

Introduction

Background

Current treatments for chronic hepatitis B (CHB) infection rely on nucleosid analogs (NUCs) and pegylated interferons (peg-IFN), which effectively suppress viral replication, but do not prevent the persistence of viral genome in the hepatocytes. Mathematical models have been used to support the development of new curative anti-HBV agents¹ that could cure CHB infection, but they often neglect the complex host/pathogen interaction, by focusing on limited short-term HBV DNA data.

Objectives

- To propose a model of HBV infection that could characterize the long-term dynamic of the main viral transcripts (namely HBV DNA, HBsAg, and HBeAg) during NUC or peg-IFN treatment.
- To predict the outcome of the combination therapy of lamivudine (NUC) and peg-IFN α .

Methods

Data

1330 HBeAg-positive² (A) or HBeAg-negative patients³ (B) were randomized to receive either peg-IFN α monotherapy (peg-IFN), lamivudine monotherapy or peg-IFN α plus lamivudine for 48 weeks (Figure 1).

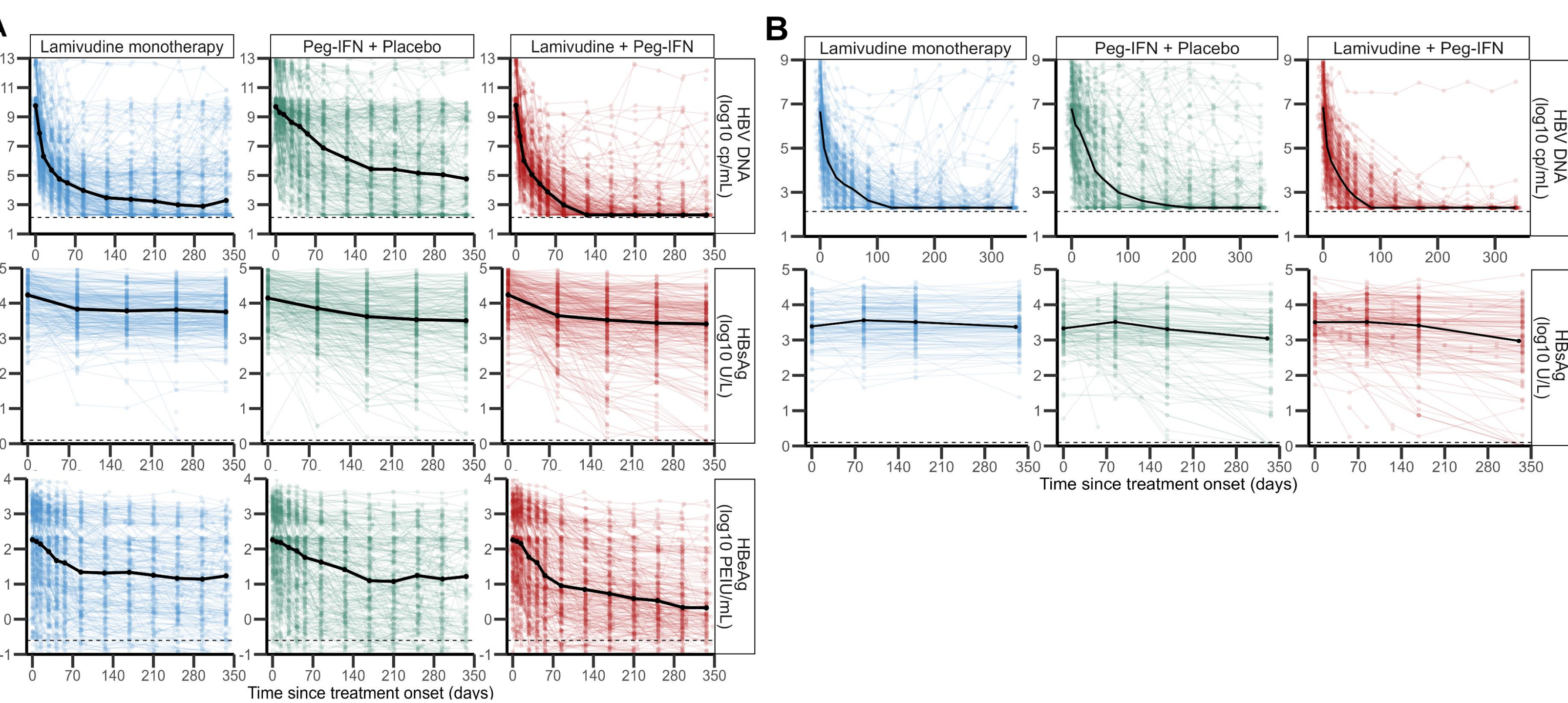


Figure 1. Dynamic of the different markers. The dashed line represents the limit of quantification (LOQ).

Modelling strategy

Models were built on patients receiving monotherapies and the same model building strategy for the drug effects was used for HBeAg-negative and HBeAg-positive patients. In both cases, the arm lamivudine+peg-IFN was used as a mean to provide an external validation of our model predictions.

A novel modeling framework for HBV viral transcripts

→ Target cells (T) are infected by virions (V) at a rate β and become I_1 cells (Figure 2).. Due to important amounts of cccDNA, I_1 cells have a large transcriptional activity and secrete HBV DNA (p_v^1), HBeAg (p_e^1) and Subviral Particles (SVPs) (p_s^1).

→ I_1 cells can die at a rate δ_1 or transit into I_2 cells at a rate δ_{tr} . I_2 cells contain lower amounts of cccDNA and/or integrated DNA, hence is less targeted by the immune system, allowing residual but sustained amount of viral production, and we note p_v^2 , p_e^2 and p_s^2 the daily rate of production of virions, HBeAg and SVPs, respectively.

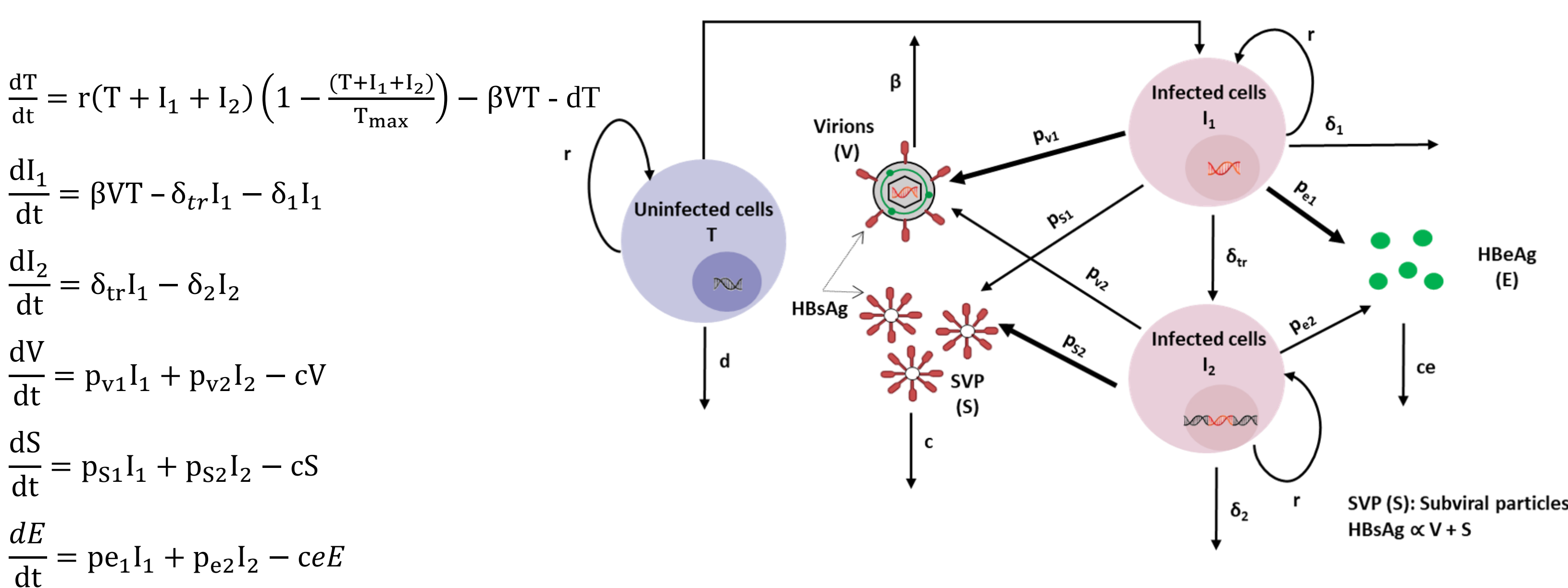


Figure 2. Schematic representation of the model

Modeling the drug effects

Models for the drug effects were developed separately for each HBeAg status, following the same strategy: A forward approach was used to select the significant drug effects. At each step, treatment effect was tested for each drug on productions and loss rates parameters, assuming a between-subject variability and a pharmacological delay.

- Only drug effects that were found significant (Wald test, pvalue < 5%) were considered.
- The model providing the best improvement of likelihood was kept, and the procedure continued until no significant improvement was found, using a corrected LRT⁴

Prediction of the combination therapy

To evaluate our framework, we predicted the virological responses (percentage of patients with undetectable HBV DNA, loss of 2 logs of HBsAg or HBeAg) after one year with combination therapy and compared them to observed data. We used a multiplicative model⁵ on the effects on the productions ($\varepsilon_{PEG+LAM}$) and an additive model on the effects on the loss rates ($\delta_{PEG+LAM}$).

$$\begin{cases} \varepsilon_{PEG+LAM} = 1 - (1 - \varepsilon_{PEG})(1 - \varepsilon_{LAM}) \\ \delta_{PEG+LAM} = \delta_{PEG} + \delta_{LAM} \end{cases}$$

Results

Infection at baseline

At baseline, almost all cells were infected. I_2 cells represented the majority of infected cells. The transcriptional activity was more important in I_1 cells than I_2 cells, except for SVPs (Table 1).

Table 1. Characteristics of the infection at baseline estimated by the model.

	I_1		I_2	
	HBeAg+	HBeAg-	HBeAg+	HBeAg-
HBV DNA (cp/cell/d) ¹	158489 (1.7)	323 (5.6)	0.016 (7.2)	0.00020 (3.2)
SVPs (U/cell/d) ¹	10471285 (1.0)	933254 (3.4)	281838 (1.7)	199526 (1.0)
HBeAg (PEIU/cell/d) ¹	4.3 .10 ⁻⁴ (1.8)	-	3.6 .10 ⁻⁸ (1.1)	-
Loss rates (d ⁻¹) ¹	$\delta_{tr} = 0.0075$ (21.5) $\delta_1 = 0.025$ (18.1)	$\delta_{tr} = 0.0846$ (5.85) $\delta_1 = 0.00024$ (126)	1.5 .10 ⁻⁵ (20.2)	9.3 .10 ⁻⁵ (26.4)
Proportion of infected cells	1.235	0.004	97.01	99.76
among T+I_1+I_2 (%) ²	[0.172 – 4.498]	[0.003 – 0.007]	[91.62 – 99.01]	[99.58 – 99.93]
¹ RSE (%)				
² Median [Q1 – Q3]				

Antiviral drug effects

Inhibition of viral replication

Lamivudine had a higher effect on blocking viral replication than peg-IFN (Table 2).

Loss cell enhancement

peg-IFN enhanced the loss of both I_1 and I_2 cells whereas lamivudine enhanced the death of I_2 in HBeAg-positive patients.

Table 2. Population parameters of the drug effects and their uncertainty (RSE%), stratified by arm and HBeAg status

	Lamivudine		Peg-IFN	
	HBeAg+	HBeAg-	HBeAg+	HBeAg-
Inhibition of HBV DNA (%)	99.9 (0.005)	99.3 (0.1)	95.1 (1.3)	91.8 (1.4)
Enhancement on loss of I_1 (n fold)	-	-	1.66 (21.5)	-
Enhancement on transit from I_1 to I_2 (n fold)	-	-	4.6 (14.0)	2.0 (18.9)
Enhancement on loss of I_2 (n fold)	7.6 (10.7)	-	7.7 (13.4)	7.9 (11.6)

Can the model predict the outcome of the combination therapy ?

In most cases, the observations of the virological responses following both monotherapies and combination were included in the prediction intervals (Figure 3).

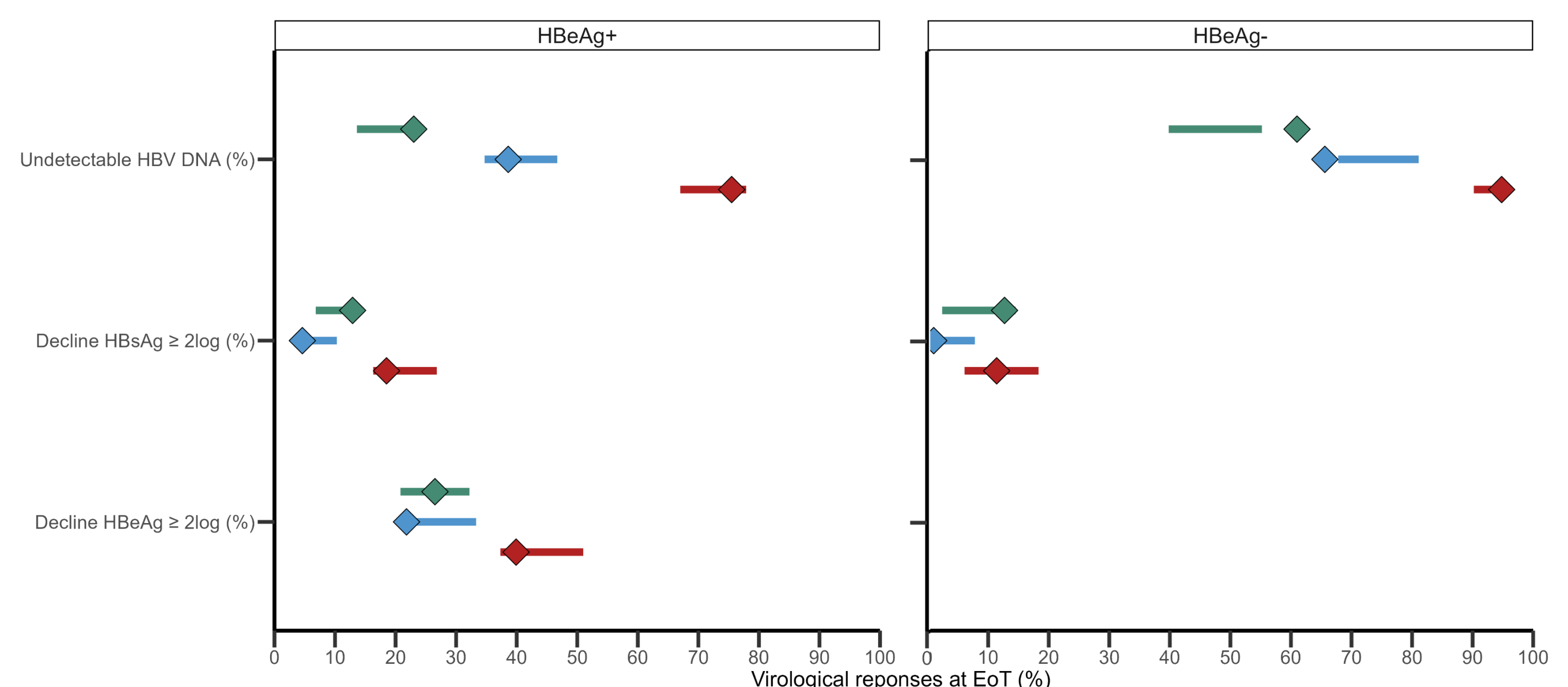


Figure 3. Prediction intervals of the virological responses after one year of lamivudine (blue), peg-IFN (green) and the combination (red). Diamonds corresponds to observations.

The model shows a benefit in using the combination after of 5 years of treatment (Figure 4)

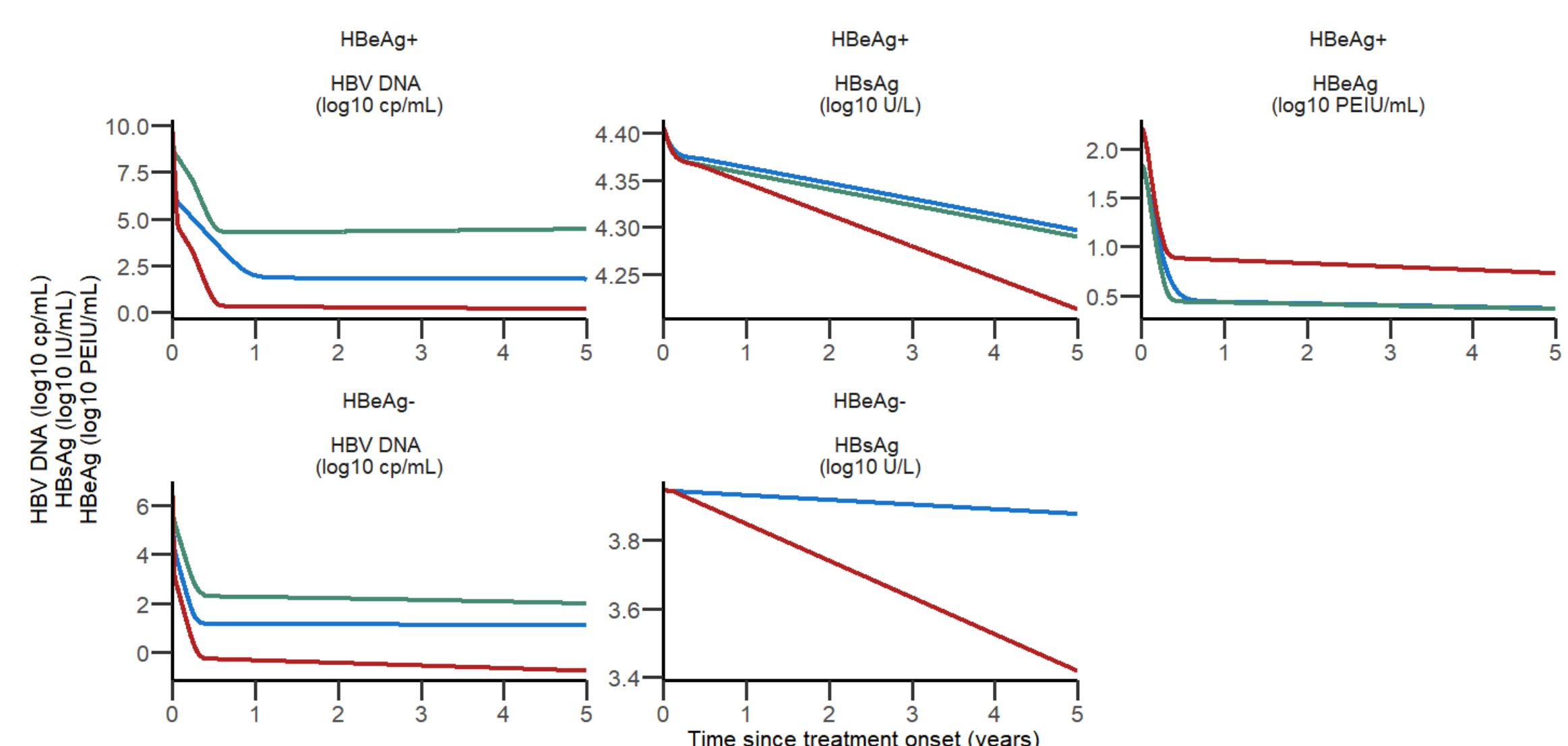


Figure 4. Typical declines following lamivudine (blue), peg-IFN (green) and the combination (red).

Conclusion

- We provide a new framework to understand the complex long-term dynamic of chronic HBV infection under standard of care therapy. It allowed to understand the relationship between the different HBV markers and the effect of the standard of care on these markers.
- This model can be a tool to optimize combination therapy with new anti-HBV agents in future analyses.

References

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