Functional control and clinical benefit 1 year following completion of REP 2139 / peg-IFN therapy in patients with chronic HBV / HDV co-infection

M. Bazinet, V. Pântea, V. Cebotarescu, L. Cojuhari, P. Jimbei, A. Krawczyk, A. Vaillant

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replicor

Infectious Disease Clinic
Toma Ciorbă Hospital

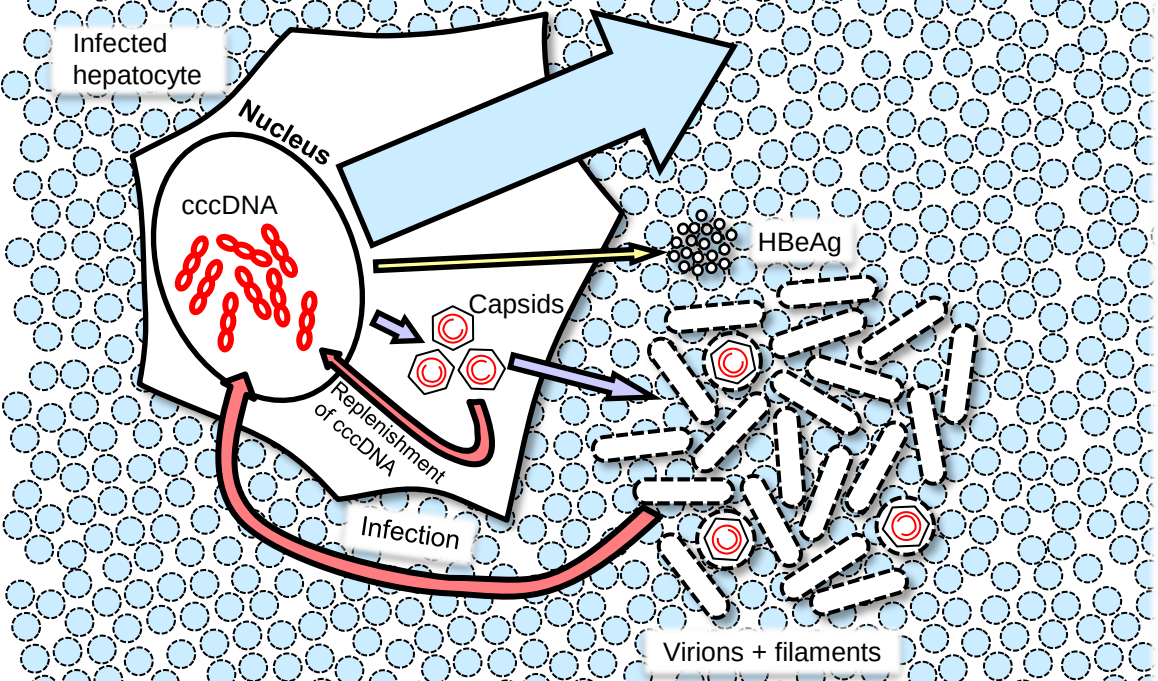
Universitätsklinikum Essen

Disclosures

M. Bazinet, A. Vaillant: Shareholder and Employee of Replicor Inc.

Particle production in HBV

SUBVIRAL PARTICLES: The bulk of circulating HBsAg



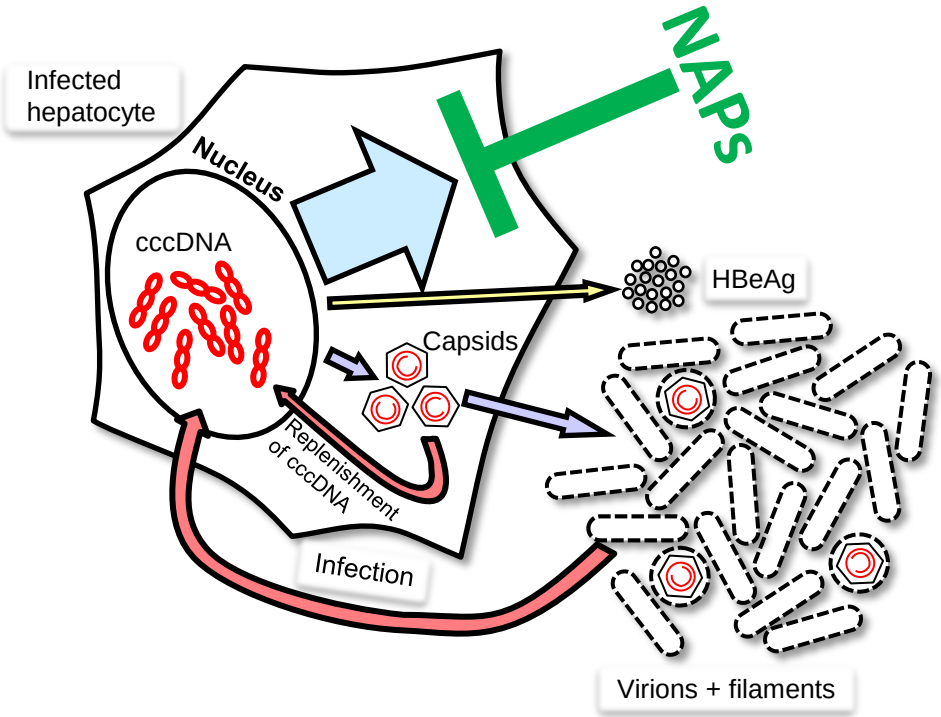
HBsAg is an immunosupressor:

- Masks anti-HBs response
- Blocks signalling mechanisms in innate and adaptive immunity
- Blocks the effect of immunotherapies
- **HBsAg clearance is critical to achieving functional control**

M. Bazinet et al., 2016 Hepatology 64: S912A
Al-Mahtab et al., 2016 PLOS One 11: e0156667
Shi et al. 2012 PLOS One 7: e44900
Woltman et al. 2011 PLOS One 6: e15324
Op den Brouw et al., 2009. Immunology, 126: 280-289
Wu et al., 2009. Hepatology, 49: 1132-11
Xu et al., 2009. Molecular immunology, 46: 2640-2646
Cheng et al., 2005. Journal of Hepatology, 43:4 65-471
Vanlandschoot et al., 2002. J. Gen. Virol., 83: 1281-1289

Nucleic Acid Polymers (NAPs)

NAPs block subviral particle release → Efficient HBsAg clearance from the blood



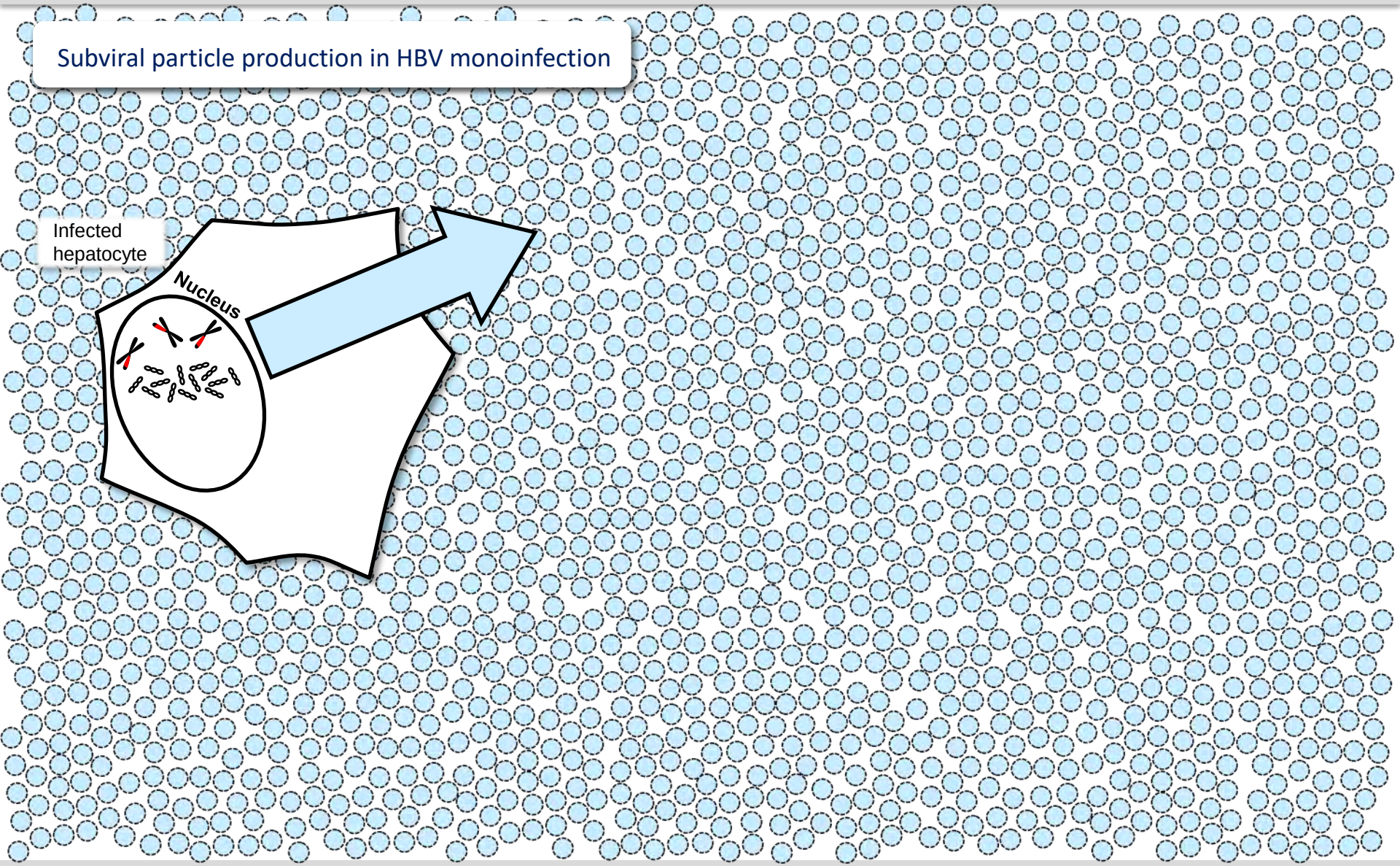
Critical effects of HBsAg clearance:

- Unmasking anti-HBs response
- Elimination of HBsAg mediated immunosupression
- Improved response to immunotherapy
- **Functional control can be established in most patients**

Vaillant, 2016. Antiviral Res. 133: 32-40
Al-Mahtab et al., 2016 PLOS One 11: e0156667
M. Bazinet et al., 2016 AASLD Abstract 1848.
Reesink et al., 2016 Hepatol. Int. 10: S2
Noordeen et al., 2015 PLOS One 10: e0140909

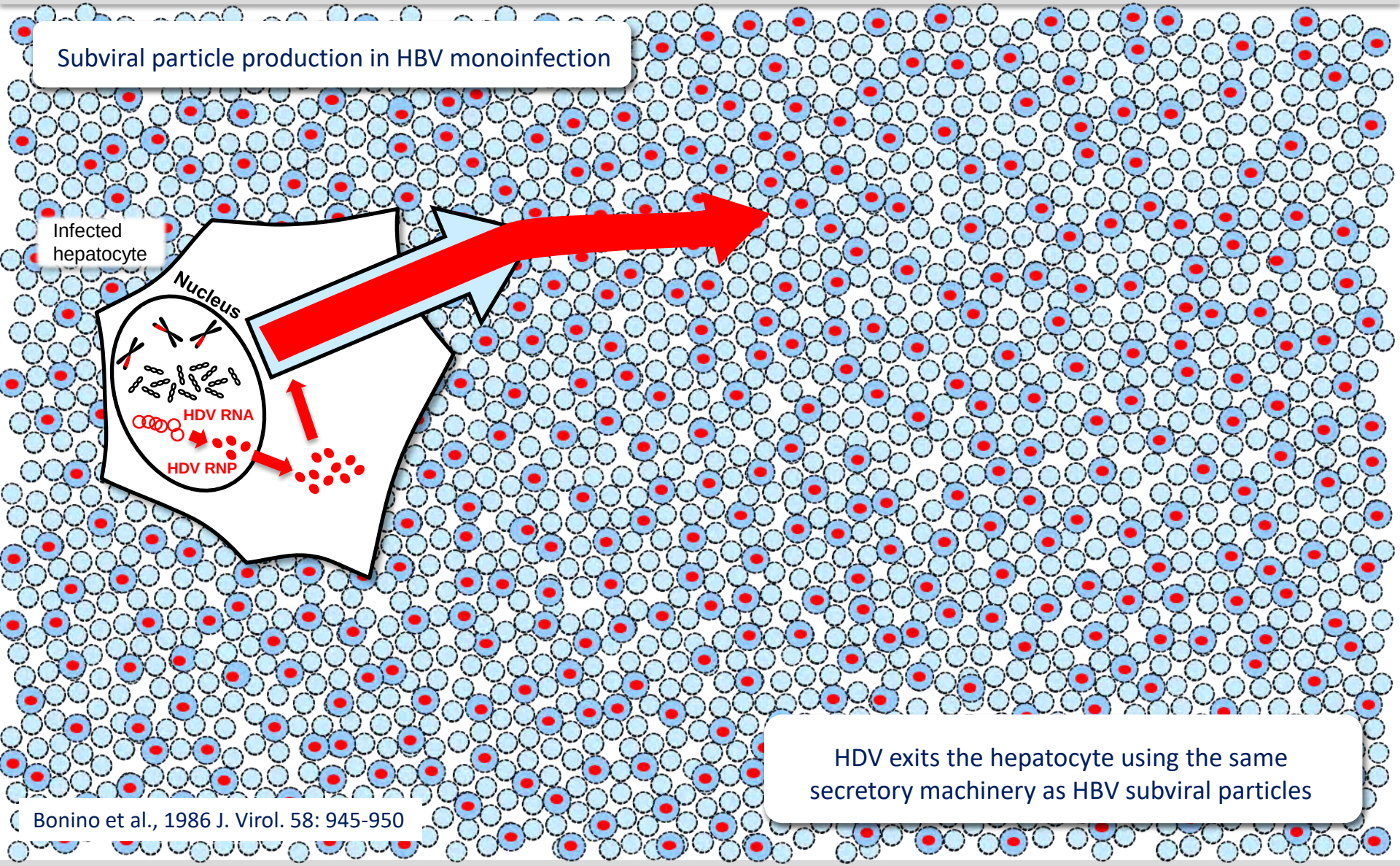
HBV vs HBV / HDV co-infection

Subviral particle production in HBV monoinfection



HBV vs HBV / HDV co-infection

Subviral particle production in HBV monoinfection



HDV exits the hepatocyte using the same secretory machinery as HBV subviral particles

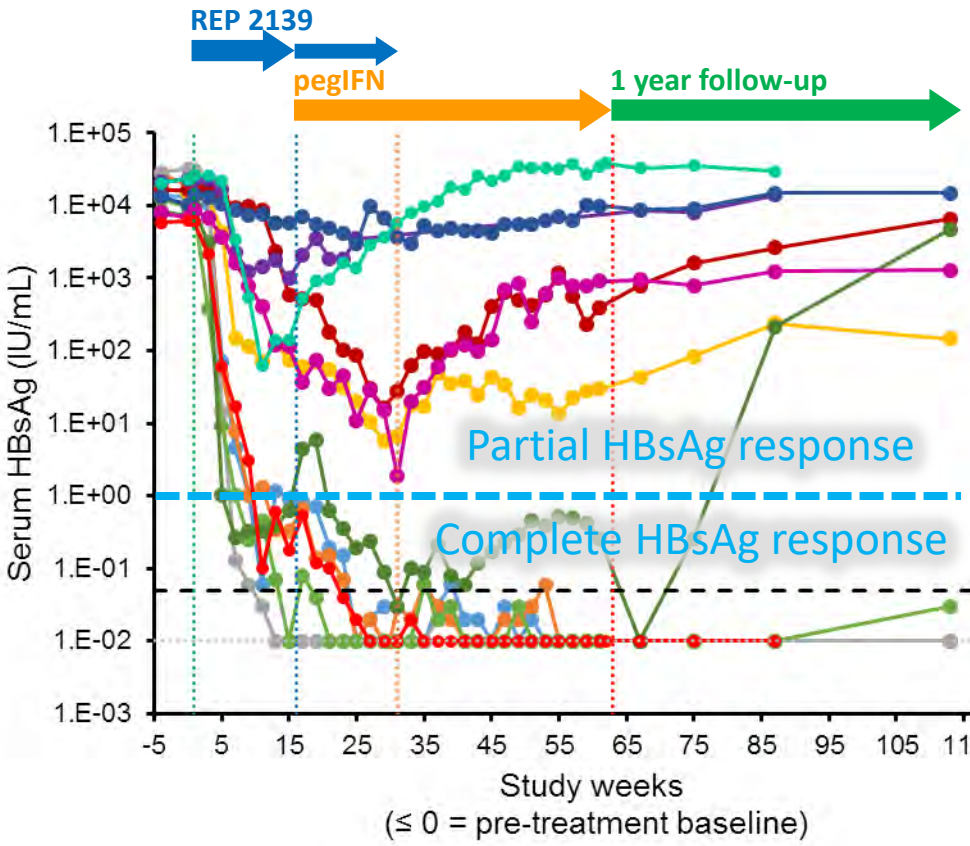
Bonino et al., 1986 J. Virol. 58: 945-950

REP 301 / 301-LTF studies

- 12 Caucasian patients with confirmed chronic HBV / HDV co-infection
- Clinicaltrials.org # NCT02233075

REP 301-LTF (NCT02876419): 3 year extension of follow-up (every 6M).

Serum HBsAg



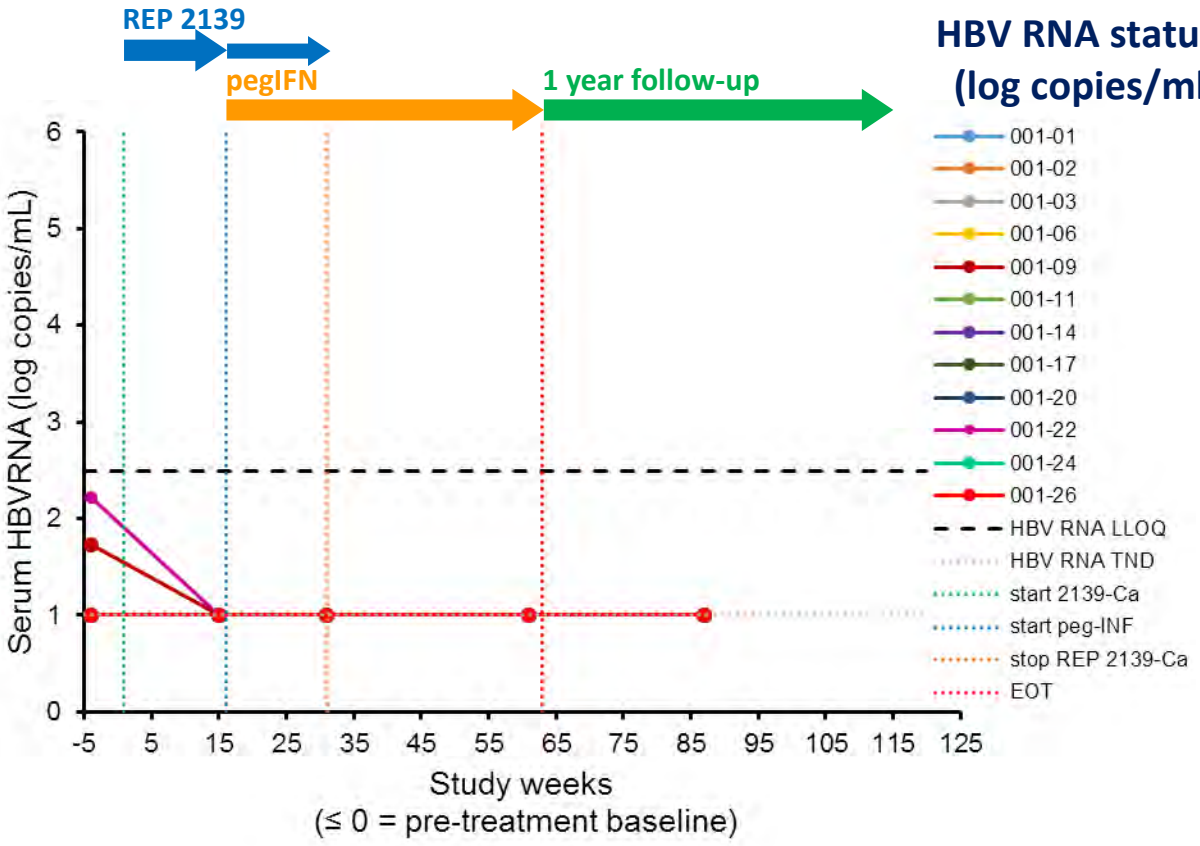
HBsAg status (IU/mL)	Baseline	24W follow-up	1 year follow-up
001-01	13998	0.00	0.00
001-02	27264	0.00	0.01
001-03	28261	0.00	0.01
001-06	17511	239	146
001-09	16426	2646	6621
001-11	12382	0.00	0.03
001-14	20869	13896	*
001-17	8314	214	4754
001-20	13430	14943	14917
001-22	7836	1225	1281
001-24	20473	29724	pending
001-26	5854	0.00	pending

5/12 patients with HBsAg control at 24W – 1 year follow-up.

An additional 2 patients have established a new HBsAg baseline

LLOQ = lower limit of quantification, TND = target not detected (0.00 IU/mL), EOT = end of treatment, * not enrolled in REP 301-LTF

Serum HBV RNA



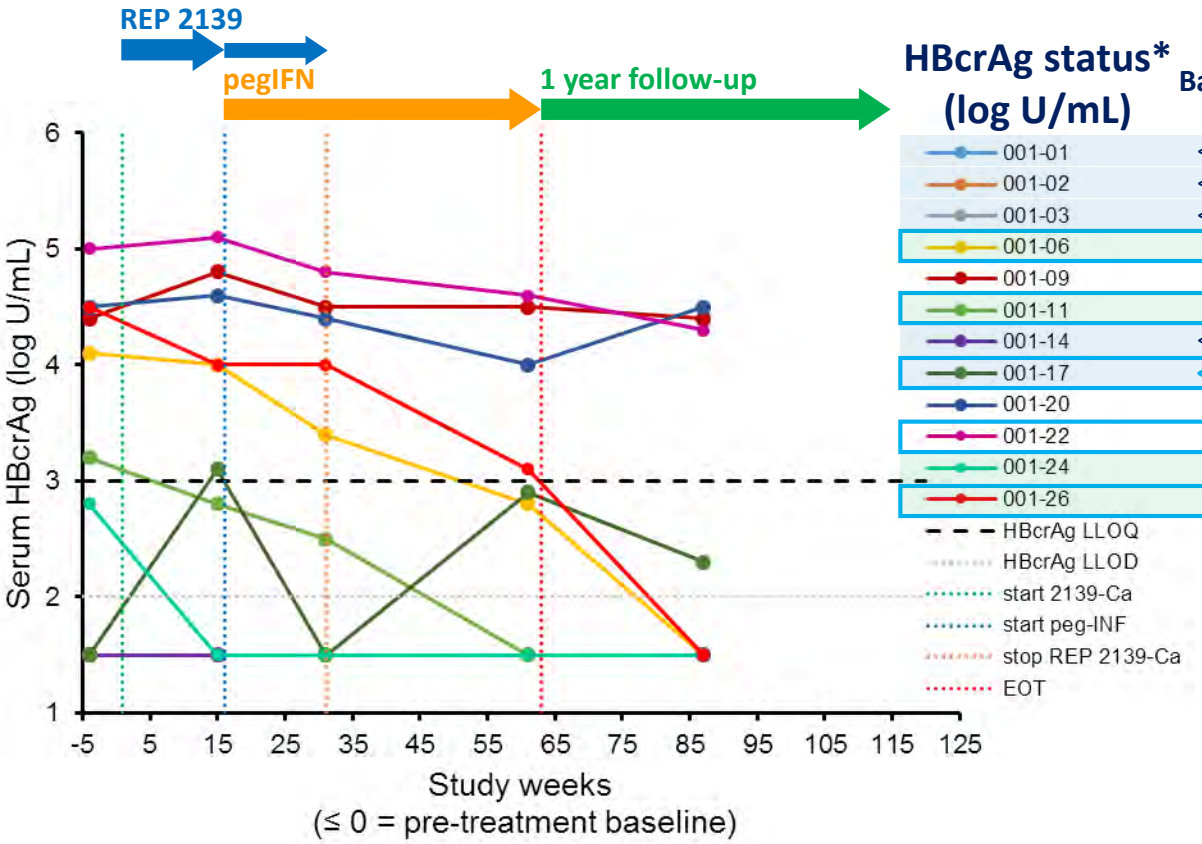
Baseline	24W follow-up	HBsAg Baseline (IU/mL)
TND	TND	13998
TND	TND	27264
TND	TND	28261
TND	TND	17511
< LLOQ	TND	16426
TND	TND	12382
TND	TND	20869
TND	TND	8314
TND	TND	13430
< LLOQ	TND	7836
TND	TND	20473
TND	TND	5854

Baseline HBV RNA is either not quantifiable or not detectable in all patients

despite significant HBsAg levels

*DDL Diagnostic, Rijswijk, The Netherlands, TND = target not detected, LLOQ = lower limit of quantification (2.49 log copies/mL)

Serum HBcrAg



HBcrAg status* (log U/mL)	Baseline	REP 2139 mono	HBsAg log reduction REP 2139 mono	24W follow-up
001-01	< LLOD	< LLOD	4.18	< LLOD
001-02	< LLOD	< LLOD	4.92	< LLOD
001-03	< LLOD	< LLOD	6.45	< LLOD
001-06	4.1	4	2.37	< LLOD
001-09	4.4	4.8	1.44	4.4
001-11	3.2	2.8	6.09	< LLOD
001-14	< LLOD	< LLOD	1.32	< LLOD
001-17	< LLOD	3.1	4.11	2.3
001-20	4.5	4.6	0.36	4.5
001-22	5	5.1	1.83	4.3
001-24	2.8	1.5	2.17	< LLOD
001-26	4.5	4	4.51	< LLOD

Baseline HBcrAg is undetectable in 5/12 patients at baseline

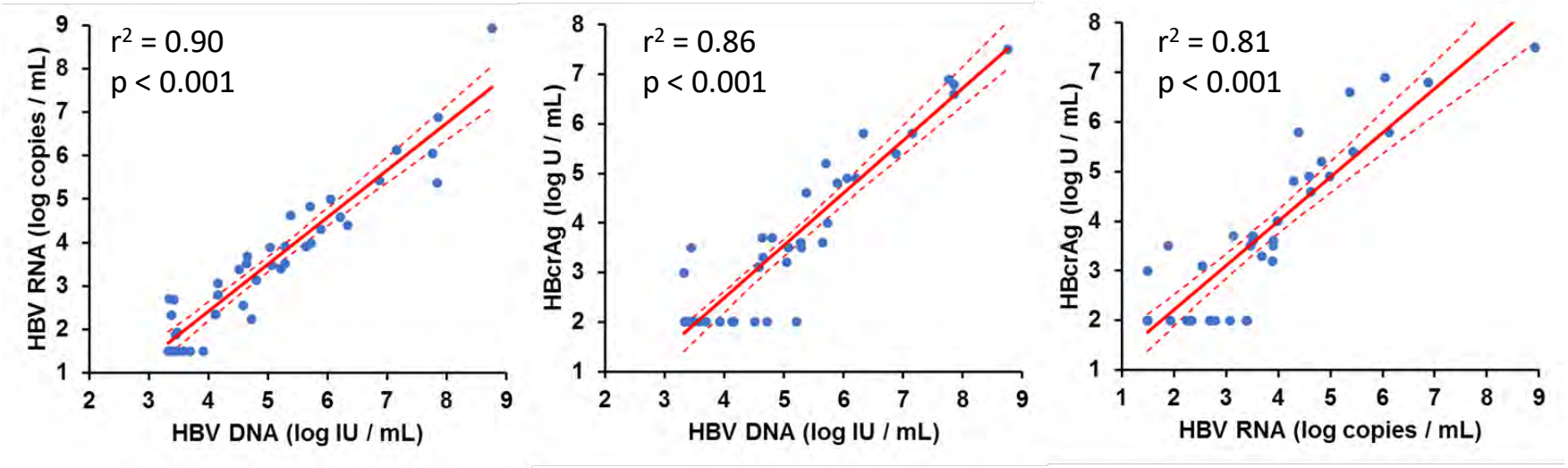
HBcrAg levels are unchanged during REP 2139 monotherapy despite substantial decreases in HBsAg (selective targeting of SVPs)

pegIFN results in HBcrAg < LLOD in 4/5 patients with HBsAg reduction > 2 log

*Fujirebio Lumipulse® (DDL Diagnostic, Rijswijk, The Netherlands), LLOD = lower limit of detection (2 log U/mL)

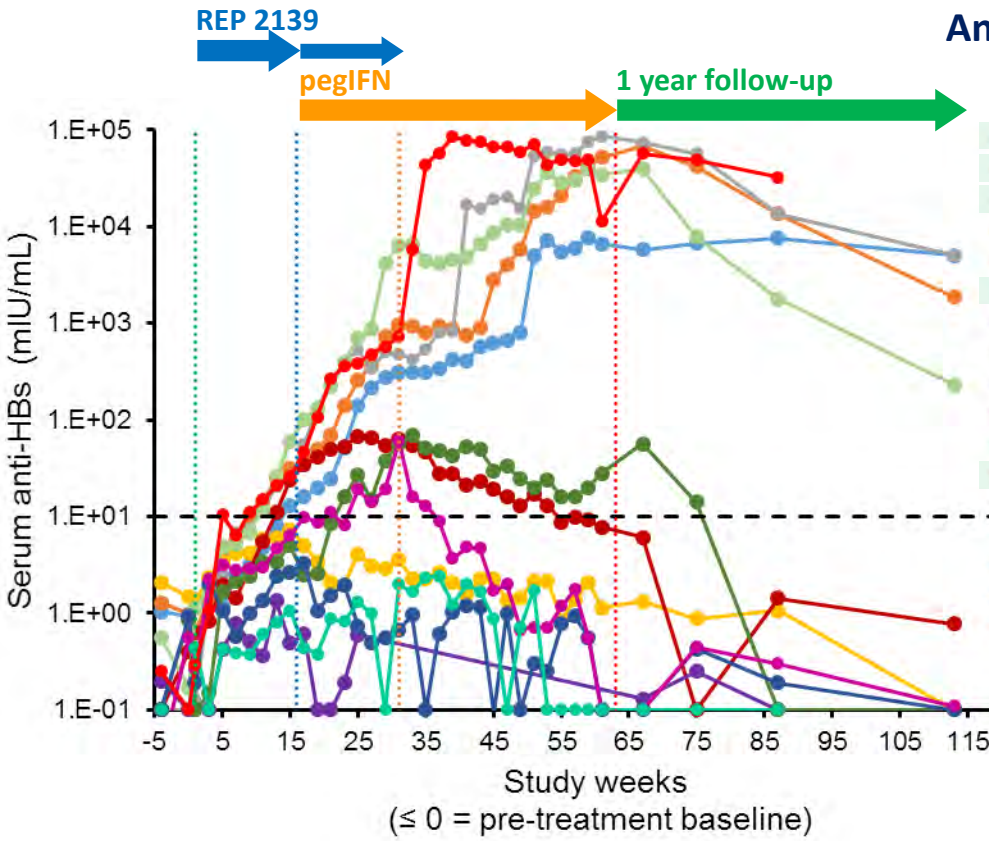
Serum HBV RNA / HBcrAg
(HBeAg negative HBV mono-infection)

Baseline measurements of 40 HBeAg- HBV mono-infected patients
(REP 401 protocol, poster THU-154)



HBV RNA deficit is specific for chronic co-infection with HDV

Anti-HBs maintenance off treatment versus HBsAg response



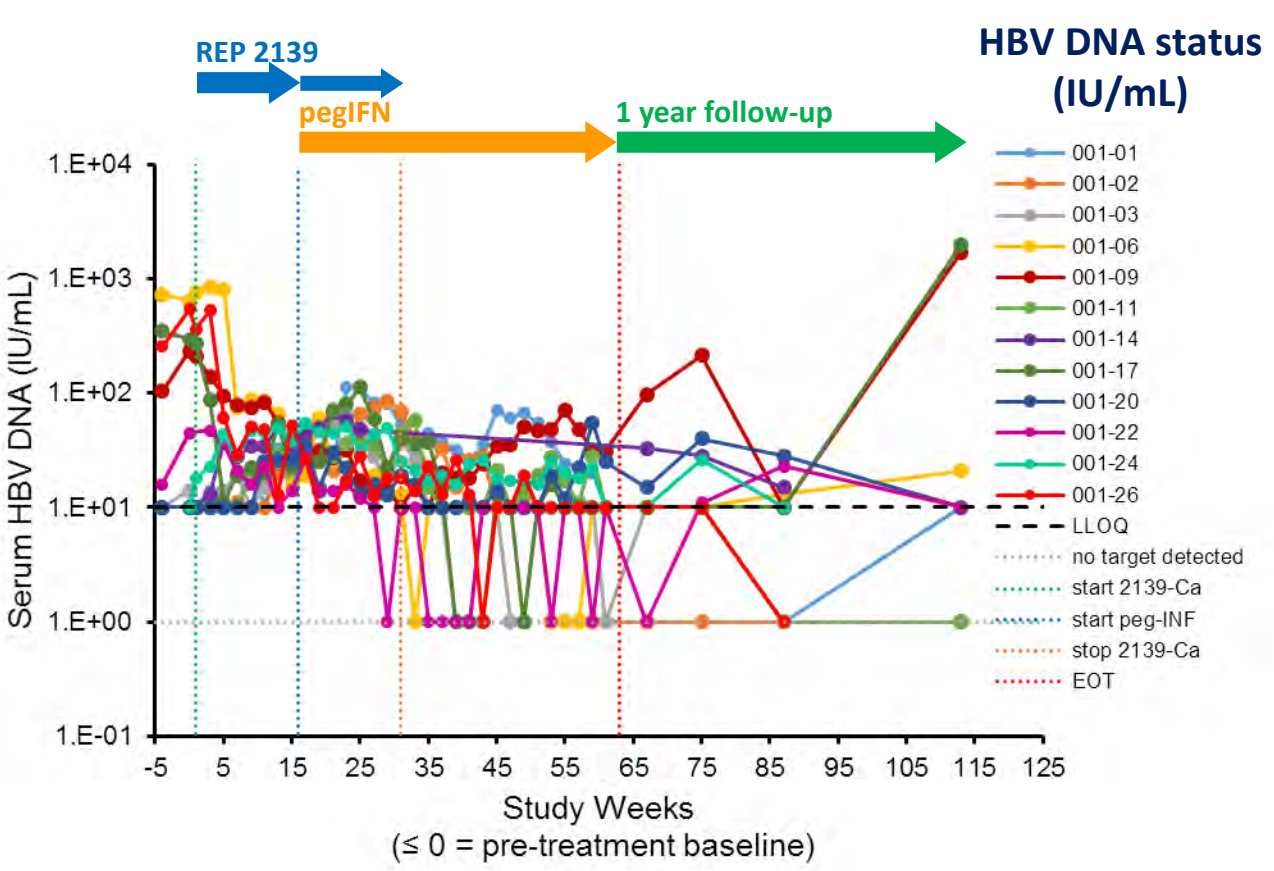
Anti-HBs status (mIU/mL)	1 year follow-up	HBsAg < 1 IU/mL before pegIFN	HBsAg 1 year follow-up
001-01	**5073**	←	**0.00**
001-02	**1873**	←	**0.01**
001-03	**5079**	←	**0.01**
001-06	< 0.1		146
001-09	0.78		6621
001-11	**231**	←	**0.03**
001-14	*		*
001-17	< 0.1	←	4754
001-20	< 0.1		14917
001-22	0.11		1281
001-24	(< 0.1)		(29724)
001-26	**(32543)**	←	**(0.00)**

protective immunity
start 2139-Ca
start peg-INF
stop REP 2139-Ca
EOT

Maintenance of anti-HBs titers at 1 year follow-up is correlated with serum HBsAg < 1 IU / at the start of peg-INF therapy

EOT = end of treatment, * not enrolled in REP 301-LTF, (24W follow-up result, 1 year follow-up result pending)

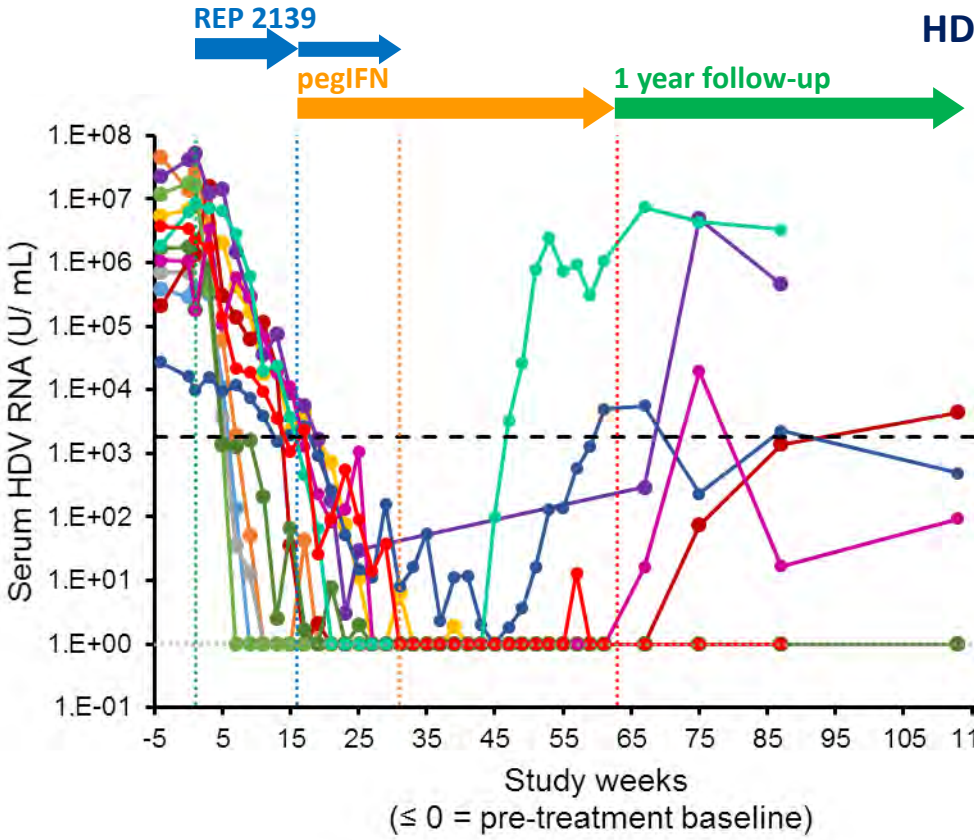
HBV DNA



HBV DNA status (IU/mL)	Baseline	1 year follow-up
001-01	< LLOQ	< LLOQ
001-02	< LLOQ	TND
001-03	< LLOQ	TND
001-06	726	21
001-09	104	1696
001-11	< LLOQ	TND
001-14	< LLOQ	*
001-17	350	1992
001-20	< LLOQ	< LLOQ
001-22	16	10
001-24	NA	(< LLOQ)
001-26	256	(TND)

EOT = end of treatment, * not enrolled in REP 301-LTF, LLOQ = lower limit of quantitation (10 IU/mL), TND = target not detected
NA = PCR result not available- inhibition observed, (24W follow-up result, 1 year follow-up result pending)

Serum HDV RNA



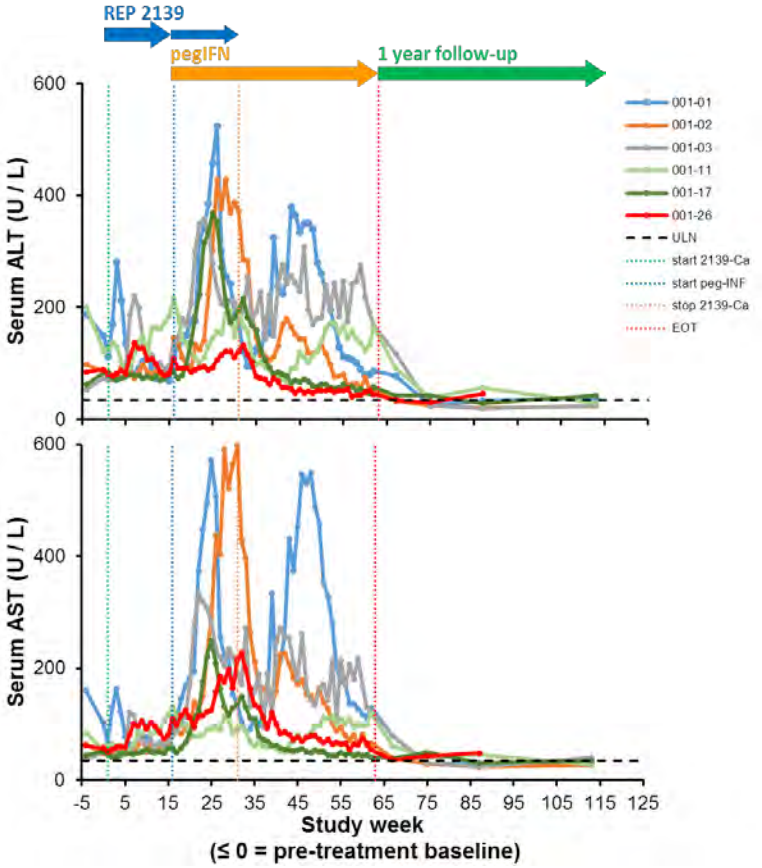
HDV RNA status (U/mL)	Baseline	EOT	24 week follow-up	1 year follow-up
001-01	3.94×10^4	TND	TND	TND
001-02	4.71×10^7	TND	TND	TND
001-03	6.97×10^5	TND	TND	TND
001-06	5.59×10^6	TND	TND	TND
001-09	2.11×10^4	TND	1390	4438
001-11	1.21×10^7	TND	TND	TND
001-14	2.30×10^7	*	4.65×10^5	*
001-17	1.68×10^6	TND	TND	TND
001-20	2.74×10^4	4920	2250	485
001-22	1.09×10^6	TND	17	94
001-24	1.89×10^6	1.09×10^6	3.28×10^6	pending
001-26	3.76×10^6	TND	TND	pending

Complete absence of HDV RNA observed at 24 weeks follow-up in 7/12 patients is stable at 1 year follow-up

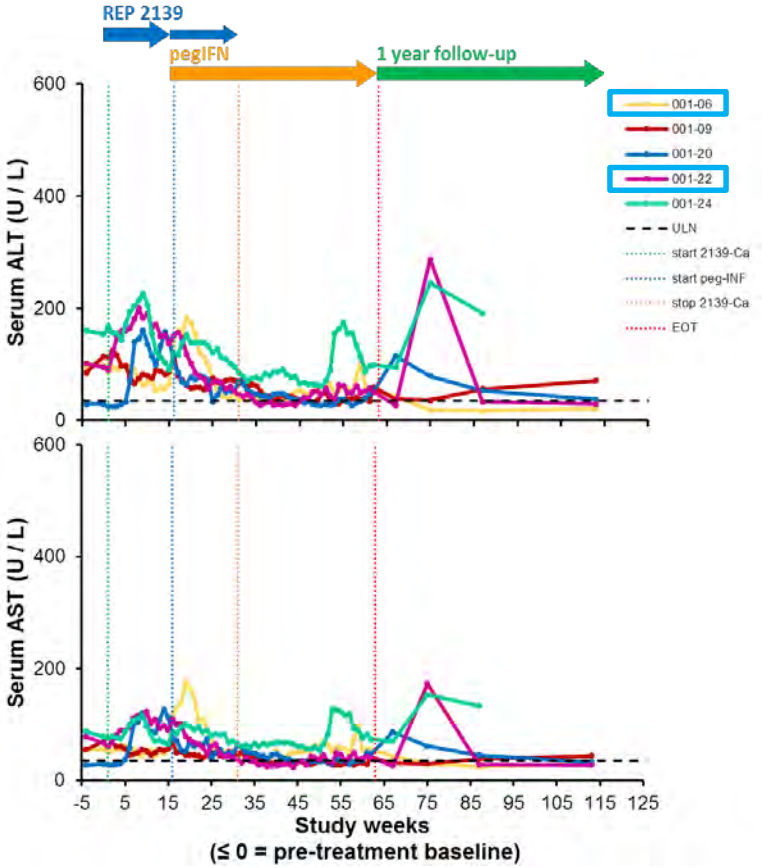
EOT = end of treatment, * early entry into REP 301 follow-up - not enrolled in REP 301-LTF, TND = target not detected

Serum ALT / AST

HBsAg < 1IU/mL prior to pegIFN



HBsAg > 1IU/mL prior to pegIFN



Serum transaminases normalize in 8/12 patients during follow-up

Serum transaminases normalize in 2 patients with lower HBsAg set points

EOT = end of treatment, ULN = upper limit of normal

Summary

HDV suppression of HBV may target HBV pregenomic RNA.

HDV infection can persist in the absence of active cccDNA.

Bulk of HBsAg in chronic co-infected patients is derived from integrated HBsAg.

REP 2139 simultaneously reduces HBsAg and HDV RNA.

HBsAg clearance threshold for activation of immunotherapy appears to be < 1 IU / ml.

Functional control of HBV infection (integration) in 5/12 patients and control of HDV infection in 7/12 patients is stable 1 year off-treatment.

Functional control rate expected to be higher with longer concomitant therapy with REP 2139 and peg-IFN and including TDF.

Next steps

Combined 48 weeks exposure with REP 2139, TDF and peg-IFN in HBV / HDV co-infected patients (in planning stages).

Transition to subcutaneous administration.

Please come and see us at EASL:

Poster THU-154: Update on REP 401 protocol (NAPs + TDF + pegINF in HBV infection).
Poster THU-155: Deep sequencing of HBsAg MHR in the presence of REP 2139.
Poster THU-156: *In vitro* modeling of post-entry NAP activity.
Poster THU-173: Modeling of HBsAg kinetics under REP 2139 treatment.
Poster LBP-507: Individual patient analysis from REP 301 / 301-LTF studies.