Achieving functional cure with nucleic acid polymers: updates on mechanistic and clinical data

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Antiviral effects of REP 2139

1 Inhibition of HBV SVP assembly / secretion and HDV envelopment

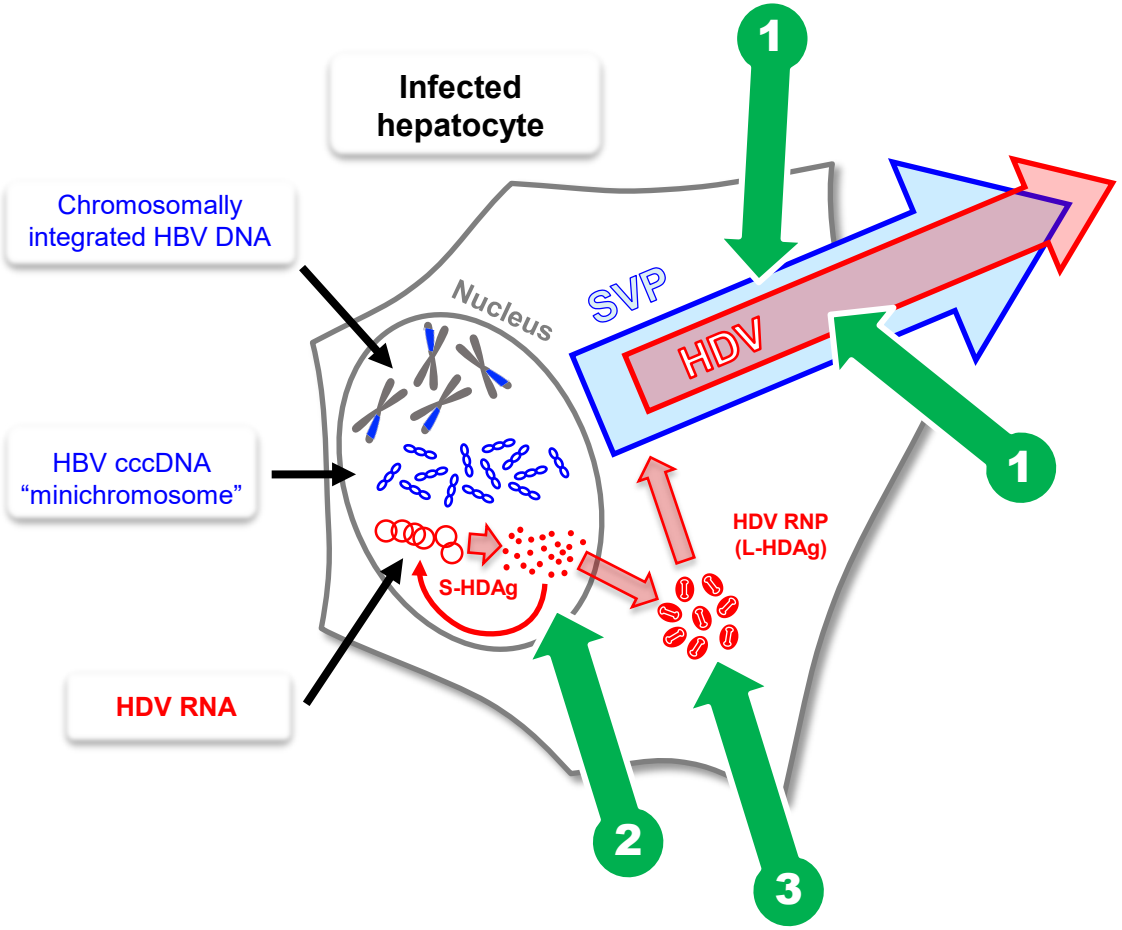
- Allows host mediated clearance of HBsAg / HDV
- Blocks release of HDV

2 Interaction with S-HDAg

- Potential upstream inhibition of HDV RNA synthesis

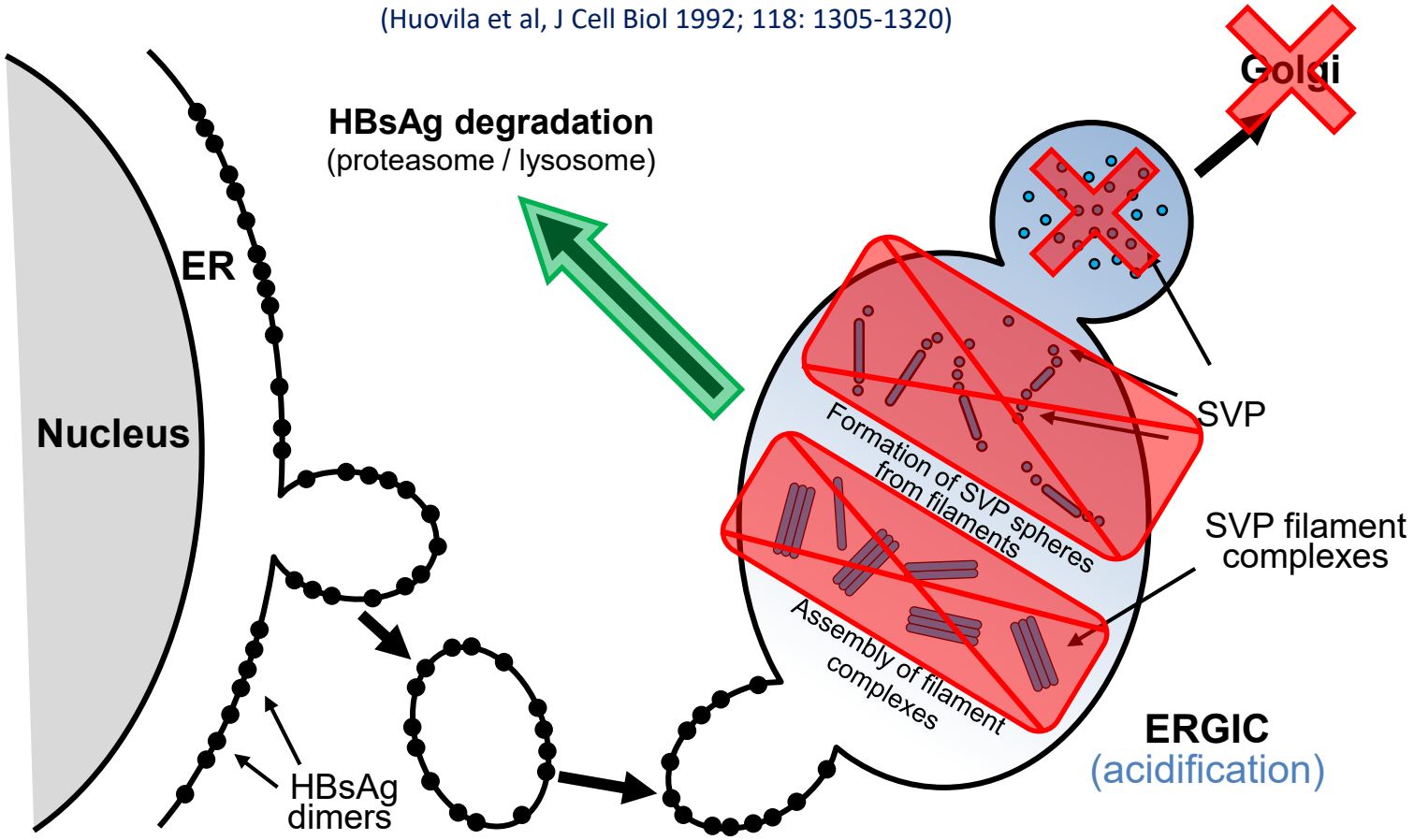
3 Interaction with L-HDAg

- Potential upstream inhibition of HDV RNP assembly



REP 2139:
A nucleic acid polymer (NAP) selectively targeting subviral particles

HBV subviral particle assembly pathway
(from cccDNA or integrated HBV DNA)
(Huovila et al, J Cell Biol 1992; 118: 1305-1320)



REP 2139 enters the ERGIC and inhibits SVP morphogenesis

Intracellular degradation of HBsAg is enhanced

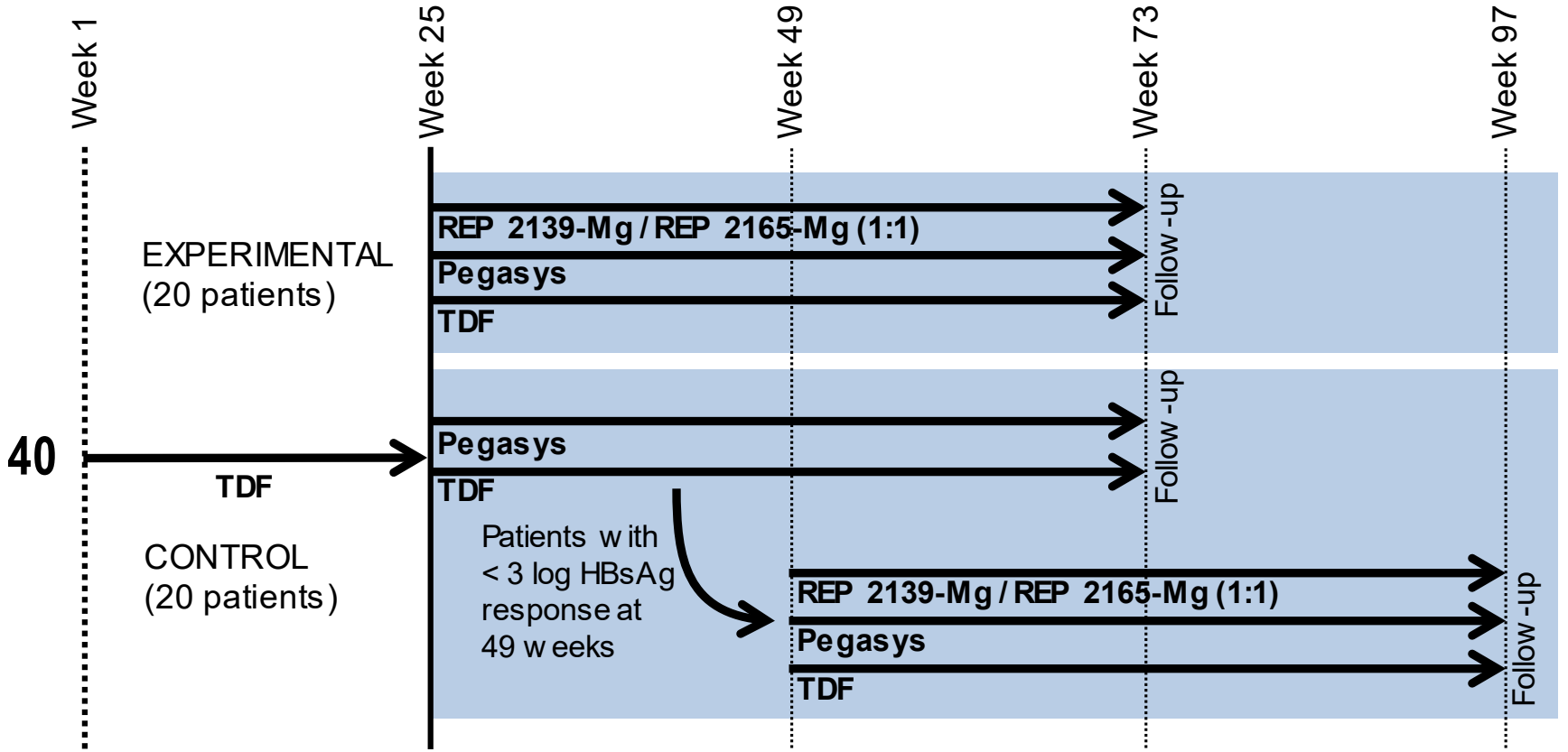
Inhibition of HBsAg secretion (from cccDNA or integrated HBV DNA) is accompanied by declines in intracellular HBsAg

Secretion of HBeAg and Dane particles is unaffected

Blanchet et al., Antiviral Res 2019; 164: 97-105
Vaillant, ACS Inf Dis 2019; 5: 675-687
Poster 241 HBV 2019 meeting
(http://replicor.com/wp-content/uploads/2019/10/Replicor-HBV-meeting-2019-flares-vs-outcome-Poster-242.pdf)

REP 401 Study

Clearing HBsAg to improve immunological recovery



TDF 300mg PO qD

Pegasys 180ug SC qW

NAPs: REP 2139-Mg or REP 2165-Mg 250mg IV qW

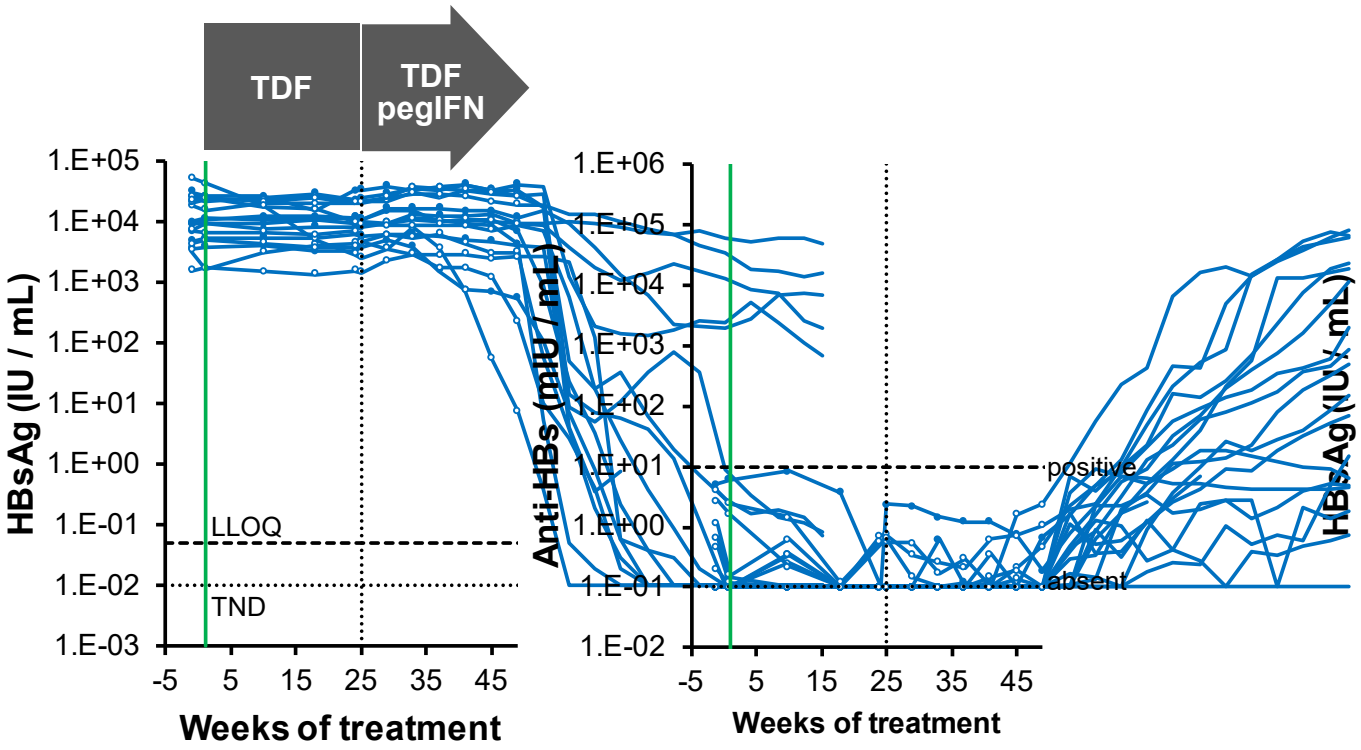
REP 2165 = REP 2139 variant with improved tissue clearance

Roehl et al., Mol Ther Nuc Acids 2017; 8: 1-12

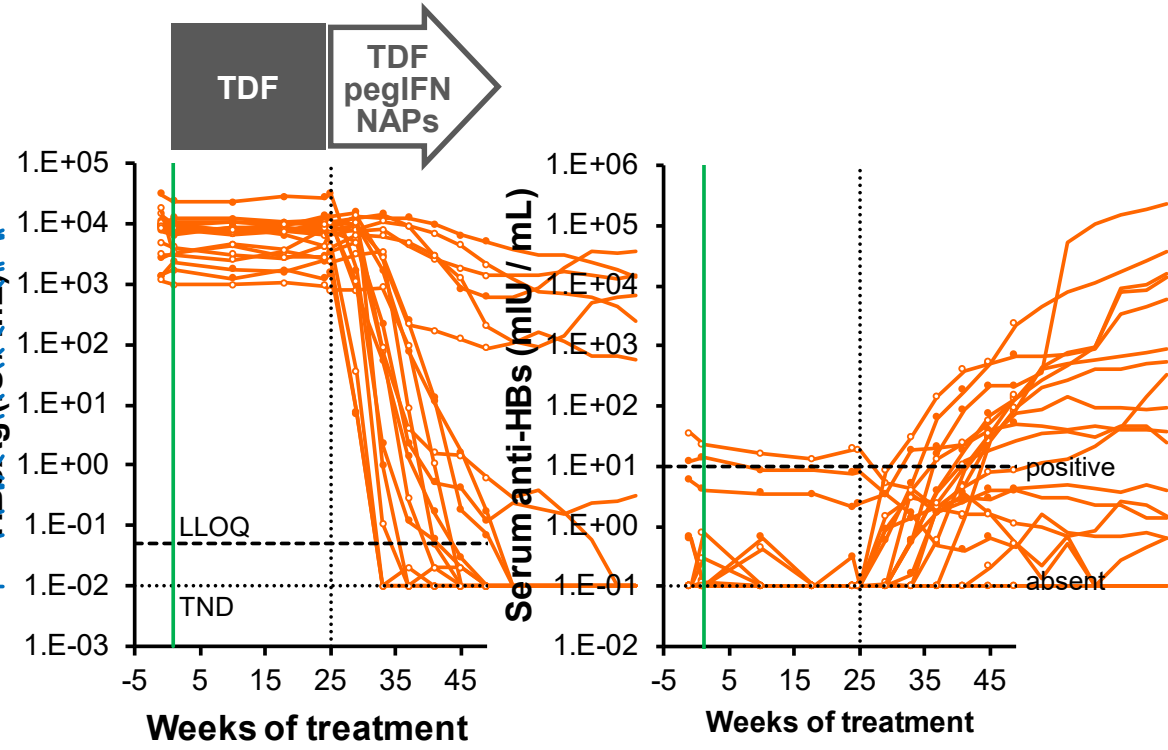
REP 401 study

Effect of NAP addition to TDF + pegIFN

Control



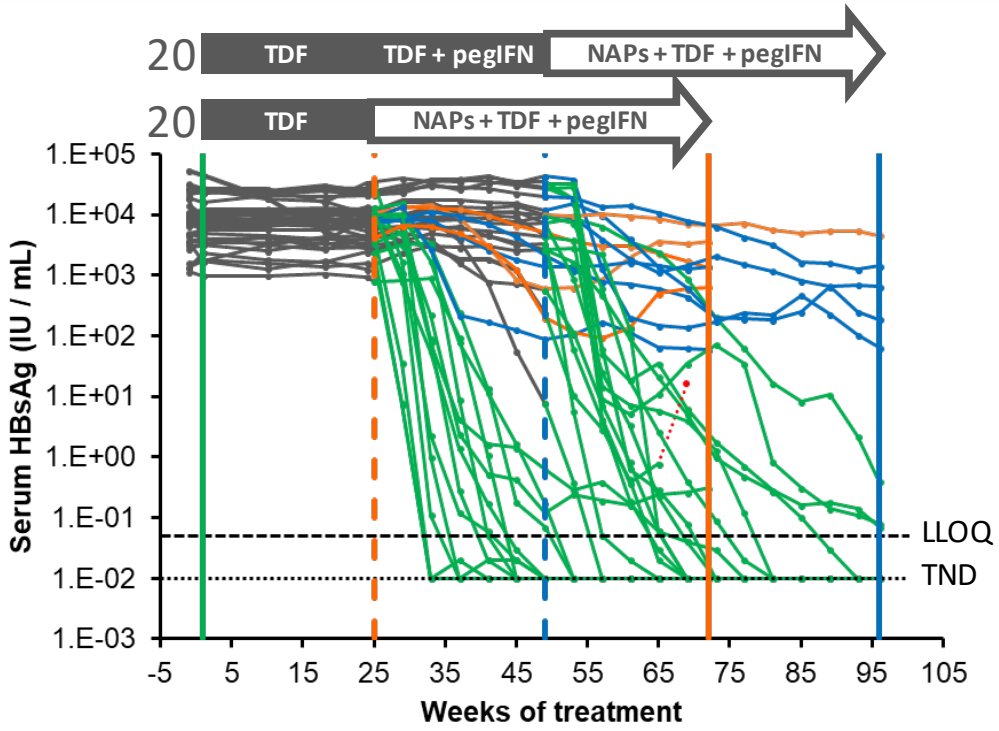
Experimental

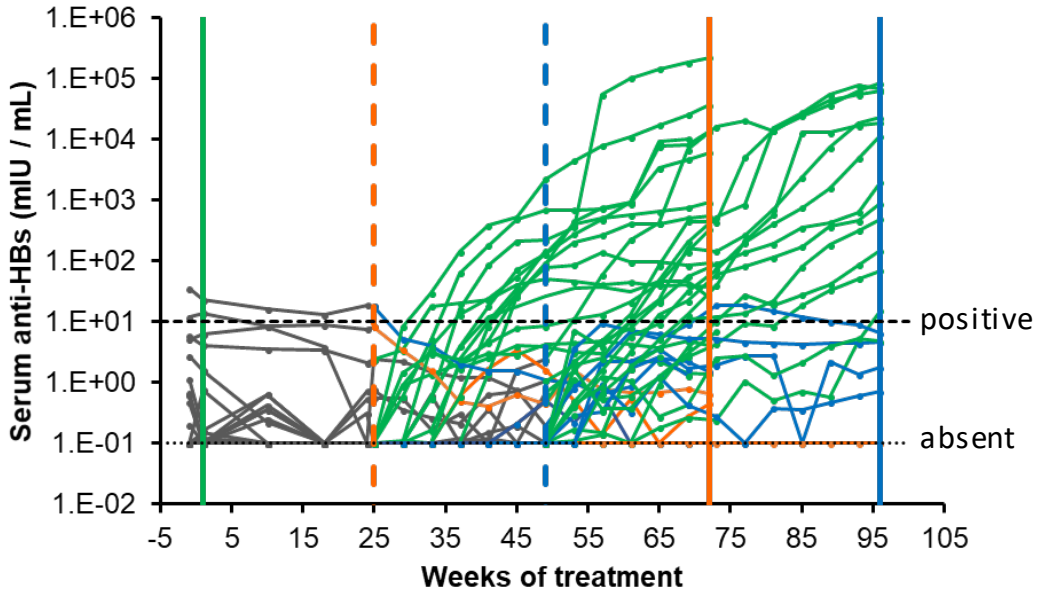


All control participants crossed over to TDF + pegIFN + NAPs

REP 401 study

HBsAg loss and seroconversion during therapy





28/40 HBsAg < 1 IU/mL

24/40 HBsAg loss (≤ 0.05 IU/mL)

(22/24 HBsAg loss in genotype D)

Previously with TDF + pegIFN: no HBsAg loss in genotype D

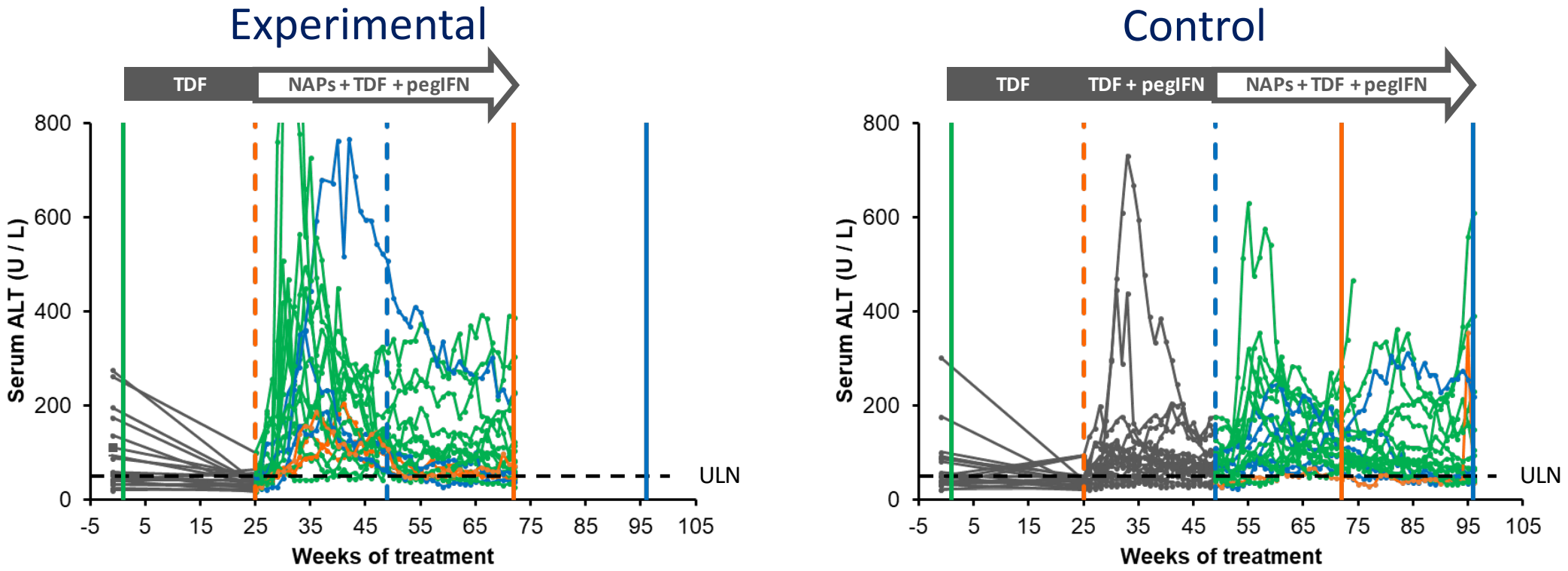
Marcellin et al., Gastroenterology 2016; 150: 134-144

Anti-HBs dramatically increased with HBsAg reduction in the presence of pegIFN

(but only in patients with HBsAg declines to < 1 IU/mL)

NAPs absent | < 1 log reduction in HBsAg | HBsAg > 1 log reduction but > 1 IU/mL | HBsAg < 1 IU/mL

REP 401 transaminase elevations



95% of participants experienced transaminase elevations during therapy

(all otherwise asymptomatic – no impact on liver function)

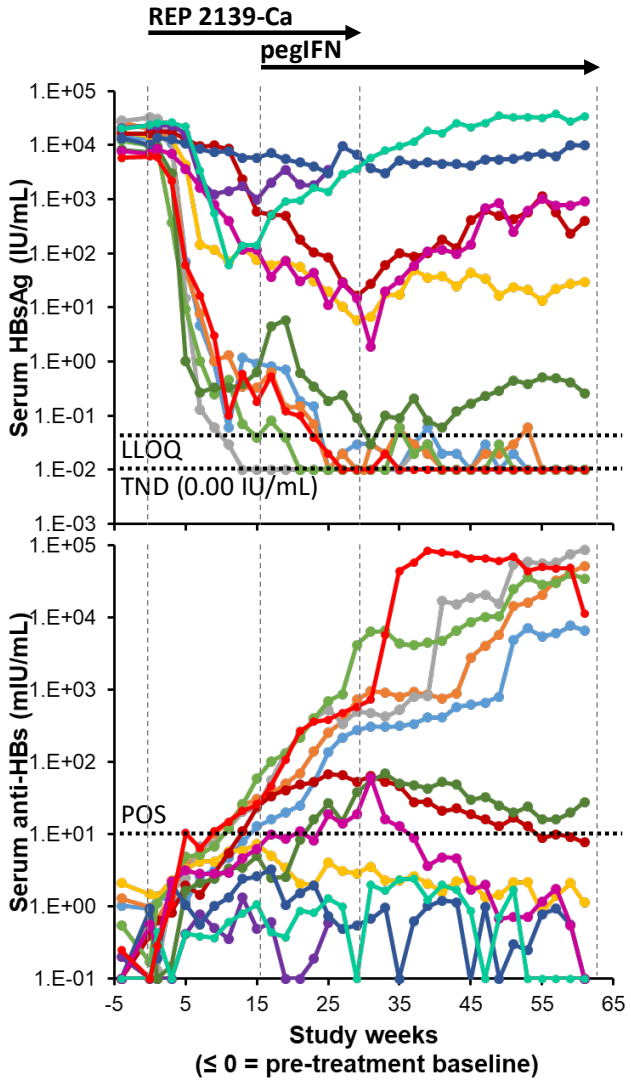
(increased intensity in patients with HBsAg declines to < 1 IU/mL)

NAPs absent | < 1 log reduction in HBsAg | HBsAg > 1 log reduction but > 1 IU/mL | HBsAg < 1 IU/mL

Final REP 401 outcome summary

Completed treatment and ≥ 24 weeks of follow-up		36 (32 completed 48 weeks of follow-up)
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	**Virologic control (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%**

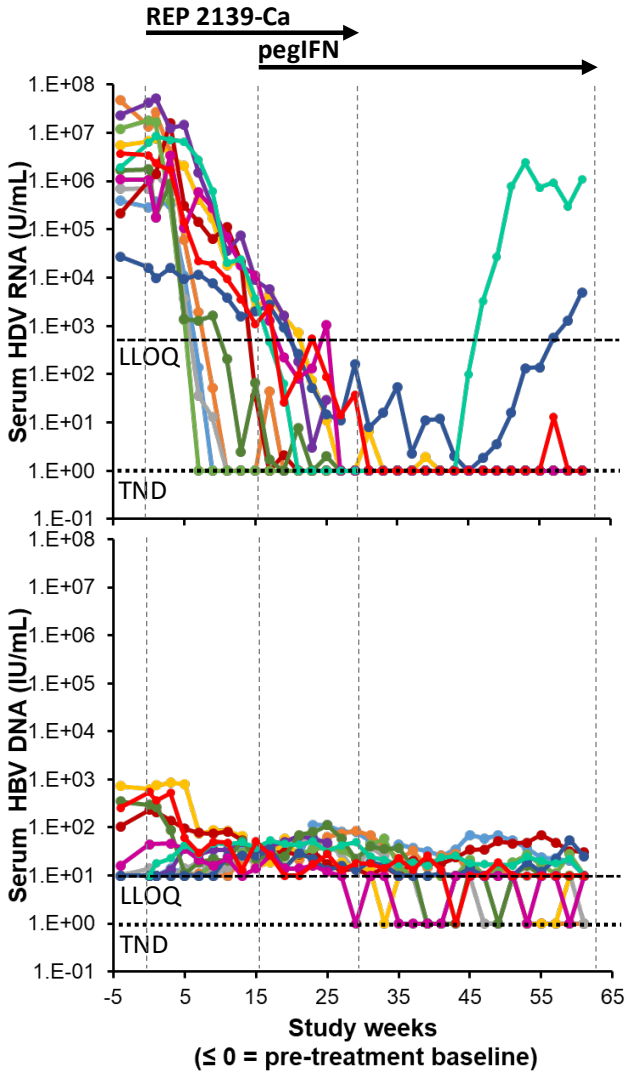
Antiviral effects during REP 2139-Ca / pegIFN in REP 301



Rapid HBsAg clearance prior to pegIFN

Rapid and dramatic increase in anti-HBs with pegIFN

Only with HBsAg < 1 IU/mL prior to pegIFN



Universal and rapid HDV RNA response

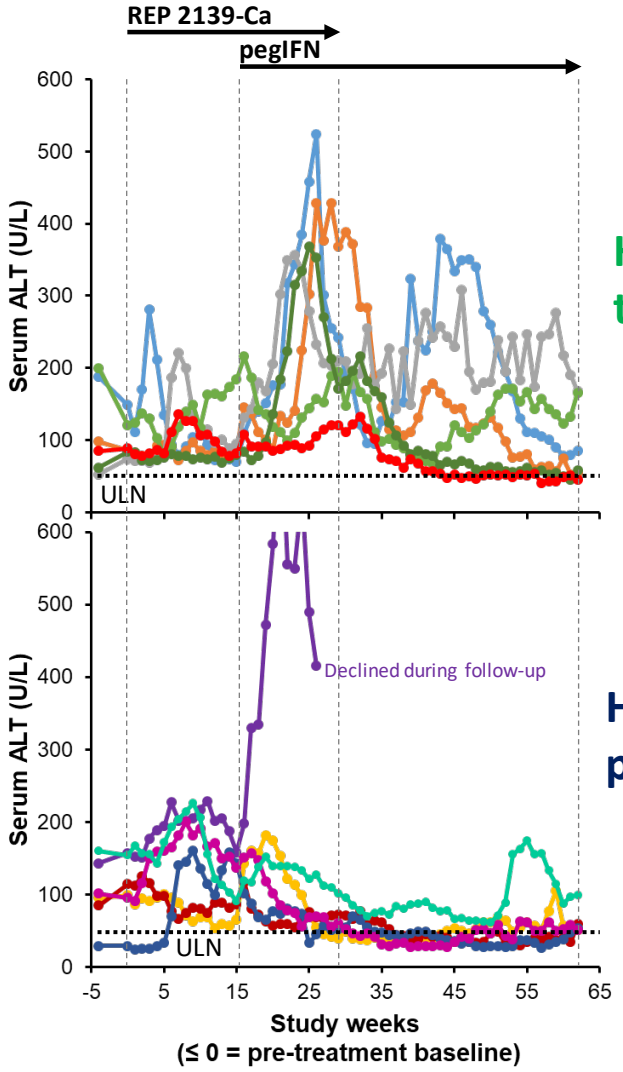
Target not detected in all participants during therapy

Even in participants with moderate HBsAg response

Likely due to upstream direct effects against HDV replication

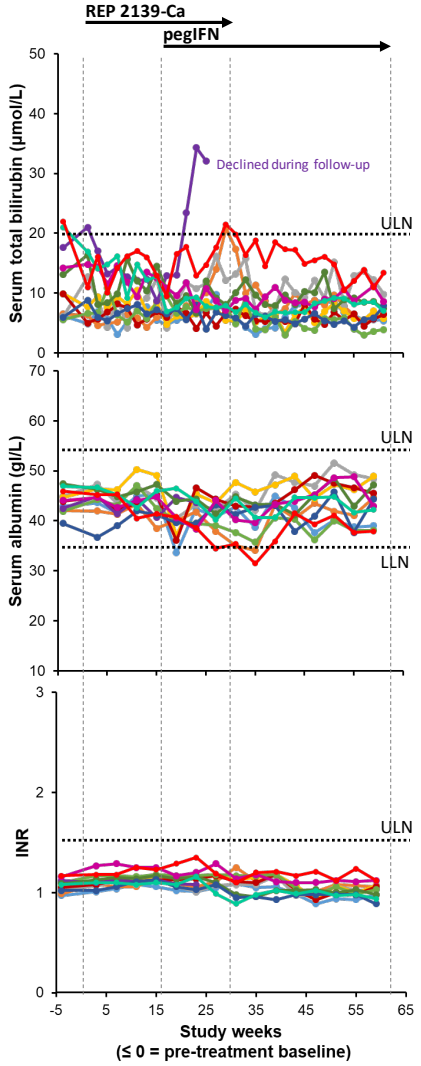
HBV DNA remains well controlled in absence of NUCs

REP 301 transaminase flares



HBsAg < 1 IU/mL prior to pegFN

HBsAg > 1 IU/mL prior to pegIFN



Liver function unaffected

(except one case of pegIFN induced DILI)

Persistent clinical, HBsAg and HDV RNA responses in REP 301-LTF

Completed treatment and 3-3.5 years of follow-up		**11**
Clinical response	Normal ALT	8/11 (73%)
	Normal / declining liver median stiffness	7/11 (64%)
HBsAg response	< 1 IU/ml	6/11 (55%)
	≤ LLOQ (0.05 IU/mL)	5/11 (42%)
	Seroconversion	4/11 (36%)
HDV RNA response	**> 2 log_{10} reduction from baseline**	**9/11 (82%)***
	TND	**7/11 (64%)**

***2 participants maintaining 2.67 and 2.12 log_{10} HDV RNA reduction from baseline at 3.5 years follow-up did not maintain normal liver function during follow-up.**

HBV outcomes in participants with persistent HDV RNA negativity

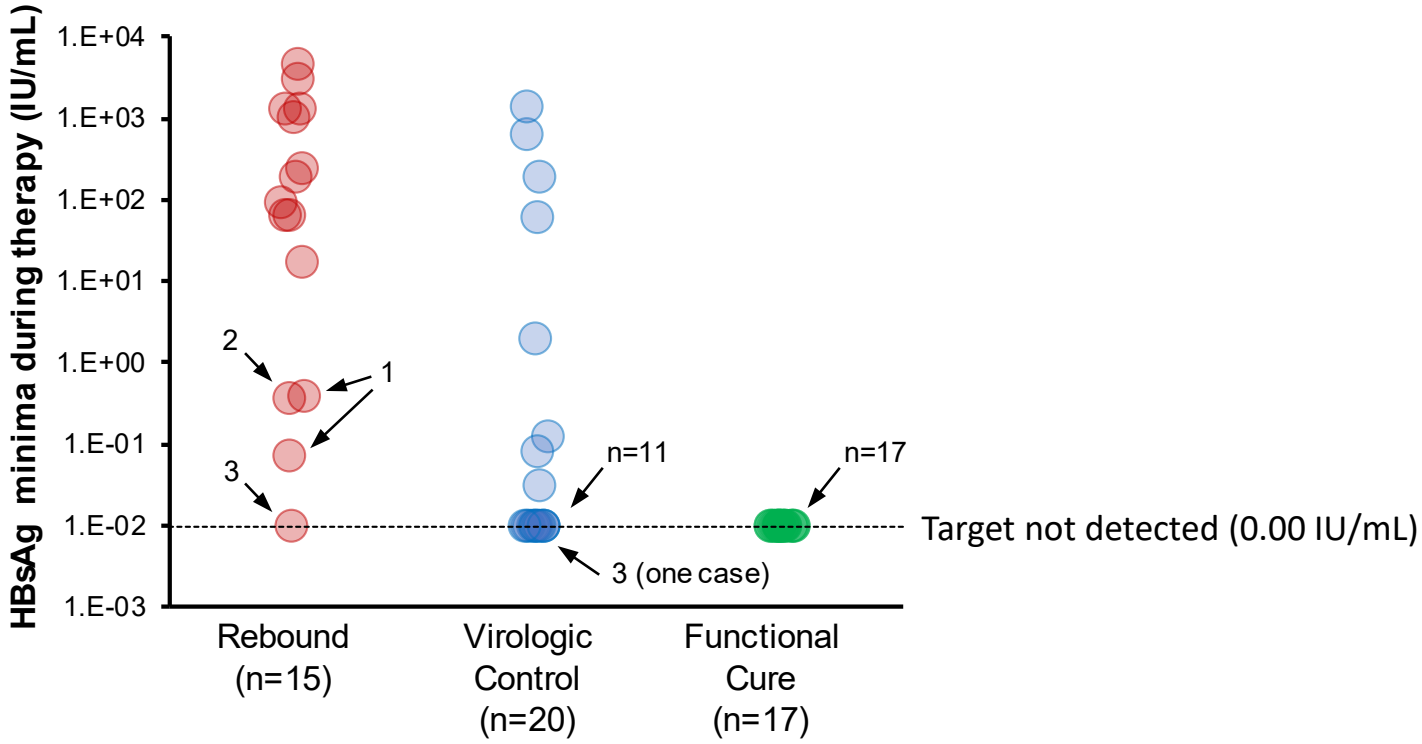
Functional cure of HDV at 3-3.5 tears of follow-up (HDV RNA TND, ALT normal)		**7**
HBV DNA response	≤ 2000 IU/mL	7/7 (100%)
	Target not detected (TND)	5/7 (71%)
HBV virologic response	Virologic control HBV (HBV DNA ≤ 2000 IU/mL, normal ALT)	3/7 (43%)
	Functional cure HBV (HBsAg < LLOQ, HBV DNA TND, normal ALT)	4/7 (57%)
	HBV clinical benefit, no therapy required (Low risk of progression, reduced risk of HCC)	**7/7 (100%)**

Predicting HBV therapeutic outcomes

All 52 participants in the REP 301 and REP 401 studies

Virologic control:
(inactive chronic HBV)
HBV DNA ≤ 2000 IU/mL
Normal ALT

Functional cure:
HBsAg < LLOQ
HBV DNA target not detected
Normal ALT



1. Late decline in HBsAg.
2. Early withdrawal from therapy due to pegIFN related depression.
3. Early withdrawal from therapy due to personal reasons not related to tolerability.

Achieving HBsAg 0.00 IU/mL during therapy appears necessary but not sufficient to achieve functional cure

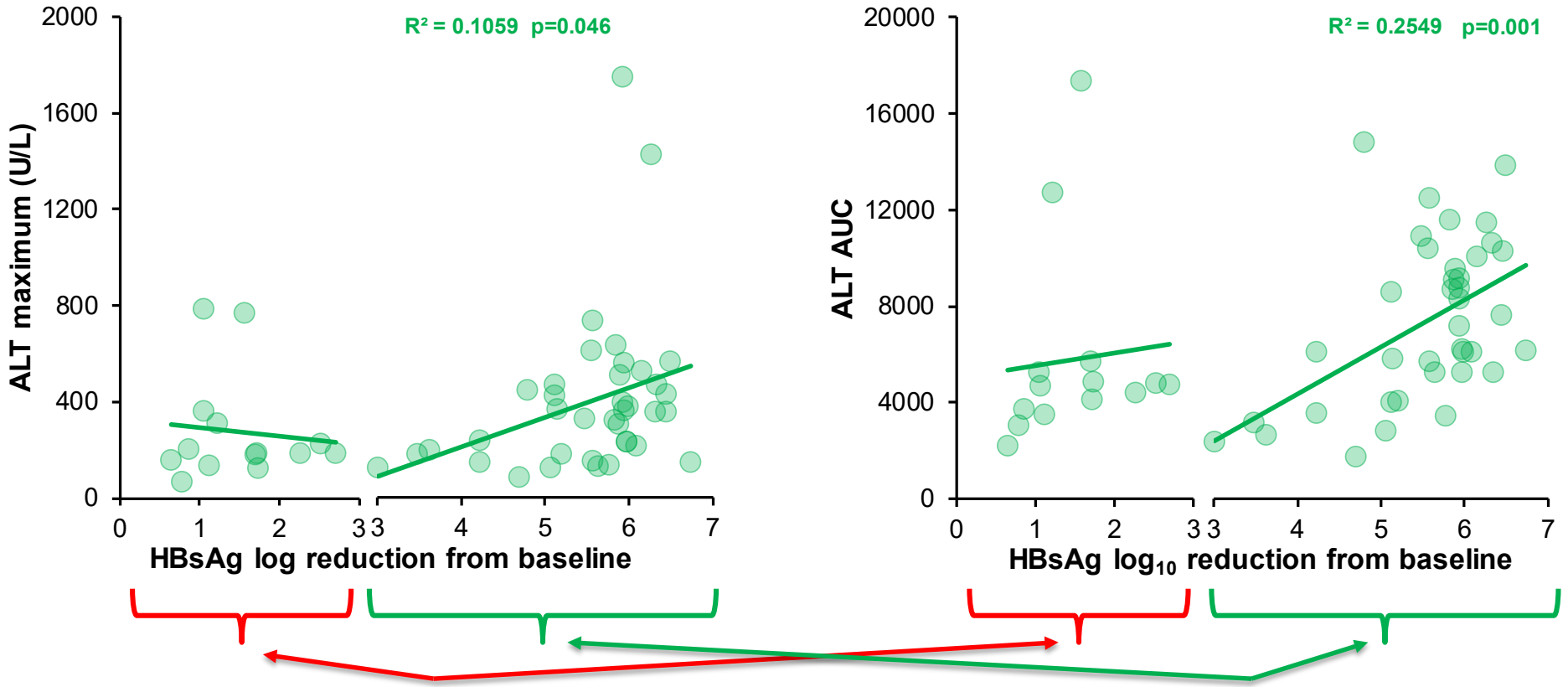
Predicting HBV therapeutic outcomes

All 52 participants in the REP 301 and REP 401 studies

Virologic control:
(inactive chronic HBV)
HBV DNA ≤ 2000 IU/mL
Normal ALT

Functional cure:
HBsAg < LLOQ
HBV DNA target not detected
Normal ALT

Increased ALT flare activity during pegIFN is correlated with HBsAg reductions ≥ 3 log_{10} from baseline



"non-productive flares"
71% rebound, 29% virologic control

"productive flares (minimal HBsAg present)"
47% functional cure, 40% virologic control, 13% rebound

Poster 242 HBV 2019 meeting

Summary

Circulating HBsAg (> 99.99% from SVP): blocks host immune function

REP 2139 selectively targets assembly and secretion of SVP

- Secretion of HBeAg and Dane particles is not affected
- **Simultaneously lowers intracellular HBsAg and blocks HBsAg replenishment in the blood.**
- Direct targeting of HDV replication by REP 2139 may help establish of functional cure of HDV

NAP-mediated HBsAg clearance during TDF + pegIFN dramatically improves outcomes

- **HBV virologic control / functional cure established in 78% of participants (HBV mono-infection)**
- Liver function normal in 89% of participants with reversal of liver inflammation / fibrosis
- TDF + pegIFN + REP 2139-Mg will achieve high rates of HBV and HDV functional cure in co-infection.

Predicting positive therapeutic outcomes

- HBsAg (0.00 IU/mL) during therapy appears necessary but not sufficient for functional cure
- Transaminase elevations are correlated with HBsAg reduction
- **Transaminase elevations while HBsAg is < 1 IU /mL during therapy occur in all participants with functional cure**
- On-therapy transaminase flares may facilitate the establishment of virologic control and functional cure

A collaborative effort !

Clinical evaluations:

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Dhaka, Bangladesh
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Chișinău, Moldova
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