

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.

AIM

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

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.
- HBV DNA levels were measured biweekly using the Roche Cobas® assay.
- Segmented linear regression analyses were performed using R 3.2.0.

RESULTS

- Mean baseline viral load (VL) and HBsAg were 7.9 ± 1.3 log cp/ml and 4.5 ± 0.7 log IU/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 ($t_{1/2} = 11.2 \pm 6.4$ d) and 6 patients had a biphasic decline consisting of a 12.0 ± 2.6 wk 1st phase ($t_{1/2} = 5.3 \pm 1.5$ d) followed by a 2nd phase plateau ($n=1$; Fig. 2B) or slower decline ($t_{1/2} = 5.0 \pm 2.3$ 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).
 - Monophasic HBsAg decline was 0.53 ± 0.25 log/wk ($t_{1/2} = 5.0 \pm 3.0$ d).
 - 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).
 - The mean 1st phase decline in the triphasic and staircase cases was 0.53 ± 0.26 log/wk ($t_{1/2} = 5.4 \pm 3.4$ 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.

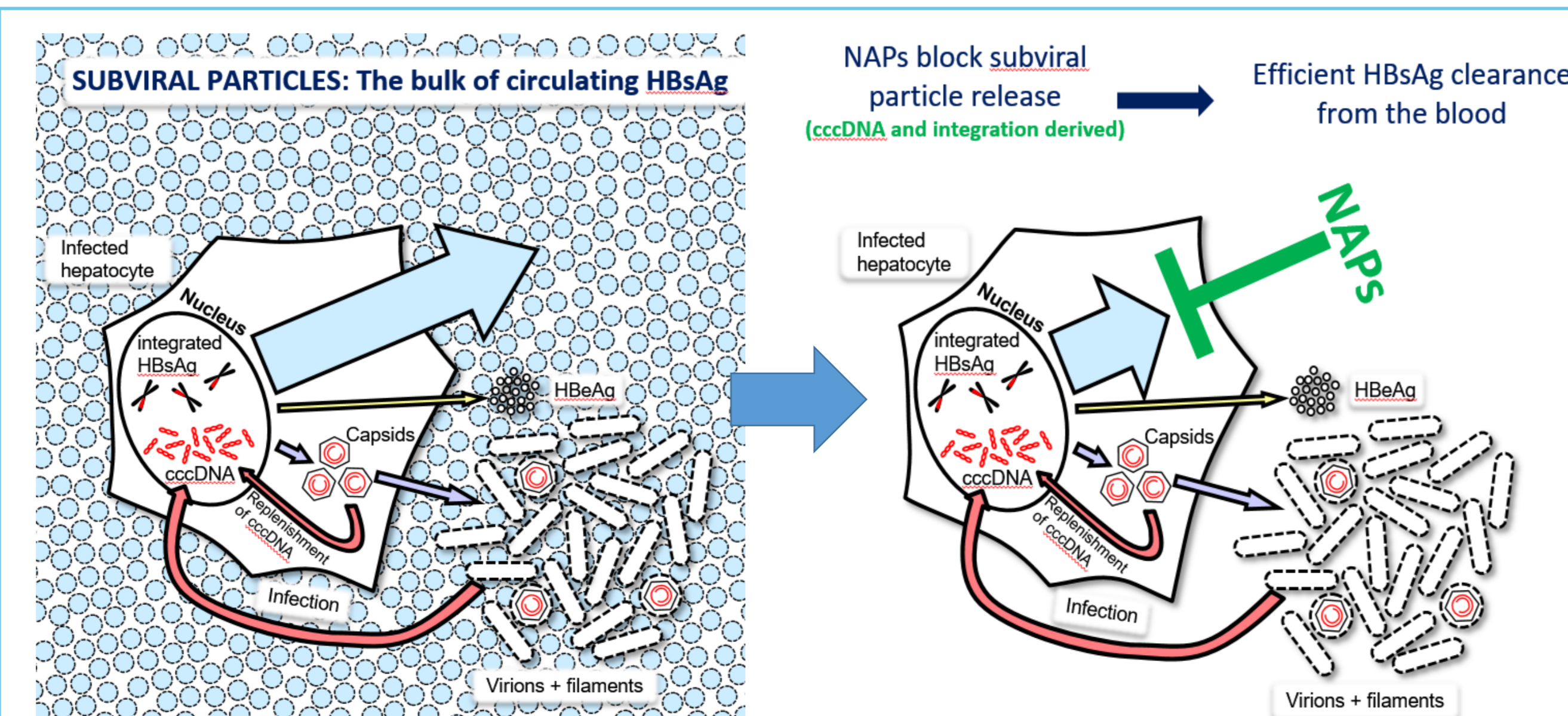
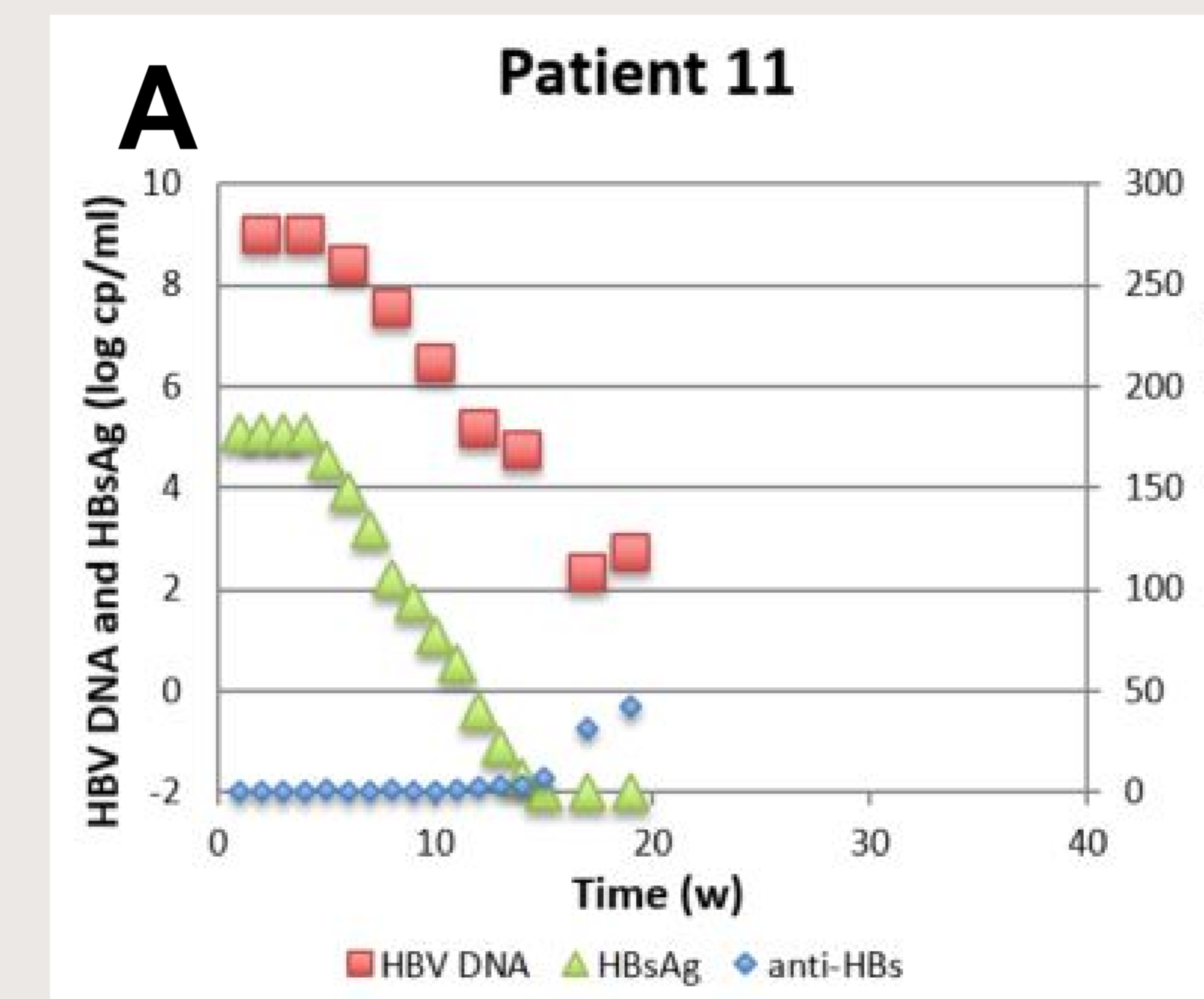
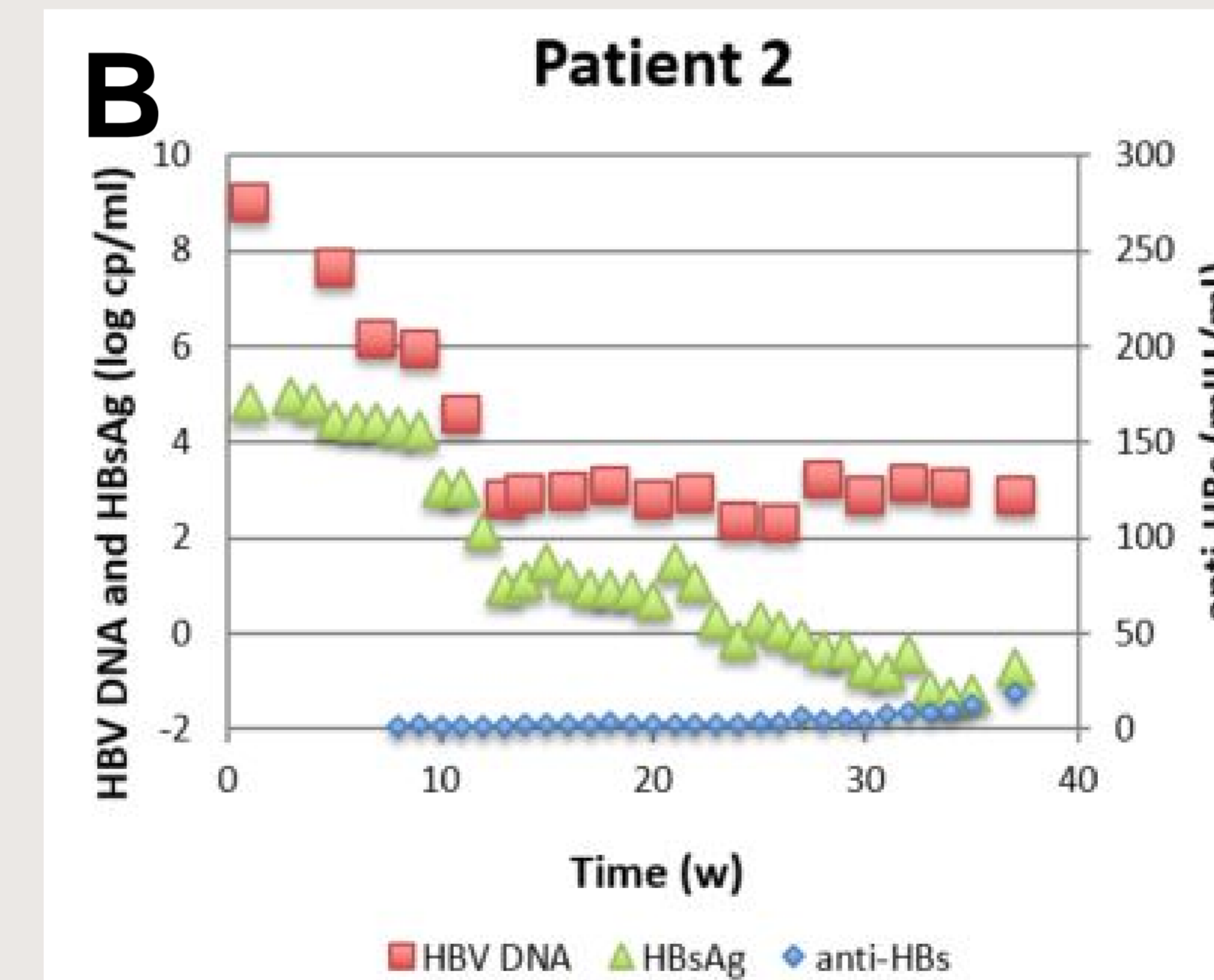


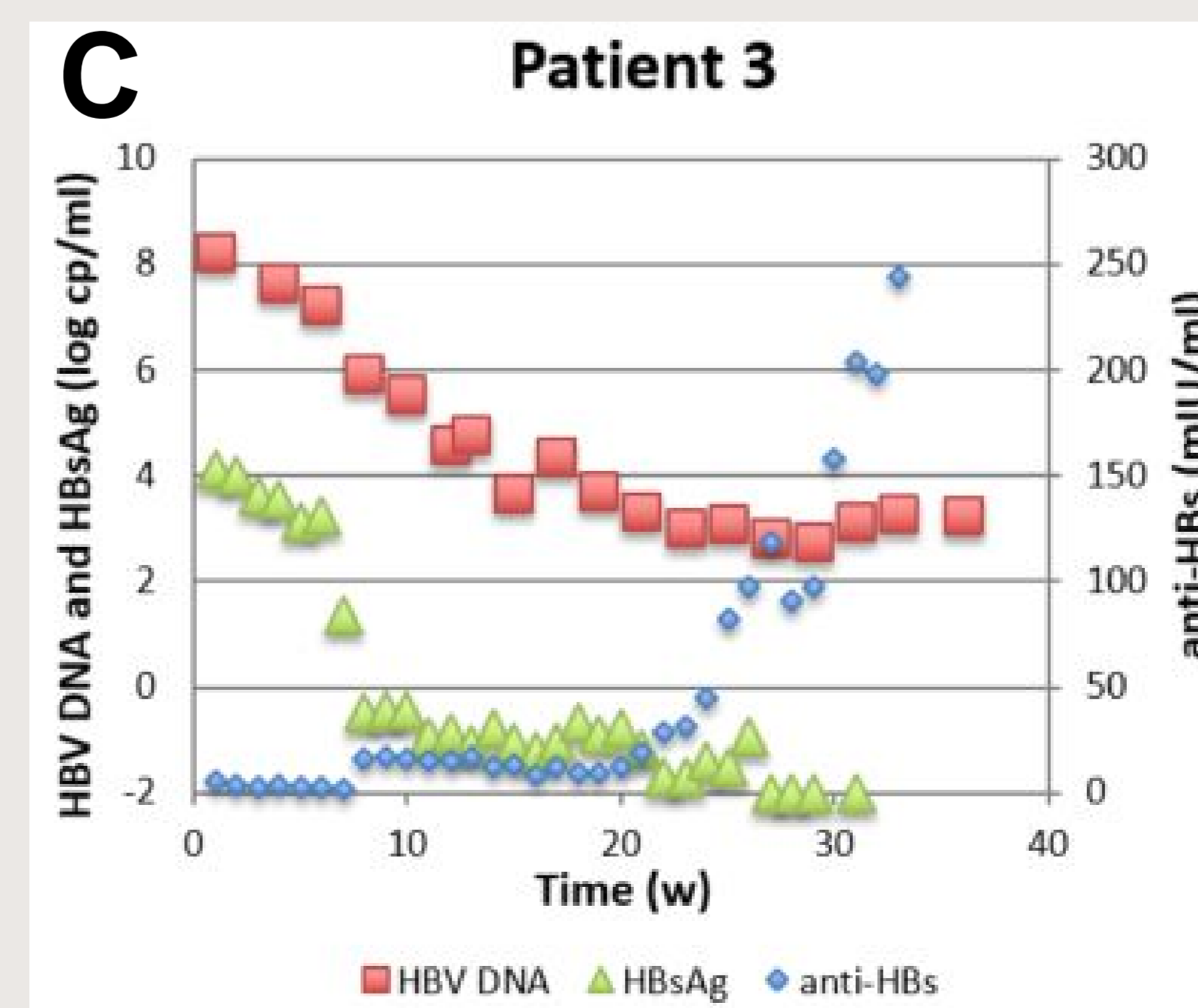
Figure 1. Mechanism of action of NAPs



Monophasic HBV DNA and HBsAg decline with anti-HBs seroconversion in 6 of those 9.



Flat partial response HBV DNA kinetic pattern and staircase HBsAg decline manner with anti-HBs appearance at week 35 post initiation of treatment.



Biphasic HBV DNA decline pattern and triphasic HBsAg decline pattern with anti-HBs appearance at week 8 post initiation of treatment.

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

CONCLUSIONS

- REP 2139 monotherapy led to a mono- or bi-phasic 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

- 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
- Neumann AU, Phillips S, Levine I, Ijaz S, Dahari H, Eren R, Dagan S, Naoumou NV. Novel mechanism of antibodies to hepatitis B virus in blocking viral particle release from cells. Hepatology (2010); Sep;52(3):875-85.
- Moucari et al. Early Serum HBsAg Drop: A Strong Predictor of Sustained Virological Response to Pegylated Interferon Alfa-2a in HBeAg-Negative Patients. HEPATOLOGY 2009;49:1151-1157.

ACKNOWLEDGEMENTS

The work was supported by Replicor Inc. and PETM.

DISCLOSURES

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

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