



Model-based Meta-analysis to Determine the Efficacy of Entecavir and Adefovir in the Treatment of Chronic Hepatitis B



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Objective:

The objectives of this study were to (1) develop a semi-mechanistic model to characterize the dynamics of viral DNA load in hepatitis B virus (HBV) infected patients who had received treatment of entecavir (ETV) or adefovir (ADV), (2) to describe the life cycle of HBV for efficacy comparison of two drugs, and (3) to identify potential covariates of virus kinetics.

Methods:

Publications were retrieved from PubMed database according to the pre-defined inclusion and exclusion criteria. Mean and individual data of HBV DNA after start of treatment were analyzed using a nonlinear mixed-effects modeling (NONMEM) approach and first-order conditional estimation with interaction (FOCE-I) Laplacian method. Variance of estimates and model robustness were assessed using sampling importance resampling (SIR) and individual visual predictive check (VPC) approaches.

Results:

Paper Search:

Item: “(HBV) AND (((((((((((pegylated interferon) OR interferon alpha-2b) OR tenofovir) OR telbivudine) OR lamivudine) OR entecavir) OR adefovir) OR IFN) OR TDF) OR LAM) OR ETV) OR ADV) OR LDT)” as the search items, “clinical trial “ as article type
Time: Before 2013.12
Database: PubMed

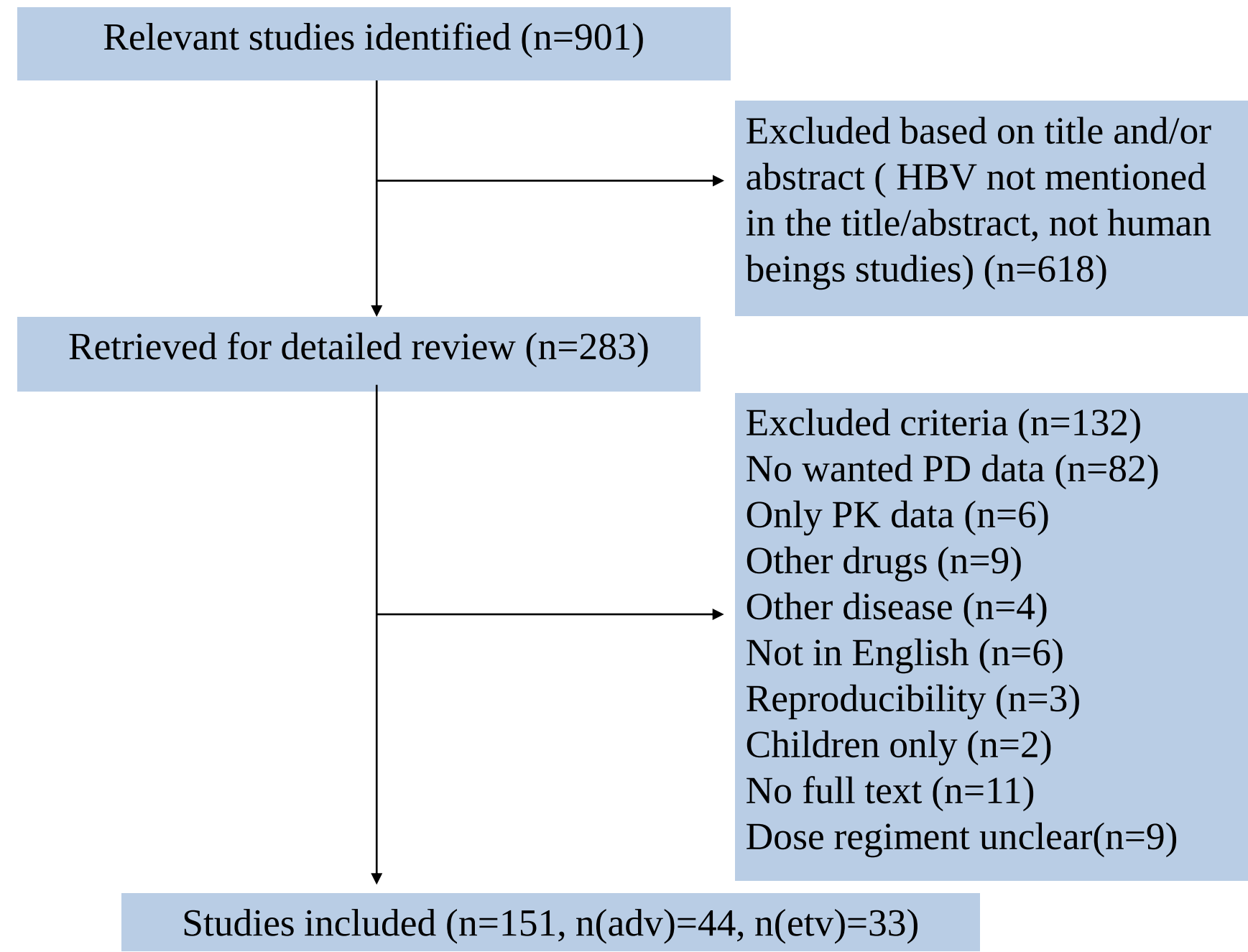


Figure 1 QUOROM flow diagram indicating study selection criteria for meta-analysis

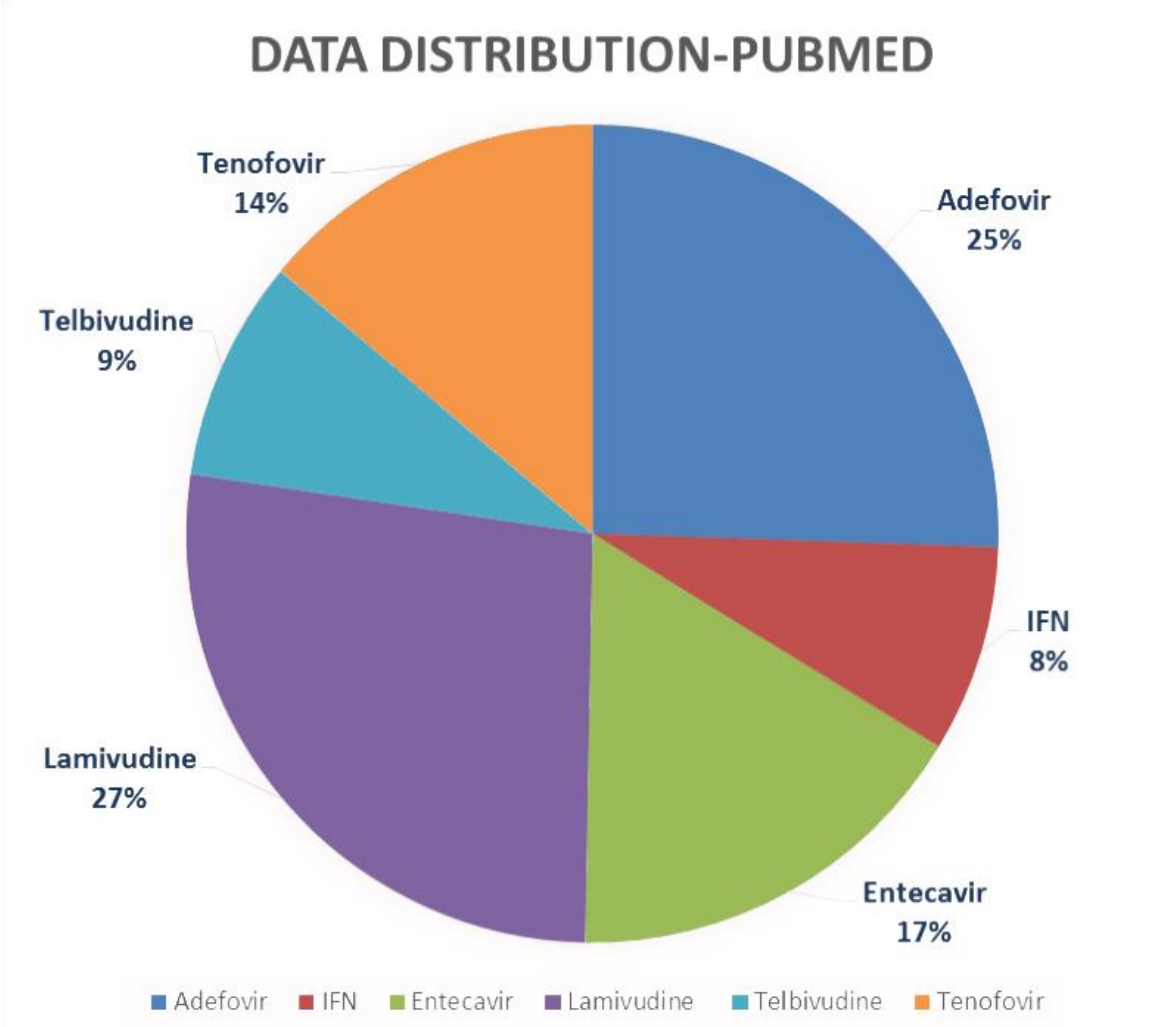


Figure 2 General data distribution

Table 1 Data distribution of ADV and ETV monotherapy and co-administrated

	Number of studies	HBV DNA mean data	HBV DNA individual data	BQL DNA percentage	ALT level	ALT Normalization	HBsAg seroconversion	HBsAg loss	HBsAg level	HBsAg loss	HBsAg level
ADV mono	23	304	344	5	132	18	83	15	10	3	15
ETV mono	29	229	235	<1%	209	0	64	56	5	12	10
ADV & ETV	4	22	0	5	0	0	4	2	0	0	0

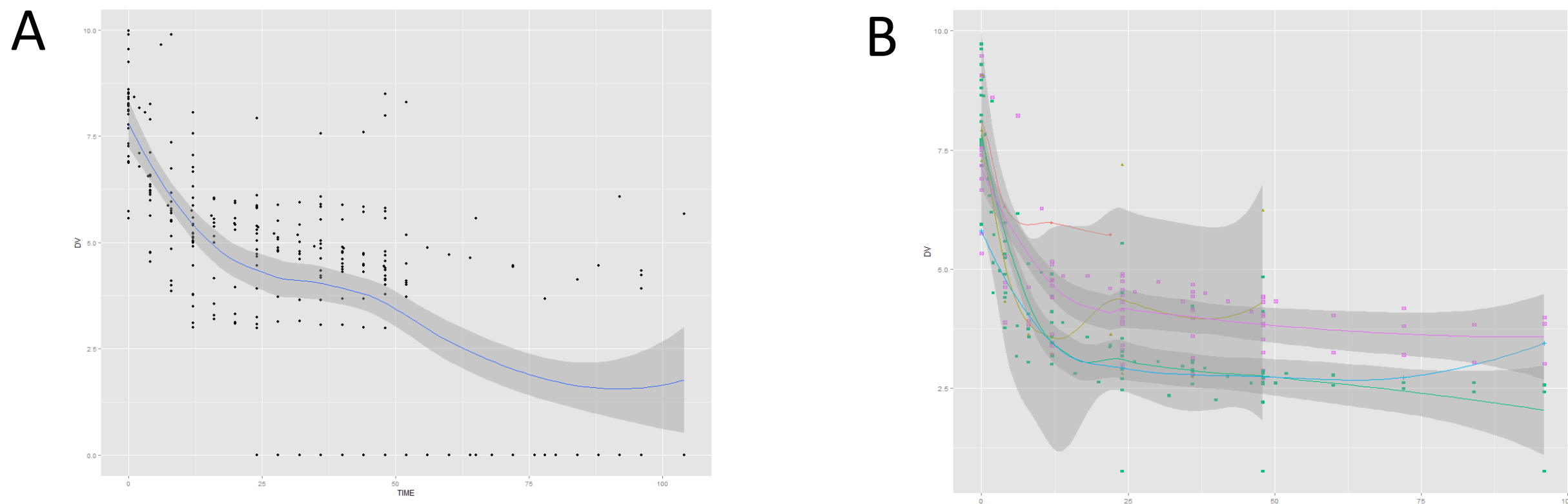


Figure 3 HBV DNA change versus time in different dose group for ADV (A) and ETV (B)

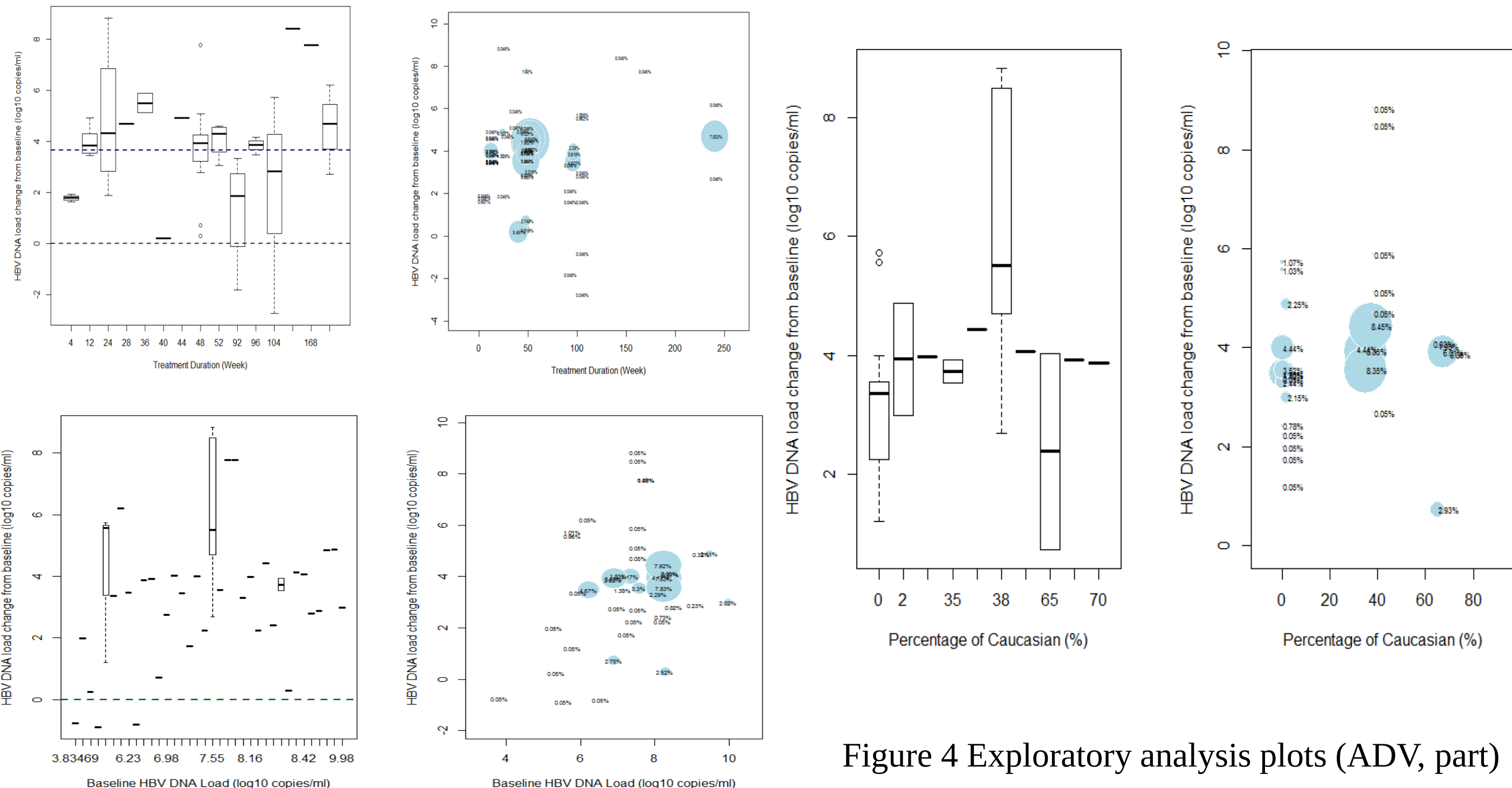


Figure 4 Exploratory analysis plots (ADV, part)

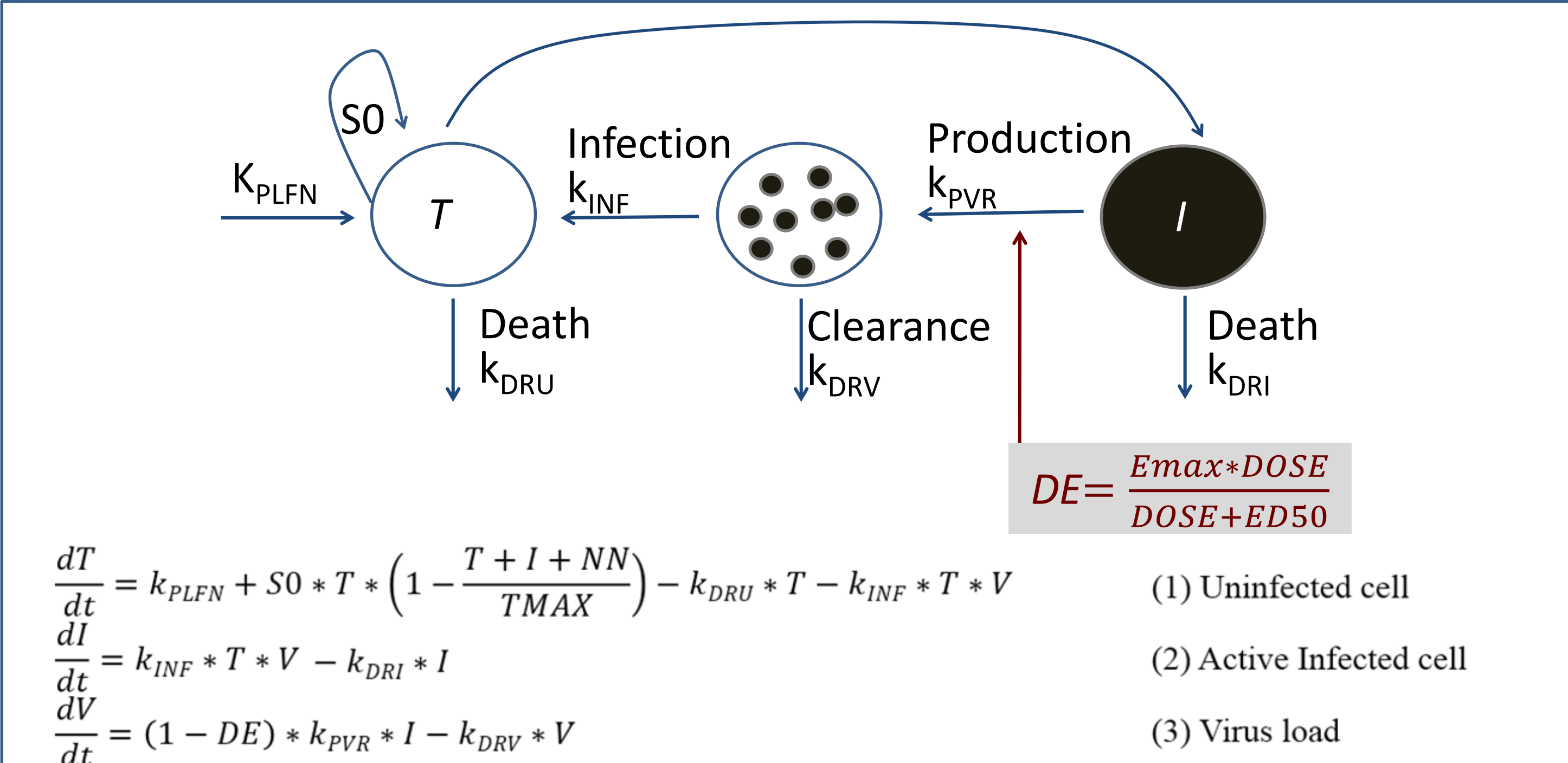


Figure 5 Representation of the HBV viral kinetic model. Virons infected target cells (T), creating productively infected hepatocytes (I). Uninfected hepatocytes are produced at the rate k_{PLFN} and die at rate k_{DRU} , infected cells die at rate k_{DRI} . A density-dependent proliferation of hepatocytes (S0) is assumed. NN represents the hepatocytes can not be infected.

Table 2 Population parameter estimates of the HBV viral kinetic model for the mean data of ADV / ETV

Parameter	Description	Unit	Typical value	RSE(%) MATRIX=S	RSE(%) SIR_INF=1	IIV (%CV)
Tmax ¹	Total number of hepatocytes per ml	Hepatocytes/ml	1.3x10 ⁷			
NN ¹	Number of hepatocytes can not be targeted per ml	Hepatocytes/ml	6.5x10 ⁶			
PLFN ²	Hepatocytes production rate	Hepatocytes/ml/day	2.6x10 ⁴			
k _{DRV}	Virion elimination rate constant	Per day	0.67			
k _{DRU} ³	Hepatocyte death rate constant	Per day	0.004			
S0	Hepatocyte proliferation rate constant	Per day	0.0151 / 0.0316	16 / 4	12 / 4	36.7 / 21.0
k _{INF}	Hepatocyte infected constant rate	ML/day/virions	1.69 / 0.979 x10 ⁻⁹	2 / 1	1 / 1	139.6 / 216.6
k _{DRI}	Infected cell death rate constant	Per day	0.0311 / 0.0428	7 / 7	6 / 7	33.9 / 68.4
k _{PVR}	Virion production rate	Virion/hepatocyte/day	67.7 / 76.2	14 / 4	11 / 4	233 / 271.9
Emax	Maximum of drug effect	1	1 FIX / 1FIX			
ED50	ED50 of Adefovir dipivoxil	mg	0.317 / 0.0055_HIS==1 0.0015_HIS==0	27 / 3 5	21 / 6.46*10 ⁻¹³ 4.84*10 ⁻¹³	122.1 / 97.2 243.0
σ ²	Additive error	Log10 copies/ml	0.0553 / 0.251	7 / 12	7 / 10	51.3 / 6.7
σ ²	Proportional error	1	0.31 / 0.242	10 / 4	8 / 4	

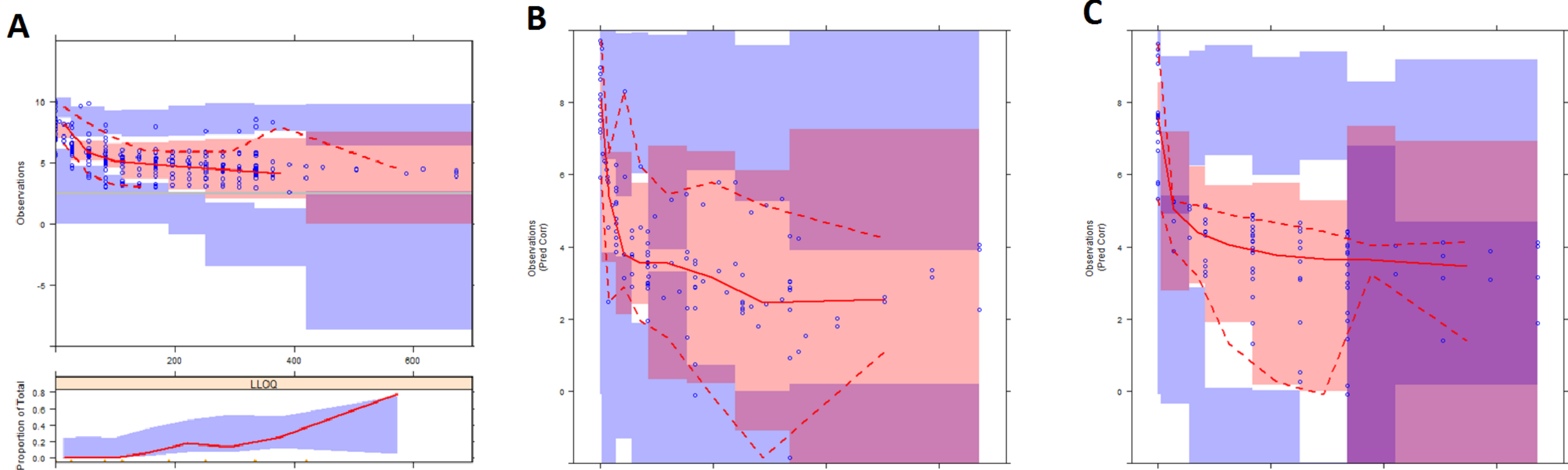


Figure 6 VPC plots for the mean data of ADV (A) and ETV (B_HIS==0, C_HIS==1). Solid lines refer to the real 50% percentile, and dash lines are the real 2.5% and 97.5% percentiles of the simulated data. The shading areas are the corresponding 95% CI.

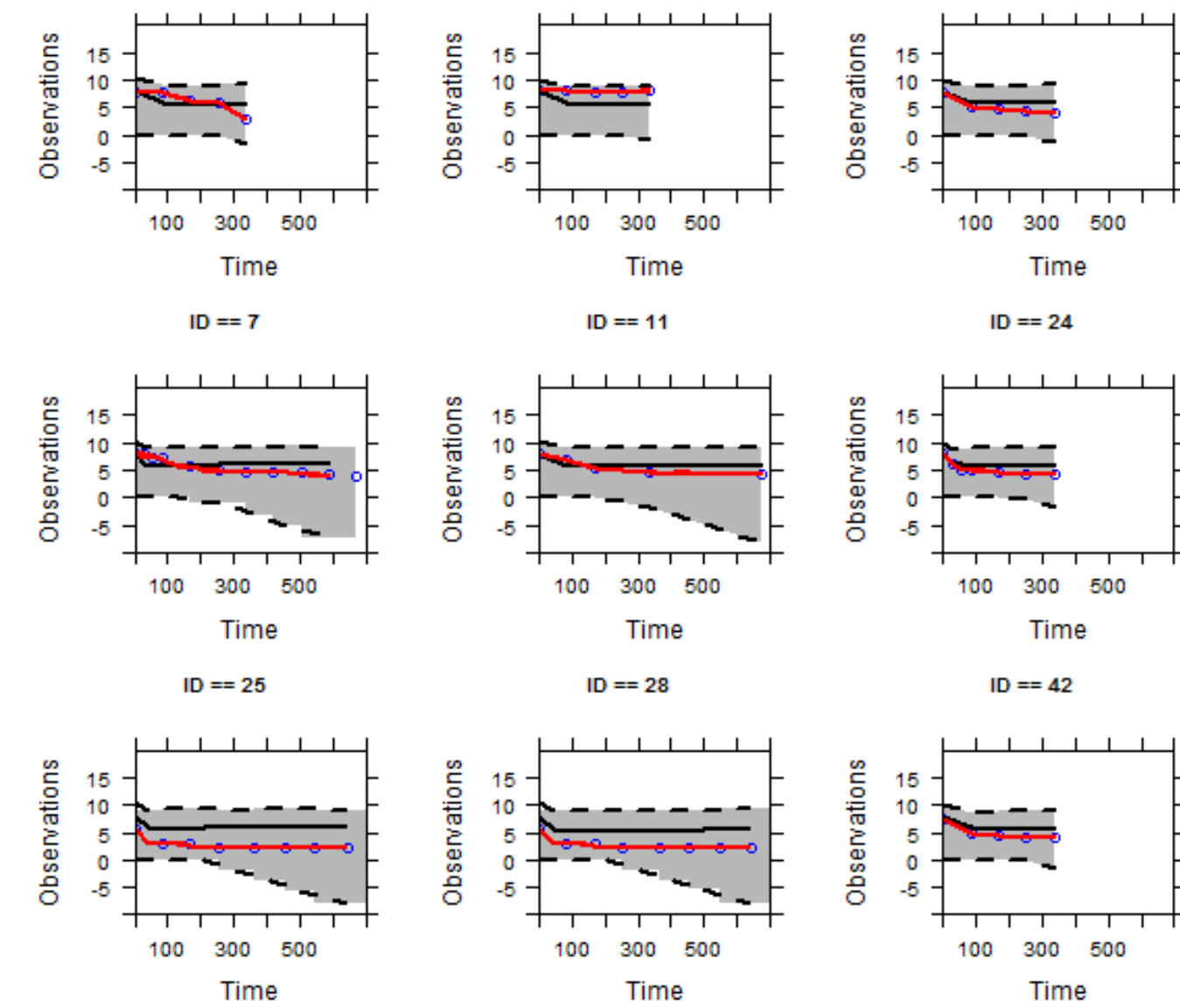


Figure 7 Individual VPC plot (part)

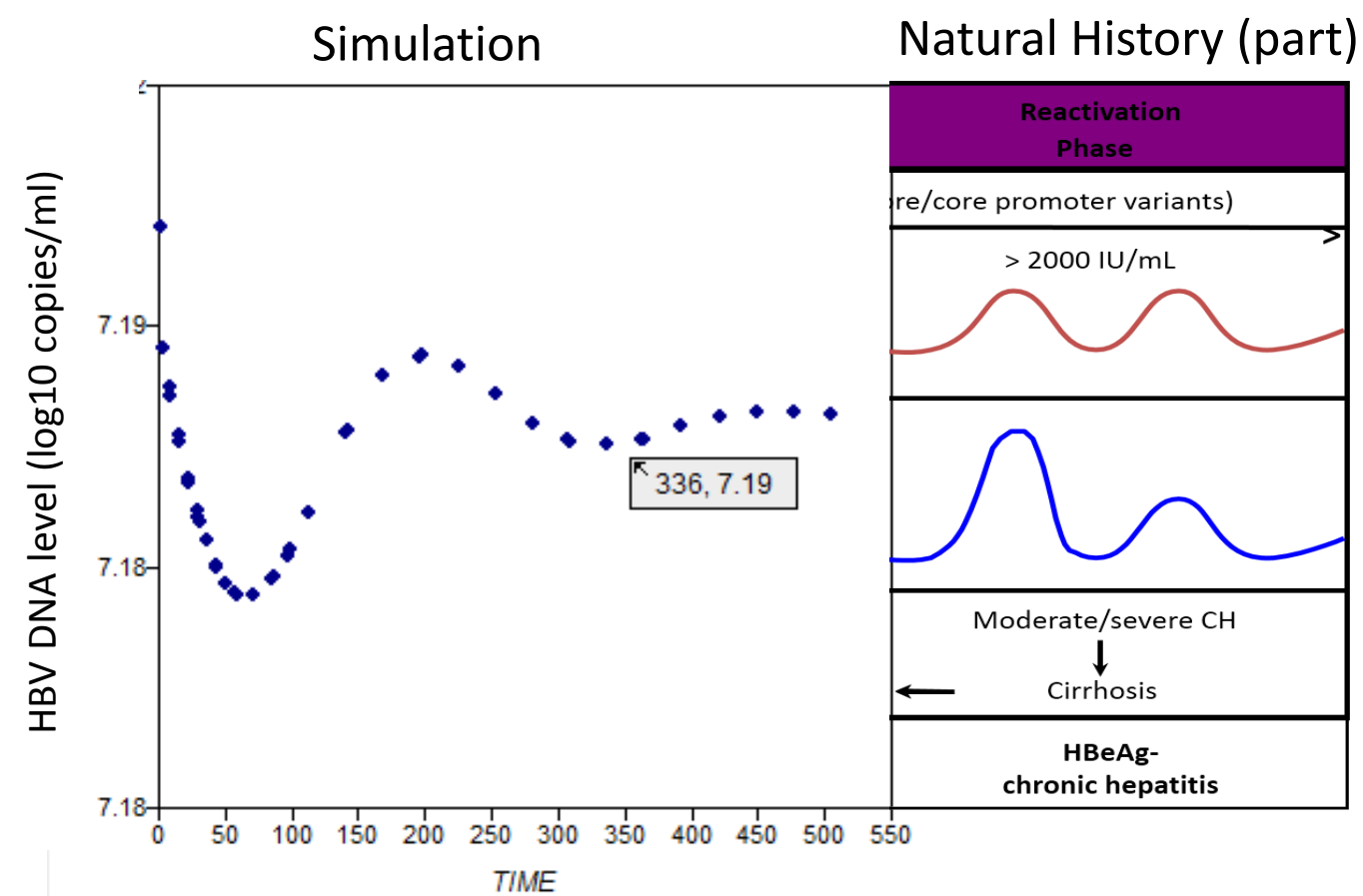


Figure 8 Simulation results vs. part of the natural history

Conclusion:

Model-based meta-analysis is useful to compare different drugs in the same class or identify significant covariates by pooling literature data and building viral kinetic models. Further development of this model may provide information about drug resistance and therefore improve understanding of this disease.

Acknowledgement:

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Reference:

1. Anne-Gaëlle Dosne, Martin Bergstrand, Mats O. Karlsson, *Application of Sampling Importance Resampling to estimate parameter uncertainty distributions. PAGE, 2013.*