Stochastic approaches to within-host viral dynamics

Daniel Coombs
Department of Mathematics & Institute of Applied Mathematics
University of British Columbia

COLD
FLAT
WET
FRENCH
BEAUFORT SEA
BAFFIN SEA
Banks Island
Victoria Island
Somerset Island
Prince of Wales Island
King William Island
Baffin Island
Davis Strait
Foxe Basin
NUNAVUT TERRITORY
YUKON TERRITORY
NORTHWEST TERRITORIES
ALASKA
US
ARCTIC CIRCLE
Great Bear Lake
Great Slave Lake
Hudson Bay
Labrador Sea
Gulf of Alaska
BRITISH COLUMBIA
ALBERTA
MANITOBA
ONTARIO
QUÉBEC
NEWFOUNDLAND
Queen Charlotte Islands
Vancouver Island
PACIFIC OCEAN
ATLANTIC OCEAN
NOVA SCOTIA
UNITED STATES
Whitehorse
Yellowknife
Iqaluit
Edmonton
Calgary
Regina
Saskatoon
Winnipeg
Vancouver
Victoria
Toronto
OTTAWA
Montréal
Québec
Halifax
St-John's
Seattle
Portland
Minneapolis
Chicago
Detroit
Boston
New York


BRITISH COLUMBIA
Port McNeill
Vancouver Island
Powell River
Strait of Georgia
Vancouver
CANADA
USA
Port Alberni
Nanaimo
Victoria
Juan De Fuca Strait
Pacific
Ocean
Everett
Seattle
WASHINGTON
50°
48°
128°
126°


Mathematics
Annex

Coombs "lab" at UBC

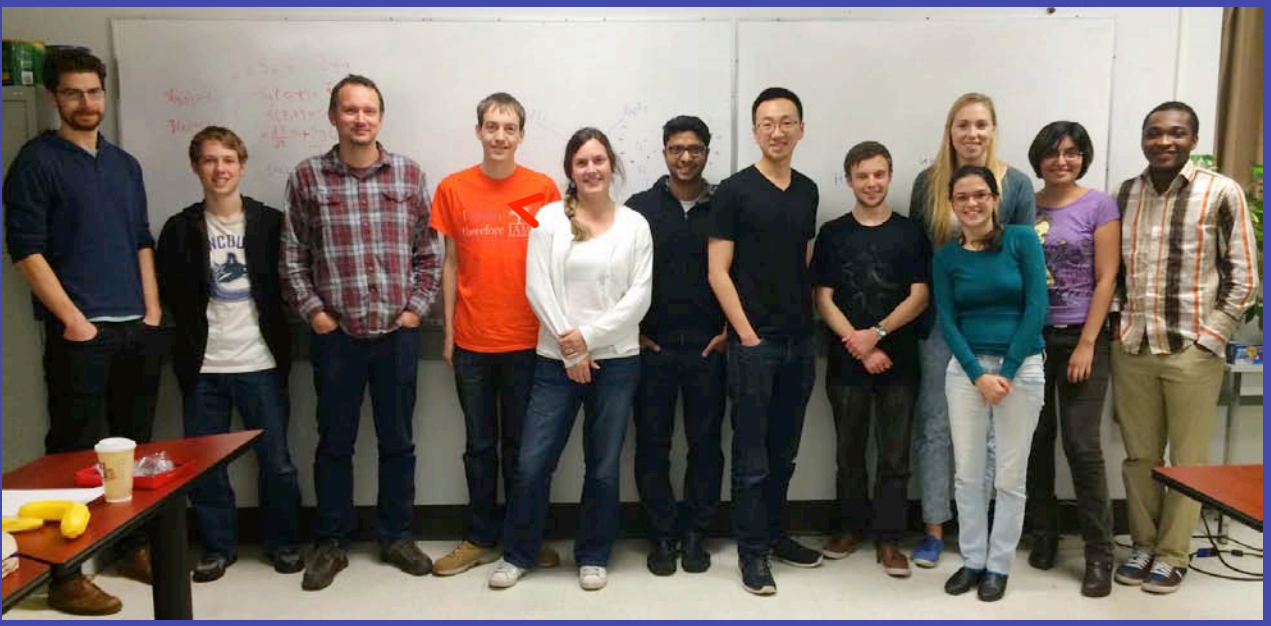
- Immune (B and T) cell signaling
  - Surface receptor motion (afternoon talk)
  - Spatial localization of receptors and signaling proteins
  - Parameter measurement and model building

- Virus dynamics, epidemiology and viral evolution
  - HIV modeling: evolution and transmission
  - Multiscale modeling of within- and between- host systems

- We collaborate with experimentalists at UBC and elsewhere and also do our own fluorescence microscopy on B cells.

NSERC CRSNG
MITACS
CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Acknowledgements

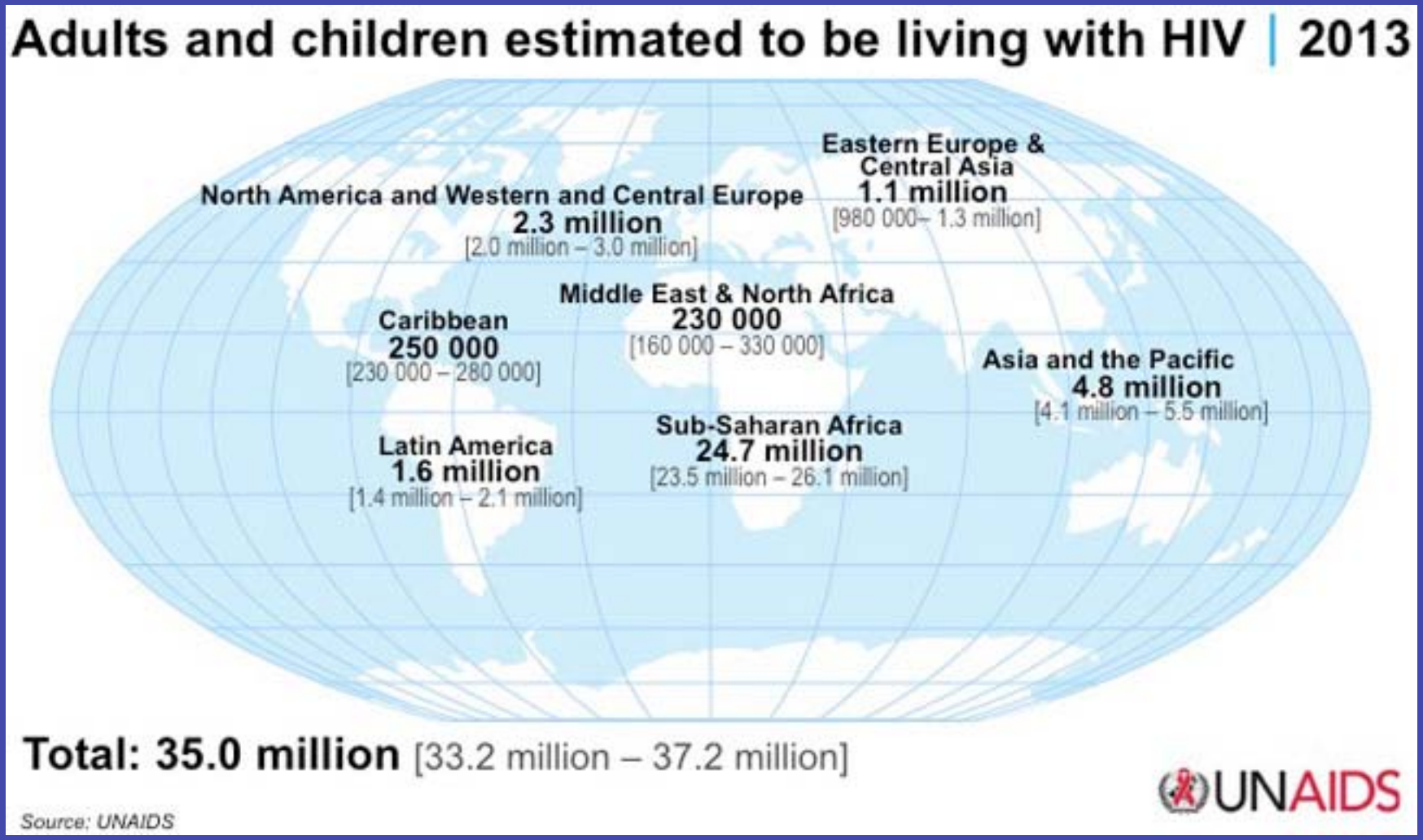


- Bernhard Konrad
- Jessica Conway

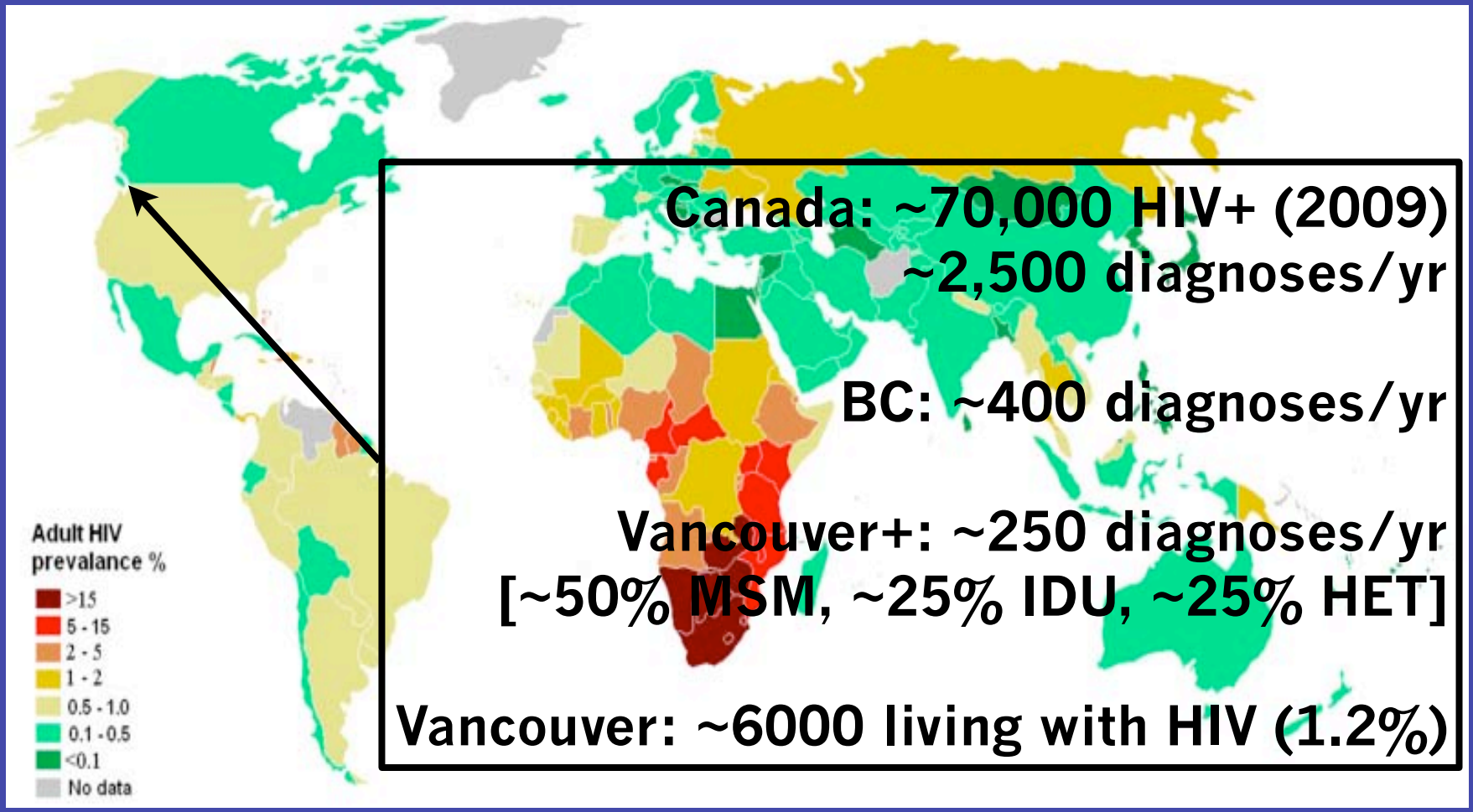
Topics for today

1. **Background on HIV epidemiology and biology**
2. Within-host mathematical models of HIV infection
3. Introduction to branching process models
4. Case studies: early and treated infection

HIV as a global epidemic

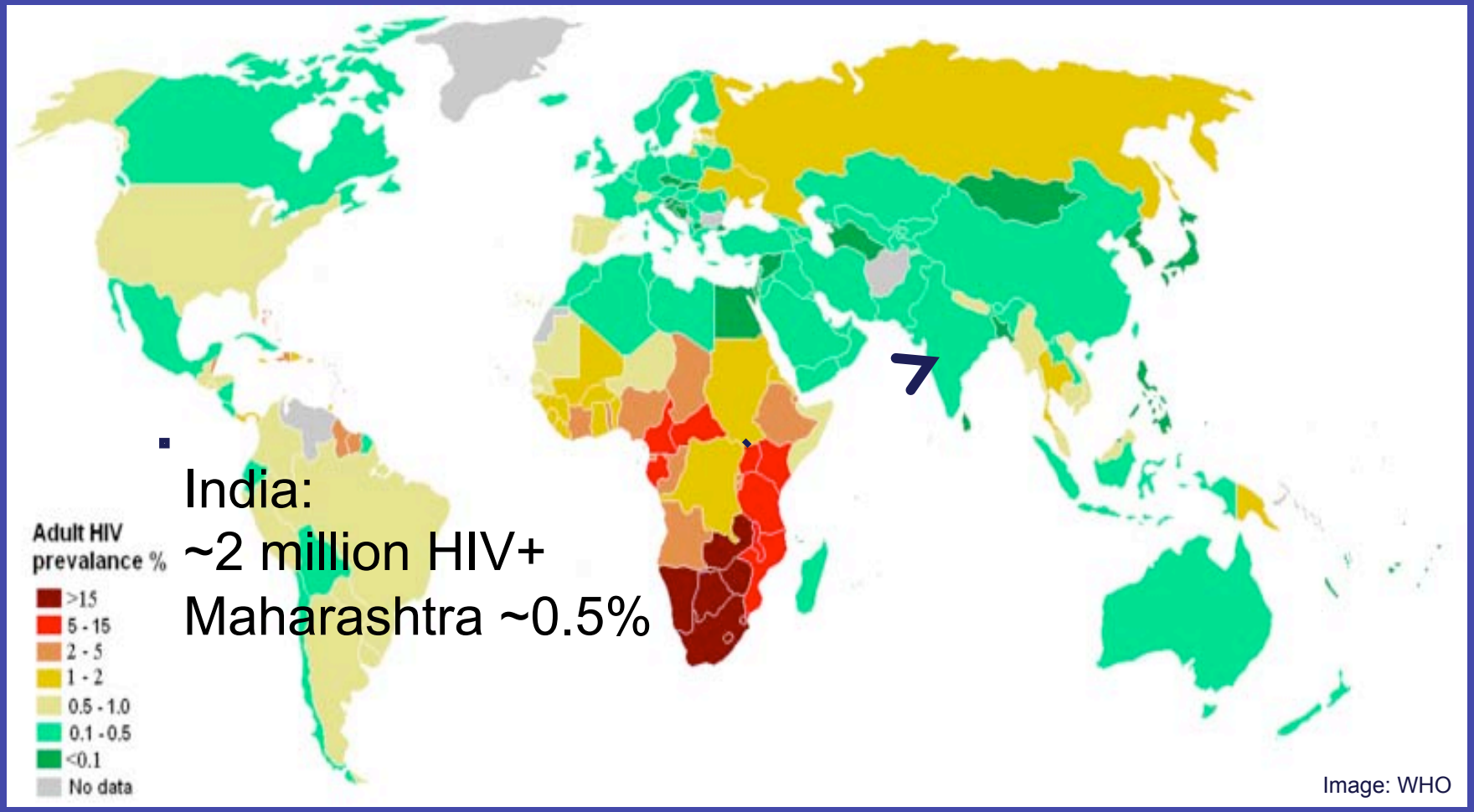


HIV as a global epidemic



Someone is infected in Canada every 3 hours

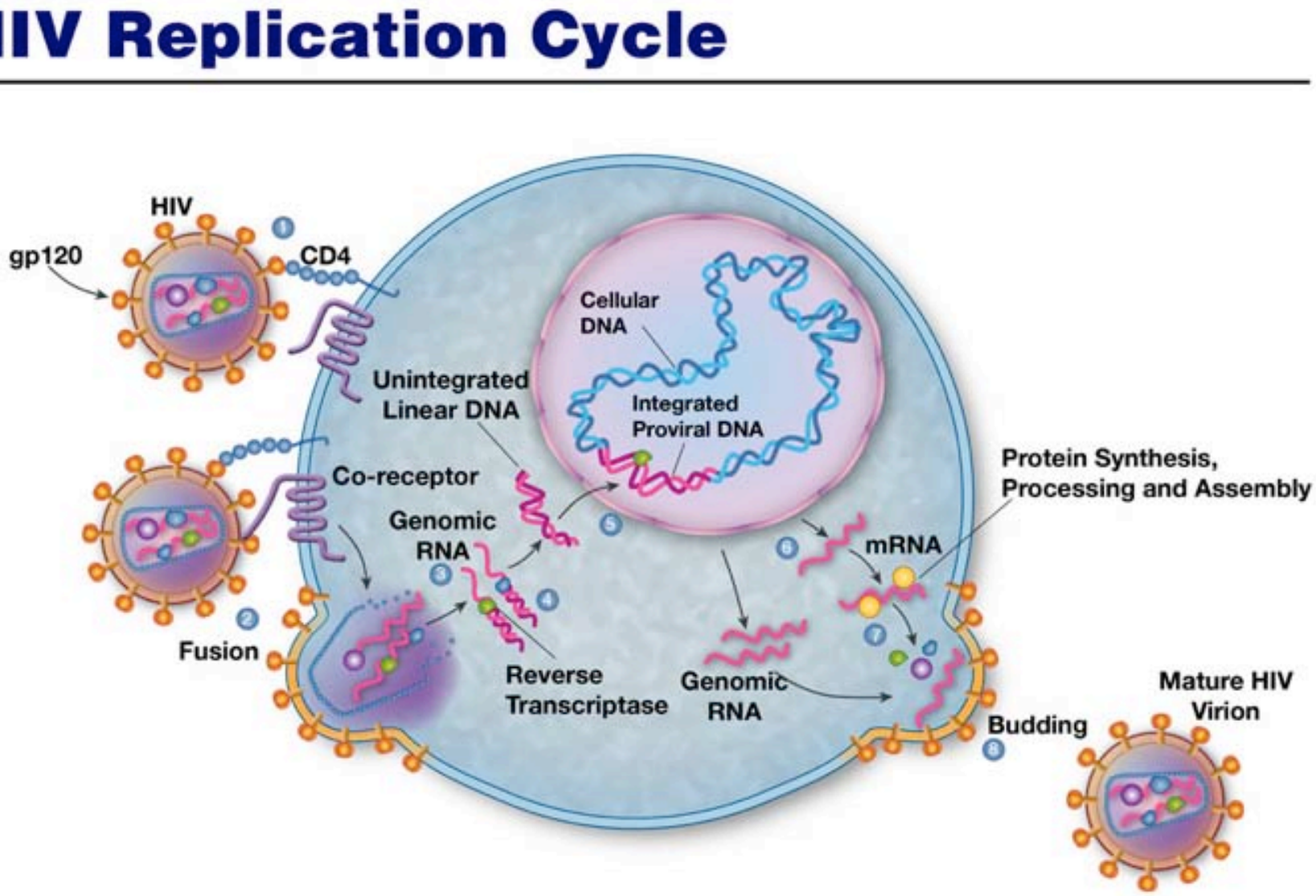
HIV as a global epidemic



History of HIV/AIDS

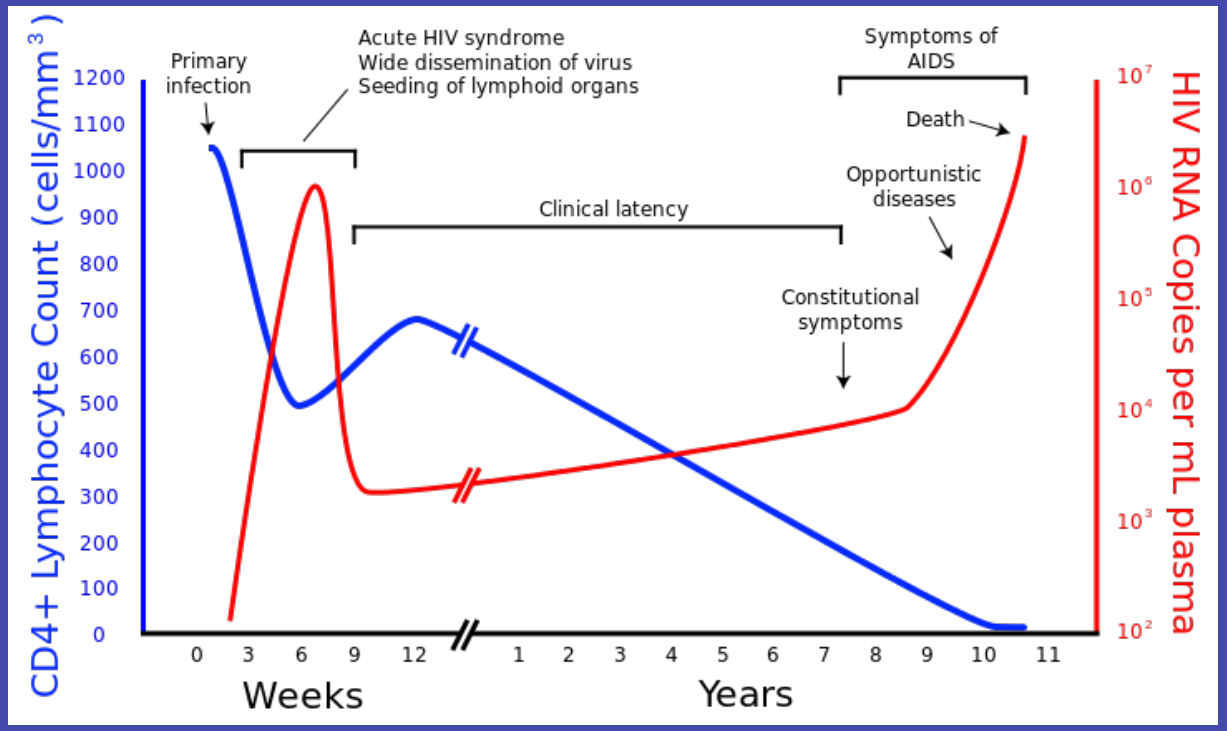
- Phylogenetics indicate simian-human transfer around 1900s
- First retroactively confirmed case – 1959
- Awareness of AIDS (hemophiliacs, MSM) in the USA – 1980
- Virus isolated and named – 1983
- Fear
- First treatment approved – 1987

Within-host HIV



Within-host HIV

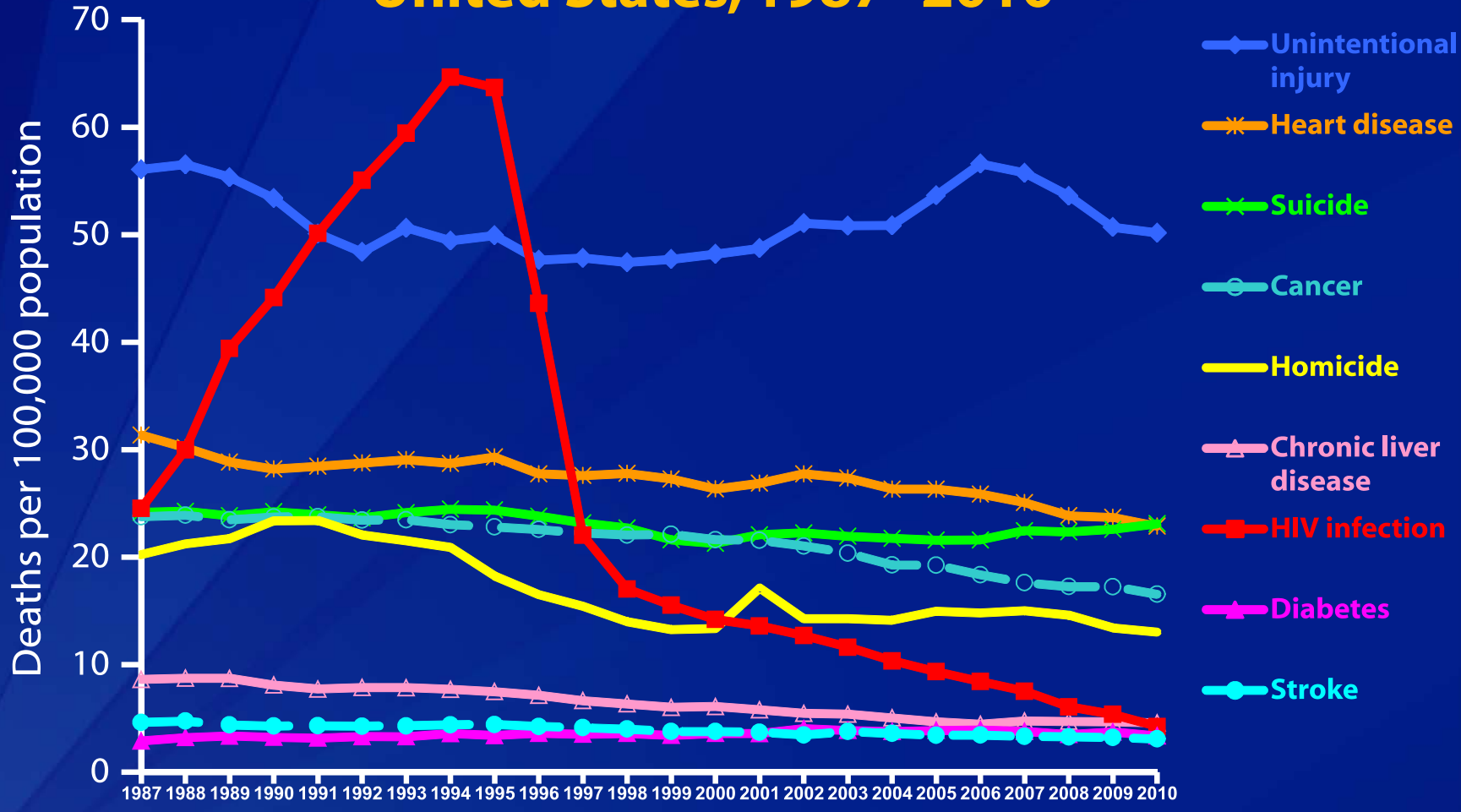
- Systemic infection (virus detectable in blood) in 10 days
- Peak viremia 21-28 days
- Decline in virus, “set point”
- Progression to AIDS ~10yr



ART (anti-retroviral therapy)

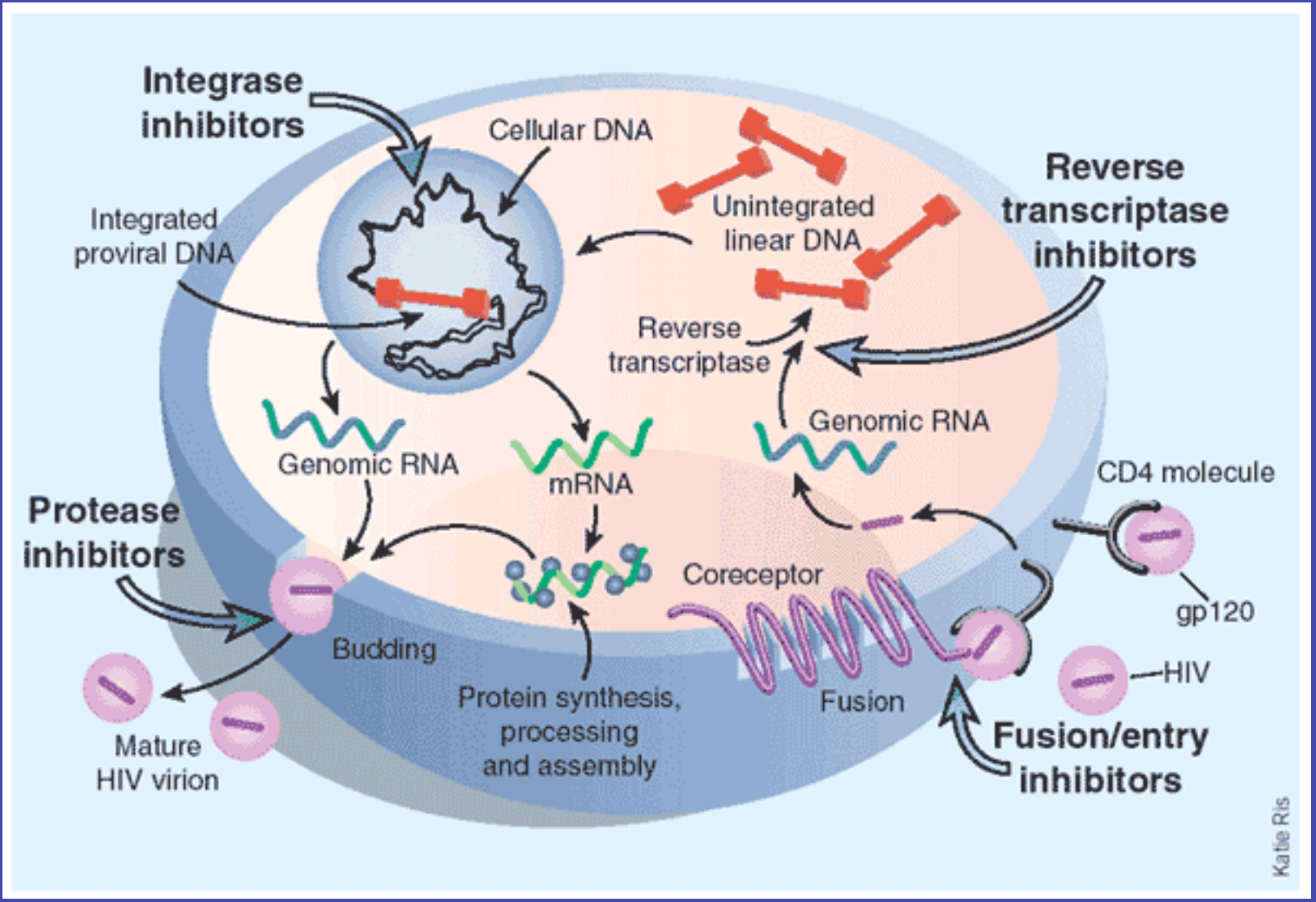
- Successful ART since mid-1990s
    - Reduces virus in blood to undetectable levels
    - Not curative
    - Immune system rebounds, mortality reduced
- Side-effects
- Cost

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

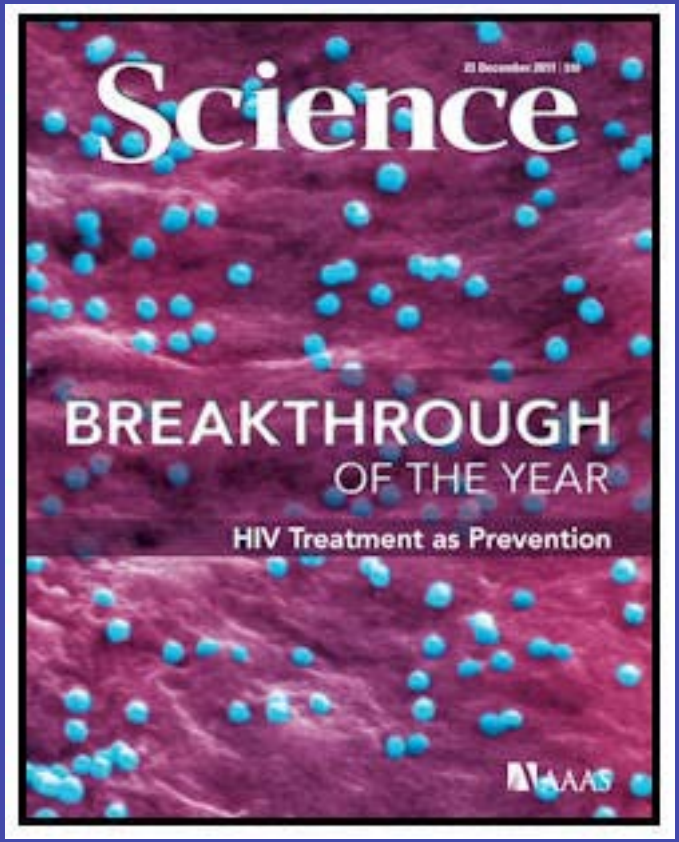


Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for *ICD-10* rules instead of *ICD-9* rules.

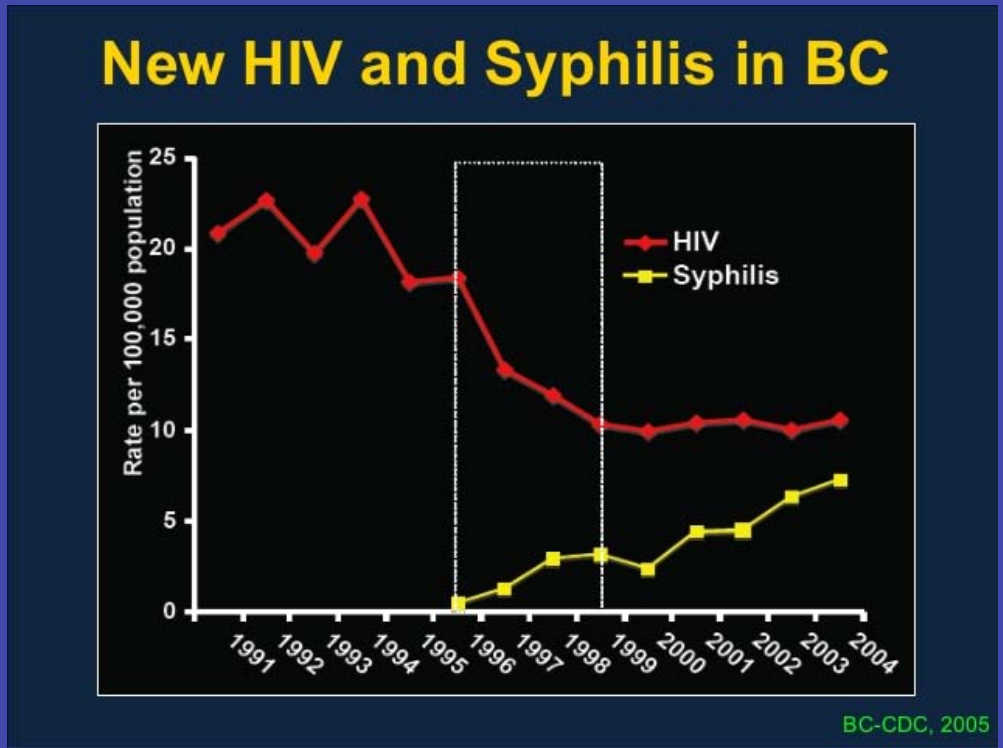
HIV Lifecycle and Drug actions



Treatment reduces transmissibility



Julio Montaner,
BC Centre for Excellence in HIV/AIDS

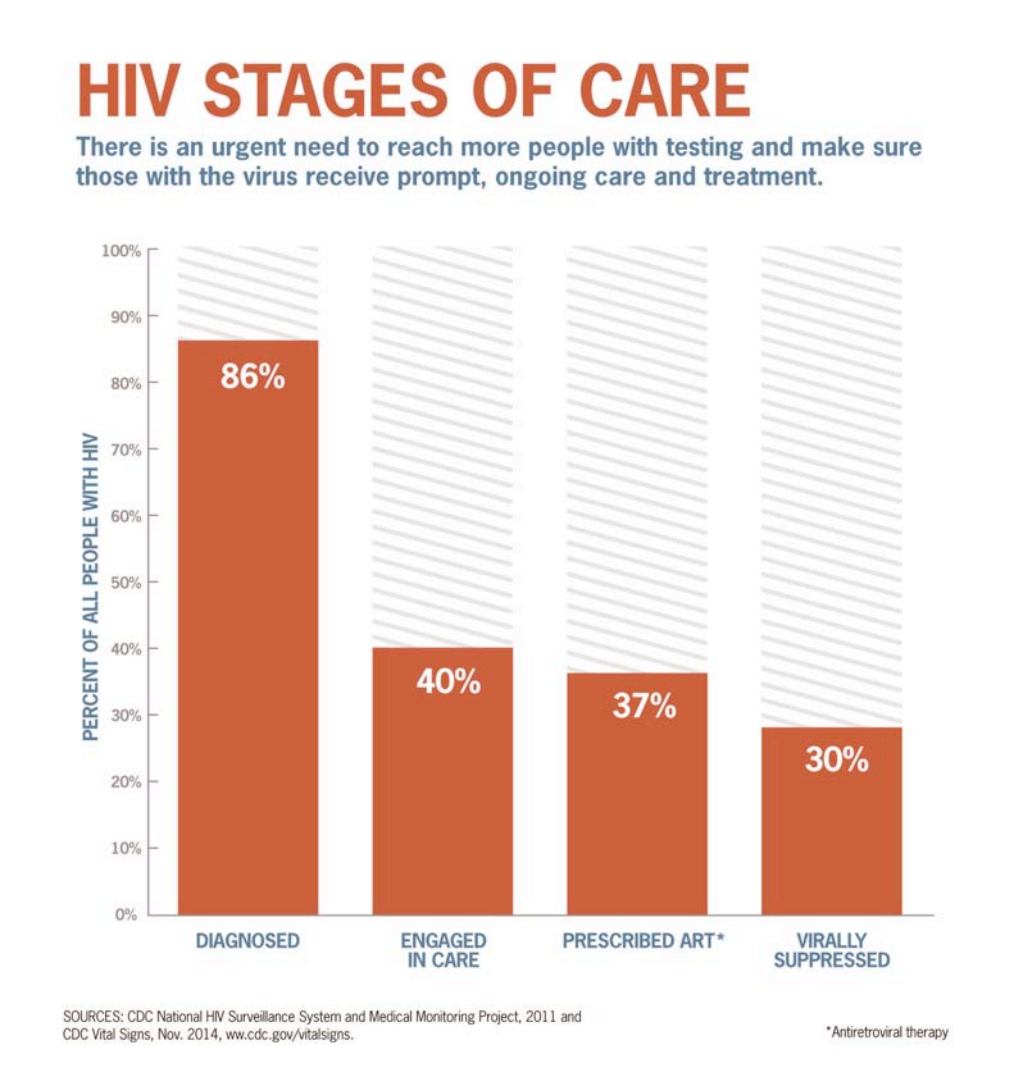


- 2008 Swiss statement

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

World AIDS day 2014: Only 3 in 10 people in the USA with HIV have virus in check (CDC)



(13% of 18-24yo)

Proceedings of the National Academy of Sciences of the United States of America

> Early Edition > Rebecca Payne, doi: 10.1073/pnas.1413339111

CrossMark click for updates

Impact of HLA-driven HIV adaptation on virulence in populations of high HIV seroprevalence

Rebecca Payne[a,1], Maximilian Muenchhoff[a,1], Jaclyn Mann[b], Hannah E. Roberts[c,d], Philippa Matthews[a], Emily Adland[a], Allison Hempenstall[a], Kuan-Hsiang Huang[c,d], Mark Brockman[e,f], Zabrina Brumme[e,f], Marc Sinclair[a], Toshiyuki Miura[g], John Frater[c,d,h], Myron Essex[i,j], Roger Shapiro[i,j], Bruce D. Walker[b,k], Thumbi Ndung'u[b,k], Angela R. McLean[c,l], Jonathan M. Carlson[m], and Philip J. R. Goulder[a,b,2]

Author Affiliations

Edited by Rafi Ahmed, Emory University, Atlanta, GA, and approved October 31, 2014 (received for review July 15, 2014)

Significance

Factors that influence the virulence of HIV are of direct relevance to ongoing efforts to contain, and ultimately eradicate, the HIV epidemic. We here investigate in Botswana and South Africa, countries severely affected by HIV, the impact on HIV virulence of adaptation of HIV to protective HLA alleles such as HLA-B*57. In Botswana, where the epidemic started earlier and reached higher adult seroprevalence than in South Africa, HIV replication capacity is lower. HIV is also better adapted to HLA-B*57, which in Botswana has no protective effect, in contrast to its impact in South Africa. Modelling studies indicate that increasing antiretroviral therapy access may also contribute to accelerated declines in HIV virulence over the coming decades.

PNAS, Dec 1 2014

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

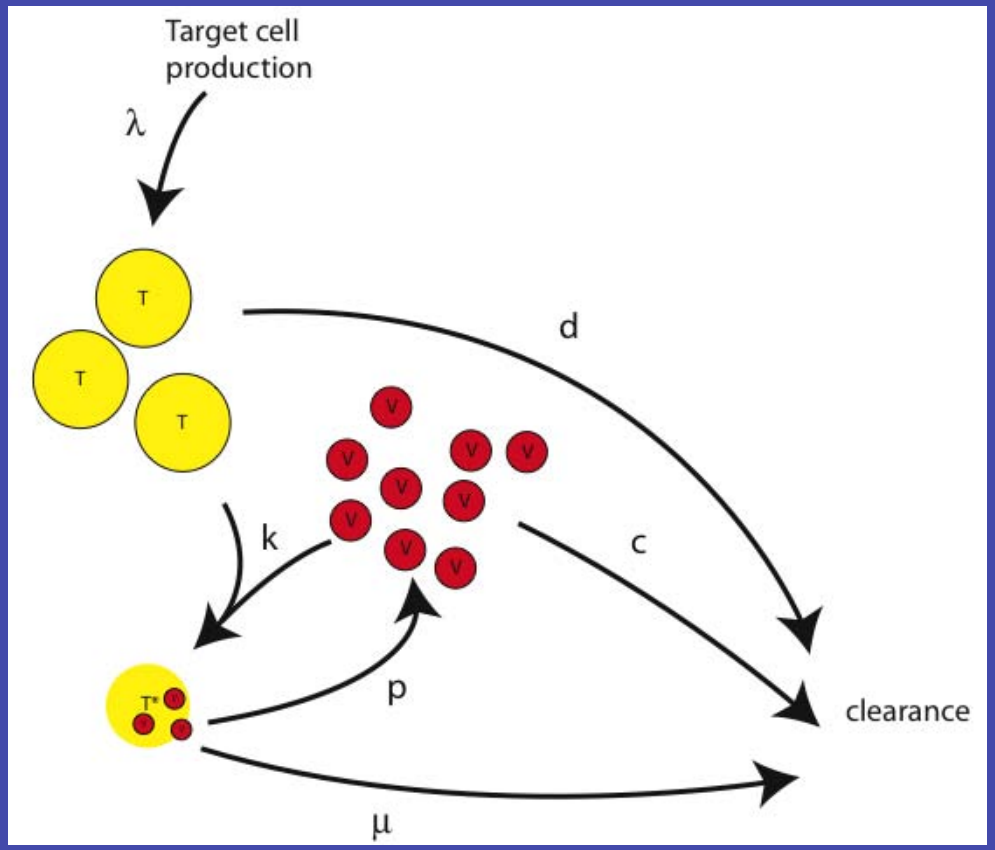
Stochastic approaches to within-host viral dynamics

Daniel Coombs
Department of Mathematics & Institute of Applied Mathematics
University of British Columbia

Topics for today

1. Background on HIV epidemiology and biology
2. **Within-host mathematical models of HIV infection**
3. Introduction to branching process models
4. Case studies: early and treated infection

"Standard" ODE model of HIV infection



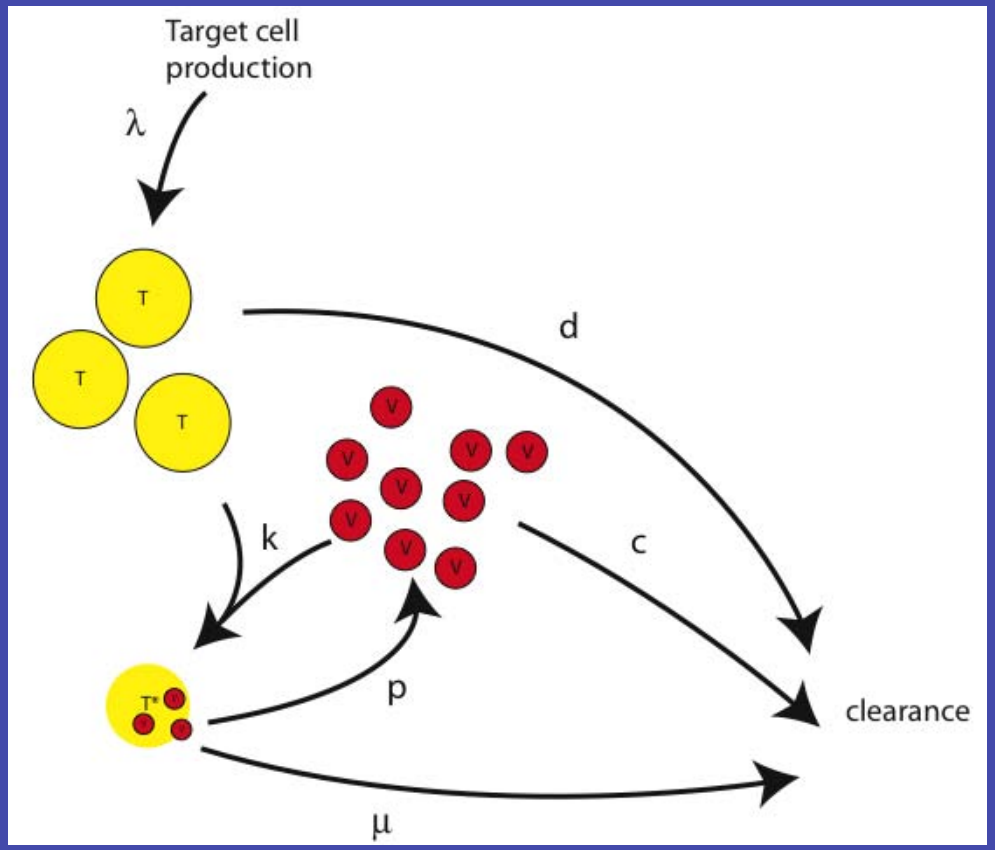
$$\frac{dT}{dt} = \lambda - kVT - dT$$

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

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

$T(t)$ = # of uninfected T cells
$T^*(t)$ = # of infected T cells
$V(t)$ = # of free virus
λ = target cell production rate
d = background T cell death rate
μ = infected cell death rate
k = mass-action infectivity
c = clearance rate of virions
p = production rate of virions

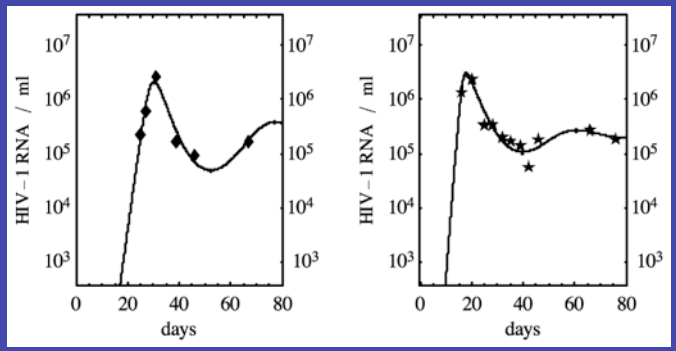
"Standard" ODE model of HIV infection



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

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

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



- 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

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

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

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

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:

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

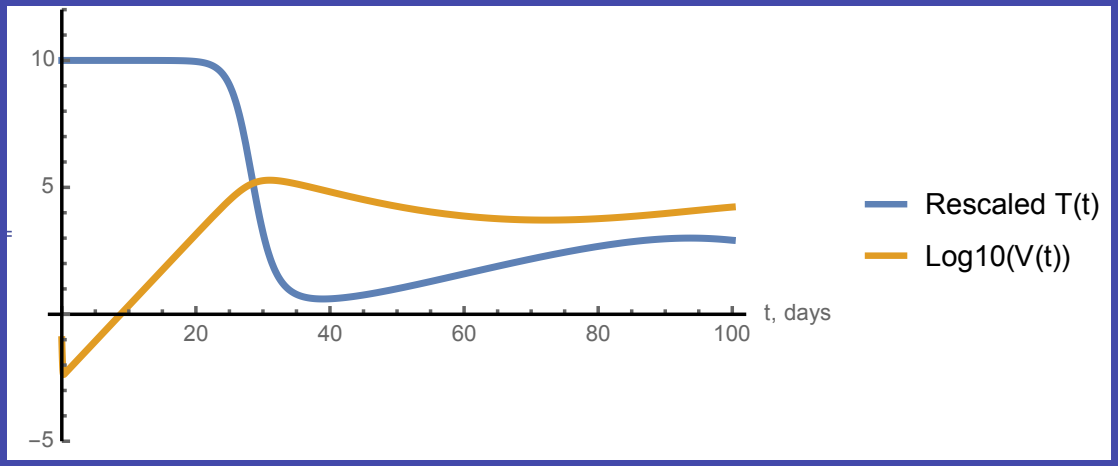
Stability condition:

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

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

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

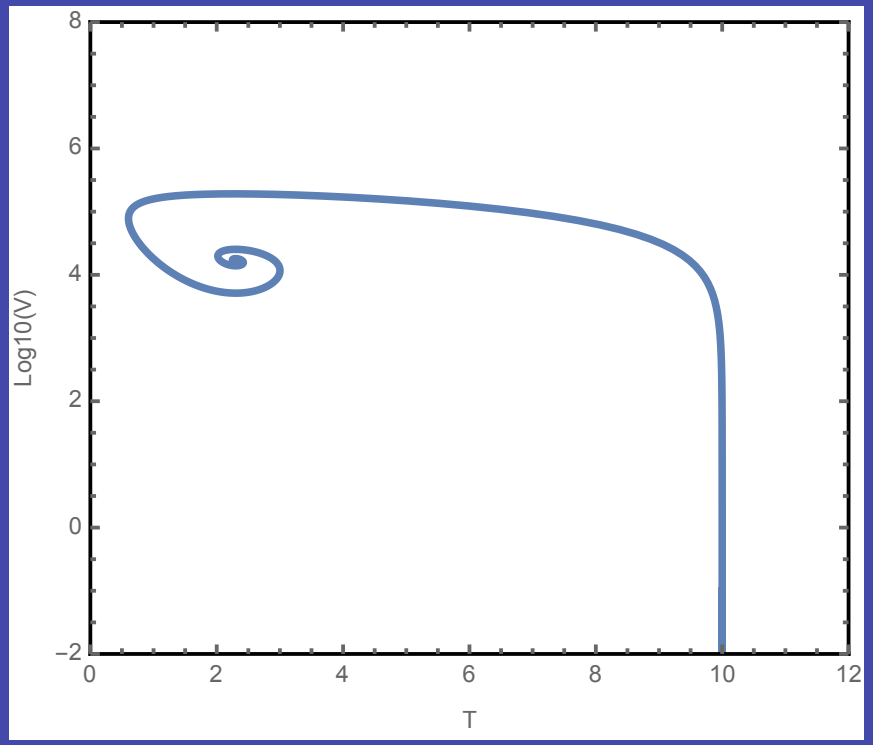
We can also (using Lyapunov functions) show that this condition controls global stability.



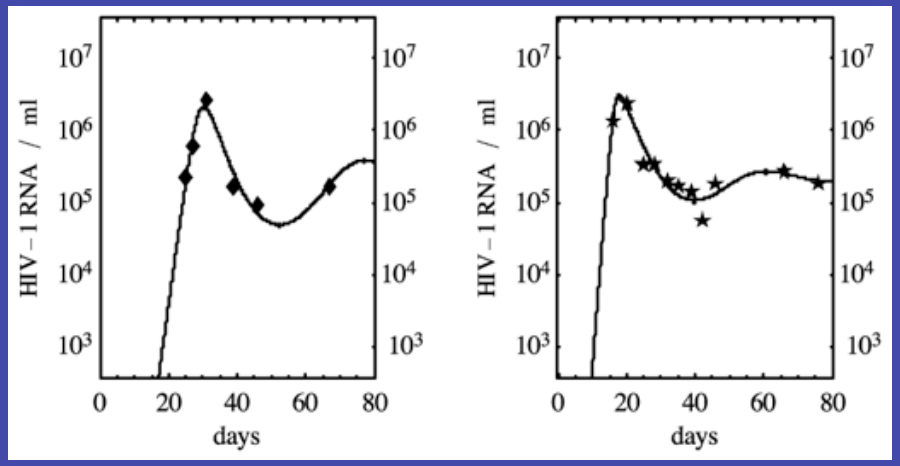
$$\frac{dT}{dt} = \lambda - kVT - dT$$

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

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



- 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

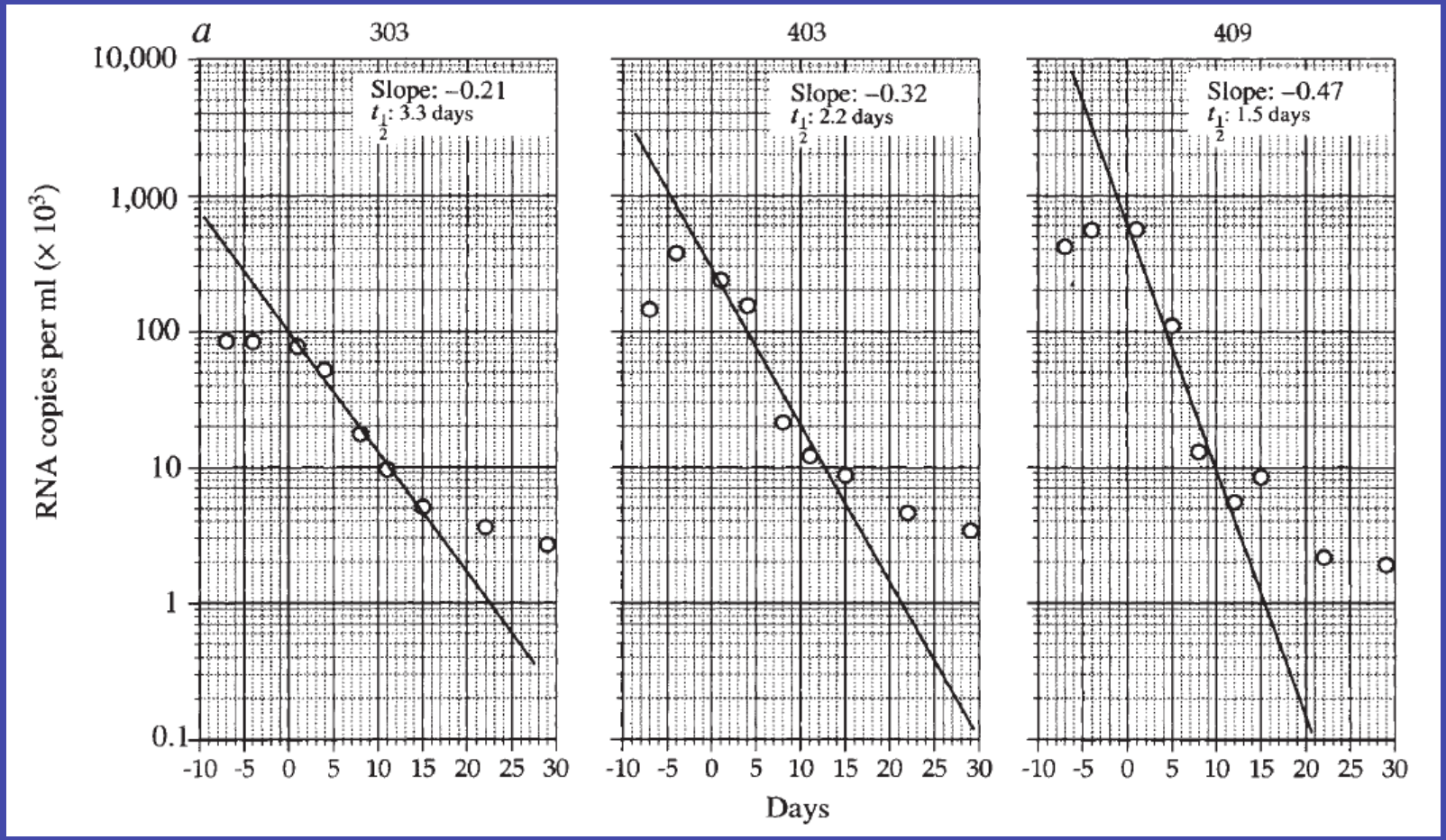
David D. Ho, Avidan U. Neumann[*†], Alan S. Perelson[†], Wen Chen, John M. Leonard[‡] & Martin Markowitz

Aaron Diamond AIDS Research Center, NYU School of Medicine, 455 First Avenue, New York, New York 10016, USA
* Santa Fe Institute, Santa Fe, New Mexico 87501, USA
† Theoretical Division, Los Alamos National Laboratory, Los Alamos, New Mexico 87545, USA
‡ Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, Illinois 60064, USA

Treatment of infected patients with ABT-538, an inhibitor of the protease of human immunodeficiency virus type 1 (HIV-1), causes plasma HIV-1 levels to decrease exponentially (mean half-life, 2.1 ± 0.4 days) and CD4 lymphocyte counts to rise substantially. Minimum estimates of HIV-1 production and clearance and of CD4 lymphocyte turnover indicate that replication of HIV-1 *in vivo* is continuous and highly productive, driving the rapid turnover of CD4 lymphocytes.

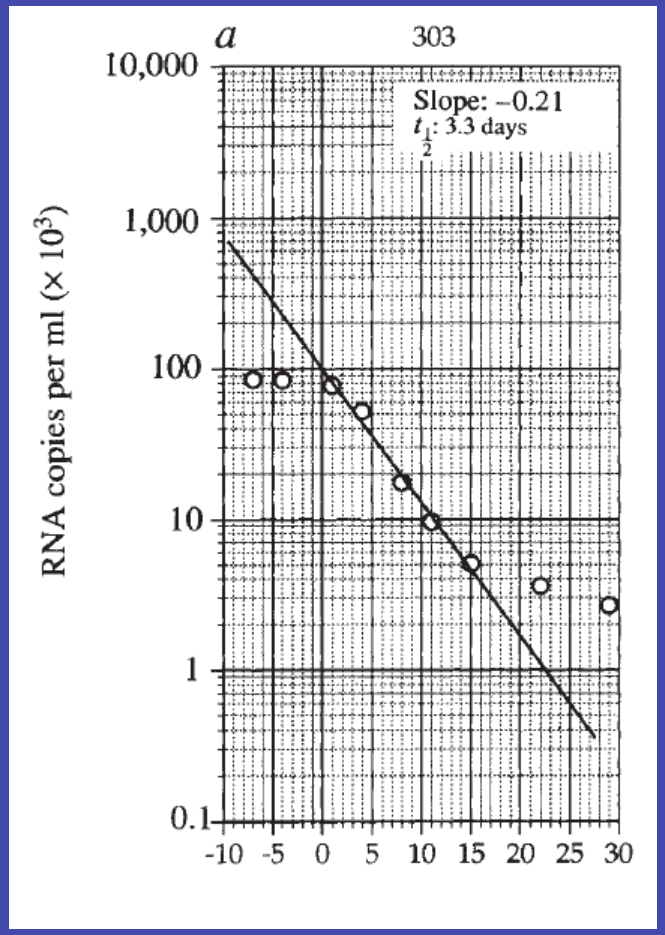
Nature, 1995

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



Patients treated with experimental HIV protease inhibitor

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



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

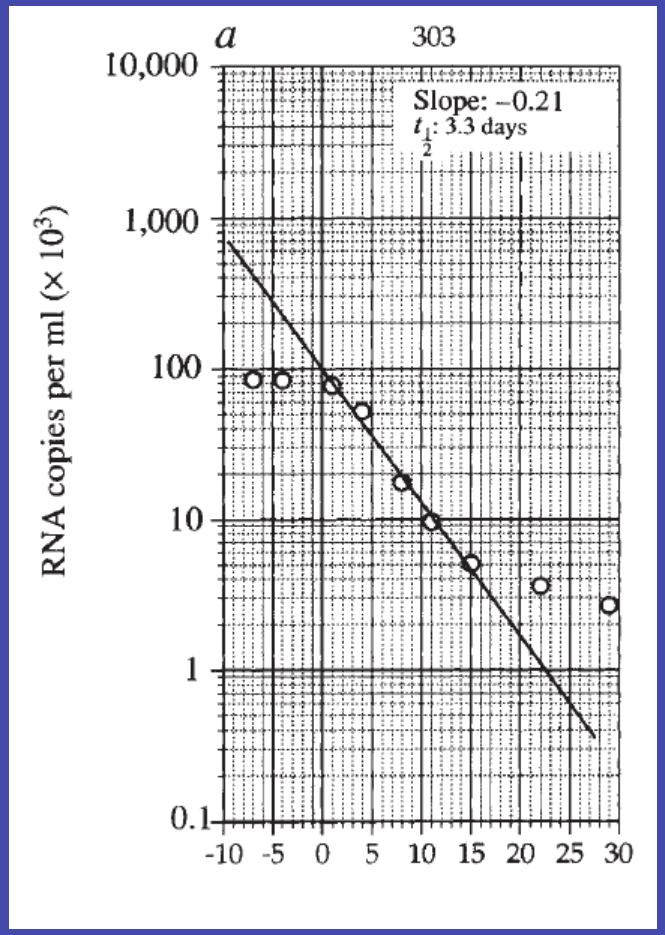
$$\frac{dT^*}{dt} = kVT - \mu T^*$$

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

- Assume st.st. pre-treatment and that T* turnover is slower than V

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

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



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

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

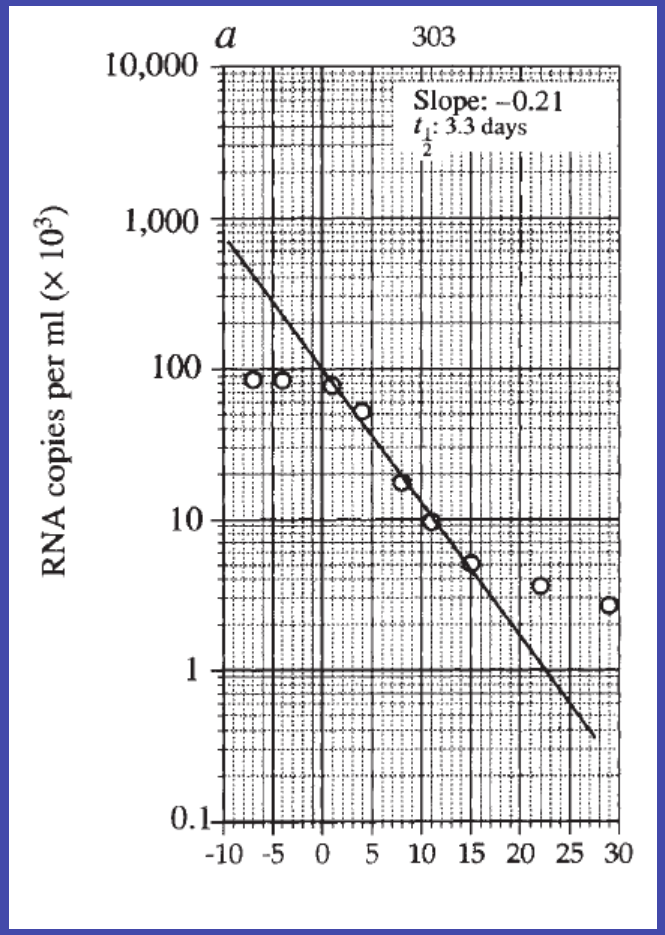
$$\frac{dV}{dt} = pT^* - cV$$

- Assume st.st. 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.
- Virus must turn over rapidly
- Lots of production and clearance
- Many mutants, immune escape
- This was a big change in 1995!

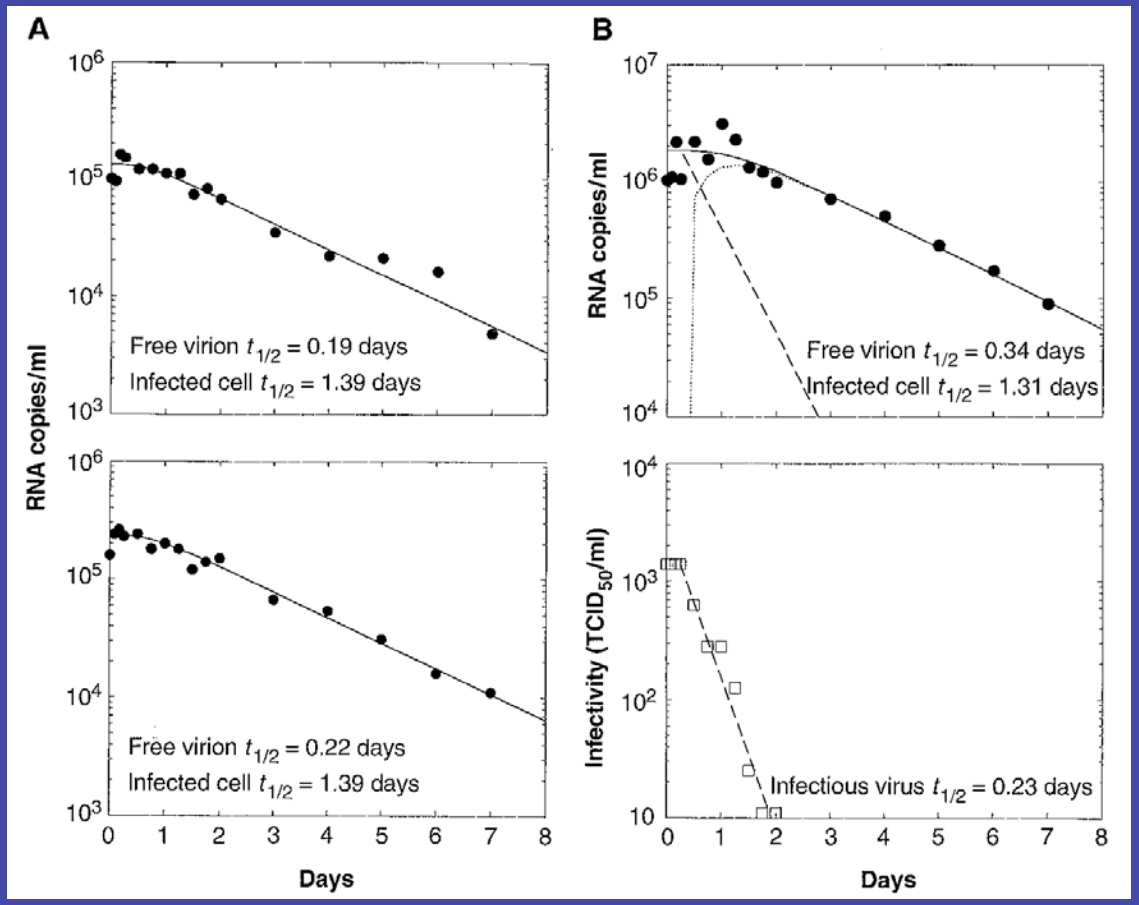
HIV-1 Dynamics in Vivo: Virion Clearance Rate, Infected Cell Life-Span, and Viral Generation Time

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

A new mathematical model was used to analyze a detailed set of human immunodeficiency virus–type 1 (HIV-1) viral load data collected from five infected individuals after the administration of a potent inhibitor of HIV-1 protease. Productively infected cells were estimated to have, on average, a life-span of 2.2 days (half-life $t_{1/2} = 1.6$ days), and plasma virions were estimated to have a mean life-span of 0.3 days ($t_{1/2} = 0.24$ days). The estimated average total HIV-1 production was 10.3×10^9 virions per day, which is substantially greater than previous minimum estimates. The results also suggest that the minimum duration of the HIV-1 life cycle in vivo is 1.2 days on average, and that the average HIV-1 generation time—defined as the time from release of a virion until it infects another cell and causes the release of a new generation of viral particles—is 2.6 days. These findings on viral dynamics provide not only a kinetic picture of HIV-1 pathogenesis, but also theoretical principles to guide the development of treatment strategies.

Science, 1996

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



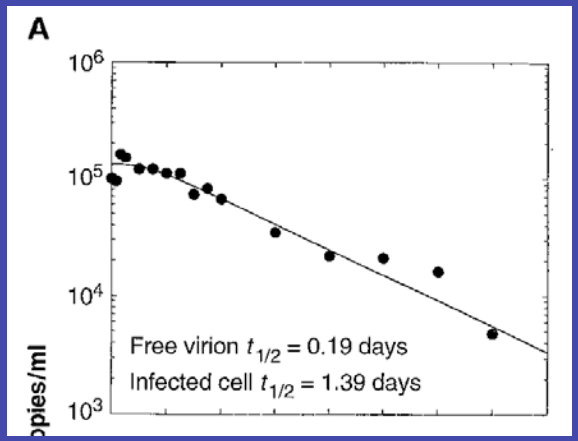
- Data taken every day!
- This drug makes all new viruses non-infectious, but still detected in assay.
- Pre-treatment: assume V, T and T* at steady state.
- Post-treatment:

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

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

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

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



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

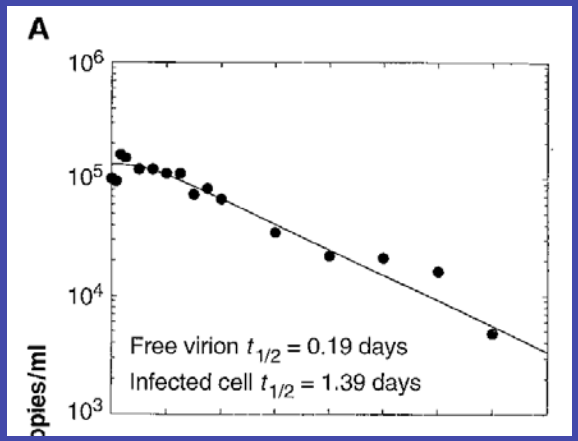
$$\frac{dV_I}{dt} = -cV_I$$

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

$$\frac{d}{dt}\begin{pmatrix} T^* \\ V_I \\ V_{NI} \end{pmatrix} = \begin{pmatrix} -\mu & kT_{SS} & 0 \\ 0 & -c & 0 \\ p & 0 & -c \end{pmatrix}\begin{pmatrix} T^* \\ V_I \\ V_{NI} \end{pmatrix}$$

Eigenvalues –c, -c and –μ

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



$$\frac{dT^*}{dt} = kT_{SS}V_I - \mu T^*$$
$$\frac{dV_I}{dt} = -cV_I$$
$$\frac{dV_{NI}}{dt} = pT^* - cV_{NI}$$

$$\frac{d}{dt}\begin{pmatrix} T^* \\ V_I \\ V_{NI} \end{pmatrix} = \begin{pmatrix} -\mu & kT_{SS} & 0 \\ 0 & -c & 0 \\ p & 0 & -c \end{pmatrix}\begin{pmatrix} T^* \\ V_I \\ V_{NI} \end{pmatrix}$$

Eigenvalues –c, -c and –μ

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

Fit c, μ, V(0) to data

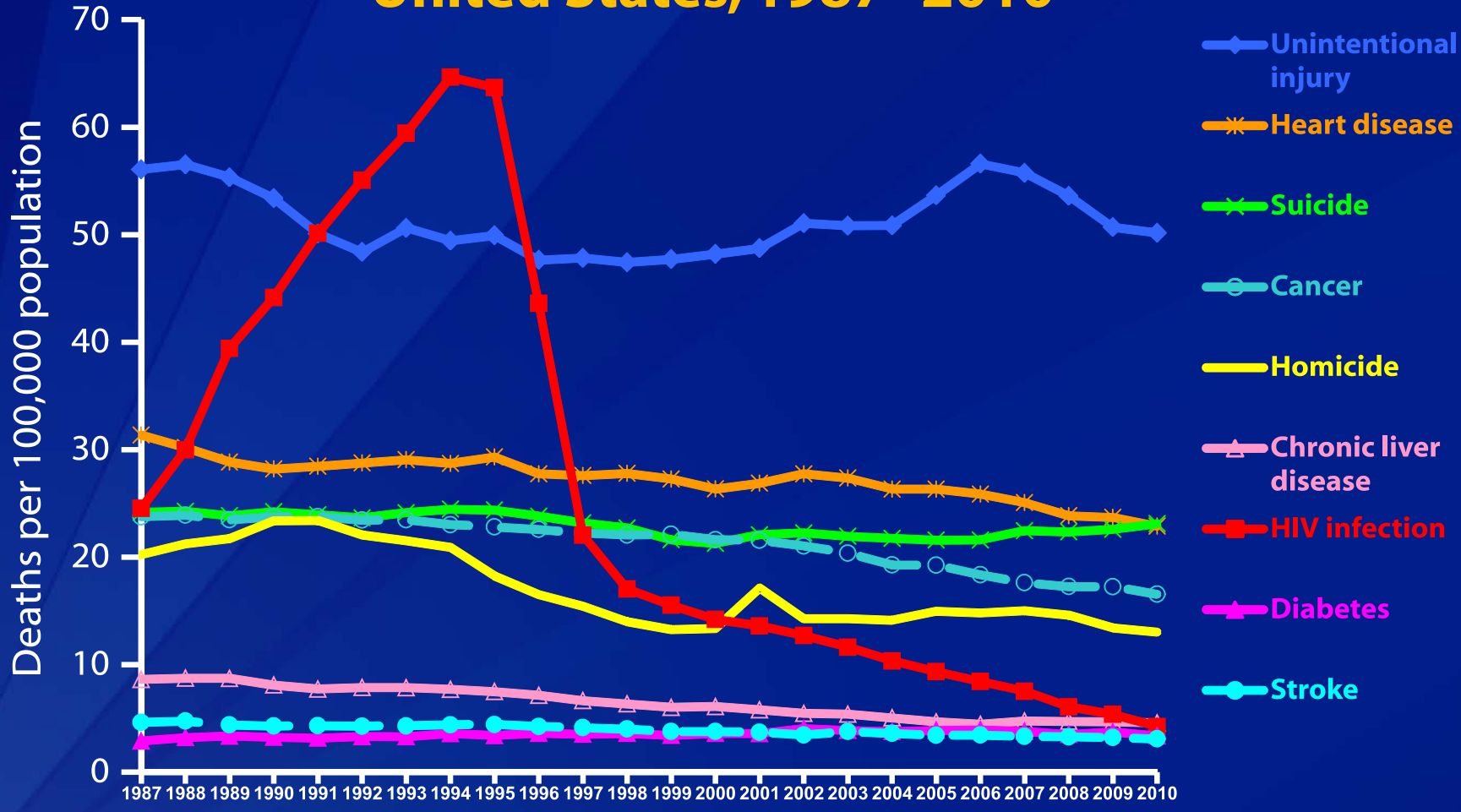
HIV-1 Dynamics in Vivo: Virion Clearance Rate, Infected Cell Life-Span, and Viral Generation Time

- Proved that massive ongoing cycle of replication and clearance of HIV accounts for loss of CD4 T cells
- Showed that
  - Any effective antiviral should work within a few days
  - HIV generates escape mutants very fast (mutates every base daily or thereabouts)

- *"The failure of the current generation of antiviral agents, when used as monotherapy, is the inievitable 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

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.

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

References

Virus Dynamics. M. Nowak and R. May. Oxford University Press.

P.W. Nelson and A.S. Perelson Mathematical analysis of HIV-1 dynamics in vivo. *SIAM Review* 41:3-44 (1999).

A.S. Perelson Modelling viral and immune system dynamics. *Nature Reviews Immunology* 2 (1), 28-36 (2002)

Stochastic approaches to within-host viral dynamics (Part 3)

Daniel Coombs
Department of Mathematics & Institute of Applied Mathematics
University of British Columbia

Topics for today

1. Background on HIV epidemiology and biology
2. Within-host mathematical models of HIV infection
3. **Introduction to branching process models**
4. Case studies: early and treated infection

Why use a stochastic model?

- **Differential equation models describe the *averaged* behaviour of the system :**
  - Apply to *many* players (cells, viruses in a human)
  - Apply to *frequent* events among the players

- **Stochastic effects are very important when numbers are small.**
  - Apply when there are few players
  - Apply when *rare events* are important

    - Me and the casino
    - Panda reproduction

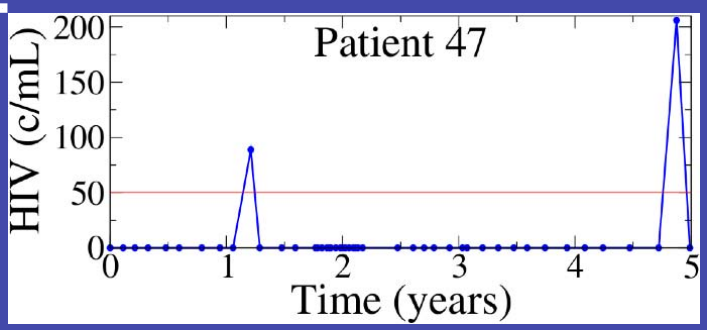
Stochastic events in HIV infection

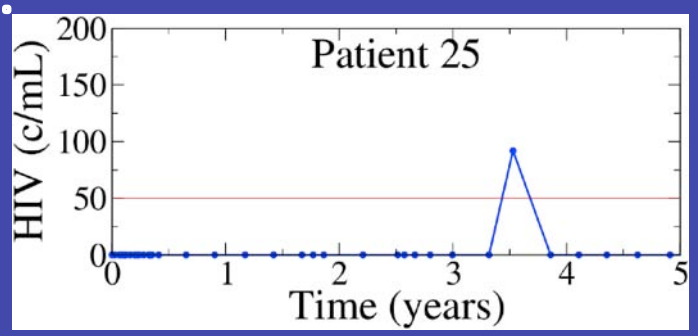
INITIAL INFECTION:

- Even *riskiest* sex or blood contact infects <2% of the time
  - Blood transfusion ~80%
- Most developed infections show a *single founder strain*
  - Suggests that the events of infection are intrinsically random

TREATED INFECTION:

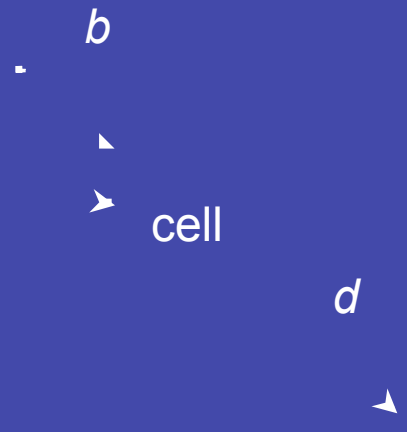
- On successful treatment, viral load is very low (5-50 copies/ml of blood)
- Viral *blips* are observed:
  - infrequent episodes of detectable but low viral load





Understanding a simpler birth-death process

- A population *N(t)* of cells that divide at rate *b* and die at rate *d*:
- ODE: $\frac{dN}{dt} = bN - dN$
- Soln: $N(t) = N_0 e^{(b-d)t}$

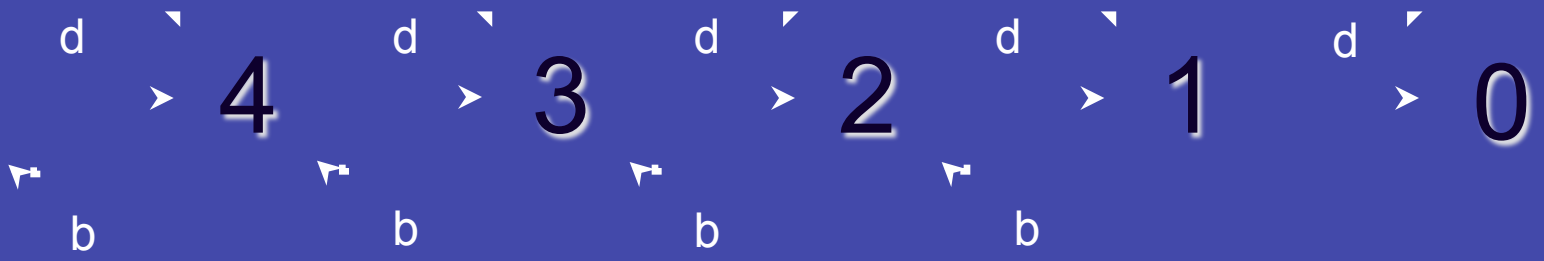


- Population becomes infinite if b > d
- Population goes extinct (in infinite time) if b < d
- How do we say “98% chance of extinction”?

Probabilistic interpretation

- Interpret d and b as the *rates* at which events happen

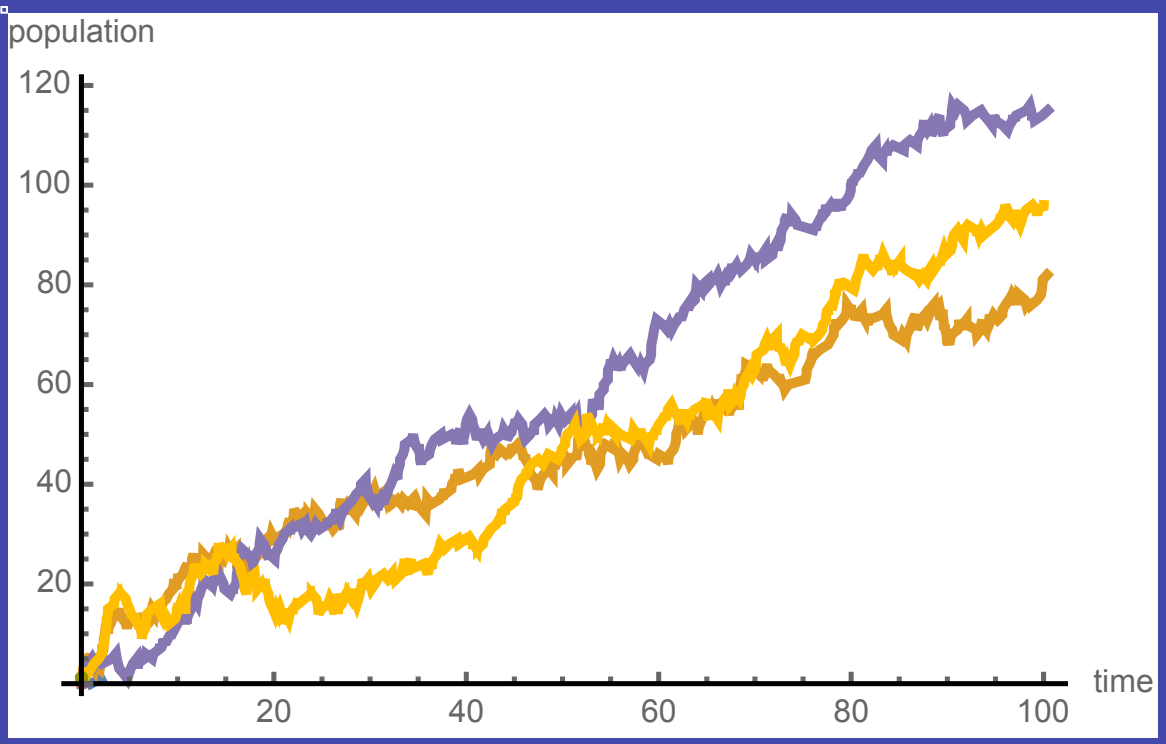
individual is born in interval Δt	$n \xrightarrow{bn\Delta t} n+1$
individual dies in interval Δt	$n \xrightarrow{dn\Delta t} n-1$



- We say that birth and death events are “exponentially distributed” or “are drawn from a Poisson process”
- Birth and death events are independent

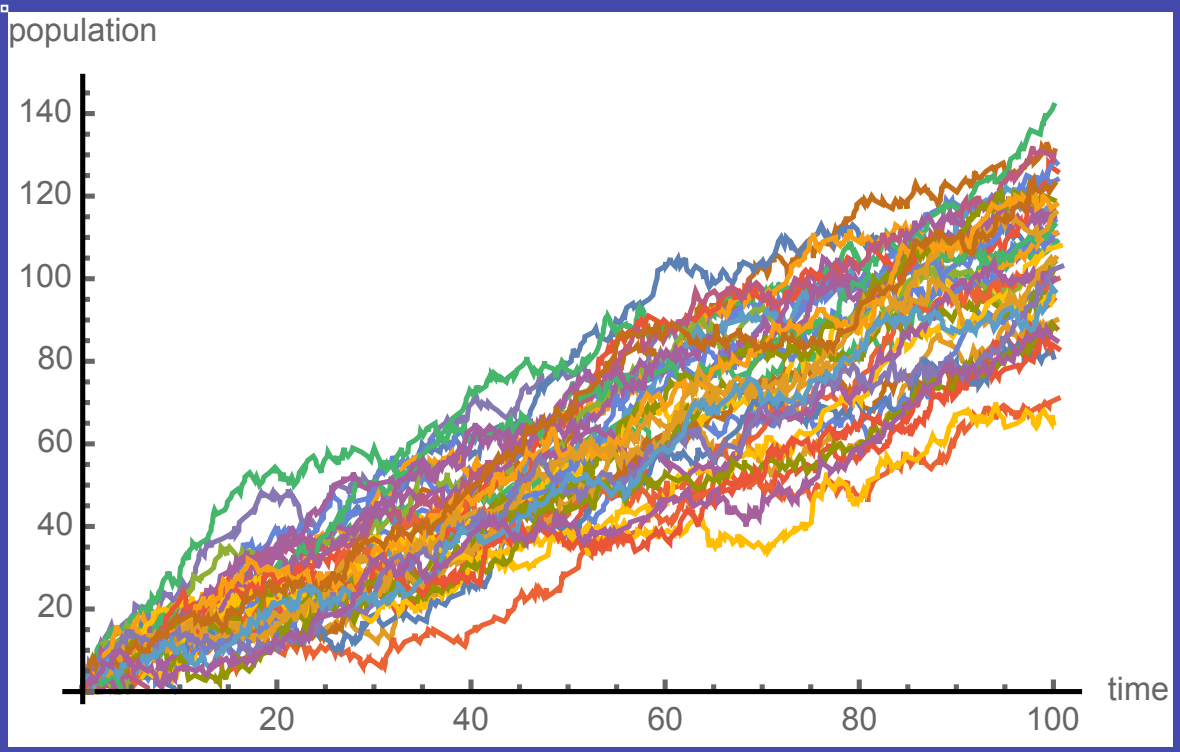
Simulations of the birth-death process

Set birth rate b=3/day; death rate d=2/day; make 10 simulations



Simulations of the birth-death process

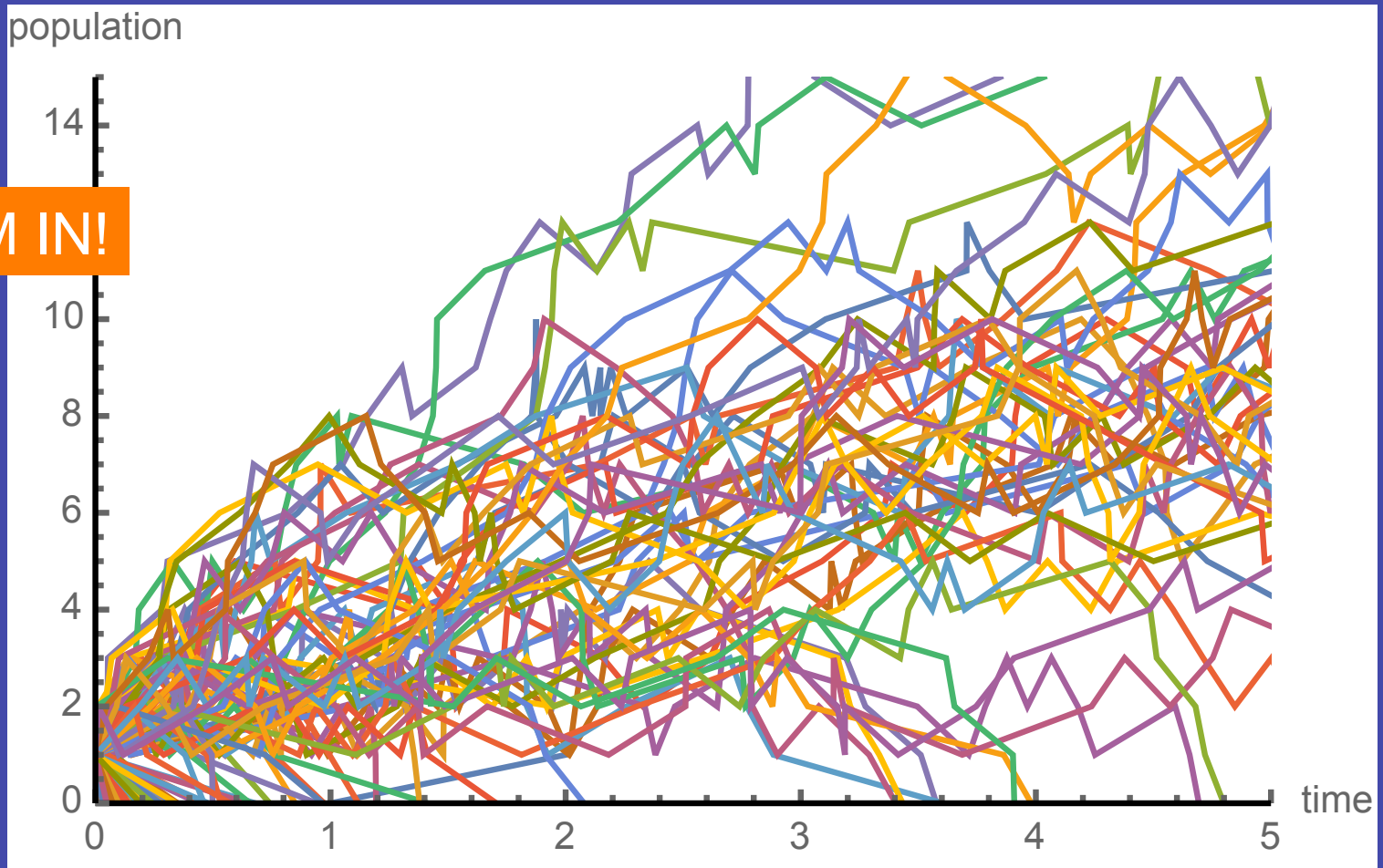
Set birth rate b=3/day; death rate d=2/day; make 100 simulations



Simulations of the birth-death process

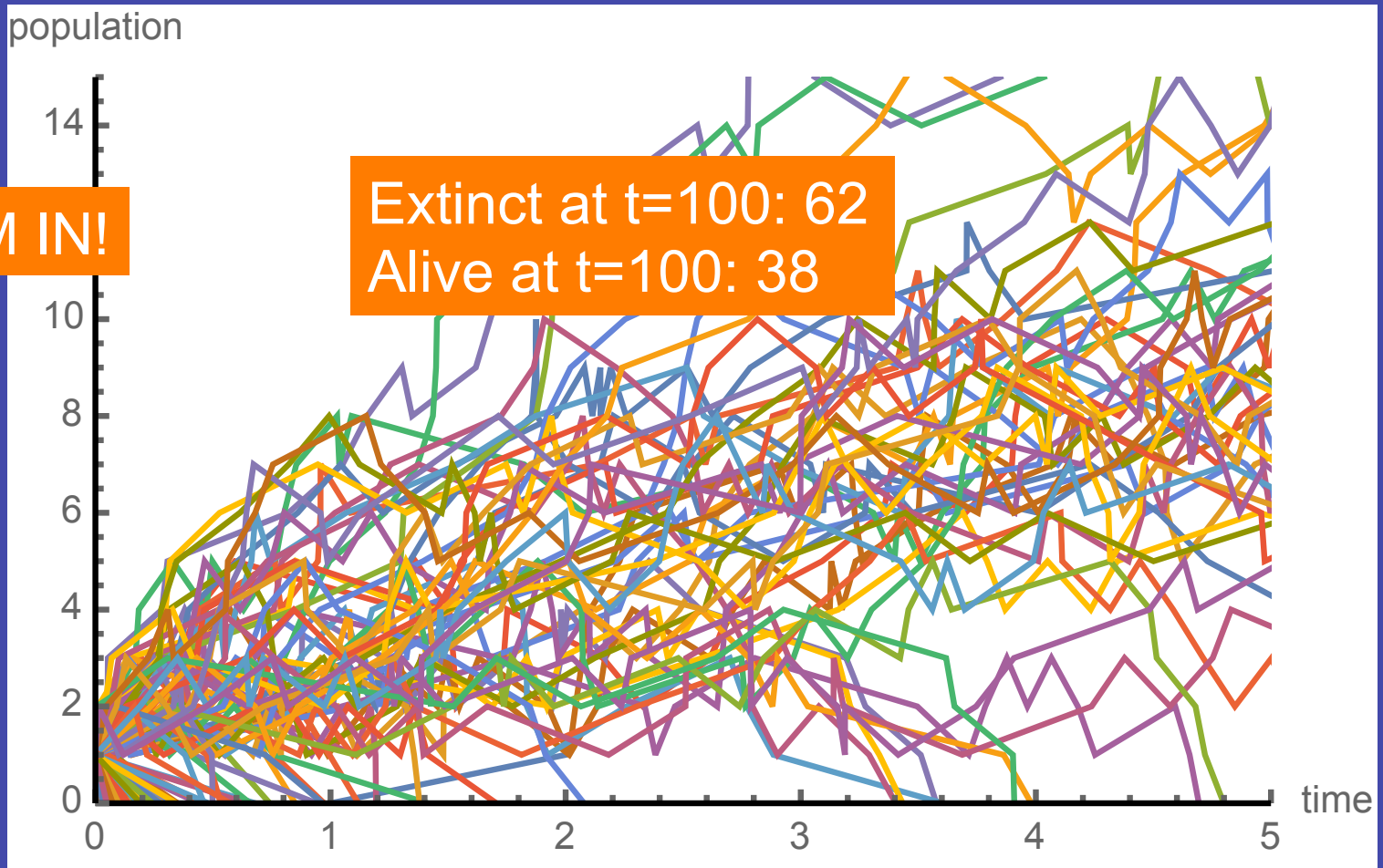
Set birth rate b=3/day; death rate d=2/day; make 100 simulations

ZOOM IN!



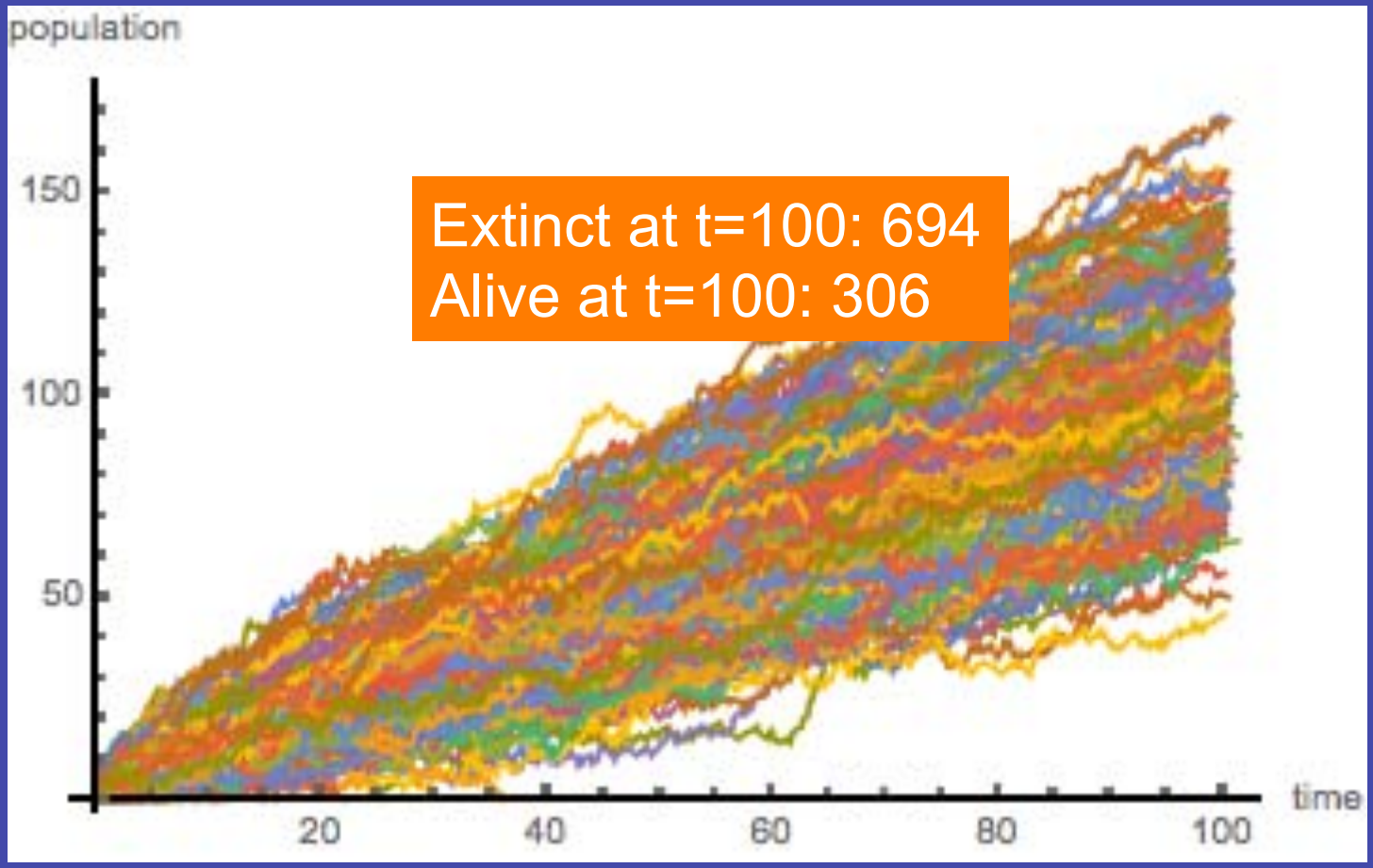
Simulations of the birth-death process

Set birth rate b=3/day; death rate d=2/day; make 100 simulations



Simulations of the birth-death process

Set birth rate b=3/day; death rate d=2/day; make **1000** simulations



Simulations of the birth-death process

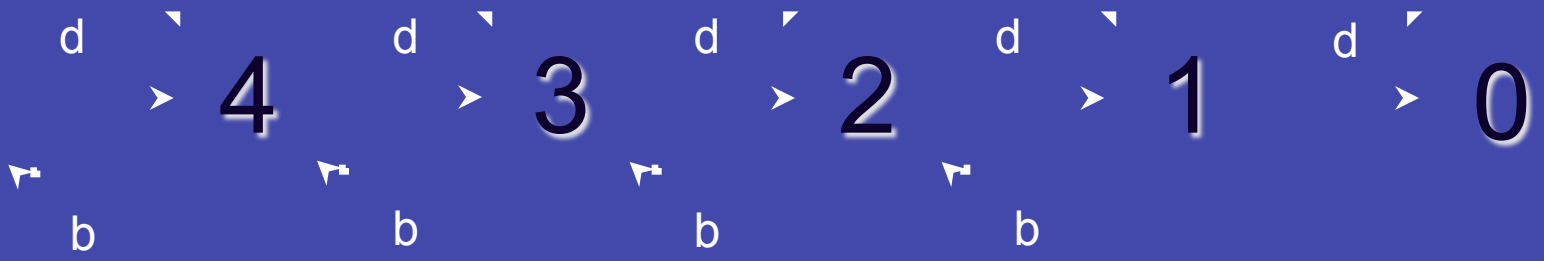
Set birth rate b=3/day; death rate d=2/day; make **10000** simulations

10000 simulations:
Extinct at t=100: 6677
Alive at t=100: 3323

Probabilistic interpretation

- Interpret d and b as the *rates* at which events happen

individual is born in interval Δt	$n \xrightarrow{bn\Delta t} n+1$
individual dies in interval Δt	$n \xrightarrow{dn\Delta t} n-1$

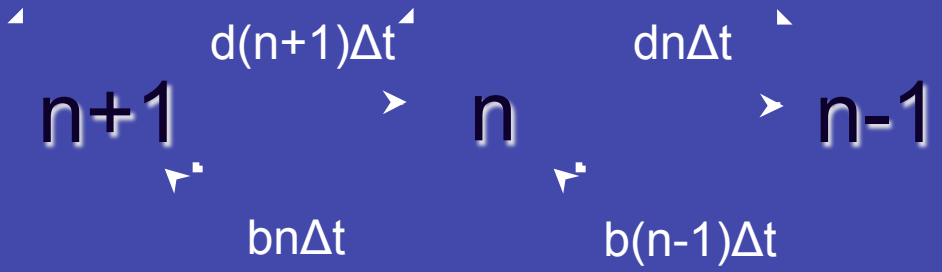


- Define

$$P_{n,n_0}(t) = \text{prob}(N(t) = n \text{ given } N(0) = n_0)$$

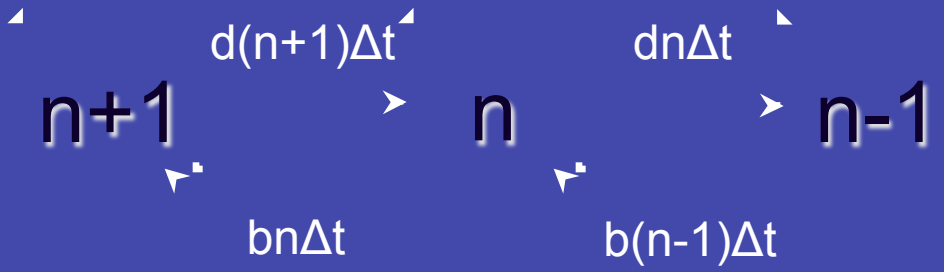
$$p_{ext}(t) \equiv P_{0,n_0}(t) = \text{prob}(\text{extinct by time } t)$$

How do the probabilities change in time?



$$P_{n,n_0}(t+\Delta t) = d(n+1)\Delta t P_{n+1,n_0}(t) + b(n-1)\Delta t P_{n-1,n_0}(t) + (1 - dn\Delta t - bn\Delta t P_{n,n_0}(t))$$

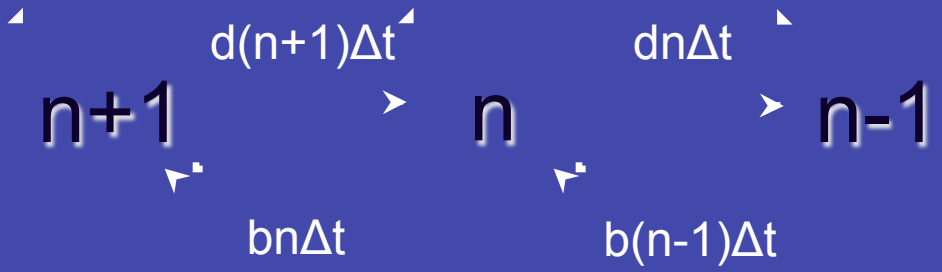
How do the probabilities change in time?



$$\frac{P_{n,n_0}(t+\Delta t) - P_{n,n_0}(t)}{\Delta t} = d(n+1)P_{n+1,n_0}(t) + b(n-1)P_{n-1,n_0}(t) - (dn+bn)\,P_{n,n_0}(t)$$

Take the limit: infinite system of differential equations

How do the probabilities change in time?



$$\frac{dP_{n,n_0}}{dt} = d(n+1)P_{n+1,n_0}(t) + b(n-1)P_{n-1,n_0}(t) - (d+b)\,nP_{n,n_0}(t)$$

This is called the Forward Kolmogorov (Master) equation

What we will do now is convert the infinite system of ODEs to a single PDE.

First we need one useful tool: the probability generating function

The Generating Function

- A very useful tool (think of it like a transform)

$$G(n_0, t, z) = \sum_{n=0}^{\infty} P_{n,n_0}(t) z^n$$

- A polynomial with the probabilities as coefficients

The Generating Function

- A very useful tool (think of it like a transform)

$$G(n_0, t, z) = \sum_{n=0}^{\infty} P_{n,n_0}(t) z^n$$

- A polynomial with the probabilities as coefficients

$$G(n_0, t, 0) = P_{0,n_0}(t) = p_{\text{ext}}(t)$$

$$\left.\frac{\partial G}{\partial z}\right|_{z=0} = P_{1,n_0}(t)$$

$$\vdots$$

$$\left.\frac{1}{N!}\frac{\partial^N G}{\partial z^N}\right|_{z=0} = P_{N,n_0}(t)$$

The Generating Function

- A very useful tool (think of it like a transform)

$$G(n_0, t, z) = \sum_{n=0}^{\infty} P_{n,n_0}(t) z^n$$

- A polynomial with the probabilities as coefficients

$$\begin{aligned} G(n_0, t, 0) &= P_{0,n_0}(t) = p_{\text{ext}}(t) \\ \left.\frac{\partial G}{\partial z}\right|_{z=0} &= P_{1,n_0}(t) \\ &\vdots \\ \left.\frac{1}{N!}\frac{\partial^N G}{\partial z^N}\right|_{z=0} &= P_{N,n_0}(t) \end{aligned}$$

- So if we can calculate *G* we know a lot!

$$G(n_0, t, z) = \sum_{n=0}^{\infty} P_{n,n_0}(t) z^n$$

>

$$\begin{aligned}\frac{dP_{n,n_0}}{dt} &= d(n+1)P_{n+1,n_0}(t) \\ &+ b(n-1)P_{n-1,n_0}(t) \\ &- (d+b)\,nP_{n,n_0}(t)\end{aligned}$$

$$G(n_0,t,z)=\sum_{n=0}^{\infty}P_{n,n_0}(t)z^n$$

>

$$\begin{aligned}\frac{dP_{n,n_0}}{dt} &= d(n+1)P_{n+1,n_0}(t)\\ &+ b(n-1)P_{n-1,n_0}(t)\\ &- (d+b)\,nP_{n,n_0}(t)\end{aligned}$$

$$\sum_{n=0}^{\infty}\frac{dP_{n,n_0}}{dt}z^n=\sum_{n=0}^{\infty}d(n+1)P_{n+1,n_0}(t)z^n+\sum_{n=0}^{\infty}b(n-1)P_{n-1,n_0}(t)z^n$$

$$-\sum_{n=0}^{\infty}(d+b)\,nP_{n,n_0}(t)z^n$$

$$\frac{\partial G}{\partial t}=??$$

$$G(n_0,t,z)=\sum_{n=0}^{\infty}P_{n,n_0}(t)z^n.$$

>

$$\begin{aligned}\frac{dP_{n,n_0}}{dt} &= d(n+1)P_{n+1,n_0}(t)\\ &\quad + b(n-1)P_{n-1,n_0}(t)\\ &\quad - (d+b)\,nP_{n,n_0}(t)\end{aligned}$$

$$\sum_{n=0}^{\infty}\frac{dP_{n,n_0}}{dt}z^n=\sum_{n=0}^{\infty}d(n+1)P_{n+1,n_0}(t)z^n+\sum_{n=0}^{\infty}b(n-1)P_{n-1,n_0}(t)z^n$$

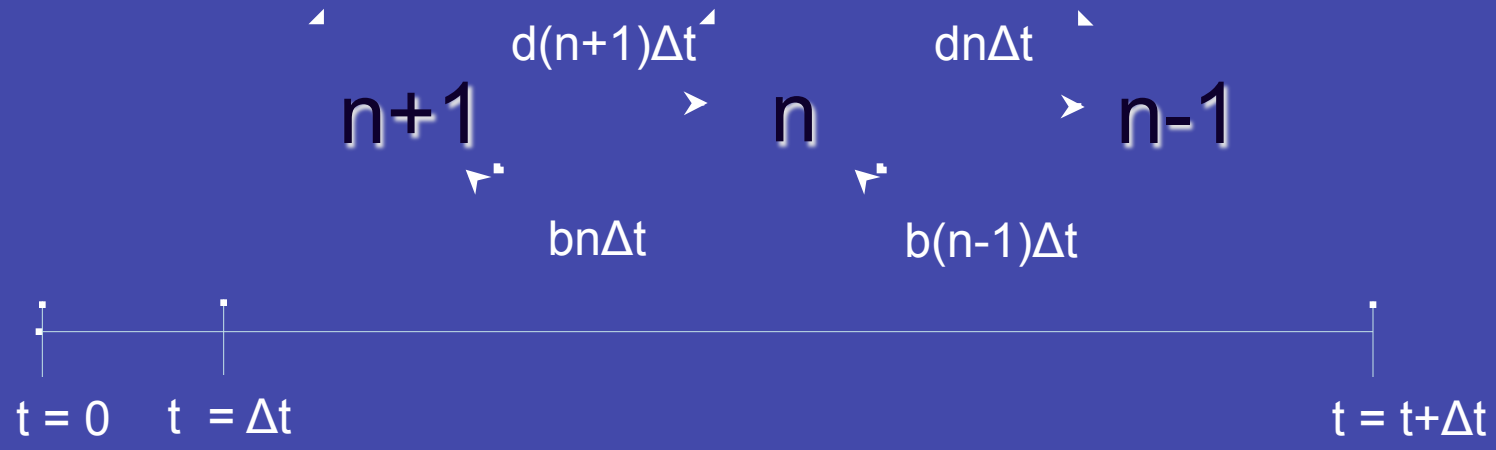
$$-\sum_{n=0}^{\infty}(d+b)\,nP_{n,n_0}(t)z^n$$

$$\frac{\partial G}{\partial t}=\left(bz^2-(b+d)z+d\right)\frac{\partial G}{\partial z}$$

$$G(n_0,0,z)=z^{n_0}$$

This is a 1st-order linear PDE for G.
We can solve via the method of characteristics (homework)!

The backward formulation:



$$
\begin{aligned}
P_{n,n_0}(t+\Delta t) &= bn_0\Delta t P_{n,n_0+1}(t) \\
&+ d(n_0)\Delta t P_{n,n_0-1}(t) \\
&+ \left(1 - dn_0\Delta t - bn_0\Delta t\right) P_{n,n_0}(t) \\
\frac{P_{n,n_0}(t+\Delta t) - P_{n,n_0}(t)}{\Delta t} &= bn_0 P_{n,n_0+1}(t) \\
&+ dn_0 P_{n,n_0-1}(t) \\
&- \left(dn_0 + bn_0\right) P_{n,n_0}(t)
\end{aligned}
$$

Again, infinite system of ODEs! How about the generating function?

$$G(n_0,t,z)=\sum_{n=0}^{\infty}P_{n,n_0}(t)z^n$$

>

$$\begin{aligned}\frac{\partial P_{n,n_0}}{\partial t} &= bn_0P_{n,n_0+1}(t)\\ &\quad + dn_0P_{n,n_0-1}(t)\\ &\quad - (dn_0+bn_0)\,P_{n,n_0}(t)\end{aligned}$$

$$\sum_{n=0}^{\infty}\frac{\partial P_{n,n_0}}{\partial t}z^n=\sum_{n=0}^{\infty}bn_0P_{n,n_0+1}(t)z^n+\sum_{n=0}^{\infty}dn_0P_{n,n_0-1}(t)z^n$$

$$-\sum_{n=0}^{\infty}(dn_0+bn_0)\,P_{n,n_0}(t)z^n$$

$$\frac{\partial}{\partial t}G(n_0,t,z)=bn_0G(n_0+1,t,z)+dn_0G(n_0-1,t,z)-(b+d)n_0G(n_0,t,z)$$

This is very different – an infinite system of ODE again!
However, it allows for an elegant solution….

- If we can assume that lineages are identical and independent, then we get a big simplification:

$$G(n_0, t, z) = \sum_{n=0}^{\infty} P_{n,n_0}(t) z^n$$

$$= E[z^n] \qquad \text{expectation of } z^n \text{ at time t}$$

- If we can assume that lineages are identical and independent, then we get a big simplification:

$$
\begin{aligned}
G(n_0, t, z) &= \sum_{n=0}^{\infty} P_{n,n_0}(t) z^n \\
&= E[z^n] \qquad \text{expectation of } z^n \text{ at time t} \\
&= E[z^{L_1 + L_2 + \cdots + L_{n_0}}]
\end{aligned}
$$

- The L_i are the individual lineages. There are n_0 of them!

- If we can assume that lineages are identical and independent, then we get a big simplification:

$$
\begin{aligned}
G(n_0, t, z) &= \sum_{n=0}^{\infty} P_{n,n_0}(t) z^n \\
&= E[z^n] \qquad \text{expectation of } z^n \text{ at time t} \\
&= E[z^{L_1 + L_2 + \cdots + L_{n_0}}] \\
&= E[z^{L_1}] E[z^{L_2}] \ldots E[z^{L_{N_0}}]
\end{aligned}
$$

- This step is valid because all the lineages are independent

- If we can assume that lineages are identical and independent, then we get a big simplification:

$$
\begin{aligned}
G(n_0,t,z) &= \sum_{n=0}^{\infty} P_{n,n_0}(t) z^n \\
&= E[z^n] \qquad \text{expectation of } z^n \text{ at time t} \\
&= E[z^{L_1+L_2+\cdots+L_{n_0}}] \\
&= E[z^{L_1}]E[z^{L_2}]\ldots E[z^{L_{N_0}}] \\
&= \left(E[z^L]\right)^{n_0} \\
&= \left(G(1,t,z)\right)^{n_0}
\end{aligned}
$$

- This step requires all the lineages are identical

- $G(n_0,t,z) = (G(1,t,z))^{n0}$

- If we can assume that lineages are identical and independent, then we get a big simplification:

$$
\begin{aligned}
G(n_0,t,z) &= \sum_{n=0}^{\infty} P_{n,n_0}(t) z^n \\
&= E[z^n] \qquad \text{expectation of } z^n \text{ at time t} \\
&= E[z^{L_1+L_2+\cdots+L_{n_0}}] \\
&= E[z^{L_1}]E[z^{L_2}]\ldots E[z^{L_{N_0}}] \\
&= \left(E[z^L]\right)^{n_0} \\
&= \left(G(1,t,z)\right)^{n_0}
\end{aligned}
$$

- Also I can do the chain rule:

$$
\frac{\partial G(n_0,t,z)}{\partial t} = \frac{\partial \left(G(1,t,z)^{n_0}\right)}{\partial t} = n_0 \frac{\partial G(1,t,z)}{\partial t} G(1,t,z)^{n_0-1}
$$

$$\sum_{n=0}^{\infty} \frac{\partial P_{n,n_0}}{\partial t} z^n = \sum_{n=0}^{\infty} b n_0 P_{n,n_0+1}(t) z^n + \sum_{n=0}^{\infty} d n_0 P_{n,n_0-1}(t) z^n - \sum_{n=0}^{\infty} (d n_0 + b n_0) P_{n,n_0}(t) z^n$$

$$\frac{\partial}{\partial t} G(n_0, t, z) = b n_0 G(n_0 + 1, t, z) + d n_0 G(n_0 - 1, t, z) - (b + d) n_0 G(n_0, t, z)$$

$$\frac{\partial G(n_0, t, z)}{\partial t} = \frac{\partial \left(G(1, t, z)^{n_0} \right)}{\partial t} = n_0 \frac{\partial G(1, t, z)}{\partial t} G(1, t, z)^{n_0 - 1}$$

$$\frac{\partial G(1, t, z)}{\partial t} = b G(1, t, z)^2 - (b + d) G(1, t, z) + d$$

- the backward equation for the generating function with n_0=1:

$$\frac{\partial G(1,t,z)}{\partial t} = bG(1,t,z)^2 - (b+d)G(1,t,z) + d$$

- It's a Riccati equation (look it up!) with solution:

$$G(1,t,z) = \left(\frac{(\sigma(t)-1) + (\frac{b}{d} - \sigma(t))z}{(\frac{b}{d}\sigma(t) - 1) + \frac{b}{d}z(1-\sigma(t))} \right)$$

$$\sigma(t) = \exp((b-d)t)$$

This is the same solution you would get from method of characteristics for the forward (PDE)!

Interpreting the generating function solution

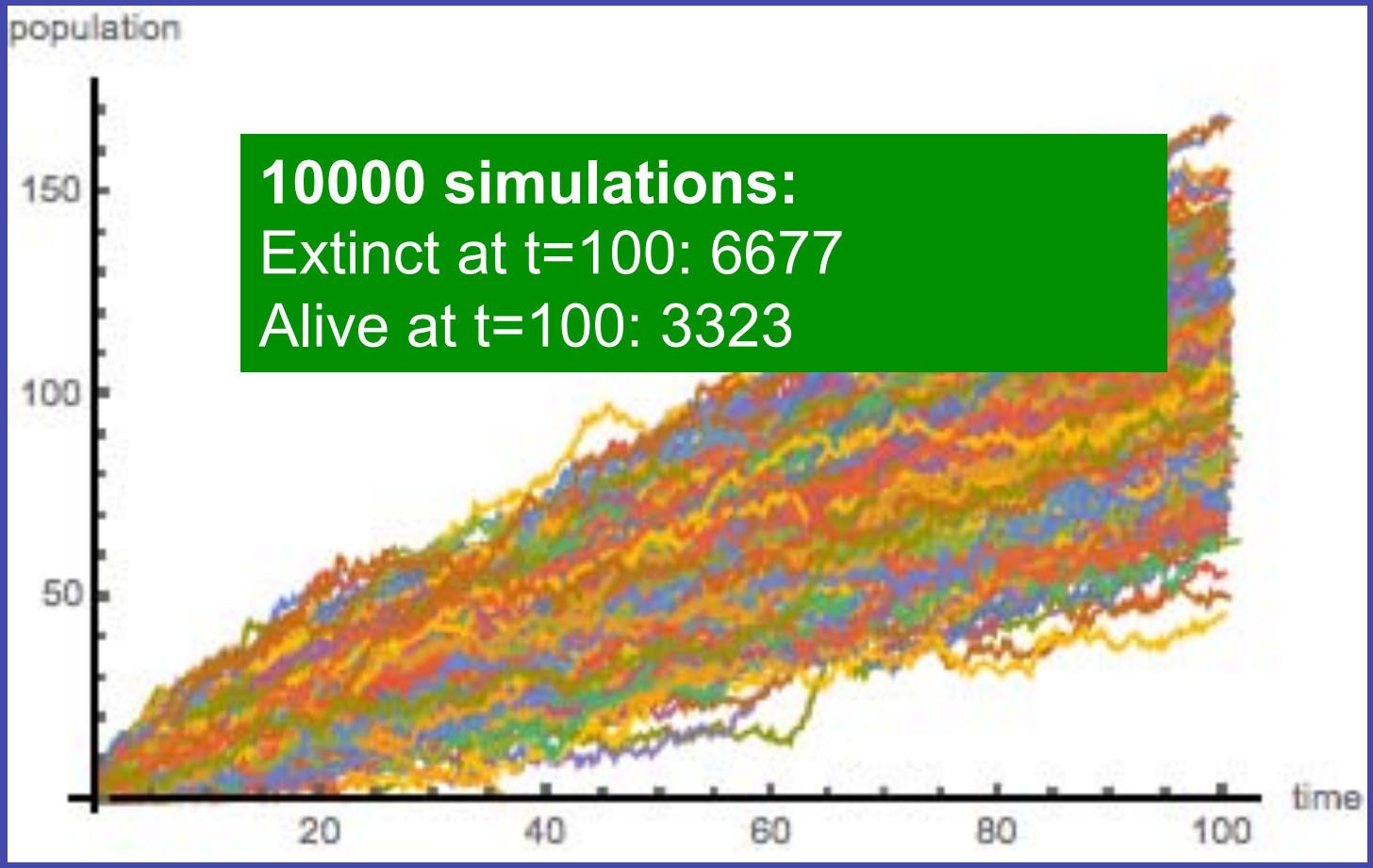
$$G(1,t,z) = \left(\frac{(\sigma(t)-1) + (\frac{b}{d} - \sigma(t))z}{(\frac{b}{d}\sigma(t) - 1) + \frac{b}{d}z(1-\sigma(t))} \right)$$

$$\sigma(t) = \exp((b-d)t)$$

- If b>d then $\sigma \rightarrow \infty$ so p_{ext} = G(1,t,0) = (d/b)
- If b>d then $\sigma \rightarrow 0$ so p_{ext} = G(1,t,0) = 1
- Notice that p_{ext} is a *fixed point* of the system governing G
- We can also find all probabilities by differentiating G(z).

Simulations of the birth-death process

Set birth rate b=3; death rate d=2; make **1000** simulations



Interpreting the generating function solution

$$G(1,t,z) = \left(\frac{(\sigma(t)-1) + (\frac{b}{d} - \sigma(t))z}{(\frac{b}{d}\sigma(t) - 1) + \frac{b}{d}z(1-\sigma(t))} \right)$$

$$\sigma(t) = \exp((b-d)t)$$

- Mean:

$$G(1,t,z) = \sum_{n=0}^{\infty} P_{n,1}(t) z^n$$

$$\frac{\partial G}{\partial z} = \sum_{n=1}^{\infty} n P_{n,1}(t) z^{n-1}$$

$$\frac{\partial G}{\partial z}(1,t,1) = \sum_{n=1}^{\infty} n P_{n,1}(t) = \bar{N} = \exp((b-d)t)$$

Interpreting the generating function solution

$$G(1,t,z) = \left(\frac{(\sigma(t)-1) + (\frac{b}{d} - \sigma(t))z}{(\frac{b}{d}\sigma(t) - 1) + \frac{b}{d}z(1-\sigma(t))} \right)$$

$$\sigma(t) = \exp((b-d)t)$$

- Variance:

$$G(1,t,z) = \sum_{n=0}^{\infty} P_{n,1}(t) z^n$$

$$\frac{\partial^2 G}{\partial z^2} = \sum_{n=2}^{\infty} n(n-1) P_{n,1}(t) z^{n-2}$$

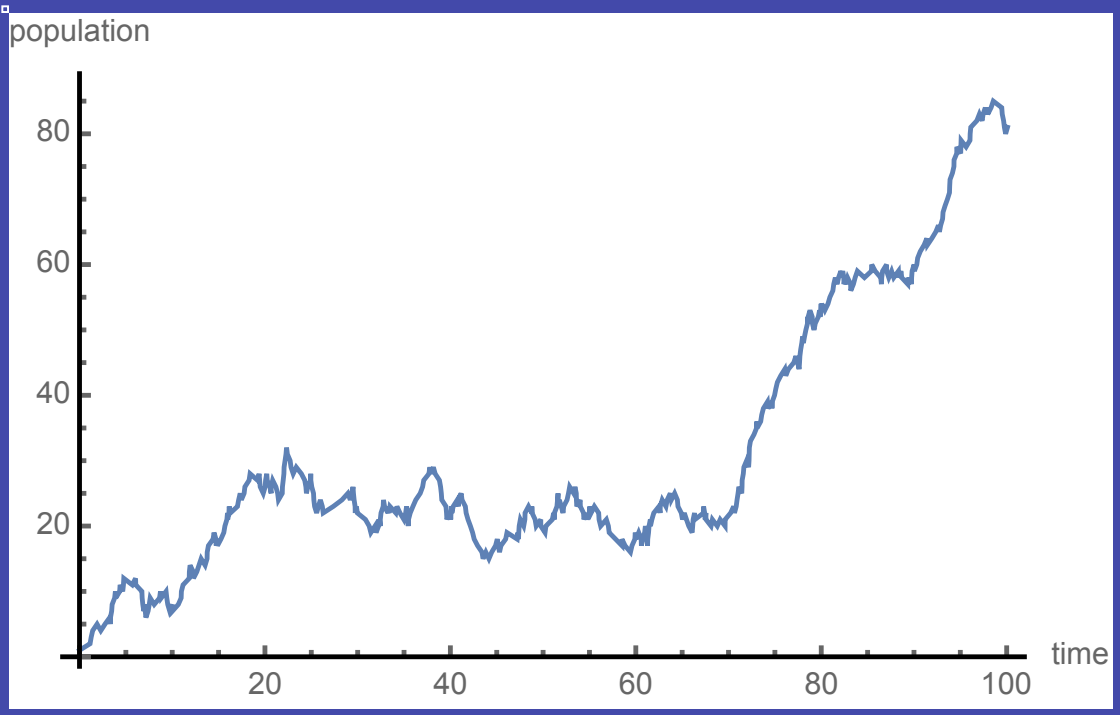
$$\cdots$$

$$\mathrm{Var}(N) = \frac{b+d}{b-d}(e^{2(b-d)t} - e^{(b-d)t})$$

What we do not know:

- Suppose we know the whole generating function.
- We know the probability of having N cells at time t

- However, we do not know anything about the *paths*. One way to get at this is to use simulation….



How to simulate (Gillespie's algorithm)

(For the birth-death process with rates b and d)

Initialize $t=0$, $N=N_0$, $i=1$.

1. Calculate the *next event time* t_i
2. Choose *which event* (birth or death) happens at t_i
3. Update:

   i++, $t=t_i$ and either N++ or N--.
4. Go to step 1 (or stop if $N=0$)

How to simulate (Gillespie's algorithm)

(For the birth-death process with rates b and d)

Initialize t=0, N=N_0, i=1.

1. Calculate the *next event time* t_i
2. Choose *which event* (birth or death) happens at t_i
3. Update:
   i++, t=t_i and either N++ or N--.
4. Go to step 1 (or stop if N=0)

Next event time: distribution of simultaneous exponential processes is exponential

$$t_i \sim \mathrm{Exp}[b+d]$$

How to simulate (Gillespie's algorithm)

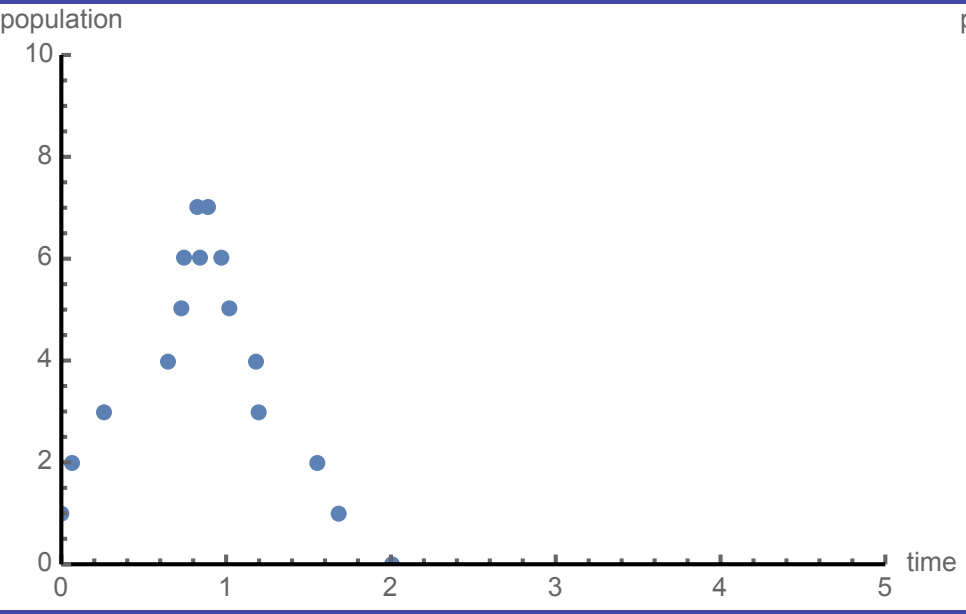
(For the birth-death process with rates b and d)

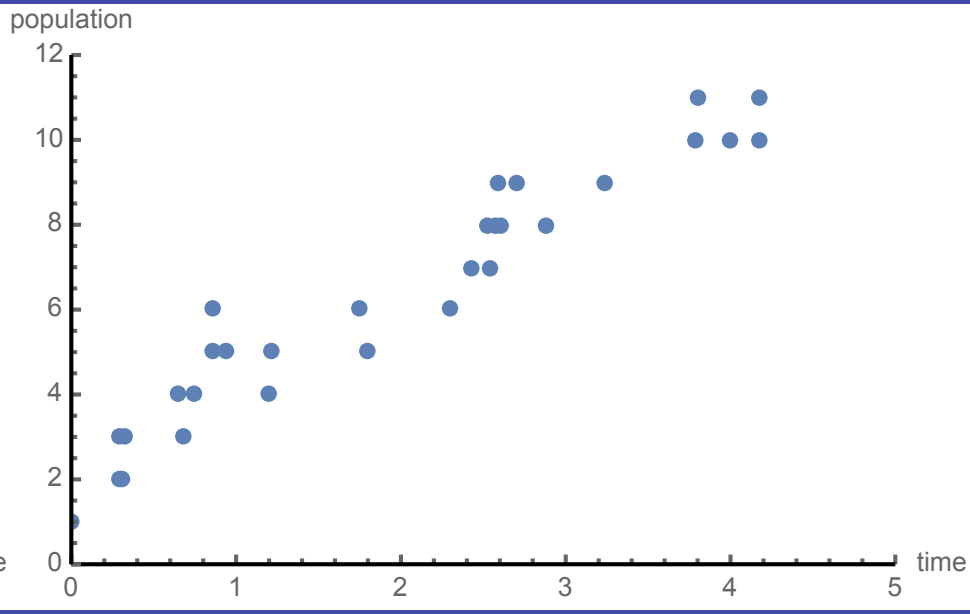
Initialize t=0, N=N_0, i=1.

1. Calculate the *next event time* t_i
2. Choose *which event* (birth or death) happens at t_i
3. Update:
   i++, t=t_i and either N++ or N--.
4. Go to step 1 (or stop if N=0)

Which event? Choose according to the event rates (propensities)!
Pick a random number x uniformly on [0,1] and choose:

$$\text{Birth if } x < \frac{b}{b+d} \qquad \text{Death if } x > \frac{b}{b+d}$$





Very efficient algorithm for simulation
(two random numbers per step)
Easily expandable to more complicated cases

But not an efficient way to sample *rare events*.

Whew….!

So far:

- Birth-death process
- Forward equation
- Backward equation
- Generating function
- 1^{st}-order linear PDE (forward generating)
- nonlinear ODE (backward generating)
- Gillespie simulations

The goal: multitype processes – inspired by HIV infection

References

A stochastic model of latently infected cell reactivation and viral blip generation in treated HIV patients
JM Conway, D Coombs
PLoS computational biology 7 (4), e1002033

Stochastic analysis of pre-and postexposure prophylaxis against HIV infection
JM Conway, BP Konrad, D Coombs
SIAM Journal on Applied Mathematics 73 (2), 904-928

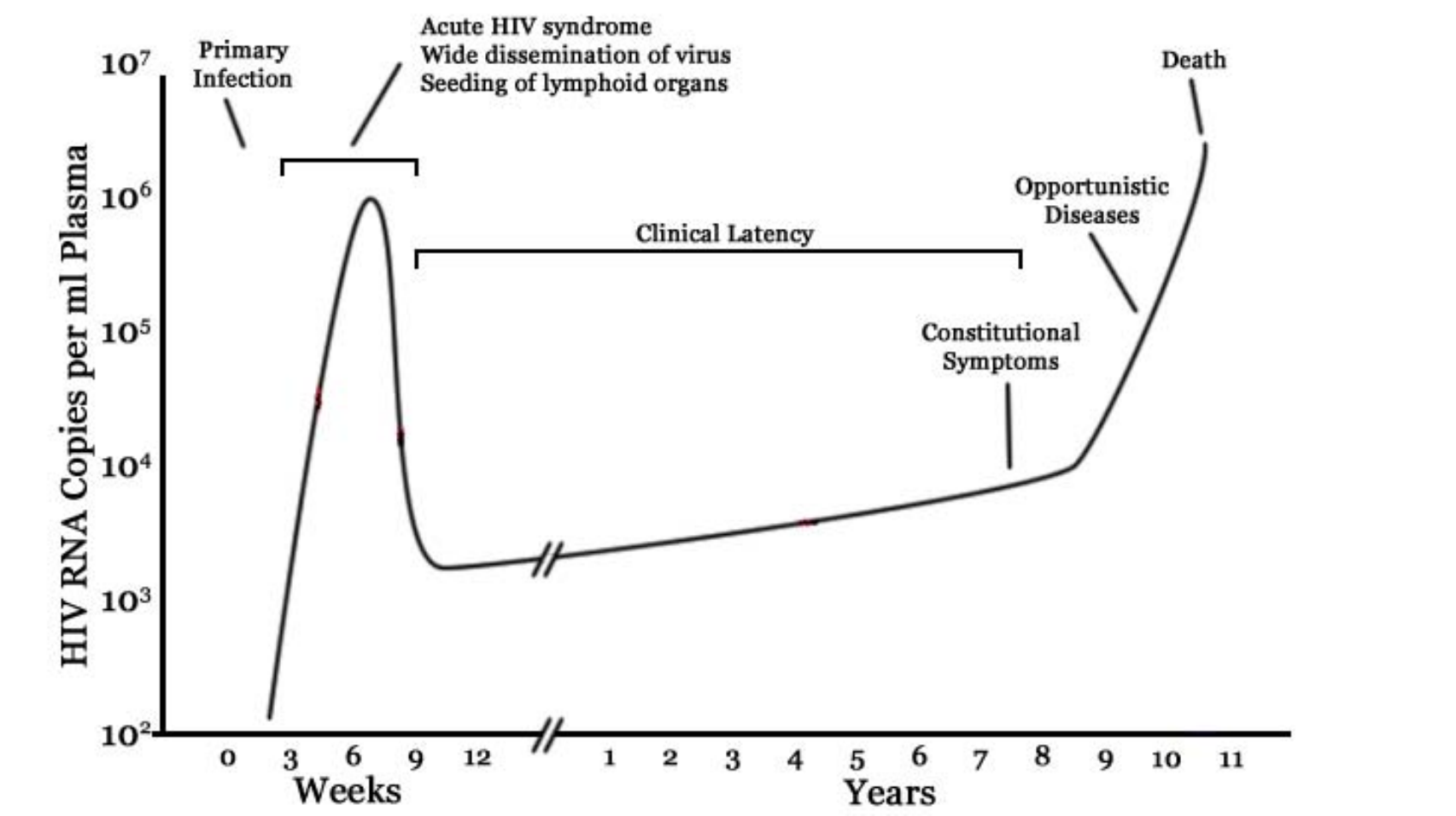
Stochastic theory of early viral infection: continuous versus burst production of virions
JE Pearson, P Krapivsky, AS Perelson
PLoS computational biology 7 (2), e1001058

Stochastic approaches to within-host viral dynamics (Part 4)

Daniel Coombs
Department of Mathematics & Institute of Applied Mathematics
University of British Columbia

HIV infection

- HIV virions infect target cells (primarily immune cells)
  - infected cells produce more virions and die
    - infection leads to loss of immune function (AIDS)



Therapy is effective

- Anti-retroviral therapy (ART) is extremely effective
  - Reduces patient viral load to “undetectable”
  - Allows rebound of immune system
  - Reduces onward transmission
  - Early treatment decreases mortality and morbidity
- Prophylactic use (pre- and post- exposure)
- Long-term continuous use
  - Side-effects can be serious
  - Drug resistance and transmission of drug resistance
  - Cost (~$500/yr in 3rd world)

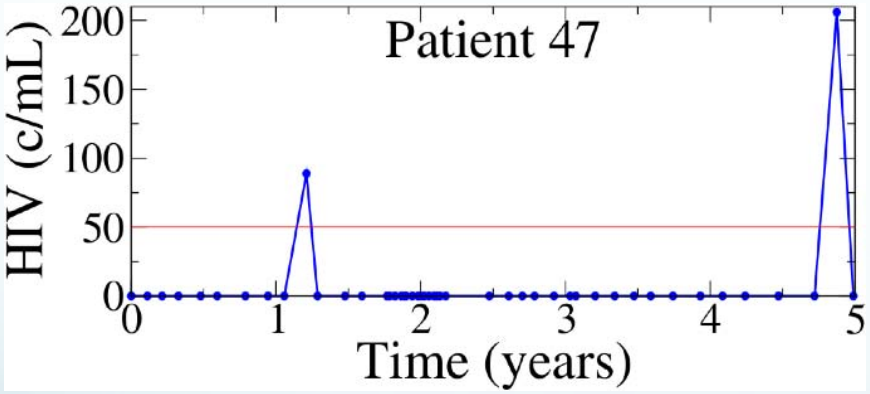
What's in this part:

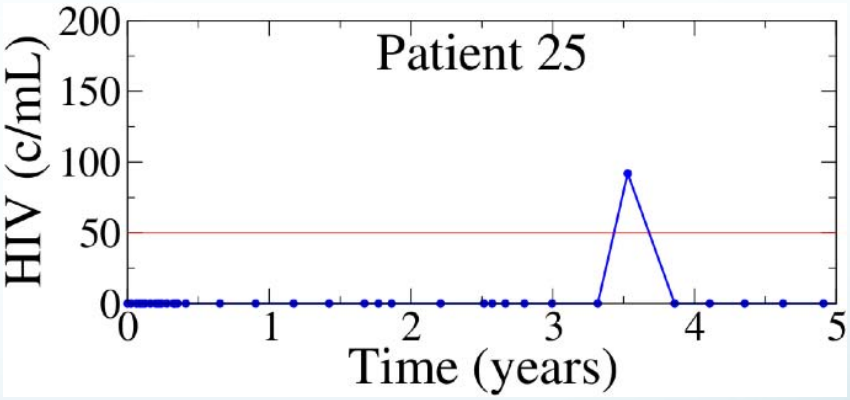
- Two projects on *treated* infection
  1. Viral load dynamics during long-term therapy
  2. Early infection and risk reduction for prophylaxis

- What are the problems?
  - Experiments are difficult during treatment
    - Building the right models without knowledge
  - Parameterizing the models (I will not discuss this)
    - Finding the right level of speculation

ART is not curative

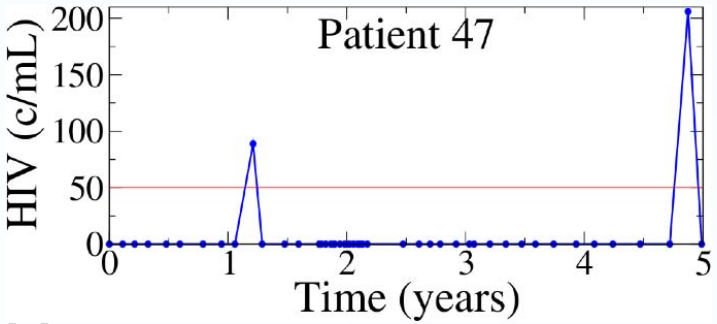
- Viral load is very low (5-50 copies/ml of blood)
- Virus remains, resurgent on drug failure
- Viral **blips** are observed:
  - infrequent episodes of detectable viral load
  - but large-amplitude blips are associated with drug failure





- We need new models of treated patients
  - older deterministic models do not capture blips well

What causes viral blips?



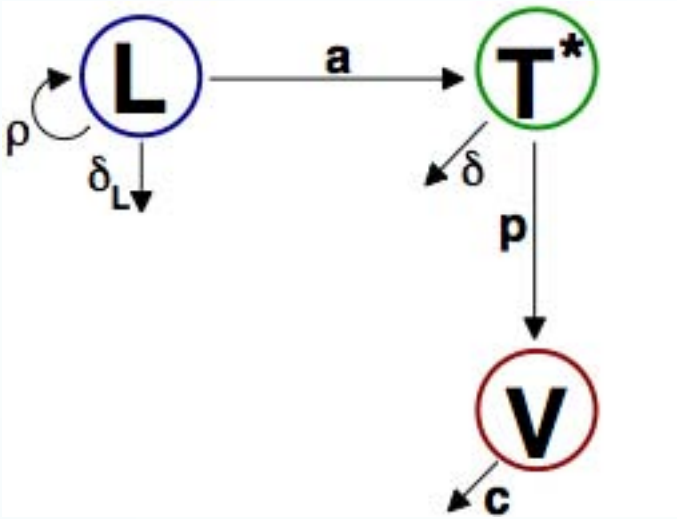
- Treatment non-adherence? Marginal.
- Secondary infection? Not always.
- Assay variation? Sometimes.

- **In any case, why is virus still present at all?**
- Where does the virus hide during ART?
- Virus that emerges during treatment interruption is very similar to pre-treatment.
  - implies minimal ongoing viral replication.
- Treatment intensification does not further reduce viral load.

Latently infected immune cell reservoir

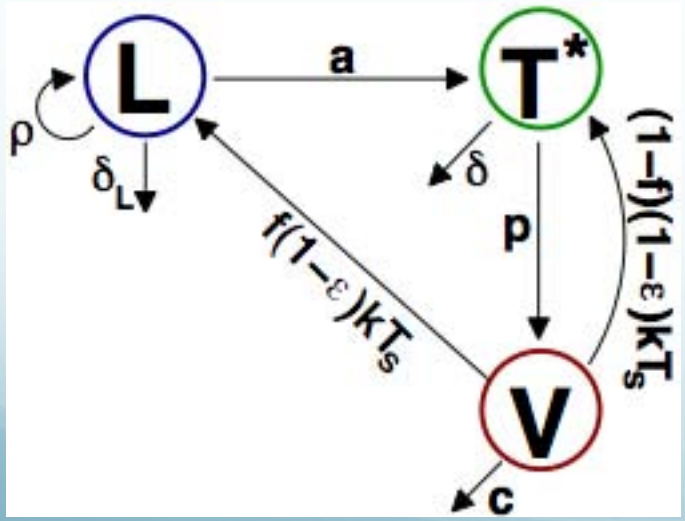
- Size of reservoir: ~$1/10^6$ cells
- Mainly memory T cells but also others
- Seeded during pre-treatment period
- Mean half-life $t_{1/2}$= 44 months
  - so >70 years to eradicate. (Siliciano 2005)
- *Hypothesis: viral blips are due to activation of latently infected cells.*

Latent cell reactivation model



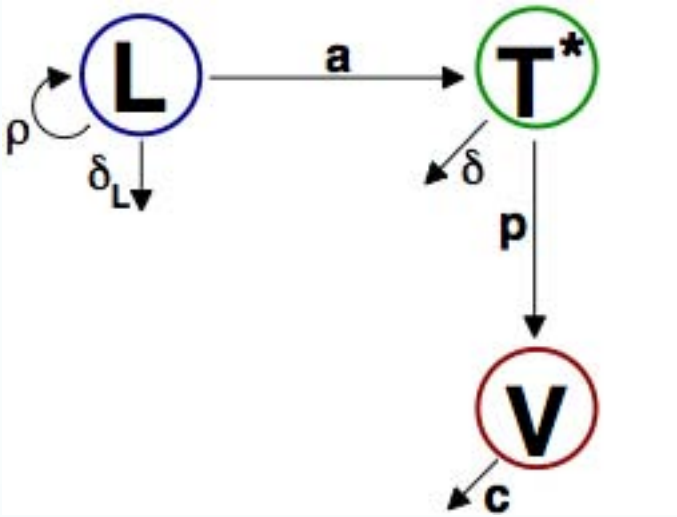
If ε=1 (drugs are perfect):

$$
\begin{aligned}
L'(t) &= (\rho - \delta_L - a)L \\
T^{*\prime}(t) &= aL - (\delta + p)T^* \\
V'(t) &= pT^* - cV
\end{aligned}
$$



If ε<1 (drugs are imperfect) then occasional rounds of replication occur

Latent cell reactivation model



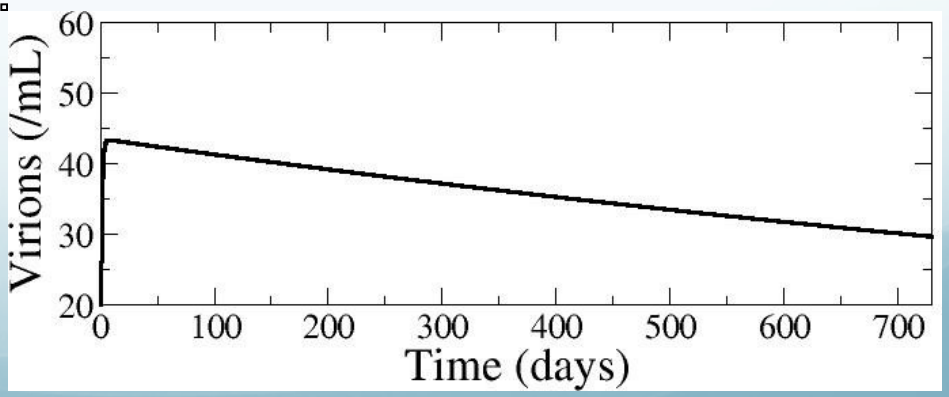
$$
\begin{aligned}
L'(t) &= (\rho - \delta_L - a)L \\
T^{*\prime}(t) &= aL - (\delta + p)T^* \\
V'(t) &= pT^* - cV
\end{aligned}
$$

Eigenvalues of linear system: $\delta = 0.1/\text{day}$

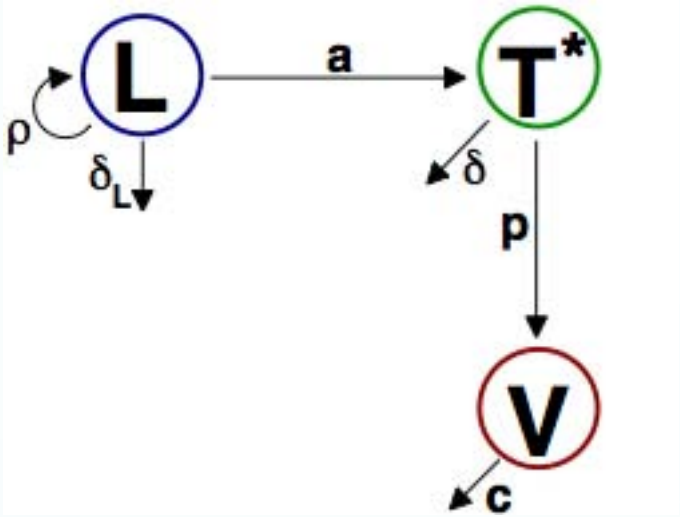
$c = 23/\text{day}$

$\rho \cdot a \cdot \delta_L = 5 \times 10^{-4}$ /day

- SLOW decay dominated by $\rho \cdot a \cdot \delta_L$



Master equation model



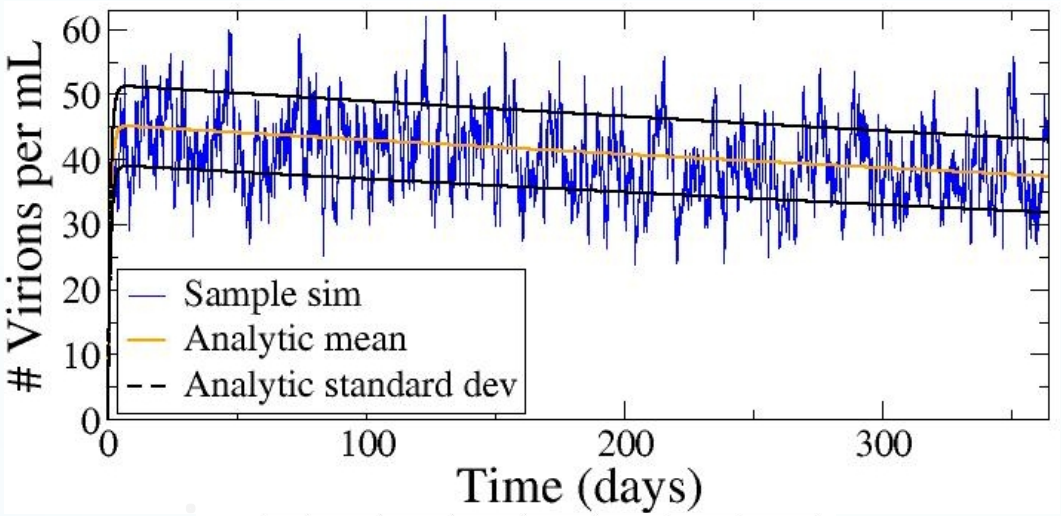
$$L \xrightarrow{a} T^* \qquad L \xrightarrow{\delta_L} \emptyset$$
$$T^* \xrightarrow{p} T^* + V \qquad T^* \xrightarrow{\delta} \emptyset$$
$$L \xrightarrow{\mu} 2L \qquad V \xrightarrow{\gamma} \emptyset$$

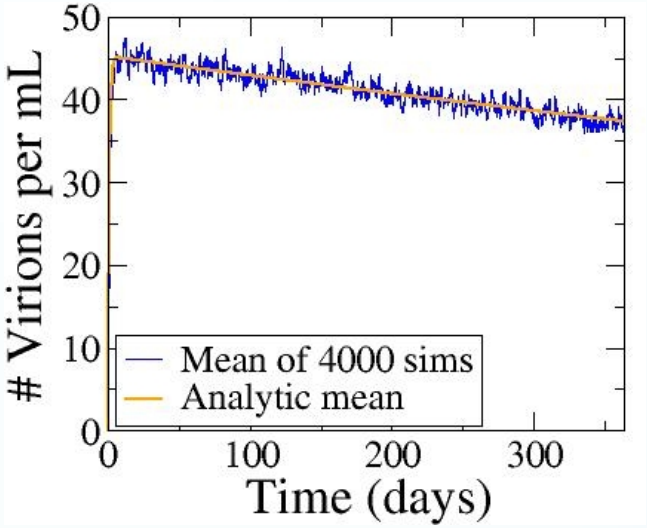
$$\begin{aligned} P'_{\ell,n,v}(t) &= a\left((\ell+1)P_{\ell+1,n-1,v}(t) - \ell P_{\ell,n,v}(t)\right) \\ &+\delta_L\left((\ell+1)P_{\ell+1,n,v} - \ell P_{\ell,n,v}\right) + \mu\left((\ell-1)P_{\ell-1,n,v} - \ell P_{\ell,n,v}\right) \\ &+\delta\left((n+1)P_{\ell,n+1,v}(t) - nP_{\ell,n,v}(t)\right) \\ &+pn\left(P_{\ell,n,v-1}(t) - P_{\ell,n,v}\right) + \gamma\left((v+1)P_{\ell,v+1,n}(t) - vP_{\ell,n,v}(t)\right) \end{aligned}$$

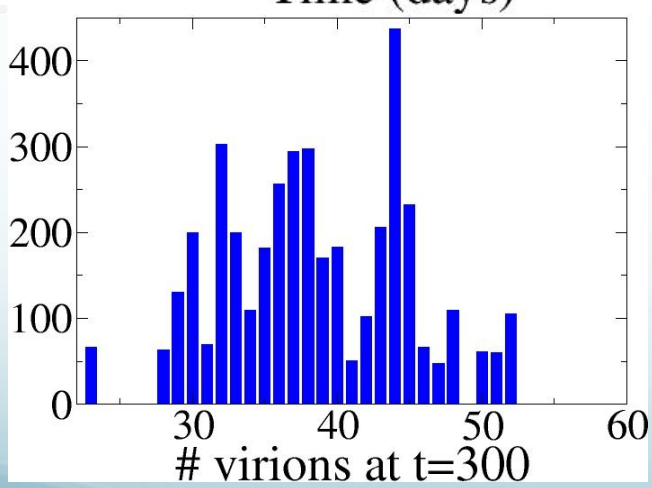
$$P_{\ell,n,v}(t) = P(L=\ell, T^*=n, V=v; t)$$

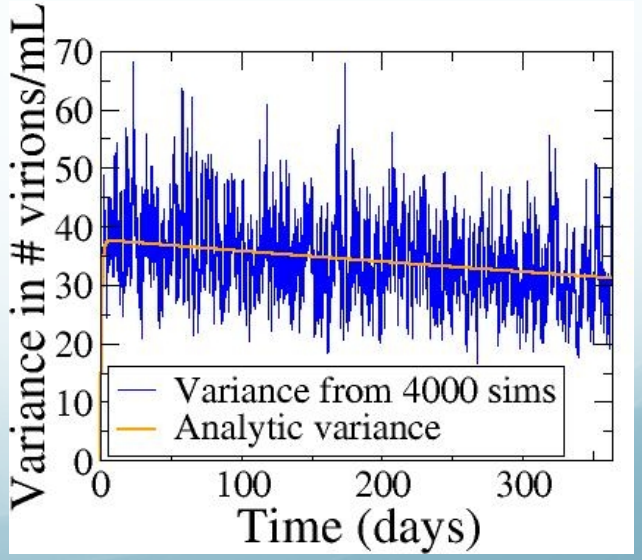
So we can simulate:

Gillespie algorithm simulations:



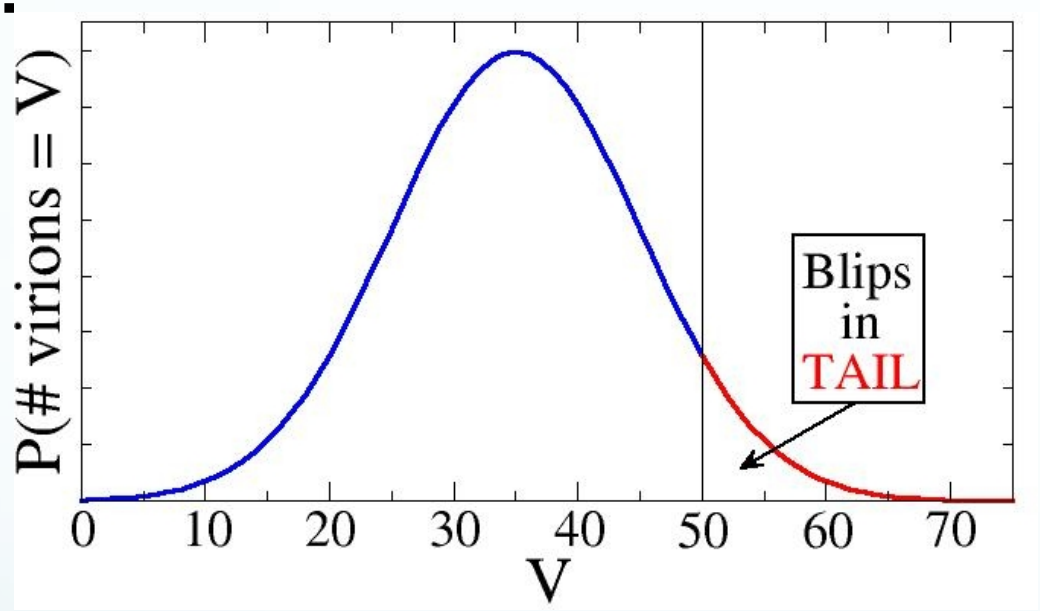


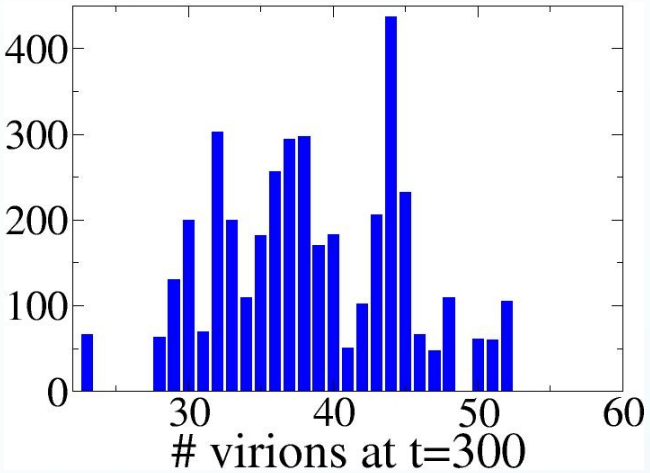




However, the problem is:

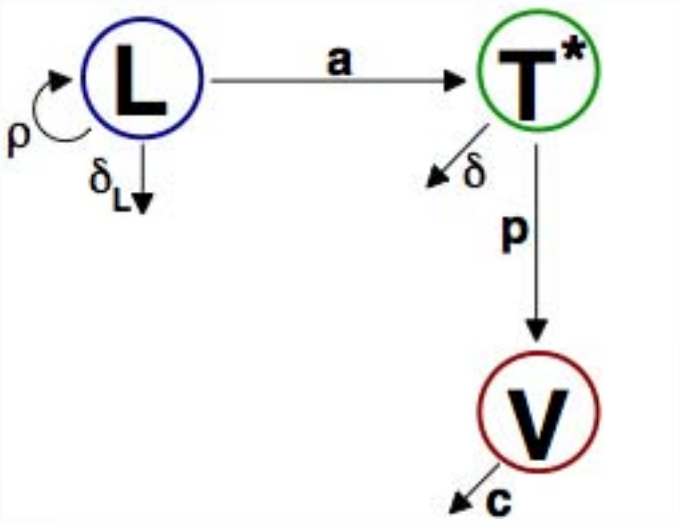
Blips are rare events.





Time-consuming to study via direct simulation.

Master equation model

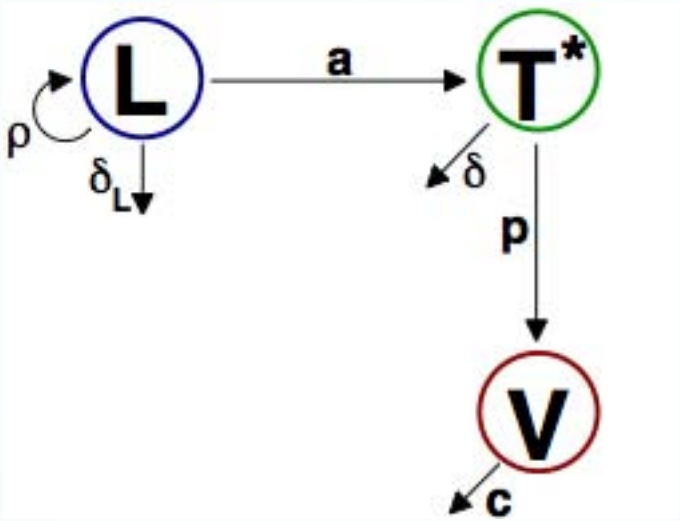


$$L \xrightarrow{a} T^* \qquad L \xrightarrow{\delta_L} \emptyset$$
$$T^* \xrightarrow{p} T^* + V \qquad T^* \xrightarrow{\delta} \emptyset$$
$$L \xrightarrow{\mu} 2L \qquad V \xrightarrow{\gamma} \emptyset$$

$$\begin{aligned} P'_{\ell,n,v}(t) &= a\left((\ell+1)P_{\ell+1,n-1,v}(t) - \ell P_{\ell,n,v}(t)\right) \\ &+\delta_L\left((\ell+1)P_{\ell+1,n,v} - \ell P_{\ell,n,v}\right) + \mu\left((\ell-1)P_{\ell-1,n,v} - \ell P_{\ell,n,v}\right) \\ &+\delta\left((n+1)P_{\ell,n+1,v}(t) - nP_{\ell,n,v}(t)\right) \\ &+pn\left(P_{\ell,n,v-1}(t) - P_{\ell,n,v}\right) + \gamma\left((v+1)P_{\ell,v+1,n}(t) - vP_{\ell,n,v}(t)\right) \end{aligned}$$

where $P_{\ell,n,v}(t) = P(L=\ell, T^*=n, V=v; t)$

Backwards Kolmogorov ODE



$$L \xrightarrow{a} T^* \qquad L \xrightarrow{\delta_L} \emptyset$$
$$T^* \xrightarrow{p} T^* + V \qquad T^* \xrightarrow{\delta} \emptyset$$
$$L \xrightarrow{\mu} 2L \qquad V \xrightarrow{\gamma} \emptyset$$

$$P_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}(t) = P(L(t) = \ell, T^*(t) = n, V(t) = v | L(0) = \tilde{\ell}, T^*(0) = \tilde{n}, V(0) = \tilde{v})$$

We can derive the backward Kolmogorov eqns:

$$\frac{dP_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}(t)}{dt} =$$
$$a\tilde{\ell}\left(P_{\tilde{\ell}-1,\tilde{n}+1,\tilde{v};\ell,n,v} - P_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}\right) + \mu\tilde{\ell}\left(P_{\tilde{\ell}-1,\tilde{n},\tilde{v};\ell,n,v} - P_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}\right)$$
$$+\rho\tilde{\ell}\left(P_{\tilde{\ell}+1,\tilde{n},\tilde{v};\ell,n,v} - P_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}\right) + \delta\tilde{n}\left(P_{\tilde{\ell},\tilde{n}-1,\tilde{v};\ell,n,v} - P_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}\right)$$
$$+p\tilde{n}\left(P_{\tilde{\ell},\tilde{n},\tilde{v}+1;\ell,n,v} - P_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}\right) + c\tilde{v}\left(P_{\tilde{\ell},\tilde{n},\tilde{v}-1;\ell,n,v} - P_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}\right)$$

$$P_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}(0) = \delta_{\ell\tilde{\ell}}\delta_{n\tilde{n}}\delta_{v\tilde{v}}$$

Probability Generating Function (pgf)

Use the BKDE to derive equations for the **pgf**.

Define the pgf $G_{\tilde{\ell},\tilde{n},\tilde{v}}(x, y, z; t)$:

$$G_{\tilde{\ell},\tilde{n},\tilde{v}}(x, y, z; t) = E[x^L y^{T^*} z^V] = \sum_{\ell=0}^{\infty} \sum_{n=0}^{\infty} \sum_{v=0}^{\infty} P_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}(t) x^{\ell} y^{n} z^{v}$$

Uses of pgf $G(x, y, z; t)$:

- Gives us moments

$$\text{e.g. Mean \# virions} = \sum_{\ell,n,v=0}^{\infty} v P_{\ell,n,v} = \left. \frac{\partial G}{\partial z} \right|_{x=y=z=1}$$

- Gives us the probability distribution of... anything!

e.g. Individual probabilities of # of virions:

$$P(V = v; t) = \left. \frac{1}{v!} \frac{\partial^v G}{\partial z^v} \right|_{x=y=1,z=0}$$

Equations for PGF

Derive from the backwards Chapman-Kolmogorov differential equation:

$$\partial_t G_{\tilde{\ell},\tilde{n},\tilde{v}} = \ldots$$

with $G_{\tilde{\ell},\tilde{n},\tilde{v}}(x,y,z;0) = x^{\tilde{\ell}} y^{\tilde{n}} z^{\tilde{v}} \ldots$ an ∞-dimensional set of equations.

Simplify - assumption of independent individual cell evolutions,

$$G_{\tilde{\ell},\tilde{n},\tilde{v}}(x,y,z;t) = (G_{100}(x,y,z;t))^{\tilde{\ell}} (G_{010}(x,y,z;t))^{\tilde{n}} (G_{001}(x,y,z;t))^{\tilde{v}}$$

3 nonlinear equations to solve, the determine PGF

$$\begin{aligned}
\partial_t G_{100} &= a\,(G_{010} - G_{100}) + \delta_L\,(1 - G_{100}) + \rho(G_{100}^2 - G_{100}) \\
\partial_t G_{010} &= \delta\,(1 - G_{010}) + p\,(G_{010} G_{001} - G_{010}) \\
\partial_t G_{001} &= c\,(1 - G_{001}) + f(1-\epsilon) k T_S\,(G_{100} - G_{001}) + (1-f)(1-\epsilon) k T_S\,(G_{010} - G_{001})
\end{aligned}$$

with initial conditions $G_{100}|_{t=0} = x$, $G_{010}|_{t=0} = y$, and $G_{001}|_{t=0} = z$.

Complex variables

From definition of generating function,

$$P(V = v; t) = \frac{1}{v!} \left. \frac{\partial^v G_{\tilde{l},\tilde{n},\tilde{v}}}{\partial z^v} \right|_{x=y=1,z=0}$$

Now apply Cauchy Integral Formula:

$$\left. \frac{d^n f(x)}{dx^n} \right|_{x=a} = \frac{n!}{2\pi i} \oint_C \frac{f(z)}{(z-a)^{n+1}} dz$$

Obtain stable algorithm for calculating probability distributions:

$$P(V = v; t) = \frac{1}{2\pi i} \int_0^{2\pi} G_{\tilde{l},\tilde{n},\tilde{v}}(1, 1, e^{i\theta}) e^{-iv\theta} d\theta$$

Obtaining viral load distributions

To calculate $P(V = v; t)$:

1. Solve DEs numerically up to time t:

$$\begin{cases} \partial_t G_{100} = f(G_{100}, G_{010}, G_{001}) \\ \partial_t G_{010} = g(G_{100}, G_{010}, G_{001}) \\ \partial_t G_{001} = h(G_{100}, G_{010}, G_{001}) \end{cases}$$

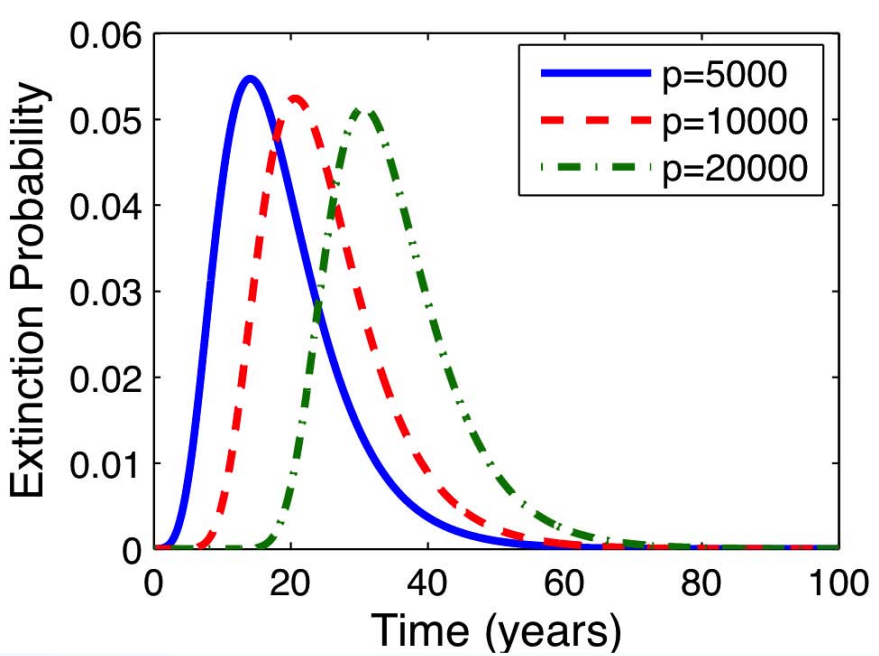
with ICs $G_{100} = 1$, $G_{010} = 1$, $G_{001} = e^{i\theta}$ for $0 \leq \theta \leq 2\pi$.

2. Set $G_{\tilde{\ell},\tilde{n},\tilde{v}}(1, 1, e^{i\theta}; t) = (G_{100})^{\tilde{\ell}}(G_{010})^{\tilde{n}}(G_{010})^{\tilde{v}}$.

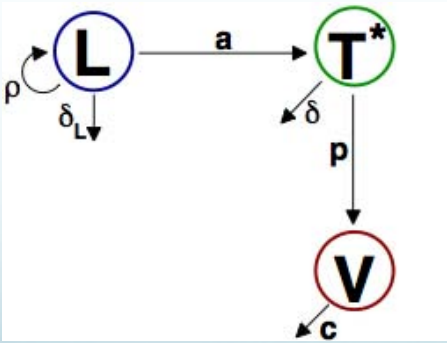
3. Integrate to calculate $P(V = v; t)$ for **any** v:

$$P(V = v; t) = \frac{1}{2\pi i} \int_0^{2\pi} G_{\tilde{\ell},\tilde{n},\tilde{v}}(1, 1, e^{i\theta}) e^{-iv\theta}\, d\theta.$$

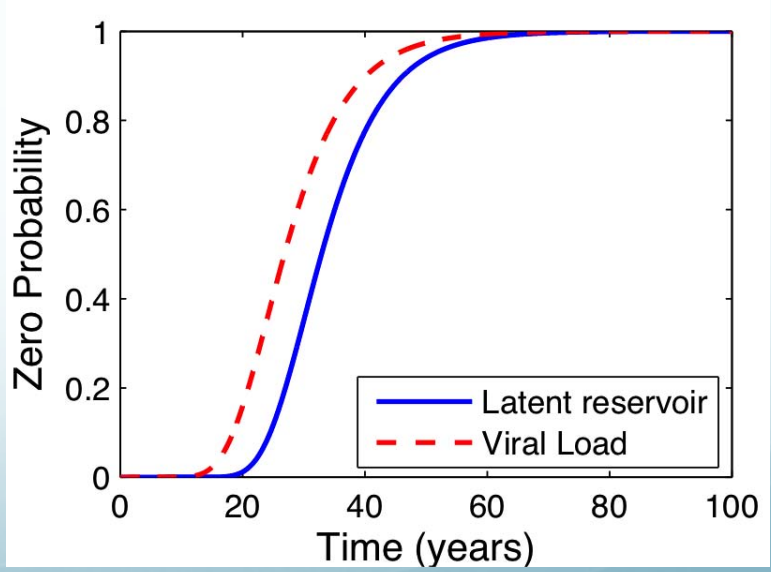
Latent cell times to extinction



- Previous estimate ~70yrs
- We allow for latent cell division - this reduces the mean time to extinction after fitting parameters

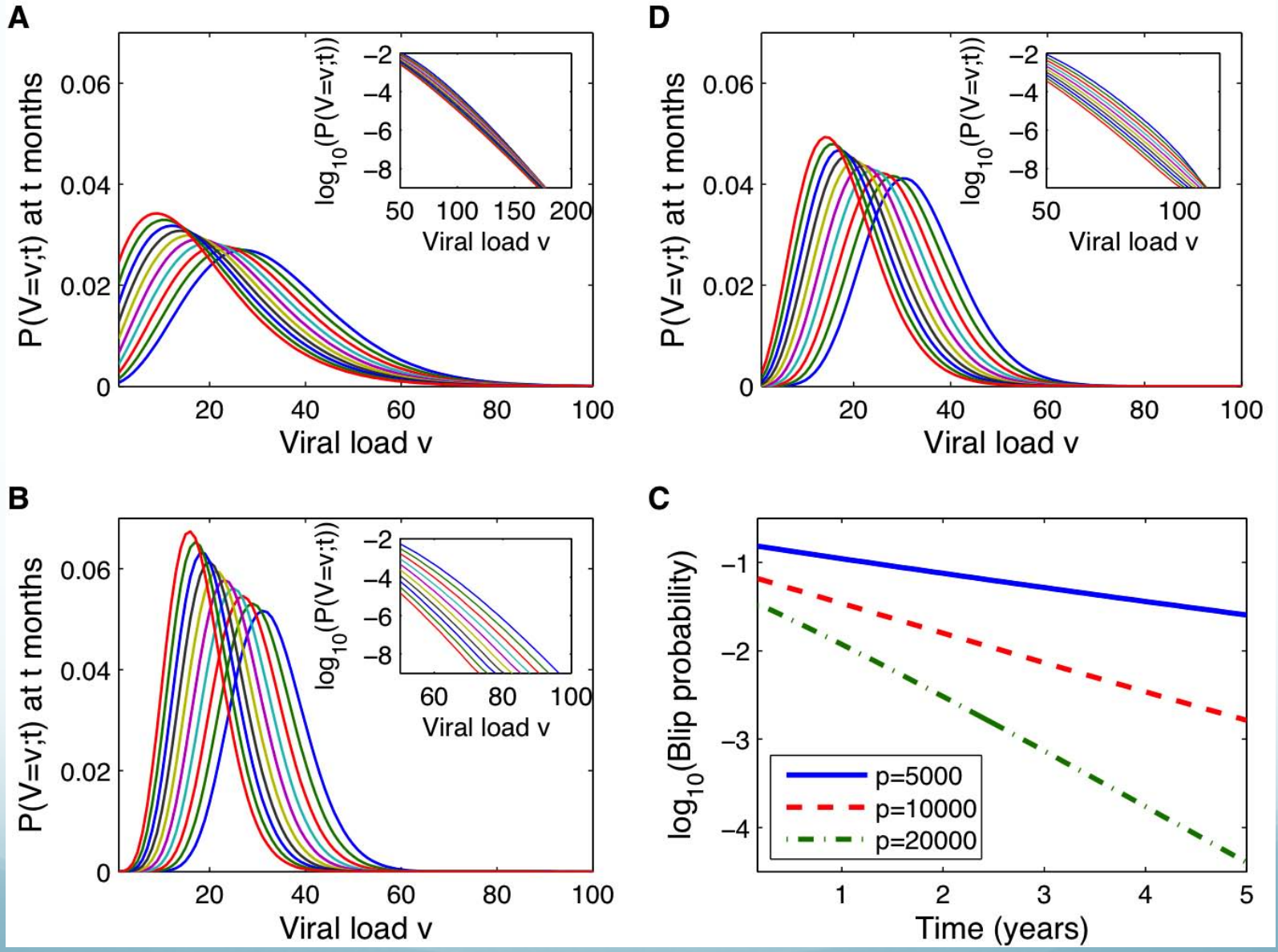


Transient viral extinction can occur:



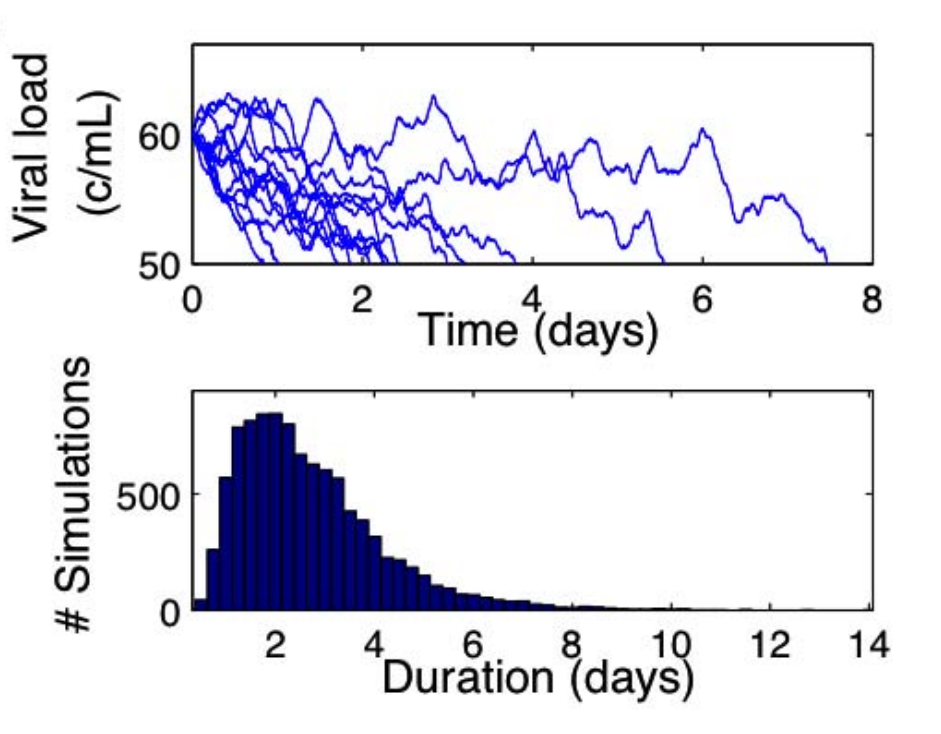
- clinical message remains depressing.....

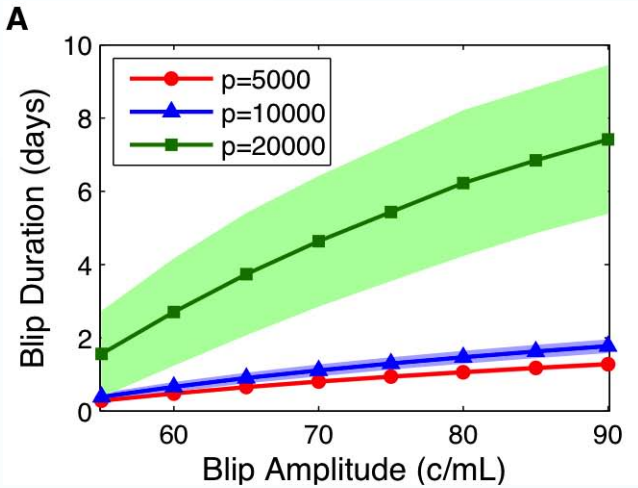
Viral blip probability (V>50)

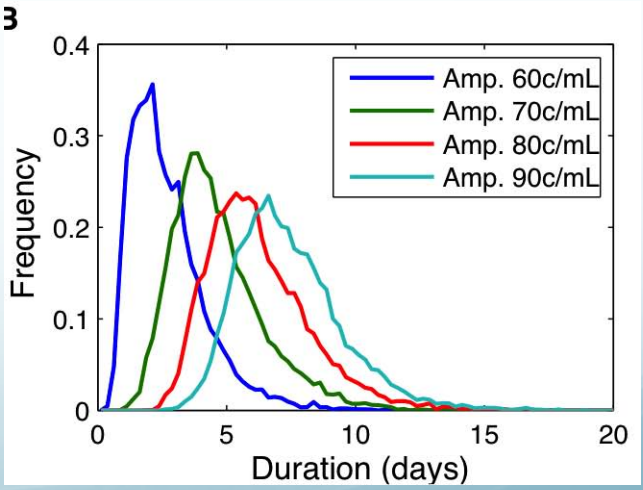


Blip durations

The generating function approach does not yield dynamic information. So we resort back to Gillespie simulations of the dynamics.







- repeat positive measurements within 8-10 days could be due to rare fluctuations rather than drug resistance or pathology.

Summary of Latent Cell Model:

- Stochastic models are essential to study stochastic events in HIV.

- Robust numerical methods to find pgf; simulate dynamics.

- Refined view of latent cell extinction in the presence of cell replication.

- It is possible that small blips are driven by stochastic reactivation of latently infected cells.
    - large blips must arise from other processes

- Two projects on *treated* infection
  1. Viral load dynamics during long-term therapy
  2. **Early infection and risk reduction for prophylaxis**

Early events in HIV infection

- Per-act infection risks are very low
  - [0.05% – 2%]
- Phylogenetic analyses support a *strong* evolutionary bottleneck at the time of infection
  - single founder strain hypothesis
- Vaccine trials have had limited success
  - Why?
- Early infection is hard to study
  - in animals and in humans
- Models of early infection will be useful
  - e.g. Pearson 2010, Yates 2011, others

Post-exposure prophylaxis (PEP)

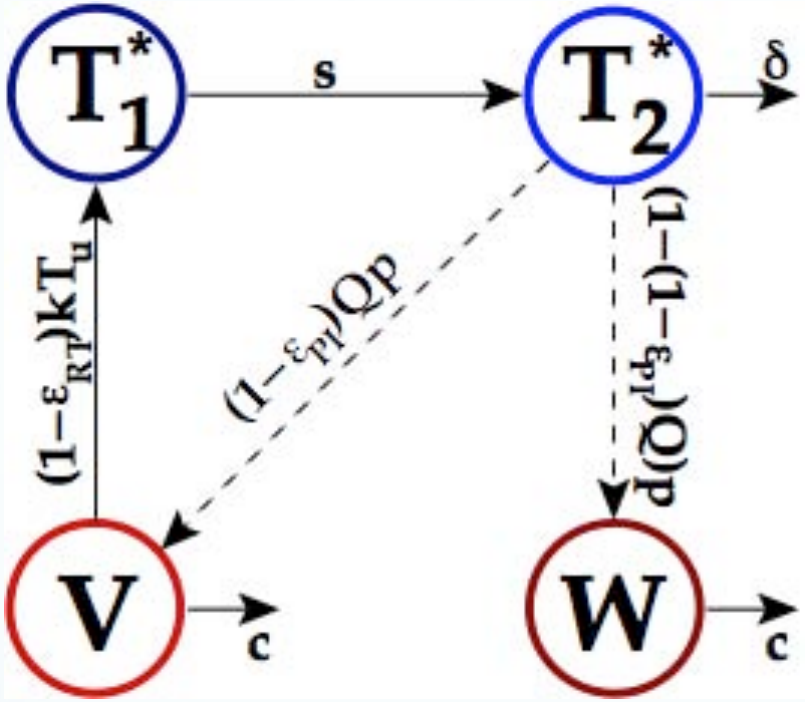
- Success in occupational exposure for 20 years
  - Guidelines: high dose of combination ART within 72 hours of exposure, continuing for 28 days
  - Reduces incidence ~80% after needlestick
  - Guidelines based on 1990s animal studies with AZT
- Non-occupational PEP trials inconclusive
  - Low adherence / completion rates

Pre-exposure prophylaxis (PrEP)

- e.g: iPReX study (2007 –)
  - 2,499 sexually active men who have sex with men
  - 11 sites in nine cities
    - Brazil, Ecuador, Peru, South Africa, Thailand, USA
  - daily tablet containing two antiretroviral drugs
  - double-blind, randomized placebo study

  - with drugs, ~44% fewer HIV infections than with placebo. ~90% protection in men whose blood samples contained blood
  - no drug resistance noted

Basic model of early infection

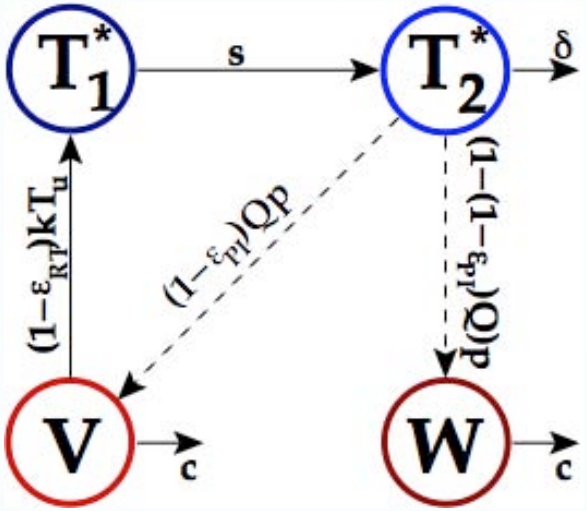


- Target cells in excess.
- include delay between infection and production (eclipse phase)
- uninfectious viruses (W)

Param.	Meaning
s	transition rate from eclipse phase
δ	death rate of T_2^*
p	production rate of virus
Q	infectious fraction of new virus

Param.	Meaning
k	mass-action infection rate
T_u	"steady" number of healthy cells
c	clearance rate of V
ε_{RT}	efficacy of RTs
ε_{PI}	efficacy of PIs

Master equation formulation



$$T_1^* \xrightarrow{s} T_2^*$$

$$T_2^* \xrightarrow{\delta} \emptyset$$

$$T_2^* \xrightarrow{(1-\epsilon_{\mathrm{RT}})kT_u} T_1^*$$

$$\dots$$

$$\frac{dP_{n,m,v,w}}{dt} = [s(n+1)]\,P_{n+1,m-1,v,w} + [\delta(m+1)]\,P_{n,m+1,v,w}$$
$$+ [(1-(1-\varepsilon_{PI})Q)pm]\,P_{n,m,v,w-1} + [(1-\varepsilon_{PI})Qpm]\,P_{n,m,v-1,w}$$
$$+ [c(w+1)]\,P_{n,m,v,w+1} + [c(v+1)]\,P_{n,m,v+1,w}$$
$$+ [(1-\varepsilon_{RT})kT_u(v+1)]\,P_{n-1,m,v+1,w}$$
$$- [sn + \delta m + (1-(1-\varepsilon_{PI})Q)pm + (1-\varepsilon_{PI})Qpm$$
$$+ cw + cv + (1-\varepsilon_{RT})kT_u v]\,P_{n,m,v,w}$$

Generating functions, etc

$$\frac{dP_{\tilde{n},\tilde{m},\tilde{v},\tilde{w}}}{dt} = s\tilde{n}P_{\tilde{n}-1,\tilde{m}+1,\tilde{v},\tilde{w}} + \delta\tilde{m}P_{\tilde{n},\tilde{m}-1,\tilde{v},\tilde{w}} + (1-(1-\varepsilon_{PI})Q)p\tilde{m}P_{\tilde{n},\tilde{m},\tilde{v},\tilde{w}+1} + (1-\varepsilon_{PI})Qp\tilde{m}P_{\tilde{n},\tilde{m},\tilde{v}+1,\tilde{w}}$$
$$+c\tilde{w}P_{\tilde{n},\tilde{m},\tilde{v},\tilde{w}-1} + c\tilde{v}P_{\tilde{n},\tilde{m},\tilde{v}-1,\tilde{w}} + (1-\varepsilon_{RT})kT_u\tilde{v}P_{\tilde{n}+1,\tilde{m},\tilde{v}-1,\tilde{w}}$$
$$-(s\tilde{n}+\delta\tilde{m}+(1-(1-\varepsilon_{PI})Q)p\tilde{m}+(1-\varepsilon_{PI})Qp\tilde{m}+c\tilde{w}+c\tilde{v}+(1-\varepsilon_{RT})kT_u\tilde{v})\,P_{\tilde{n},\tilde{m},\tilde{v},\tilde{w}}$$

$$+$$

$$G_{\tilde{n},\tilde{m},\tilde{v},\tilde{w}}(x,y,z,r;t) = \sum_{n=0}^{\infty}\sum_{m=0}^{\infty}\sum_{v=0}^{\infty}\sum_{w=0}^{\infty} P_{\tilde{n},\tilde{m},\tilde{v},\tilde{w};n,m,v,w}x^n y^m z^v r^w$$

$$=$$

$$\frac{\partial G_{\tilde{n},\tilde{m},\tilde{v},\tilde{w}}}{\partial t} = s\tilde{n}G_{\tilde{n}-1,\tilde{m}+1,\tilde{v},\tilde{w}} + \delta\tilde{m}G_{\tilde{n},\tilde{m}-1,\tilde{v},\tilde{w}} + (1-(1-\varepsilon_{PI})Q)p\tilde{m}G_{\tilde{n},\tilde{m},\tilde{v},\tilde{w}+1} + (1-\varepsilon_{PI})Qp\tilde{m}G_{\tilde{n},\tilde{m},\tilde{v}+1,}$$
$$+c\tilde{w}G_{\tilde{n},\tilde{m},\tilde{v},\tilde{w}-1} + c\tilde{v}G_{\tilde{n},\tilde{m},\tilde{v}-1,\tilde{w}} + (1-\varepsilon_{RT})kT_u\tilde{v}G_{\tilde{n}+1,\tilde{m},\tilde{v}-1,\tilde{w}}$$
$$-(s\tilde{n}+\delta\tilde{m}+(1-(1-\varepsilon_{PI})Q)p\tilde{m}+(1-\varepsilon_{PI})Qp\tilde{m}+c\tilde{w}+c\tilde{v}+(1-\varepsilon_{RT})kT_u\tilde{v})\,G_{\tilde{n},\tilde{m},\tilde{v},\tilde{w}}$$
$$G_{\tilde{n},\tilde{m},\tilde{v},\tilde{w}}(x,y,z,r;0) = x^{\tilde{n}}y^{\tilde{m}}z^{\tilde{v}}r^{\tilde{w}}$$

(This is the **Backward Chapman-Kolmogorov** system of equations)

Extinction probabilities

- We're particularly interested in the probability that the infection goes extinct (patient is “cured”):

$$q = \lim_{t \to \infty} P_{\tilde{n},\tilde{m},\tilde{v},\tilde{w};0,0,0,0}(t)$$

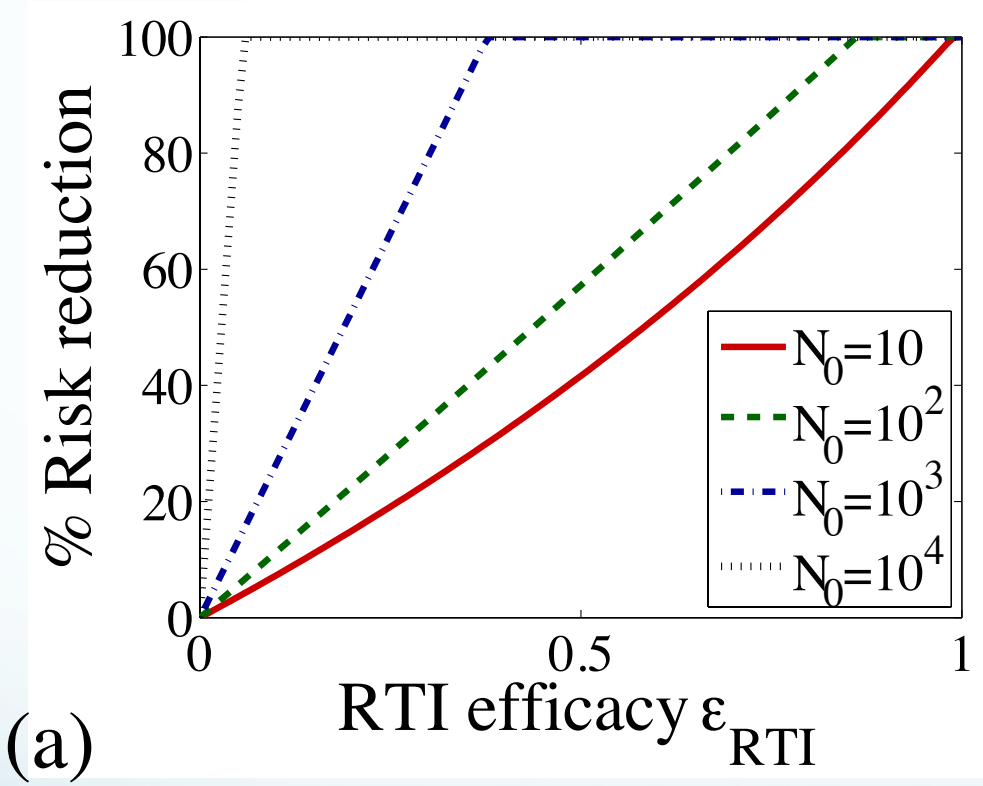
- This limit is a *fixed point* of the ODE system.
  - Can find this using algebra!

$$q = \left(\frac{\delta(c + (1 - \varepsilon_{RT})kT_u)}{pQ(1 - \varepsilon_{PI})kT_u(1 - \varepsilon_{RT})} \right)^{\tilde{n}+\tilde{m}} \left(\frac{\delta(c + (1 - \varepsilon_{RT})kT_u) + Qpc(1 - \varepsilon_{PI})}{pQ(1 - \varepsilon_{PI})(c + (1 - \varepsilon_{RT})kT_u)} \right)^{\tilde{v}}$$

where $\tilde{n}, \tilde{m}, \tilde{v}$ are initial conditions.

Risk reduction for PrEP

- RTIs only (consistent with clinical trials).

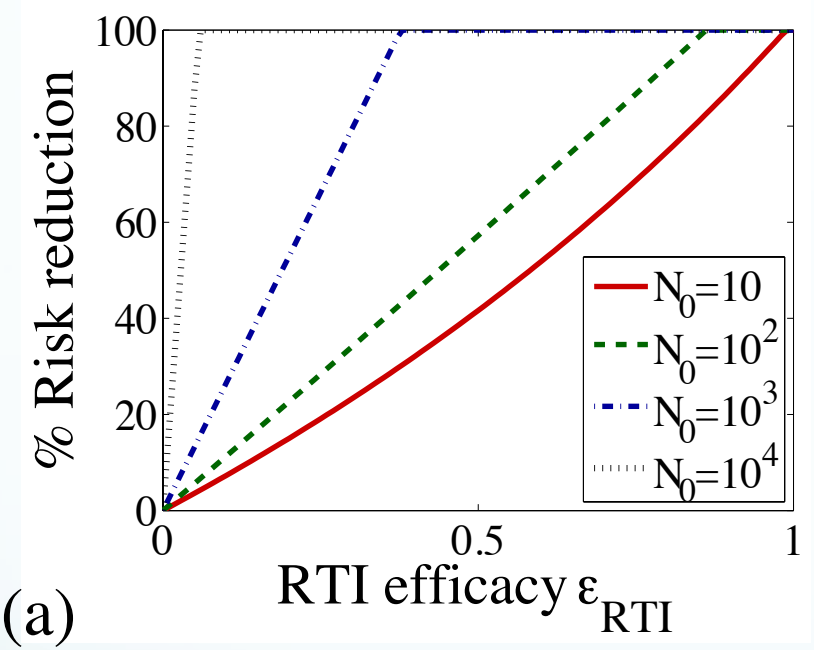


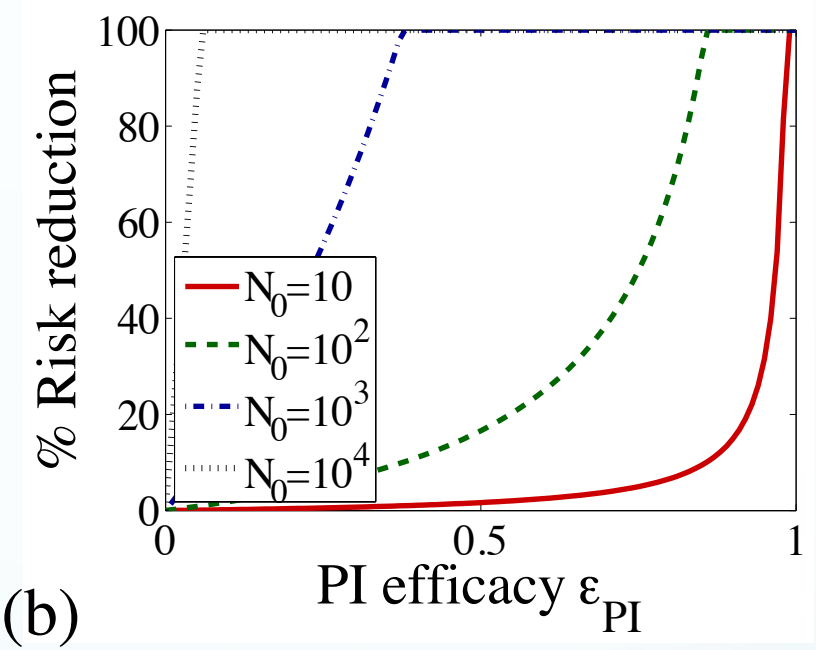
- Higher risk reductions for higher inoculum sizes.
- High inoculum size forces a lower cell infection rate kT in order to get the same 0.3% risk without treatment

- Predict excellent risk reductions for high RTI efficacy
- *NB recent reports of low drug concentrations in tissue*

Risk reduction for PrEP

- Comparison of RTI and PI drugs (monotherapy)

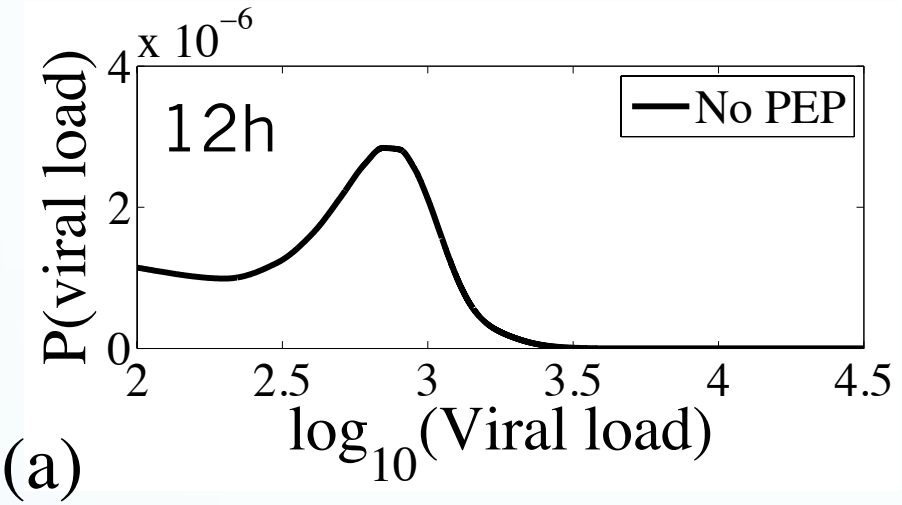


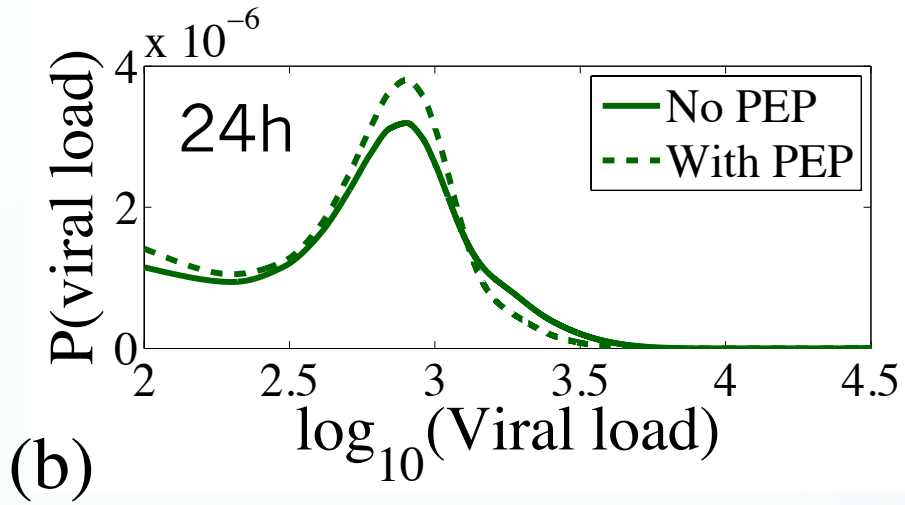


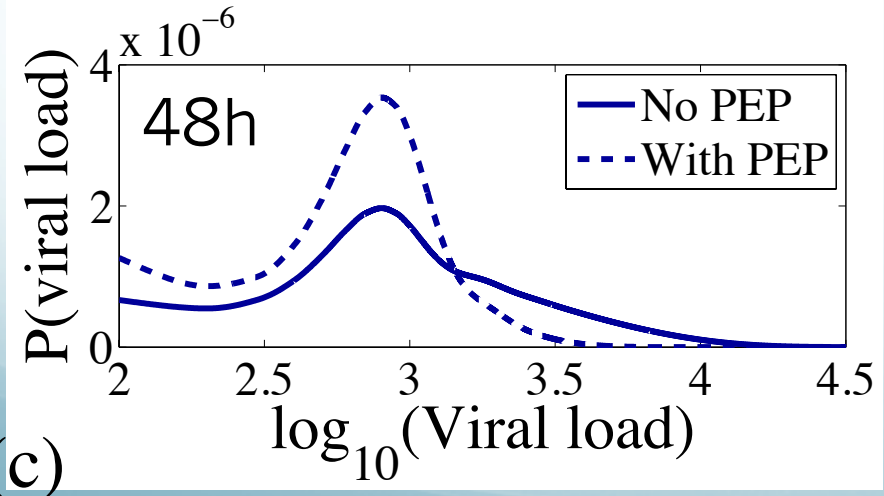
- PIs work only once cells are infected
- Hence, PIs are less effective as PrEP monotherapy
- Combination approach even more effective
  - (needed if drugs are weak at infection site?)

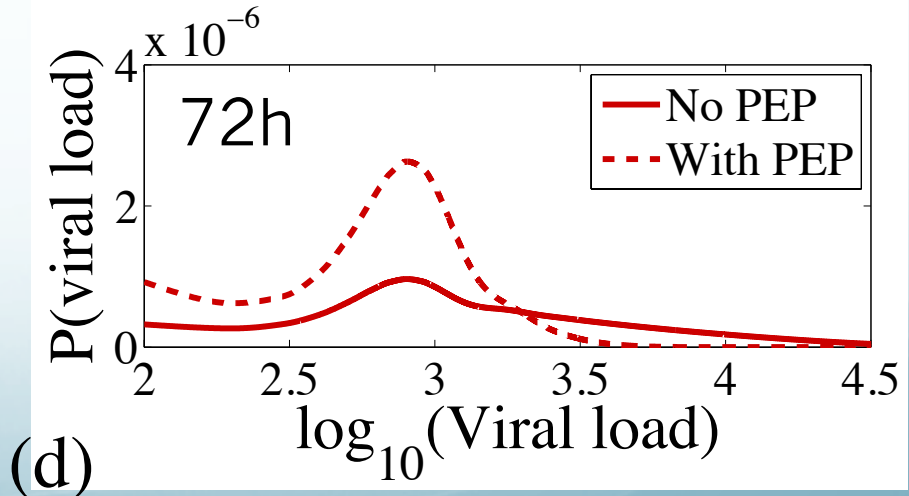
Viral population dynamics with PEP

RTI monotherapy starting at 12h post-exposure; efficacy = 0.9 (AZT)

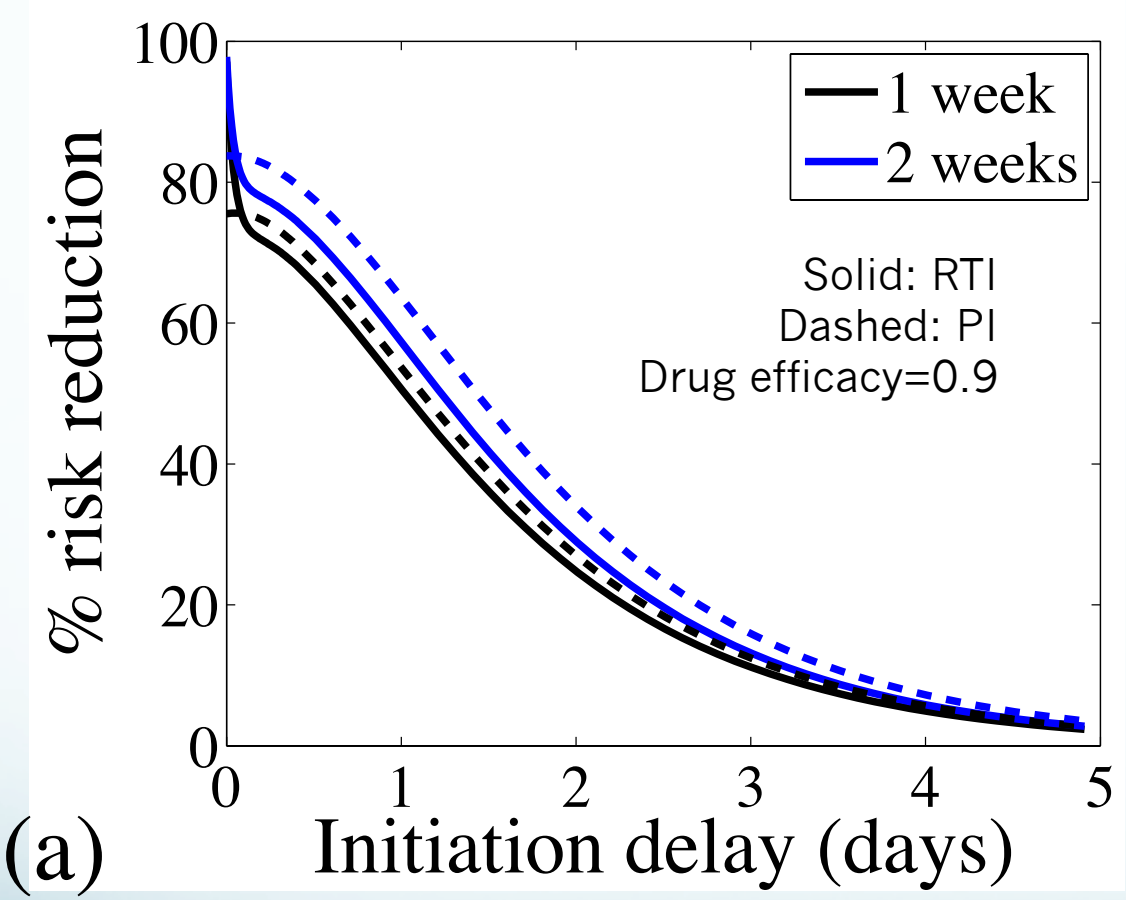






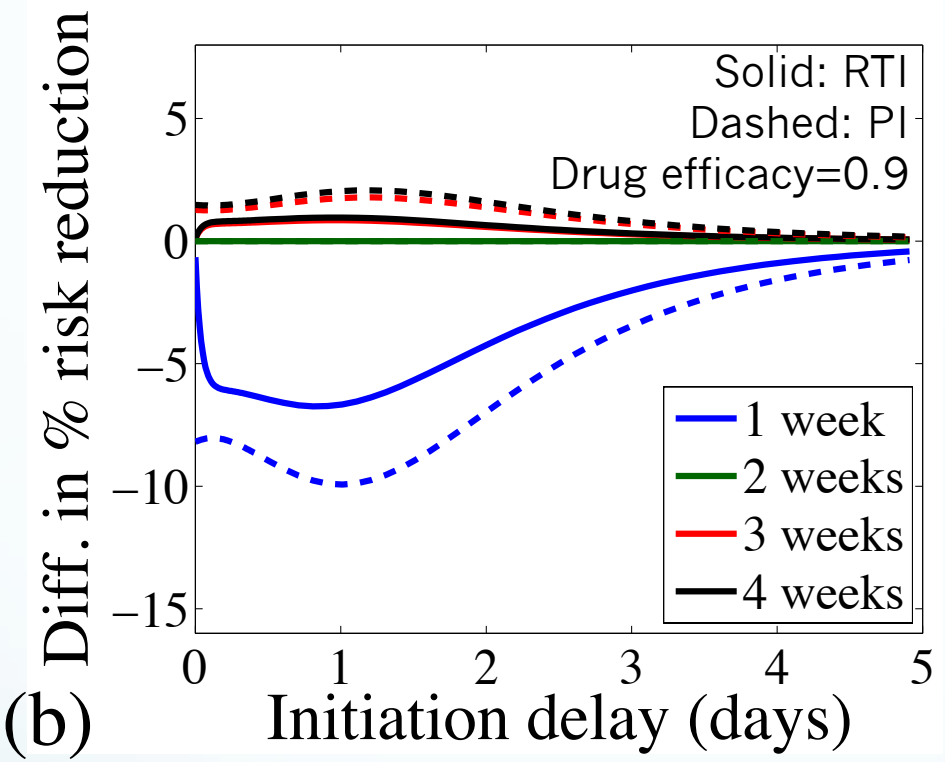


Early initiation of PEP is essential



- Start within **24h** for 50% risk reduction
- Clinical guideline: start no later than 72h
- PI and RTI essentially equivalent for single-drug PEP

Duration of PEP less important



- 2 weeks ~ 4 weeks
- RTI better for 1 week single-drug PEP
- 1990s animal studies:
  - 4-week PEP after 24h is effective
  - 10-day PEP is 50% effective
  - 3-day PEP is ineffective
  - NB big inoculum size

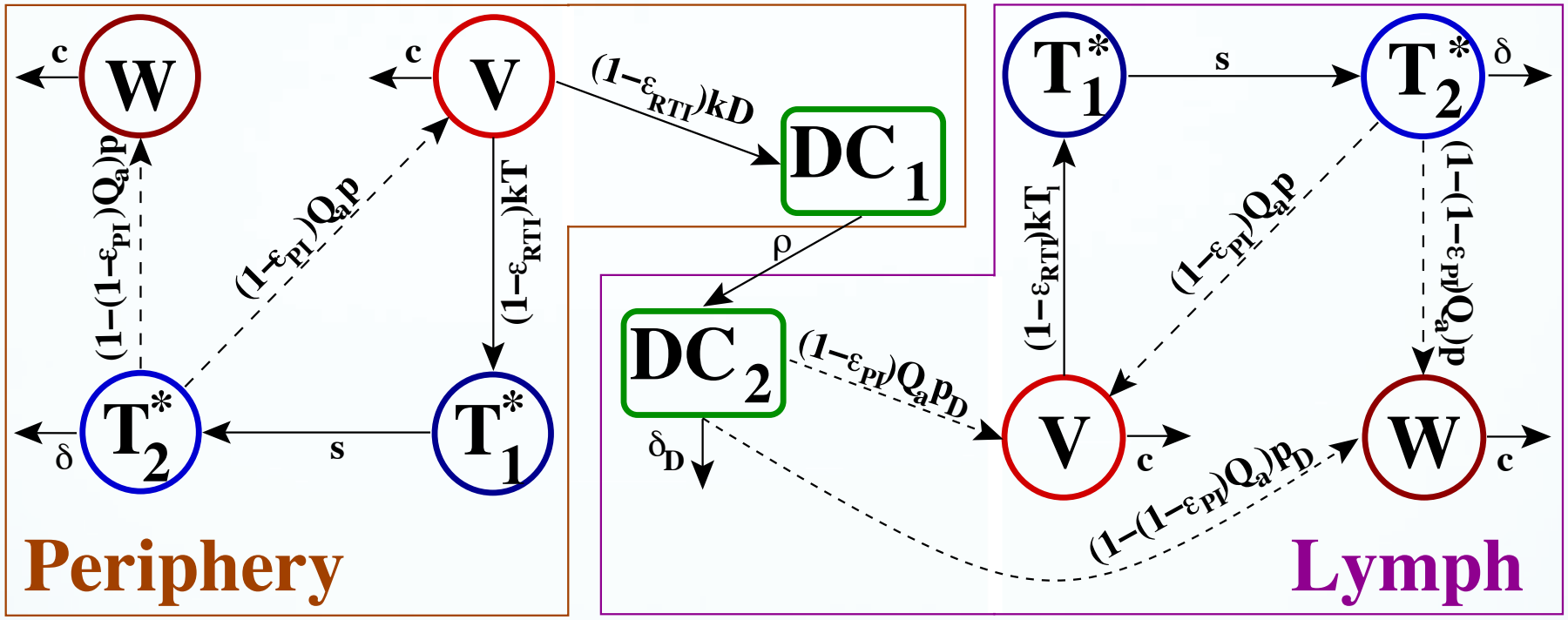
- Clinical guidelines call for multi-drug approach. We agree.

2 weeks of RTI+PI therapy started at 48h

=

4 weeks of RTI monotherapy started at 24h

Two-compartment model of early infection



- Travel time for DC to lymph 2 days
- Lifetime of DC in lymph 7 days
- DC infectibility and burst size smaller than T cell equivalents
- Other parameters are equal in both compartments
- Analysis is longer but same idea as basic model

Summary:

- Stochastic methods essential to study stochastic events
- One- and two- compartment models predict:
  - small inoculum of 10 – 1000 virions
  - consistent with few founder strains (1 or 2)
- PrEP predicted to be effective
  - combination therapy needed if drug efficacies are low
- PEP should be started within 24 – 36 hours of exposure
  - pointless after 100 hours of exposure
  - 2 weeks may be as good as 4 weeks
- Need better parameter estimates and mechanistic insight

Future directions:

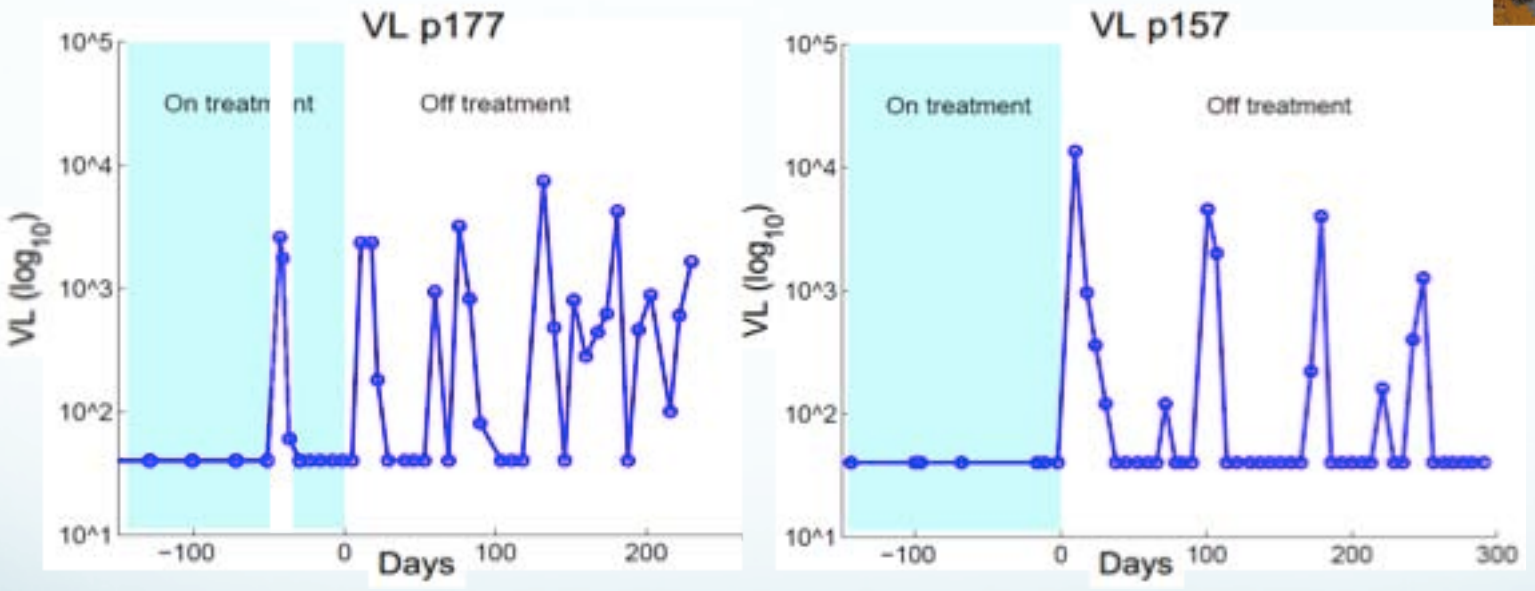
- Latent cell reservoir in long-term therapy
  - Characterize and destroy long-lived cells?
  - Collaboration on SIV infection in macaques

- PrEP and PEP in the clinic?
  - Potential for drug-resistance
  - Variable drug efficacy and improved models
    - link to population models; need practical expertise

- Modeling early infection without treatment
  - Sparse experimental data
  - Clues: PEP, PrEP findings
    HIV-test manufacturer data
    Early – disease studies
  - Modeling HIV vaccine

Functional cure for SIV?

- Two macaques with SIV who were treated with strong, latent-infection-reducing therapy.
- Viral "blips" following the end of treatment



- Deterministic models do not capture blips well

I.L. Shytaj, et al. PLoS Pathogens, 8(6):e1002774, 2012.

References

- J.M. Conway and D. Coombs. *A stochastic model of latently infected cell reactivation and viral blip generation in treated HIV patients*. PLoS Comp Biol (2011).
- J.M. Conway, B.P. Konrad and D. Coombs. *Stochastic analysis of pre- and post-exposure prophylaxis against HIV infection*. SIAM J Appl Math (2013).
- B.P. Konrad et al. *On the duration of the undetectable phase of HIV infection.* Under preparation.