Modeling Kinetics of HBV Infection and Recommendations for Moving Forward

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HBV Models

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Medical Sciences

Viral dynamics in hepatitis B virus infection

(lamivudine/antiviral treatment/liver/viral turnover/mathematical model)

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Biphasic Clearance Kinetics of Hepatitis B Virus From Patients During Adefovir Dipivoxil Therapy

Hepatology 1999

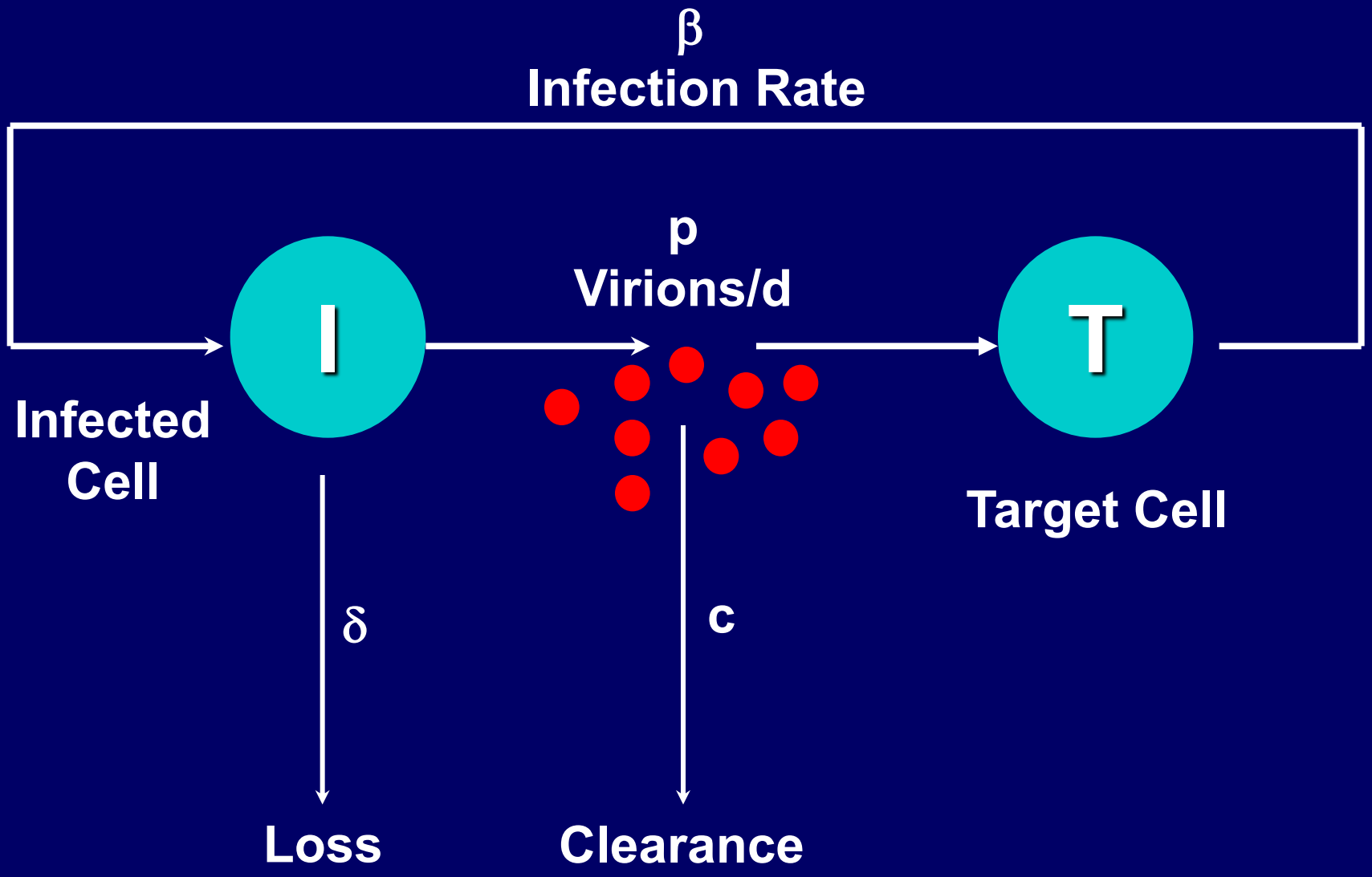
MANUEL TSIANG, JAMES F. ROONEY, JOHN J. TOOLE, AND CRAIG S. GIBBS

Tsiang model similar to HCV model, Science 1998

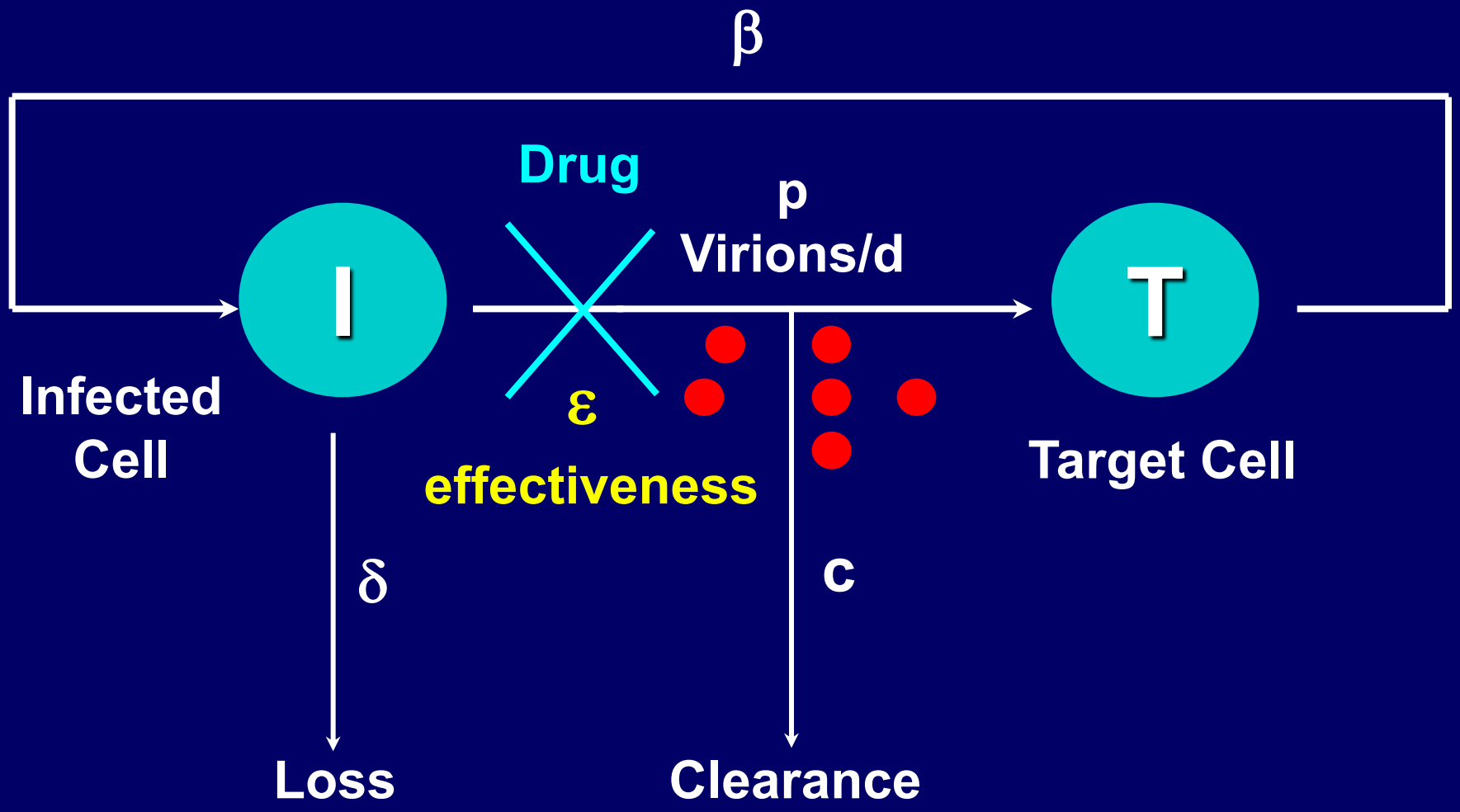
Hepatitis C Viral Dynamics in Vivo and the Antiviral Efficacy of Interferon-α Therapy

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

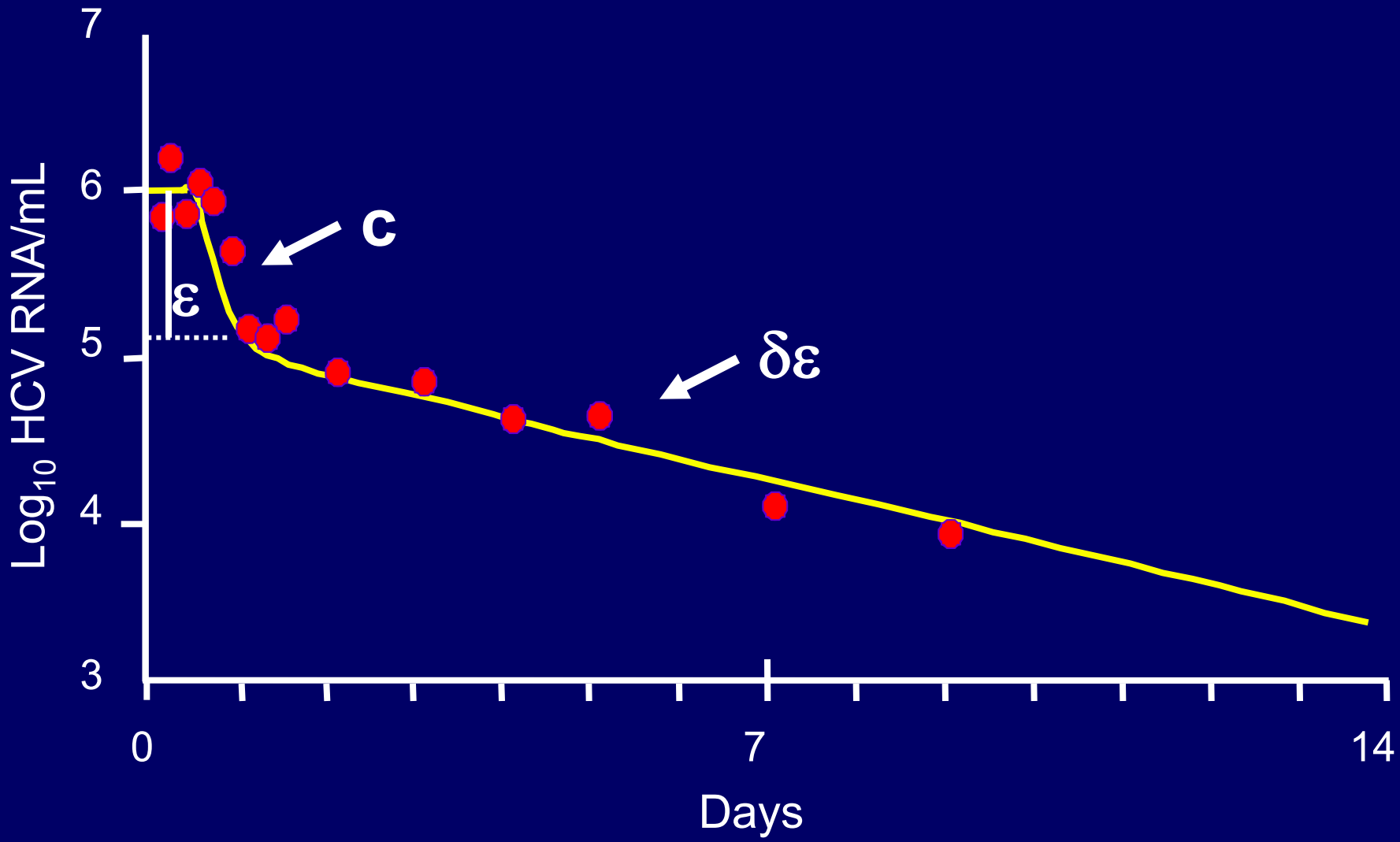
Model of Viral Infection



Drug (e.g. IFN, Adefovir) Partially Blocks Viral Production

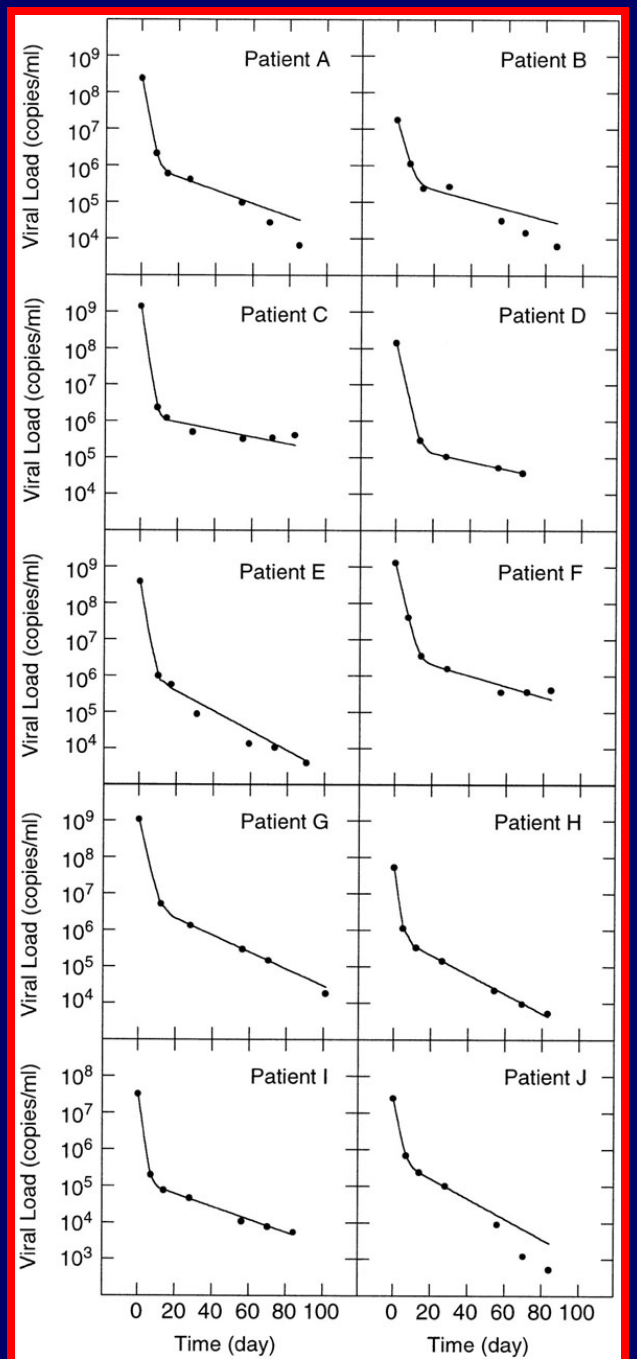


15 MU IFN-α



Neumann Perelson Science 1998

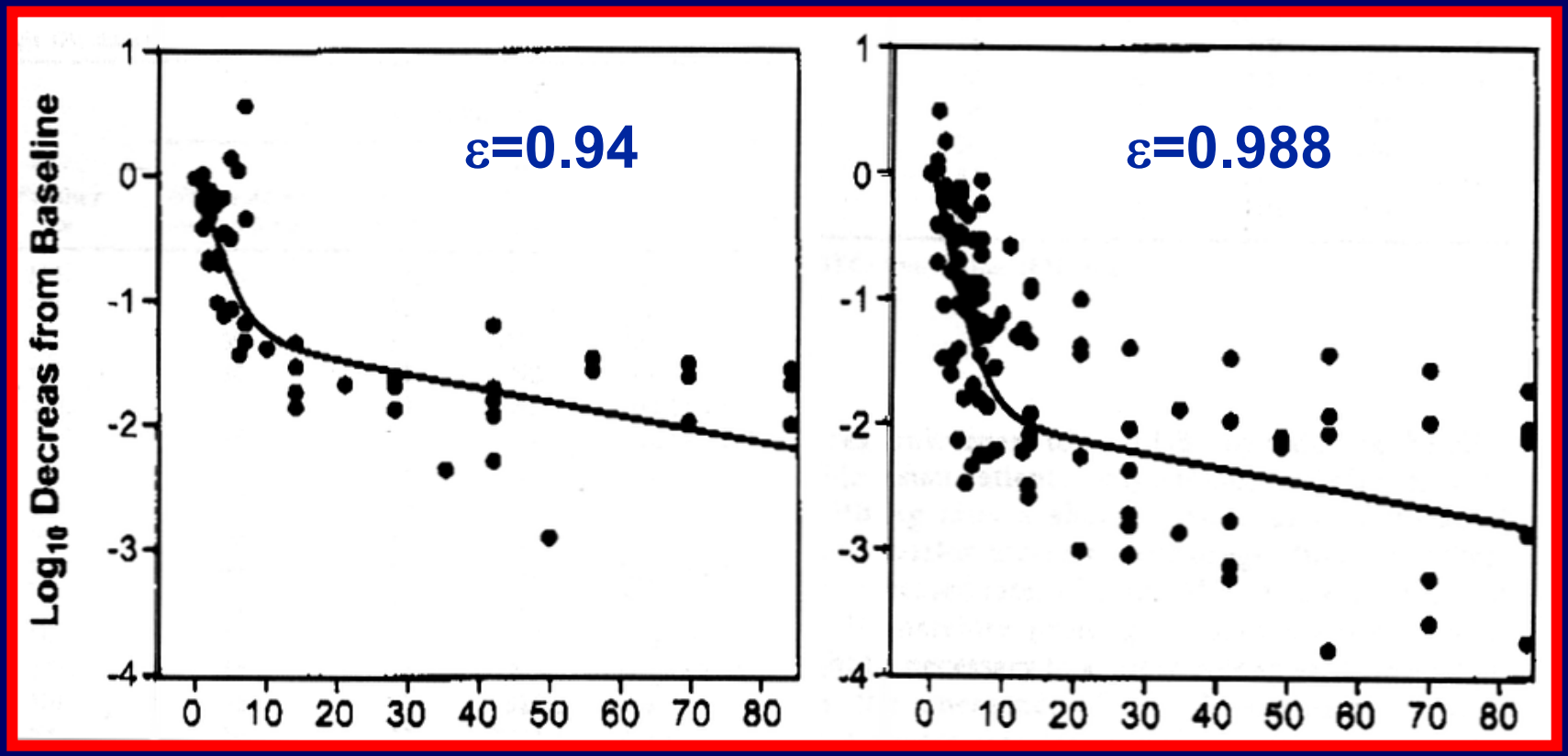
Biphasic Decay of HBV DNA with Adefovir Treatment



Tsiang et al.

Hepatology *29:1863* 1999

Enhanced efficacy of lamivudine/famciclovir compared with lamivudine alone

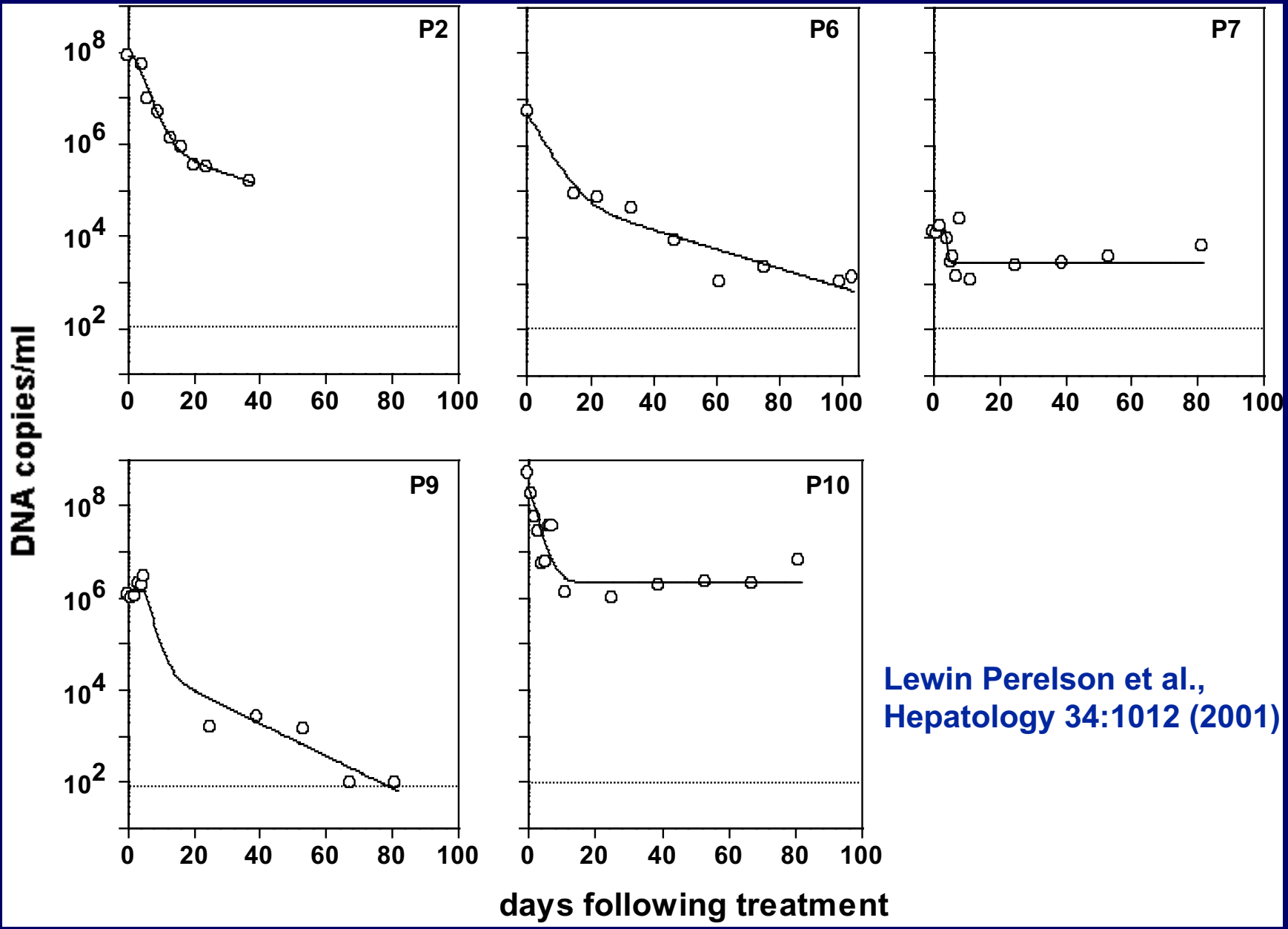


lamivudine

lamivudine/famciclovir

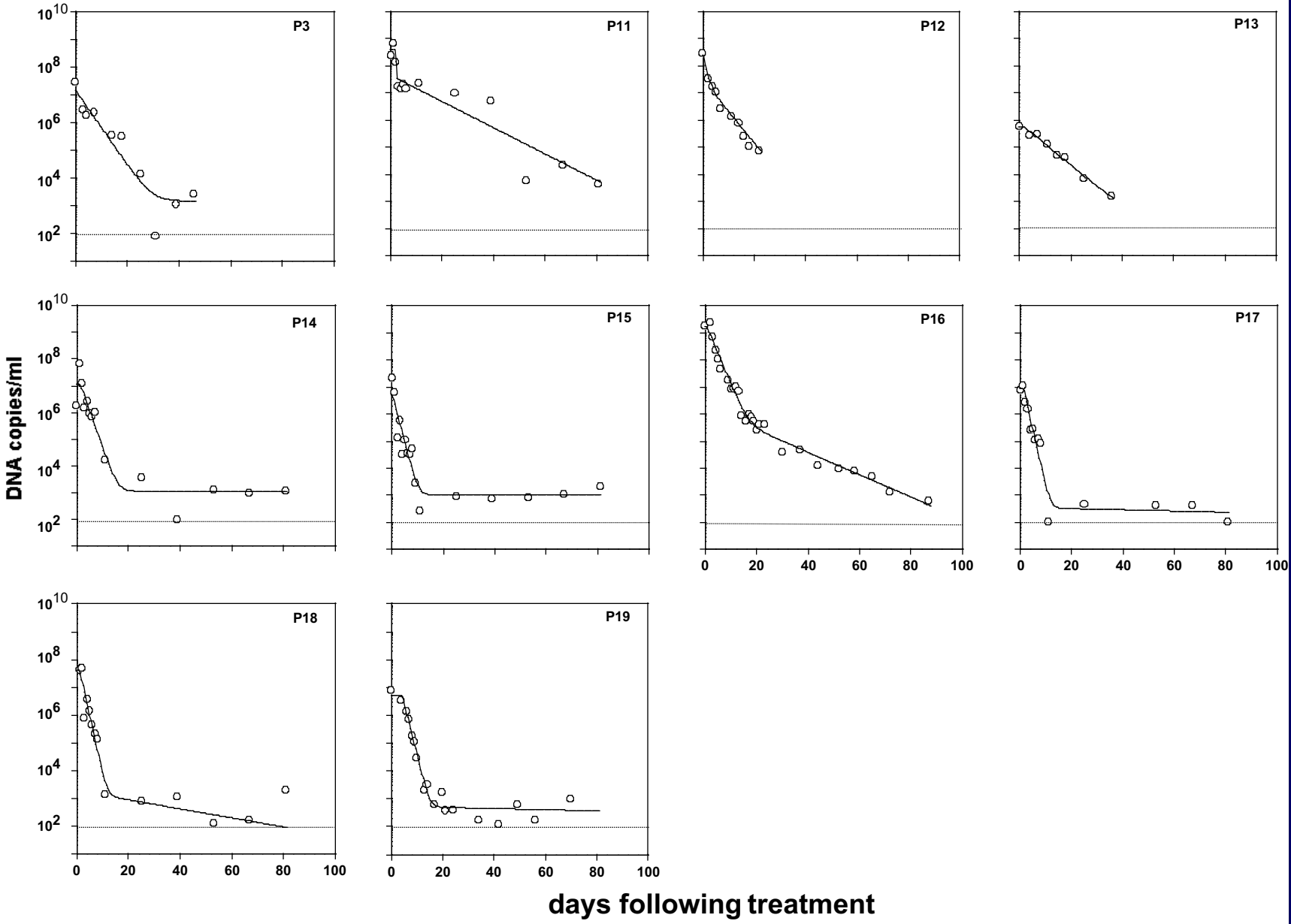
Lau et al. Hepatology, 2000

LMV Treatment



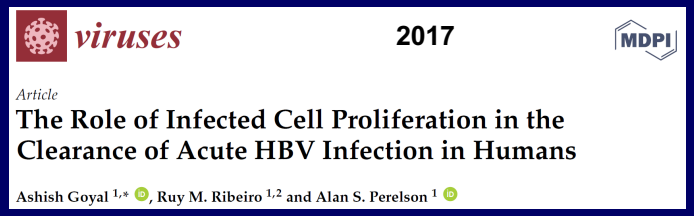
Lewin Perelson et al.,
Hepatology 34:1012 (2001)

LMV/FCV Treatment

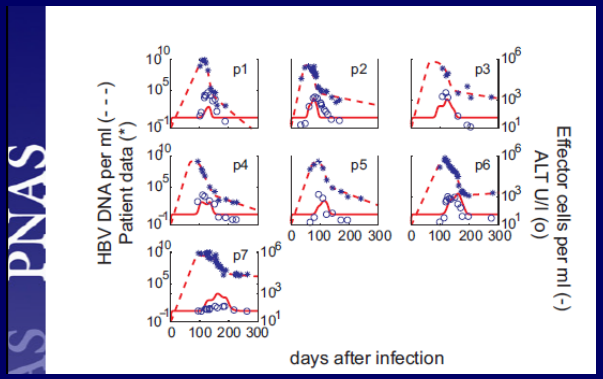


Expanded Models

- Include cell proliferation
- Include cccDNA and dilution or loss upon cell division



- Include immune responses (Ab or cell-mediated)

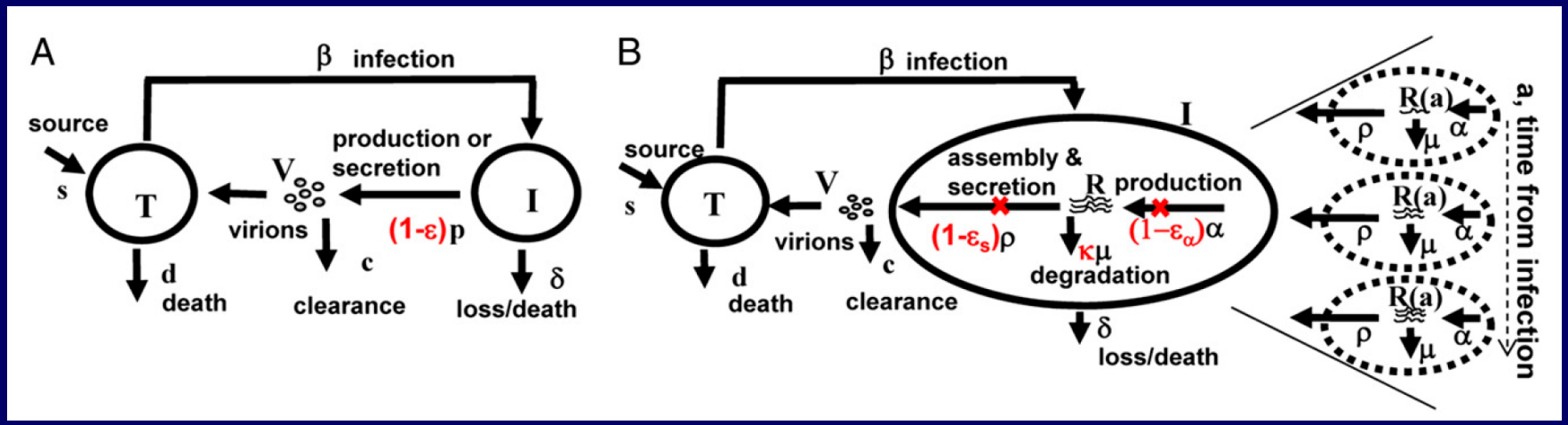


What should we do now in age of new agents and cure research?

Ciupe Perelson et al PNAS 2007

For HCV – New Models

- In order to understand the mode of action of direct acting antivirals – DAAs – new multiscale models were needed.



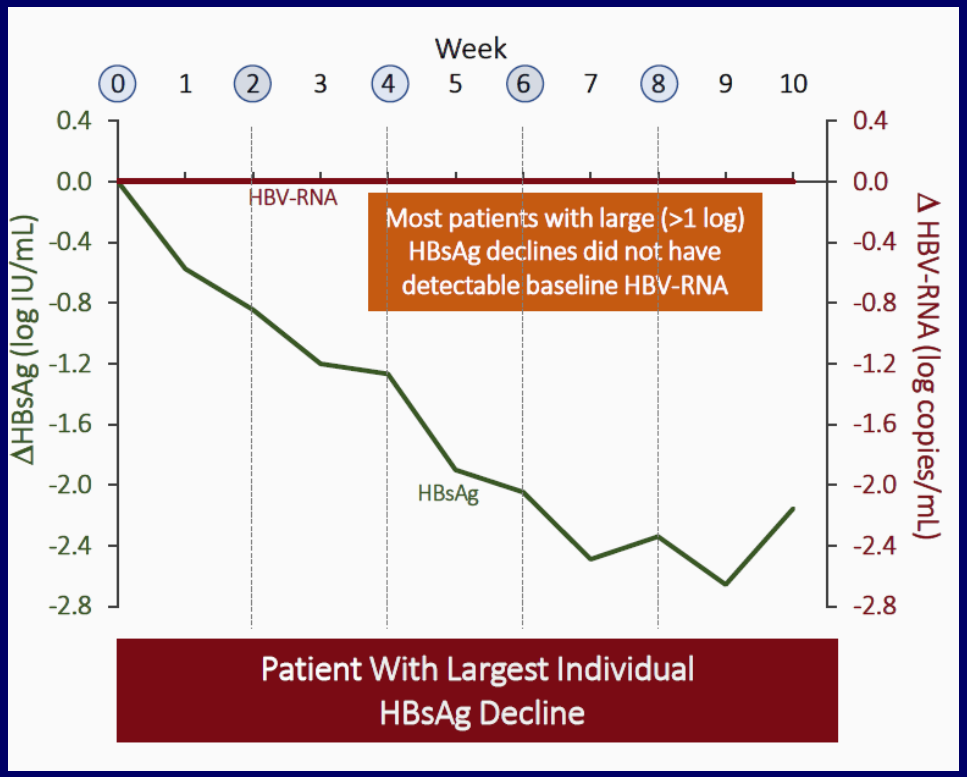
Standard model **Multiscale model**

Such models should be applicable to HBV infection

siRNA with lipid nanoparticle delivery

HBcrAg, HBV-RNA Declines in A Phase 2a Study Evaluating the Multi-Dose Activity of ARB-1467 in HBeAg-Positive and Negative Virally Suppressed Patients With Hepatitis B AASLD 2017

Kosh Agarwal[1], Ed Gane[2], Wendy Cheng[3], William Sievert[4], Stuart Roberts[5], Sang Hoon Ahn[6], Yoon Jun Kim[7], Adrian Streinu-Cercel[8], Jill Denning[9], William Symonds[9], Patricia Mendez[9]



HbsAg decline is linear for the first 7 wks and leads to a 2.4 log decline. Since HbsAg is produced by infected cells, if we assume this loss reflects the loss of residual infected cells in this HBV DNA- pt, then the loss rate of infected cells, δ = 0.11 /day (t1/2 = 6.1 days).

This is similar to the estimated death rate of HCV infected cells, δ = 0.14 /day (t1/2 = 6.3 days), Neumann Science 1998. If we estimate number of infected cells we can calculate time to cure under this drug regime if decline can be sustained. ALT data could help establish if this decline is due to loss of infected cells.

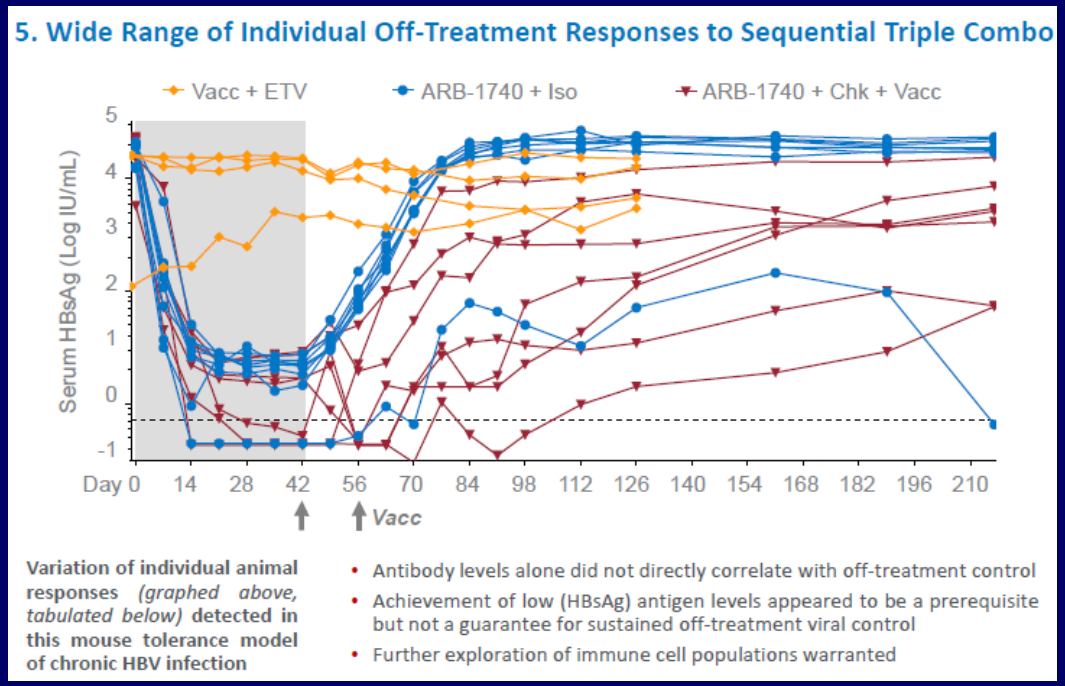
If drug is ~ 100% effective decline could reflect clearance of HbsAg but t1/2 seems very long for an antigen.

After wk 7 decay slows – maybe 2 phase decline like that of HBV DNA with Mycludex B, which would lengthen time to cure.

Patient on nucleos(t)ide therapy, HBV DNA negative

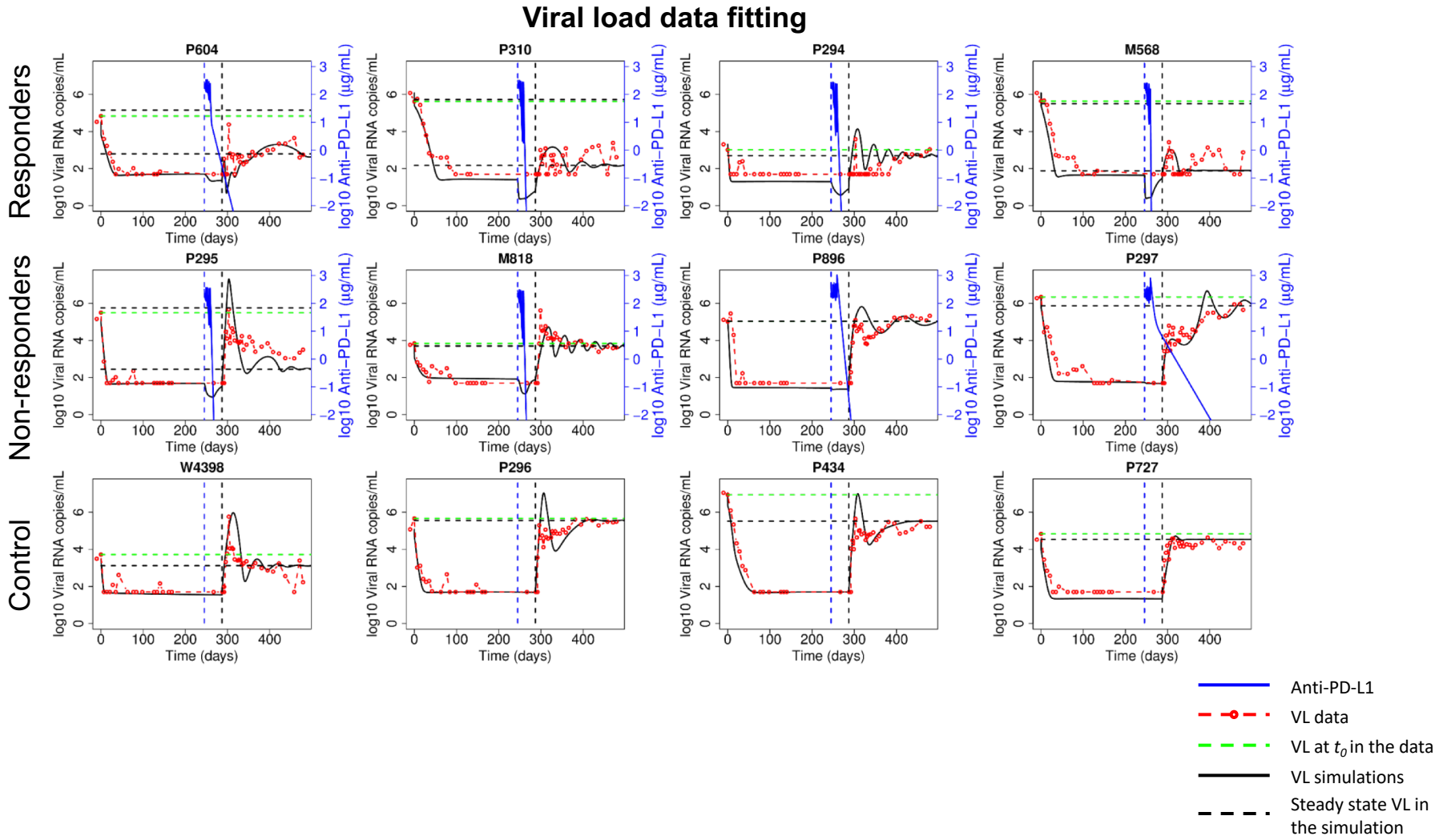
In Vivo Study of a LNP siRNA Investigational Agent Applied Sequentially with Immunomodulatory Treatments for Chronic Hepatitis B Infection

AASLD 2017

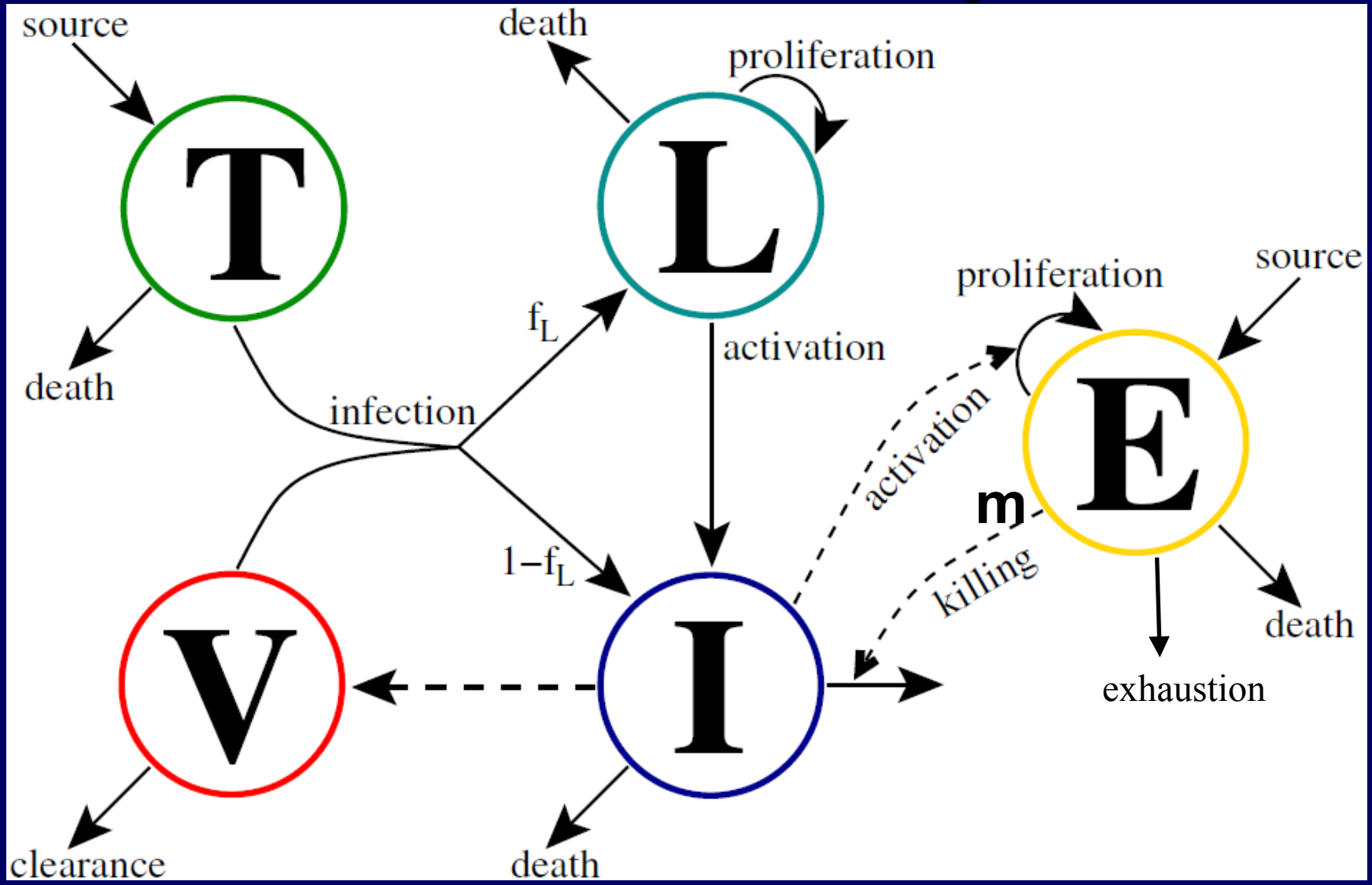


In AAV mouse model of chronic HBV, after therapy with siRNA, anti-PDL1 and Energix B vaccine, HBV DNA does not go back to baseline in most vaccinated animals (red).

We have seen the same thing in HIV/SIV infection and have an explanation.


Viral load data fitting
Responders
Non-responders
Control
P604
P310
P294
M568
P295
M818
P896
P297
W4398
P296
P434
P727
log10 Viral RNA copies/mL
log10 Anti−PD−L1 (μg/mL)
Time (days)
Anti-PD-L1
VL data
VL at t_0 in the data
VL simulations
Steady state VL in the simulation

Model with 2 set-points



Conway and Perelson Post-treatment control of HIV, PNAS 2015

Recommendations for Moving Forward with New Therapies

- Need to monitor baseline viral load to see if at steady state
- Would be informative to measure cccDNA, level of infected cells and biomarkers (ALT, HbsAg, HbeAg), proliferation of cells (Ki67, PCNA), immune responses (tetramer + CD8 cells, ICS) – but difficult due to biopsy limitations; could use humanized mice or animal models
- Develop multiscale models that allow multiple effects of single drugs and combinations.
- These models may need to take into account cccDNA content of infected cells as rate of HBV, HBsAg and HbeAg production may depend on cccDNA level.
- Models also need to allow for infected cell proliferation and its effect on cccDNA.
- Need to develop better models of the immune system's interaction with HBV as it is important for cure, to explain ALT flares and the effects of immunotherapy.