Virus dynamics

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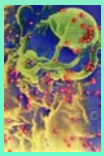
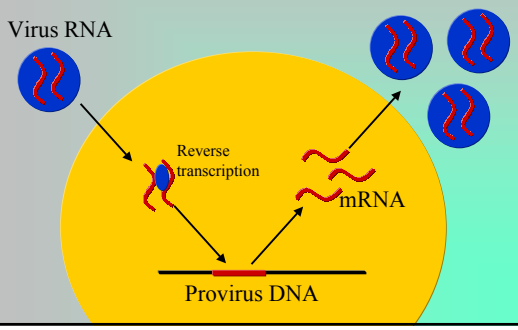


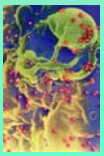
Collaborators

- Robert May (Oxford)
- Sebastian Bonhoeffer (Zurich)
- Dominik Wodarz (Seattle)
- Marc Lipsitch (Harvard)
- Alun Lloyd (Princeton)
- George Shaw (Birmingham, Alabama)
- Andrew McMichael (Oxford)
- Charles Bangham (London)
- Jeff Lifson (Washington)

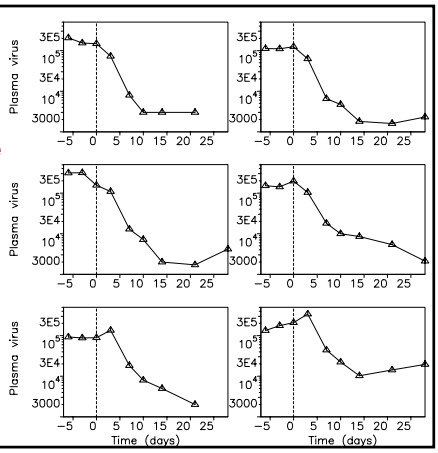
HIV is a retrovirus



How fast does HIV reproduce in vivo ?

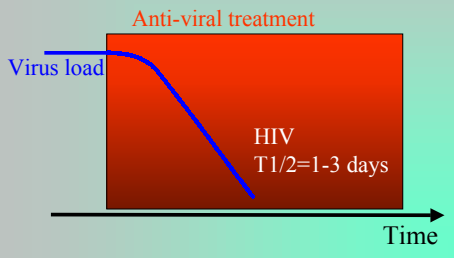


1994:
protease inhibitors
and
quantitative PCR

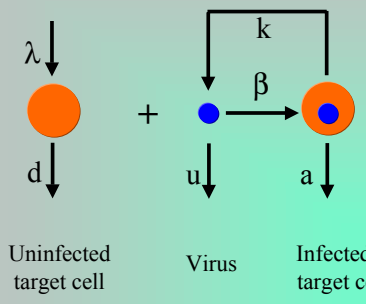


George Shaw

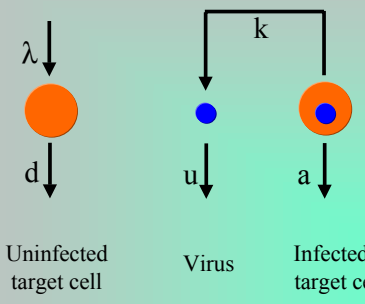
Treatment leads to a rapid decline in virus load



Virus dynamics



Virus dynamics with treatment



The basic model of virus dynamics

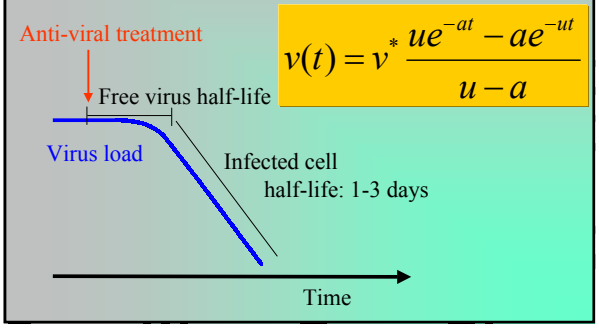
Uninfected cells	$\dot{x} = \lambda - dx - \beta xv$
Infected cells	$\dot{y} = \beta xv - ay$
Free virus	$\dot{v} = ky - uv$

Micro-epidemiology within infected host

Anti-viral treatment

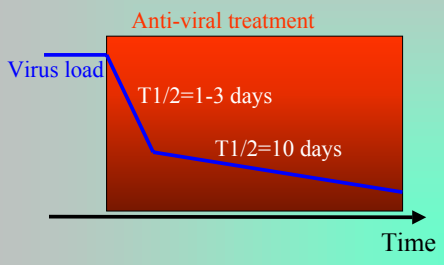
Uninfected cells	$\dot{x} = \lambda - dx - \beta xv$
Infected cells	$\dot{y} = \beta xv - ay$
Free virus	$\dot{v} = ky - uv$

Virus declines as



$$v(t) = v^* \frac{ue^{-at} - ae^{-ut}}{u - a}$$

Latently infected cells



An extended model of virus dynamics

Uninfected cells

Productively infected cells

Latently infected cell

Cells with defective provirus

Free virus

$$\dot{x} = \lambda - dx - \beta xv$$

$$\dot{y}_1 = q_1 \beta xv - a_1 y_1 + \alpha y_2$$

$$\dot{y}_2 = q_2 \beta xv - a_2 y_2 - \alpha y_2$$

$$\dot{y}_3 = q_3 \beta xv - a_3 y_3$$

$$\dot{v} = k y_1 - uv$$

HIV-1 half-lives

- Productively infected cells : 1-3 days
- Latently infected cells : 10 days
- Defective provirus : 100 days
- Free virus : hours

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HIV eradication requires 1-3 years of effective therapy.

HIV-1 half-lives

- Productively infected cells : 1-3 days
- Latently infected cells : 10-100 days
- Defective provirus : 100 days
- Free virus : hours

HIV eradication requires >10 years of effective therapy and is most likely impossible.

What kills productively infected cells?

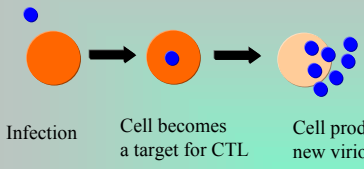
- **viral cytopathicity**
- **CTL responses**

Note that all patients have very similar decay slopes corresponding to half-lifes of 1-3 days.

Comparing HIV and HBV dynamics:

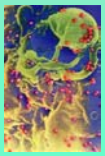
- Half-life of productively infected cells:
- HIV: 1-3 days
- HBV: 10-100 days

Viral cytopathicity leads to a constant half-life despite different CTL activity



The experiment is biased toward those cells that produce plasma virus. CTL can greatly reduce virus production without affecting the half-life.

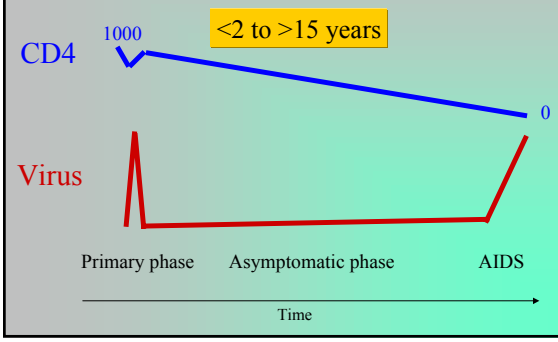
What is the mechanism of HIV disease progression?



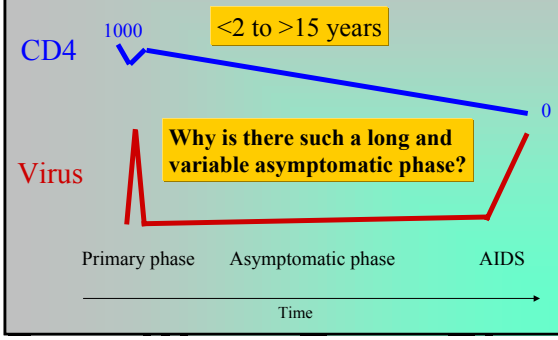
Evolution of virulence

- The closest relatives of HIV-1 and HIV-2 are SIVs.
- All SIVs appear to be apathogenic in their natural hosts.
- SIV can be transferred to other species, where it induces AIDS.

HIV-1: clinical profile



HIV-1: clinical profile

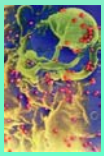


A mechanism of disease progression

- .. has to explain why the steady state of virus dynamics (with a timescale of days) shifts over many years.
- 2 possibilities:
  - the immune system changes
  - the virus changes

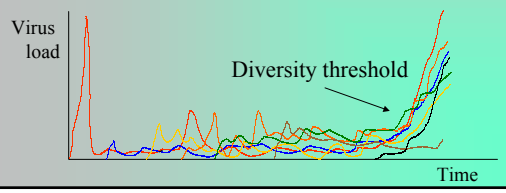
HIV is a quasispecies

- Viral replication is error prone.
- HIV reverse transcriptase and RNA polymerase have error rates of about 10^{-4}
- The virus population in any one patient is extremely heterogeneous.
- HIV can escape from immune responses.



Evolution toward disease

- Escape from immune responses
- Faster replicating, more aggressive strains
- Broader cell tropism



Antigenic variation

virus mutant i

immune response against mutant i

$$\dot{v}_i = rv_i - px_iv_i \qquad i = 1,\ldots,n$$
$$\dot{x}_i = cv_i - bx_i$$

Each mutant goes to equilibrium:

$$v_i = \frac{br}{cp} \qquad x_i = \frac{r}{p}$$

Add new mutants over time.

Antigenic variation

Total virus load is proportional to antigenic diversity.

$$v := \sum_i v_i = n\frac{br}{cp}$$

Antigenic variation

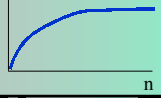
virus mutant i

specific immune response

cross reactive immune response

$$\dot{v}_i = v_i(r - px_i - qz)$$
$$\dot{x}_i = cv_i - bx_i \qquad i = 1,\ldots,n$$
$$\dot{z} = kv - bz$$

Virus load:



$$v = \frac{brn}{cp + kqn}$$

Antigenic variation of HIV

virus mutant i

specific immune response

cross reactive immune response

$$\dot{v}_i = v_i(r - px_i - qz)$$
$$\dot{x}_i = cv_i - bx_i - uvx_i \qquad i = 1,\ldots,n$$
$$\dot{z} = kv - bz - uvz$$

Virus load:

$$v = \frac{brn}{cp - (ru - kq)n}$$

Antigenic variation of HIV

Virus load:

$$v = \frac{brn}{cp - (ru - kq)n}$$

Diversity threshold:

$$n_c = \frac{cp}{ru - kq}$$

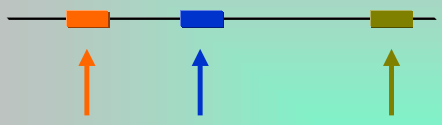
The 'diversity threshold' model has 3 possible outcomes

1. Disease after long asymptomatic period.
   $kq < ru < kq + cp$

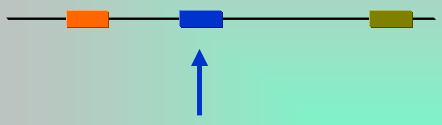
2. Indefinite virus control.
   $ru < kq$

3. Immediate disease.
   $kq + cp < ru$

Immune responses to multiple epitopes



Immune responses to multiple epitopes



Immunodominance

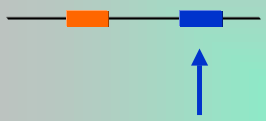
Multiple epitope theory

$$\dot{v}_{ij} = v_{ij}(r_{ij} - p_i x_i - q_j y_j)$$

$$\dot{x}_i = \eta\ c_i v_{i*} + x_i(c_i v_{i*} - b)$$

$$\dot{y}_j = \eta\ k_j v_{*j} + y_j(k_j v_{*j} - b)$$

Antigenic variation in presence of multiple epitopes



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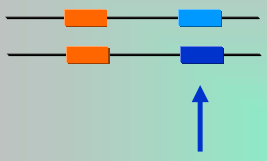
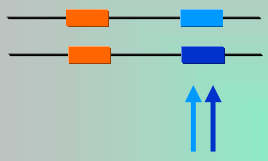


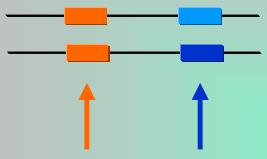
a new mutant arises

Antigenic variation in presence of multiple epitopes



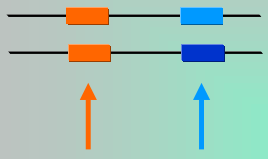
Diversification in the immunodominant epitope

Antigenic variation in presence of multiple epitopes



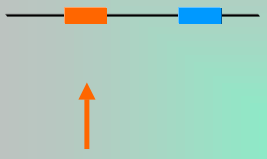
Partial shift in immunodominance, no response to new variant

Antigenic variation in presence of multiple epitopes



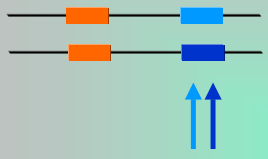
Partial shift in immunodominance, response to new variant
loss of response to old variant

Antigenic variation in presence of multiple epitopes



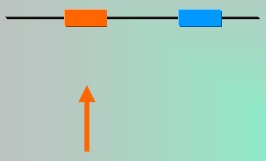
Complete shift in immunodominance
loss of old variant

Antigenic variation in presence of multiple epitopes



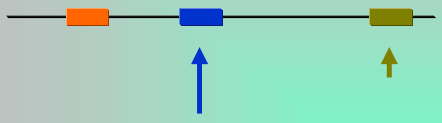
Immune response against variable epitope selects **for** viral diversity.

Antigenic variation in presence of multiple epitopes



Immune response against conserved epitope selects **against** viral diversity.

Immune responses to multiple epitopes



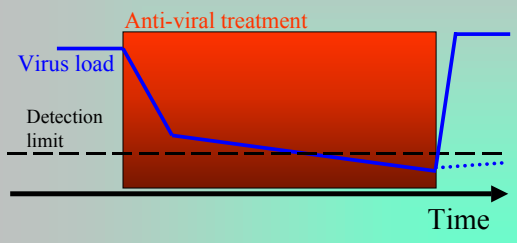
Immunodominance
breadth of the response is related to immune memory

Dominik Wodarz

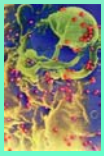
HIV disease progression according to this model

- There is a highly dynamic balance between the virus and the immune system with rapid virus turnover.
- The evolutionary adaptation of the virus in individual patients is the mechanism of disease progression.

The virus will return if therapy is withdrawn



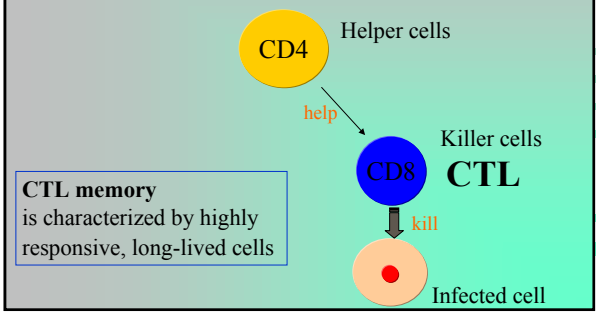
Is it possible to treat and help the patient's immune system to gain control of the virus?



A new theory of CTL memory

- Long lived **CTL responses** can eliminate virus infections or reduce virus load to low levels.

Cytotoxic T lymphocytes CTL



CTL memory
is characterized by highly responsive, long-lived cells

HIV

- HIV kills CD4 cells which are needed for CTL memory.
- Failure to establish a CTL memory response leads to persistent infection, high virus load and rapid disease progression
- A good CTL memory response leads to virus elimination (rare ?) or low virus load and slow disease progression

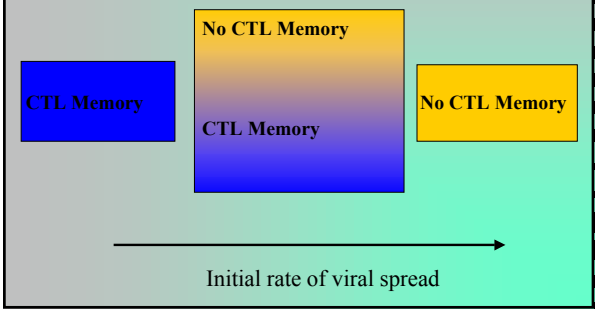
HIV: rate of disease progression

Fast progressors: high virus load

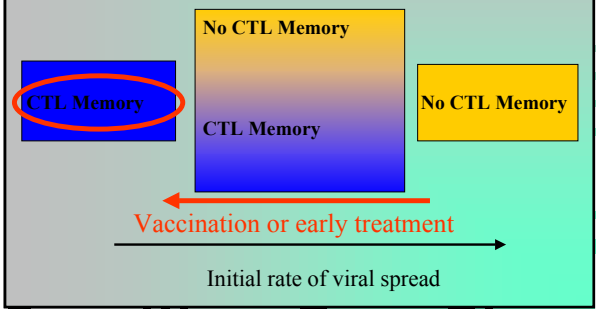
CTL memory makes the difference.

Slow progressors: low virus load

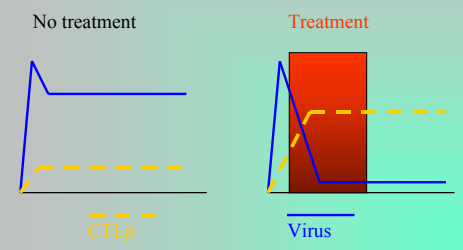
HIV replication and establishment of memory



HIV replication and establishment of memory



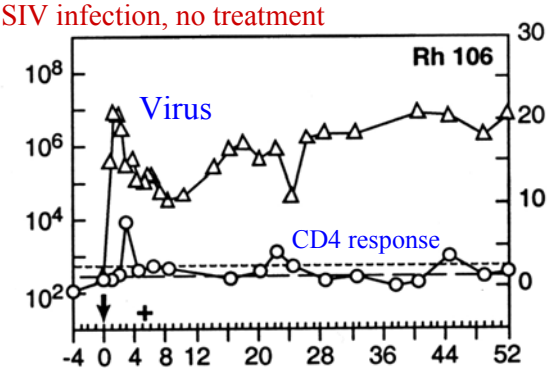
Treatment during primary infection



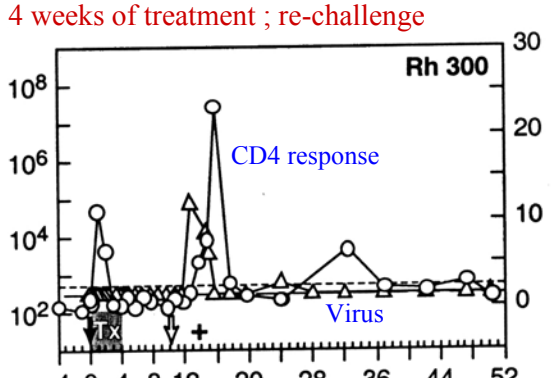
SIV: Jeff Lifson

HIV: Bruce Walker

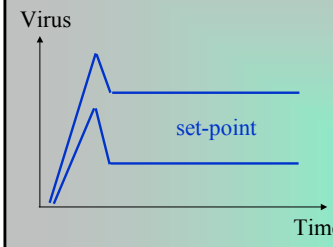
SIV infection, no treatment



4 weeks of treatment ; re-challenge



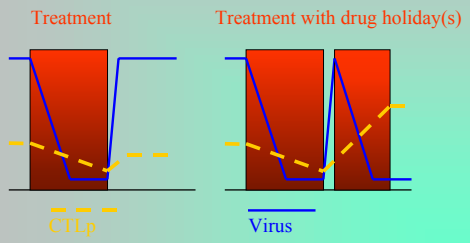
SIV primary infection without treatment



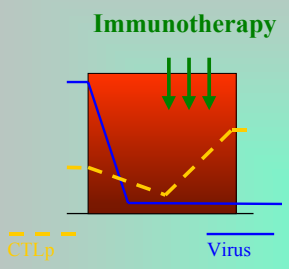
Virus load in the first week of infection is correlated with **set-point** is correlated with **survival.**

Jeff Lifson: 12 monkeys, 12 authors

Treatment during chronic HIV infection



Anti-viral treatment and immunotherapy



HIV therapy

- **For primary infection:** Use vaccination and early treatment to reduce the initial viral growth rate and bring patients into a state of long term non-progression.
- **For chronic infection:** Use treatment and immunotherapy to switch patients into a state of long term non-progression.

Summary

- HIV dynamics
- Disease progression
- CTL memory / virus control

Collaborators

- Robert May (Oxford)
- Sebastian Bonhoeffer (Zurich)
- Dominik Wodarz (Seattle)
- Marc Lipsitch (Harvard)
- Alun Lloyd (Princeton)
- George Shaw (Birmingham, Alabama)
- Andrew McMichael (Oxford)
- Charles Bangham (London)
- Jeff Lifson (Washington)

Three possible mechanisms of HIV disease progression

- Evolution of the virus
- Slow break-down of the immune system
- Accumulation of opportunistic infections