Nucleic acid polymer REP2139 monotherapy reveals a short half-life of serum HBsAg in HBeAg+ chronically infected HBV patients

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INTRODUCTION
- Previous efforts to estimate the half-life (t_{1/2}) of serum HBsAg were confounded by slow or absent HBsAg decline during therapy.
- Nucleic acid polymers (NAPs) are a new class of antiviral that significantly reduce circulating HBsAg by blocking its release from infected hepatocytes (Fig. 1) and therefore provide a unique opportunity to estimate HBsAg t_{1/2} and study HBV-host dynamics.

METHODS
- HBeAg positive patients with confirmed chronic infection were enrolled in the REP 102 protocol who were treatment naive, non-cirrhotic with baseline ALT < 5X ULN.
- Twelve HBeAg+ chronically infected HBV patients were given weekly 500mg IV infusions of REP 2139 for 20-40 weeks [1].
- HBsAg and anti-HBs levels were measured weekly using quantitative Abbott Architect® assays.

AIM
To characterize HBV DNA and HBsAg inhibition kinetics during monotherapy with REP2139 in the REP 102 protocol (NCT02646189).

RESULTS
- Mean baseline viral load (VL) and HBsAg were 7.9±1.3 log cp/ml and 4.5±0.7 log I/U/ml, respectively. All patients had anti-HBs<10 mIU/ml. Three patients with no decline in VL or HBsAg were excluded (not shown).
- VL remained at baseline 0-14 weeks before 3 patients (Fig. 2A) had a monophasic decline (t_{1/2}=11.2±6.4 d) and 6 patients had a biphasic decline consisting of a 12.0±2.6 wk 1st phase (t_{1/2}=5.3±1.5 d) followed by a 2nd phase plateau (n=1, Fig. 2B) or slower decline (t_{1/2}=5.0±2.3 wk; Fig. 2C).
- HBsAg kinetic patterns were more complex. After a 0-16 week delay (Fig. 2), HBsAg decline was monophasic (n=3, Fig. 2A), biphasic (n=1, not shown), triphasic (n=3, Fig. 2C) or staircase (n=2, Fig. 2B).
  a) Monophasic HBsAg decline was 0.53±0.25 log/wk (t_{1/2}=5.0±3.0 d).
  b) Biphasic HBsAg decline exhibited a rapid phase (0.56 log/wk; t_{1/2}=3.8 d) followed by a slower phase (0.09 log/wk; t_{1/2}=24 d).
  c) The mean 1st phase decline in the triphasic and staircase cases was 0.53±0.26 log/wk (t_{1/2}=5.4±3.4 d), followed by complex kinetic patterns.
- Anti-HBs appearance in 6 patients (>10 mIU/ml) was not associated with VL or HBsAg inhibition patterns (Fig. 2). One patient (Fig. 2C) had extremely rapid increase in anti-HBs levels.

CONCLUSIONS
- REP 2139 monotherapy led to a mono- or biphasic HBV VL decline and complex HBsAg inhibition patterns in 9 of 12 patients, with anti-HBs seroconversion in 6 of those 9.
- Kinetic analysis of the 1st HBsAg decline phase indicates a mean HBsAg t_{1/2} of 5.3±3.2 d, which is strikingly shorter than estimated under approved medications, e.g., lamivudine [2] (t_{1/2}=38 d) and pegylated interferon-alpha [3] (t_{1/2}=32 d) suggesting REP2139 inhibits HBsAg release from infected hepatocytes.
- Further efforts are needed to refine the understanding of the modes of action of NAPs against HBV and HBV-host dynamics during treatment.

REFERENCES
1. Al-Mahtab, Bazinet M, Vaillant A. Safety and Efficacy of Nucleic Acid Polymers in Monotherapy and Combined with Immunotherapy in Treatment-Naive Bangladeshi Patients with HBeAg+ Chronic Hepatitis B Infection. 2016 PLOS One 11:e0156667 .

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DISCLOSURES
MB and AV are employees of and shareholders in Replicor Inc. The other authors have nothing to disclose.

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Figure 1. Mechanism of action of NAPs

Figure 2. Representative HBV DNA, HBsAg and anti-HBs kinetic patterns during REP 2139 monotherapy (adapted from [1]).