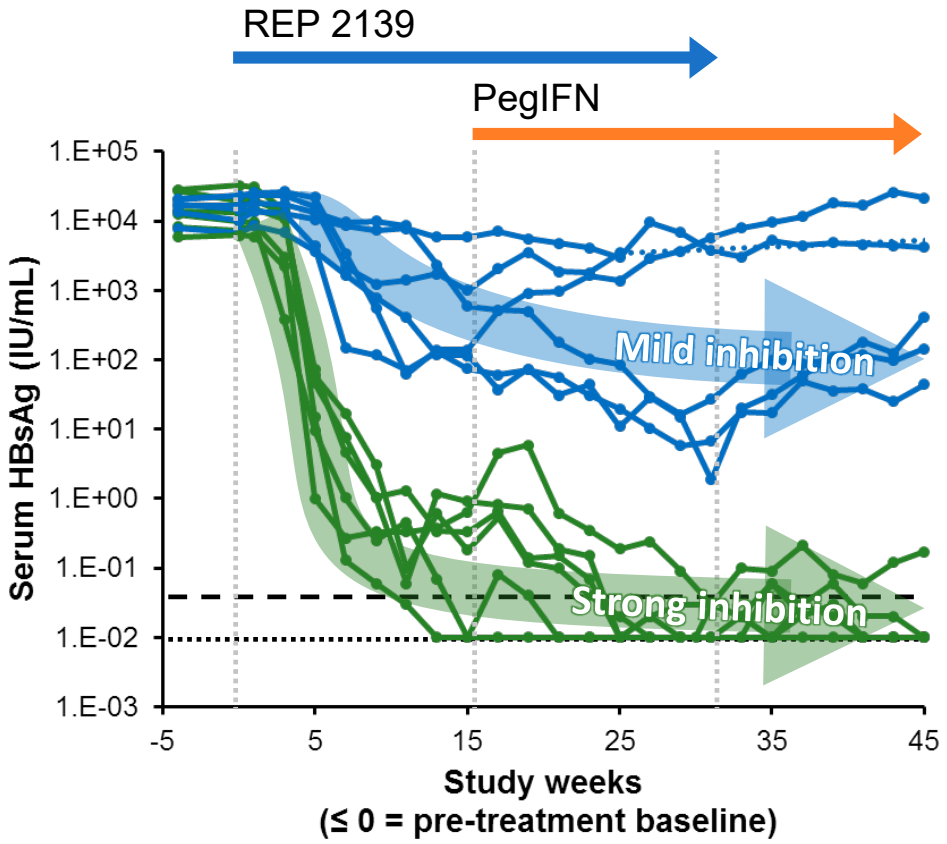
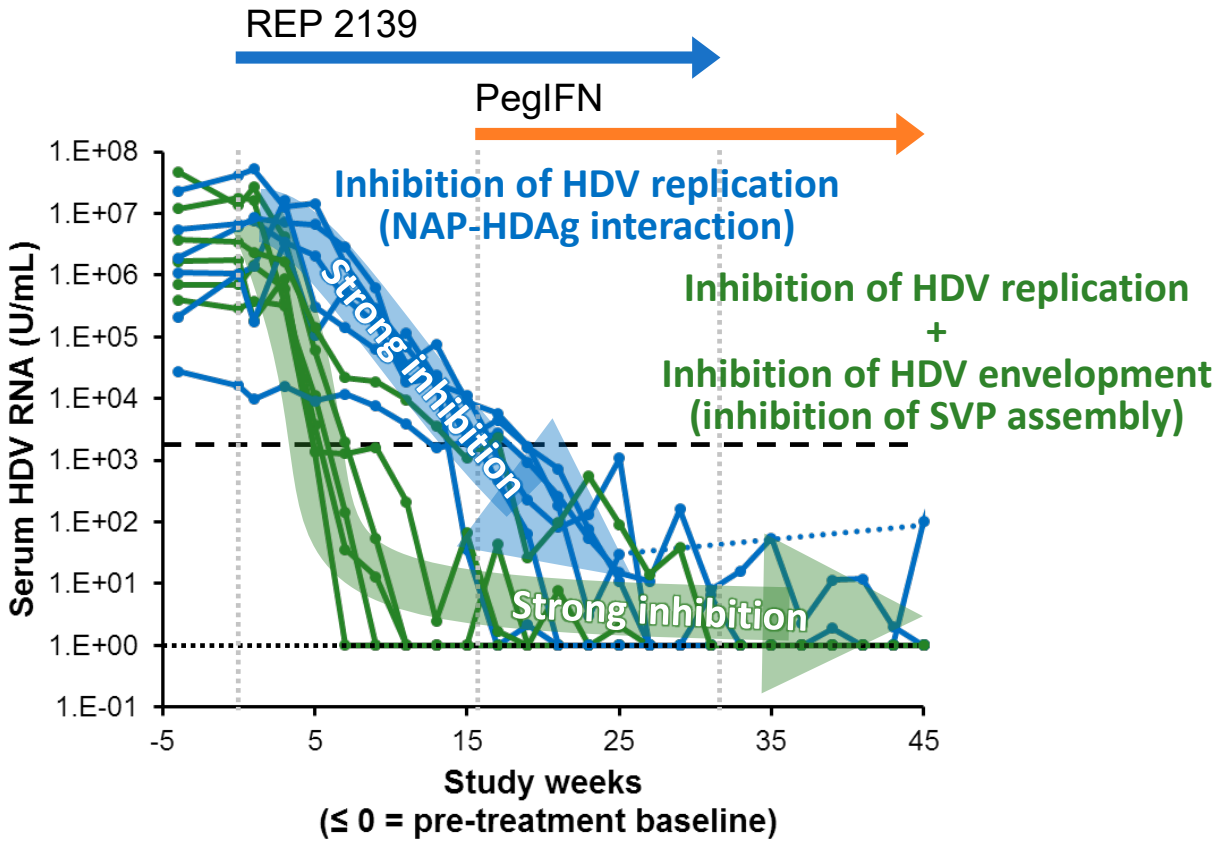


Understanding clinical responses to NAPs in HBV / HDV

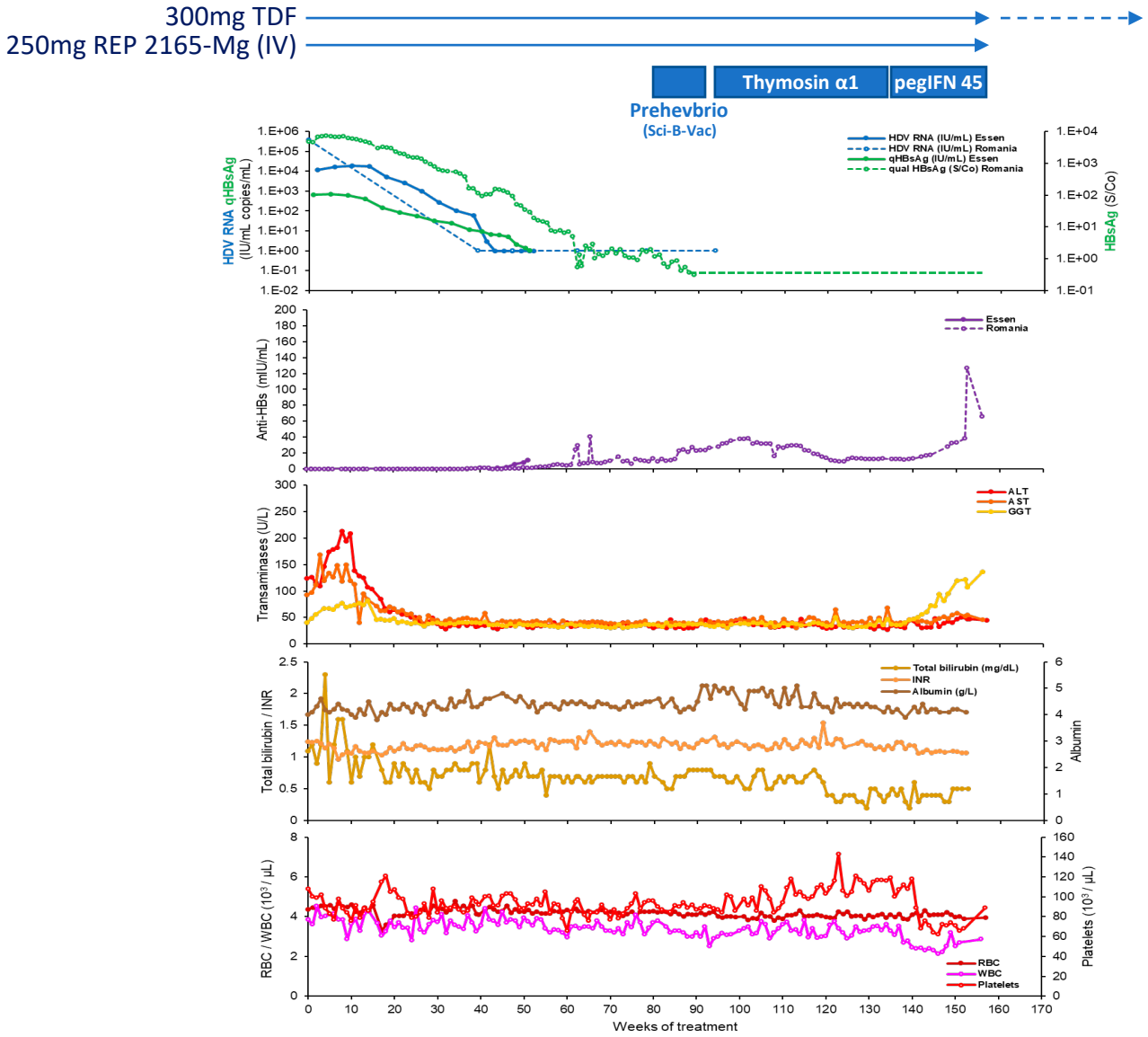
Strong HDV RNA declines with NAPs occur even when inhibition of SVP assembly is attenuated





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

TDF now discontinued

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

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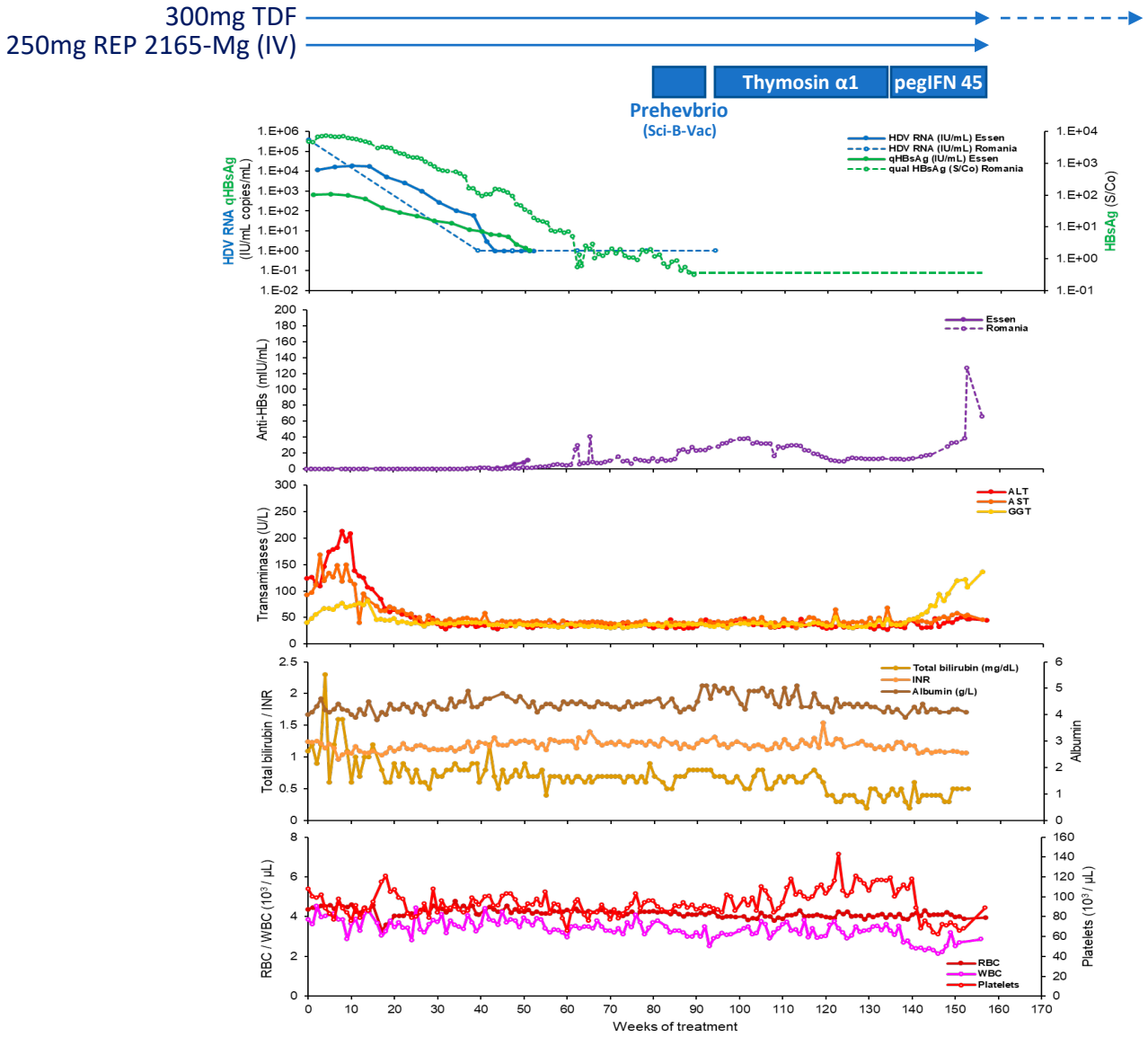

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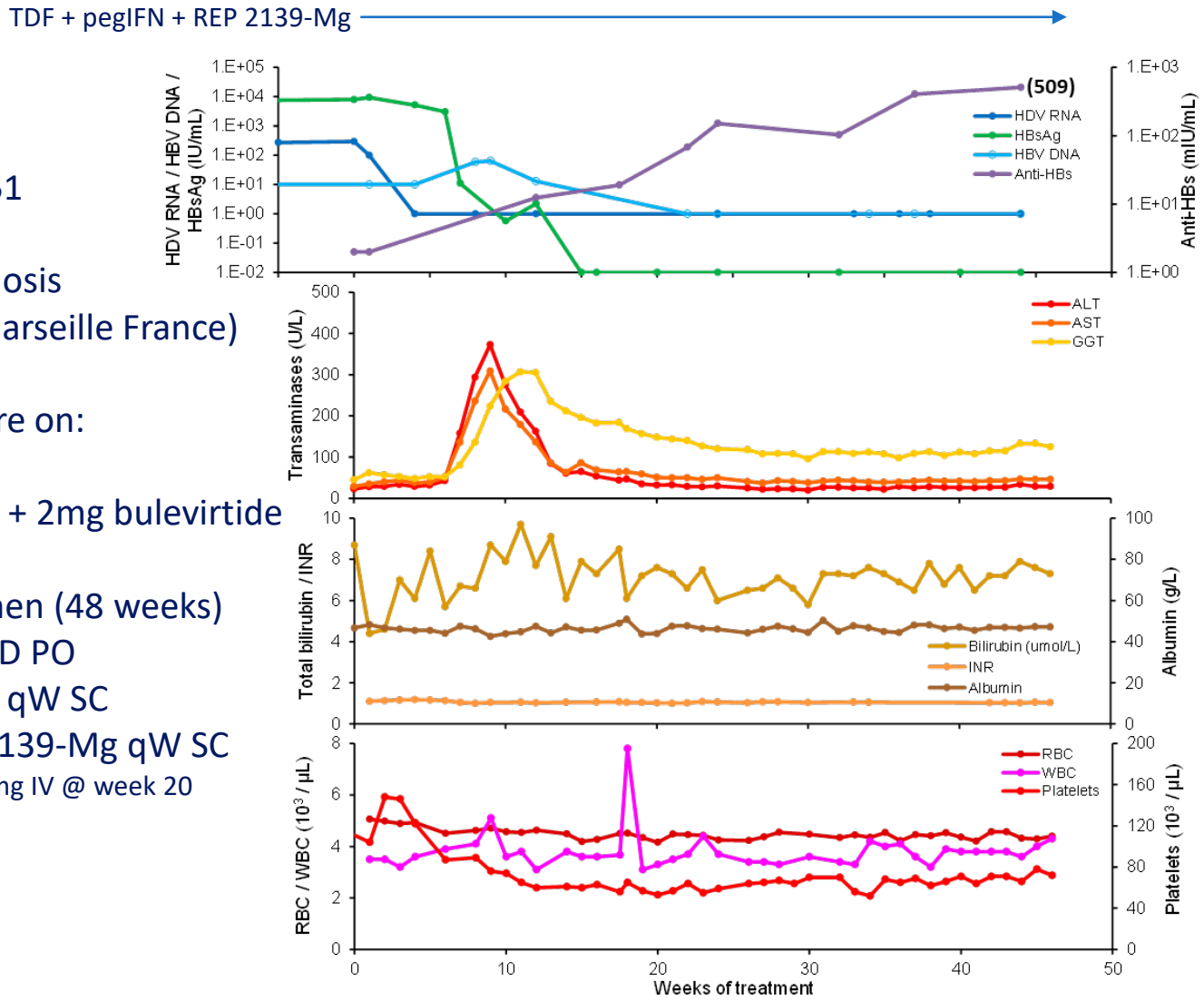
WBC 4.31 x 10^3/µL (recovering)

Transition of REP 2139-Mg to subcutaneous administration

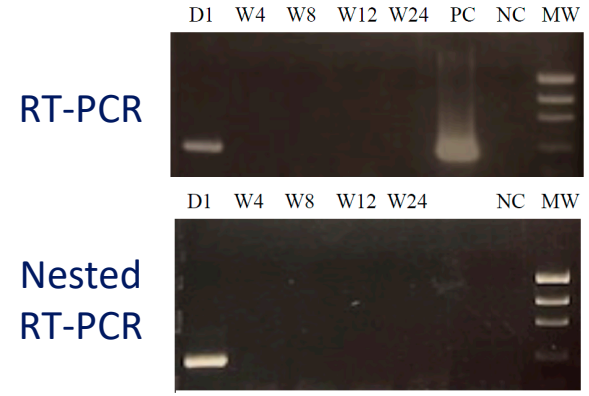
Patient #2
Senegalese male, 51
HBV / HDV (GT5)
Compensated cirrhosis
(Marc Bourlière, Marseille France)

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

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 (2 months)

HBsAg not detected (< 0.05 IU/mL)
Anti-HBs 983 mIU/mL (509 at EOT)
HBV DNA target not detected
HDV RNA pending…..

ALT 26, AST 35, GGT 84 U/L
T-BIL 6.6 µmol/L, ALB 51 g/L, INR 1.13

Platelets 129x10^3 /µL (recovering)

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 + bulevirtide 2mg

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

SC administration well tolerated
9 weeks: HBsAg target not detected (baseline 4650 IU/mL)
≤ 4 weeks: HDV RNA target not detected (baseline 5.78 $\log_{10}$ IU/mL)
Latest LFT: ALT 59 U/L, GGT 120 U/L, Bilirubin 12µmol/L

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

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

NAPs are multifunctional agents against HDV

1. direct acting antiviral activity (via HDAg interactions)
   enhanced via progressive nuclear accumulation with repeated dosing
2. inhibit HDV envelopment and secretion (as HBV SVP)
   maintained by transient movement of NAPs through ERGIC with each dose

Successful transition to subcutaneous administration (REP 2139-Mg from REP 401 study)

well tolerated
activity appears more potent than IV administration

Safety and efficacy established in patients with compensated and non-compensated cirrhosis.

host mediated transaminase flares are asymptomatic
effective salvage therapy for bulevirtide non-response / resistance
persistent control of HBV and HDV infection established in the absence of therapy

Multicountry expansion of compassionate use access to REP 2139-Mg

HBV monoinfection
HBV/HDV, HBV/HIV and HBV/HCV co-infection
Expand safety and efficacy envelope in difficult to treat patients with advanced liver disease