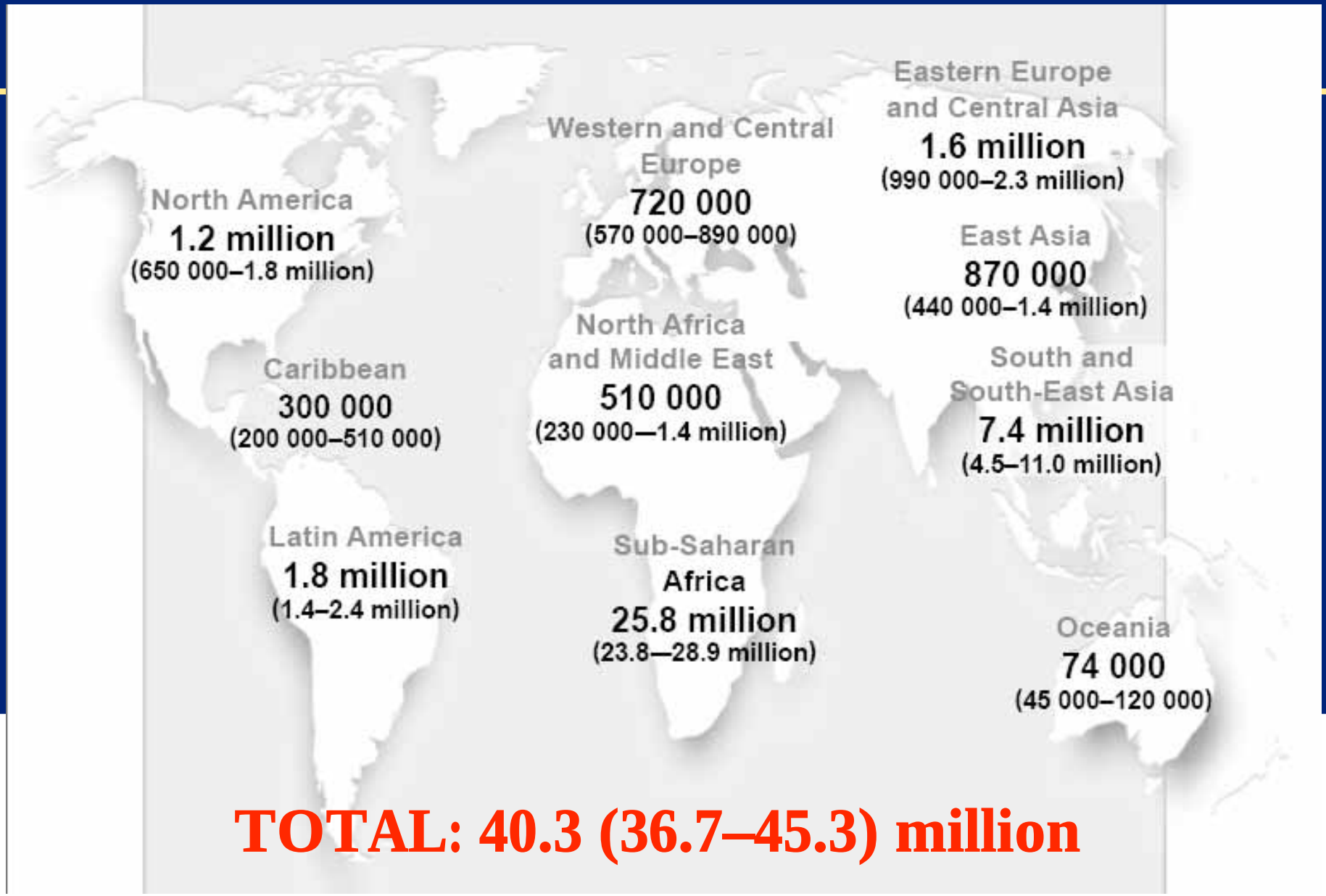
Viral Dynamics

Alan S. Perelson, PhD

Theoretical Biology & Biophysics
Los Alamos National Laboratory
Los Alamos, NM

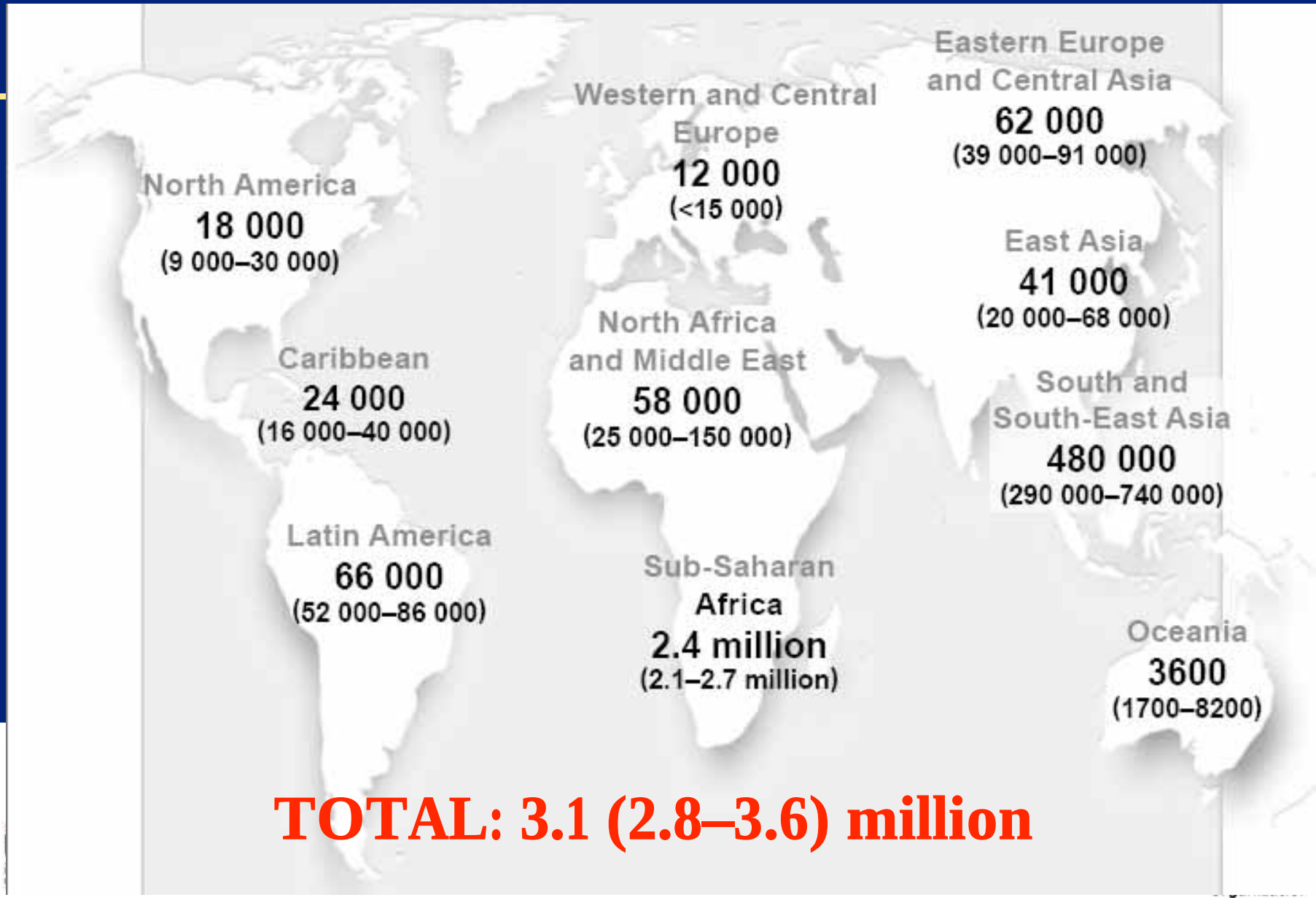
asp@lanl.gov

People living with HIV (2005)



TOTAL: 40.3 (36.7–45.3) million

Deaths resulting from HIV (2005)

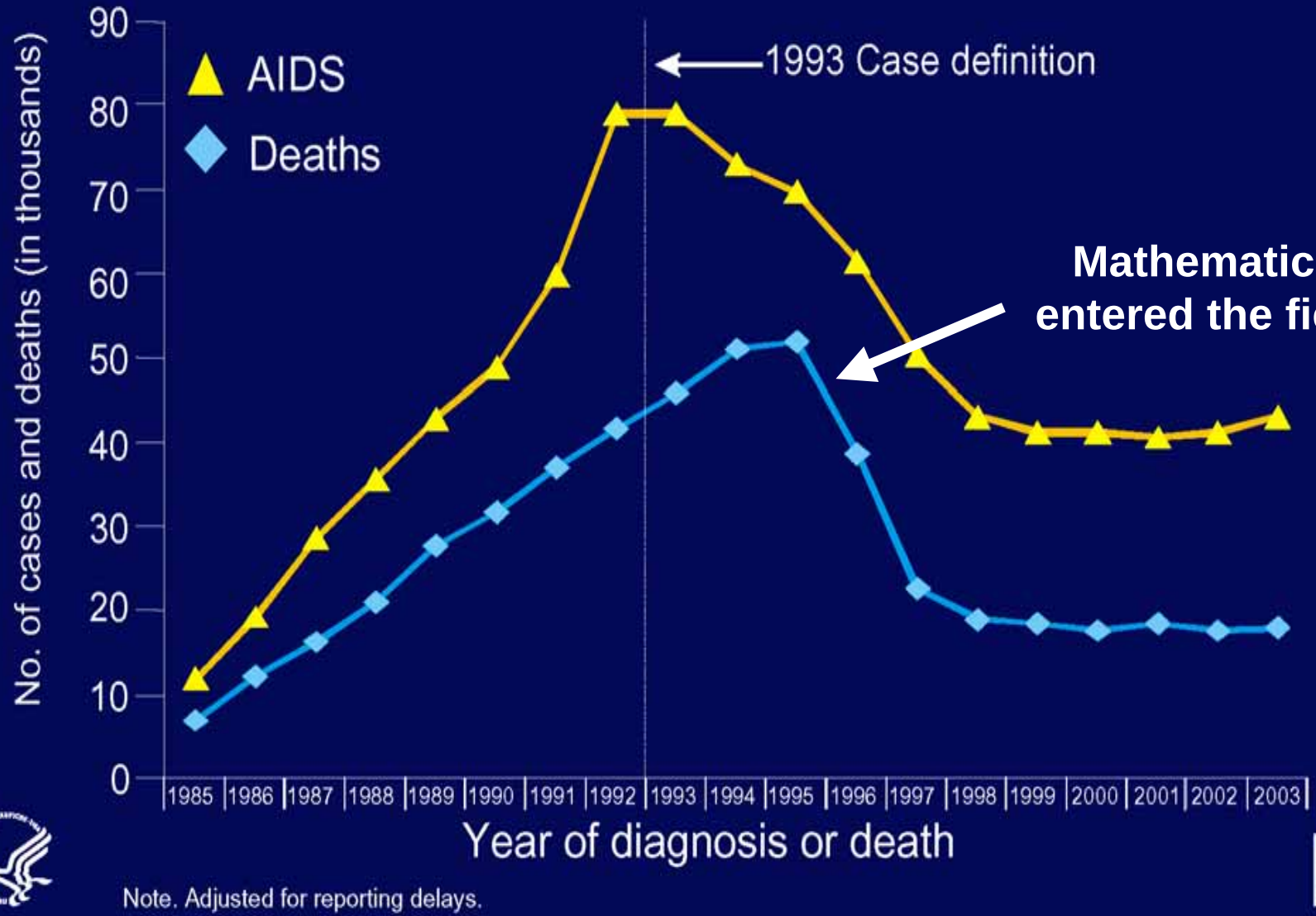


TOTAL: 3.1 (2.8–3.6) million

New infections with HIV (2005)

TOTAL: 4.9 (4.3–6.6) million

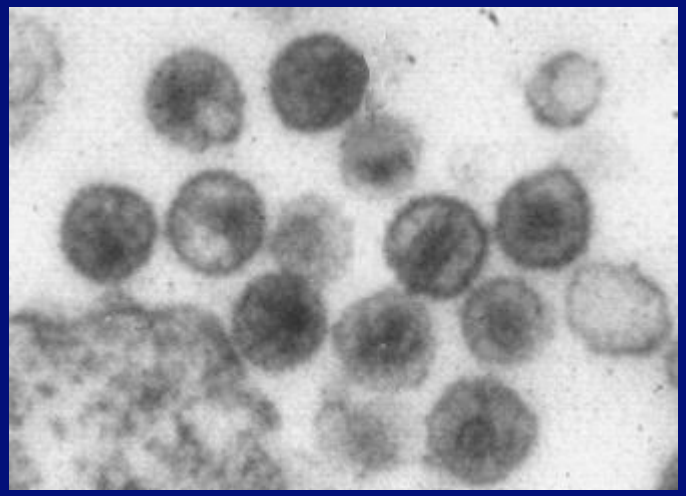
Estimated Number of AIDS Cases and Deaths among Adults and Adolescents with AIDS, 1985–2003—United States



Note. Adjusted for reporting delays.

What is HIV infection?

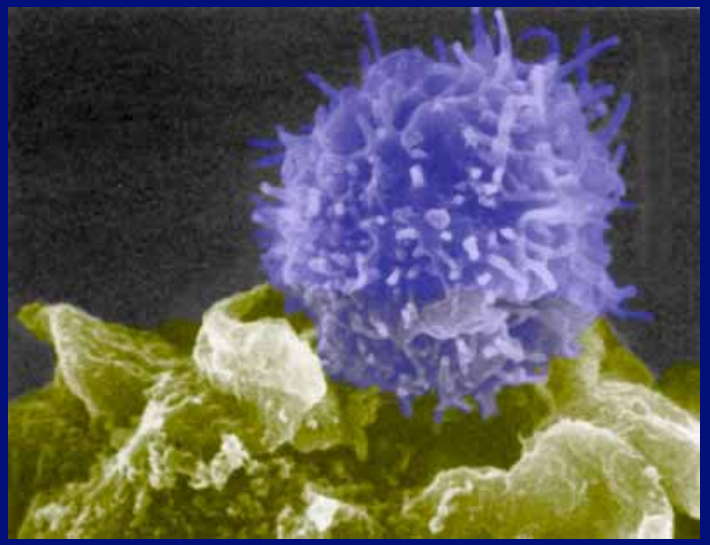
The virus



A retrovirus

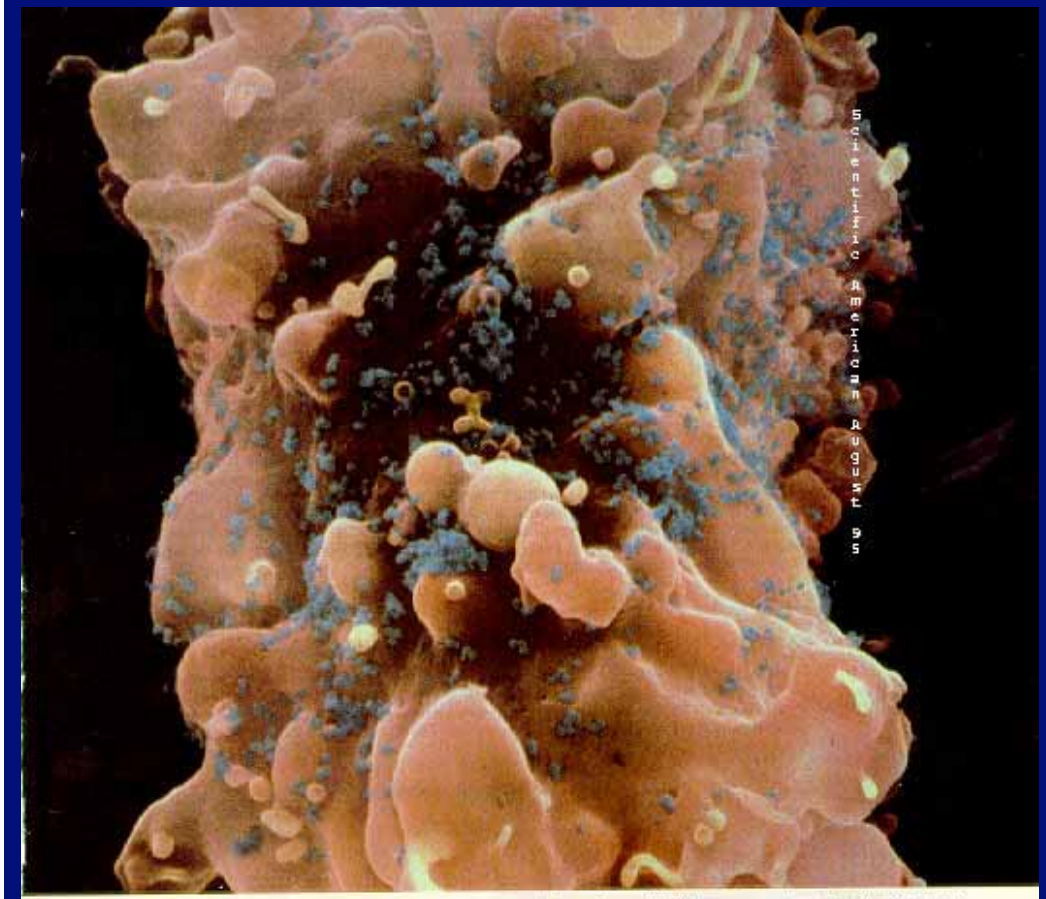
Infects immune cells bearing:
CD4 & CCR5/CXCR4

The host

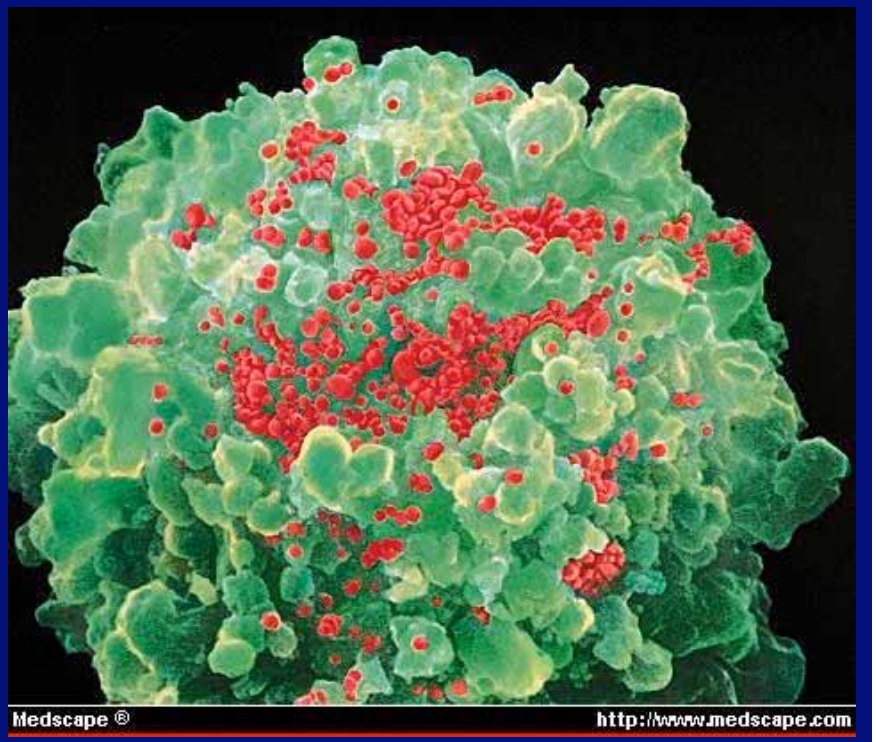


CD4+ T-cells (or helper T cells)

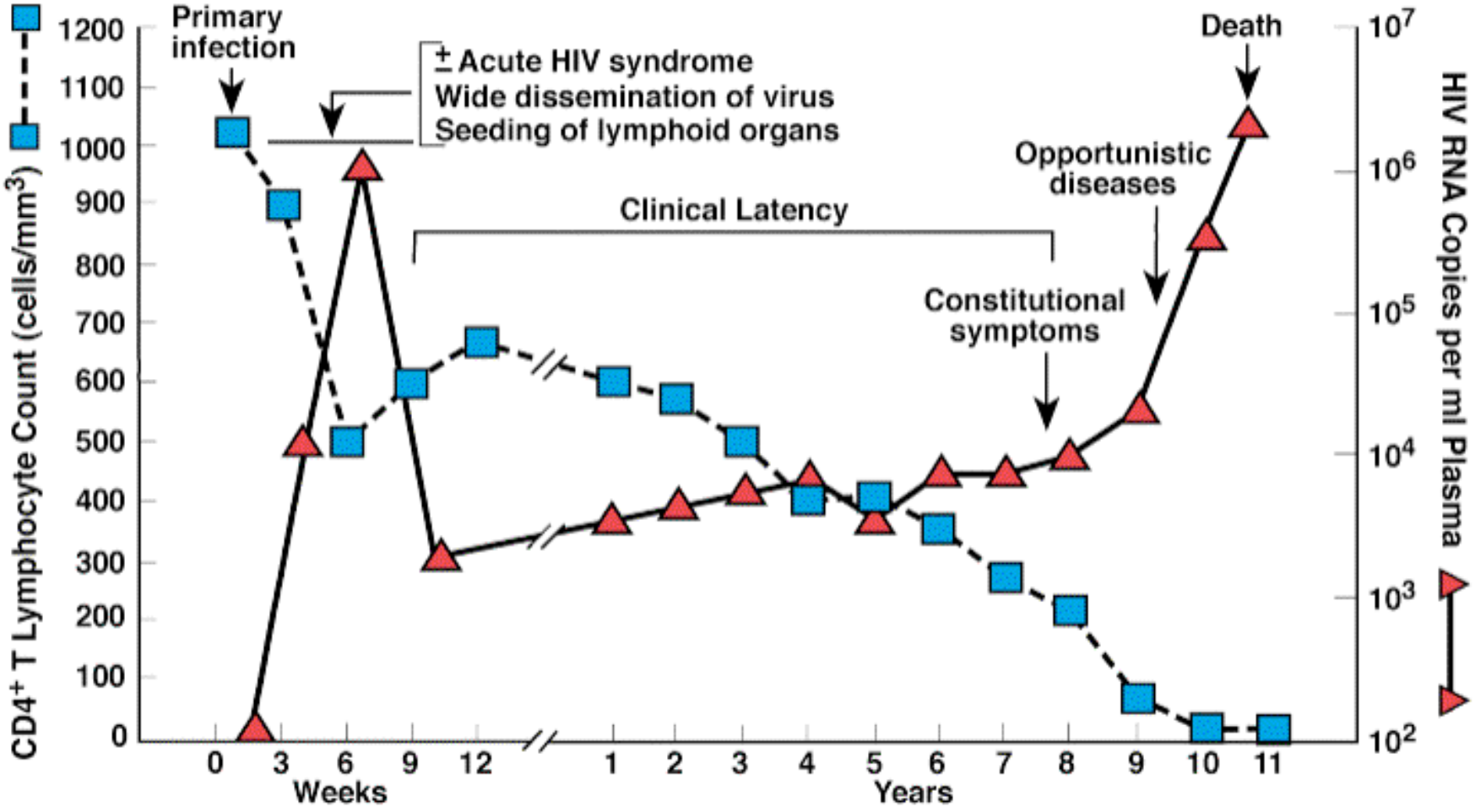
Macrophages and dendritic cells



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.



Typical Course of HIV Infection

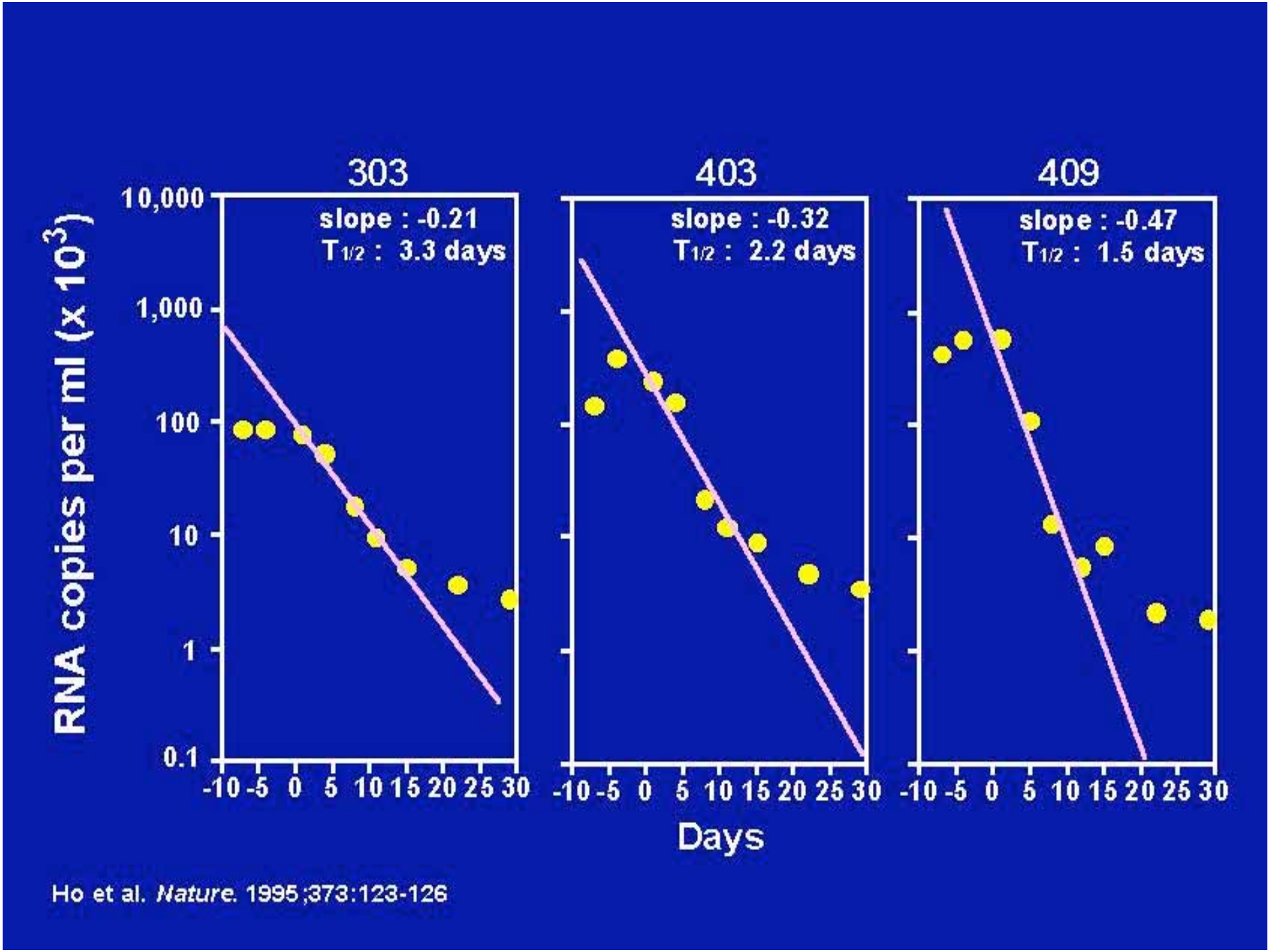


Modified From: Fauci, A.S., et al, *Ann. Intern. Med.*, 124:654, 1996

No treatment

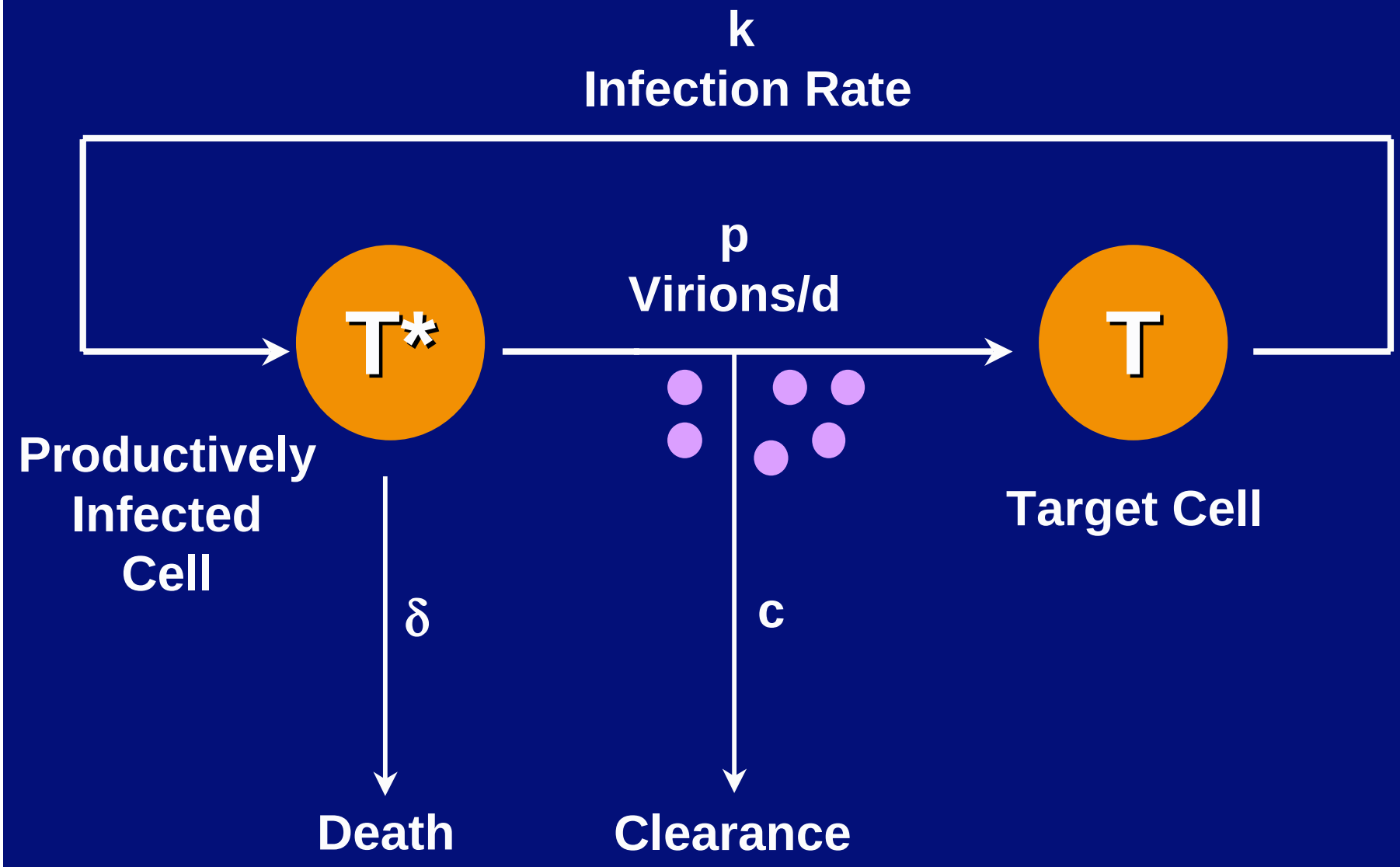
Drug Therapy

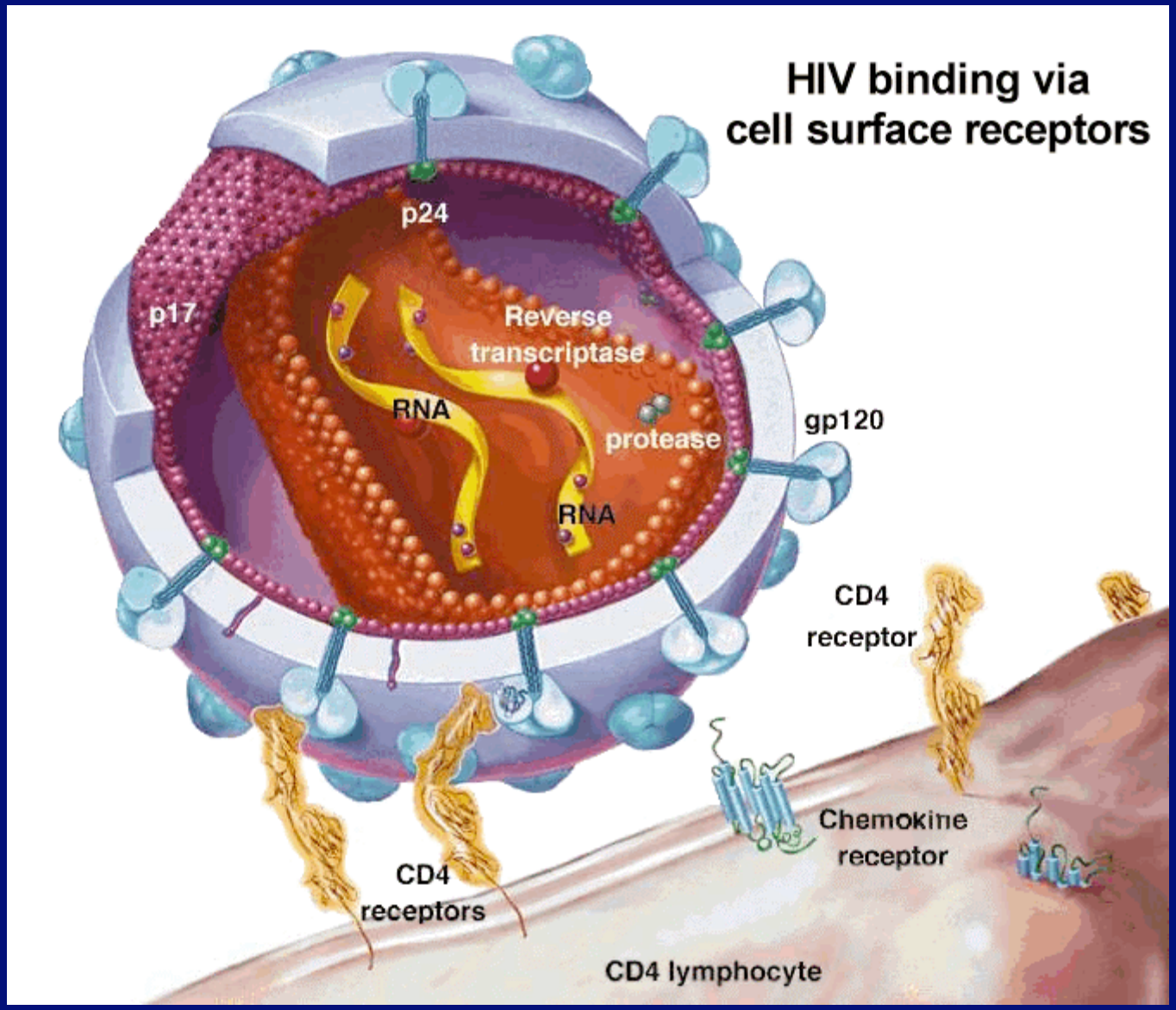
- Medical: a means of interfering with viral replication – treat or cure disease
- Mathematical: a means of perturbing a system and uncovering its dynamics



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

Model of HIV Infection




HIV binding via
cell surface receptors
p24
p17
Reverse
transcriptase
RNA
protease
RNA
gp120
CD4
receptor
Chemokine
receptor
CD4
receptors
CD4 lymphocyte

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 Used for Drug Perturbation Studies

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

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

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

Drug efficacy

ε_{RT} ε_{PI}

Subscripts:

"I": infectious

"NI": non-infectious

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

Solution of Model Equations Assuming 100% Efficacy of Protease Inhibitor Therapy; Target Cells Assumed Constant

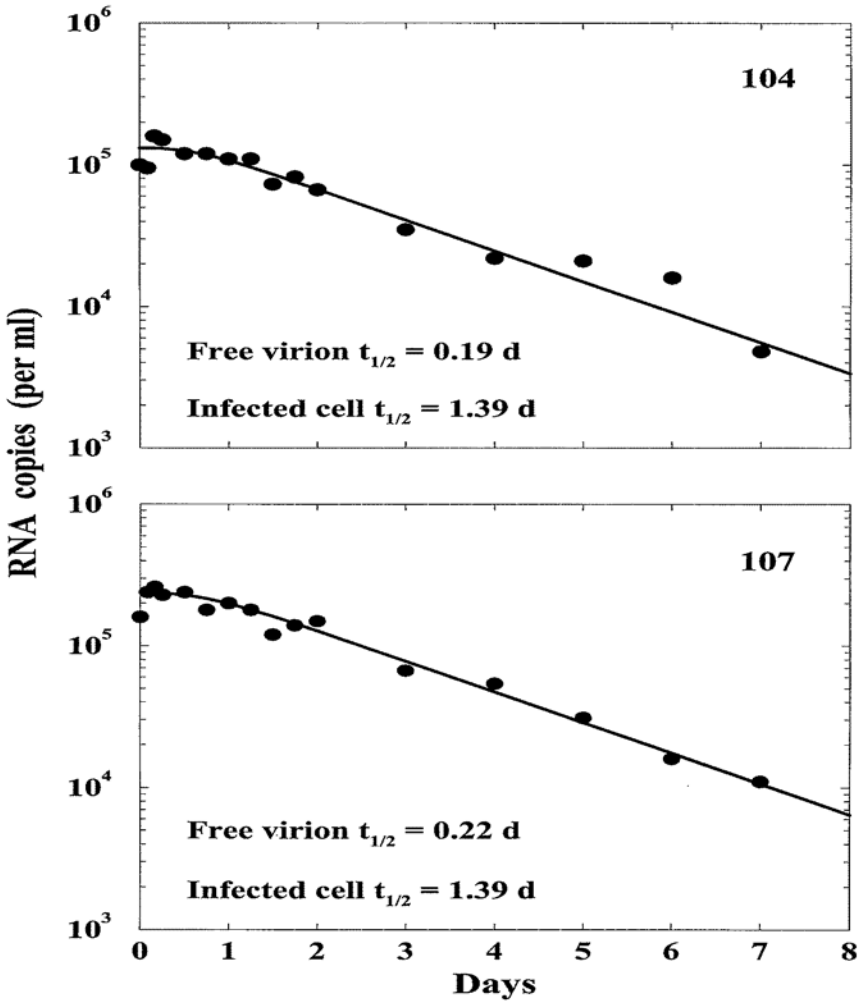
$$V(t) = V_0 \exp(-ct) + \frac{cV_0}{c-\delta}\left\{\frac{c}{c-\delta}\left[\exp(-\delta t) - \exp(-ct)\right] - \delta t \exp(-ct)\right\}$$

Solution has two parameters:

c – clearance rate of virus

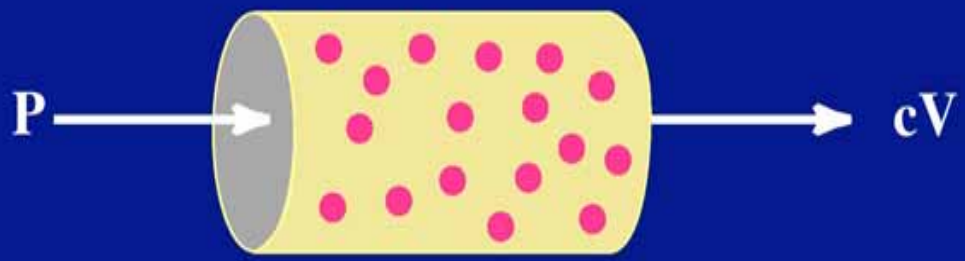
δ – death rate of infected cells

HIV-1: First Phase Kinetics

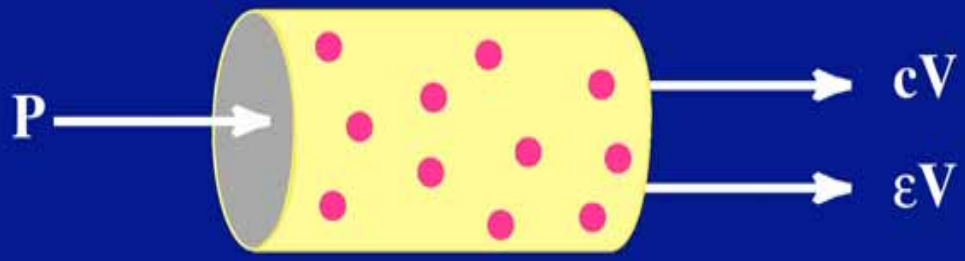


Perelson et al. Science 271, 1582 1996

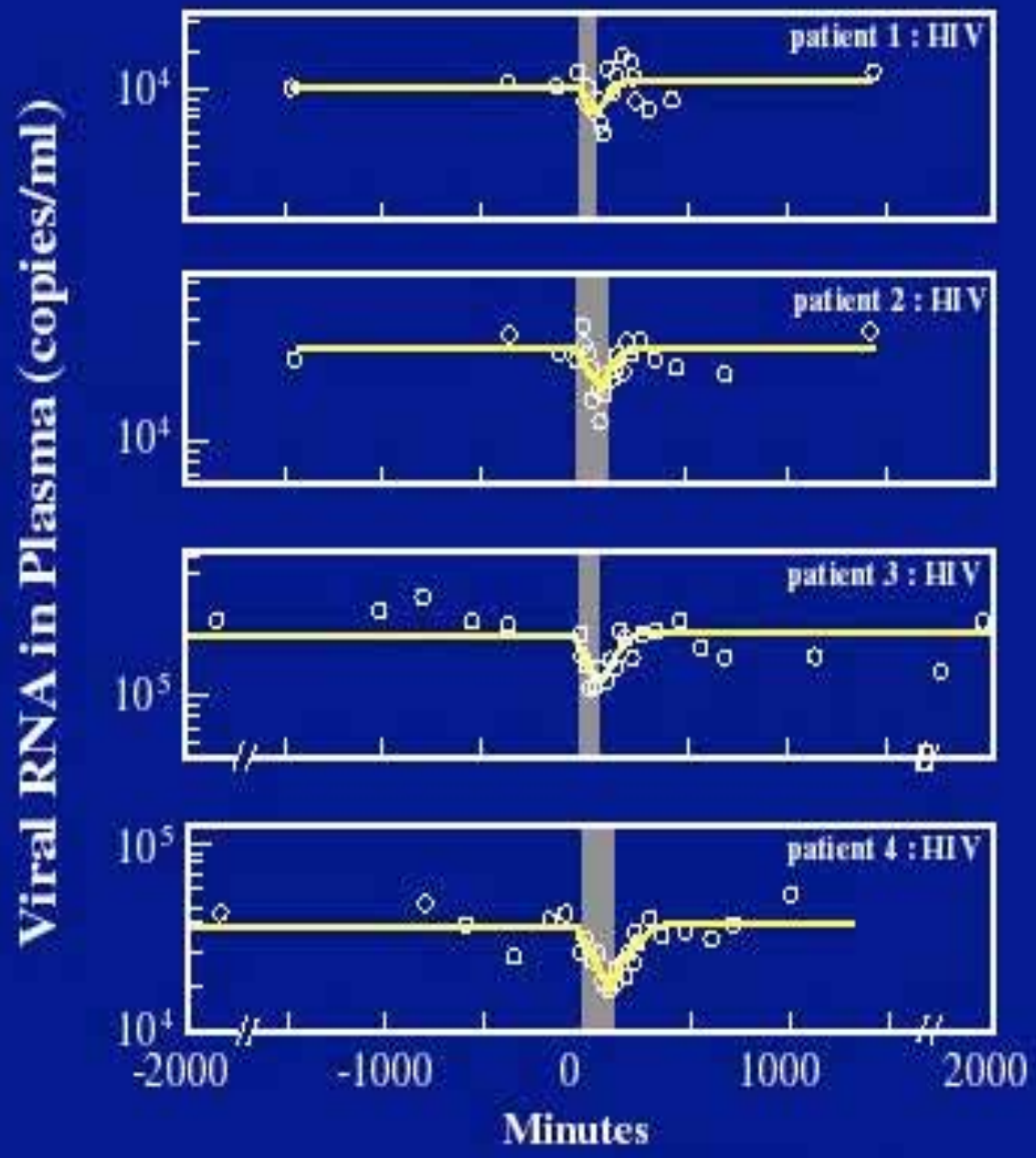
before and after apheresis



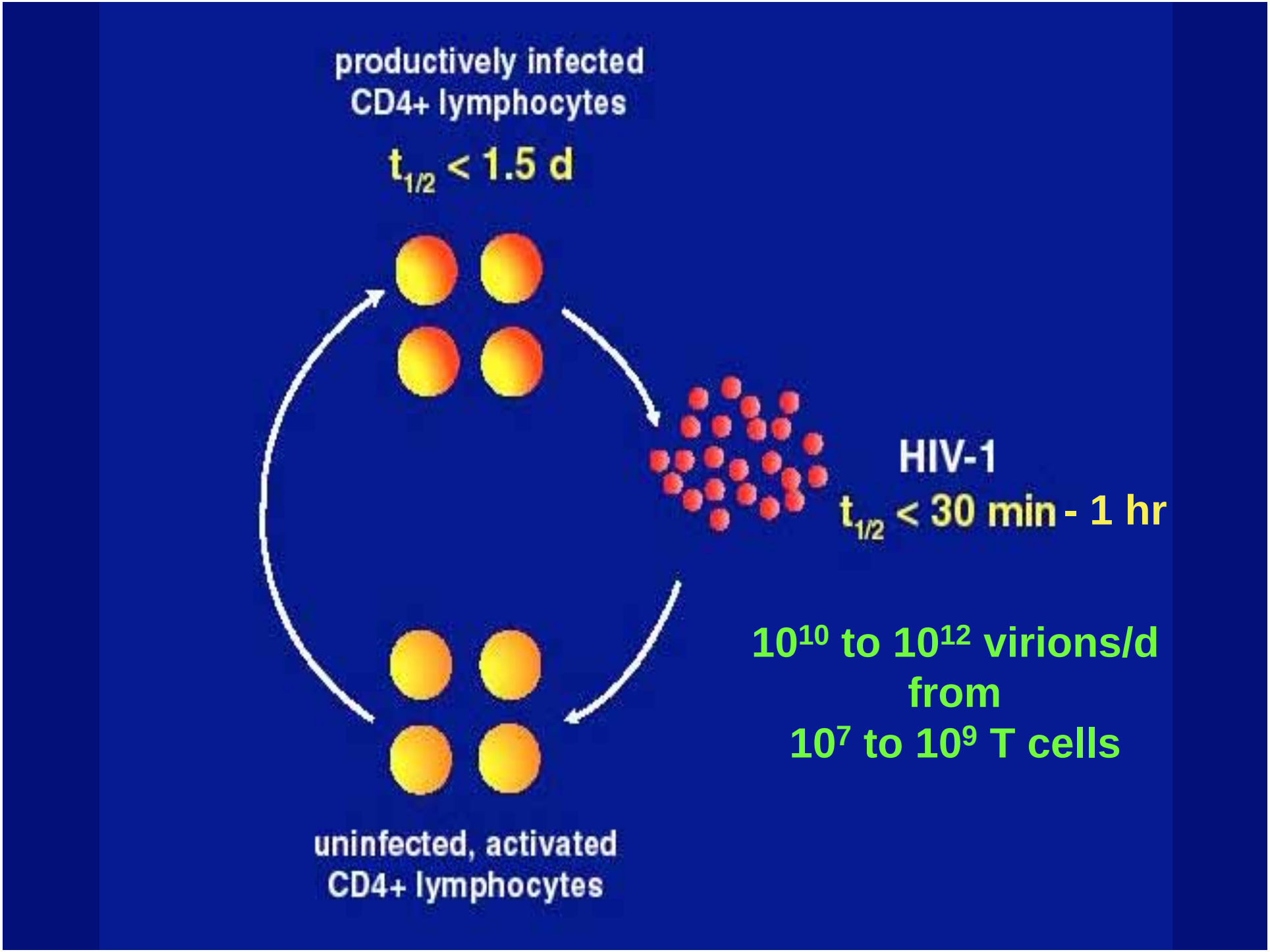
during apheresis



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

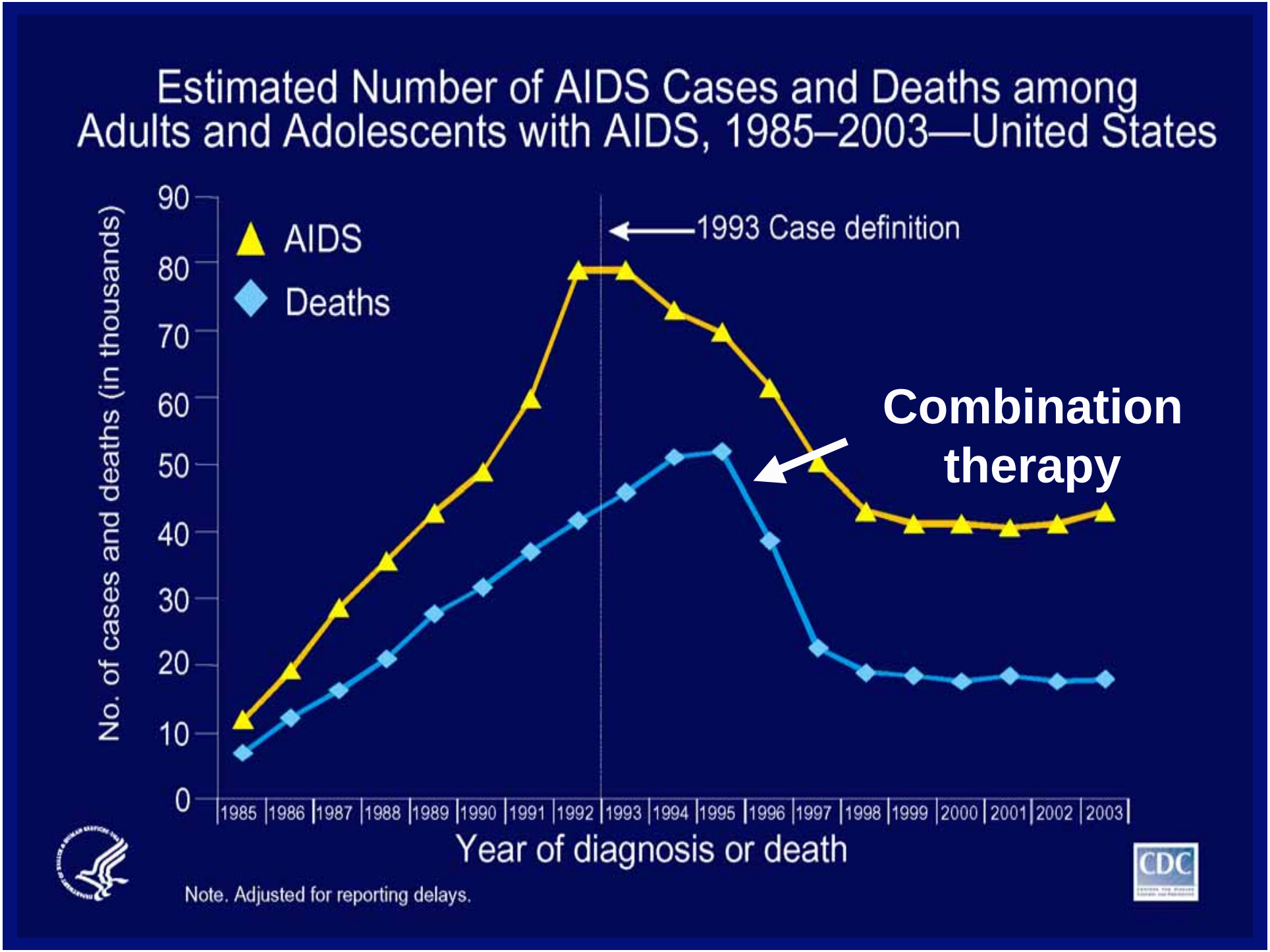
Implications

- 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

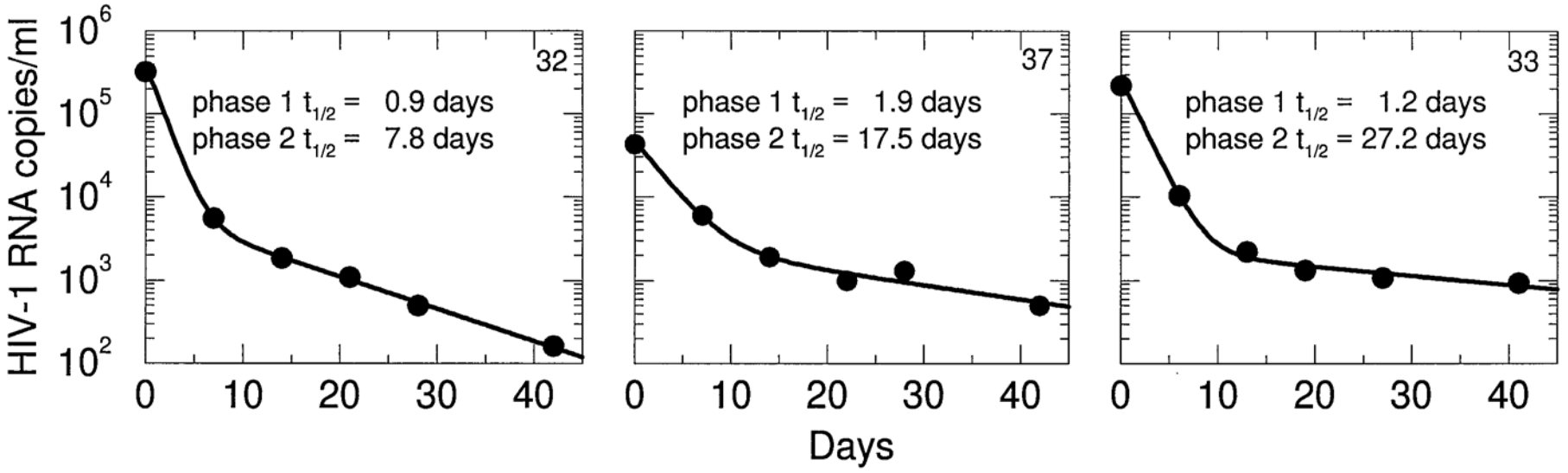
Rate of generation of HIV-1 mutants

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

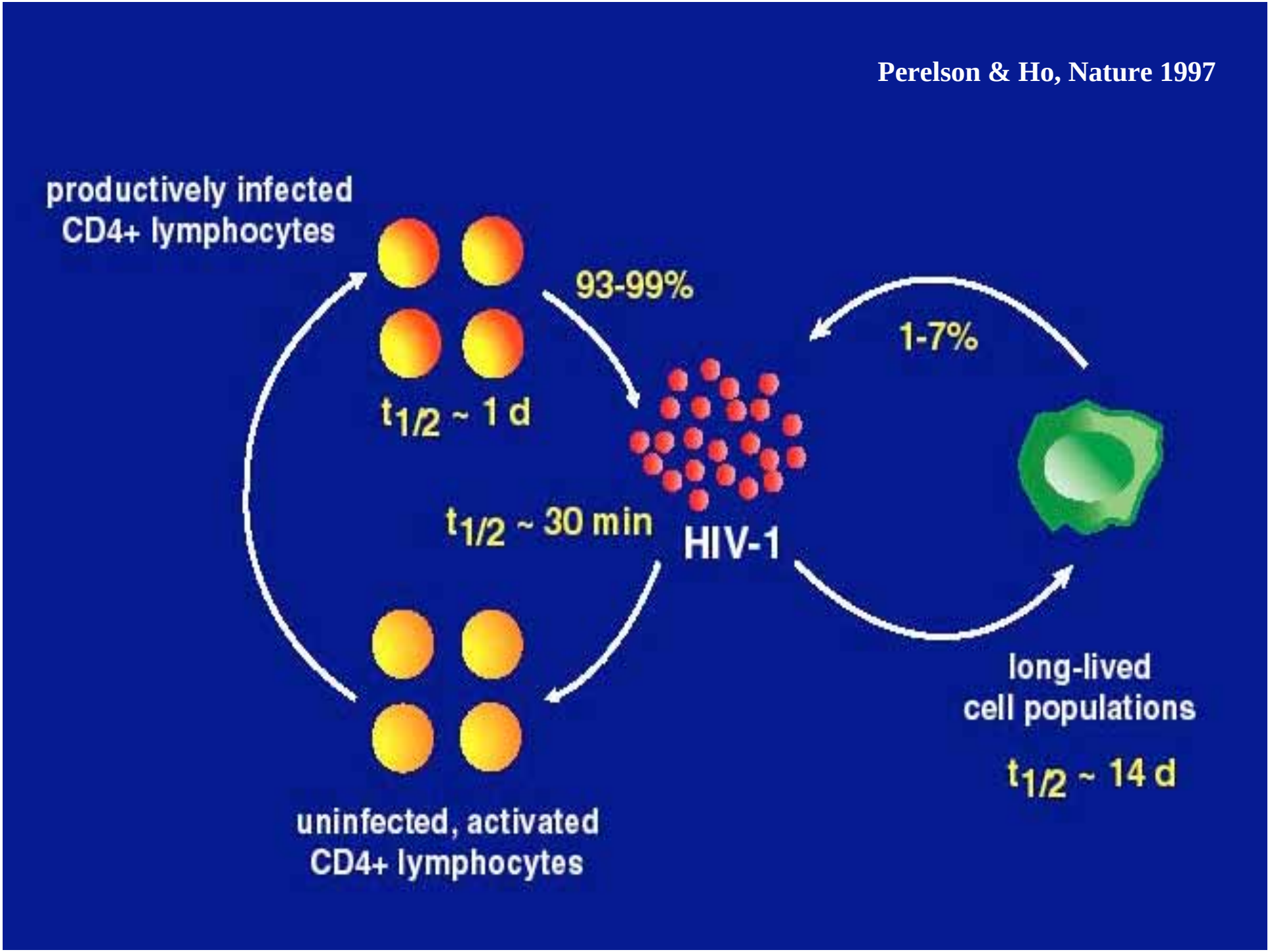

Estimated Number of AIDS Cases and Deaths among Adults and Adolescents with AIDS, 1985–2003—United States
No. of cases and deaths (in thousands)
90
80
70
60
50
40
30
20
10
0
AIDS
Deaths
1993 Case definition
Combination therapy
1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003
Year of diagnosis or death
Note. Adjusted for reporting delays.
CDC

HIV-1: Two Phase Kinetics Combination Therapy

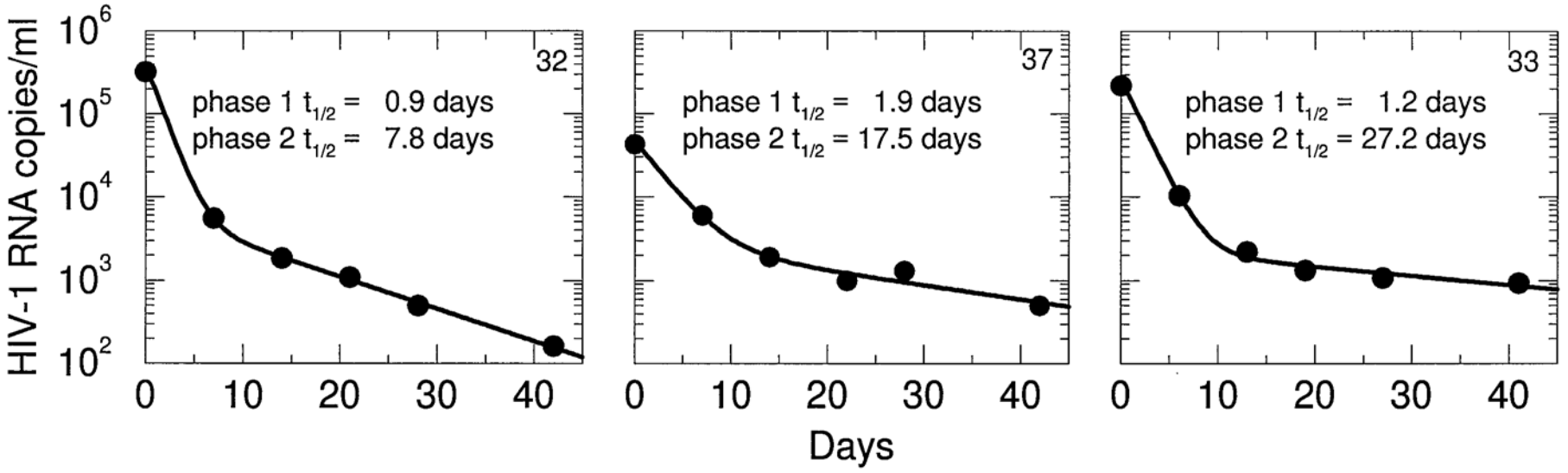


Perelson et al. Nature 387, 186 (1997)

Perelson & Ho, Nature 1997

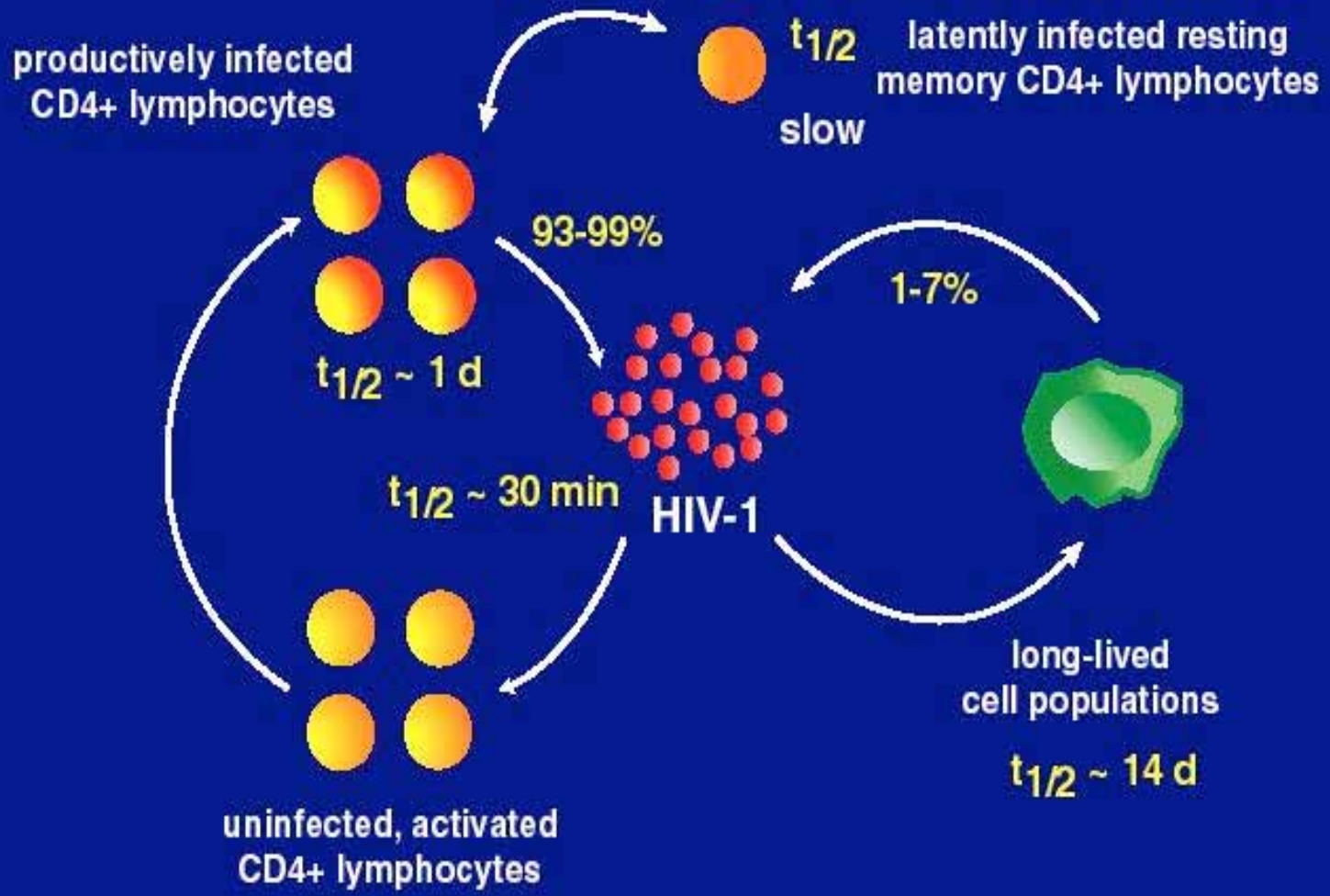


HIV-1: Two Phase Kinetics

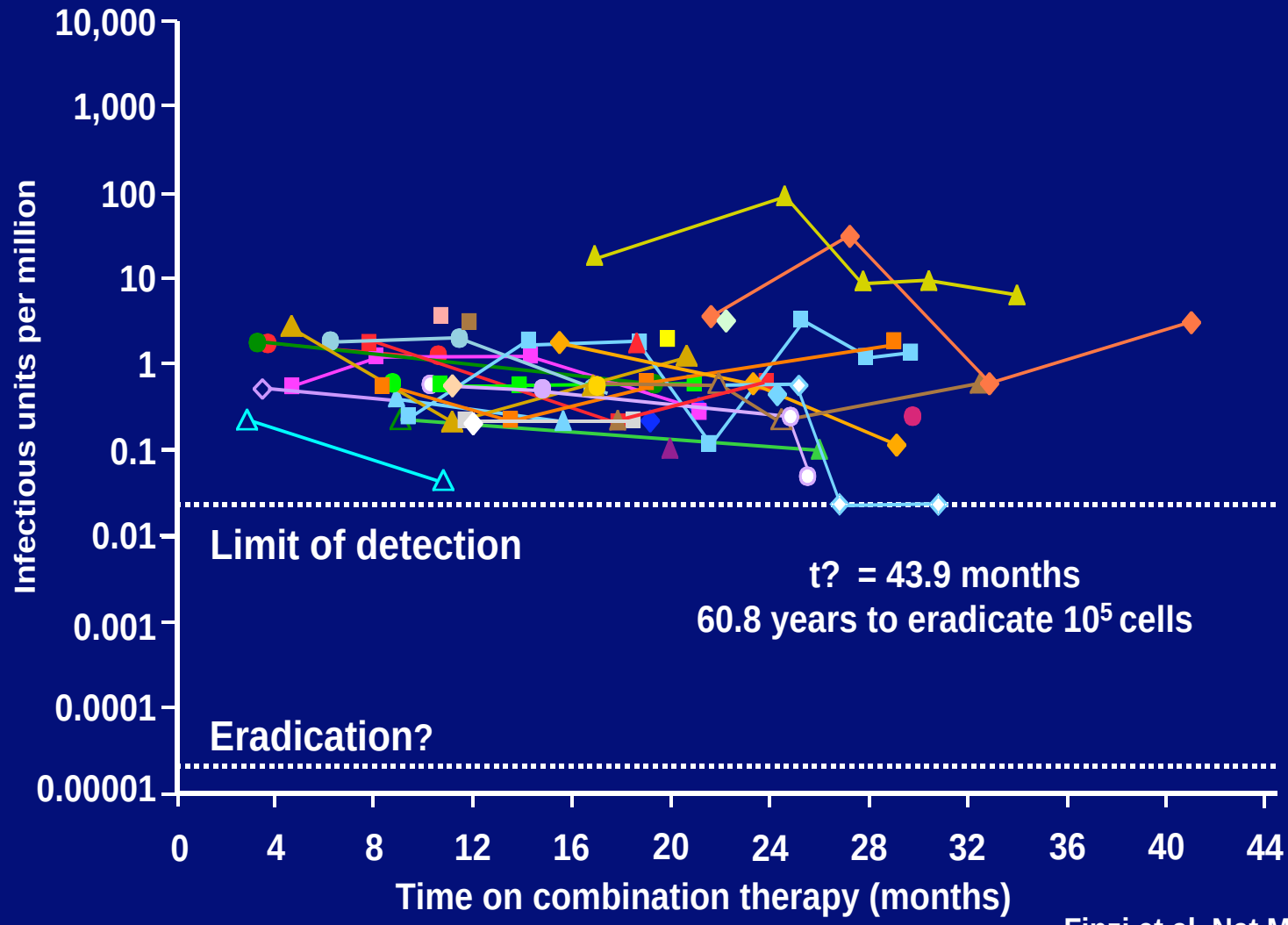


Perelson et al. Nature 387, 186 (1997)

Dynamics of HIV-1



Decay of latent reservoir on HAART



Finzi et al. Nat Med 1999

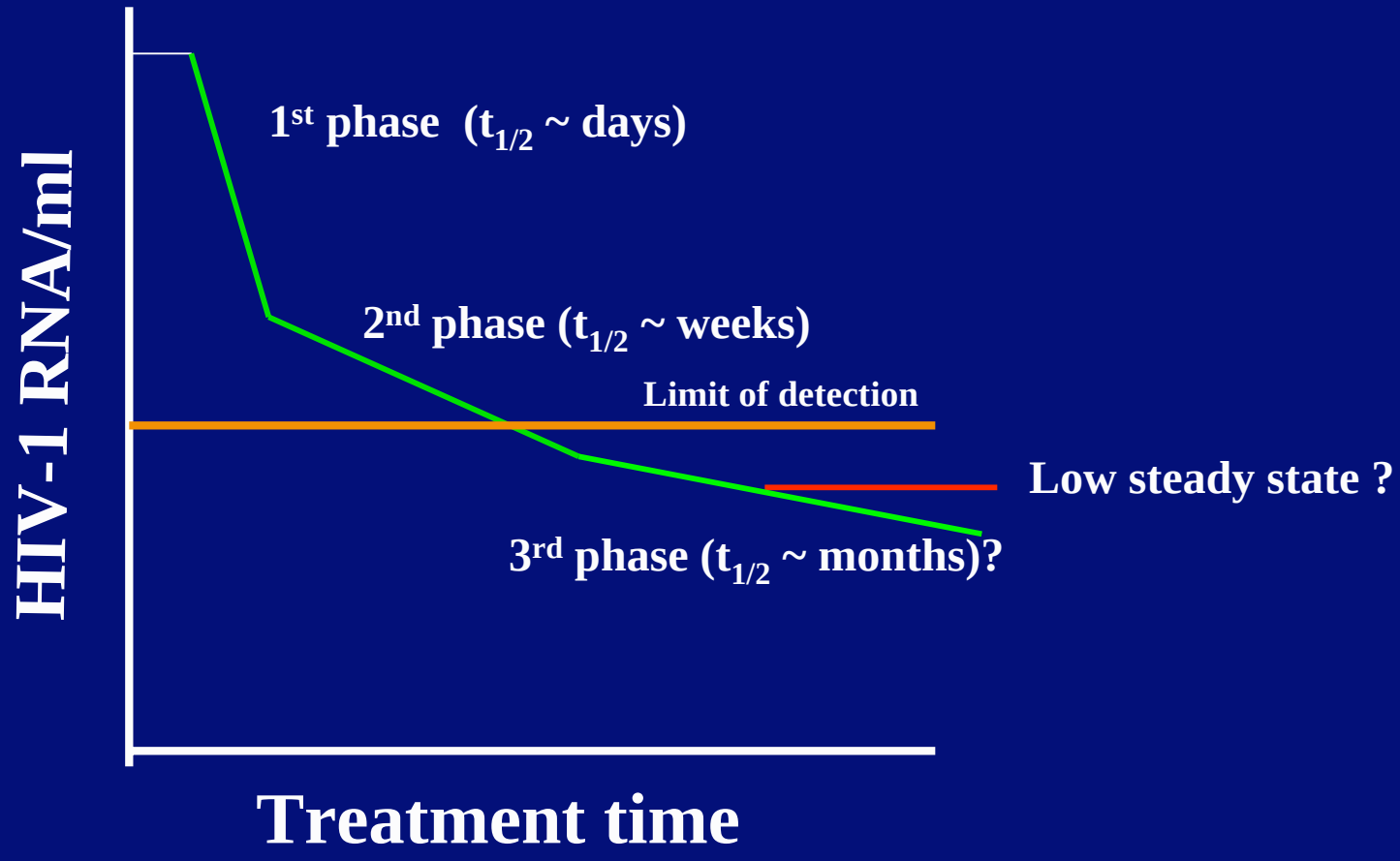
Basic Biology of HIV-1 In Vivo Revealed by Modeling

	$t_{1/2}$	Contribution to viral load
Virions:	< 1 hr	$>10^{10}$/day
Infected T cells:	0.7 d	93-99%
Infected long-lived cells:	14 d	1-7%
Latently infected T cells:	months - years	< 1 %

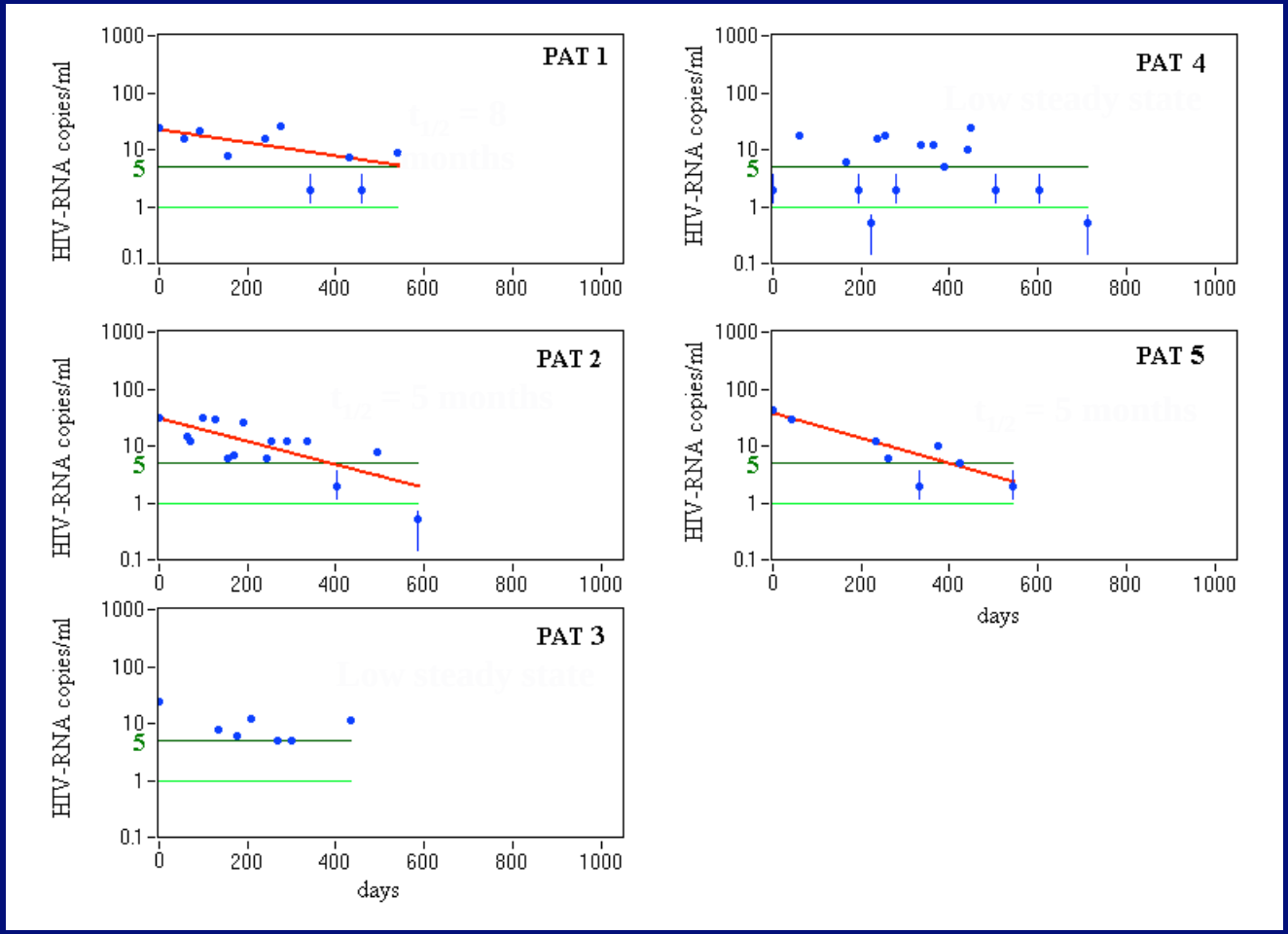
Implications

- Due to long-lived infected cell populations, would need to treat HIV infected individuals for many years with 100% effective drugs to eradicate the virus. Initial estimates were 3-4 years of treatment, new estimates at least 10 years.
- But, do not have 100% effective therapy

What happens after the limit of detection is reached?

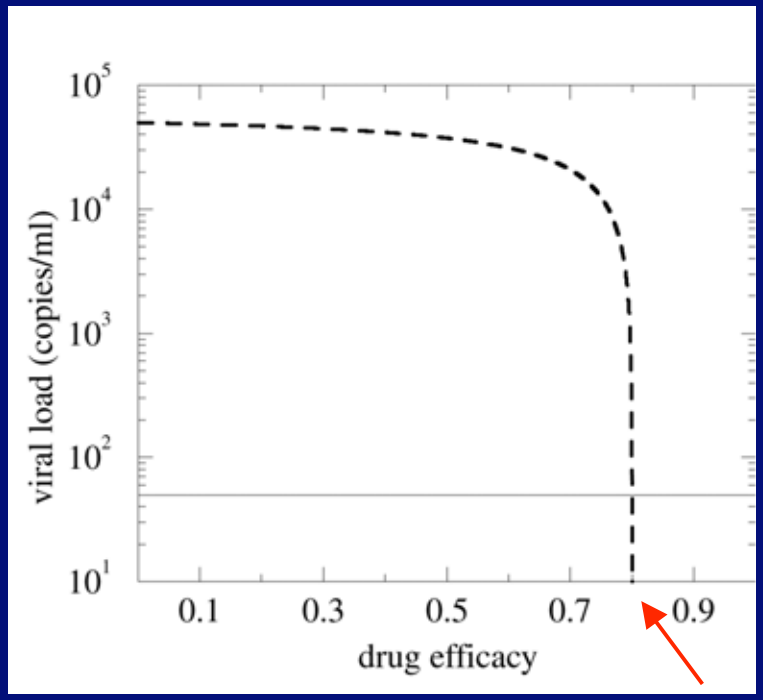


Pomerantz – supersensitive RT-PCR



Di Mascio, M. et al., J. Virol., 2003

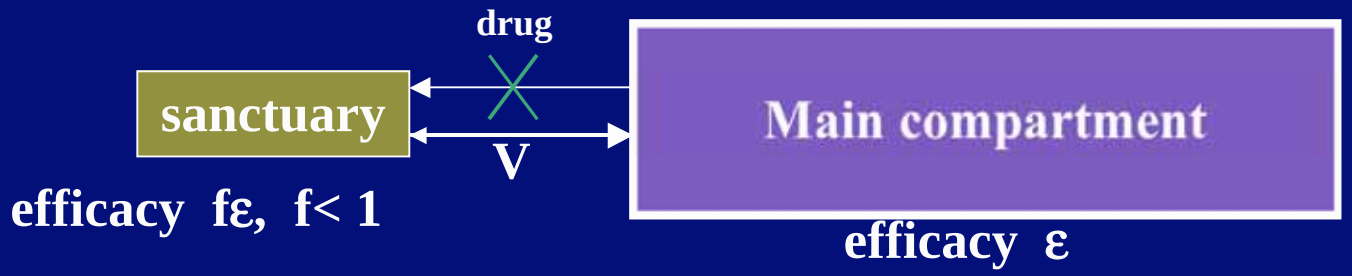
How to explain low steady state?



For the standard model Bonhoeffer et al. JV 71:3275 1997 showed that there was a sensitive dependence of steady state VL on drug efficacy

Two-Compartment Drug Sanctuary Model

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



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

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

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

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

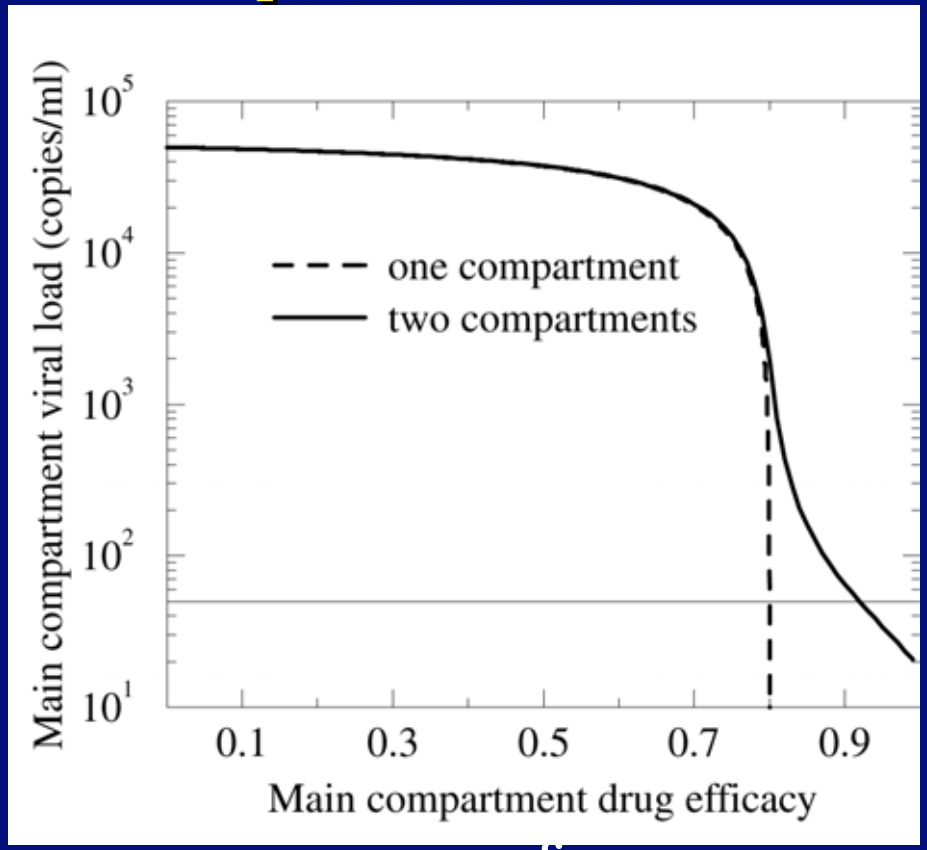
$$\dot{C}_1^* = \alpha(1-\varepsilon)kV_1T_1 - \mu C_1^*$$

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

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

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

Drug sanctuary solves the problem



Two compartment model does not have sensitive dependence on ε

Part II

Hepatitis C Virus Modeling

Viral Hepatitis - Overview

	Type of Hepatitis				
	A	B	C	D	E
Source of virus	feces	blood/ blood-derived body fluids	blood/ blood-derived body fluids	blood/ blood-derived body fluids	feces
Route of transmission	fecal-oral	percutaneous permucosal	percutaneous permucosal	percutaneous permucosal	fecal-oral
Chronic infection	no	yes	yes	yes	no
Prevention	pre/post-exposure immunization	pre/post-exposure immunization	blood donor screening; risk behavior modification	pre/post-exposure immunization; risk behavior modification	ensure safe drinking water

Estimates of Acute and Chronic Disease Burden for Viral Hepatitis, United States

	HAV	HBV	HCV	HDV
Acute infections (x 1000)/year*	125-200	140-320	35-180	6-13
Fulminant deaths/year	100	150	?	35
Chronic infections	0	1-1.25 million	3.5 million	70,000
Chronic liver disease deaths/year	0	5,000	8-10,000	1,000

* Range based on estimated annual incidence, 1984-1994.

Hepatitis C and B Virus

- HCV is a positive strand RNA virus
  - Genome is about 9.3kb, approximately the same size as HIV
  - No vaccine; therapy successful in 50% of people treated
- HBV is a DNA virus
  - Genome is very small, ~ 3.2kb,
  - Takes the form of a partially closed circle
  - Vaccine; therapy to control not cure

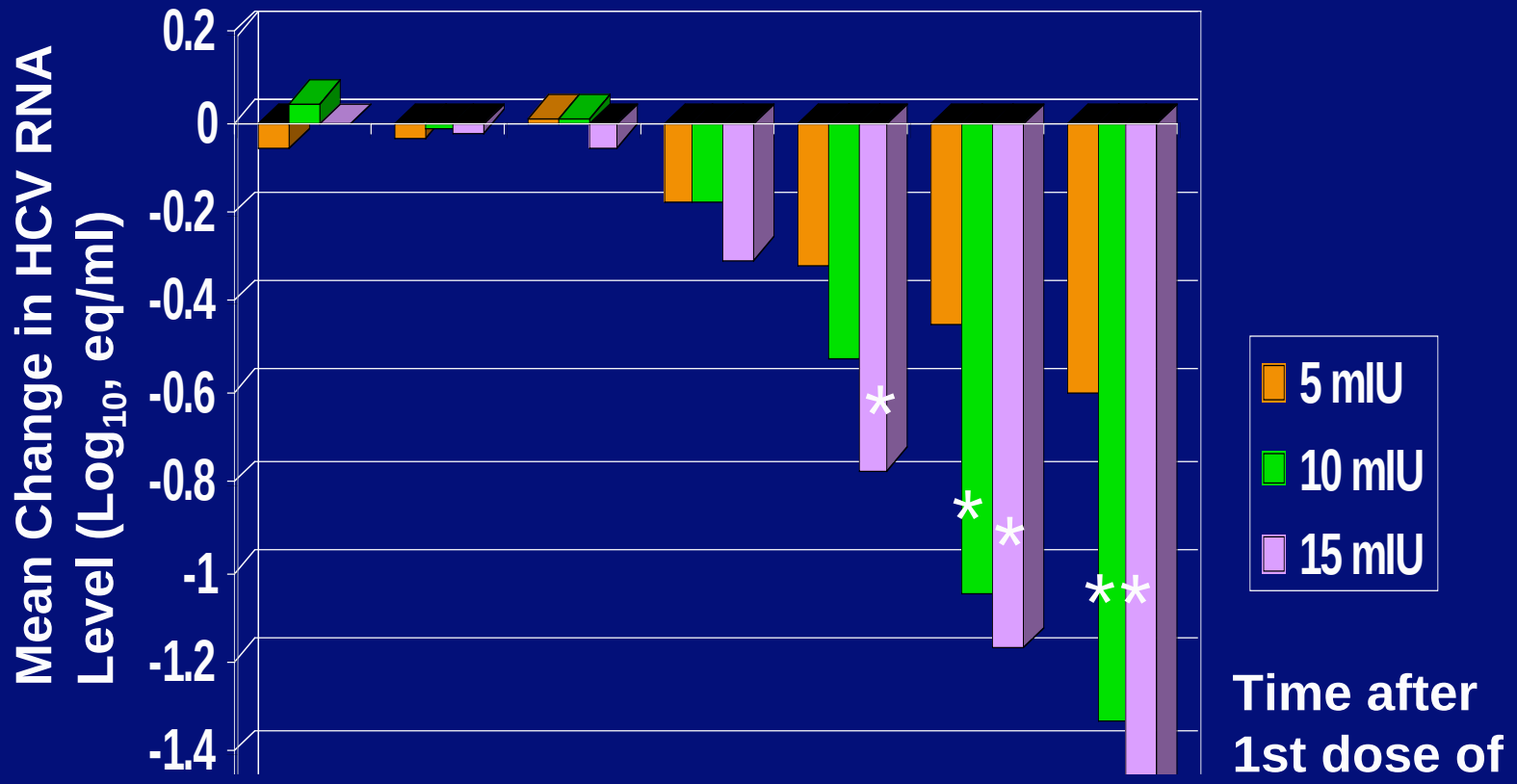
Treatment of HCV

- Two drugs are currently used to treat HCV infection
  - Interferon – α (IFN), which is naturally made cytokine involved in protection against viral infections
  - Ribavirin (RBV), which is a nucleoside analog of guanosine. Its mechanism of action is controversial but it may act as a mutagen

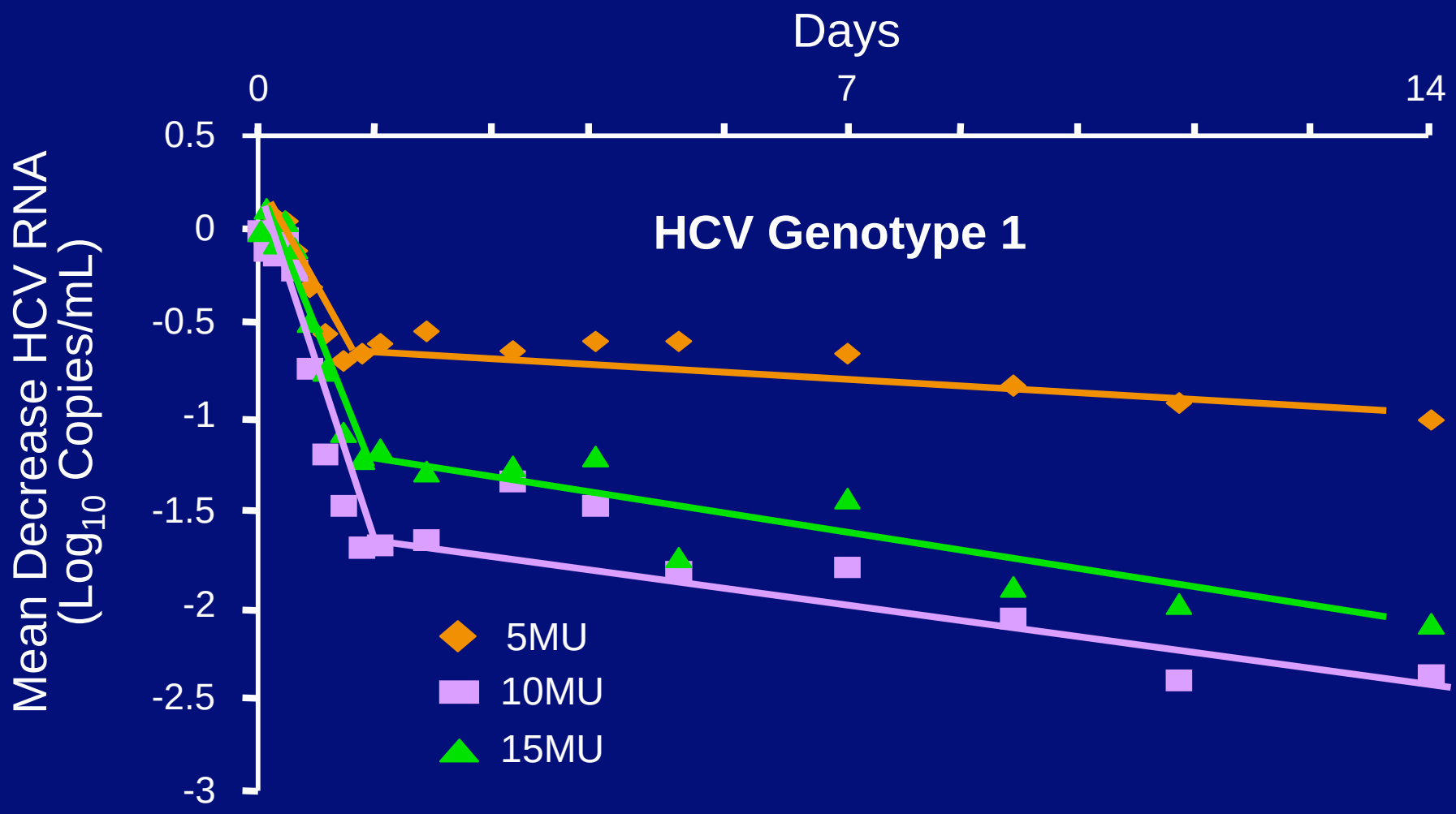
Effects of Treatment

- Virus particles (called virions) are made in the liver but are transported throughout the body via the blood
- Each virion contains one HCV RNA molecule that encodes the genome for the virus.
- Experimentalists can accurately measure the amount of HCV RNA per ml of blood (plasma or serum).
- Treatment should lower the amount of HCV RNA

Acute Changes in HCV RNA Level Following First Dose of IFN-α

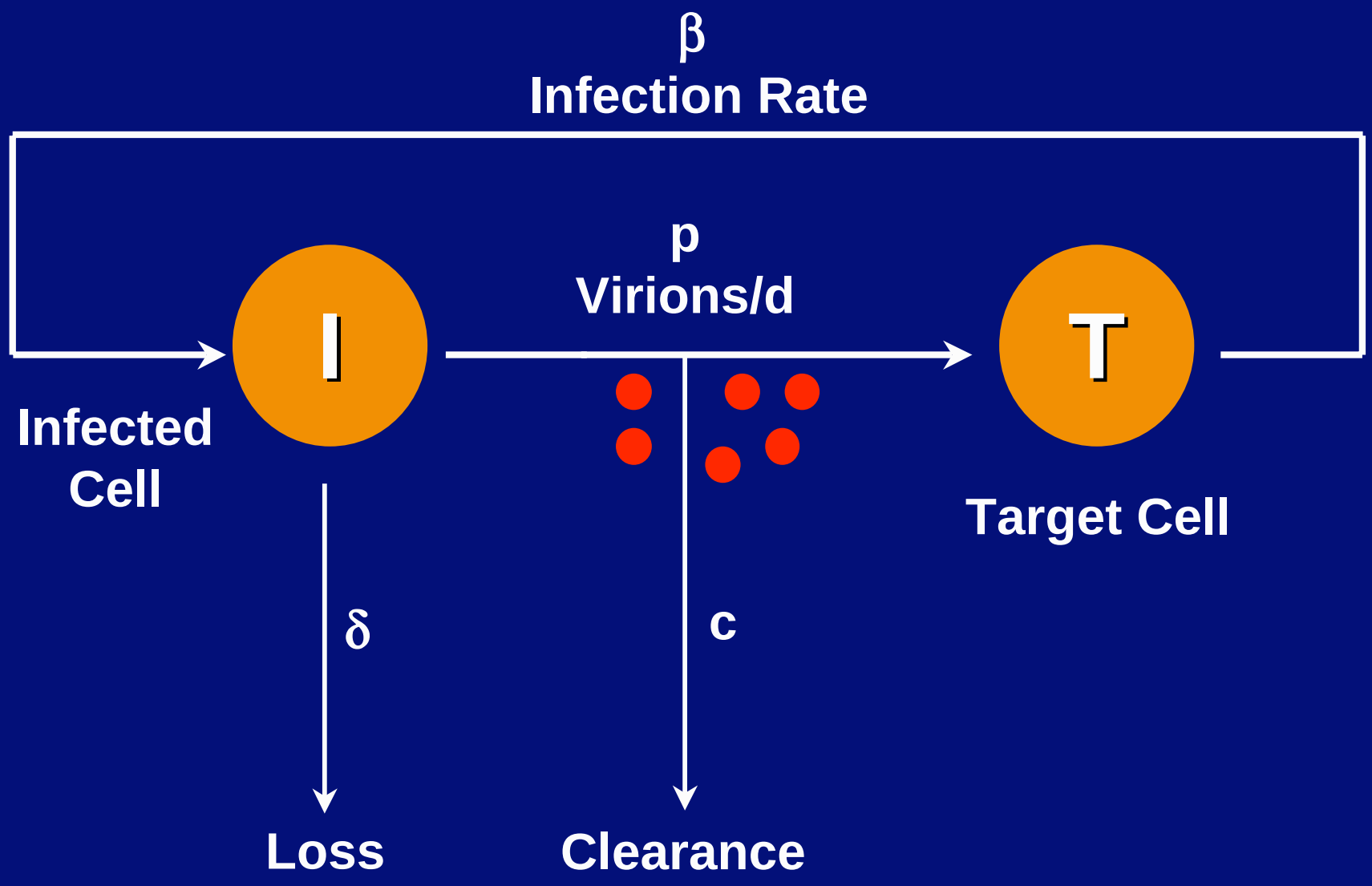


Mean Decrease in HCV RNA Levels Over First 14 Days of QD IFN-α Treatment

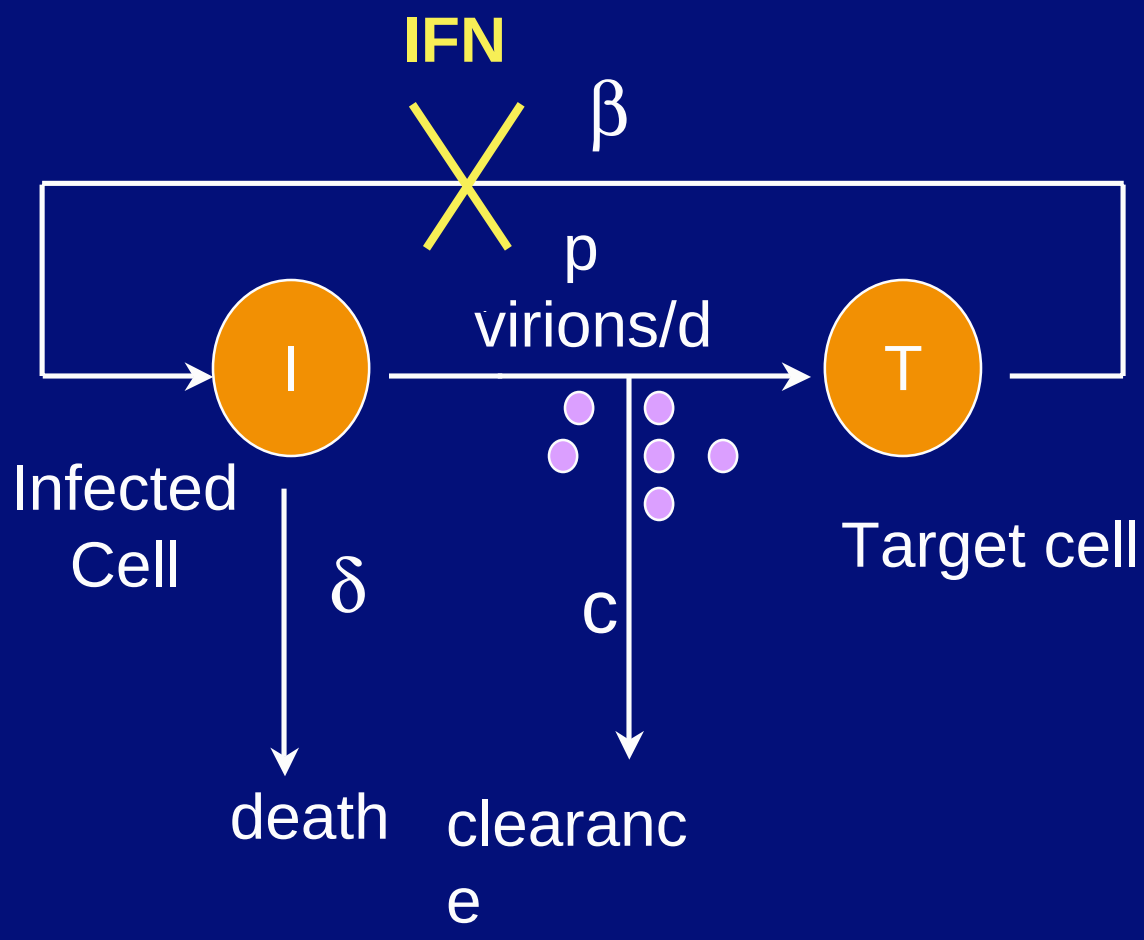


Lam N. DDW. 1998 (abstract L0346).

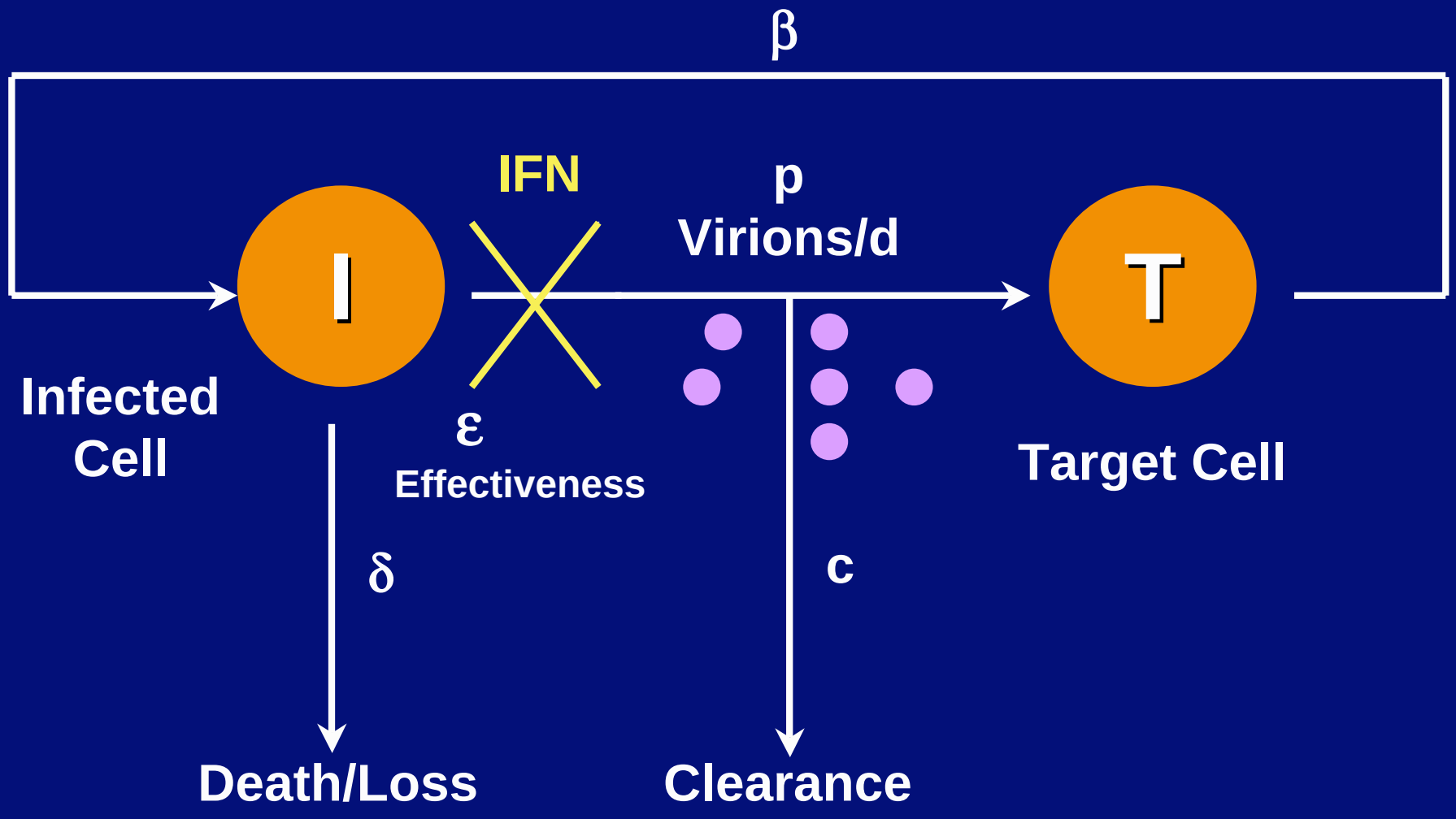
Model of HCV Infection



What if IFN blocks infection?



What if IFN Blocks Production?



What if IFN blocks production?

- If IFN treatment totally blocks virus production, then
- $dV/dt = -cV \Rightarrow V(t)=V_0 e^{-ct}$
- Viral load should fall exponentially with slope c. However, data shows an acute exponential fall followed by slower fall.

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

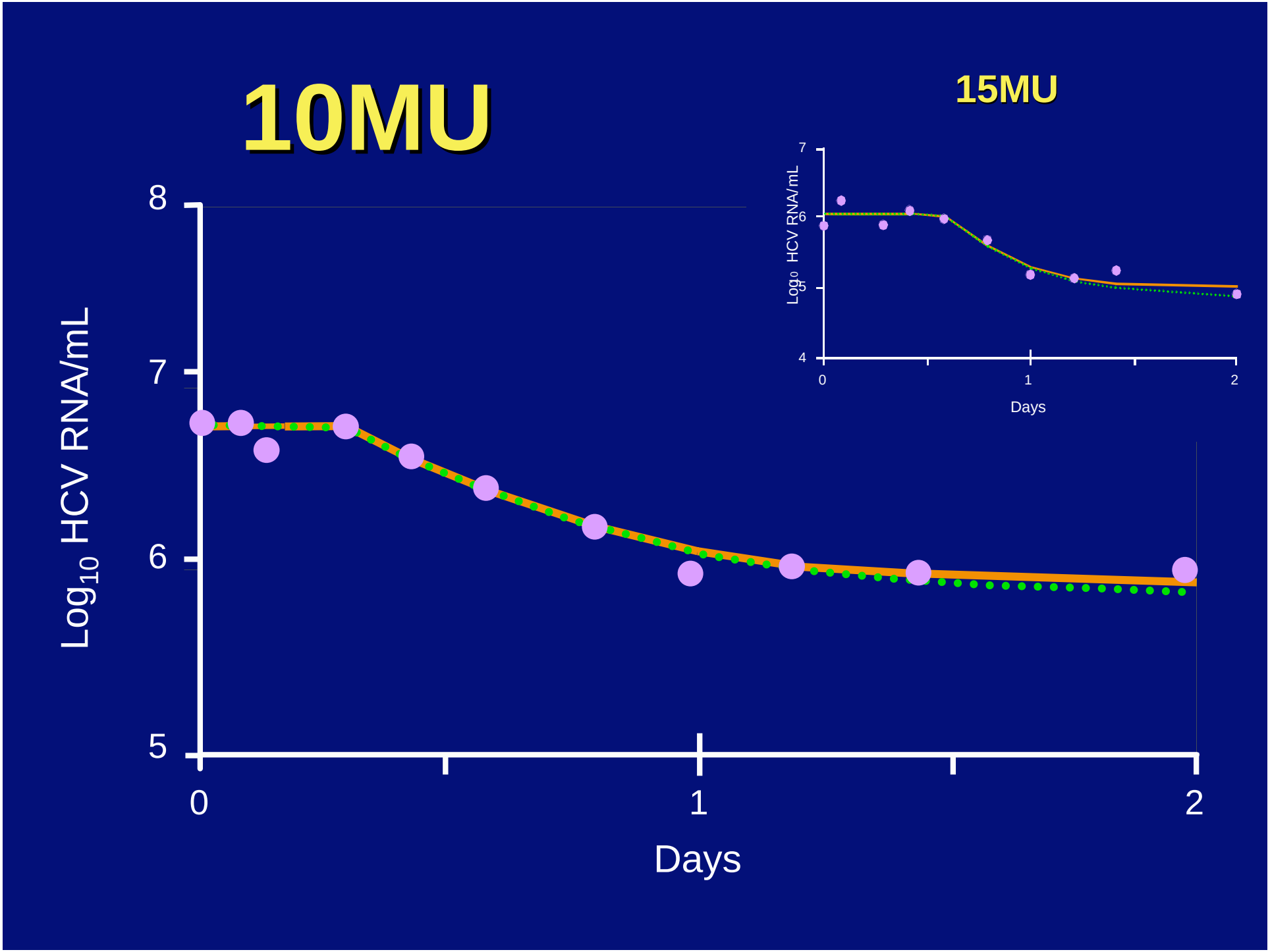
$$dV/dt = (1-\varepsilon)pI - cV = (1-\varepsilon)cV_0 - cV,\ V(0)=V_0$$

- 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.

- Thus drug effectiveness can be determined within the first few days!


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

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
- δ 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

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

$I(0) = I_0$

Assume Steady State

- Before treatment patient is generally in a steady state.

$$\frac{dI}{dt} = \beta V_0 T_0 - \delta I_0 = 0$$

$$\frac{dV}{dt} = pI_0 - cV_0 = 0$$

Hence

$$\beta V_0 T_0 = \delta c V_0 / p \quad or \quad \beta T_0 = \delta c / p$$

and

$$\frac{dI}{dt} = \beta V T_0 - \delta I = \delta (c / p) V - \delta I$$

$$\frac{dV}{dt} = pI - cV$$

Solution: Change in Viral Load

- Assuming $T = T_0$ =constant,

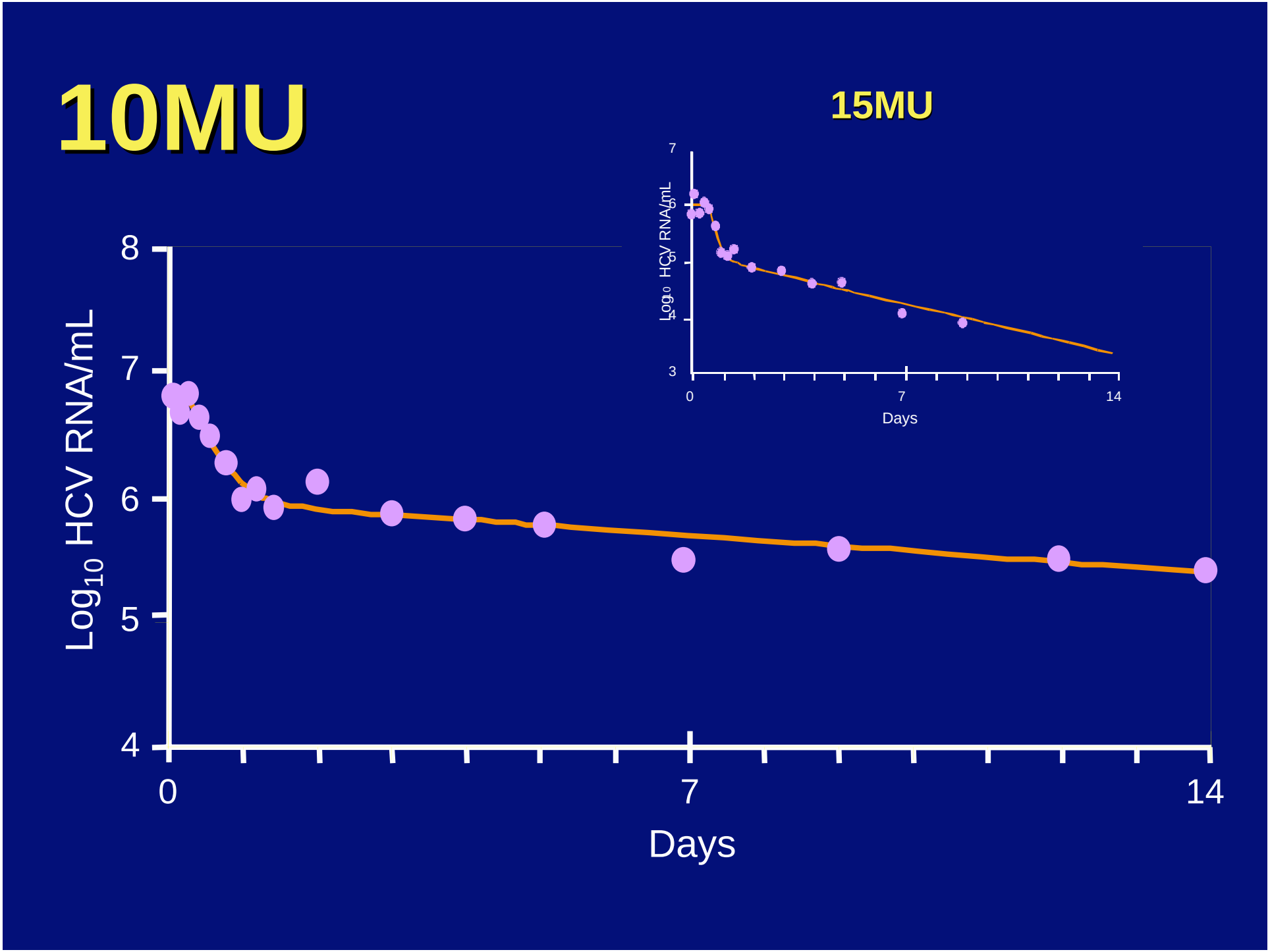
$$V(t) = \frac{1}{2} V_0 [(1 - \frac{c + \delta - 2\varepsilon c}{\theta}) e^{-\lambda_1 (t - t_0)} + (1 + \frac{c + \delta - 2\varepsilon c}{\theta}) e^{-\lambda_2 (t - t_0)}]$$

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

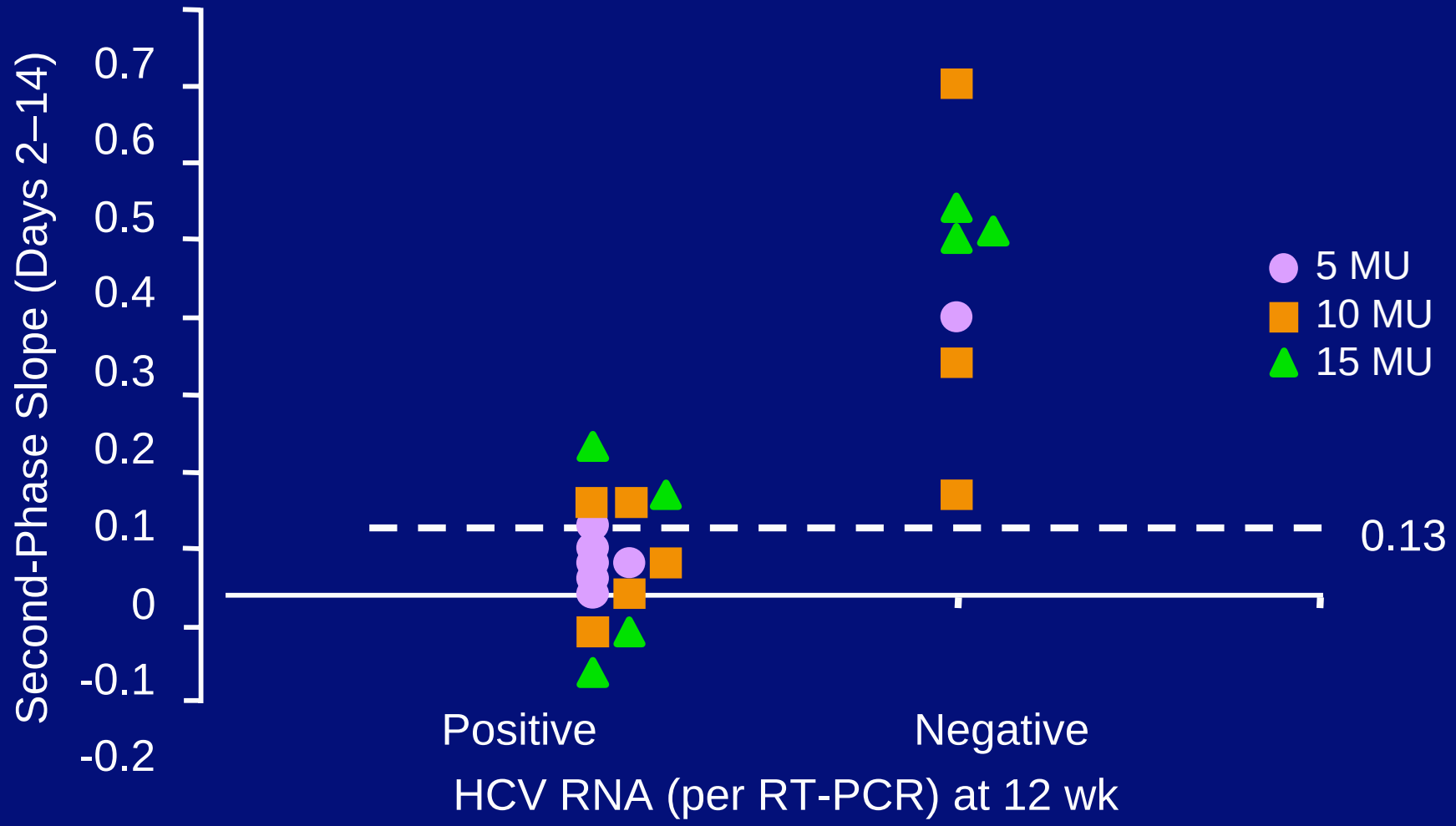
- When c>>δ, $\lambda_1 \approx c$ and $\lambda_2 \approx \varepsilon\delta$


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

High Second-Phase Slope Is Predictive of HCV Being Undetectable at 12 Weeks



HCV Viral Kinetics : Summary

- Biphasic clearance of serum HCV RNA
- 1st phase rapid; depends on IFN-α dose
  - This appears to be due to dose-dependent efficacy in blocking HCV production
- 2nd phase slower. Slope appears to be a measure of rate of infected cell loss