Achieving functional cure with nucleic acid polymers: final results of the REP 401 study

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HBV
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Breaking the chronicity of chronic HBV infection

Chronic HBV infection still persists in up to 292 million people. **WHY?**

HBsAg involved in preventing the establishment of immune control

HBsAg is an important immune checkpoint inhibitor in chronic HBV infection

- Inhibits innate and adaptive immunity[1-5]
- Exhausts the HBsAg specific immune response[6-10]
- Limits the effectiveness of immunotherapies[11-15]

HBsAg is the most abundant circulating viral antigen

- > 99.99% derived from subviral particles
  - Assembled and secreted independently from virions
  - Assembled and secreted in part independently of cccDNA (from integrated HBV DNA)

Difficult to target with direct acting antivirals

1. Kondo et al., ISRN Gastro 2013;2013:935295 (review)
2. Lebosse et al., J Hepatol 2017**;** *66:* 897-909.
3. Aillot et al., Anti Microb Agents Chemother 2018; 62: e01741
4. Wang et al., J Immunol 2013; 190: 5142-5151
5. Tout et al., J Immunol 2018; 201: 2331-2344
6. Yang et al., Int Immunopharmacol 2016; 38: 291-297
7. Rydell et al., Virology 2017; 509: 67-70
8. Moffat et al., Vaccine 2013; 31: 2310-2316
9. Ferrari, Liver Int 2015; 35 Suppl 1: 121-128 (review)
10. Boni et al., J Virol 2007; 81: 4215-4225
11. Zhu et al. J Immunol 2016; 196: 3079-3087.
12. Xu et al., Biochem Biophys Res Comm 2016; 473: 219-223.
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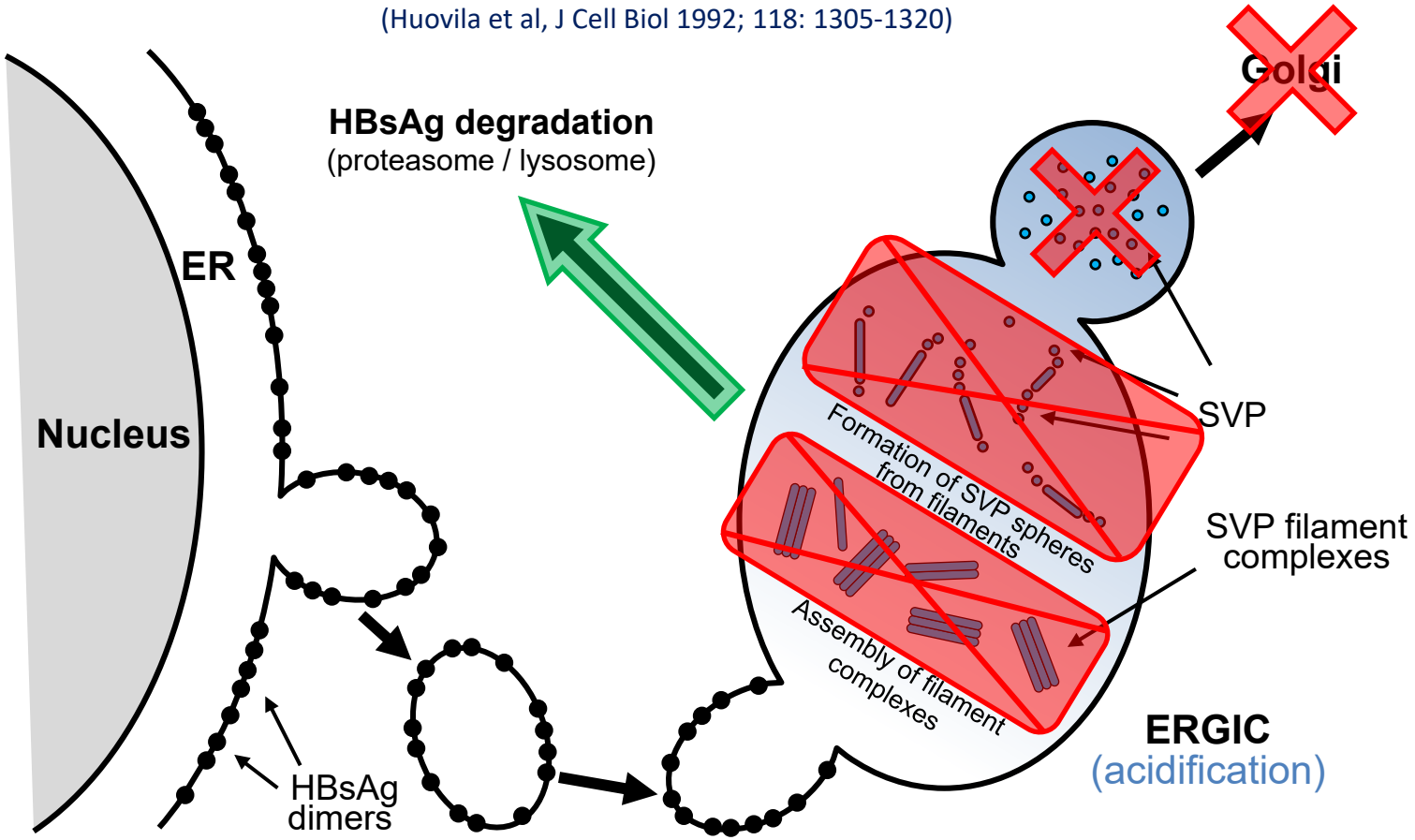
REP 2139:
a nucleic acid polymer (NAP) selectively targeting subviral particles

HBV subviral particle assembly pathway
(from cccDNA or integrated HBV DNA)

(Huovila et al, J Cell Biol 1992; 118: 1305-1320)



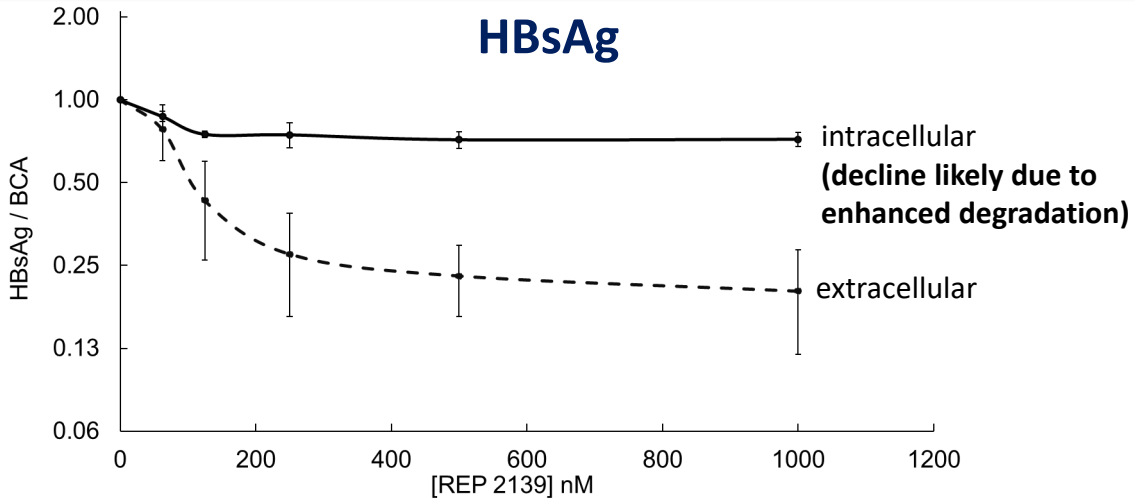
REP 2139 enters the ERGIC and inhibits SVP morphogenesis

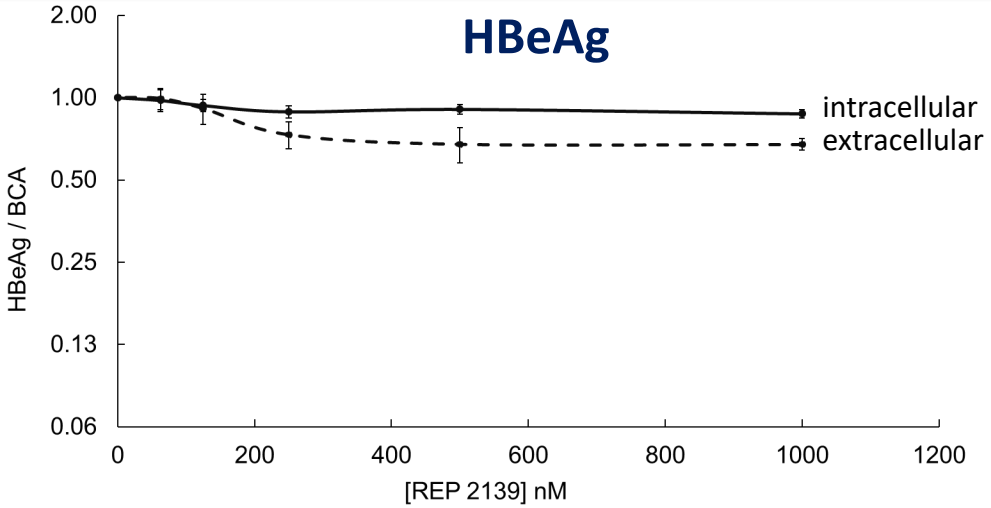
Intracellular degradation of HBsAg is enhanced

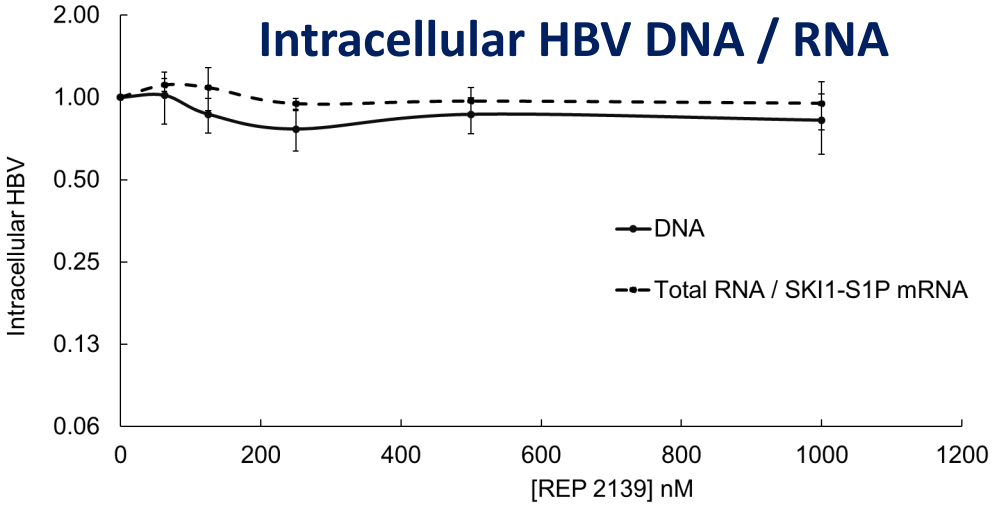
Inhibition of HBsAg secretion (from cccDNA or integrated HBV DNA) is accompanied by declines in intracellular HBsAg

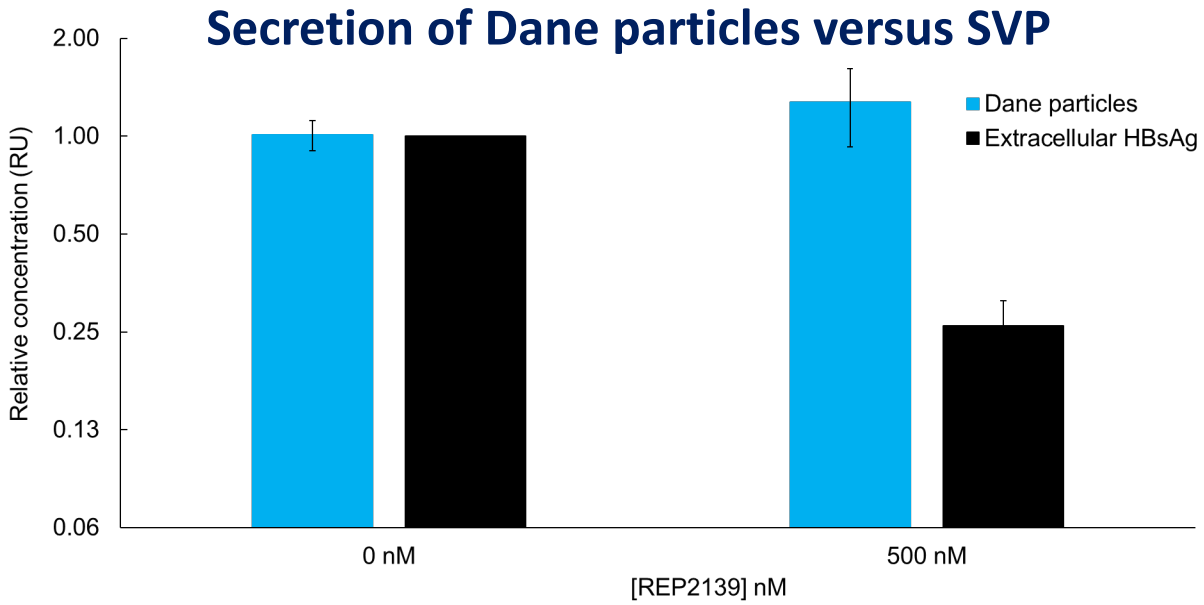
Blanchet et al., Antiviral Res 2019; 164: 97-105
Vaillant, ACS Inf Dis 2019; 5: 675-687

REP 2139 selectively targets subviral particles
(HepG2.2.15 cells)









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Previous effects of NAPs *in vivo* and in humans

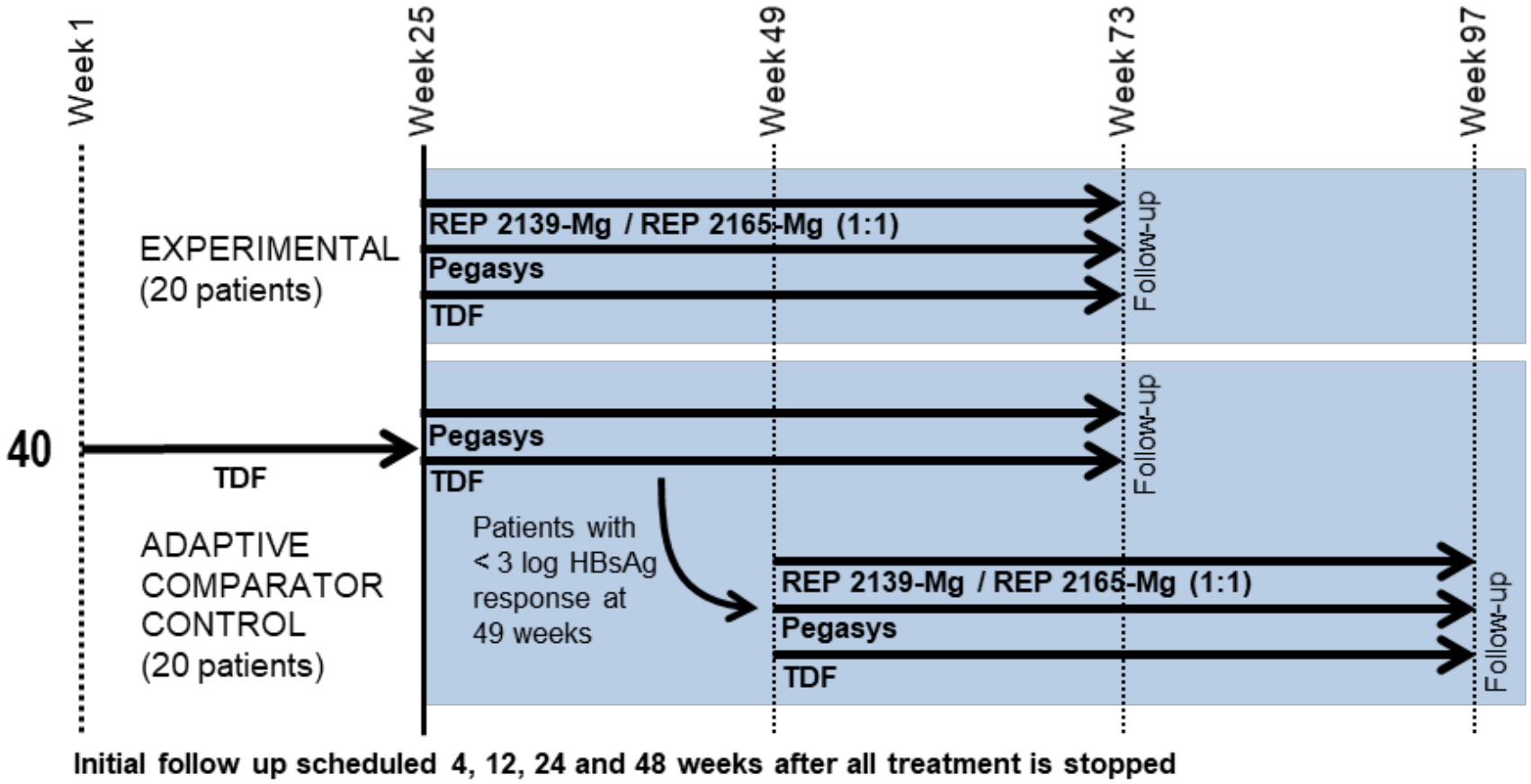
Monotherapy *in vivo* (DHBV)
Clearance of serum HBsAg, increased anti-HBs, clearance of serum HBV DNA
Early declines in cccDNA and liver HBV DNA
Clearance of HBsAg, HBcAg and multilog reduction in cccDNA and HBV DNA in the liver
Control of serum and liver virema persists after removal of therapy

Monotherapy in humans
Clearance of HBsAg, HBeAg, HBsAg and HBeAg seroconversion, multilog reduction / clearance of HBV DNA
Clearance of HDV RNA (in HBV / HDV co-infection)
Asymptomatic transaminase flares in subjects achieving HBsAg < 1 IU/mL
Establishment of virologic control / functional cure of HBV infection off-therapy, normalization of liver function (in some subjects)

REP 2139 monotherapy followed by add on immunotherapy (pegIFN or thymosin alpha 1)
Increased speed of HBsAg clearance, dramatic increase in anti-HBs production
Increased magnitude and incidence of asymptomatic transaminase flares (when HBsAg is < 1 IU/mL)
Increased rates of virologic control / functional cure of HBV, persistent elimination of HDV off therapy
Normalization of liver function and reversal of liver inflammation / fibrosis off therapy

Vaillant, ACS Inf Dis 2019; 5: 675-687

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

TDF + pegIFN + REP 2139-Mg or REP 2165-Mg

TDF: **Block production of infectious virus and replenishment of cccDNA**

Control of serum HBV DNA by TDF is unaffected by addition of pegIFN or NAPs

TDF + pegIFN: **Addition of immunotherapy to restore immune control**

HBsAg declines < 0.5 $\log_{10}$ from baseline in 17/20 patients after 24 weeks – further treatment futile

TDF + pegIFN + NAPs: **Lower intrahepatic HBsAg and block replenishment of serum HBsAg**

REP 2139-Mg = REP 2165-Mg over 48 weeks of triple combination therapy

Rapid HBsAg reduction (> 5 $\log_{10}$ reduction to 0.00 IU/mL [TND] as quickly as 10 weeks)

90% HBsAg response (> 1 $\log_{10}$ from baseline), 60% TND (within 24 weeks)

60% HBsAg seroconversion (up to 233,055 mIU/mL)

Transaminase flares (> 3X ULN) occurred in 95% of participants

Concomitant with NAP-induced HBsAg declines in the presence of pegIFN

Not accompanied by alteration in liver function or any signs of hepatic decompensation

(consistent with overall positive impact of transaminase flares during therapy of chronic HBV[1-10])

1. Nair and Perillo, Hepatology 2001; 34: 1021-1026
2. Ter Borg et al., J Clin Virol 2008; 42: 160-1643
3. Sonneveld et al., Clin Inf Dis 2013; 56: 100-105
4. Nagaoka et al., Hepatol Res 2016; 46: E89-E99
5. Chi et al., J Gastroenterol Hepatol 2016; 31: 1882-1887
6. Seo et al., Clin Mol Hepatol 2017; 23: 154-159
7. Yano et al., Biomed Rep 2017; 7: 257-262.
8. Jeng et al., J Viral Hep 2018; 25: 421-428
9. Wong et al., Liver Int 2018; 38: 1760-1769.
10. Bramania et al., Clin Gastroenterol Hepatol 2019; Epub Feb 9

Final REP 401 outcome summary

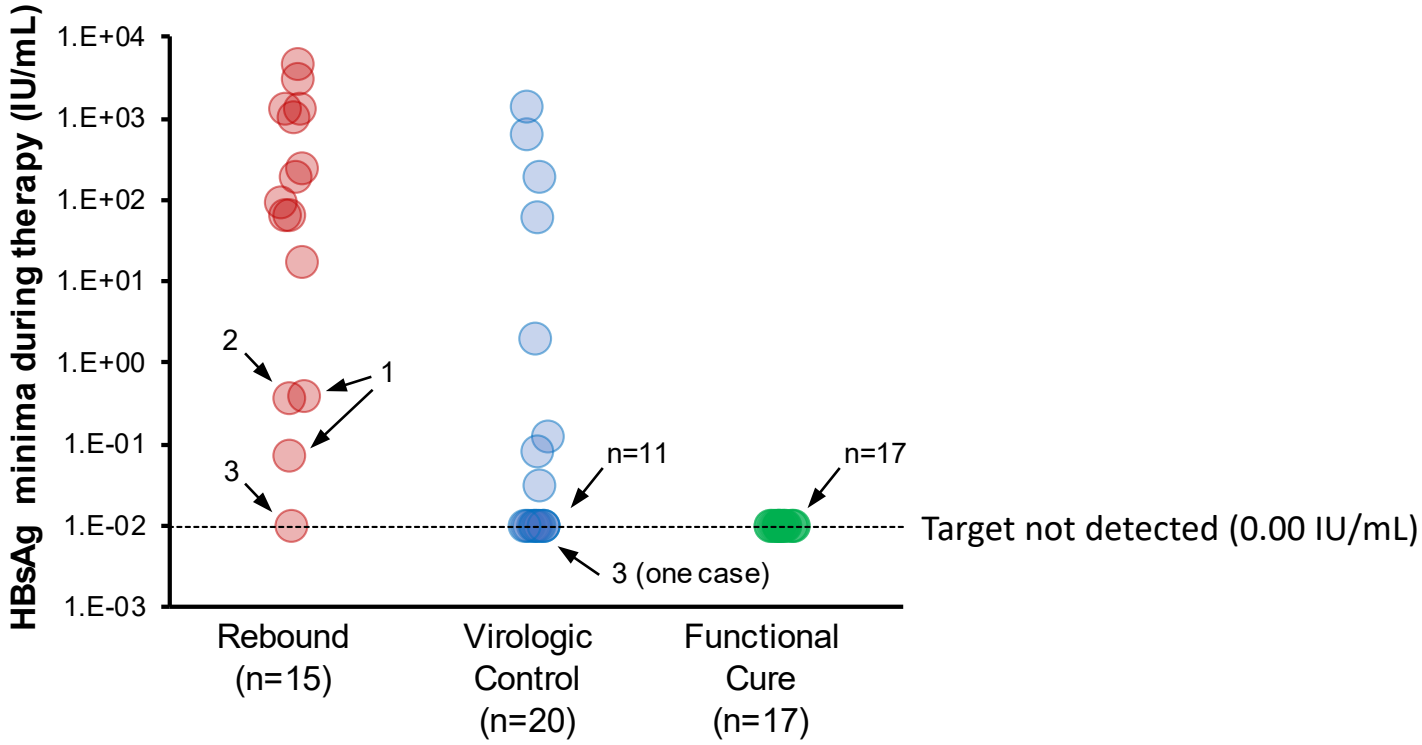
Completed treatment and ≥ 24 weeks of follow-up		36 (32 completed 48 weeks of follow-up)
Clinical response	Normal ALT	89%
	Normal liver median stiffness	56%
HBsAg response	< 1000 IU/mL	72%
	< 1 IU/ml	50%
	≤ LLOQ (0.05 IU/mL)	42%
	Seroconversion	53%
HBV DNA response	≤ 2000 IU/mL	78%
	Target not detected (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%**

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

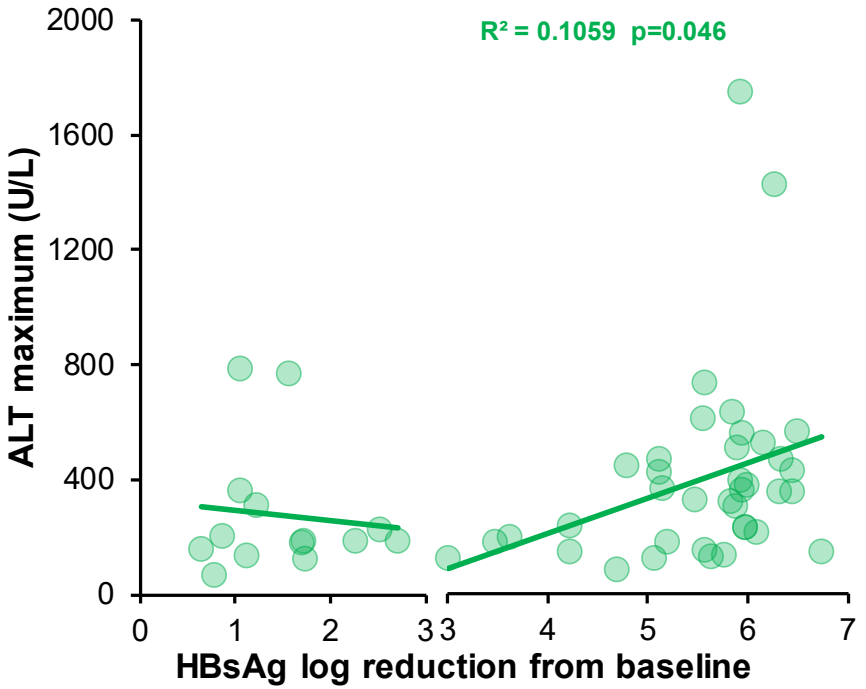
Predicting virologic outcomes

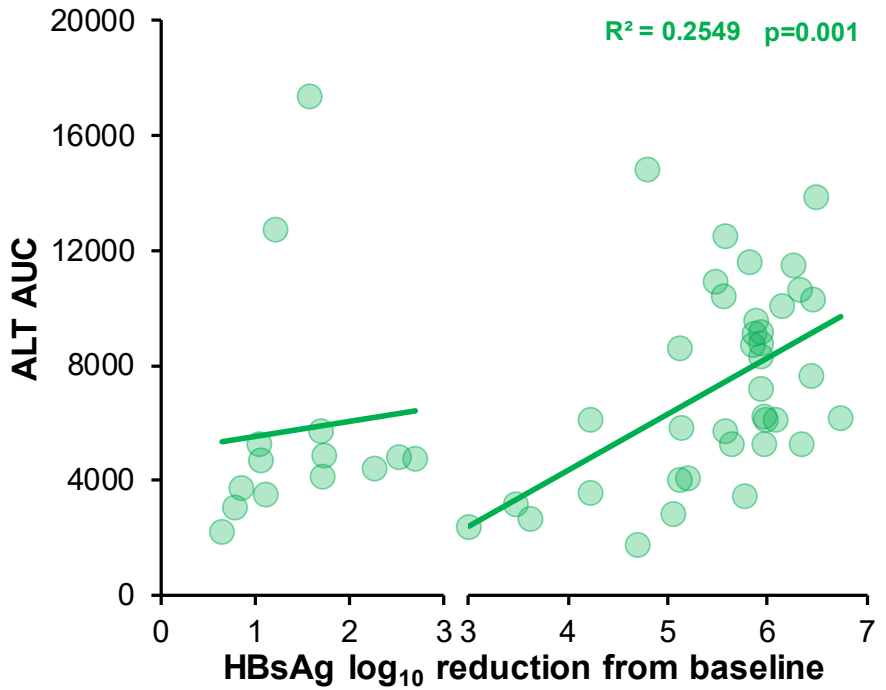
All 52 participants in the REP 301 and REP 401 studies

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

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Summary

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.
- Host target interface is characterized and identification is underway.

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

Establishment of virologic control / functional cure of chronic HBV infection in 78% of participants

Liver function normal in 89% of participants with reversal of liver inflammation / fibrosis

Predicting 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 are highly correlated with functional cure**
- On-therapy transaminase flares may facilitate the establishment of virologic control and functional cure

Next steps

Long term follow-up now at 3 years in the REP 301-LTF study (HBV / HDV)
Results to be presented at AASLD

Long term follow-up of participants in REP 401 trial (2 additional years)

Examine immunologic responses in upcoming trials:

REP 2139-Mg transition from IV to SC with TDF + pegIFN
- To be assessed in upcoming REP 501 trial in HBV / HDV co-infection

REP 2139-Mg + pegIFN in NUC experienced HBeAg negative subjects
- Phase IIA US study in collaboration with ACTG / DAIDS (A5382)

A collaborative effort !

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