

On-treatment reduction of HBsAg and HDV RNA with REP 2139-Ca and pegylated interferon alpha 2a in Caucasian patients with chronic HBV / HDV co-infection

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BACKGROUND & AIMS

- 15-20 million patients are affected by HBV / HDV co-infection
- Most aggressive form of viral hepatitis with the fastest progression to cirrhosis.
- No approved therapy: Interferon-based treatment can infrequently achieve functional cures with long-term exposure
- HBsAg is a critical component of the HDV life cycle:
 - HBsAg not produced by HDV but is required for its assembly
 - HDV infection only occurs with HBV infection
 - HDV assembly may be linked to the assembly of HBV subviral particles (SVP) (1)
- NAPs have the ability to reduce HBsAg concentration in the serum (2, 3)

○ Hypothesis: Impairing the assembly of SVP may also block HDV virion morphogenesis and/or secretion

MATERIALS & METHODS

Caucasian patients treated in Chisinau, Moldova
 CRO monitored trial compliant with EU GCP
 Clinicaltrials.org # NCT02233075

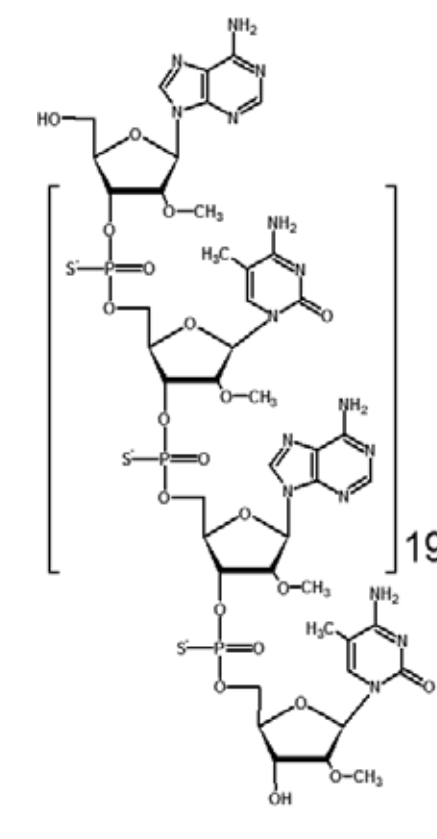
- 12 patients enrolled with HBV / HDV co-infection at the start of treatment:
- Anti-HDAG (+),
 - Serum HBsAg > 1000 U / ml
 - HBeAg (-),
 - Compensated liver disease, mild to moderate fibrosis, non cirrhotic.

- Viremia monitored at University of Duisburg-Essen, Germany:
- Abbott PCR (HBV DNA)
 - Abbott Architect Quantitative (HBsAg and anti-HBs)
 - Robogene RT-PCR (HDV RNA) – validated at two external sites.
 - Diasorin (anti-HDAG)

Dosing in three stages:

1. 15 weeks REP 2139-Ca (calcium chelate complex of REP 2139) 500mg qW IV
2. 15 weeks REP 2139-Ca 250mg qW IV plus pegylated interferon alpha 2a (peg-IFN, 180 ug qW SC)
3. 33 weeks peg-IFN (180 ug qW SC)

24 weeks of follow-up is planned at the end of peg-IFN therapy



CONCLUSIONS & PERSPECTIVE

- REP 2139-Ca is able to simultaneously reduce HBsAg and HDV RNA in patients with chronic HBV / HDV co-infection.
- Pharmacologic effect of NAPs on serum HBsAg observed in Asian patients in previous trials is replicated in Caucasian patients.
- REP 2139-Ca is well tolerated.
- Increased anti-HBs production and/or liver flares correlated with the start of peg-IFN exposure appears to be related to the extent of clearance of serum HBsAg.
- Longer combination treatment with immunotherapy will likely result in a higher proportion of patients with a full HBsAg response (< 1 IU / ml).
- NAP-based antiviral therapy may become an important new treatment option for patients with HBV / HDV co-infection.

REFERENCES

- (1) Bonino et al., 1986 J. Virol. 58: 954-950
- (2) Noordeen et al., 2015 PLoS ONE 10: e0140909
- (3) Mahtab et al., 2013 J. Hepatol. 58: S316

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RESULTS

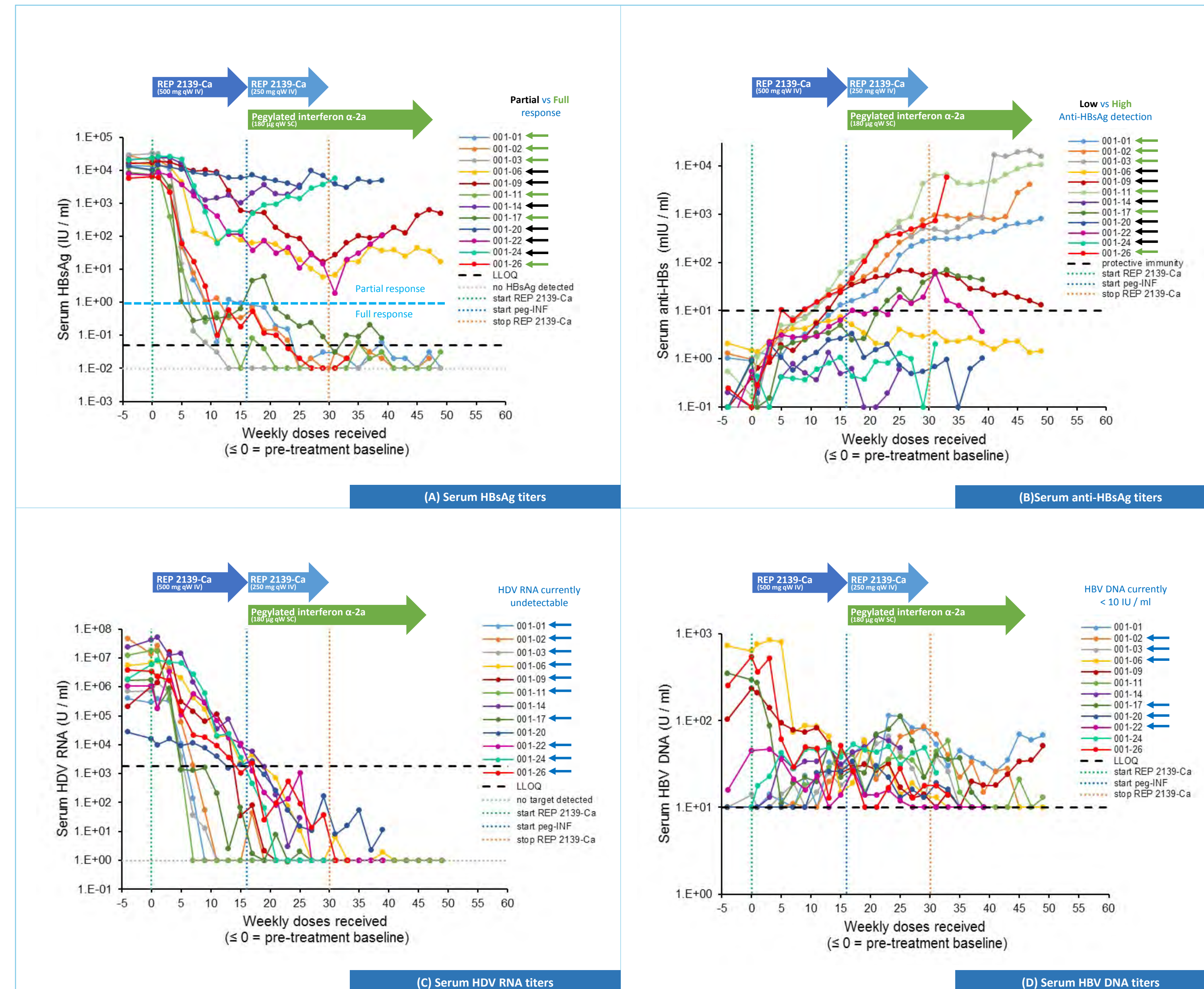


Figure 1. Efficacy of REP 2139-Ca and peg-IFN combined treatment in HBV/HDV coinfected patients. (A) REP 2139-Ca monotherapy results in up to ~ 6 log reductions in serum HBsAg. Full responders are defined by serum HBsAg is < 1 IU / ml prior to peg-IFN addition and partial responders are defined as having serum HBsAg > 1 IU/ml prior to peg-IFN addition. (B) Serum anti-HBsAg in treated patients. Substantial anti-HBsAg titers ranging from > 10² to >10⁴ mIU/ml are observed with the start of peg-IFN therapy. (C) Serum HDV RNA reductions are profound in all patients with 10/12 patients currently having no detectable serum HDV RNA. Importantly, reduction of serum HBsAg was not a prerequisite for the loss of serum HDV RNA, suggesting an additional inhibitory effect of NAPs in HDV lifecycle. (D) Serum HBV DNA appears to be partially and transiently de-repressed with reduction in serum HDV RNA in patients 01, 02, 03, 14, 20, 22 and 24. However after de-repression, significant reduction of HBV DNA concentration is observed in many of these patients with the addition of peg-IFN, and serum HBV DNA < 10 IU/ml is currently observed for 6 patients.

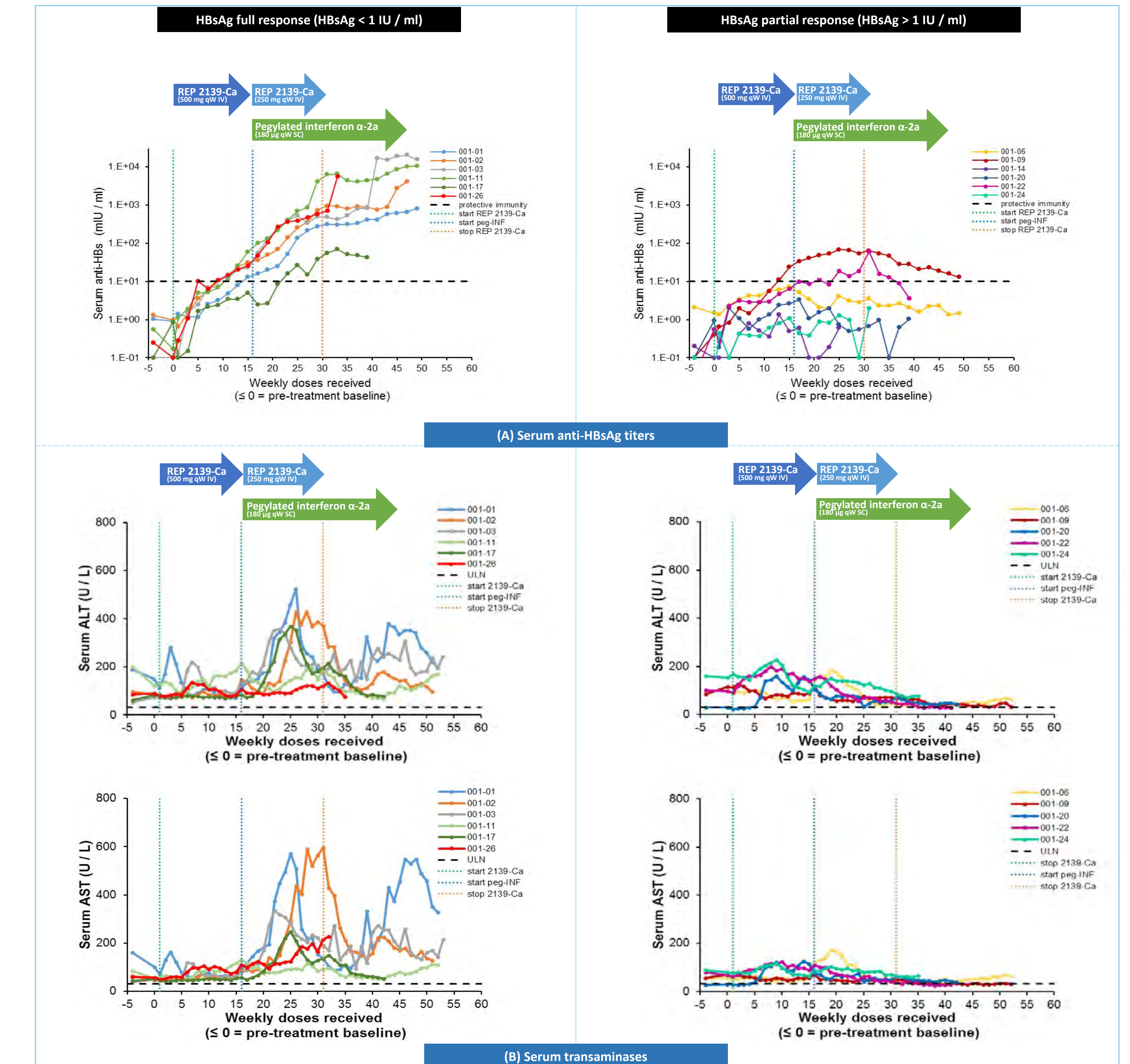


Figure 2. Correlation between serum HBsAg reductions and anti-HBsAg and liver transaminase levels with the start of peg-IFN therapy. (A) Serum anti-HBsAg from full HBsAg responders (left panel) and partial HBsAg responders (right panel) as defined in Figure 1. (B) Serum ALT and AST response to treatment. No significant flares are visible with REP 2139-Ca / Pegylated interferon α-2a treatment in partial responders (right panel) and serum transaminase levels appear to normalize as treatment progresses. In the case of full responders (serum HBsAg < 1 IU / ml), significant serum ALT / AST flares are observed upon addition of peg-IFN to the therapy regimen.