Modeling of viral kinetics in patients chronically infected with hepatitis B and D

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Introduction - Virus kinetic models

- The dynamics of a virus population in vivo could be described by a simple ODE (Bonhoeffer et al., 1997; Nowak and May, 2000)

$$\frac{dT}{dt} = \lambda - mT - \beta TV$$

$$\frac{dI}{dt} = \beta TV - \delta I$$

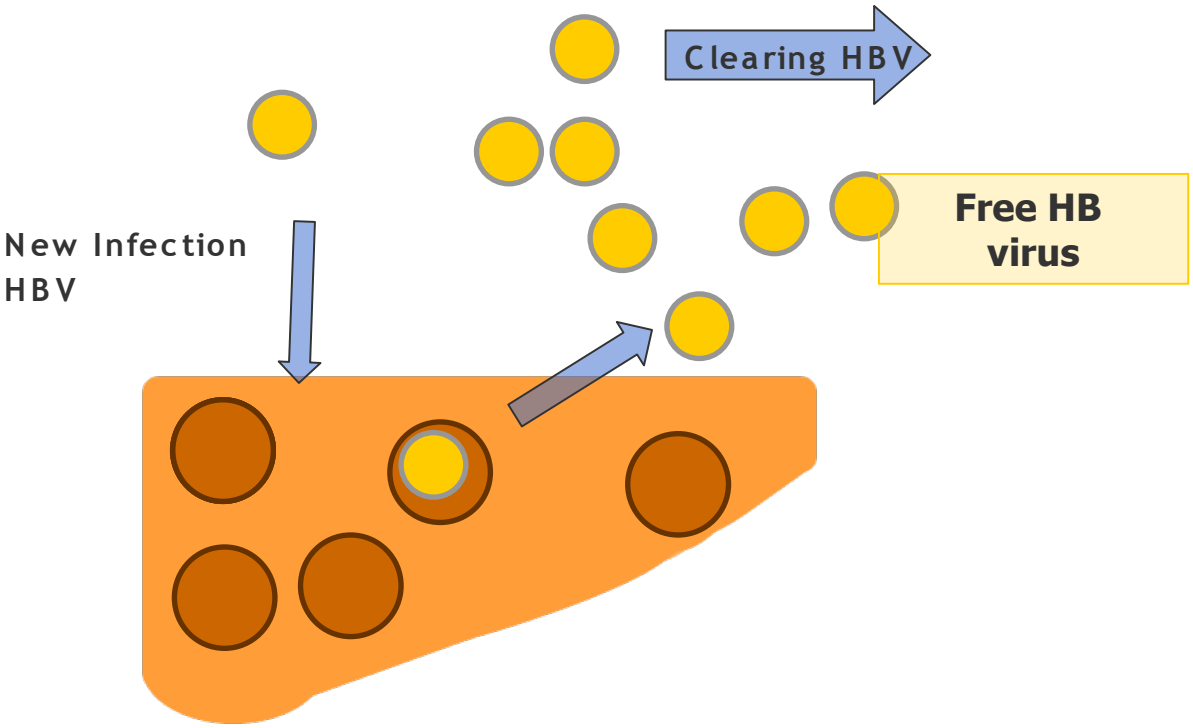
$$\frac{dV}{dt} = pI - cV$$

Introduction - Virus kinetic models

- Models for HIV, HBV, HCV monoinfection are an important tool for
  - Understanding dynamics of several viruses diseases
  - Quantifying effectiveness of anti-viral therapy
  - Comparing and optimizing anti-viral therapy
- Now: Introducing HBV-HDV-Viral kinetic model

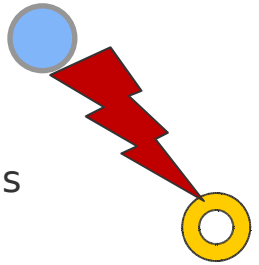
Medical background - HBV

- Hepatitis B is a disease caused by HBV (hepatitis B virus) which infects the liver and causes an inflammation called hepatitis



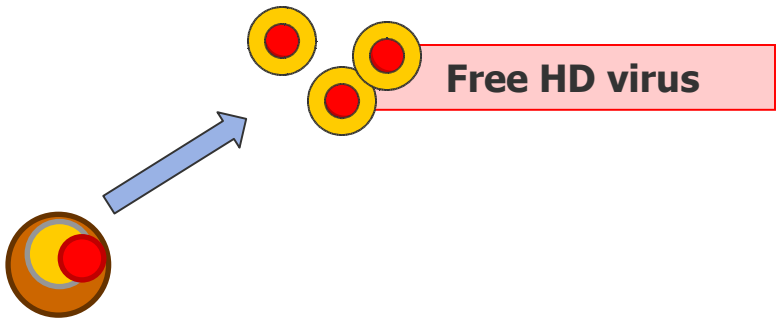
Medical background - HBV

- HBsAg: Hepatitis B surface Antigen
  - Vast amount of HBsAg particles in blood serum
  - Produced in liver cells
  - HDV life-cycle relies on HbsAg
  - HDV uses HBsAg as surface protein
- Anti-HBs: Hepatitis B surface antibody
  - Anti-HBs neutralizes HBsAg particels
  - Anti-HBs makes HBV noninfectious but cannot cure infected liver cells
- HBIG: Hepatitis B immune globulin
  - Blood plasma product administered after liver transplantation (LTX)
  - HBIG contains Anti-HBs and can prevent hepatitis B reinfection

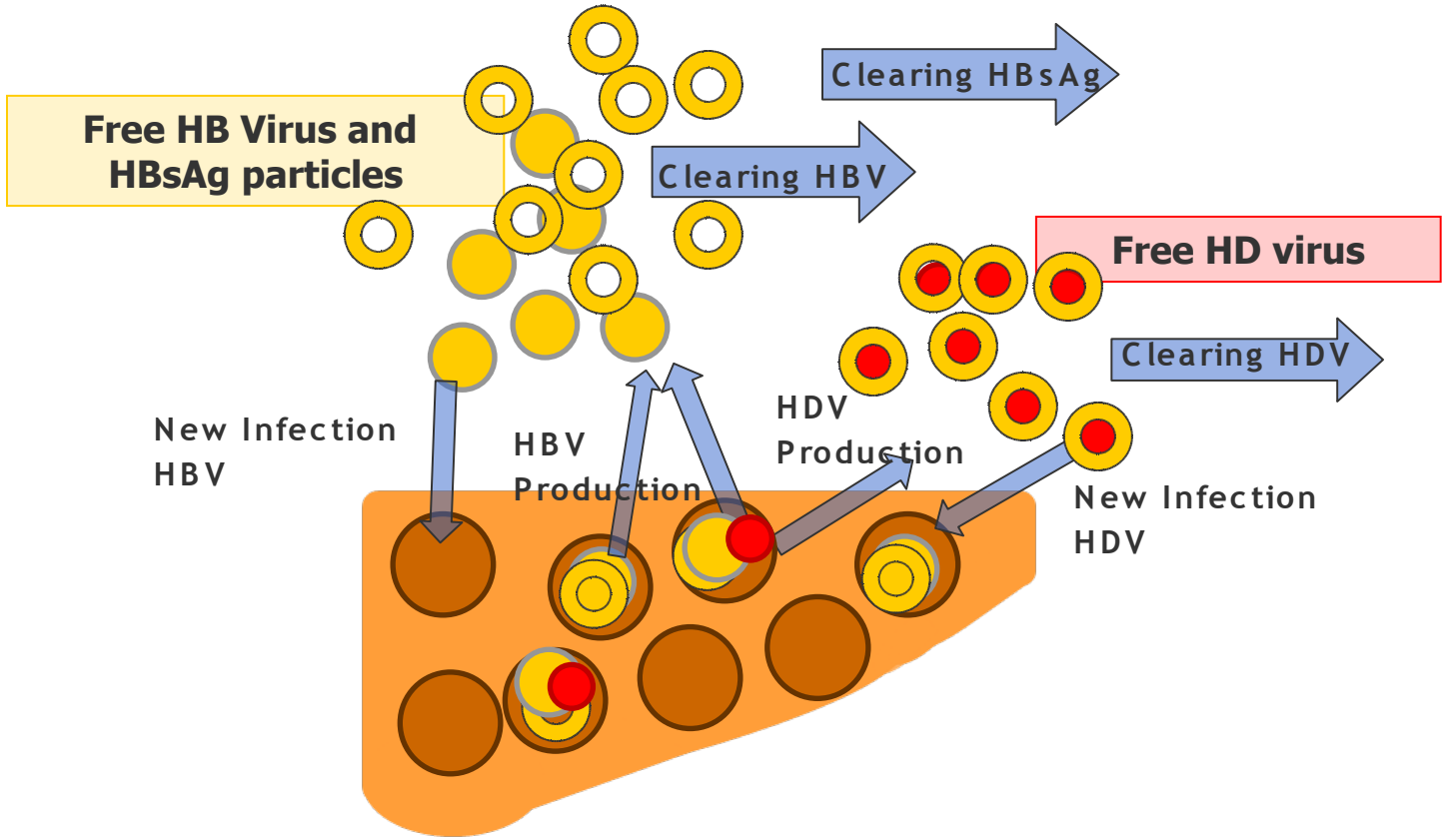


Medical background - HDV

- Delta hepatitis is the most severe form of chronic viral hepatitis
  - Frequently leading to end-stage liver disease and hepatocellular carcinoma
- Hepatitis D virus ● is a defective virus that is dependent for its life cycle on HBV-particles (HBsAg) ○
  - Therefore HDV-infection can only occur as coinfection or as superinfection with HBV-infection
  - Produced in liver cells which contain HBV and released to blood



HBV-HDV-host-interaction



Material and Methods

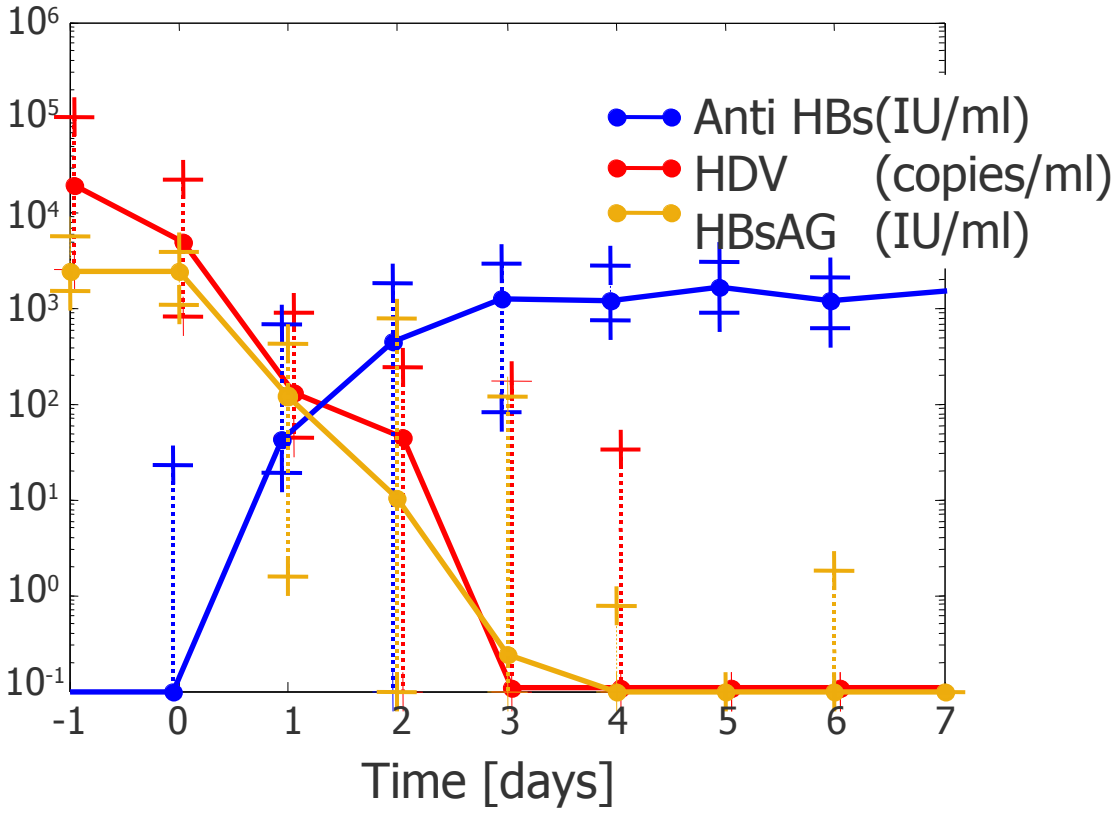
- The data: **25 coinfected patients who underwent liver transplantation**

- Measured was:
  - HB Virus load (qualitative)
  - HD Virus load
  - HbsAg-level
  - Anti-HBs-level after transplantation
  - HBIG dose after transplantation

- Measured once before LTX and every 1,2,3 days after LTX
  - Until HBsAg became negative
    (Range: 1-13 days, except one patient who didn't achieved negativity at all)

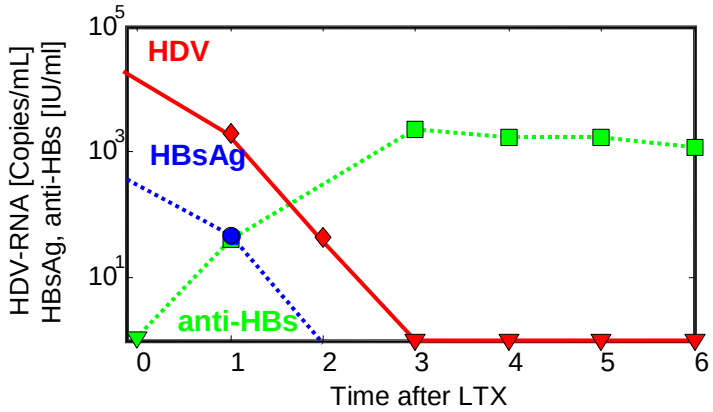
Virus dynamics after Liver Transplantation

Median values – Anti HBs, HDV, HBsAG



Virus dynamics after Liver Transplantation

Kinetics of HDV-RNA, HBsAg and anti-HBs in representative patients



Virus dynamics after Liver Transplantation

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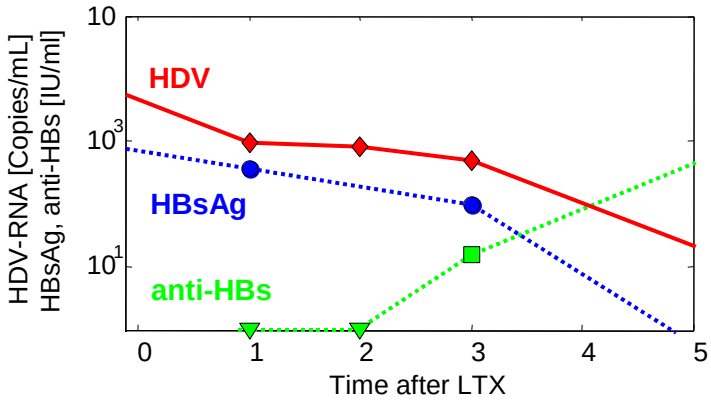
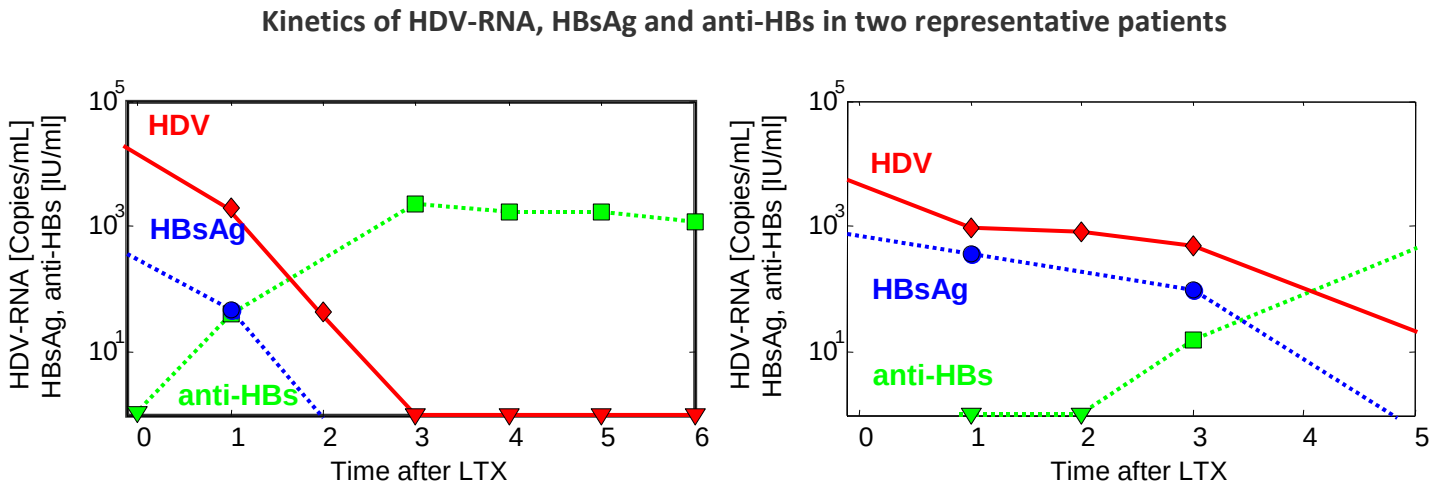


Virus dynamics after Liver Transplantation



Model after liver transplantation

- Assume clearing of HBsAg and HDV due to anti-HBs
- No reinfection of the liver

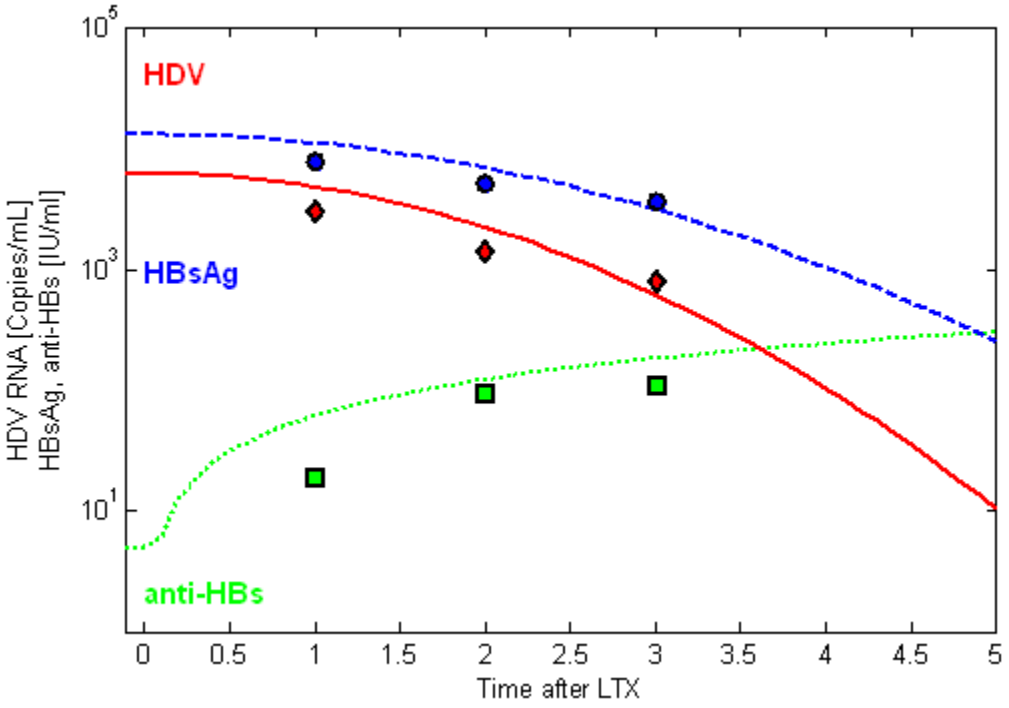
$$A = k_0 + (k_{max} - k_0) \cdot (1 - \exp(-kt))$$

$$\frac{dV_D}{dt} = -A\, c_D\, V_D$$

$$\frac{dH}{dt} = -A\, c_H\, H$$

Compartments	Kinetic parameters
A : Anti - HBs	c_D : Clearance of free HDV
V_D : Hepatitis D viremia	c_H : Clearance of free HBsAg
H : HBsAg	k_0 : Initial anti - HBs level
	k : Rate of saturation
	k_{max} : Maximal saturation

Fitting results



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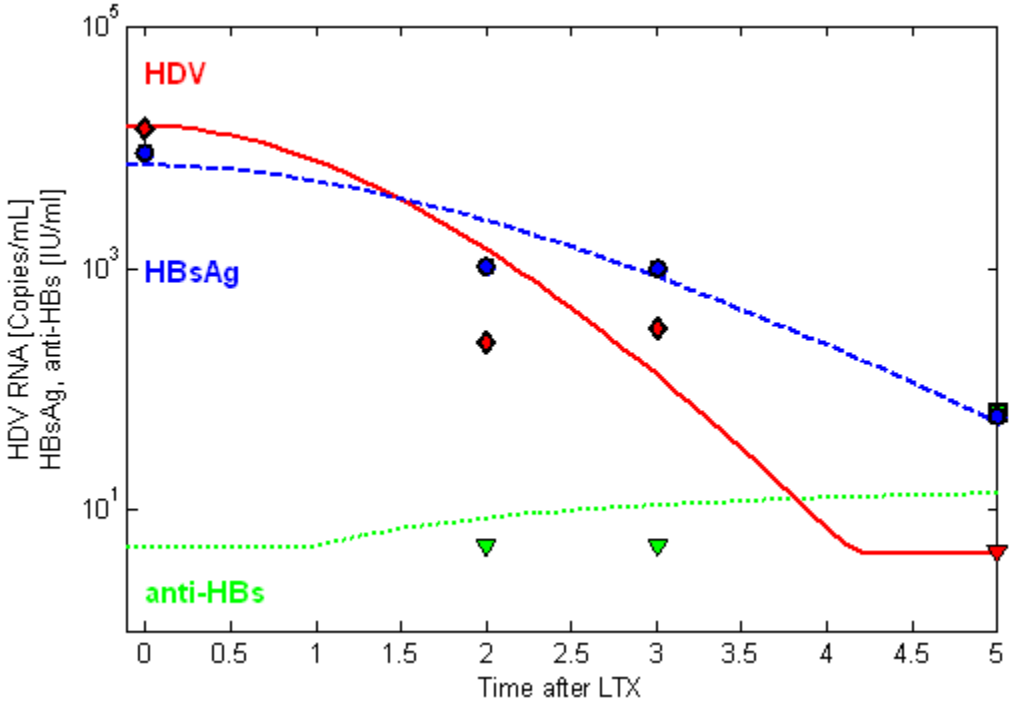

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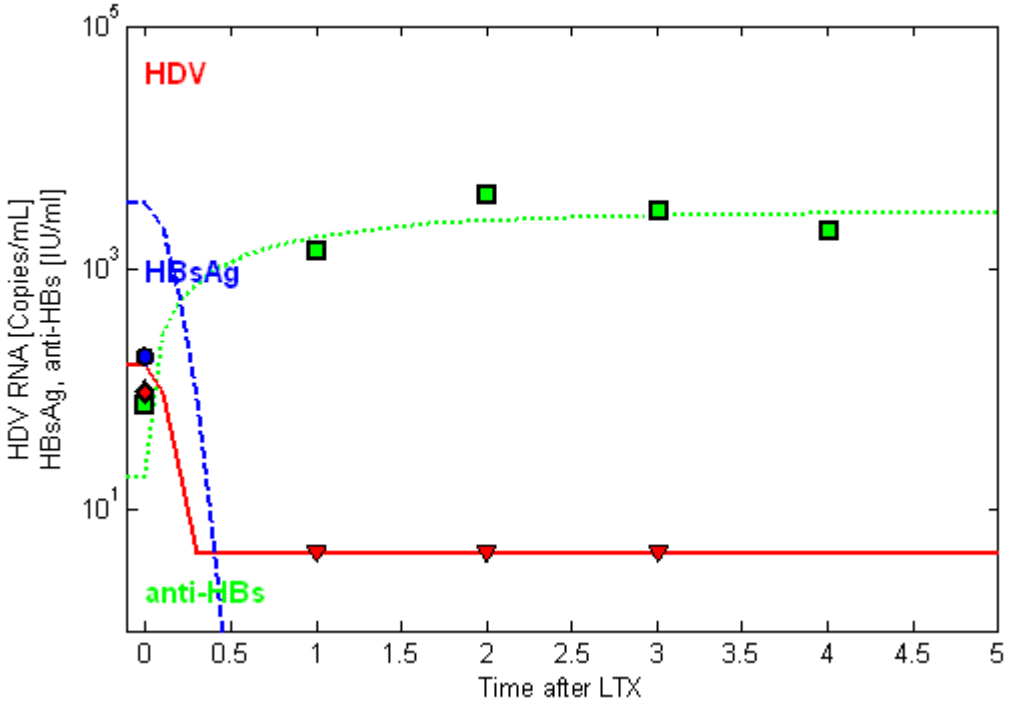

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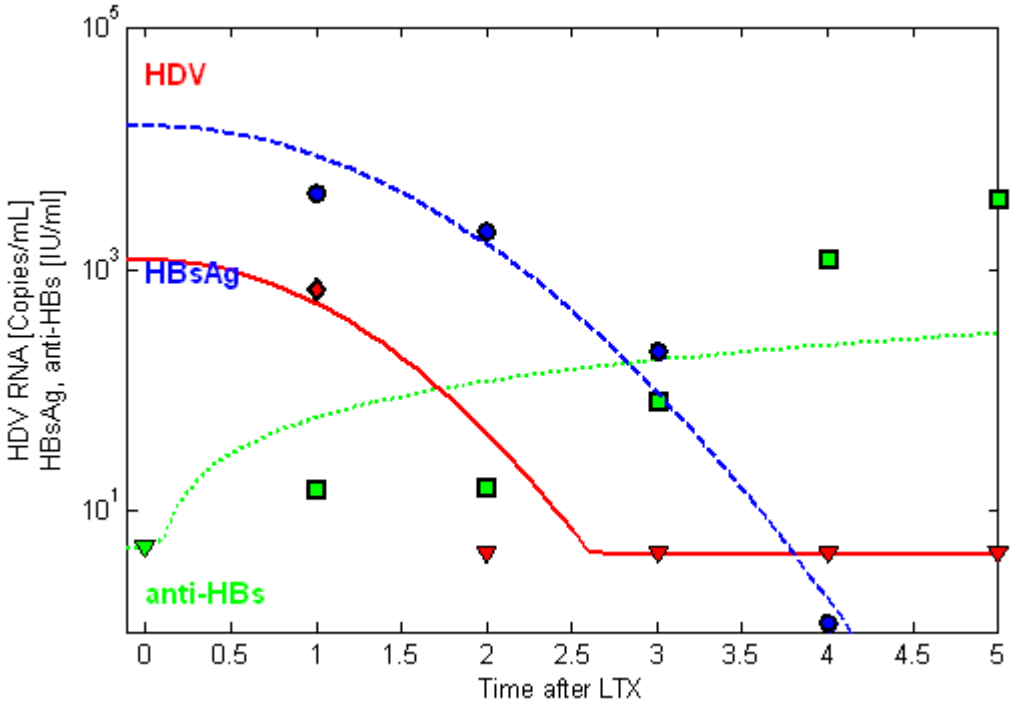

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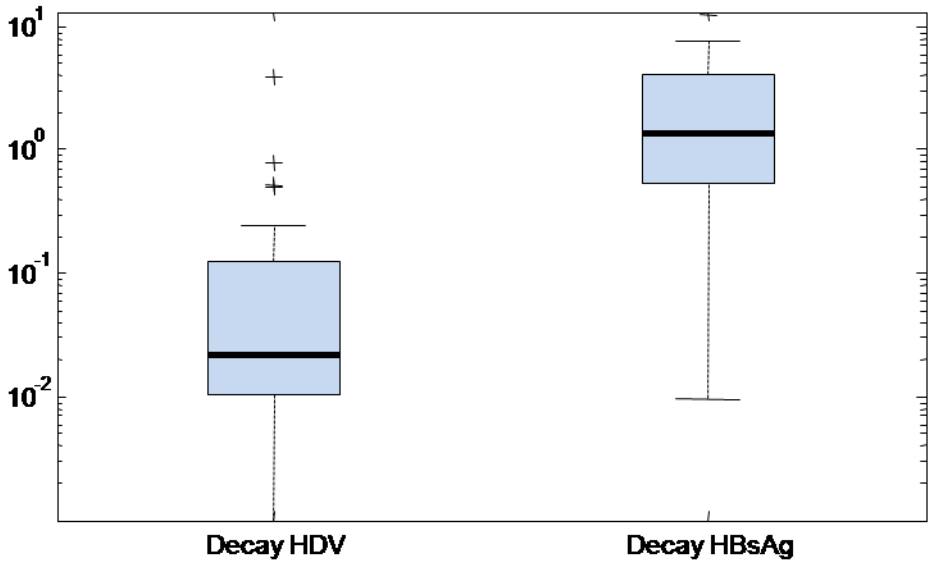

Results and Outline

- Overall similar kinetic pattern in HDV and HBsAG decline
  - Early HDV-RNA decline and HBsAg decline paralleled almost exactly in all 25 patients
- Nevertheless, two kinetic profiles were observed:
  - Most patients showed a relatively linear decrease (in logarithmic scale)
  - Some show a plateau phase in both, HBsAg and HDV DNA:
- Model modification to account for these profiles:
  - Directly model the single doses of HBIG in a PK-PD approach
  - Inclusion of possible time lags
  - Analyze if these plateaus can be explained by reinfection

Outline - the full model

- **Modelling virus-virus-host-interaction**

$$\frac{dV_B}{dt} = p_B I_B - A c_B V_B + p_{DB} I_{DB}$$

$$\frac{dV_D}{dt} = p_D I_D - A c_D V_D$$

$$\frac{dI_B}{dt} = \beta_B T V_B - \delta_B I_B - \beta_D I_B V_D$$

$$\frac{dI_{DB}}{dt} = \beta_D I_B V_D - \delta_{DB} I_{DB}$$

$$\frac{dH}{dt} = p_H I_B - A c_H H + p_{HD} I_{DB}$$

$$A = k_0 + (k_{max} - k_0) \cdot (1 - \exp(-kt))$$

$$T = T_{max} - I_B$$

Compartments

V_B : Hepatitis B viremia
V_D : Hepatitis D viremia
I_B : Monoinfected cells
I_{DB} : Coinfected cells
T : Target cells
T_{max} : Maximal contingent of target cells
H : HBsAg
A : Anti-HBs

Kinetic parameters

p_B : Viral production rate (free HBV)
p_{DB} : Viral production rate (free HBV)
p_D : Viral production rate (free HDV)
p_H : HBsAg production rate (free HBsAg)
p_{HD} : HBsAg production rate (free HBsAg)
c_B : Clearance of free HBV
c_D : Clearance of free HDV
c_H : Clearance of free HBsAg
β_B : De novo monoinfection rate
β_D : De novo coinfection rate
δ_B : Monoinfected cell loss rate
δ_{DB} : Coinfected cell loss rate
k : Treatment effect due to HBIG administration

Conclusions and Outlook

- It seems as if HDV fully parallels HbsAg kinetics without differences in degradation rates
- The dynamics does not yet indicate reinfection but this has to be analyzed with more detailed data
- Modeling the observed plateau phase by introducing time lags
  - Considering time lags - using the full model
  - Introduce pharmacokinetics (HBIG) as well
- Modeling appraoch may help to individualize HBIG dosing schemes in patients undergoing HBV/HDV-indicated or HBV-indicated liver transplantation
  - Up to now HBIG is given at a fixed dose until HBsAG level is negative

References

- Roseneau J, Kreutz T, Kujawa M, et al.: HBsAg level at time of liver transplantation determines HBsAg decrease and anti-HBs increase and affects HBV DNA decrease during early immunoglobulin administration. Journal of Hepatology 2007, 46: 635-644.
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Thank you for your attention.