Modelli bio-matematici delle dinamiche virali per la personalizzazione della terapia antivirale

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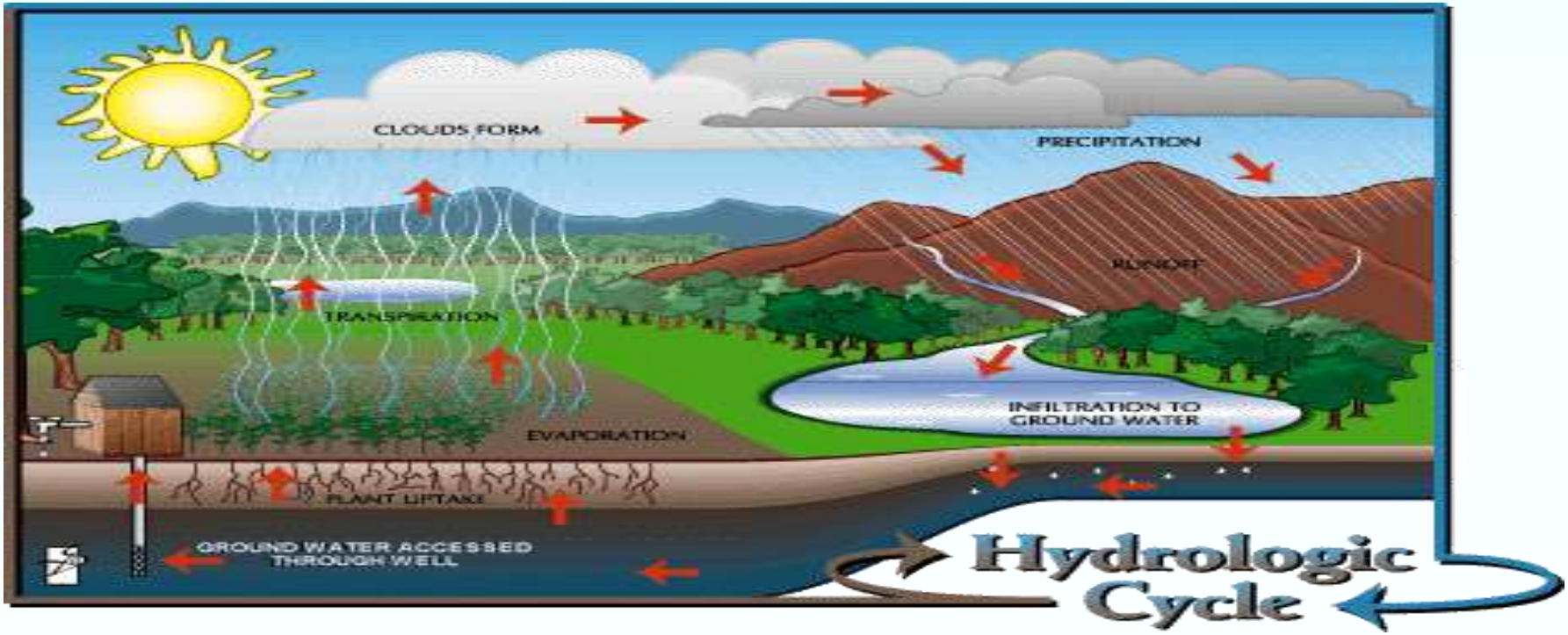
Modelling a physical / biological process is an evolving investigational approach

<u>Definition</u>: the simulation of a physical process by means of mathematical equations based on evidences, assumptions and hypothesis aimed to uncover the major forces driving the process.

The model can progressively increase its accuracy by comparing experimental to predicted data.



Modeling of HCV infection dynamics during antiviral therapy can allow for:

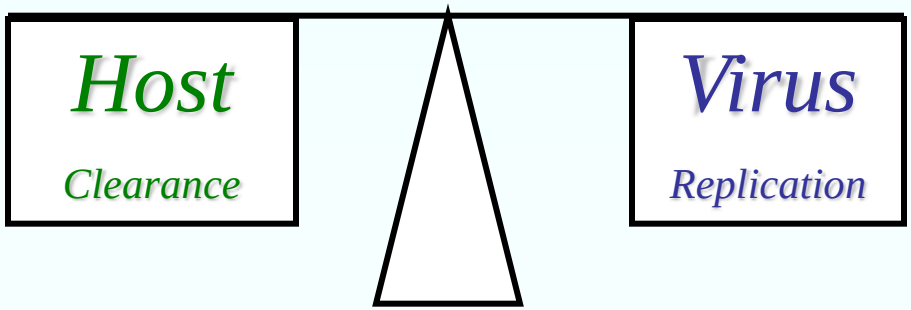
- the calculation of relevant biological variables not accessible to direct measurement (virion and infected cell clearance rate constants)
- the accurate characterization of the antiviral effects to compare the mechanisms and the efficacy of different antiviral regimens
- the identification of infected cell and viremia decline patterns that correlate with different treatment outcomes

Application of modelling in the clinical practice could warrant treatment tailoring at the indivudual patient level

Viral kinetics:

viral load variations measured at short intervals of time

viral load steady state



Biological process

Mathematical description

Model fitting of experimental data

HCV RNA and ALT kinetics during IFN therapy: a single exponential decline?

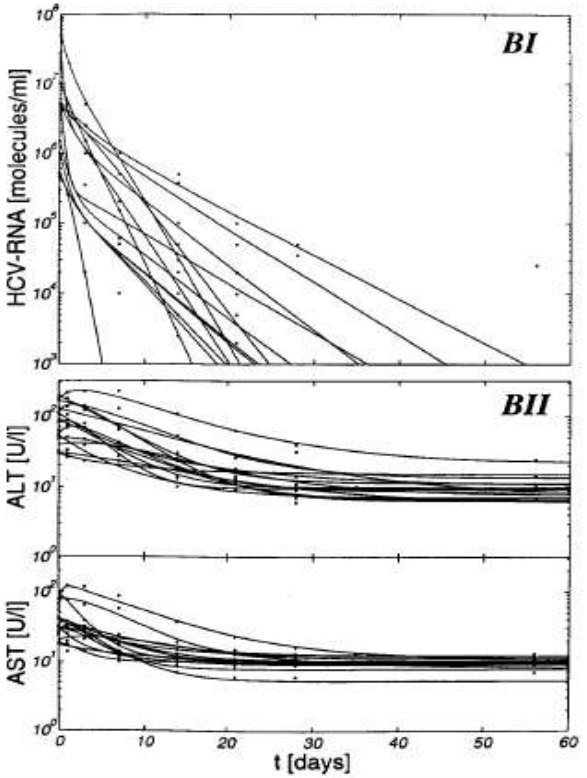
Rapid Communication

HEPATOLOGY Vol. 23, No. 2, 1996

Effect of Interferon Alfa on the Dynamics of Hepatitis C Virus Turnover *In Vivo*

STEFAN ZEUZEM,[1] JÜRGEN M. SCHMIDT,[2] JUNG-HUN LEE,[1] BRIGITTE RÜSTER,[3] AND W. KURT ROTH[3]

In about 30% to 40% of patients with chronic hepatitis C, treatment with recombinant interferon alfa (r-IFNα) causes a decrease of serum aminotransferases and hepatitis C virus (HCV) RNA. The antiviral mechanism of interferon alfa (IFNα) *in vivo* is unknown. From serial measurements of serum HCV-RNA concentrations following IFNα induced perturbation of the balance between virus production and clearance, we obtained kinetic information on the pretreatment steady-state of HCV. In patients with chronic hepatitis C responding to IFNα, HCV-RNA declined exponentially with a half life of approximately 2 days. Modeling of the data predicts that in patients with chronic hepatitis C responding to IFNα this cytokine predominantly acts as an inhibitor of *de novo* infection of susceptible cells. HCV is released



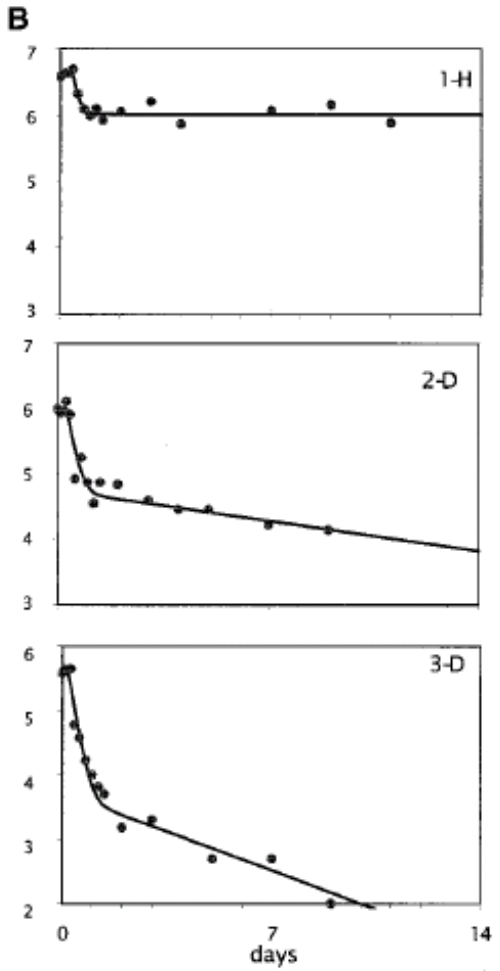
From a single exponential decline to the biphasic model

Hepatitis C Viral Dynamics in Vivo and the Antiviral Efficacy of Interferon-α Therapy

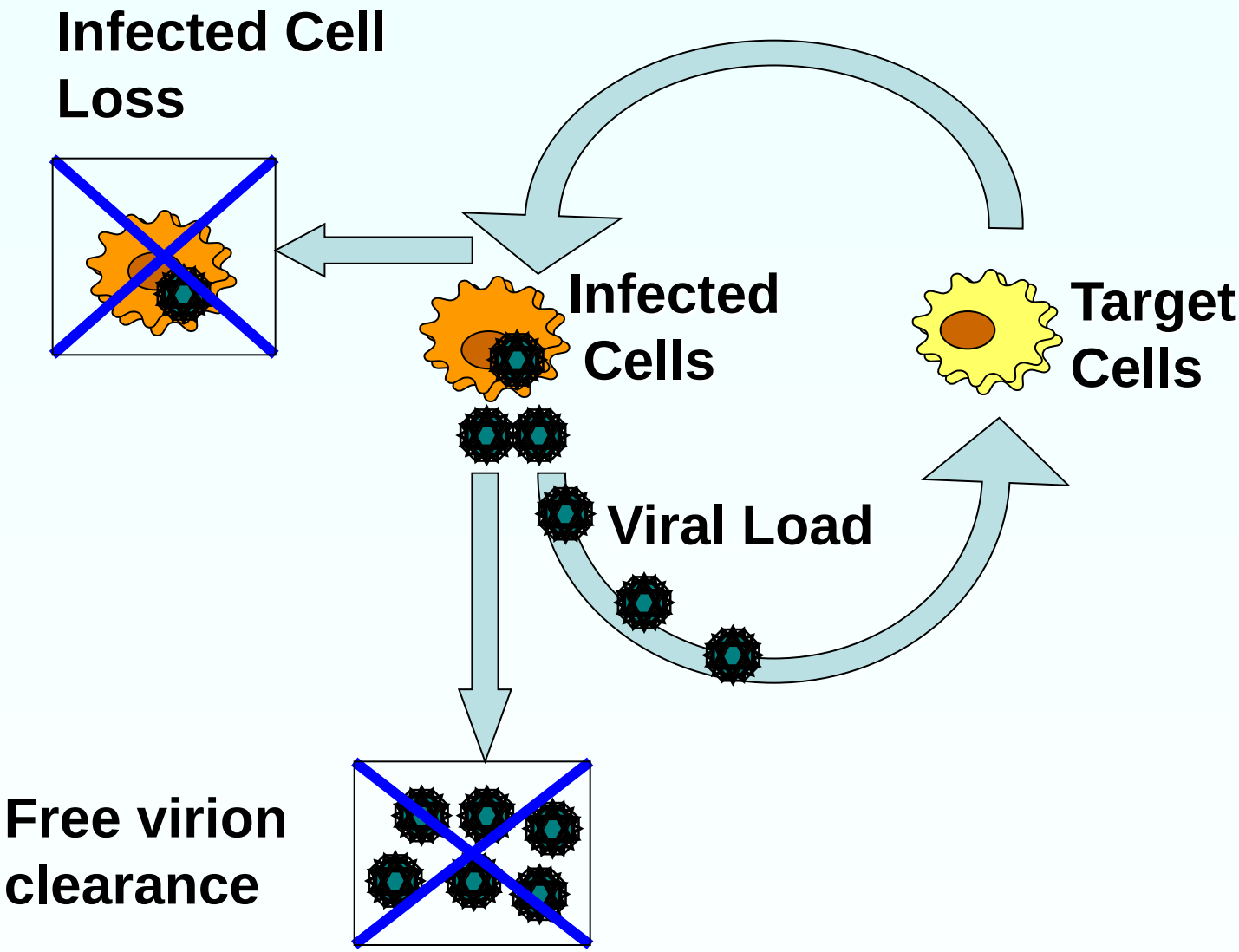
Avidan U. Neumann,*† Nancy P. Lam,*‡ Harel Dahari, David R. Gretch, Thelma E. Wiley, Thomas J. Layden, Alan S. Perelson

To better understand the dynamics of hepatitis C virus and the antiviral effect of interferon-α-2b (IFN), viral decline in 23 patients during therapy was analyzed with a mathematical model. The analysis indicates that the major initial effect of IFN is to block virion production or release, with blocking efficacies of 81, 95, and 96% for daily doses of 5, 10, and 15 million international units, respectively. The estimated virion half-life ($t_{1/2}$) was, on average, 2.7 hours, with pretreatment production and clearance of 10^{12} virions per day. The estimated infected cell death rate exhibited large interpatient variation (corresponding $t_{1/2}$ = 1.7 to 70 days), was inversely correlated with baseline viral load, and was positively correlated with alanine aminotransferase levels. Fast death rates were predictive of virus being undetectable by polymerase chain reaction at 3 months. These findings show that infection with hepatitis C virus is highly dynamic and that early monitoring of viral load can help guide therapy.

www.sciencemag.org SCIENCE VOL 282 2 OCTOBER 1998



Schematic representation of the standard biphasic model of chronic HCV infection



Mathematical description of the standard model

3 differential equations describing:

1. The change in the number of uninfected cells (**Target cells, T**)

$$dT/dt = s - dT - (1-\eta)\beta VT$$

2. The change in the number of infected cells (**Infected cells, I**)

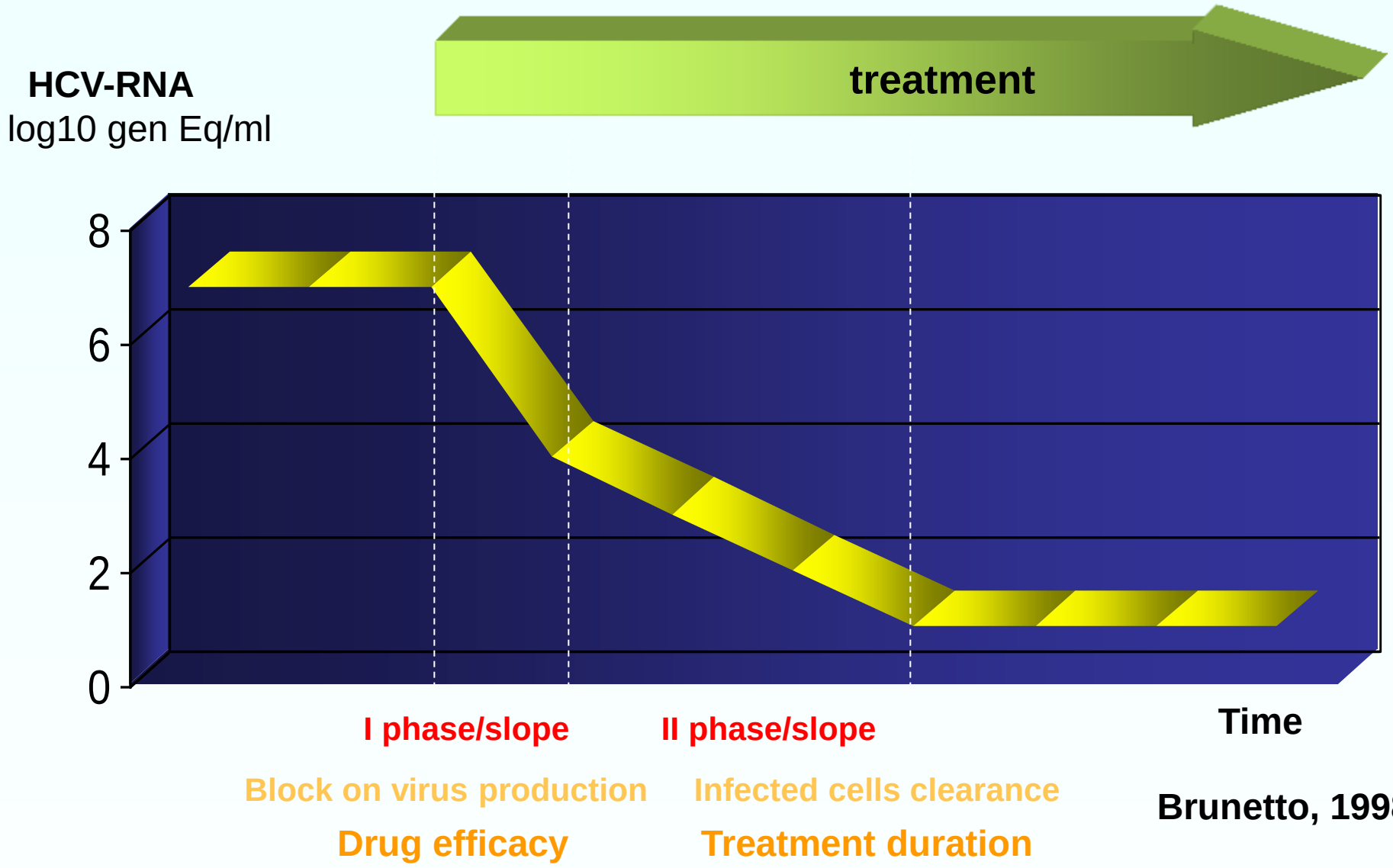
$$dI/dt = (1-\eta)\beta VT - \delta I$$

3. The change of **viral load (V)**

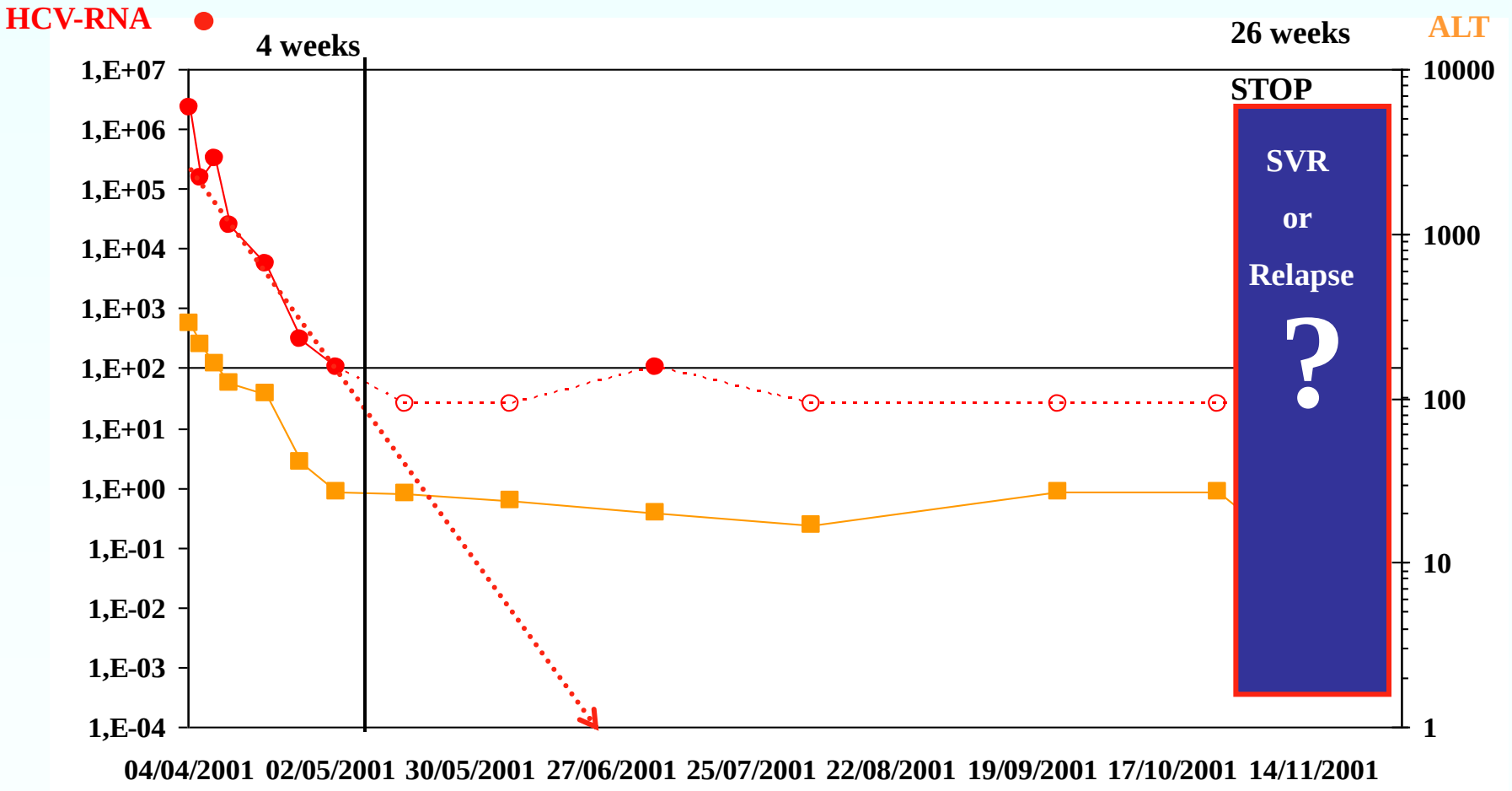
$$dV/dt = (1-\varepsilon)\Psi I - \lambda V$$

s = production rate of T; d = death rate of T;
β = infection rate of T; η = reduction of cell susceptibility to the infection;
δ = clearance rate of I; Ψ = production rate of virions;
ε = reduction of virus production rate
λ = clearance rate of virions

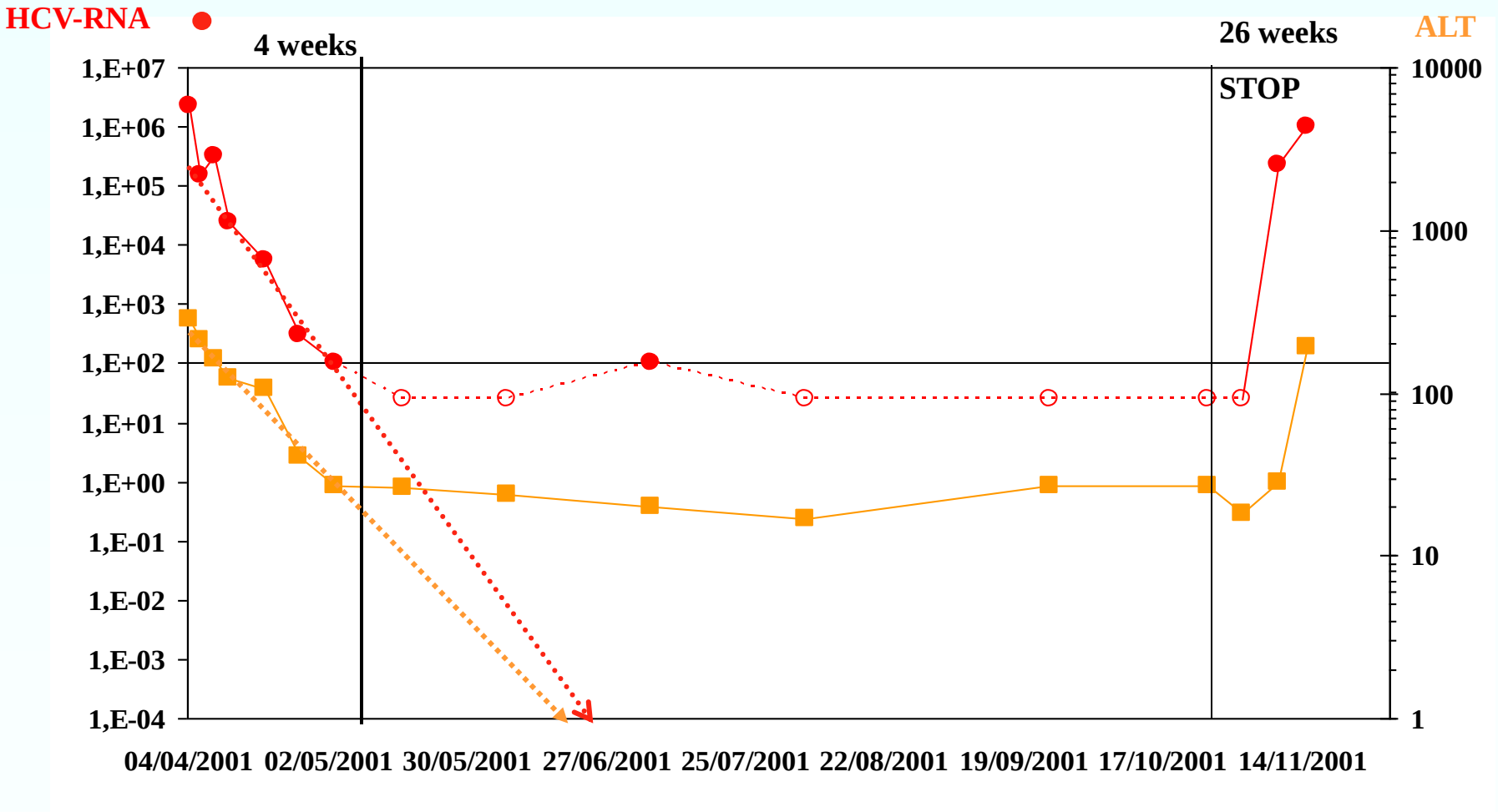
Potential application of the quantitative analysis of viral load decline in clinical practice



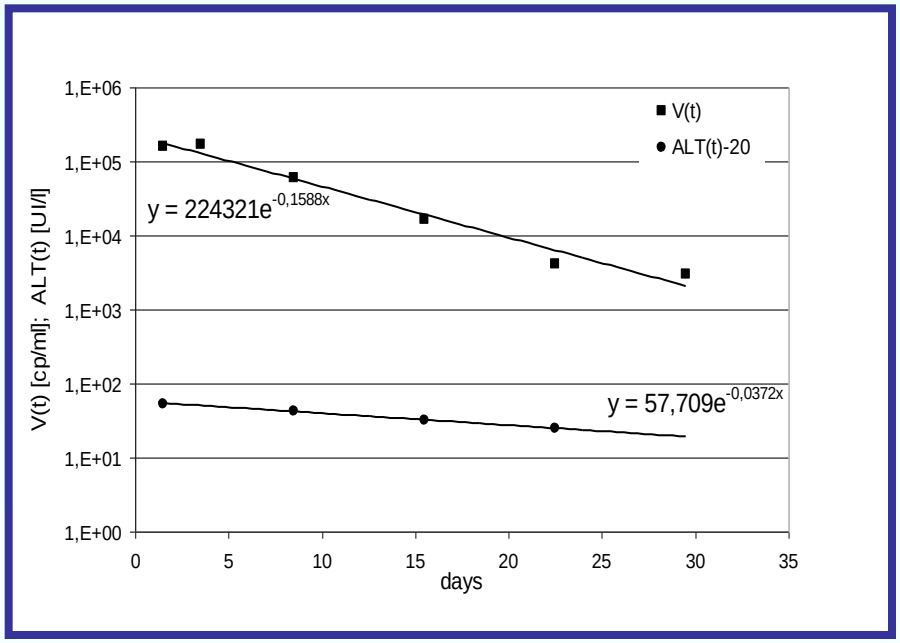
Application of the biphasic model to HCV RNA decline during effective antiviral treatment



The simple biphasic model of HCV RNA decline does not predict treatment outcome



Combined analysis of ALT and HCV RNA kinetics



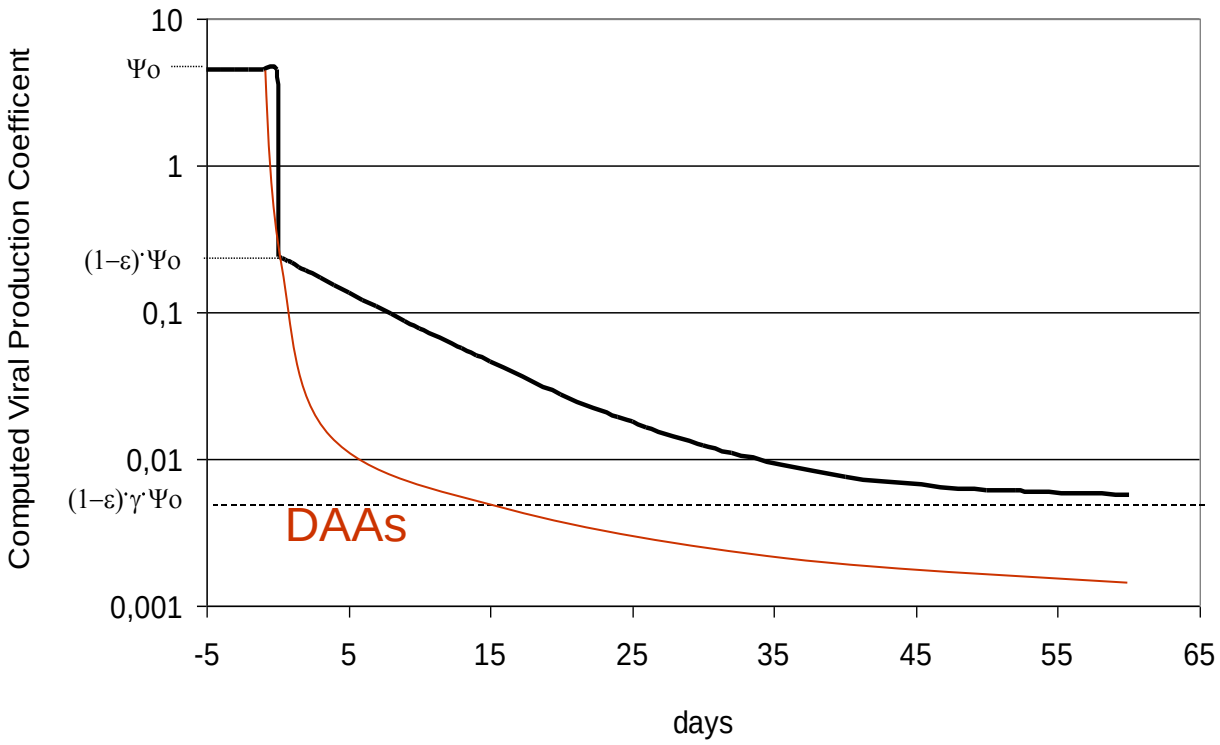
A discrepancy in Log decrease of ALT and HCV-RNA is present during the 2nd phase attributed to the infected cell clearance.

IN OUR MODEL:

- the discrepancy betwen ALT and HCV-RNA Log decline is attributed to a further decrease of the virus production rate constant (Ψ_0) during the 2nd phase
- the infected cell clearance rate constant (δ_0) is computed by fitting the ALT decline during the 1st month

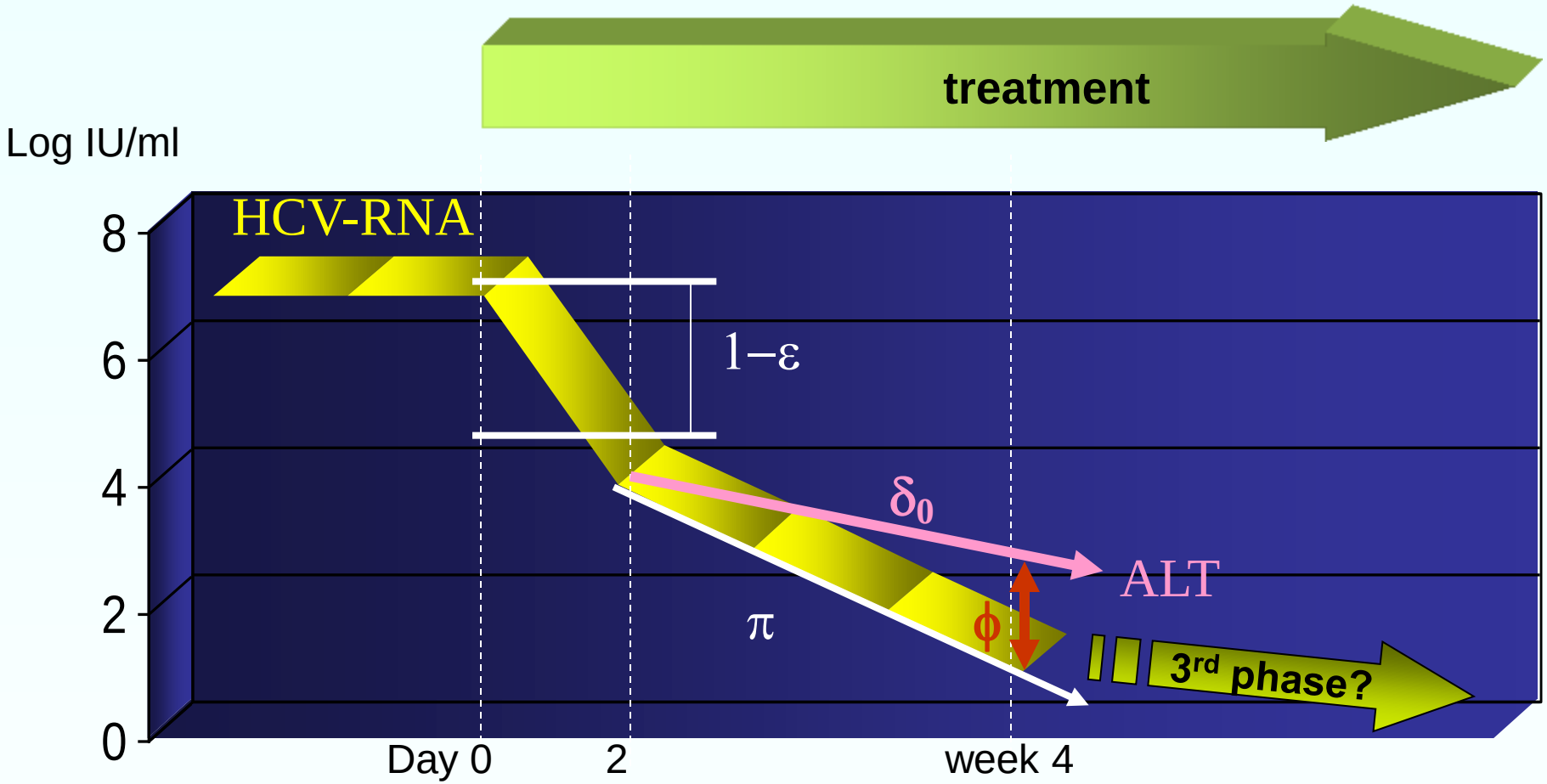
Colombatto P et al.. Antiv Ther, 2003

kinetics of the inhibitions of virus replication



Brunetto MR, WJG 2009 Rev.

Model for early viral kinetics analysis



Block on virus production (ε)

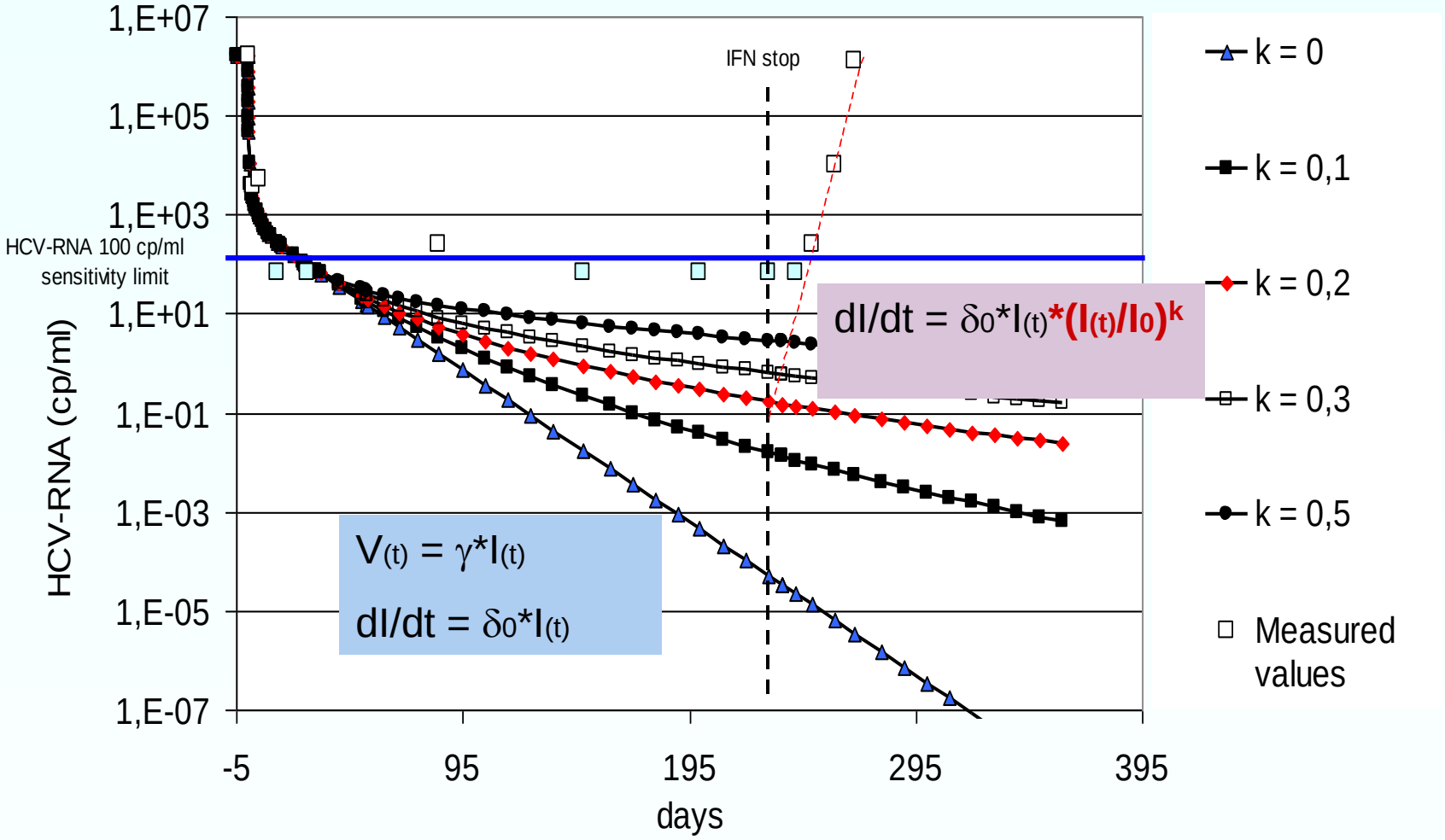
Drug effectiveness

Infected cells clearance (δ_0)

Immune system activity

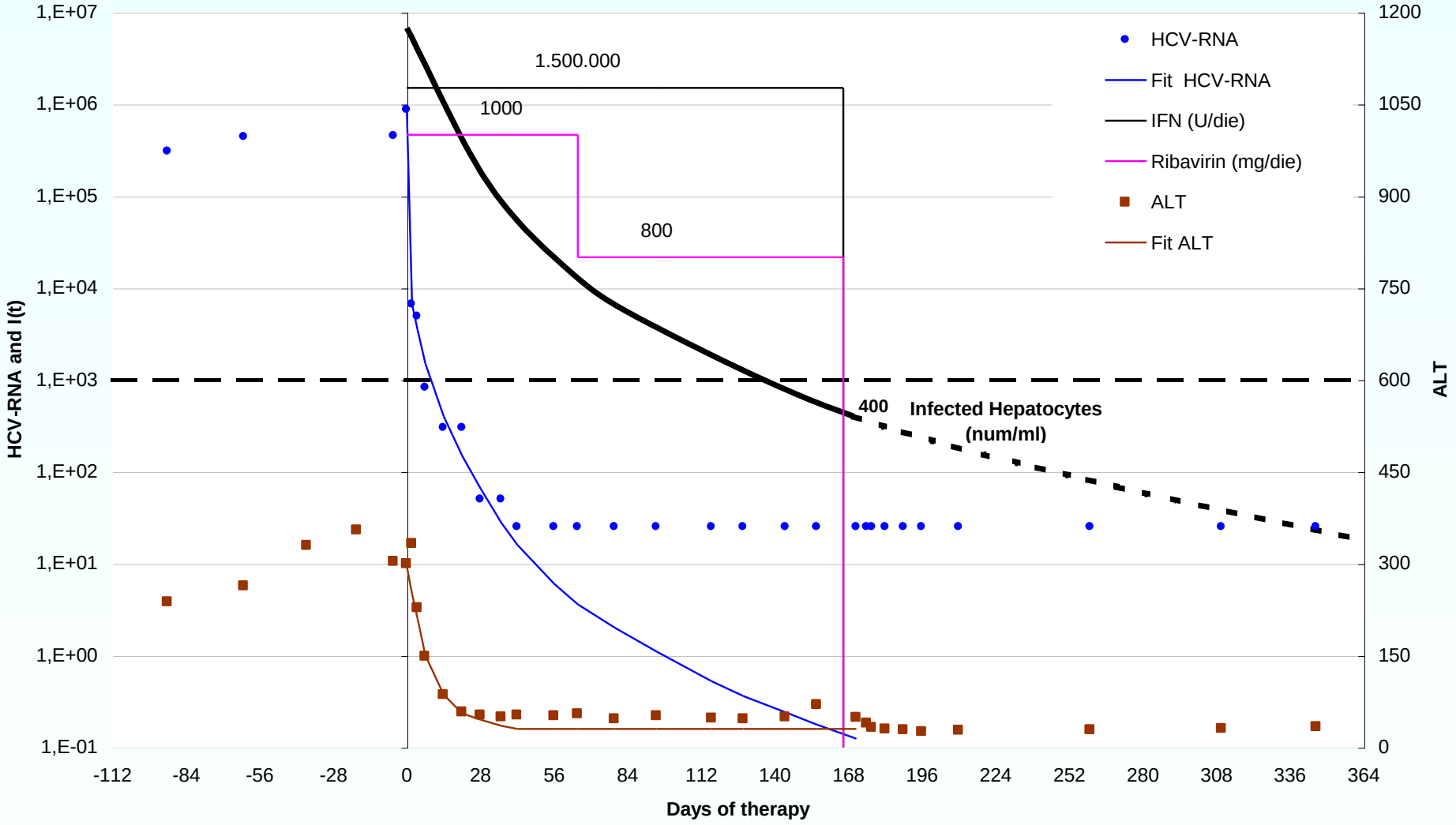
Colombatto P et al.. Antiv Ther, 2003

Model of long term viral kinetics

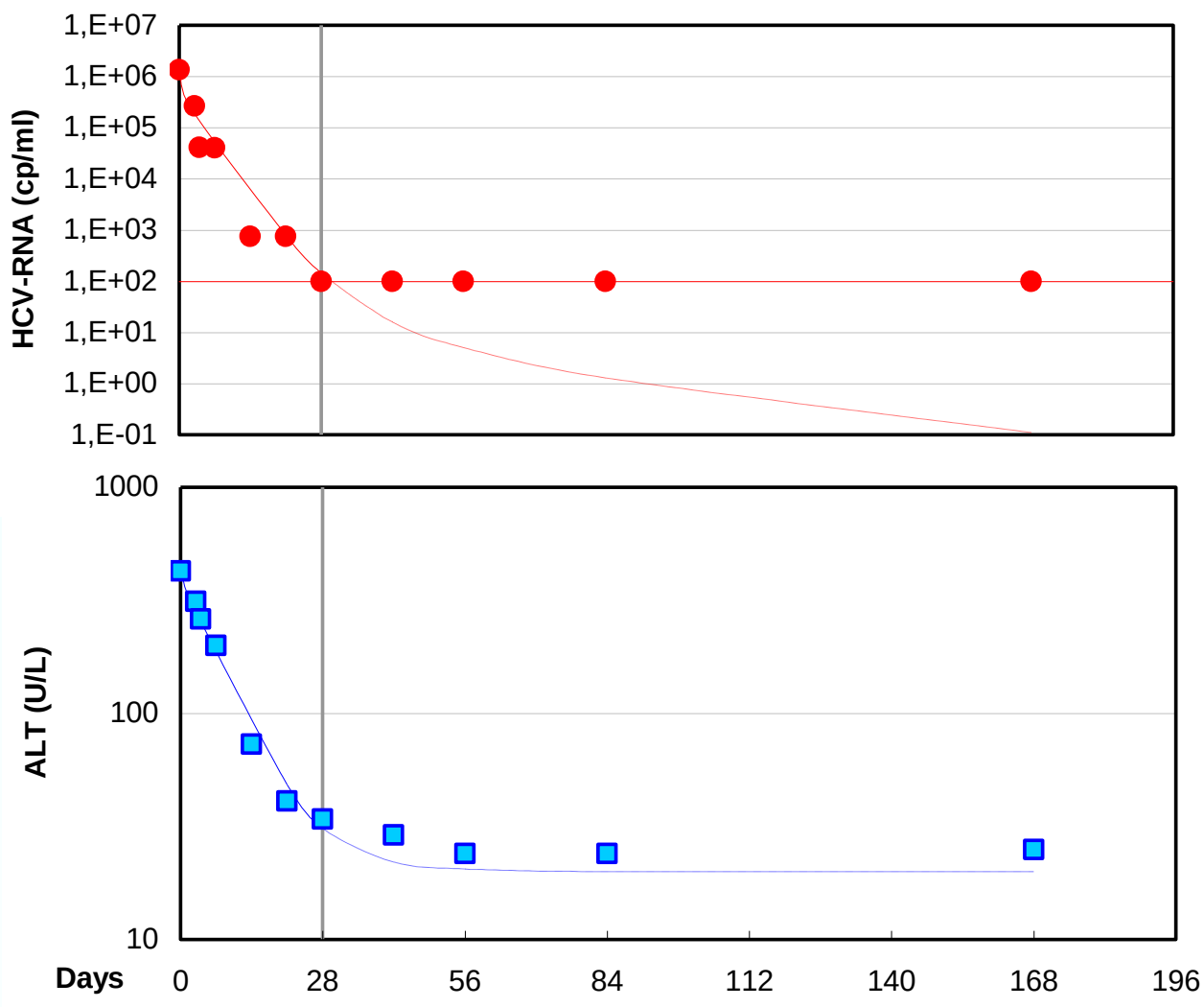


Colombatto P et al.. Antiv Ther, 2003

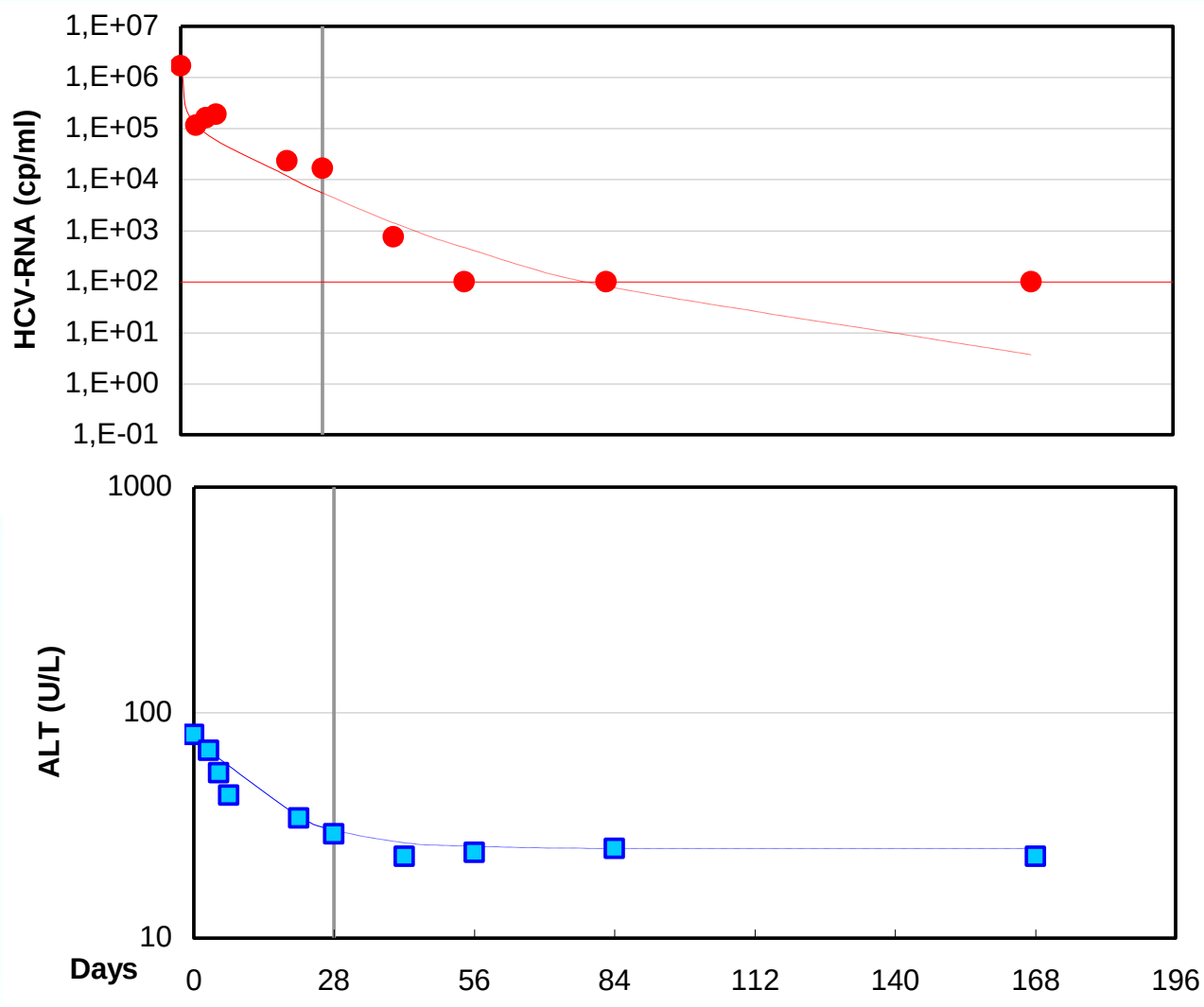
Fitting of **HCV-RNA** and **ALT** allows the model to compute an index correlated to the residual amount of the **I**nfected cells at the **e**nd **o**f **t**herapy (I_{eot})



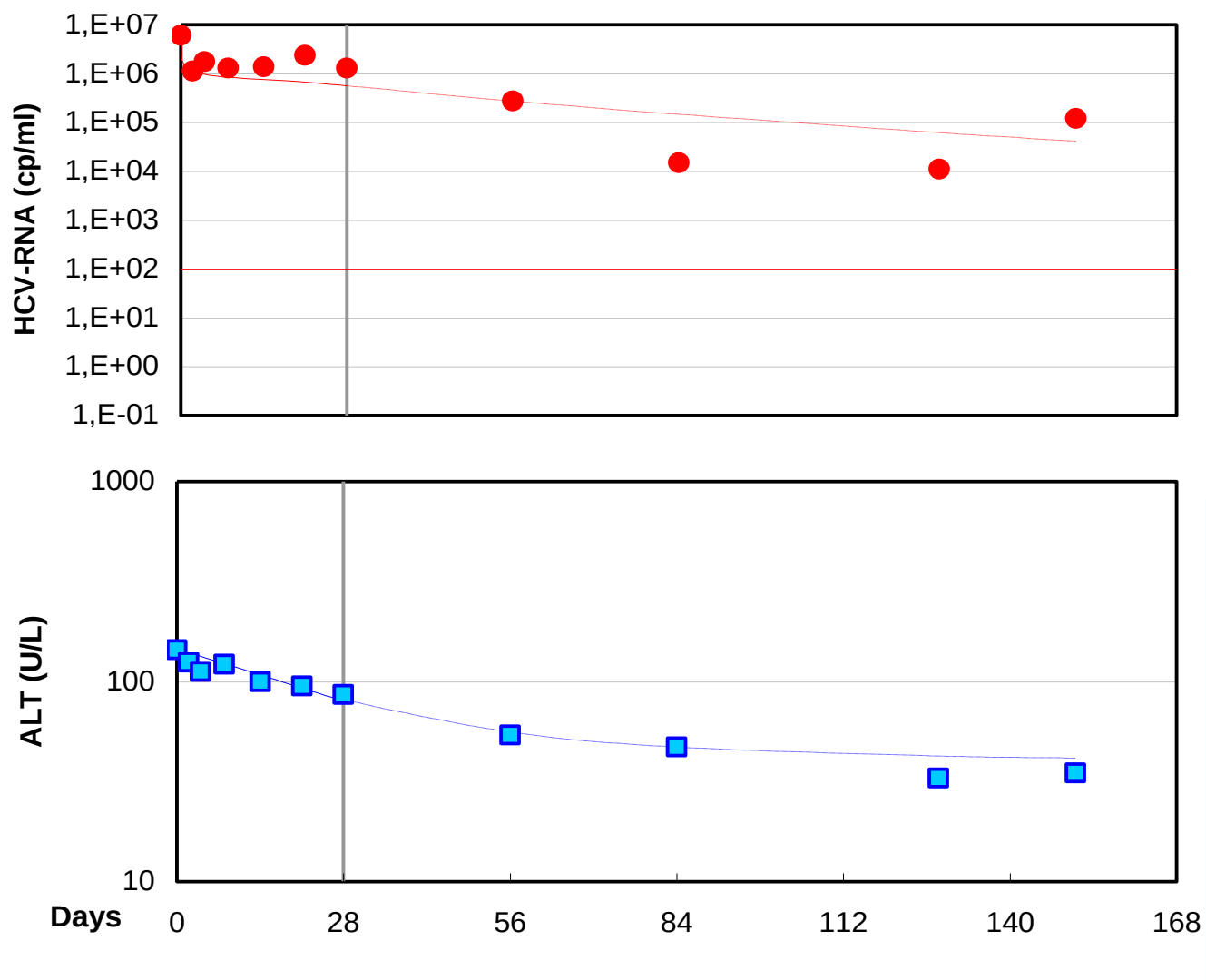
Model fitting and predictions in SVR pt (HCV gt 2 / peg-IFN2b+RBV)



Model fitting and predictions in REL pt (HCV1b / peg-IFN2b+RBV)



Model fitting and predictions in NR pt (HCV1b / peg-IFN2b+RBV)

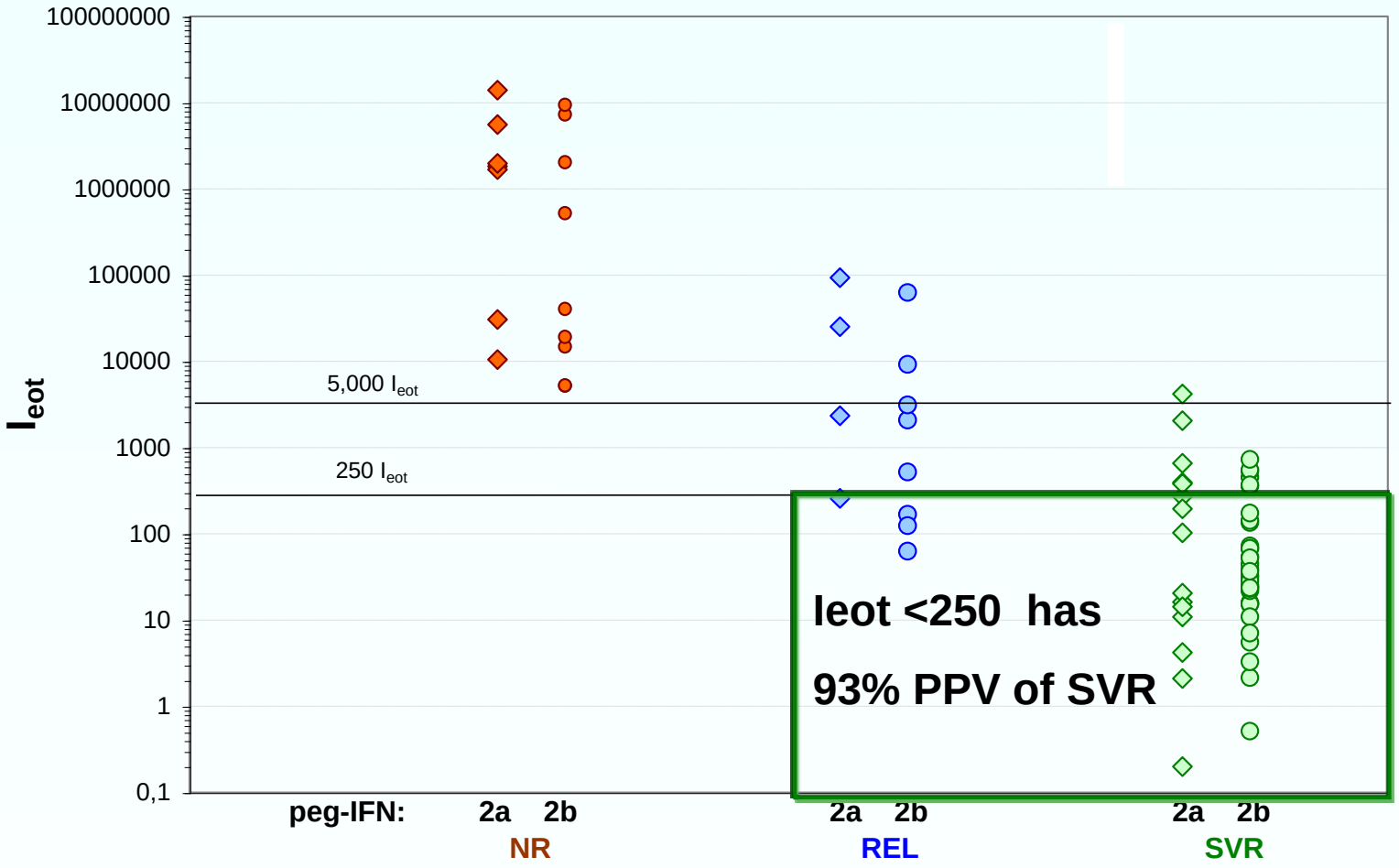


Modelling in patients treated with standard therapy

	Total Pts (n=97)	Peg-IFN 2a (n=35)	Peg-IFN 2b (n=62)
Sex			
Male	76	29	47
Female	21	6	15
Age (years)			
Mean ± SD	47 ± 11	47 ± 10.6	48 ± 12
Body mass index (Kg/m^2)			
Mean ± SD	24.8± 2.8	24.6±3.1	24.9±2.7
HCV genotype			
1 - 4	56 - 5	22 - 1 (66%)	34 - 4 (61%)
2 - 3	23 - 13	5 - 7	18 - 6
Cirrhosis			
Present	27	12 (34%)	14 (23%)
Absent	70	23	48
Steatosis			
Present	64	25 (71%)	22 (35%)
Assent	31	9	39
Not known	2	1	1
Baseline ALT (U/L)			
Mean ± SD	130 ± 126	132 ± 100	129 ± 140
Baseline HCV-RNA (IU/mL)			
Mean ± SD	5.9E+06 ± 5.5E+05	1.61E+06 ± 1.73E+06	1.46E+06 ± 1.61E+06
Prior treatment response			
Naive	53	20 (57%)	33 (53%)
Relapser	33	6	27
Non Responder	11	9	2

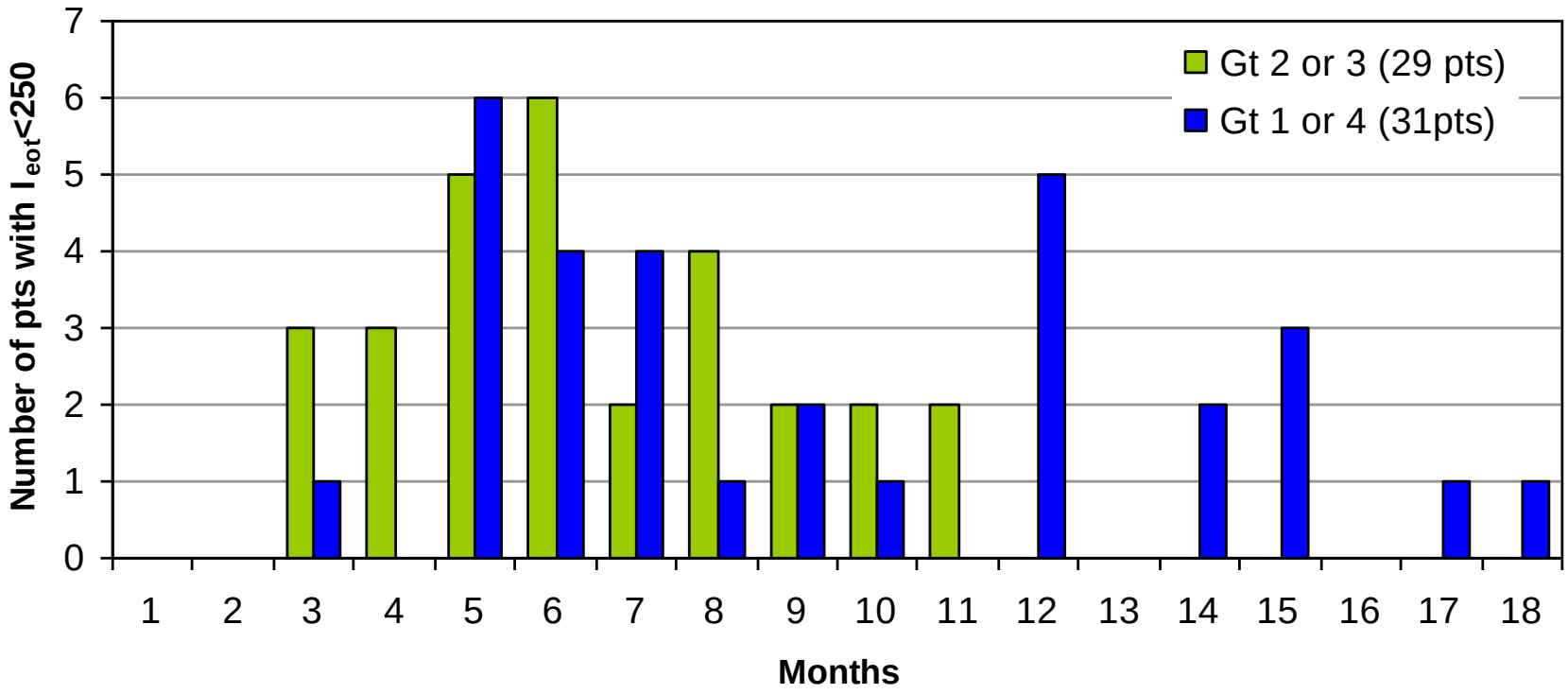
Early and Accurate Prediction of Peg-IFNs/ Ribavirin Therapy Outcome in the Individual Patient With Chronic Hepatitis C by Modeling the Dynamics of the Infected Cells

P Colombatto[1], P Ciccorossi[1], AM Maina[1–3], L Civitano[1–3], F Oliveri[1], B Coco[1], V Romagnoli[1], F Bonino[2,3] and MR Brunetto[1]



CLINICAL PHARMACOLOGY & THERAPEUTICS (2008)

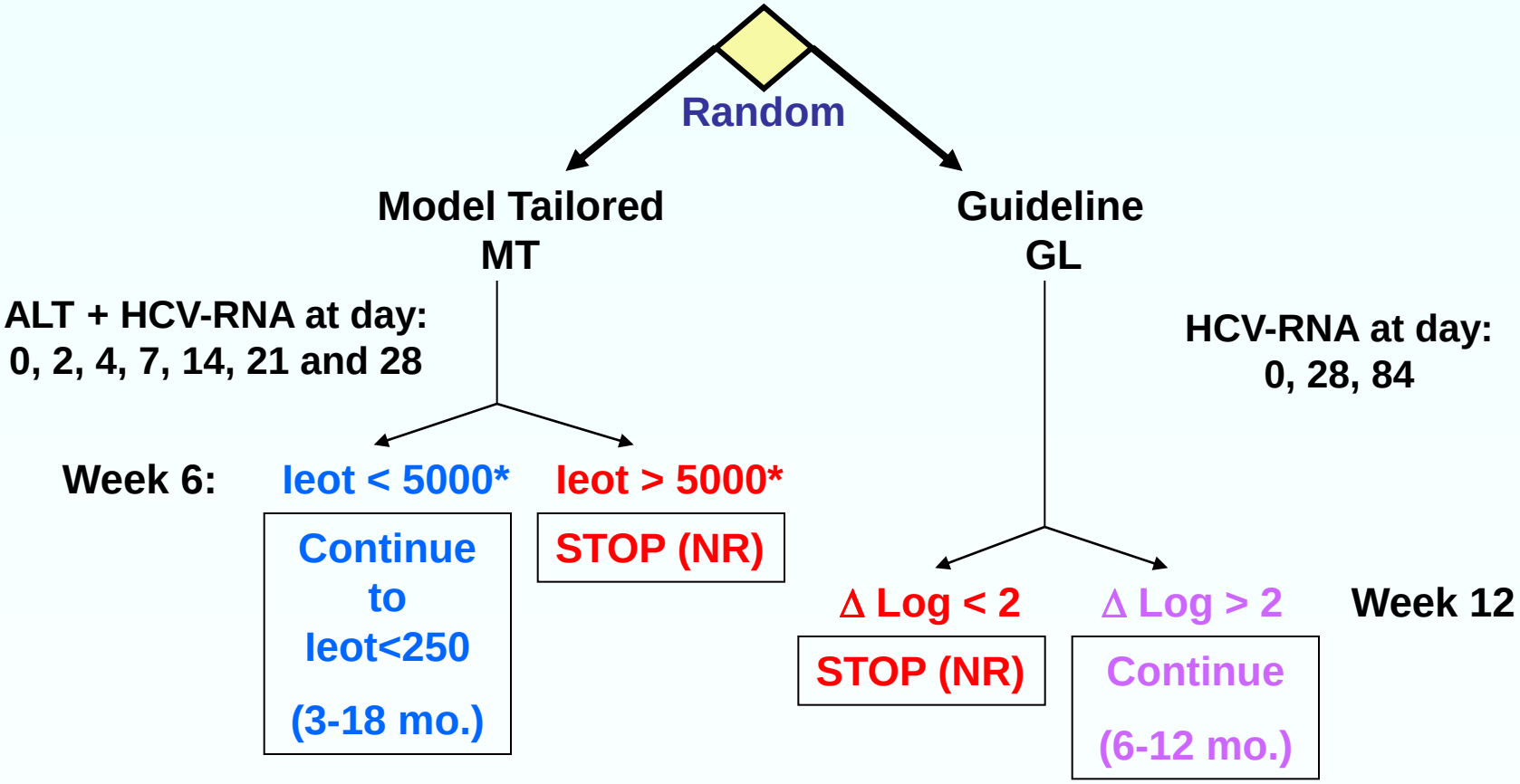
Predicted treatment duration to reach Ieot<250 according to HCV genotype



Prospective Randomized Trial (EudraCT: 2006−002483−26)

After stratification by:

- **HCV genotype (1 - 4 vs 2 - 3)**
- **treatment exposure (Naives vs Relapsers)**
- **peg-IFN type (alpha-2a vs alpha-2b)**



* Ieot >5000 at GL duration: 6 mo. for G2-3 and 12 mo. for G1-4.

Interim Results (31/12/2010)

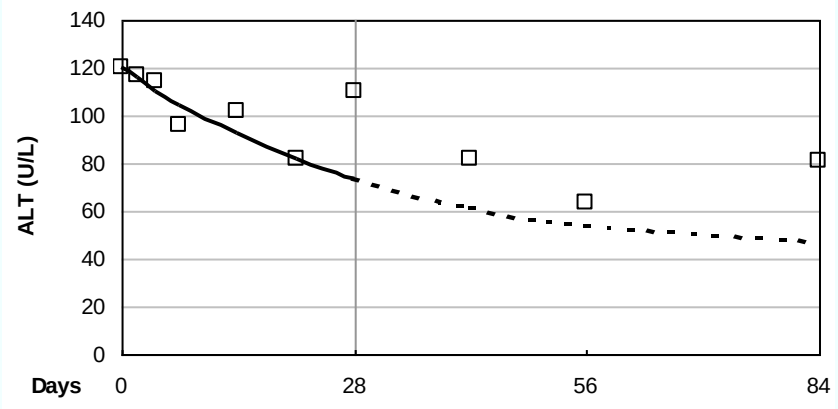
Randomized patients: **112** → 1 pt NO START

Study completed in: **107 pts**

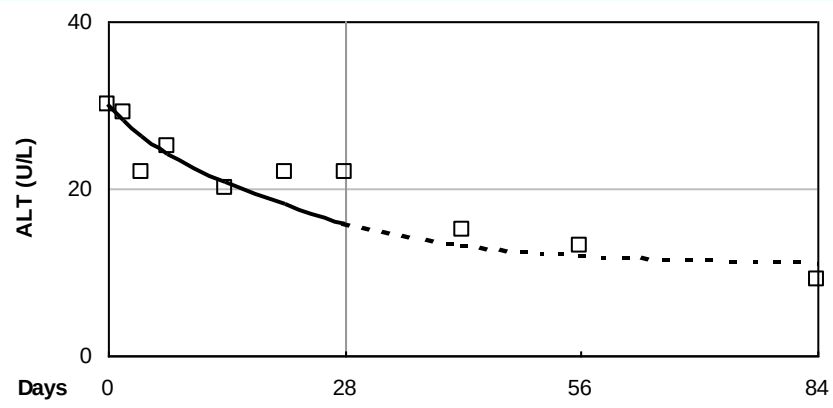
	Model Tailored: 55	**Guideline: 52**
No model fit: 8 (15%)	not included in the analysis	
	47	**52**
Drop out due to		
AE:	**9**	**6**
Prot. Viol.:	**5**	**5**
Analysed pts:	**33**	**41**

Major reasons for ALT fitting failure:

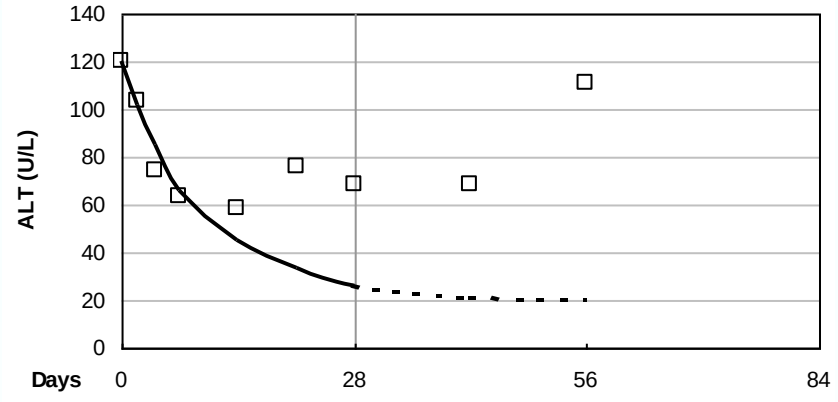
A: scattered ALT
(Peg-IFN2a+RBV)



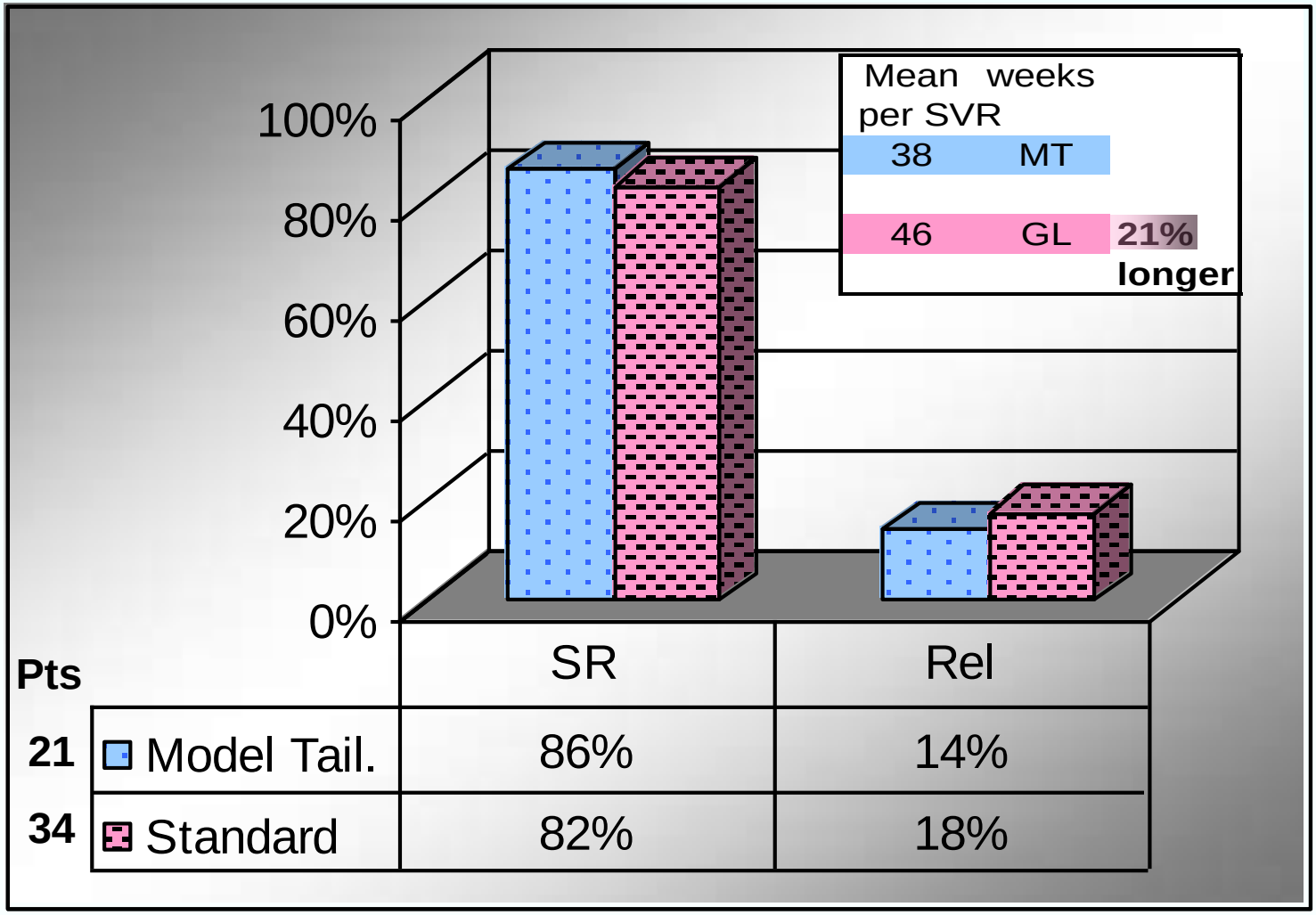
B: normal ALT
(Peg-IFN2b+RBV)



C: ALT decline with rebound
(Peg-IFN2a+RBV)

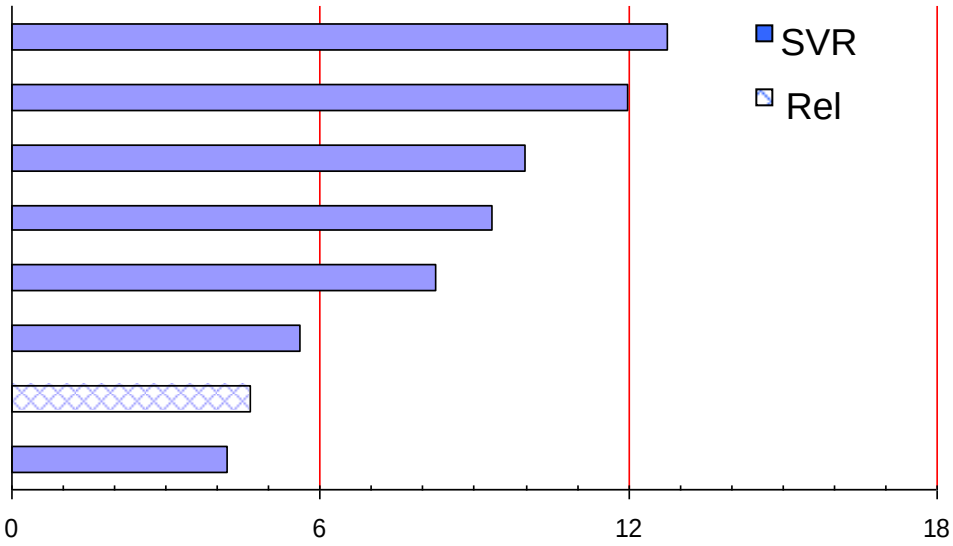


Rate of SVR in Responder patients

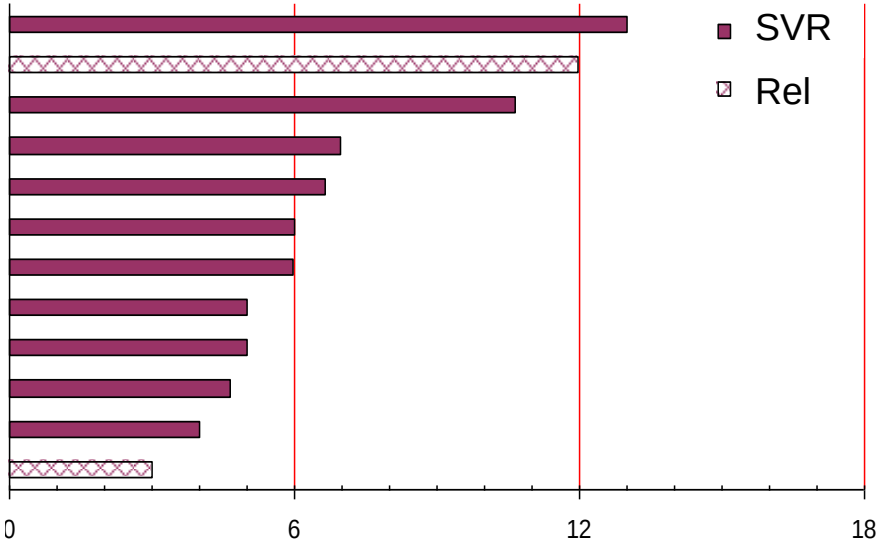


Outcome and individual treatment durations in MT patients

Genotype 1 pts



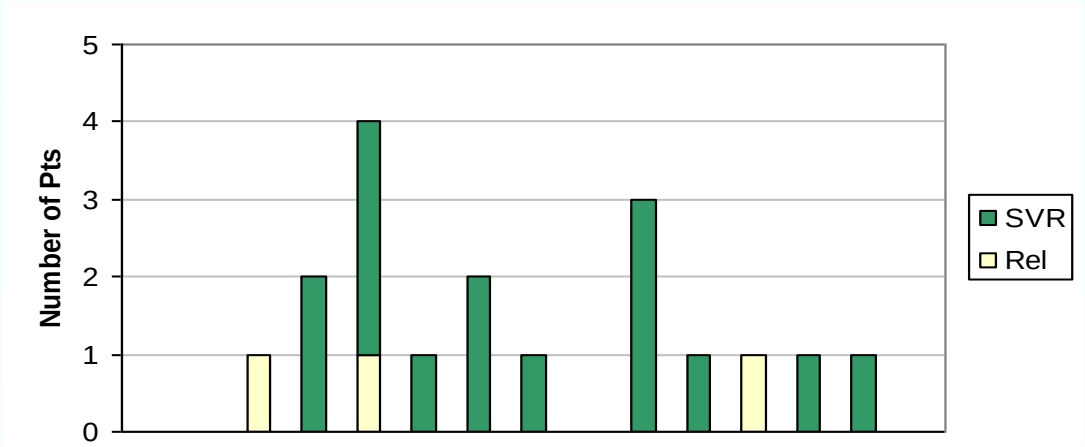
Genotype 2-3 pts



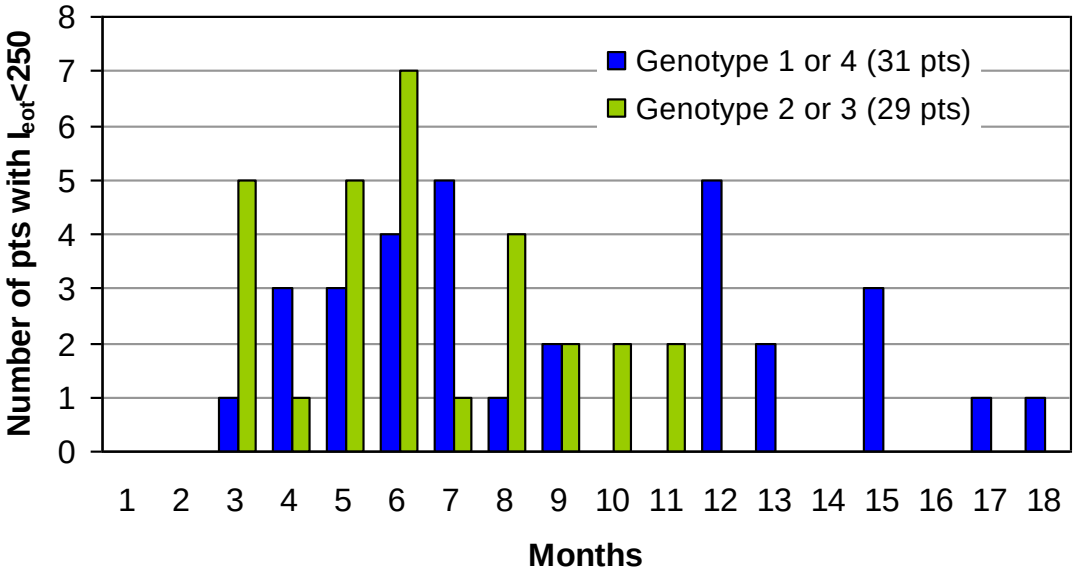
Months of therapy

Individual treatment duration according to the Model Tailored schedules

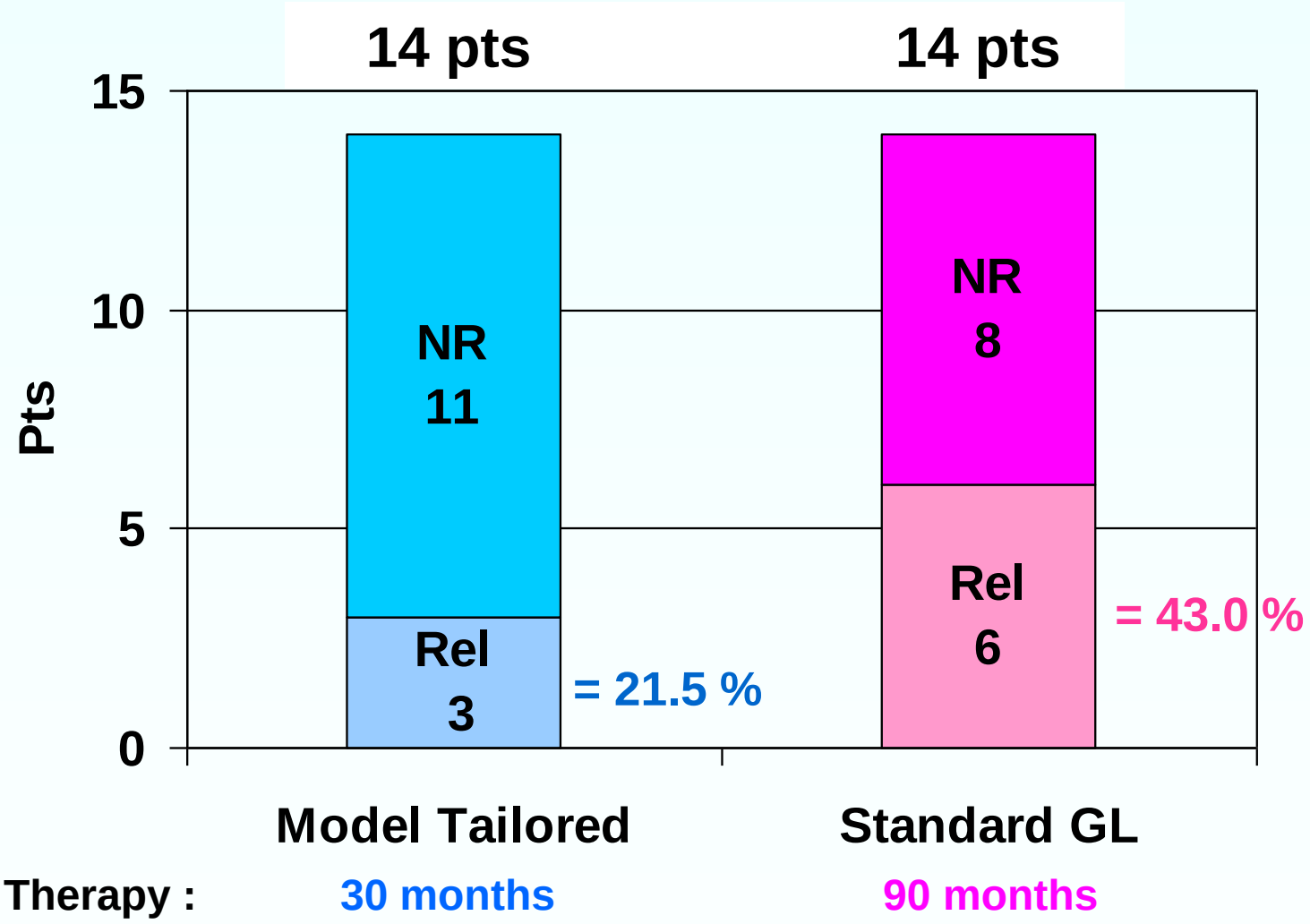
Prospective Study (real duration)



Retrospective Study (predicted duration)

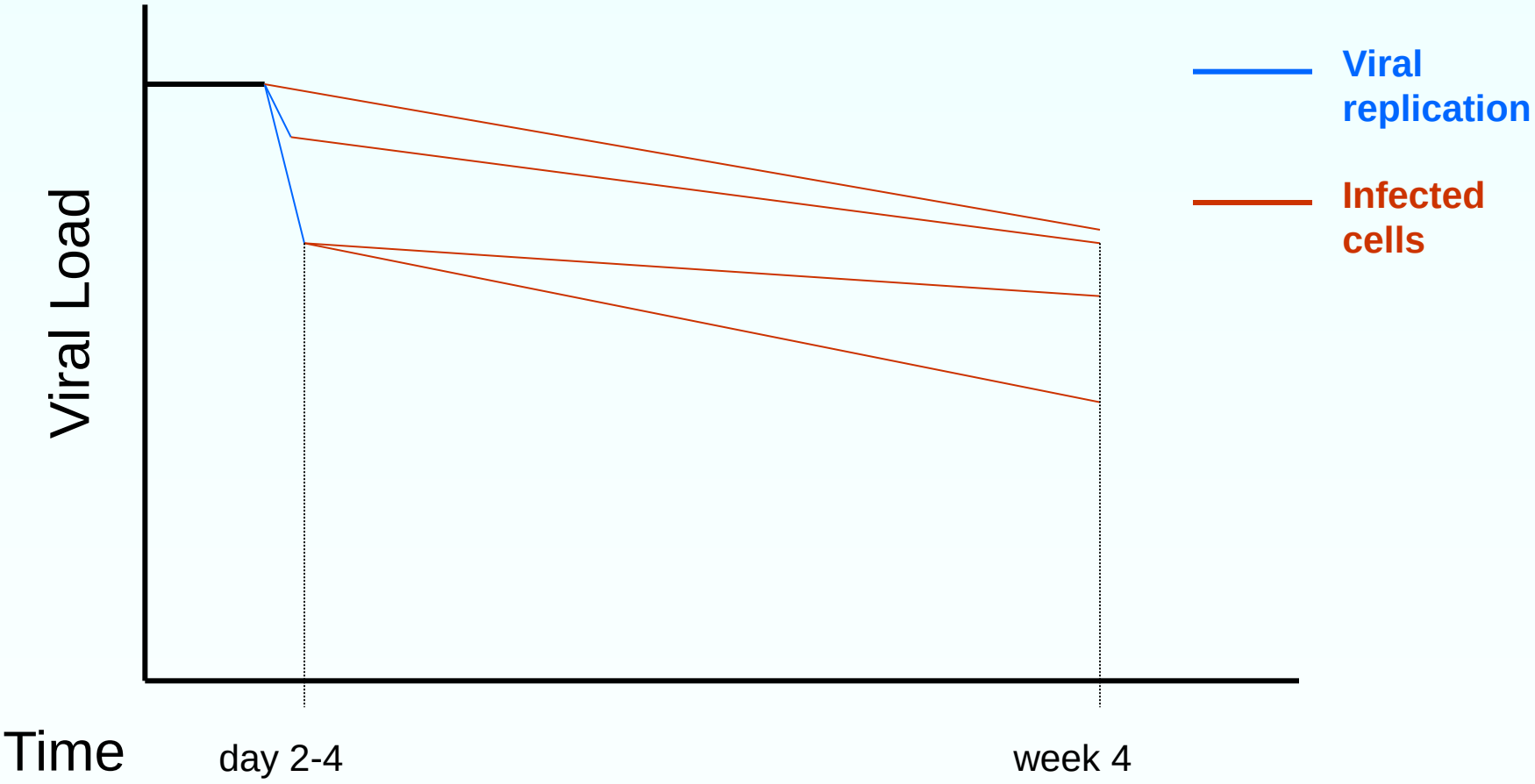


Reasons for treatment failures in the two arms

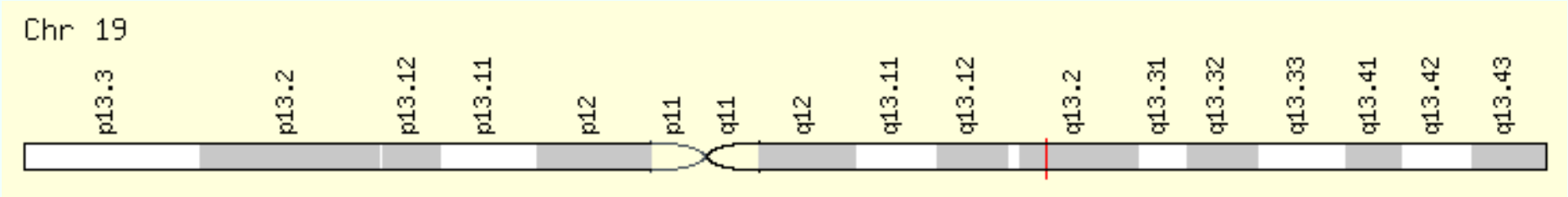


Total Therapy : 30 months 90 months

Prototypes of viral kinetics in treatment failures

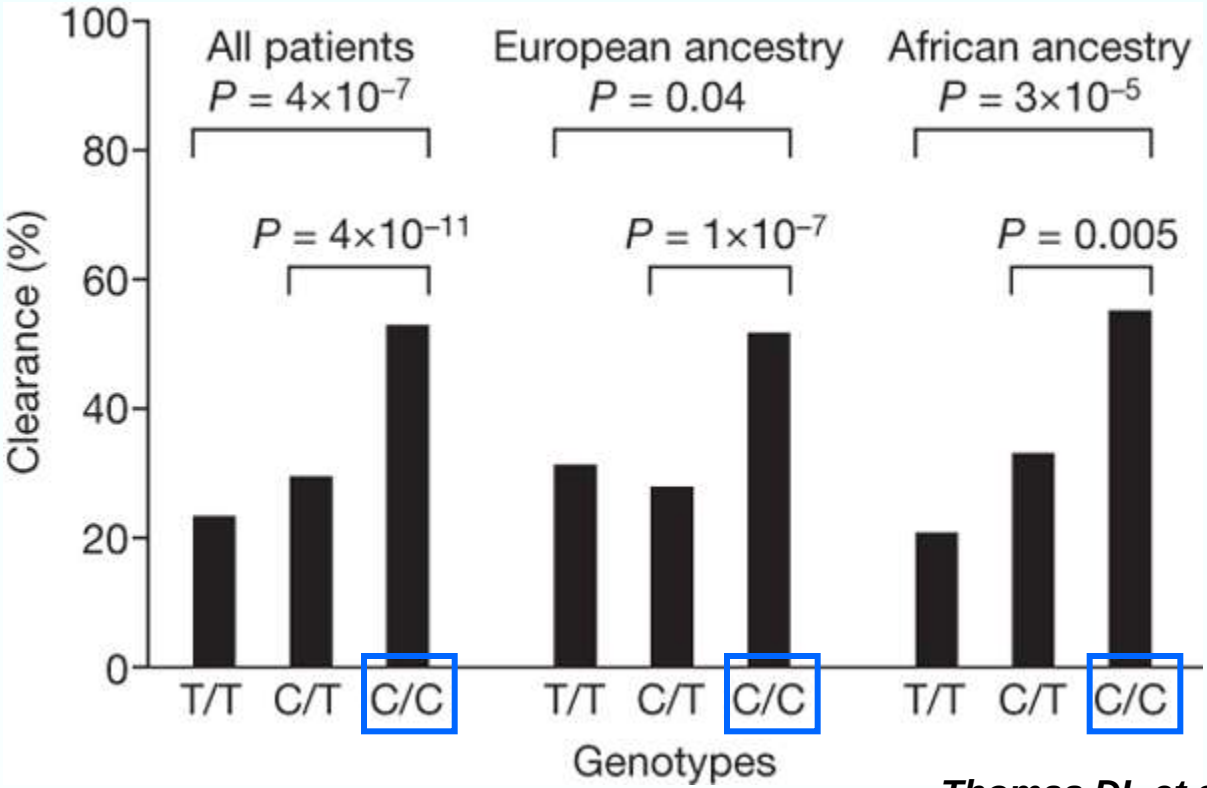


Interleukin 28B (IFN, lambda 3) and HCV clearance



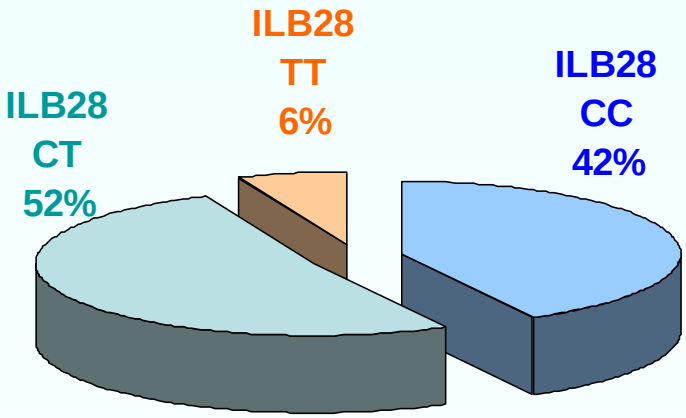
IL28B Gene in genomic location

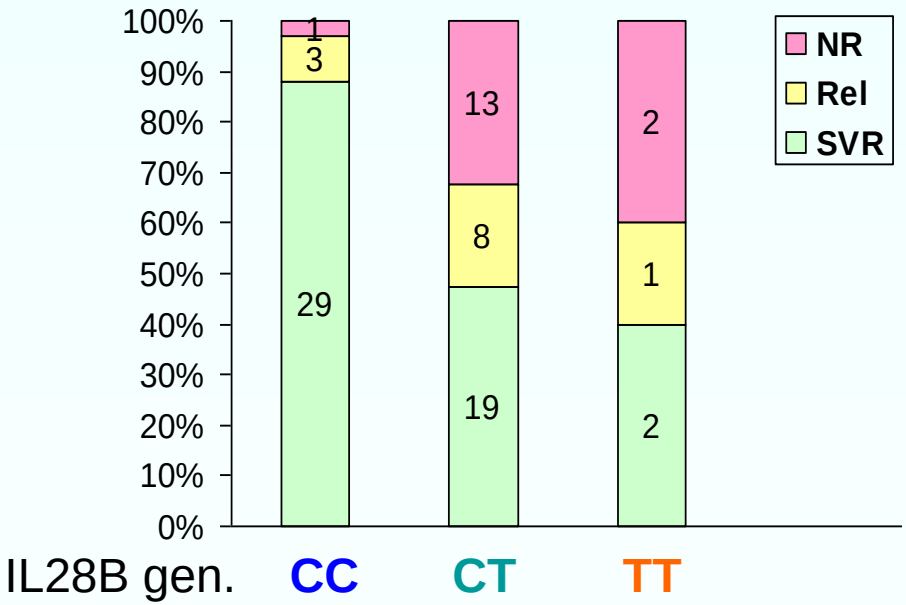
Percentage of HCV clearance by rs12979860 genotype.



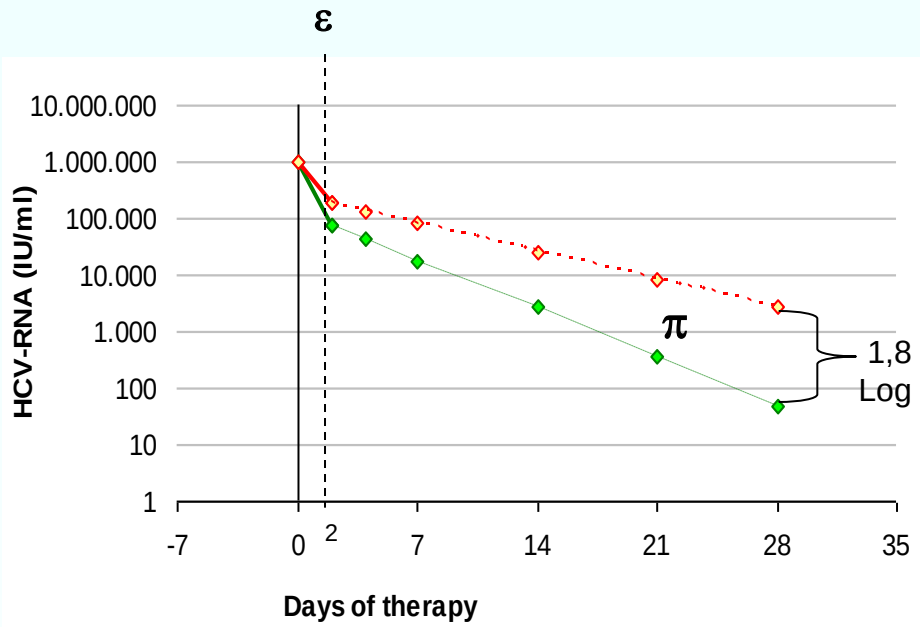
***Thomas DL et al. Nature Oct* 2009**

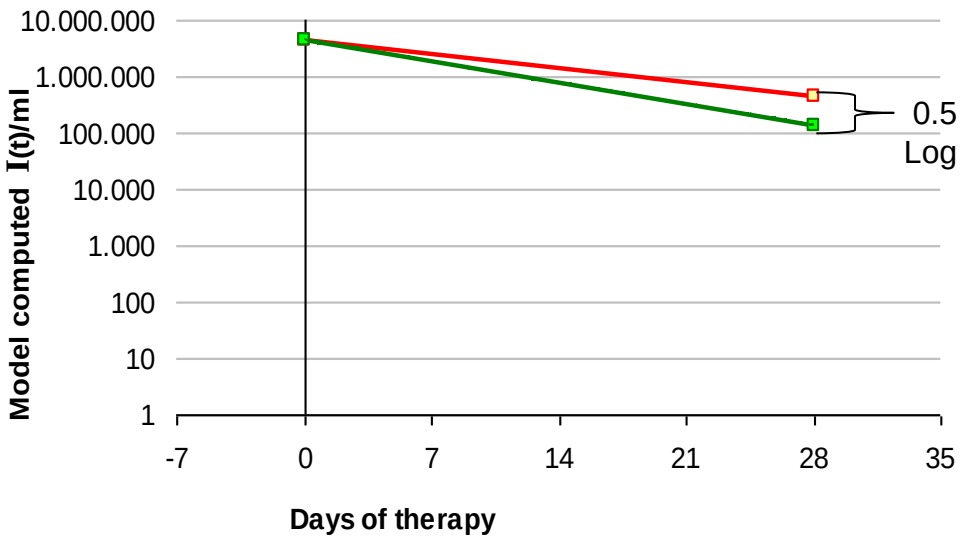
IL28B genotype characterization in 78 retrospective patients analysed by the model





Differences in the early viral kinetics according to IL28B genotype

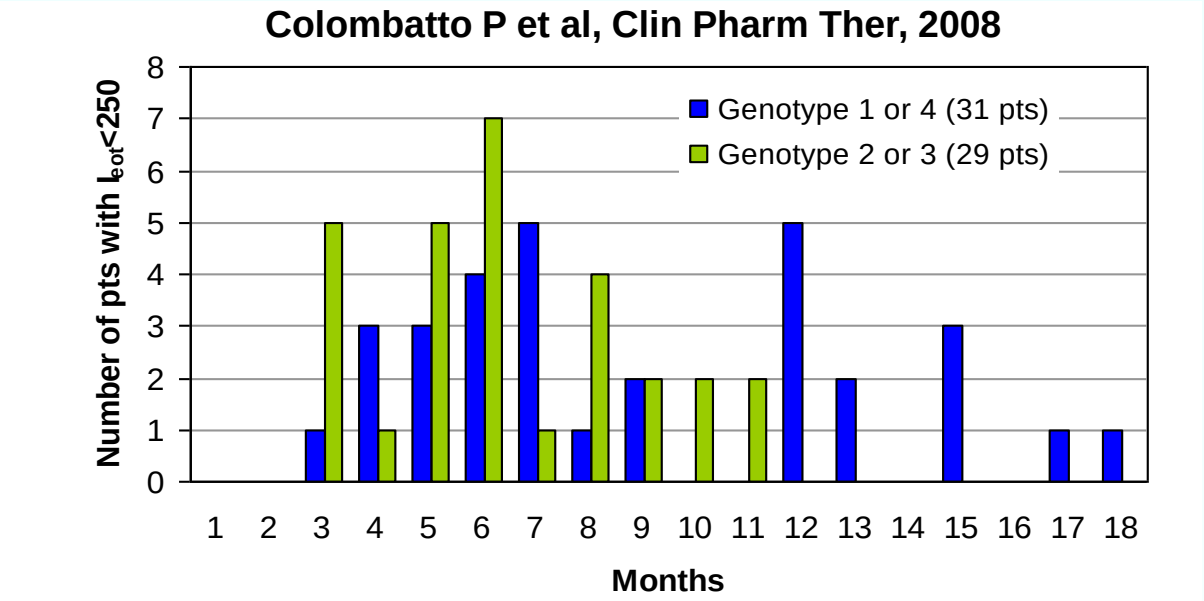




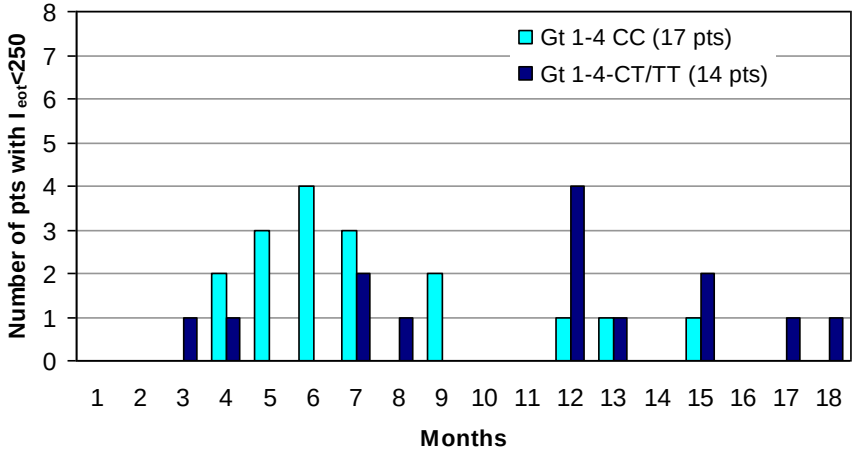
Patients with IL28B-CC pts had:

- higher block of viral replication (**ε**: 0.9264 vs 0.8142, p=0.006)
- faster 2nd phase HCV-RNA declines (π: 0.2829 vs 0.1626 days^{-1}; p< 0.001)
- faster infected cell declines computed by ALT (δ: 0.1238 vs 0.0816 days^{-1}; p=0.002).

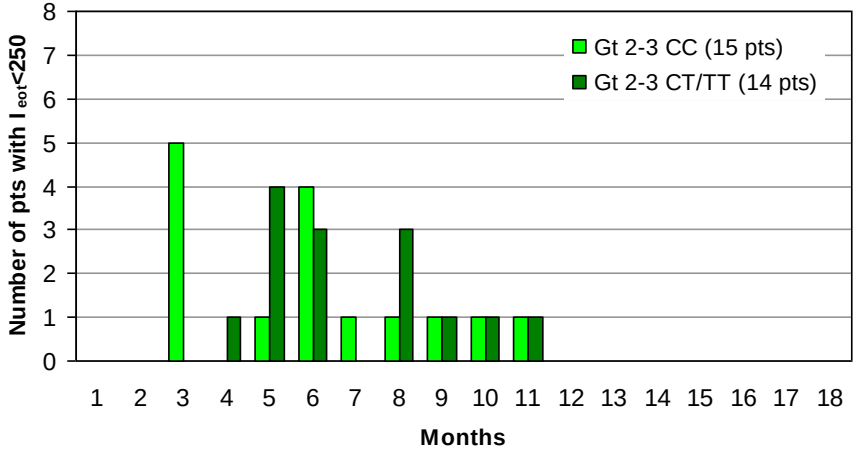
Model computed treatment duration to reach I_{eot}<250



Genotype 1 or 4

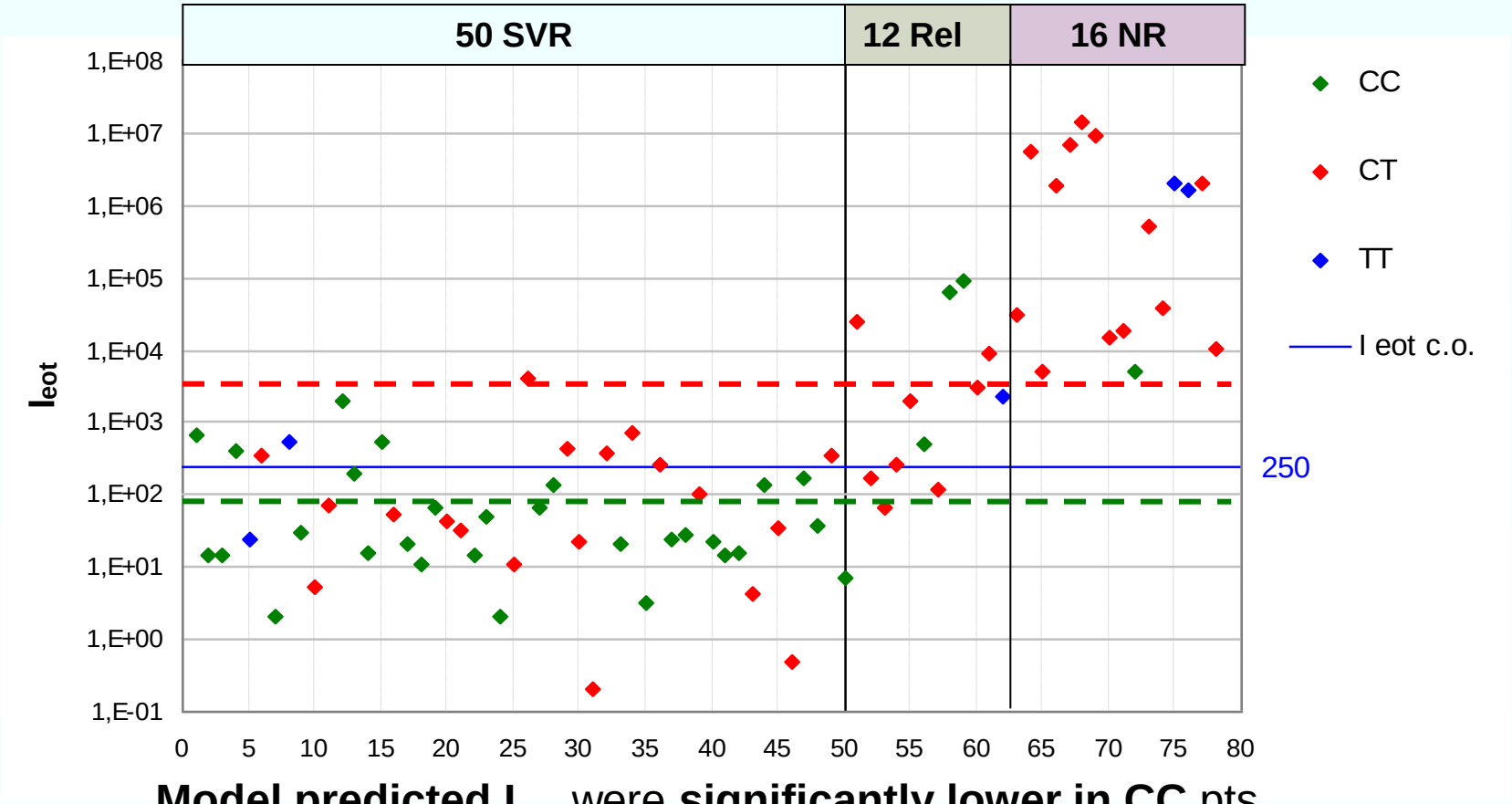


Genotype 2 or 3



Ieot

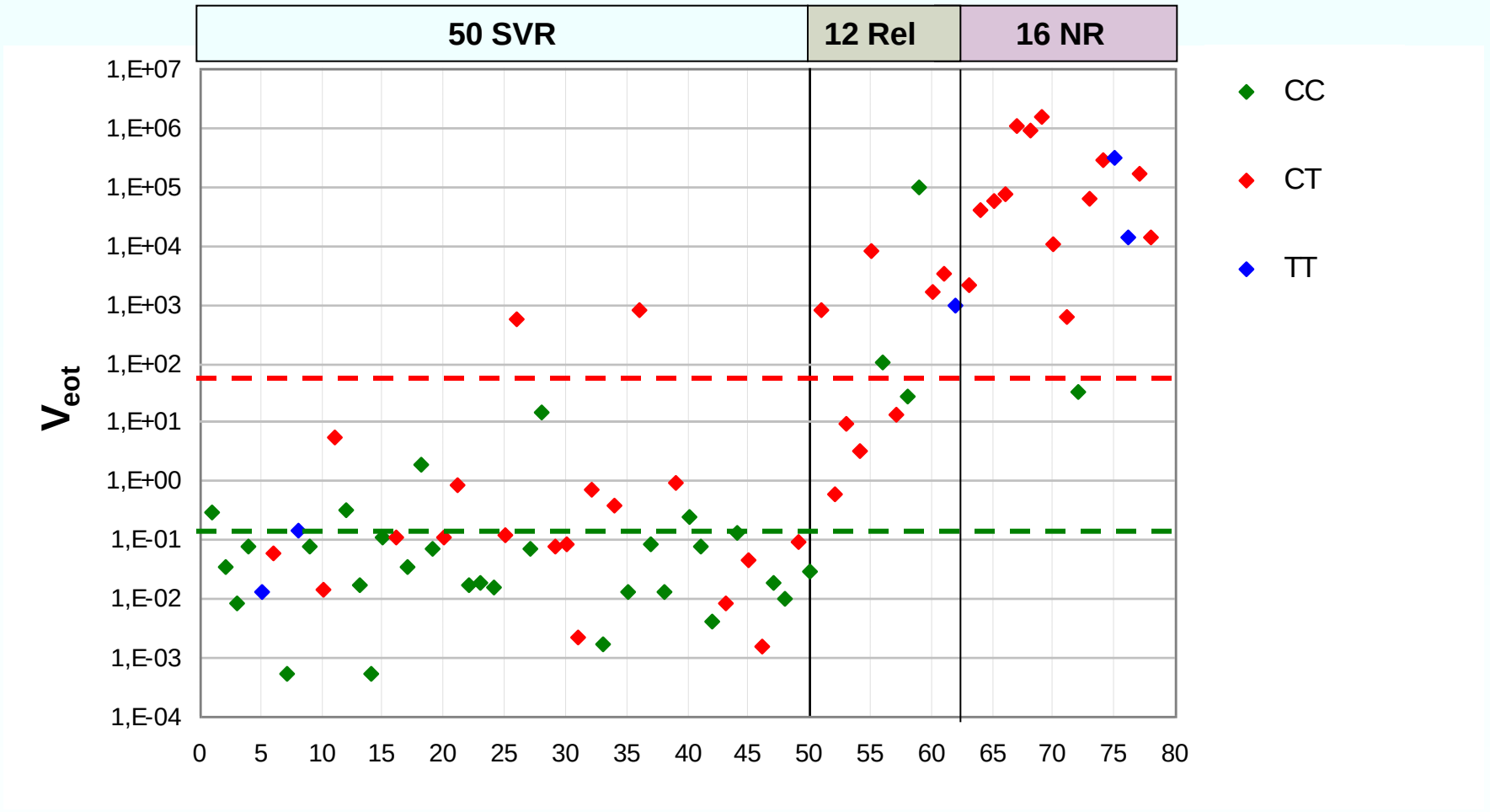
Residual number of infected cells at the end of treatment (I_{eot}) computed by the model in the 78 patients according to treatment outcome and IL28B genotype



Model predicted I_{eot} were **significantly lower in CC** pts (Log I_{eot}: **1.87** vs **3.27**; p=0.001).

Veot

Also **residual Viral load (V_{eot}) computed by the model was lower in CC pts** (Log V_{eot}: **-0.95** vs **1.69**; p< 0.001) and independently correlated with SVR at multivatiate analysis.



Prediction of SVR by HCV genotype, IL28B genotype and model parameters

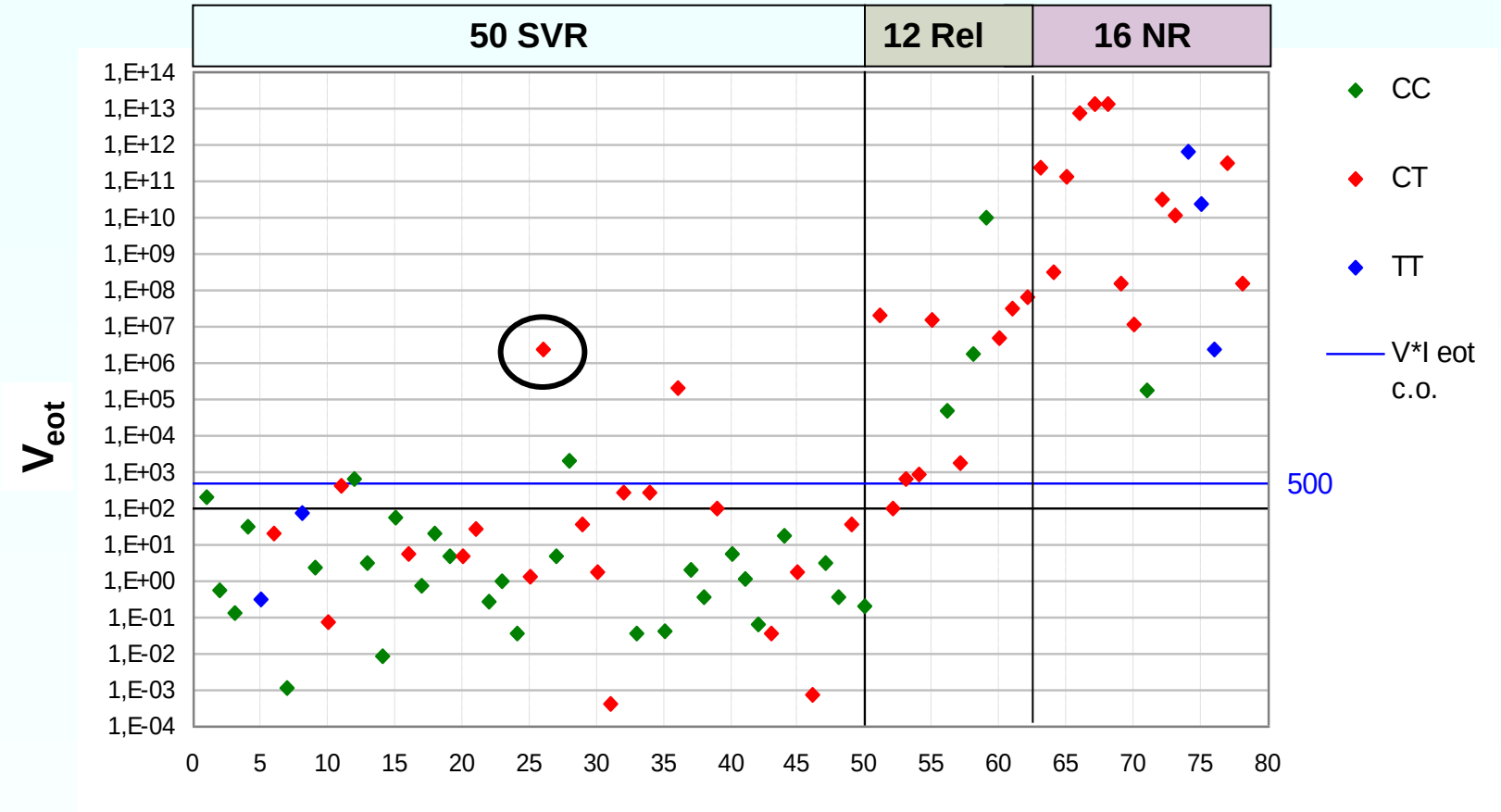
Pts	Predictor of SVR	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
78	IL28B-CC	58.0%	85.7%	87.9%	53.3%	67.9%
78	HCV Gen. 2 or 3	56.0%	92.9%	93.3%	54.2%	69.2%
78	RVR	60.0%	100%	100%	94.4%	74.4%
33	**IL28B-CC and Ieot<500**	100%	100%	**100%**	100%	**100%**
45	**IL28B-CT/TT and Ieot<1000**	95.2%	83.3%	**83.3%**	95.2%	**88.9%**
33	**IL28B-CC and Veot<5**	96.6%	100%	**100%**	80.0%	**97.0%**
45	**IL28B-CT/TT and Veot<1**	86.4%	95.8%	**95.0%**	88.5%	**91.3%**
78	**Ieot*Veot < 500**	92.0%	96.4%	**97.9%**	87.1%	**93.6%**

In 100 treated pts, the outcome is mispredicted by:

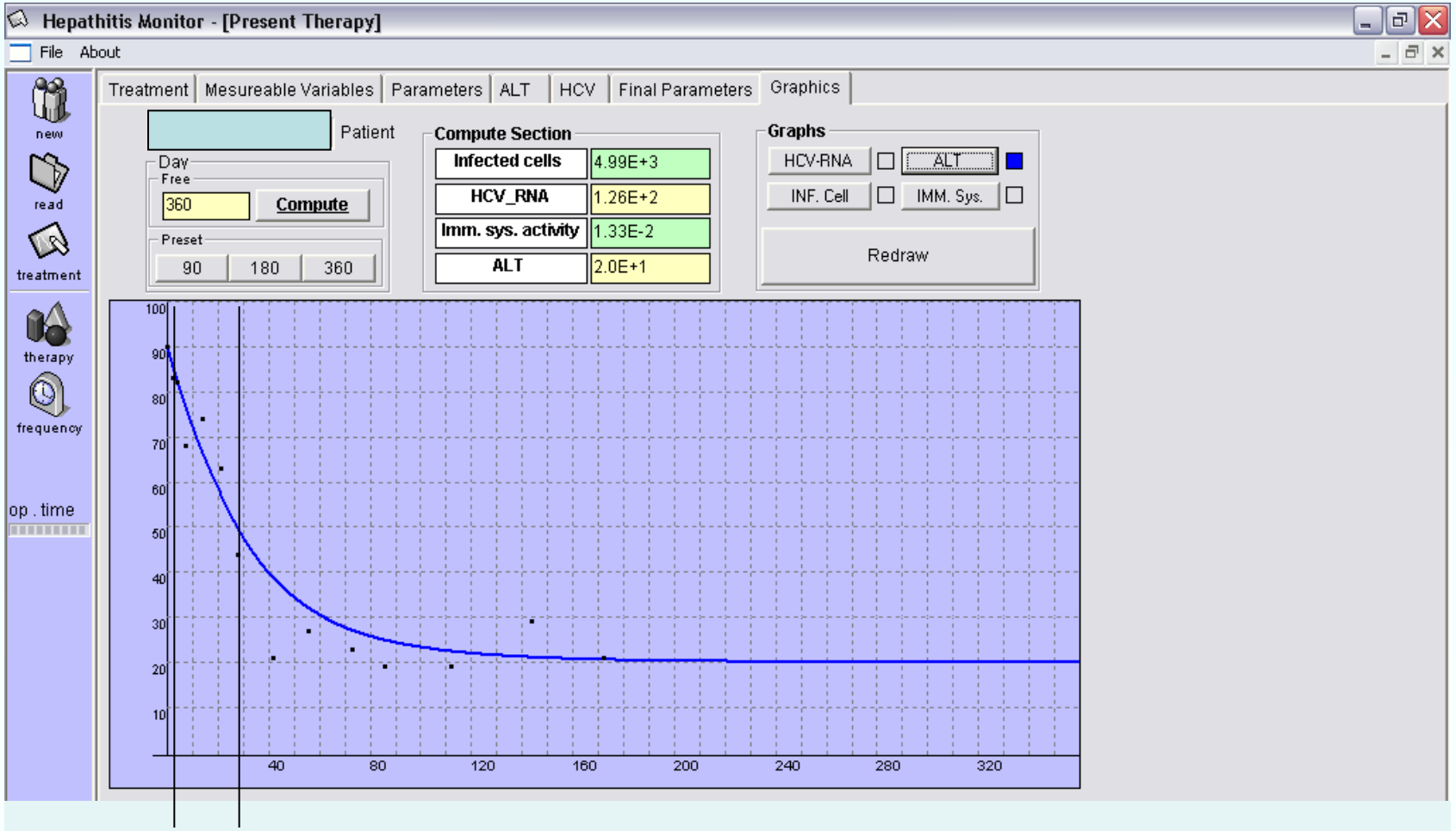
- **Ieot*Veot in: 6**

- **IL28B – HCV gt - RVR in: 26-32**

Ieot*Veot


50 SVR
12 Rel
16 NR
1,E+14
1,E+13
1,E+12
1,E+11
1,E+10
1,E+09
1,E+08
1,E+07
1,E+06
1,E+05
1,E+04
1,E+03
1,E+02
1,E+01
1,E+00
1,E-01
1,E-02
1,E-03
1,E-04
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
500
CC
CT
TT
V*I eot c.o.
Veot

Model misprediction of SVR

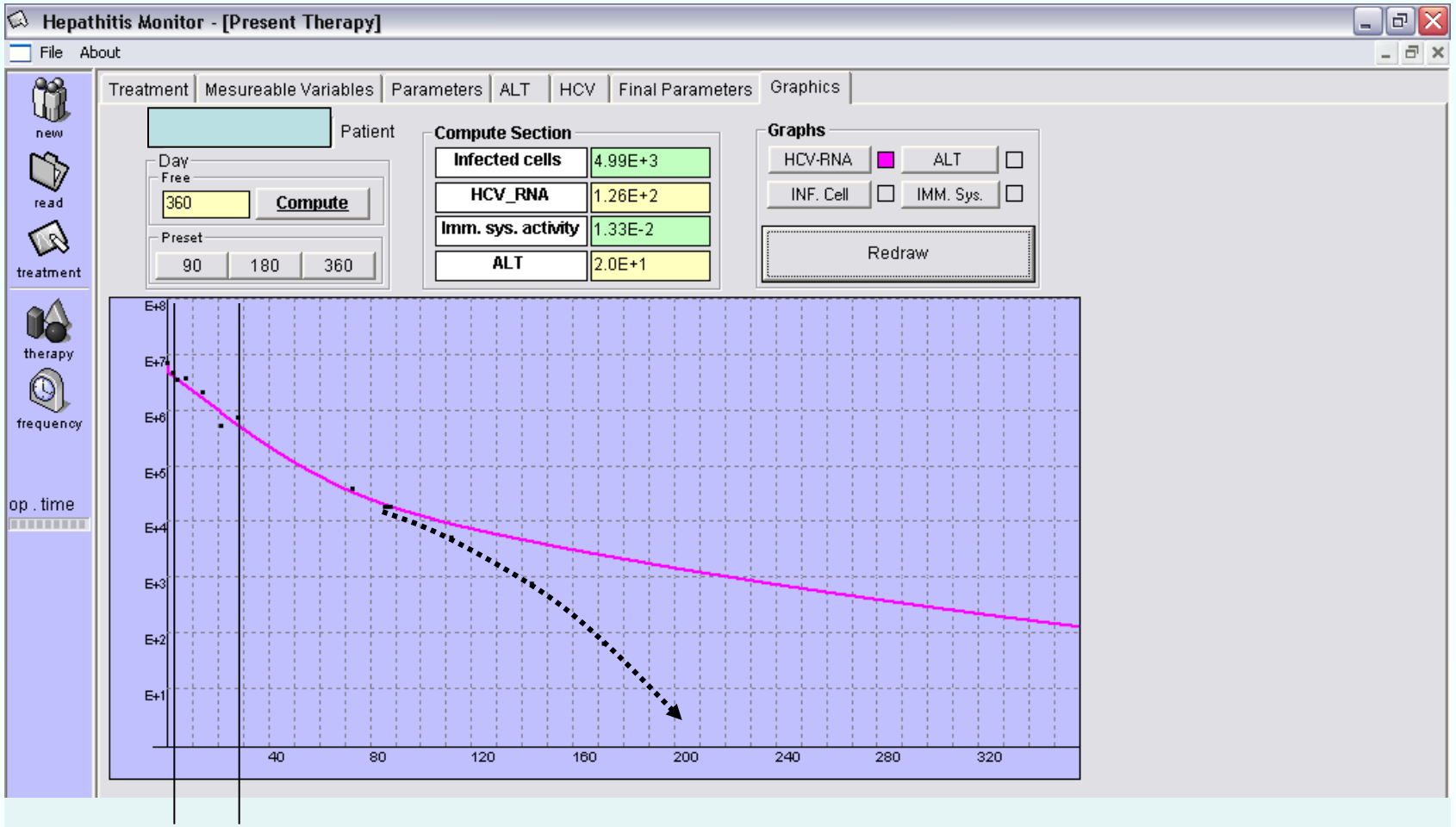


fitting window

prediction

ALT kinetics

Model misprediction of SVR

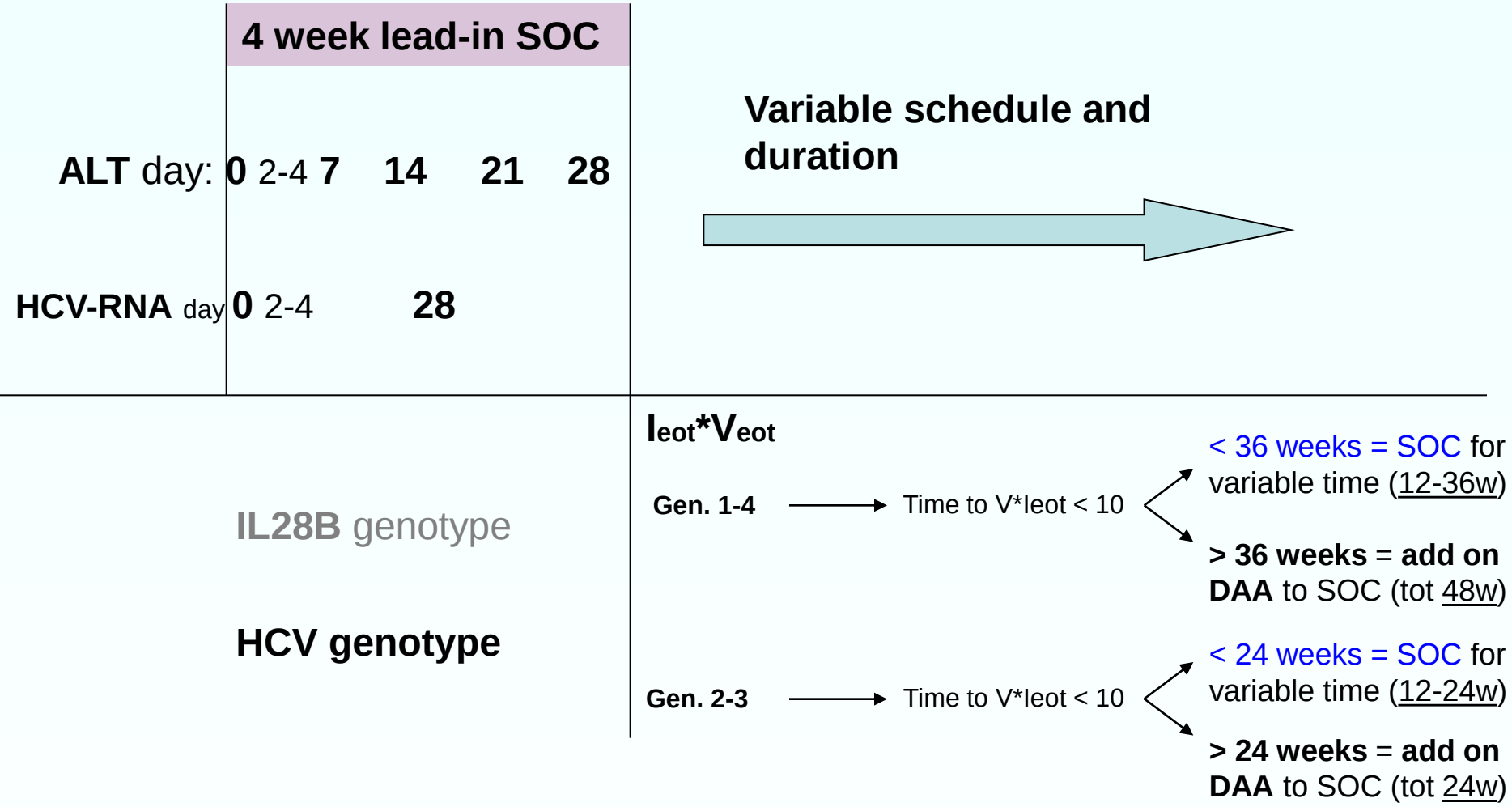


fitting window

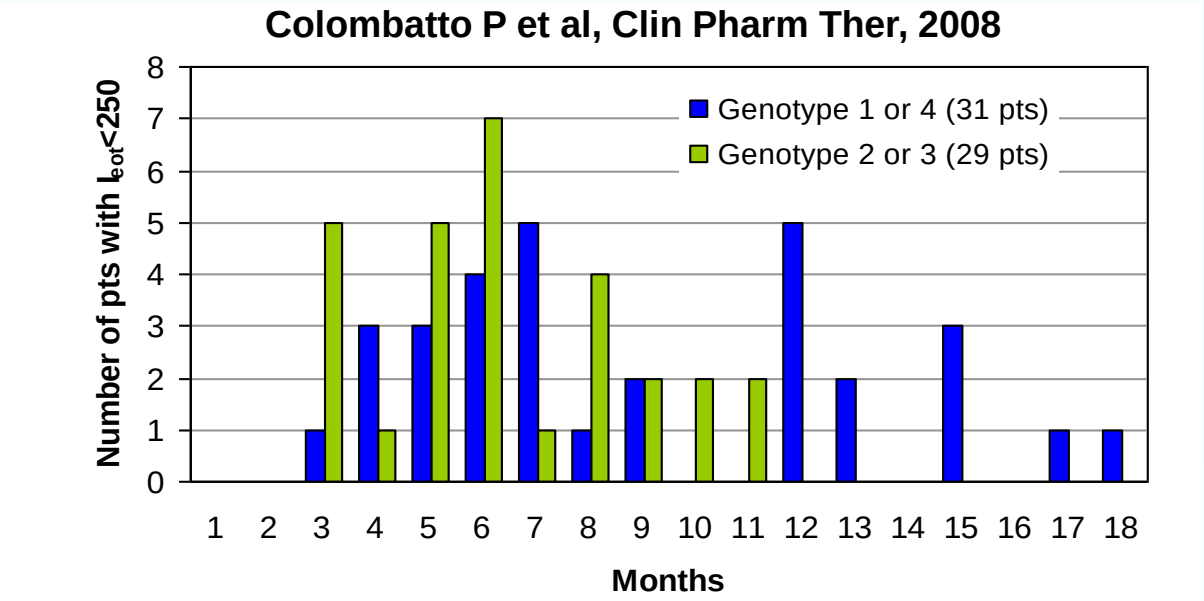
prediction

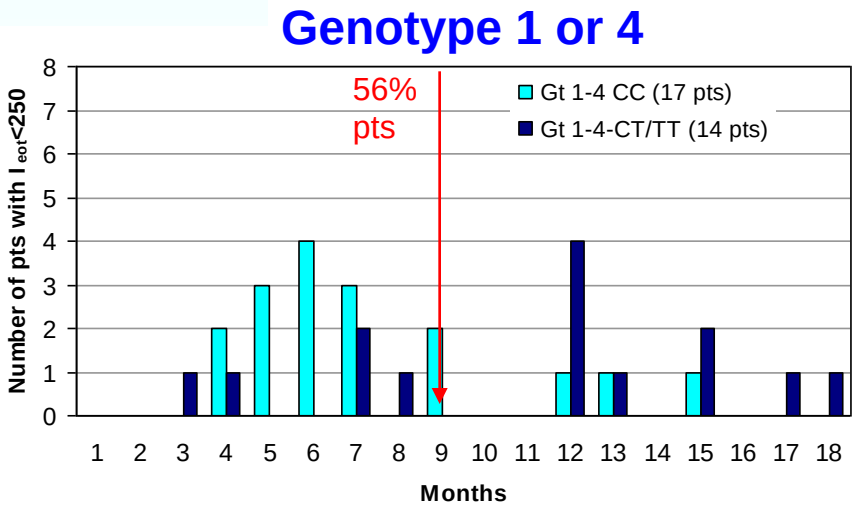
HCV RNA kinetics

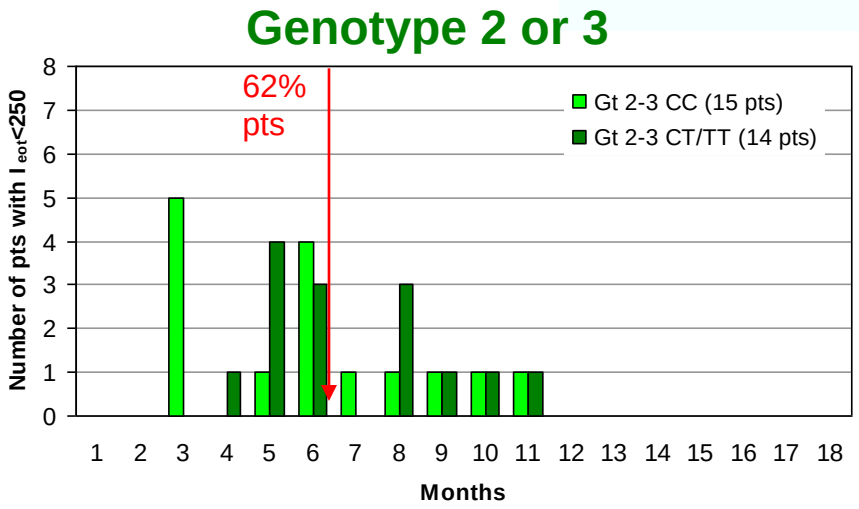
Proposal of individualized HCV therapy management in the era of the new DAAs



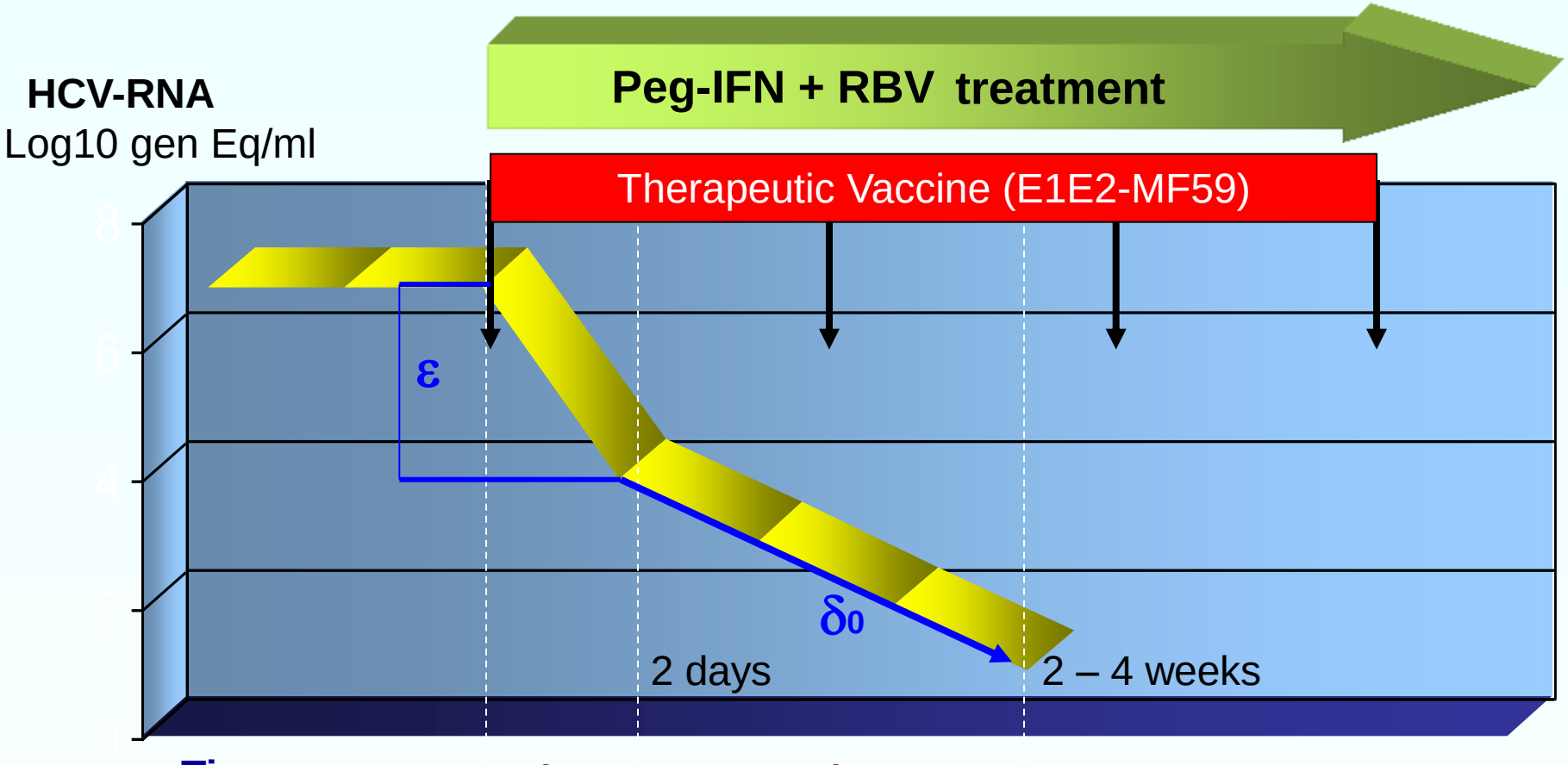
Model computed treatment duration to reach I_{eot}<250





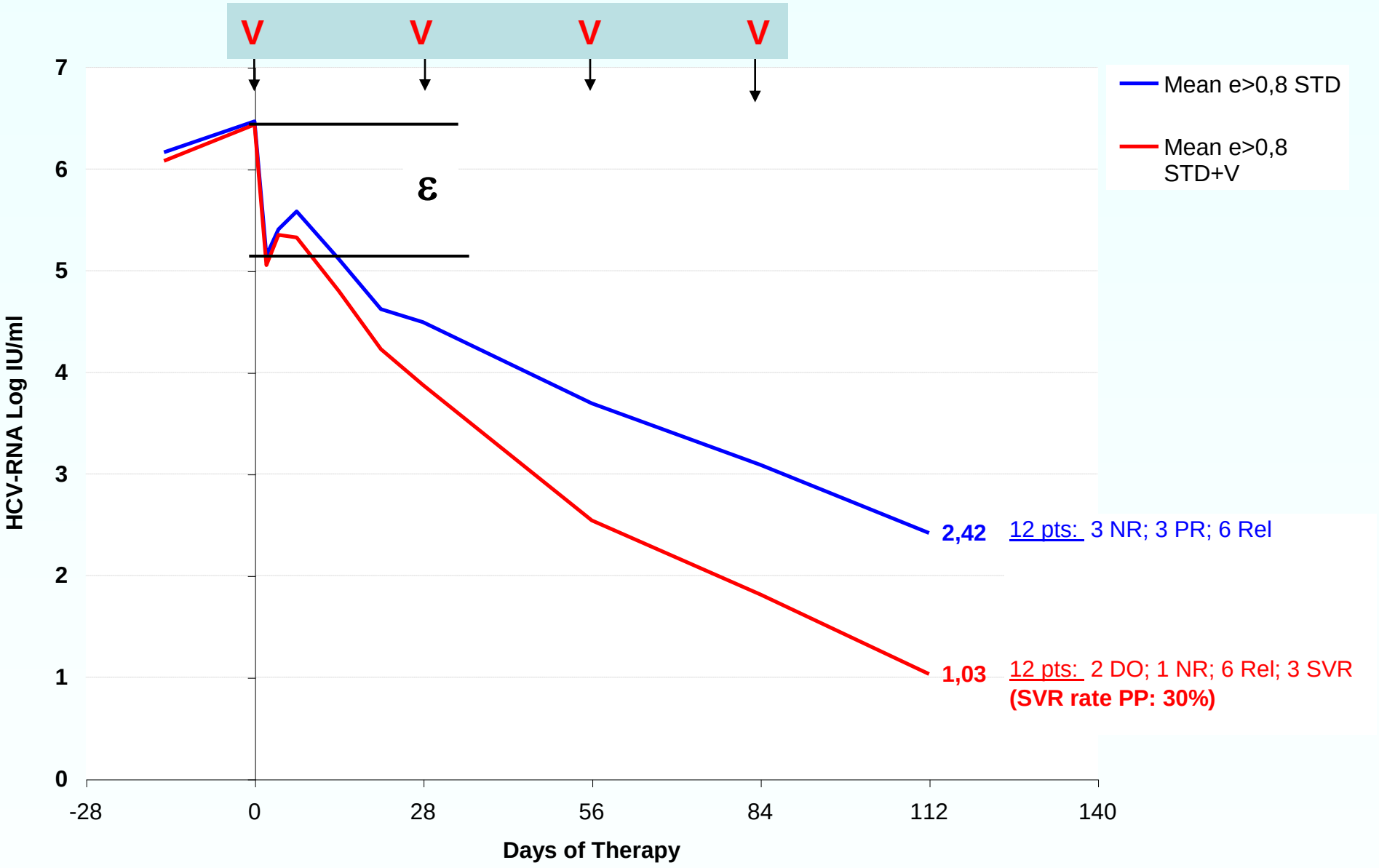


Boosting anti-HCV immune response by combining SOC and Therapeutic Vaccines



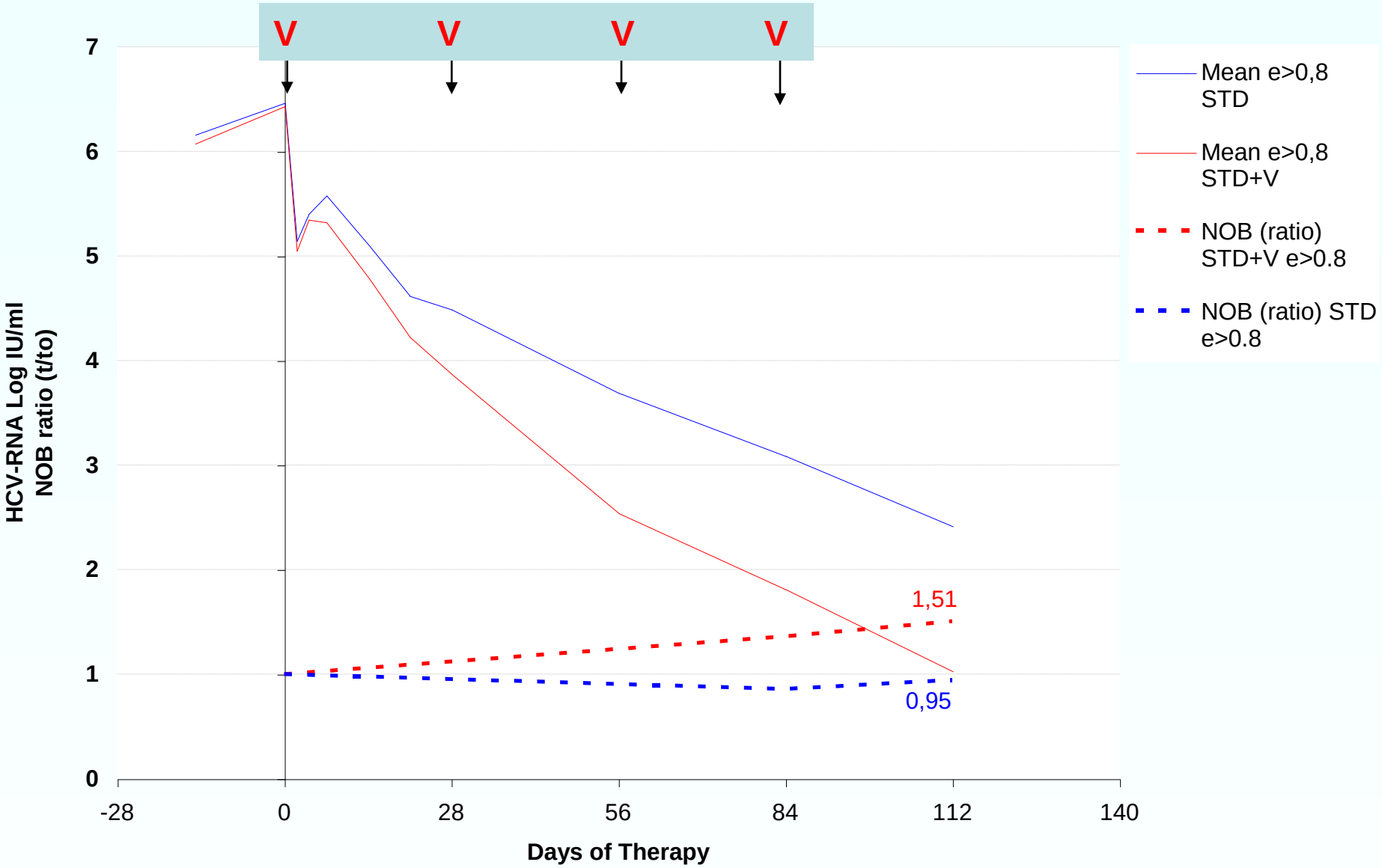
Colombatto et al., ISVHLD Washington 2009 (manuscript in preparation)

Viral dynamics: 2nd phase HCV-RNA decline in patients with ε > 0.8

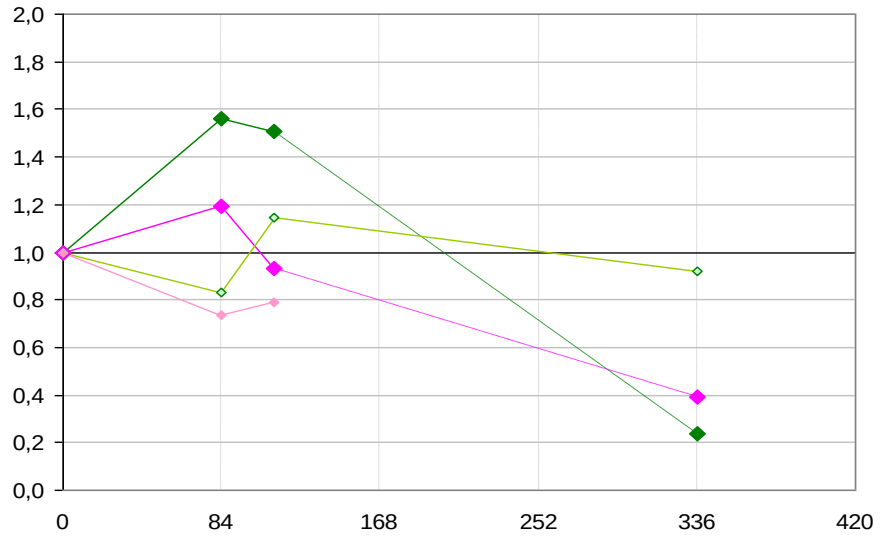


Immunology: Neutralizing Ab (NOB) and viral load decline

NOB titer and Viral Load kinetics in patients with ε >0.8

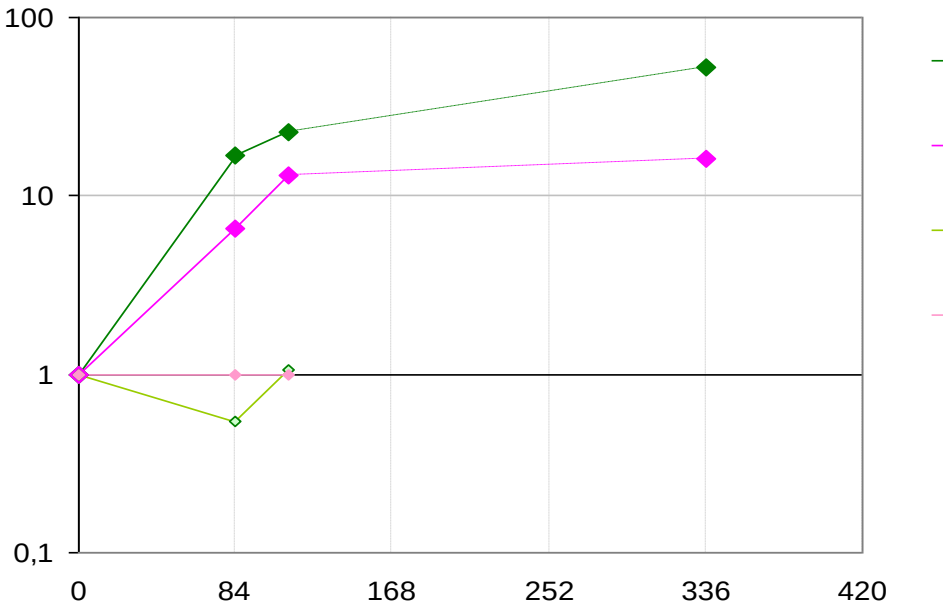


Neutralizing Ab (NOB) and Lymphocyte Proliferation Assay (LPA) changes in SVR and REL during SOC or SOC+V



NOB Titer

(ratio to baseline)



LPA index

CONCLUSIONS

- an **accurate definition by mathematical modelling of treatment duration at the single patient level is feasible in clinical practice** showing that the duration to achieve SVR is a continuous variable with wide individual differences

- Tailoring treatment to Ieot<250 showed **SVR rates comparable** to standard treatment (85% vs 82%) with a **significant reduction of non-effective and non appropriate treatments**.

- Treatment **duration required to reach these I_{eot}/V_{eot} thresholds** that warrant an high chance of SVR is **influenced by HCV genotype** and **IL28B polymorphism**, but retains a wide range of individual variability.

- **In the facing era of the new antivirals model-computed parameters (week 4) will help to optimize treatment strategy and duration at the single patient level**

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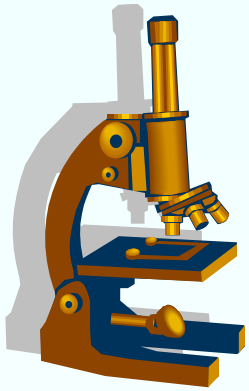

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