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

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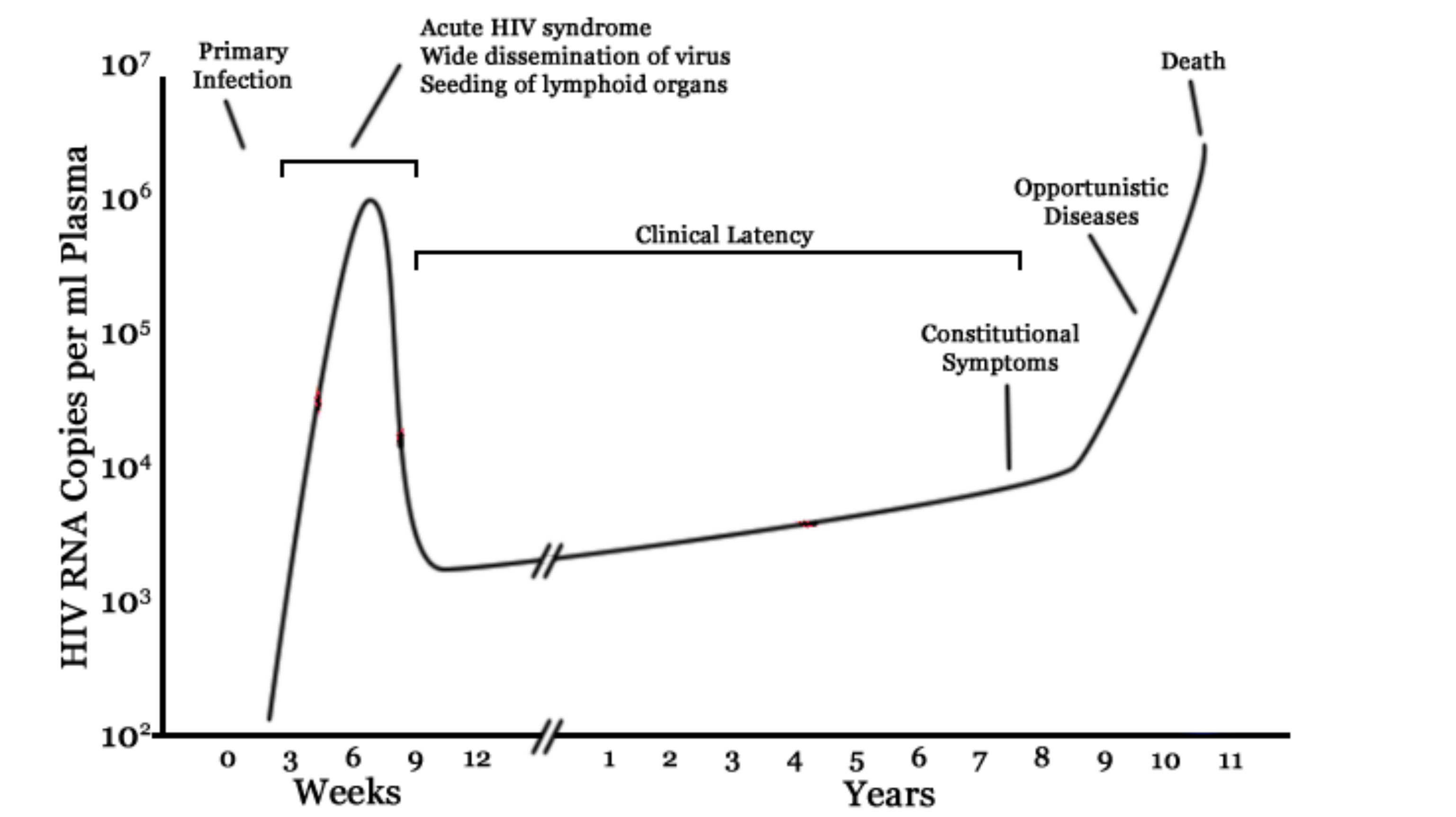
HIV infection

- 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)

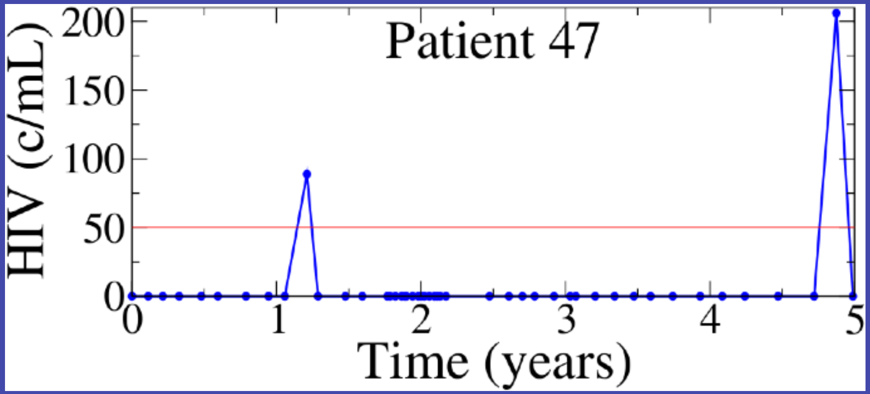
- Long-term continuous use
  - Side-effects can be serious
  - Drug resistance and transmission of drug resistance
  - Cost (~$500/yr in 3rd world)

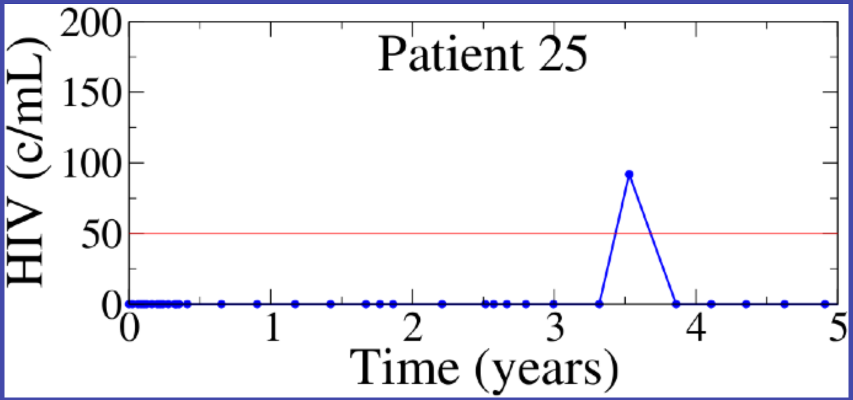
What's in this talk:

- 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

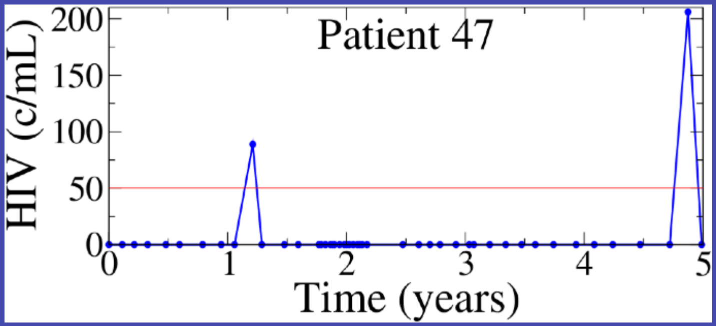
- Viral load is very low (5-50 copies/ml of blood)
- Virus remains, resurgent on drug failure
- Viral **blips** are observed:
  - infrequent episodes of <u>detectable</u> viral load
  - but large-amplitude blips are associated with drug failure





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

What causes viral blips?



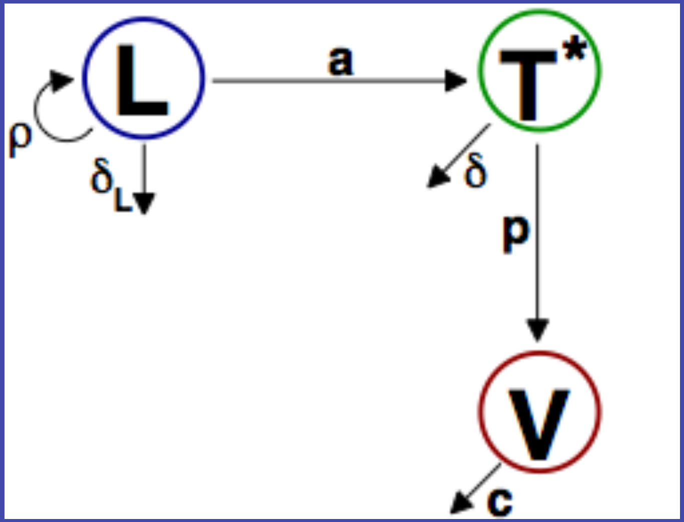
- Treatment non-adherence? Marginal.
- Secondary infection? Not always.
- Assay variation? Sometimes.

- **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

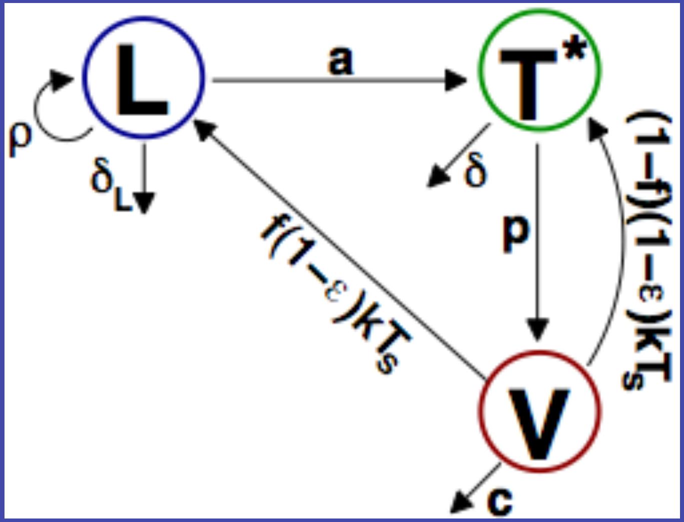
- Size of reservoir: ~$1/10^6$ cells
- Mainly memory T cells but also others
- Seeded during pre-treatment period
- Mean half-life $t_{1/2}$= 44 months
  - so >70 years to eradicate. (Siliciano 2005)
- *Hypothesis: viral blips are due to activation of latently infected cells.*

Latent cell reactivation model



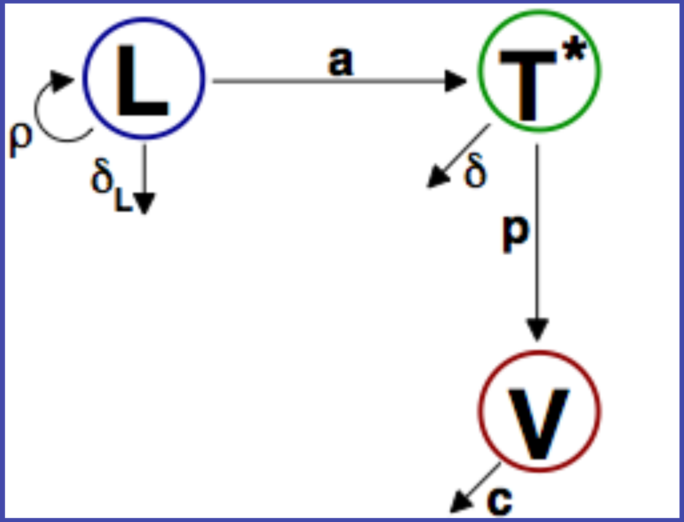
If ε=1 (drugs are perfect):

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



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

Latent cell reactivation model



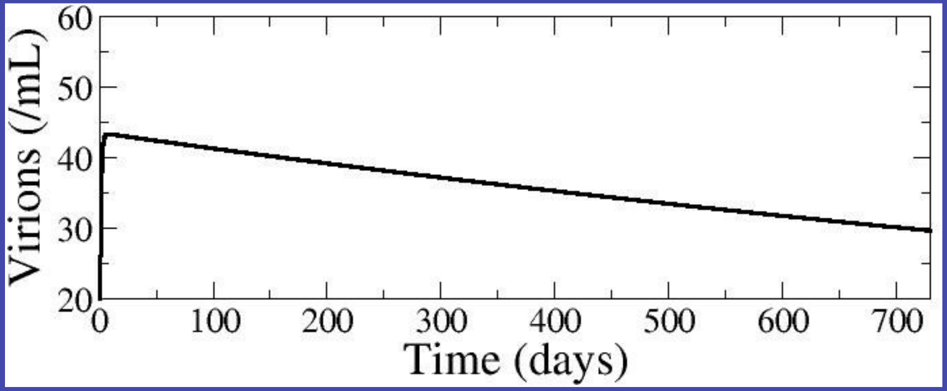
$$
\begin{aligned}
L'(t) &= (\rho - \delta_L - a)L \\
T^{*\prime}(t) &= aL - (\delta + p)T^* \\
V'(t) &= pT^* - cV
\end{aligned}
$$

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

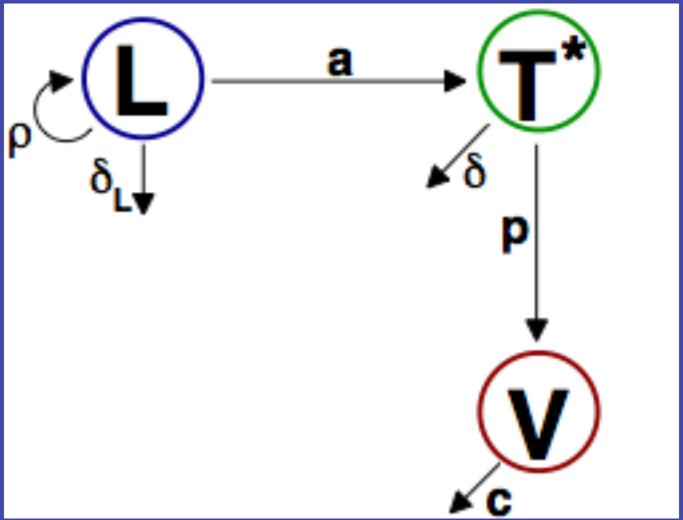
$c = 23$/day

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

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



Master equation model



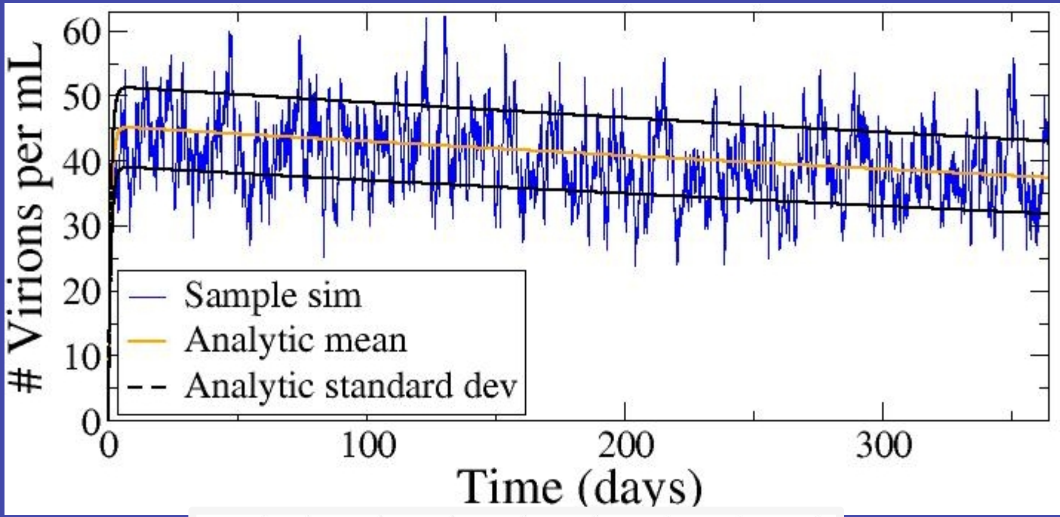
$$L \xrightarrow{a} T^* \qquad L \xrightarrow{\delta_L} \emptyset$$
$$T^* \xrightarrow{p} T^* + V \qquad T^* \xrightarrow{\delta} \emptyset$$
$$L \xrightarrow{\mu} 2L \qquad V \xrightarrow{\gamma} \emptyset$$

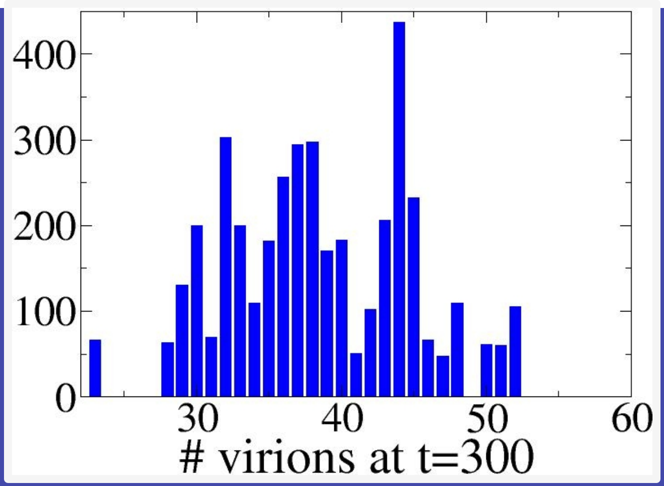
$$\begin{aligned} P'_{\ell,n,v}(t) \quad = \quad & a\left((\ell+1)P_{\ell+1,n-1,v}(t) - \ell P_{\ell,n,v}(t)\right) \\ & +\delta_L\left((\ell+1)P_{\ell+1,n,v} - \ell P_{\ell,n,v}\right) + \mu\left((\ell-1)P_{\ell-1,n,v} - \ell P_{\ell,n,v}\right) \\ & +\delta\left((n+1)P_{\ell,n+1,v}(t) - nP_{\ell,n,v}(t)\right)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

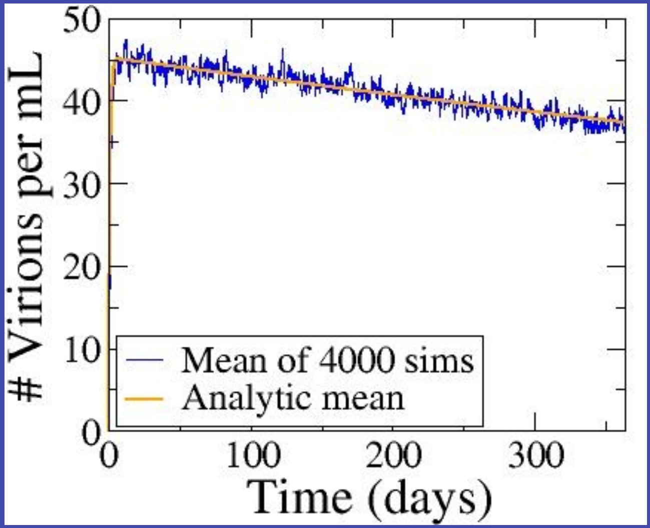
$$P_{\ell,n,v}(t) = P(L = \ell, T^* = n, V = v; t)$$

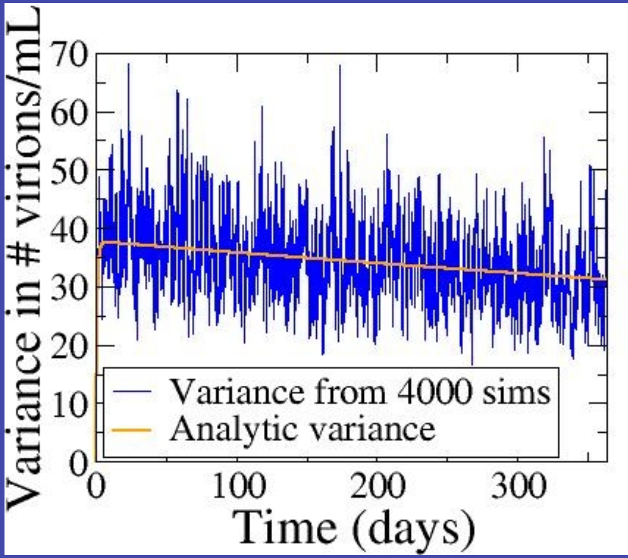
So we can simulate:

Gillespie algorithm simulations:



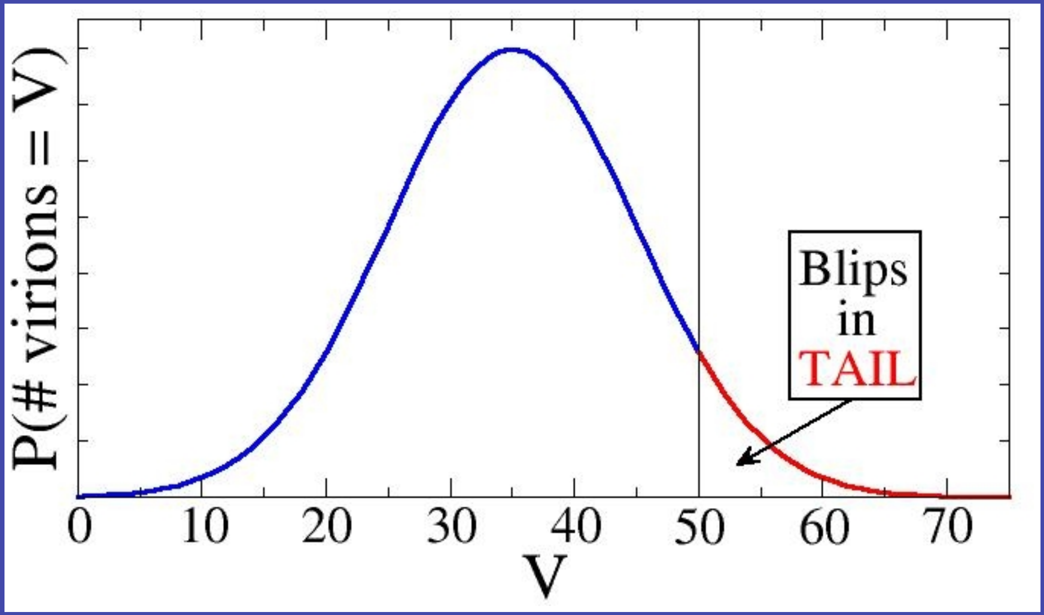


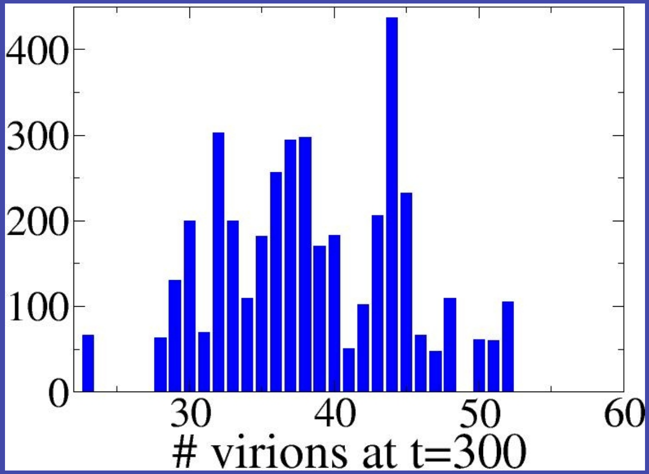




However, the problem is:

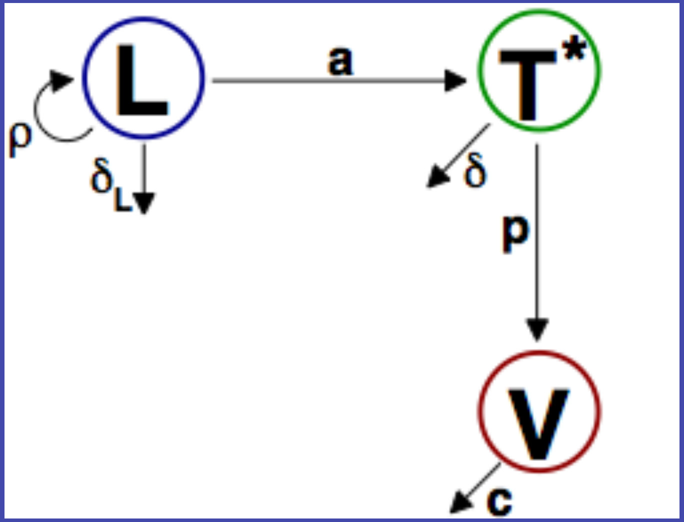
Blips are rare events.





Time-consuming to study via direct simulation.

Master equation model



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

Backwards Kolmogorov ODE

Defining

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

We can derive the backward Kolmogorov eqns:

$$\begin{aligned}
\frac{dP_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}(t)}{dt} = \quad & a\tilde{\ell}\left(P_{\tilde{\ell}-1,\tilde{n}+1,\tilde{v};\ell,n,v} - P_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}\right) + \mu\tilde{\ell}\left(P_{\tilde{\ell}-1,\tilde{n},\tilde{v};\ell,n,v} - P_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}\right) \\
& +\rho\tilde{\ell}\left(P_{\tilde{\ell}+1,\tilde{n},\tilde{v};\ell,n,v} - P_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}\right) + \delta\tilde{n}\left(P_{\tilde{\ell},\tilde{n}-1,\tilde{v};\ell,n,v} - P_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}\right) \\
& +p\tilde{n}\left(P_{\tilde{\ell},\tilde{n},\tilde{v}+1;\ell,n,v} - P_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}\right) + c\tilde{v}\left(P_{\tilde{\ell},\tilde{n},\tilde{v}-1;\ell,n,v} - P_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}\right) \\
P_{\tilde{\ell},\tilde{n},\tilde{v};\ell,n,v}(0) = \quad & \delta_{\ell\tilde{\ell}}\delta_{n\tilde{n}}\delta_{v\tilde{v}}
\end{aligned}$$

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

  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

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

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,

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

Now apply Cauchy Integral Formula:

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

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:

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

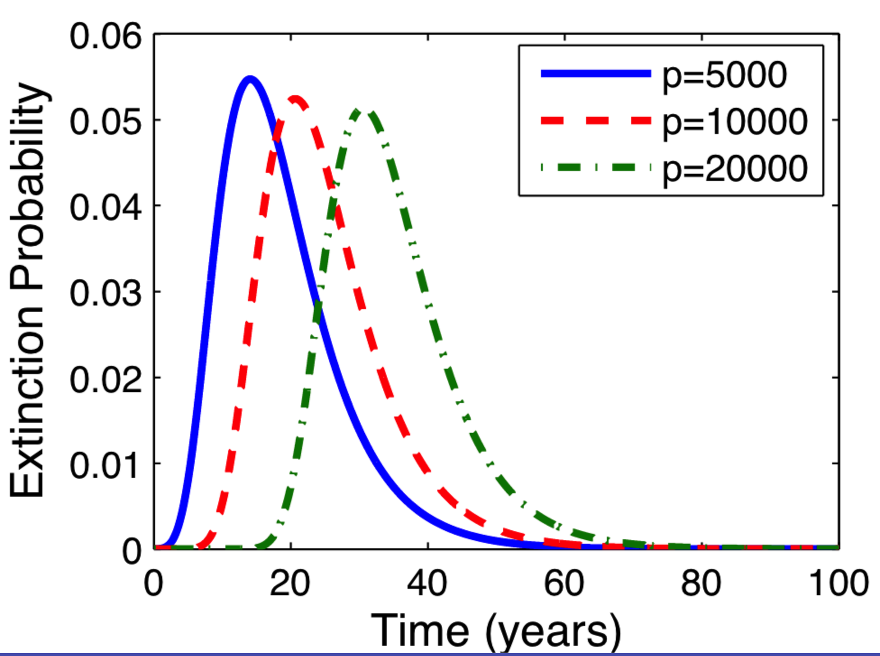
with ICs $G_{100} = 1$, $G_{010} = 1$, $G_{001} = e^{i\theta}$ for $0 \leq \theta \leq 2\pi$.

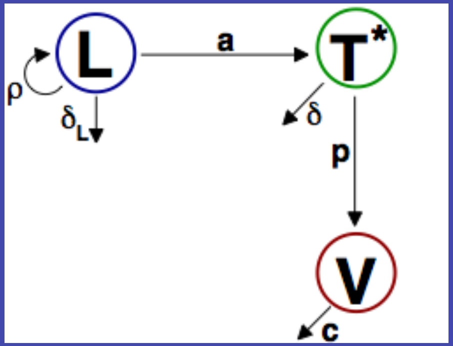
2. Set $G_{\tilde{\ell},\tilde{n},\tilde{v}}(1, 1, e^{i\theta}; t) = (G_{100})^{\tilde{\ell}}(G_{010})^{\tilde{n}}(G_{010})^{\tilde{v}}$.

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

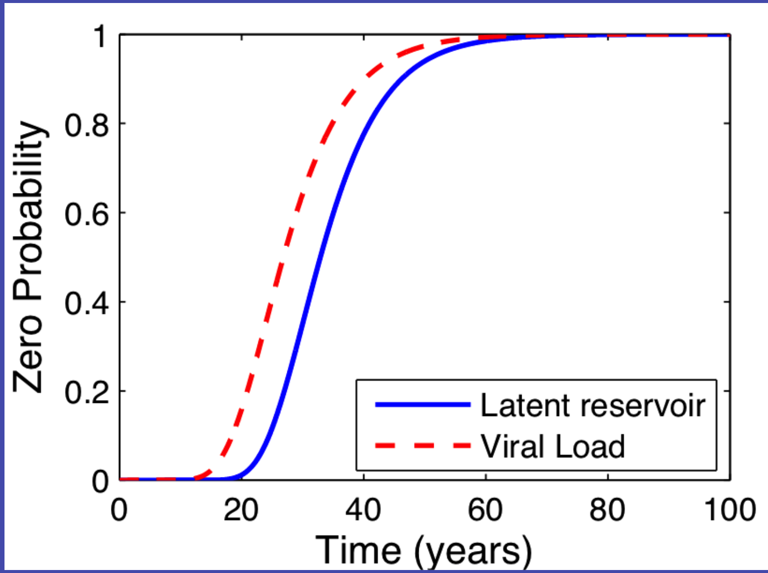




- Previous estimate ~70yrs

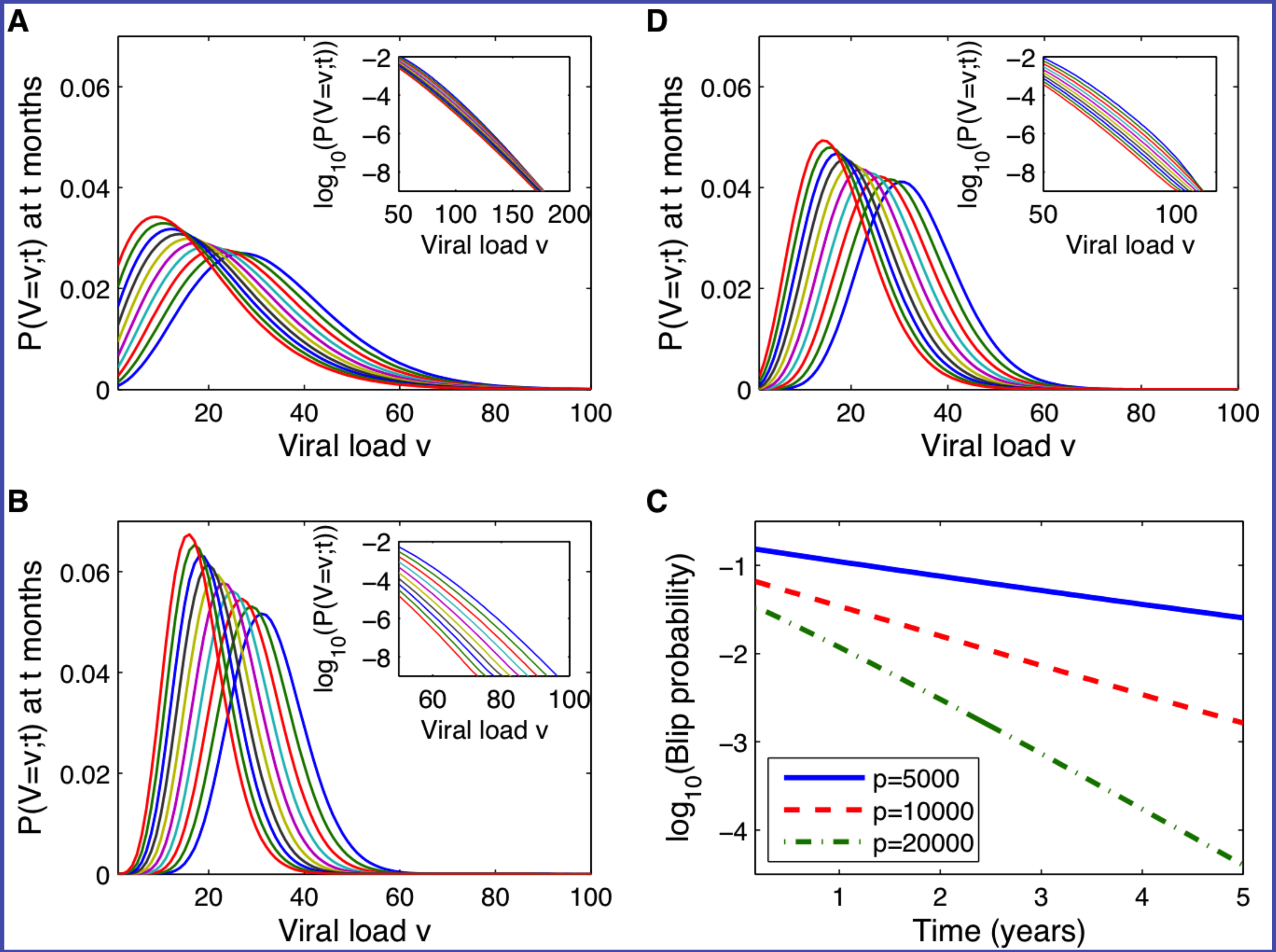
- We allow for latent cell division
- this reduces the mean time to extinction after fitting parameters

Transient viral extinction can occur:



- clinical message remains depressing…..

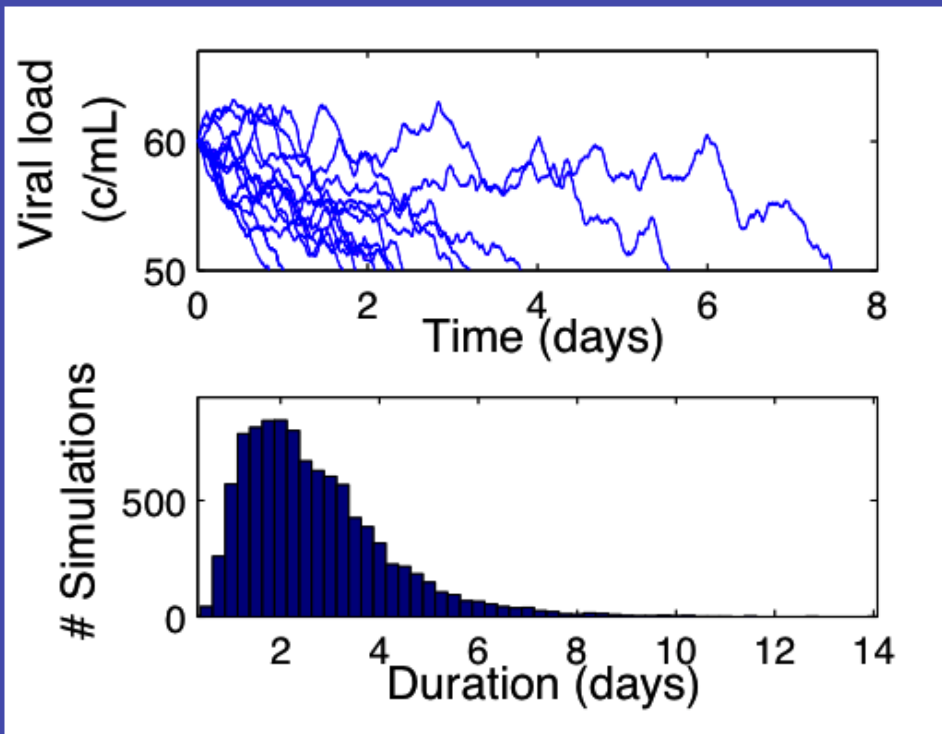
Viral blip probabilities

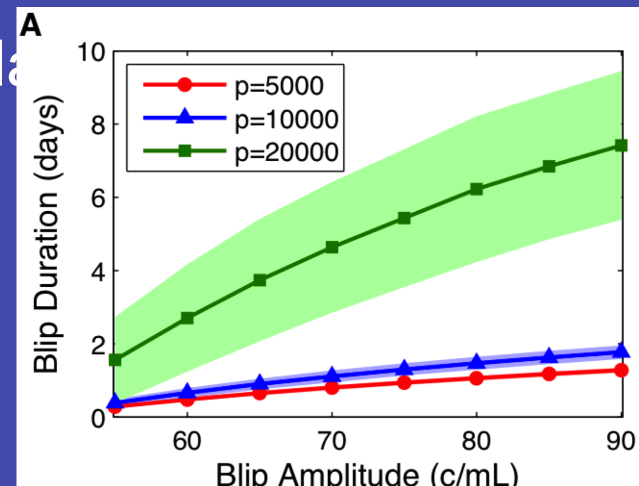


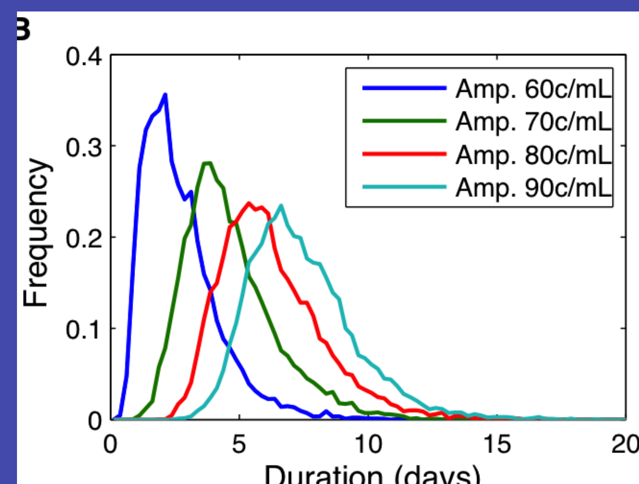
Blip durations

The generating function approach does not yield dynamic information.

simula







• 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

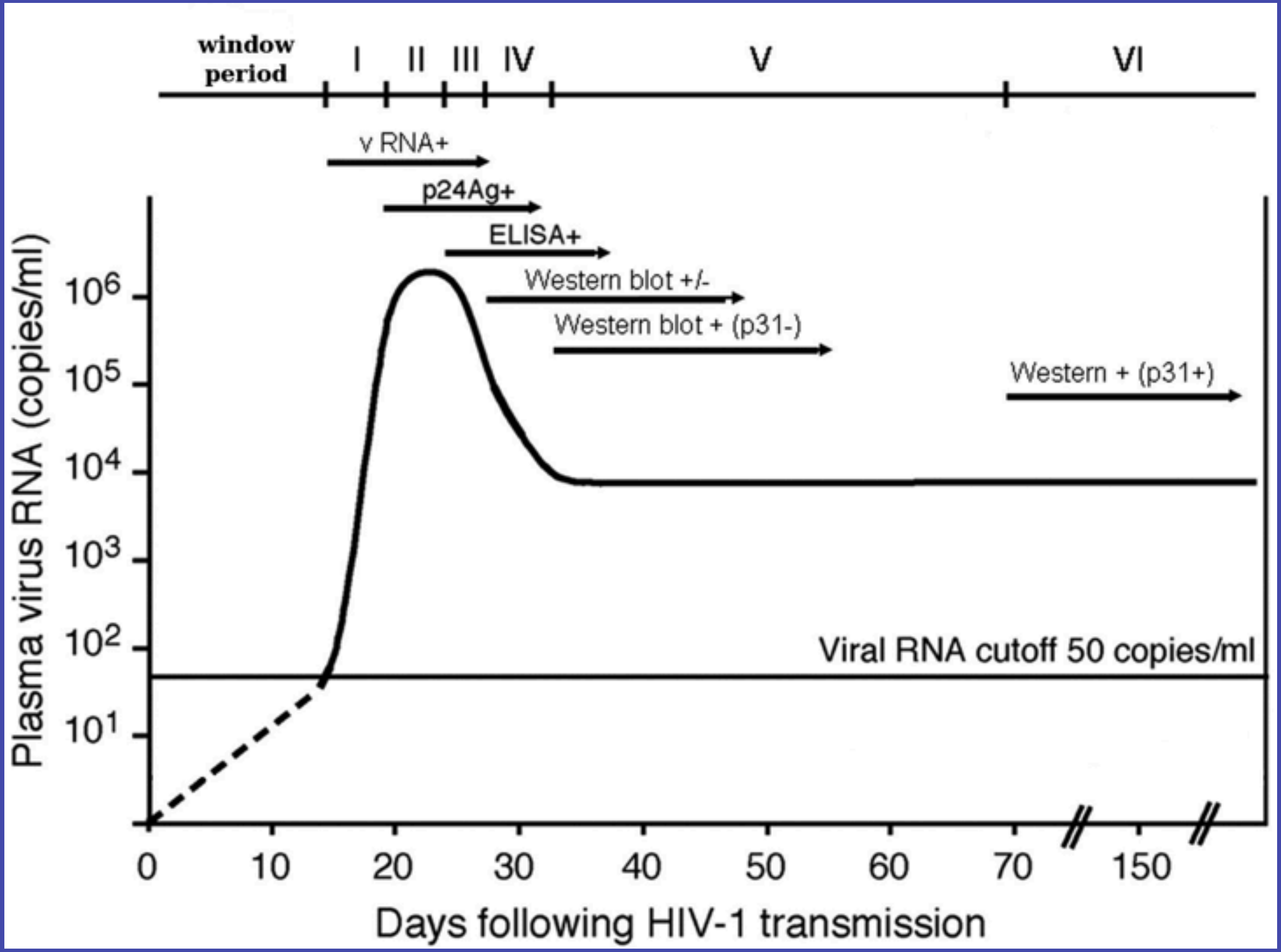
Early events in HIV infection

- Per-act infection risks are very low
    - [0.05% – 0.5%]
- 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

Case Study 1: Estimating the window period for HIV-RNA tests

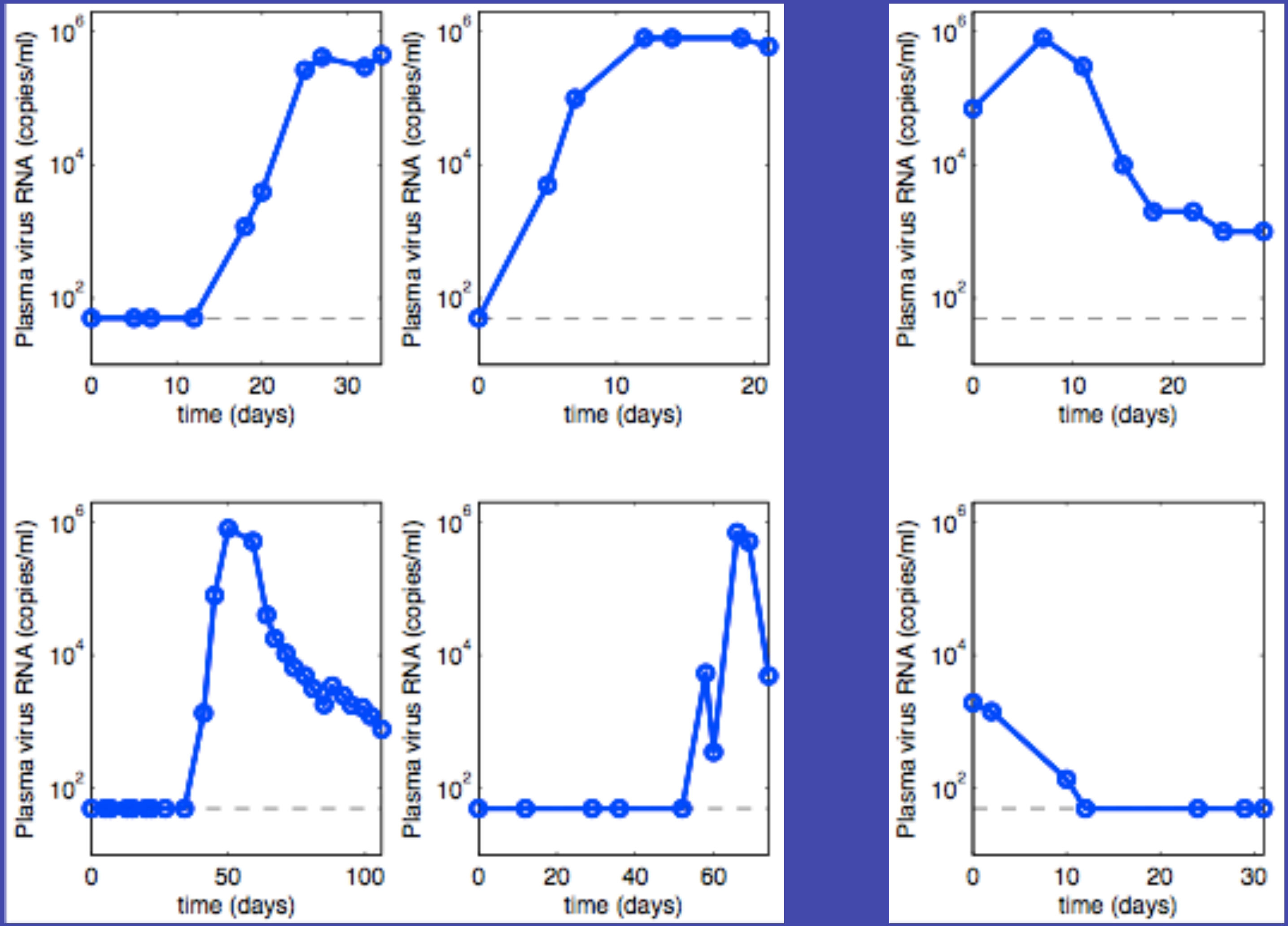
- What is the **time-gap** between *risky exposure* and a *positive HIV test?*
- If a patient reports a risky event, *t* days previously, what is the value of a negative HIV test?
- **Problems?**
  - Per-act risks very low [0.05% – 1.5%]
  - Animal experiments difficult to interpret,
  - Early patients hard to find
- **Background:**
  - RNA test, detection limit 30-50 copies/ml.
  - Clinical guidelines on RNA window period: fuzzy

- Relative window periods for different tests are well known.

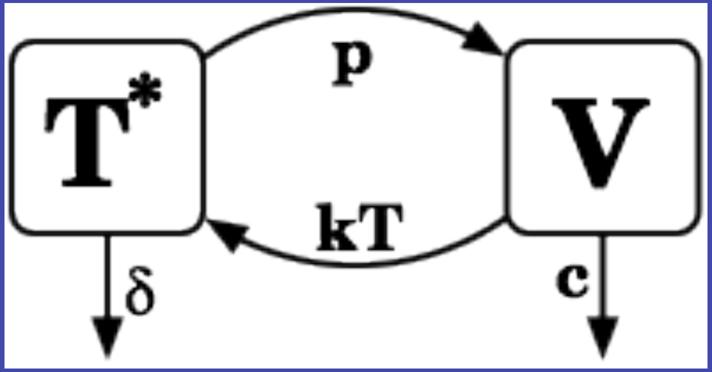


Fiebig et al, AIDS 2003

- Our approach: combine data from ~50 plasma donors with a stochastic model of early infection.



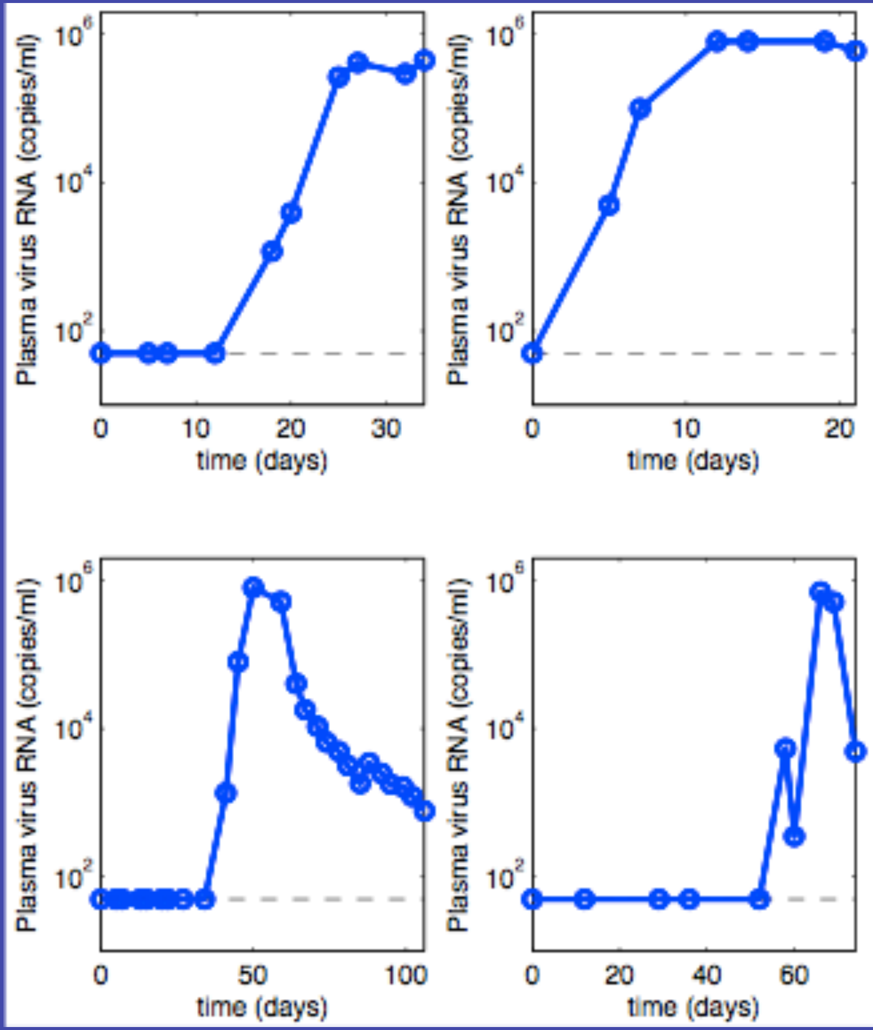
- A simple-enough model for early infection:



- Possible improvements:
  - Time delay between cell infection and production
  - Time-varying immune response

- Stochastic approaches: Gillespie method, master-equation for branching process

- Back to the patient data.



- The data are *biased* - all patients are **infected**.
- **Condition** process on viral non-extinction.
- Define q = probability of extinction (non-infection)
- Bayes (for the simple birth-death model):

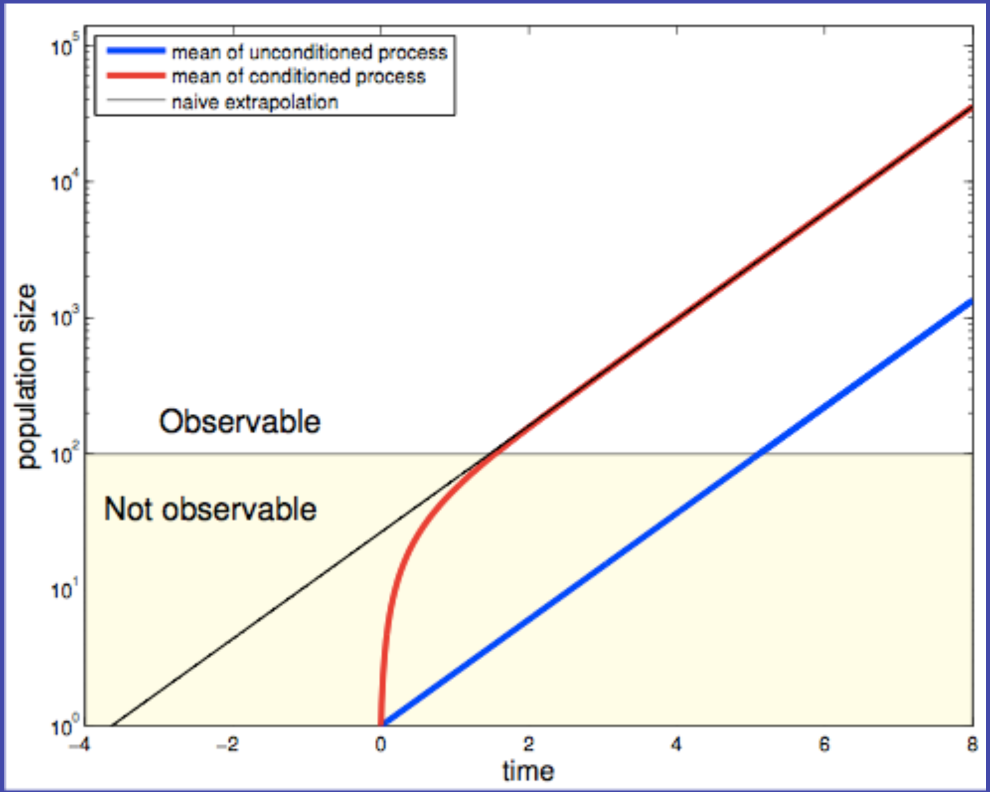
$$
\begin{aligned}
P[N(t) = N | N(\infty) \neq 0] &= P[N(t) = N] \frac{P[N(\infty) \neq 0 | N(t) = N]}{P[N(\infty) \neq 0]} \\
&= \frac{1}{1 - q^{N_0}} \left(P(N, N_0, t) - P(N, N_0, t) q^N \right)
\end{aligned}
$$

- *q* is a fixed point of the system and is easy to find

$$
\tilde{G}(n_0, t, z) = \frac{G(n_0, t, z) - G(n_0, t, qz)}{1 - q^{n_0}}
$$

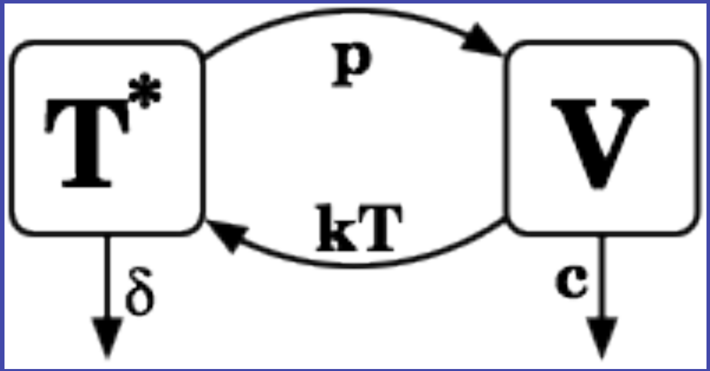
- We fit the mean of the conditioned process to the data:

$$E[\tilde{N}] = \left.\frac{\partial \tilde{G}(N_0, t, z)}{\partial z}\right|_{z=1}$$
$$= N_0 \frac{\left(e^{(b-d)t} - q^{N_0} e^{-(b-d)t}\right)}{1 - q^{N_0}}$$



Naive extrapolation is inaccurate when many trajectories go extinct.

- Back to the T*V model



Generating function:

$$G(N_0, V_0, t, z_1, z_2) = \sum_N \sum_V P(N, V, N_0, V_0, t) z_1^N z_2^V$$

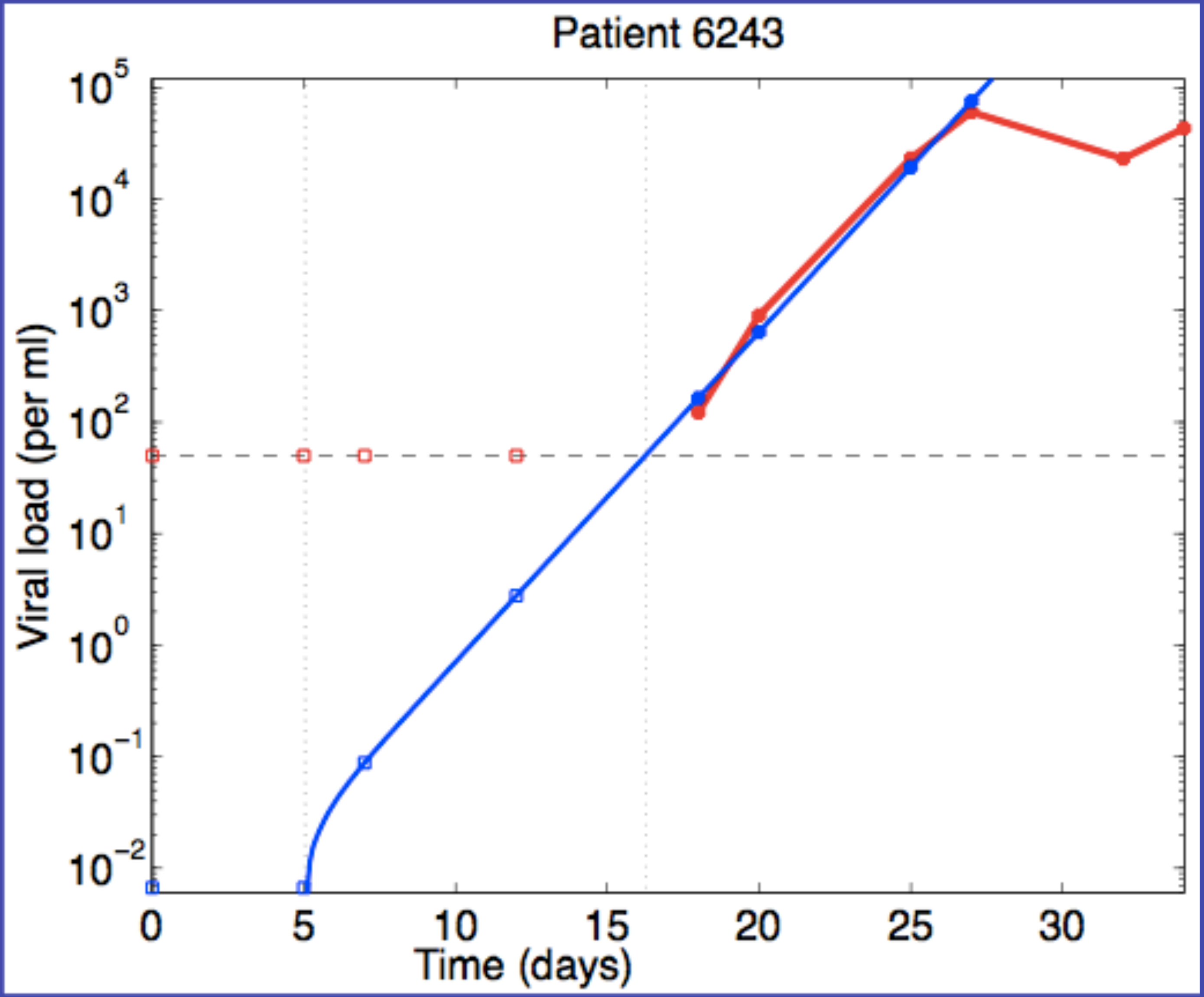
Backwards generating function formulation:

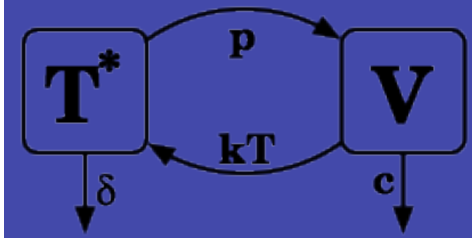
$$\frac{\partial G_{10}}{\partial t} = \delta\left(1 - G_{10}\right) + p\left(G_{10}G_{01} - G_{10}\right)$$

$$\frac{\partial G_{01}}{\partial t} = kT\left(G_{10} - G_{01}\right) + c\left(1 - G_{01}\right)$$

Solve numerically...........

- Results: fitting mean of **conditioned T*V model**

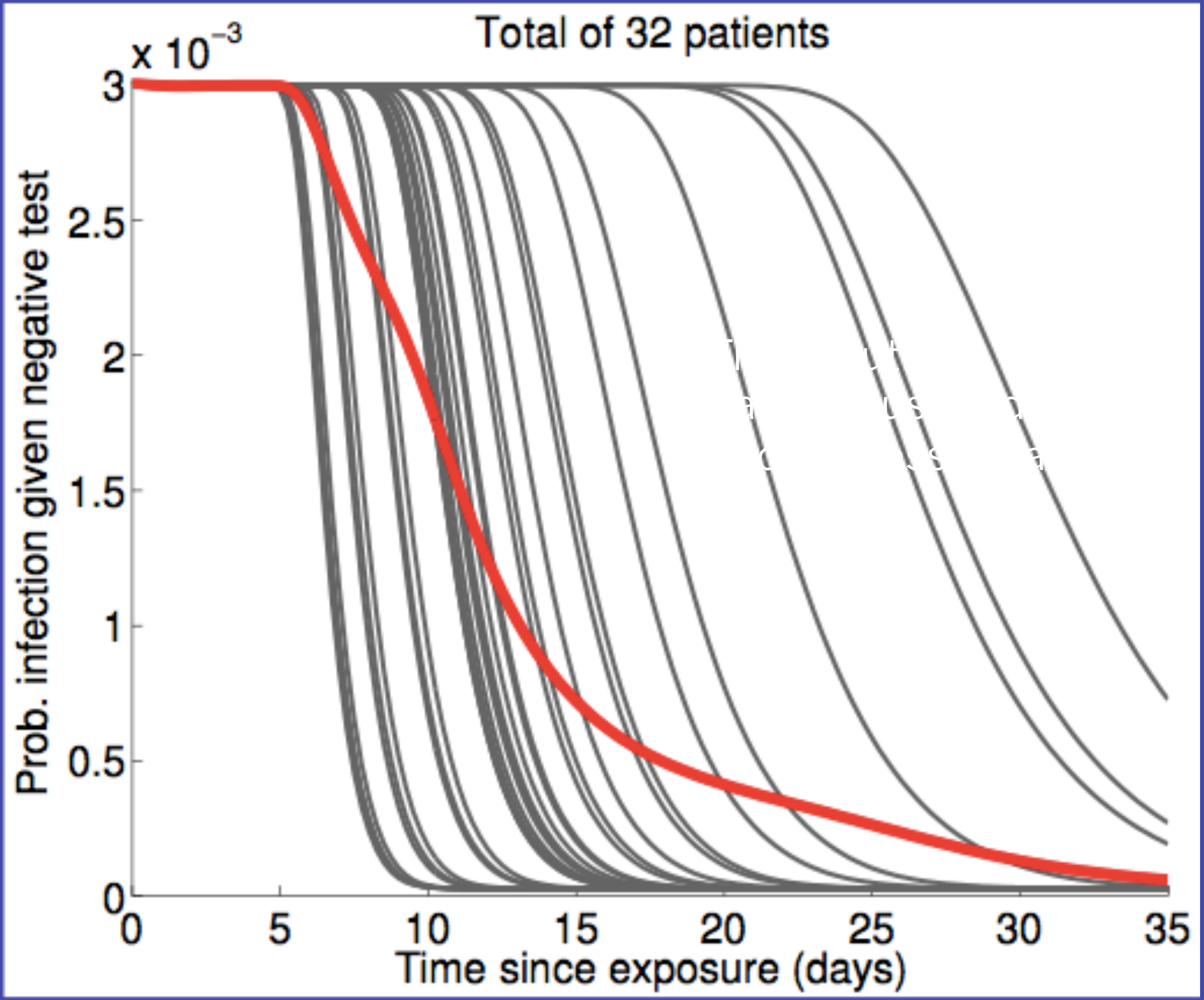




Fixed:
p = 2000/day
δ = 1/day
c = 23/day
V(0) = 50
T(0) = 0

Fit:
t0 = 5.1 days
kT = 0.02 /day

- Probability of infection given a negative test:



Post-exposure prophylaxis (PEP)

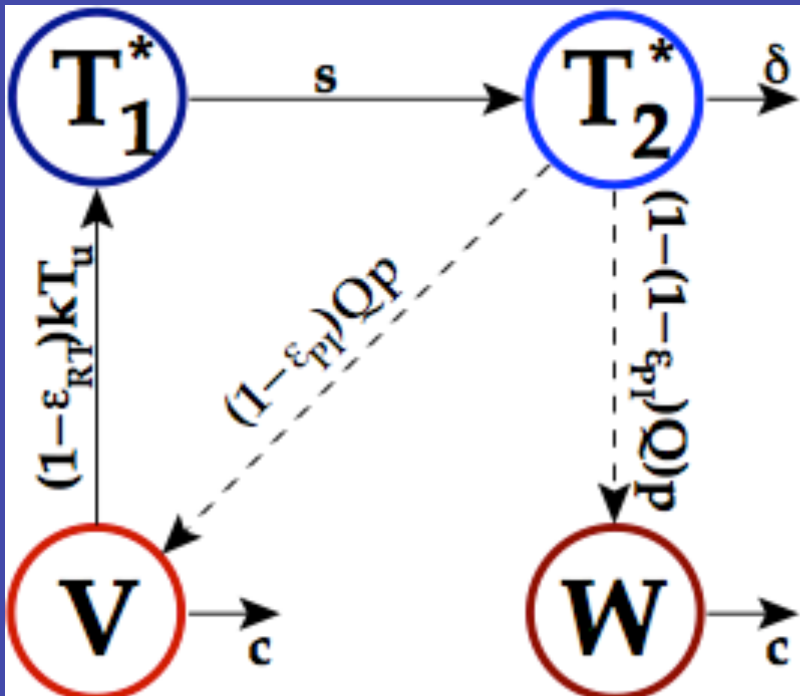
- Success in occupational exposure for 20 years
  - Guidelines: high dose of combination ART within 72 hours of exposure, continuing for 28 days
  - Reduces incidence ~80% after needlestick
  - Guidelines based on 1990s animal studies with AZT
- Non-occupational PEP trials inconclusive
  - Low adherence / 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.
  - no drug resistance noted

Basic model of early infection

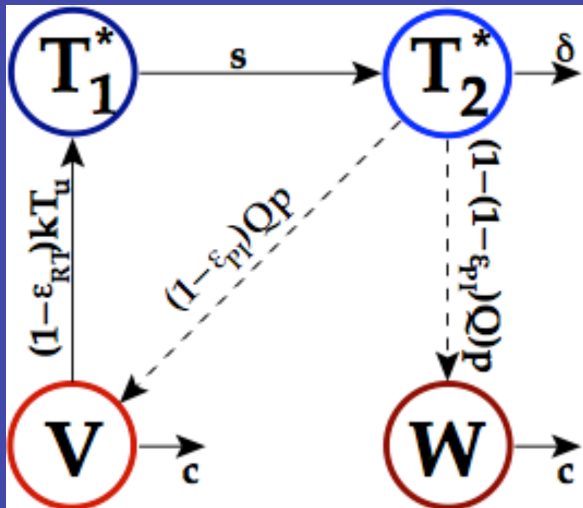


- Target cells in excess.
- include delay between infection and production (eclipse phase)
- uninfectious viruses (W)

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



$$
\begin{array}{ccc}
T_1^* & \xrightarrow{s} & T_2^* \\
T_2^* & \xrightarrow{\delta} & \emptyset \\
T_2^* & \xrightarrow{(1-\epsilon_{\mathrm{RT}})kT_u} & T_1^* \\
 & \cdots &
\end{array}
$$

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

Generating functions, etc

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

+

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

=

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

Extinction probabilities

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

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

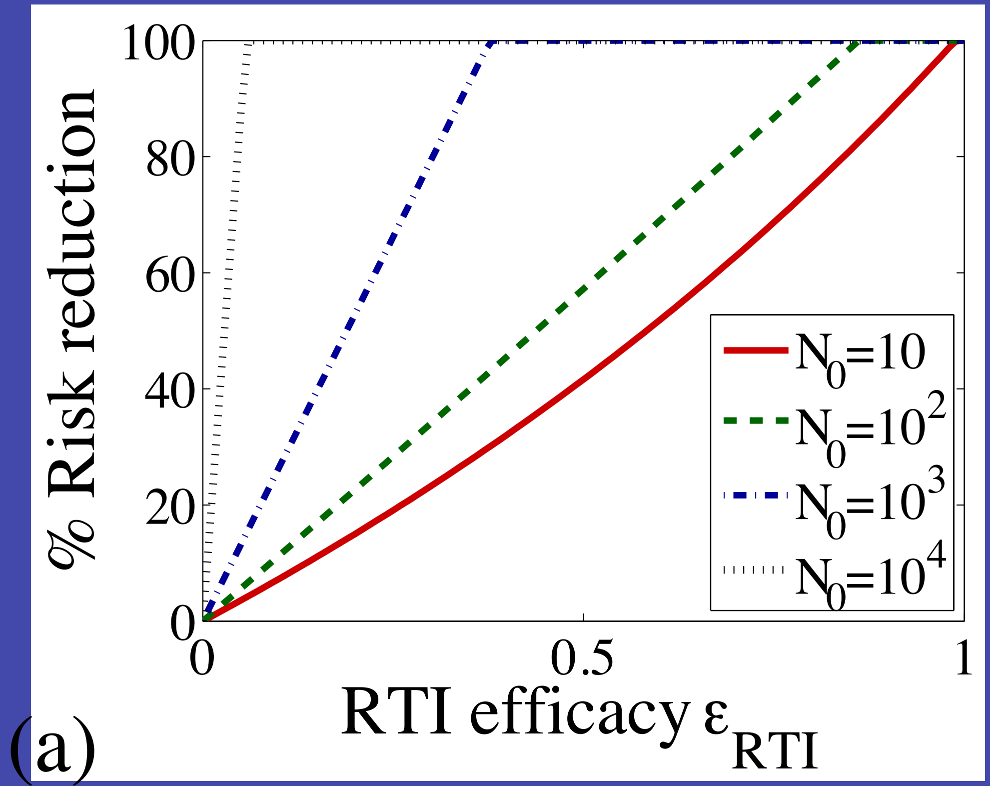
- This limit is a *fixed point* of the ODE system.
  - Can find this using algebra!

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

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

Risk reduction for PrEP

- RTIs only (consistent with clinical trials).

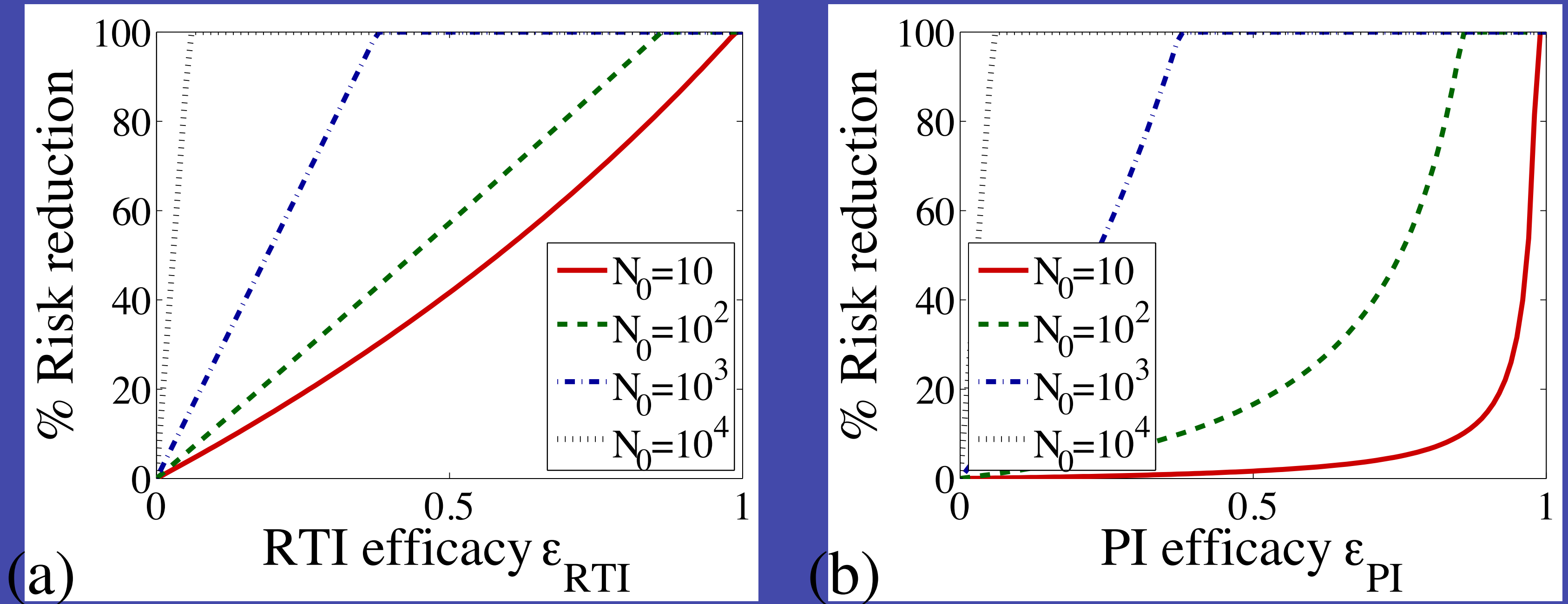


- Higher risk reductions for higher inoculum sizes.
- High inoculum size forces a lower cell infection rate kT in order to get the same 0.3% risk without treatment

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

Risk reduction for PrEP

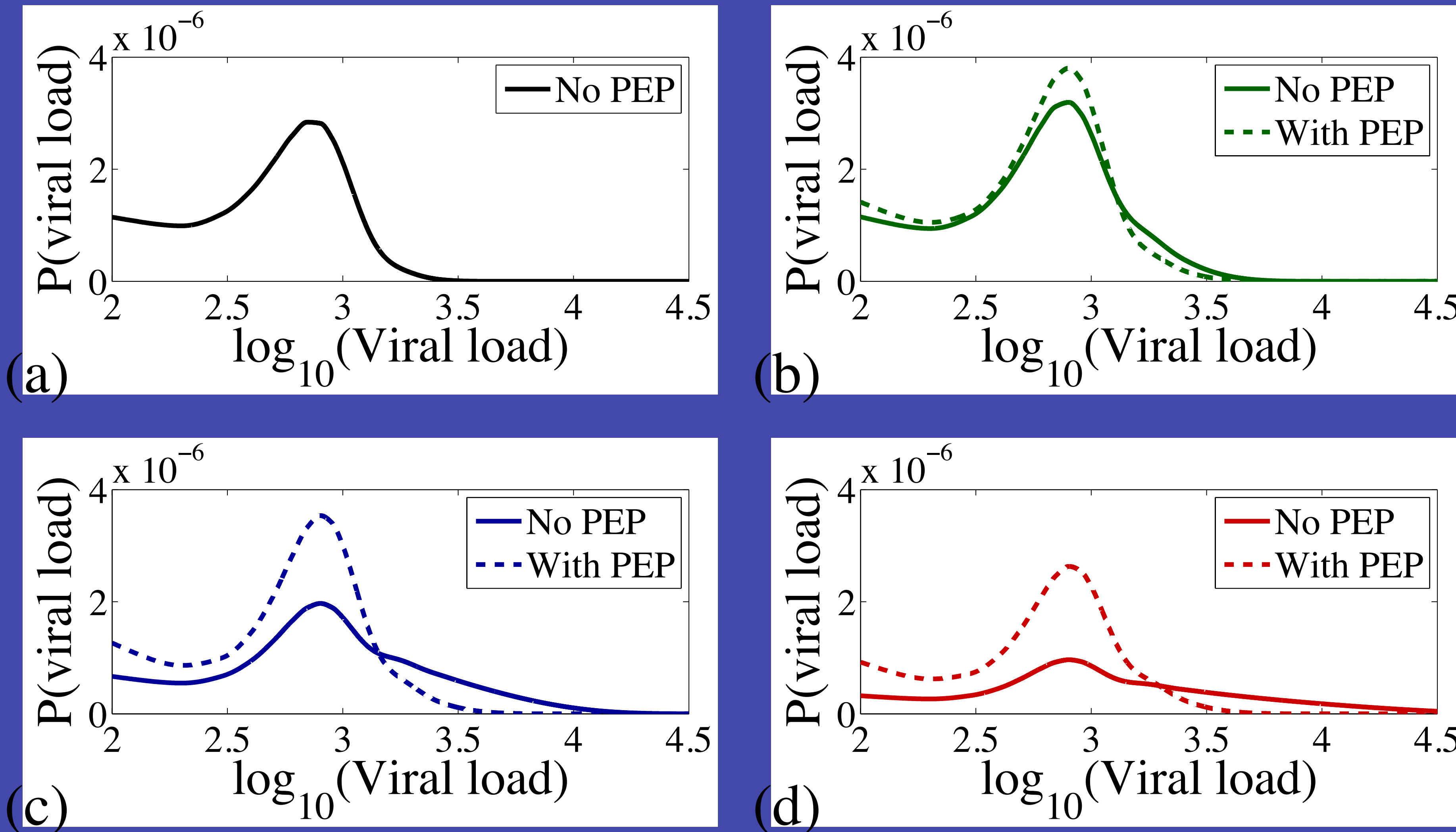
- Comparison of RTI and PI drugs (monotherapy)



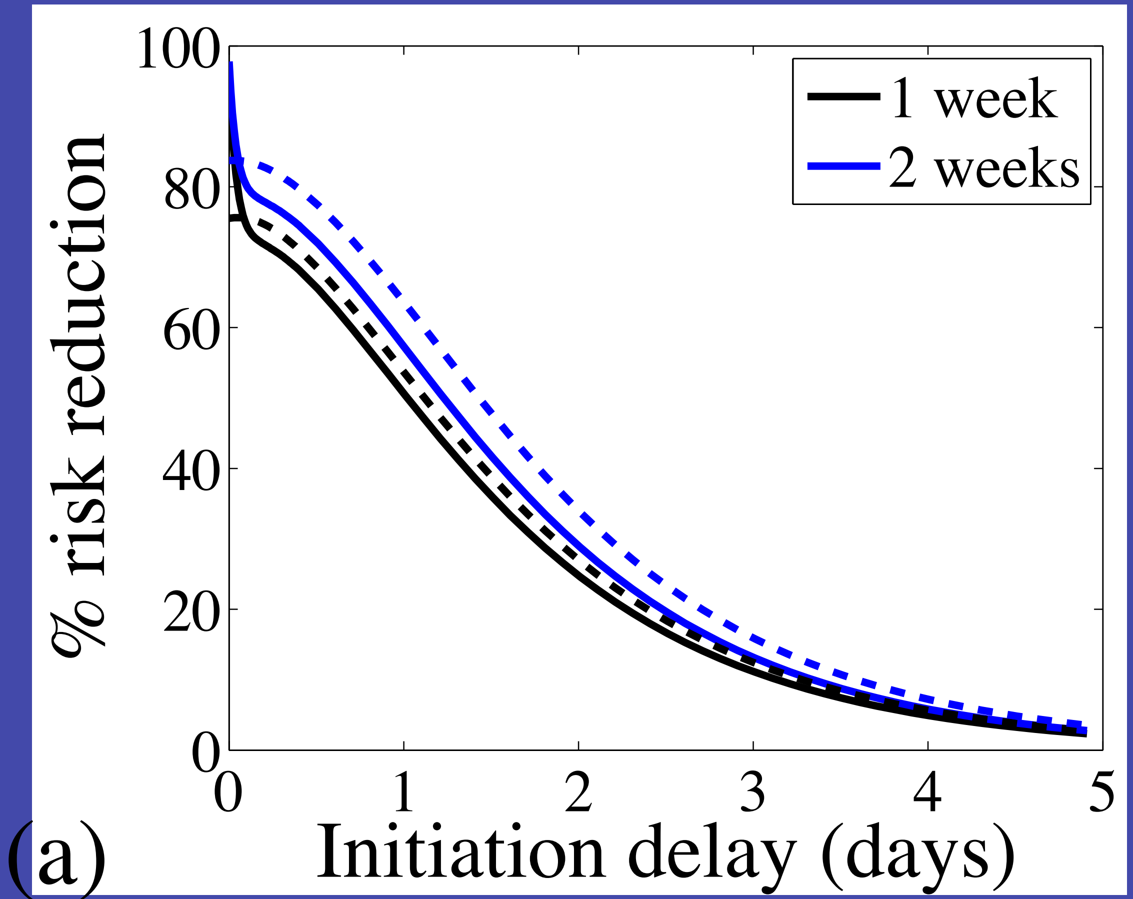
- PIs work only once cells are infected
- Hence, PIs are less effective as PrEP monotherapy
- Combination approach even more effective
    - (needed if drugs are weak at infection site?)

Viral population dynamics with PEP

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

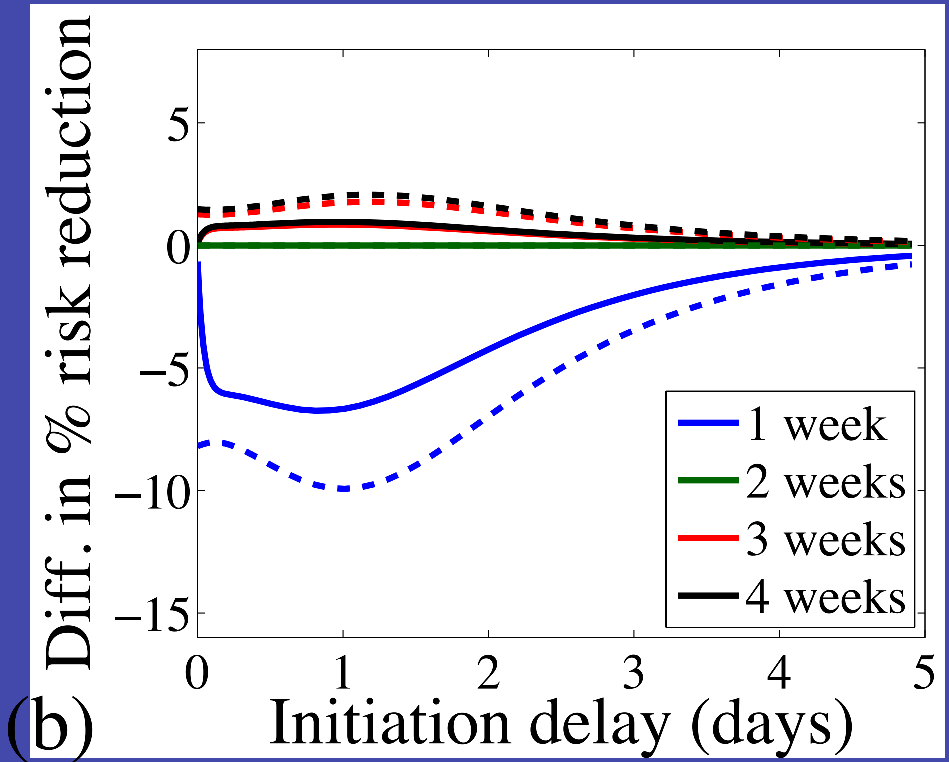


Early initiation of PEP is essential



- 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

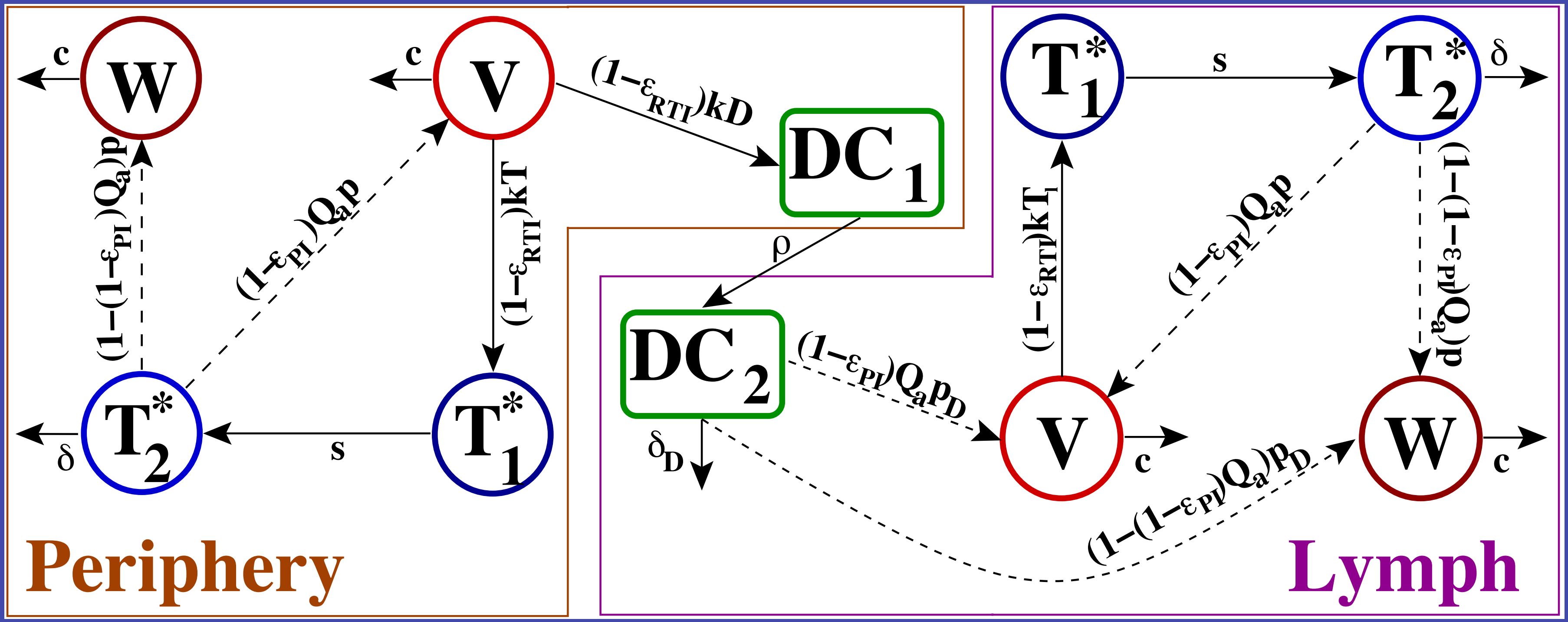
- Clinical guidelines call for multi-drug approach. We agree.

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

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.* Epidemics (2017).