Within-host viral dynamics

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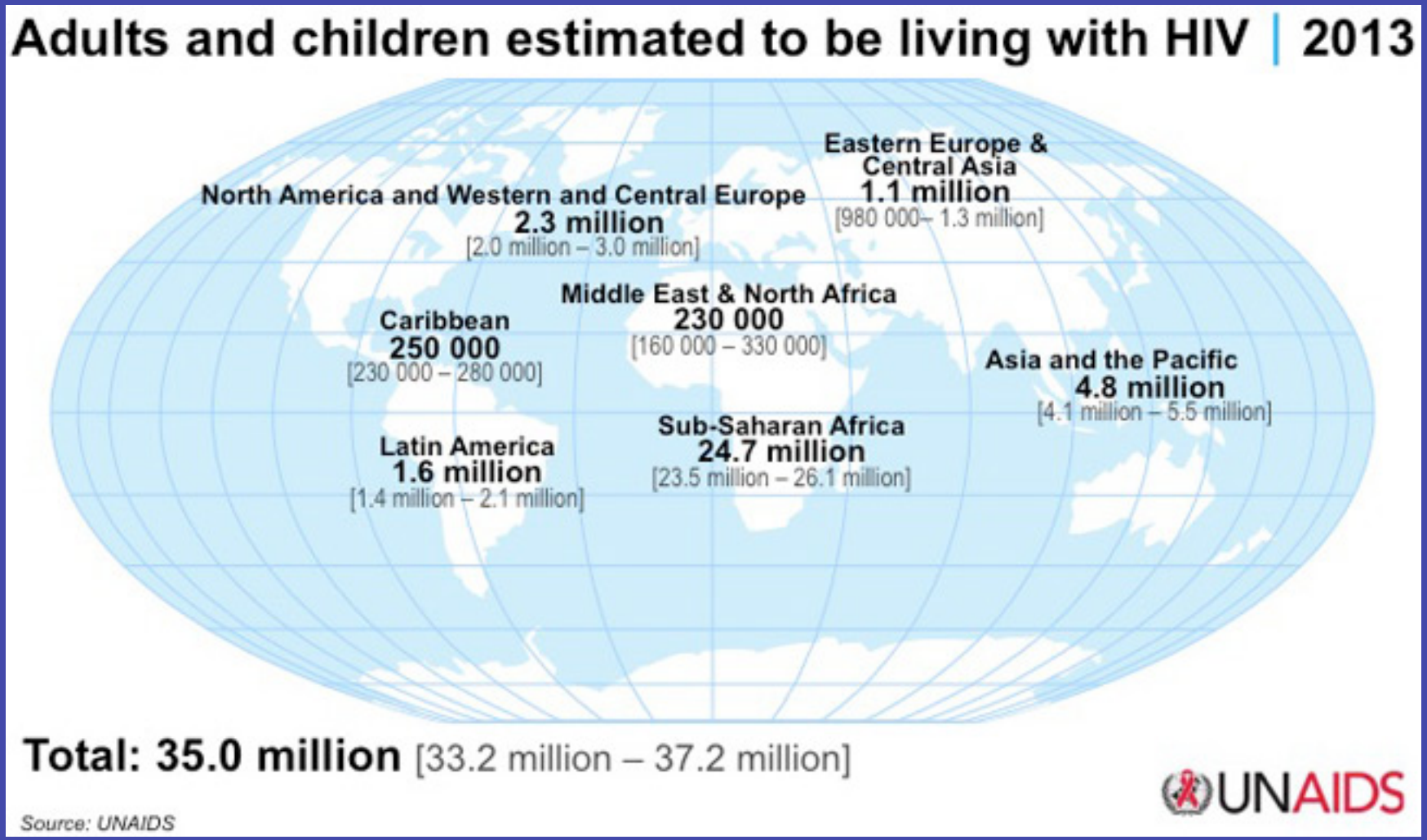
Topics for today

1. **Background on HIV epidemiology and biology**
2. Within-host mathematical models of HIV infection
3. Introduction to branching process models

HIV as a global epidemic

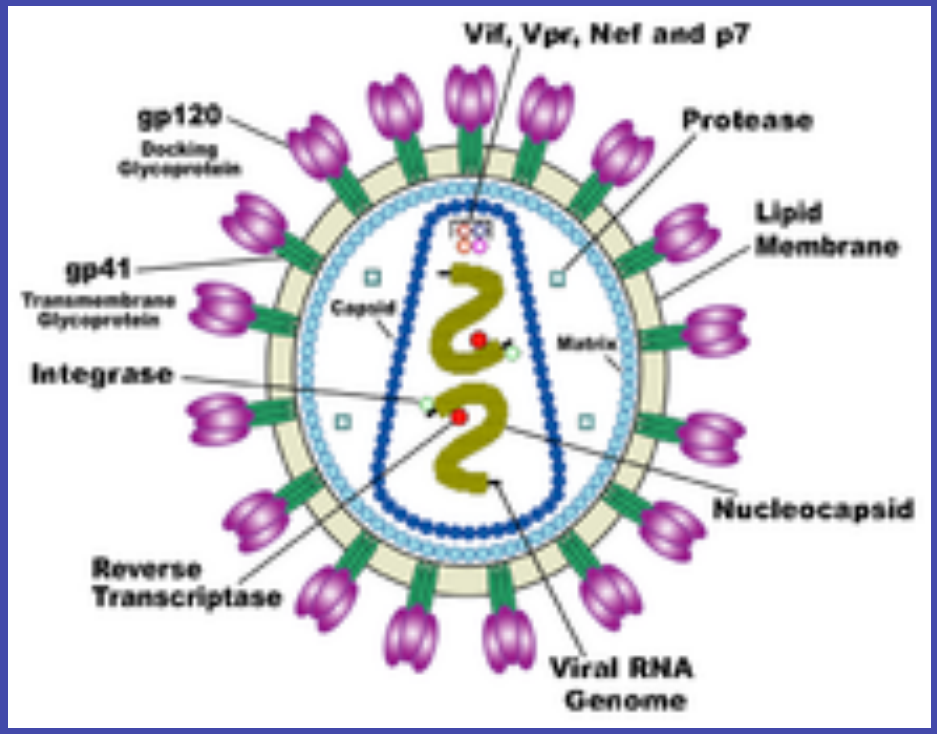


History of HIV/AIDS

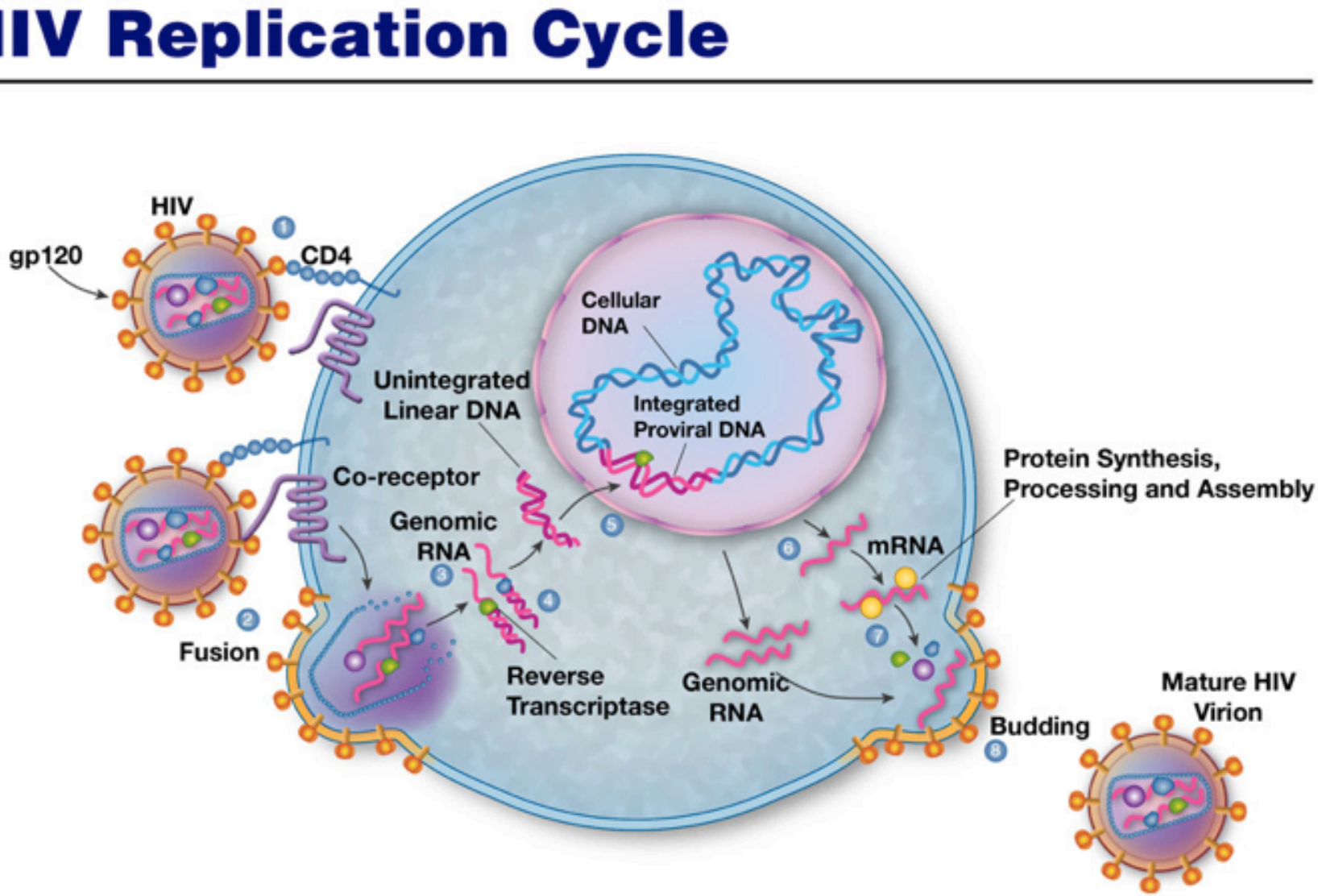
- Phylogenetics indicate simian-human transfer around 1900s
- First retroactively confirmed case – 1959
- Awareness of AIDS (hemophiliacs, MSM) in the USA – 1980
- Virus isolated and named – 1983
- Fear
- First treatment approved – 1987

Within-host HIV

- Transmission via sex or blood contact
- Virus infects CD4+ immune cells
  - Helper T cells
  - Macrophages
- Systemic infection (virus detectable in blood) in 10 days
- Widespread dissemination through the body

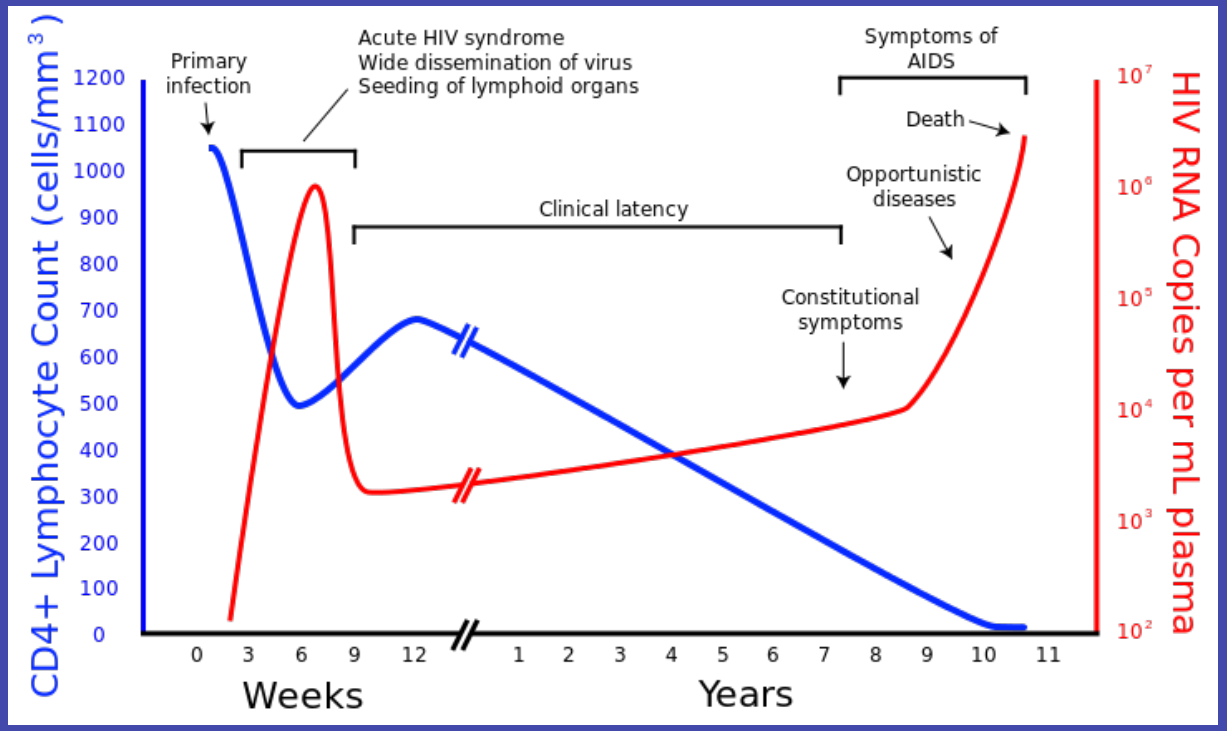


Within-host HIV



Within-host HIV

- Systemic infection (virus detectable in blood) in 10 days
- Peak viremia 21-28 days
- Decline in virus, “set point”
- Progression to AIDS ~10yr

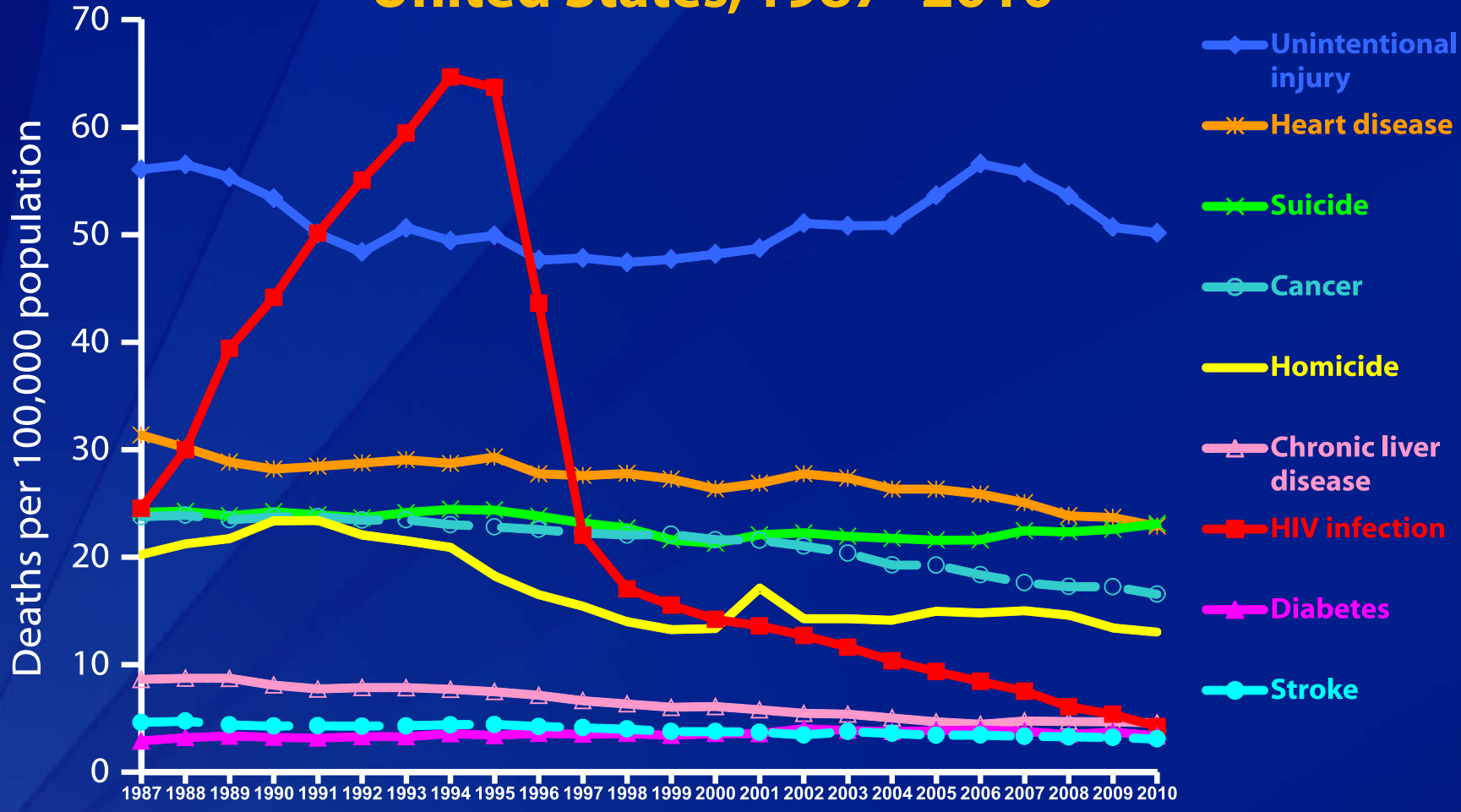


ART (anti-retroviral therapy)

- Successful ART since mid-1990s
  - Reduces virus in blood to undetectable levels
  - Not curative
  - Immune system rebounds, mortality reduced
- Side-effects
- Cost

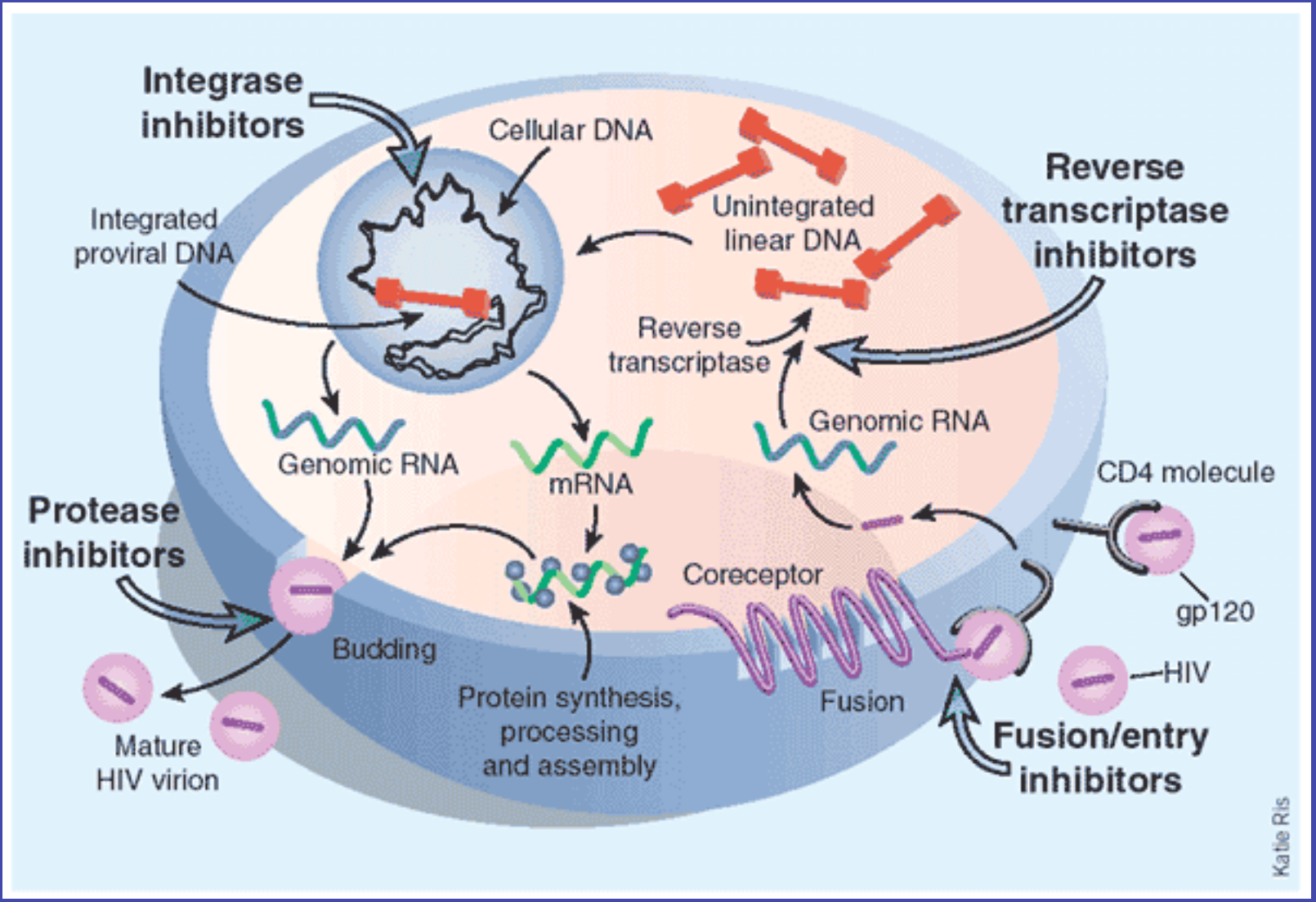
- How many people have been cured of HIV?

Trends in Annual Rates of Death due to the 9 Leading Causes among Men 25–44 Years Old, United States, 1987–2010



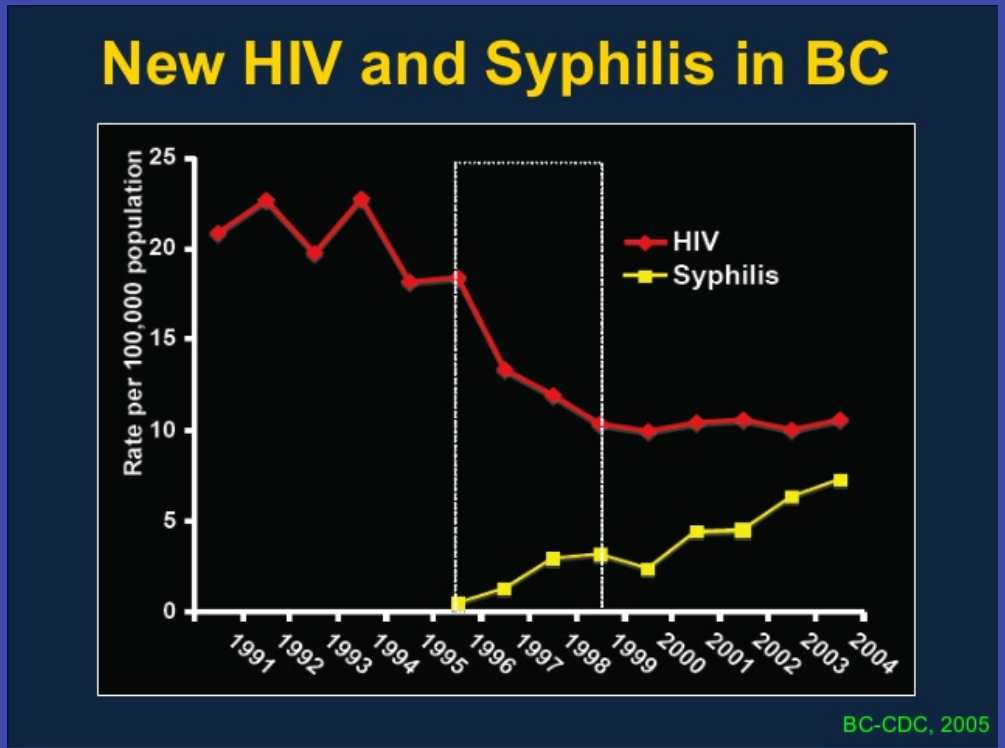
Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for *ICD-10* rules instead of *ICD-9* rules.

HIV Lifecycle and Drug actions



Treatment reduces transmissibility

Julio Montaner,
BC Centre for Excellence in HIV/AIDS



- 2008 Swiss statement

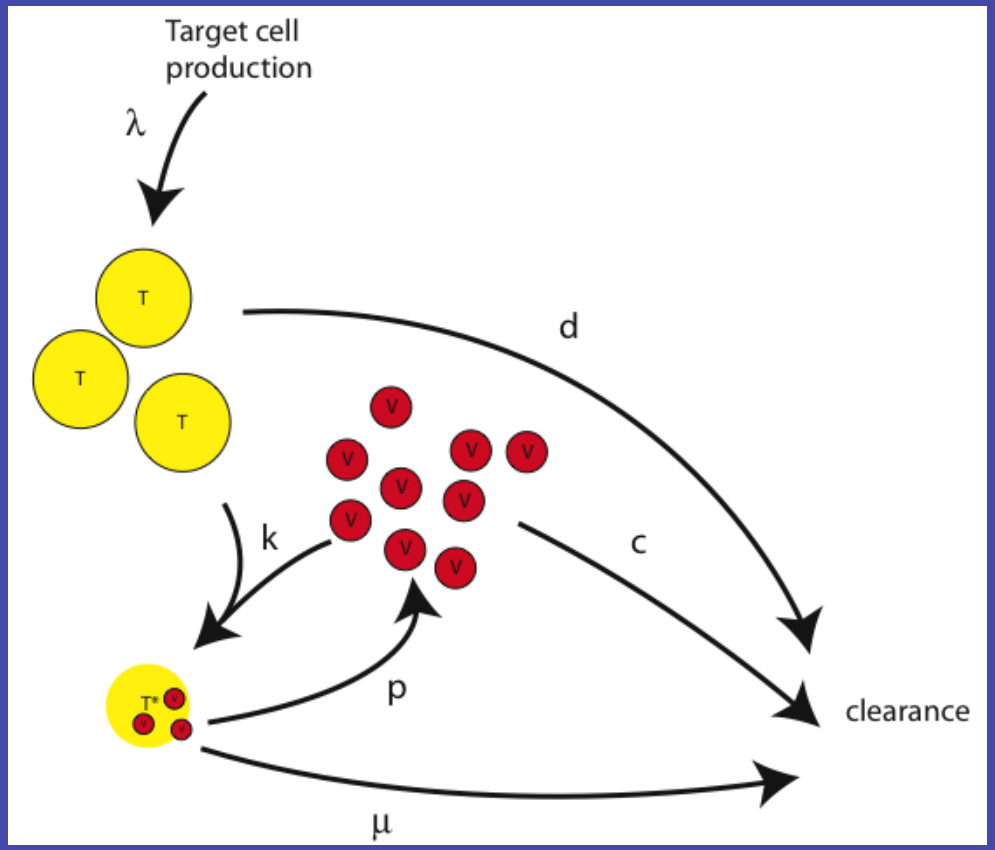
Post-exposure and Pre-Exposure Prophylaxis (PEP and PrEP)

- Prospective treatment BEFORE detectable infection
- PEP – prescribed for healthcare workers since 1990s
  - now also prescribed for non-occupational exposure
- PrEP – a daily pill to prevent infection
  - 44% protection in MSM study (92% for those who provably took the pills)
  - Similar results for heterosexuals, IDUs
  - Long-term effects on epidemic unknown

Summary:

- HIV infects and depletes CD4+ T cells; development to AIDS ~10yr
- One person has been cured, ever (same as Rabies)
- Continuing transmission worldwide
- Modern treatment options (ART)
    - Restore normal life expectancy
    - Reduce new infections
    - Not curative
- Vaccine development slow

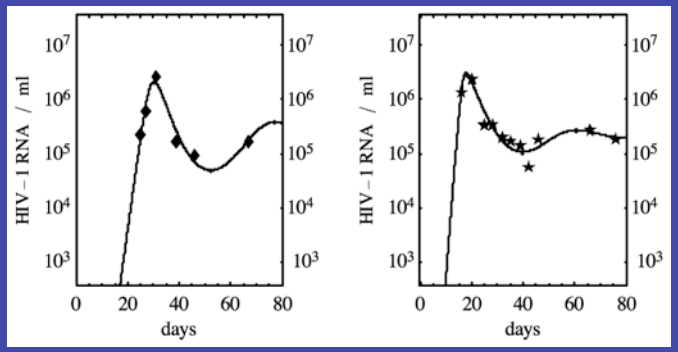
"Standard" ODE model of HIV infection



$$\frac{dT}{dt} = \lambda - kVT - dT$$

$$\frac{dT^*}{dt} = kVT - \mu T^*$$

$$\frac{dV}{dt} = pT^* - cV$$



- Successful deterministic models of *untreated* infection
  - Biological parameters can be fit
  - Hypotheses can be made interpreting the parameters

Linear Analysis of the Standard Model

$$\frac{dT}{dt} = \lambda - kVT - dT$$
$$\frac{dT^*}{dt} = kVT - \mu T^*$$
$$\frac{dV}{dt} = pT^* - cV$$

$$T = \lambda/d$$
$$T^* = 0$$
$$V = 0$$

Uninfected st.st.

$$T = \frac{c\mu}{kp}$$
$$T^* = \frac{\lambda}{\mu} - \frac{cd}{kp}$$
$$V = \frac{kp\lambda}{ck\mu} - \frac{d}{k}$$

Infected st.st.

Steady state

$$T = \lambda/d$$
$$T^* = 0$$
$$V = 0$$

Nonlinear system

$$\frac{dT}{dt} = \lambda - kVT - dT$$
$$\frac{dT^*}{dt} = kVT - \mu T^*$$
$$\frac{dV}{dt} = pT^* - cV$$

Perturbation variables

$$T = \lambda/d + \hat{T}$$
$$T^* = 0 + \hat{T}^*$$
$$V = 0 + \hat{V}$$

$$\frac{d}{dt}\begin{pmatrix} \hat{T} \\ \hat{T}^* \\ \hat{V} \end{pmatrix} = \begin{pmatrix} -d & 0 & -\frac{k\lambda}{d} \\ 0 & -\mu & \frac{k\lambda}{d} \\ 0 & p & -c \end{pmatrix} \begin{pmatrix} \hat{T} \\ \hat{T}^* \\ \hat{V} \end{pmatrix}$$

Linearized system

Eigenvalues:

$$r_1 = -d$$
$$r_2 = \frac{1}{2}\left(-(c+\mu) \pm \sqrt{(c-\mu)^2 + \frac{4k\lambda p}{d}}\right)$$

Stability condition:

$$\frac{\lambda p k}{d\mu c} < 1$$

Steady state

$$T = \frac{c\mu}{kp}$$

$$T^* = \frac{\lambda}{\mu} - \frac{cd}{kp}$$

$$V = \frac{kp\lambda}{ck\mu} - \frac{d}{k}$$

Nonlinear system

$$\frac{dT}{dt} = \lambda - kVT - dT$$

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Perturbation variables

$$T = \frac{c\mu}{kp} + \hat{T}$$

$$T^* = \frac{\lambda}{\mu} - \frac{cd}{kp} + \hat{T}^*$$

$$V = \frac{kp\lambda}{ck\mu} - \frac{d}{k} + \hat{V}$$

$$\frac{d}{dt}\begin{pmatrix} \hat{T} \\ \hat{T}^* \\ \hat{V} \end{pmatrix} = \begin{pmatrix} -\frac{kp\lambda}{c\mu} & 0 & -\frac{c\mu}{p} \\ \frac{kp\lambda}{c\mu} - d & -\mu & \frac{c\mu}{p} \\ 0 & p & -c \end{pmatrix} \begin{pmatrix} \hat{T} \\ \hat{T}^* \\ \hat{V} \end{pmatrix}$$

Linearized system

Eigenvalues:

$$r^3 + \left(\frac{k\lambda p}{c\mu} + c + \mu\right) r^2 + \frac{k\lambda p(c+\mu)}{c\mu} r + (k\lambda p - cd\mu) = 0$$

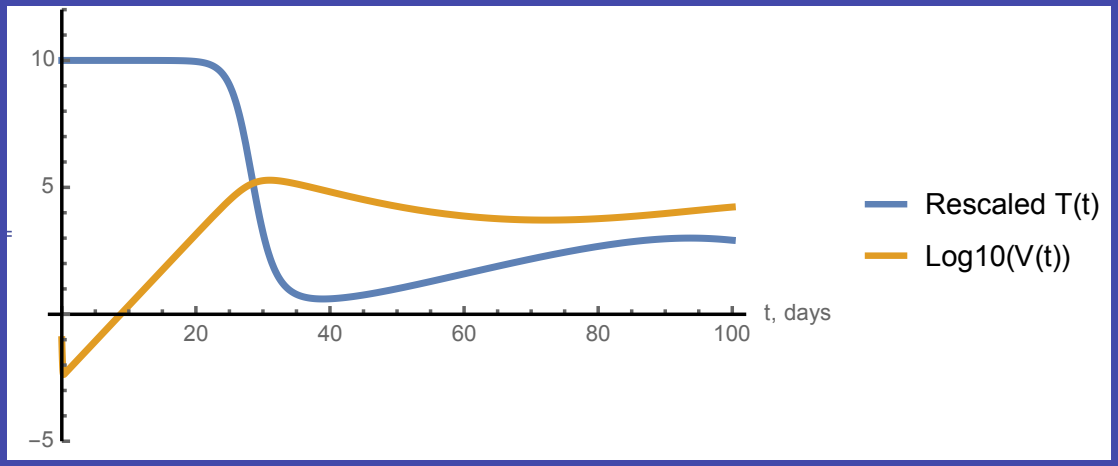
Stability condition:

$$\frac{\lambda pk}{d\mu c} > 1$$

The uninfected and infected steady states exchange local stability when the *basic reproductive number* R_0 crosses one.

$$\frac{\lambda p k}{d \mu c} > 1 \longrightarrow R_0 = \frac{\lambda p k}{d \mu c}$$

We can also (using Lyapunov functions) show that this condition controls global stability.



$$\frac{dT}{dt} = \lambda - kVT - dT$$

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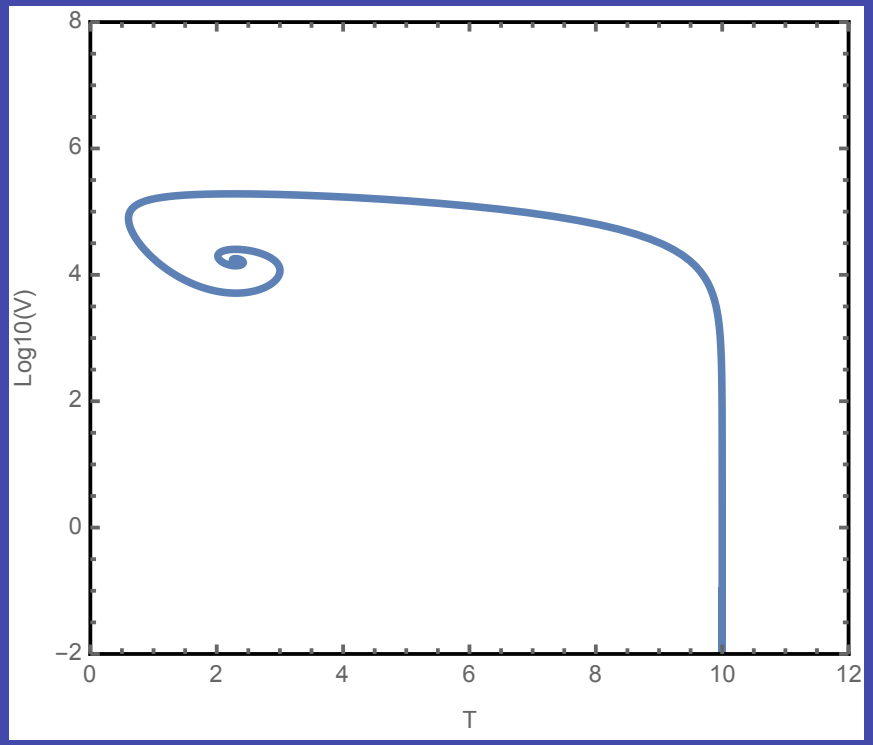
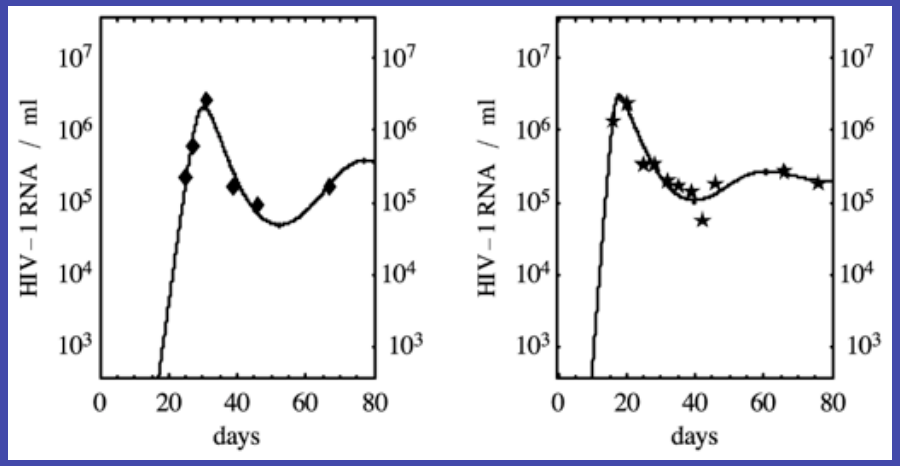


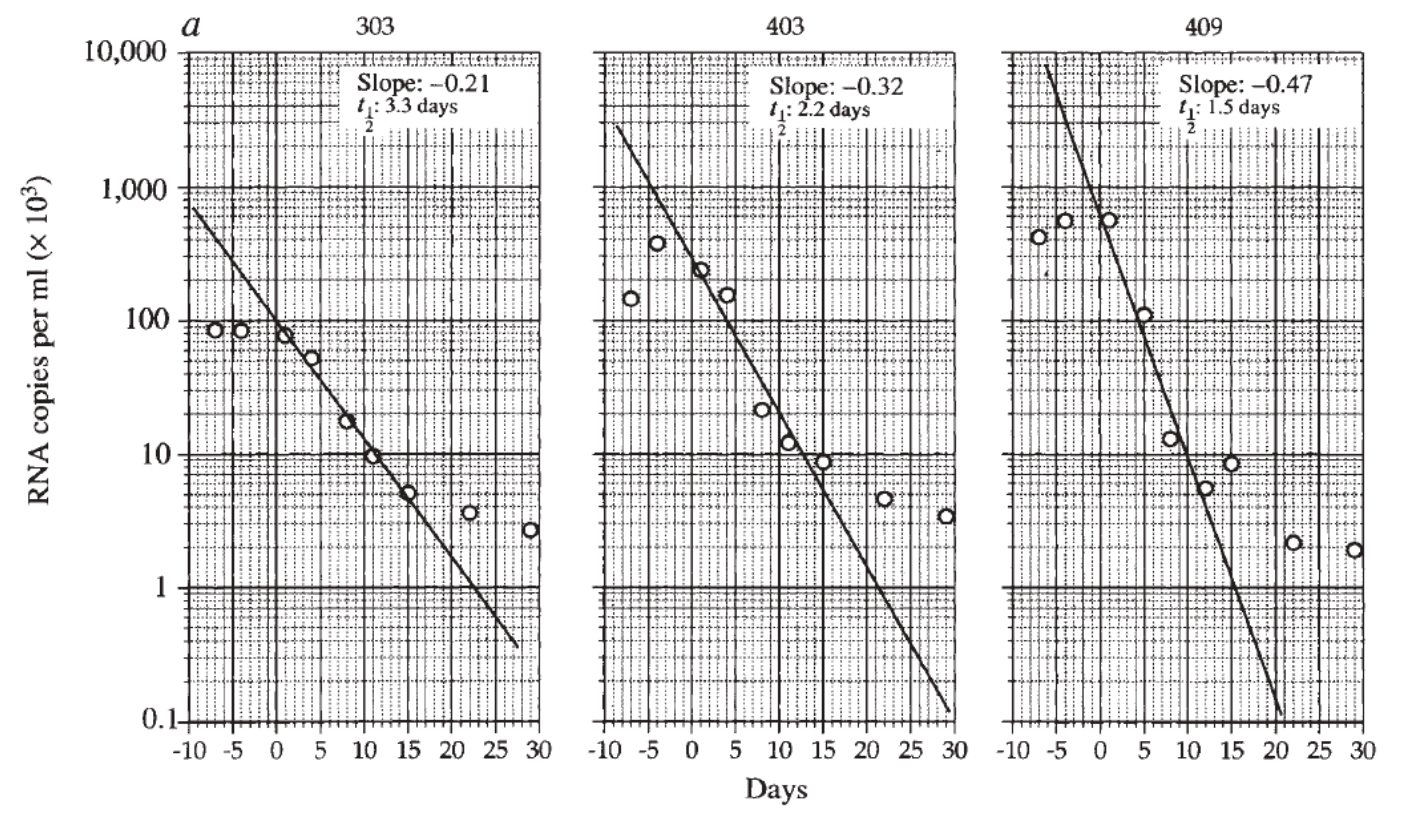
- Infected st.st. can be a spiral point or a stable node, depending on parameters



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

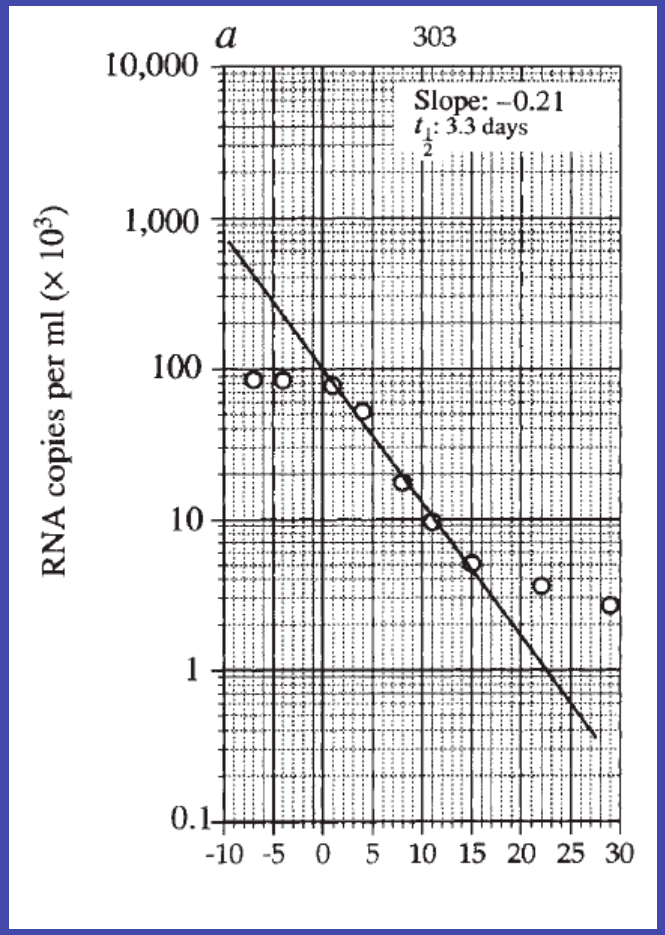
David D. Ho, Avidan U. Neumann*†, Alan S. Perelson†, Wen Chen, John M. Leonard‡ & Martin Markowitz

1995



Patients treated with experimental HIV protease inhibitor

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



$$\frac{dT}{dt} = \lambda - kVT - dT$$

$$\frac{dT^*}{dt} = kVT - \mu T^*$$

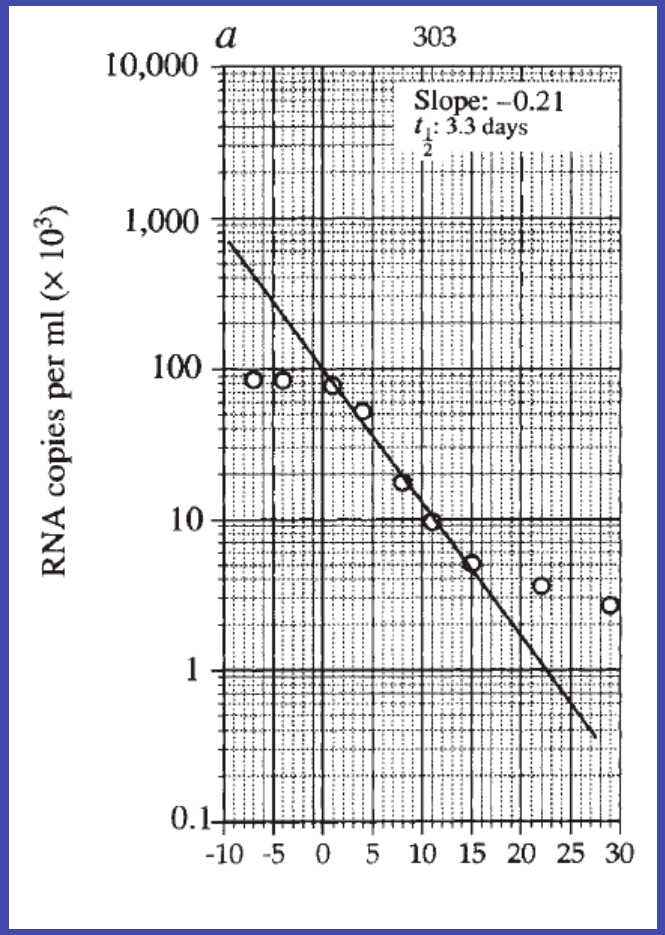
$$\frac{dV}{dt} = pT^* - cV$$

- Assume steady state pre-treatment and that T* turnover is slower than V

$$\frac{dV}{dt} = pT_{SS}^* - cV \qquad V(0) = V_{SS}$$

$$V(t) = \frac{pT_{SS}^*}{c}\left(1 - e^{-ct}\right) + V_{SS}e^{-ct}$$

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



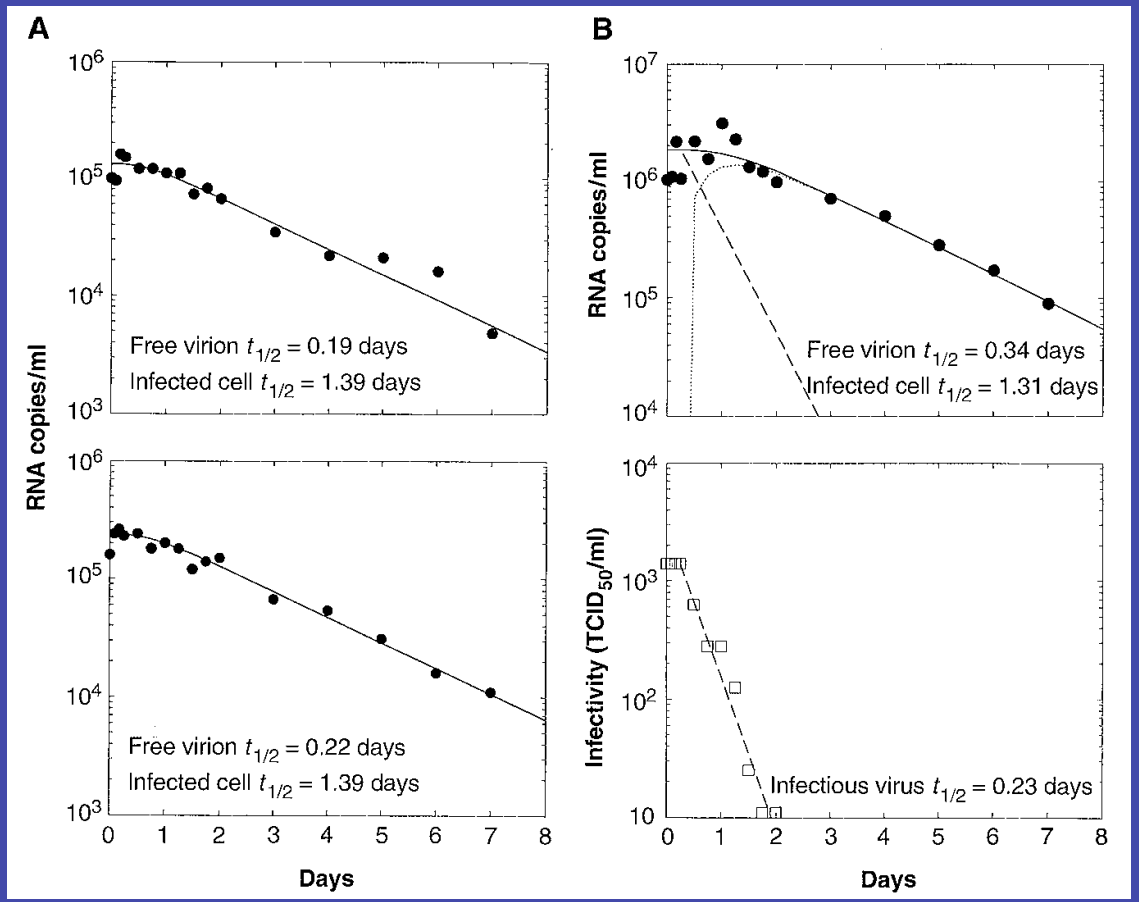
$$V(t) = \frac{pT^*_{SS}}{c}\left(1 - e^{-ct}\right) + V_{SS}e^{-ct}$$

- If drug is perfect then p=0 and the slope of the log data is c
- Imperfect drug: c > slope

- Model+data tells us that viral half-life *in-vivo* is short (<1day).
- Virus must turn over rapidly
- Lots of production and clearance
- Many mutants, immune escape
- This was a big change in 1995!

HIV-1 Dynamics in Vivo: Virion Clearance Rate, Infected Cell Life-Span, and Viral Generation Time

Alan S. Perelson, Avidan U. Neumann, Martin Markowitz, John M. Leonard, David D. Ho*



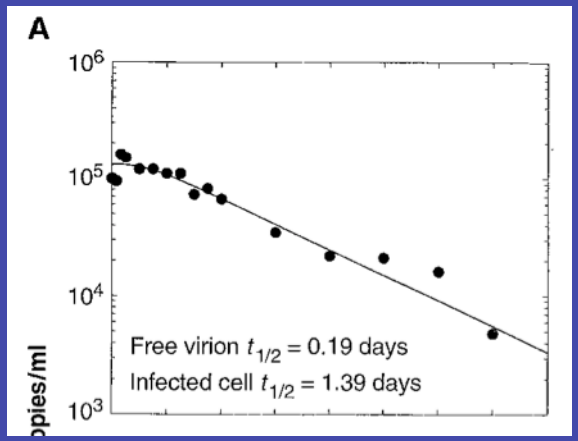
- This drug makes all new viruses non-infectious, but still detected in assay.
- Pre-treatment: assume V, T and T* at steady state.
- Post-treatment:

$$\frac{dT^*}{dt} = kT_{SS}V_I - \mu T^*$$

$$\frac{dV_I}{dt} = -cV_I$$

$$\frac{dV_{NI}}{dt} = pT^* - cV_{NI}$$

HIV-1 Dynamics in Vivo: Virion Clearance Rate, Infected Cell Life-Span, and Viral Generation Time



$$\frac{dT^*}{dt} = kT_{SS}V_I - \mu T^*$$

$$\frac{dV_I}{dt} = -cV_I$$

$$\frac{dV_{NI}}{dt} = pT^* - cV_{NI}$$

$$V(t) = V(0)e^{-ct} + \frac{cV_0}{c-\mu}\left(\frac{c}{c-\mu}\left[e^{-\mu t} - e^{-ct}\right] - \mu t e^{-ct}\right)$$

Fit c, μ, V(0) to data
Obtain half-life of virus of <6hrs

HIV-1 Dynamics in Vivo: Virion Clearance Rate, Infected Cell Life-Span, and Viral Generation Time

- Proved massive ongoing replication and clearance of HIV
- Showed that
  - Any effective antiviral should work within a few days
  - HIV generates escape mutants very fast (mutates every bp daily)
- *"The failure of the current generation of antiviral agents, when used as monotherapy, is the inevitable consequence of the dynamics of HIV replication. Effective treatment must instead force the virus to mutate simultaneously at multiple positions by means of a combination of multiple, potent antiretroviral agents."*

1996

Summary

$$\frac{dT}{dt} = \lambda - kVT - dT$$

$$\frac{dT^*}{dt} = kVT - \mu T^*$$

$$\frac{dV}{dt} = pT^* - cV$$

- The standard model has been used in hundreds (thousands?) of disease studies.
- Hepatitis C, influenza, measles, …
- Major success of mathematical biology
- Extended to include different target cells, multiple strains, changes over time,…

Main Criticism:
The infection is controlled only by loss of target cells – no immune system