Decline in TRECs with age and HIV infection

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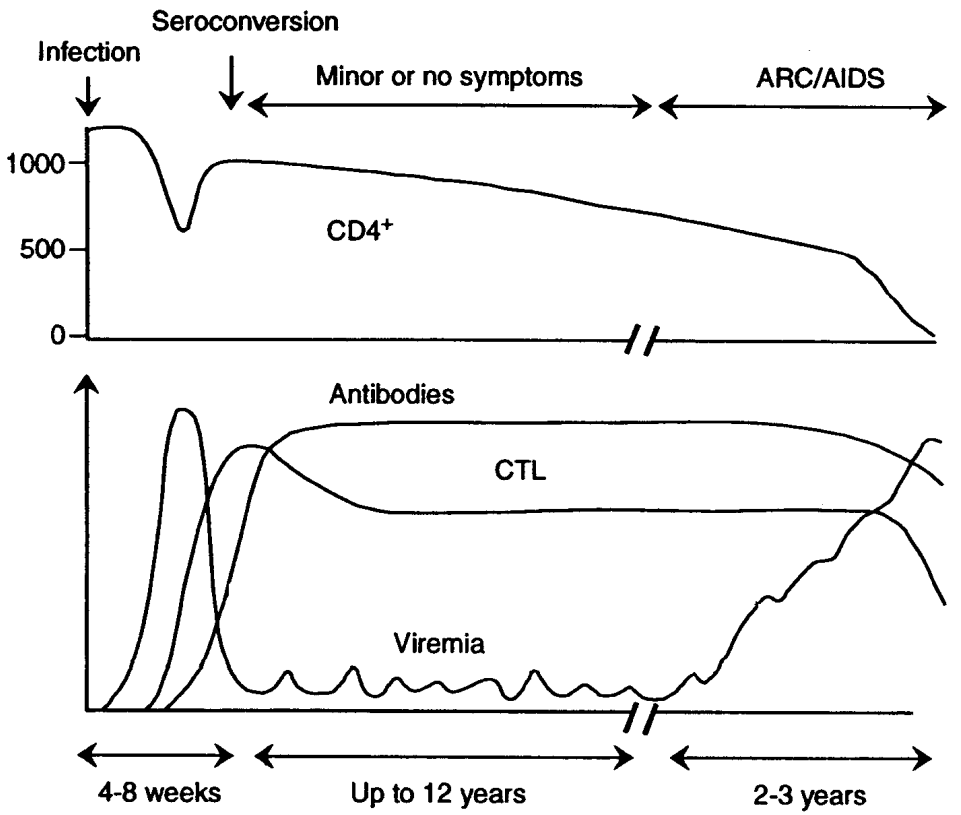
HIV infection: decrease in $CD4^+$ T cell counts

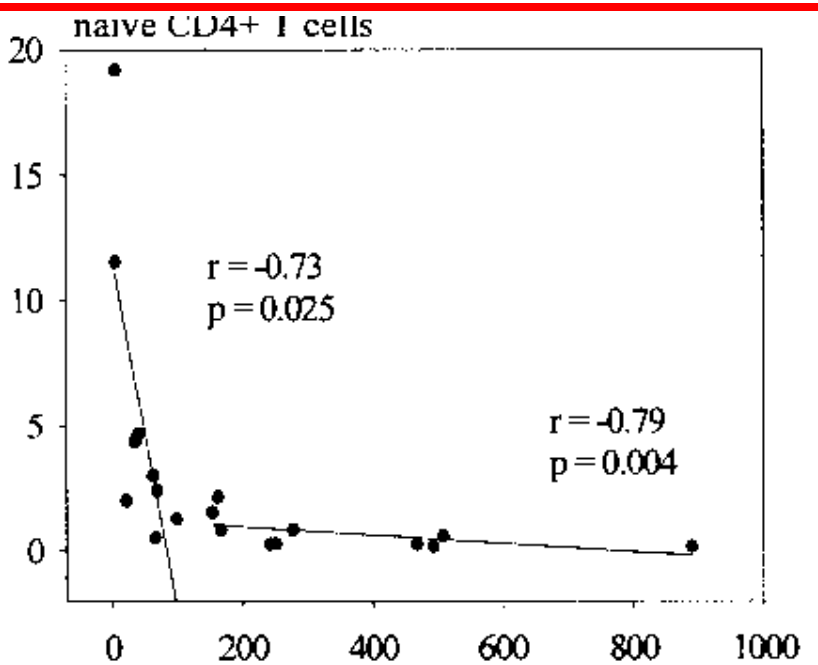


Today: naive T cells

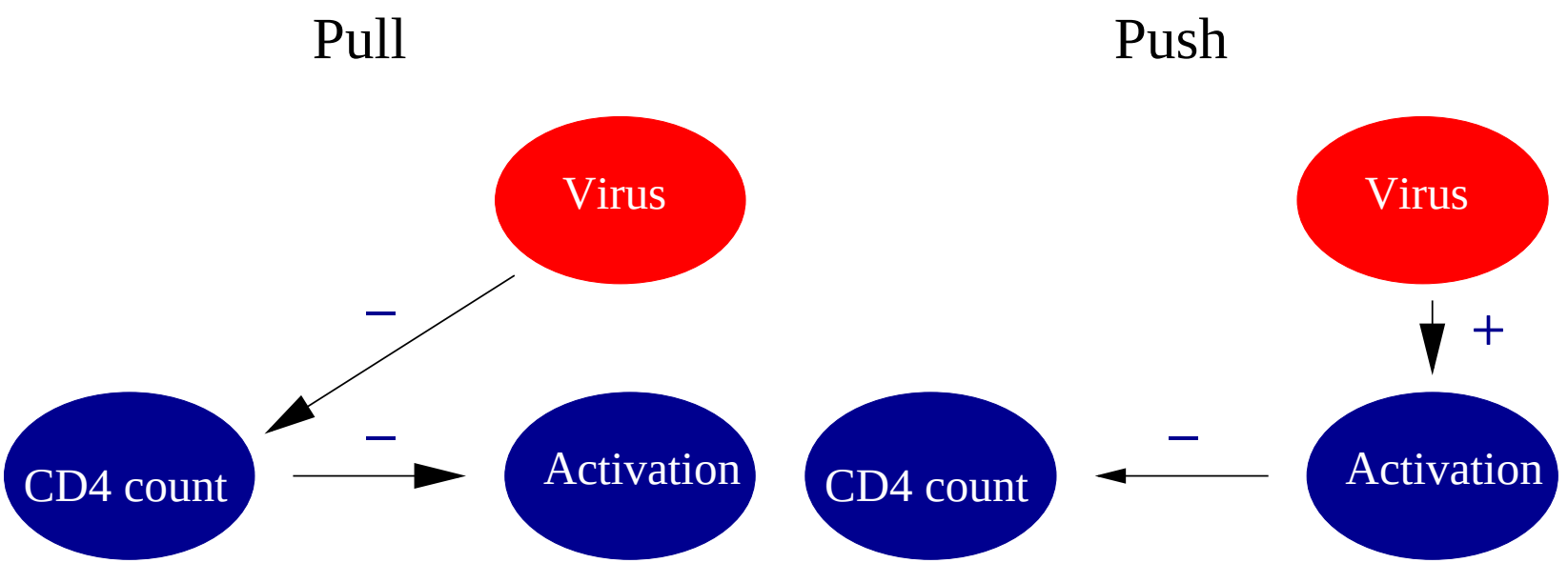
Both $CD4^+$ and $CD8^+$ naive T cell counts decline

Is this due to HIV infection of the thymus?

Hazenberg et al., Blood, 2000

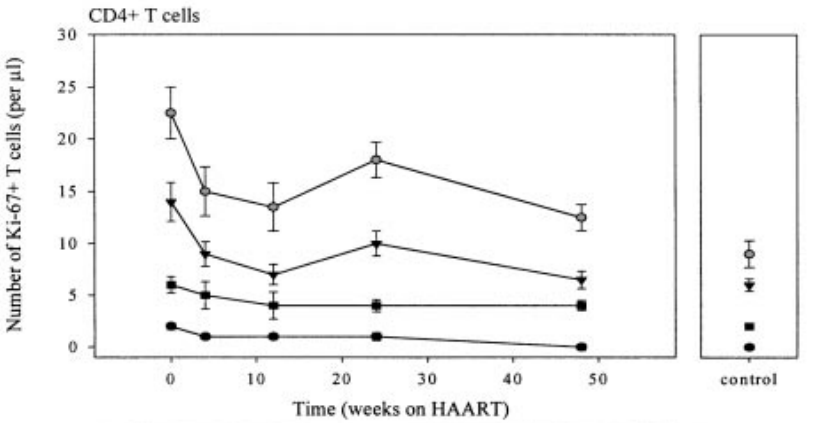


%Ki67 as a function of number of naive $CD4^+$ T cells:
At very low counts large fraction dividing naive T cells
Similar data for naive $CD8^+$ T cells



Activation caused by homeostasis due to low counts?
Or activation (due to virus) responsible for low counts?

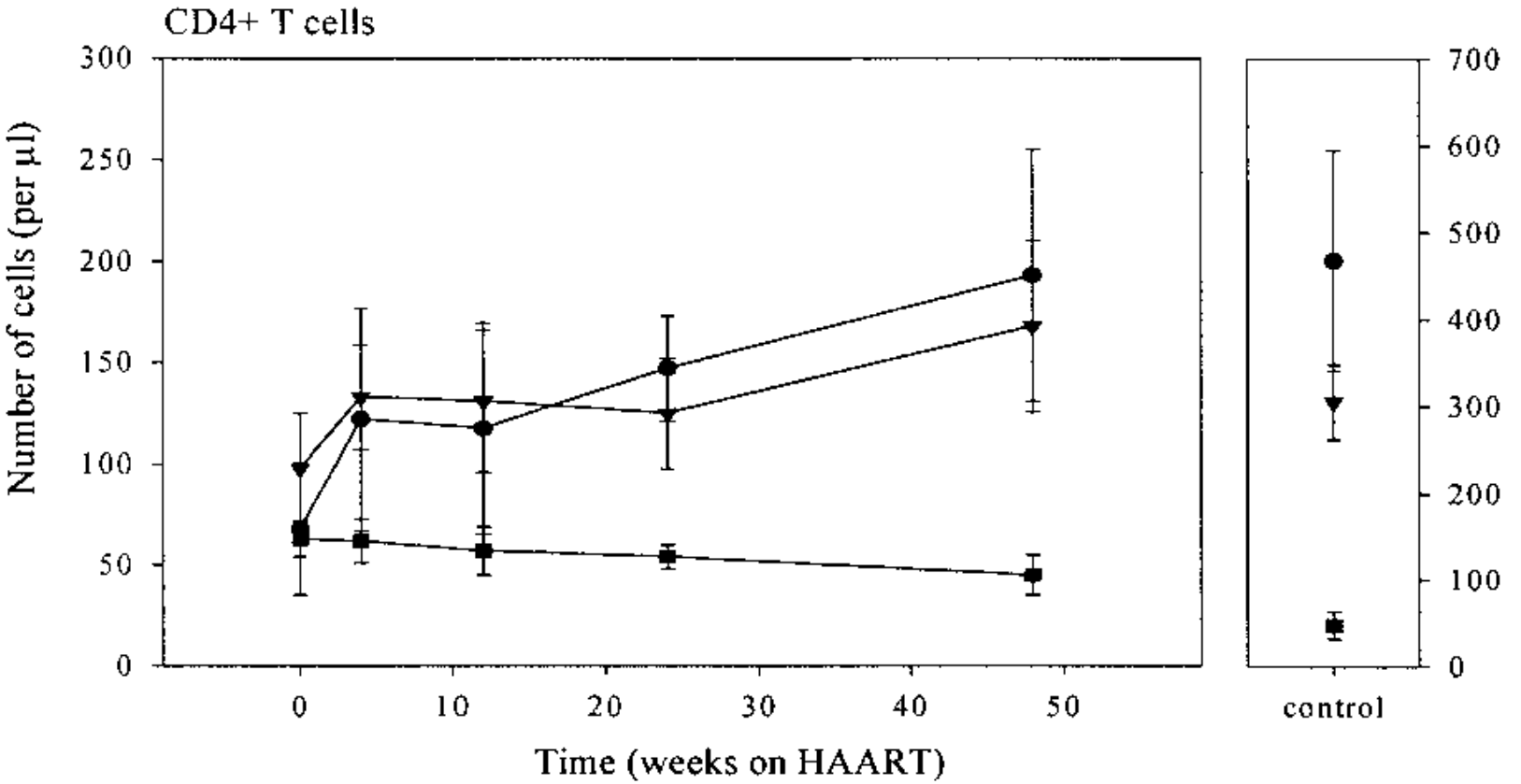
During therapy rapid normalization of division



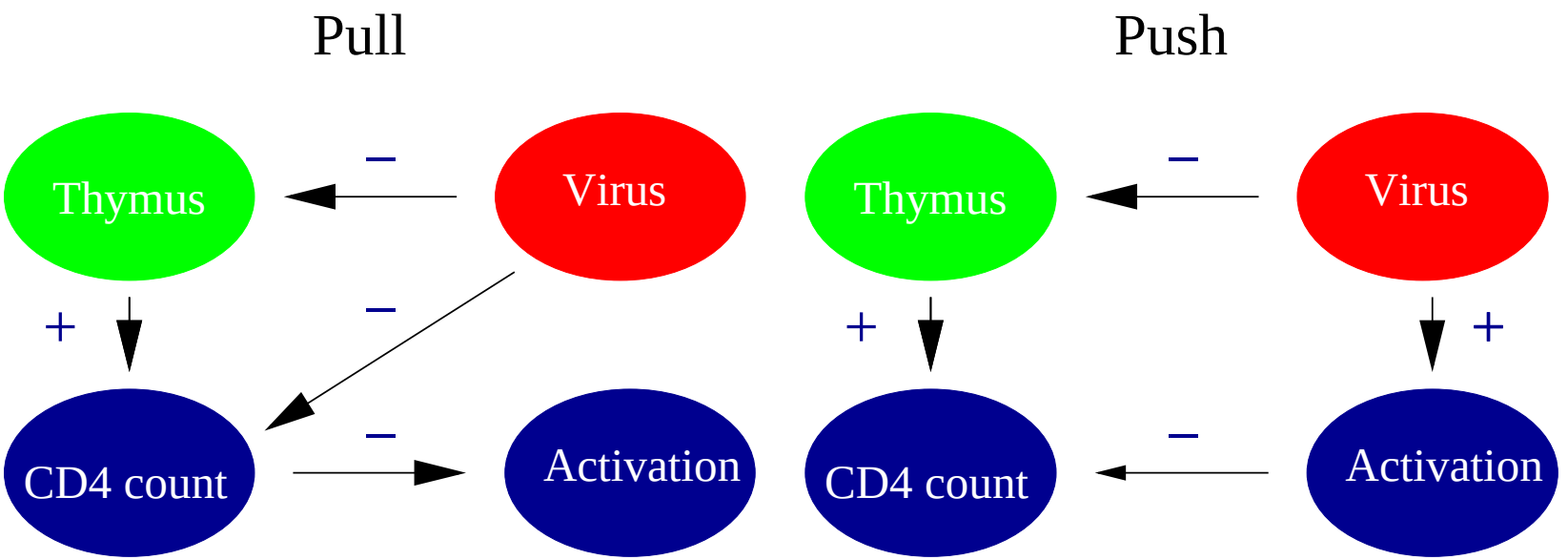
•: naive, triangle: $CD27^+$ memory, squares: $CD27^-$ memory, gray circles: total

From: Hazenberg *et al.*, Blood, 2000

Counts recover much slower

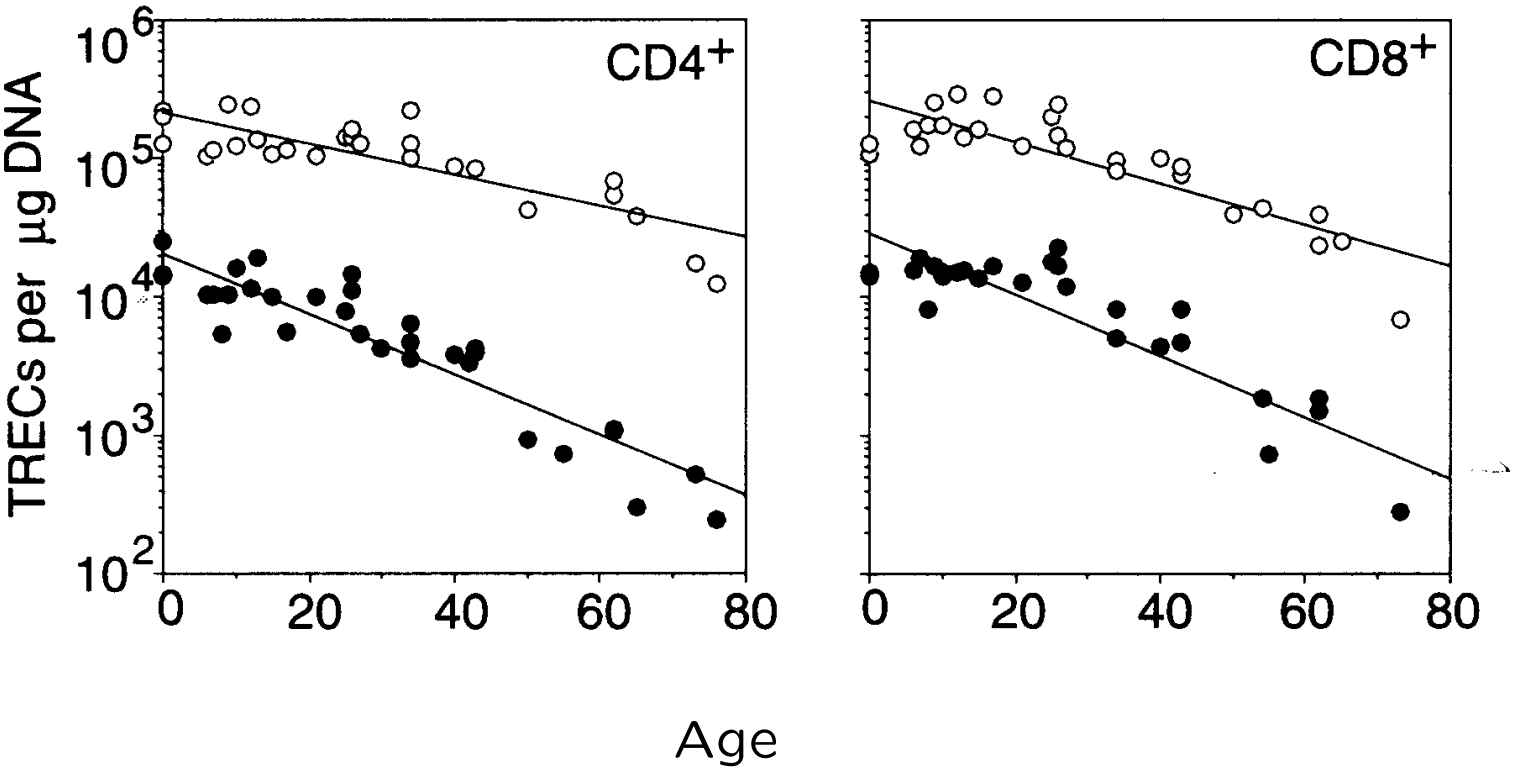


From: Hazenberg *et al.*, Blood, 2000



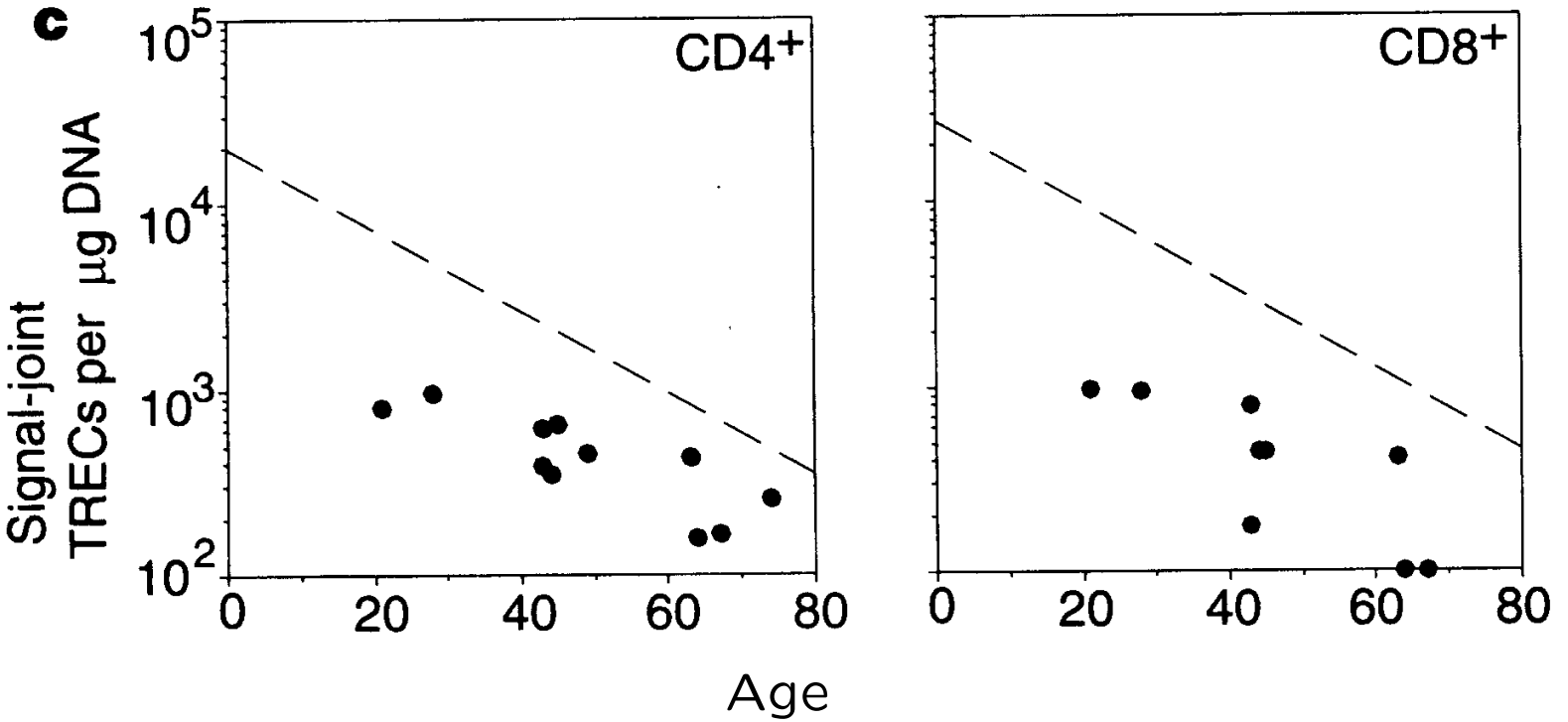
Or is infection of thymus responsible for low naive counts?

TREC content declines one or two logs with age



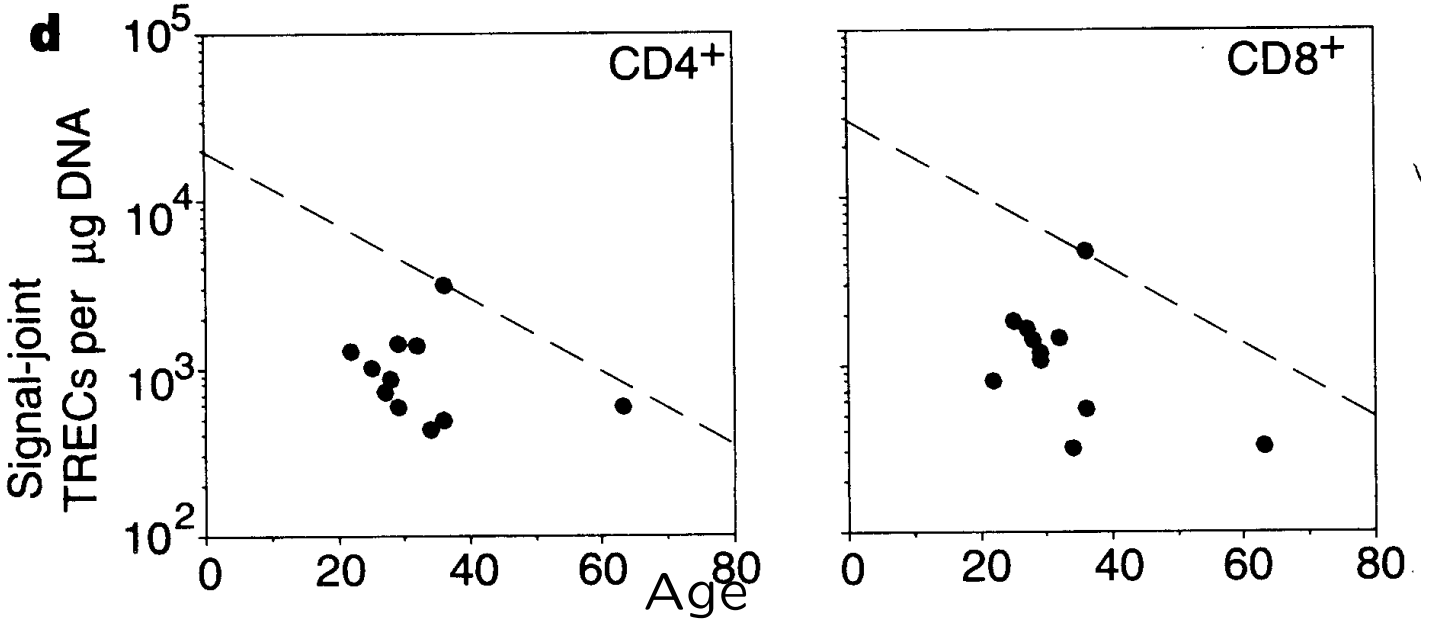
Total CD4 or CD8 (from: Douek *et al.*, Nature, 1998).

Thymectomy affects TREC content



From: Douek *et al.*, Nature, 1998.

TREC content decreased in HIV-1$^+$ patients



→ Evidence for decreased thymic output during HIV infection

TREC content rapidly increases during therapy:

→ Evidence for recovery of thymic output during therapy.

TREC model: Hazenberg et al., NM, 2000

In an attempt to resolve existing confusion on interpreting TREC data we developed a **simple** model:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \sigma(t) + [\rho(N) - \delta(N)]N$$

$$\frac{\mathrm{d}T}{\mathrm{d}t} = c\sigma(t) - [\delta(N) + \delta_I]T$$

for naive T cells N and the total TRECs T.

c represents the TREC content of a RTE.

Note that total TREC content is **not** diluted by division.

Examples of functions

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \sigma(t) + [\rho(N) - \delta(N)]N \ , \qquad \frac{\mathrm{d}T}{\mathrm{d}t} = c\sigma(t) - [\delta(N) + \delta_I]T$$

Thymic production:

$$\sigma(t) = \sigma_0 \mathrm{e}^{-vt}$$

Density dependent renewal:

$$\rho(N) = \frac{\rho_{\mathrm{max}}}{1 + (N/h)^k}$$

Density dependent death:

$$\delta(N) = \delta_{\mathrm{min}} + (\epsilon N)^m$$

Average TREC content per naive T cell

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \sigma(t) + [\rho(N) - \delta(N)]N \ , \qquad \frac{\mathrm{d}T}{\mathrm{d}t} = c\sigma(t) - [\delta(N) + \delta_I]T$$

Define $A \equiv T/N$ and derive that

$$\frac{\mathrm{d}A}{\mathrm{d}t} = \frac{\sigma(t)}{N}\ (c - A) - [\delta_I + \rho(N)]A$$

$$\bar{A} = \frac{c}{1 + [\delta_I + \rho(N)]N/\sigma(t)}$$

- no homeostasis, i.e., $N \propto \sigma(t)$, no decline in $\bar{A}$
- when $\delta_I = \rho(N) = 0$, $\bar{A} = c$
- **increasing division $\rho(N)$ similar to decreasing $\sigma(t)$**

No homeostasis: no decrease in TREC content

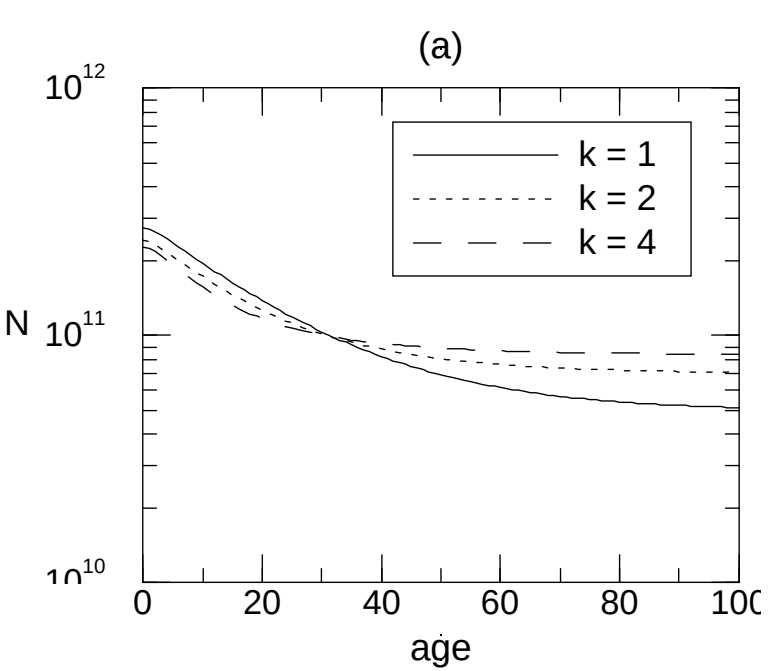
$$\frac{\mathrm{d}N}{\mathrm{d}t} = \sigma(t) + [\rho - \delta]N \ , \qquad \bar{N} = \sigma(t)/(\delta - \rho)$$

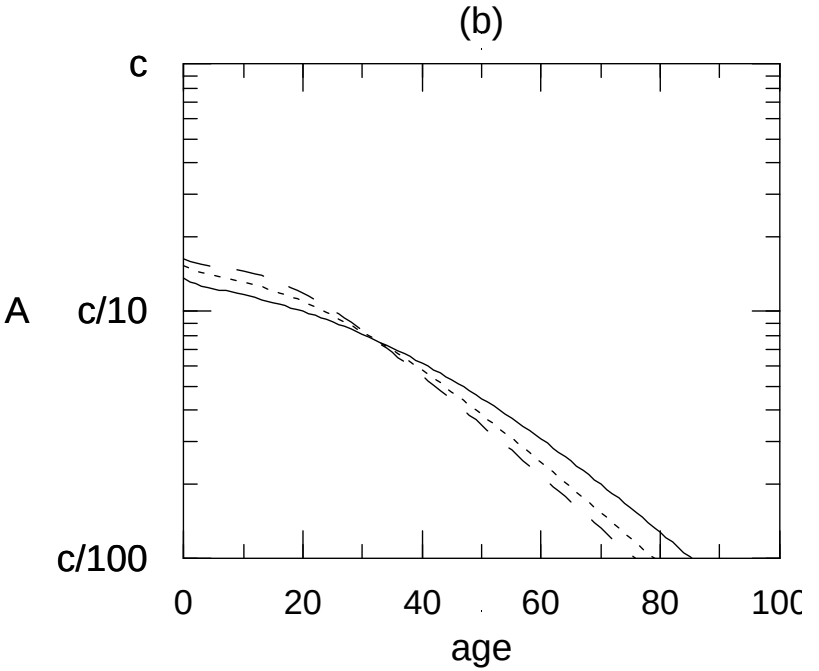
$$\bar{A} = \frac{c}{1 + [\delta_I + \rho]/(\delta - \rho)}$$

In the absence of density dependent renewal or death functions, the average TREC content will go to a steady state depending on renewal, death, and intracellular degradation.

TREC data evidence for existence of homeostasis

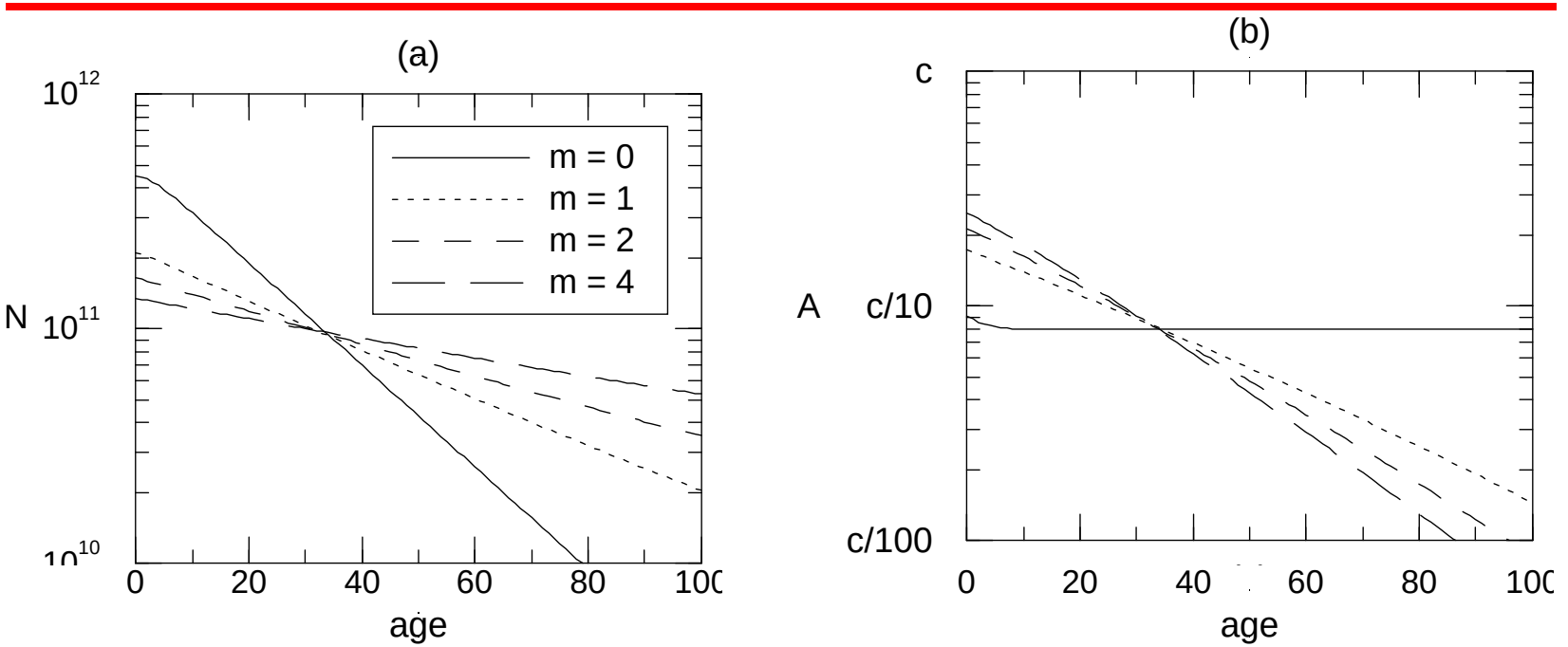
Density dependent renewal





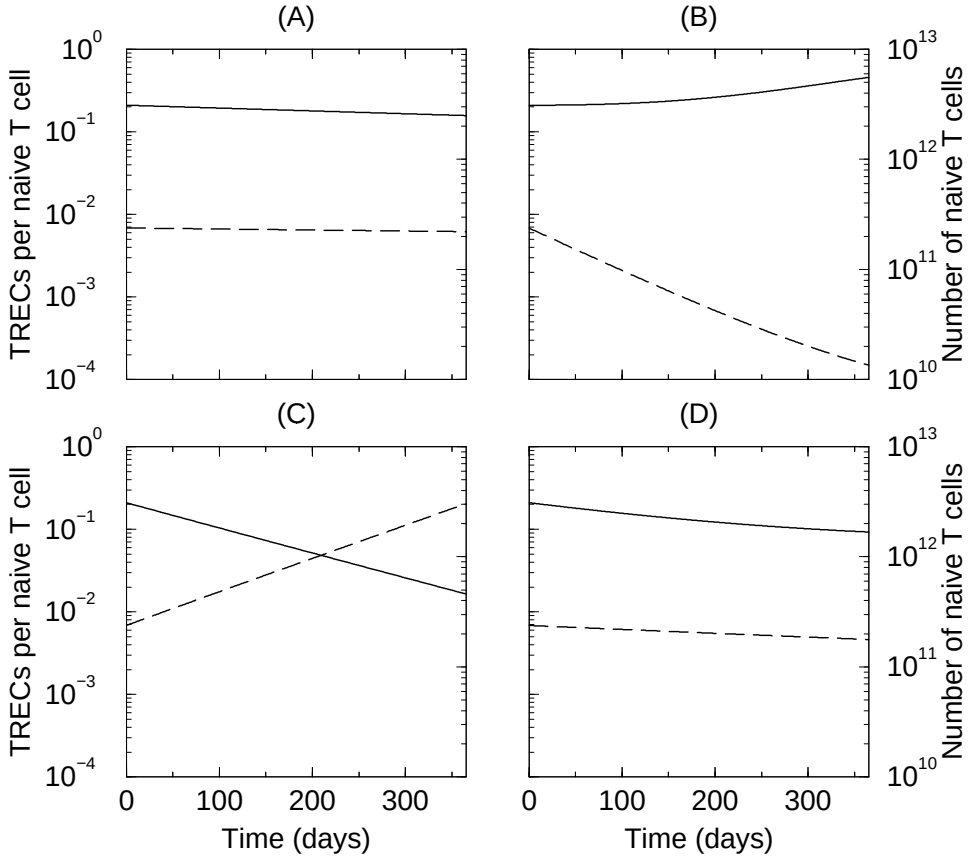
$\delta_I = 0$, δ is fixed

Density dependent death



Needs either a small intracellular decay (δ_i) or low frequency of division (ρ).

HIV infection



TRECs (solid line), Naive T cells (dashed line)
At age 30 we set: (a) $\sigma(t) = 0$, (b) 10-fold increase δ (c) 10-fold increase ρ (d) 5-fold increase of ρ & δ

Conclusion: many factors determine TREC content

- opposite effect of thymus and division

$\longrightarrow$ effect of thymus is slow

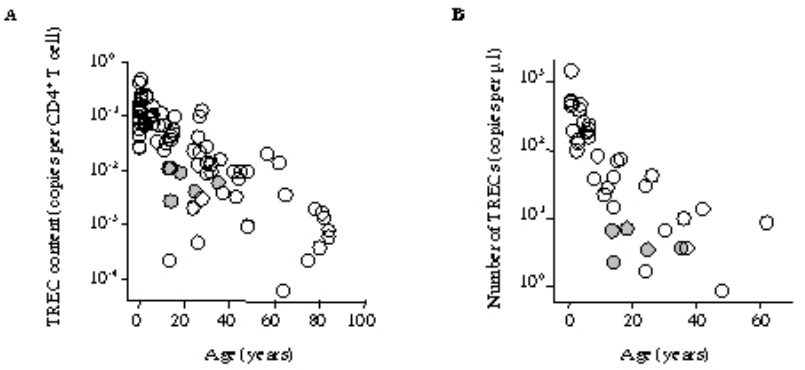
$\longrightarrow$ effect of division is fast

- increasing death increased TREC content

$\longrightarrow$ rapid changes in HIV-patients due to changes in division?

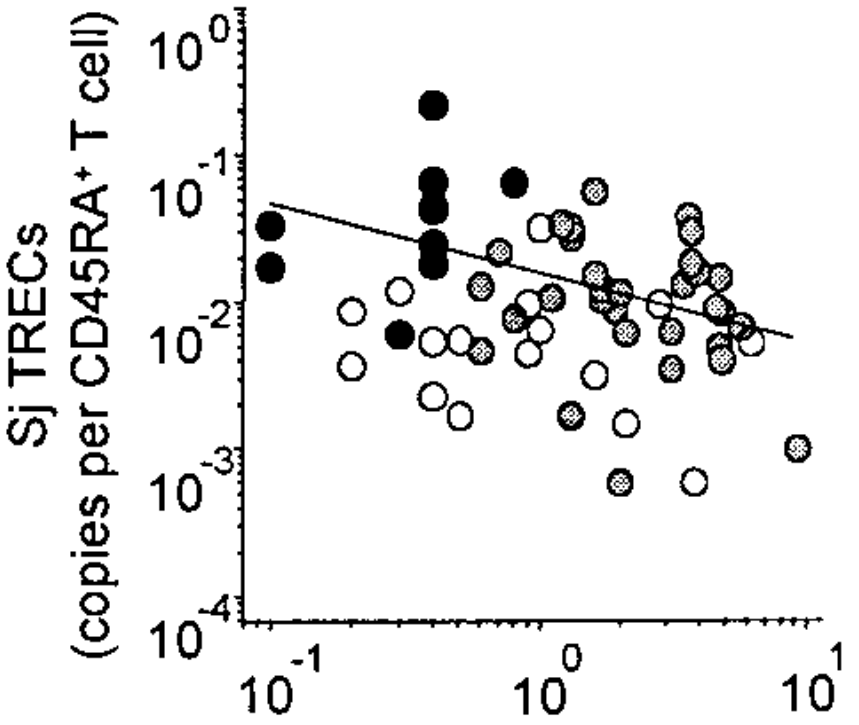
Is this in agreement with data?

Thymectomy



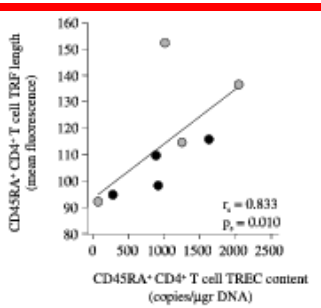
- juvenile macaques: TRECs $\approx$ constant over a year
- **Sempowski, JI, 2001**: thymectomy in Myasthenia gravis patients affects TRECs only after > 3 months
- $\sigma = 0$: nevertheless a decline in TREC content

Division: Hazenberg et al., Nat. Med., 2000



Douek, JI, 2001: similar negative correlation between TREC content and BrdU uptake

Division: Hazenberg et al., submitted



TREC content is reflecting replicative history

black: healthy, gray HIV-1 infected patients

Another confounding factor: TRECs/total T cells

TREC content is typically measured per total $CD4^+$ or total $CD8^+$ T cells, and is sometimes compared to division in whole population.

Because the TREC content of naive T cells is much larger than that of memory cells, whereas their division rate is lower, such TREC measurements are easily confounded by changes in the ratios of naive/memory cells.

Conclusion

TREC content declines with age because thymic output decreases.

TREC content is not a quantitative measurement of thymic output because it is confounded by division and the (possible density dependent) longevity of naive T cells.

Lower TREC content in HIV patients cannot be used as evidence for impairment of thymic production.

Whether or not HIV infection of thymus has an impact on the loss of naive T cells remains an open question.

Not due to equilibrium assumption

Fixed death rate:

$$\frac{\mathrm{d}N(t)}{\mathrm{d}t} = \sigma \mathrm{e}^{-vt} - dN(t) \ , \quad \frac{\mathrm{d}T(t)}{\mathrm{d}t} = c\sigma \mathrm{e}^{-vt} - dT(t) \ ,$$

has the solution:

$$N(t) = \frac{\sigma}{d-v} \left(\mathrm{e}^{-vt} - \mathrm{e}^{-dt}\right) \ , \quad T(t) = cN(t)$$

Hence the TREC content $A \equiv T/N = c$.

TRECs are diluted by division