Safety and efficacy of REP 2139-Mg in hepatitis D patients with advanced liver disease: an international compassionate use program

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*On behalf of the RCAP investigators

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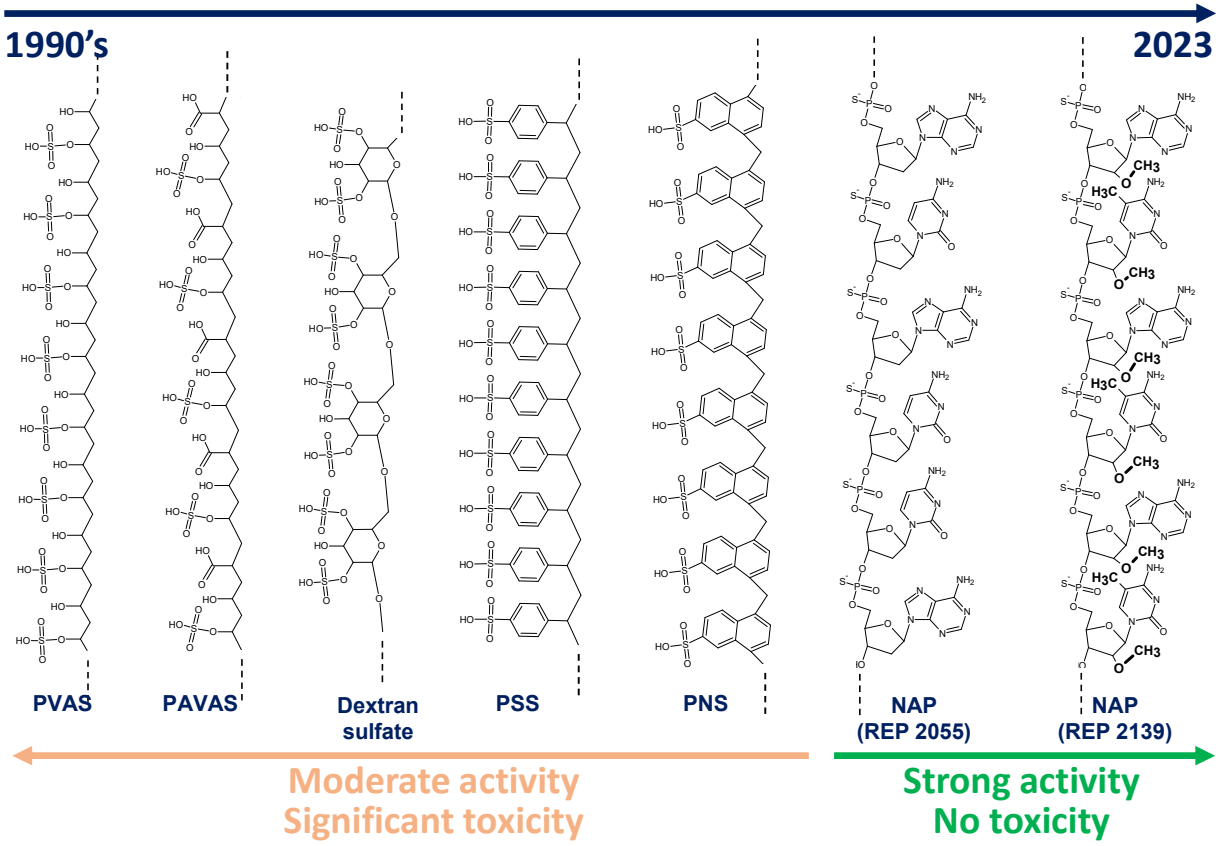
Conflict of interest

- Consultant: EchoSens
- Speaker: Hologic, Gilead
- Stock options: Gilead

- Except for M. Bazinet and A. Vaillant, no authors have a conflict of interest with Replicor Inc.

Nucleic Acid Polymers (NAPs): well-known class effects



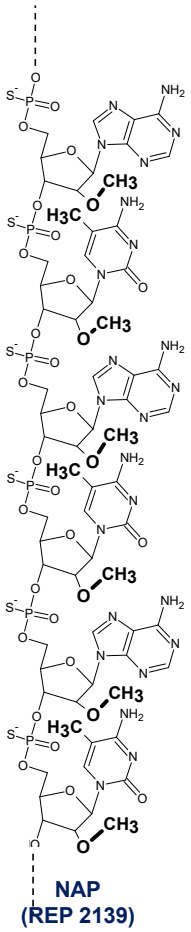
NAPs = **broad-spectrum antiviral** compounds active against diverse enveloped viruses and other agents

Interact with the exposed hydrophobic surfaces of **amphipathic α-helix proteins**

Primary accumulation in the liver = 250-500 mg required for effective hepatocyte accumulation (IV or SC)

Roehl et al, Mol Ther Nuc Acids 2017. Yu et al, Mol Ther Nuc Acids 2015. Geary et al, Biochem Pharmacol. 2009.

REP 2139 in HDV patients: *in vitro* data



NAP
(REP 2139)

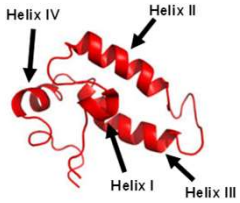
40mer oligonucleotide polymer of alternating adenosine and cytidine =

strong activity, prevents host genome interactions and immunostimulation

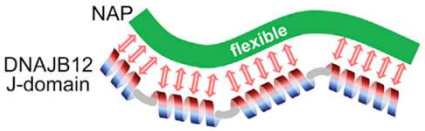
Mechanism of action

Passage through secretory pathway (transient)

- Target the host HSP40 chaperone DNAJB12
- Inhibition of HBV SVP assembly
- Blocks envelopment of HDV RNP



J-domain crystal structure of DNAJB12 at neutral pH
(4 linked alpha helices)



Flexible nature of NAPs adapts to minor alterations in α-helical confirmation, maintaining high affinity interactions

Accumulation in nucleus

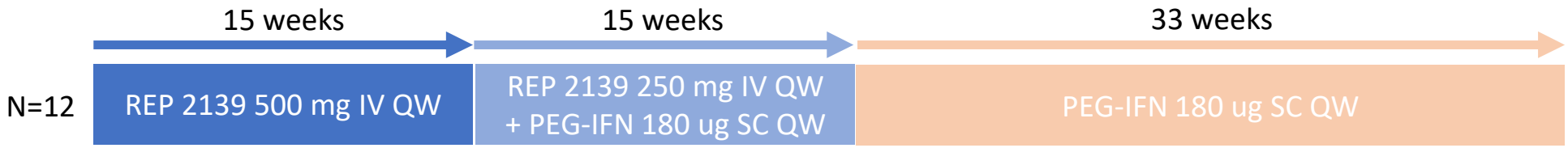
- Targets S-HDAg and L-HDAg
- Inhibits HDV RNA replication
- Blocks HDV RNA interaction with HDAg during HDV RNP morphogenesis
- **Nuclear accumulation is more efficient**
- Anti-HDV effects are easier to achieve

HDAg
crystal structure

Vaillant A, ACS Inf Dis 2019. Vaillant A, Antiviral Res 2016. Levrero M *et al*, AASLD 2023.

REP 2139 in HDV patients: phase II clinical trial data

Study REP 301: HDV patients, non-cirrhotics, HBeAg negative



	REP 2139 monotherapy	End of combination therapy	End of treatment
HBsAg reduction (log from baseline)	3·31 (1·99)	4·15 (2·24)	3·45 (2·70)
HBsAg negative*	2 (17%)	4 (33%)	5 (42%)
Anti-HBs positive†	5 (42%)	6 (50%)	6 (50%)
HDV RNA reduction (log from baseline)	4·21 (1·99)	5·68 (1·14)	5·34 (2·34)
HDV RNA negative‡	4 (33%)	10 (83%)	9 (75%)

Long-term follow-up study up to 7.4 years:

- 64% (7/11) HDV RNA undetectable
- 4 (36%) with HBsAg loss (HBV functional cure)

Replicor compassionate access program

- Compassionate access to REP 2139-Mg (RCAP, NCT05683548) in eligible patients:
  - Previous virologic or biochemical failure or rebound during therapy with pegIFN and/or bulevirtide
  - Patients with HBV / HDV decompensated cirrhosis
  - Utilizes remaining drug supply from phase II trial, but transitioning to weekly SC administration of 250mg as same pharmacokinetics observed for NAPs with IV or SC administration

- Patients enrolled worldwide:
  - France (18 patients, 8 centers)
  - Israel (1 patient, 1 center)
  - Austria (3 patients, 1 center)
  - Turkey (4 patients, 1 center)
  - Germany (1 patient, 1 center)
  - Italy (4 patients, 1 center)
  - Australia (1 patient, 1 center)
  - Canada (1 patient, 1 center)

Objective

- To evaluate the real-life safety and efficacy of REP 2139 in HDV patients with advanced liver disease in an international compassionate access program (RCAP, NCT05683548)

Patients and methods

- All 33 HDV patients enrolled in the compassionate access program were included
- Patients received the following treatment for a planned duration of 48 weeks:
  - **REP 2139-Mg 250 mg QW SC (n=33)**
  - **TDF 245 mg QD PO (n=28) or TAF QD PO (n=5)**
  - **PegIFN 45-180ug qW SC if compensated disease and no contra-indication (n=18)**
- Safety and liver function were monitored weekly and antiviral response every 4 weeks with standard assays for quantitative HBsAg and anti-HBs, HBV DNA, HDV RNA and HIV RNA (in 2 HIV co-infected patients).

RCAP baseline characteristics

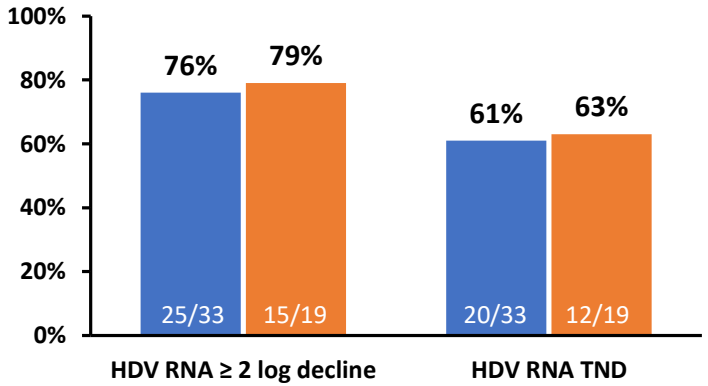
	N = 33
Age (years)[#]	47 (21 – 69)
Male Sex (n, %)	21 (64 %)
Ethnicity	24 Caucasian, 5 African, 2 Middle Eastern, 1 Asian, 1 Central Asian
Previous failure to pegIFN (n, %)	24 (73 %)
Previous BLV treatment (n, %) *	20 (61 %)
Liver fibrosis (n) Advanced fibrosis F3 Compensated cirrhosis Decompensated cirrhosis	 5 22 6
Positive HBeAg at baseline (n)	6
HDV genotype (n) GT1 / GT5 / GT7 / Unknown	 19 / 4 / 1 / 9
HIV co-infection (n)	2
HDV RNA (IU/mL) [#]	1.96 x10^6 (295-1.68x10^7)
HBsAg (IU/mL) [#]	8307 (626-33559)
HBV DNA (IU/mL) [#]	1234 (TND-3440)
ALT (U/L) [#]	88 (19-266)
Bilirubin (µmol/L) [#]	17 (3.4-34)

[#] Mean (range)

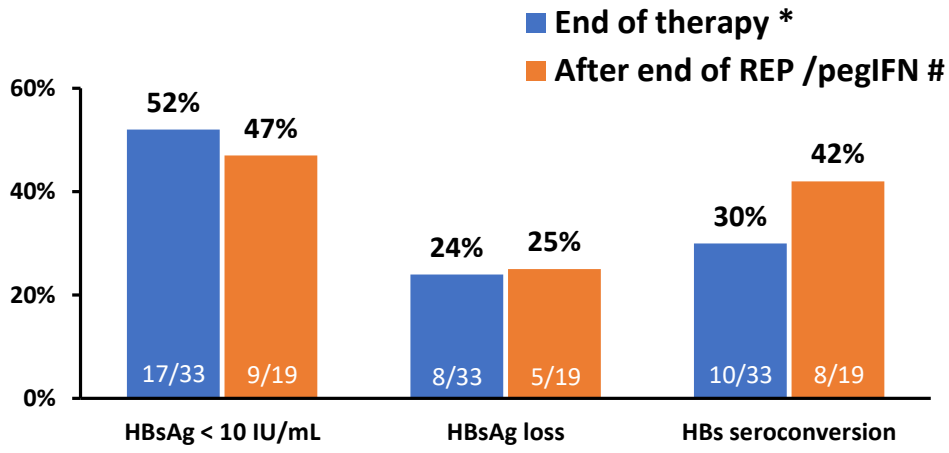
*9 non response (< 2 $\log_{10}$ in HDV RNA) and 11 HDV RNA rebound during therapy

Virological results on therapy and after REP 2139 treatment

HDV RNA response



HBsAg response



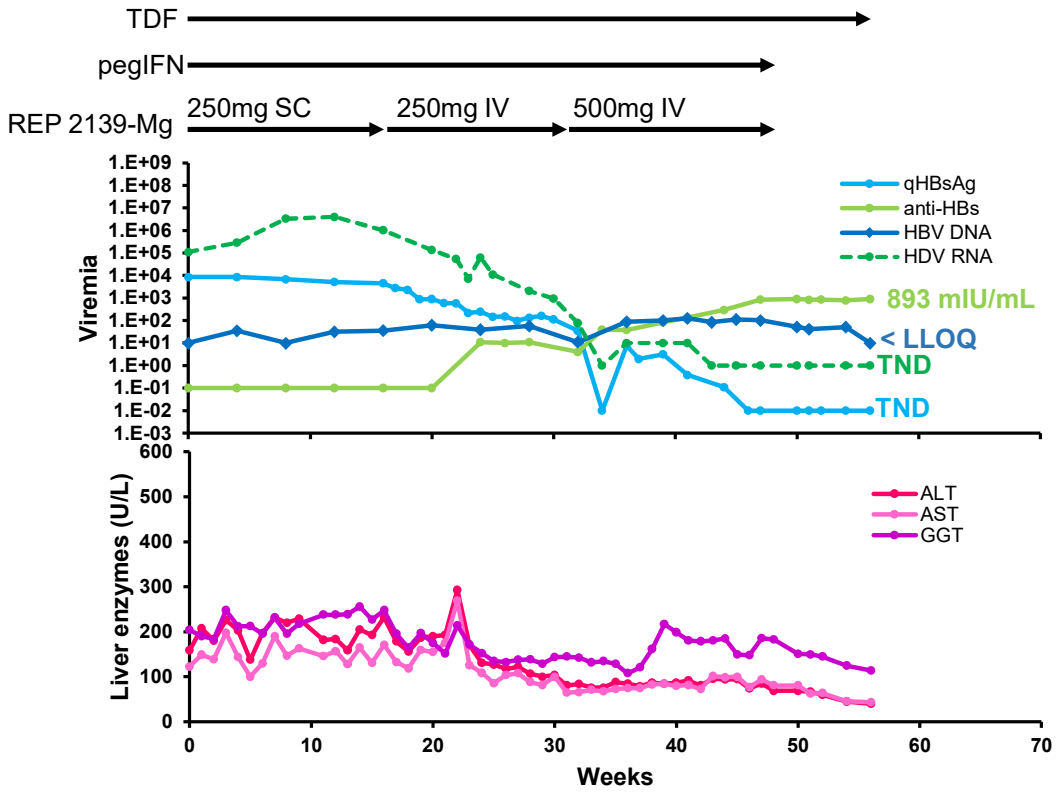
ALT normalized in 47% (9/19) after end of REP / pegIFN

Removal of all therapy in three patients:
all with HDV TND and HBV functional cure (24 weeks of follow-up)

* 3 patients still on therapy: 1 has < 16 weeks, 2 on extension therapy > 48 weeks. 7 patients halted therapy prior to 48 wks; 2 due to LT, 2 due to poor IV access, 1 due to unrelated burst varices, 1 for futility and 1 due to lost contact.
# With available follow-up (4-48 weeks) after completion of at least 48 weeks of therapy. Four patients completed extension therapy totalling 60-80 weeks.

Suboptimal virological response can be improved with REP 2139 dose modification and/or therapy extension

RCAP #31: Christoph Neumann-Haefelin, Germany



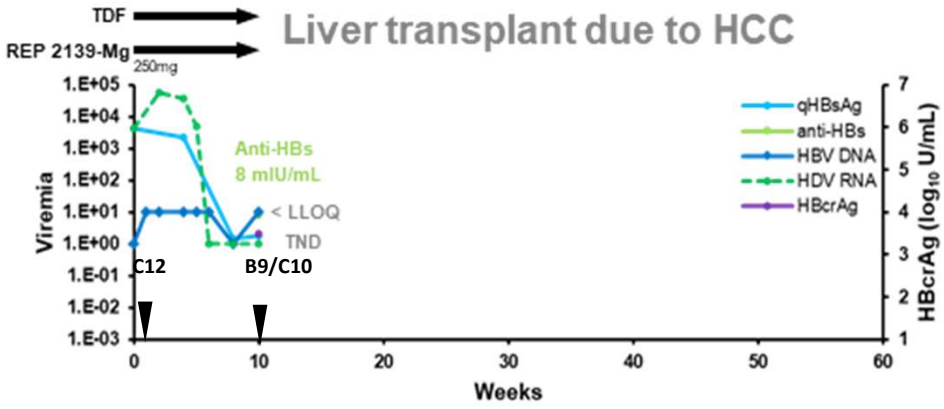
- 47 year old, Asian male, compensated cirrhosis with previous failure on pegIFN + BLV
- Initial poor response to 250mg SC is effectively rescued by modifying dosing to increase C_{max}
- HDV-RNA TND at W43 and HBsAg loss at W46

Patient maintains HDV RNA TND and HBsAg loss with seroconversion 8 weeks off therapy (TDF only)

Rescue of HDV RNA response in all 6 patients with therapy extension

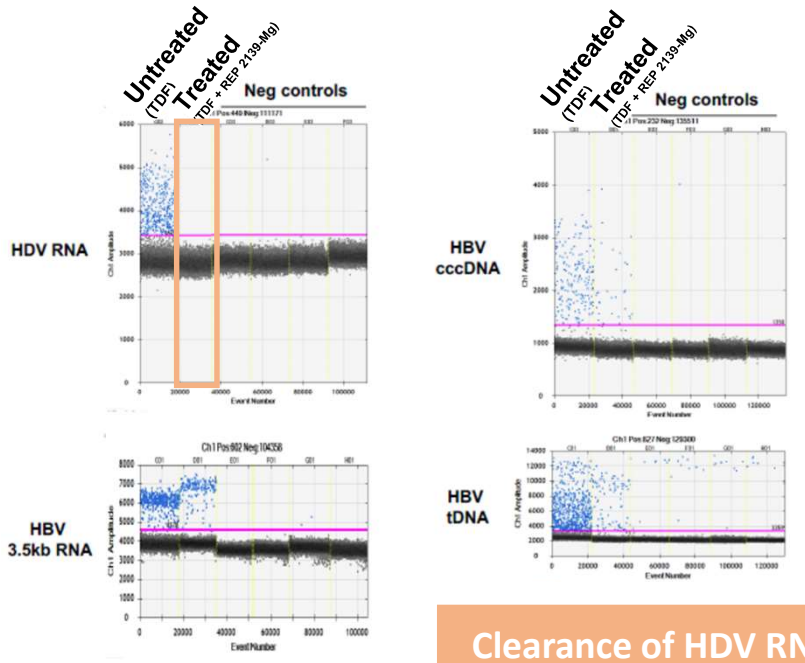
Clearance of HDV RNA from the liver after 10 wks of REP therapy

56 years old, African female, GT5, HBeAg -



- Significant reduction of ascites at week 4
- No progression of HCC, no ALT flare, no systemic AE
- **Transplant after 10 weeks of REP 2139**
- Explant has normal histology (non HCC regions)
  - No steatosis
  - Well differentiated HCC with no vascular emboli
  - **No ground glass hepatocytes**

Intrahepatic analysis of HDV and HBV markers in the liver explant

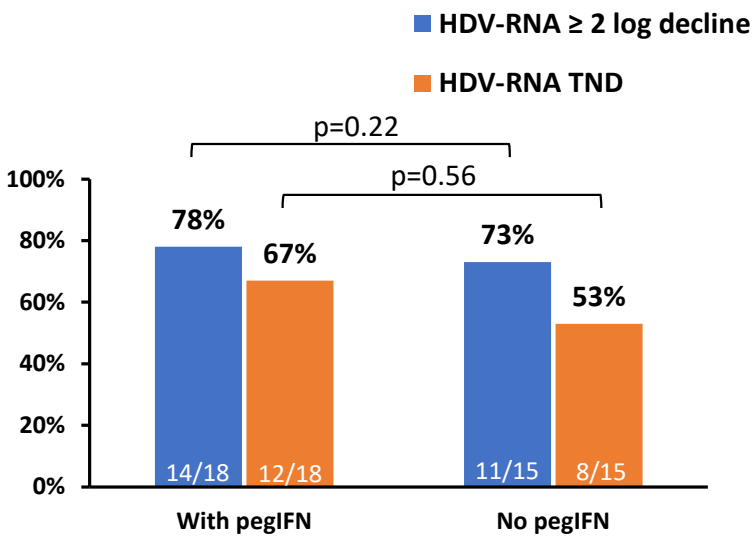


Clearance of HDV RNA from the liver explant with very low levels of cccDNA present

No baseline predictive factors of virological response

Baseline parameter	HDV RNA TND during therapy	HBsAg log reduction from baseline during therapy
Age	p=0.94[B]	p=0.87[A]
Sex	p=0.99[E]	p=0.62[B]
Ethnicity Caucasian versus non-Caucasian	p=0.46[E]	p=0.36[B]
BMI	p=0.29[B,C]	p=0.25[A,C]
ALT	p=0.57[B]	p=0.63[A]
Liver disease Compensated cirrhosis / fibrosis versus decompensated cirrhosis	p=0.06[E,F]	p=0.76[B]
HDV RNA	p=0.54[B]	p=0.79[A]
HBsAg	p=0.82[B]	p=0.99[A]
Absence of pegIFN during therapy	p=0.56[E]	p=0.25[B,D,G]

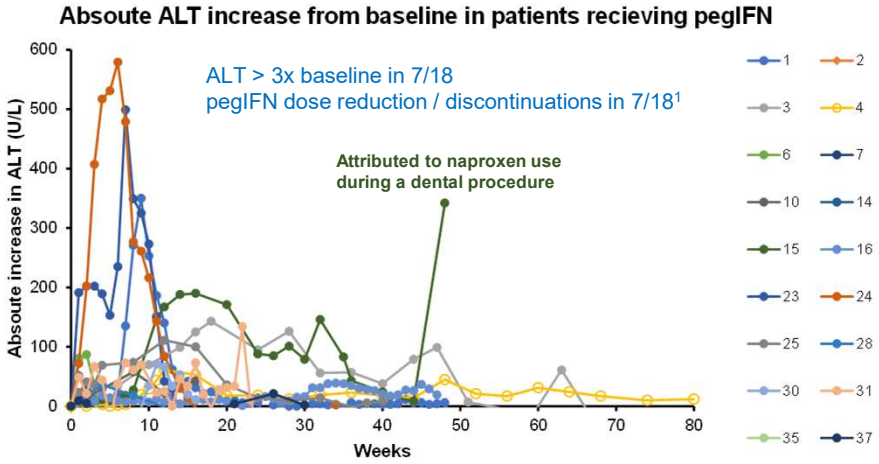
Virological response according to pegIFN therapy

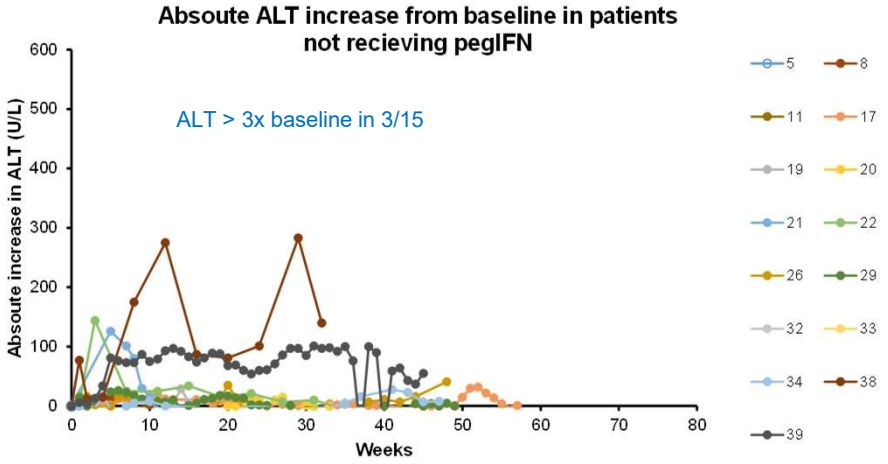


A. Regression analysis
B. T-test
C. Baseline BMI is not available for 10 patients
D. No significant differences in baseline HDV RNA (p=0.37) or HBsAg (p=0.88) were present between –pegIFN and +pegIFN groups.
E. X^2 analysis
F. May reflect bias due to small sample size (decompensated cirrhosis n=6) and 3/6 decomps halted therapy early (2 transplant, 1 burst varices not related to REP 2139-Mg exposure).
G. Change to lack of significance from original abstract submission is attributed to additional REP 2139-Mg dose escalation and or therapy extension since submission of abstract.

REP 2139 is safe and well tolerated in HDV cirrhotics

- No SAE related to REP 2139-Mg
- Reported REP 2139-Mg AE: 1. transient mild injection site reactions (55%)
  2. grade 1-2 thrombocytopenia (18%) self resolving after removal of REP 2139-Mg
- ALT flares are asymptomatic and self resolving (mainly with pegIFN)
  - lower in intensity and prevalence than observed in prior clinical trials





1. one transient reduction (lip lesions), 1 discontinuation due to unavailability (switch in manufacturer) and 5 discontinuations due to AE (fatigue, anemia, petechial hemorrhages, hyperbilirubinemia[2])
2. in one patient with previous poor tolerability to pegIFN, pegIFN was halted to reverse hyperbilirubinemia, REP 2139-Mg dosing was not altered

Summary

- REP 2139-Mg SC is well tolerated and safe in compensated and decompensated HDV cirrhosis
- HDV cure and HBV functional cure is possible in these difficult to treat patients, even in the absence of pegIFN
- In patients with suboptimal response to 250mg SC, increasing REP 2139 doses, transitioning to IV or therapy extension can improve antiviral response
  - Using dose transitioning to improve Cmax is well established for phosphorothioate oligonucleotides
  - A novel SC formulation of REP 2139-Mg is currently in development to improve Cmax in all HDV patients
- ALT flares are asymptomatic but are less intense and prevalent than in non-cirrhotic patients in previous trials

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Additional RCAP patient data

Suboptimal virological response can be improved with REP 2139 dose modification and/or therapy extension

Extension therapy > 48 weeks in 6 patients

- Rescue of initial poor HDV RNA response in 5 patients (6th achieved early HDV RNA TND)
  - 3 HDV RNA TND, 1 HDV RNA < LLOQ, 1 HDV RNA > 2 log decline
- Rescue of HBsAg response in 5 patients
  - Two TND, 2 < 10 IU/mL, 1 < 1 IU/mL
- Three patients completed extension therapy:
  - All HDV RNA TND
  - One HBsAg TND, one HBsAg < 10 IU/mL, one HBsAg rebound (non-compliance issues)

REP 2139 induces HDV cure and HBV functional cure

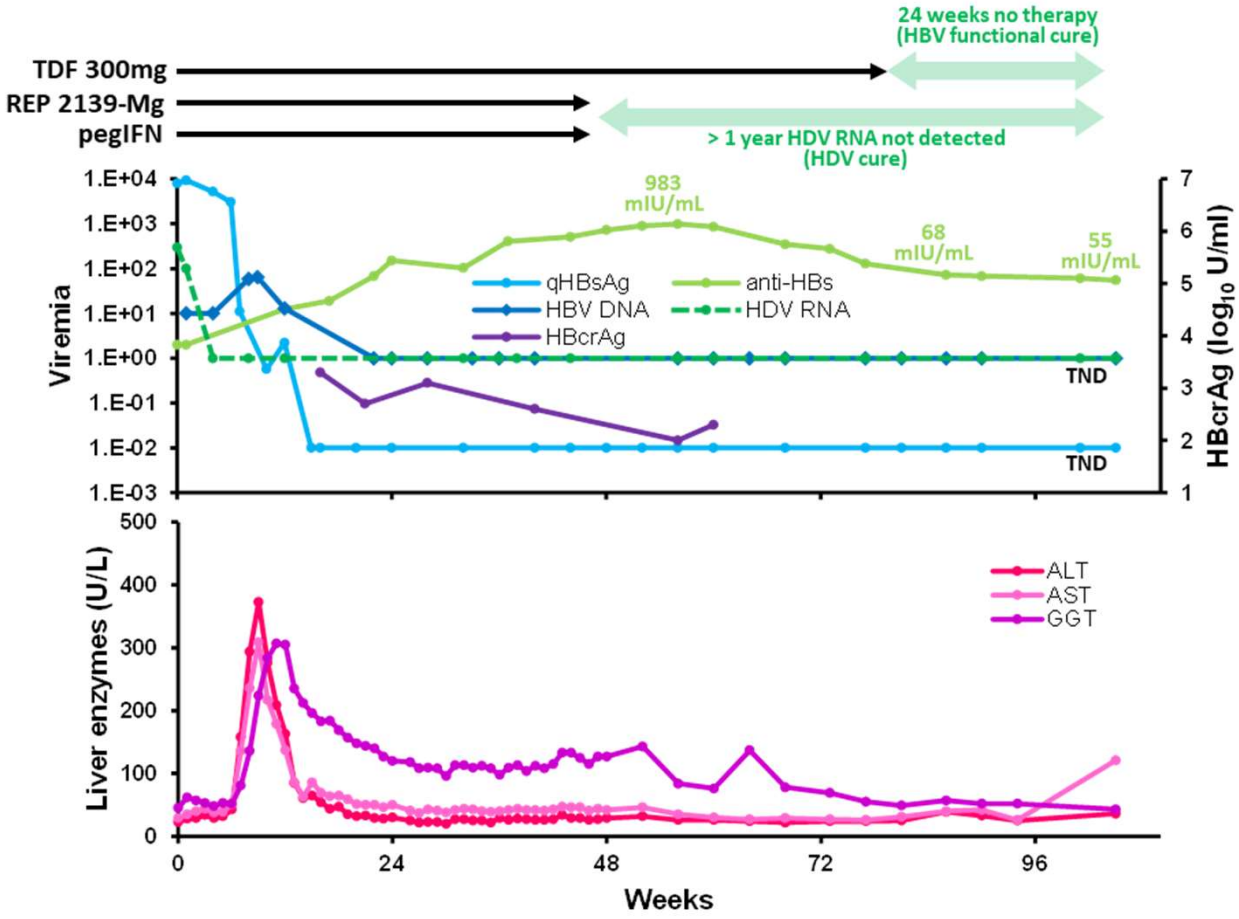
RCAP #1

Marc Bourliere, Marseille, France

Senegalese male, 51 years old
HDV GT-5, cirrhosis Child A5
Previous failure on pegIFN
Previous failure of pegIFN + BLV

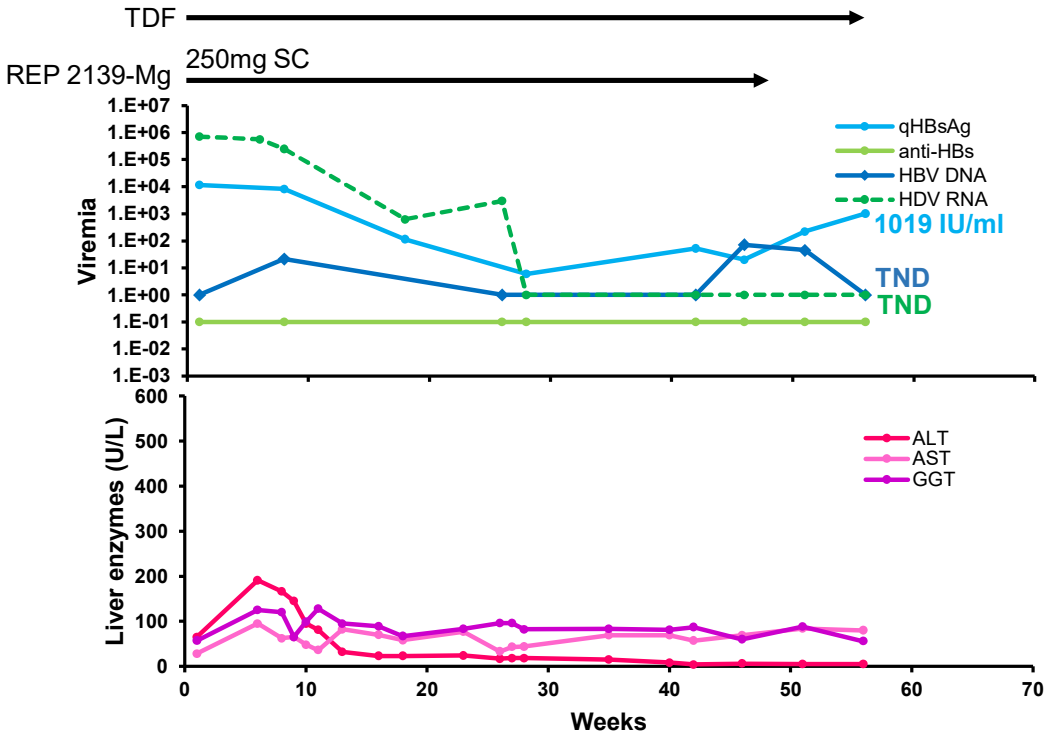
Supervised by Marc Bourliere
Marseille, France

HDV cure established
Functional cure of HBV established



RCAP #21

Magdalena Meszaros, Montpellier, France



48 year old Caucasian female
Compensated cirrhosis

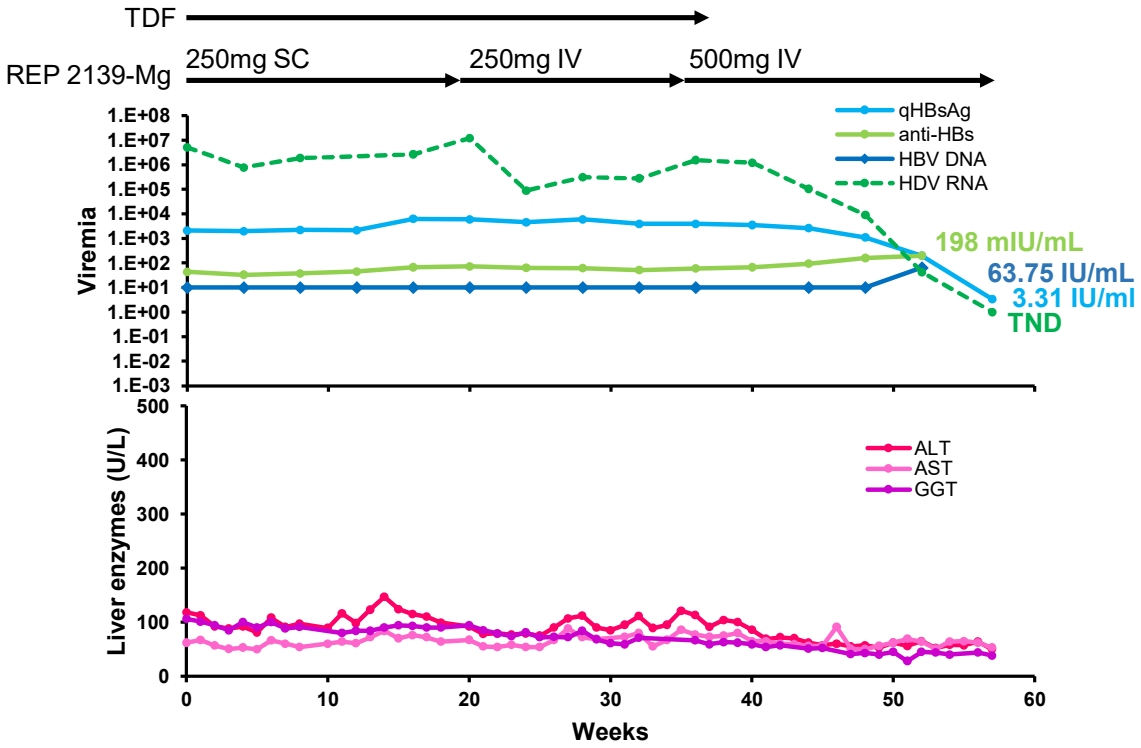
Previous failure during 2mg BLV

- 250mg SC sufficient for HDV RNA clearance but HBsAg decline only to 6 IU/mL during therapy
- Dose increase / extension not possible due limited drug supply

HDV RNA TND and ALT normal are maintained off therapy

RCAP #19

Cihan Yurdaydin, Istanbul, Turkey



30 year old Caucasian male
Compensated cirrhosis

No prior pegIFN or BLV exposure

- No effect at 250mg SC
- Mild effect at 250mg IV (increased C_{max})
- Strong antiviral effect at 500mg IV (further increased C_{max})

Therapy scheduled for 72 weeks is expected to produce HDV cure and HBV functional cure

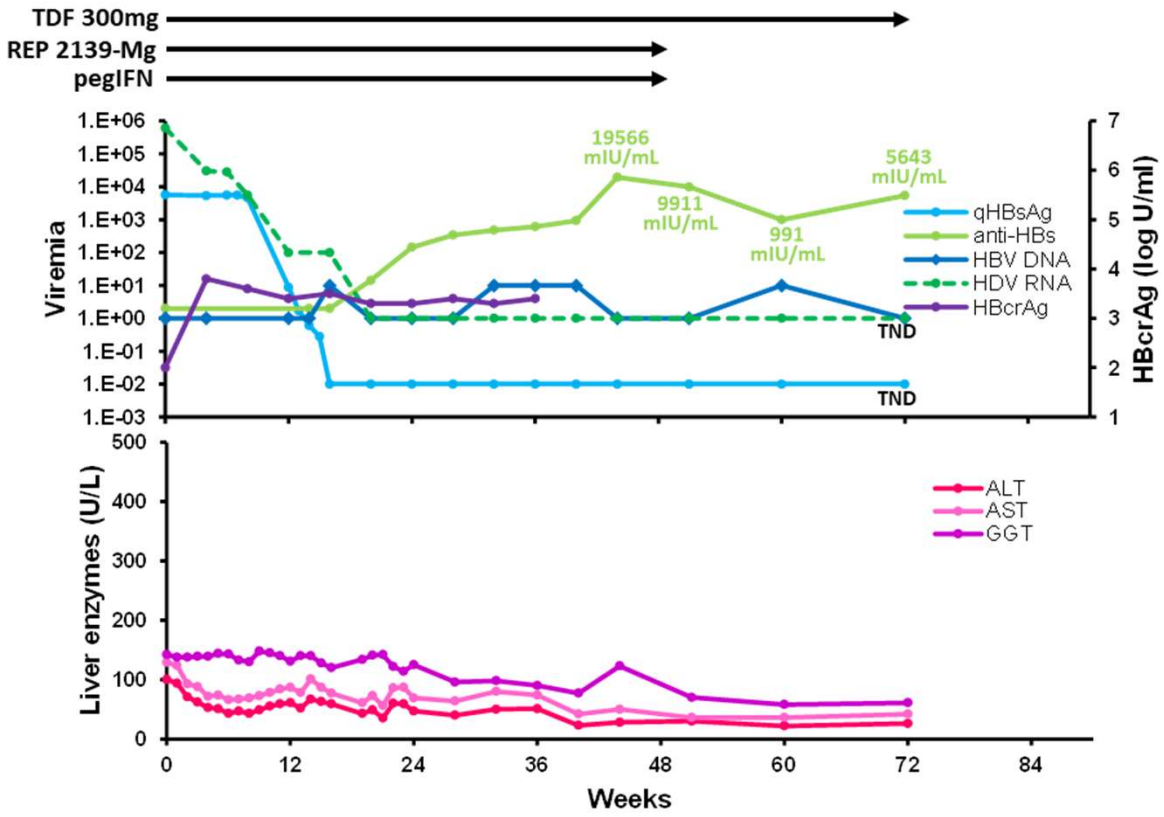
RCAP #2

Veronique Loustaud-Ratti, Limoges, France

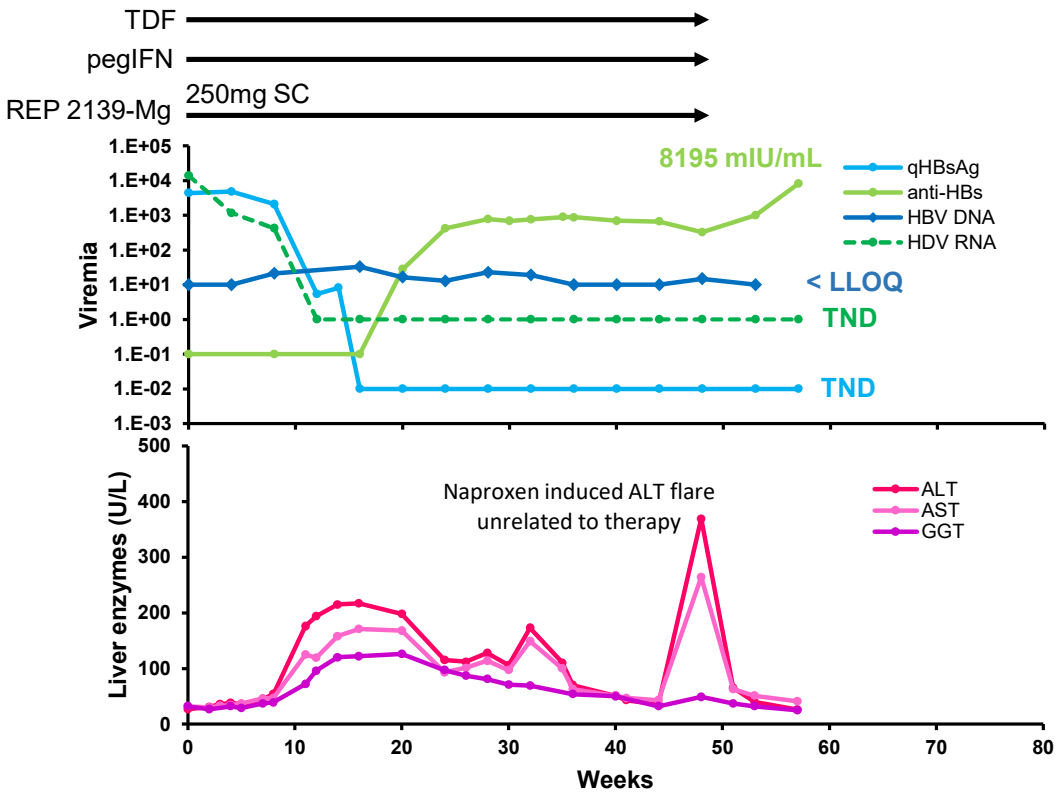
Caucasian male, 47 years old
HDV GT-1, cirrhosis, stage 1 varices
Previous failure to pegIFN
Previously HDV rebound on pegIFN + 2mg BLV

Supervised by Veronique Loustaud-Ratti
Limoges, France

HDV cure established
Persistent HBsAg loss established
(strong indication of HBV functional cure)



RCAP #15
Cihan Yurdaydin, Istanbul, Turkey



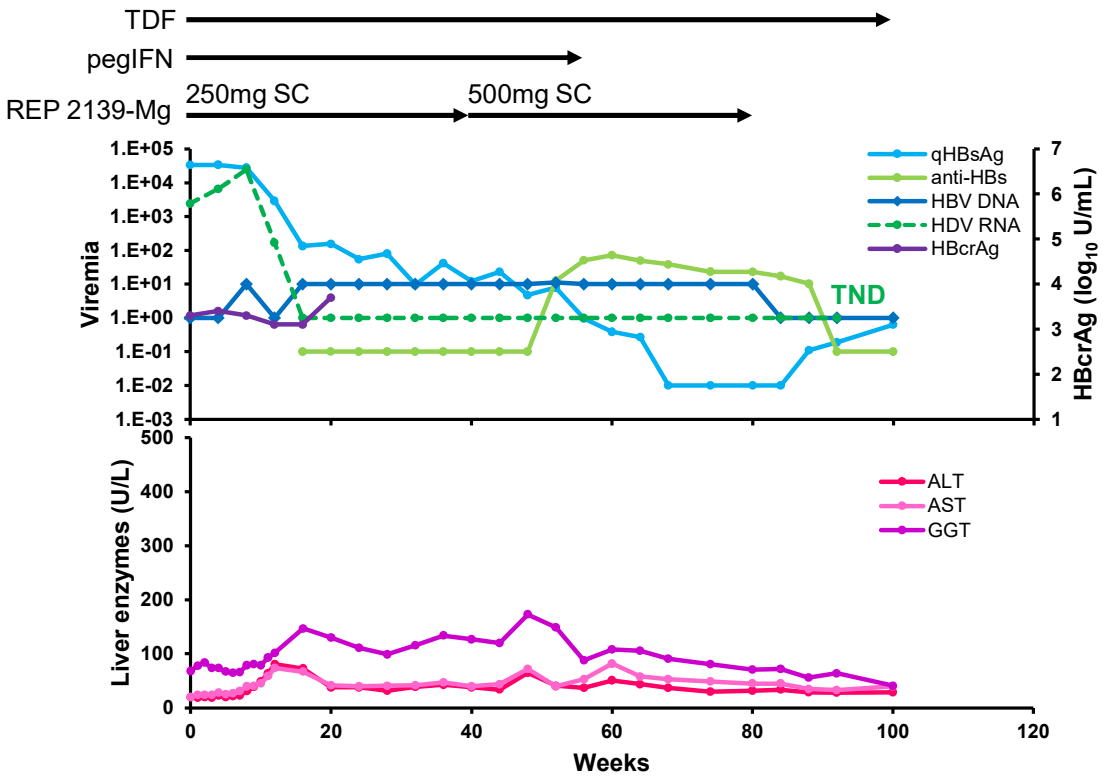
53 year old Caucasian male
Compensated cirrhosis

Previous failure to:
pegIFN

- 250mg SC achieves HDV RNA and HBsAg loss and seroconversion
- Establishes HDV cure and HBV functional cure in combination with pegIFN

RCAP #4

Veronique Loustaud-Ratti, Limoges, France



59 year old Caucasian female
F3 fibrosis

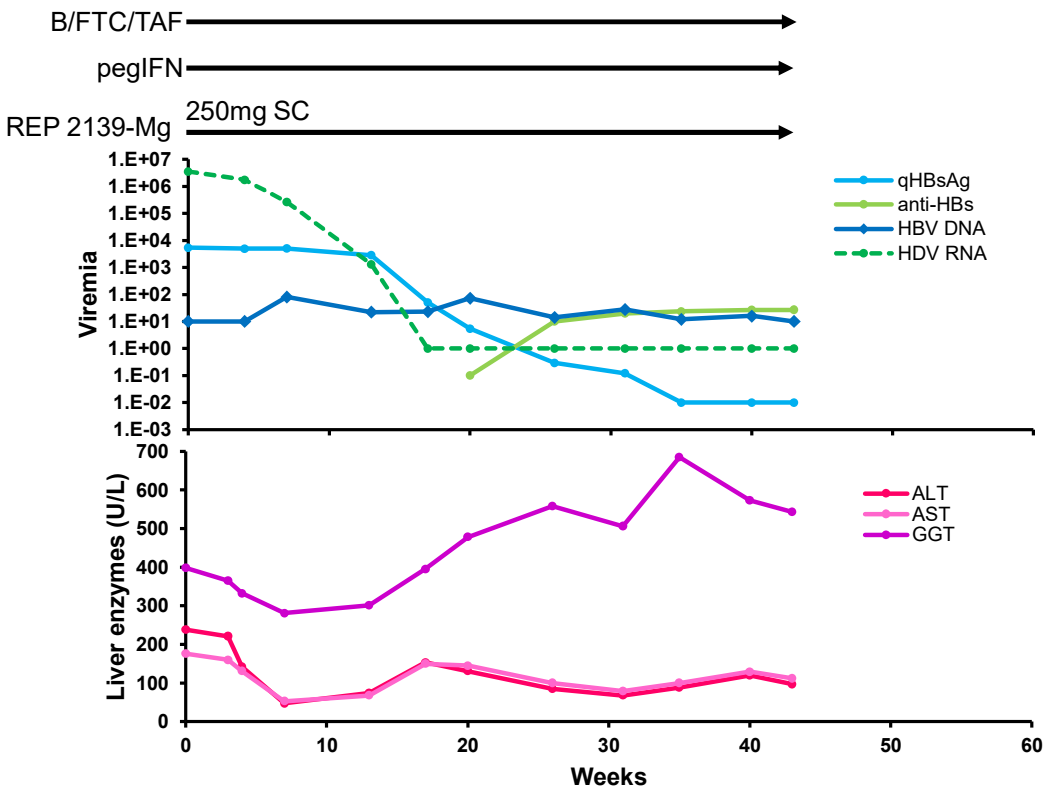
Previous failure to:
pegIFN (poor tolerability)
2mg BLV, 10mg BLV

- pegIFN tolerability improved with REP 2139-Mg
- early HDV RNA clearance with 250mg SC
- 500mg SC increases frequency of REP 2139 loading into hepatocytes
- improves HBsAg response
- Achieves HBsAg loss and seroconversion

HDV TND, normal ALT are maintained off therapy

RCAP #35

Veronique Loustaud-Ratti, Limoges, France



45 year old African female
F3 fibrosis
HIV co-infected

Previous failure on pegIFN + BLV

- HIV suppression is stable on therapy
- 250mg SC achieves HDV RNA loss and HBsAg loss and seroconversion

Scheduled therapy for 48 weeks is expected to achieve HDV cure and HBV functional cure

RCAP #5
Christiane Stern, Versailles, France

Caucasian female, 45 years old
HDV GT-1, decompensated cirrhosis
Pronounced ascites – awaiting liver transplant
pegIFN and BLV contraindicated

Supervised by Christiane Stern
Paris, France

Rapid elimination of ascites at week 4
Recompensation of cirrhosis (Child B8 to A6)
No ALT flare, no systemic AE

Persistent HDV RNA and HBsAg loss 6 months following removal of REP 2139-Mg

Patient has been removed from the transplant list