Evolutionary origin on HIV

- The closest relatives of HIV-1 and HIV-2 are simian immunodeficiency viruses (SIV).
- There is evidence for multiple transmissions from SIV into humans.
- HIV-1 is very closely related to SIV from chimpanzees.
Evolution of virulence

- All SIVs appear to be apathogenic in their natural hosts.
- SIV can be transferred to other species, where it induces AIDS.
- ‘Short-sighted’ evolution of virulence.
HIV is a quasispecies

- Viral replication is error prone.
- HIV reverse transcriptase and RNA polymerase have error rates of about 1E-4.
- The virus population in any one patient is extremely heterogeneous.
- HIV can escape from drug treatment.
- HIV can escape from immune responses.
Evolution toward disease

- Escape from immune responses
- Increasing viral diversity
- Faster replicating strains

![Virus load over time graph]

Diversity threshold
Antigenic variation

virus mutant \( i \)

immune response against mutant \( i \)

Each mutant goes to equilibrium:

\[
\begin{align*}
\dot{v}_i &= rv_i - px_i v_i \\
\dot{x}_i &= cv_i - bx_i
\end{align*}
\]

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

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

Virus load:

\[ v = \frac{brn}{cp + kqn} \]
Antigenic variation of HIV

\[ \dot{v}_i = v_i (r - px_i - qz) \]

\[ \dot{x}_i = cv_i - bx_i - uvx_i \quad i = 1, \ldots, n \]

\[ \dot{z} = kv - bz - uvz \]

Virus load:

\[ v = \frac{brn}{cp - (ru - kq)n} \]
Antigenic variation of HIV

Virus load:

\[ \nu = \frac{brn}{cp - (ru - kq)n} \]

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

Immunodominance

breadth of the response is related to immune memory
Immune responses to multiple epitopes

Antigenic variation can lead to shifting immunodominance
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.
Three possible mechanisms of HIV disease progression

- Evolution of the virus
- Slow break-down of the immune system
- Accumulation of opportunistic infections
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?
The primary role of CTL memory is to eliminate virus infections or to reduce virus load to low levels.

Dominik Wodarz
CTL memory is characterized by highly responsive and long-lived CTL precursors (high c and low b).

CTL memory requires CD4 cell help.
The basic model with CTL

\[ \dot{x} = \lambda - dx - \beta xy \]
\[ \dot{y} = \beta xy - ay - pyz \]
\[ \dot{w} = cyw (1 - q) - bw \]
\[ z = cqw - hz \]
2 possible outcomes:

1. Virus elimination
2. Persistent infection
HIV specific model

\[
\begin{align*}
    \cdot & \quad \dot{x} = \lambda - dx - \beta xy \\
    \cdot & \quad \dot{y} = \beta xy - ay - pyz \\
    \cdot & \quad \dot{w} = cxyw - cqyw - bw \\
    \cdot & \quad \dot{z} = cqyw - hz
\end{align*}
\]
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 at least 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

Initial rate of viral spread
HIV replication and establishment of memory

- CTL Memory
- No CTL Memory

Vaccination or early treatment

Initial rate of viral spread
Treatment during primary infection

SIV: Jeff Lifson

HIV: Bruce Walker
SIV infection, no treatment

Time (weeks)

Virus

CD4 response
4 weeks of treatment; re-challenge

CD4 response

Virus

Time (weeks)
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

- Treatment
- Treatment with drug holiday(s)

CTLP

Virus
Anti-viral treatment and immunotherapy

Immunotherapy

CTLp

Virus
A new approach for 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.