The Dynamics of Virus Infection and Treatment

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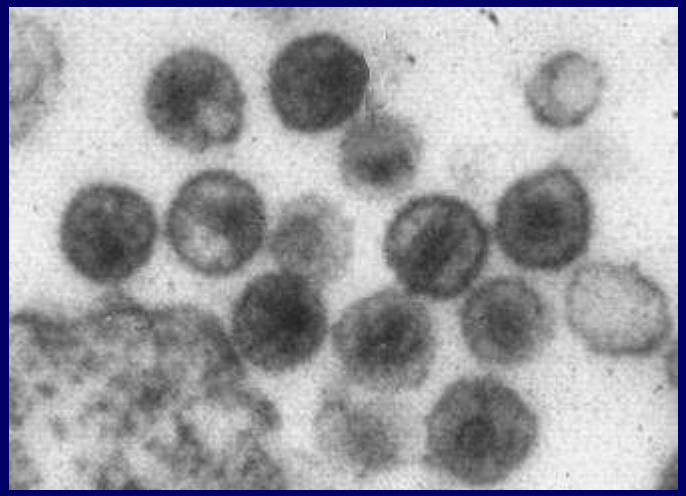
What is HIV infection?

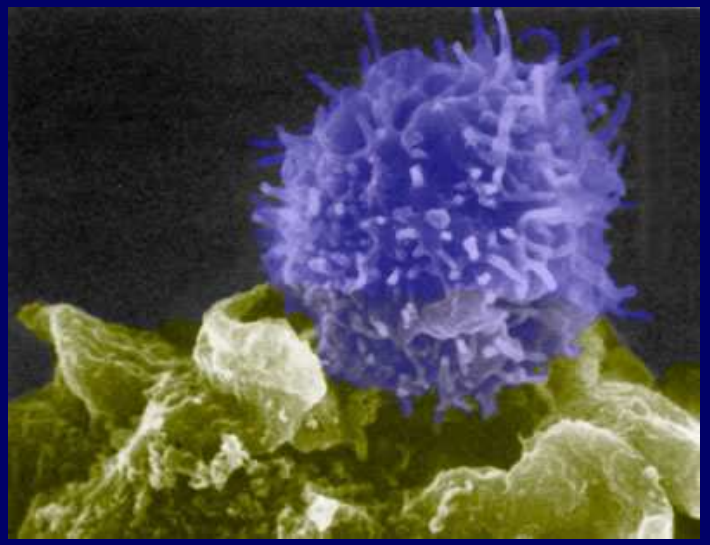
The virus



A retrovirus

Infects immune cells bearing:
CD4 & CCR5/CXCR4

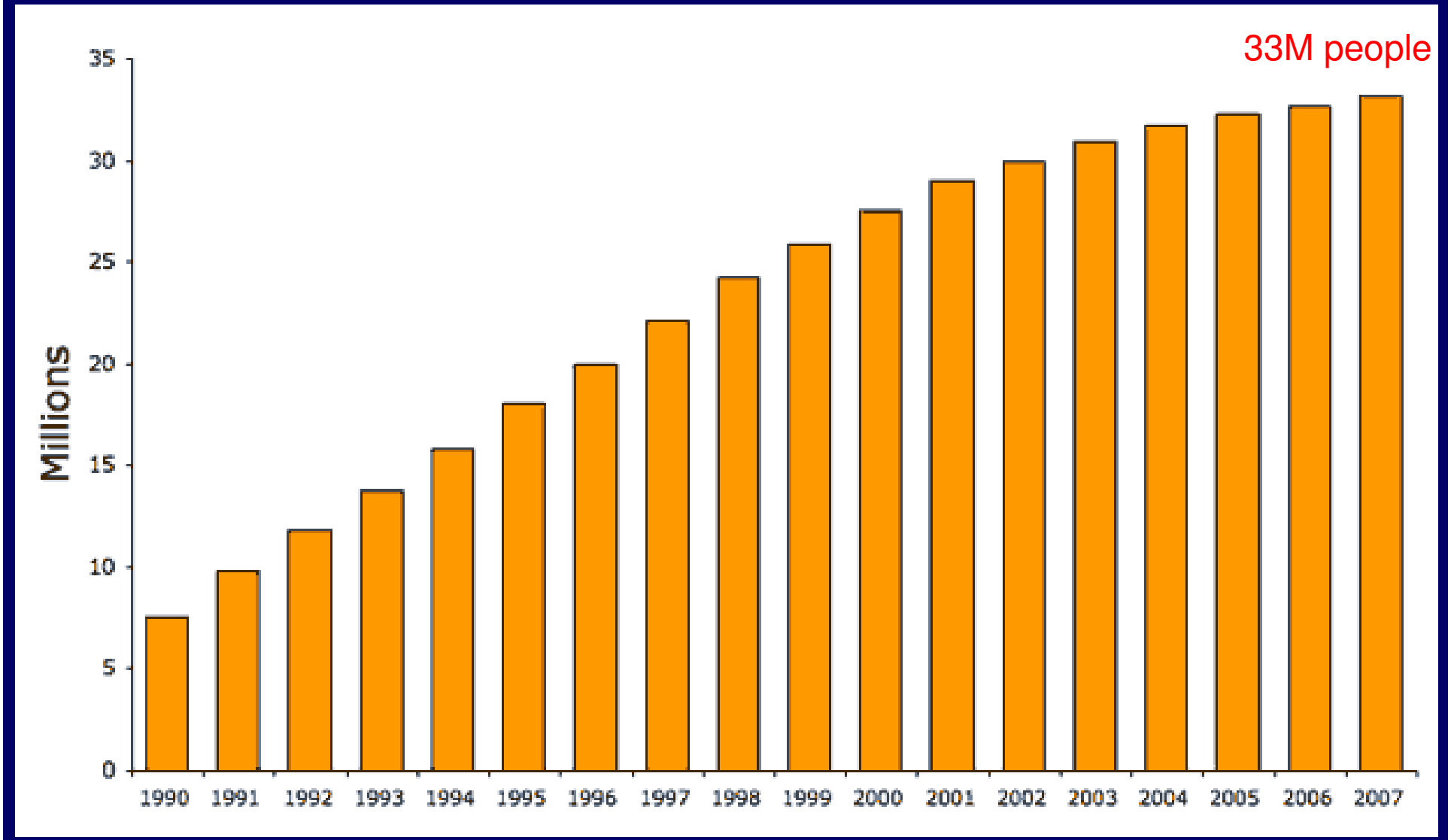
The host



CD4+ T-cells (or helper T cells)

Macrophages and dendritic cells

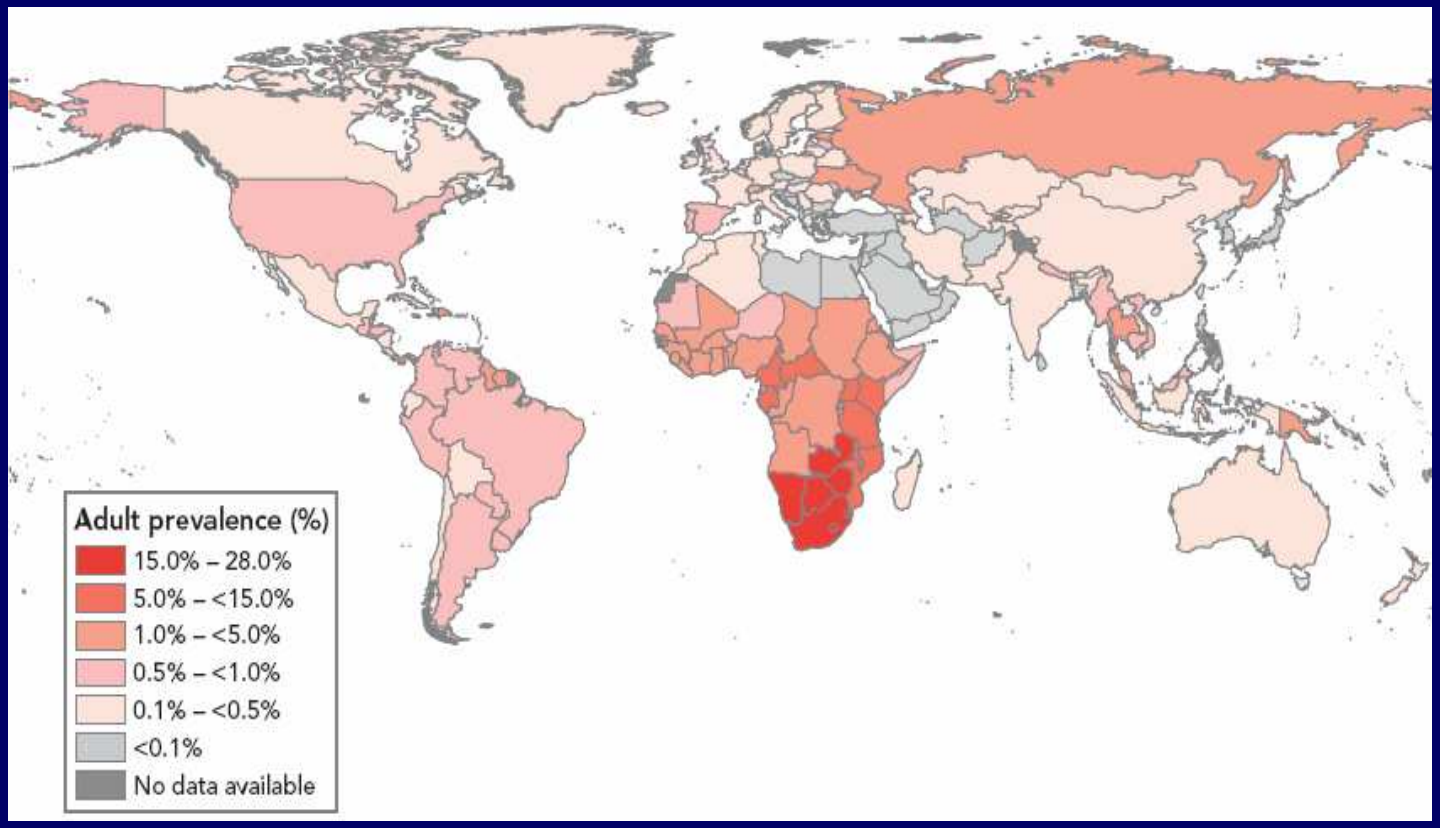
Number of people infected



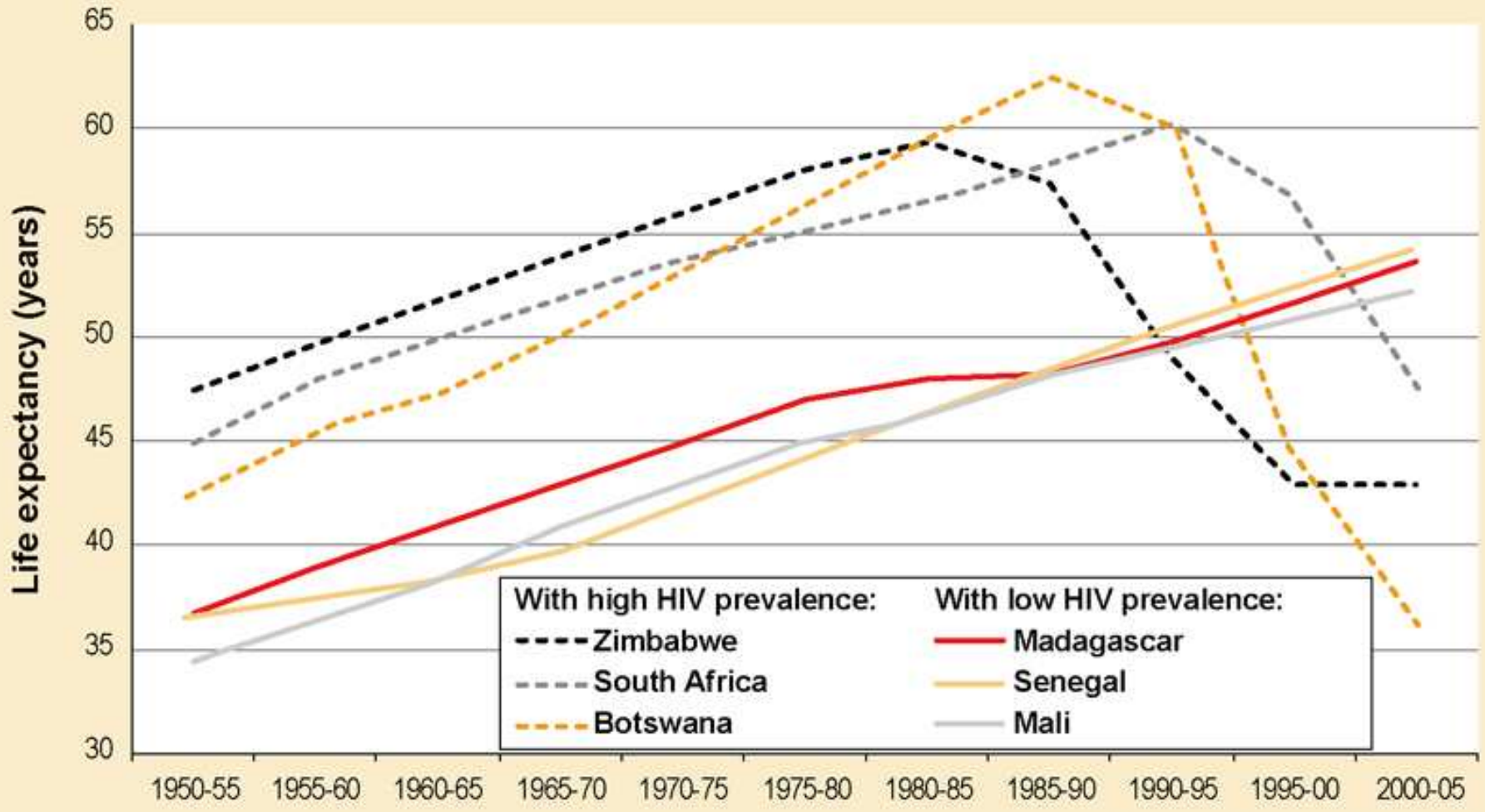
UNAIDS, 2007

A global view of HIV infection

33 million people [30–36 million] living with HIV, 2007

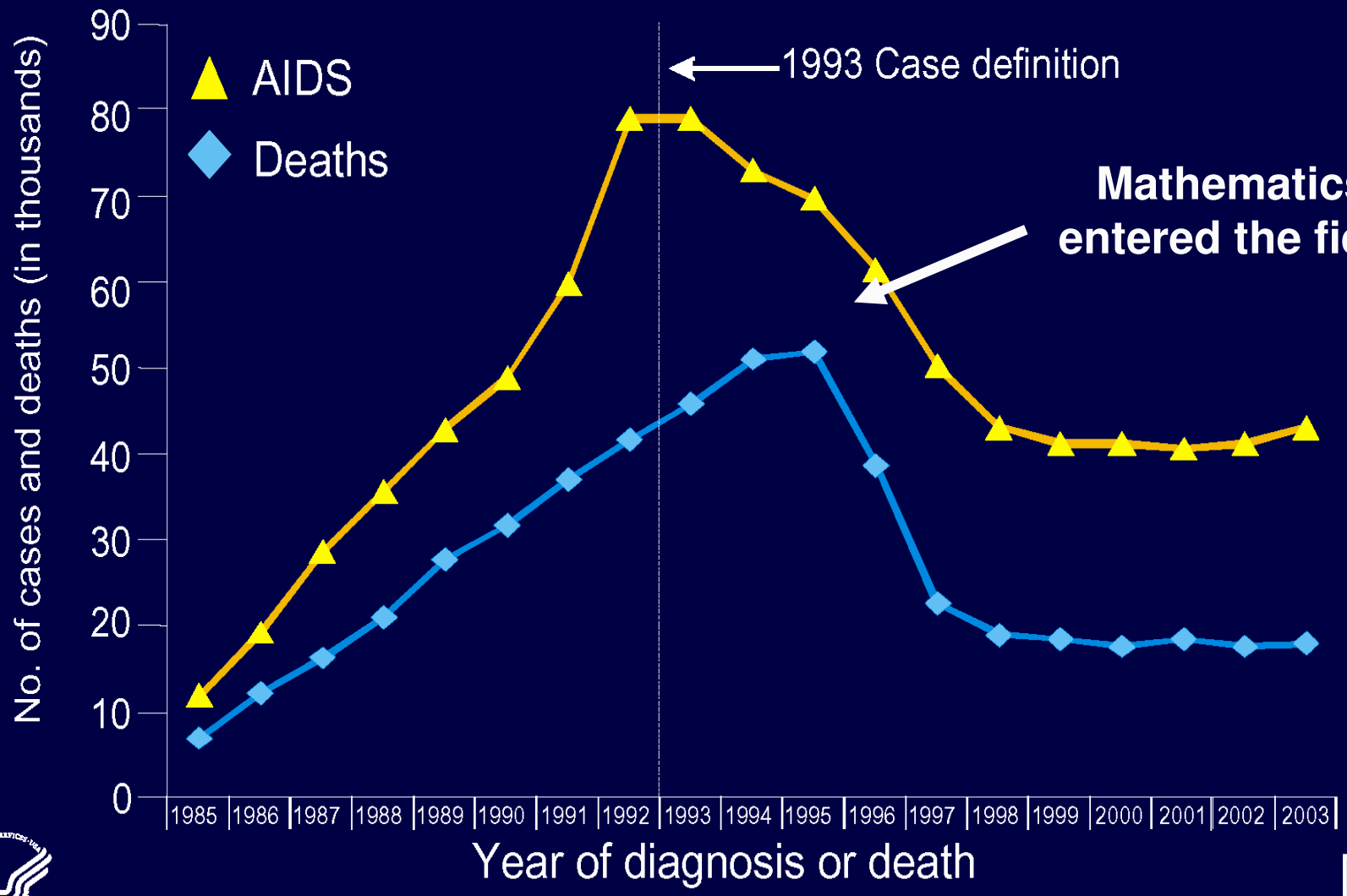


Life expectancy in African countries



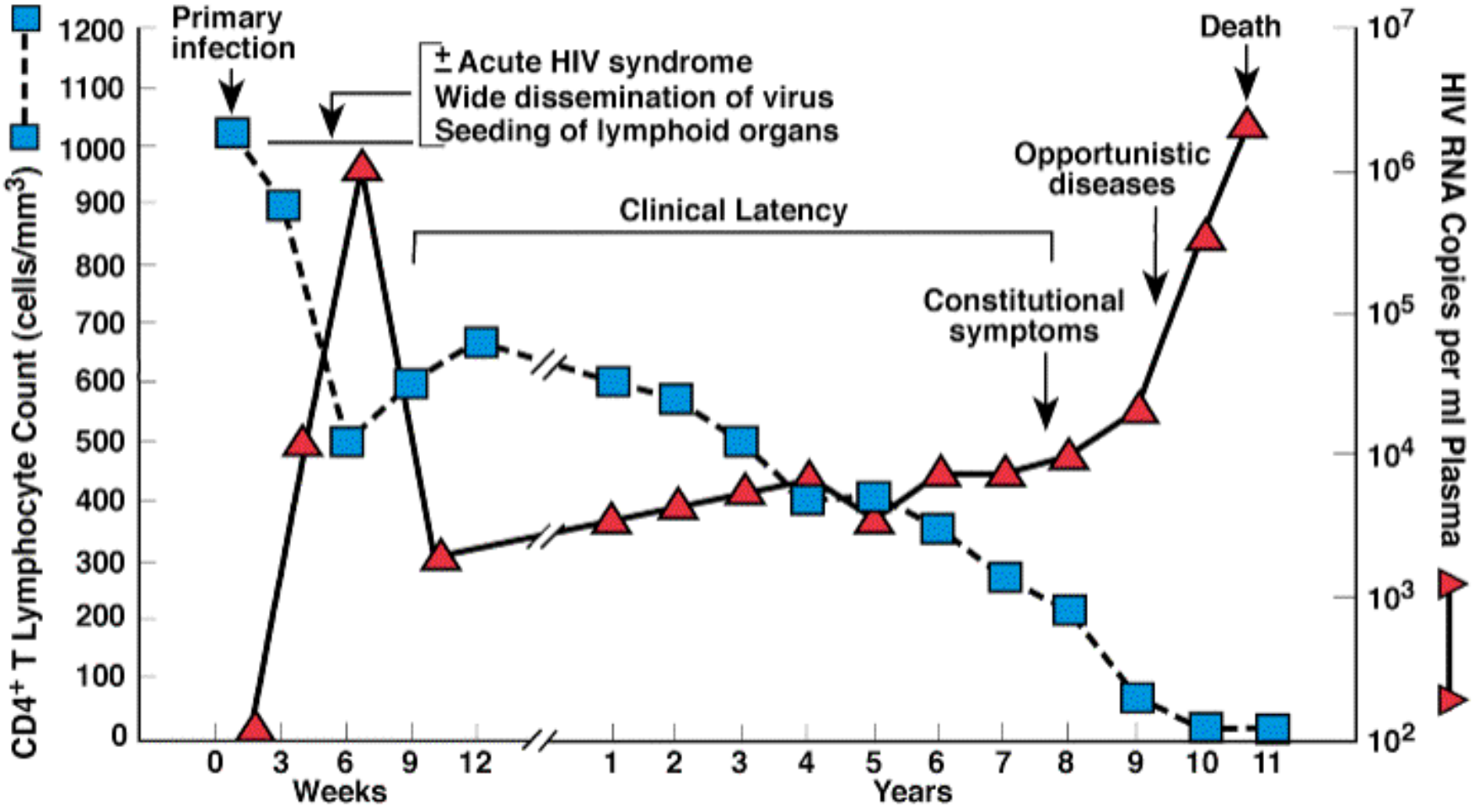
Source: UN Department of Economic and Social Affairs (2001) *World Population Prospects, the 2000 Revision*

Estimated Number of AIDS Cases and Deaths among Adults and Adolescents with AIDS, 1985–2003—United States



Note. Adjusted for reporting delays.

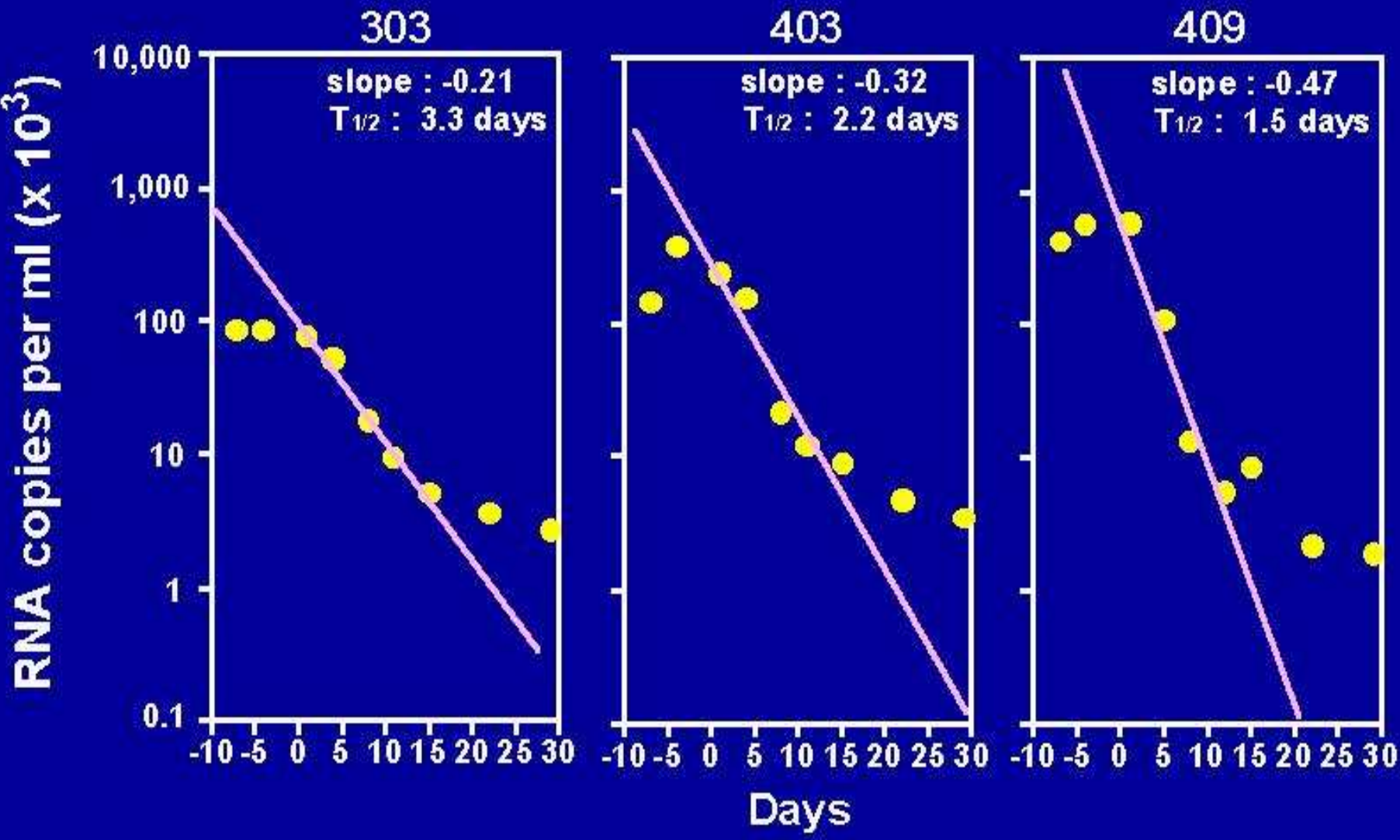
Typical Course of HIV Infection



Modified From: Fauci, A.S., et al, *Ann. Intern. Med.*, 124:654, 1996

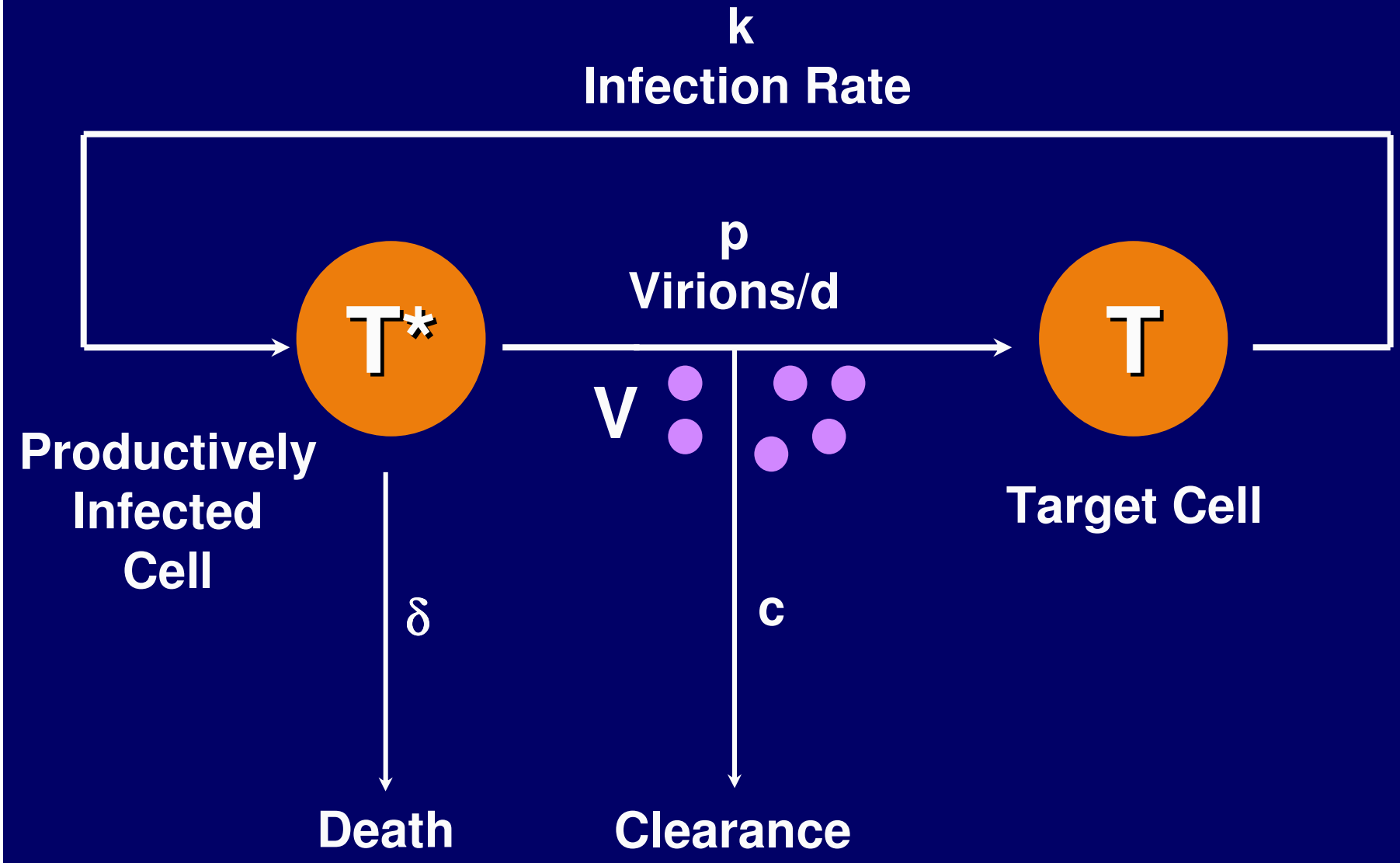
No treatment

HIV-1 protease inhibitor (ritonavir) given at t=0



Ho et al. *Nature*. 1995;373:123-126

Model of HIV Infection



Model of HIV Infection

$$\frac{dT(t)}{dt} = \lambda - dT - kTV$$

$$\frac{dT^*(t)}{dt} = kTV - \delta T^*$$

$$\frac{dV(t)}{dt} = N\delta T^* - cV$$

$$T(0) = T_0$$

$$T^*(0) = 0$$

$$V(0) = V_0$$

Variables

- T Target Cell Density
- T^* Infected Target Cell Density
- V Virus Concentration

Parameters

- λ Supply of target cells
- d Net loss rate of target cells
- k Infectivity rate constant
- δ Infected cell death rate
- $N\delta = p$ Virion production rate
- c Virion clearance rate constant

Model derived by trying to explain effects of antiretroviral drugs; Here T=constant=T_0

$$\frac{dT^*(t)}{dt} = (1-\varepsilon_{RT})kV_I T_0 - \delta T^*$$

$$\frac{dV_I(t)}{dt} = (1-\varepsilon_{PI})N\delta T^* - cV_I$$

$$\frac{dV_{NI}(t)}{dt} = \varepsilon_{PI} N\delta T^* - cV_{NI}$$

Drug efficacy

ε_{RT} ε_{PI}

Subscripts:

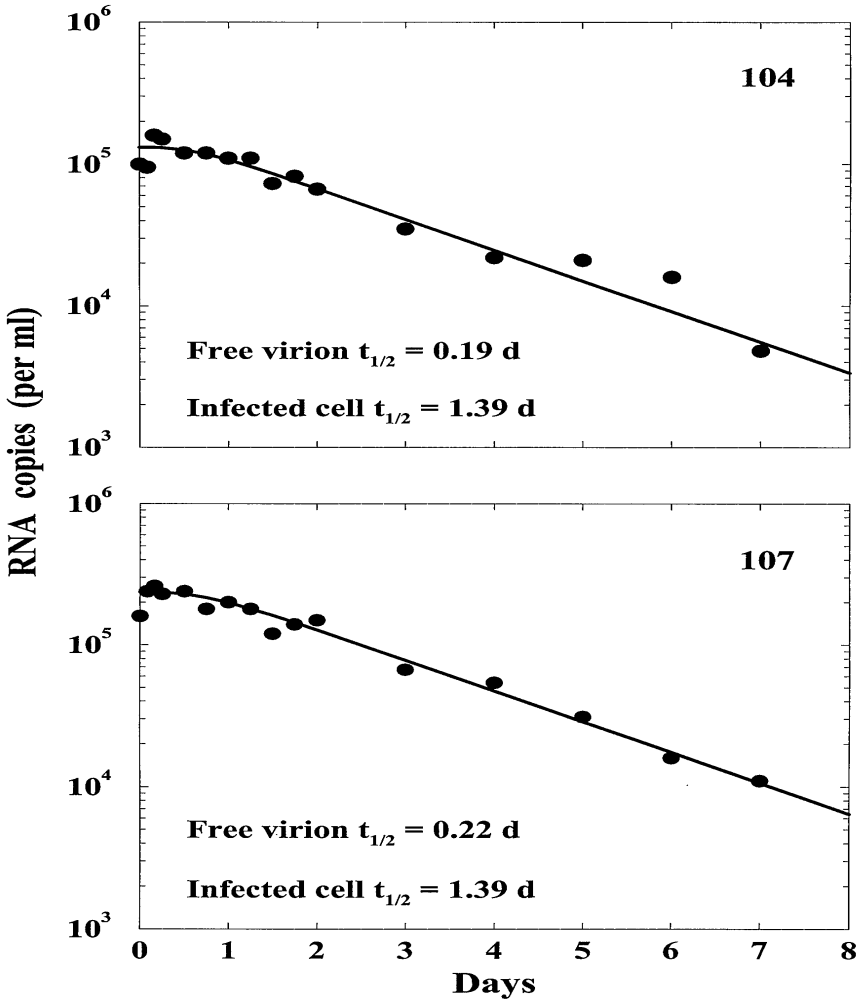
"I": infectious

"NI": non-infectious

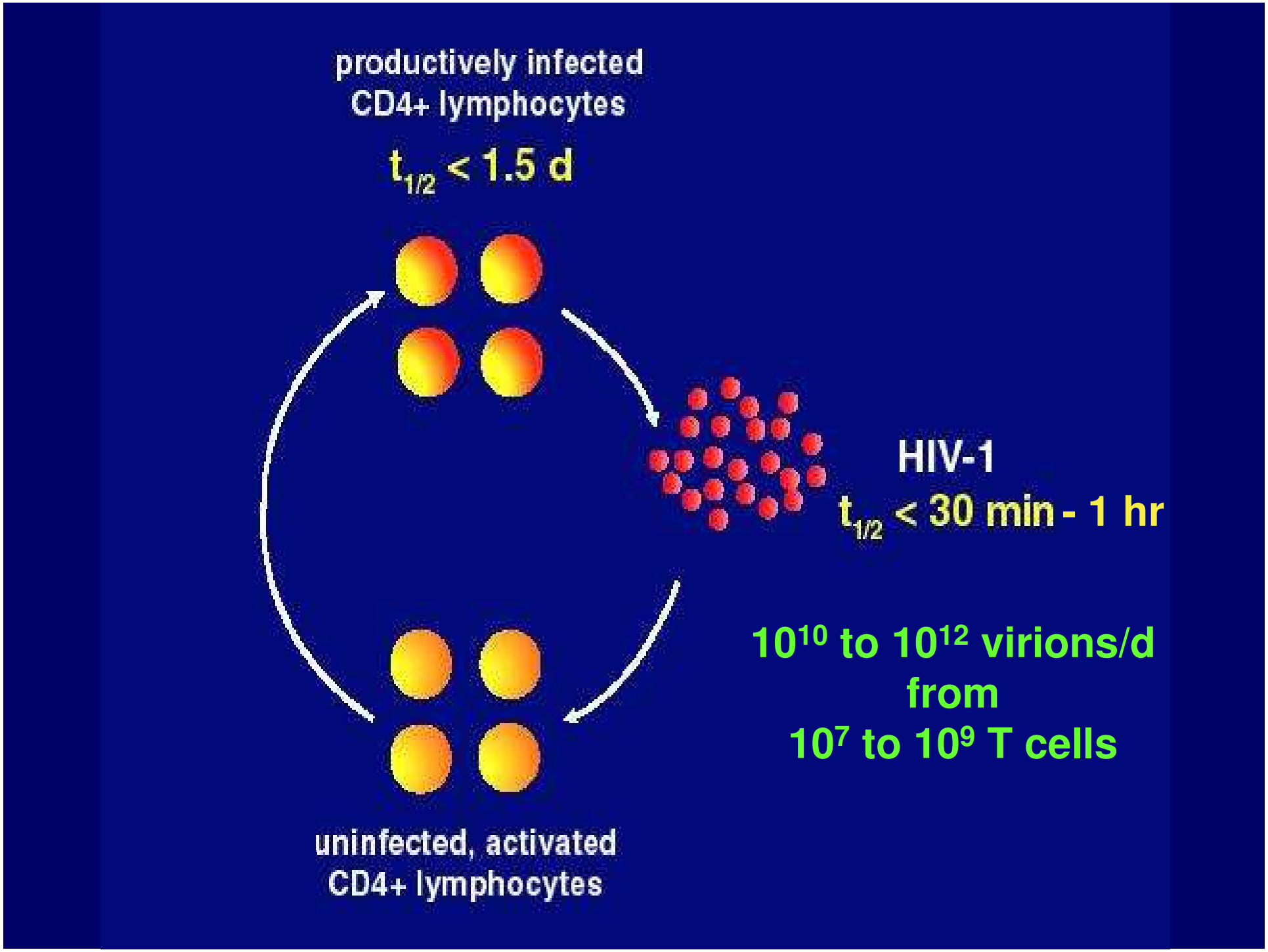
From *HIV-Dynamics in Vivo: …*,

Perelson, *et al*, Science, 1996

HIV-1: First Phase Kinetics



Perelson et al.
Science 271, 1582
1996


productively infected
CD4+ lymphocytes
$t_{1/2}$ < 1.5 d
HIV-1
$t_{1/2}$ < 30 min - 1 hr
10^{10} to 10^{12} virions/d
from
10^{7} to 10^{9} T cells
uninfected, activated
CD4+ lymphocytes

Implications

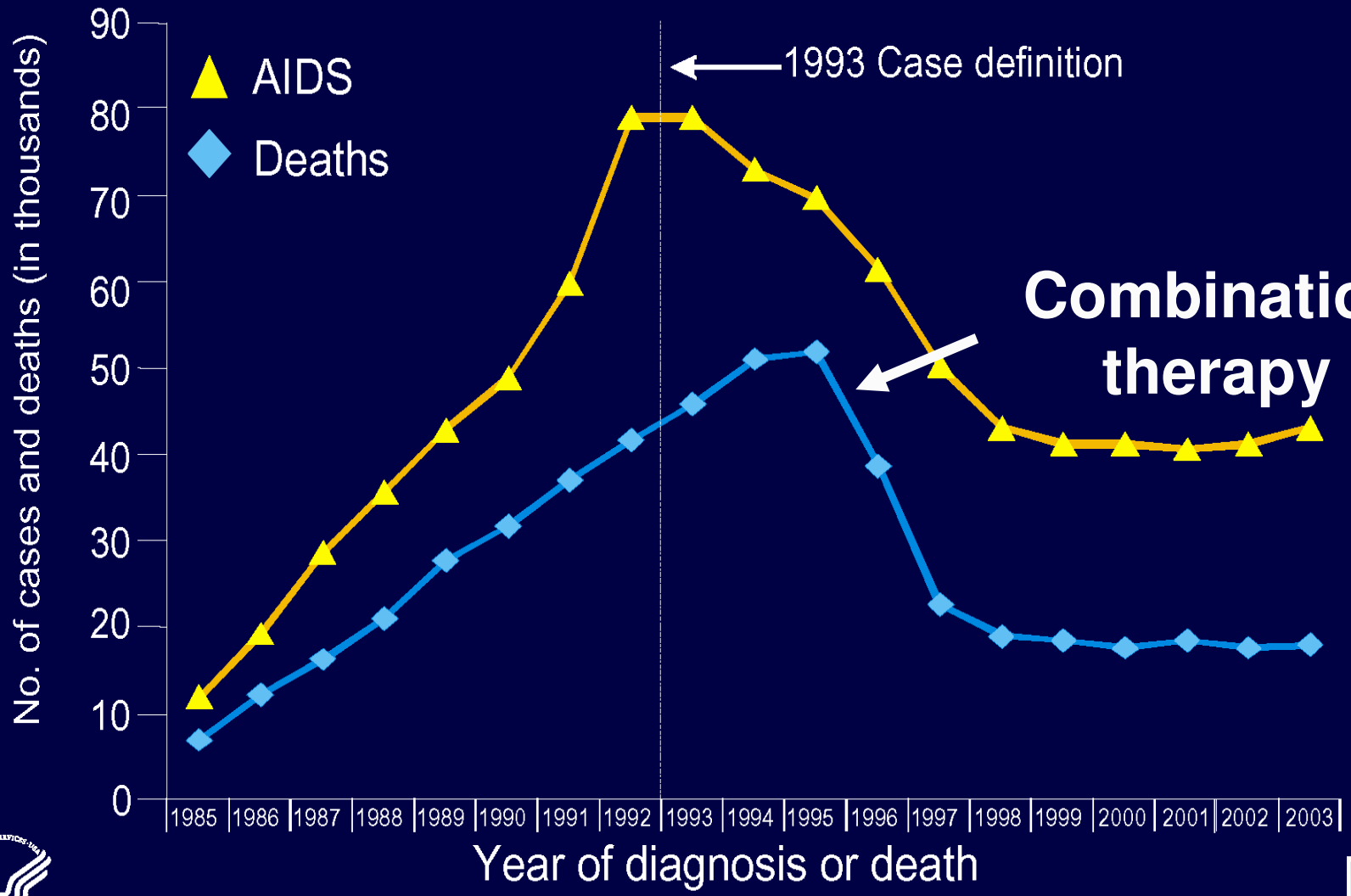
- HIV infection is not a slow process.
- Virus replicates rapidly and is cleared rapidly – can compute to maintain set point level > 10^{10} virions produced/day.
- Most cells infected by HIV are killed rapidly.
- Rapid replication implies HIV can mutate and become drug resistant.
- Calculations showed the need for triple combination therapy to overcome resistance.

Rate of generation of HIV-1 mutants

Base Changes	Probability of mutant	Number created/day	Number of possible mutants	Fraction of all possible mutants created/day
0	0.74	7.4×10^{7}	1	
1	0.22	2.2×10^{7}	3.0×10^{4}	1
2	0.033	3.3×10^{6}	4.5×10^{8}	7.4×10^{-3}
3	0.0033	3.3×10^{5}	4.5×10^{12}	7.4×10^{-8}

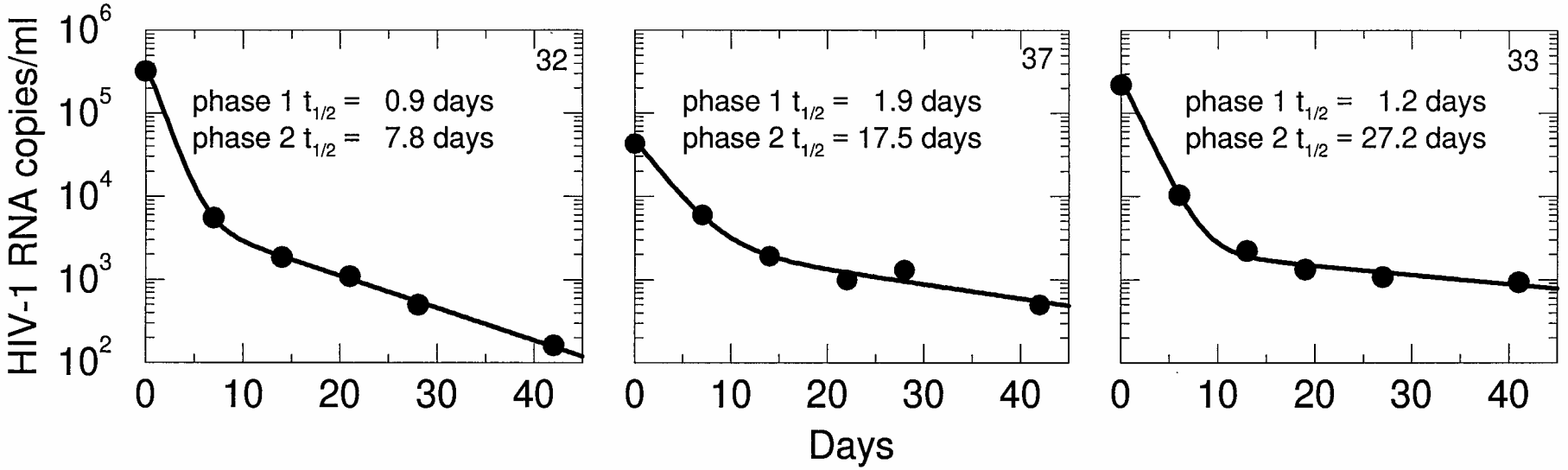
Perelson, Essunger & Ho, AIDS 1997

Estimated Number of AIDS Cases and Deaths among Adults and Adolescents with AIDS, 1985–2003—United States



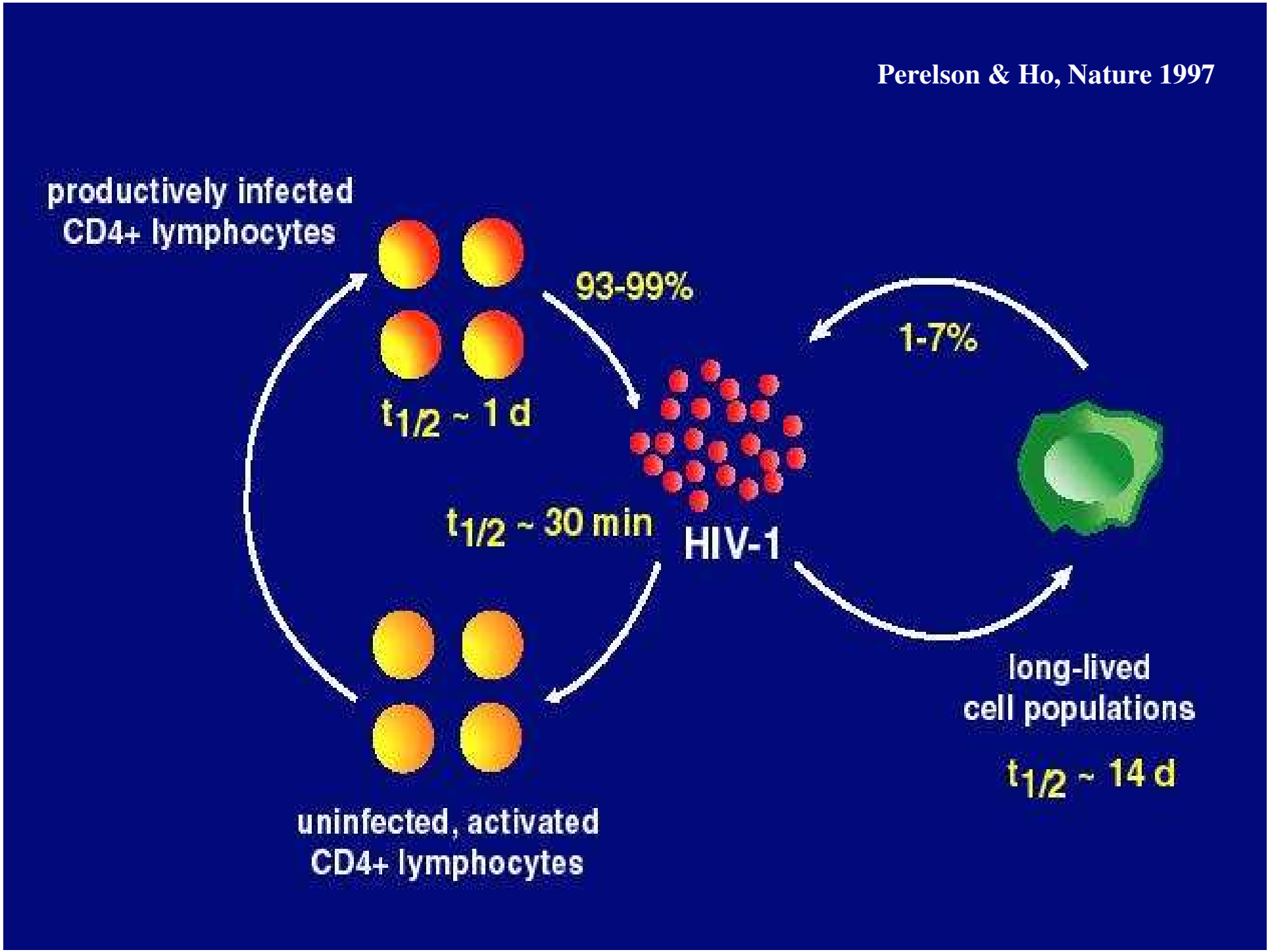
Note. Adjusted for reporting delays.

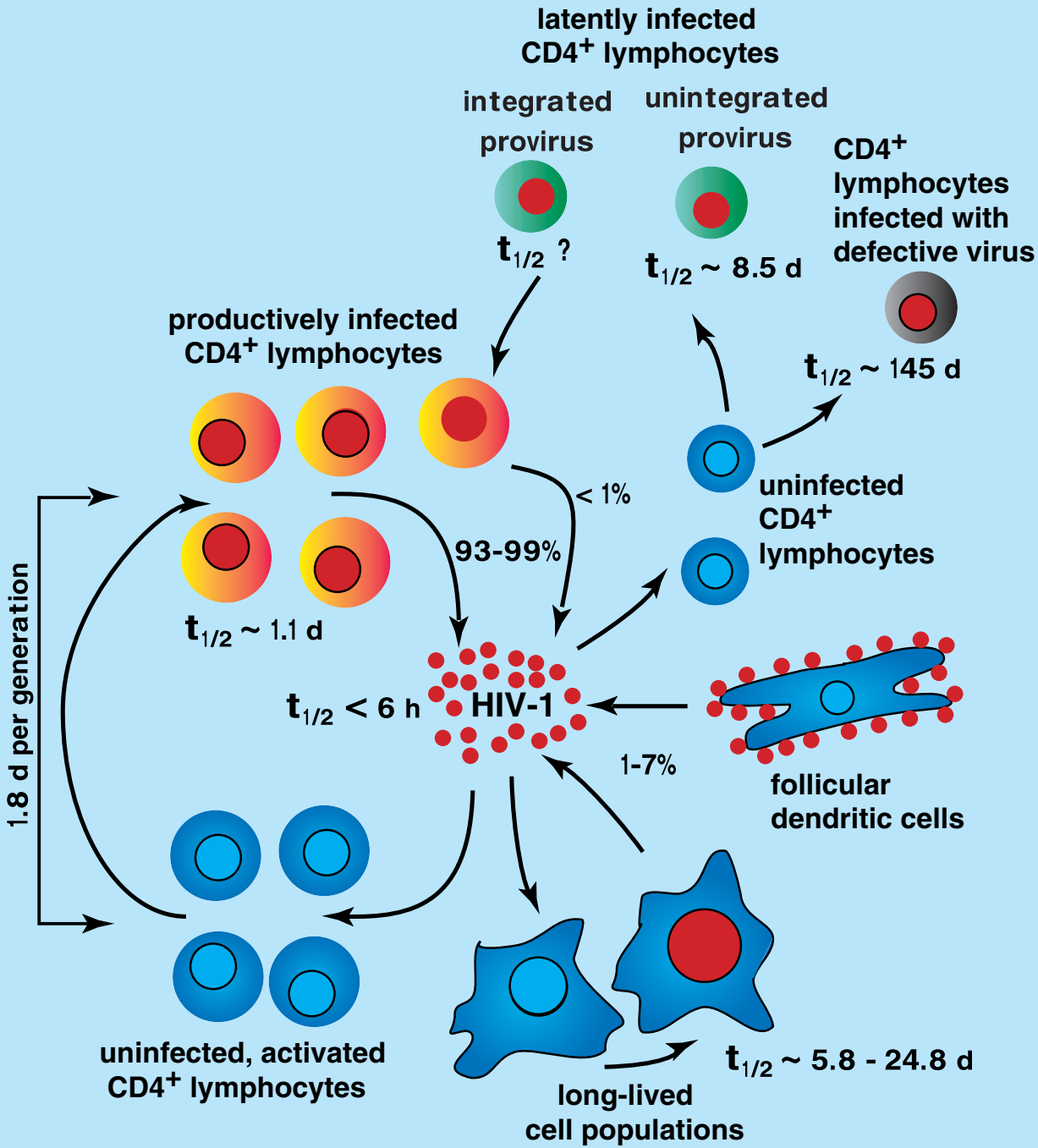
HIV-1: Two Phase Kinetics (Combination Therapy)

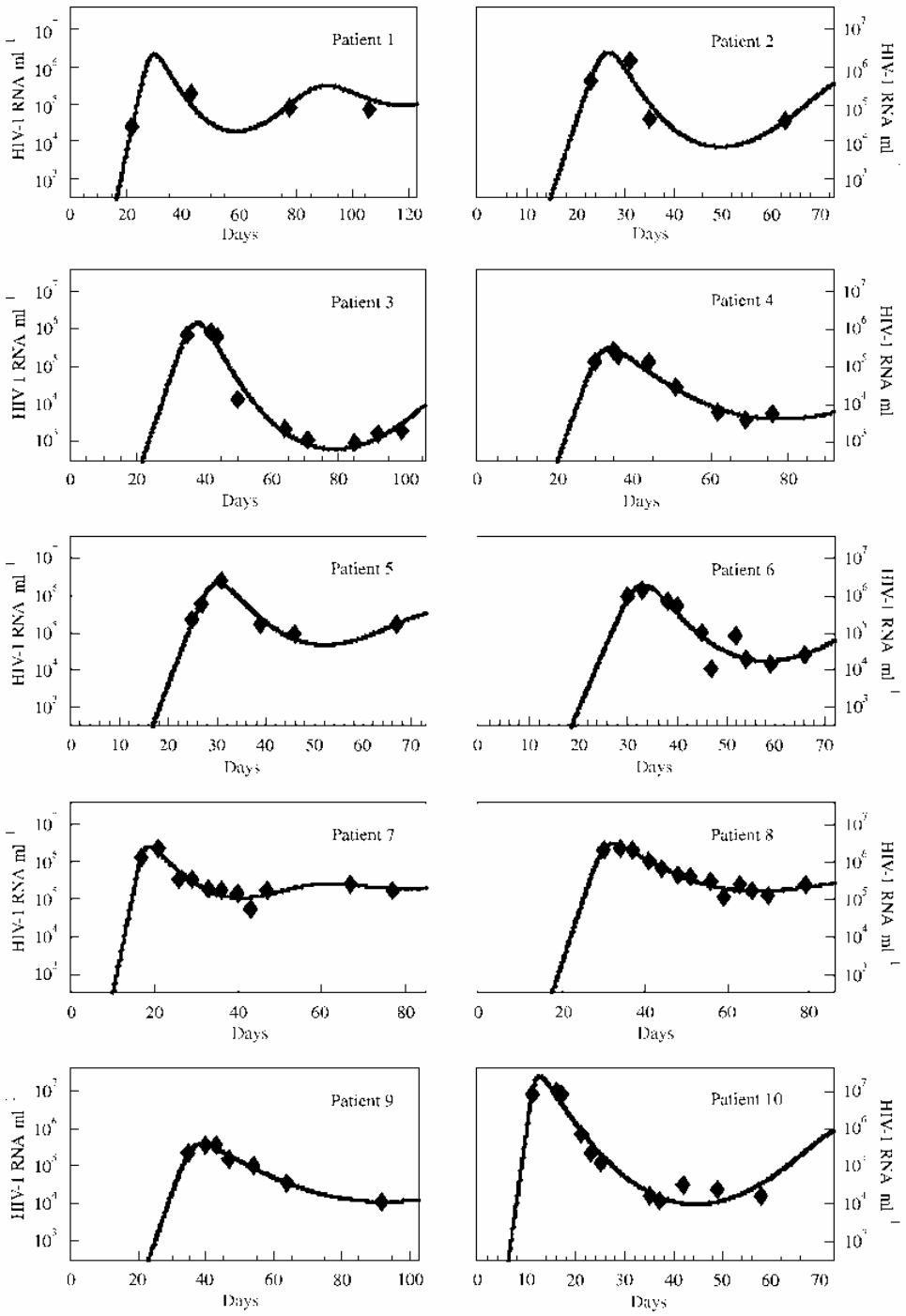


Perelson et al. Nature 387, 186 (1997)

Perelson & Ho, Nature 1997




latently infected
CD4+ lymphocytes
integrated
provirus
unintegrated
provirus
CD4+
lymphocytes
infected with
defective virus
t1/2 ?
t1/2 ~ 8.5 d
t1/2 ~ 145 d
productively infected
CD4+ lymphocytes
< 1%
uninfected
CD4+
lymphocytes
93-99%
t1/2 ~ 1.1 d
1.8 d per generation
t1/2 < 6 h
HIV-1
1-7%
follicular
dendritic cells
uninfected, activated
CD4+ lymphocytes
t1/2 ~ 5.8 - 24.8 d
long-lived
cell populations



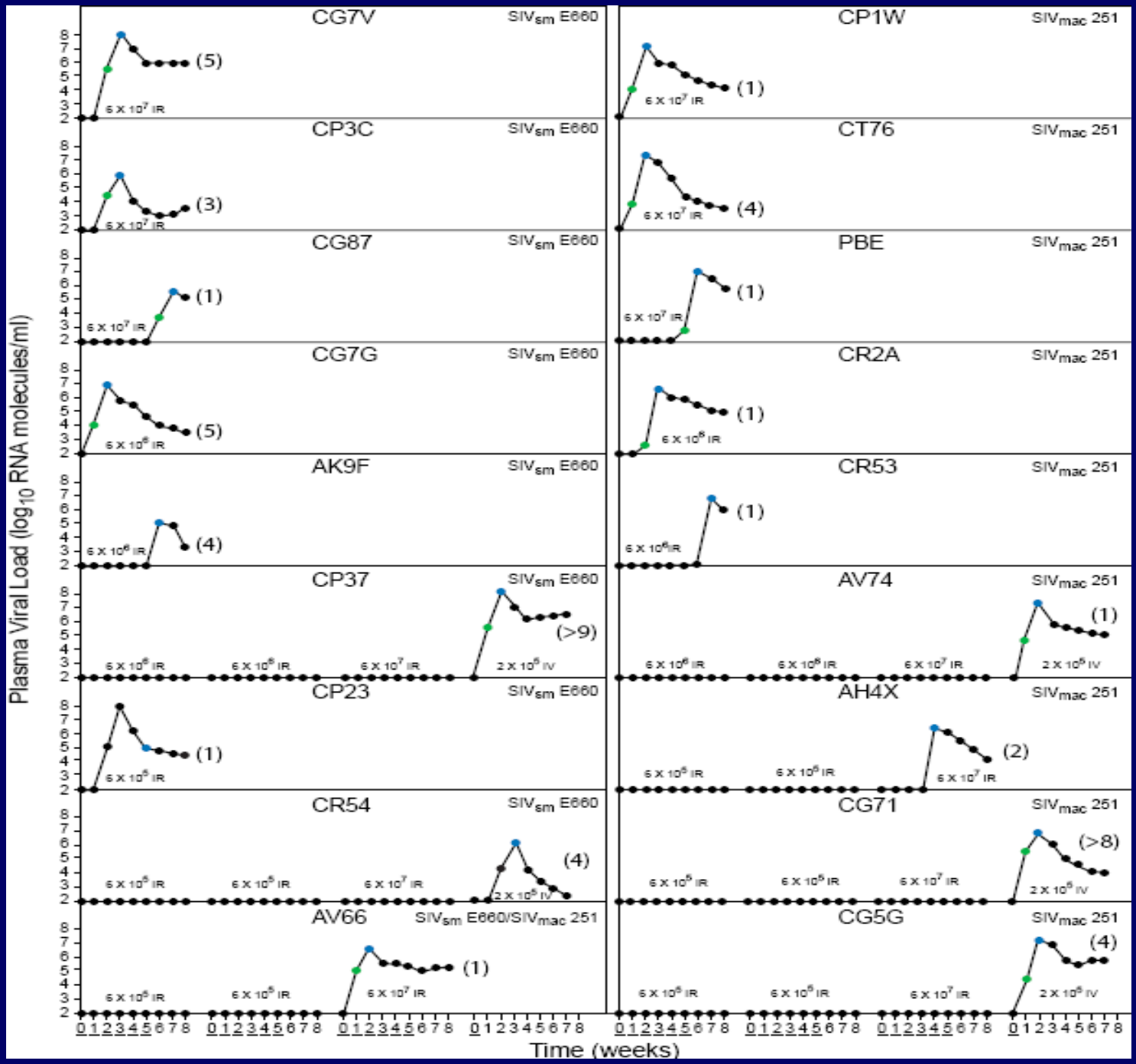
Model also fits primary infection data.

Stafford et al.
J Theoret Biol.
203: 285 (2000)

Note virus is not visible at early times = eclipse phase
1 – 3 weeks in humans

Requirements for Infection

- Prob. HIV transmitted/ sex act ~ .001 - .01
- Inject low doses of SIV into monkeys – many times no noticeable infection results
- Suggests early events are stochastic and not all encounters with virus lead to infection.

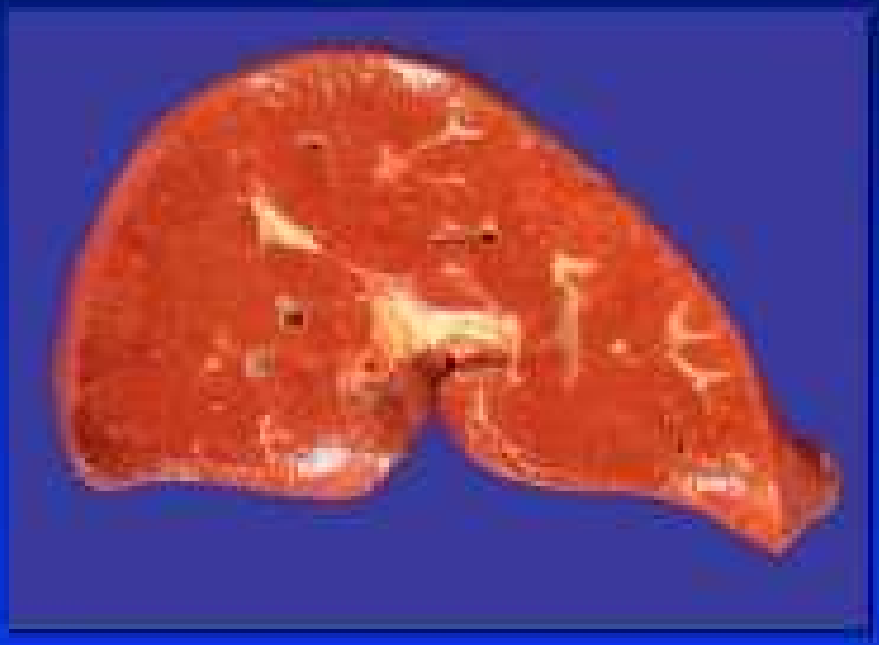

CG7V
SIVsm E660
(5)
6 X 10^7 IR
CP3C
SIVsm E660
(3)
6 X 10^7 IR
CG87
SIVsm E660
(1)
6 X 10^7 IR
CG7G
SIVsm E660
(5)
6 X 10^6 IR
AK9F
SIVsm E660
(4)
6 X 10^6 IR
CP37
SIVsm E660
(>9)
6 X 10^6 IR
6 X 10^6 IR
6 X 10^7 IR
2 X 10^6 IV
CP23
SIVsm E660
(1)
6 X 10^5 IR
CR54
SIVsm E660
(4)
6 X 10^5 IR
6 X 10^5 IR
6 X 10^7 IR
2 X 10^6 IV
AV66
SIVsm E660/SIVmac 251
(1)
6 X 10^5 IR
6 X 10^5 IR
6 X 10^7 IR
CP1W
SIVmac 251
(1)
6 X 10^7 IR
CT76
SIVmac 251
(4)
6 X 10^7 IR
PBE
SIVmac 251
(1)
6 X 10^7 IR
CR2A
SIVmac 251
(1)
6 X 10^6 IR
CR53
SIVmac 251
(1)
6 X 10^6 IR
AV74
SIVmac 251
(1)
6 X 10^6 IR
6 X 10^6 IR
6 X 10^7 IR
2 X 10^6 IV
AH4X
SIVmac 251
(2)
6 X 10^5 IR
6 X 10^5 IR
6 X 10^7 IR
CG71
SIVmac 251
(>8)
6 X 10^5 IR
6 X 10^5 IR
6 X 10^7 IR
2 X 10^6 IV
CG5G
SIVmac 251
(4)
6 X 10^5 IR
6 X 10^5 IR
6 X 10^7 IR
2 X 10^6 IV
Plasma Viral Load (log10 RNA molecules/ml)
Time (weeks)

Hepatitis C Virus Infection

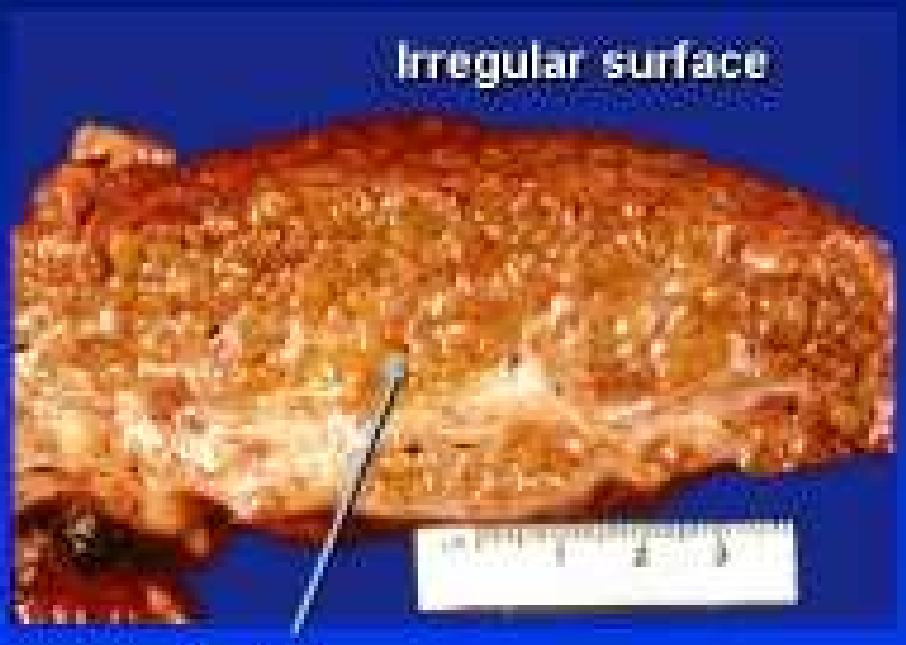
- HCV is a positive strand RNA virus that infects the liver
- It can lead to cirrhosis and liver cancer with a varying time course, from a few years (fulminant hepatitis) to > 30 years
- ~ 4 million infected in the US
- Can be treated with interferon (IFN), but ~50% of people fail to respond to best available therapy.
- No vaccine available.

Cirrhosis

Normal



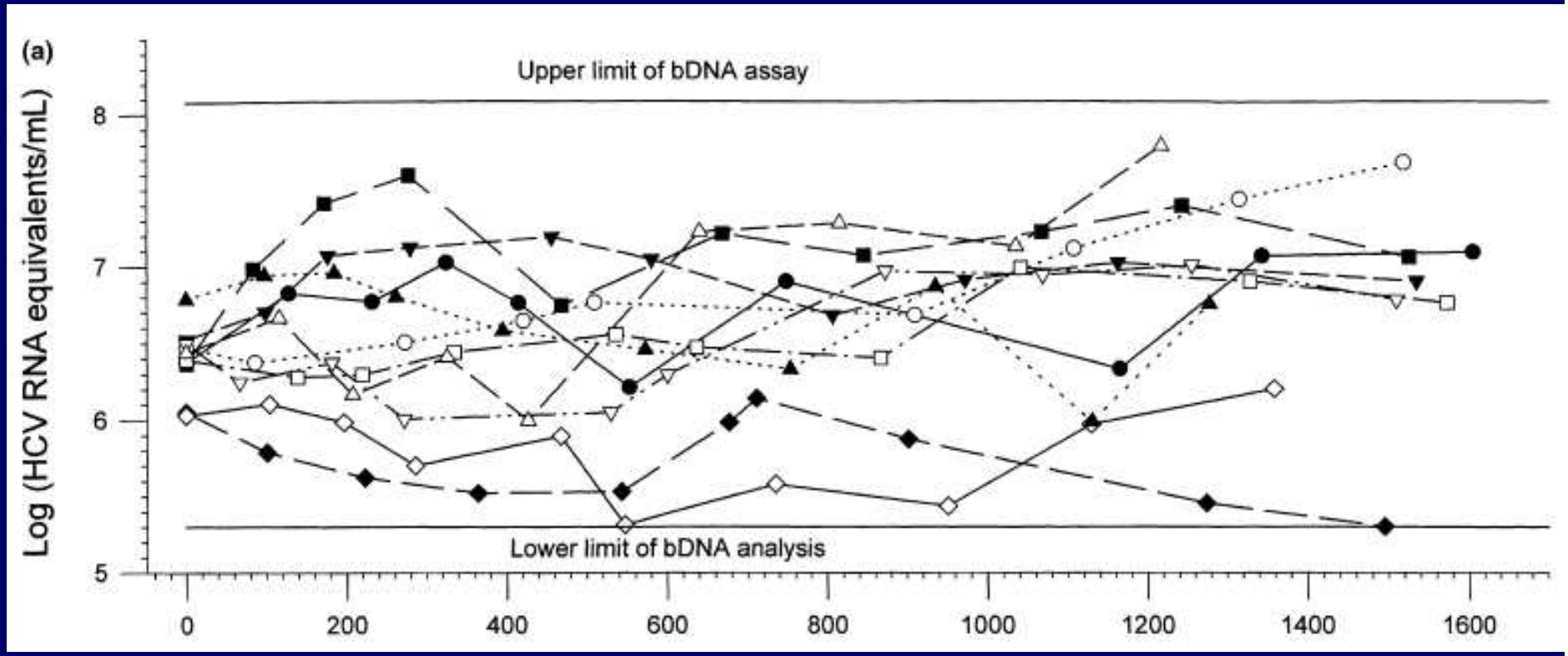
Cirrhosis



HCV treatment

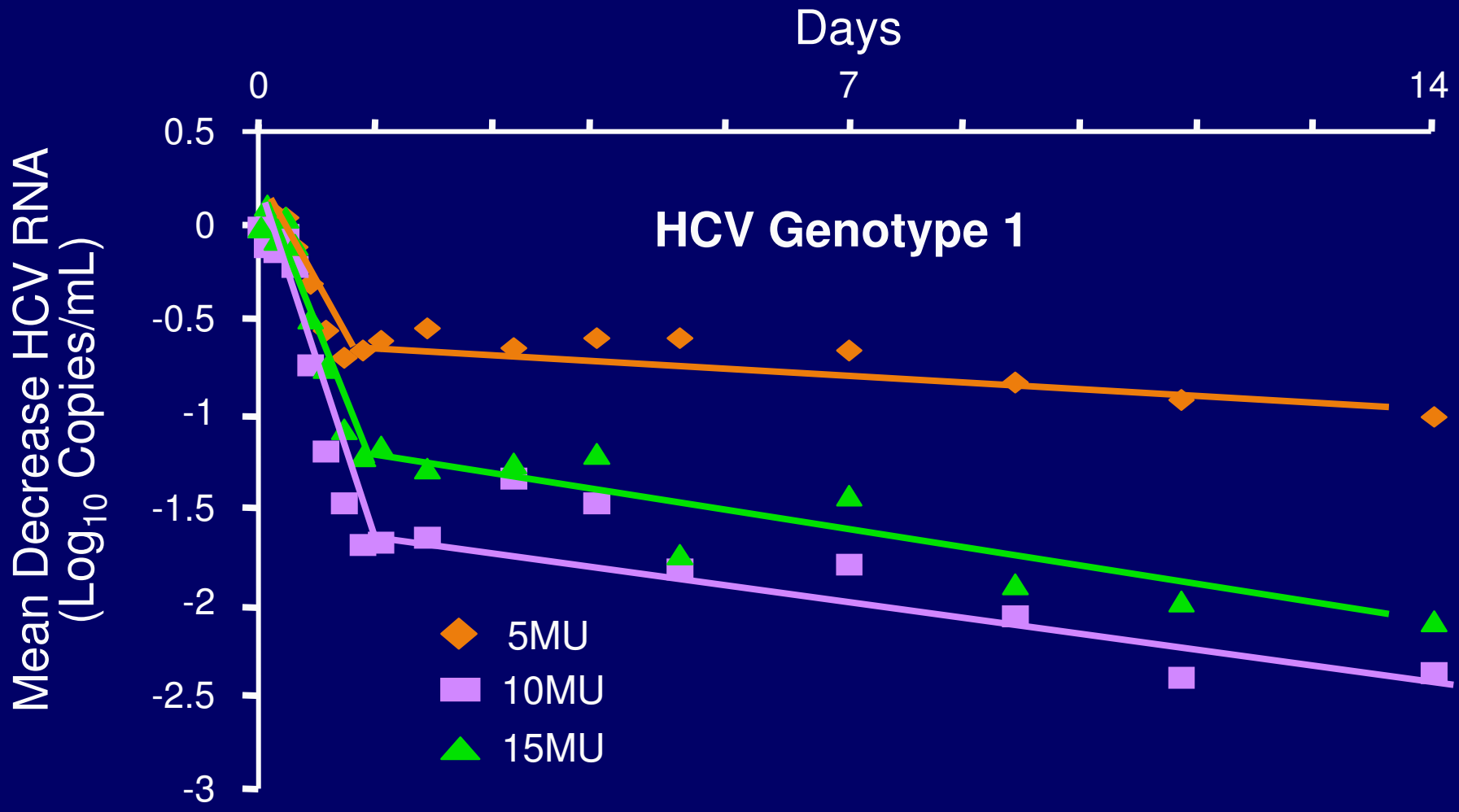
- Current standard therapy, consisting of pegylated interferon and ribavirin, is effective in only ~50% of treated HCV patients; serious adverse effects in some patients
- A number of small molecule drugs, including protease inhibitors and polymerase inhibitors, are being developed and evaluated in clinical trials.

HCV RNA stable in chronic infection



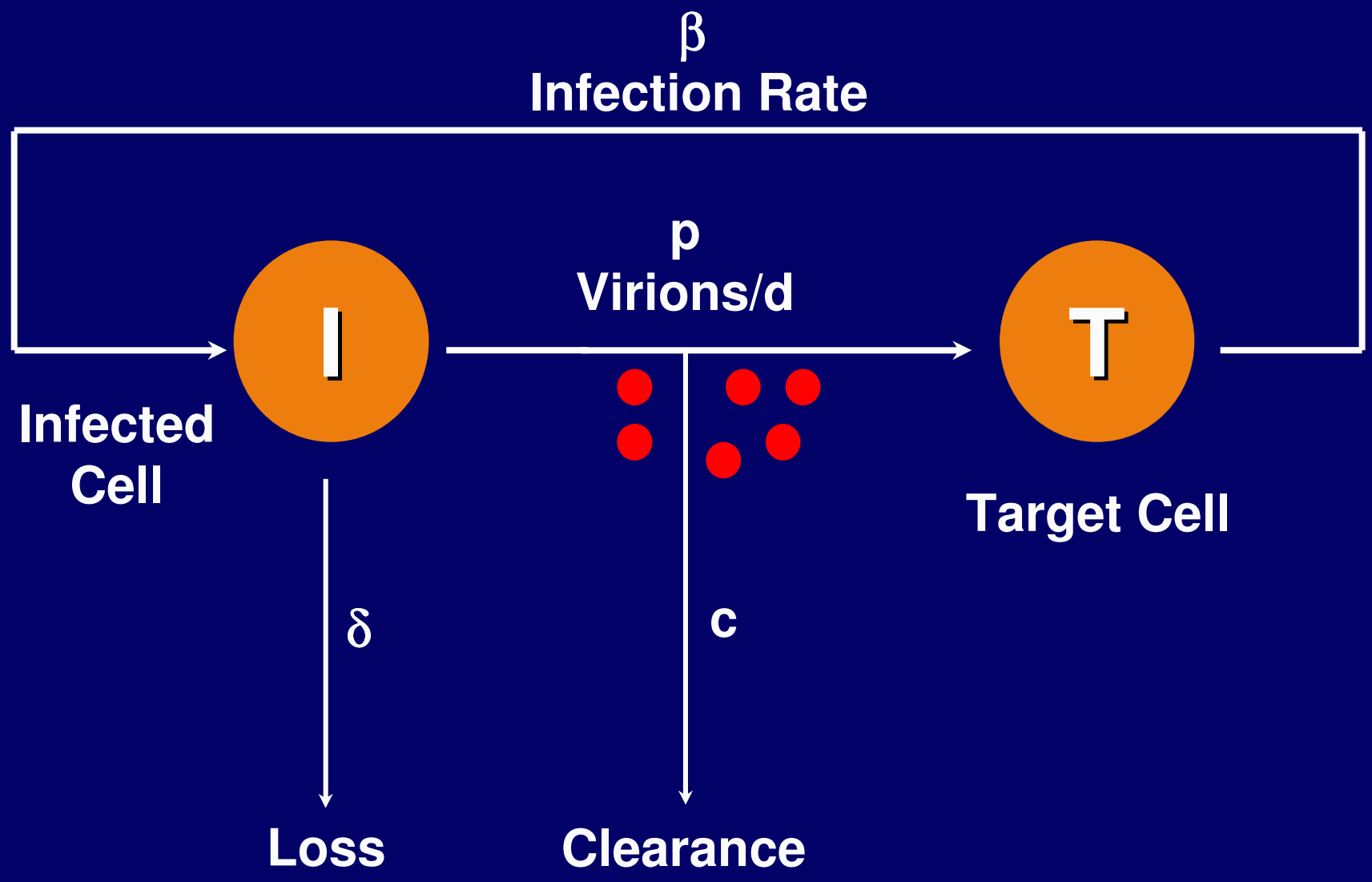
Yeo et al. J. Viral Hepat. 8:256 2001

Mean Decrease in HCV RNA Levels Over First 14 Days of Daily IFN-α Treatment

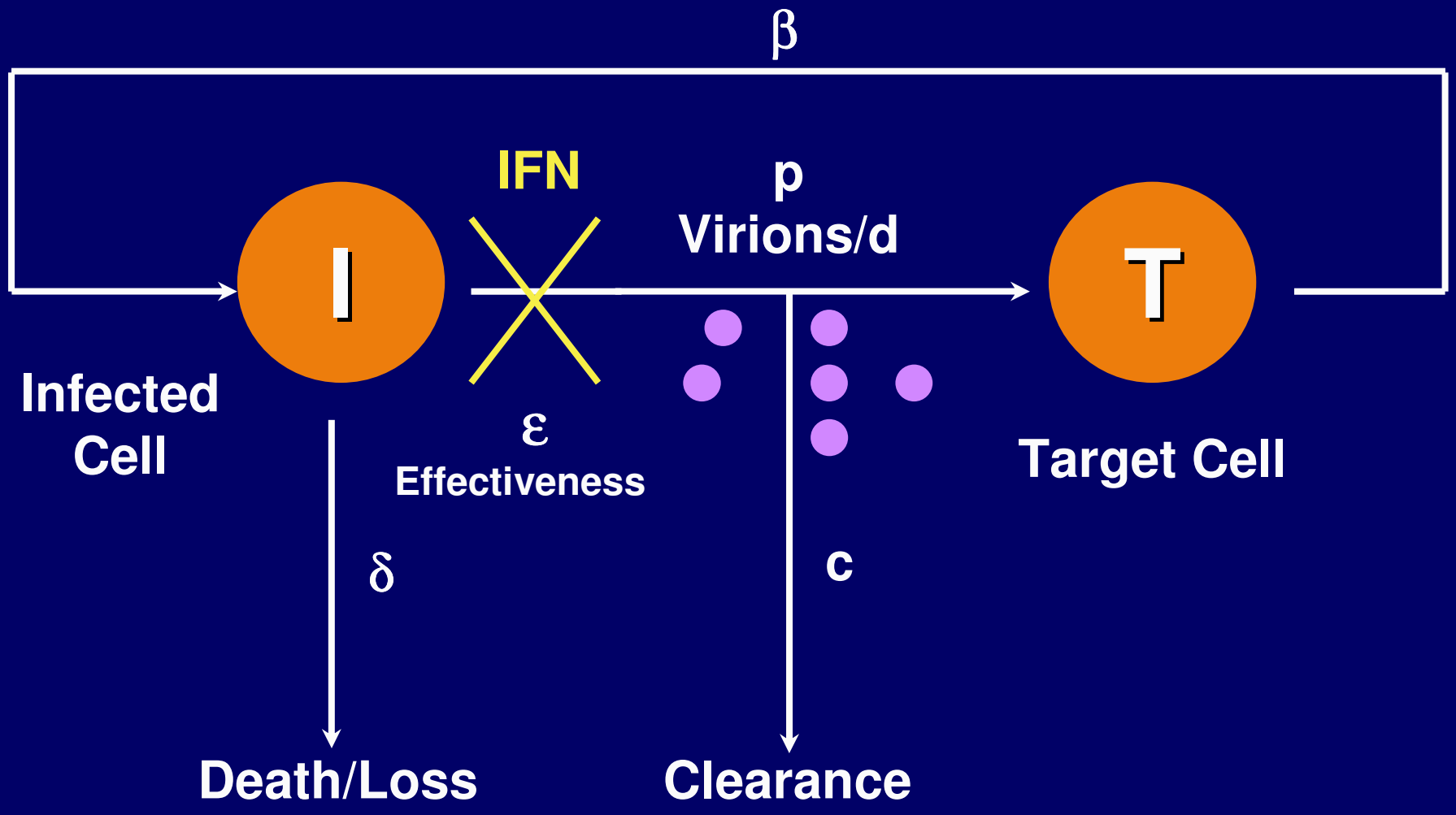


Lam N. DDW. 1998 (abstract L0346).

Model of HCV Infection



IFN Partially Blocks Production



IFN Effectiveness in Blocking Production

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

Early Kinetic Analysis

- Before therapy, assume steady state so that $pI_0 = cV_0$. Also, assume at short times, I=constant=I_0, so that

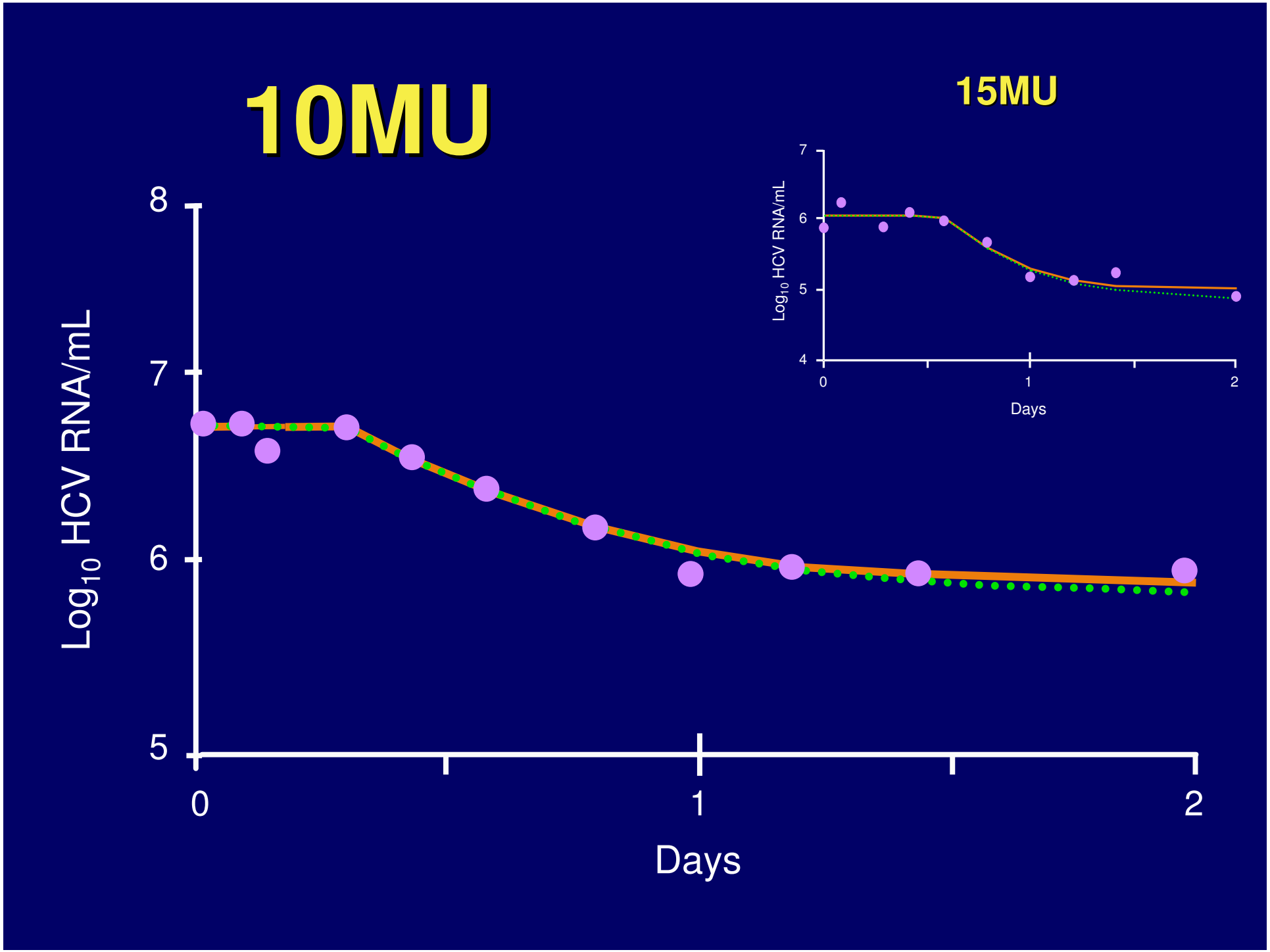
$$dV/dt = (1-\varepsilon)pI - cV = (1-\varepsilon)cV_0 - cV,\ V(0)=V_0$$

- Model predicts that after therapy is initiated, the viral load will initially change according to:

$$\mathbf{V(t) = V_0[1 - \varepsilon + \varepsilon\, exp(-ct)]}$$

- This equation can be fit to data and **c** and ε estimated.

- This suggests drug effectiveness can be determined within the first few days of treatment!

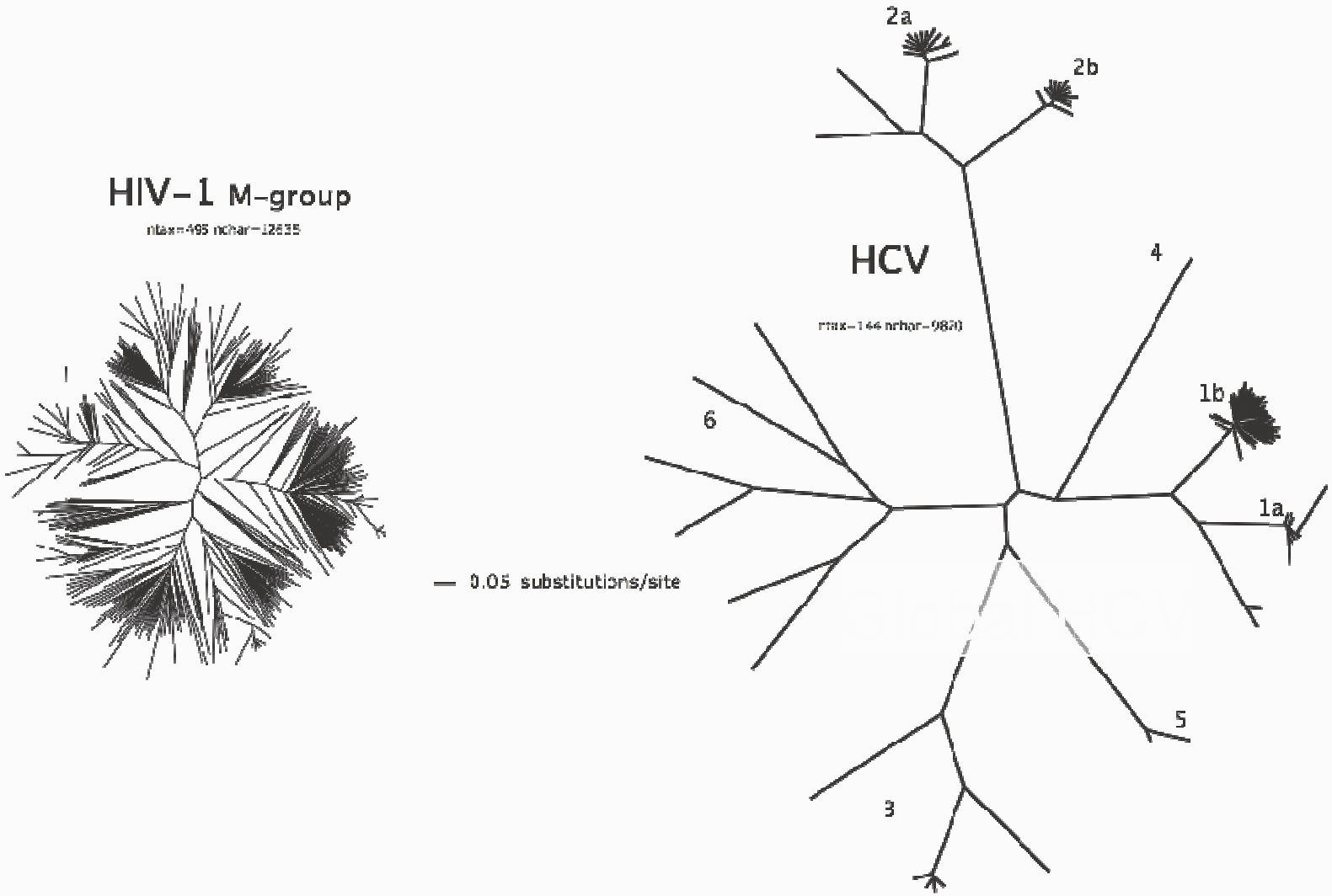

10MU
15MU
Log10 HCV RNA/mL
8
7
6
5
0
1
2
Days
Log10 HCV RNA/mL
7
6
5
4
0
1
2
Days

Viral Kinetics of HCV Genotype 1

	Drug Efficacy	Viral Clearance Constant (1/d)	Half-life of Virions (Hours)	Production & Clearance Rates (10^{12} Virions/d)
5MU	81 ± 4%	6.2 ± 0.8	2.7	0.4 ± 0.2
10MU	95 ± 4%	6.3 ± 2.4	2.6	2.3 ± 4
15MU	96 ± 4%	6.1 ± 1.9	2.7	0.6 ± 0.8

$t_{1/2}$ estimates independently validated;
Ramratnam et al. Lancet 1999

Inter-subtype distances are greater for HCV than for HIV-1



Standard Model of HCV Dynamics

Equations

$$\frac{dT}{dt} = \lambda - dT - \beta VT$$

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

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

Parameters

- λ Supply of target cells
- d Net loss rate of target cells
- β Infectivity rate constant
- δ Infected cell death rate
- ε Drug efficacy
- p Virion production rate
- c Virion clearance rate constant

Variables

- T Target Cell Density
- I Infected Cell Density
- V Virus Concentration

Initial Conditions

$T(0) = T_0$ $\quad V(0) = V_0$

$I(0) = I_0$

Solution: Change in Viral Load

- Assuming $T = T_0$=constant, and pretreatment steady state $\beta T_0 = c\delta/p$

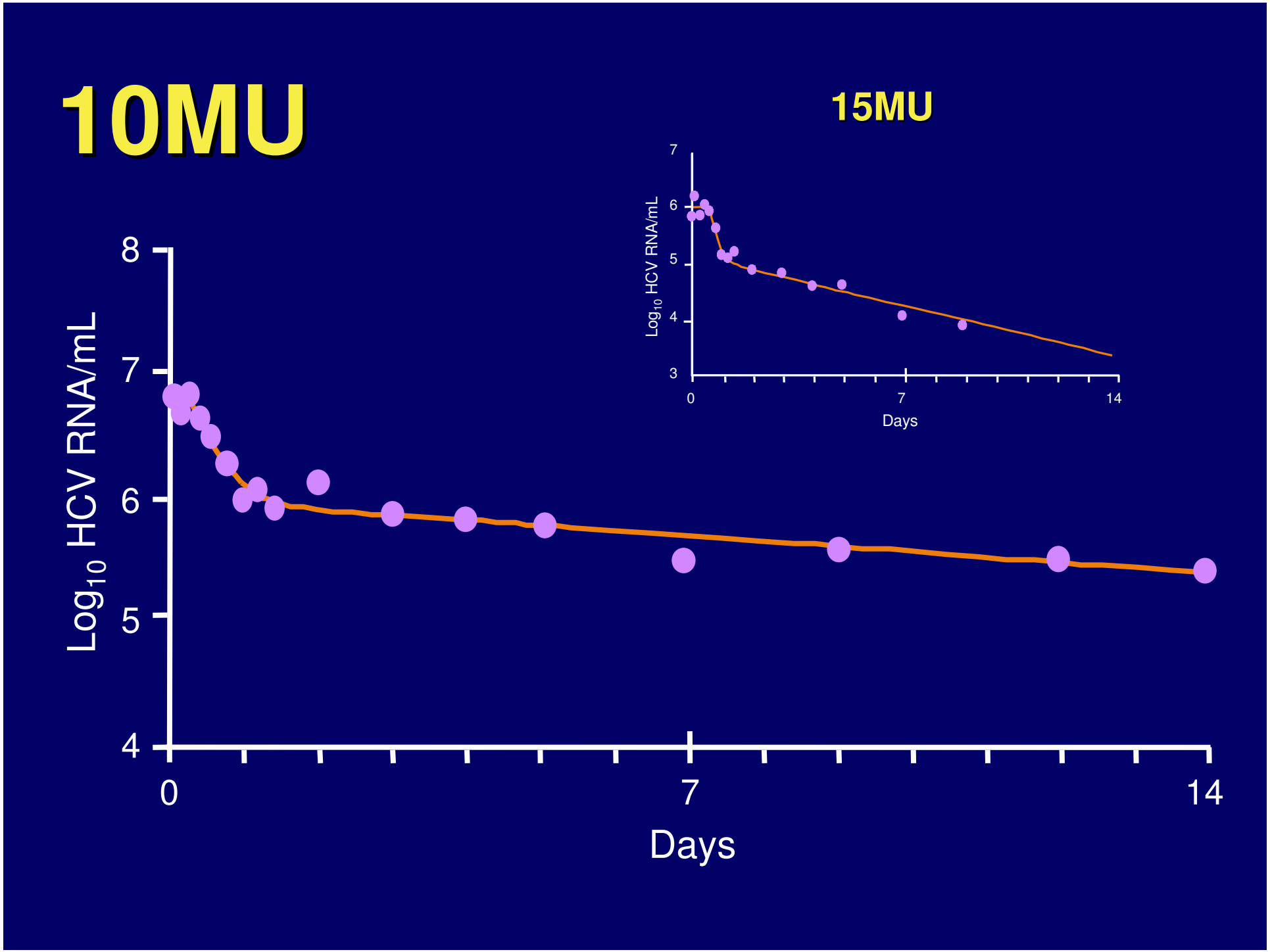
$$V(t) = \frac{1}{2} V_0 [(1 - \frac{c + \delta - 2\varepsilon c}{\theta}) e^{-\lambda_1 (t - t_0)} + (1 + \frac{c + \delta - 2\varepsilon c}{\theta}) e^{-\lambda_2 (t - t_0)}]$$

where

$$\lambda_1 = \frac{1}{2}(c + \delta + \theta) \qquad \lambda_2 = \frac{1}{2}(c + \delta - \theta) \qquad \theta = \sqrt{(c - \delta)^2 + 4(1 - \varepsilon) c\delta}$$

t_0 = delay between treatment commencement and onset of effect

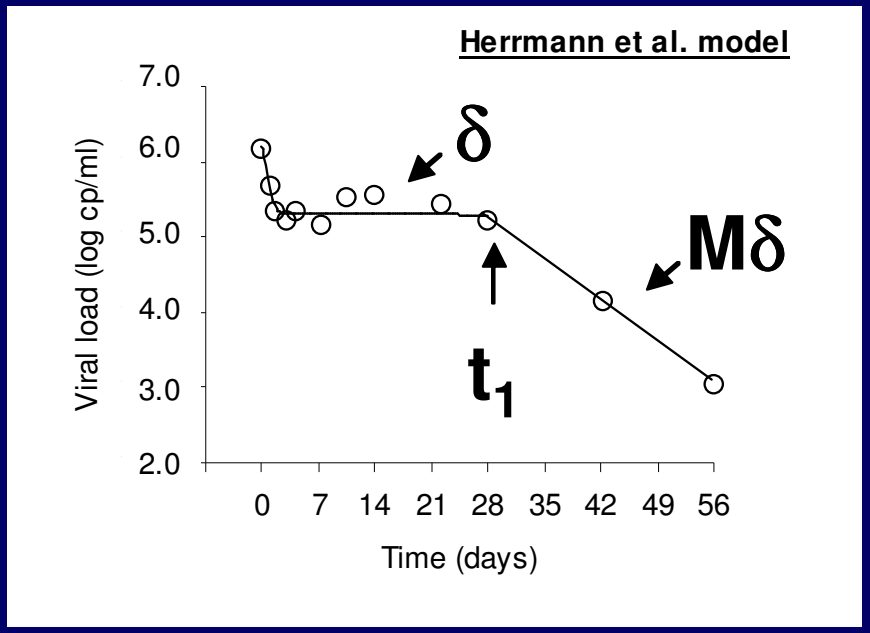
- When c>>δ, $\lambda_1 \approx c$ and $\lambda_2 \approx \varepsilon\delta$

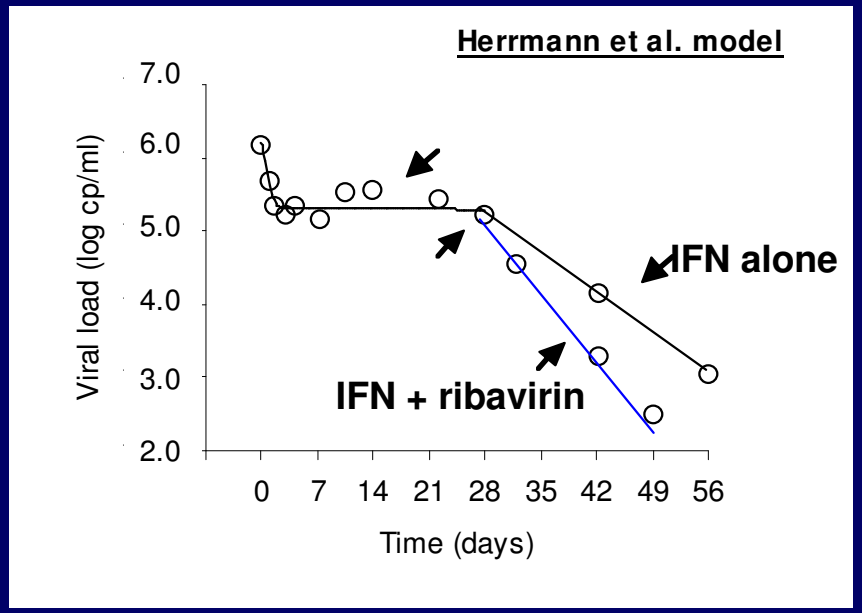

10MU
15MU
Log10 HCV RNA/mL
8
7
6
5
4
0
7
14
Days
Log10 HCV RNA/mL
7
6
5
4
3
0
7
14
Days

Viral Kinetics of HCV Genotype 1

	Drug Efficacy	Second Phase Decay Constant, δ (1/d)	Half-life of Infected Cells (Days)
5MU	81 ± 4%	0.09 ± 0.14	2.2–69.3
10MU	95 ± 4%	0.10 ± 0.05	4.3–17.3
15MU	96 ± 4%	0.24 ± 0.15	1.7–6.3

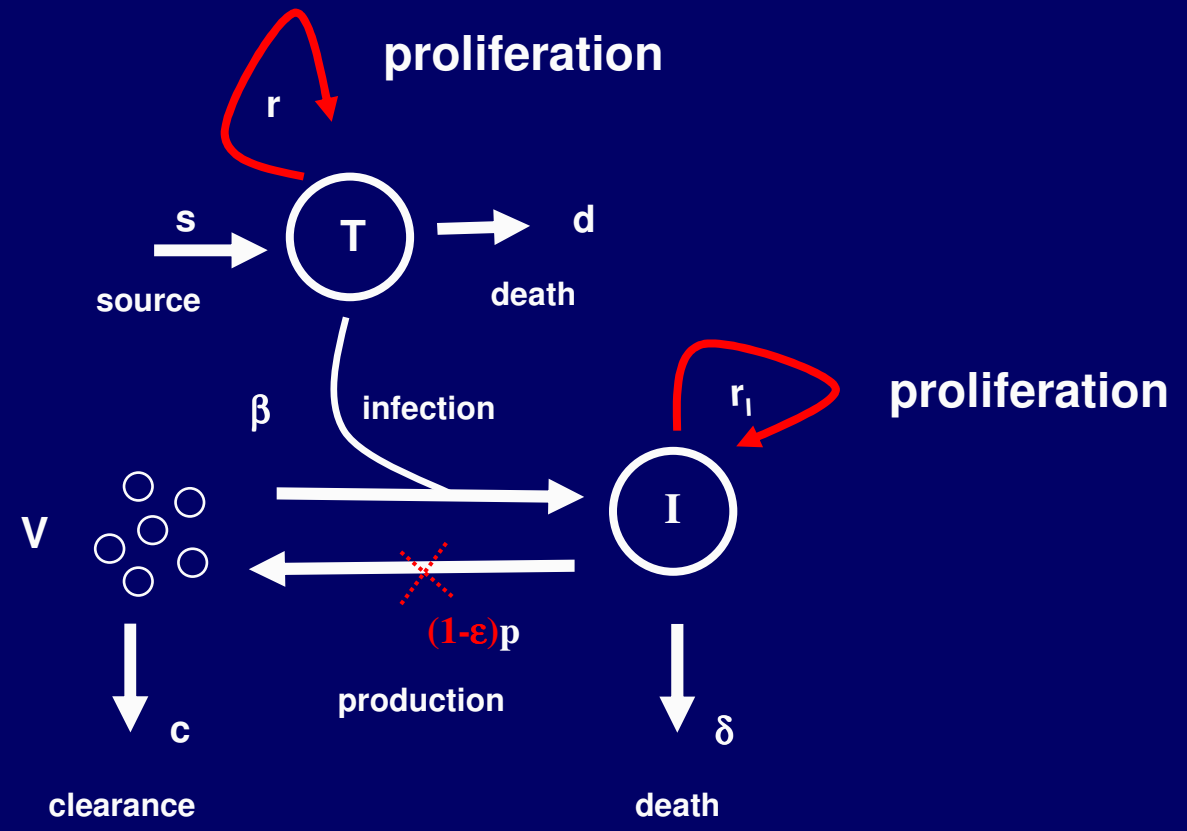
Triphasic Decay





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

Extended Model: Proliferation



Dahari et al., Hepatology 2007; JTB 2007

Model with proliferation

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

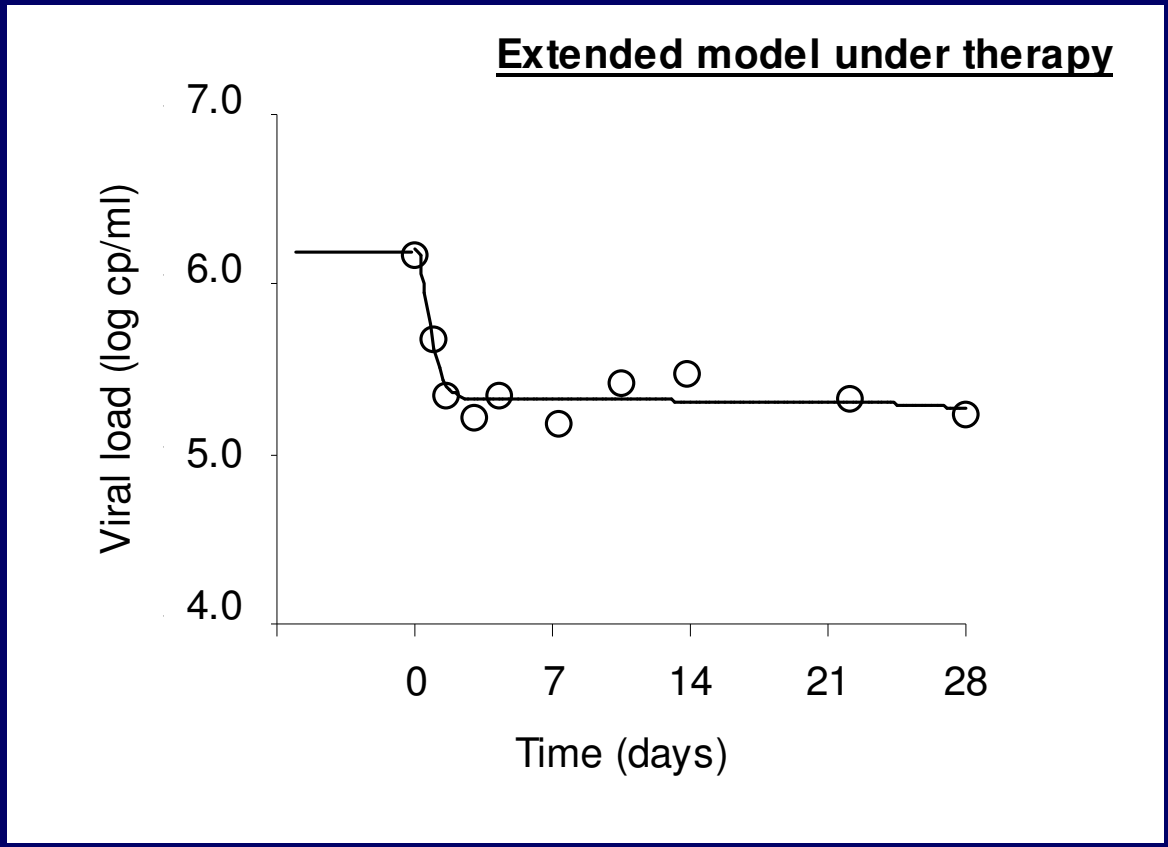
$$\frac{\mathrm{d}I}{\mathrm{d}t} = (1-\eta)\beta VT + rI\left(1 - \frac{T+I}{T_{max}}\right) - \delta I,$$

$$\frac{\mathrm{d}V}{\mathrm{d}t} = (1-\varepsilon_p)pI - cV,$$

Critical Drug Efficacy

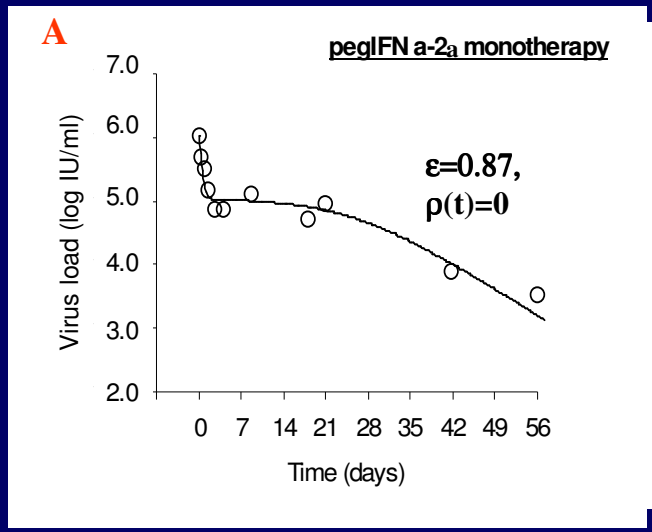
- Drug effectiveness ε:
  - $1-\varepsilon = (1-\varepsilon_p)(1-\eta)$.
- There exists a drug effectiveness, called the critical effectiveness, ε_c, at which the infected steady state amount of virus goes to zero.
- Thus, with $\varepsilon > \varepsilon_c$ model predicts elimination of virus.

$\varepsilon < \varepsilon_c$ Flat 2nd phase

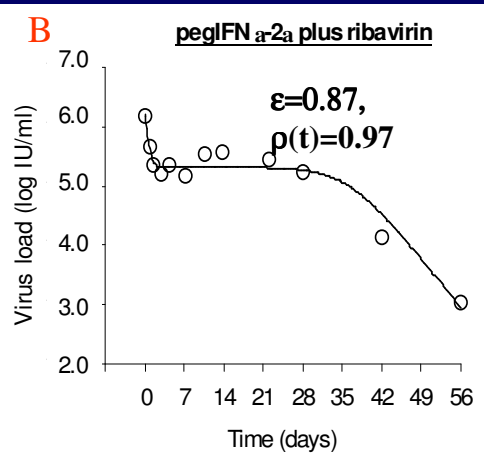


Can have flat 2nd phase with $\delta > 0$ since infected cells replaced by replication and new infection

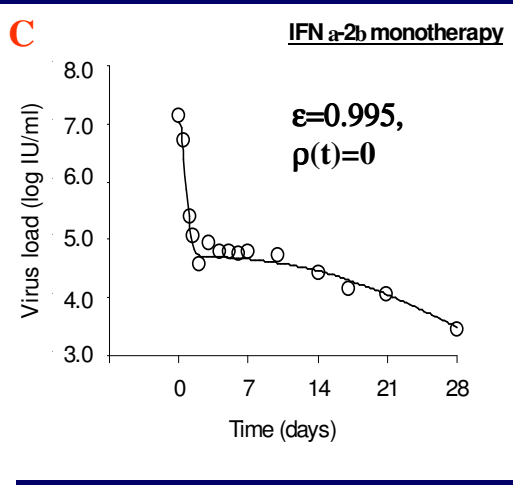
Extended model: Fits to data



Herrmann et al.
(Hepatology 2003)



Herrmann et al.
(Hepatology 2003)

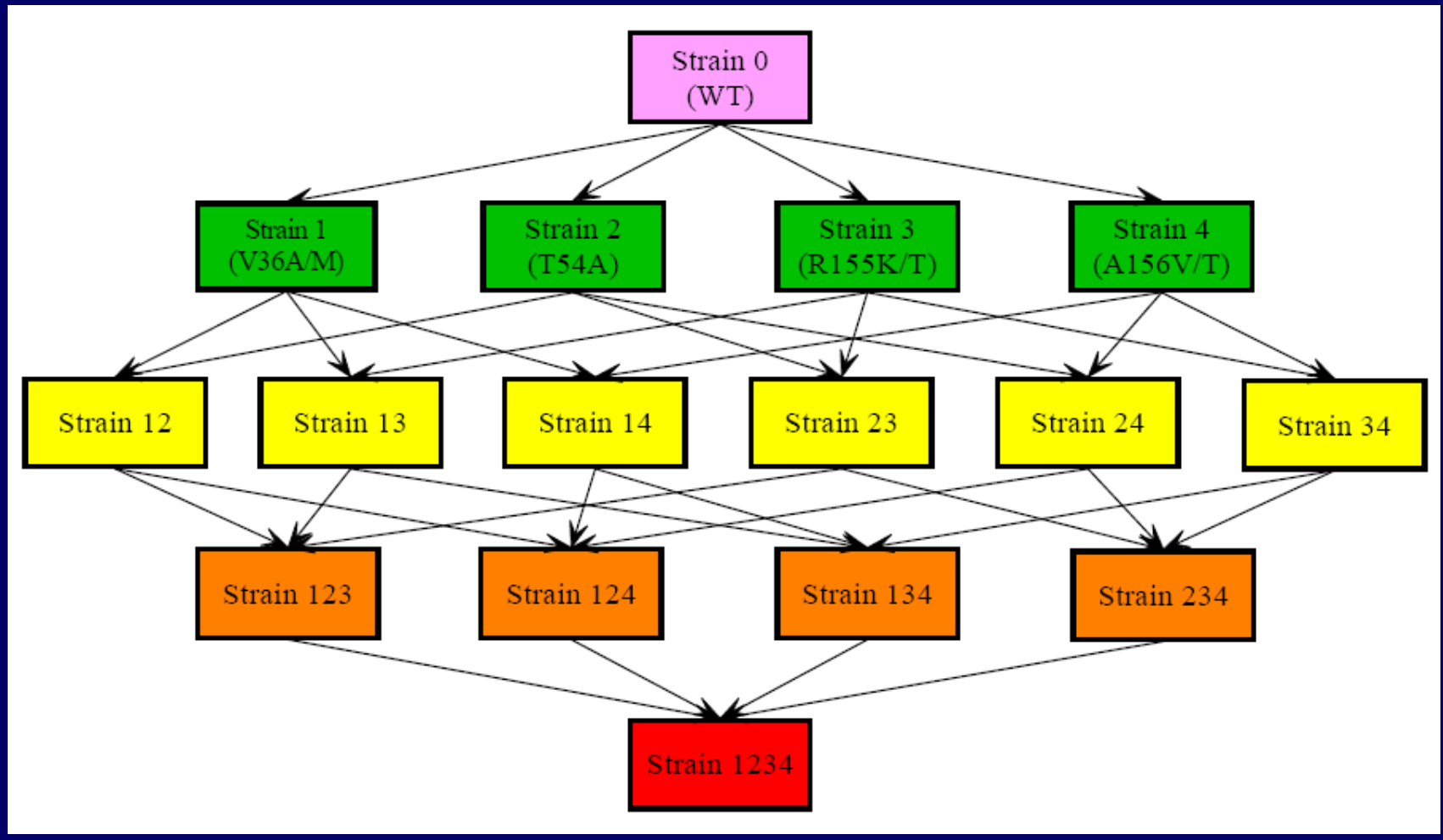


Bekkering et al.
(BMC Gastro 2001)

We fit the extended model to data from patients treated with pegylated interferon a-2a alone (A) or in combination with ribavirin (B), and with daily therapy with interferon a-2b alone (C).

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

Mutations between multiple strains



Conclusions

- Mathematics can have a large impact in medicine. I have given you two examples (HIV and HCV). Within the infectious disease community this type of work is being accepted and valued. There are enormous opportunities in this area, not only in infectious disease, but also in cancer, metabolic diseases, immunology,…..

Collaborators (HIV)

- John Pearson, LANL
- Paul Krapivsky, Boston Univ

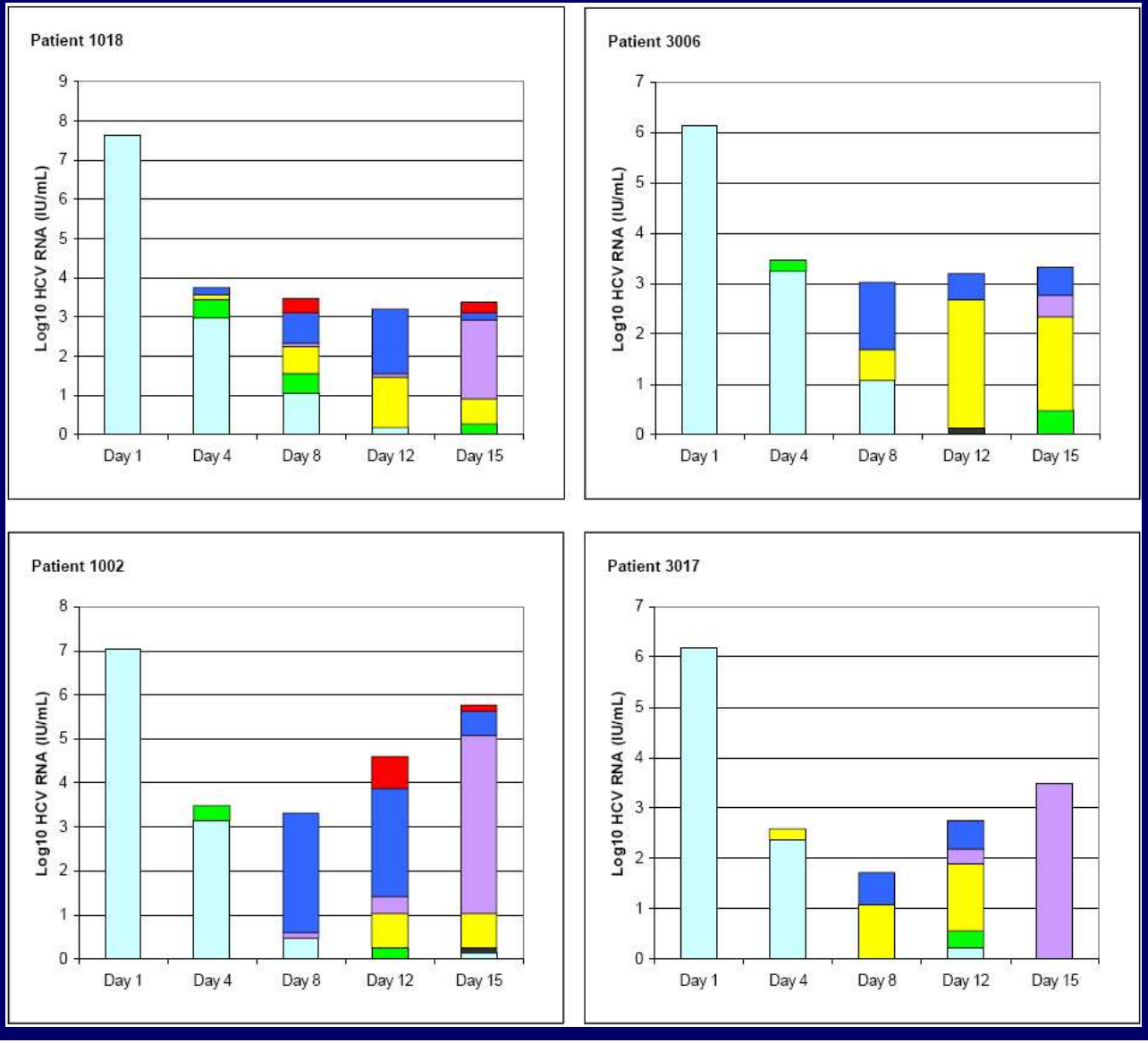
Collaborators (HCV)

- Avidan Neumann, Bar-Ilan Univ
- Harel Dahari, Libin Rong, Emi Shudo and Ruy M. Ribeiro, Los Alamos
- Tim Reluga, Penn State

A new drug against HCV

- Telaprevir (Vertex Pharmaceuticals): a new HCV protease inhibitor
- Demonstrates substantial antiviral activity even as monotherapy
- Drug resistant variants are 5%-20% of the total virus population as early as day 3 after treatment initiation (Kieffer, et al. Hepatology, 2007)
- Such rapid appearance of drug resistance has not been seen with monotherapy for either HIV or hepatitis B virus (HBV) infection

Rapid emergence of resistance



Two-strain model

$$\frac{dT(t)}{dt} = s - dT - \beta_s V_s T - \beta_r V_r T$$

$$\frac{dI_s(t)}{dt} = \beta_s V_s T - \delta I_s$$

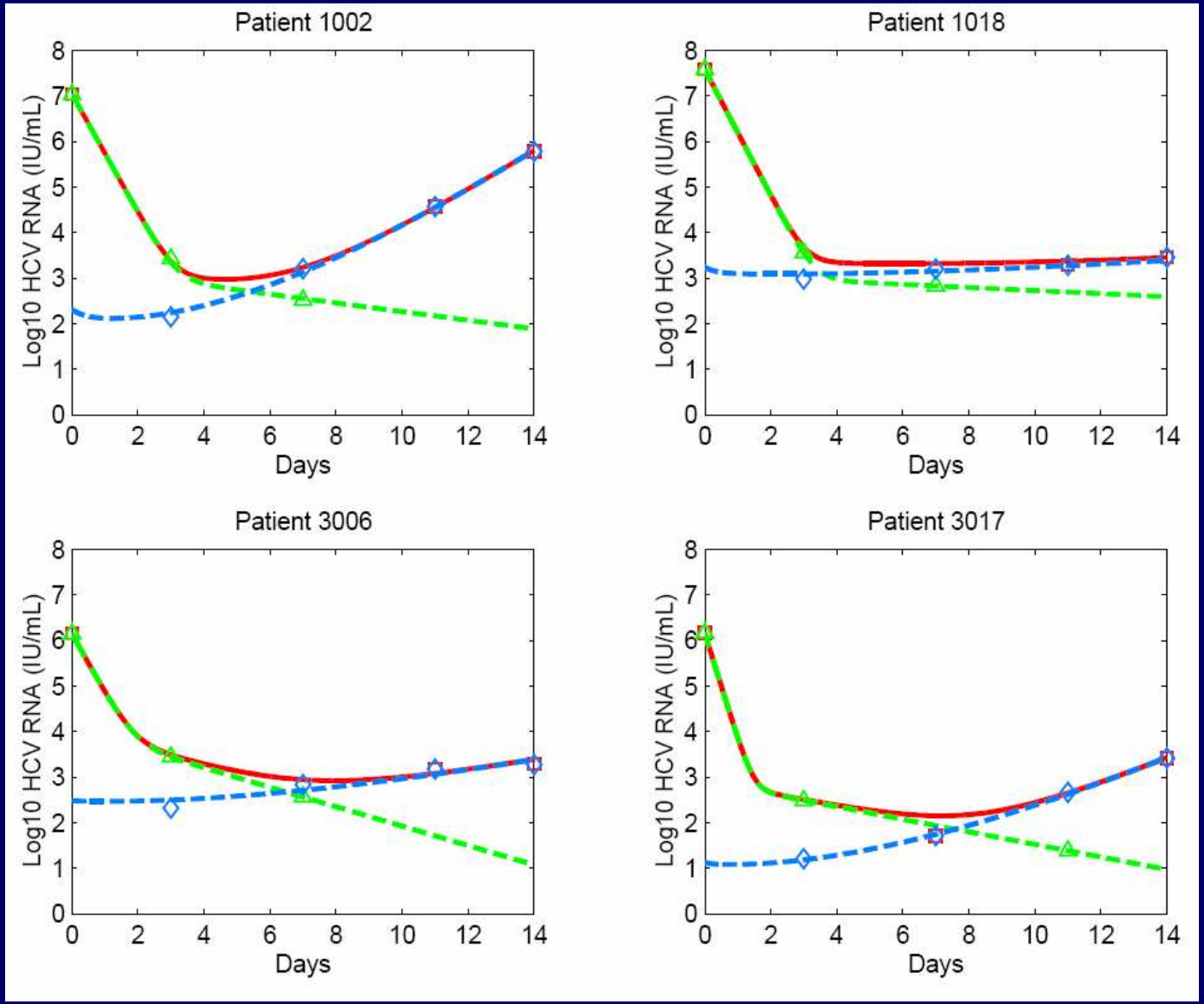
$$\frac{dI_r(t)}{dt} = \beta_r V_r T - \delta I_r$$

$$\frac{dV_s(t)}{dt} = (1-\mu)(1-\varepsilon_s) p_s I_s - cV_s$$

$$\frac{dV_r(t)}{dt} = \mu(1-\varepsilon_s) p_s I_s + (1-\varepsilon_r) p_r I_r - cV_r$$

s=drug sensitive, r=drug resistant

Model fits

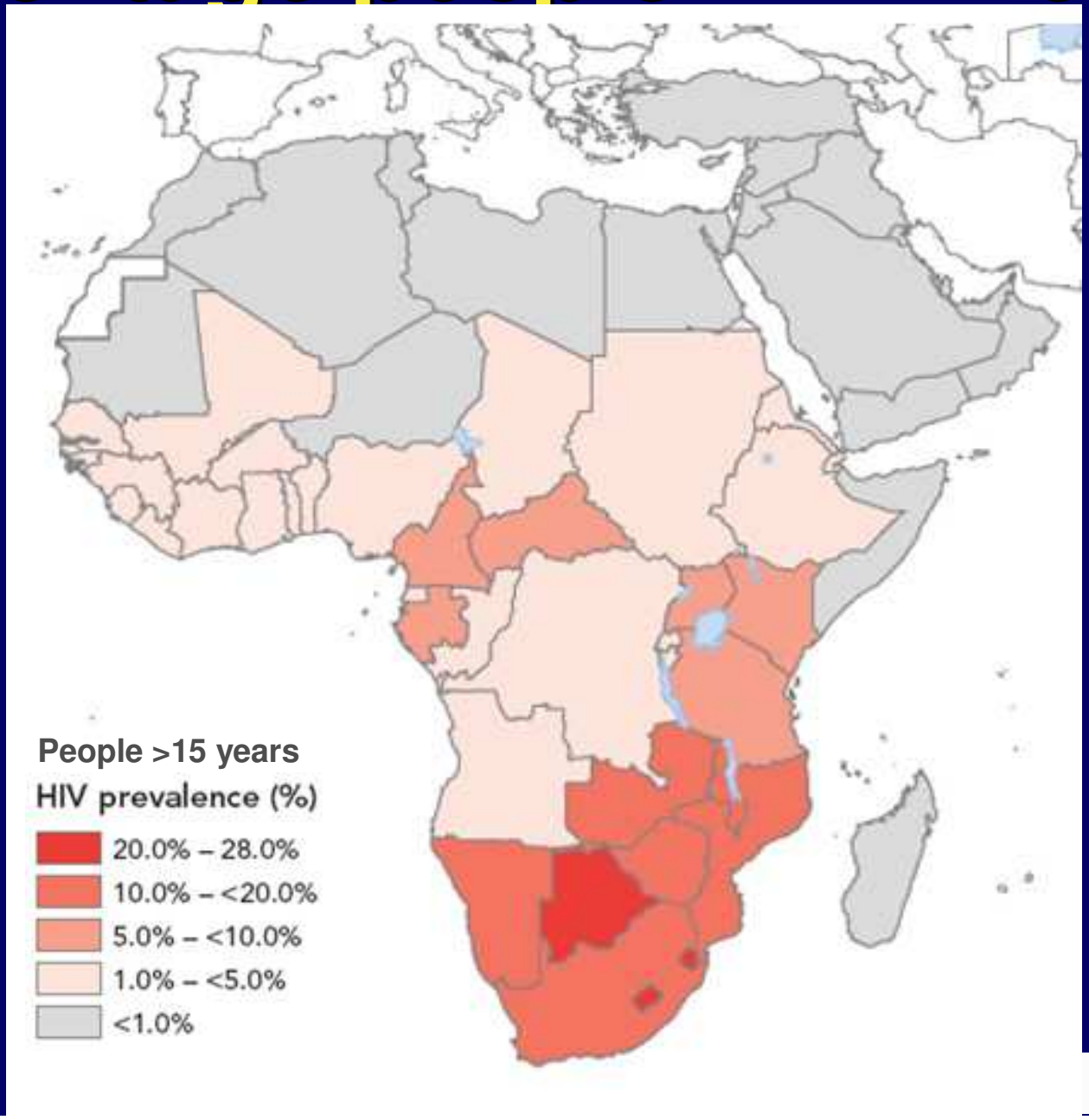

Patient 1002
Patient 1018
Patient 3006
Patient 3017
Log10 HCV RNA (IU/mL)
Days
0
1
2
3
4
5
6
7
8
0
2
4
6
8
10
12
14

Parameter estimates

Patients	δ (day^{-1})	μ (10^{-6})	ε_s	ε_r	β_s (10^{-8} mL day^{-1} $virion^{-1}$)	p_s (virions $cell^{-1}$ day^{-1})	f_p	c (day^{-1})
1018	0.08	12.75	0.99997	0.001	0.77	17.1	0.72	3.2
3006	0.50	3.03	0.99431	0.023	7.06	5.6	0.98	3.0
1002	0.22	6.70	0.99988	0.015	13.64	10.4	0.64	3.0
3017	0.32	0.88	0.99952	0.013	25.85	4.2	0.90	5.4
Average ± SD	0.28 ± 0.18	5.84 ± 5.20	0.99842 ± 0.0027	0.013 ± 0.009	11.83 ± 10.72	9.33 ± 5.82	0.81 ± 0.16	3.65 ± 1.17

Drug efficacy of telaprevir against resistant virus

Percentage people HIV infected



UNAIDS, 2008