Establishment of High Rates of Functional Cure of HBeAg Negative Chronic HBV Infection with REP 2139-Mg Based Combination Therapy: Ongoing Follow-up Results from the REP 401 Study

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Breaking the chronicity of chronic HBV infection

HBV infection has occurred in ~ 2 billion people:

- Typically resolved and well controlled by host immunity.

Chronic HBV infection still persists in up to 350 million people. **WHY?**

HBsAg likely prevents the establishment of immune control:

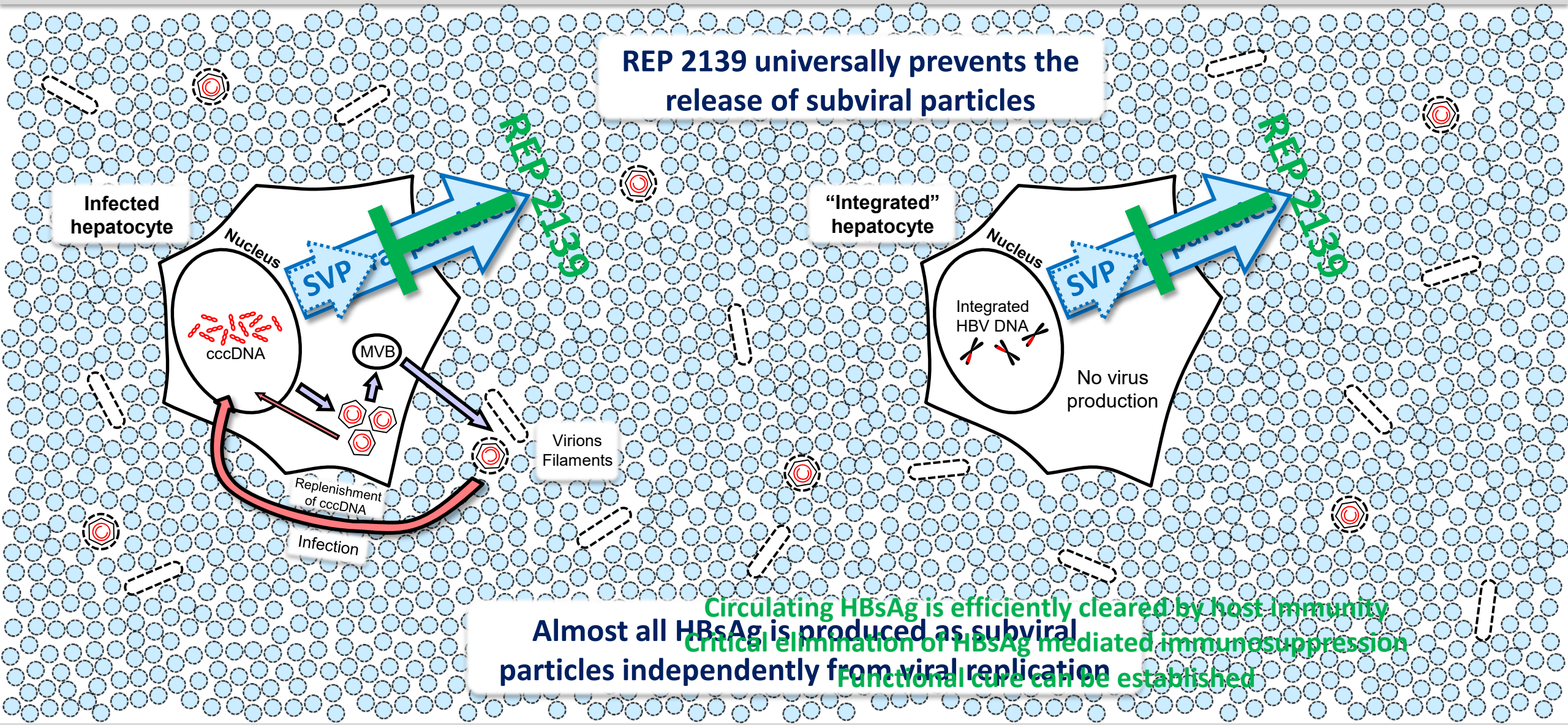
HBsAg is the most abundant circulating viral antigen

- Produced independently from virions (as subviral particles)
- Largely derived from integrated HBV DNA
- **Cannot be targeted by direct acting antivirals**

HBsAg is an important immune checkpoint inhibitor in chronic HBV infection

- Inhibits innate and adaptive immunity
- Exhausts the HBsAg specific B- and T-cell response

Controlling HBsAg with REP 2139

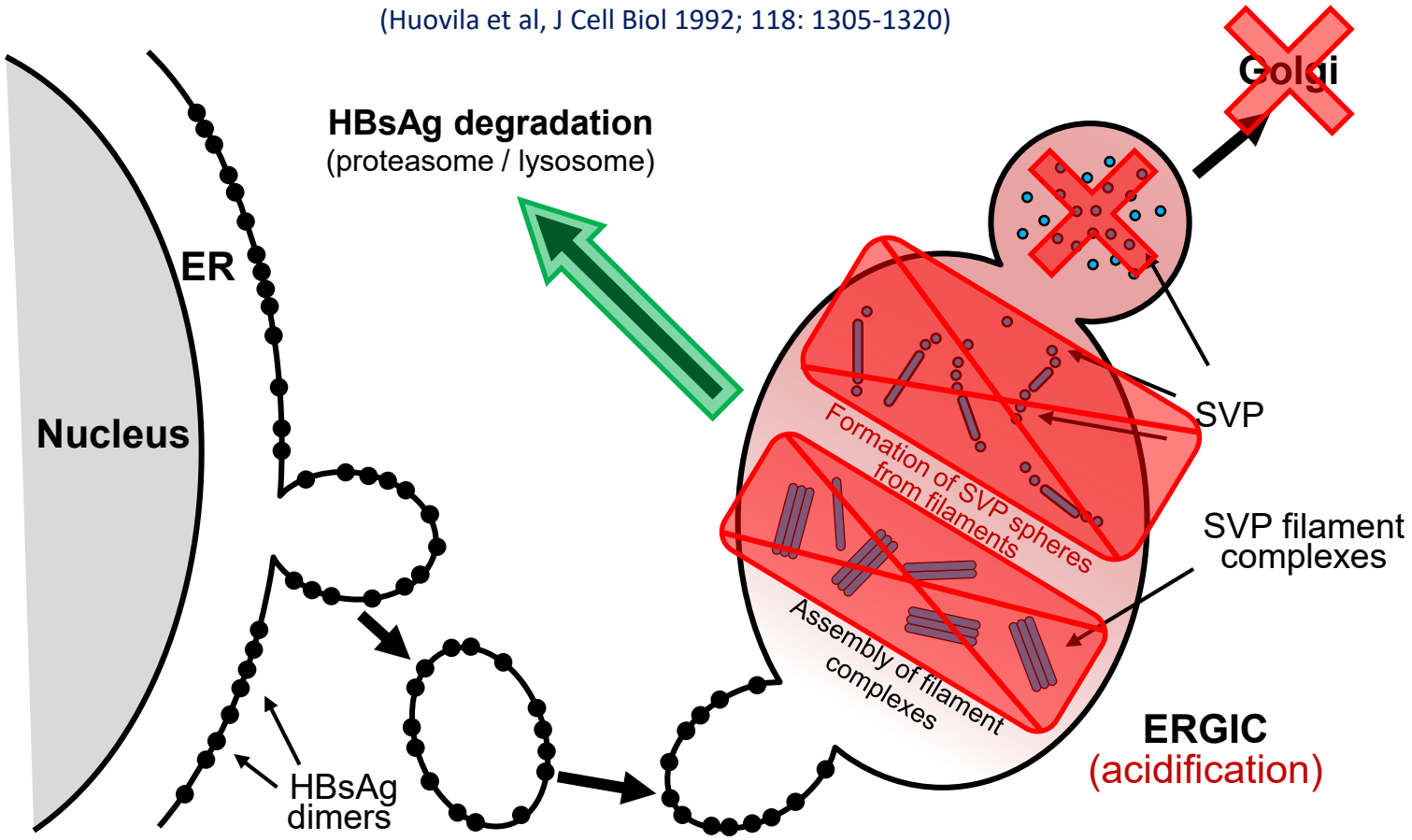


Mechanism of action of REP 2139 in HBV

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 (host target currently unknown)

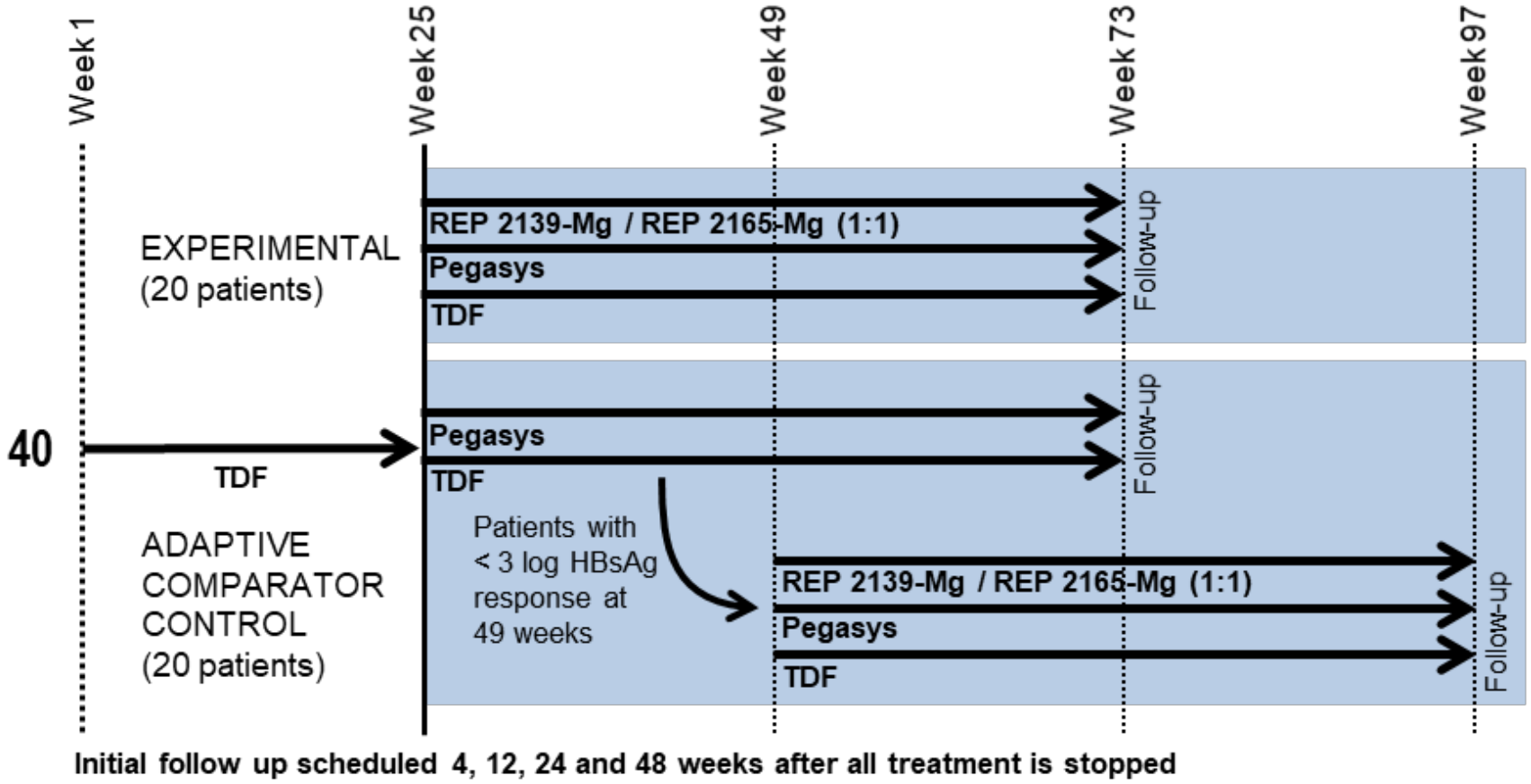
Intracellular degradation of HBsAg is enhanced

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

Blanchet et al., Antiviral Res 2019; 164: 87-105

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

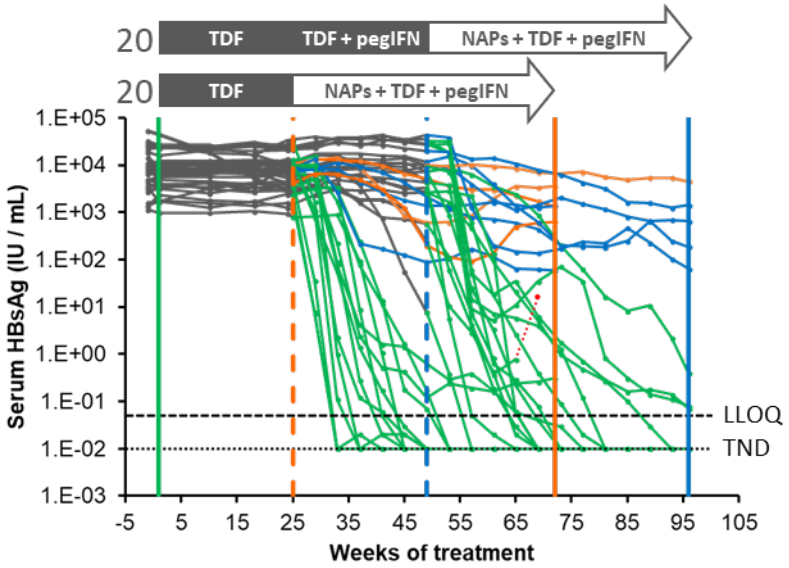
REP 2165 = REP 2139 variant with improved tissue clearance

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

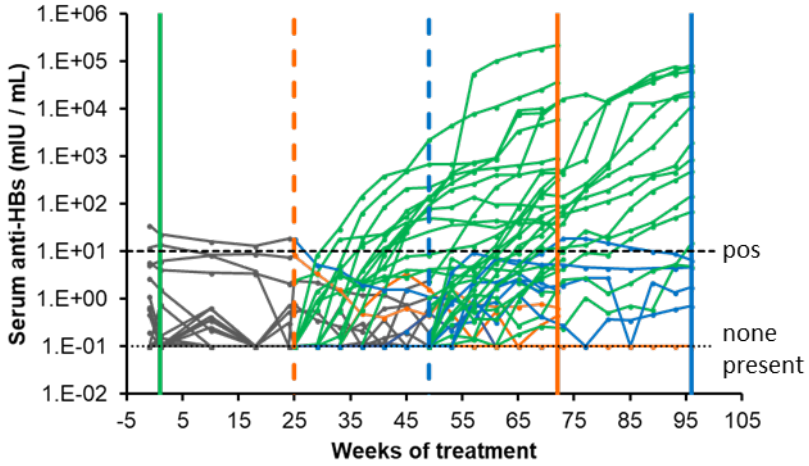
REP 401 on-treatment HBsAg response

LLOQ = lower limit of quantification (0.05 IU/mL)
TND = HBsAg not detected (0.00 IU/mL)

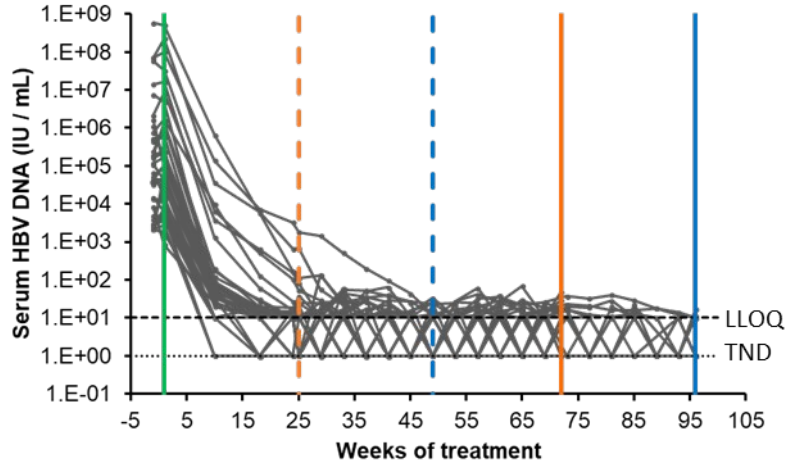
pos = threshold for protective immunity (10 mIU / mL)
none present = no significant anti-HBs present (≤ 0.1 mIU / mL)



Rapid declines in HBsAg with the introduction of NAPs
(REP 2139-Mg = REP 2165-Mg)
2/20 response during TDF/pegIFN
4/40 non-responders
8/40 HBsAg > 1 log reduction but > 1 IU/mL
28/40 HBsAg < 1 IU/mL
24/40 HBsAg loss (≤ 0.05 IU/mL)



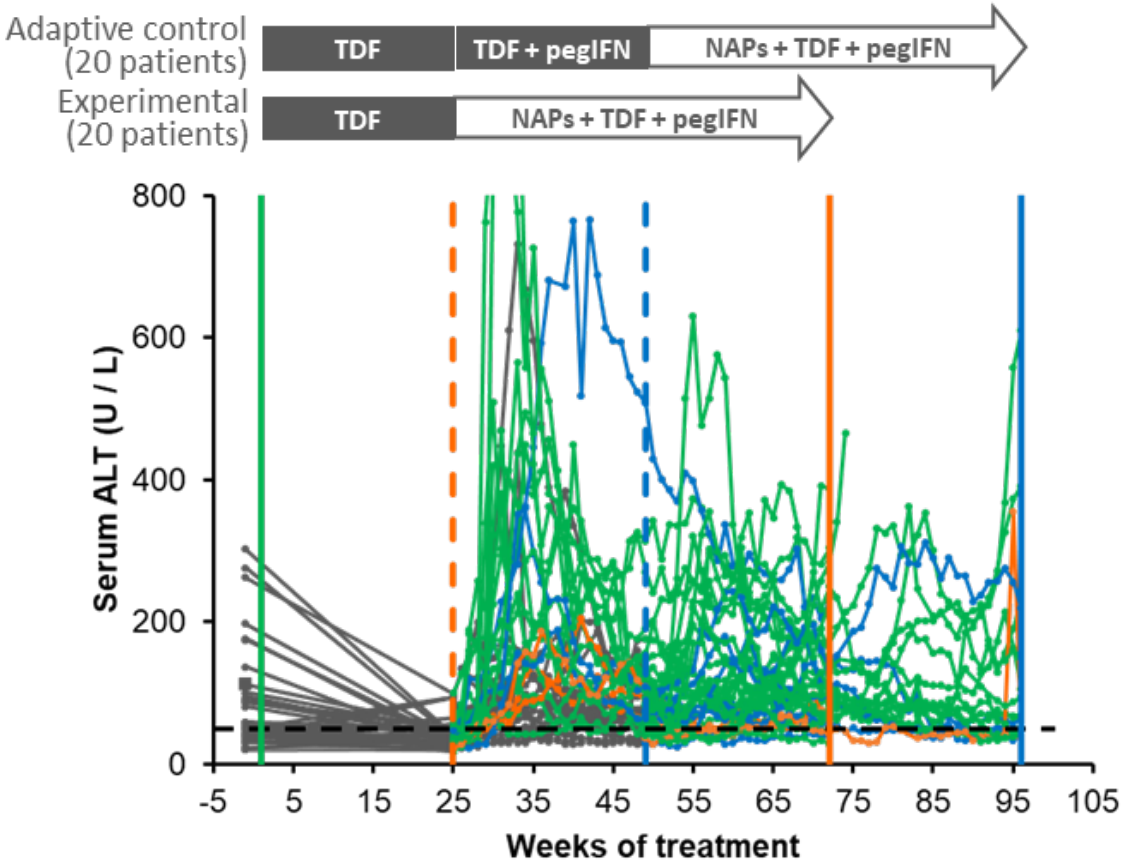
Anti-HBs dramatically increased with the introduction of pegIFN
(but only in patients with HBsAg declines to < 1 IU/mL)



TDF-induced HBV DNA declines unaffected during therapy
(no negative drug-drug interactions)

Standard of care only | < 1 log reduction in HBsAg | HBsAg > 1 log reduction but > 1 IU/mL | HBsAg < 1 IU/mL

Clearance of infected / integrated hepatocytes



Transaminase flares occur in 38/40 patients

Appear to be immune-mediated:

- Timing correlated with antiviral response
- Strength correlated with HBsAg response
- All self-resolving either during therapy or follow-up
- Liver function is continually normal throughout (bilirubin, albumin, INR)
- Otherwise asymptomatic

Correlated with the establishment functional control

For additional data please visit poster P03-01

Standard of care only | < 1 log reduction in HBsAg | HBsAg > 1 log reduction but > 1 IU/mL | HBsAg < 1 IU/mL

Interim REP 401 response summary

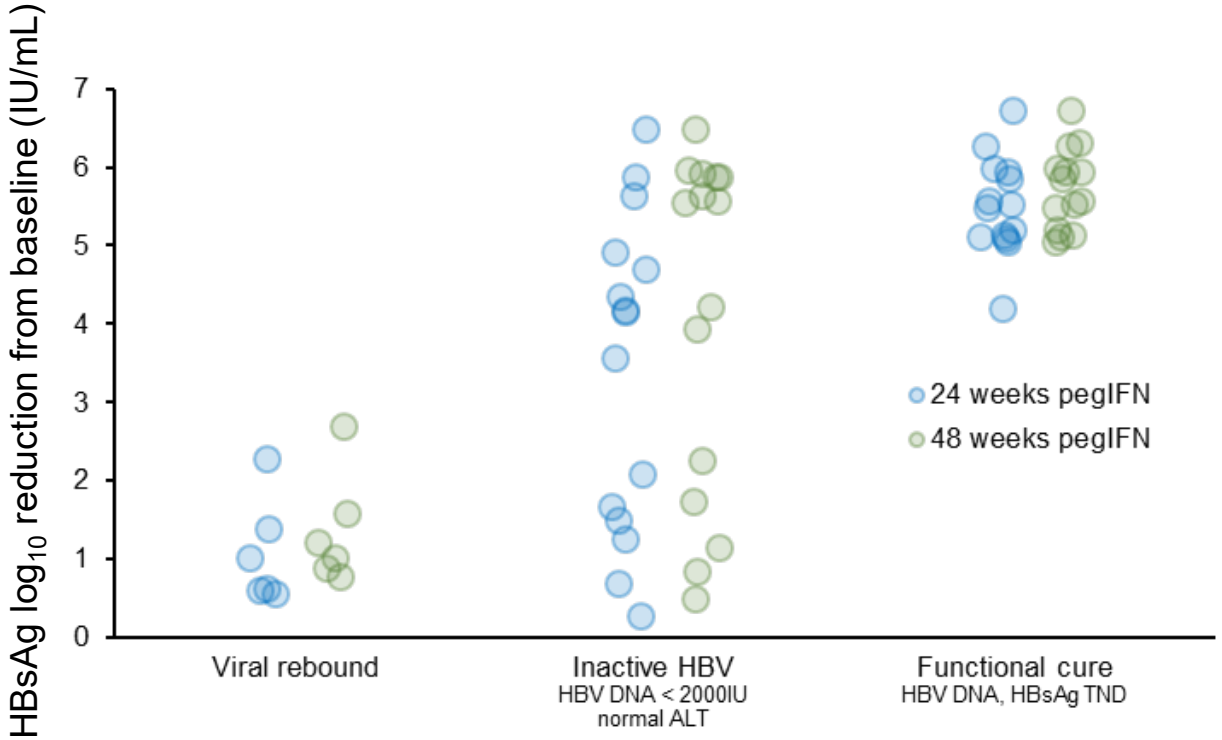
Patients entered into trial		**40**
End of treatment HBsAg response	> 1 log from baseline	36
	< 1 IU/mL	27
	≤ 0.05 IU/mL	24
Patients currently completed treatment and ≥ 24 weeks of follow-up		**34**
Inactive HBV (HBV DNA ≤ 2000 IU/mL, normal ALT)		44%
Functional cure (HBsAg and HBV DNA target not detected)		41%
Clinical benefit, no therapy required (Low risk of progression, reduced risk of HCC)		**85%**

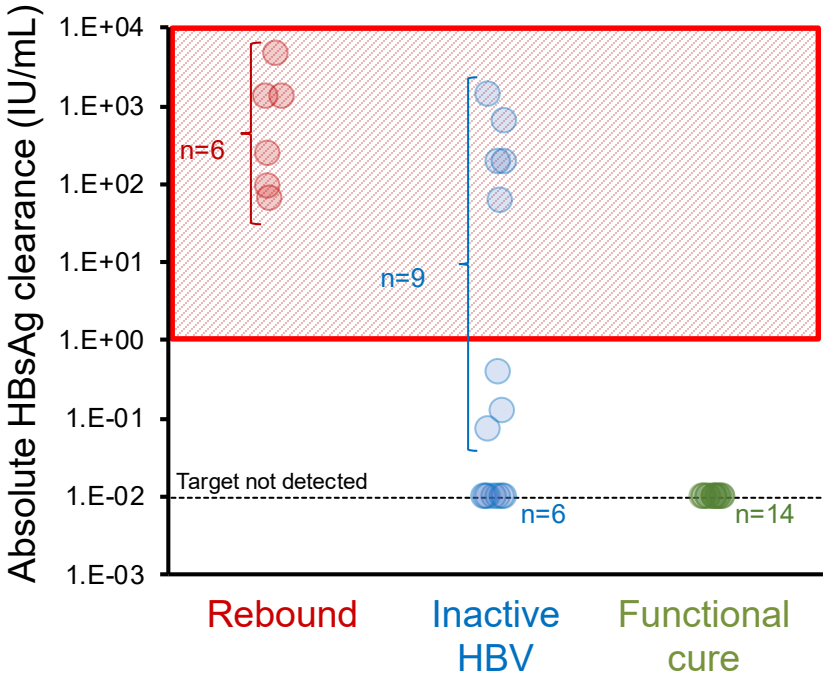
Accompanied by normalization of liver function and reversal of fibrosis (as measured by Fibroscan)

For additional data please visit poster OP-02

Predicting outcomes during REP 2139-based therapy

Outcome after removal of all therapy





HBsAg response at week 24 predicts HBsAg response at the end of therapy (48 weeks)

Achieving functional cure requires achieving HBsAg target not detected during therapy (0.00 IU/mL)

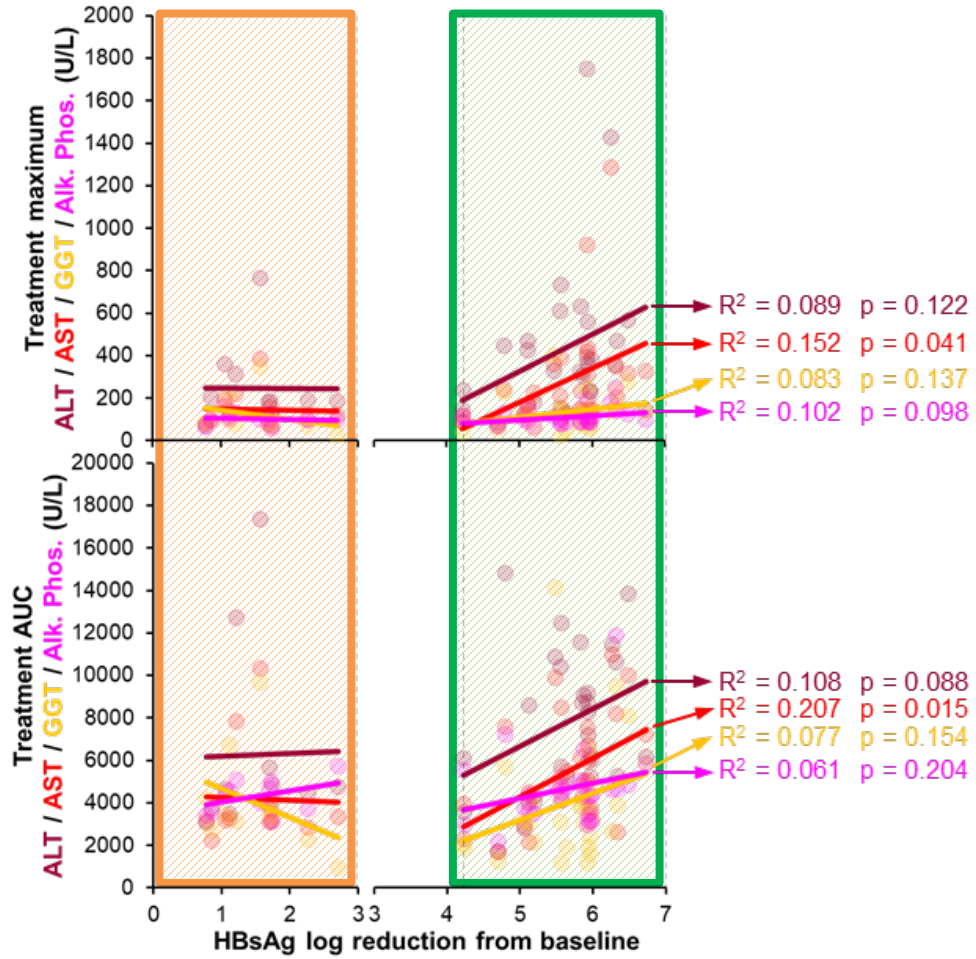
Poor rate of functional control when HBsAg remains > 1 IU/mL

Predicting outcomes during REP 2139-based therapy

Analysis of transaminase maxima and AUC during therapy reveal two flare populations

Maxima during therapy

AUC during therapy



"Non-productive flares"

(substantial HBsAg still present)

not correlated with HBsAg response

5 inactive chronic HBV

6 HBV rebound

"Productive flares"

(occur with efficient clearance of HBsAg)

correlated with HBsAg response

14 HBV functional cure*

10 inactive chronic HBV*

2 HBV rebound

(both withdrew early from therapy)

*1 additional REP 401 patient has inactive chronic HBV at 12 weeks of follow-up
1 additional REP 401 patient has HBV functional cure at 12 weeks of follow-up

REP 2139-Mg next steps

Transition of REP 2139-Mg to subcutaneous dosing

- REP 2139-Mg SC formulation is administered via IV in the REP 401 protocol
- Transition expected to be well tolerated with similar efficacy against HBV and HDV

Initiation of phase IIA triple combination trial in the US

- In collaboration with the ACTG (DAIDS / NIH)
- Will use same regimen and administration as in the REP 401 trial (NUCs + pegIFN + REP 2139-Mg)

Assessing other immunotherapies

- PegIFN is much better tolerated in HBV than in HCV but results in loss of T-cells during therapy

  Marcellin et al., Liv Int 2008; 28: 477-485
  Micco et al., J Hepatol 2013; 58: 225-233

- Functional cure rates may improve with other immunotherapies
  - Thymosin alpha 1 (T-cell agonist)
  - Pattern recognition receptor agonists
  - Therapeutic vaccines

A collaborative effort !

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