How to Model HIV Infection

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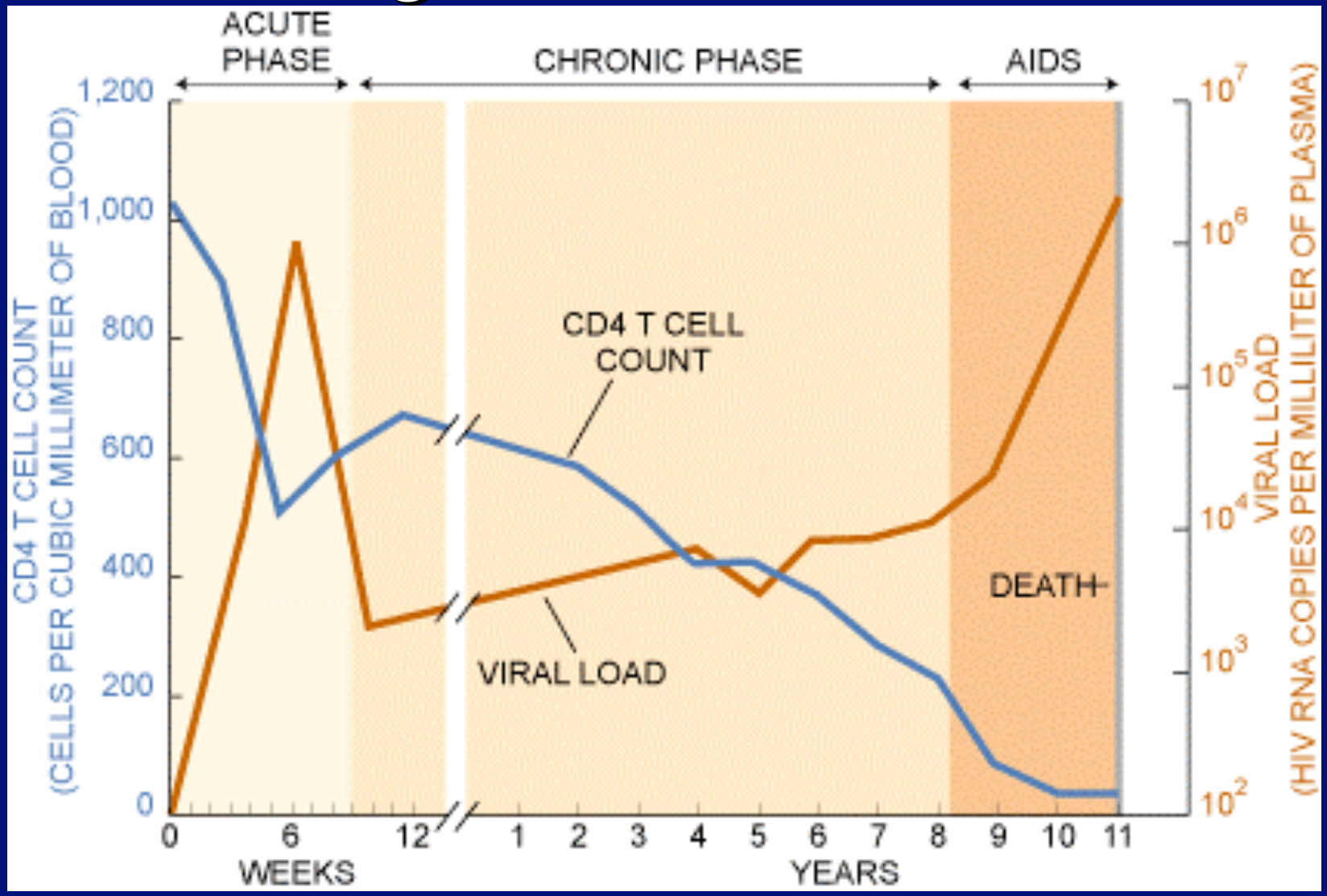
Progression to AIDS



Improving HIV Therapy

Bartlett and Moore, Scientific American, June 1998

http://www.sciam.com/1998/0798issue/0798bartlett.html

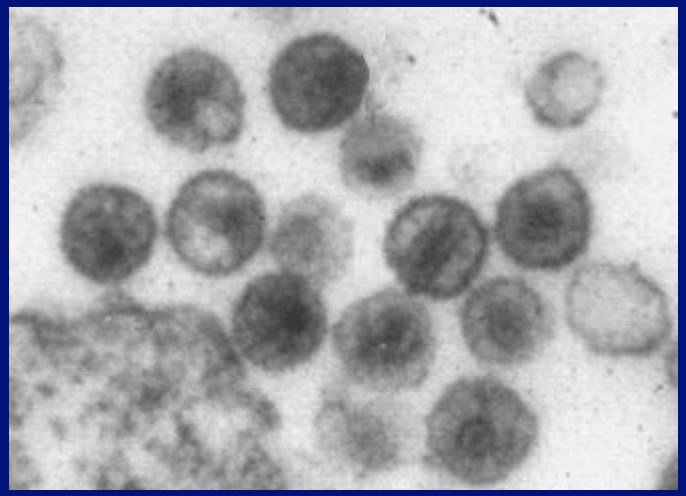
Unresolved Problems

- What causes T cell depletion?
- What determines the 10 year timescale?
- What determines the viral setpoint?
- Why does viral level increase late in disease?

Long time scale is one of the features that led Peter Duesberg, Berkeley, to argue that HIV does not cause AIDS.

What is HIV infection?

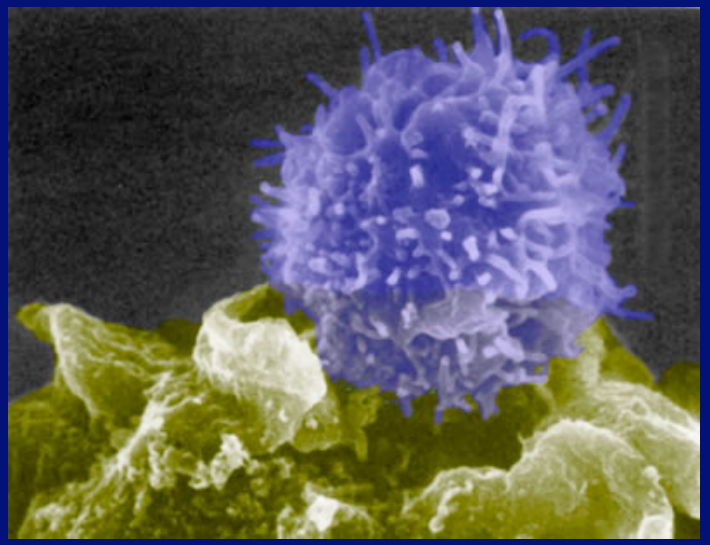
The virus



A retrovirus

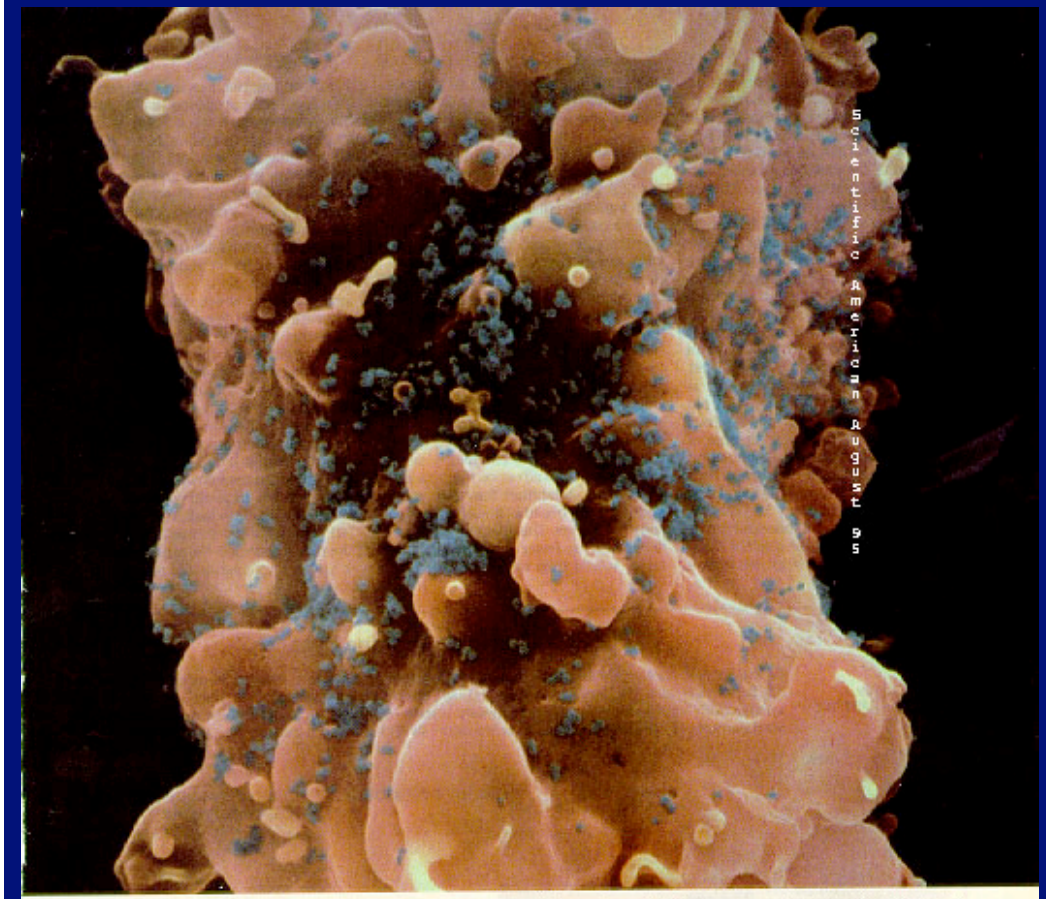
Infects immune cells bearing:
CD4 & CCR5/CXCR4

The host

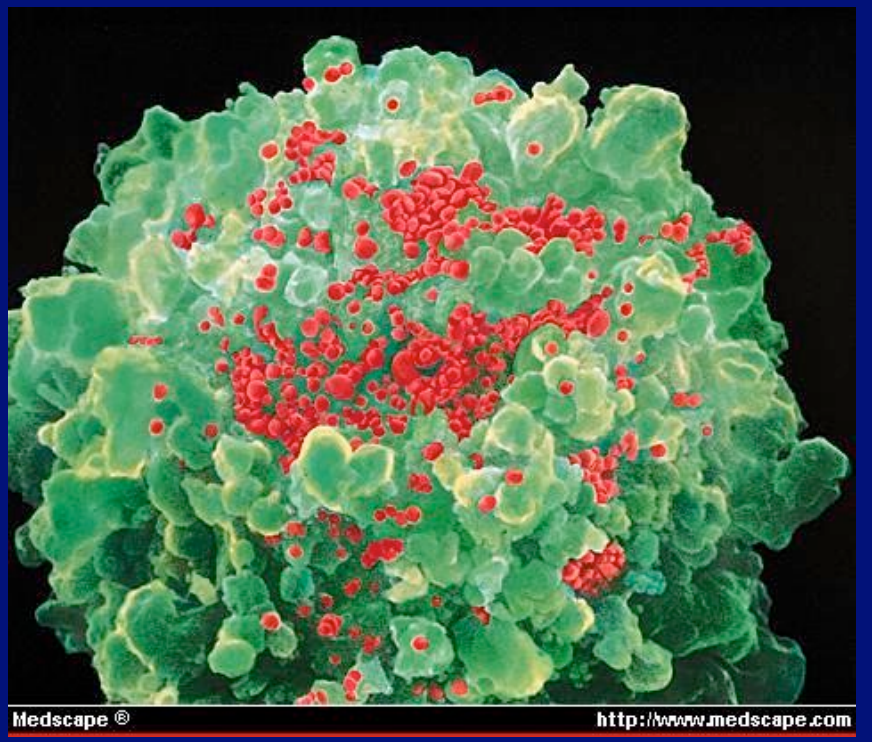


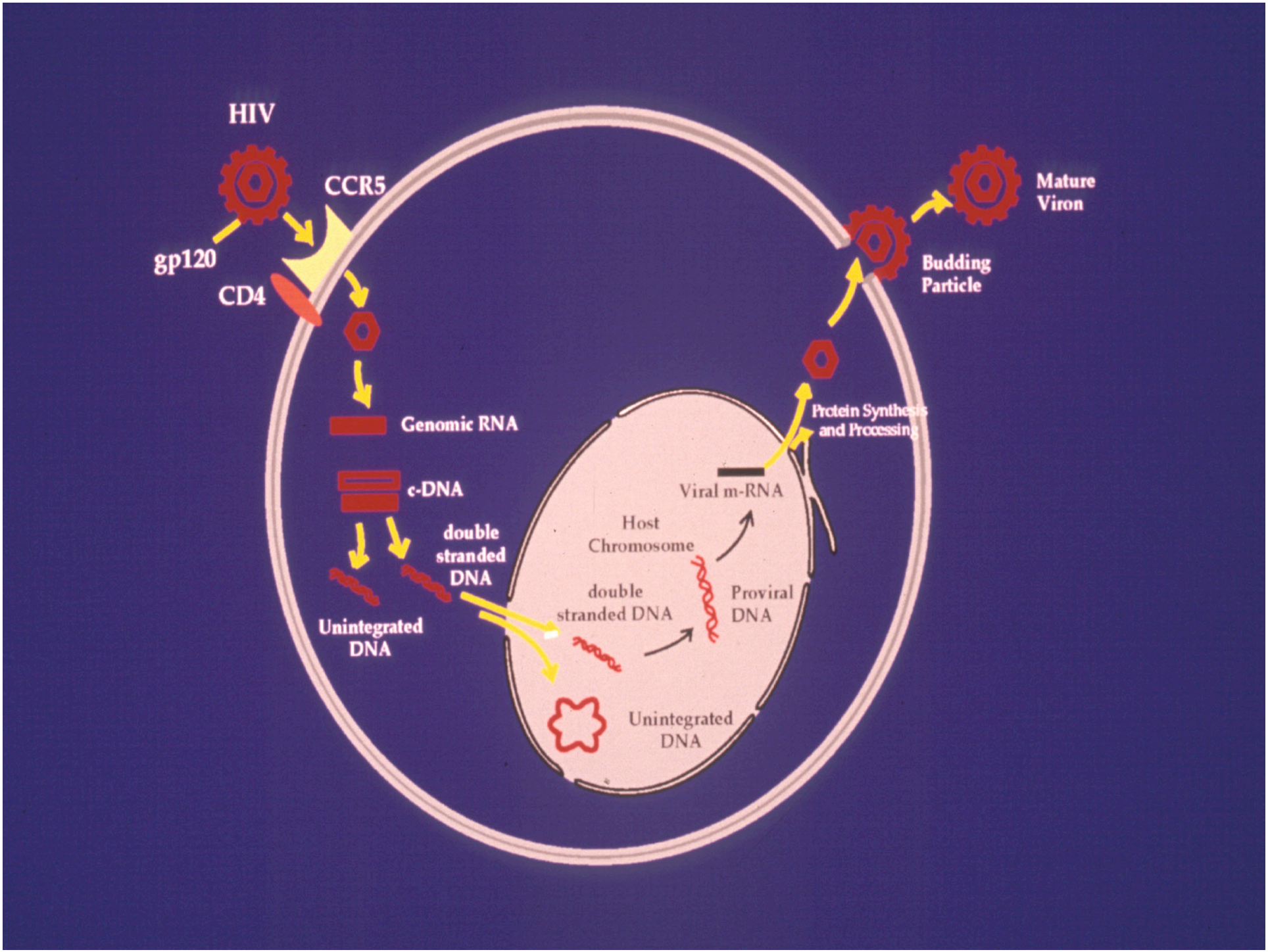
CD4+ T-cells (or helper T cells)

Macrophages and dendritic cells

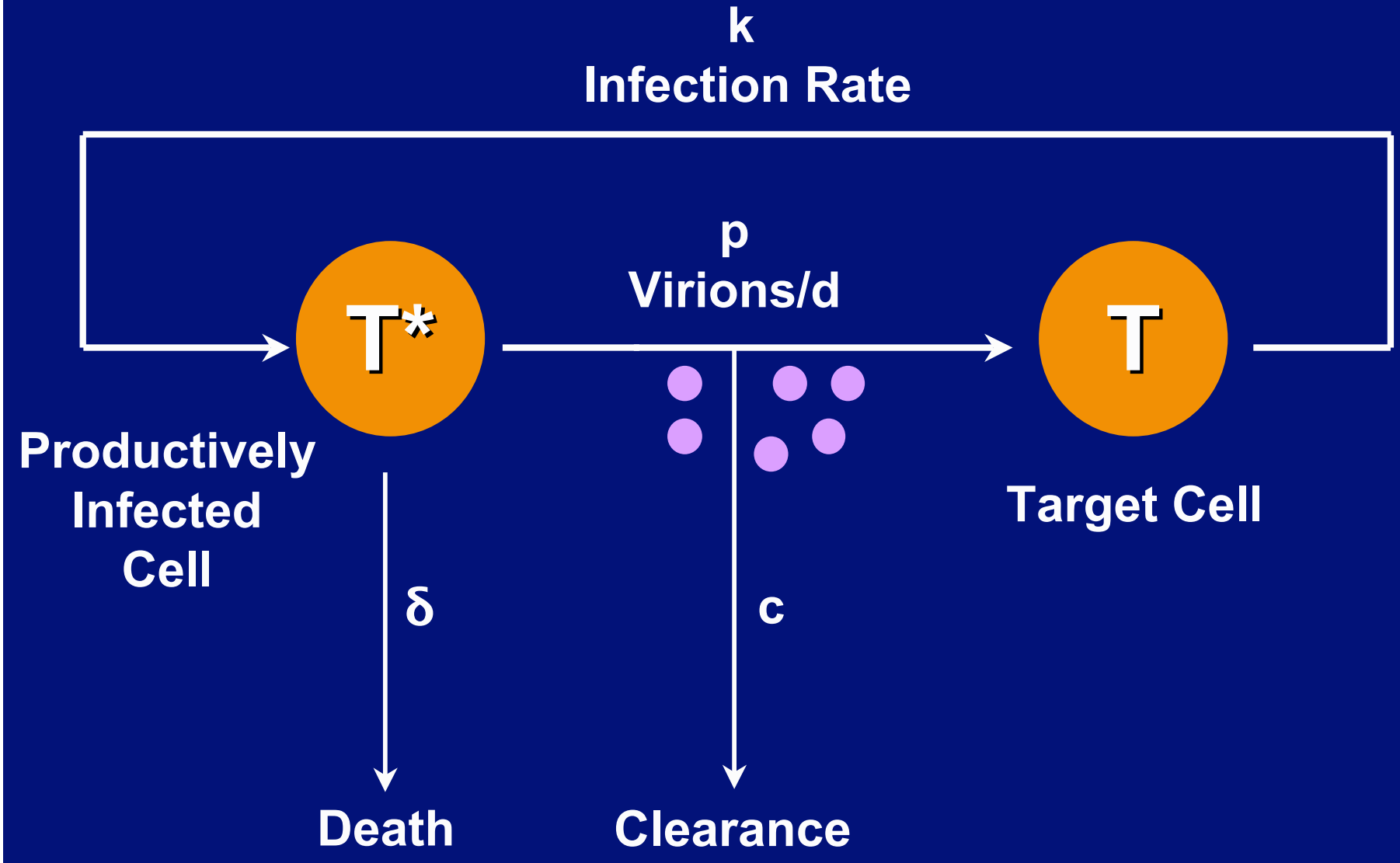


PARTICLES OF HIV (*blue spheres*), the virus that causes AIDS, bud from an infected white blood cell before moving on to infect other cells. The immune system controls such spread at first but is eventually outmaneuvered by the virus.




HIV
gp120
CCR5
CD4
Genomic RNA
c-DNA
double stranded DNA
Unintegrated DNA
Host Chromosome
double stranded DNA
Proviral DNA
Unintegrated DNA
Viral m-RNA
Protein Synthesis and Processing
Budding Particle
Mature Viron

Model of HIV Infection



Model of HIV Infection

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

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

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

$$T(0) = T_0$$

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

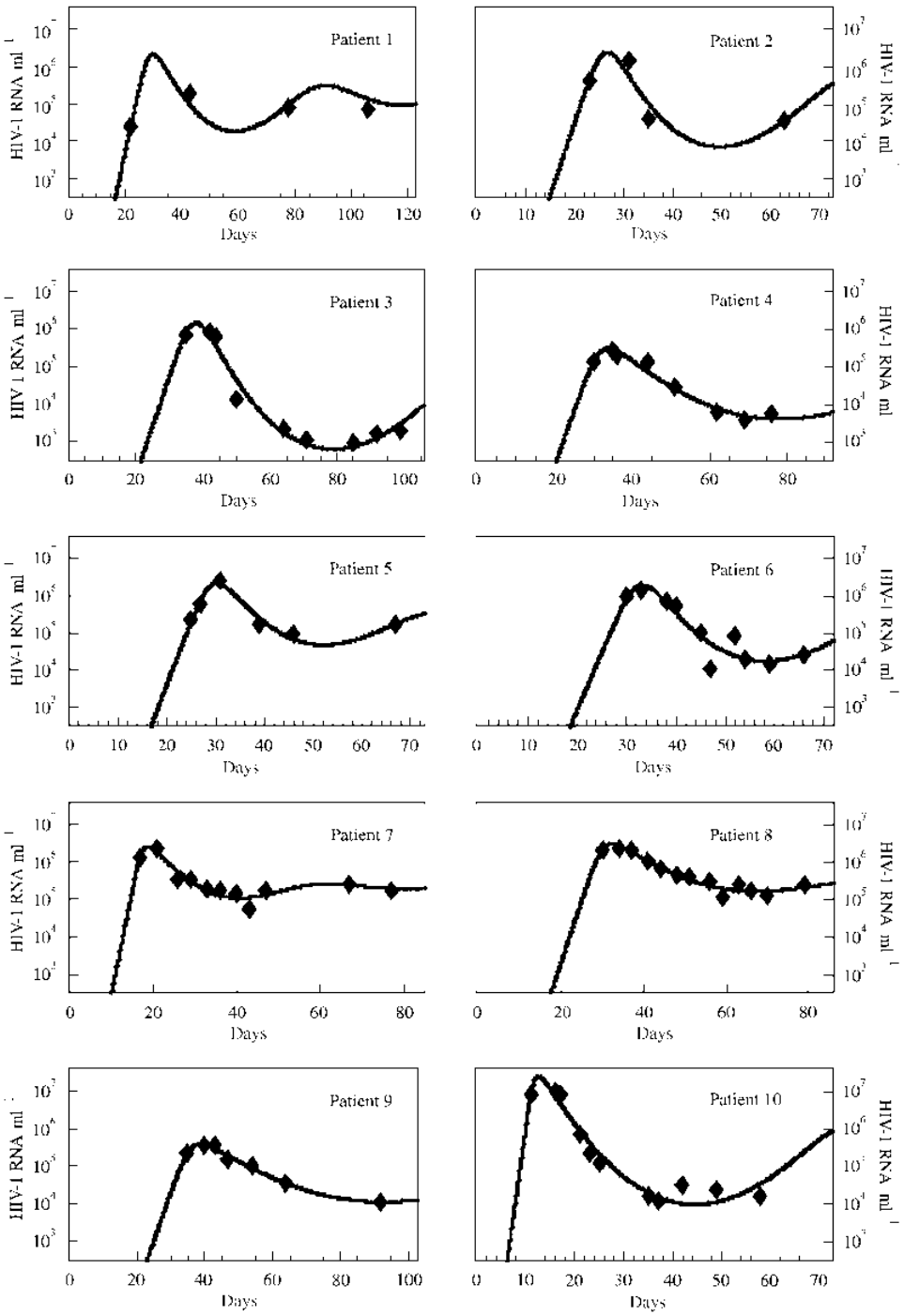
$$V(0) = V_0$$

Variables

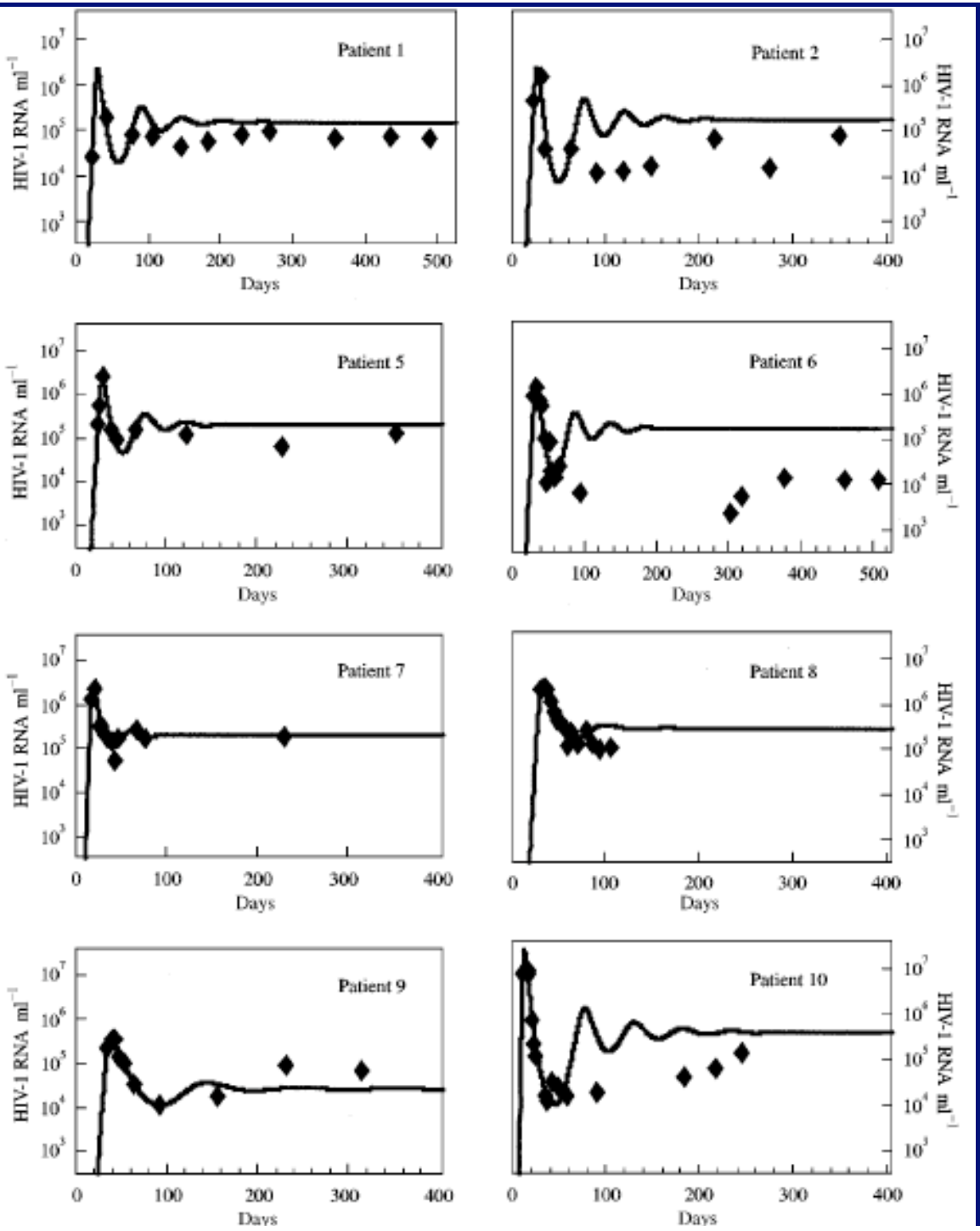
- T Target Cell Density
- T^* Infected Target Cell Density
- V Virus Concentration

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



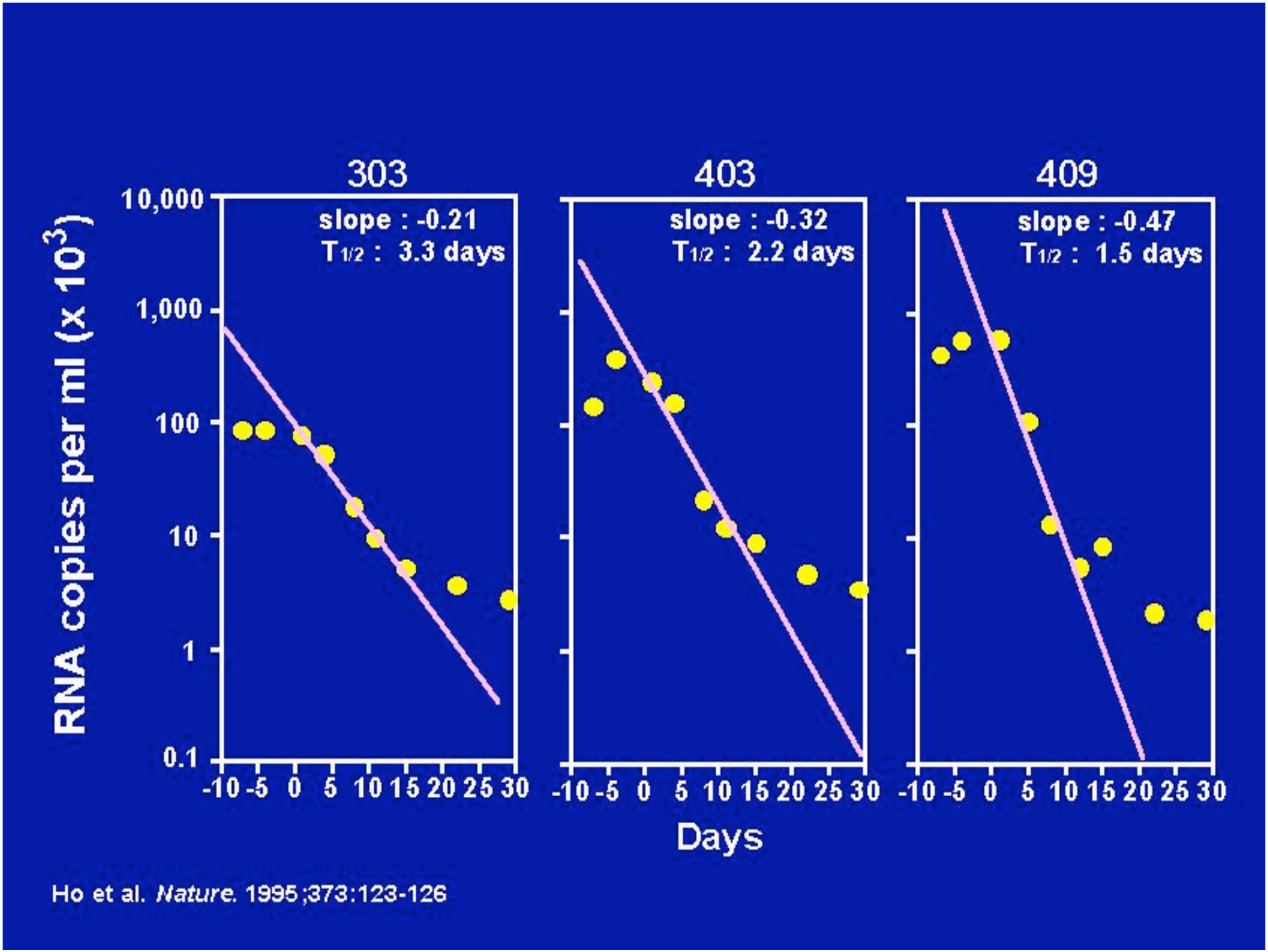
Stafford et al.
J Theoret Biol.
203: 285 (2000)



At longer times virus below prediction -> Immune response

Drug Therapy: Interferes with Viral Replication

- Medical: treat or cure disease
- Mathematical: a means of perturbing a system and uncovering its dynamics



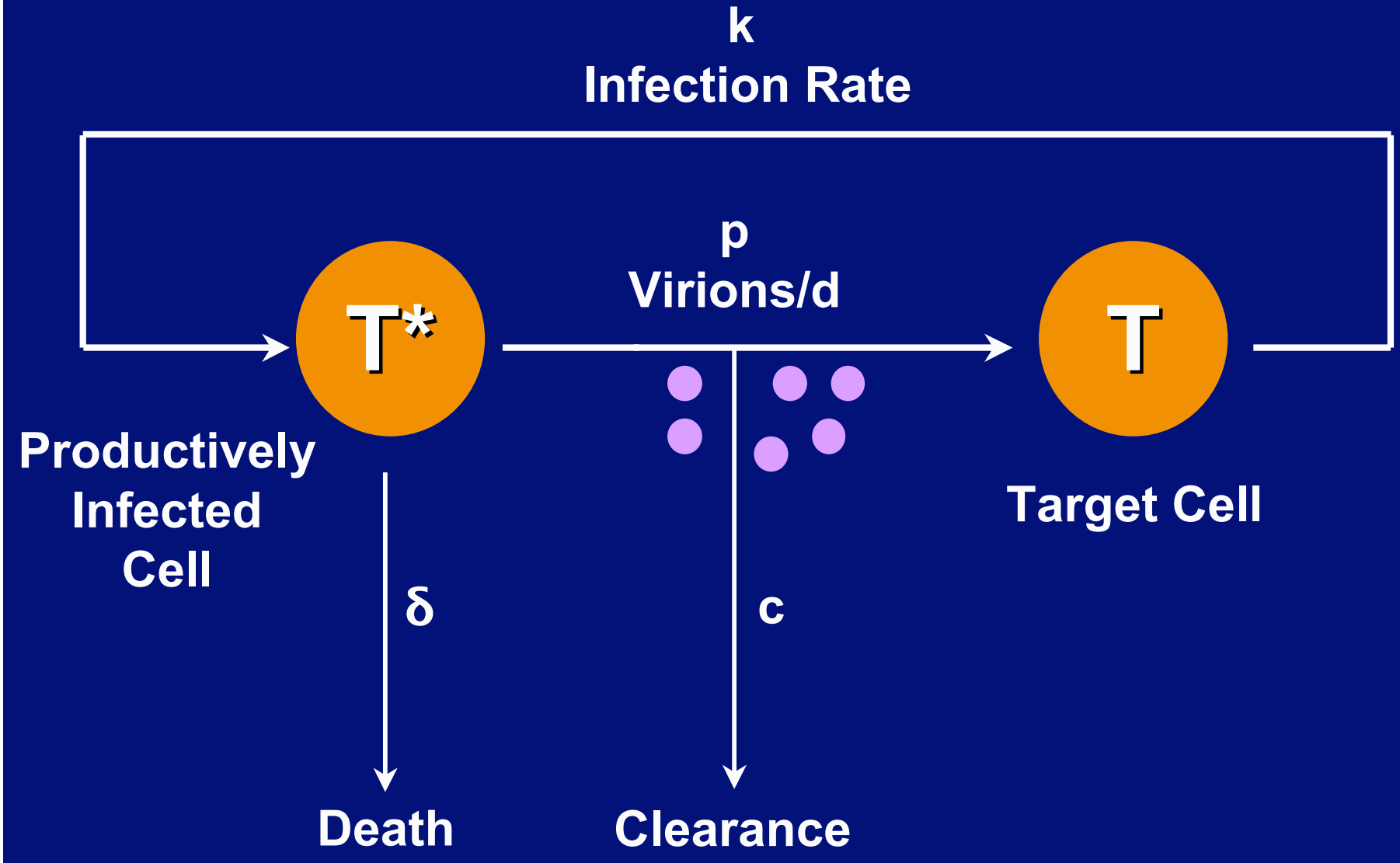
Ho et al. *Nature*. 1995;373:123-126

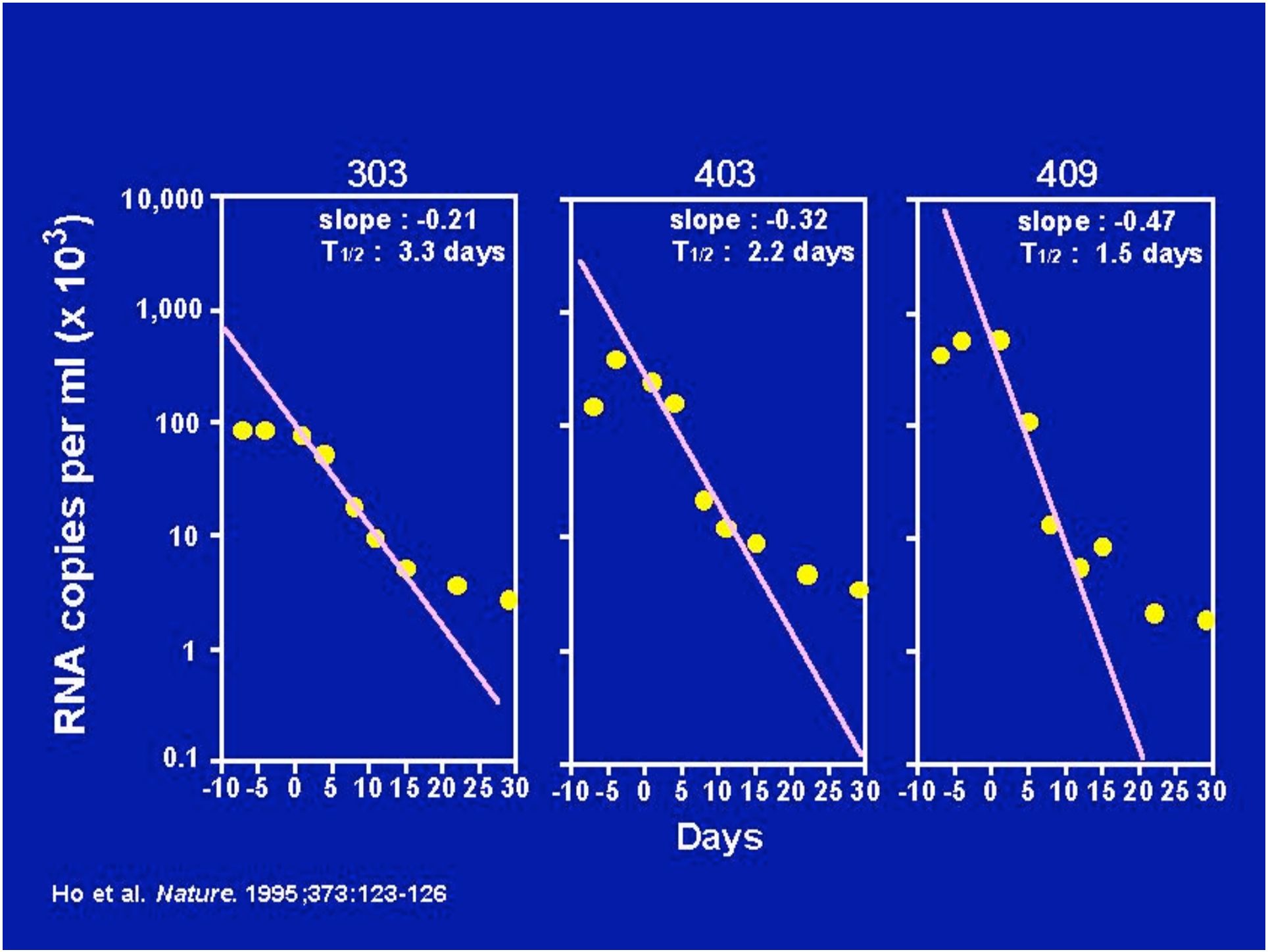
Features in Data

- Before therapy virus level is constant
  - This implies a quasi-steady state
- After therapy virus declines exponentially
  - Simplest model:
  - $dV/dt = P - cV$,
  - P = rate of viral production
  - c = rate of virion clearance (per virion)

If drug causes P=0, then $V=V_0 e^{-ct}$

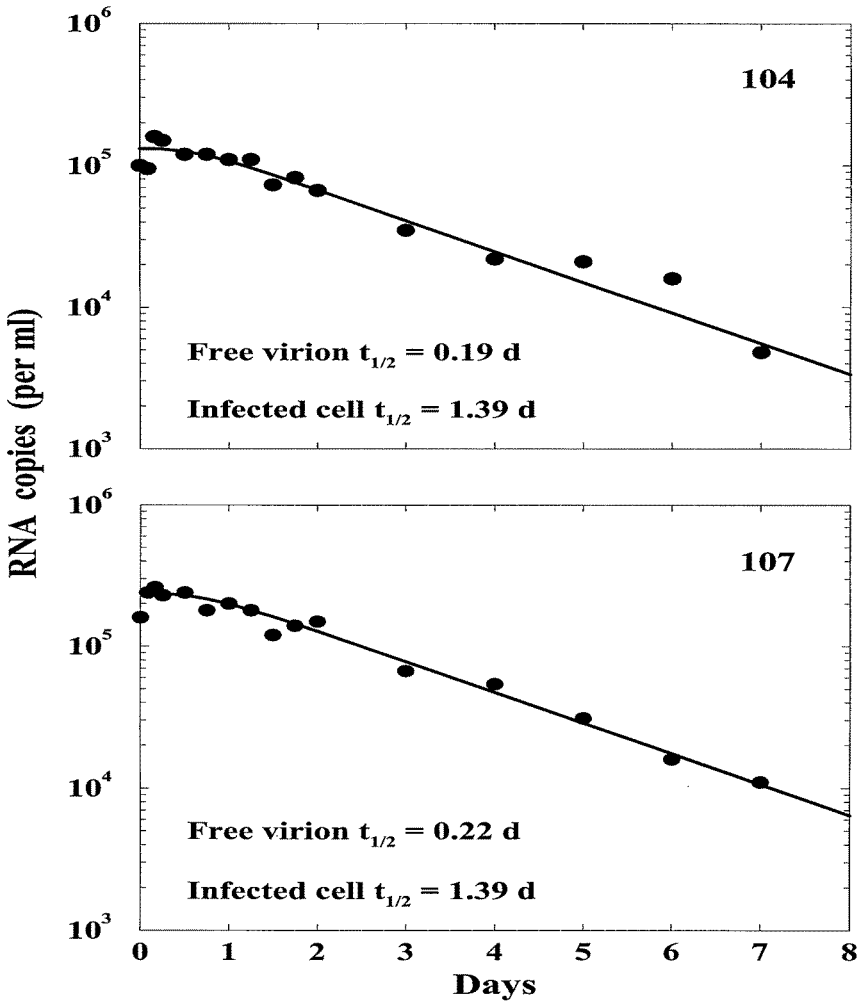
Model of HIV Infection





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

Same experiment with more frequent sampling

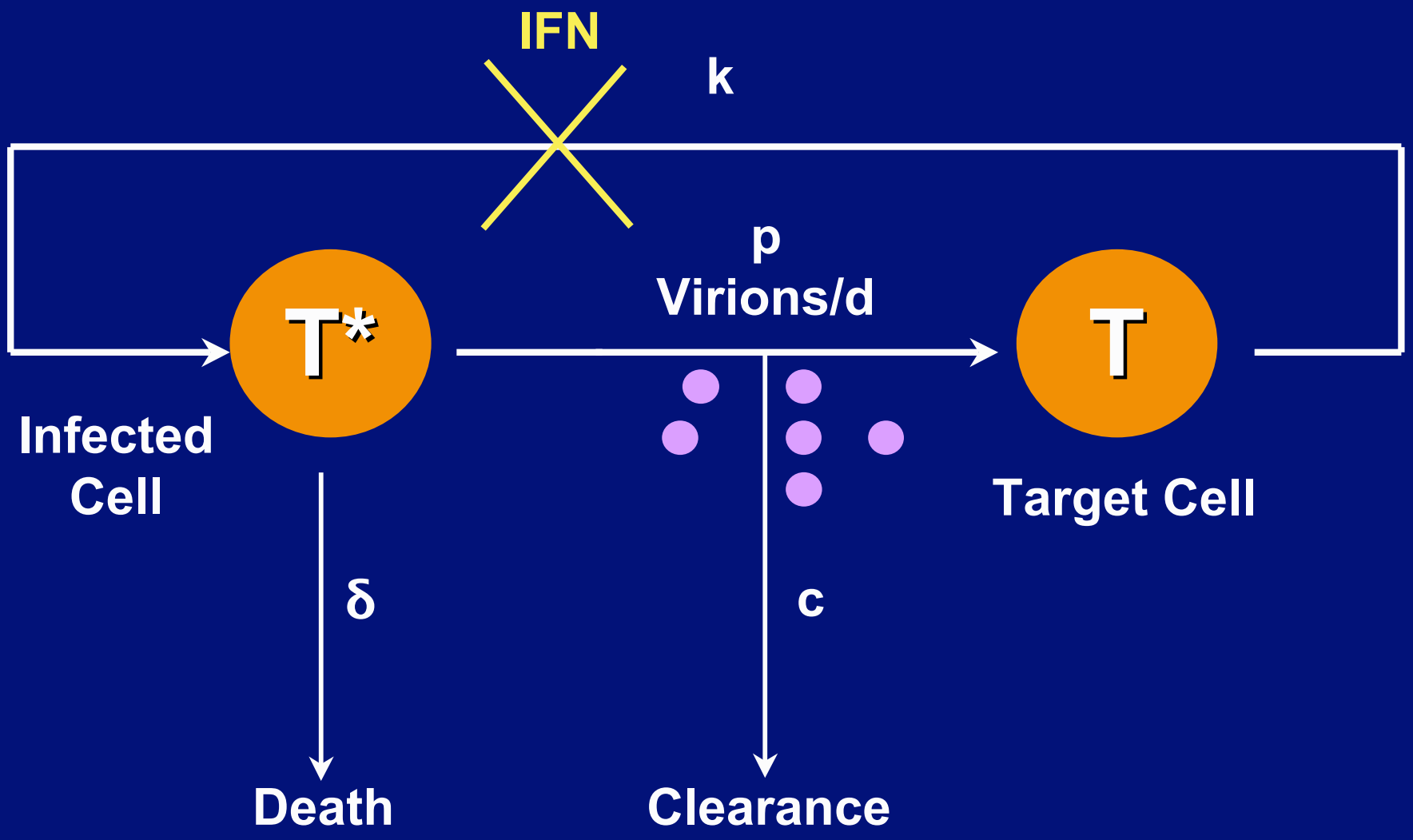


Perelson et al.
Science 271, 1582
1996

Features in Data

- Decline is no longer a single exponential
- Shoulder phase followed by an exponential decline
- Data suggests drug does not simply cause P=0

What If Drug Blocks Infection?



Action of Antiretroviral Drugs

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

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

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

Drug efficacy

ϵ_{RT} ϵ_{PI}

Subscripts:

"I": infectious

"NI": non-infectious

From *HIV-Dynamics in Vivo: …*,
Perelson, *et al*, Science, 1996

Have assumed T=constant=T_0

Solution of Model Equations Assuming 100% Efficacy of Protease Inhibitor Therapy, Target Cells Constant.

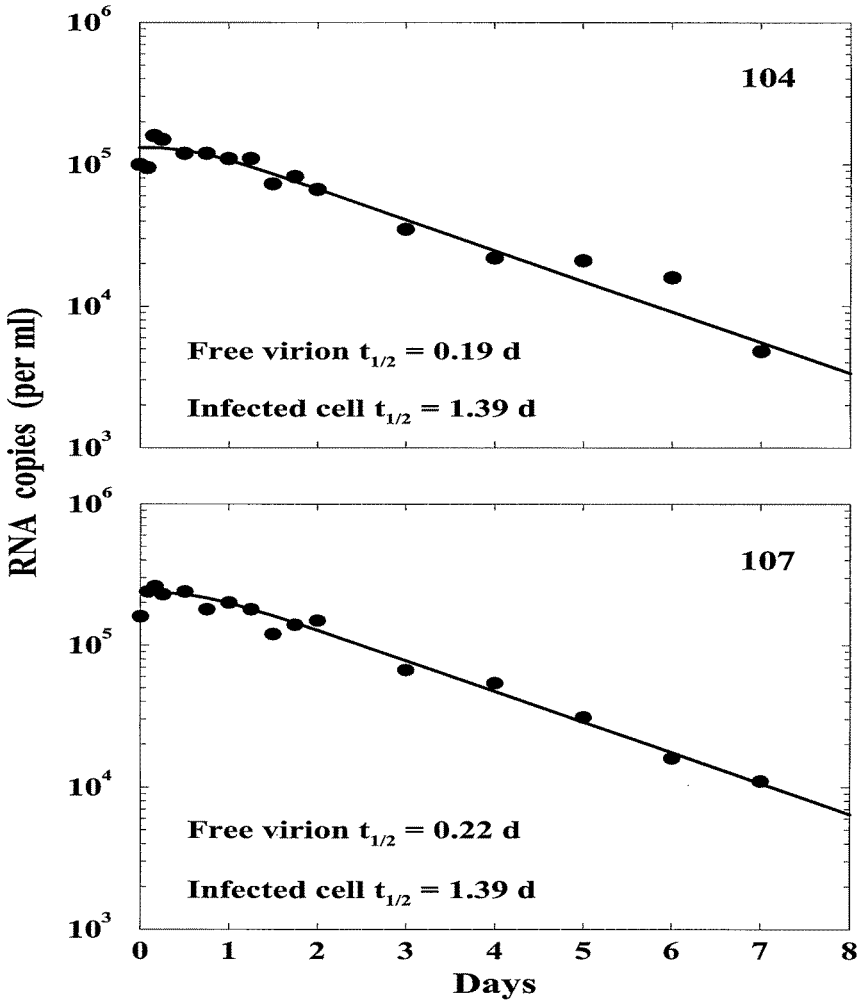
$$V(t) = V_0 \exp(-ct) + \frac{cV_0}{c-\delta}\left\{\frac{c}{c-\delta}\left[\exp(-\delta t) - \exp(-ct)\right] - \delta t \exp(-ct)\right\}$$

Solution has two parameters:

c – clearance rate of virus

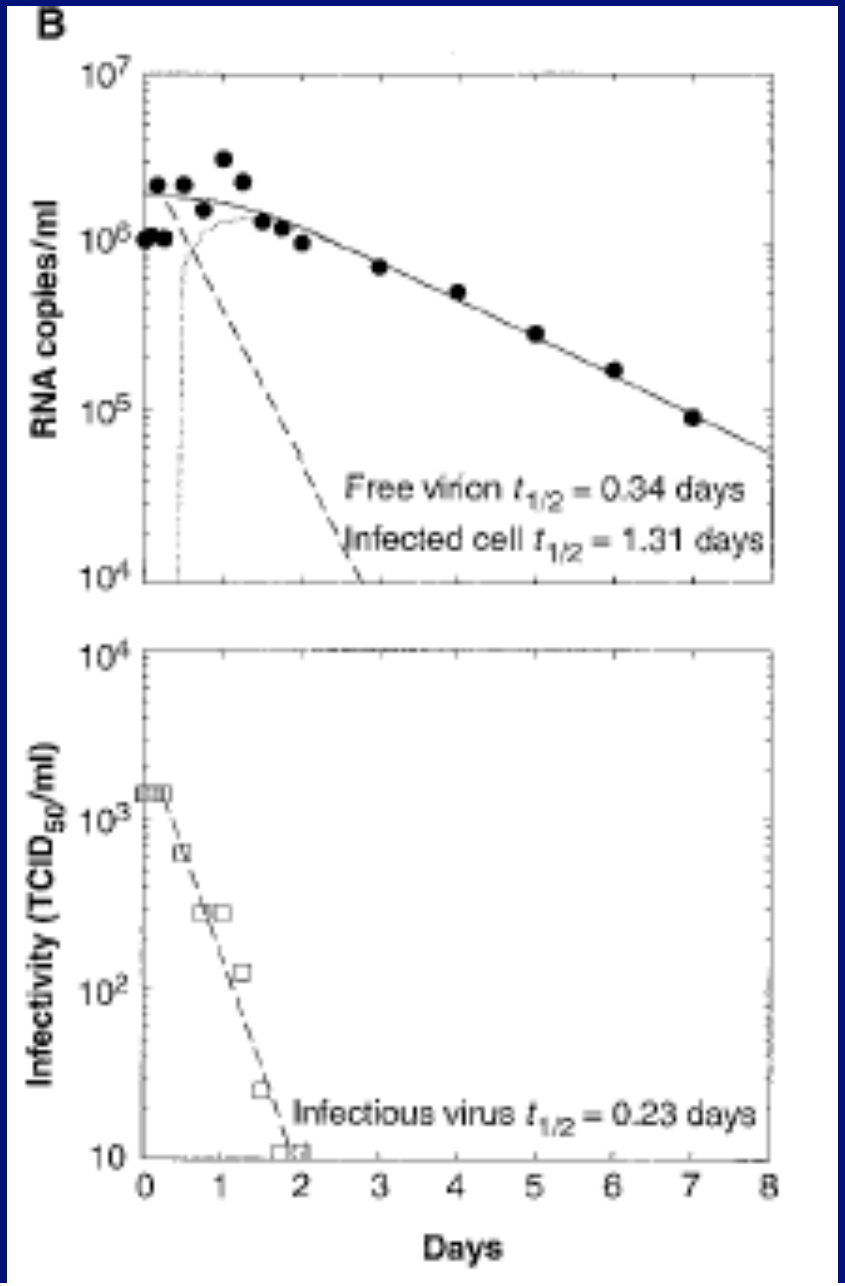
δ – death rate of infected cells

HIV-1: First Phase Kinetics

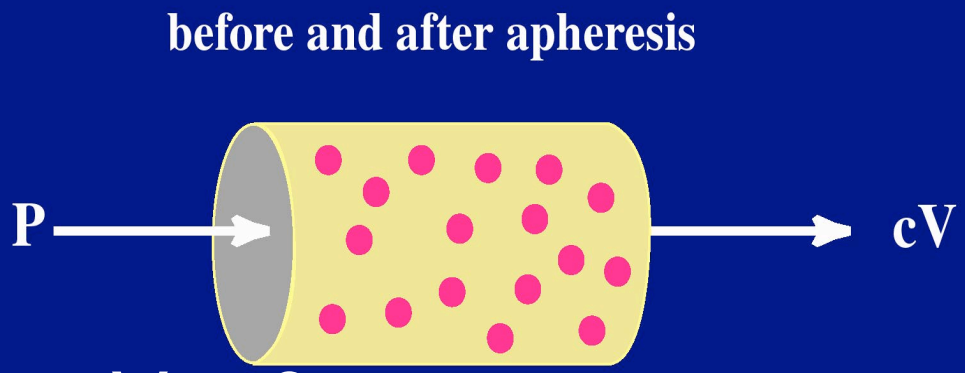


Perelson et al.
Science 271, 1582
1996

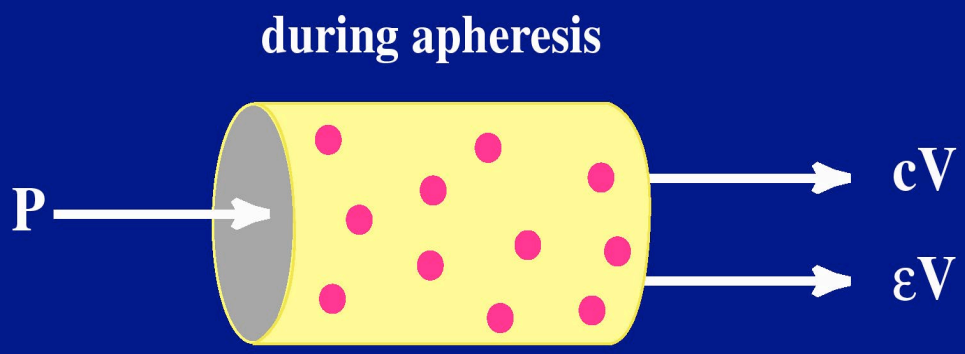
Infectious virions decay



An experiment to measure clearance



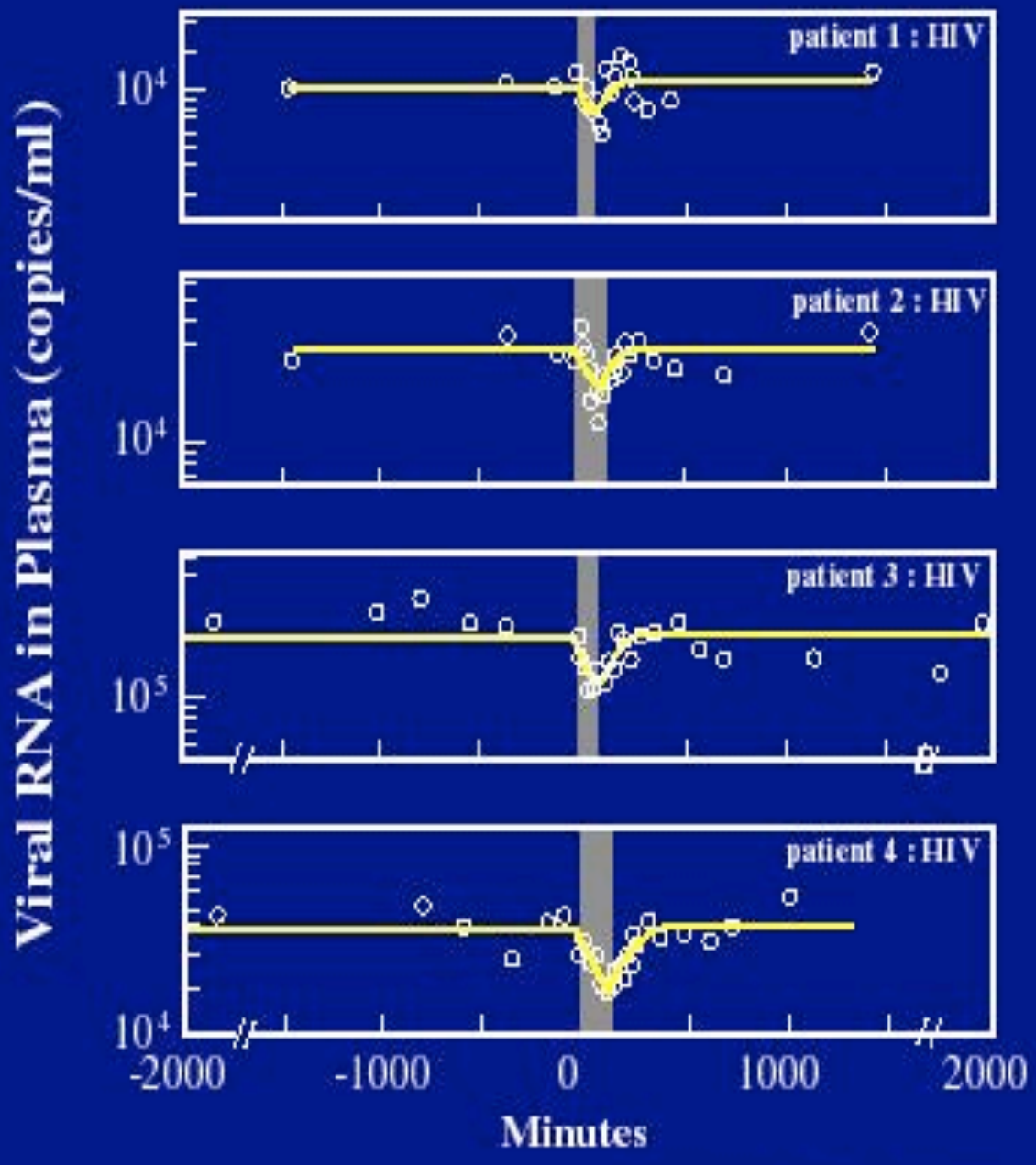
$dV/dt = P - cV = 0$



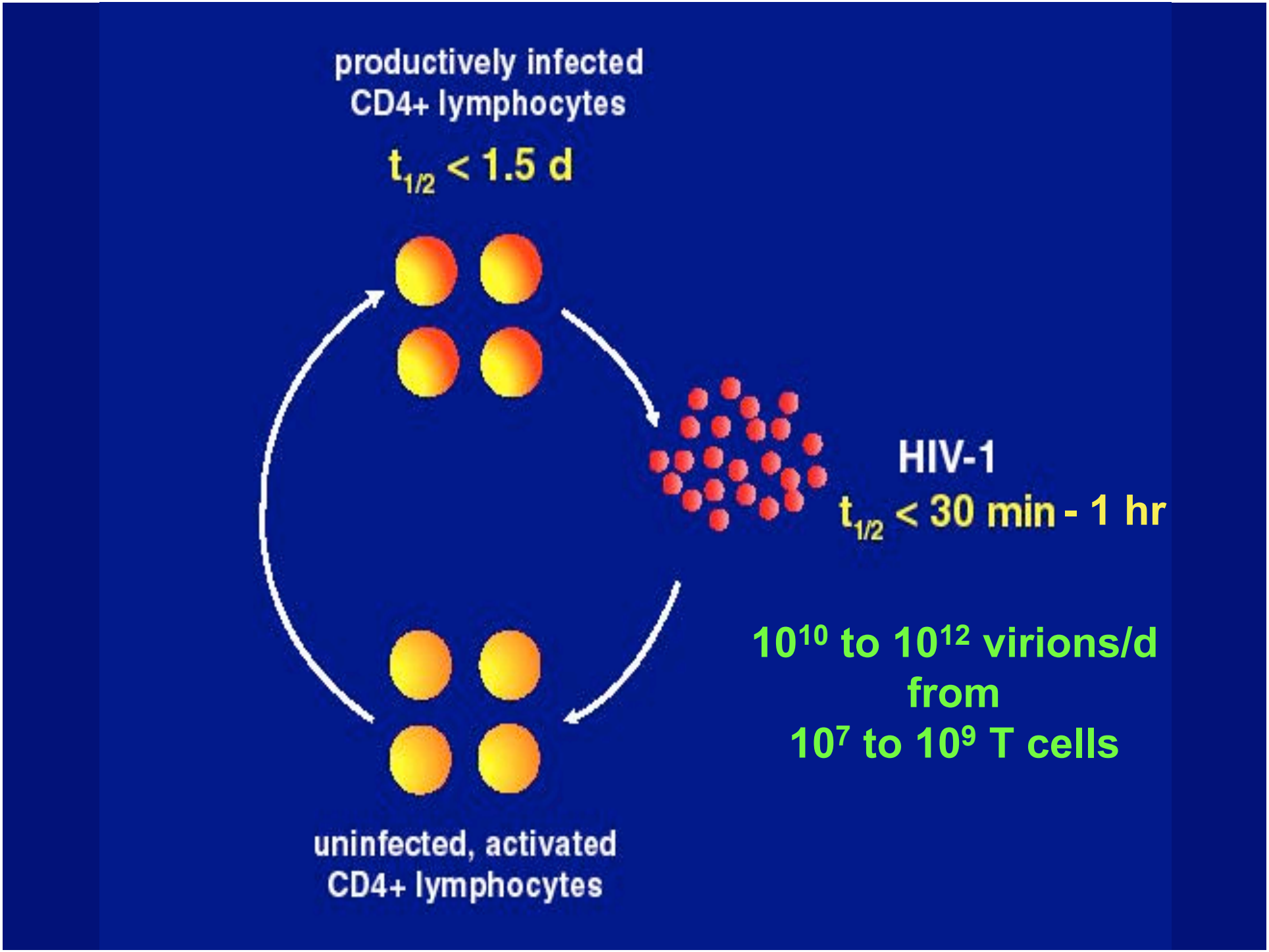
$dV/dt = P - cV - \epsilon V$

$= cV_0 - cV - \epsilon V, \quad V(0) =$

Ramratnam & Ho, Lancet, 1999



Ramratnam & Ho, Lancet, 1999


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

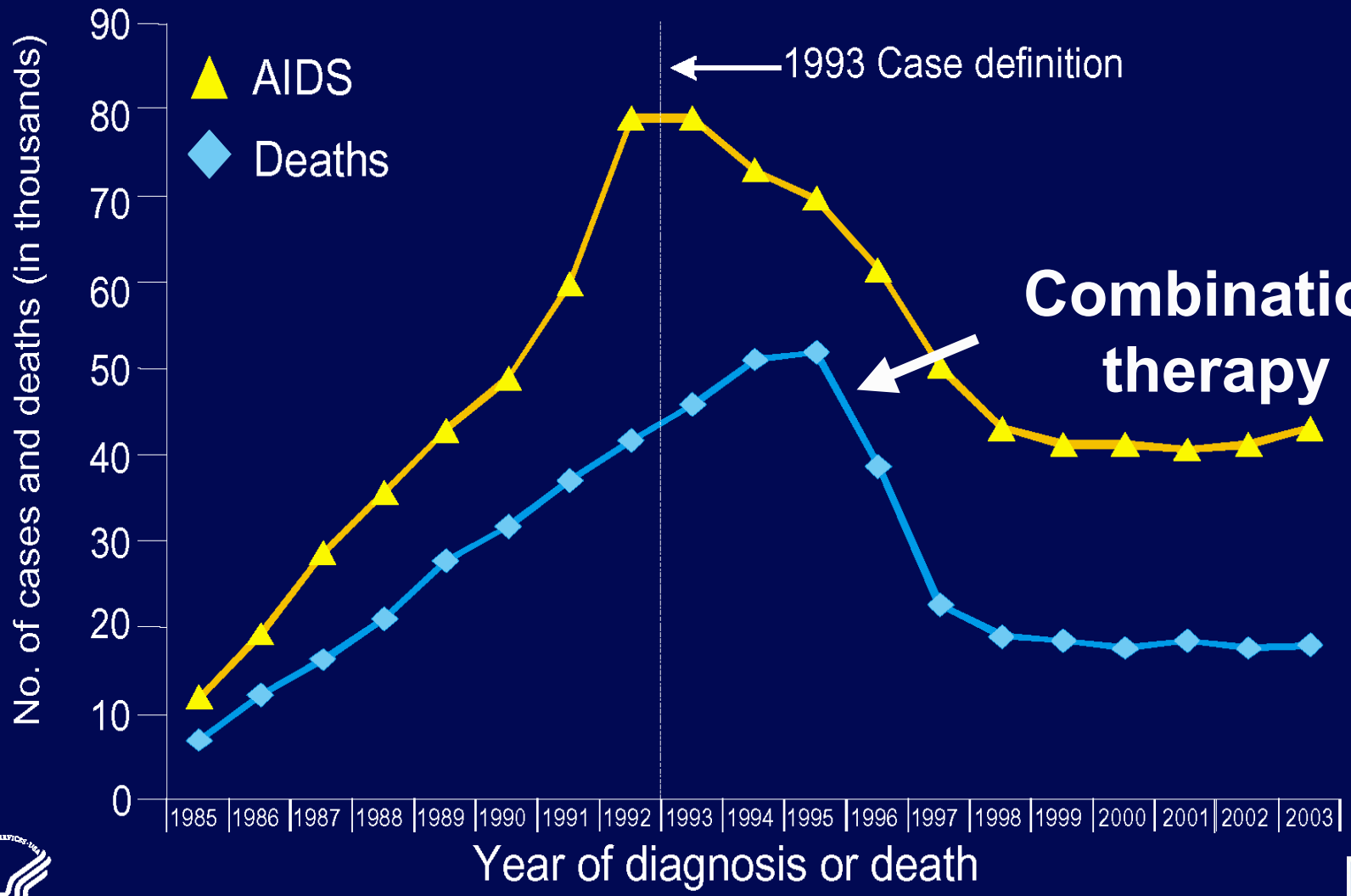
- HIV infection is not a slow process
- Virus replicates rapidly and is cleared rapidly – can compute to maintain set point level > 10^{10} virions produced/day
- Cells infected by HIV are killed rapidly
- Rapid replication implies HIV can mutate and become drug resistant

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}

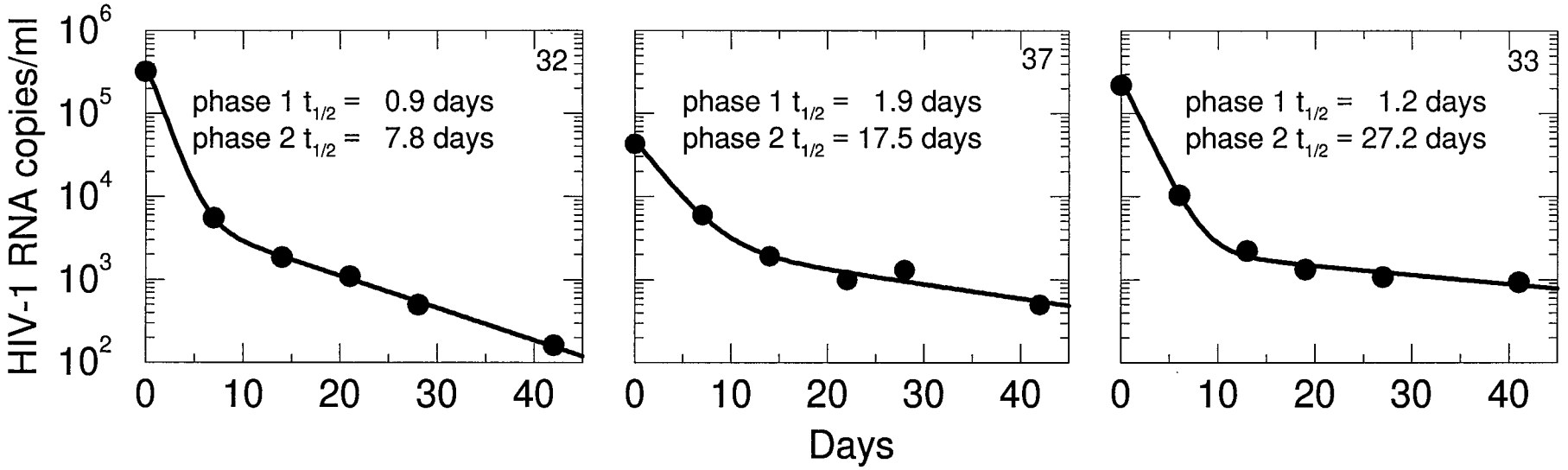
Perelson, Essunger & Ho, AIDS 1997

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



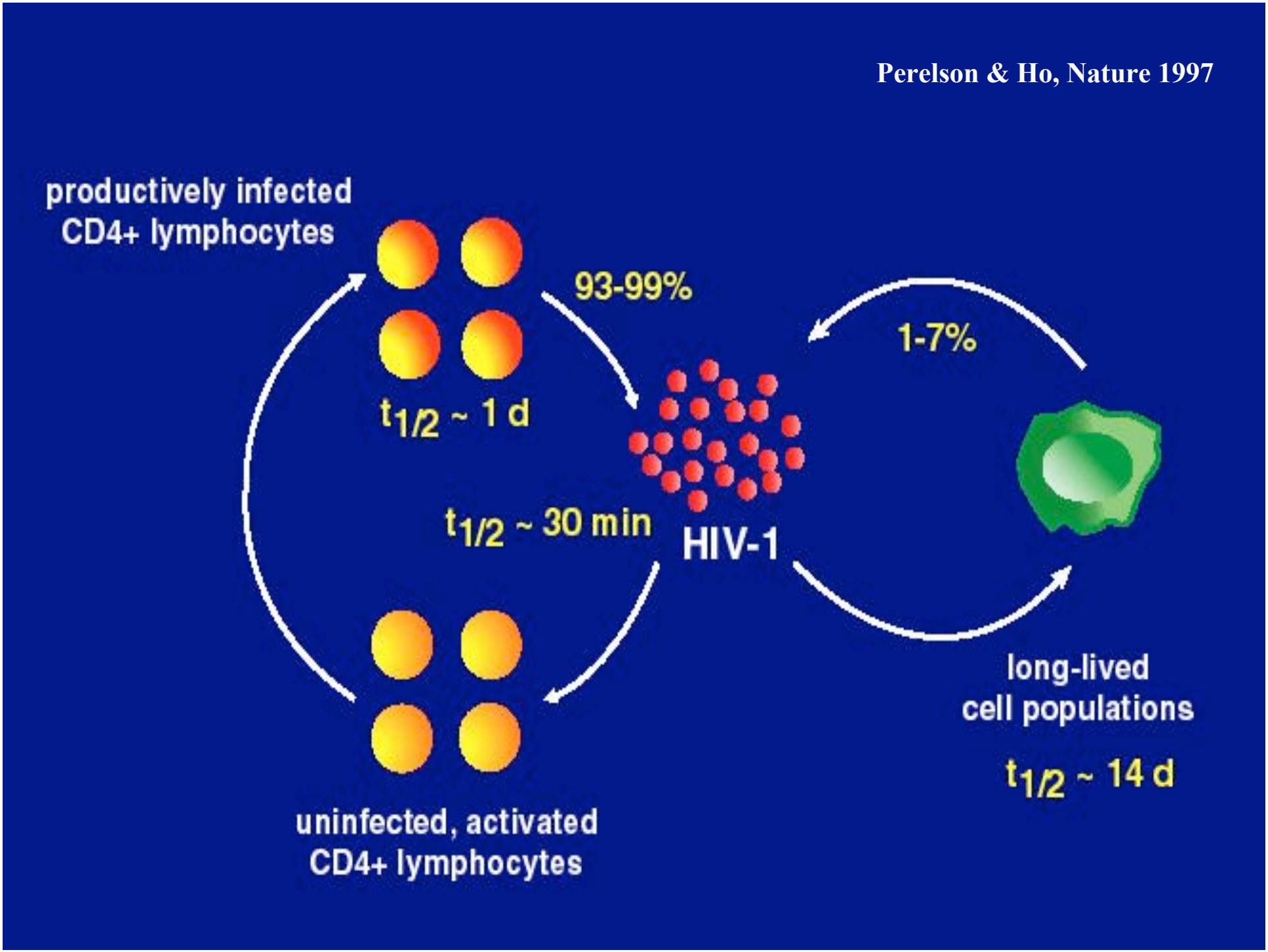
Note. Adjusted for reporting delays.

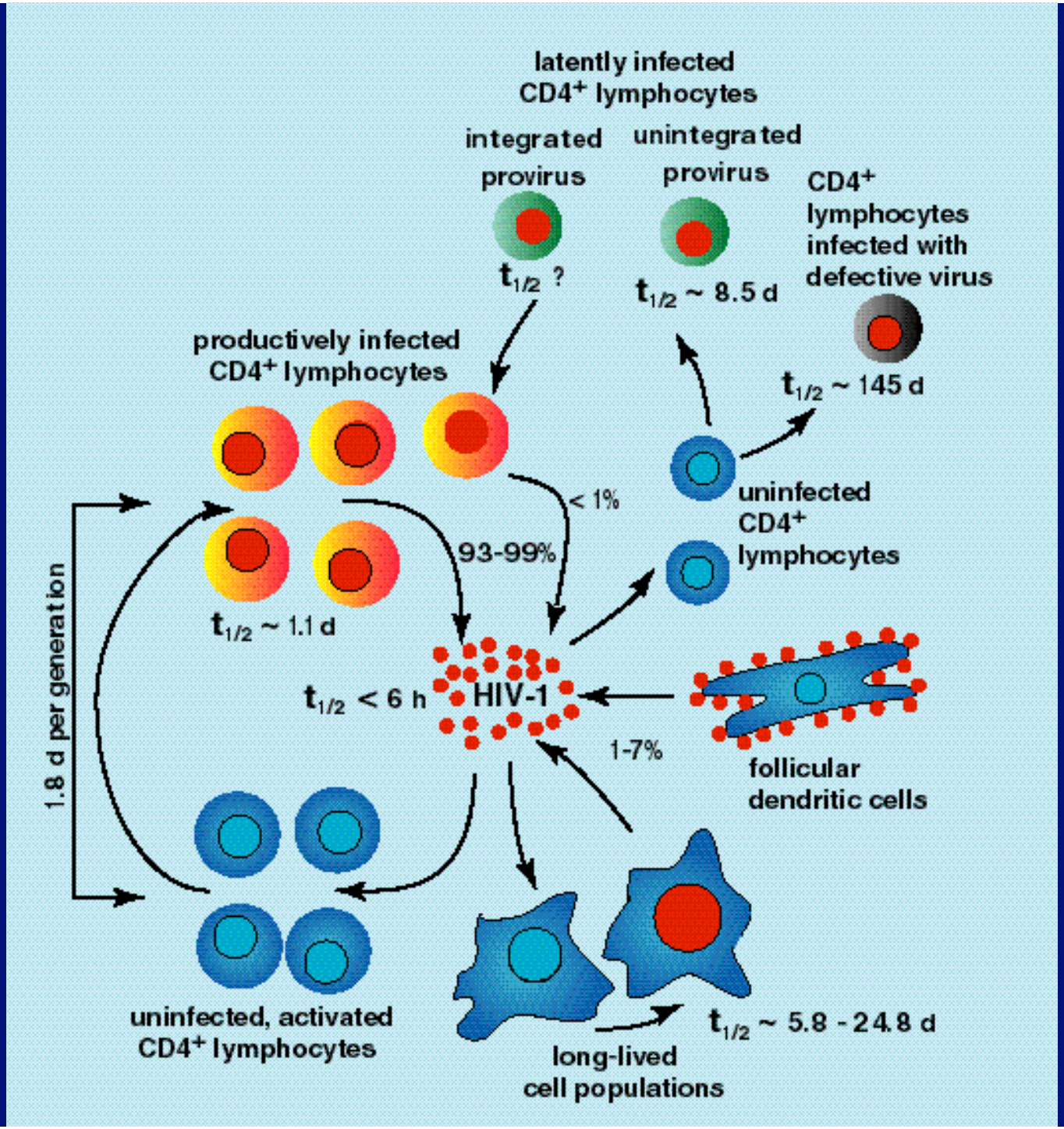
HIV-1: Two Phase Kinetics (Combination Therapy)



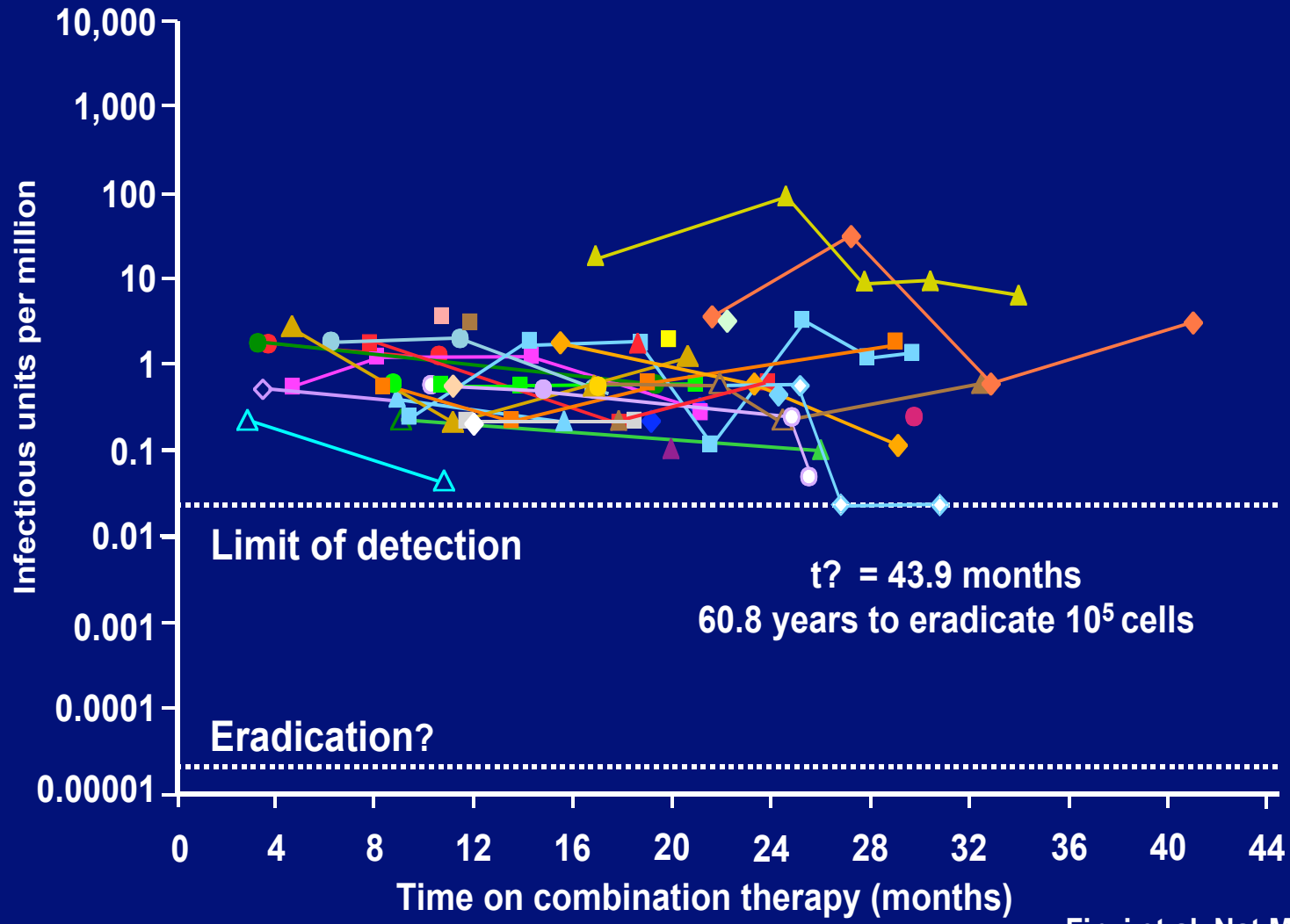
Perelson et al. Nature 387, 186 (1997)

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

Decay of latent reservoir on HAART



Finzi et al. Nat Med 1999

Basic Biology of HIV-1 In Vivo Revealed by Patient Studies

	$T_{1/2}$	Contribution to viral load	Generations per year
Virions:	~45 min		
Infected T cells:	0.7 d	93-99%	~180
Infected long-lived cells:	14 d	1-7%	~20
Latently infected T cells:	months		few

Problems with Standard Model

T cell kinetic equation and parameters not known

Labeling studies BrdU, d-glucose have provided some insights

What are target cells?

- **Most assume target cells = activated (Ki67+) cells**
- **Haase et al. suggest resting cells are also targets**

No good estimates of the infection rate k. Is mass-action correct?

- **find correlation between N and k; at steady state $NkT_0 = c$.**
- **solution very sensitive to value of k**
- **value of k may vary between isolates**

No good estimates of the burst size N

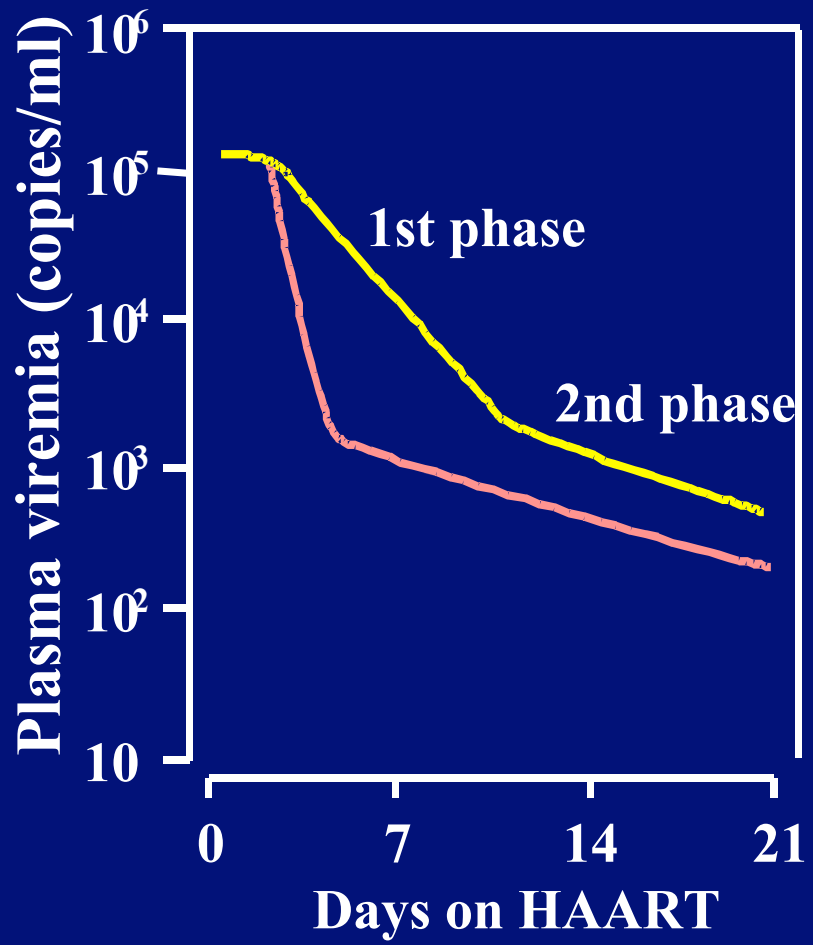
- **Haase Science 1996 N ~ 100 based on # HIV-1 RNA/ cell**
- **Hockett et al. J Exp Med 1999, N ~ 4,000**
- **Yuen et al. PNAS 2007, N ~ 50,000 (SIV)**

No good estimates of drug efficacy – generally assumed high

What is the magnitude of HIV-1 residual replication on standard HAART?

Models discussed so far have assumed drugs are 100% effective

Viral Dynamics and Drug Efficacy



1st phase slope ~ $\delta\epsilon$, where δ is the death rate of productively infected CD4 T cells, and ϵ is the efficacy of the antiretroviral regimen.

Recent impression:

- ϵ approaching 100%
- δ yields $t_{1/2}$ of ~1 day

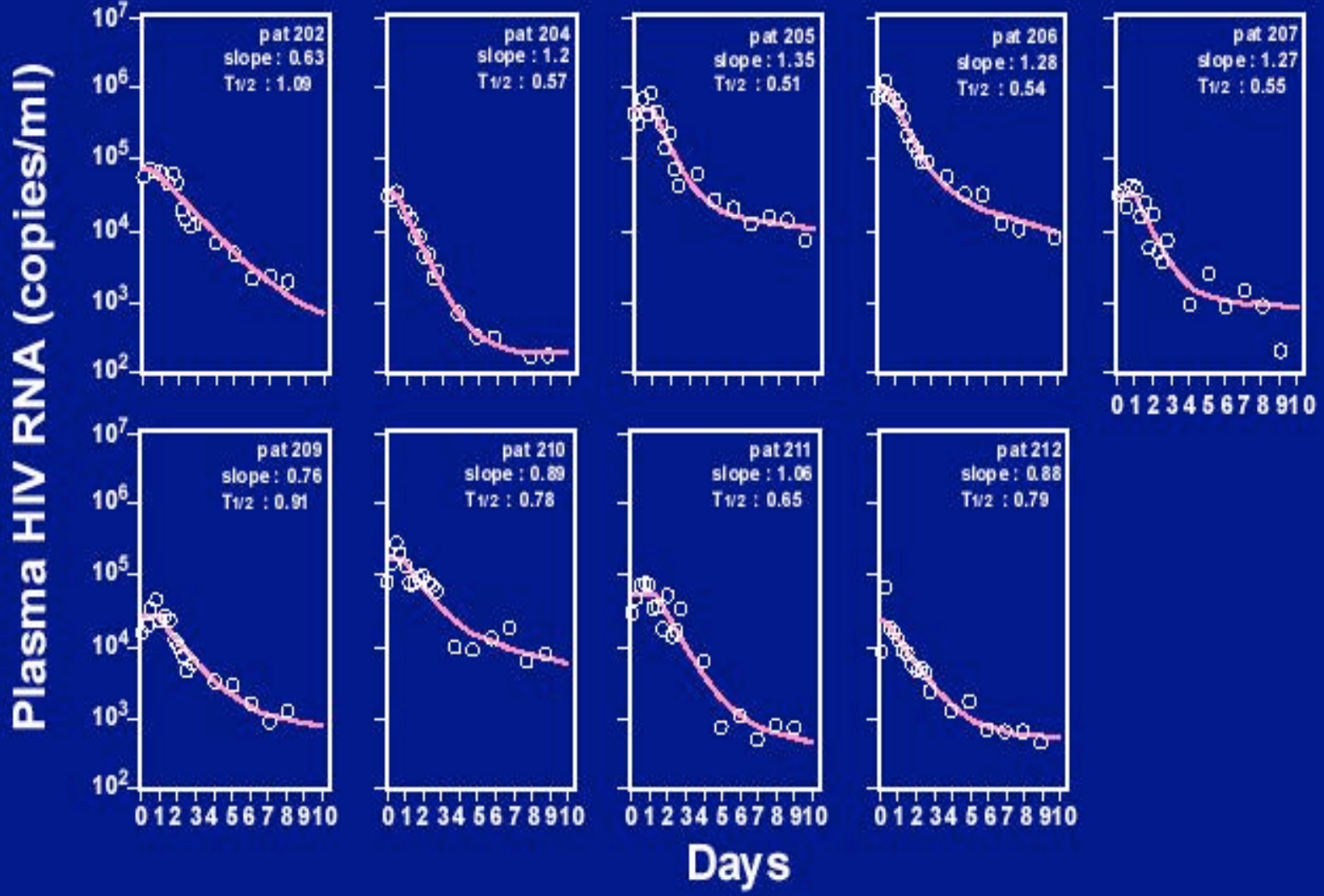
Study 377 (Louie, Hurley, Markowitz, Sun)

Drugs: lopinavir/ritonavir, tenofovir, lamivudine & efavirenz

Patients: drug-naïve or drug-sensitive

Objectives: measure the increased potency of the regimen based on sharper 1st phase decline in plasma viremia

First phase of viral decay after initiation of LPV/EFV/TFV/3TC



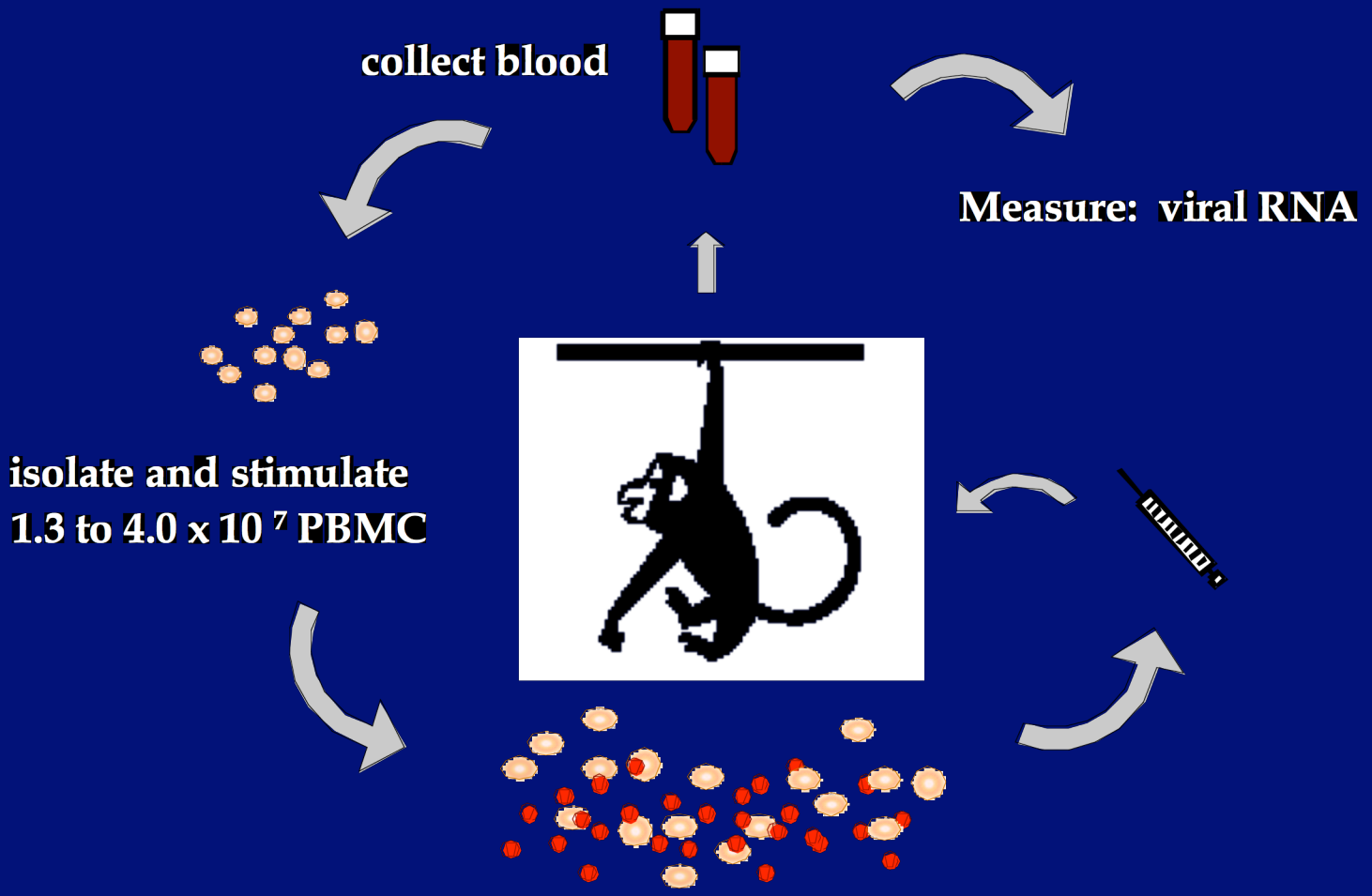
	Mean Slope (/d)	Mean $T_{1/2}$ (d)	Relative Efficacy
Study 377	0.99_	0.7	1.00
Standard HAART	~0.45-0.80	~0.9-1.5	≤0.80

Slope = death rate of infected T cells x relative efficacy

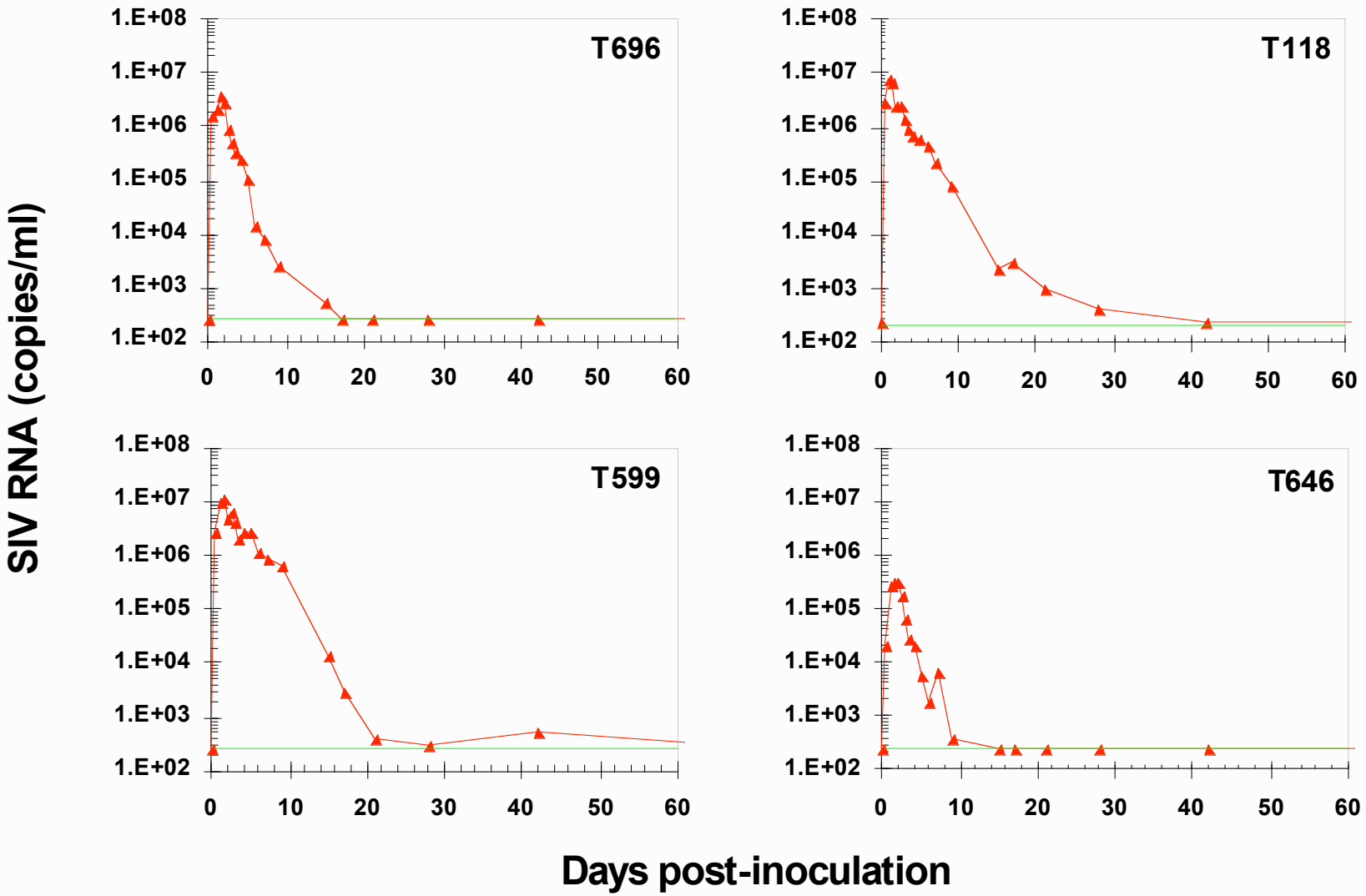
Estimating Burst Size

How many viruses does an infected cell produce in its lifetime?

Experimental Procedure



SIV RNA vs. Days Post-inoculation



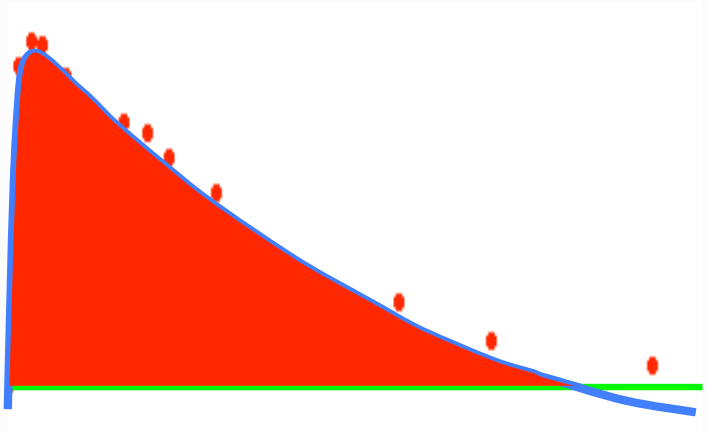
Method 1: Area Under the Curve

$$dV/dt = N\delta T^* - cV$$

$$V(\infty) - V(0) = N \equiv \delta T^*(0) e^{-\delta t} - c \equiv V dt = 0$$

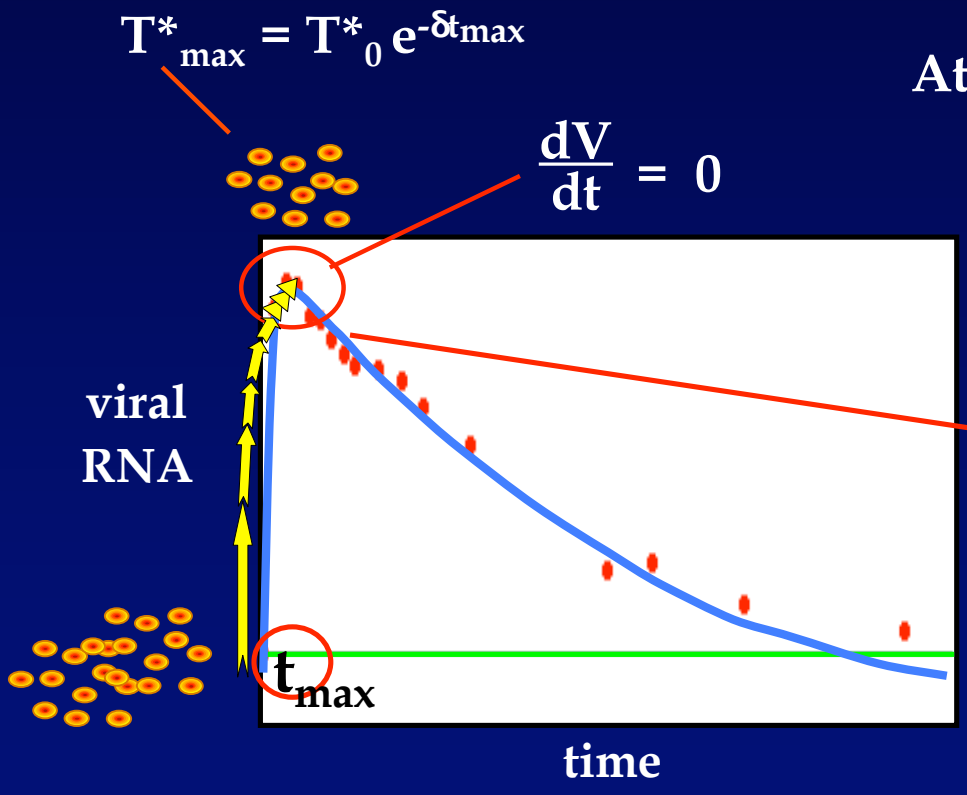
$$NT^*(0) = c \equiv V dt$$

total production = total clearance



$$N = \frac{c \equiv V dt \text{ [total virions produced]}}{T^*_0 \text{ [total number of cells infected]}}$$

Method 2: Steady-state at the Peak



At peak, $N\delta T^* = cV$

$$N = \frac{cV_{max}}{\delta T^*_{max}}$$

Estimate δ from slope

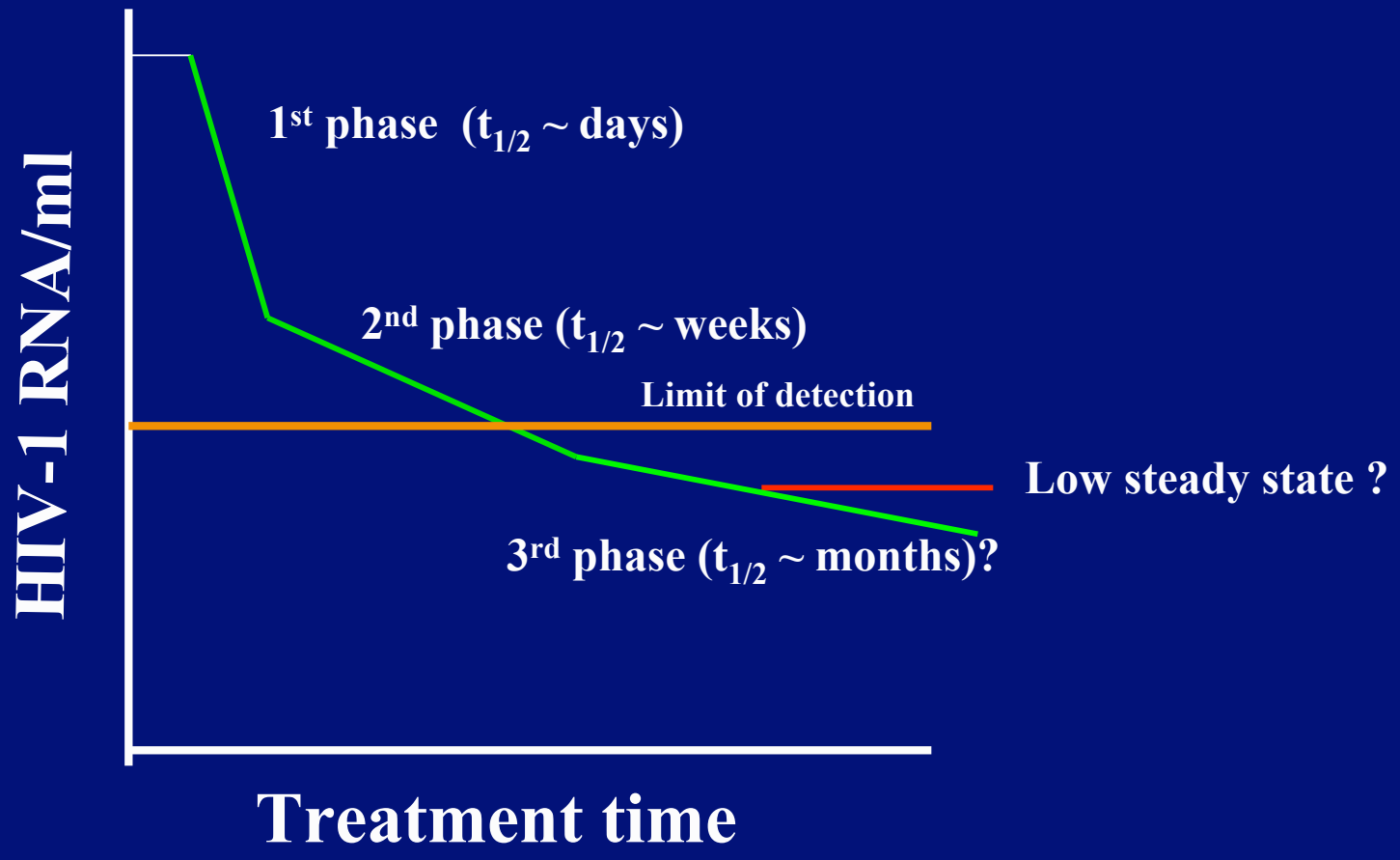
Estimates of Burst Size, N

Rhesus macaque	Method 1 Area Under the Curve	Method 2 Steady-state at Peak
T696 / 2	1.3×10^4	2.1×10^4
T118 / 1	4.0×10^4	4.9×10^4
T599 / 1	5.9×10^4	6.1×10^4
T646 / 1	4.7×10^4	7.0×10^4
mean	4.0×10^4	5.0×10^4

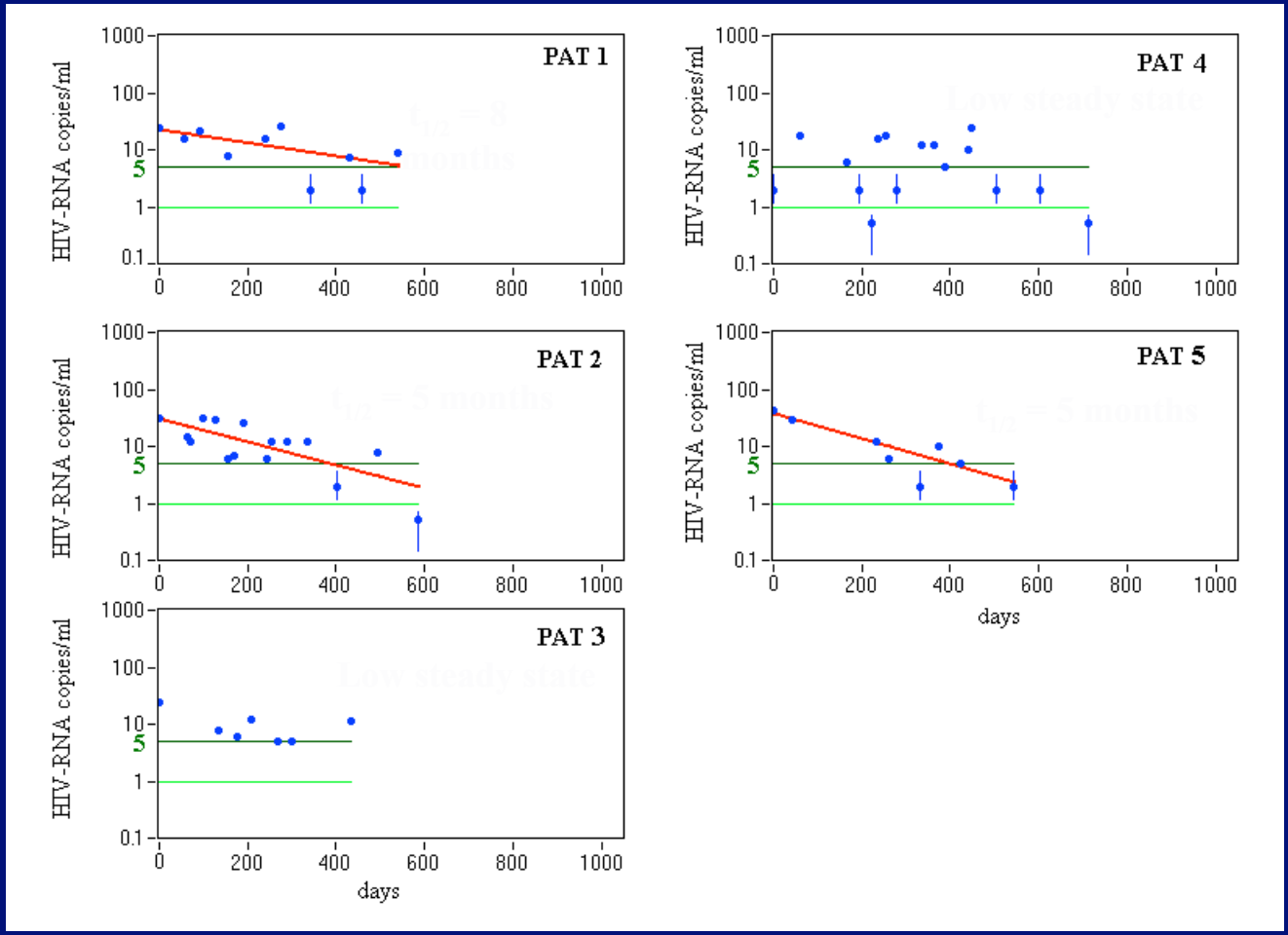
With current therapy (HAART)

- Viral levels in most patients driven below the limit of detection of standard assays
- Does this mean a patient is cured?
- Can we get information about what is happening in the patient after virus becomes undetectable?

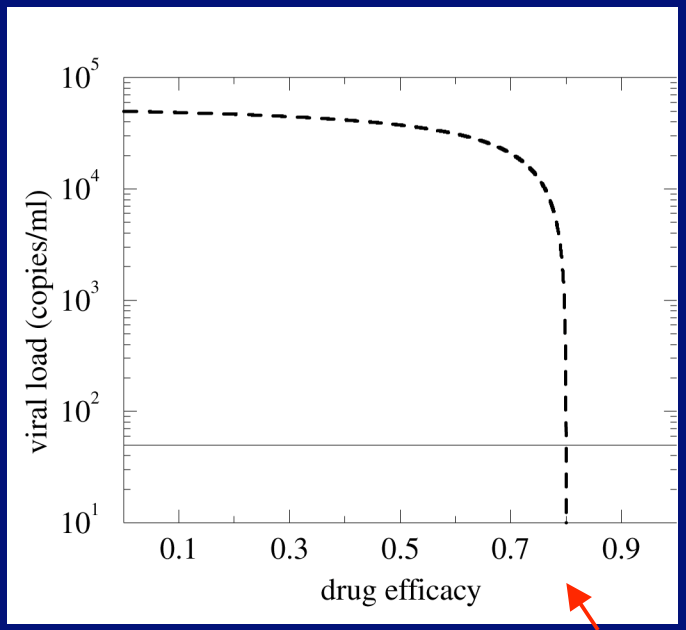
What happens after the limit of detection is reached?



Pomerantz – supersensitive RT-PCR



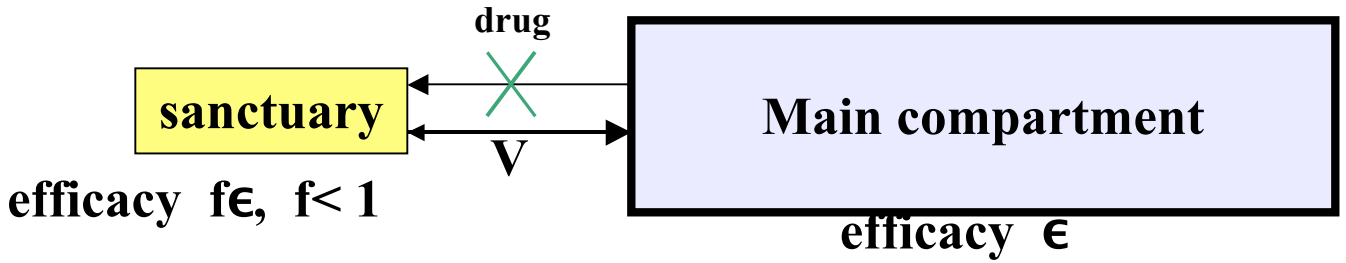
How to explain low steady state?



For the standard 3-eqn model one can show that there is a sensitive dependence of steady state VL on drug efficacy

Two-Compartment Drug Sanctuary Model

(Duncan Callaway, Bull. Math. Biol. 64:29 2002)



$$\dot{T}_1 = \lambda_1 - dT_1 - (1-\varepsilon)kV_1T_1$$

$$\dot{T}_2 = \lambda - dT_2 - (1-f\varepsilon)kV_2T_2$$

$$\dot{T}_1^* = (1-\alpha)(1-\varepsilon)kV_1T_1 - \delta T_1^*$$

$$\dot{T}_2^* = (1-\alpha)(1-f\varepsilon)kV_2T_2 - \delta T_2^*$$

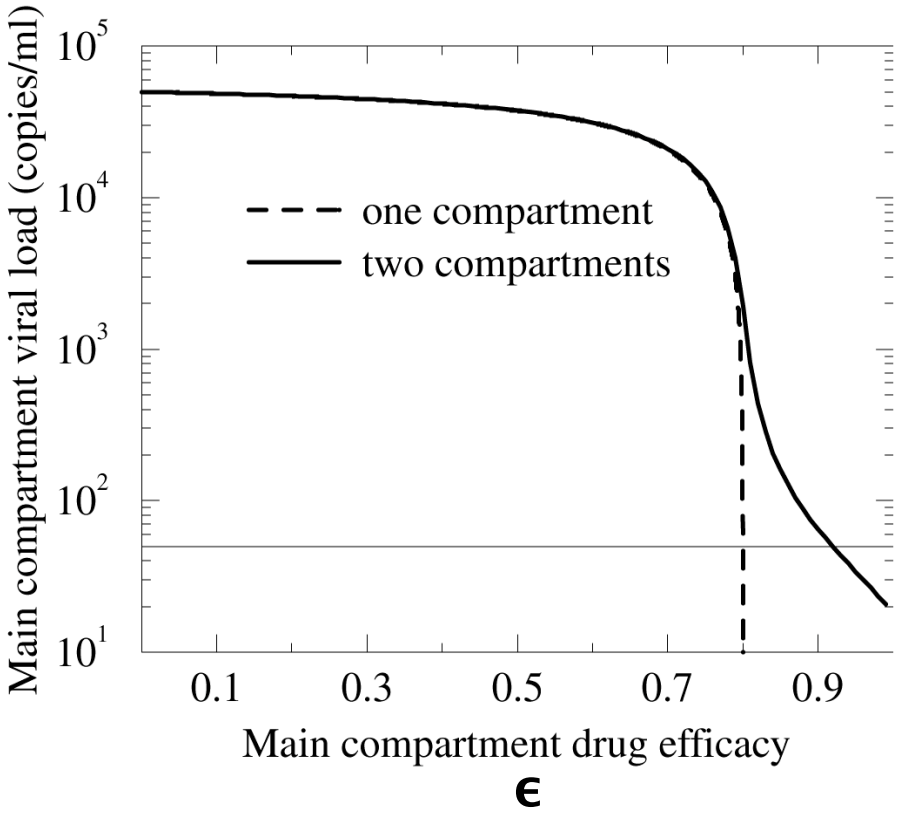
$$\dot{C}_1^* = \alpha(1-\varepsilon)kV_1T_1 - \mu C_1^*$$

$$\dot{C}_2^* = \alpha(1-f\varepsilon)kV_2T_2 - \mu C_2^*$$

$$\dot{V}_1 = N_T\delta T_1^* + N_C\mu C_1^* - cV_1 + D_1(V_2 - V_1)$$

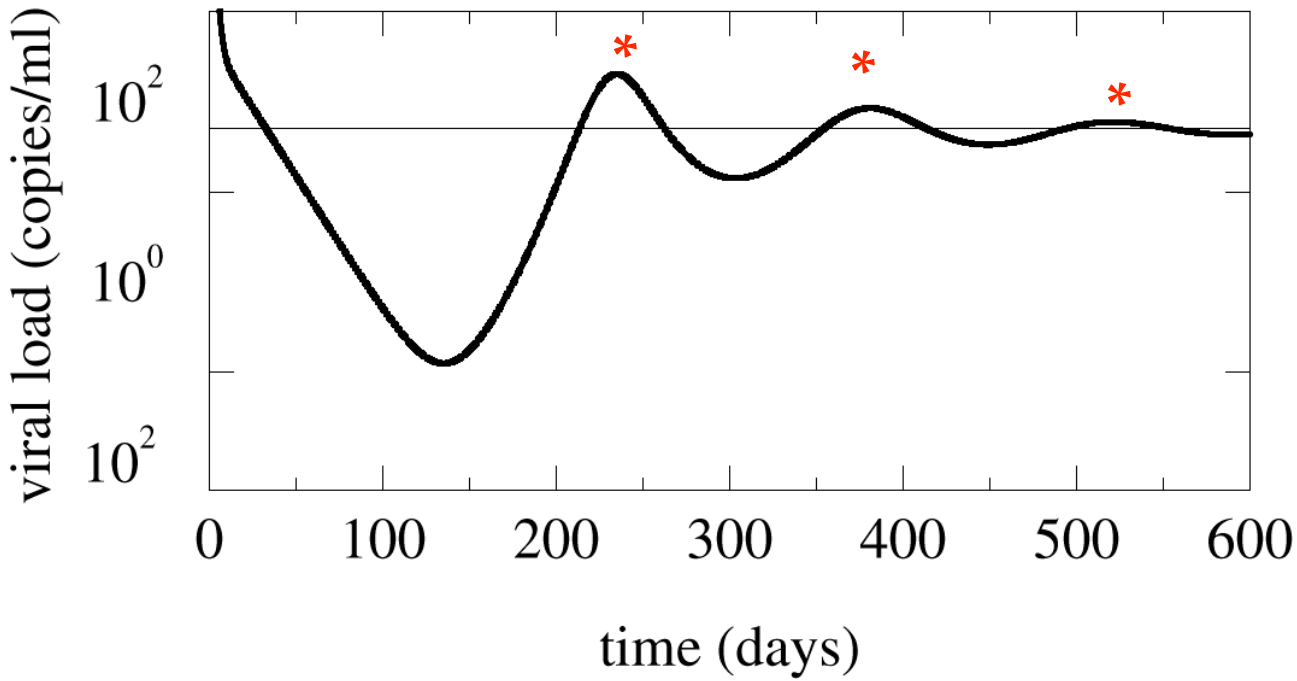
$$\dot{V}_2 = N_T\delta T_2^* + N_C\mu C_2^* - cV_2 + D_2(V_1 - V_2)$$

Drug sanctuary solves the problem (sort of)



Two compartment model does not have sensitive dependence on ϵ

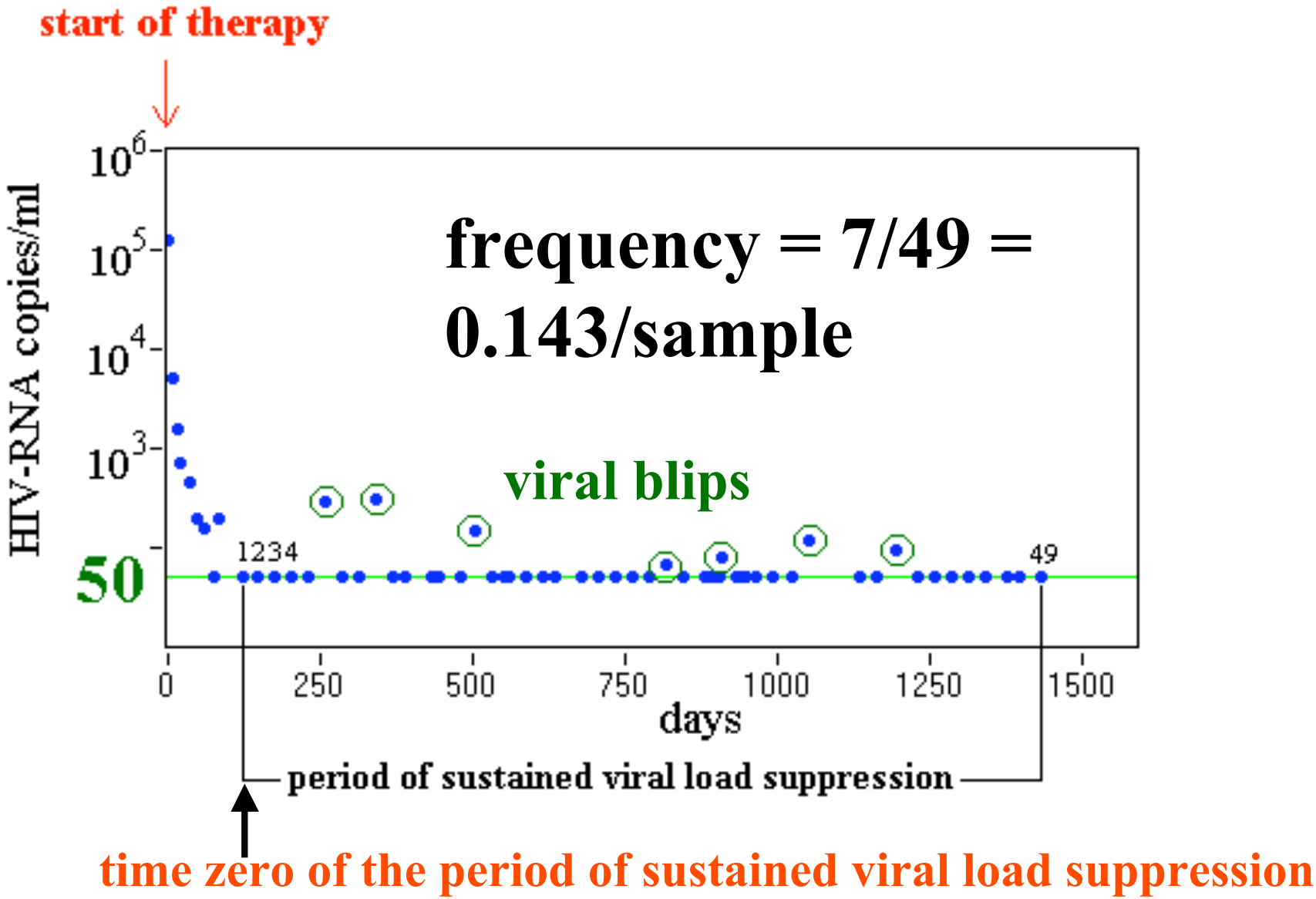
Approach to steady state generates “blips”

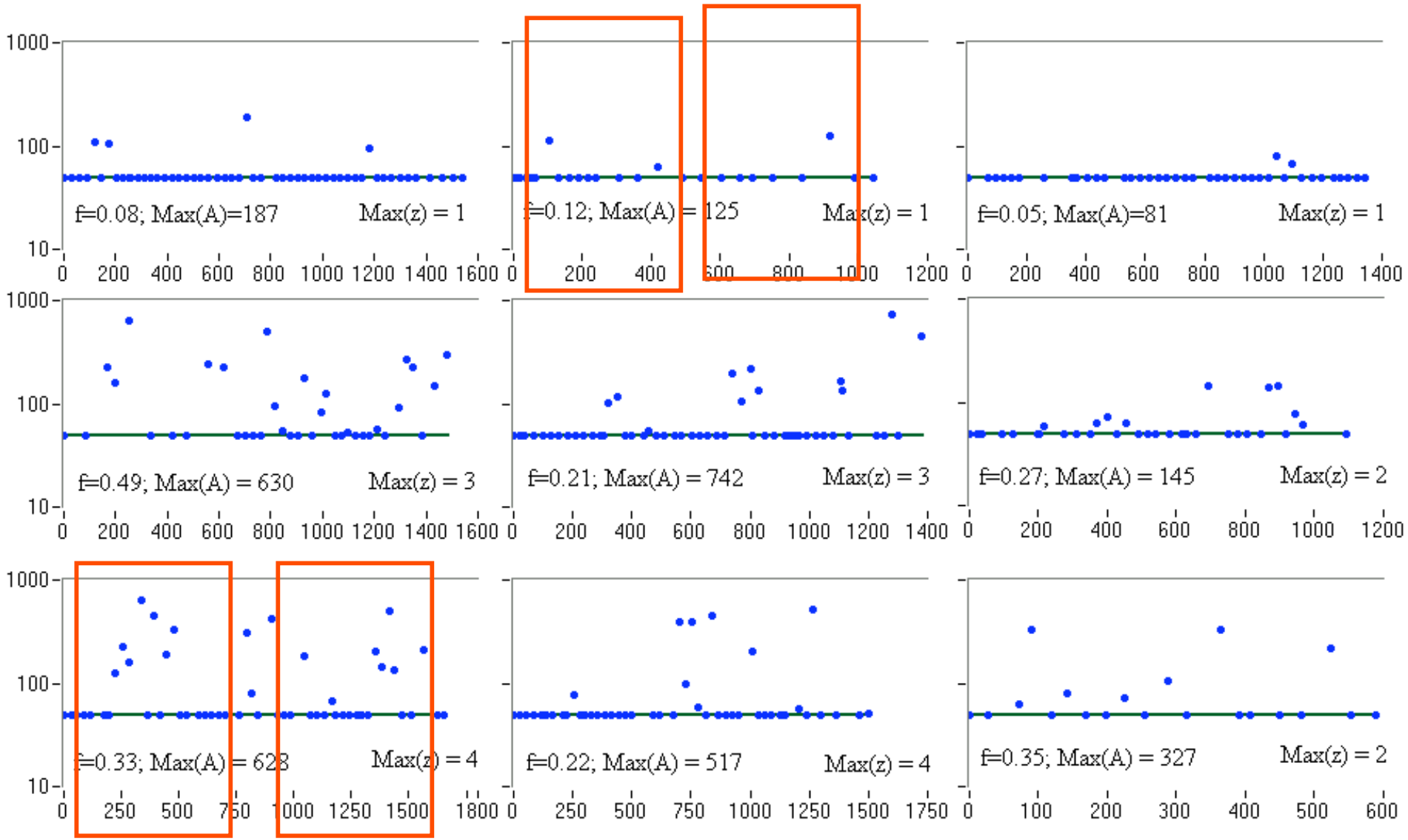


Here blips are generated by viral dynamics – no clinical relevance except they suggest that a drug sanctuary may exist

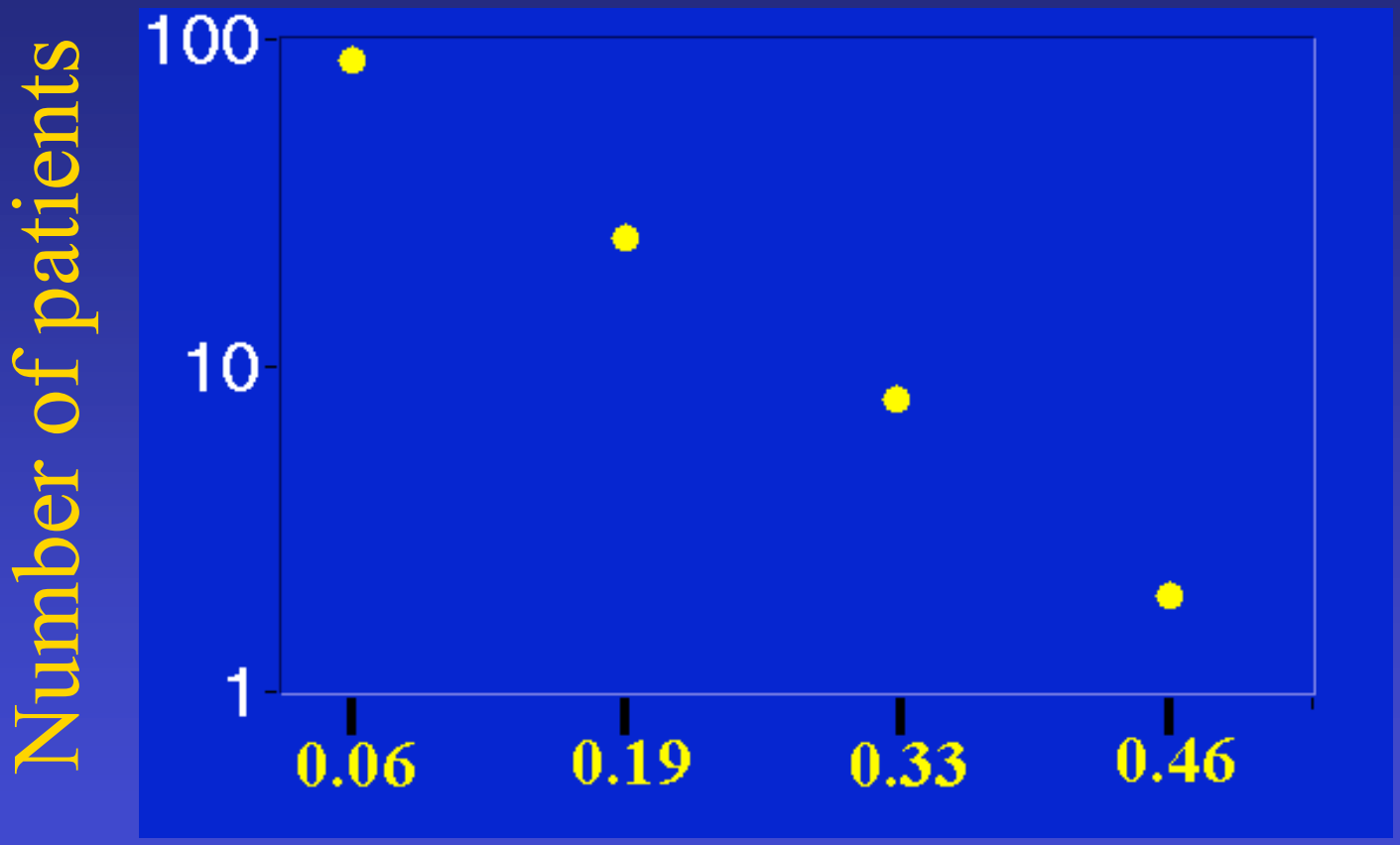
number of samples = 49

number of blips = 7

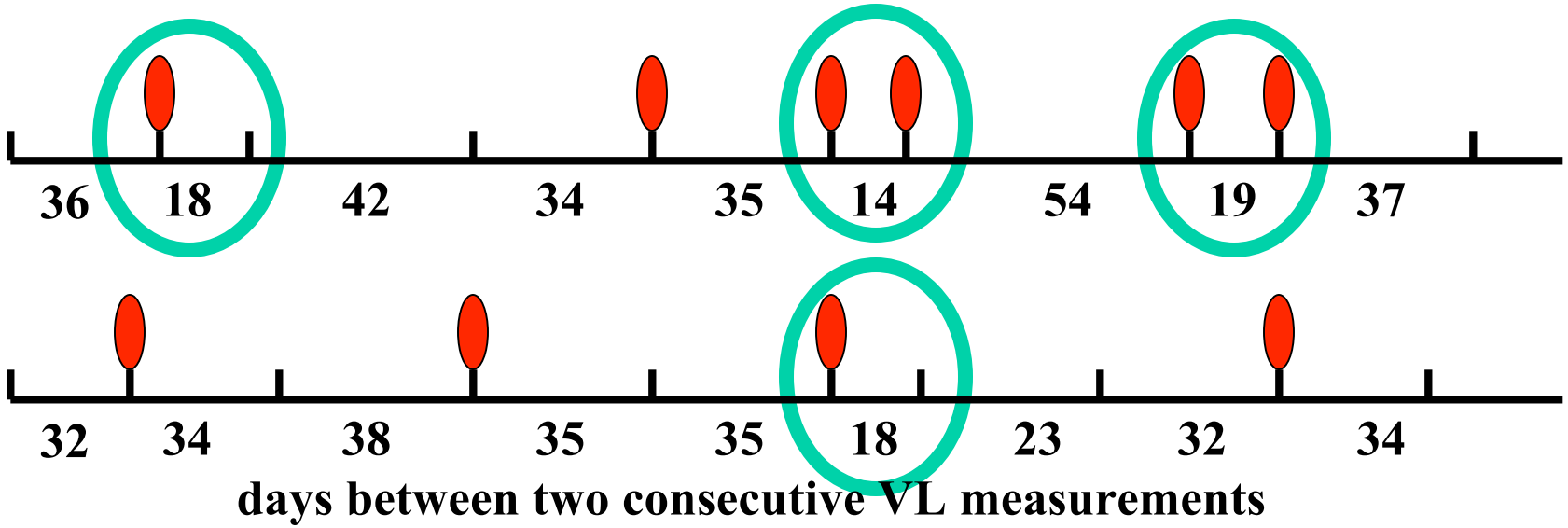



f=0.08; Max(A)=187
Max(z) = 1
f=0.12; Max(A) = 125
Max(z) = 1
f=0.05; Max(A)=81
Max(z) = 1
f=0.49; Max(A) = 630
Max(z) = 3
f=0.21; Max(A) = 742
Max(z) = 3
f=0.27; Max(A) = 145
Max(z) = 2
f=0.33; Max(A) = 628
Max(z) = 4
f=0.22; Max(A) = 517
Max(z) = 4
f=0.35; Max(A) = 327
Max(z) = 2

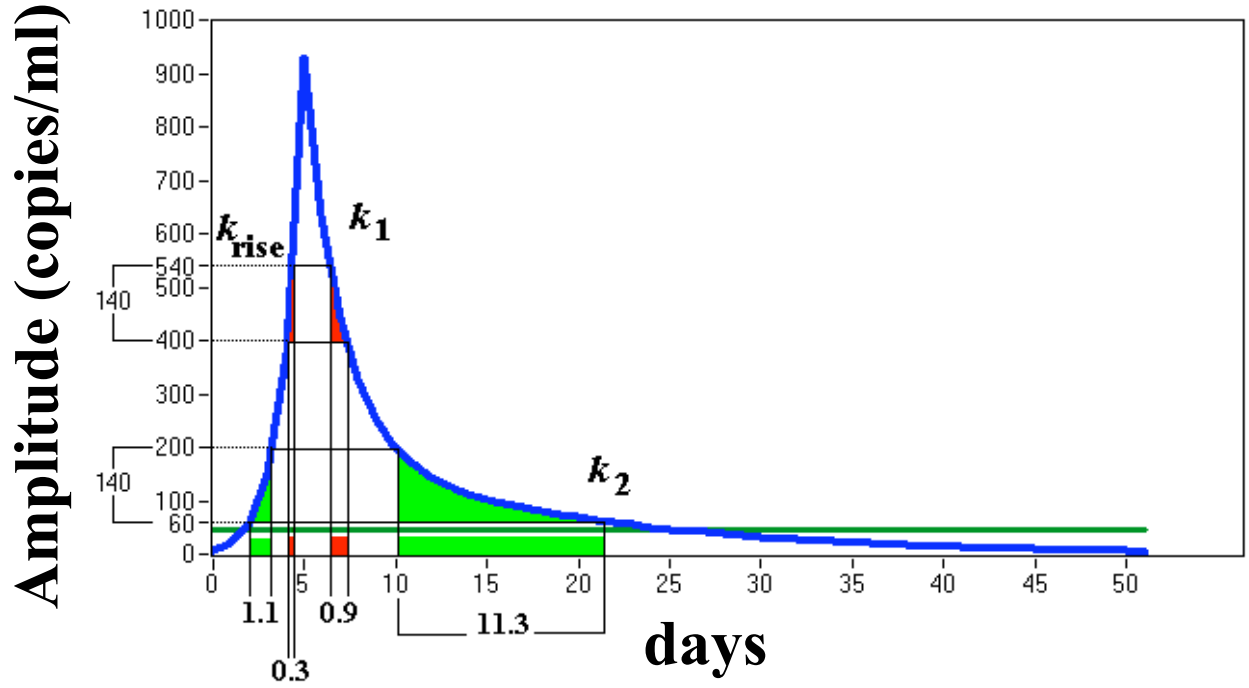
Distribution of viral blip frequencies

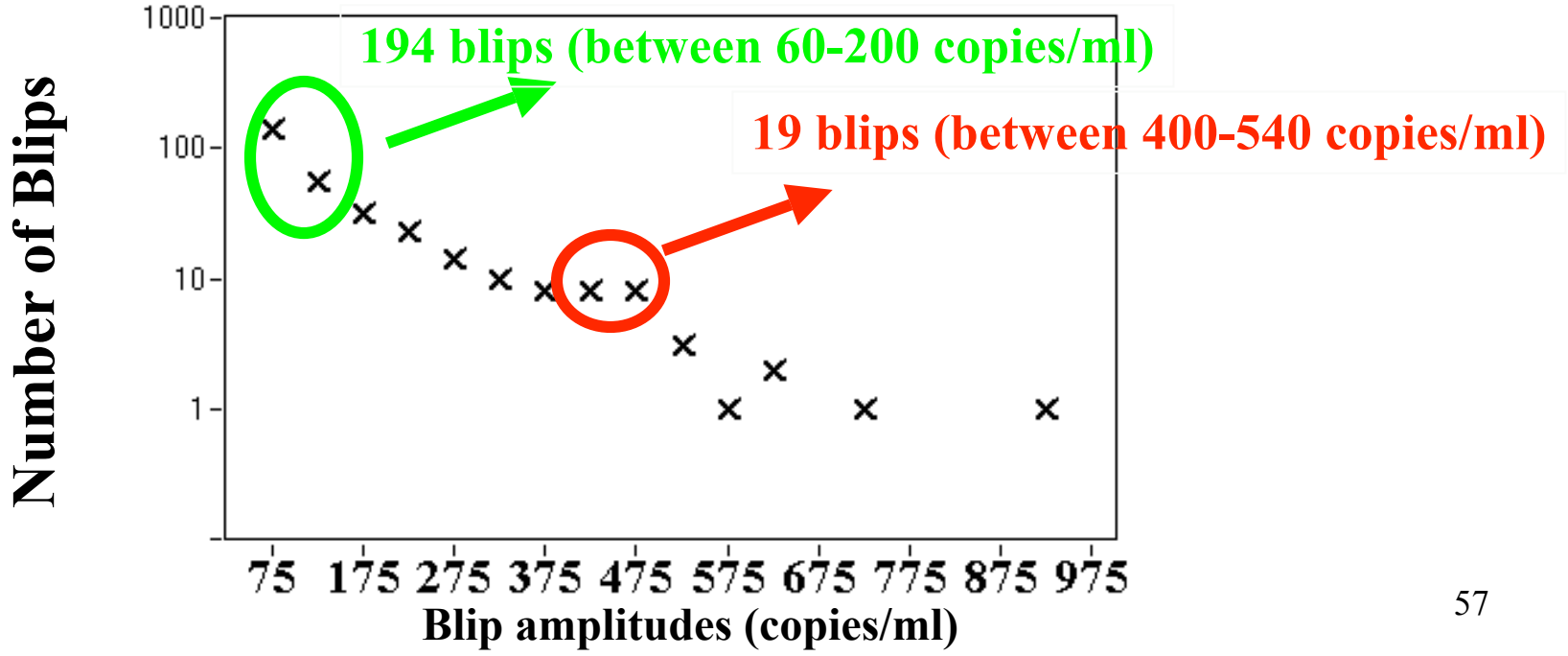


Are blips correlated in time?



- Yes, up to about 3 weeks, suggests virus is elevated for about 3 weeks


Amplitude (copies/ml)
1000
900
800
700
600
540
500
400
300
200
100
60
0
140
140
k_{rise}
k_1
k_2
0
5
10
15
20
25
30
35
40
45
50
1.1
0.9
11.3
0.3
days


Number of Blips
1000
100
10
1
194 blips (between 60-200 copies/ml)
19 blips (between 400-540 copies/ml)
75
175
275
375
475
575
675
775
875
975
Blip amplitudes (copies/ml)

What causes blips?

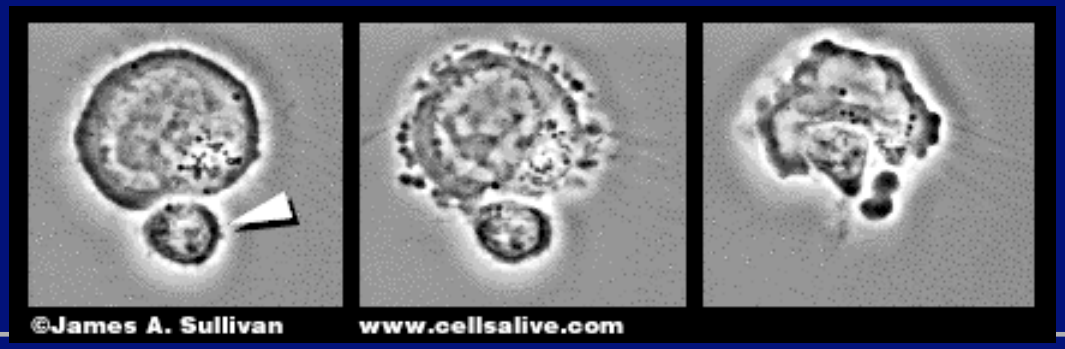
- Assay error
- Stochastic events
  - – activation of cells due to concurrent infection with another virus
  - - Stochastic release of virus from a reservoir

Immune Response

Antibodies and/or cytotoxic T cells

CYTOTOXIC T-LYMPHOCYTE:
A specialized white blood cell responsible for eliminating unwanted body cells (e.g. cancer) is killing a cell infected with the influenza virus

Cytotoxic T Lymphocytes



CTLs can kill virus-infected cells. Here, a CTL (arrow) is attacking and killing a much larger influenza virus-infected target cell.

http://www.cellsalive.com/

Models of CTL Response

$dT/dt = \lambda - dT - kVT$

$dT^*/dt = kVT - \delta_V T^* - \delta_E E T^*$

$dV/dt = pT^* - cV$

$dE/dt = k_E E T^* - \mu E$ CTL Effectors

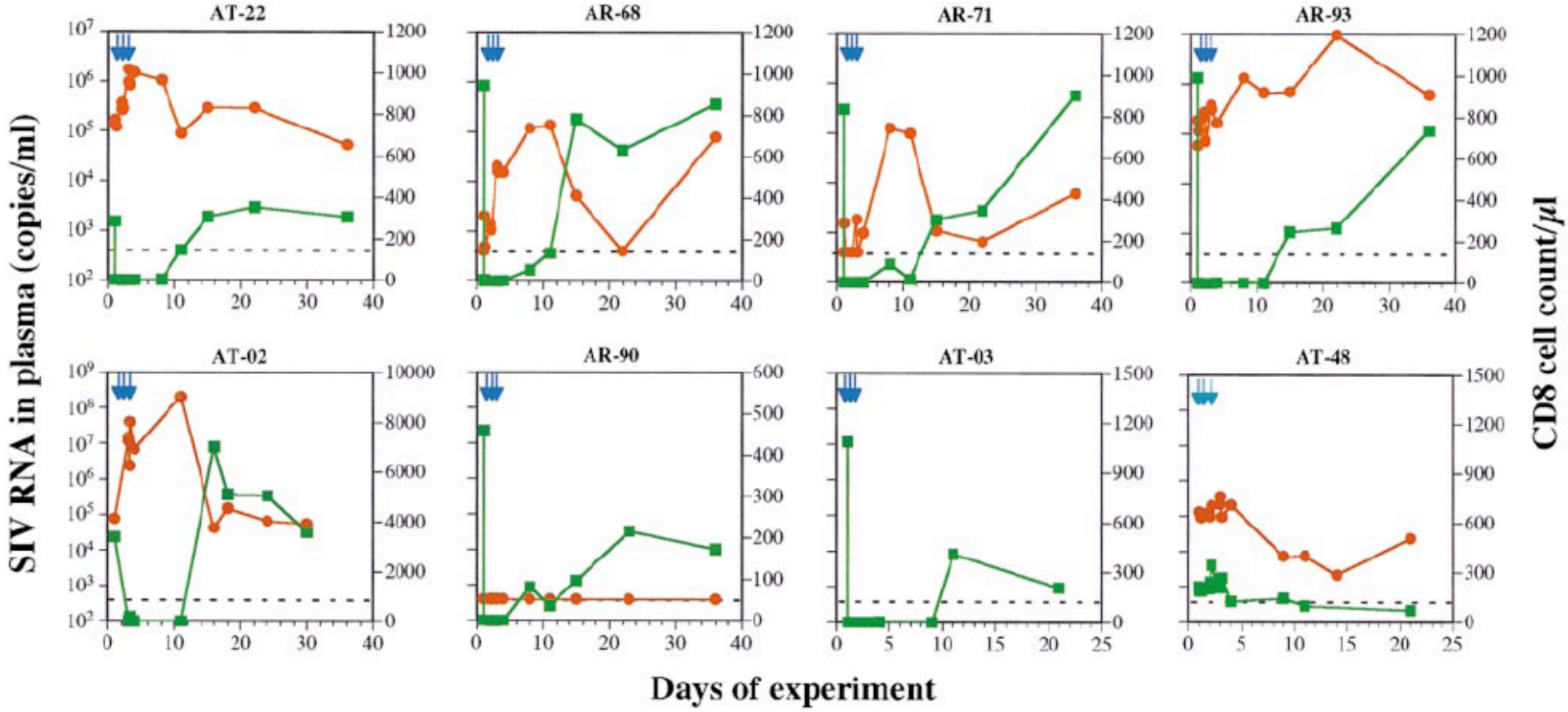
Nowak and Bangham, *Science* **272**, 74 1996

Is this an appropriate model?

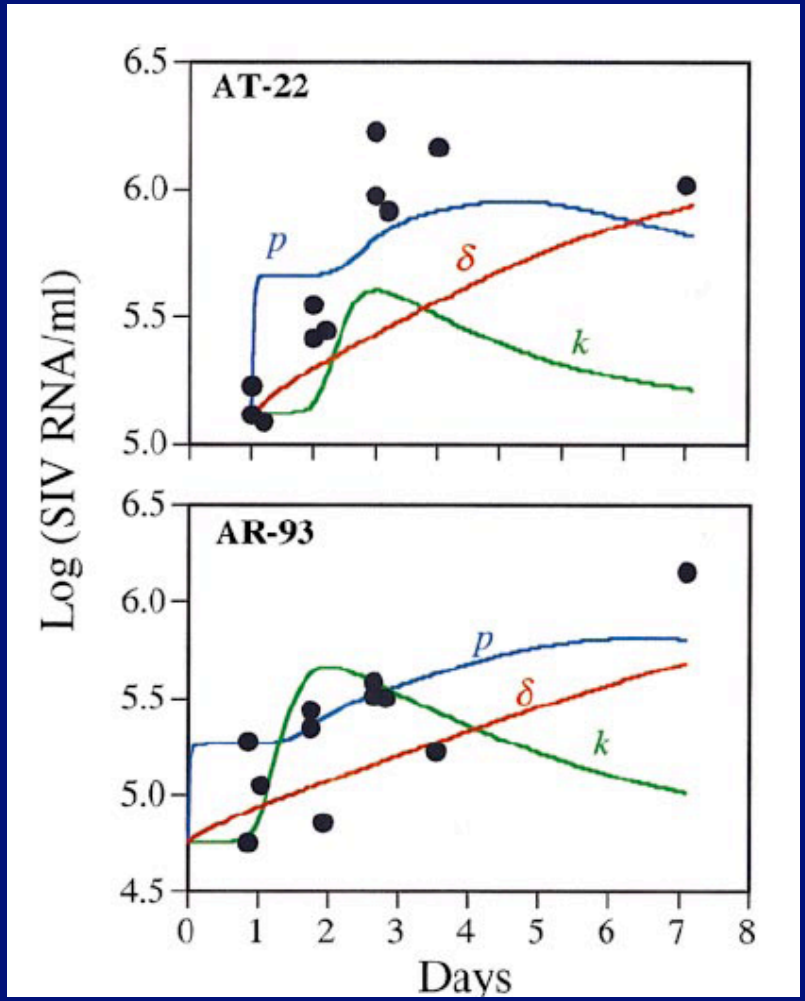
- Do perturbation experiments!
  - Vaccinate to increase CD8 numbers
  - Deplete animals of CD8 cells

Then fit model to data

Depleting CD8 T cells leads to dramatic increase in V



Possible effects of CD8 depletion



Collaborators

- David Ho, Rockefeller Univ
- Many postdocs, students, visitors to LANL- Ruy Ribeiro, Avidan Neumann, Miles Davenport, Leor Weinberger, Michele Di Mascio