Viral and CD4+ T-cell dynamics in HIV infection

and... the contribution of mathematical models

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HIV infects CD4+ (T helper) cells

Central role of CD4 T cells

CD4+ T cell decline is a hallmark of HIV-1 infection

Is HIV a latent virus?

Continuous low viral production
or
High viral production and loss
**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

Viral load decreases according to:

\[ V(t) = V(0) \ e^{-St} \]

Mean slope = 0.34/day

Half-life \( t_{1/2} \) of the virus derived from:

\[ 0.5 = e^{-St_{1/2}} \]  
\[ \text{i.e.} \quad t_{1/2} = \ln(2)/S \]

i.e. mean half-life of the virus = 2 days !!!

**From viral latency to clinical latency**

**Why are CD4+ T-cells gradually lost?**
What is the cause of CD4 T cell loss?

- HIV induced cytopathicity
- Telomere shortening due to high T cell turnover
- Interference with thymic output
- Chronic immune activation

HIV infects and can kill CD4+ T cells, but...

- Number of apoptotic cells >> number of infected cells
- Most apoptosis in CD8 T cell population (which cannot be infected)
- Few infected cells undergo apoptosis
- Few apoptotic cells are infected

HIV-infected cells are not in apoptosis and apoptotic cells are not infected

What is the cause of CD4 T cell loss?

- HIV induced cytopathicity
- Telomere shortening due to high T cell turnover
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- Chronic immune activation

Finkel et al. 1995
-red = apoptotic  green = HIV infected
Similar to decline in viral load after start treatment…

Increase in CD4+ T cell numbers after start treatment

High CD4+ T cell turnover in HIV infection!

Ho et al. Nature 1995:
- HAART causes rapid increase in CD4 T cells
- Thus, lots of CD4 T cell destruction pre-HAART
- Rapid CD4 T cell turnover exhausts the immune system

Redistribution of CD4 and CD8 memory cells contributes to the early rise in CD4+ T cells following start of HAART

Pakker et al, Nature Medicine, 1998

In fact CD4 T cell turnover in HIV is only 5-fold increased, not 100-fold

Vrisekoop et al. AIDS 2015
Evidence for immune exhaustion during HIV?

T-cell telomere lengths

Telomeres shorten 50-100 bp with each cell division
Marker of replicative history of T cells
Telomere shortening associated with cell senescence

Naive and memory T-cell telomere lengths: decline with age

Modeling telomere lengths

\[
\frac{dn_t}{dt} = 2p_x n_{t-1} - (p_x + d_x)n_t
\]
\[
\frac{dm_t}{dt} = 2p_md_{t-1} - (p_md + d_md)m_t + \gamma C n_t \]

Translate into mean division index of naive ($\mu_N$) and memory ($\mu_M$) cells
And then to average telomere lengths...
Naive and memory T-cell telomere lengths: decline with age

Are CD4+ T cell telomeres shortening more rapidly in HIV infection? Weng et al. PNAS 1995

What is the cause of CD4 T cell loss?

- HIV induced cytopathicity
- Telomere shortening due to high T cell turnover
- Interference with thymic output
- Chronic immune activation
Interference with thymic output

- HIV infects the thymus of SCID-hu mice (McCune)
- Intrathymic (!) HIV injection leads to loss of thymocytes
- Thymus biopsies from HIV+ children show thymocyte loss

- Effect of thymus loss on CD4 T cell pool unclear, especially in adults…

Formation and detection of T-cell receptor excision circles (TRECs)

Formation and detection of T-cell receptor excision circles (TRECs)

Measuring thymic output:
TRECs formed during V(D)J rearrangement

TRECs as a marker for thymus output?

- Only source is the thymus
- Not copied during cell proliferation

- Typically measured as TRECs per cell (TREC content)
- Note: no measure of current thymus output, because TRECs and naive T cells are long-lived
TREC decline with age has been interpreted to reflect thymus decline

Mathematical model for TREC dynamics

T cells:
\[ \frac{dN}{dt} = \sigma(t) + pN - dN \]

TRECs:

TREC content:

Adapted from Hazenberg et al. 2000

TREC decline in HIV infection

Due to HIV-induced thymic impairment?

How is the average TREC content affected when thymic output declines?

Because not only TRECs but also naive T-cell numbers decline

Hazenberg et al. 2000; Dutih et al. 2003
What explains TREC decline with age?

If naive T cells divide more when thymic output declines…

Proliferation strongly influences TREC contents!

Thymic output per se does not…

Chronic activation of CD4 (and CD8 T cells) during HIV infection

What is the cause of CD4 T cell loss?

• HIV induced cytopathicity
• Telomere shortening due to high T cell turnover
• Interference with thymic output
• Chronic immune activation
Is the immune system trying to compensate for the loss of CD4 T cells?

Naive T cell division seems density dependent...

Increased T cell division in HIV-1 infection is not a homeostatic response to T cell depletion, but reflects persistent activation of the immune system

Immune activation correlates with HIV progression
Even better predictor than viral load

NB: CD8 T cell proliferation rates during HIV increased while CD8 T cell numbers are not reduced
Even high levels of immune activation pre-seroconversion predict fast progression

Hazenberg et al. 2003

CD70 low

CD70 high

(Silvestri et al. 2003)

Rhesus macaque:
High viral load, immune activation, AIDS

Chimpanzee:
Low viral load, no disease

Sooty Mangabey:
High viral load, no immune activation, no disease

What is the cause of CD4 T cell loss?

• HIV induced cytopathicity
• T cell exhaustion
• Interference with thymic output
• Chronic immune activation

It’s even causing e.g. cardiovascular problems in HIV patients

Little evidence

CD4 and CD8 T-cell proliferation in sooty mangabeys versus rhesus macaques

Immune activation in HIV

What is causing it?

I. Severe depletion of CD4+ T cells from lamina propria in humans

- Early in HIV infection independent of peripheral blood CD4 T cell depletion
- Persists during chronic infection
- Results in breaching of the gut barrier and displacement of bacterial products such as LPS to the blood
- LPS concentrations in the circulation of HIV patients correlate strongly with T-cell activation levels

“Theoretical Immunologists are people who make oversimplified models and do not even feel embarrassed”

Lee Segel

“Mathematics is no more – but no less – than a way of thinking clearly”

Martin Nowak

Robert May