

# **Insights into the Impact of HBV and HCV Viral Dynamics on Antiviral Therapy**

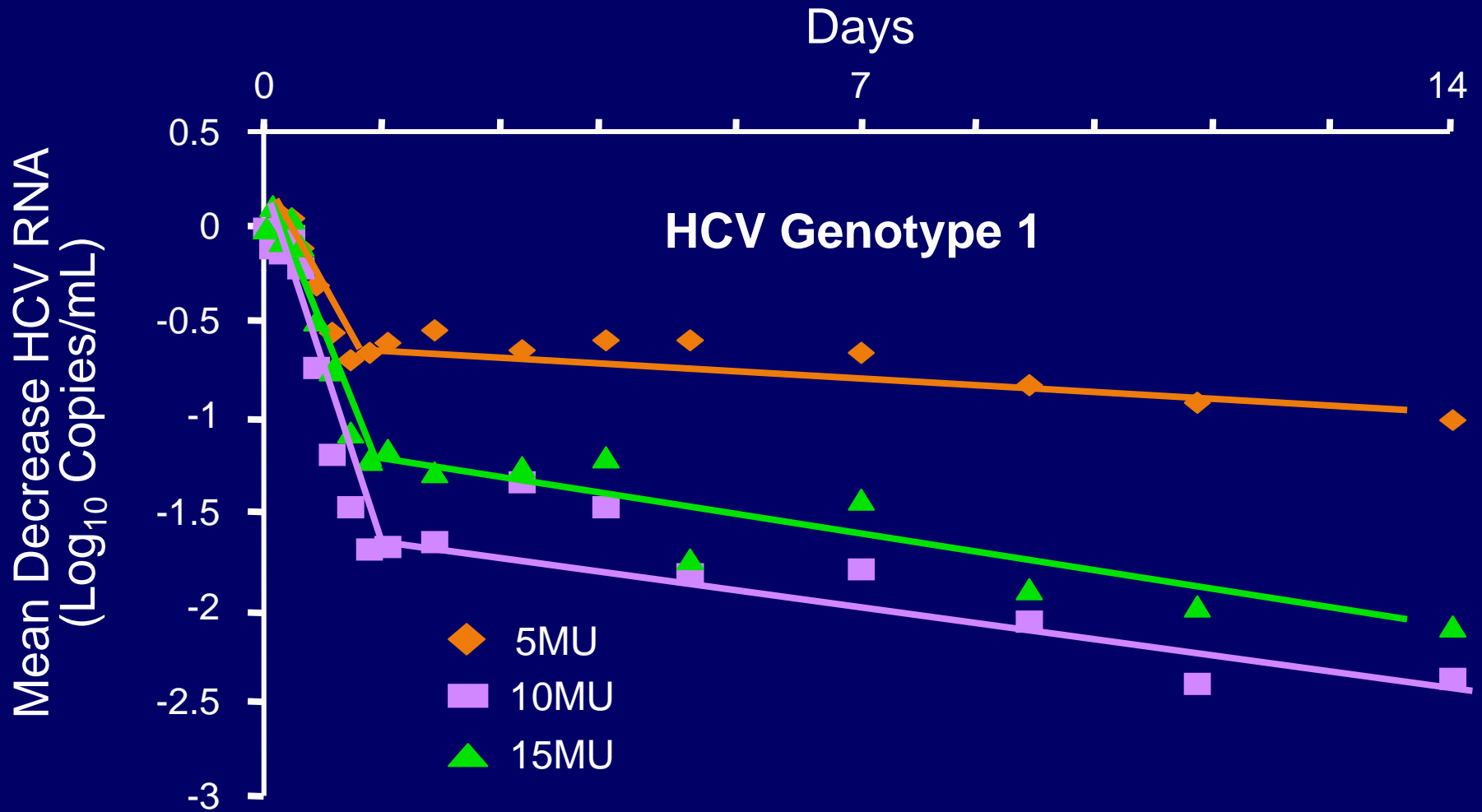
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# With QD IFN- $\alpha$ treatment HCV RNA typically has biphasic decline



Lam N. DDW. 1998 (abstract L0346).

# First phase: Blocking production

- Let  $\varepsilon$  = *effectiveness* of IFN in blocking production of virus
  - $\varepsilon = 1$  is 100% effectiveness
  - $\varepsilon = 0$  is 0% effectiveness
- $dV/dt = (1 - \varepsilon)pl - cV$

## Second Phase: Loss of infected cells

- Cells with reduced HCV RNA production are ultimately lost, either through death or cessation of viral production.
- From the “second phase” decay slope we can estimate the rate of infected cell loss,  $\delta$ .

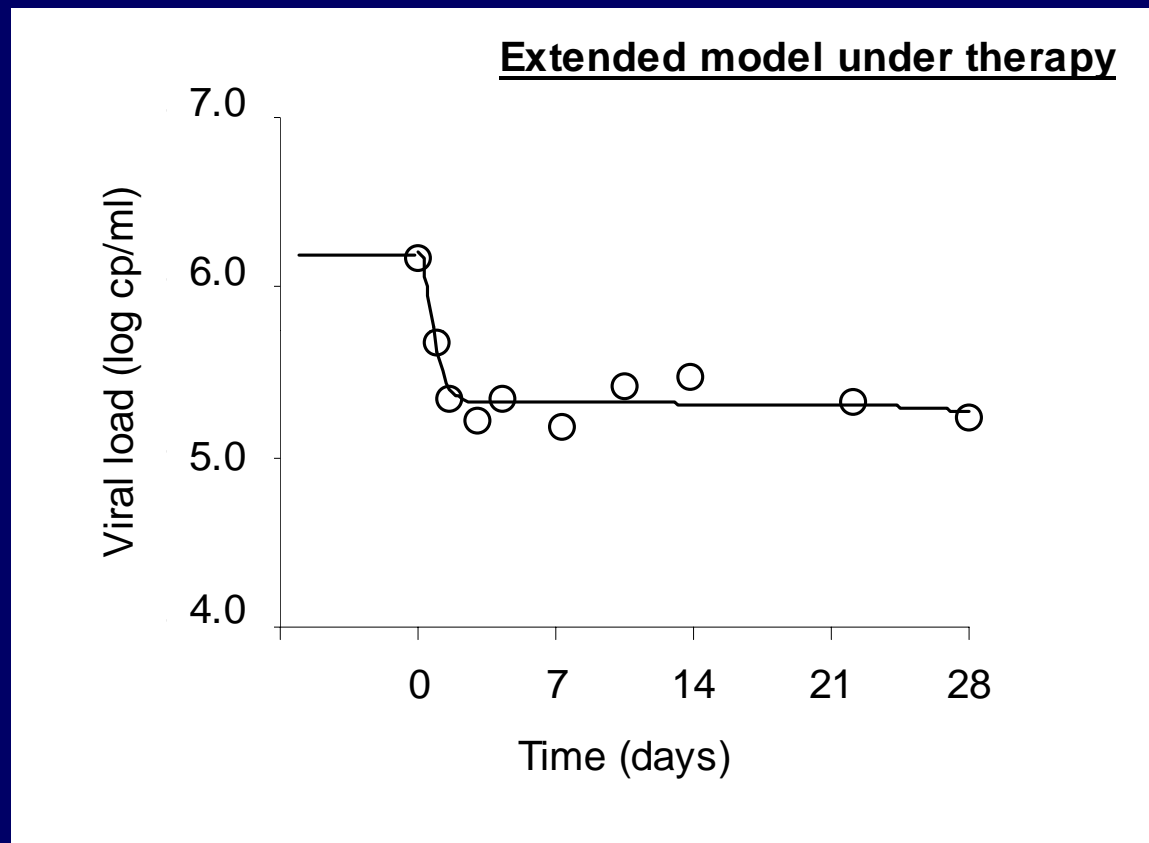
# HBV

- The same theory has been applied to treatment of HBV and 1<sup>st</sup> and 2<sup>nd</sup> phases defined in the same way.
- In models, noncytolytic cure of infected cell has been included but that has not changed the interpretation of 1<sup>st</sup> and 2<sup>nd</sup> phase declines

**More complex patterns of decay arise in both HCV and HBV**

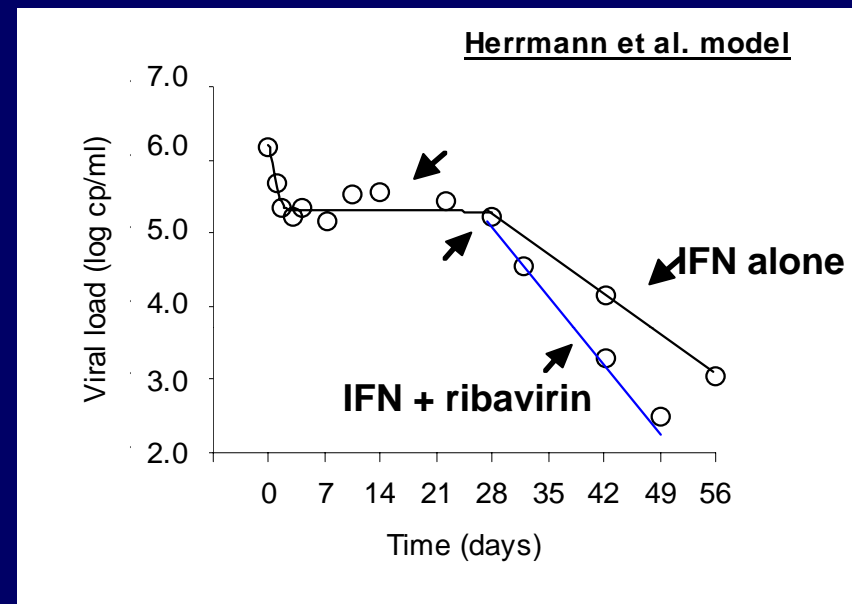
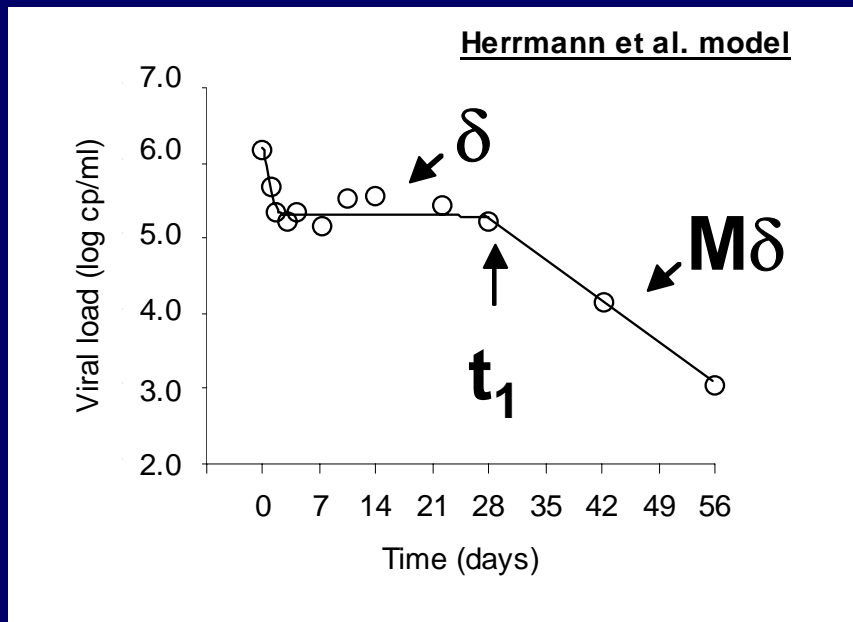
**Not all viral decays are biphasic**

# Flat 2<sup>nd</sup> phase



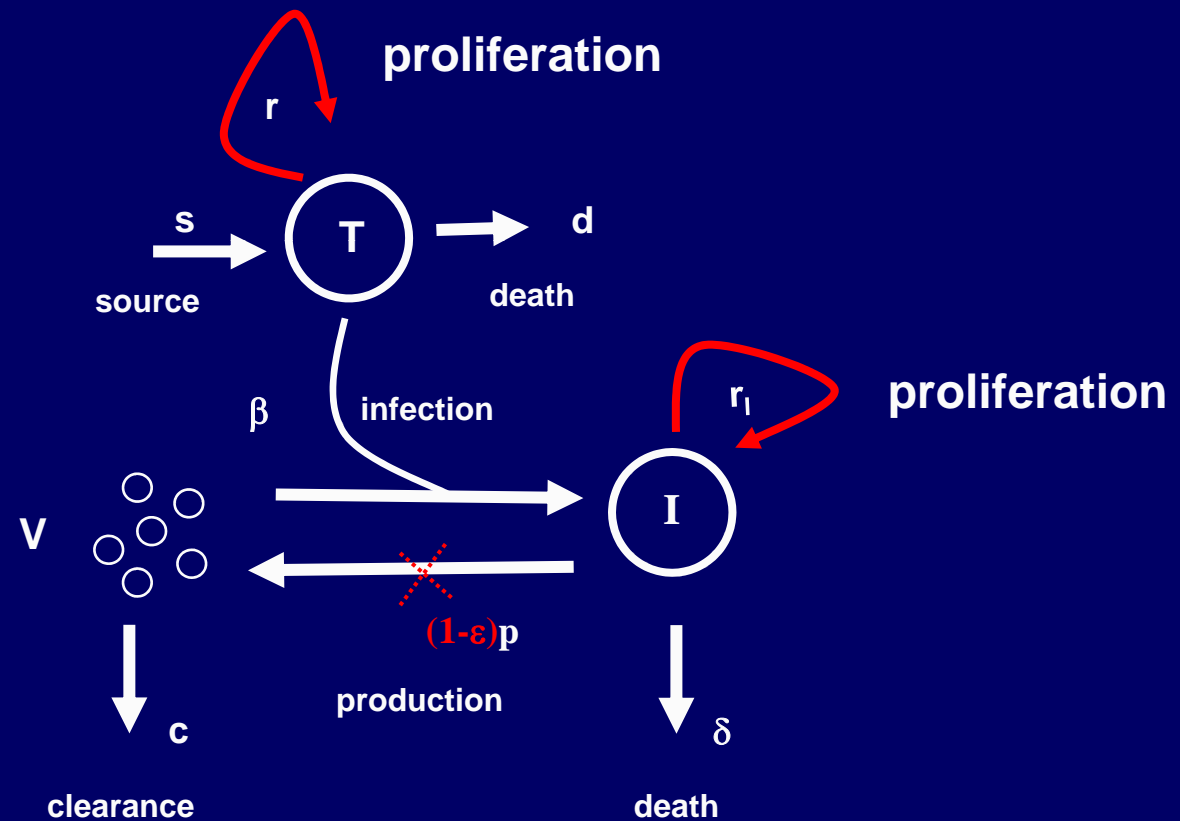
**Flat 2<sup>nd</sup> phase implies  $\delta=0$ . But can have flat 2<sup>nd</sup> phase with  $\delta > 0$  if infected cells proliferate.**

# Triphasic Decay



Herrmann et al., Hepatol. 37: 1351 (2003) suggest the pretreatment infected cell loss rate  $\delta$  is increased to a treatment-enhanced infected cell loss rate  $M\delta$  at a time  $t_1$ . RBV increases  $M$ .

# Model with Proliferation



Dahari et al., Hepatology 2007.

# Model with proliferation

$$\frac{dT}{dt} = s + rT \left( 1 - \frac{T + I}{T_{max}} \right) - dT - (1 - \eta)\beta VT,$$

$$\frac{dI}{dt} = (1 - \eta)\beta VT + rI \left( 1 - \frac{T + I}{T_{max}} \right) - \delta I,$$

$$\frac{dV}{dt} = (1 - \varepsilon_p)pI - cV,$$

# Model has an infected steady state

$$\bar{V} = \frac{(1 - \varepsilon_p)p\bar{I}}{c}, \quad \bar{I} = \bar{T}(A - 1) + T_{max} - B,$$

$$\bar{T} = \frac{1}{2} \left[ -D + \sqrt{D^2 + \frac{4sT_{max}}{rA^2}} \right],$$

where

$$A = \frac{(1 - \eta)(1 - \varepsilon_p)p\beta T_{max}}{cr}, \quad B = \frac{\delta T_{max}}{r},$$

$$D = \frac{1}{A} \left( T_{max} + \frac{dB}{\delta A} - B \left( \frac{1}{A} + 1 \right) \right).$$

**At high enough  $\varepsilon$ ,  $V = 0$**

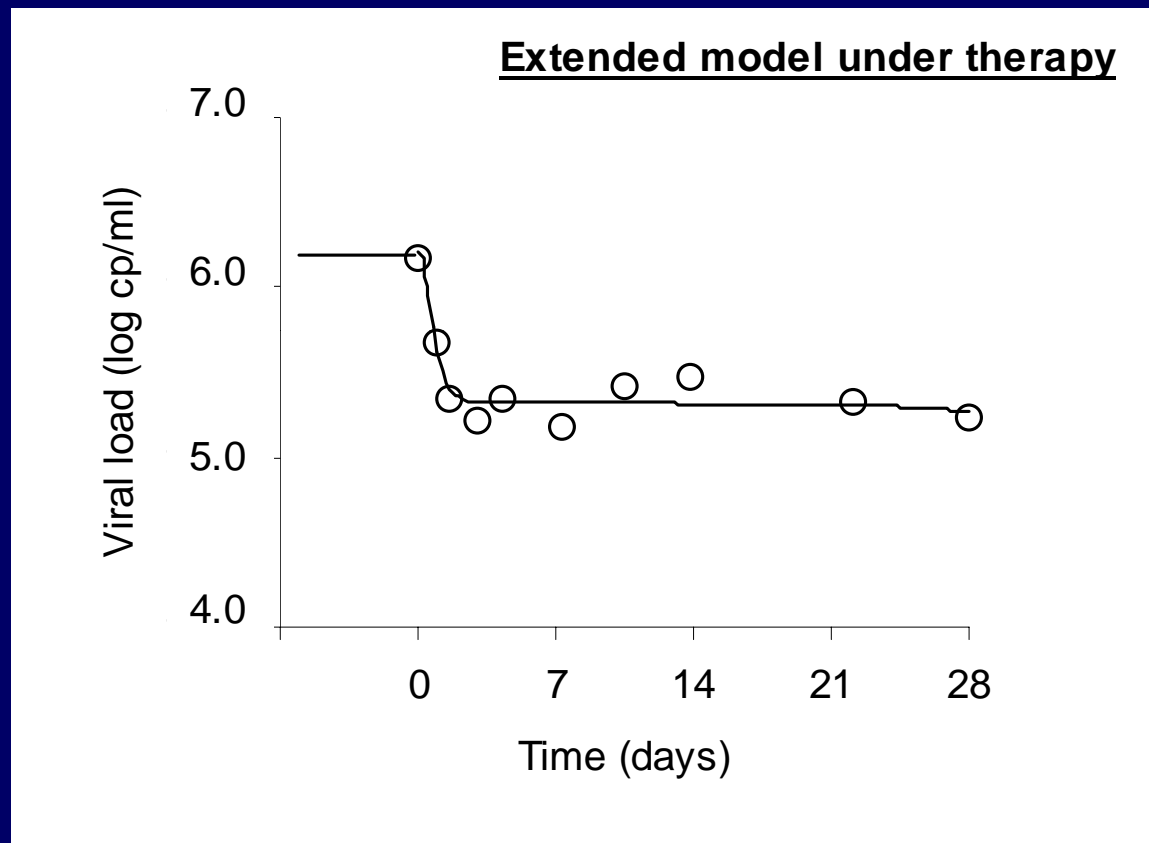
# Critical Drug Efficacy

- There exists a drug effectiveness, called the critical effectiveness,  $\varepsilon_c$ , at which the infected steady state amount of virus goes to zero.
- Thus, with  $\varepsilon > \varepsilon_c$  model predicts elimination of virus.
- Patient and viral dependent parameters ( $c, \delta, \beta, p$ ) determine  $\varepsilon_c$ .
- Patients with higher baseline VL have higher  $\varepsilon_c$ .

## When $\varepsilon < \varepsilon_c$

- The model now predicts viral load will decrease to an infected steady state with less virus than pre-treatment, but virus will not be eliminated.
- This pattern is seen in many patients, who are said to have failed therapy. Also, when therapy is terminated viral levels go back to pre-treatment level.

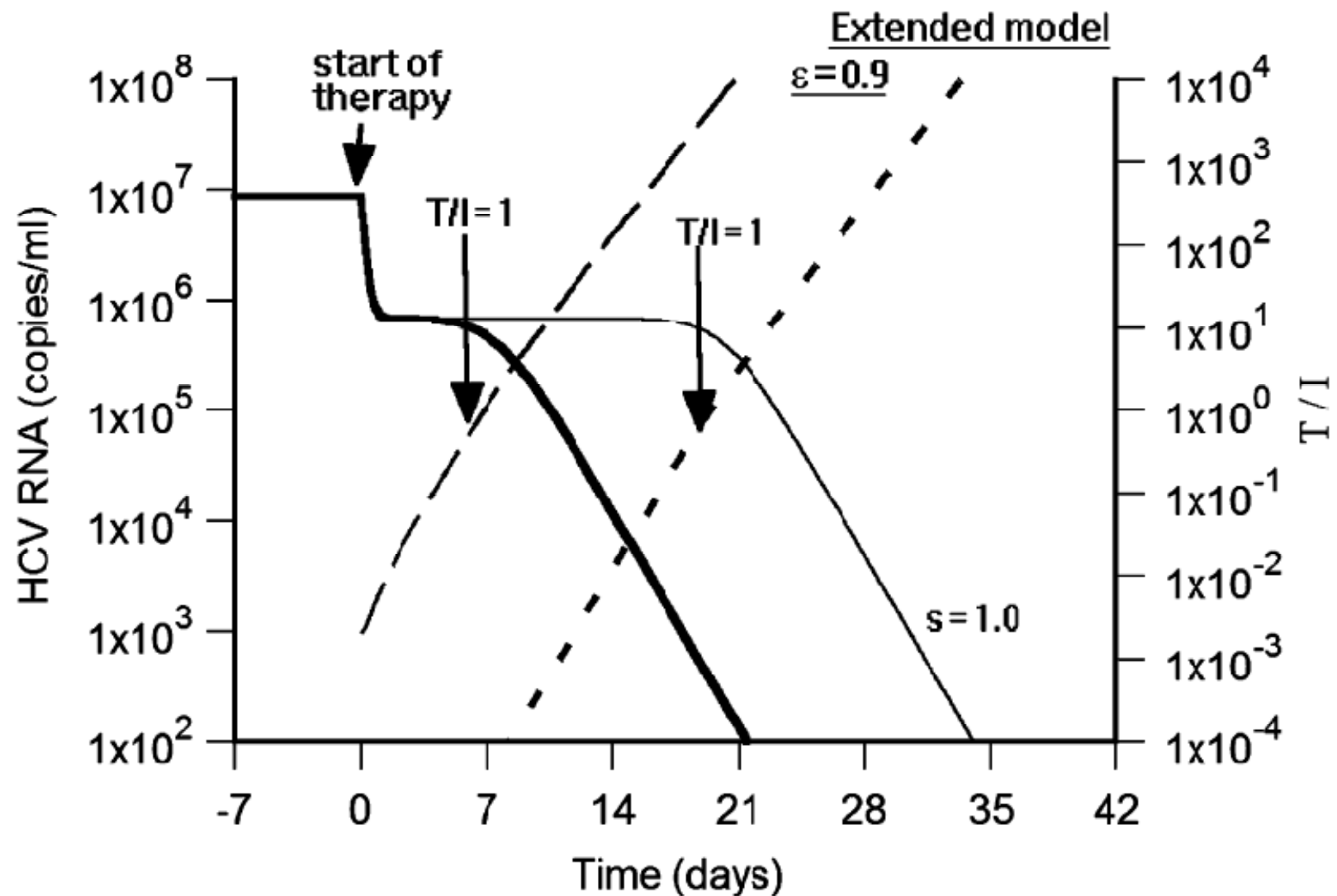
# Extended Model: Flat 2<sup>nd</sup> phase



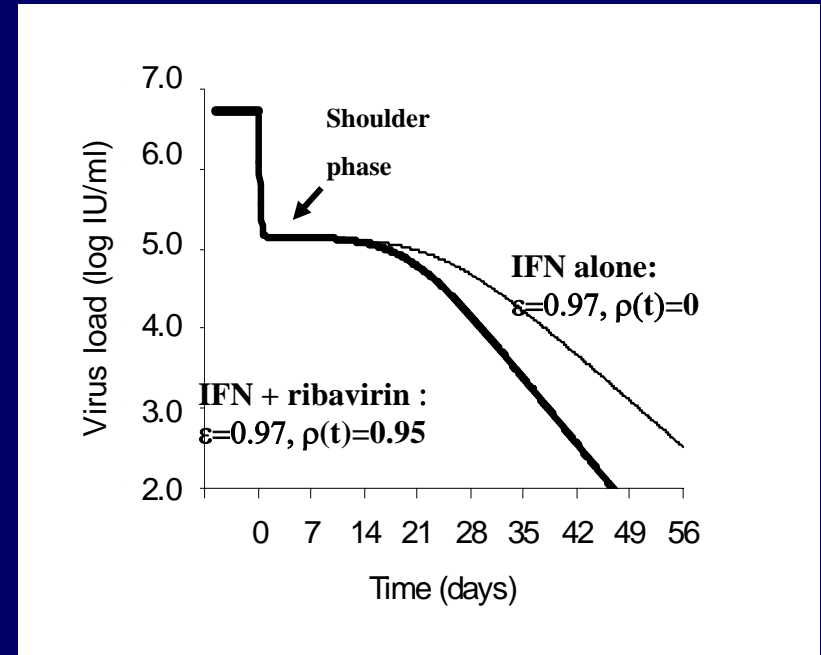
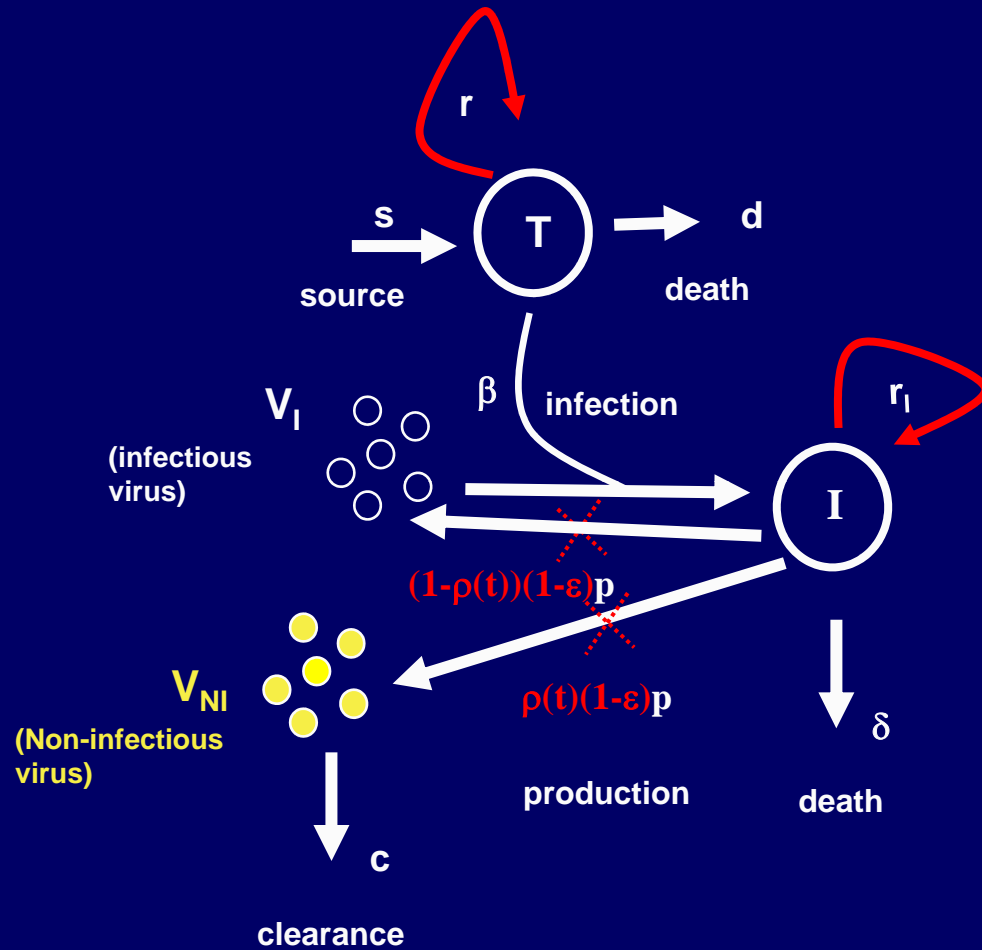
$$\varepsilon < \varepsilon_c$$

Can have flat 2<sup>nd</sup> phase with  $\delta > 0$  since infected cells can be replaced by replication

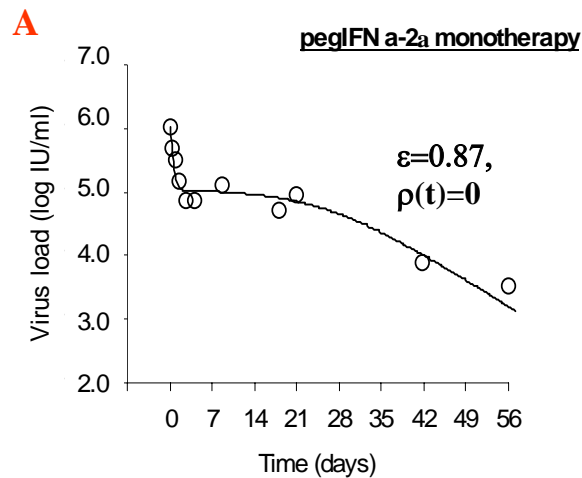
# Triphasic response: $\varepsilon > \varepsilon_c$



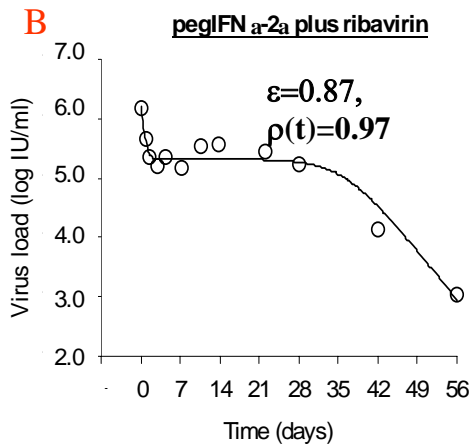
# Extended model: ribavirin mutagenesis and triphasic viral decay



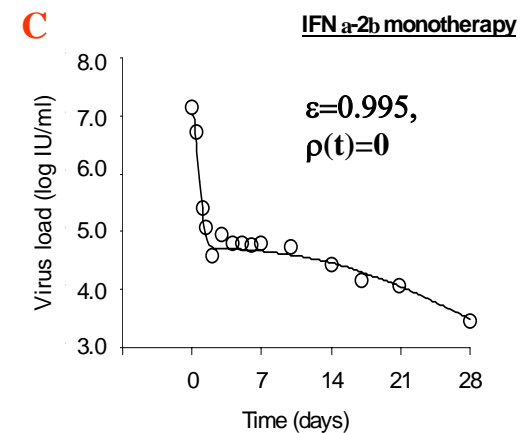
# Extended model: Fits to data



Herrmann et al.  
(Hepatology 2003)



Herrmann et al.  
(Hepatology 2003)

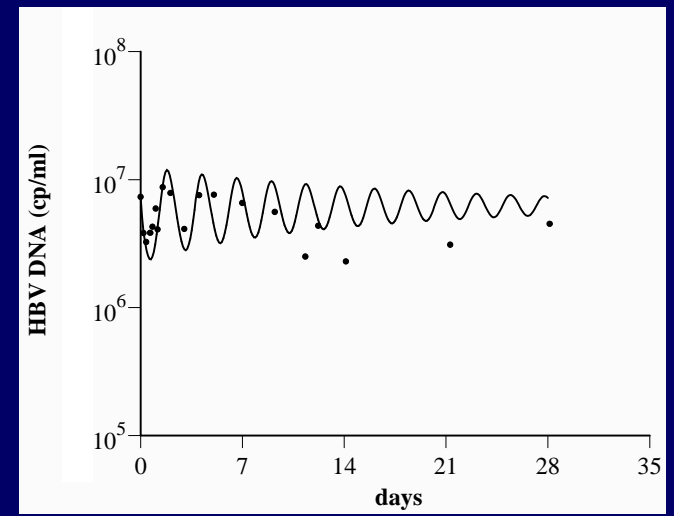
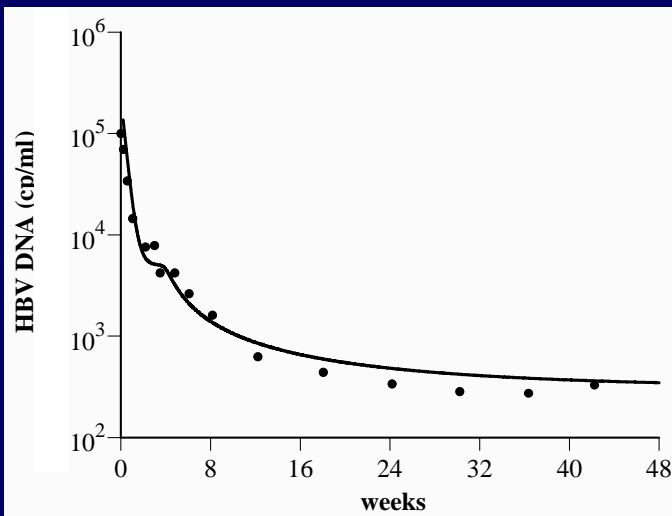
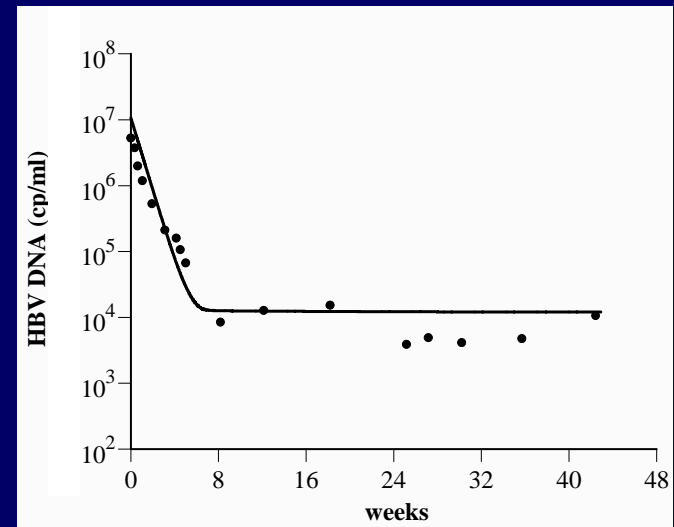
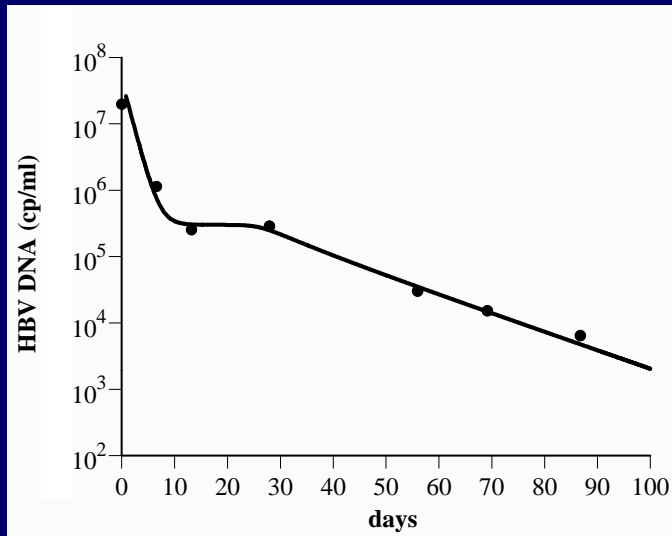


Bekkering et al.  
(BMC Gastro 2001)

Pegylated interferon a-2a alone (A). combination pegIFN ribavirin (B), daily interferon a-2b alone (C).

**Can explain triphasic response and enhancement of final phase slope without invoking immunomodulation**

# HBV Decays



# Summary

- Complex patterns of decay that arise in both HCV and HBV- flat 2<sup>nd</sup> phase, triphasic, rebound can be explained by new models
- Critical efficacy  $\varepsilon_c$ ; if  $\varepsilon < \varepsilon_c$  virus will not be eliminated – non responder, rebounder, flat 2<sup>nd</sup> phase
- Due to rebounds with peg-IFN a2b new decreasing efficacy models may be useful.
- Drug resistance; all single and double point mutants pre-exist. With monotherapy compensatory mutations likely.

# Collaborators

- Harel Dahari, Univ Illinois
- Emi Shudo and Ruy M. Ribeiro, Los Alamos