

Modelling hepatitis B kinetics in mice treated by a novel TLR7 agonist, alone or in combination with entecavir

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Introduction

Background

- Current antiviral strategies against Hepatitis B virus, such as entecavir (ETV), suppress viremia but do not result in cure from the infection.
- One major obstacle to cure is the existence of subviral particles that carry the surface antigen of HBV (HBsAg) and are not targeted by ETV¹.
- Toll-like receptor 7 agonists (aTLR7) are a novel therapy that stimulate antigen presentation² and antibody production potentially leading to a substantial decrease of HBsAg.

Objectives

- To characterize the complex interplay between virions, HBsAg and anti-HBs upon aTLR7 therapy developing a specific mathematical model.
- To estimate the effects of aTLR7 on viral particles and immune effectors.
- To describe the possible synergisms between ETV and aTLR7.

Data & Methods

Data

We analysed the dynamics of virus, HBsAg and anti-HBsAg of 118 mice in the AAV/HBV model³, a model where cells are transfected at baseline without further cell reinfection. Each mouse received either a placebo, ETV, aTLR7 or ETV+aTLR7 at various dosing regimen during 6 to 9 weeks. While ETV only reduces HBV DNA levels and does not affect HBsAg and anti-HBsAg, aTLR7 leads to a reduction of both HBV DNA and HBsAg titres in addition to an increase of antibodies titers.

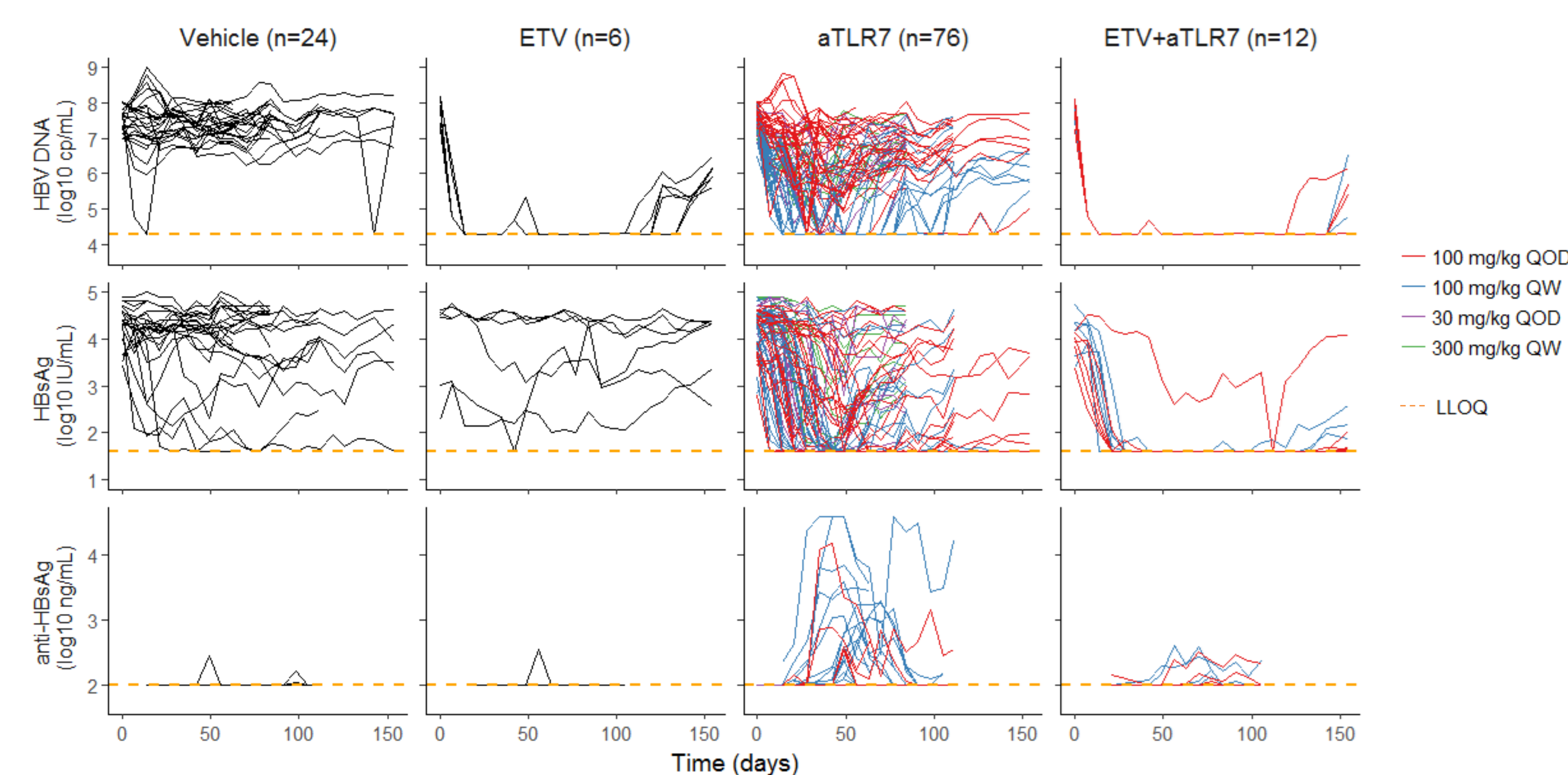


Figure 1: Spaghetti plot of HBV DNA, HBsAg and anti-HBsAg kinetics

A new model of HBV dynamics

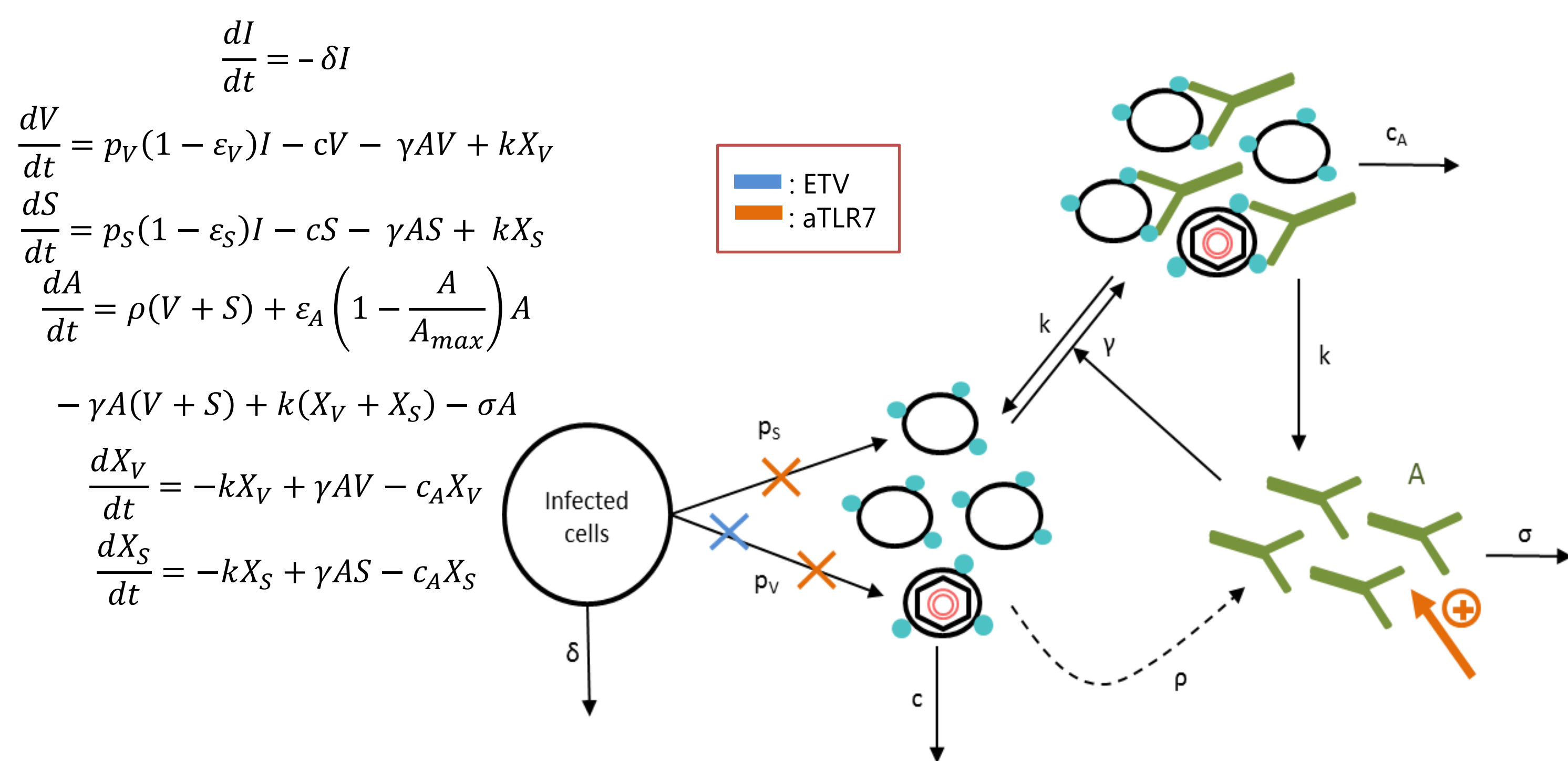


Figure 2: Schematic representation of the model

Infected cells (I) produce virions (V) and SVPs (S). Anti-HBsAg bind to V and S, that both harbour HBsAg, and complexes are rapidly eliminated⁴. The $t_{1/2}$ of infected cells was fixed to the value from the vehicle data ($t_{1/2} = 123$ d). Assuming that all cells are infected at baseline, and that both V and S carry 96 HbsAg molecules⁵, an approximated steady-state value can be found where $S \gg V$, i.e., reflecting the fact that antigen is mostly carried by non-infectious subviral particles. When treatment is initiated, we assumed that aTLR7 has 3 possible mechanisms of action: 1) reduce HBV DNA production; 2) reduce SVP production; 3) stimulate anti-HbsAg. ETV acts only by blocking virus production.

Parameter estimation

Parameter were estimated using the SAEM algorithm in Monolix software v2016R1. Correlation between efficacy related parameters were tested in case of correlation in the EBE (P-value<0.1) and were included using a forward procedure if it improved BIC by more than 2 points.

Results

Efficacy of aTLR7 and ETV on HBV DNA and HBsAg

After an initial delay, aTLR7 at the highest dose had a strong effect on HBV DNA, albeit lower than ETV ($\varepsilon_V^{aTLR7} = 99.96\%$ vs. $\varepsilon_V^{ETV} = 99.9999\%$). ETV had no effect on SVPs and therefore not reduce HBsAg titers. On the contrary aTLR7 had a strong effect on SVPs with an efficacy of 99.90%.

ETV enhances the efficacy of aTLR7 against HBsAg reduction

The efficacy of aTLR7 was significantly larger in mice treated with ETV+aTLR7 than in those receiving aTLR7 monotherapy (P=0.004, Wald test), leading to an efficacy of 99.994%. No effect of the combination could be detected on anti-HBsAg.

Stimulating antibody production

Finally aTLR7 stimulated antibody production with an efficacy estimated to 22.5% corresponding to an increase in anti-HBsAg titers over 100 ng/mL. After week 7, that led to a renewed decline of HBV DNA and HBsAg decline. The model predicted that this decline may pursue up to W20, and could lead to a decline in HBV DNA and SPV of more than 3 logs at the highest dose.

After treatment cessation, viral load returned to baseline value, consistent with the absence of infected cell elimination in this model.

Table 1: Parameter estimates

Efficacies	Fixed effects (RSE%)
ETV vs. virions	0.999999 (<1)
aTLR7 vs. virions	0.9964 (<1)
aTLR7 _{mono} vs. SVPs	0.9990 (<1)
aTLR7 _{combo} vs. SVPs	0.99994 (<1)
aTLR7 vs. antibodies	0.2250 (10)

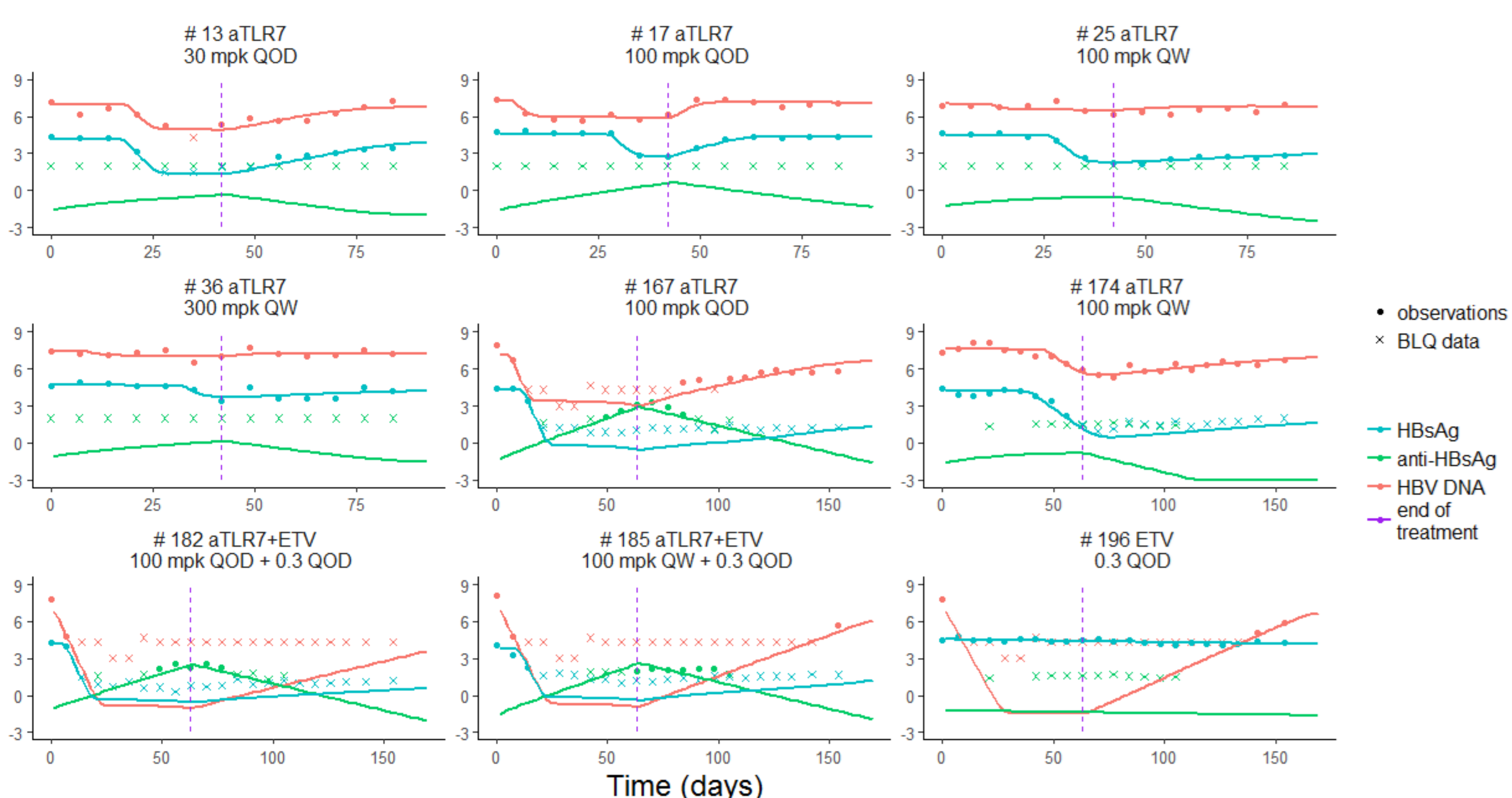


Figure 3: Individual predictions of representative individuals

Simulated long-term HBV kinetics over one year of treatment

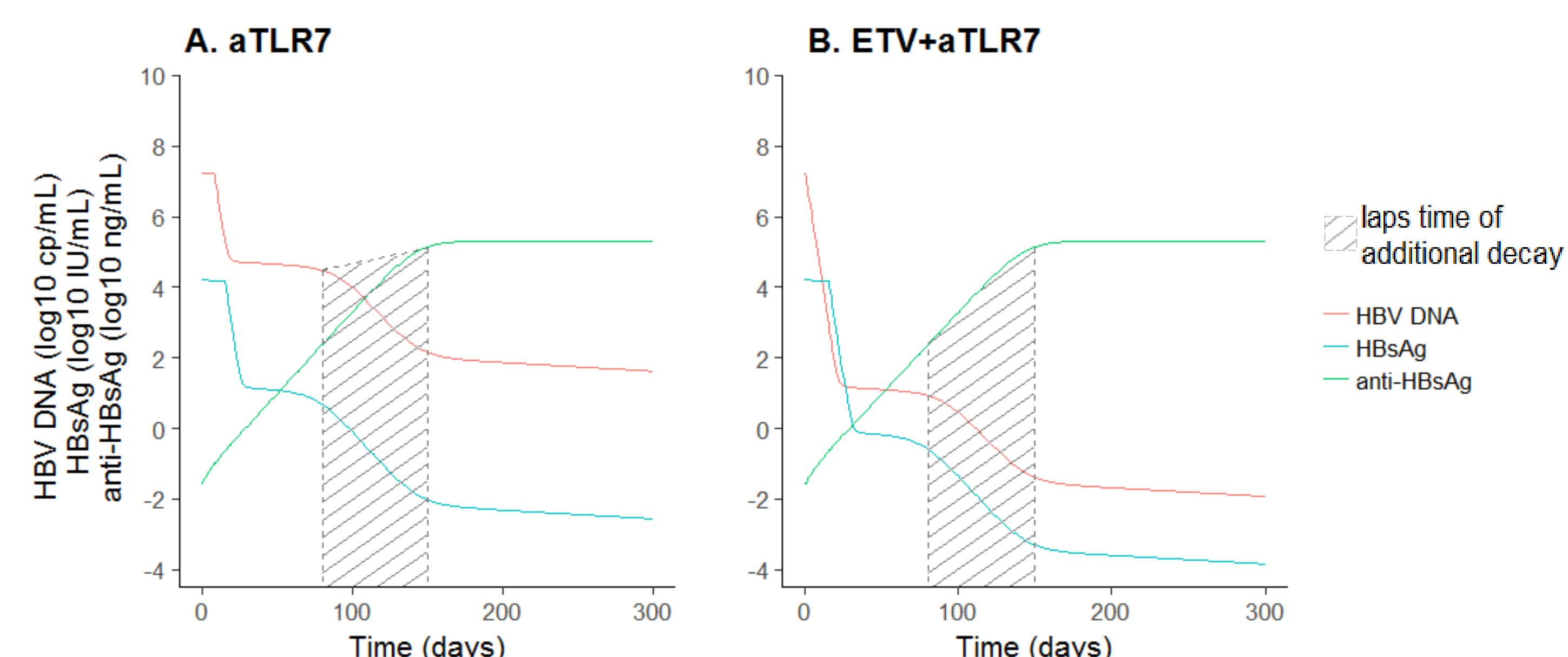


Figure 4: Simulations of long-term kinetics over 1 year treatment by aTLR7

Conclusion

- We provided a novel modeling framework of HBV that takes into account the interaction between virus, subviral particles and the immune system.
- Our model suggests that aTLR7 has a 3 modes of action by strongly destabilizing viral and subviral production and stimulating antibody production.
- There was a significant synergism of ETV and aTLR7 on reducing SVP production and hence HBsAg levels.
- These results support that combination of ETV and aTLR7 may be relevant in chronically infected patients, but more data will be needed to evaluate the time needed to maximize anti-HBsAg production and the possibility to reduce the number of infected cells and cure the infection.

References:

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