Updated follow-up analysis in the REP 401 protocol: Treatment of HBeAg negative chronic HBV infection with REP 2139 or REP 2165, tenofovir disoproxil fumarate and pegylated interferon α-2a

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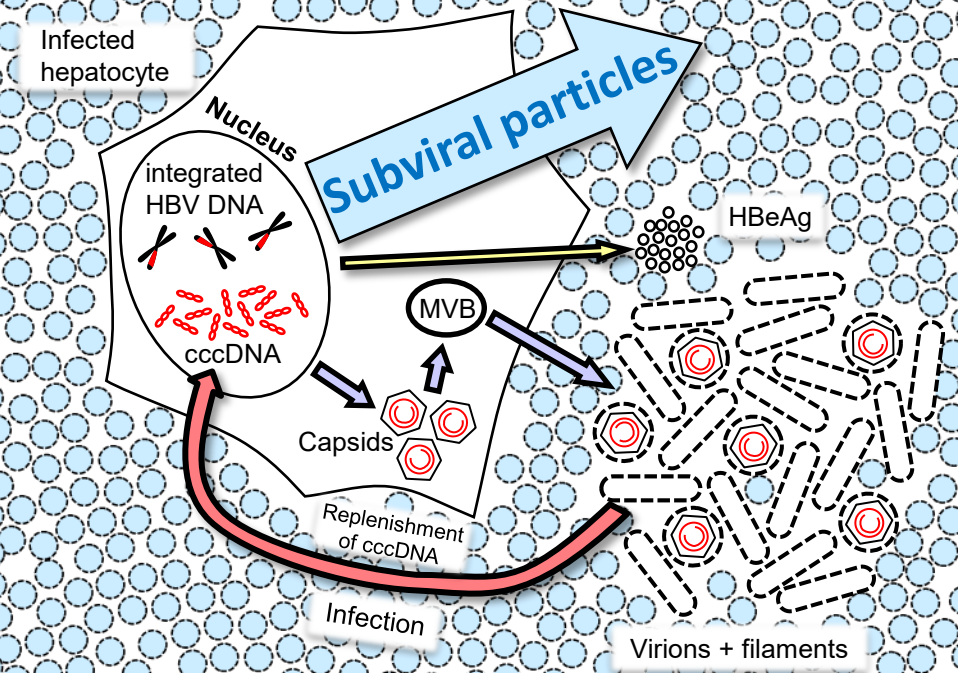
GLOBAL HEPATITIS SUMMIT 2018 TORONTO CANADA
THE 16TH INTERNATIONAL SYMPOSIUM ON VIRAL HEPATITIS AND LIVER DISEASE, ISVHLD JUNE 14-17, 2018

replicor

The HBV-derived checkpoint inhibitor: subviral particles

almost all HBsAg is derived from subviral particles which are mostly derived from integrated HBV DNA
not affected by targeting viral replication



HBsAg clearance is crucial to restoring functional control of HBV infection

Subviral particles are the primary immunosuppressive agent:

- Mask the anti-HBs response
- Block signalling mechanisms required for innate and adaptive immune function
- Exhaust B- and T-cell responses
- Inhibit the activity of immunotherapy
  - cytokine or TLR-based
  - therapeutic vaccines

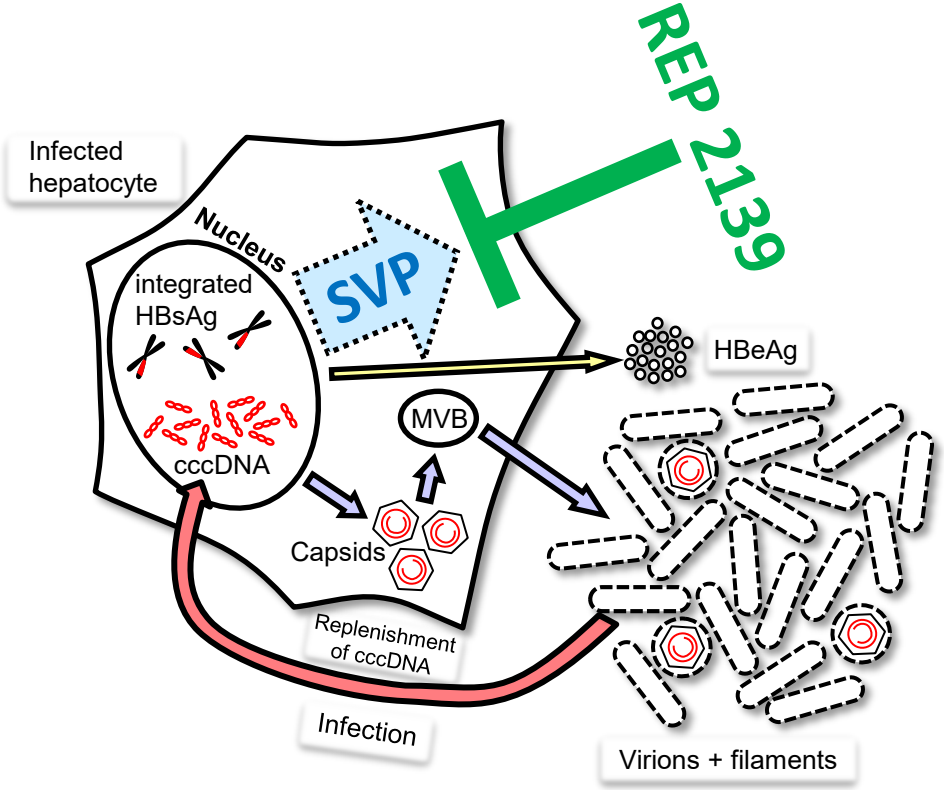
Dembeck et al., Curr. Op. Virol. 2018; 30: 58-67.
Aillot et al., Antimicro. Agents Chemother. 2018; 62: e01741-17
Rydell et al., Virol. 2017; 509: 67-70
Bazinet et al., 2017 Lancet Gastro. Hep 2: 877-889
Al-Mahtab et al., 2016 PLOS One 11: e0156667
Yang et al., Int. Immunopharmacol. 2016; 38: 291-297
Jiang et al., J. Viral Hep. 2014; 21: 860-872
Wang et al., J. Immunol. 2013; 190: 5142-5151
Kondo et al., ISRN Gastro. 2013; 2013:935295

REP 2139 mechanism of action in HBV

REP 2139 blocks subviral particle assembly and release
from cccDNA or integrated HBV DNA

→ Efficient HBsAg clearance from the blood

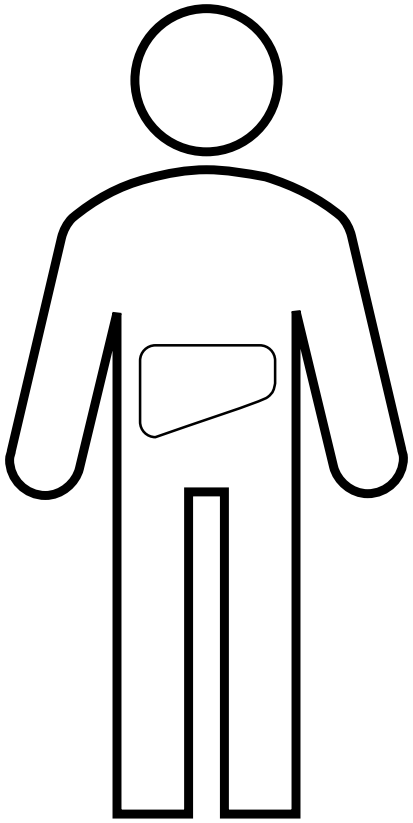
Inhibition of SVP release is associated with reduction in intracellular HBsAg



REP 2139 only prevents replenishment of circulating HBsAg

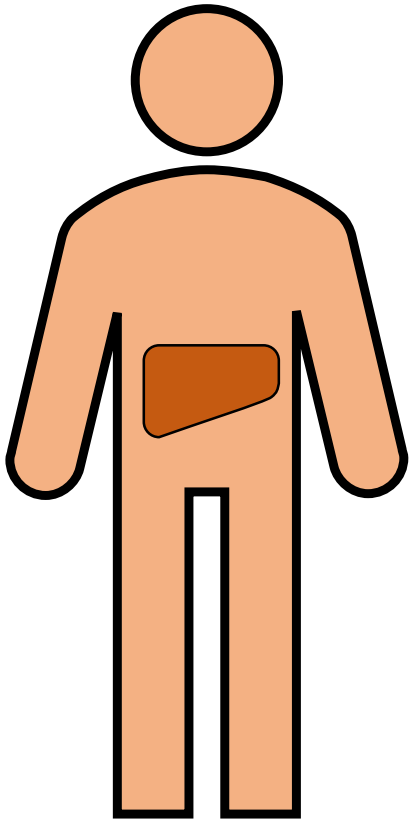
HBsAg clearance is dependent on the clearance of SVP by host immune function.

REP 2139 effects on systemic HBsAg burden



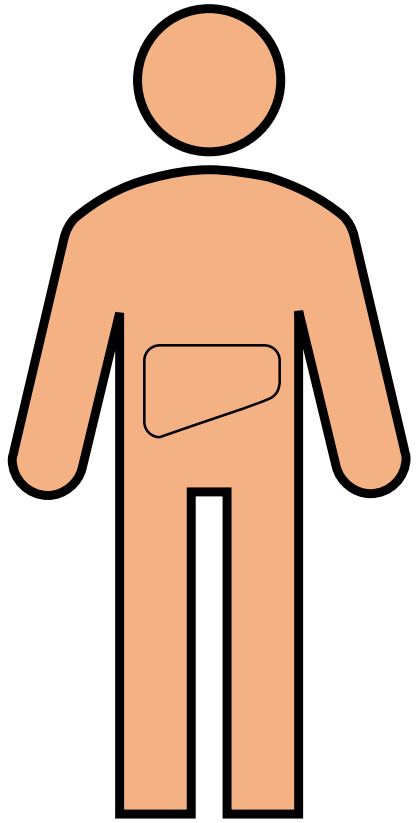
Healthy individual

Treatment naive



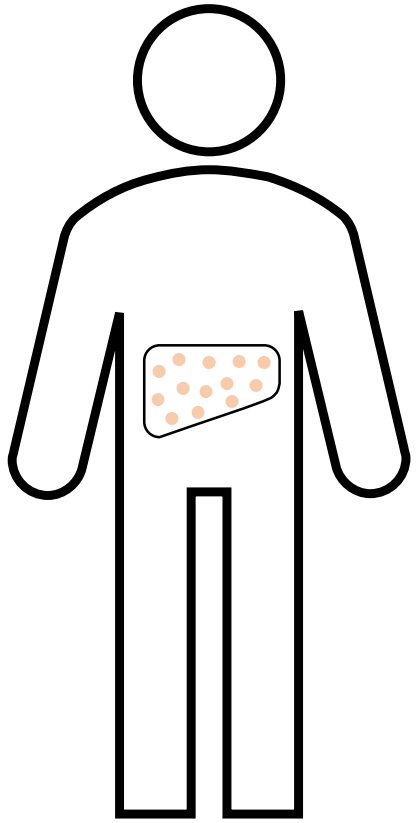
Chronic HBV infection
Abundant circulating HBsAg
Local intrahepatic HBsAg likely elevated

Early in REP 2139 exposure



Inhibition of HBsAg release likely leads to rapid equilibration of intrahepatic HBsAg and circulating HBsAg
Potential for early reactivation of intrahepatic immune function

Continued REP 2139 exposure



Circulating HBsAg is cleared by host immune response leading to further reduction of intrahepatic HBsAg
Potential for restoration of functional control of HBV infection

REP 2139 effects in monotherapy

Antiviral response	In vivo (DHBV infected Pekin ducks)	HBeAg positive chronic HBV infection	HBeAg negative chronic HBV/HDV co-infection
Blood	**HBsAg reduction to < LLOQ** HBV DNA reduction to < LLOQ (decoupled from HBsAg clearance)	**HBsAg reduction to < 1 IU/mL** Anti-HBs unmasking HBeAg seroconversion HBV DNA and RNA reduction (decoupled from HBsAg clearance)	**HBsAg reduction to < 1 IU/mL** Anti-HBs unmasking **HDV RNA clearance** **(target not detected)**
Liver	Clearance of HBsAg and HBcAg Transcriptional inactivation of cccDNA 2-3 log_{10} reduction in cccDNA	Strong, self resolving, asymptomatic transaminase flares (when HBsAg becomes < 1 IU/mL)	Weak transaminase flares (strong following pegIFN add-on when HBsAg < 1 IU/mL)
Functional control after removal of therapy (HBsAg and HBV DNA)	**55-66%** **(blood and liver)**	25% 5 years of follow-up	**36% (HBsAg)*** **55% (HBV DNA)*** **63% (HDV RNA)*** (2 years of follow-up)

*suboptimal combination regimen (15 weeks REP 2139-Ca + pegIFN)

Decoupling of HBsAg and HBV DNA declines a result of selective targeting of SVP assembly / release

HBsAg clearance is accompanied multiple positive effects on immune response to HBV infection

Immunological damage present in chronic infection likely prevent many patients from restoring immune function with HBsAg clearance alone

Potent and distinct antiviral mechanism is active against HDV

Noordeen et al., PloS One 2015
Roehl et al., Mol. Ther. Nuc. Acids 2017; 8: 1-12
Quinet et al., Hepatol. 2018; 67: 2127-2140
Janssen et al., J. Hepatol. 2015;62: S250
Al-Mahtab et al., PLOS One 2016; 11: e0156667
Bazinet et al., Lancet Gastro. Hep. 2017; 2: 877-889

Building an effective combination therapy

Functional control of chronic HBV infection can only be achieved by restoring immune control

Adding immunotherapy is essential to assist in recovering immunological damage caused by chronic HBsAg exposure

- **synergistic activation requires HBsAg reduction to < 1 IU/mL**
  - Enhanced rates of HBsAg loss
  - Rapid elevations in anti-HBs (to > 10,000 mIU/mL)
  - Strong therapeutic transaminase flares now occur in HBeAg negative patients
  - Increased rates of functional control persisting off therapy (HBV and HDV)
  - **Occurs with cytokine-based (pegIFN α2a) or TLR-based (thymosin α1) immunotherapies**

A direct acting antiviral agent may further improve outcomes → tenofovir pro-drugs are currently the best option:

- Efficiently inhibits the HBV RT with minimal resistance→ reduces cccDNA levels in the liver
- **Stimulates the production of antiviral cytokines (TNFα and INFγ and INFλ3)**
- Improved liver partitioning of next generation tenofovir prodrugs (i.e. TXL) may further enhance these effects

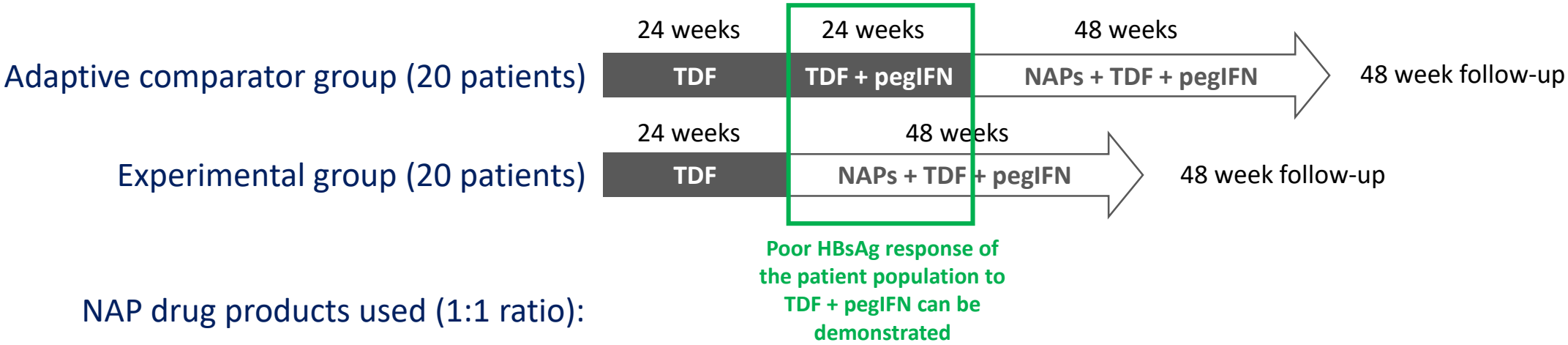
Bazinet et al., 2017 Lancet Gastro. Hep 2: 877-889
Al-Mahtab et al., 2016 PLOS One 11: e0156667

Cathcart et al., J. Hepatol. 2018;66: S476
Lai et al., J. Hepatol. 2017; 66: 275-281
Zidek et al., Nucleosides Nucleotides. 1999; 18: 959-961
Zidek et al., Antimicrob. Agents Chemother. 2001; 45: 3381-3386
Zidek et al., Eur. J. Pharmacol. 2003; 475: 149-159

Kmoníčková et al., Eur. J. Pharmacol. 2006; 530: 179-187
Potměšil et al., Eur. J. Pharmacol. 2006; 540: 191-199
Zidek et al., Eur. J. Pharmacol. 2007; 574: 77-84
Kostecká et al., Int. Immunopharmacol. 2012; 12: 342-349
Murata et al., Gut. 2018; 76: 362-371

Putting the pieces together: the REP 401 study

NCT02565719
Treatment naive chronic HBeAg negative infection, HBsAg > 1000 IU/mL, HBV DNA > 10,000 IU /mL
Advanced fibrosis allowed but cirrhosis excluded



NAP drug products used (1:1 ratio):

250mg REP 2139-Mg qW IV
lead candidate
250mg REP 2165-Mg qW IV
suitable for high frequency dosing to rescue the small proportion patients with weak HBsAg response (< 1 log reduction)

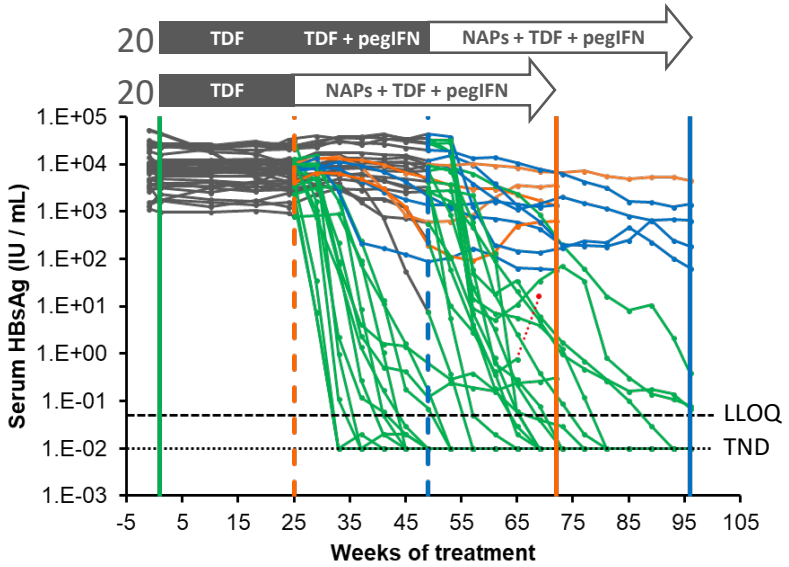
These are SC formulations administered via IV infusion

Safety in the REP 401 study

Treatment	Common Adverse events
TDF monotherapy	none
TDF + pegIFN	• asymptomatic thrombocytopenia and leucopenia (easily managed with pegIFN dose reduction and or eltrombopag) • typical symptoms associated with pegIFN (fever, aches, joint pain) 1 patient withdrew due to pegIFN associated depression
TDF + pegIFN + NAPs (REP 2139-Mg or REP 2165-Mg)	• no change in platelet / WBC dynamics or pro-inflammatory symptoms (vs TDF + pegIFN) • NAP IV administration now asymptomatic over 48 weeks **ready for transition to SC administration** **(normal mode of administration used for this drug class)**

Antiviral Response in the REP 401 study

HBsAg



REP 2139-Mg = REP 2165-Mg

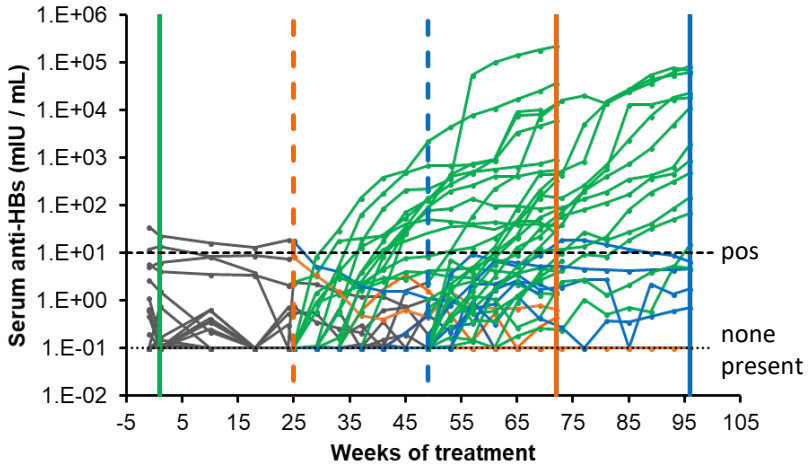
4/40 non-responders (HBsAg reduction < 1 $\log_{10}$)

8/40 HBsAg > 1 $\log_{10}$ reduction but < 1 IU/mL

28/40 HBsAg < 1 IU/mL

24/40 HBsAg loss (0.00 – 0.05 IU/mL)

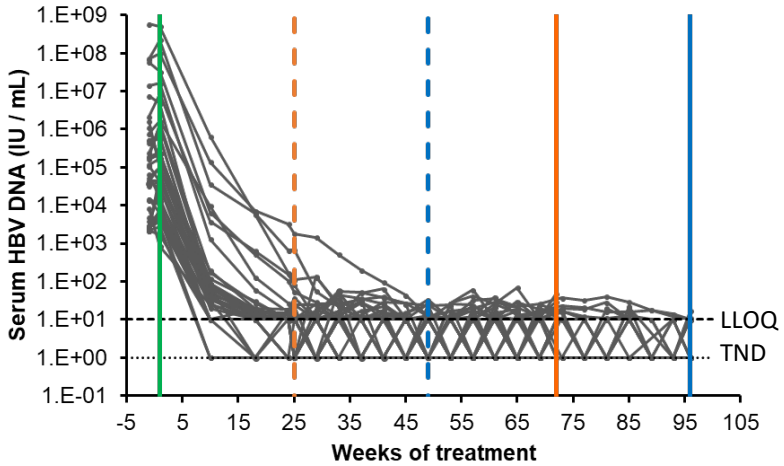
Anti-HBs



Anti-HBs dramatically increased with the introduction of pegIFN

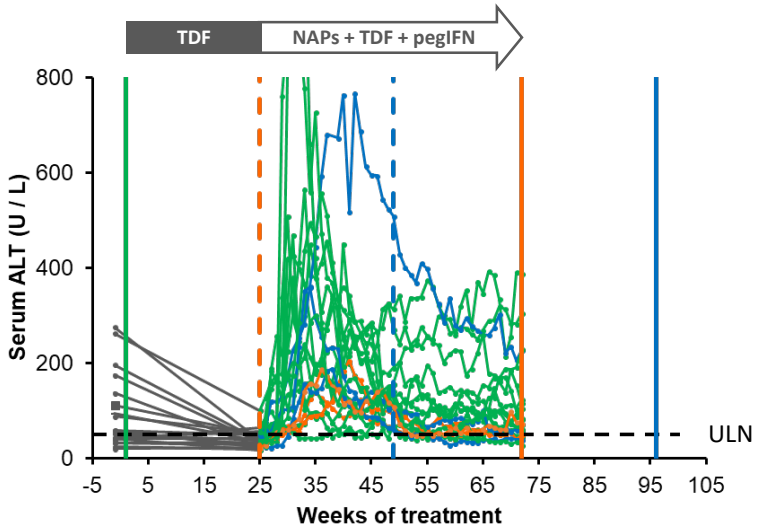
(but only in patients with HBsAg declines to < 1 IU/mL)

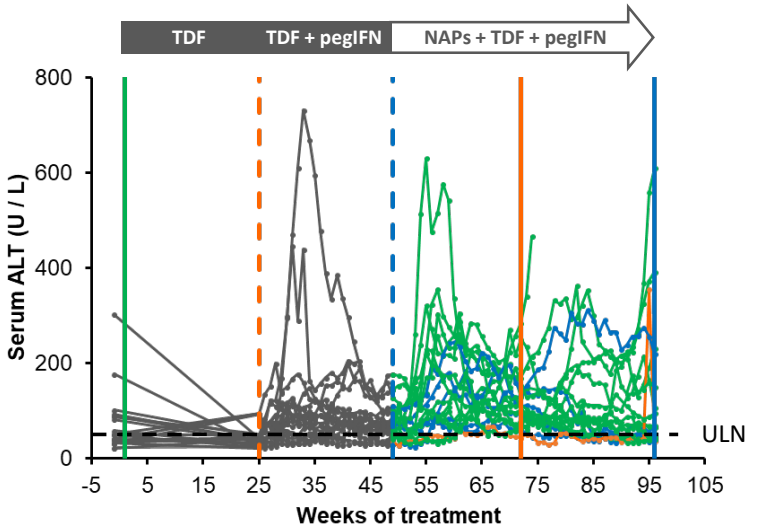
HBVDNA



TDF-induced HBV DNA declines unaffected during therapy

Therapeutic transaminase flares in the REP 401 study





ALT flares observed during immunotherapy
(all otherwise asymptomatic)
(increased intensity in patients with HBsAg declines to < 1 IU/mL)

Flares present but attenuated when NAPs introduced following 24 weeks of pegIFN
Likely due to loss of CD8+ T-cells during pegIFN exposure
(Micco et al. J. Hepatol. 2013; 58: 225-233)

ALT / AST declines in all patients during follow-up and normalizes in patients with persistent functional control

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

REP 401 interim follow-up
(June 1, 2018)

30 patients have reached 24 weeks of follow-up:

26/30 (87%) have functional repression (HBV DNA < 1000 IU/mL)
- 20/26 with HBsAg < 10 IU/mL
- 24/26 with normal liver function
- 12 patients now at 48 weeks of follow-up

21/30 (70%) have functional remission (HBV DNA < LLOQ)
- 18/21 with HBV DNA target not detected
- 14/21 with HBsAg target not detected (0.00 IU/mL)
- 9 patients now at 48 weeks of follow-up

Summary

48 weeks of REP 2139-Mg/REP 2165-Mg, TDF and pegIFN are well tolerated

- pegIFN side effects are mild, easily managed and not altered by NAP exposure
- **pegIFN is much better tolerated in combination setting than when used with ribavirin in HCV infection**

Leads to a high rate (90%) of > 1 log_{10} HBsAg reduction within the first 24 weeks of NAP exposure

- 70% of patients experience HBsAg reduction to < 1 IU/mL or target not detected
  - Rapid and profound increases in anti-HBs
  - Strong, self revolving and otherwise asymptomatic (therapeutic) transaminase flares

High rates of functional control are present at 24 weeks follow-up

- 87% functional repression (HBV DNA < 1000 IU/mL)
- 70% functional remission (HBV DNA < LLOQ)
- Normalization of liver function

Next steps:

- REP 103 / A5382 trial in the US (in collaboration with ACTG): REP 2139-Mg + pegIFN in NUC supressed patients
- Transition REP 2139-Mg to SC administration
- REP 2139-Mg + TDF + pegIFN in HBV / HDV co-infection
- Compare other immunotherapies to pegIFN in this combination therapy setting

Acknowledgments

A collaborative effort!

Clinical evaluations:

Montreal, Canada
Michel Bazinet

Dhaka, Bangladesh
Mamun Al-Mahtab

Chișinău, Moldova
Victor Pântea
Valentin Cebotarescu
Lilia Cojuhari
Pavlina Jimbei
Gheorghe Placinta
Liviu Iarovoi
Valentina Smesnoi
Tatiana Musteata
Iurie Moscalu
Alina Jucov

US (ACTG)
Marion Peters
Mark Sulkowski

Clinical virology and assay validation:

Essen, Germany
Adalbert Krawczyk

Munich, Germany
Michael Roggendorf
Hadi Karimzadeh
Hrvoje Mijočević
Zainab Usman

Los Angeles, USA
Peter Schmid
Jeffrey Albrecht

Bobigny, France
Emmanuel Gordien
Frédéric Le Gal

Pre-clinical evaluations:

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Celia Brikh
Jonathan Quinet
Catherine Jamard

Essen, Germany
Michael Roggendorf
Katrin Schöneweis
Mengji Lu
Pia Roppert
Dieter Glebe

Logan, Utah, USA
John Morrey
Neil Motter

Reno, Nevada, USA
Doug Kornbrust

Mechanistic studies:

Montreal, Canada
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Patrick Labonté

Paris, France
Camille Sureau
Frauke Beilstein
Matthieu Lemasson

Essen, Germany
Ruth Broering
Catherine Real
Joerg Schlaak

Ness Ziona, Israel
Raphael Mayer
Merav Merom Shamur
Ronny Peri-Naor