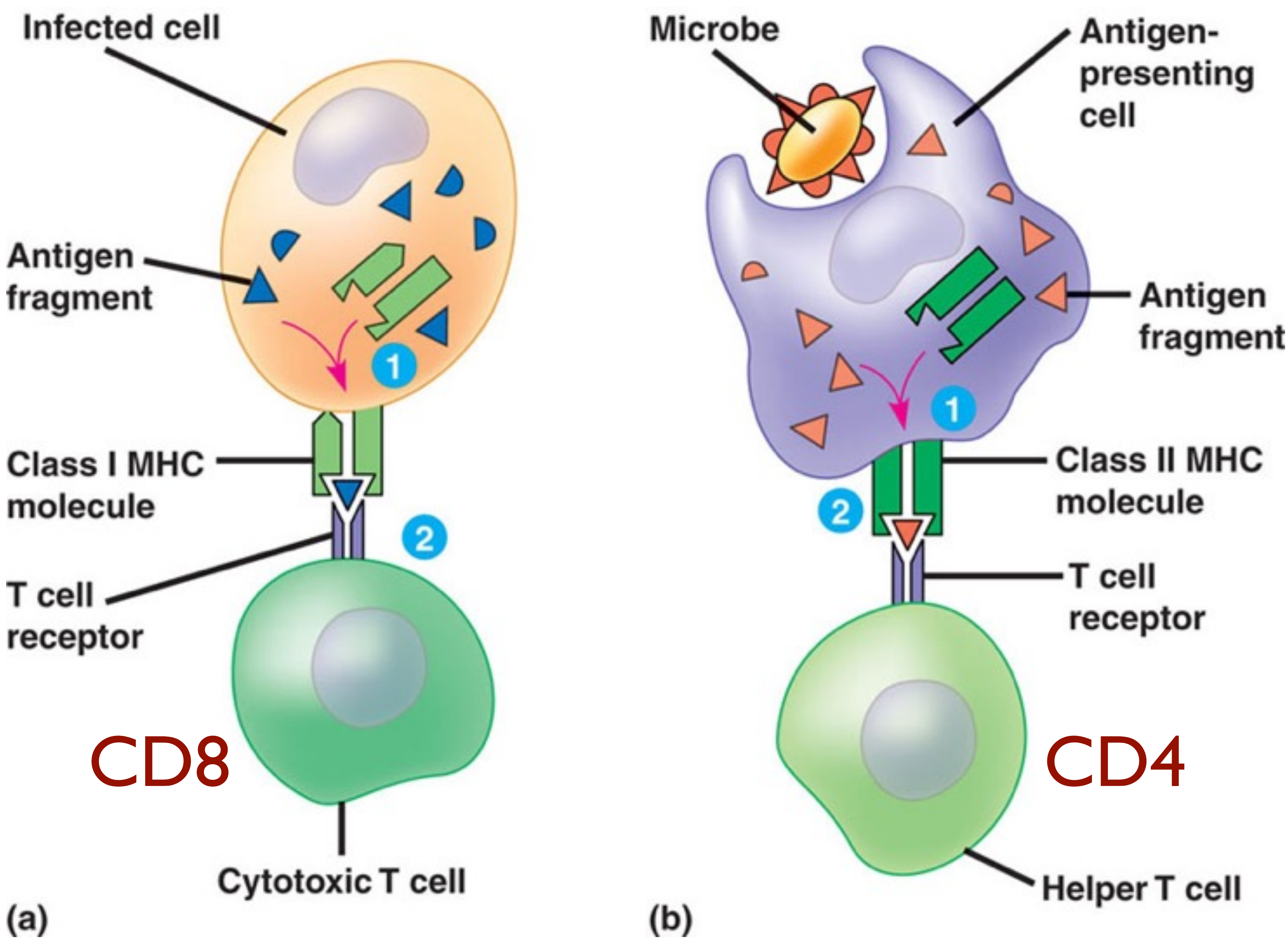
Chapter 8:

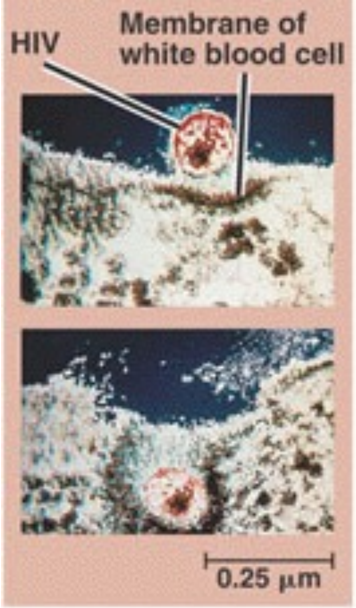
Immune reactions
to
chronic viruses

Theoretical Biology
2016

CD4 and CD8 T cells

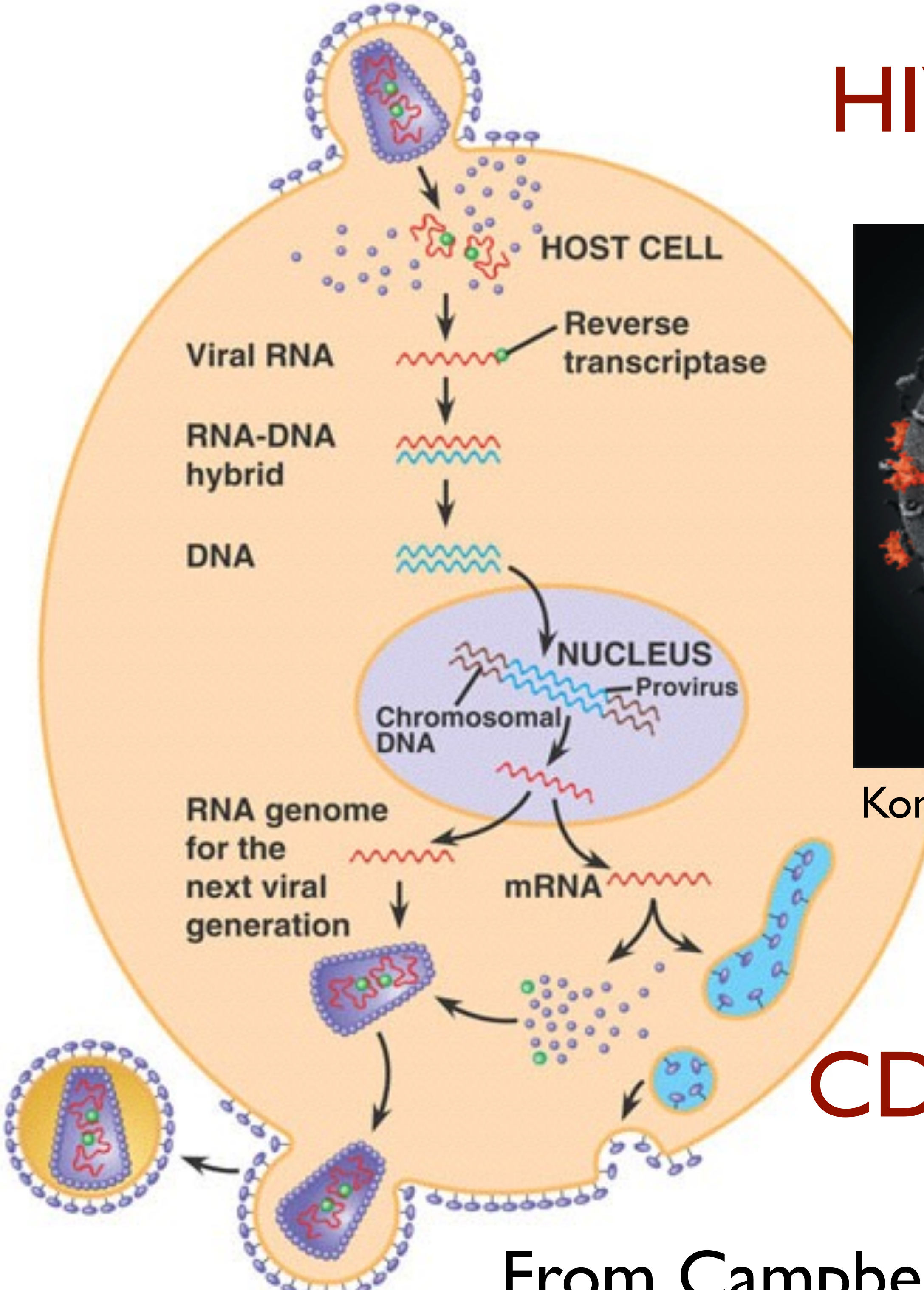


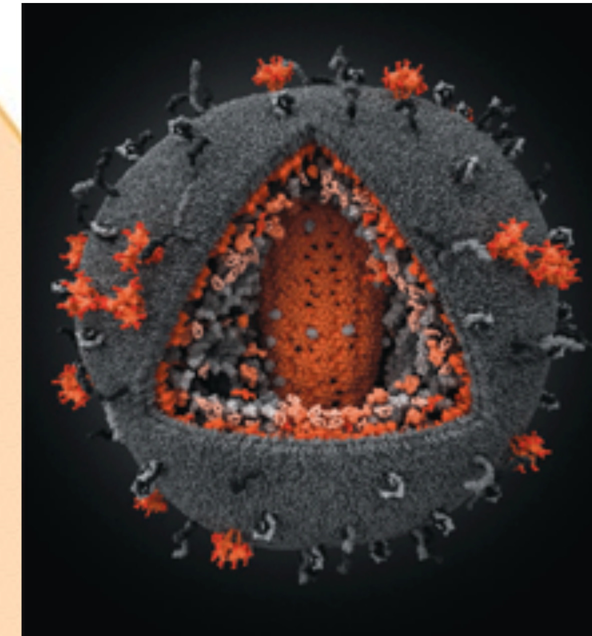
HIV life cycle



HIV entering a cell


New HIV leaving a cell

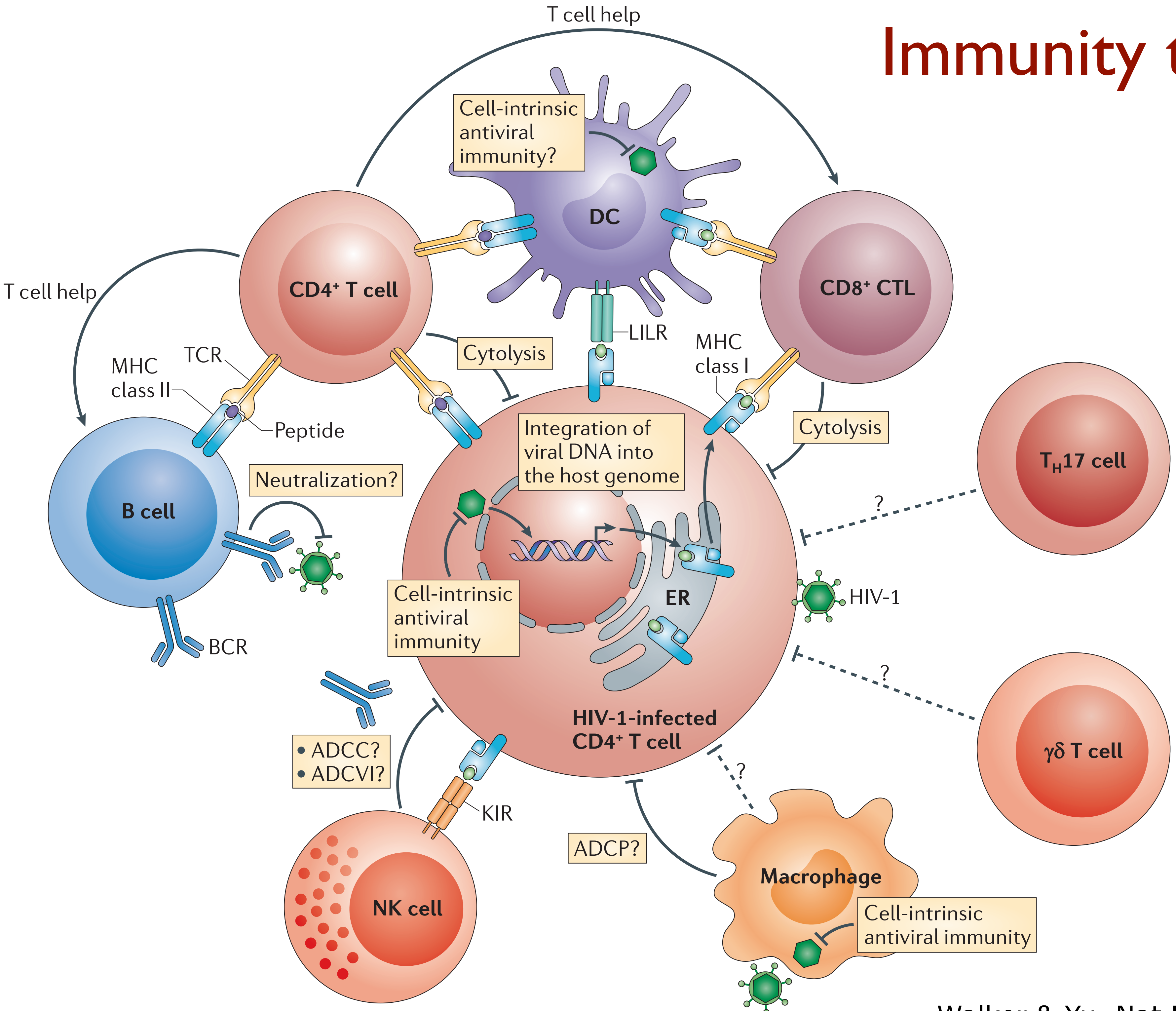



Konstantinov Science 2011

CD4^{+} T cell

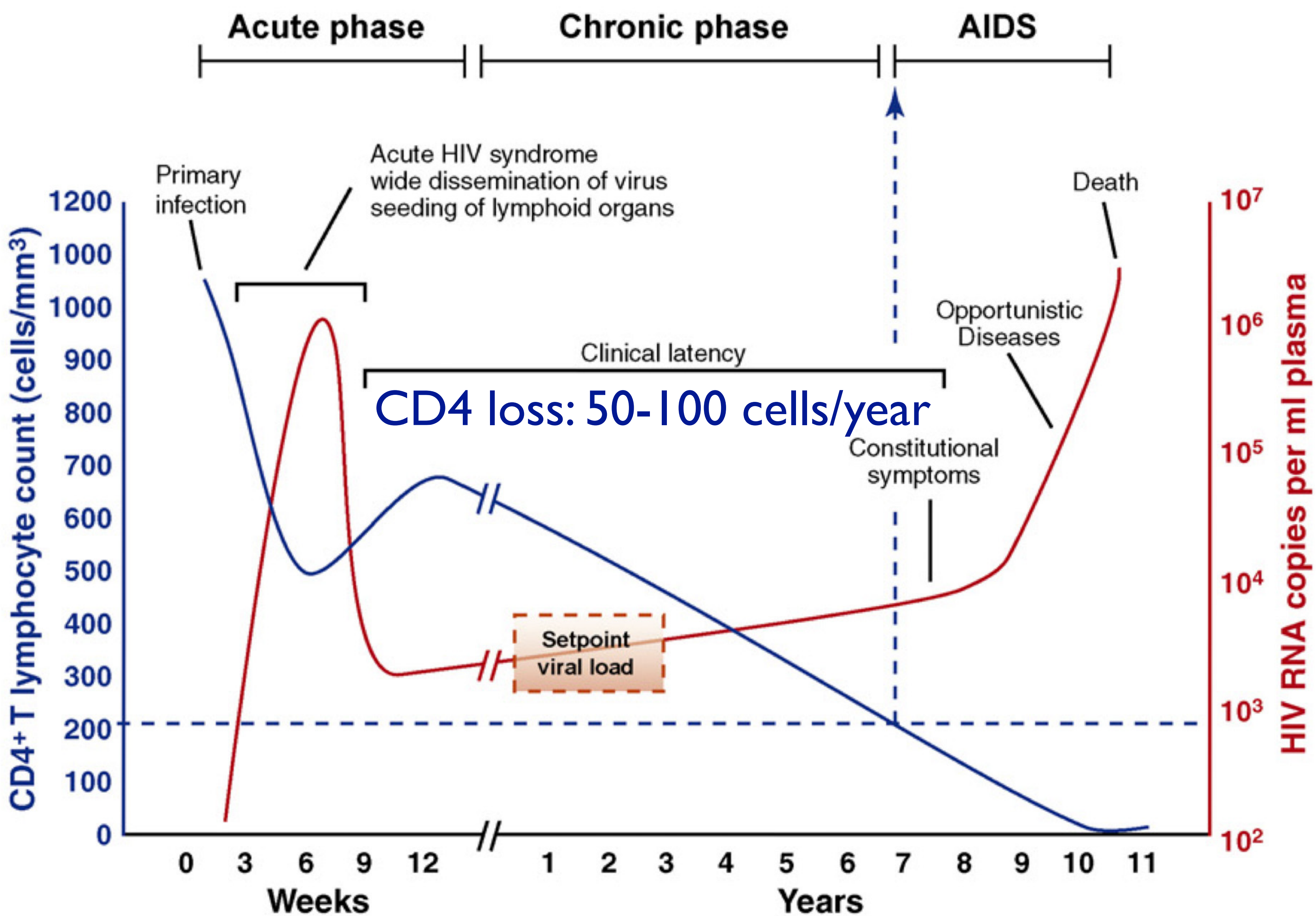
From Campbell

Immunity to HIV



Walker & Yu, Nat Rev Imm 2013

Time course of an HIV infection

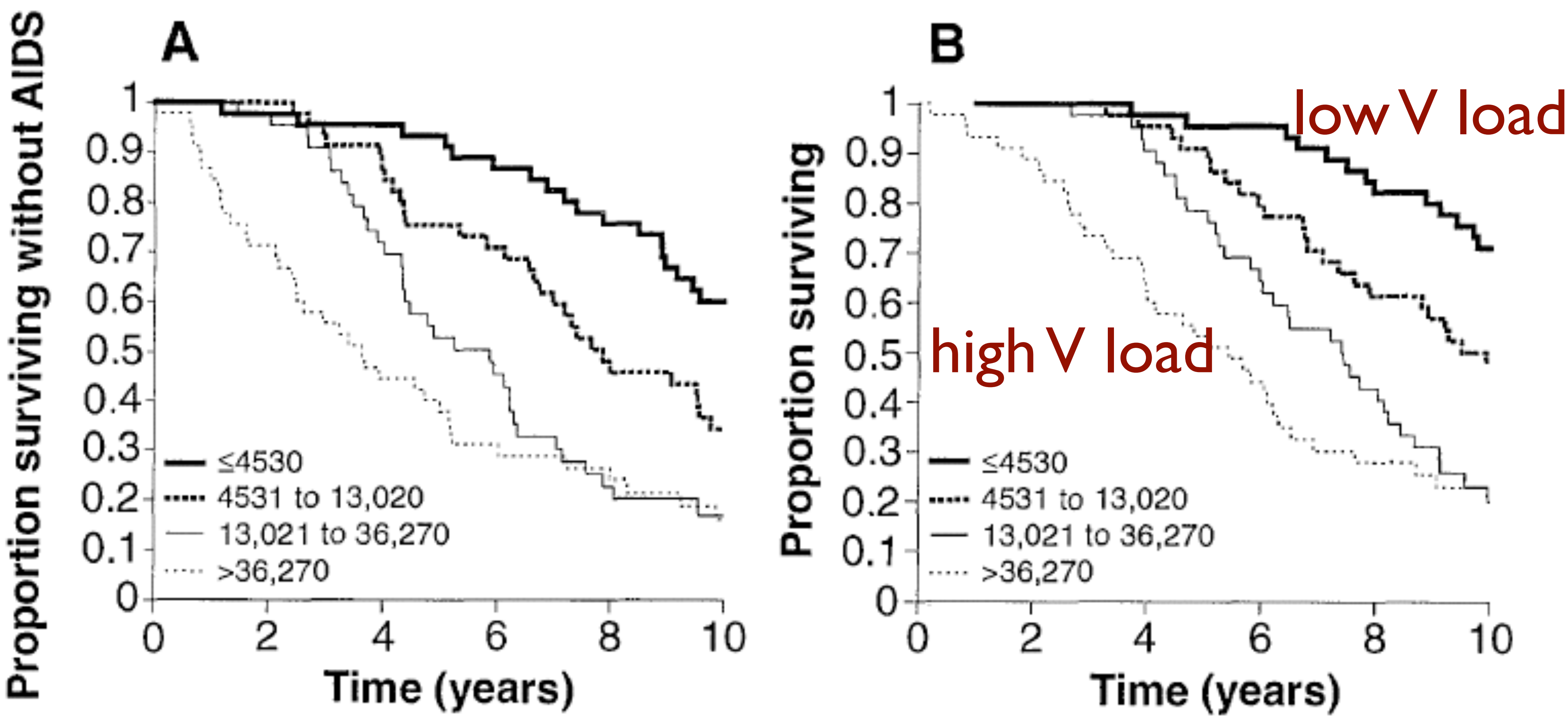


O'Brien & Hendrickson, Genome Biol. 2013

Slow decline of CD4$^+$ T cells: AIDS due to loss of immunity

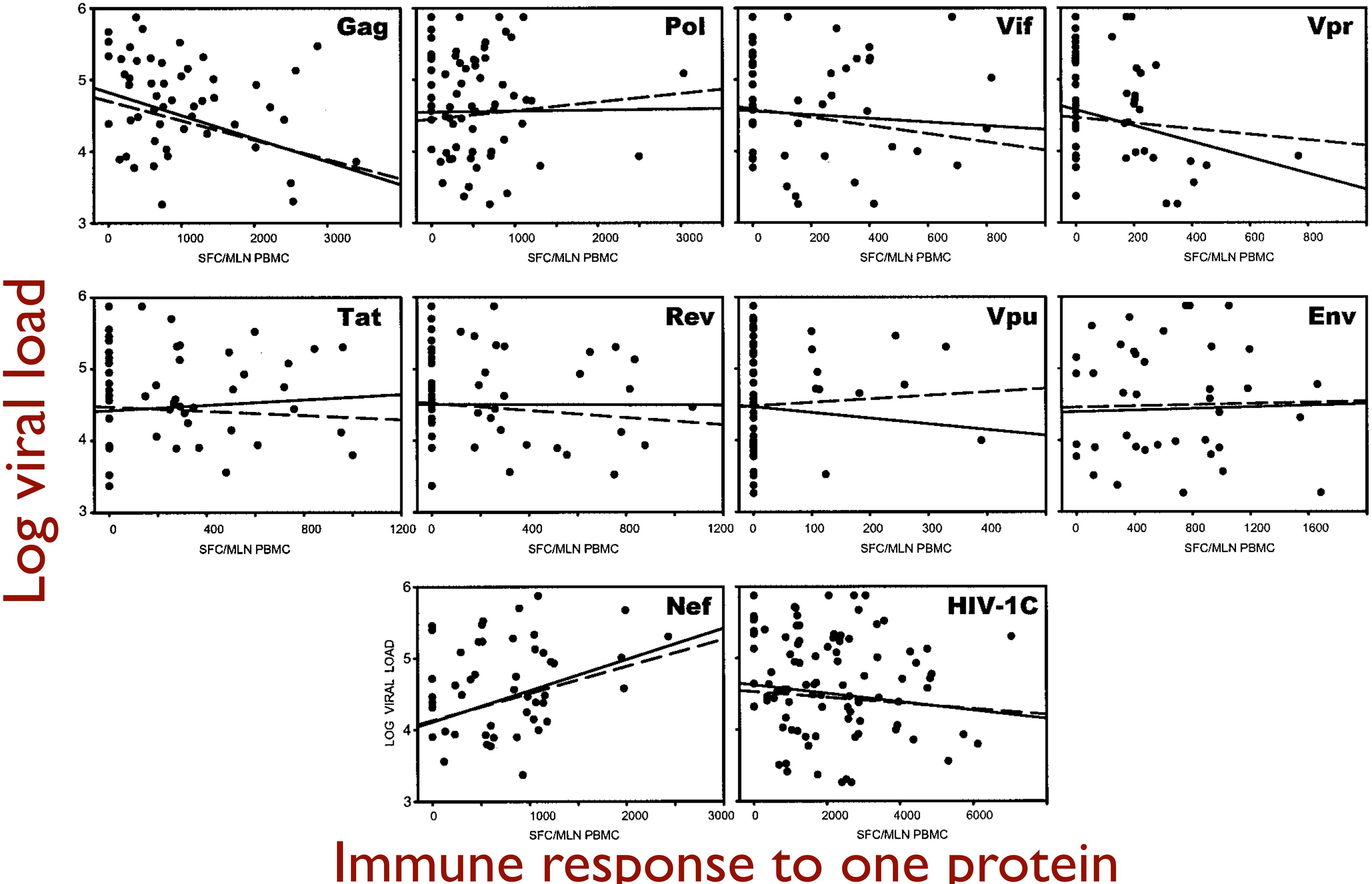
Fairly stable viral setpoint for many years: time to AIDS

Viral load predicts rate of disease progression



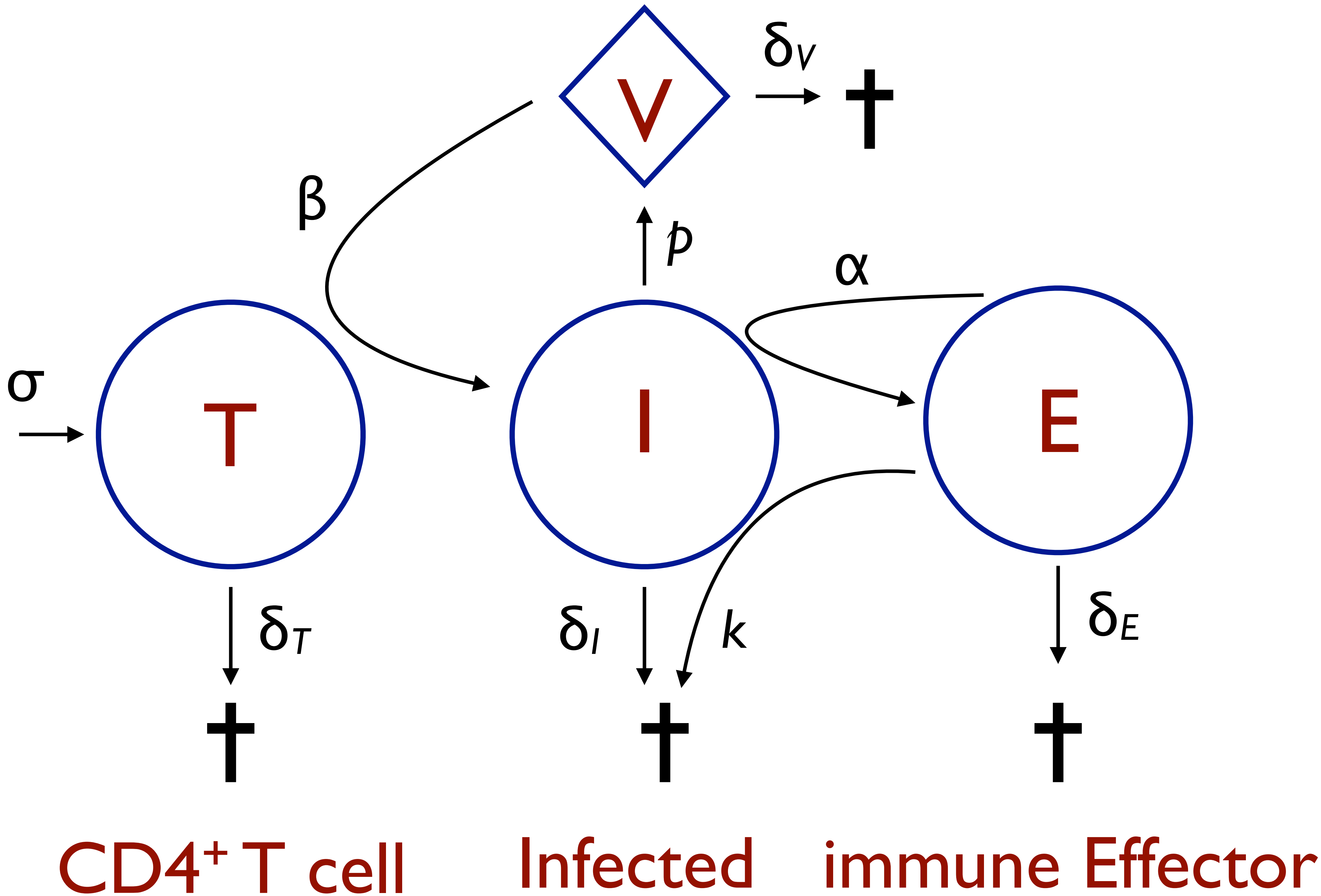
From: Mellors et al. Science 1996

Immune response does not correlate with viral load



From: Novitsky et al. J Virol. 2003

Caricature scheme



Mathematical model

$$
\begin{aligned}
\frac{\mathrm{d}T}{\mathrm{d}t} &= \sigma - \delta_T T - \beta T V \ , \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta T V - \delta_I I - k E I \ , \\
\frac{\mathrm{d}V}{\mathrm{d}t} &= p I - \delta_V V \ , \\
\frac{\mathrm{d}E}{\mathrm{d}t} &= \alpha E I - \delta_E E \ .
\end{aligned}
$$

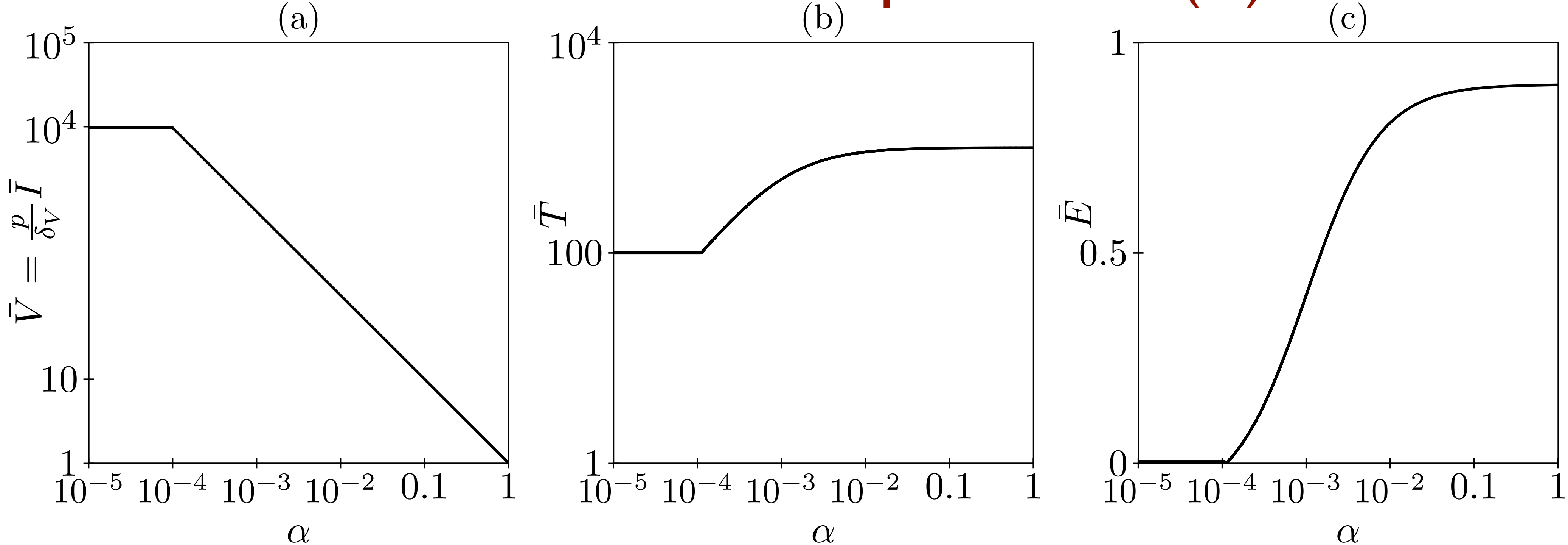
Set $\delta_I > \delta_T$ to allow for cytopathic effects of the virus

Steady state

$$\begin{aligned}
\bar{I} &= \frac{\delta_E}{\alpha} \\
\bar{V} &= \frac{p}{\delta_V}\bar{I} = \frac{p\delta_E}{\alpha\delta_V} \\
\bar{T} &= \frac{\sigma}{\delta_T + \beta\bar{V}} = \frac{\alpha\sigma\delta_V}{\alpha\delta_T\delta_V + p\beta\delta_E} \\
\bar{E} &= \frac{p\beta}{k\delta_V}\bar{T} - \frac{\delta_I}{k} \\
&= \frac{p\beta\alpha\sigma}{k(\alpha\delta_T\delta_V + p\beta\delta_E)} - \frac{\delta_I}{k}
\end{aligned}$$

Only the rate at which immune cells are activated, α, determines the viral burden *I*.

Viral load (V), targets (T) and immune response (E) as a function of activation parameter (α)



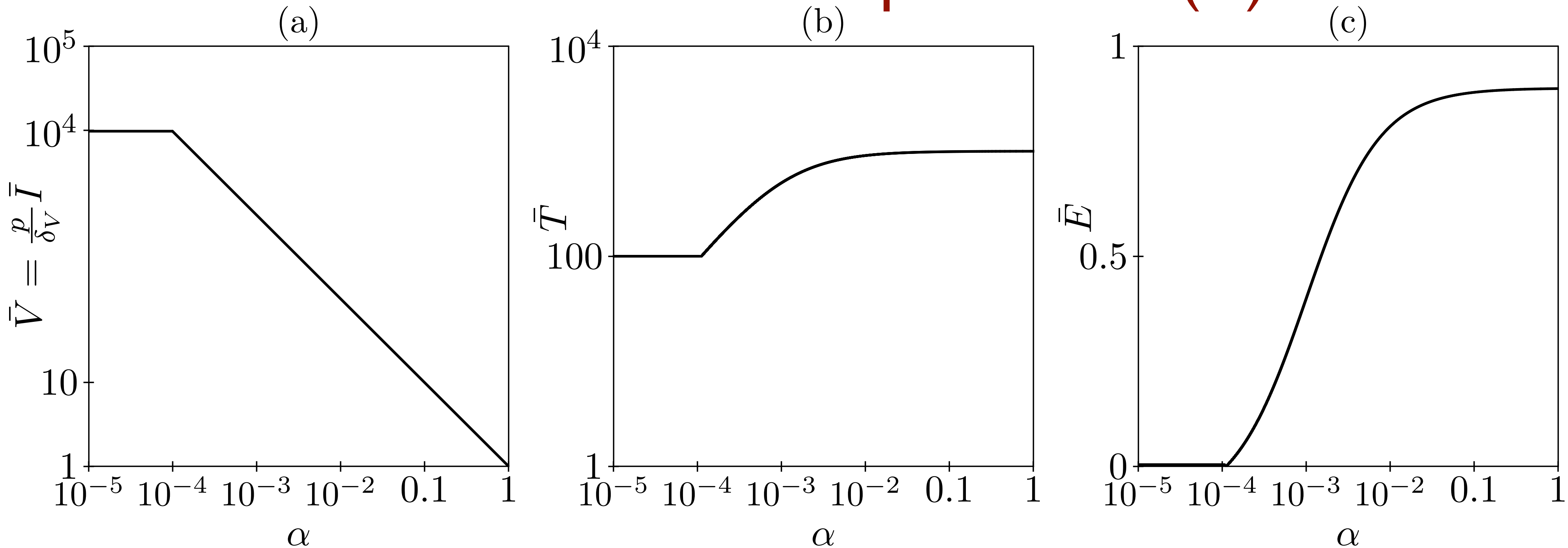
When α>0.01 the immune response hardly changes, but the viral load (V or I) changes markedly.

Patients having similar immune response can have very different viral loads!

What happens at α=10^{-4}?

$$\bar{V} = \frac{p\delta_E}{\alpha\delta_V}$$

Viral load (V), targets (T) and immune response (E) as a function of activation parameter (α)

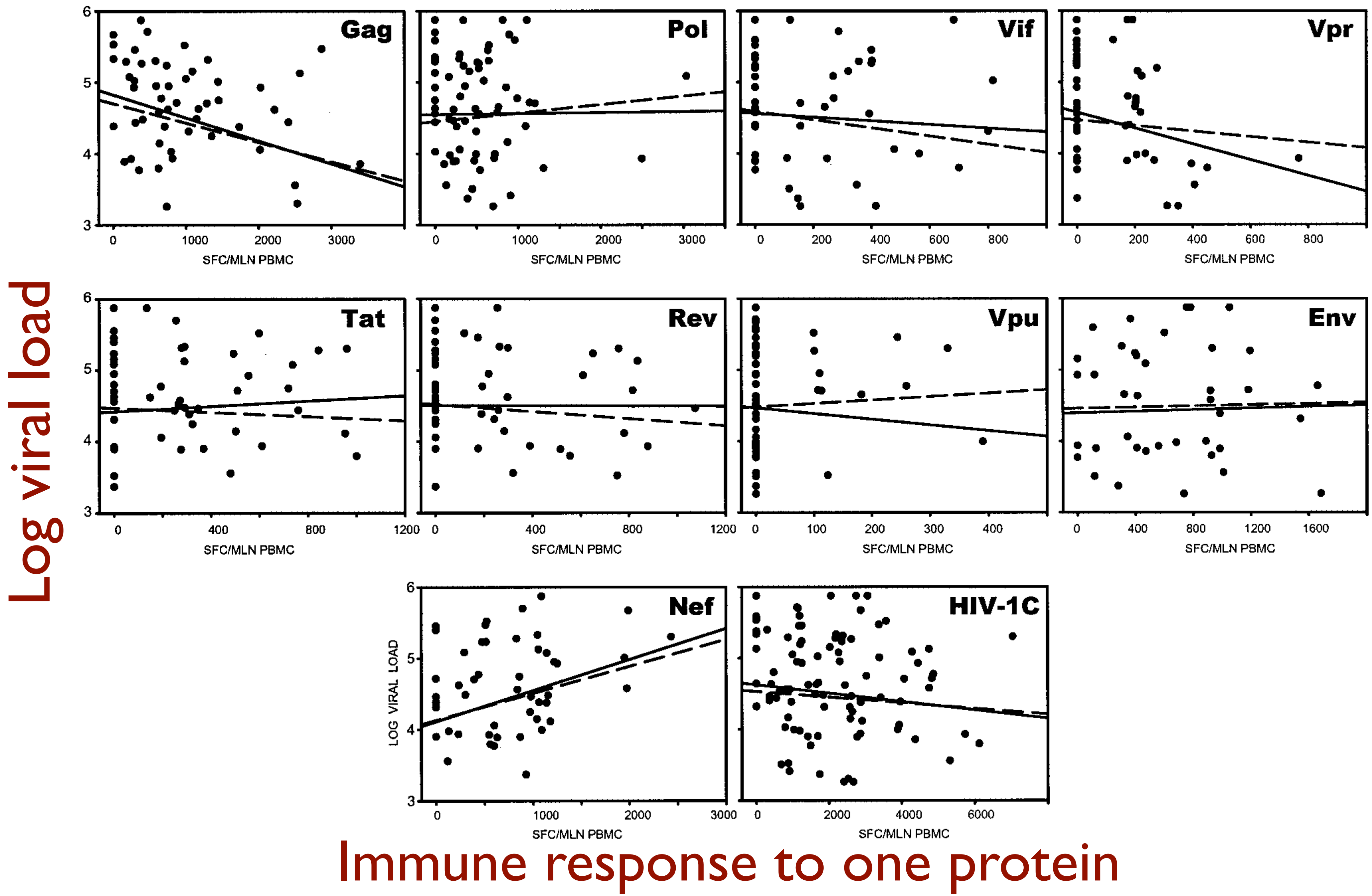


When α>0.01 the immune response hardly changes, but the viral load (*V* or *I*) changes markedly.

Patients having similar immune response can have very different viral loads!

Bifurcation at $\alpha=10^{-4}$: Immune response disappears

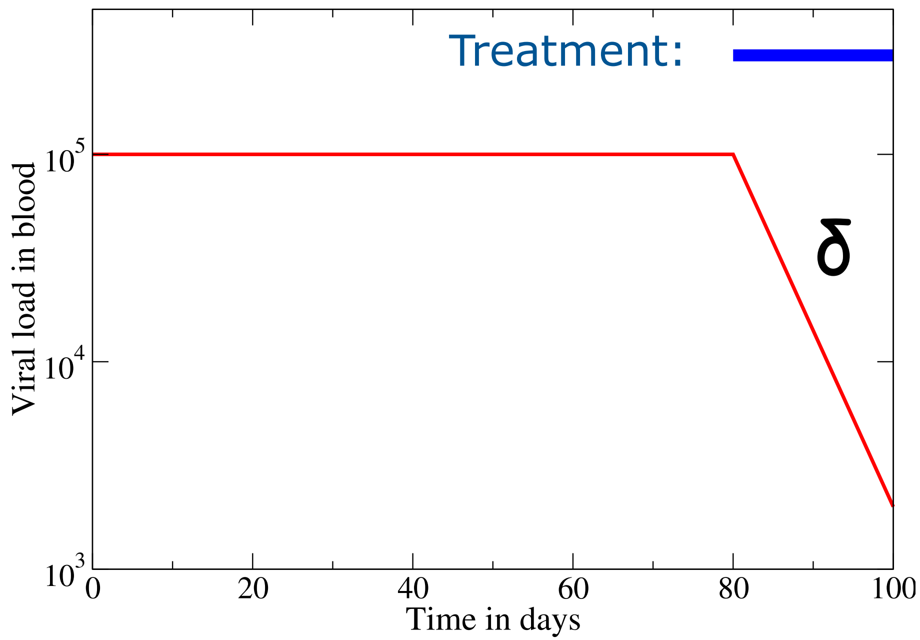
Immune response does not correlate with viral load

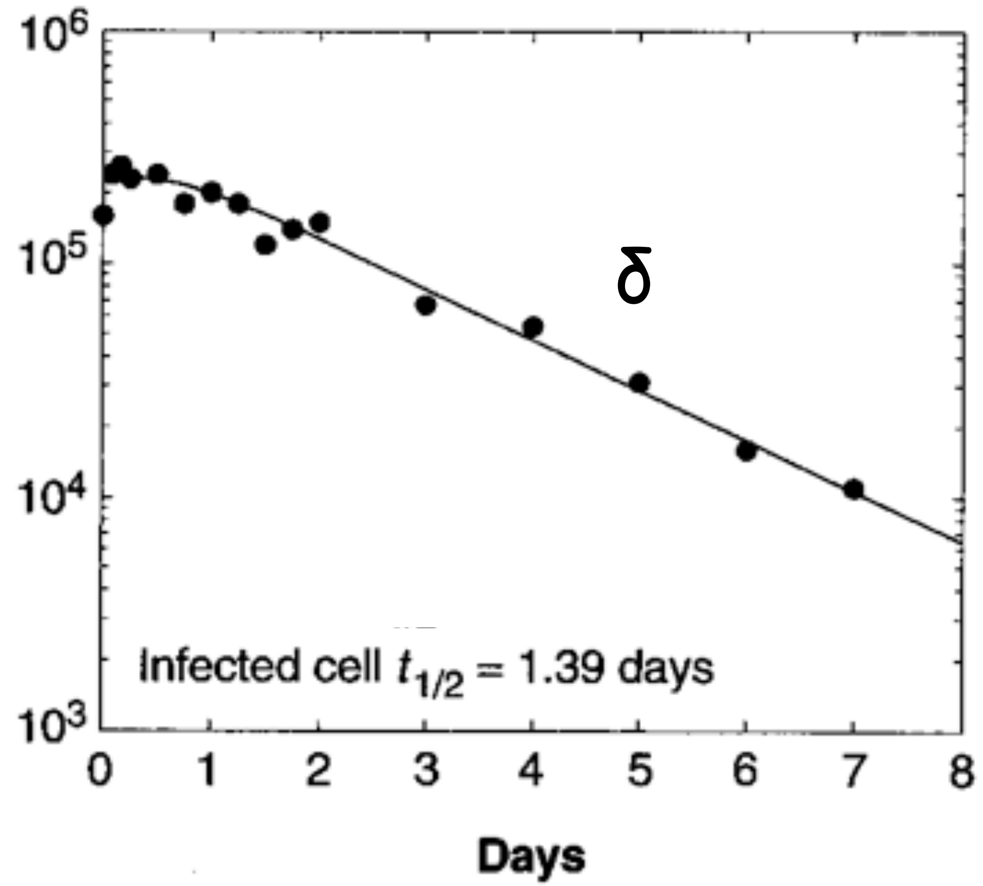


From: Novitsky et al. J Virol. 2003

Perturb the steady state by treatment (ART)

Ho and Perelson, Nature 1995, Science 1998





$$
\begin{aligned}
\frac{\mathrm{d}T}{\mathrm{d}t} &= \sigma - \delta_T T - \cancel{\beta T V} \ , \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \cancel{\beta T V} - \delta_I I - kEI \ , \\
\frac{\mathrm{d}V}{\mathrm{d}t} &= pI - \delta_V V \ , \\
\frac{\mathrm{d}E}{\mathrm{d}t} &= \alpha EI - \delta_E E \ .
\end{aligned}
$$

What can this downslope δ tell us?

Separation of time scales: QSSA

Setting $dV/dt=0$ we obtain $V=(p/\delta_V)I$,
i.e., V becomes proportional to I:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = \sigma - \delta_T T - \beta' T I \ ,$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta' T I - \delta_I I - k E I \ ,$$

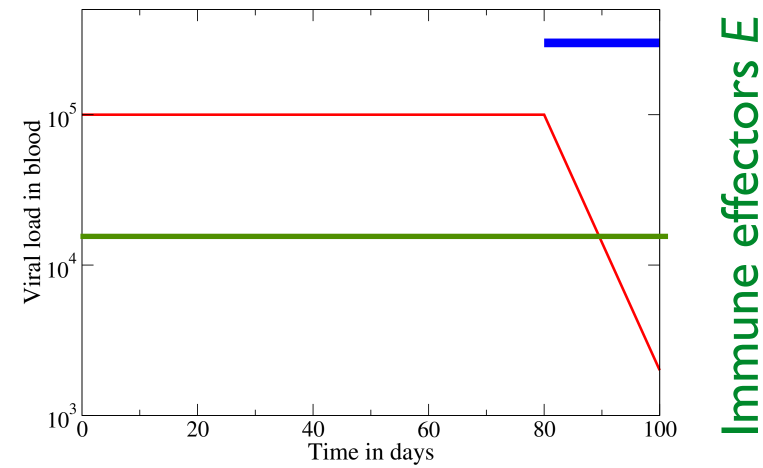
$$\frac{\mathrm{d}E}{\mathrm{d}t} = \alpha E I - \delta_E E \ ,$$

where $\beta' = p\beta/\delta_V$

Separation of time scales: *E*=constant

Setting δ = δ$_I$ + *kE* we obtain from

$$\frac{\mathrm{d}T}{\mathrm{d}t} = \sigma - \delta_T T - \beta' T I \ ,$$
$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta' T I - \delta_I I - kEI \ ,$$
$$\frac{\mathrm{d}E}{\mathrm{d}t} = \alpha E I - \delta_E E \ ,$$



$$\frac{\mathrm{d}T}{\mathrm{d}t} = \sigma - \delta_T T - \beta' T I \ , \qquad \frac{\mathrm{d}I}{\mathrm{d}t} = \beta' T I - \delta I$$

which we have seen before and has one steady state:

$$\bar{T} = \frac{\delta}{\beta'} \quad \text{and} \quad \bar{I} = \frac{\sigma}{\delta} - \frac{\delta_T}{\beta'}$$

Use this model to infer viral dynamics from data

Nature 1995

ARTICLES

Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection

David D. Ho, Avidan U. Neumann[*†], Alan S. Perelson[†], Wen Chen, John M. Leonard[‡] & Martin Markowitz

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* Santa Fe Institute, Santa Fe, New Mexico 87501, USA
† Theoretical Division, Los Alamos National Laboratory, Los Alamos, New Mexico 87545, USA
‡ Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, Illinois 60064, USA

Treatment of infected patients with ABT-538, an inhibitor of the protease of human immunodeficiency virus type 1 (HIV-1), causes plasma HIV-1 levels to decrease exponentially (mean half-life, 2.1 ± 0.4 days) and CD4 lymphocyte counts to rise substantially. Minimum estimates of HIV-1 production and clearance and of CD4 lymphocyte turnover indicate that replication of HIV-1 *in vivo* is continuous and highly productive, driving the rapid turnover of CD4 lymphocytes.

This paper changed the field: HIV-1 is not slow at all.
Utterly simple model teaches us a new biology.

$$\frac{\mathrm{d}T}{\mathrm{d}t} = \sigma - \delta_T T - \beta'\cancel{T}I \ , \qquad \frac{\mathrm{d}I}{\mathrm{d}t} = \beta'\cancel{T}I - \delta I$$

Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection

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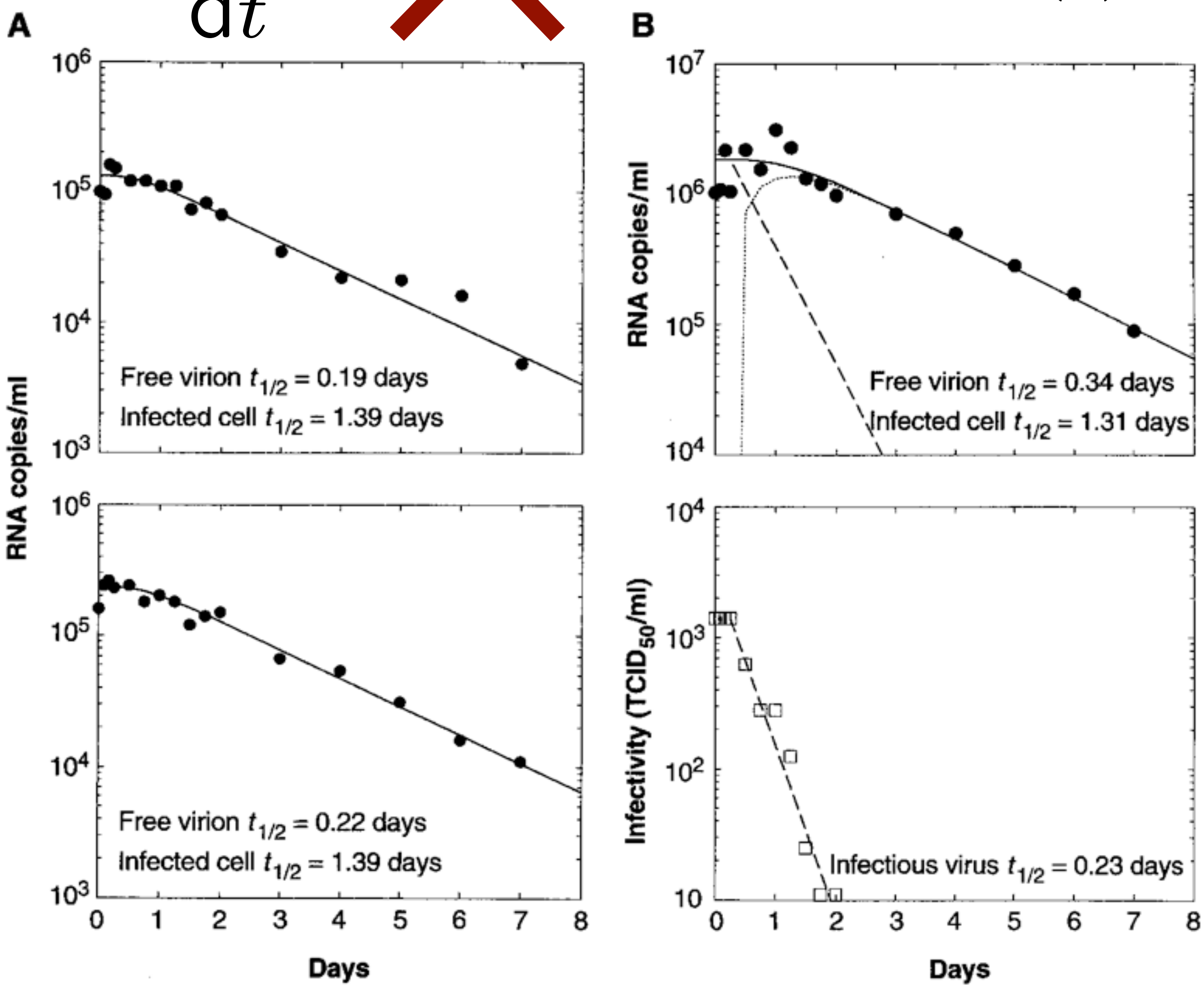
Use model to infer viral dynamics from data

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \cancel{\beta VT}I - \delta I \qquad I(t) = I(0)\mathrm{e}^{-\delta t}$$



Famous papers: HIV is not slow but has a generation time of 1-2 days

Employing the fitness R_0

In this model
$$R_0 = \frac{\beta' \sigma}{\delta_T \delta}$$

and we can rewrite the steady state as:

$$\bar{T} = \frac{\sigma}{\delta_T R_0} = \frac{K}{R_0} \quad \text{and} \quad \bar{I} = \frac{\sigma}{\delta}\left(1 - \frac{1}{R_0}\right)$$

where K is the carrying capacity of the target cells.

If R_0>>1 the steady state of the infected cells should remain approximately σ/δ