Viral and CD4+ T-cell dynamics in HIV infection

and... the contribution of mathematical models

Jose Borghans
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 Luc Montagnier and Françoise Barré-Sinoussi

Robert 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
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

HIV load after protease inhibitor ABT-538
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:
\[ 0.5 = e^{-S t_{1/2}} \quad i.e. \quad t_{1/2} = \ln(2)/S \]

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

- Continuous low viral production
- High viral production and loss

![Graph showing CD4+ T Lymphocyte Count and HIV RNA Copies per ml Plasma over weeks and years. Key stages include Primary Infection, Acute HIV syndrome, Wide dissemination of virus, Seeding of lymphoid organs, Clinical Latency, Constitutional Symptoms, Opportunistic Diseases, and Death.]
Why are CD4+ T-cells gradually lost?
What is the cause of CD4 T cell loss?

- HIV induced cytopathicicy
- 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
- 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

red = apoptotic  green = HIV infected

Finkel et al. 1995
What is the cause of CD4 T cell loss?

- HIV induced cytopathicility
- 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

T-cell production

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

See the exercise today

Weng et al. PNAS 1995
Modeling telomere lengths

Naive T cells

Memory T cells
\[
\frac{dn_i}{dt} = 2p_N n_{i-1} - (p_N + d_N) n_i
\]

\[
\frac{dm_i}{dt} = 2p_M m_{i-1} - (p_M + d_M) m_i + \gamma C n_{i-K}
\]

Translate into mean division index of naive ($\mu_N$) and memory ($\mu_M$) cells

And then to average telomere lengths…
\[
\frac{dn_i}{dt} = 2p_n n_{i-1} - (p_n + d_n) n_i
\]

mean division index:

\[
\frac{d\mu_N}{dt} = 2p_N
\]

Telomeric length:

\[
T_N = T_{n0} - L \mu_N \\
T_M = T_{m0} - L \mu_M
\]

\[
\frac{d\mu_M}{dt} = 2p_M - \gamma C \frac{N}{M} (\mu_M - \mu_N - K)
\]

\[
\frac{dm_i}{dt} = 2p_M m_{i-1} - (p_M + d_M) m_i + \gamma C n_{i-K}
\]

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

Are CD4+ T cell telomeres shortening more rapidly in HIV infection?

See the exercise today

Weng et al. PNAS 1995
Shortening of telomeres in CD8 from HIV-infected persons

CD4 T cells

CD8 T cells

Wolthers et al. Science 1996
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…
Measuring thymic output:
TRECs formed during V(D)J rearrangement

Kuby Immunology 6th edition
Formation and detection of T-cell receptor excision circles (TRECs)

Rodewald Nature 1998
TRECs as a marker for thymus output?

- 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.


Rodewald Nature 1998

Child

Adult
TREC decline in HIV infection

Thymectomized patients

HIV patients (early stage)

Due to HIV-induced thymic impairment?

Douek et al. 1998
Mathematical model for TREC dynamics

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

TRECs:
\[ \frac{dT}{dt} = c\sigma(t) - dT \]

TREC content:
\[ \frac{dA}{dt} = \frac{\sigma(t)(c - A)}{N} - pA \]

Adapted from Hazenberg et al. 2000
How is the average TREC content affected when thymic output declines?

Because not only TREC counts but also naive T-cell numbers decline

Hazenberg et al. 2000, Dutilh 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…
TREC decline in HIV infection:

Douek et al. 1998 Due to decreased thymic output?

Hazenberg et al. 2000 Increased T-cell proliferation!

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

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

Naive T cell division seems density dependent...

Hazenberg et al, Blood 2000
...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
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
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.
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)
CD4 and CD8 T-cell proliferation in sooty mangabeys *versus* rhesus macaques

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
Immune activation in HIV

What is causing it?
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!

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

Brenchley et al. JEM 2004

Stained for CD4
Severe depletion of CD4 T cells from gut

- 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

But… bacterial translocation persists during treatment (when immune activation subsides)

Cassol et al. JID 2010
Source of immune activation II: Innate response to TLR7 stimulation by HIV

Innate response much lower in SM; Due to polymorphism in TLR7/9 signaling?

Mandl et al. Nat Med 2008
“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
T-cell receptor excision circle and T-cell dynamics after allogeneic stem cell transplantation are related to clinical events

Mette D. Hazenberg, Sigrid A. Otto, Elmar S. de Pauw, Helene Roelofs, Willem E. Fibbe, Dörte Hamann, and Frank Miedema

It is generally believed that homeostatic responses regulate T-cell recovery after peripheral stem cell transplantation (PSCT). We studied in detail immune recovery in relation to T-cell depletion and clinical events in a group of adult patients who underwent PSCT because of hematologic malignancies. Initially, significantly increased proportions of dividing naive, memory, and effector CD4+ and CD8+ T cells were found that readily declined, despite still very low numbers of CD4+ and CD8+ T cells. After PSCT, increased T-cell division rates reflected immune activation because they were associated with episodes of infectious disease and graft-versus-host disease (GVHD). T-cell receptor excision circles (TRECs) were measured to monitor thymic output of naive T cells. Mean TREC content normalized rapidly after PSCT, long before naive T-cell numbers had significantly recovered. This is compatible with the continuous thymic production of TREC+ naive T cells and does not reflect homeostatic increases of thymic output. TREC content was decreased in patients with GVHD and infectious complications, which may be explained by the dilution of TRECs resulting from increased proliferation. Combining TREC and Ki67 analysis with repopulation kinetics led to the novel insight that recovery of TREC content and increased T-cell division during immune reconstitution after transplantation are related to clinical events rather than to homeostatic adaptation to T-cell depletion. (Blood. 2002;99:3440-3453)