

Establishing functional cure of chronic HBV infection with nucleic acid polymers: Final results from the REP 401 study

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Breaking the chronicity of chronic HBV infection

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

- > 99.99% derived from subviral particles

 - Assembled and secreted independently from virions

 - Assembled and secreted in part independently of cccDNA (from integrated HBV DNA)

Cannot be effectively targeted by direct acting antivirals

HBsAg is an important immune checkpoint inhibitor in chronic HBV infection

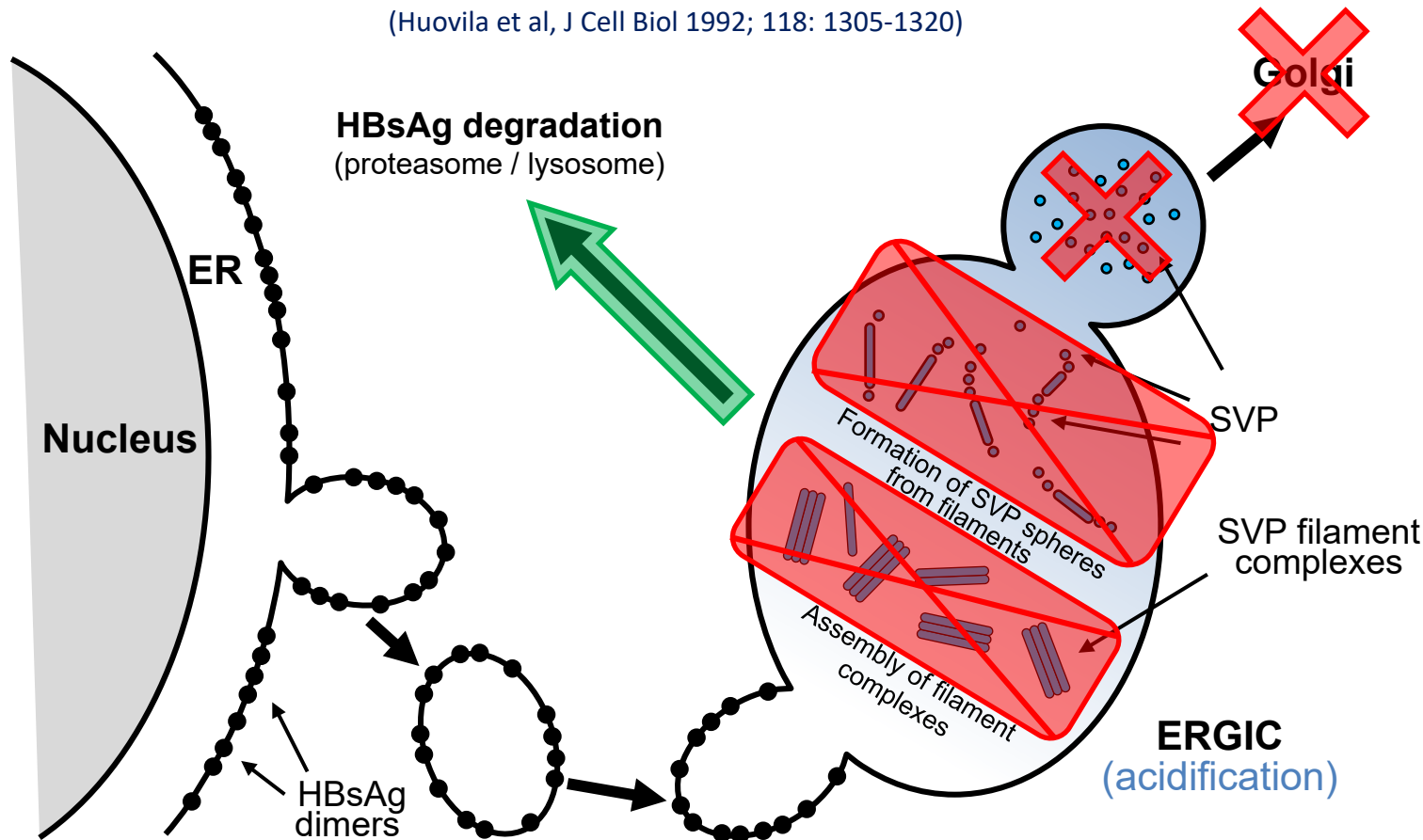
- Inhibits innate and adaptive immunity

- Exhausts the HBsAg specific B- and T-cell responses

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

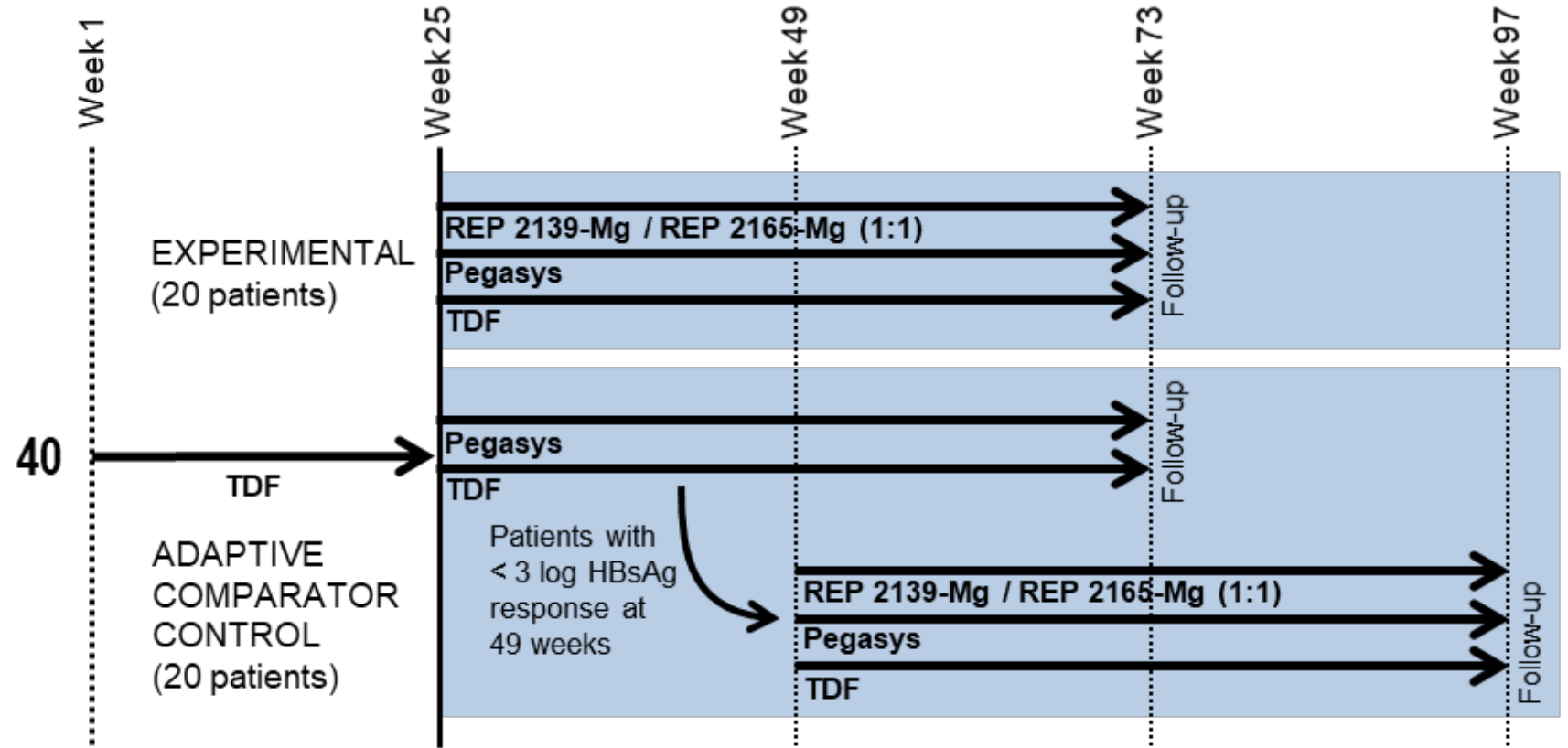
REP 2139 does not directly affect virus production

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

REP 401 Study

Clearing HBsAg to improve immunological recovery

Participant population
18-55 years old
HBeAg negative
HBsAg > 1000 IU/mL
HBV DNA > 2000 IU/mL
No HDV, HIV, HCV, active CMV
No current therapy
No immunotherapy > 6M



Initial follow up scheduled 4, 12, 24 and 48 weeks after all treatment is stopped

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

Quality control in the REP 301 and REP 401 studies

REP 301 (HBV / HDV) and REP 401 (HBV) studies are fully EU GCP compliant

- Participants managed by 3 independent and experienced principle investigators and 7 associate investigators with decades of experience in treating viral hepatitis.
- Share similar trial sites and investigators with recent JNJ-56136379 trial (NCT02662712) – Dr. Iurie Moscalu, ARENSIA Clinical Trial Unit, Republican Clinical Hospital, Chişinău, Moldova.
- Study oversight, audit and data management by independent CROs (Clinical Accelerator / Planimeter)

Safety assessments and sample management

- Managed by Synevo Central Labs (German-headquartered) with a fully integrated quality system.
- GCLP:2011 accredited
- ISO 15189:2007 certified

Virologic testing

- Performed at the Institute for Virology, University of Duisburg-Essen (Germany)
- Recognized EU center for excellence in virologic testing.
- Independently supervised by Drs. Ulf Dittmer and Adalbert Krawczyk

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 was 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 (from SVP)**
Allow host mediated clearance of 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 HBsAg declines following addition of NAPs

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

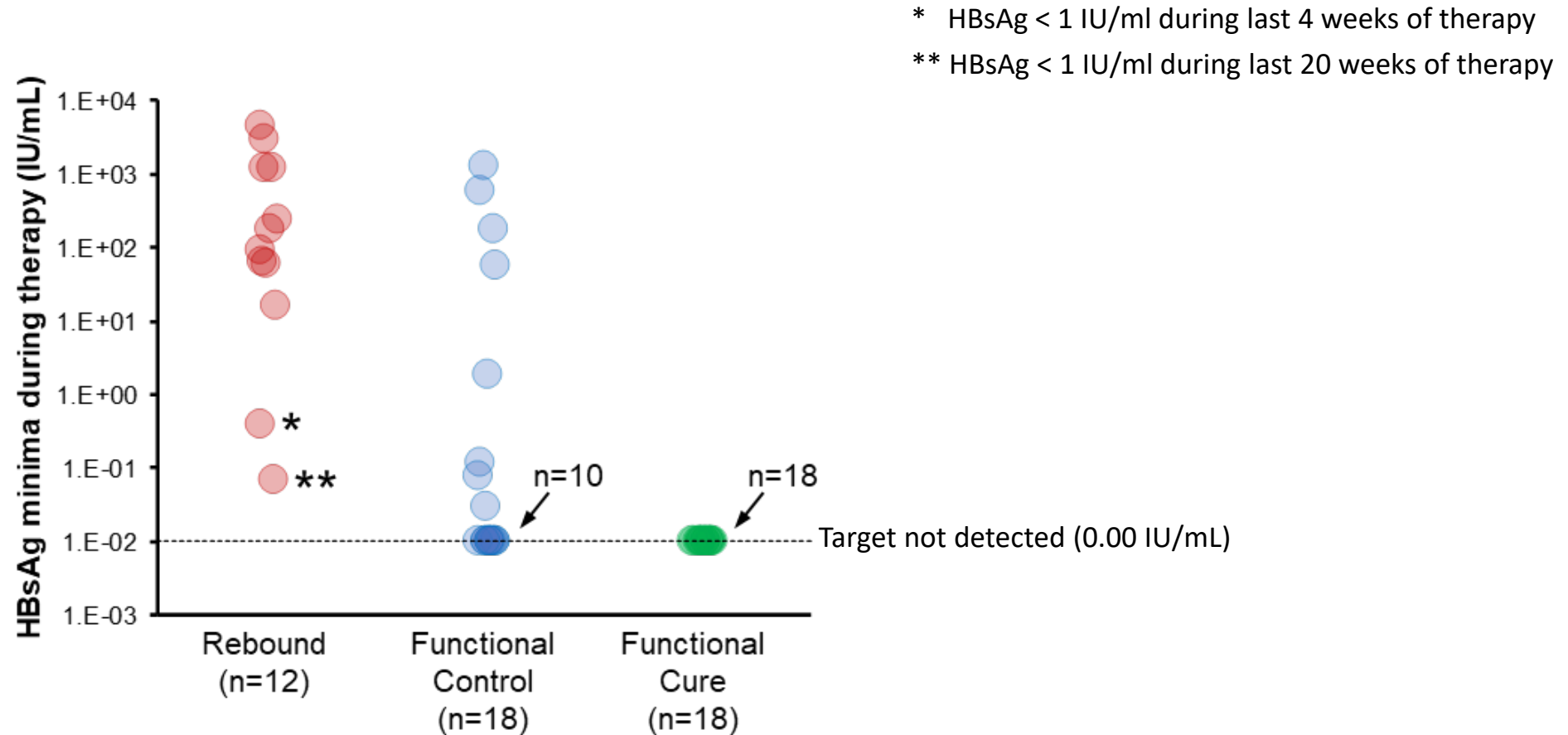
(consistent with overall well tolerated and positive impact of transaminase flares in chronic HBV)

Final REP 401 outcome summary

Completed treatment and ≥ 24 weeks of follow-up		35 (32 completed 48 weeks of follow-up)
Clinical response	Normal ALT	91%
	Normal median hepatic stiffness	57%
HBsAg response	< 1000 IU/mL	74%
	< 1 IU/ml	51%
	\leq LLOQ (0.05 IU/mL)	43%
	Seroconversion	54%
HBV DNA response	≤ 2000 IU/mL	83%
	< 100 IU/mL	63%
	Target not detected (TND)	49%
Virologic response	Functional control (HBV DNA ≤ 2000 IU/mL, normal ALT)	43%
	Functional cure (HBsAg $< \text{LLOQ}$, HBV DNA TND, normal ALT)	40%
	Clinical benefit, no therapy required (Low risk of progression, reduced risk of HCC)	83%

Predicting virologic outcomes

Meta analysis of HBeAg negative patients completing therapy in the REP 301 and REP 401 studies

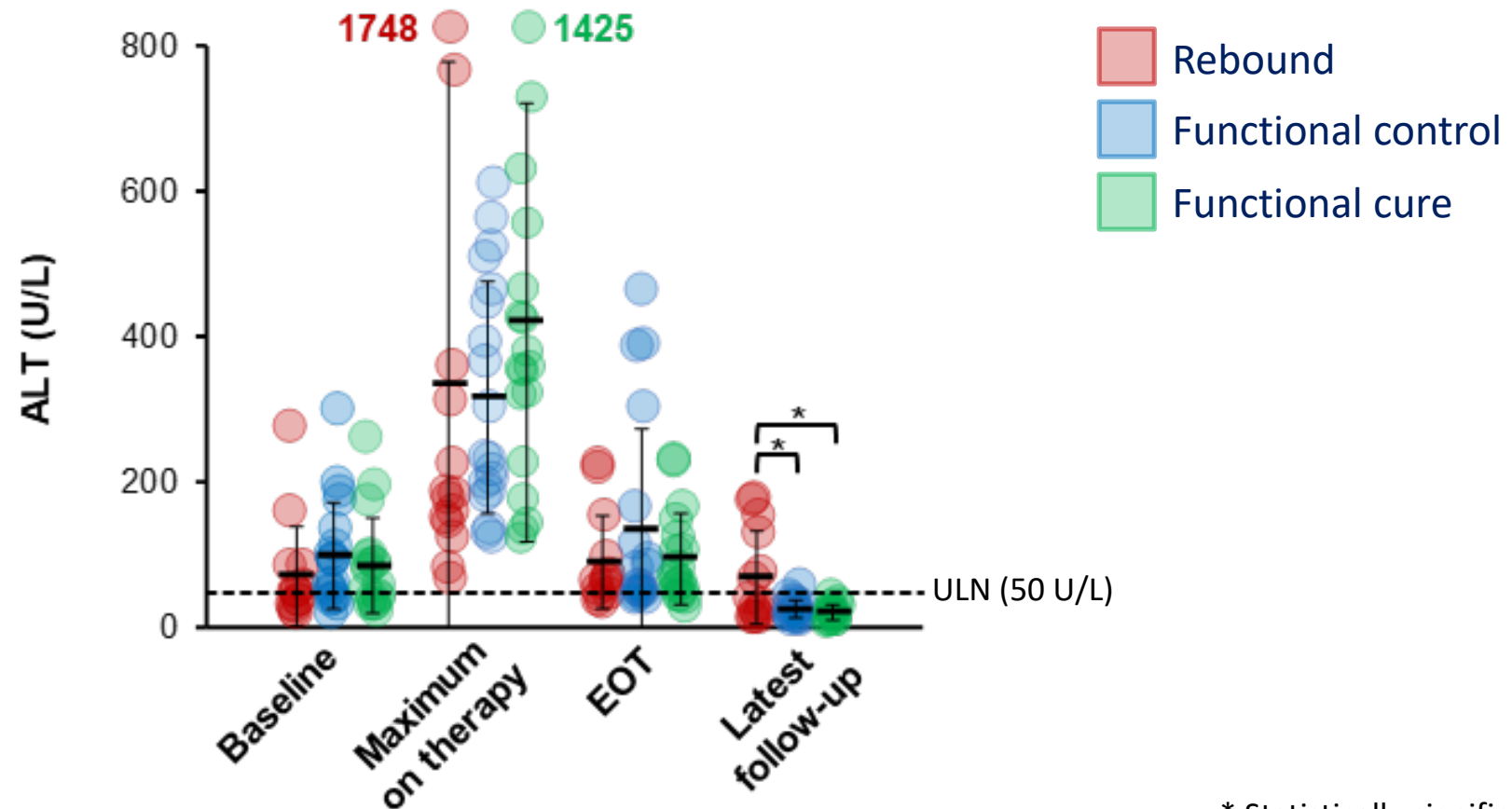


Achieving HBsAg 0.00 IU/mL during therapy was necessary but not sufficient to achieve functional cure

Predicting virologic outcomes

Meta analysis of HBeAg negative patients in the REP 301 and REP 401 studies

ALT flares are prevalent during therapy leading to rebound, functional control or functional cure



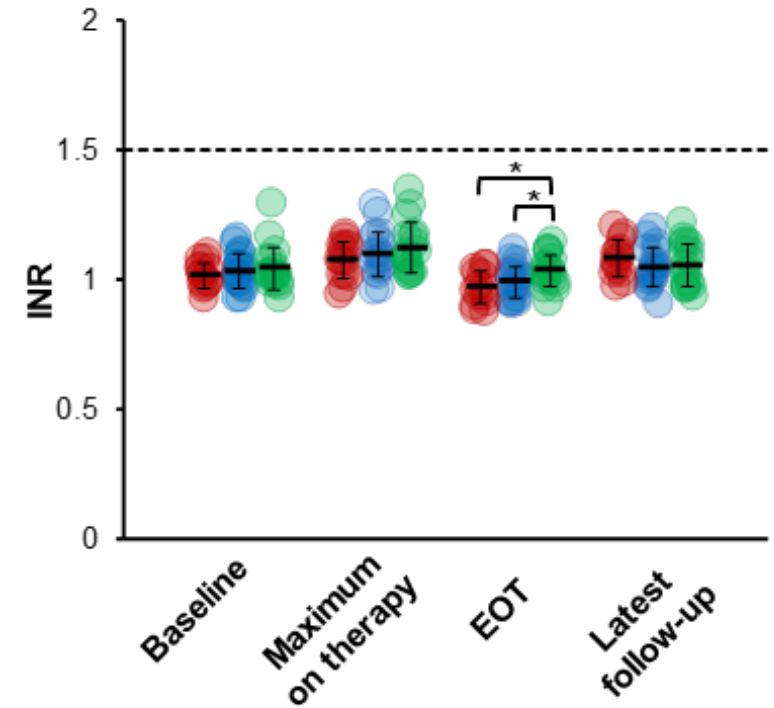
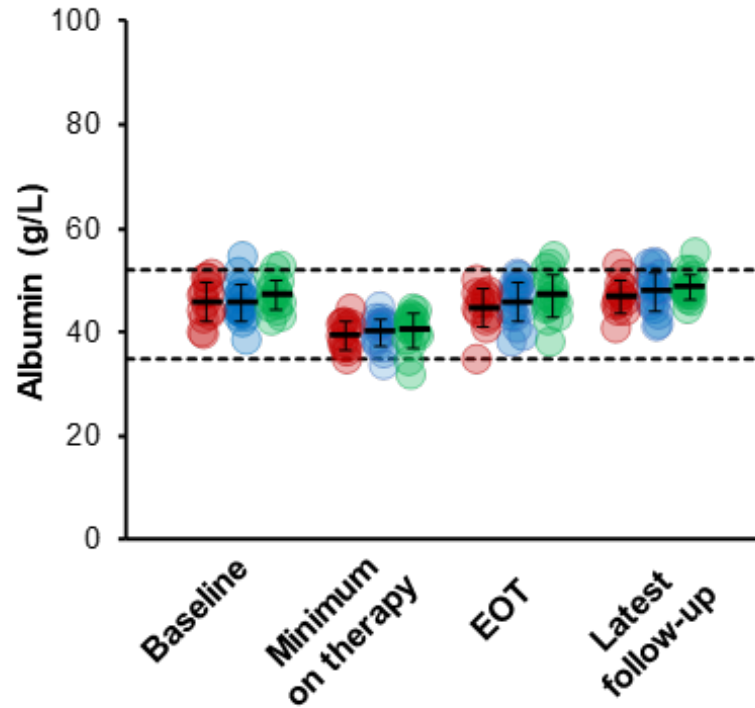
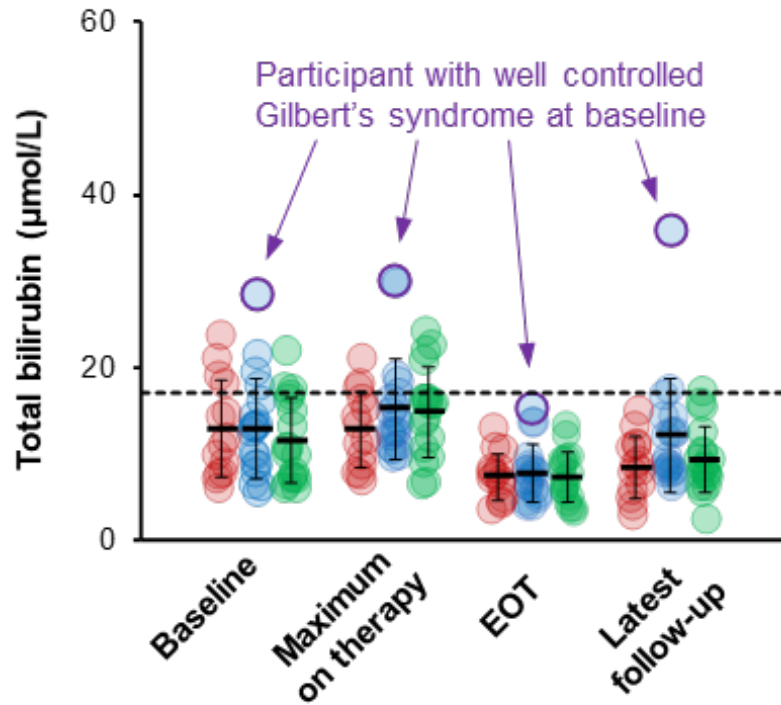
* Statistically significant with $p < 0.05$

Predicting virologic outcomes

Meta analysis of HBeAg negative patients in the REP 301 and REP 401 studies

Liver function is unaffected during ALT flares
(otherwise asymptomatic)

- Rebound
- Functional control
- Functional cure



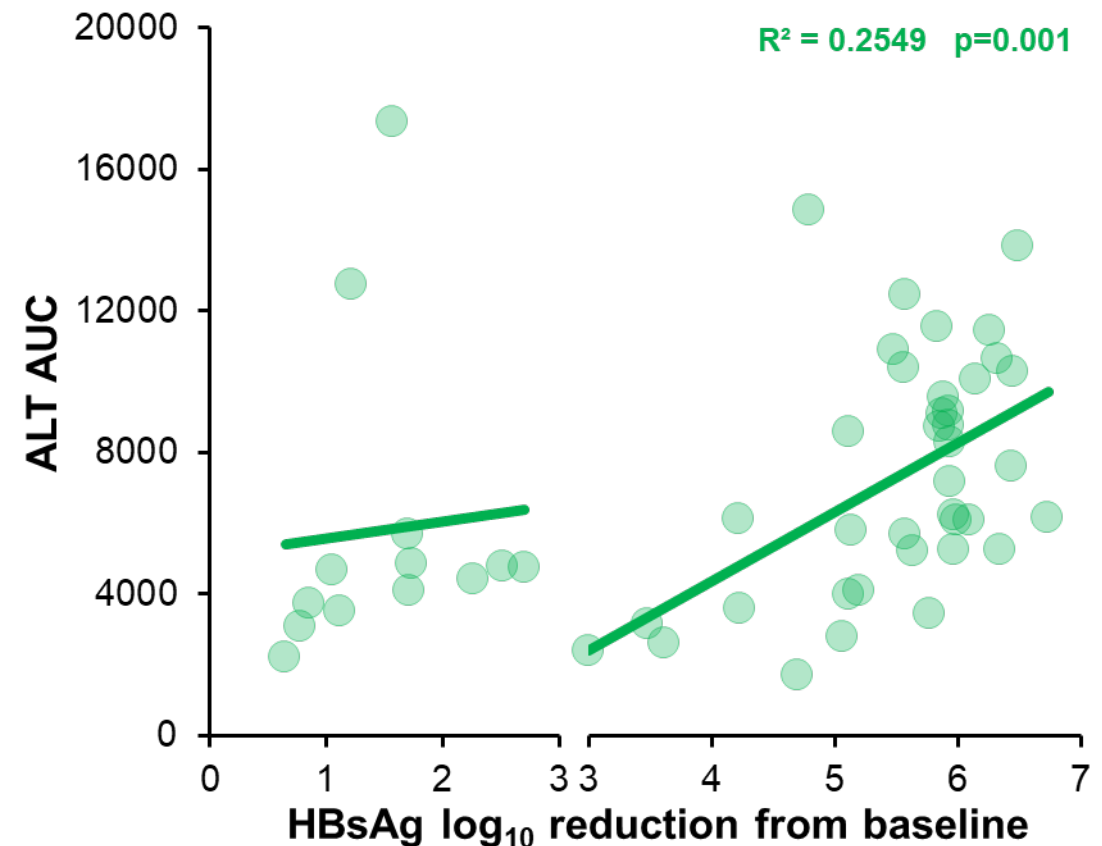
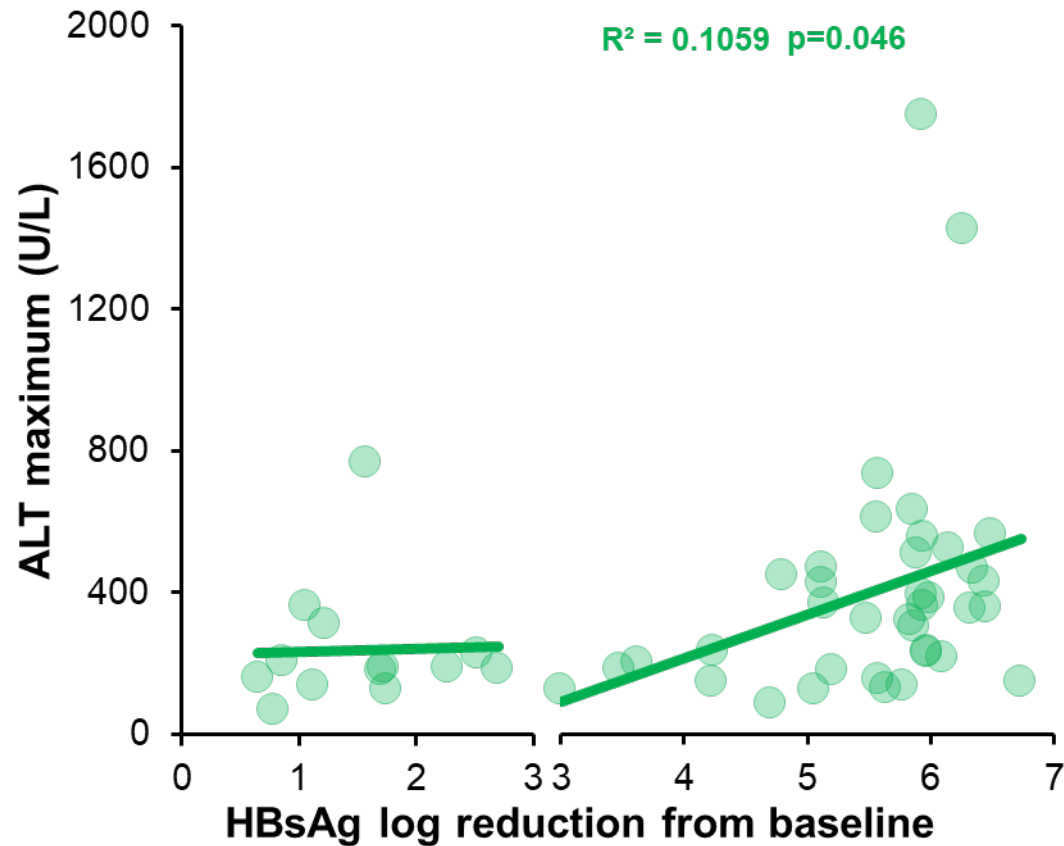
----- ULN or normal range

* Statistically significant with $p < 0.05$

Predicting virologic outcomes

Meta analysis of HBeAg negative patients in the REP 301 and REP 401 studies

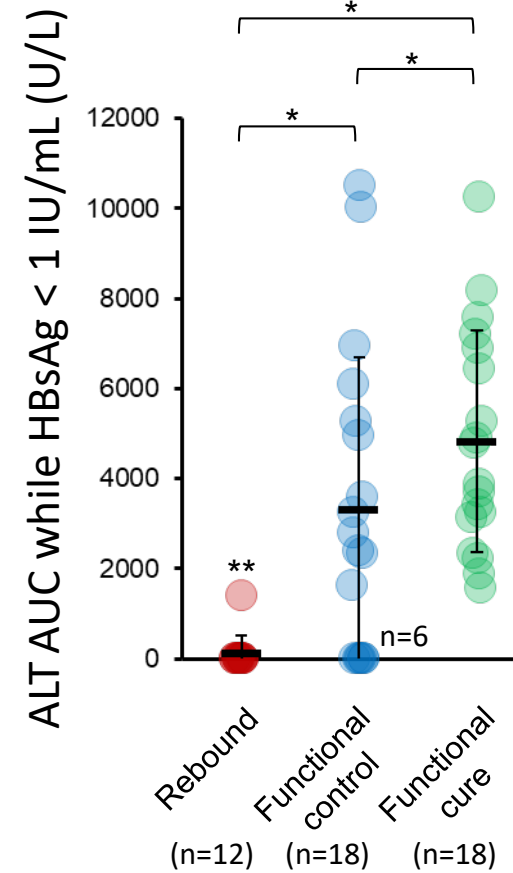
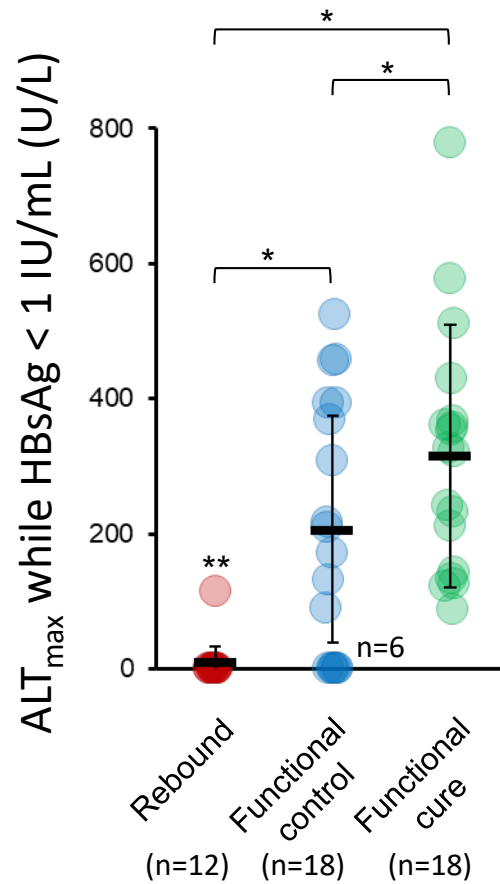
Increased ALT flare activity is correlated with HBsAg reductions $\geq 3 \log_{10}$ from baseline



Predicting virologic outcomes

Meta analysis of HBeAg negative patients completing therapy in the REP 301 and REP 401 studies

ALT flare activity while HBsAg < 1 IU/mL was correlated with virologic outcome



* Statistically significant with p < 0.05
** HBsAg < 1 IU/ml during last 20 weeks of therapy

Summary

Addition of NAPs to TDF + pegIFN dramatically improves outcomes off therapy

- Liver function normal in 91% of participants
- Reversal of inflammation / fibrosis
- Establishment of functional control / functional cure of chronic HBV infection in 83% of participants

Extent of ALT flare activity while HBsAg is < 1 IU/mL predicts outcomes after therapy

- No flare activity with HBsAg < 1 IU/mL typically leads to rebound and no functional cure
- Stronger flare activity while HBsAg is < 1 IU/mL increases probability of achieving functional cure
- Restoration of HBsAg specific immune function during therapy (T-cell mediated?) may drive establishment of functional cure

REP 2139-Mg transition to SC with TDF + pegIFN is expected to further improve HBsAg response and have similar or better outcomes against HBV / HDV co-infection as observed in REP 401 study (to be assessed in upcoming REP 501 trial).

IV Phase IIA US study (ACTG A5382) will confirm optimal REP 2139-Mg dose to allow early entry into a phase IIB pivotal study with SC administration.

A collaborative effort !

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