Evolutionary origin on HIV

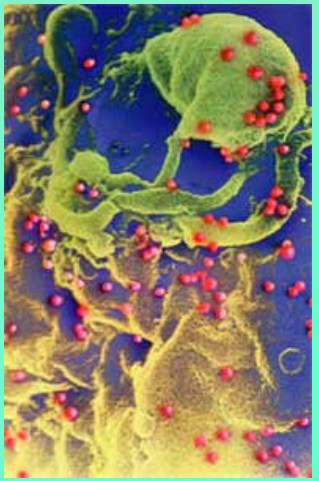
- The closest relatives of HIV-1 and HIV-2 are simian immunodeficiency viruses (SIV).
- There is evidence for multiple transmissions from SIV into humans.
- HIV-1 is very closely related to SIV from chimpanzees.

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.

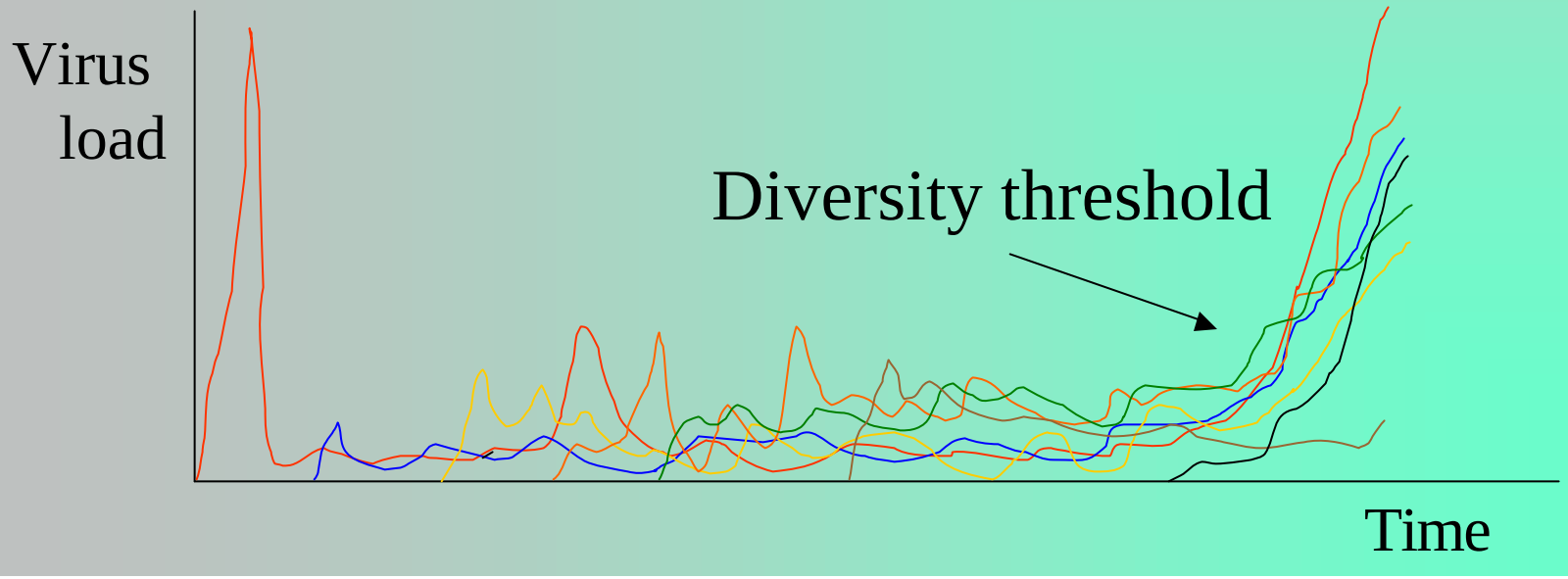
HIV is a quasispecies

- 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



Antigenic variation

virus mutant i

immune response against mutant i

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

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

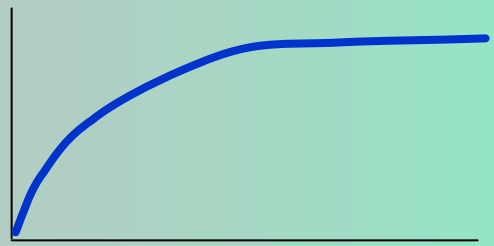
cross reactive immune response

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

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

$$\dot{z} = kv - bz$$

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:

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

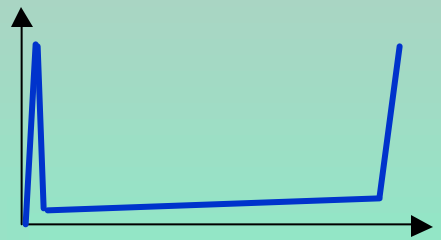
Diversity threshold:

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

The ‘diversity threshold’ model has 3 possible outcomes

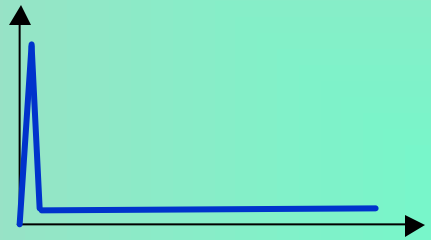
1. Disease after long asymptomatic period.

$$kq < ru < kq + cp$$



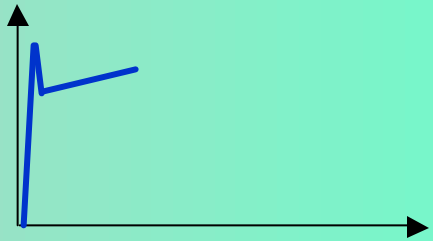
2. Indefinite virus control.

$$ru < kq$$

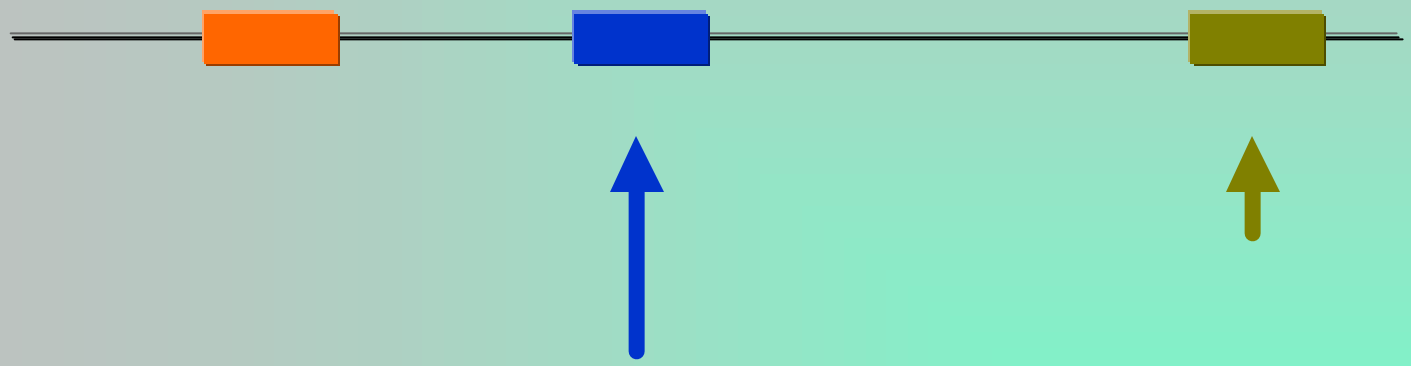


3. Immediate disease.

$$kq + cp < ru$$



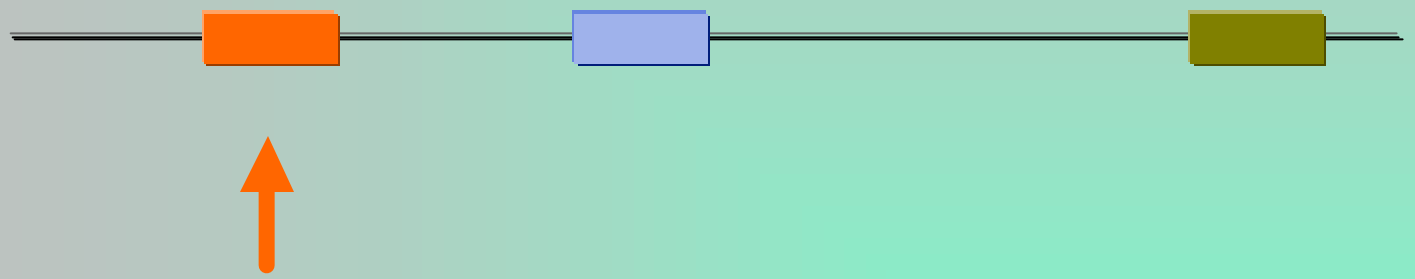
Immune responses to multiple epitopes



Immunodominance

breadth of the response is related to immune memory

Immune responses to multiple epitopes



Antigenic variation can lead to **shifting immunodominance**

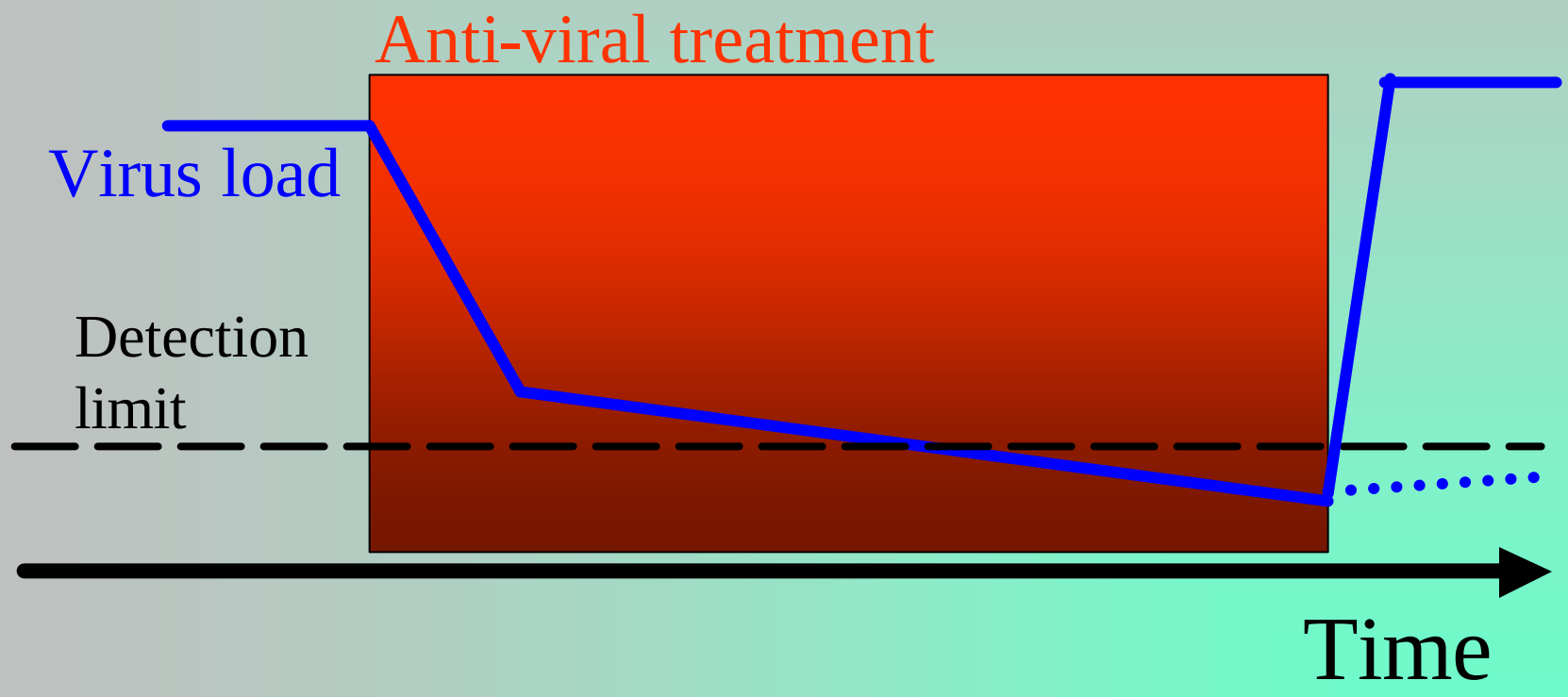
HIV disease progression according to this model

- 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.

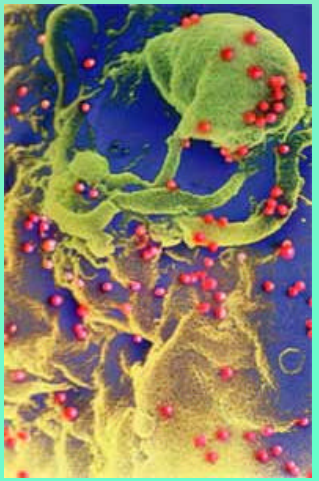
Three possible mechanisms of HIV disease progression

- 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?

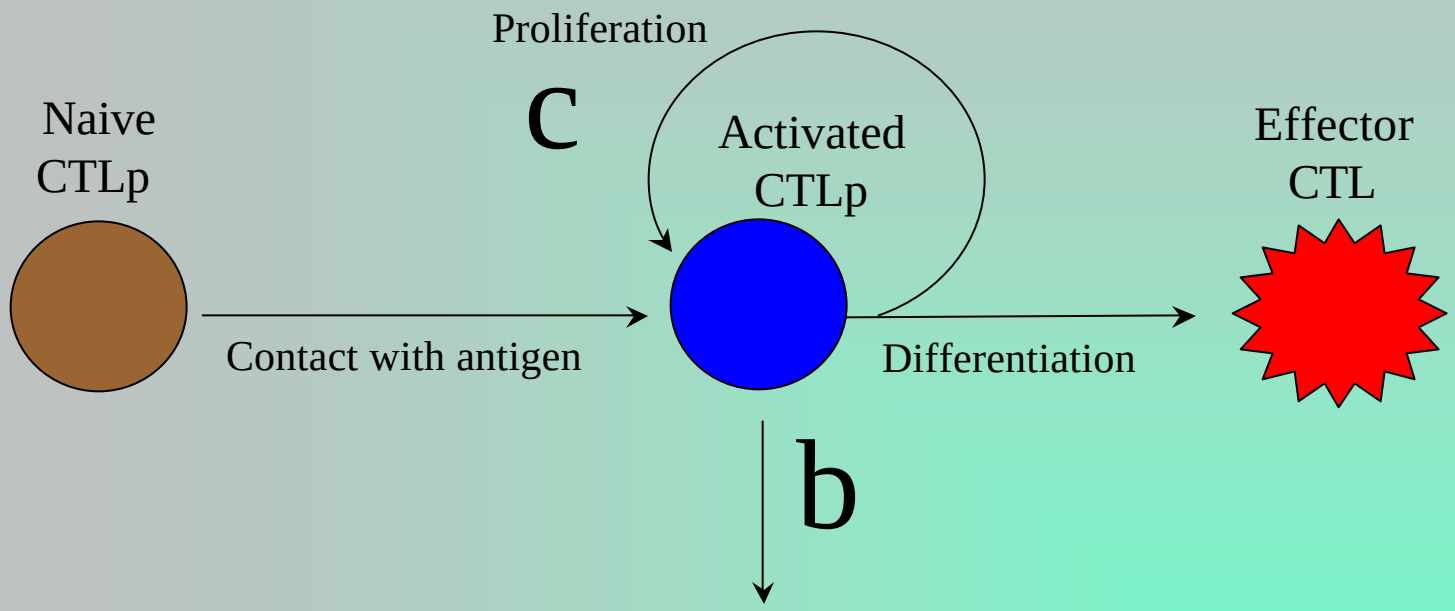


A new theory of CTL memory

- The primary role of **CTL memory** is to eliminate virus infections or to reduce virus load to low levels.

Dominik Wodarz

CTL dynamics



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

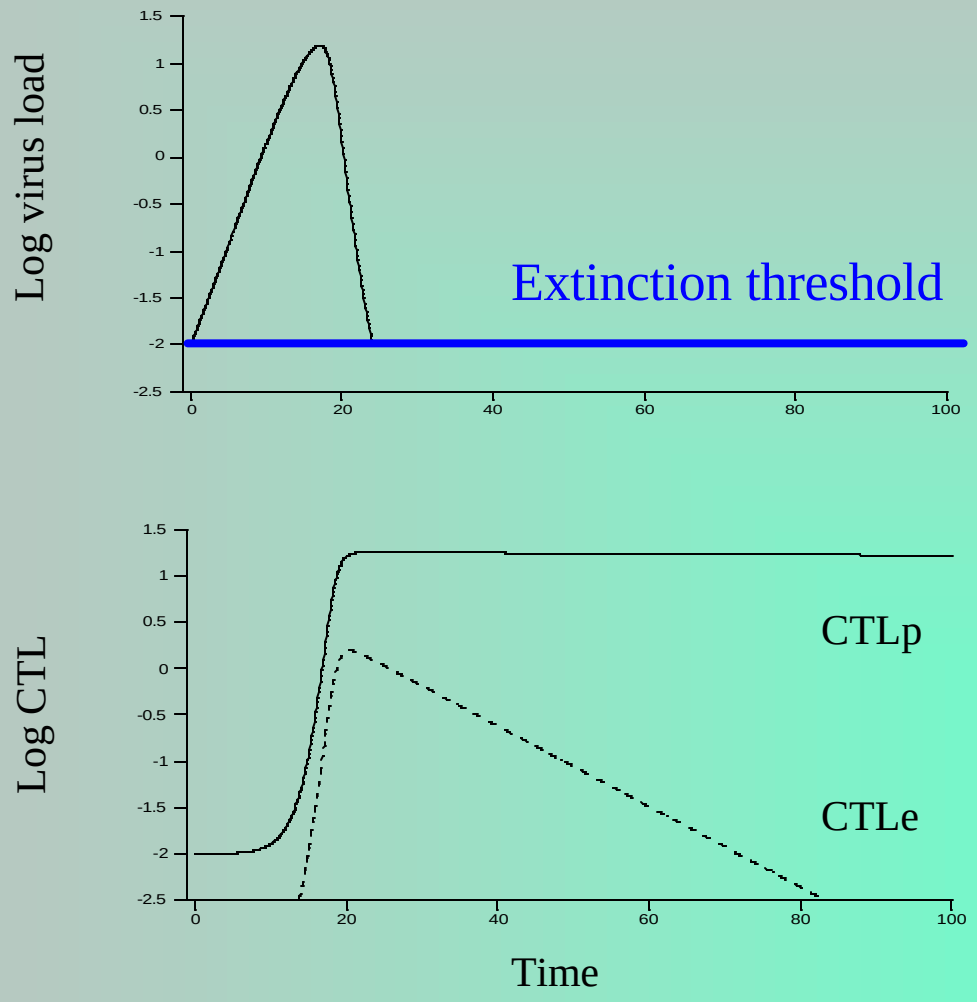
$$\dot{x} = l - dx - b\,xy$$

$$\dot{y} = b\,xy - ay - pyz$$

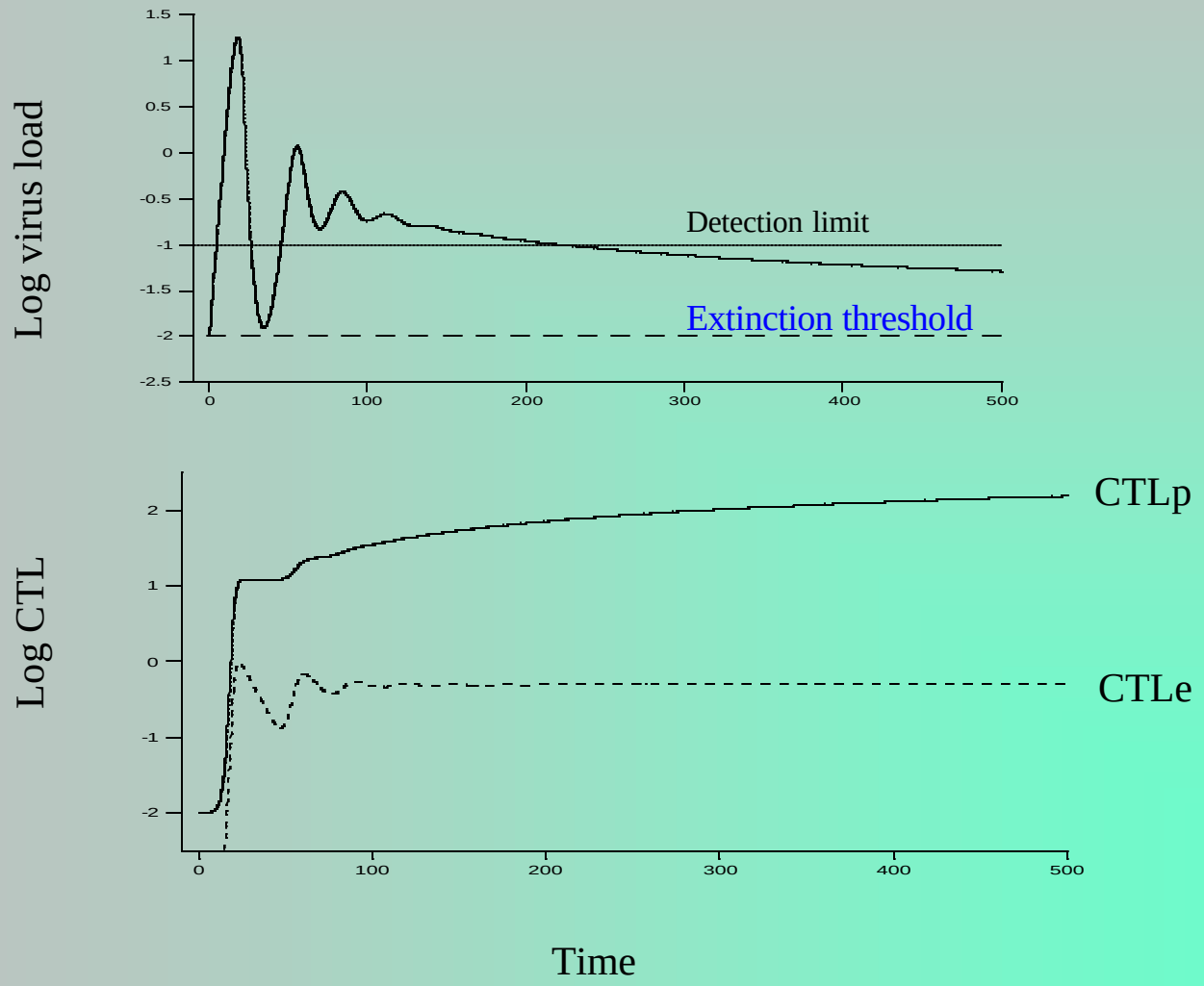
$$\dot{w} = cyw\,(1 - q) - bw$$

$$\dot{z} = cqyw - hz$$

2 possible outcomes:
1. Virus elimination



2. Persistent infection



HIV specific model

$$\dot{x} = l - dx - b\,xy$$

$$\dot{y} = b\,xy - ay - pyz$$

$$\dot{w} = cxyw - cqyw - bw$$

$$\dot{z} = cqyw - hz$$

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

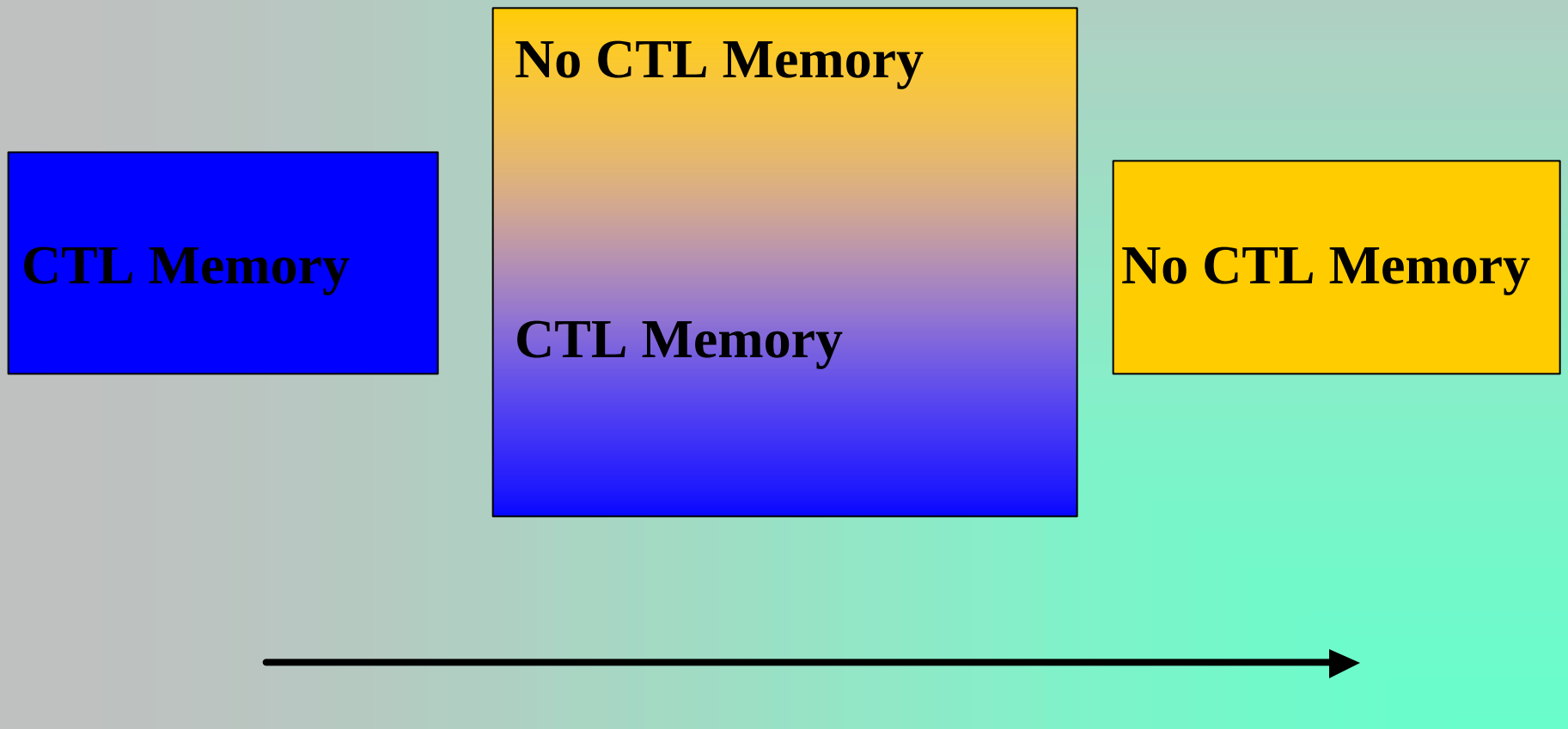
HIV: rate of disease progression

Fast progressors: high virus load

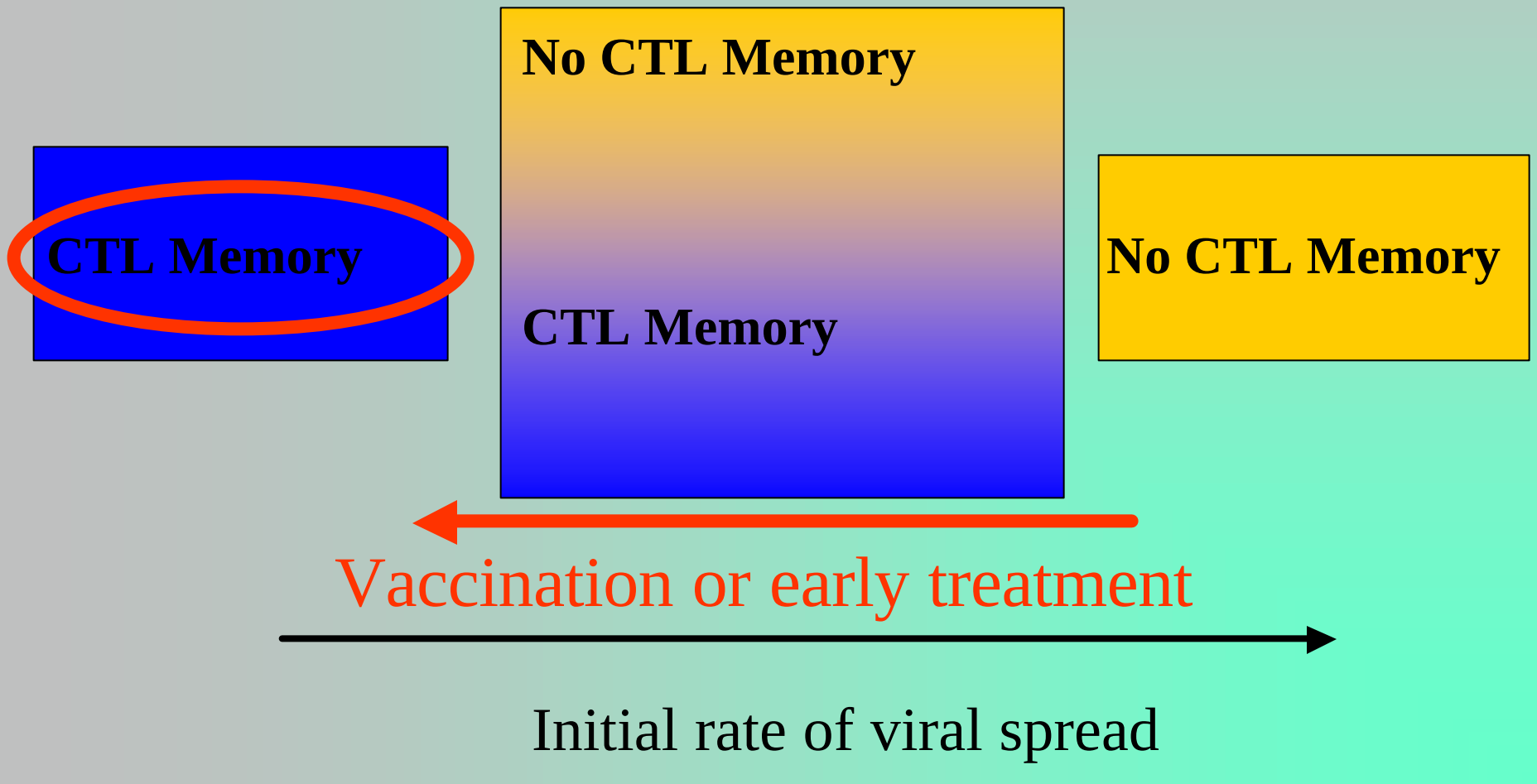
CTL memory makes the difference.

Slow progressors: low virus load

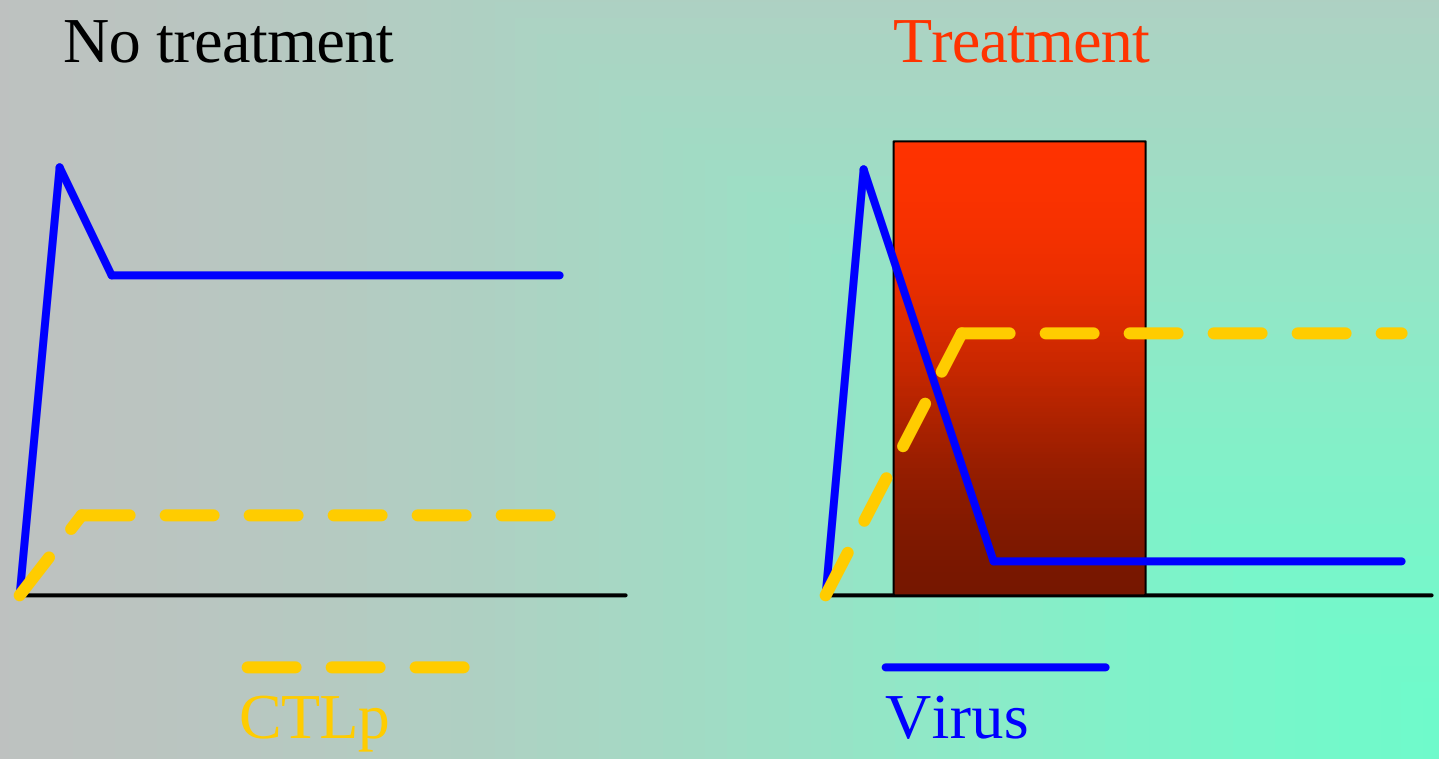
HIV replication and establishment of memory



HIV replication and establishment of memory



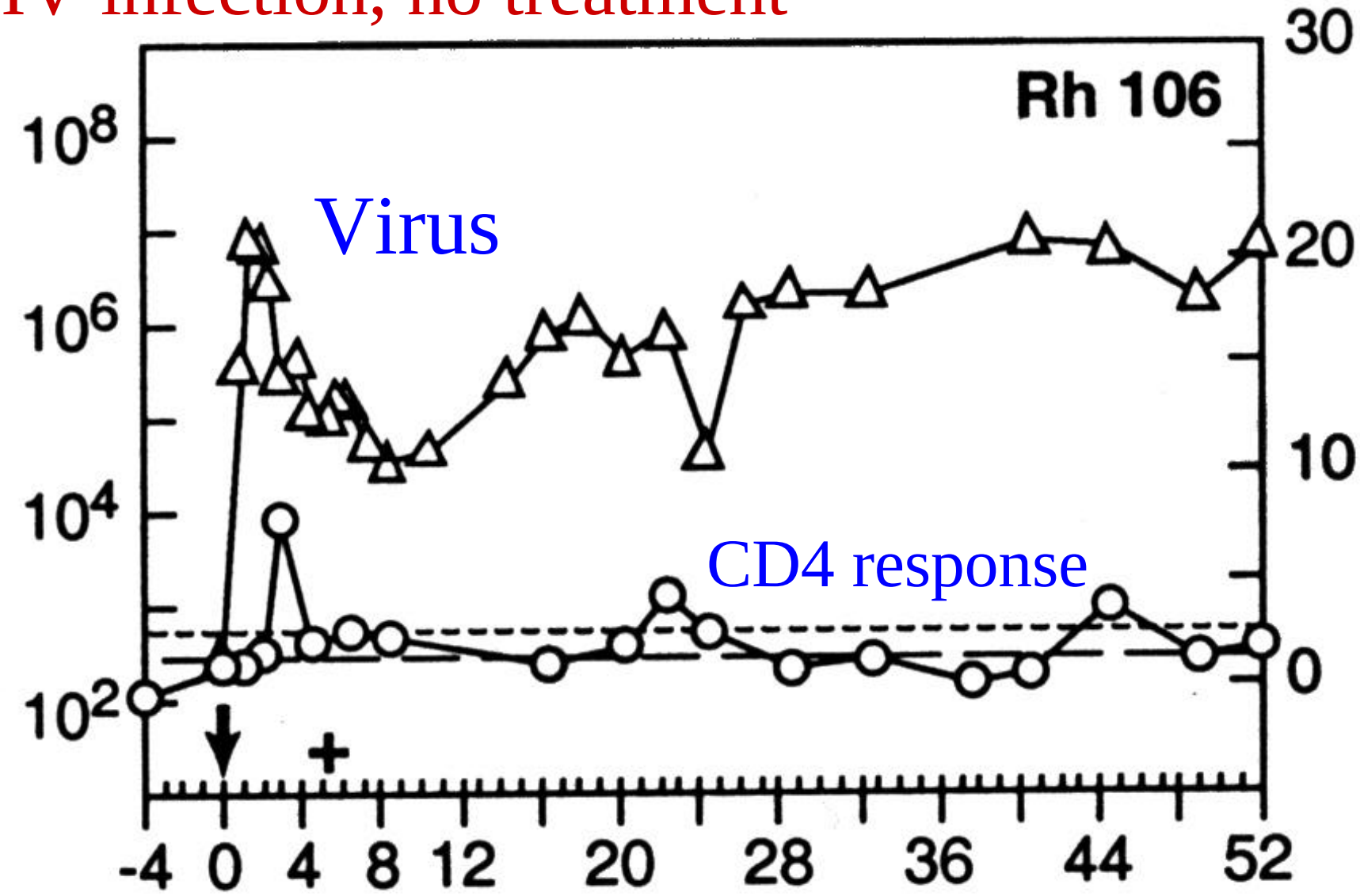
Treatment during primary infection



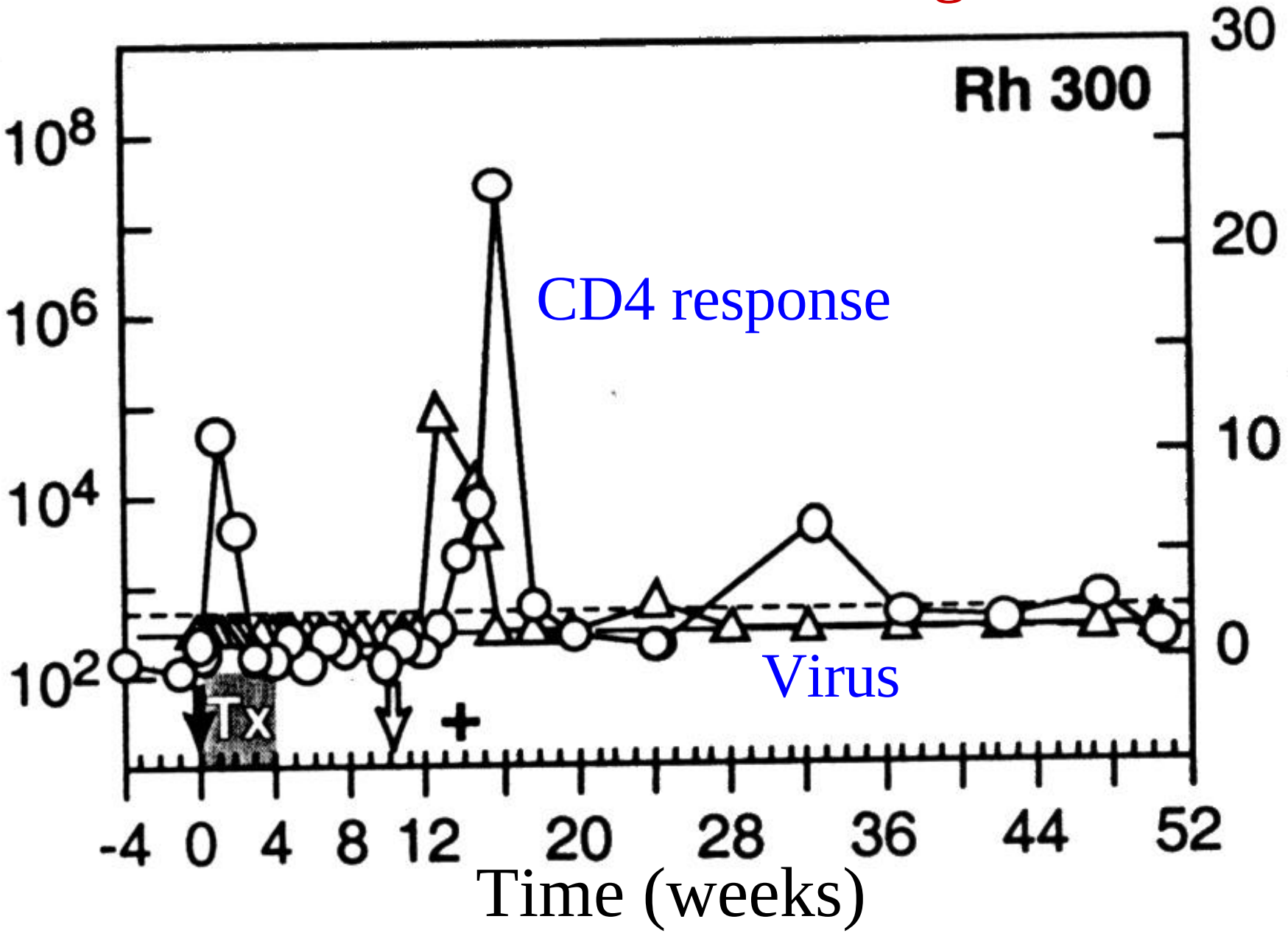
SIV: Jeff Lifson

HIV: Bruce Walker

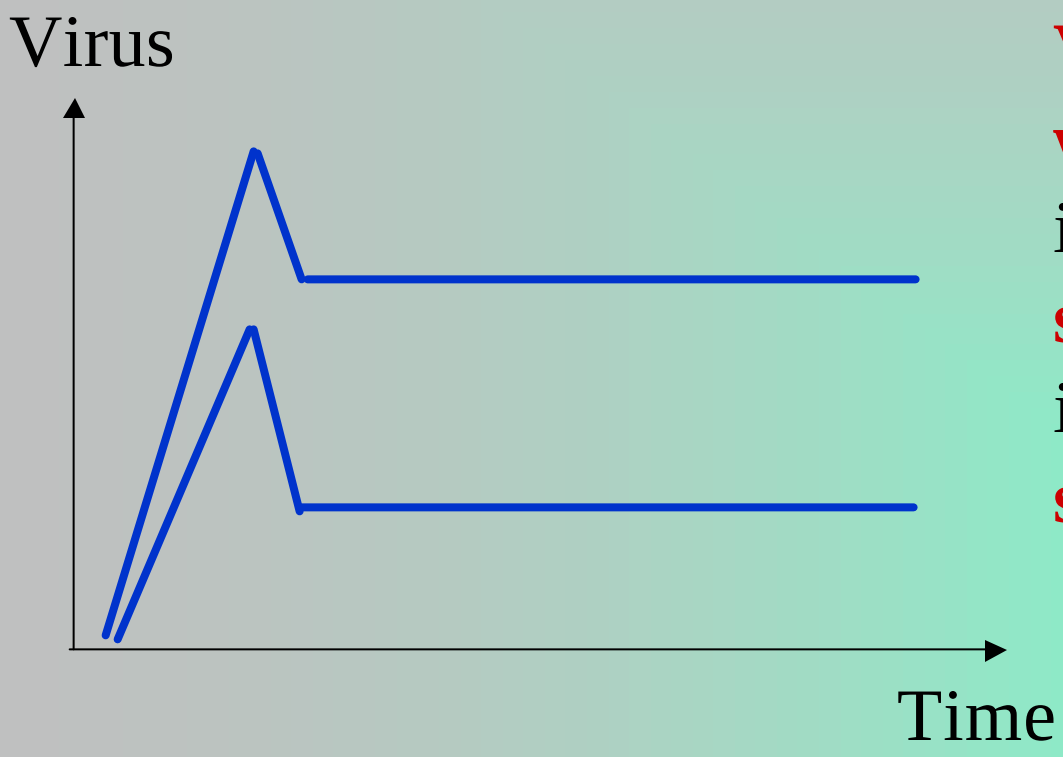
SIV infection, no treatment



4 weeks of treatment ; re-challenge



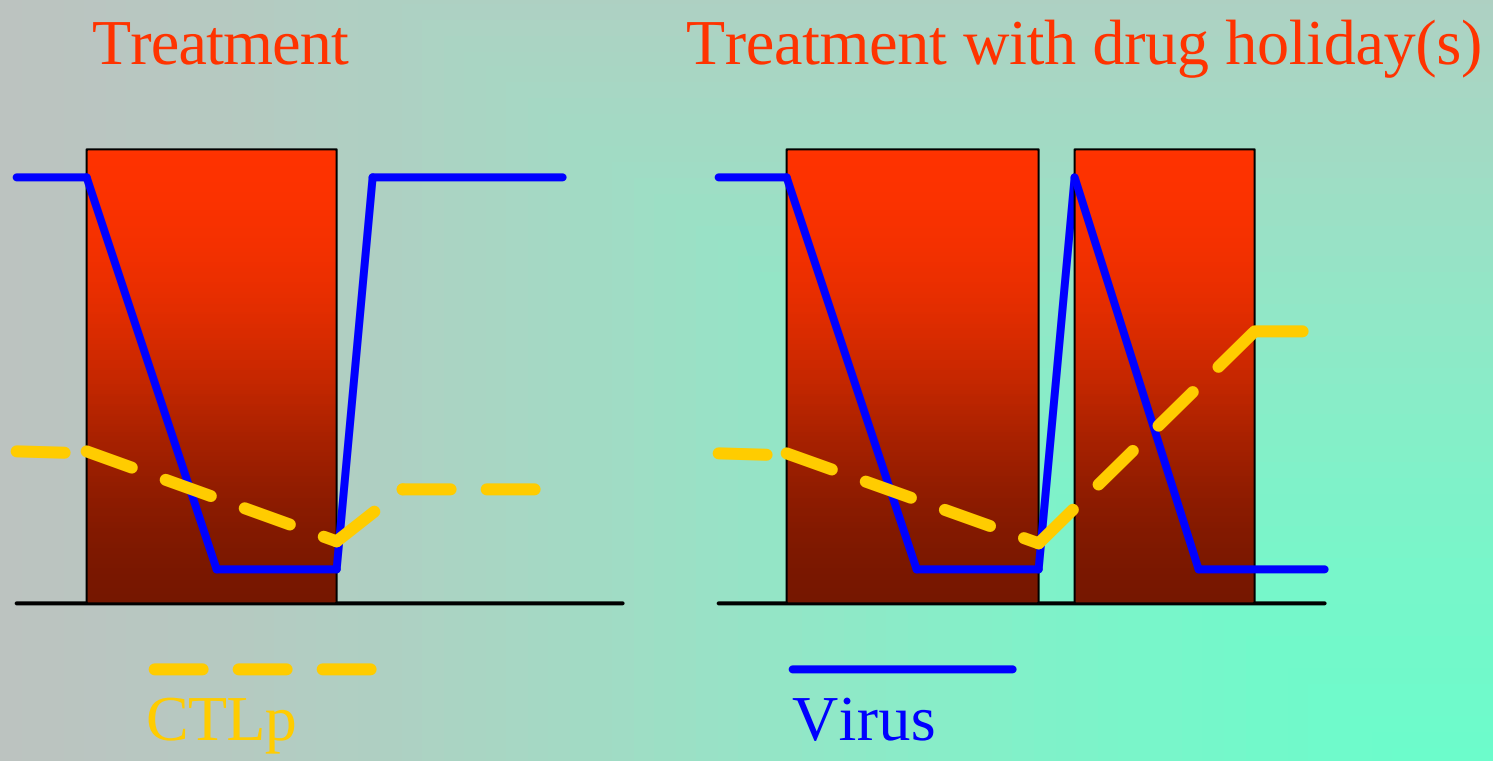
SIV primary infection without treatment



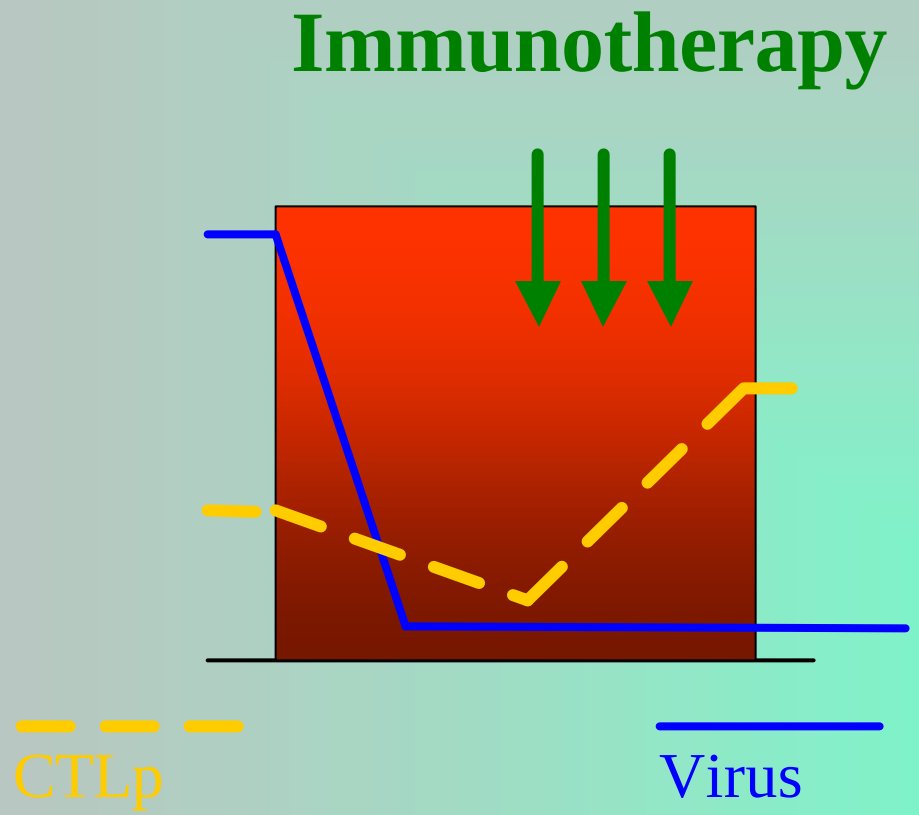
Virus load in the first week of infection
is correlated with
set-point
is correlated with
survival.

Jeff Lifson: 12 monkeys, 12 authors

Treatment during chronic HIV infection



Anti-viral treatment and immunotherapy



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.