Viral and CD4+ T-cell dynamics in HIV infection

and... the contribution of mathematical models

Julia Drylewicz
Dpt. Immunology
University Medical Center Utrecht

Acquired immune deficiency syndrome (AIDS)

In 1981 young men in LA, NY and SF presented with:
• Opportunistic infections by intracellular pathogens
  - viruses, fungi, mycobacteria
• Opportunistic tumors:
  - Kaposi sarcoma, EBV-related Non-Hodgkin’s lymphoma

Due to T cell immune deficiency

The AIDS-virus: HIV human immunodeficiency virus

1983 HIV discovered by Montagnier Gallo et al: HIV causes AIDS

HIV infects CD4+ T helper cells

• Central role of CD4 T cells

• HIV infects CD4+ T cells, macrophages and dendritic cells
CD4+ T cell decline is a hallmark of HIV-1 infection

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


Nature 1995

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:

\[ 0.5 = e^{-St_{1/2}} \]

i.e. \( t_{1/2} = \ln(2)/S \)

i.e. mean half-life of the virus = 2 days !!!
From viral latency to clinical latency

- Continuous low viral production
- High viral production and loss

Why are CD4+ T-cells gradually lost?

- HIV induced cytopathicity
- T cell exhaustion 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
- Few apoptotic cells are infected
- Most apoptosis in CD8 T cell population
  (which cannot be infected)
- Few infected cells undergo apoptosis
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
- T cell exhaustion due to high T cell turnover
- Interference with thymic output
- Chronic immune activation

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

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

Modeling telomere lengths

\[
\frac{dN_0}{dt} = \sigma(a) - (p + d)N_0, \\
\frac{dN_n}{dt} = 2pN_{n-1} - (p + d)N_n, \quad n = 1, 2, \ldots, \infty,
\]

where \( n \) is the division number

\[
L(t) = \sum_n (L_0 - nL_{\Delta}) N_n(t) N(t) = L_0 - L_{\Delta} \sum_n nN_n(t) N(t)
\]

\( L_0 \) is the average telomere length of RTE \( N_0 \) and \( L_{\Delta} \) is the telomere loss per division.

Taking the derivative gives:

\[
\frac{dL}{dt} = -2pL_{\Delta} + (L_0 - L) \frac{\sigma(a)}{N}.
\]
For memory cells:

\[
\frac{dM_n}{dt} = 2\rho M_{n-1} - (\rho + d_M) M_n + \alpha N \lambda N - K
\]

\(a_n\) is the activation rate of naive T cells and \(c_n\) their clonal expansion and \(K\) the average loss during clonal expansion.

The mean division index is:

\[
\frac{dM}{dt} = 2\rho - \alpha N \lambda N \left(\mu - \mu_N - K\right)
\]

See the exercise today

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
- T cell exhaustion 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)

- Only source is the thymus
- 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:

TRECs:

TREC content:

TREC decline in HIV infection

Due to HIV-induced thymic impairment?

Mathematical model for TREC dynamics

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

Because not only TRECs but also naive T-cell numbers decline
If naive T-cell numbers are homeostatically regulated, TREC contents do decline.

Homeostasis by increasing T-cell division or survival rates increases number of cells but not TREC's.

Proliferation strongly influences TREC contents!

\[ A = c \left( 1 - \frac{p}{d} \right) \]

TREC decline in HIV infection:

- Douek et al. 1998: Due to decreased thymic output?
- Hazenberg et al. 2000: Increased T-cell proliferation!

What is the cause of CD4 T cell loss?

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

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

Hazenberg et al, Blood 2000
Is the immune system trying to compensate for the loss of CD4 T cells?

Hazenberg et al, Blood 2000

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

Hazenberg et al, Blood 2000

Cause
CD4 T cell loss
Effect
Increased CD4 T cell proliferation

Effect
Increased CD4 T cell proliferation
Cause
CD4 T cell loss

...but rapidly declines during HAART while CD4 T cell counts are still low

NB: CD8 T cell proliferation rates during HIV increased while CD8 T cell numbers are not reduced

Immune activation correlates with HIV progression

Even better predictor than viral load

Hazenberg et al. 2003
Even high levels of immune activation pre-seroconversion predict fast progression

![Graph showing CD70 low and CD70 high over time](image)

Hazenberg et al. 2003

Chronic immune activation in HIV: what is causing it?

‘Getting to the guts of HIV pathogenesis…’

First conclusive evidence for involvement of intestinal CD4+ T cells was obtained in SIV-infected macaques.

SIV infection immediately eliminates activated CD4 memory T cells from the gastro-intestinal tract!


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

![Images showing the effects of HIV on CD4+ T cells](image)

Brenchley et al. JEM 2004

Rhesus macaque:
High viral load, immune activation, AIDS

Chimpanzee:
Low viral load, no disease

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

(Silvestri et al. 2003)
Severe depletion of CD4 T cells from gut

- Early in HIV infection independent of peripheral blood CD4 T cell depletion
- Persists during chronic infection and during treatment
- 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


What is the cause of CD4 T cell loss?

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

Little evidence

Central role for chronic immune activation

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