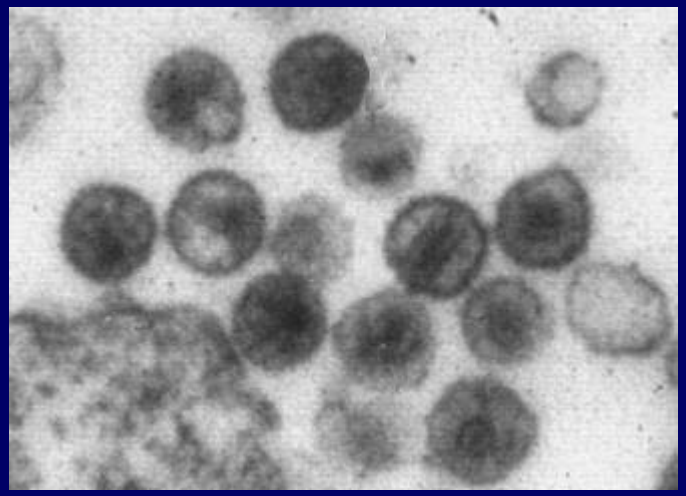
HIV: Models and Data

Alan S. Perelson, PhD
Theoretical Biology & Biophysics
Los Alamos National Laboratory
Los Alamos, NM

What is HIV infection?

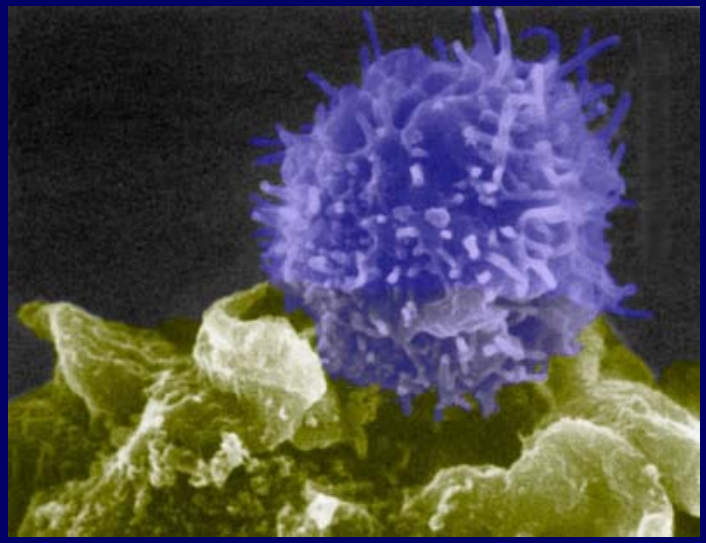
The virus



A retrovirus

Infects immune cells bearing:
CD4 & CCR5/CXCR4

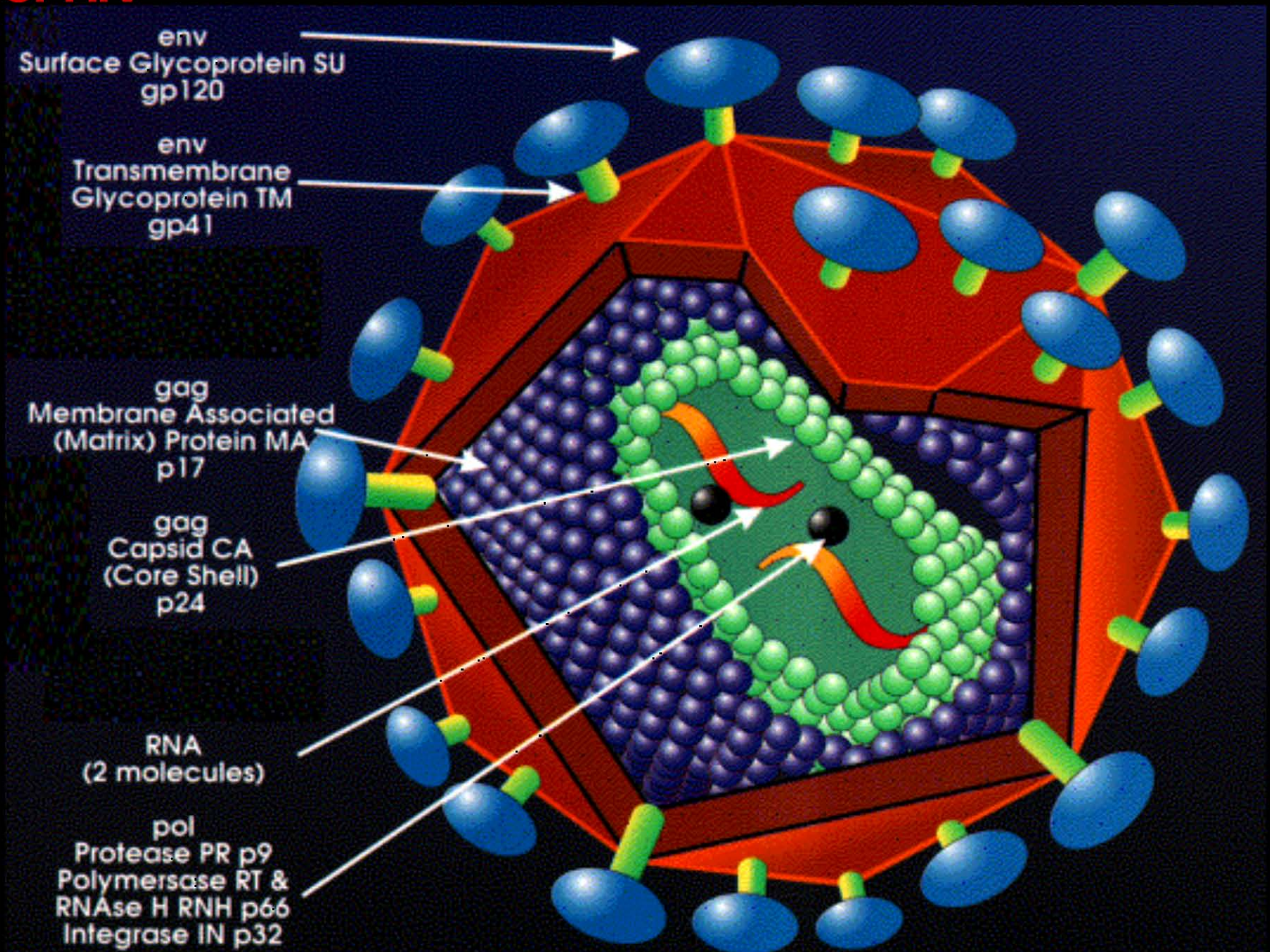
The host



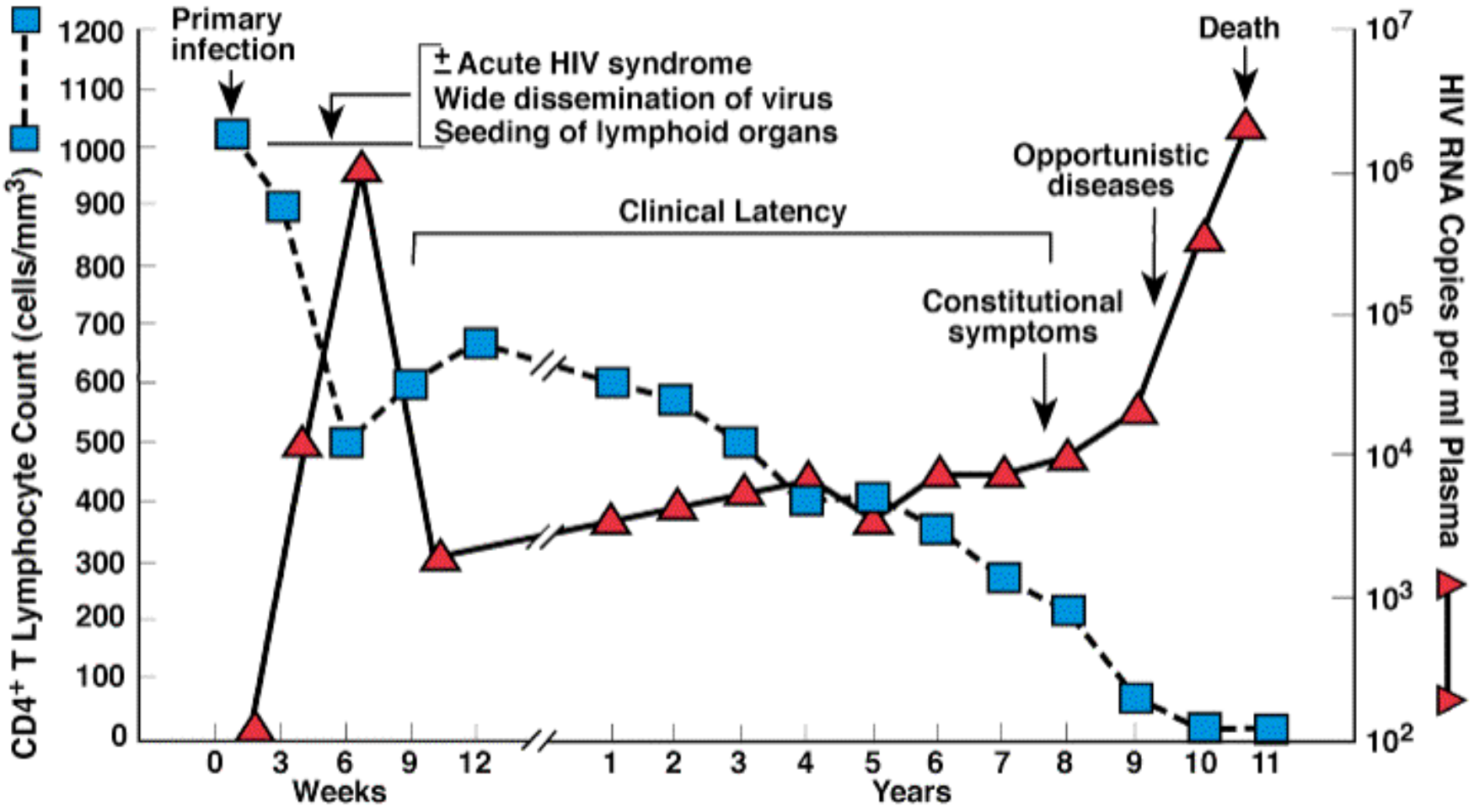
CD4+ T-cells (or helper T cells)

Macrophages and dendritic cells

Structure of HIV



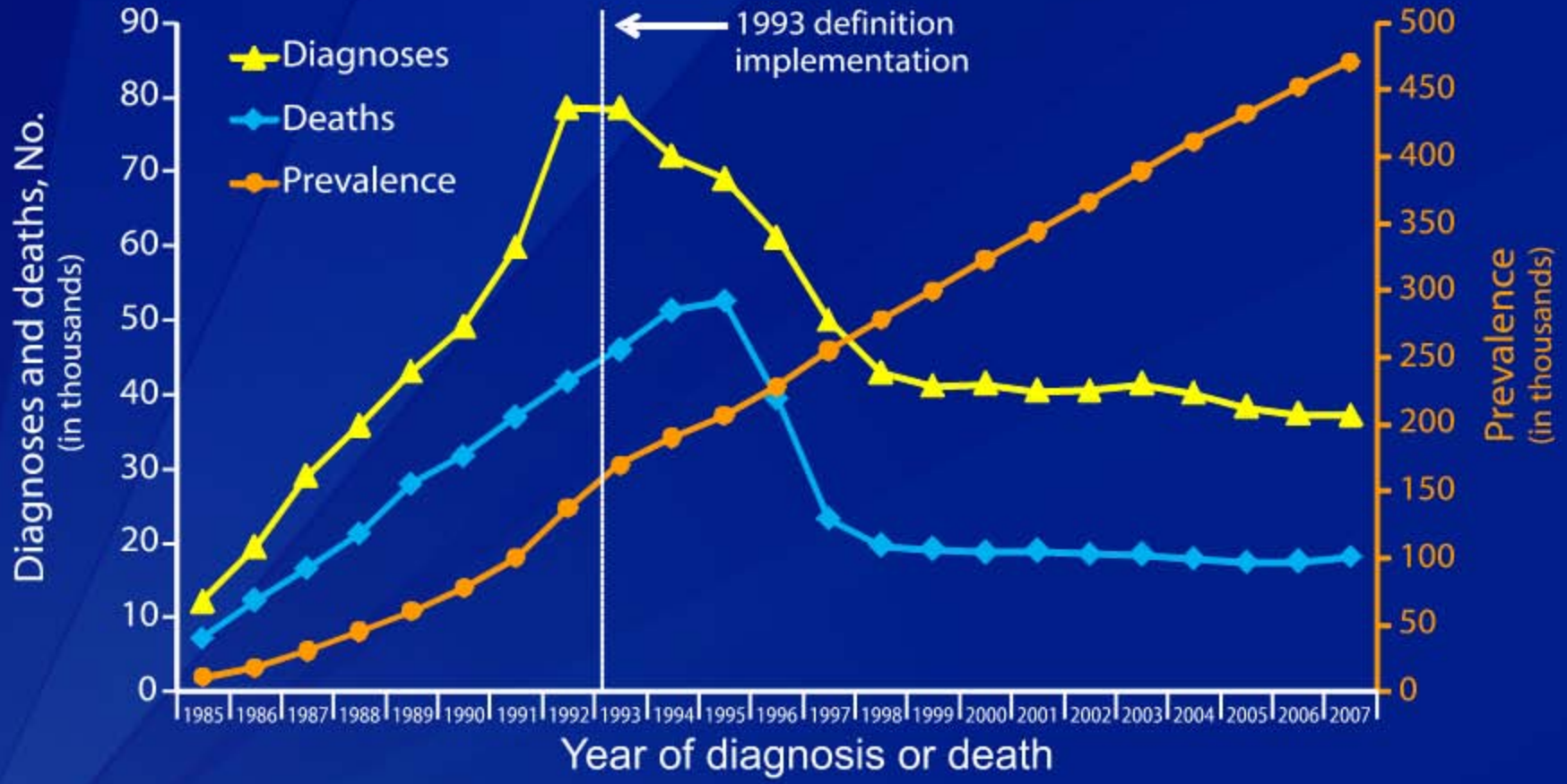
Typical Course of HIV Infection



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

No treatment

AIDS Diagnoses, Deaths, and Persons Living with AIDS, 1985–2007—United States and Dependent Areas



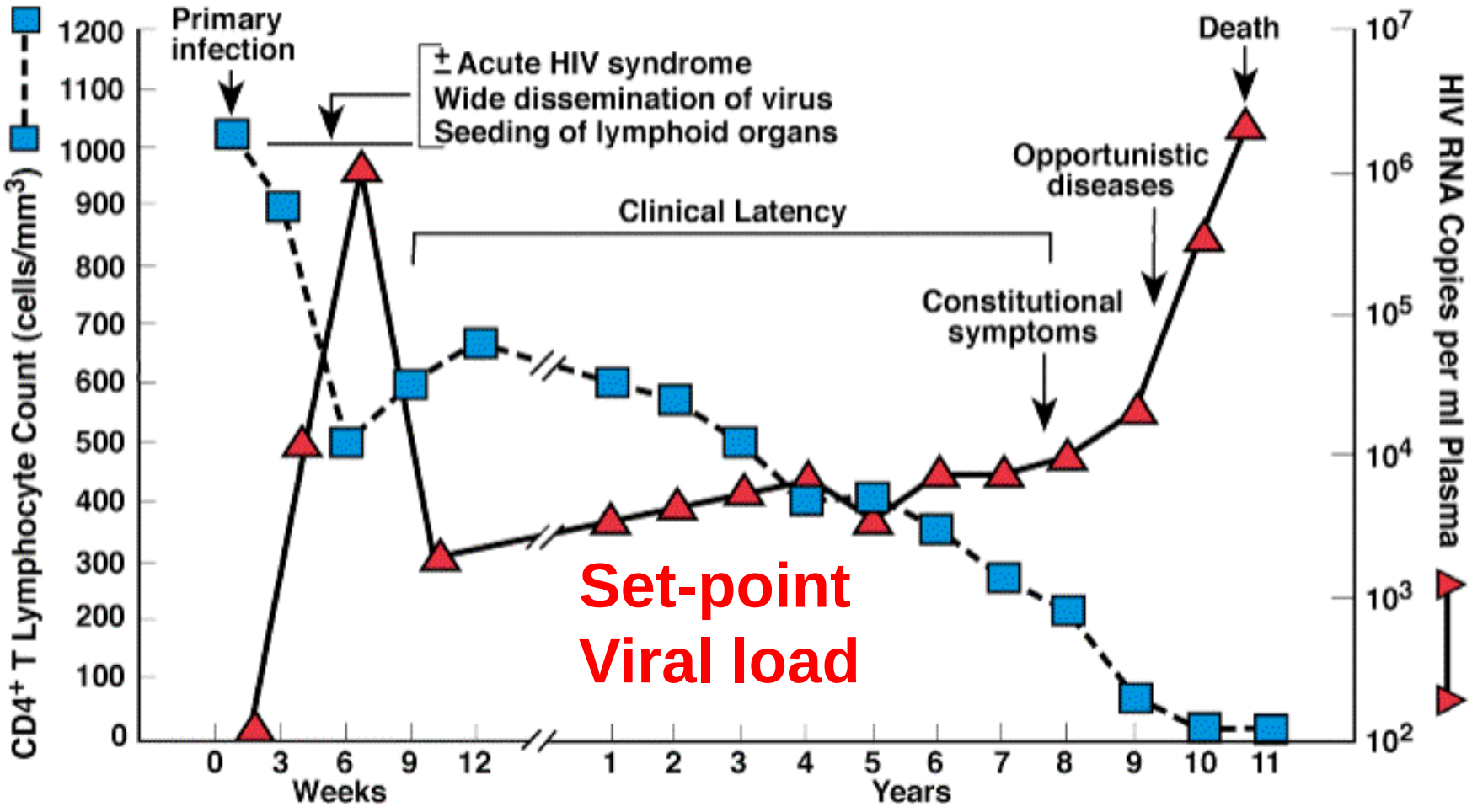
Note. All displayed data have been estimated. Estimated numbers resulted from statistical adjustment that accounted for reporting delays, but not for incomplete reporting.

CDC

Problems

- Why can’t an infected person clear HIV infection?
- Why can’t we develop a vaccine?

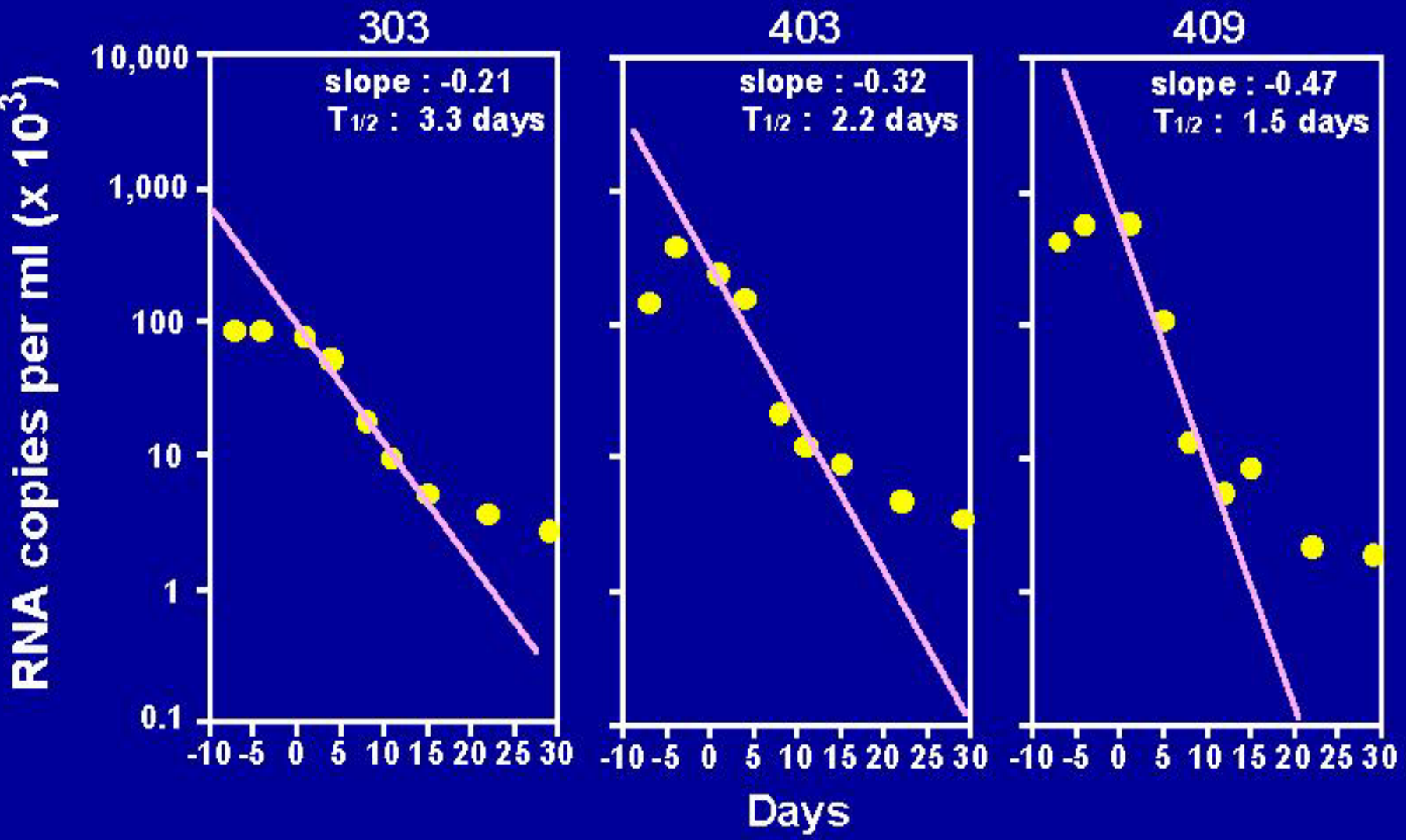
Typical Course of HIV Infection



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

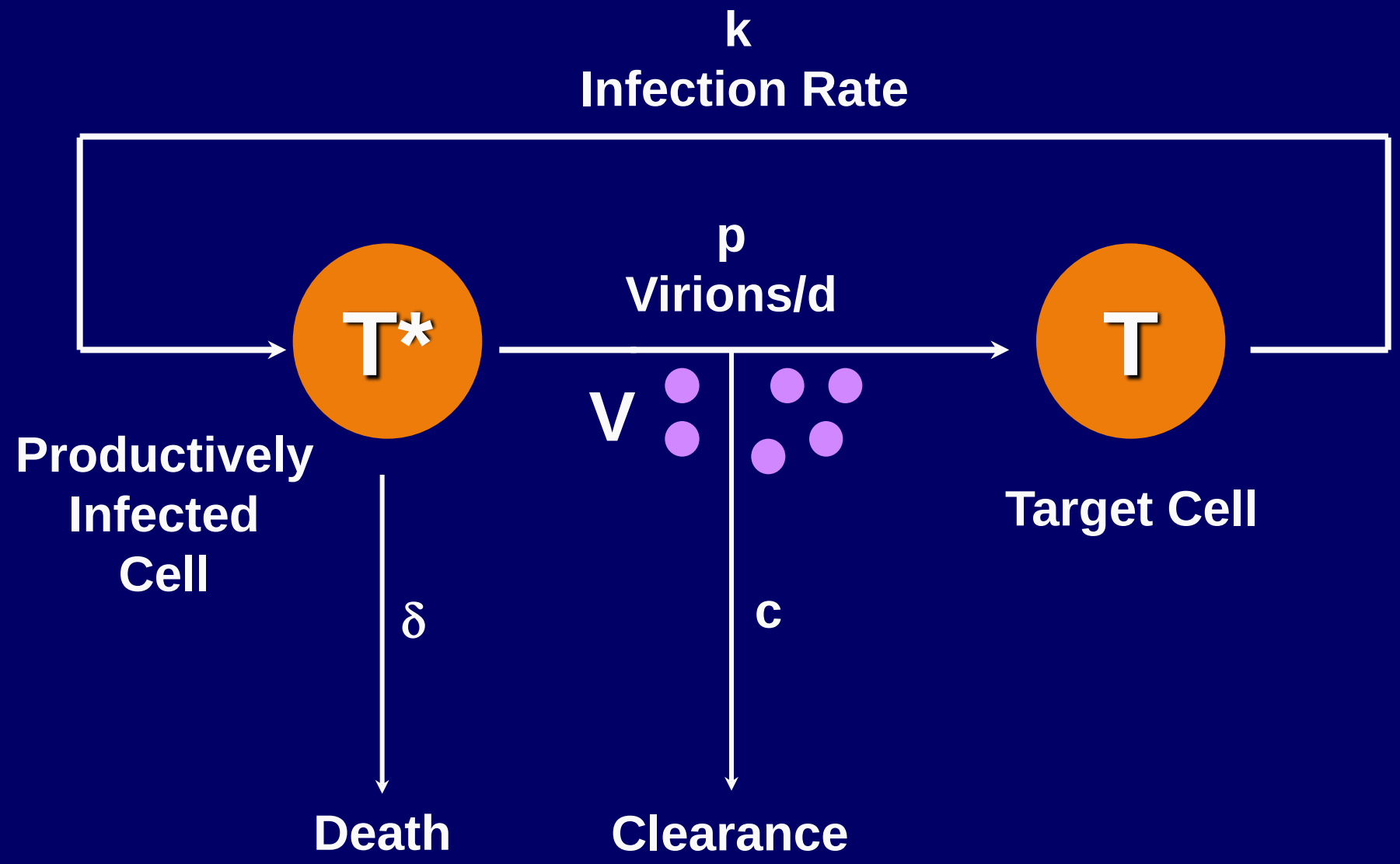
No treatment

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

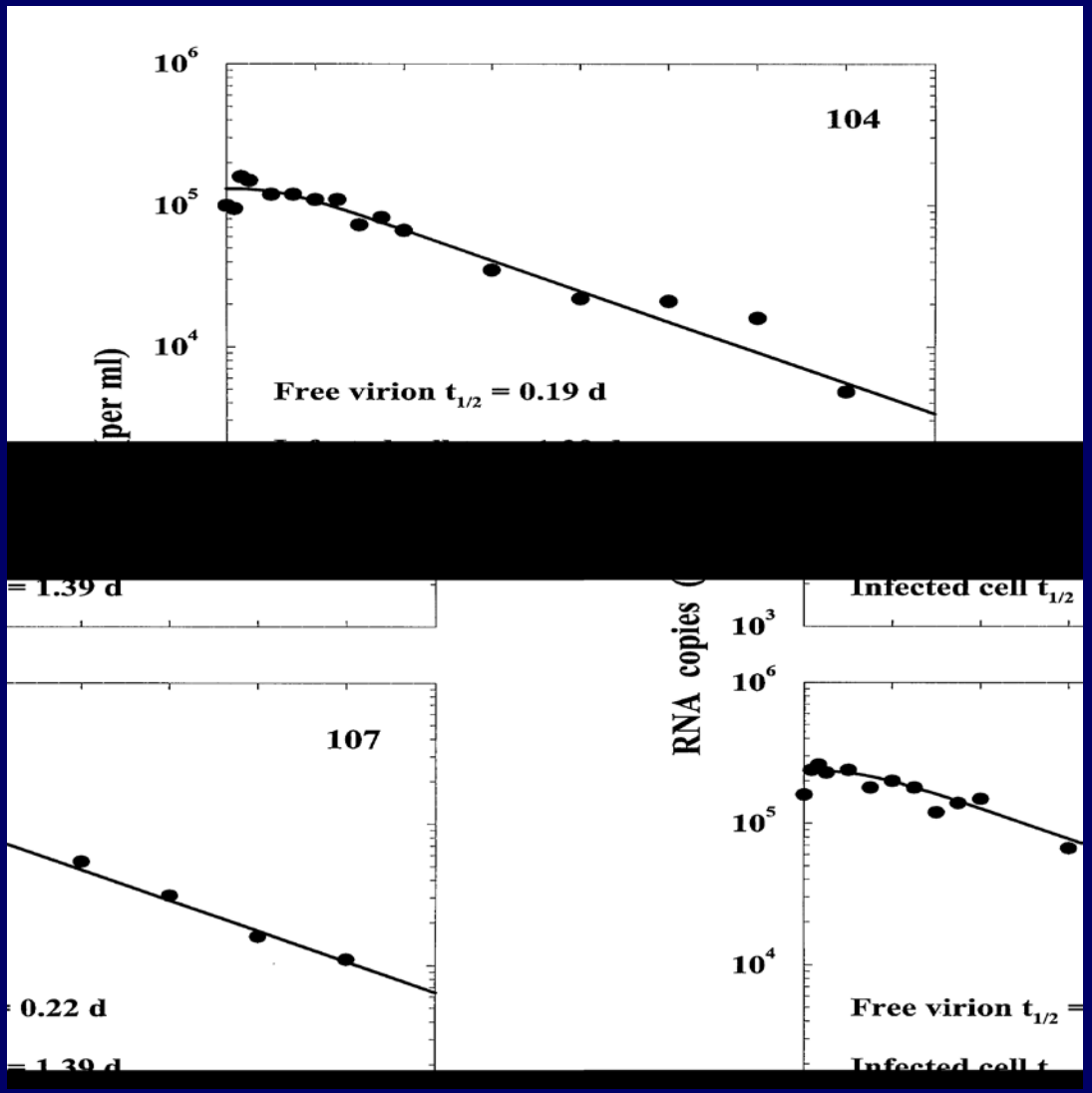
From *HIV-Dynamics in Vivo: …*,

Perelson, *et al*, Science, 1996

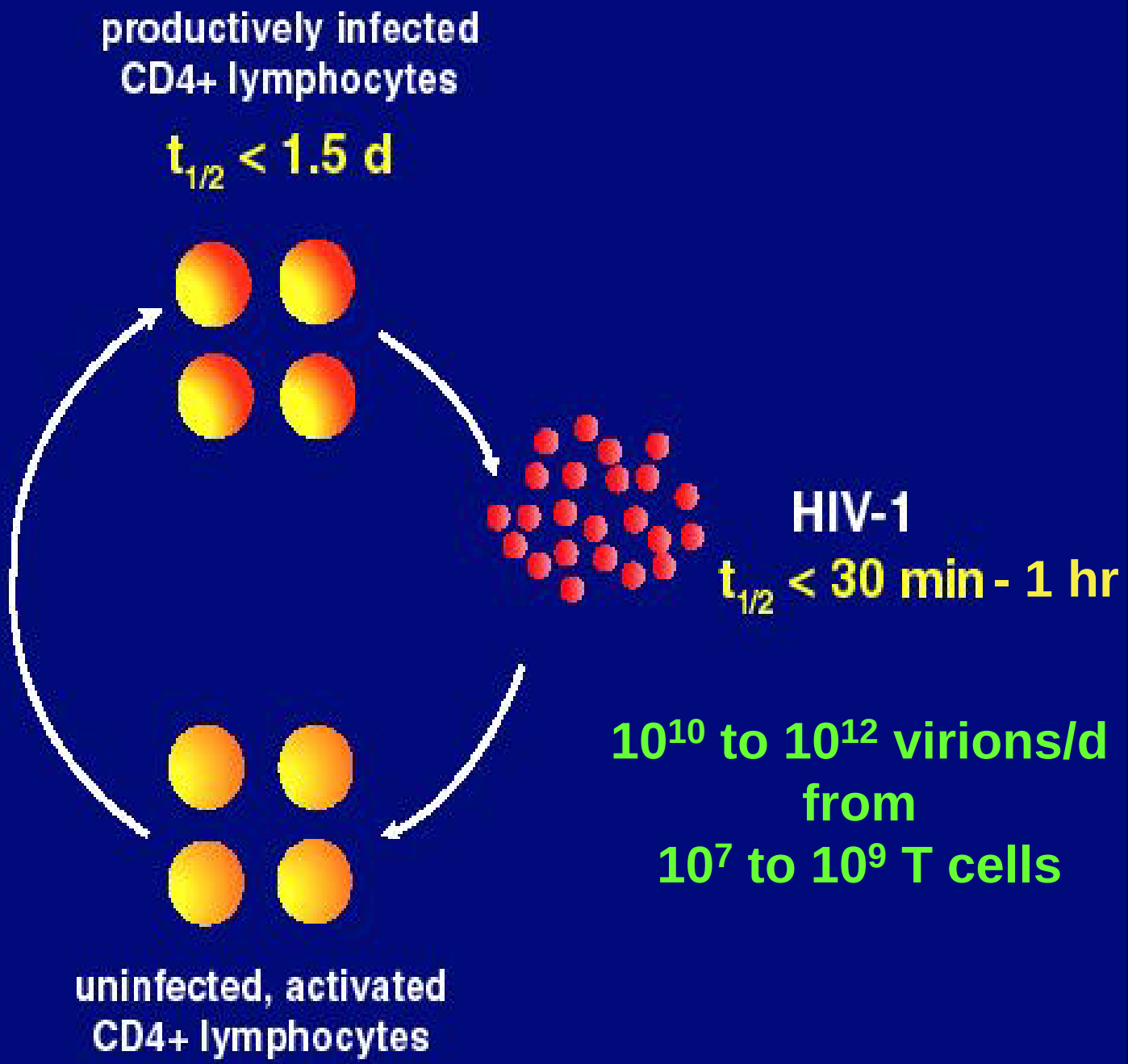
Solution of Model Equations Assuming 100% Efficacy of Protease Inhibitor Therapy

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

HIV-1: First Phase Kinetics



Perelson et al. Science 271, 1582 1996

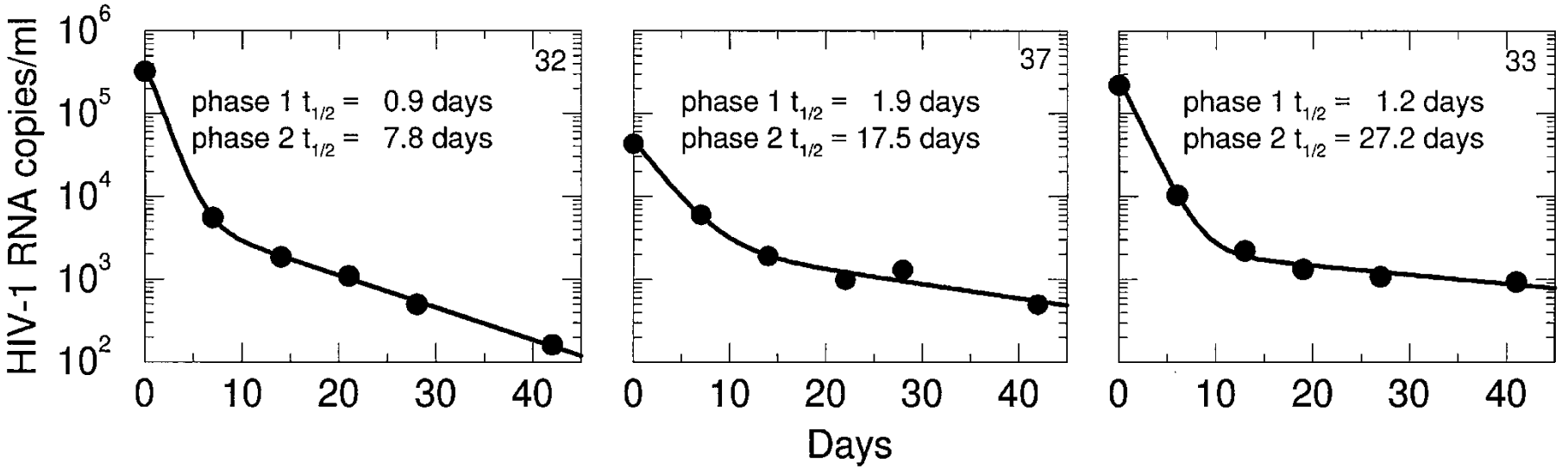

productively infected
CD4+ lymphocytes
$t_{1/2}$ < 1.5 d
HIV-1
$t_{1/2}$ < 30 min - 1 hr
10^{10} to 10^{12} virions/d
from
10^{7} to 10^{9} T cells
uninfected, activated
CD4+ lymphocytes

Rate of generation of HIV-1 mutants

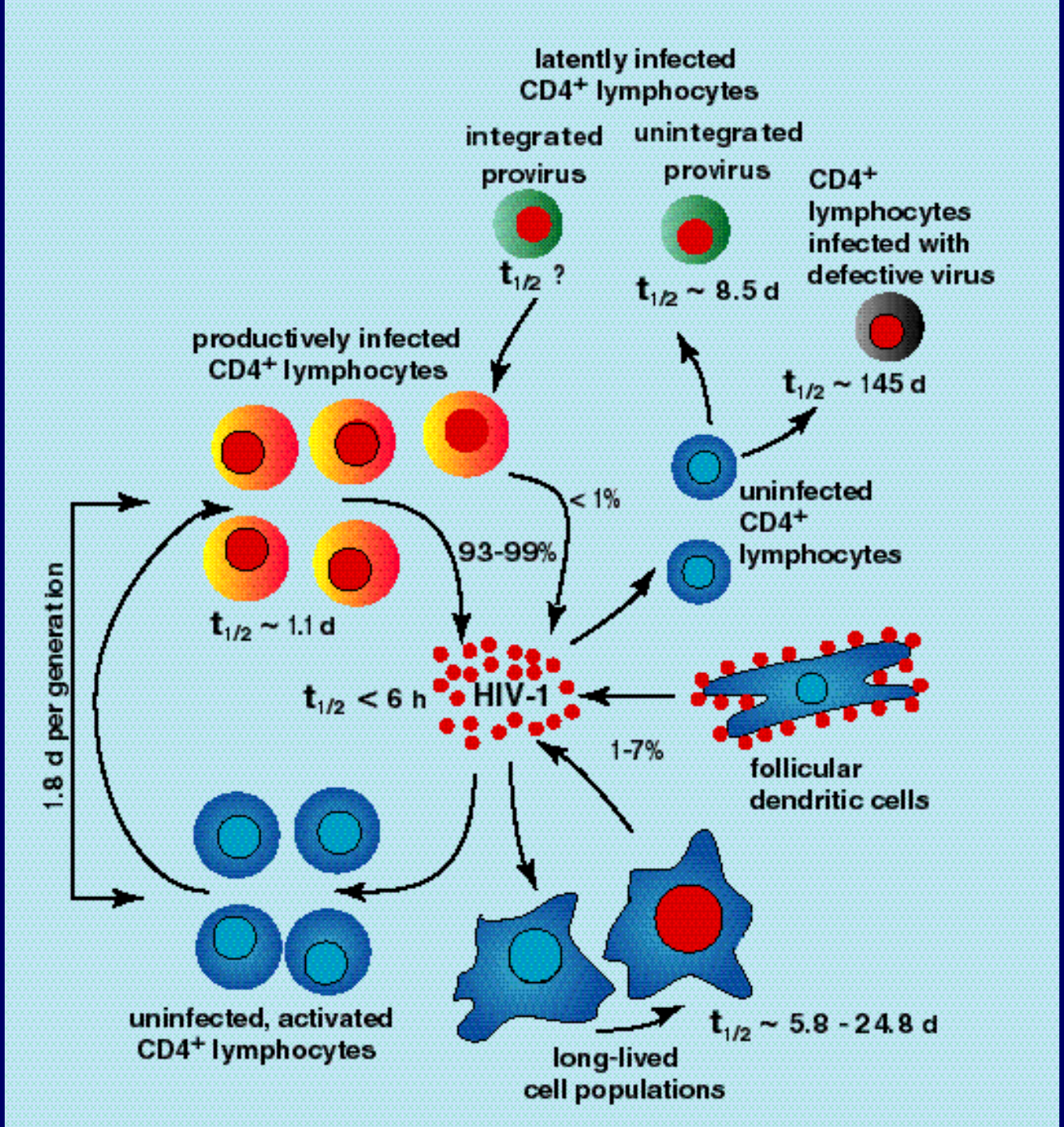
Base Changes	Probability of mutant	Number created/day	Number of possible mutants	Fraction of all possible mutants created/day
0	0.74	7.4×10^{7}	1	
1	0.22	2.2×10^{7}	3.0×10^{4}	1
2	0.033	3.3×10^{6}	4.5×10^{8}	7.4×10^{-3}
3	0.0033	3.3×10^{5}	4.5×10^{12}	7.4×10^{-8}

Perelson, Essunger & Ho, AIDS 1997

HIV-1: Two Phase Kinetics Combination Therapy

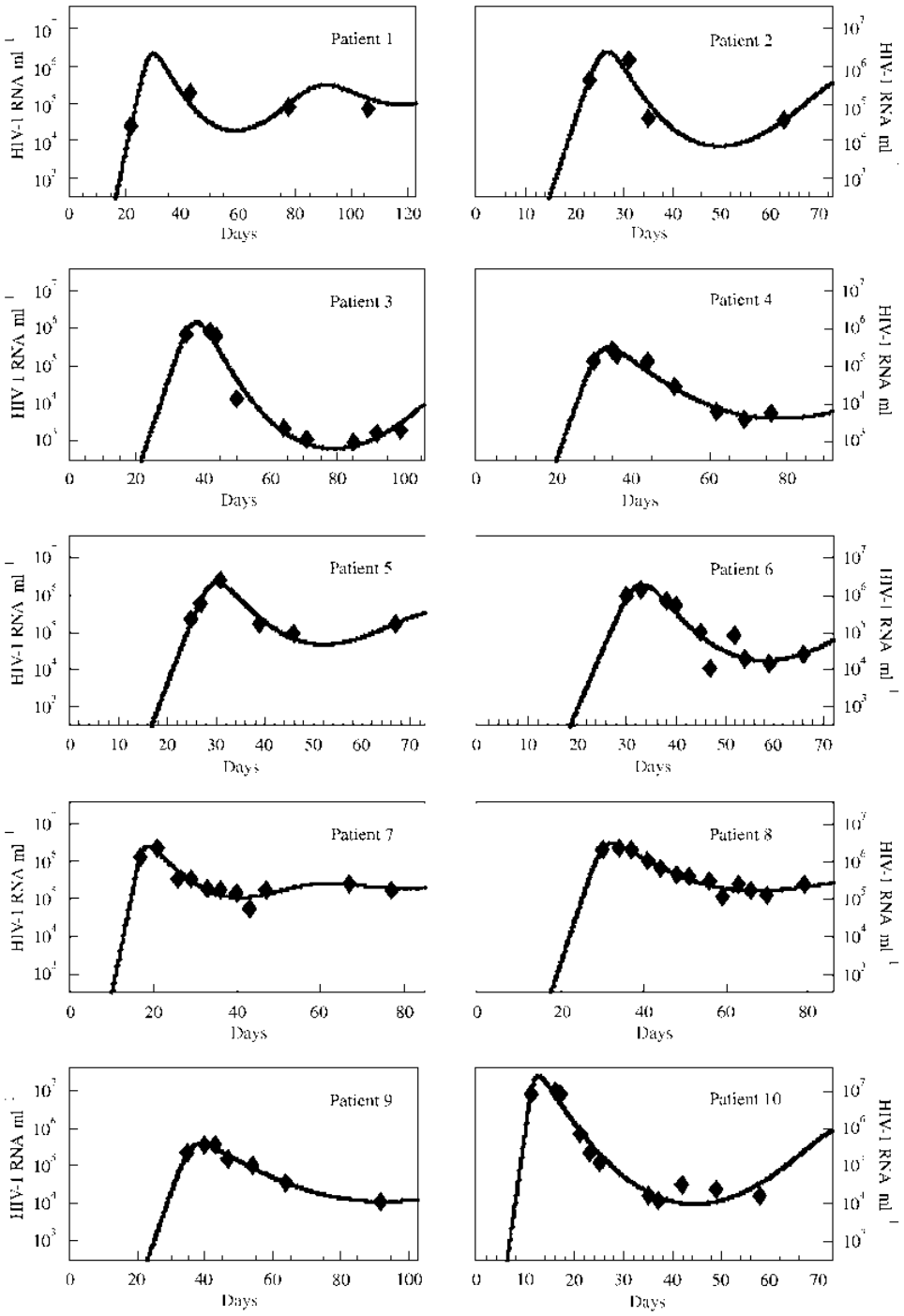


Perelson et al. Nature 387, 186 (1997)


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

Acute HIV Infection

1) Single Transmitted/Founder Virus
2) Escape from Immune Responses
3) Stochastic Model of Early Infection



Model fits primary infection data.

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

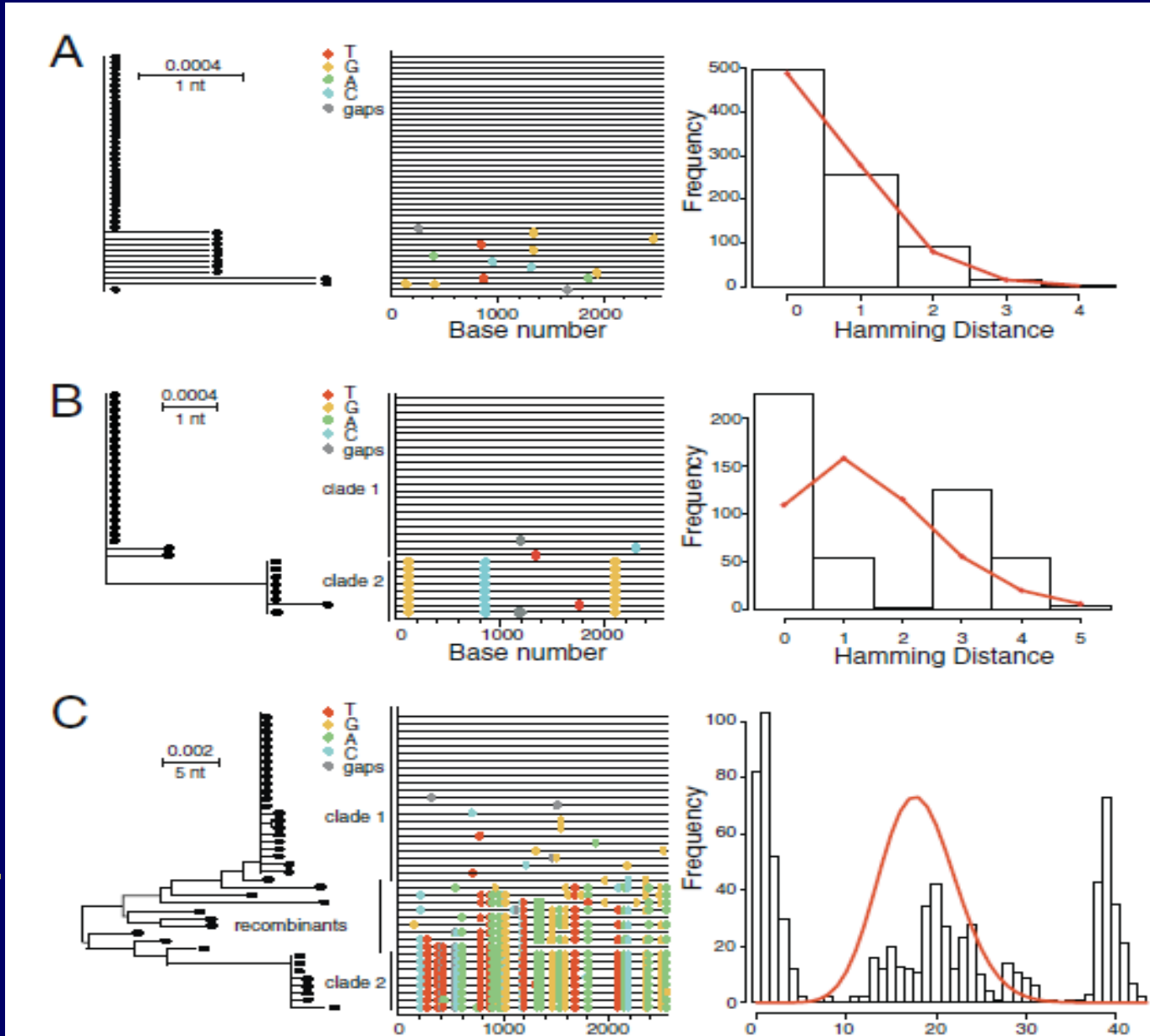
Note virus is not visible at early times = eclipse phase
1 – 3 weeks in humans

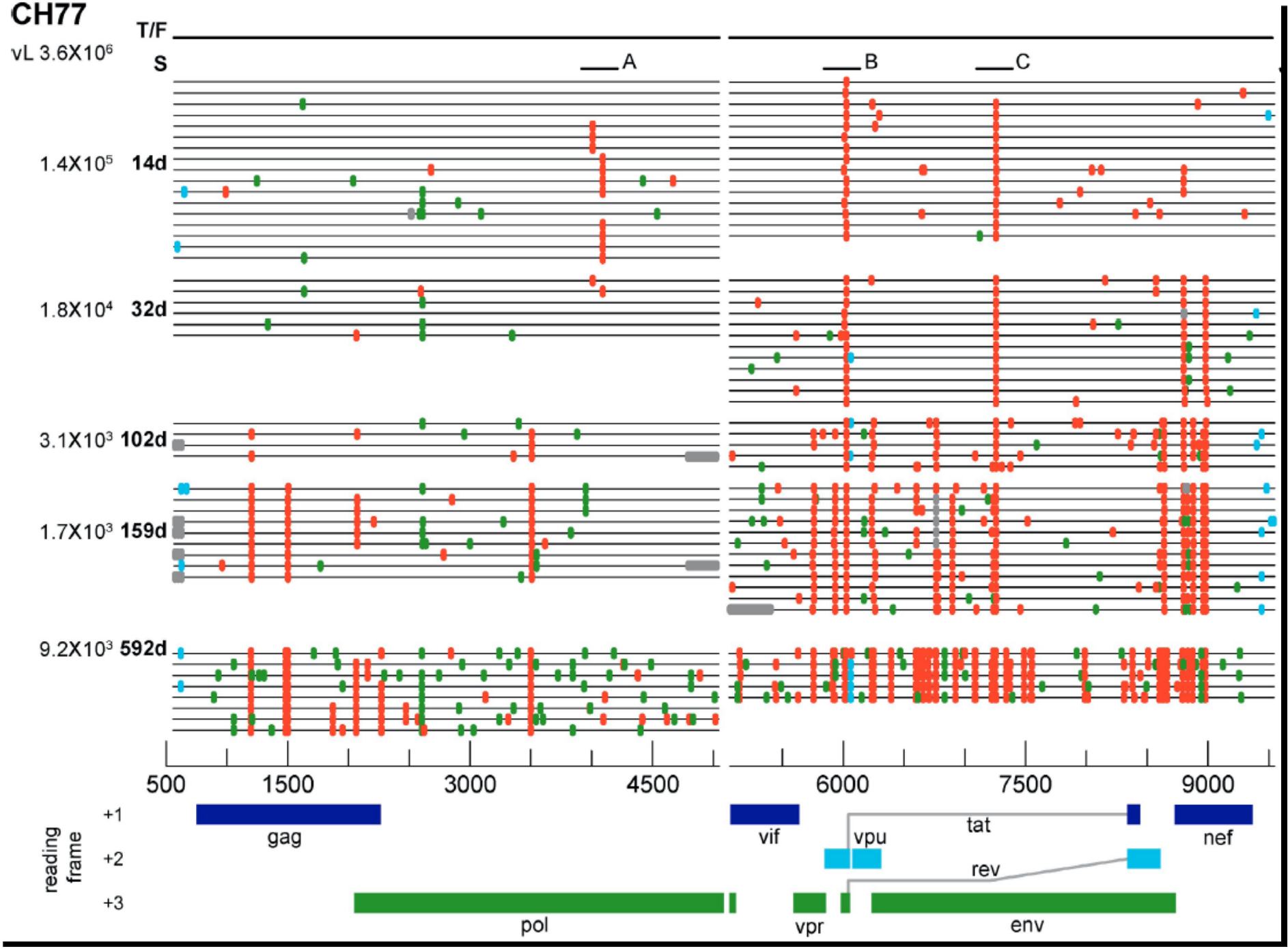
78 of 102 pts had single founder virus

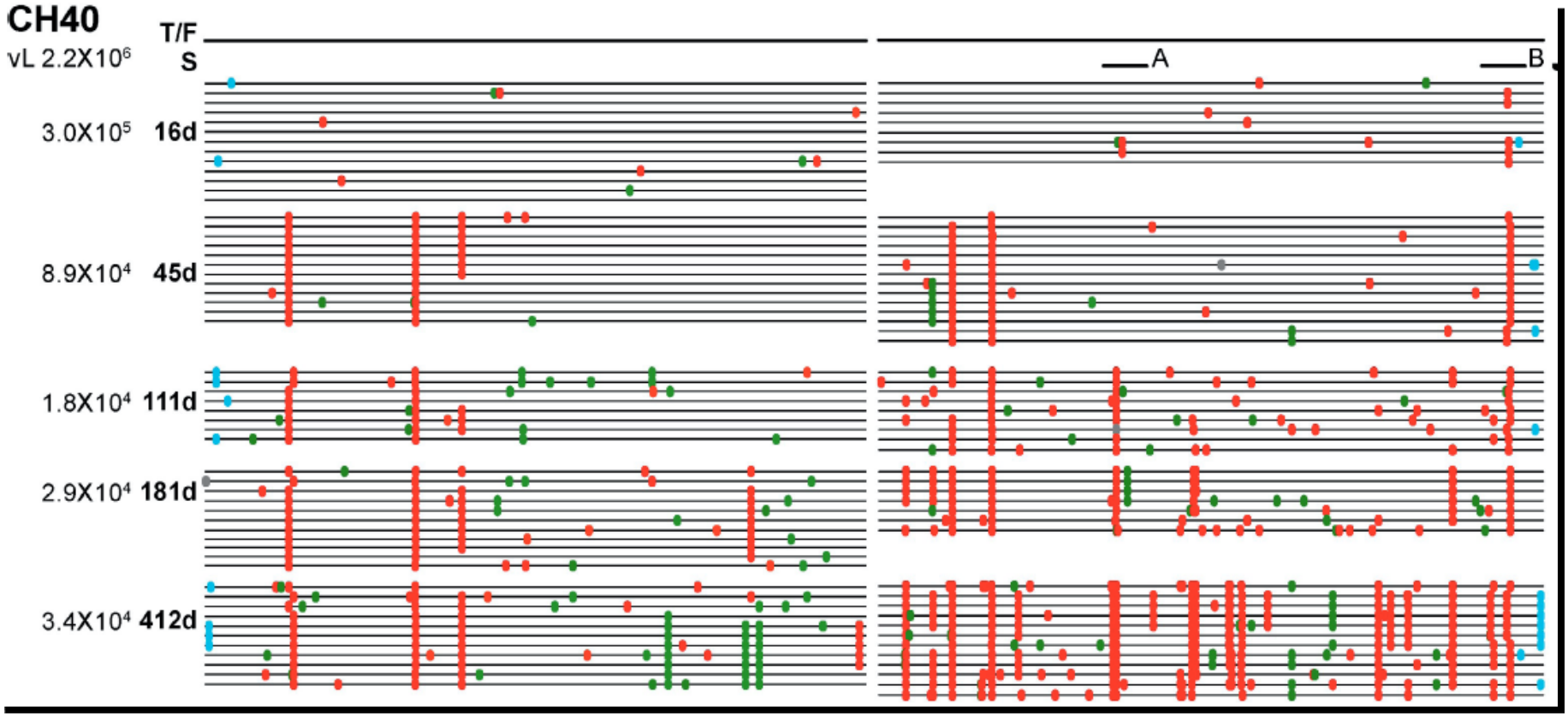
Lee et al.
JTB 261:
341 (2009)

Keele et al
PNAS 105:
7552 (2008)

Salazar-Gonzalez
J Exp Med 206:
1273 (2009)

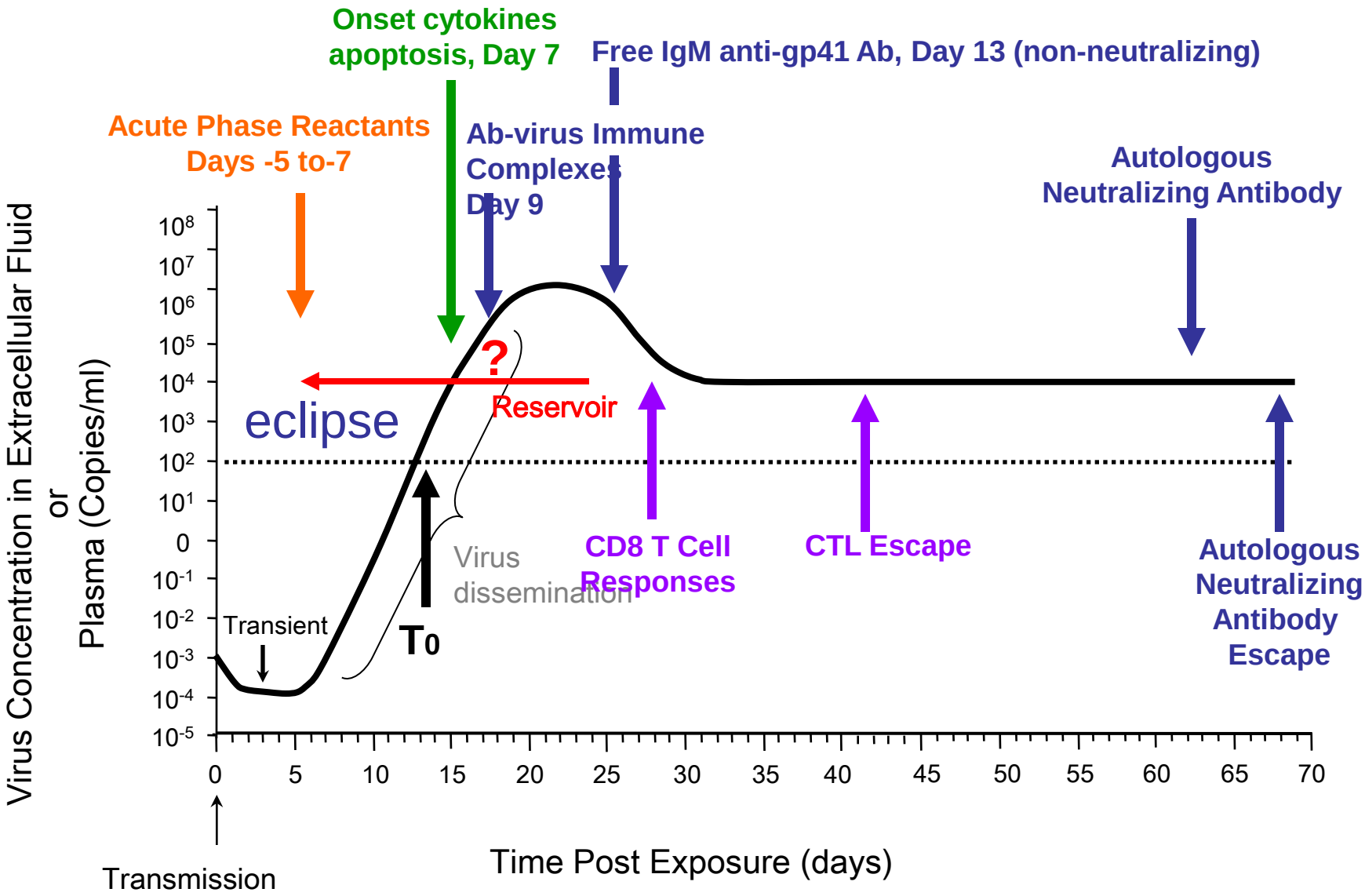



CH77
T/F
vL 3.6X10^6
S
A
B
C
1.4X10^5 14d
1.8X10^4 32d
3.1X10^3 102d
1.7X10^3 159d
9.2X10^3 592d
500
1500
3000
4500
6000
7500
9000
reading frame
+1
+2
+3
gag
pol
vif
vpu
tat
rev
vpr
env
nef



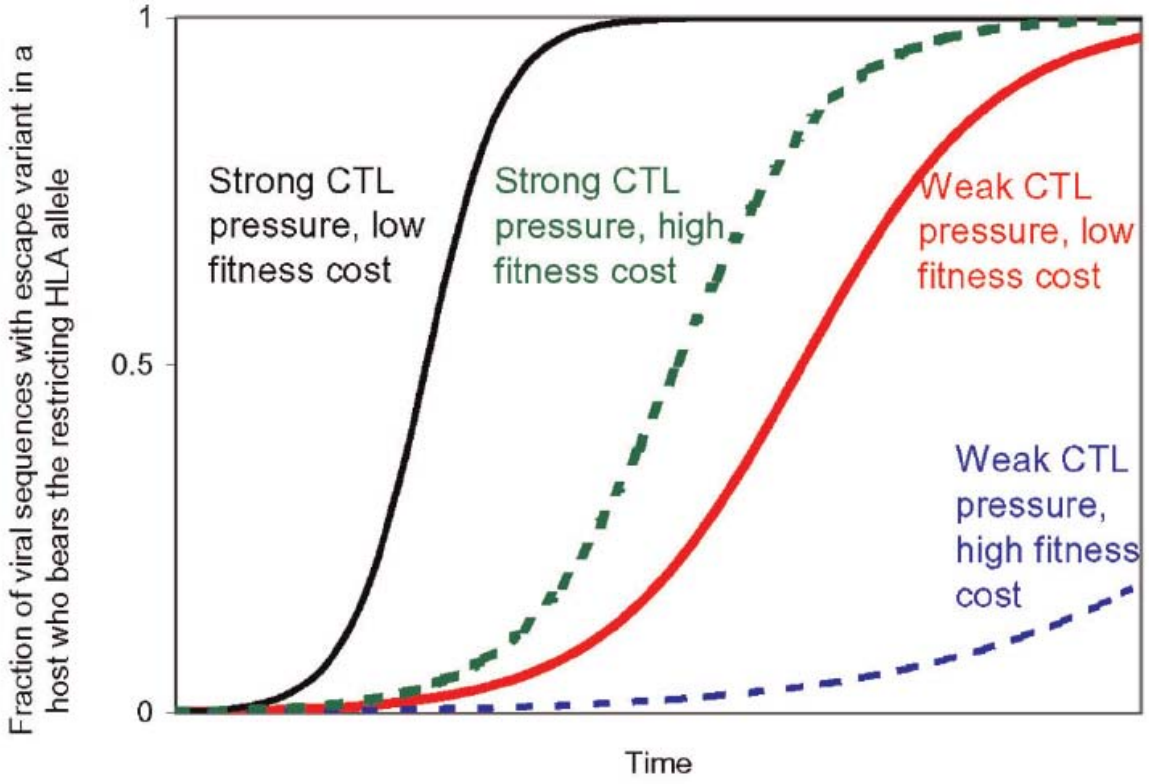
Red=NS in a coding gene; green = synonymous; blue non-coding

Acute HIV-1 Infection



CHAVI
CENTER FOR HIV/AIDS VACCINE IMMUNOLOGY

Escape from CTL pressure



Idea: By examining rate of escape one can estimate the CTL pressure on the virus

Asquith et al., PLoS Biol 2006

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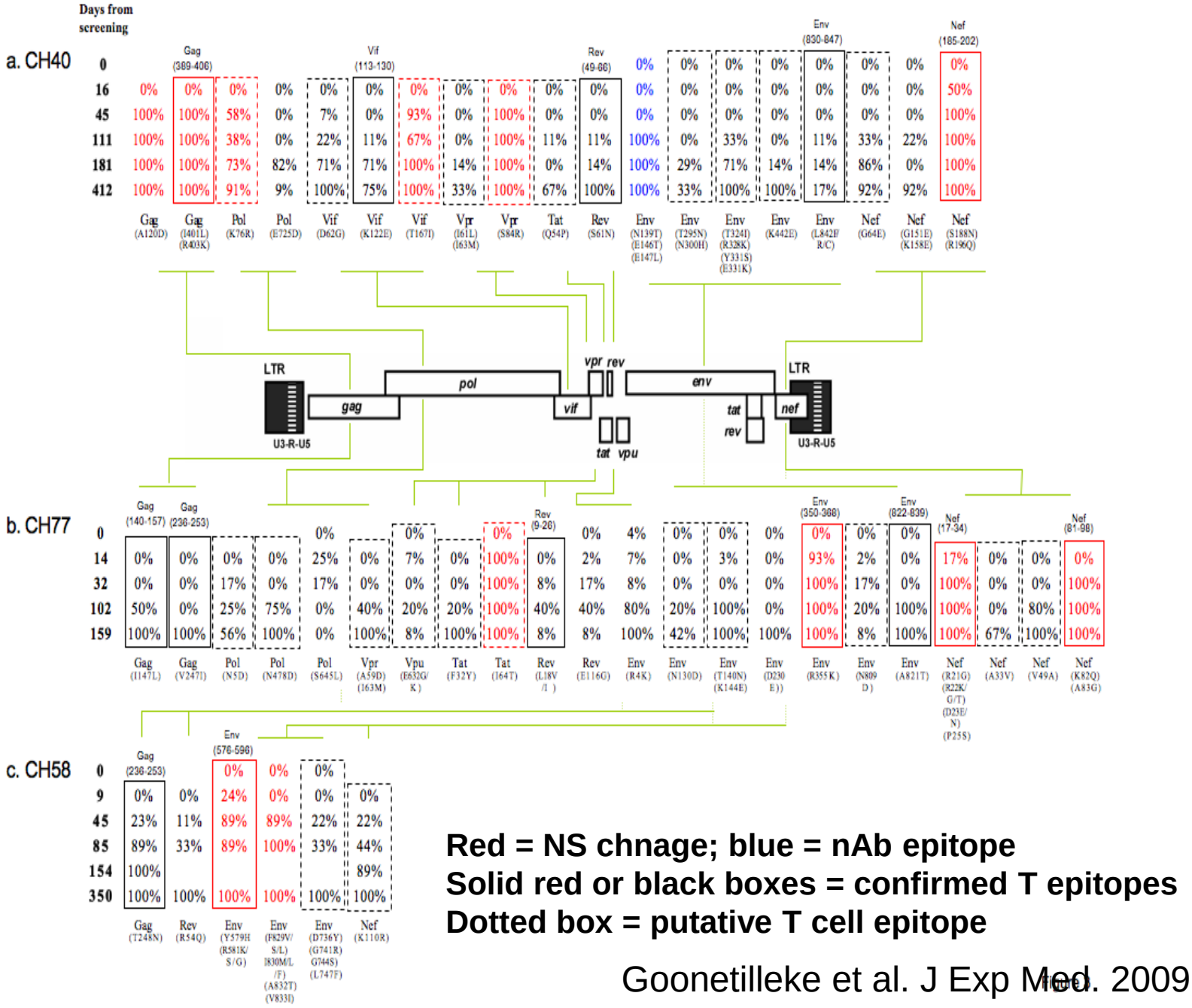
National Institute of Allergy and Infectious Diseases



Goonetilleke et al. J Exp Med. 2009

Model

$$
\begin{aligned}
\frac{\mathrm{d}T}{\mathrm{d}t} &= s(T_0 - T) - \beta T(V_w + V_m), \\
\frac{\mathrm{d}I_w}{\mathrm{d}t} &= \beta T V_w - \delta I_w - k_E I_w E, \\
\frac{\mathrm{d}I_m}{\mathrm{d}t} &= \beta T V_m - \delta I_m, \\
\frac{\mathrm{d}V_w}{\mathrm{d}t} &= p_w I_w - c_V V_w, \\
\frac{\mathrm{d}V_m}{\mathrm{d}t} &= p_m I_m - c_V V_m,
\end{aligned}
$$

QSS: dV/dt =0; $V_w = I_w p_w/c$ and $V_m = I_m p_m/c$.

$r = p_w \beta T/c$ $c = 1 - p_m/p_w$, $w = I_w$, $m = I_m$, $k = k_E E_w$,

Escape from CTL pressure

CTL killing

$$\frac{dw}{dt} = rw - \delta w - kw$$

Wildtype virus (infected cells)

$$\frac{dm}{dt} = r'm - \delta m$$

Escape mutant (infected cells)

Replication rate = r(1-c)

For WT, δ +k = total rate of killing
Note, k/(δ+k) is fraction of killing attributed to CTL

Fitness cost, c=0 no cost, c=1 maximal cost

Time course of escape variants

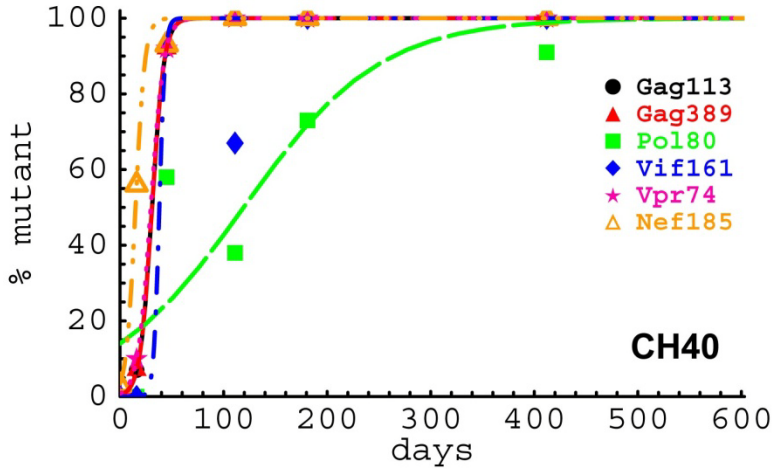
Proportion of mutant virus over time

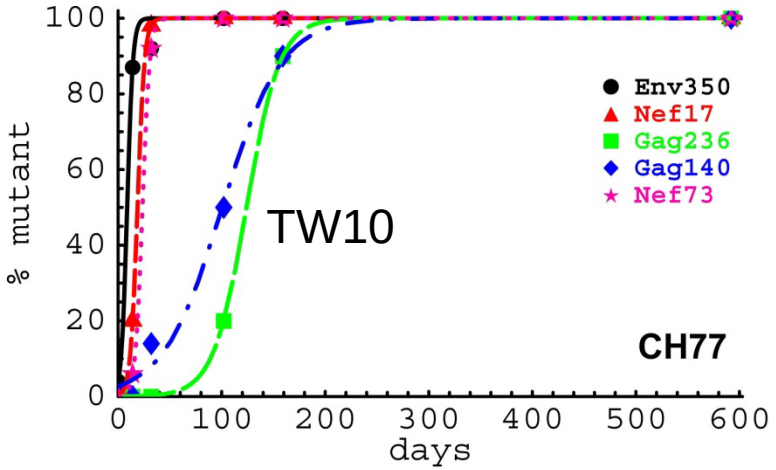
$$p(t) = \frac{m(t)}{w(t) + m(t)} = \frac{1}{\frac{w(0)}{m(0)} e^{-\varepsilon t} + 1}$$

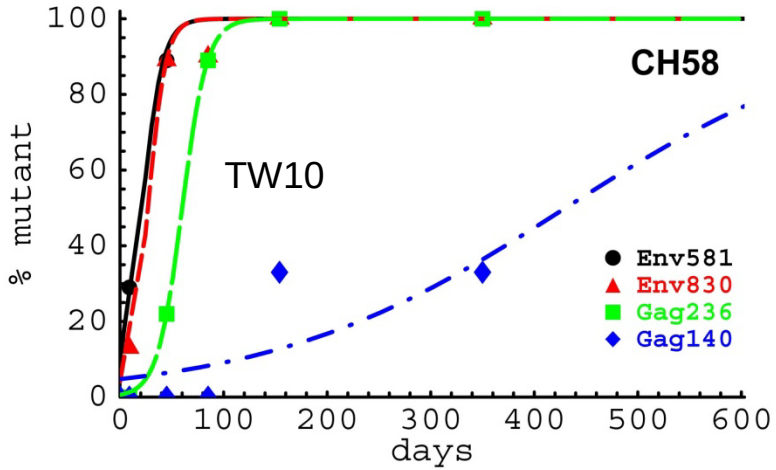
We can use this equation to fit data and estimate the rate of escape $\varepsilon = k - cr$. More generally, Since parameters depend on *T(t)*

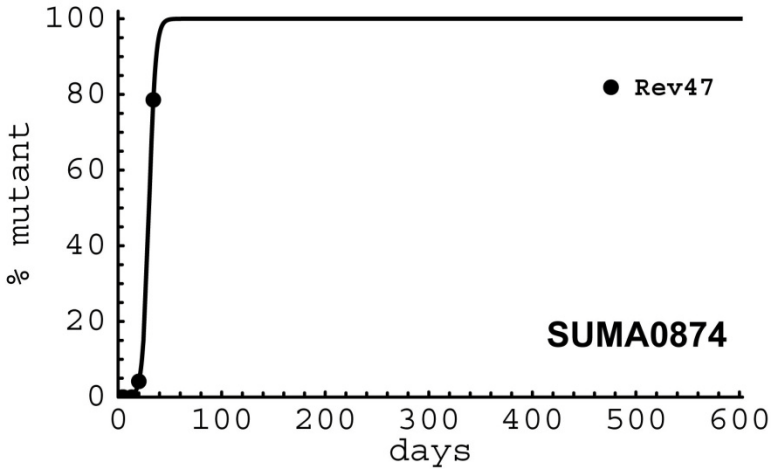
$$\varepsilon = \frac{1}{t} \int_0^t [k(t') - c(t')r(t')] \mathrm{d}t' = \langle k - cr \rangle$$

Model Fits to Kinetics of HIV-1 Escape from CTL Responses in Acute Infection









Escape rates and epitopes

Patient	Mutations	Escape rate (day^{-1})	$t_{50\%}$ (days)	CD8 T cell epitope	Confirmed T cell response (HXB2 position)
CH40	Nef S188R/N, R196Q	0.22	15	yes	Yes, (Nef185-202)
	Gag A120D	0.17	31	no	no
	Gag I401L, R403K	0.17	31	yes	Yes (Gag389-406)
	Vpr S84R	0.16	31	yes	no
	Vif T167I	0.37	38	yes	no
	Pol K76R	0.015	119	yes	Yes, (Pol73-90)
CH77	Env R355K/S/N,T358A	0.36	9	yes	Yes, (Env350-368)
	Nef R21K/G, R22K/G/,TD23E/N, P25S	0.30	19	yes	Yes, (Nef17-34)
	Nef K82Q/T/P, A83G, L85H, L87I	0.29	24	yes	Yes, (Nef81-98)
	Gag I147L	0.035	101	yes	Yes, (Gag140-157) IW9
	Gag T242N,V247I, G248E/S	0.063	124	yes	Yes, (Gag236-253) TW10
CH58	Env Y586H	0.10	21	yes	Yes, (Env576-596)
	Env F829V/S/L, I830M/L/F, A832T, V833I	0.12	27	no	no
	Gag T248N, G254E	0.085	60	yes	Yes, (Gag236-253) TW10
	Gag I147L	0.007	430	yes	Yes , (Gag140-157) IW9
SUMA0874	Rev R48K, Q51H, Q53R, S54L, L55I	0.32	30	yes	Yes, (Rev47-55)
Median		**0.17**	**30**		

Elispot / IFN g staining

Results: Median rate of CTL escape = 0.17/d; Maximum rate of CTL escape = 0.37/d
Avg death rate of productively-infected cells on HAART = 1/d.

Conclusions

- Escapes measured here are faster than previously seen:
  - Median ε =0.17 day^{-1}, max ε =0.37 day^{-1}
  - Asquith *et al. (2006)*, median ε = 0.04 day^{-1}
- Comparing rate of escape with the death rate of infected cells, δ+k= 1 day^{-1} (HAART data) one sees CTL pressure to one epitope is high and accounts for as much as 37% of the killing rate and on average 17%. However, virus rapidly escapes this pressure.
- Current theory too simple – need to account for escape at multiple epitopes.

$$\frac{\mathrm{d}w}{\mathrm{d}t} = \left[r - \sum_{i=1}^{n} k_i - \delta \right] w,$$

$$\frac{\mathrm{d}m_{\mathbf{i}}}{\mathrm{d}t} = \left[(1 - c_{\mathbf{i}})r - \sum_{i \in \mathbf{i}} k_i - \delta \right] m_{\mathbf{i}},$$

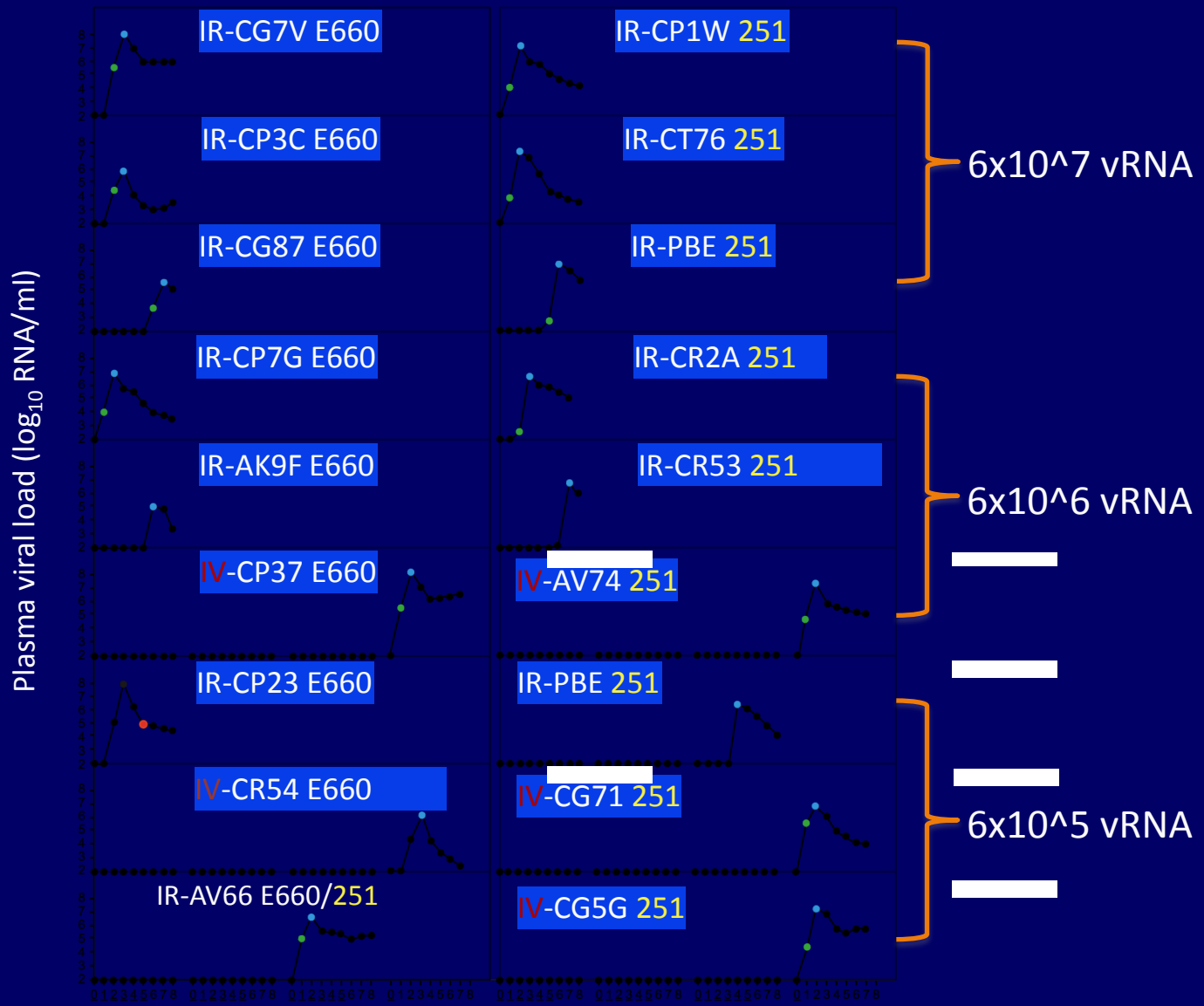
Infection: Stochastic?

- Prob. HIV transmitted/ sex act ~ .001 - .01
- About 80% of infections result from a single viral genome
- Inject low doses of SIV into monkeys – many times no infection results

- Suggests early events are stochastic and not all encounters with virus lead to infection.

Inoculation scheme, infection kinetics, and sampling timepoints in 18 rhesus macaques

Keele et al.
J Exp Med 2009



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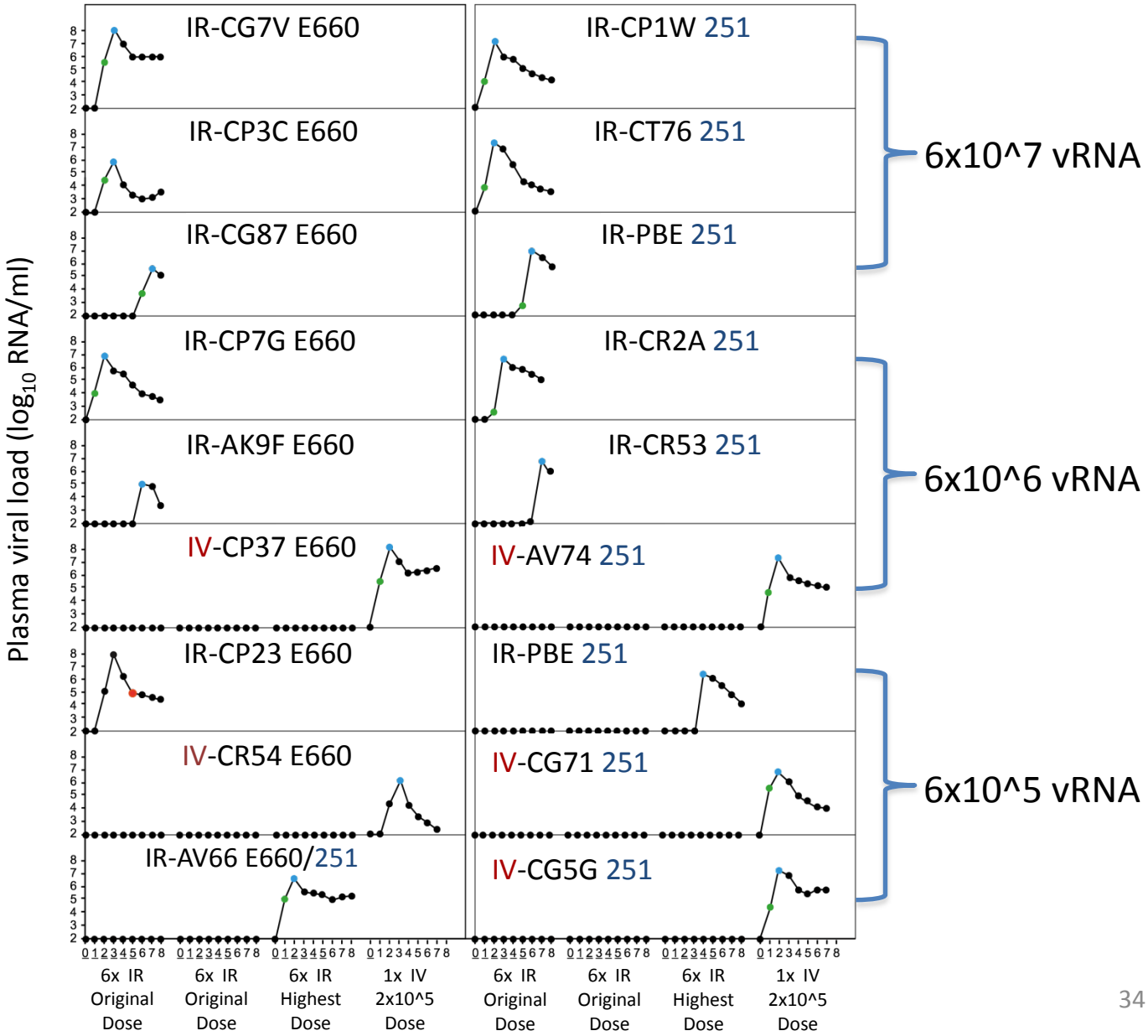
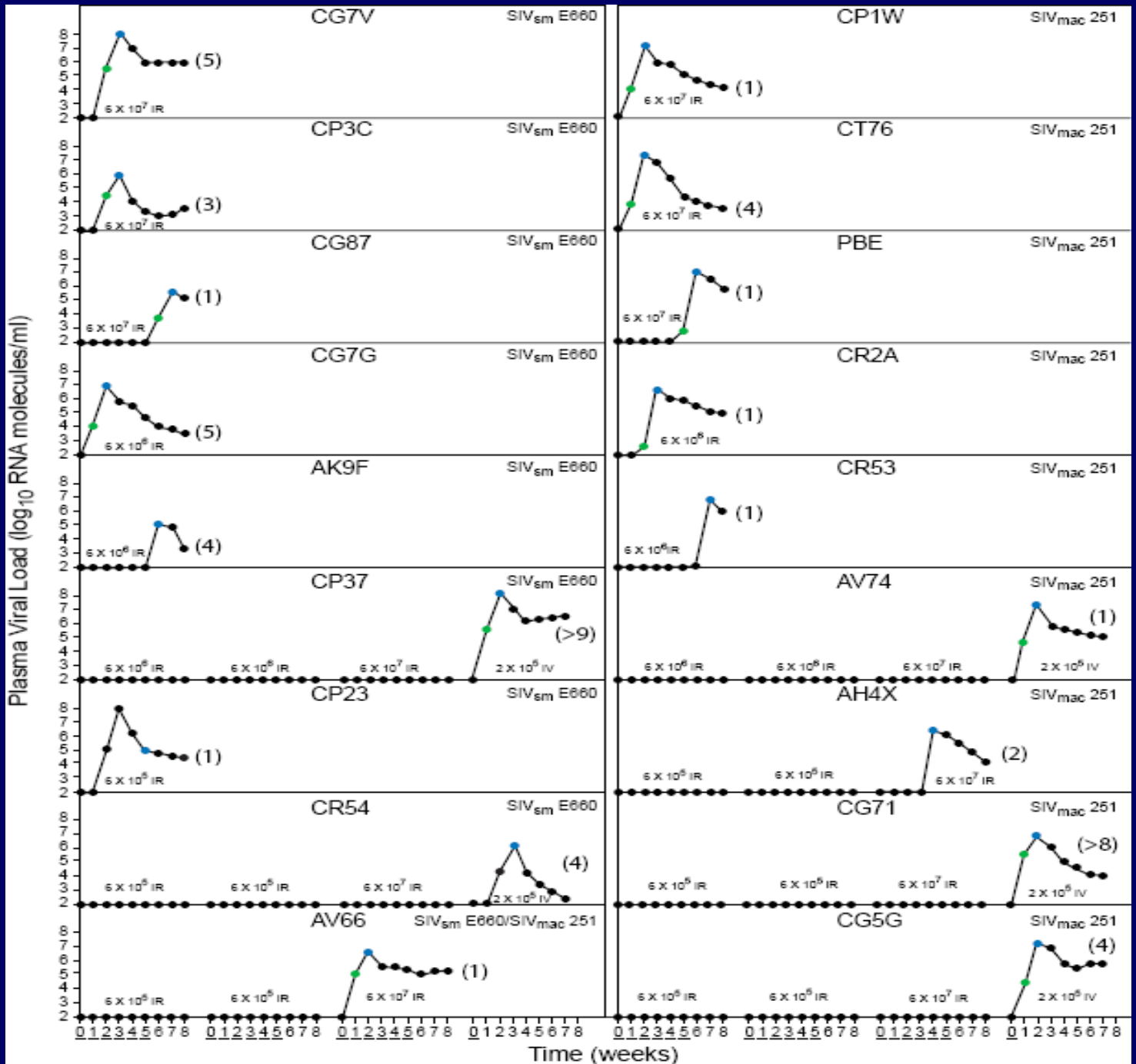
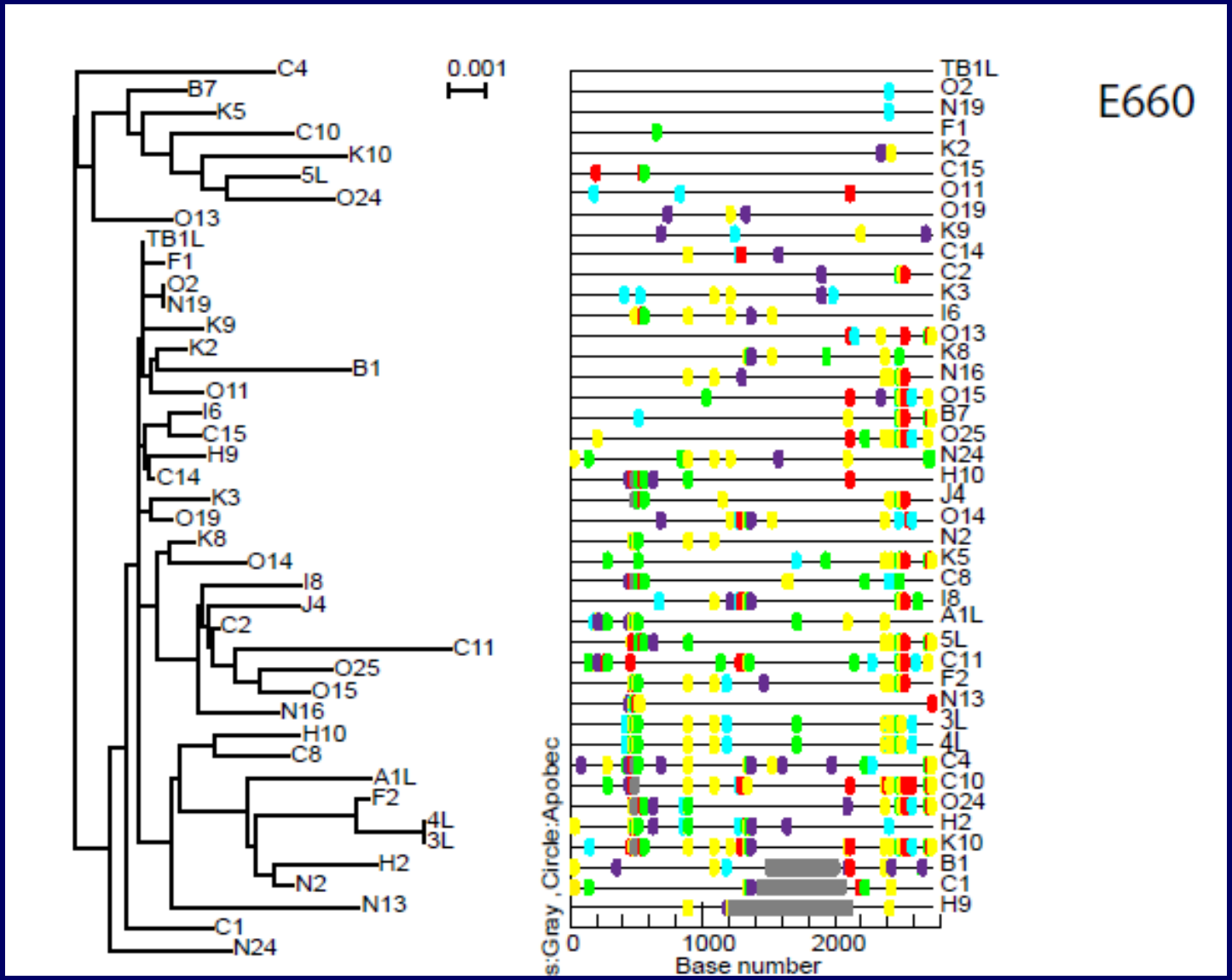




Keele (2009) J Exp Med 206:1117

Viral stock diverse

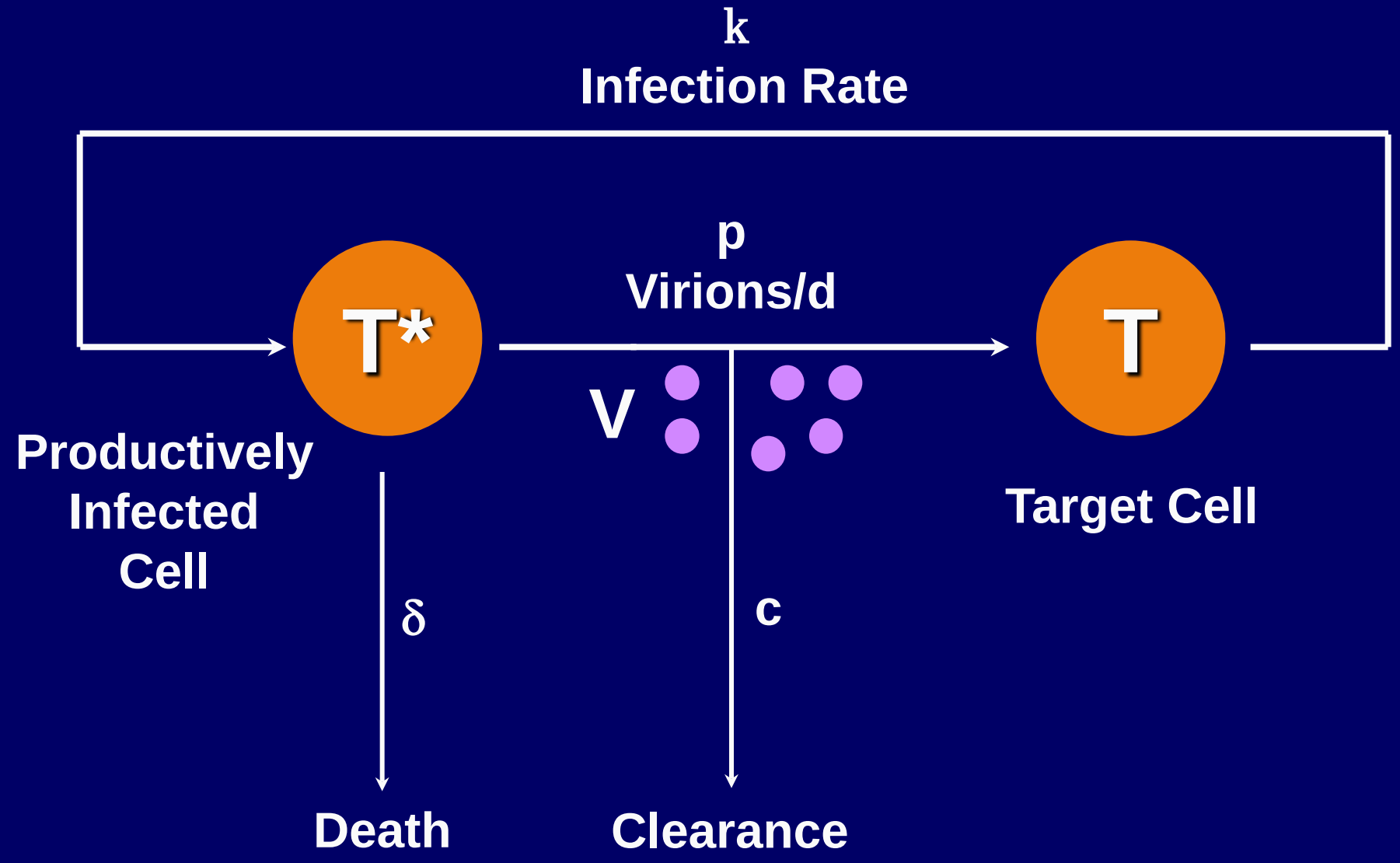


Stochastic Model

- Master equation approach – follow the fate of each virion and infected cell.

Done in collaboration with John Pearson (LANL) and Paul Krapivsky (BU)

Model of HIV Infection



Processes (Continuous Viral Production)

$$
\begin{aligned}
&(1) \quad V + T \xrightarrow{k} I \\
&(2) \quad I \xrightarrow{N\delta} I + V \\
&(3) \quad I \xrightarrow{\delta} \emptyset \\
&(4) \quad V \xrightarrow{c} \emptyset,
\end{aligned}
$$

Assume T is constant early in infection

$$
\begin{aligned}
&(1) \quad V \xrightarrow{kT} I \\
&(2) \quad I \xrightarrow{N\delta} I + V \\
&(3) \quad I \xrightarrow{\delta} \emptyset \\
&(4) \quad V \xrightarrow{c} \emptyset.
\end{aligned}
$$

State Transitions

Table 1: The elementary microscopic model

Process	$n \to m$	$r_{n \to m}$
1	$(n_v, n_I) \to (n_v - 1, n_I + 1)$	kTn_V
2	$(n_v, n_I) \to (n_v - 1, n_I)$	cn_V
3	$(n_v, n_I) \to (n_v + 1, n_I)$	pn_I
4	$(n_v, n_I) \to (n_v, n_I - 1)$	δn_I

n_V = # of virions
n_I = # of infected cells
$n = (n_V, n_I)$

Master Eqn.
Gillespie simulations

Prob of Extinction

- $\Pi(\boldsymbol{n})$ = prob of a process starting in state ***n*** reaching (0,0).
- Because clearing each virus or infected cell is independent

$$\Pi(n) = \rho_V^{n_V} \rho_I^{n_I}$$

where ρ_v (ρ_I) is prob of going extinct starting with a single virus (infected cell). Further,

$$\Pi(n) = \sum_m p_{n\to m} \Pi(m)$$

Probability of reaction

$$p_i(\vec{n}) = \frac{r_i(\vec{n})}{Z(\vec{n})}$$

$$Z(\vec{n}) = \sum_i^{n_{max}} r_i(\vec{n}).$$

p_i = prob of i^{th} reaction

r_i = rate of i^{th} reaction

Plugging in

$$\rho_V^{n_V}\,\rho_I^{n_I} = \frac{kTn_V}{Z}\rho_V^{(n_V-1)}\,\rho_I^{(n_I+1)} + \frac{N\delta n_I}{Z}\rho_V^{(n_V+1)}\,\rho_I^{n_I} + \frac{\delta n_I}{Z}\rho_V^{n_V}\,\rho_I^{(n_I-1)} + \frac{cn_V}{Z}\rho_V^{n_V-1}\,\rho_I^{n_I} \ .$$

Simplifying yields:

$$\begin{aligned}\rho_V &= \gamma\rho_I + (1-\gamma) \\ \rho_I &= \frac{N}{N+1}\rho_V\,\rho_I + \frac{1}{N+1}\end{aligned}$$

which is a quadratic eqn with solns:

$\rho_v=\rho_I=1$ $R_0\leq 1$,

$\rho_v=1-(R_0-1)/N$

and

$\rho_I=1/R_0$ $R_0>1$;

where $R_0= N\ kT/(kT+c)= N\gamma$,

γ = prob a virion infects a cell

Viral Production via a Burst

Here viral production and cell death occur simultaneously, so only 3 rxns

$$
\begin{array}{lcc}
(1) & V & \xrightarrow{kT} & I \\
(2) & I & \xrightarrow{\delta} & NV \\
(3) & V & \xrightarrow{c} & \emptyset
\end{array}
$$

Leads to different master eqn and different extinction probability.

Burst Model

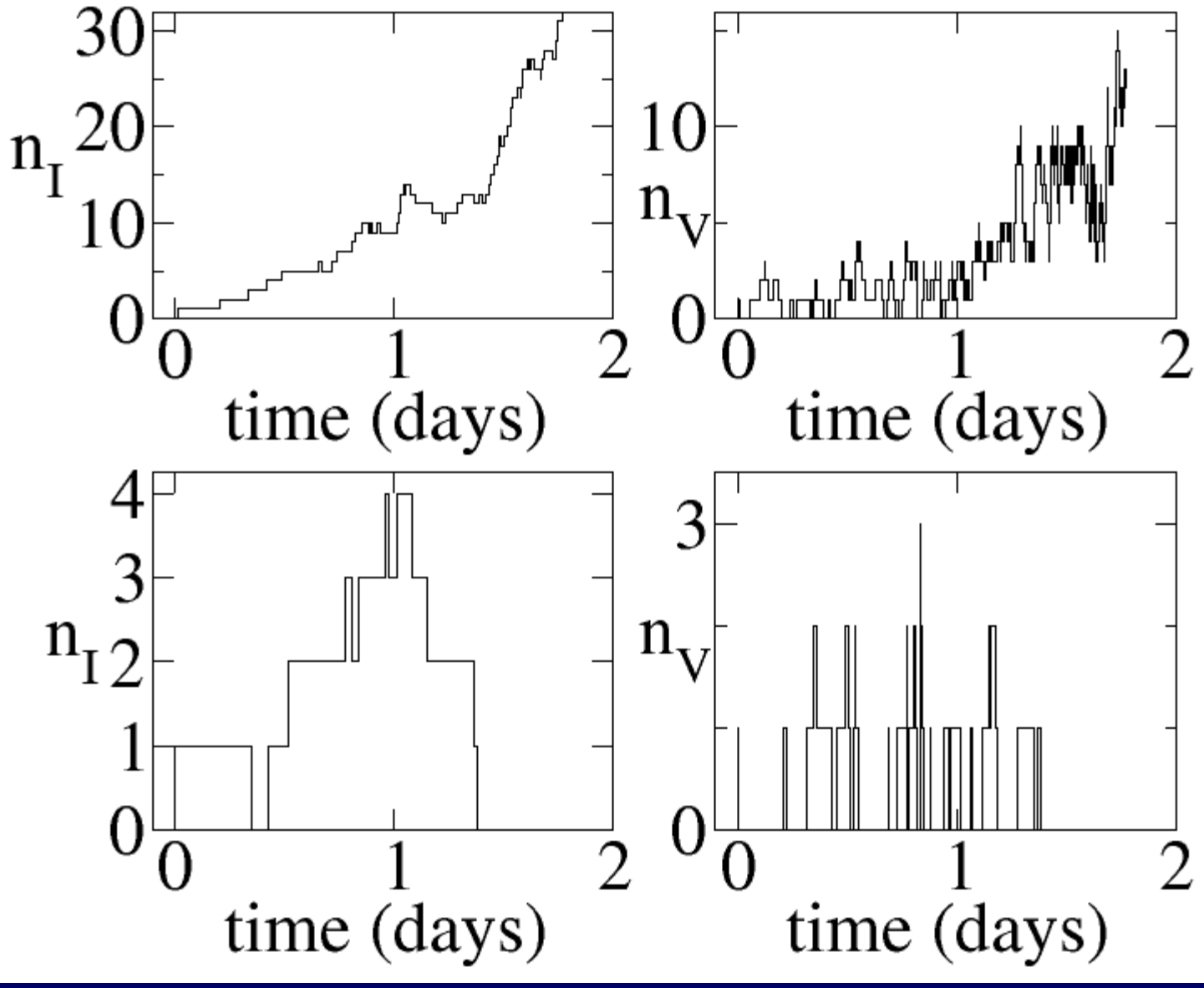
$$\begin{aligned} \rho_V^{burst} &= min(\rho_V^*, 1) \\ \rho_I^{burst} &= min((\rho_V^*)^N, 1) \end{aligned}$$

where ρ_V^* is the positive real root of:

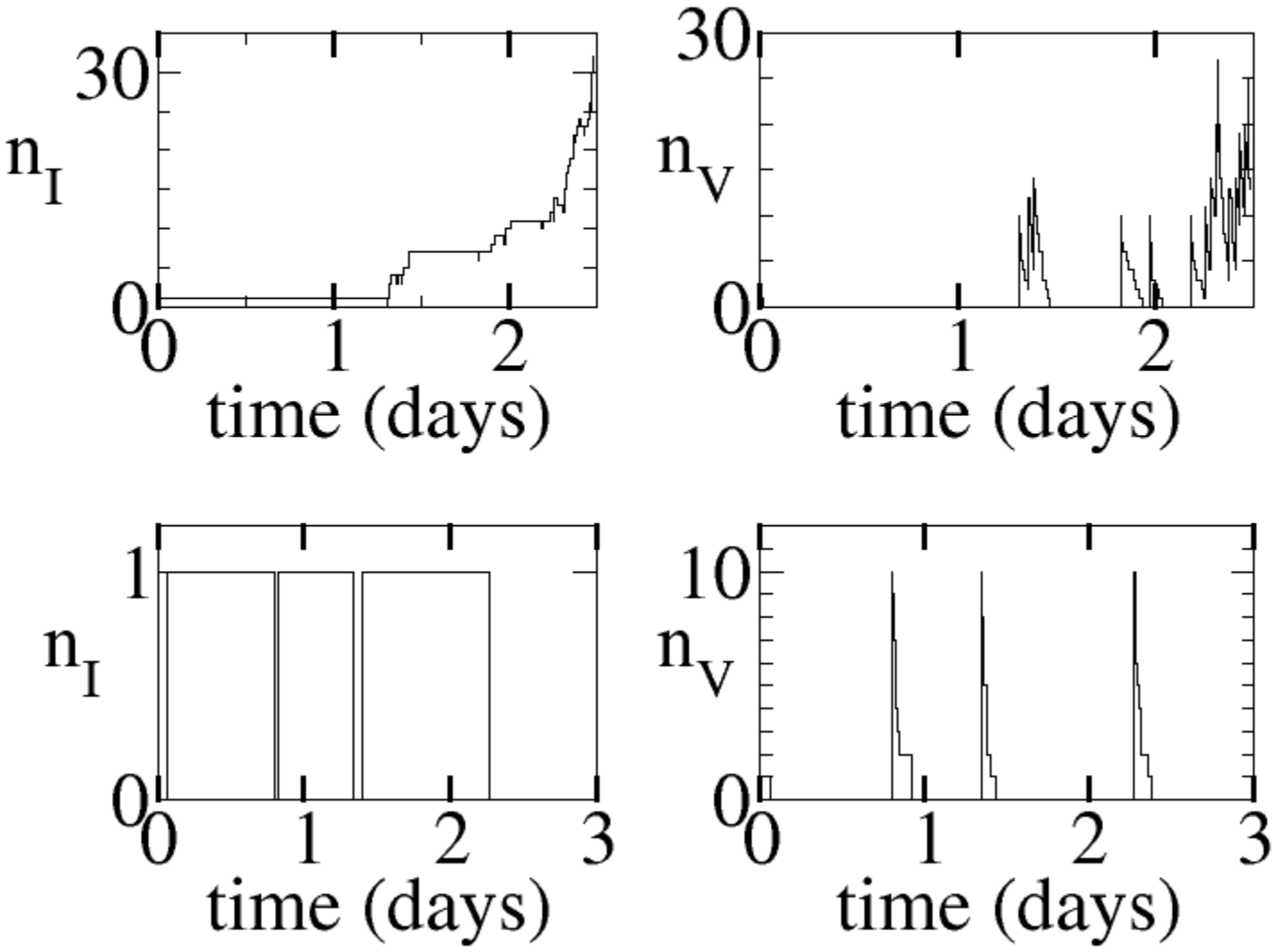
$$\frac{1-\rho_V^*}{1-(\rho_V^*)^N} = \gamma$$

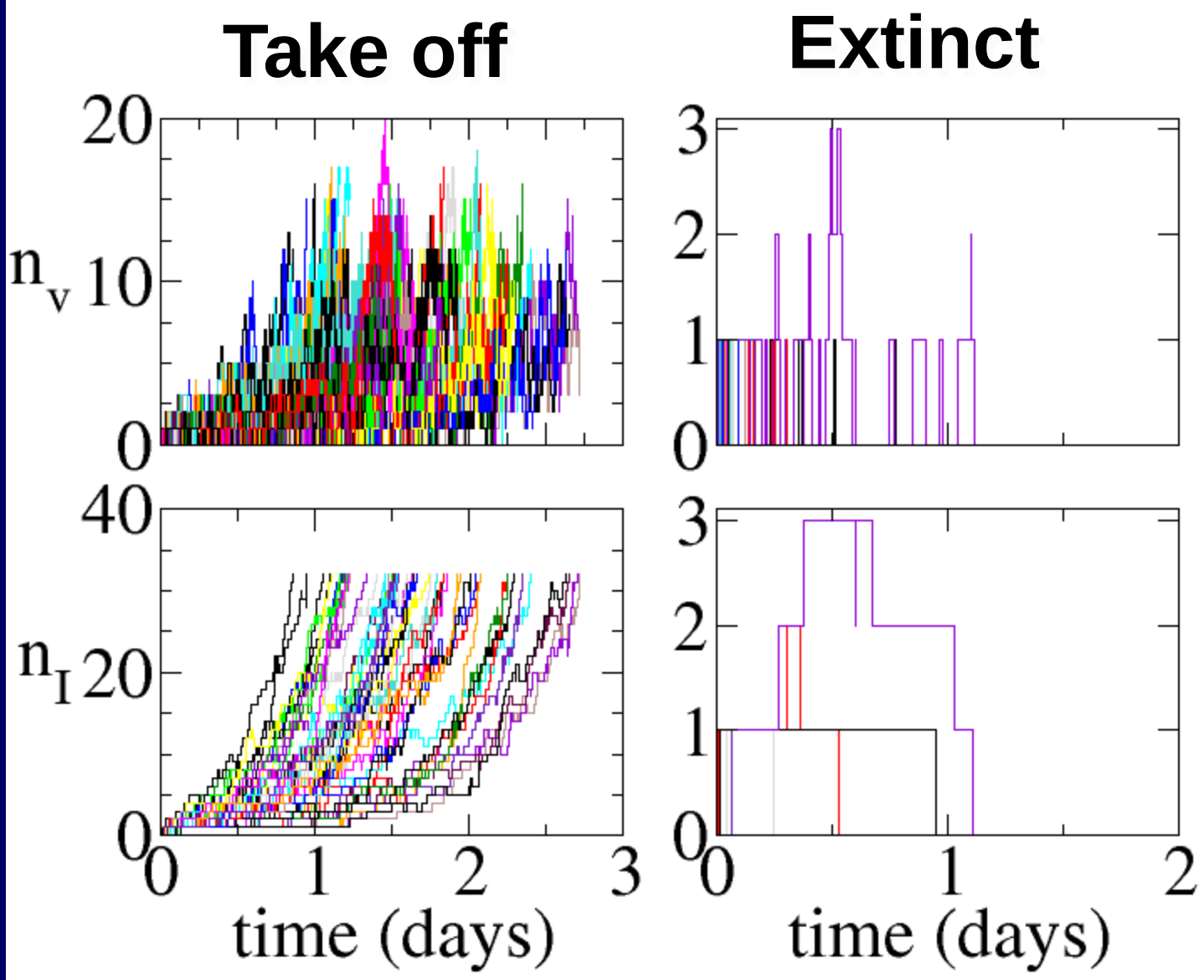
and $\gamma = kT/(c+kT) = R_0/N$.

Dynamics: Continuous Production

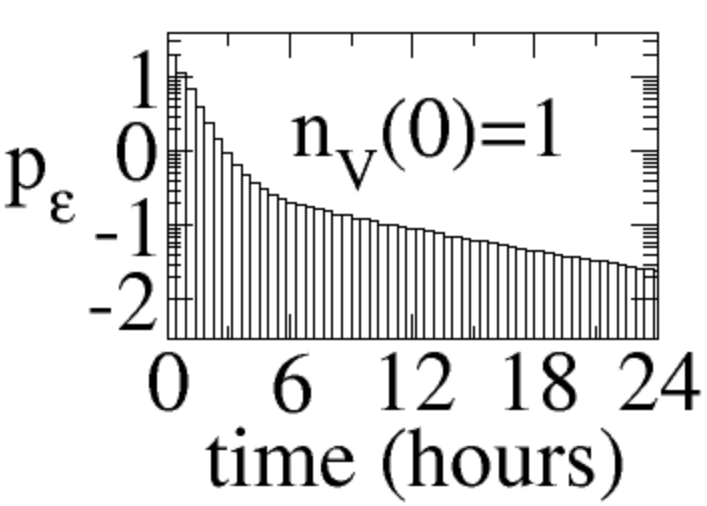


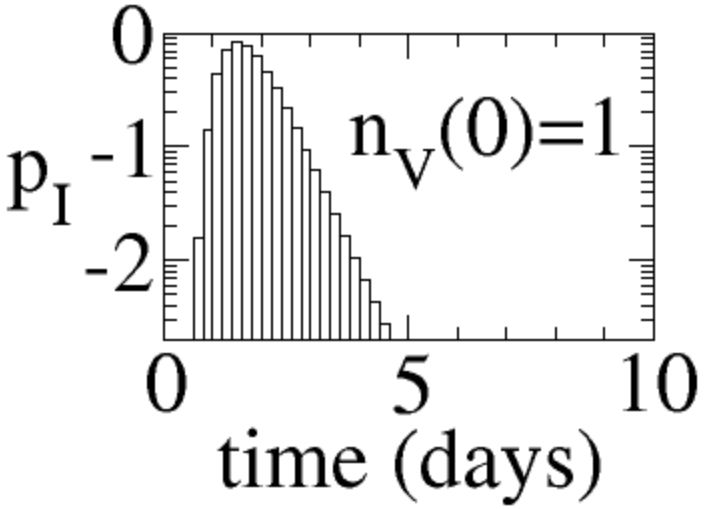
Dynamics: Burst Model

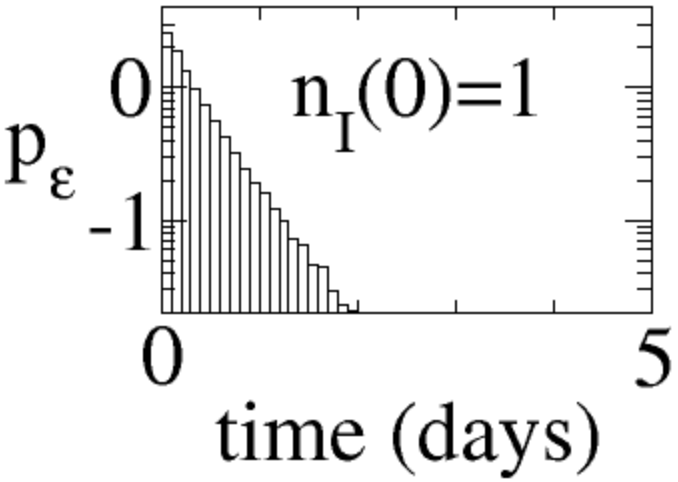


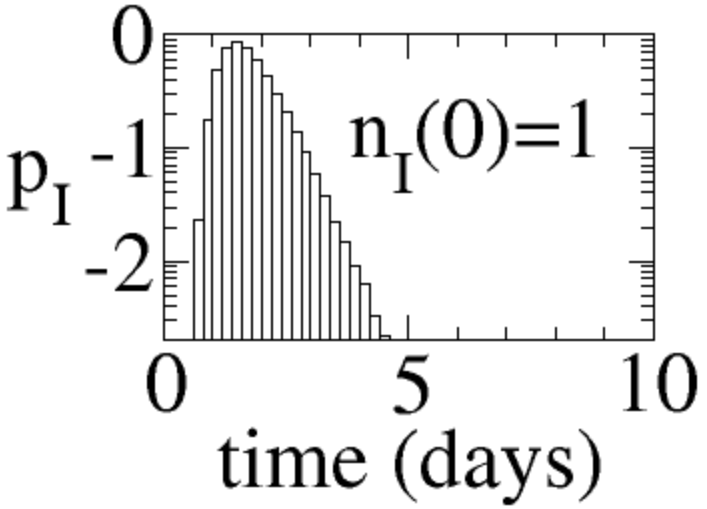

Take off
Extinct
20
10
0
n_v
40
20
0
n_I
0
1
2
3
time (days)
3
2
1
0
0
1
2
time (days)

Continuous

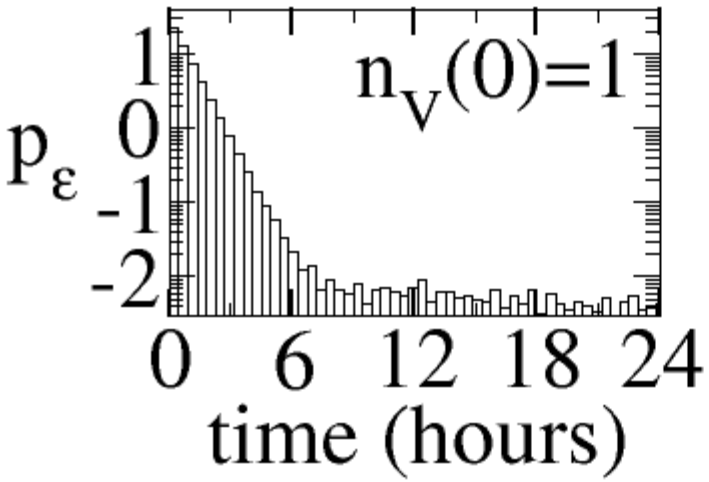

p_ε
1
0
-1
-2
$n_V(0)=1$
0
6
12
18
24
time (hours)

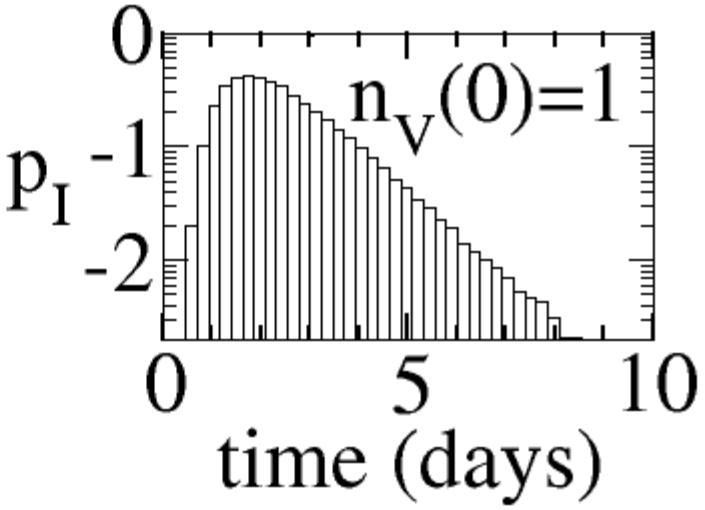

p_I
0
-1
-2
$n_V(0)=1$
0
5
10
time (days)

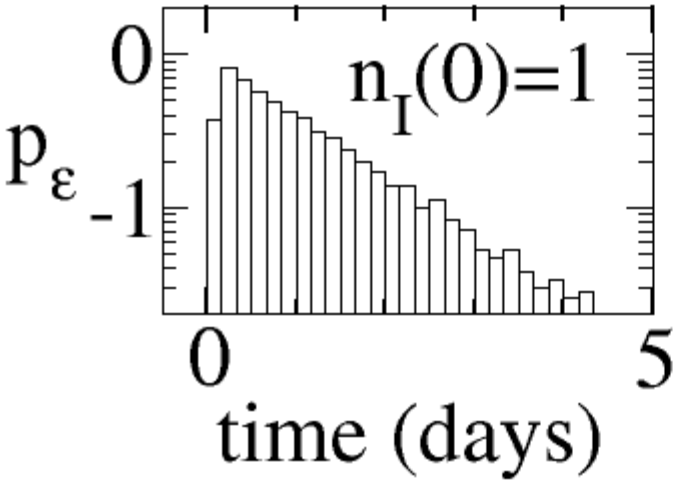

p_ε
0
-1
$n_I(0)=1$
0
5
time (days)

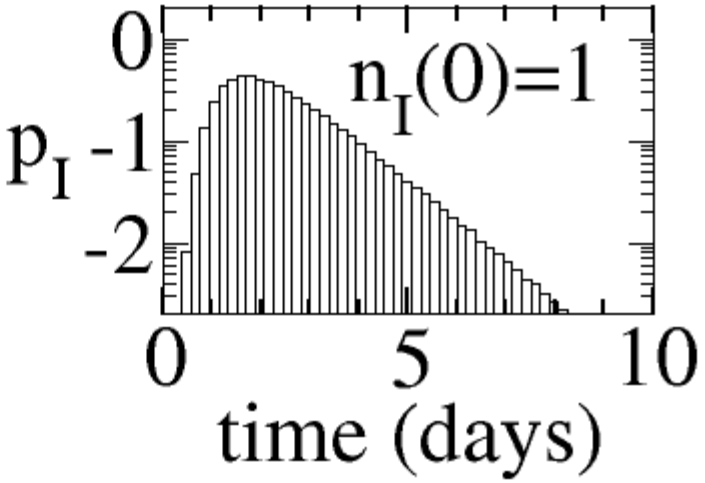

p_I
0
-1
-2
$n_I(0)=1$
0
5
10
time (days)

Burst

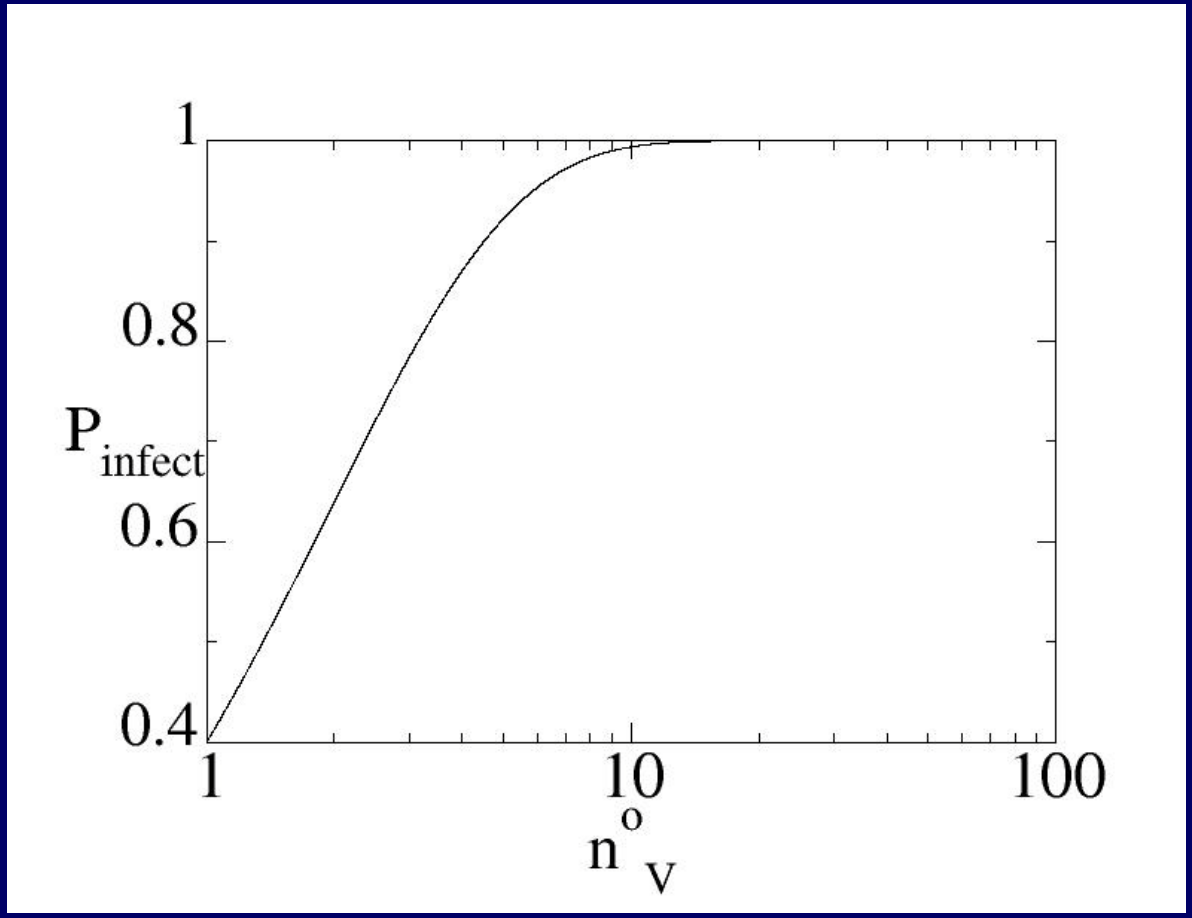

$n_V(0)=1$
p_ε
1
0
-1
-2
0 6 12 18 24
time (hours)


$n_V(0)=1$
p_I
0
-1
-2
0 5 10
time (days)


$n_I(0)=1$
p_ε
0
-1
0 5
time (days)


$n_I(0)=1$
p_I
0
-1
-2
0 5 10
time (days)

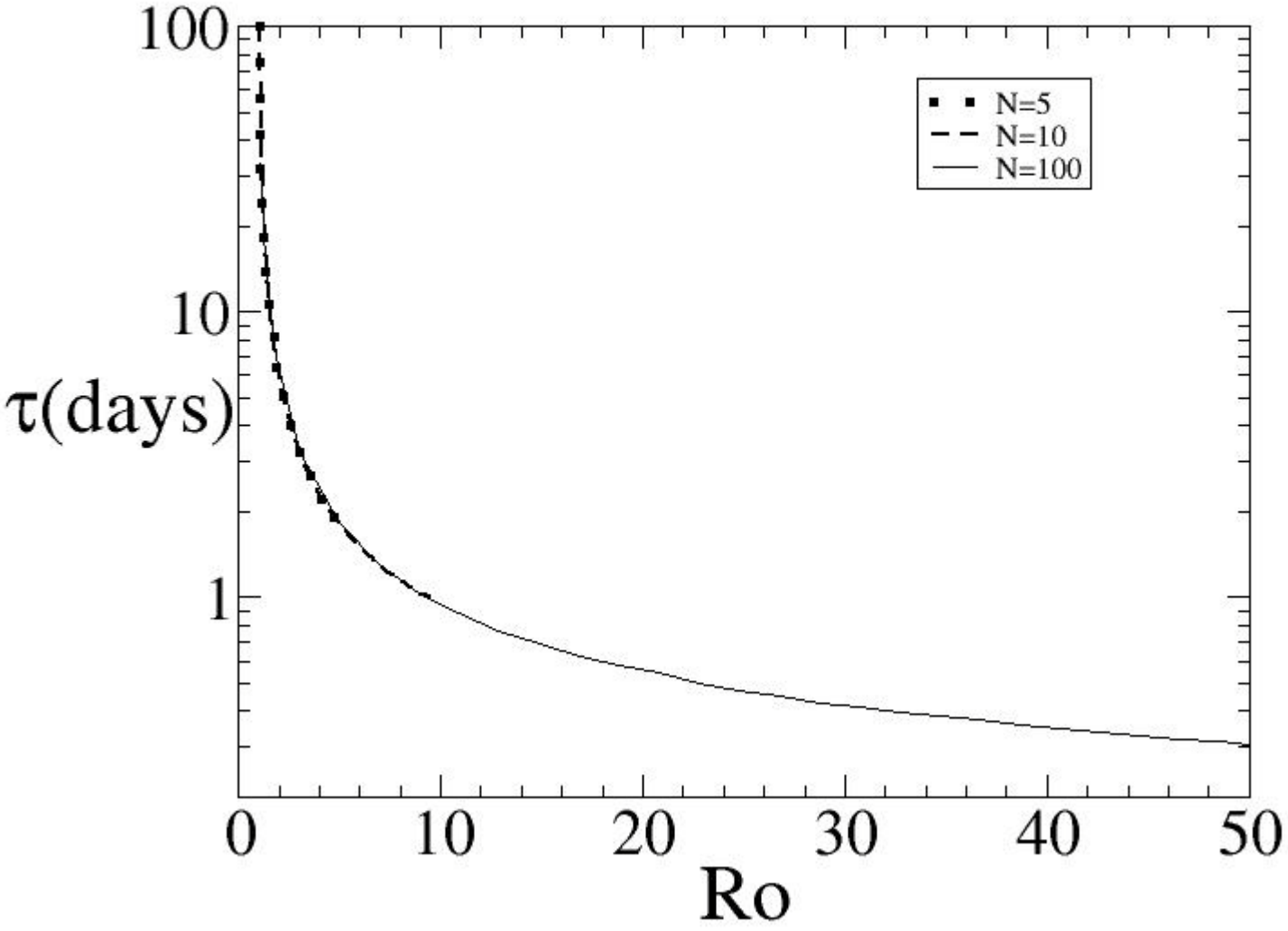
Prob of infection



P_{infect} = 1-prob extinction

R_0=5, N=10

Time to measureable infection



R_0

$$R_0 = N\,kT/(kT+c),$$

where T = number of target cells.

If T is small R_0 can be < 1 or close to one.

As infection proceeds immune response can lead to cell activation increasing T or virus can spread to regions where more targets are available.

Two-Compartment Model

- Add rate limiting step – transport out of mucosal layer
  - Could be diffusion of virus or more likely transport of virus by antigen carrying dendritic cells
  - Currently being modeled as another process with a fixed transition probability

Implications

- If eclipse phase is typically long, this means there is a large window of opportunity for intervening (eg with ART) and hopefully preventing infection.
- If an increase in target cells, T, is driving an increase in R_0, then strategies that lead to activation of the immune system are problematic.

Vaccines

- Vaccines tend to activate cells, and such activation is thought to be behind the failure of the Merck vaccine. Activation might have to be highly specific so as not to increase R_0, but because of the diversity of HIV current vaccines are being made more broad. Stimulation of innate responses, eg NK cells, may avoid increasing T.
- If transport out of mucosal tissue is behind the long eclipse phase then novel strategies aimed at reducing such targets need to be explored.