Can the viral reservoir of latently infected $CD4^+$ T cells be eradicated with antiretroviral HIV drugs?

Robert Smith?

Department of Mathematics and Faculty of Medicine
The University of Ottawa

Outline

- Mechanics of latently infected cells
- Mathematical model
- Impulsive differential equations
- Limiting results for infinite amount of drug
- More realistic dosing regimens
- Implications.

Antiretroviral HIV drugs

- If drugs are taken sufficiently often, the virus will be controlled
- However, it is not eradicated from the body
- Viral rebound occurs when drugs are stopped.

Viral reservoirs

This rebound occurs due to reservoirs, eg

- eyes
- brain
- testicles
- follicular dendritic cells
- latently infected cells

Viral reservoirs

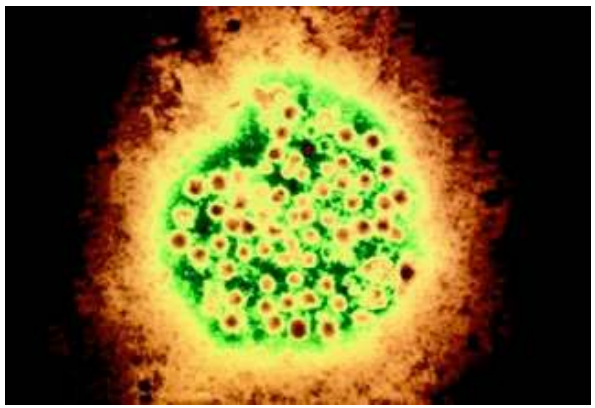
This rebound occurs due to reservoirs, eg

- eyes
- brain
- testicles
- follicular dendritic cells
- latently infected cells

It's been suggested that these are the primary reservoir for viral rebound.

Latently infected cells

- Virologically quiescent (Chun *et al*, J Clin Invest 2005)
- <1 latently infected cell per million resting $CD4^+$ T cells (Chun *et al*, Nature 1997)
- 10^3-10^6 cells per patient (Ramratran *et al*, Nat Med 2000)
- Halflife of 6-44 months (Finzi *et al*, Nat Med 1999)
- Do not produce virus until activated (Blankson *et al*, Annu Rev Med 2002).

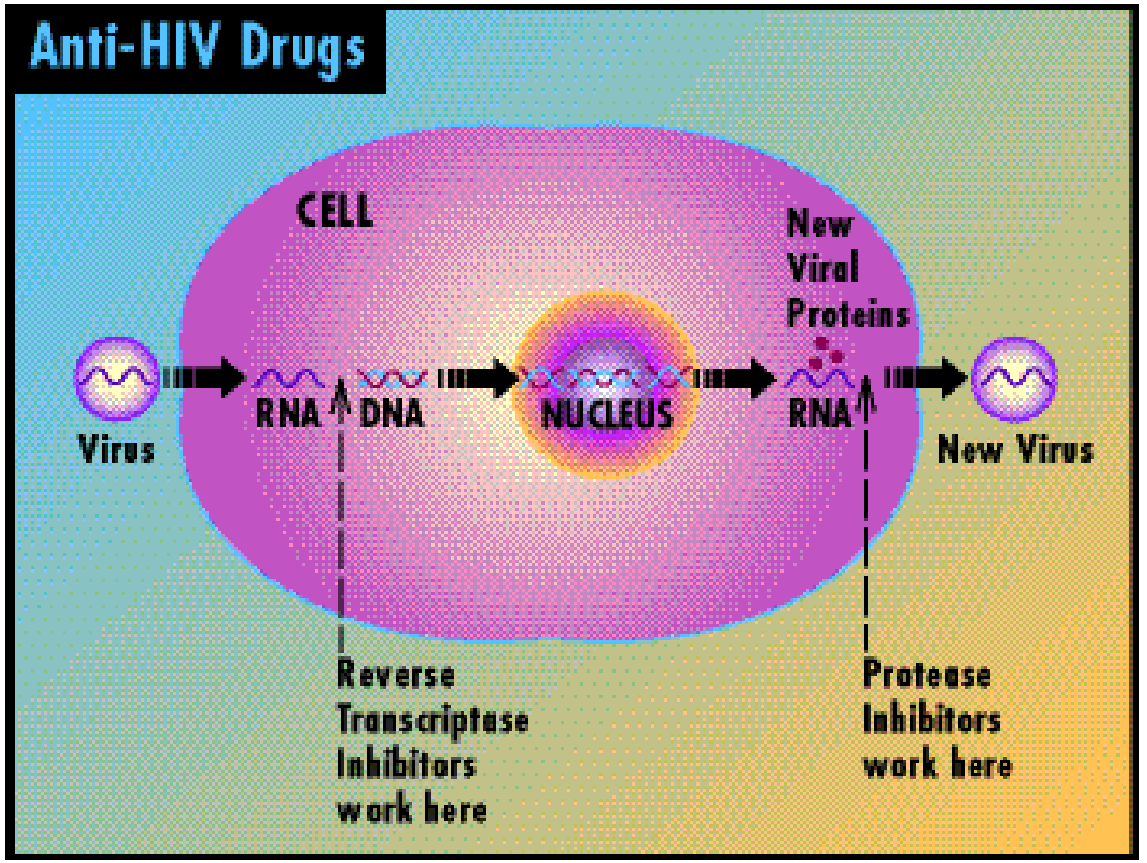


Current therapy

- Current HIV therapy consists of a combination of antiretroviral drugs
- These are primarily drawn from two major classes:
  - Reverse Transcriptase Inhibitors (RTIs)
  - Protease Inhibitors (PIs).

The two drug classes

- Reverse Transcriptase Inhibitors prevent viral infection of a T cell
- Protease Inhibitors result in the creation of noninfectious virus, thus preventing new cells from becoming infected.



Assumptions

We assume that

- drugs have no effect on latently infected cells

  (likely true for RTIs, not for PIs)
- latently infected cells live for maximal time: as long as susceptible cells

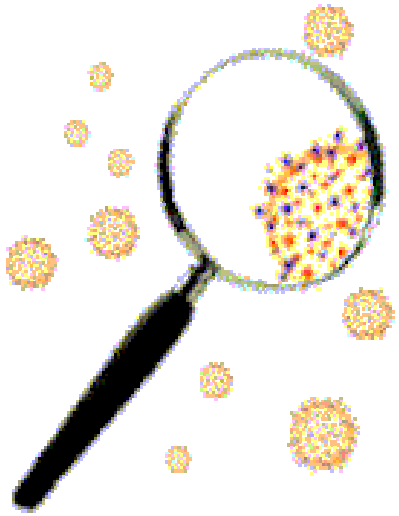
  (and hence much longer than productively infected cells)

This is the most extreme scenario.

RTI=reverse transcriptase inhibitor
PI=protease inhibitor

Modelling latently infected cells

- We model latently infected cells via a separate compartment
- They become infected at rate α_L
- They are not productively infected until leaving the latent state at rate p_L.



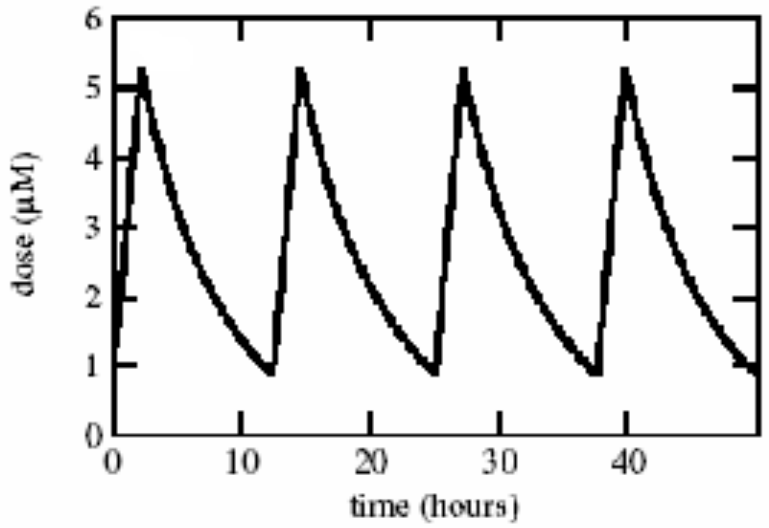
Modelling $CD4^+$ T cells

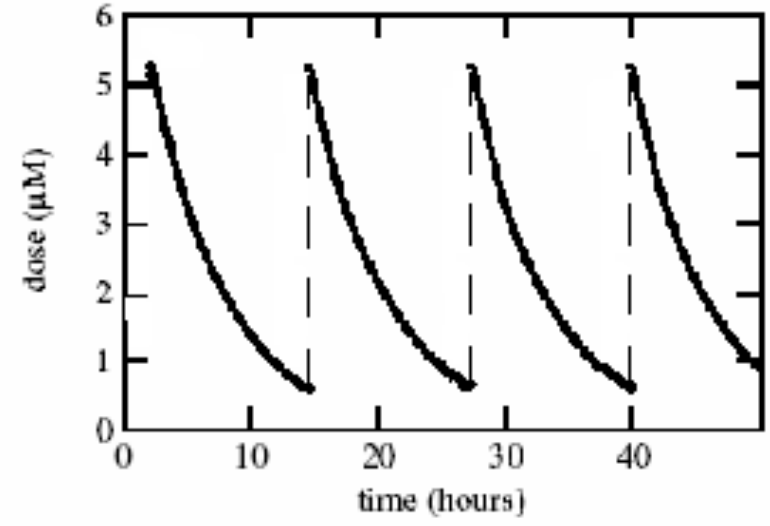
- Susceptible cells may be inhibited with RTIs, PIs or both
- Infected cells may be inhibited by PIs
- Cells inhibited with RTIs cannot be infected while they remain in this state
- Drug effects wear off at different rates for each drug.

RTI=reverse transcriptase inhibitor
PI=protease inhibitor

Impulsive Differential Equations

- Assume drug effects are instantaneous
- That is, the time-to-peak is assumed to be negligible
- This results in a system of *impulsive differential equations*.





Impulsive effect

- According to impulsive theory, we can describe the nature of the impulse at time r_k via the difference equation

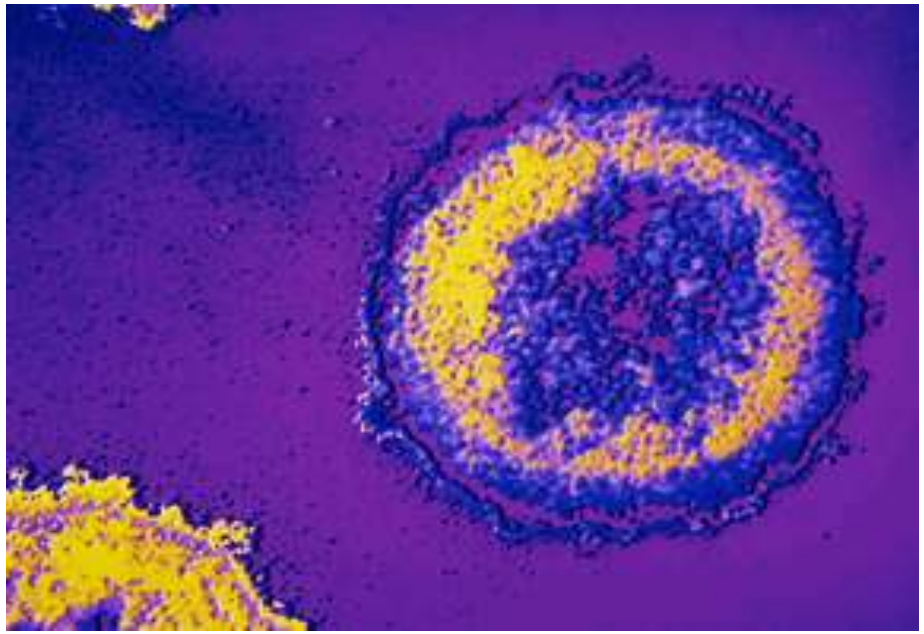
$$\Delta y \equiv y(r_k^+) - y(r_k^-) = f(r_k, y(r_k^-))$$

Difference equation

Depends on the time of impulse and the state immediately beforehand.

Impulsive DEs

- Solutions are continuous for $t \neq r_k$
- Solutions undergo an instantaneous change in state when $t = r_k$
- Such approximations are reasonable when the cycle time is sufficiently large, compared to the time-to-peak.



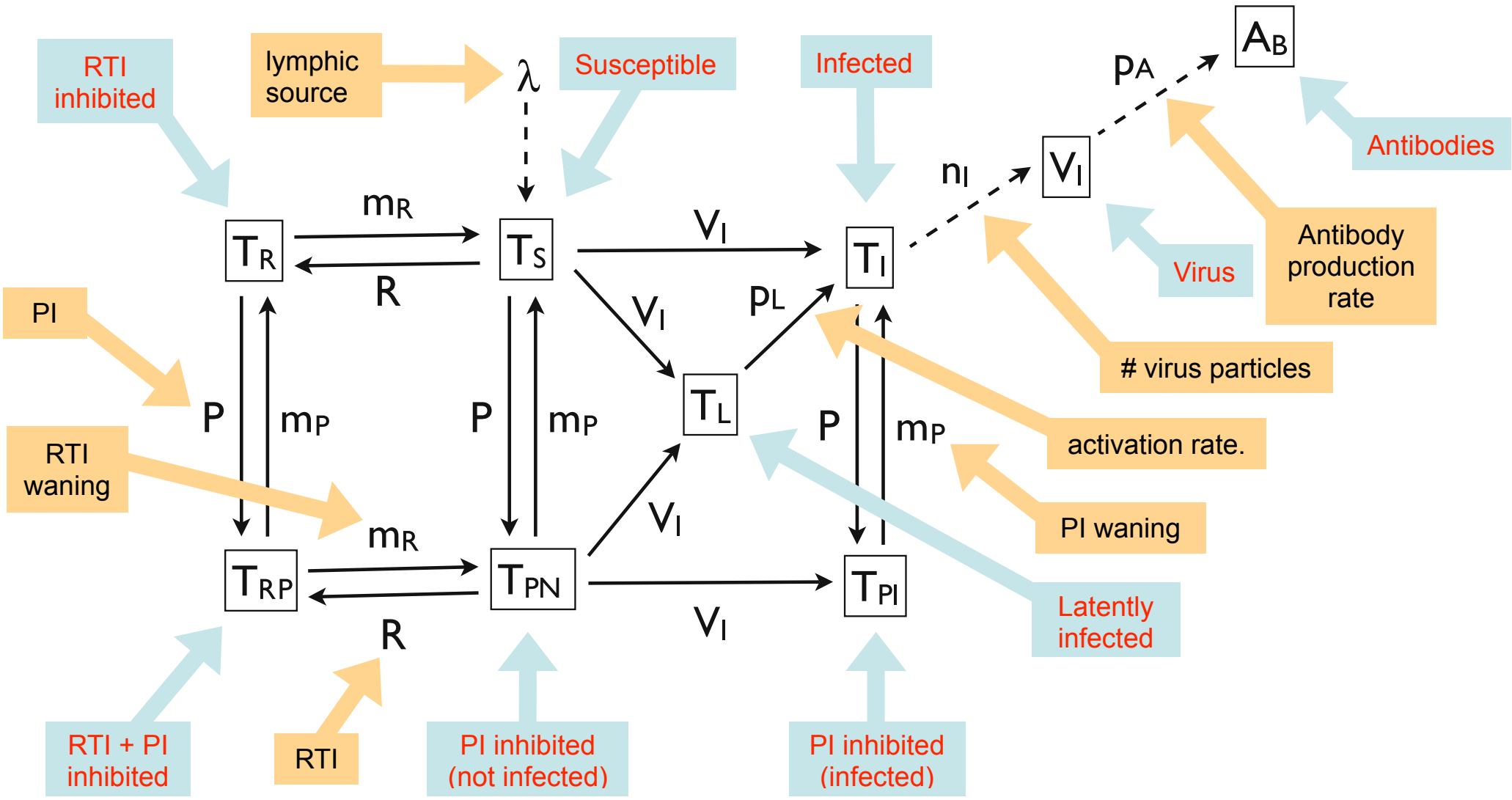
Thousands of HIV particles emerging from an infected T-cell

r_k=impulse time

Putting it together

- The model thus consists of a system of ODEs (virus and T cells) together with an ODE and a difference equation (drugs).

The model (figure)



The model (equations)

$$\frac{dV_I}{dt} = n_I T_I - d_V V_I$$
$$\frac{dA_B}{dt} = p_A V_I - d_A A_B$$
$$\frac{dT_S}{dt} = \lambda - r_I T_S V_I - d_S T_S - r_R T_S R - r_P T_S P + m_R T_R + m_P T_{PN}$$
$$\frac{dT_I}{dt} = q_I T_S V_I - d_I T_I + p_L T_L - \delta_A A_B T_I - r_P T_I P + m_P T_{PI}$$
$$\frac{dT_L}{dt} = \alpha_L T_S V_I + \alpha_L T_{PN} V_I - d_L T_L - p_L T_L$$
$$\frac{dT_R}{dt} = r_R T_S R - d_S T_R + m_P T_{RP} - m_R T_R - r_P T_R P$$
$$\frac{dT_{RP}}{dt} = r_R T_{PN} R - d_S T_{RP} - m_P T_{RP} - m_R T_{RP} + r_P T_R P$$
$$\frac{dT_{PN}}{dt} = r_P T_S P - d_S T_{PN} - r_I T_{PN} V_I - r_R T_{PN} R - m_P T_{PN} + m_R T_{RP}$$
$$\frac{dT_{PI}}{dt} = q_I T_{PN} V_I - d_I T_{PI} - \delta_A A_B T_{PI} + r_P T_I P - m_P T_{PI}$$

T_S=Susceptible T cells T_I=Infected T_R=RTI inhibited T_{RP}=RTI + PI inhibited λ=lymphic source T_{PN}=PI inhibited (not infected) T_{PI}=PI inhibited (infected) T_L=Latently infected A_B=antibodies R=Reverse Transcriptase Inhibitor P=Protease Inhibitor n_I=# particles m_R,m_P=RTI, PI waning rates p_L= activation rate p_A=antibody production rate d_S,d_I,d_L,d_V,d_A=death rates r_I,α_V,q_I=infection rates r_R,r_P=drug inhibition rates δ_A=antibody clearance rate

…with the (impulsive) dynamics of the drugs:

$$
\begin{aligned}
\frac{dR}{dt} &= -d_R R & t &\neq t_k \\
\frac{dP}{dt} &= -d_P P & t &\neq s_k \\
\Delta R &= R^i & t &= t_k \\
\Delta P &= P^i & t &= s_k \,.
\end{aligned}
$$

R=Reverse Transcriptase Inhibitor P=Protease Inhibitor
d_R,d_P=drug clearance rates R^i=RTI dosage P^i=PI dosage
t_k=RTI dosage times s_k=PI dosage times

Absence of drugs

- There's a disease-free equilibrium

$$(V_I, A_B, T_S, T_I, T_L, T_R, T_{RP}, T_{PN}, T_{PI}) = \left(0, 0, \frac{\lambda}{d_S}, 0, 0, 0, 0, 0, 0\right)$$

and an endemic equilibrium of the form

$$(V_I, A_B, T_S, T_I, T_L, T_R, T_{RP}, T_{PN}, T_{PI}) = (\bar{V}_I, \bar{A}_B, \bar{T}_S, \bar{T}_I, \bar{T}_L, 0, 0, 0, 0)$$

- We can prove: the disease-free equilibrium is unstable in the absence of drugs

Proof: Smith? & Aggarwala, 2009.

T_S=Susceptible T cells T_I=Infected (wild type) λ=lymphic source T_R=RTI inhibited
T_{RP}=RTI + PI inhibited T_{PNI}=PI inhibited (not infected) T_{PI}=PI inhibited (infected)
T_L=Latently infected A_B=antibodies d_S=susceptible cell death rate

The presence of drugs

- There are no equilibria, due to impulses
- Instead, there are impulsive orbits with variation in the state variables, due to the drug dynamics
- The disease-free impulsive orbit is in the form

$$(V_I, A_B, T_S, T_I, T_L, T_R, T_{RP}, T_{PN}, T_{PI}) = \left(0, 0, \hat{T}_S, 0, 0, \hat{T}_R, \hat{T}_{RP}, \hat{T}_{PN}, 0\right).$$

T_S=Susceptible T cells T_I=Infected (wild type) T_R=RTI inhibited
T_{RP}=RTI + PI inhibited T_{PN}=PI inhibited (not infected)
T_{PI}=PI inhibited (infected) T_L=Latently infected A_B=antibodies

The drugs satisfy a recursion relation

$$R(t) = R(t_k^+)e^{-d_R(t-t_k)} \qquad t_k < t \leq t_{k+1}$$
$$R(t_k^+) = R(t_k^-) + R^i$$

R=drug
d_R=decay rate
R^i=dosage
t_k=impulse time

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Hence

$$R(t_k^+) \rightarrow \frac{R^i}{1 - \mathrm{e}^{-d_\mathrm{R}\tau}}.$$

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Hence

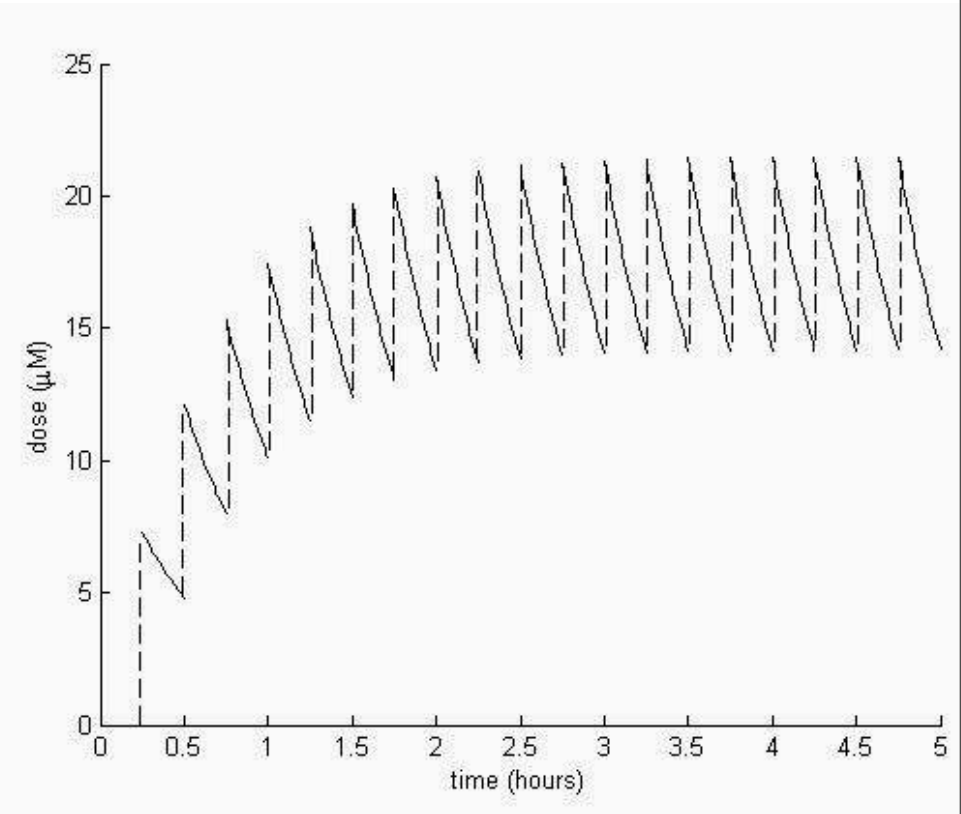
$$R(t_k^+) \to \frac{R^i}{1 - \mathrm{e}^{-d_\mathrm{R}\tau}}.$$

as $k \to \infty$, where $\tau = t_{k+1} - t_k$ is the dosing interval.

R=drug
d_R=decay rate
R^i=dosage
t_k=impulse time

Impulsive periodic orbit

- Thus, for the drugs, there is a unique, positive impulsive periodic orbit with one impulse per cycle
- It can also be shown that the endpoints of each cycle monotonically approach the endpoints of this periodic orbit.



Disease-free orbit

- The disease-free orbit satisfies

$$\hat{T}_{PN} = \frac{r_P P \hat{T}_S + m_R \hat{T}_{RP}}{d_S + r_R R + m_P} \qquad \hat{T}_S = \frac{f_1}{f_2} T_{RP}$$

$$\hat{T}_R = \frac{r_R R \hat{T}_S + m_P \hat{T}_{RP}}{d_S + m_R + r_P P} \qquad \hat{T}_{RP} = \frac{\lambda}{f_3}$$

where

$$f_1 = d_S(d_S + r_P P + m_R)(d_S + r_R R + m_P) + m_P(d_S + m_R)(d_S + r_R R + m_P) + m_R(d_S + m_P)(d_S + r_P P + m_R)$$

$$f_2 = r_R R r_P P(2d_S + m_R + m_P + r_R R + r_P P)$$

$$f_3 = \left[d_S + r_R R + r_P P - \frac{m_R r_R R}{d_S + r_P P + m_R} - \frac{m_P r_P P}{d_S + r_R R + m_P} \right] \frac{f_1}{f_2} - \frac{m_R m_P}{d_S + r_P P + m_R} - \frac{m_R m_P}{d_S + r_R R + m_P}$$

Intermediate calculations

- We have

$$\lim_{r_P P \to \infty} f_1 = \infty$$

$$\lim_{r_P P \to \infty} f_2 = \infty$$

$$\lim_{r_P P \to \infty} \frac{f_1}{f_2} = 0.$$

$$\begin{aligned} f_1 &= d_S(d_S + r_P P + m_R)(d_S + r_R R + m_P) \\ &\quad + m_P(d_S + m_R)(d_S + r_R R + m_P) \\ &\quad + m_R(d_S + m_P)(d_S + r_P P + m_R) \\ f_2 &= r_R R r_P P(2d_S + m_R + m_P + r_R R + r_P P) \end{aligned}$$

R=reverse transcriptase inhibitor
P=protease inhibitor
d_S=susceptible cell death rates
m_R,m_P=RTI, PI waning rates
r_R,r_P=drug inhibition rates

Further calculations

$$r_P P \frac{f_1}{f_2} = \frac{d_S(d_S + r_R R + m_P)(d_S + r_P P + m_R)}{r_R R(2d_S + m_P + m_R + r_P P + r_R R)} + \frac{m_R(d_S + m_P)(d_S + r_P P + m_R) + m_P(d_S + m_R)(d_S + r_R R + m_P)}{r_R R(2d_S + m_P + m_R + r_P P + r_R R)}$$

Limiting values

$$\begin{aligned}\lim_{r_P P\to\infty} T_S &= \lim_{r_P P\to\infty} \frac{f_1}{f_2} \lim_{r_P P\to\infty} T_{RP} \\ &= 0\end{aligned}$$

$$\begin{aligned}\hat{T}_S &= \frac{f_1}{f_2} T_{RP} \\ \hat{T}_{RP} &= \frac{\lambda}{f_3} \\ \hat{T}_{PN} &= \frac{r_P P \hat{T}_S + m_R \hat{T}_{RP}}{d_S + r_R R + m_P} \\ \hat{T}_R &= \frac{r_R R \hat{T}_S + m_P \hat{T}_{RP}}{d_S + m_R + r_P P}\end{aligned}$$

PIs can also control virus

- We have thus proved the following:
- If PIs are taken with sufficient frequency, then

$$T_{RP} + T_{PN} \rightarrow \frac{\lambda}{d_S}$$

λ/d_S = *the level of CD4⁺ T cells in the uninfected body*

as the dosing interval shrinks to zero

- It follows that, with sufficient application, PIs can theoretically control the virus.

PI=protease inhibitor T_{PN}=PI inhibited (not infected) λ=lymphic source T_{RP}=RTI+PI inhibited d_S=susceptible cell death rate

RTIs theoretically control virus

- Similarly:
- If RTIs are taken with sufficient frequency, then

$$T_R + T_{RP} \rightarrow \frac{\lambda}{d_S}$$

λ/d_S = *the level of CD4⁺ T cells in the uninfected body*

as the dosing interval shrinks to zero

- It follows that, with sufficient application, RTIs can theoretically control the virus.

RTI=reverse transcriptase inhibitor d_S=susceptible cell death rate
T_R=RTI inhibited T_{RP}=RTI+PI inhibited λ=lymphic source

Both drugs together

- If RTIs and PIs are taken with sufficient frequency, then

$$T_{RP} \rightarrow \frac{\lambda}{d_S}$$

λ/d_S = *the level of CD4⁺ T cells in the uninfected body*

as the dosing interval shrinks to zero

- Thus, with sufficient application, combination therapy can theoretically control the virus
- In particular, the latently infected cells are driven to extinction.

RTI=reverse transcriptase inhibitor PI=protease inhibitor λ=lymphic source T_{RP}=RTI+PI inhibited d_S=susceptible cell death rate

Why is this? (Mathematically)

- As $P \to \infty$, $T_I' \to -\infty$ unless $T_I \to 0$

$$
\begin{aligned}
\frac{dV_I}{dt} &= n_I T_I - d_V V_I \\
\frac{dA_B}{dt} &= p_A V_I - d_A A_B \\
\frac{dT_S}{dt} &= \lambda - r_I T_S V_I - d_S T_S - r_R T_S R - r_P T_S P + m_R T_R + m_P T_{PN} \\
\frac{dT_I}{dt} &= q_I T_S V_I - d_I T_I + p_L T_L - \delta_A A_B T_I - r_P T_I P + m_P T_{PI} \\
\frac{dT_L}{dt} &= \alpha_L T_S V_I + \alpha_L T_{PN} V_I - d_L T_L - p_L T_L \\
\frac{dT_R}{dt} &= r_R T_S R - d_S T_R + m_P T_{RP} - m_R T_R - r_P T_R P \\
\frac{dT_{RP}}{dt} &= r_R T_{PN} R - d_S T_{RP} - m_P T_{RP} - m_R T_{RP} + r_P T_R P \\
\frac{dT_{PN}}{dt} &= r_P T_S P - d_S T_{PN} - r_I T_{PN} V_I - r_R T_{PN} R - m_P T_{PN} + m_R T_{RP} \\
\frac{dT_{PI}}{dt} &= q_I T_{PN} V_I - d_I T_{PI} - \delta_A A_B T_{PI} + r_P T_I P - m_P T_{PI}
\end{aligned}
$$

P=protease inhibitor T_S=Susceptible T cells T_I=Infected T_R=RTI inhibited T_{PI}=PI inhibited (infected) T_L=Latently infected A_B=antibodies

Why is this? (Biologically)

- As RTIs$\rightarrow\infty$,T_S cells instantly become T_R cells and cannot be infected
- As PIs$\rightarrow\infty$, cells instantly become T_{PN} or T_{PI} cells and don't produce infectious virus
- Essentially, the drugs "overwhelm" the virus.

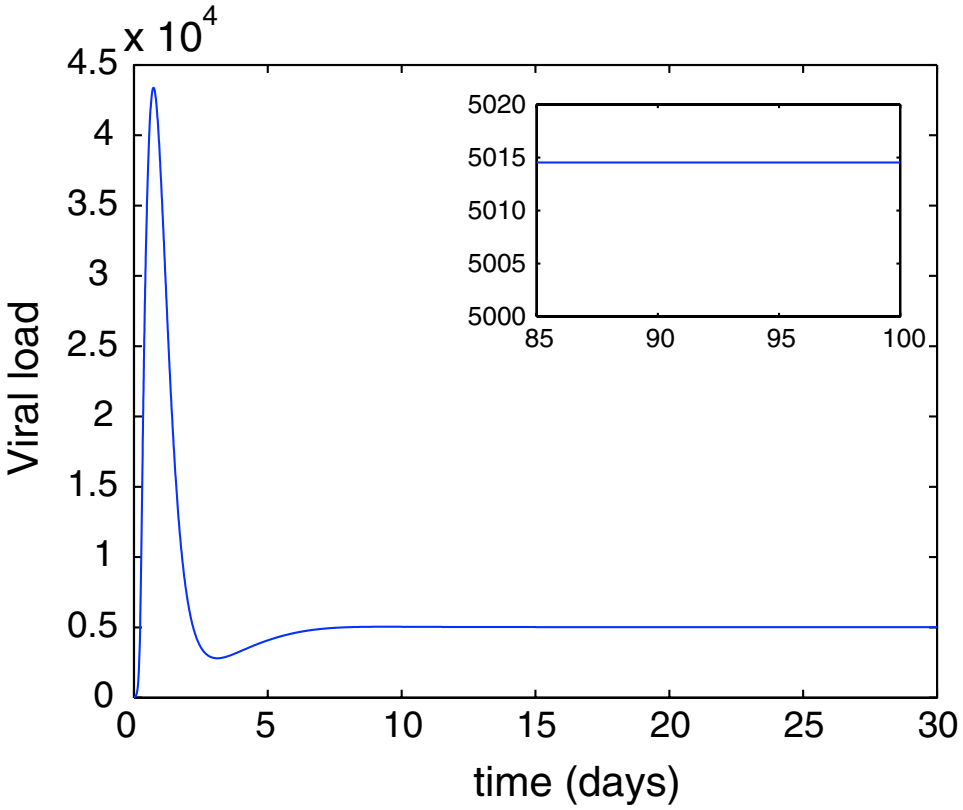
RTI=reverse transcriptase inhibitor PI=protease inhibitor T_S=Susceptible cells T_{PNI}=Protease inhibited (not infected) T_{PN}=protease inhibited (not infected) T_{PI}=protease inhibited (infected) T_R=RTI inhibited

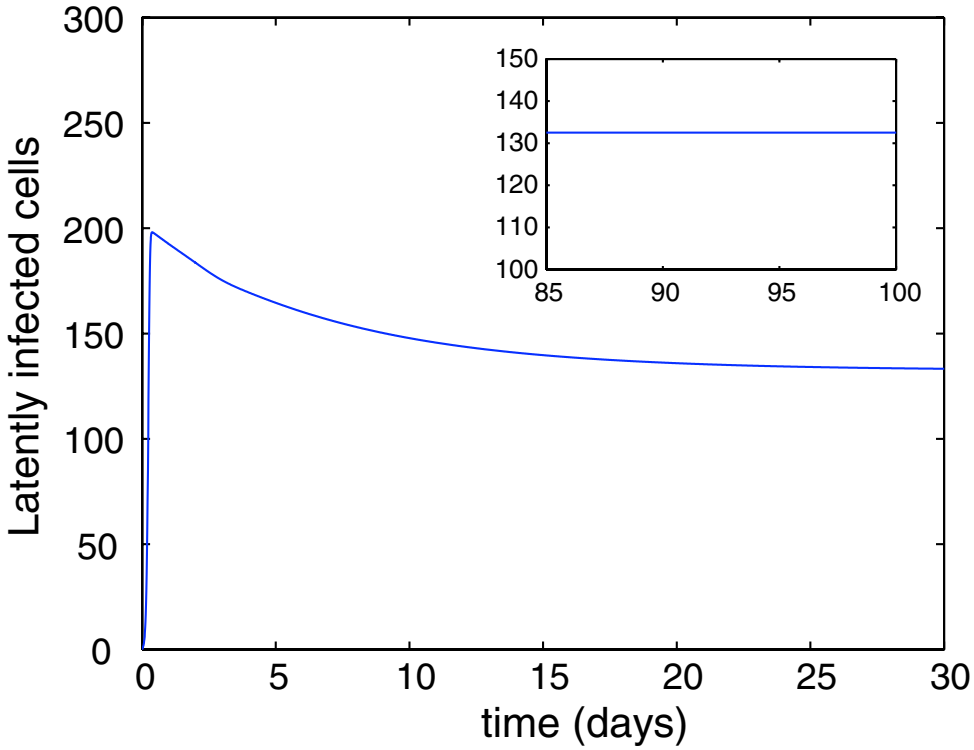
Realistic regimens

- Of course, we can't take drugs infinitely often
- Too much drug is toxic for the patient
- But these theoretical results match more realistic dosing regimens
- We simulated Didanosine, supplemented by a low-level PI.

RTI=reverse transcriptase inhibitor
PI=protease inhibitor

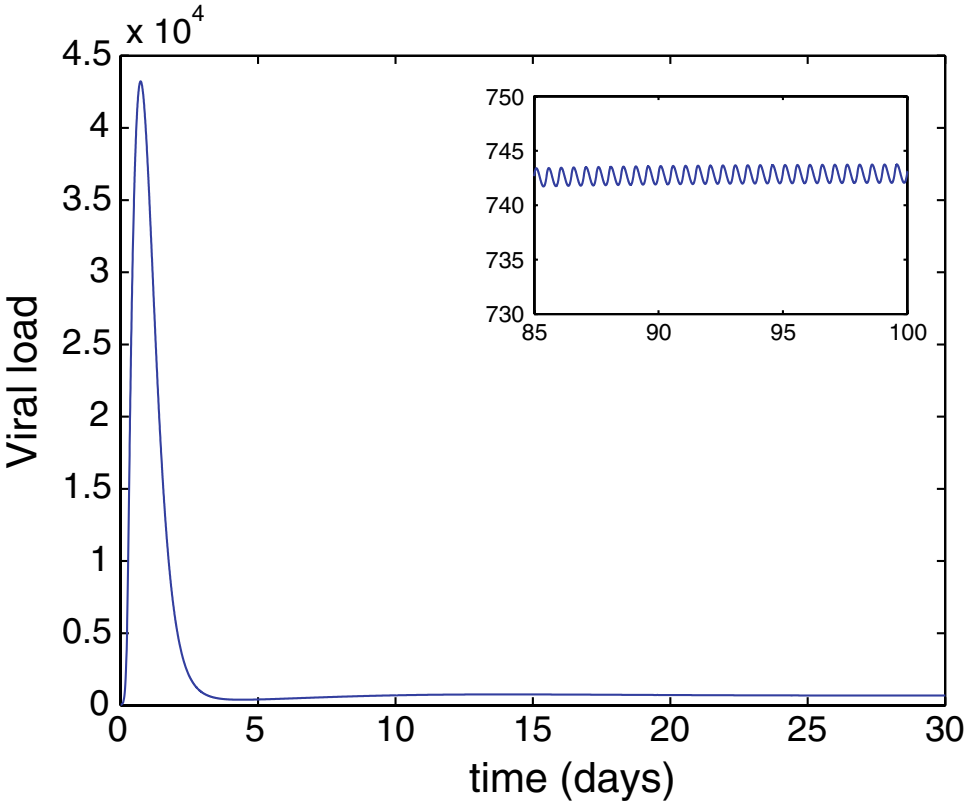
The case of no drugs

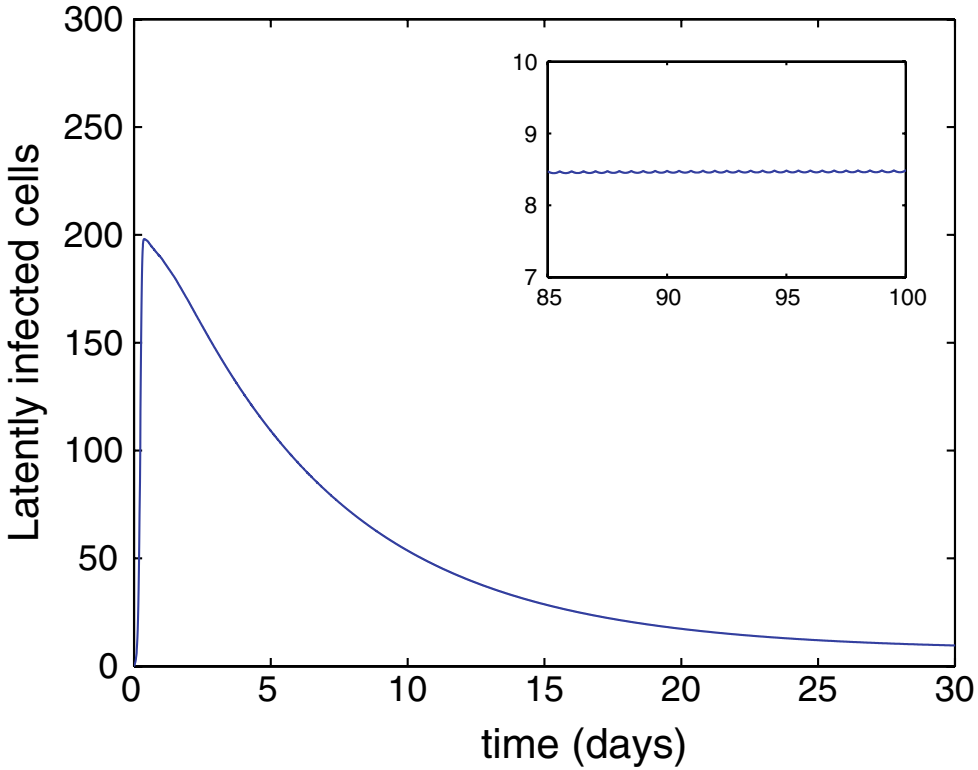




- High viral load, high reservoir of latently infected cells.

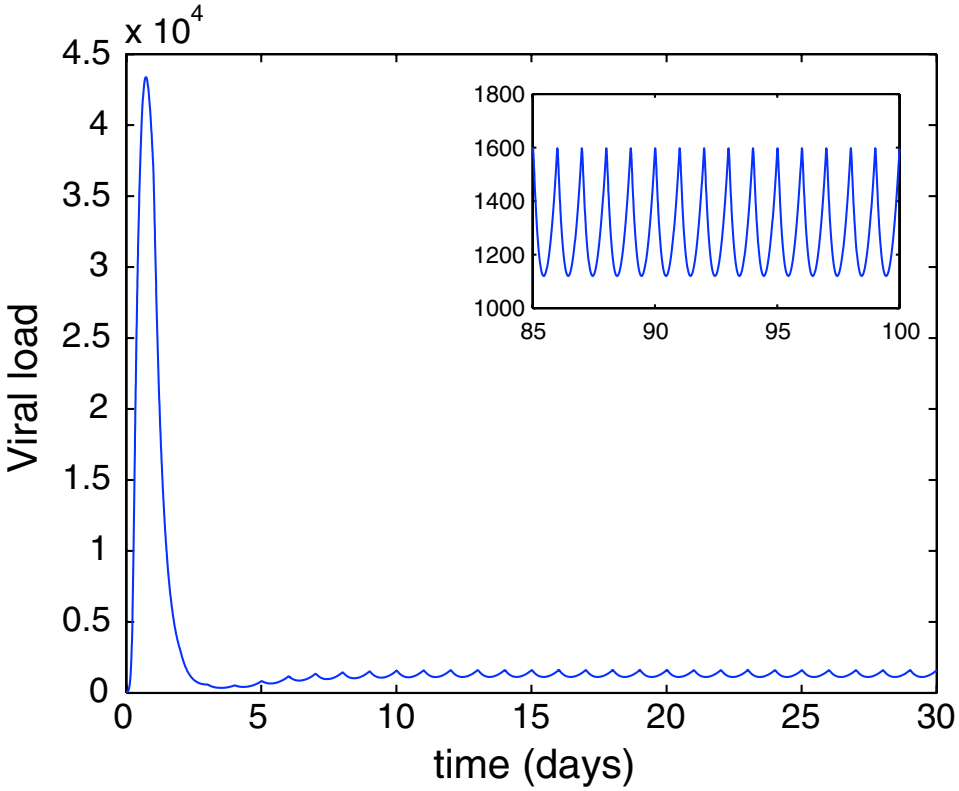
RTIs taken twice daily, no PIs

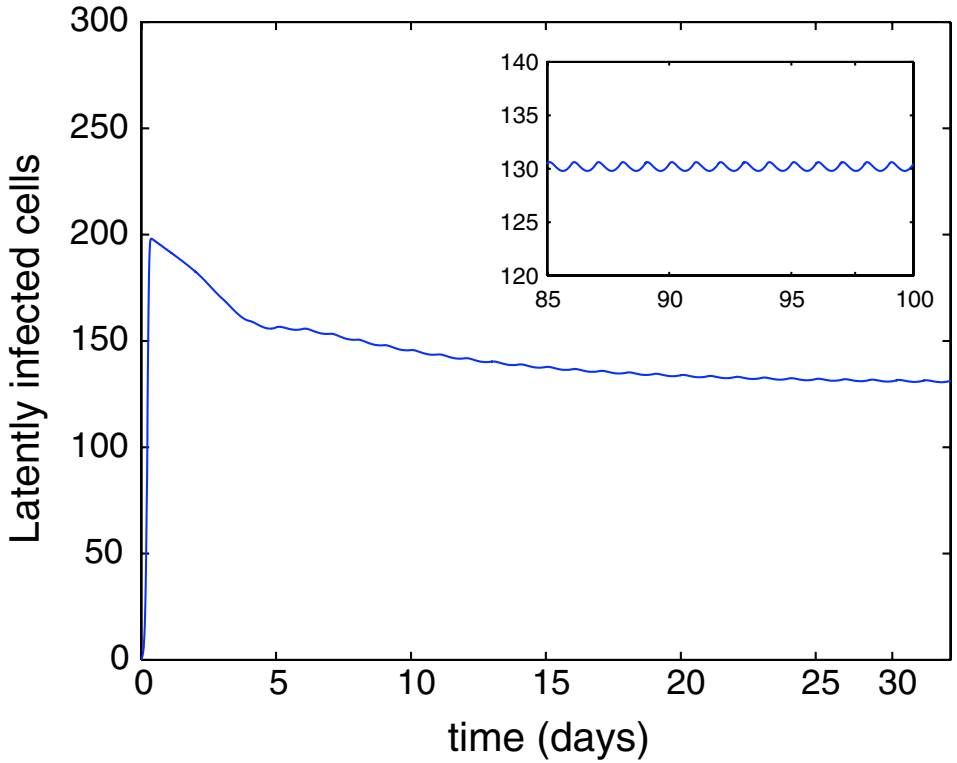




- Moderate viral load, low reservoir of latently infected cells.

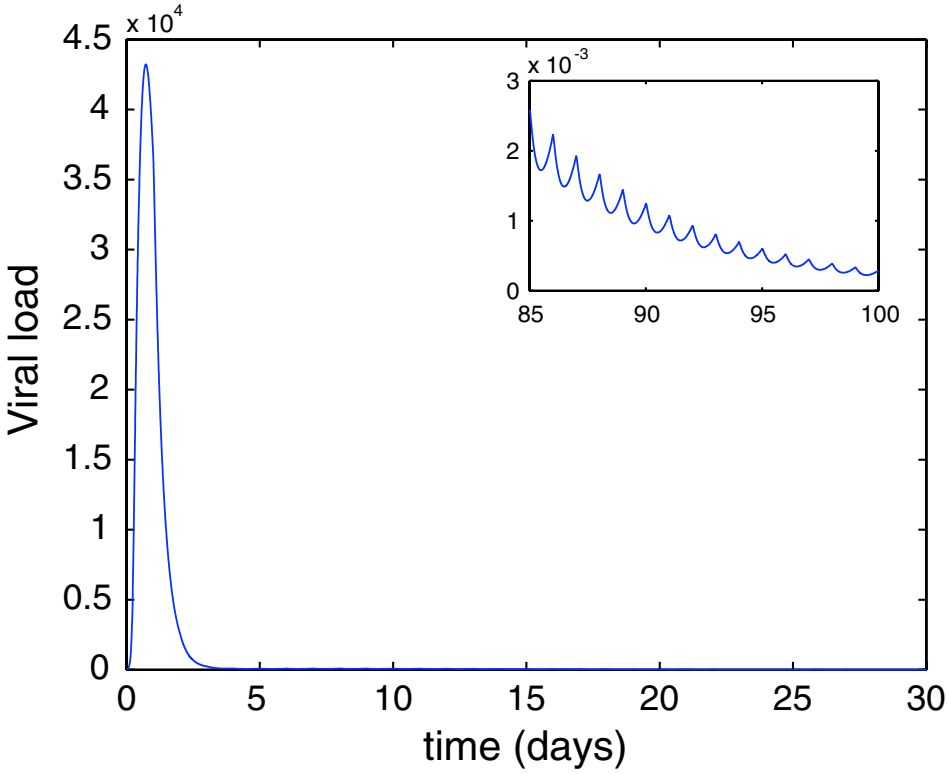
Low-level PI, no RTIs

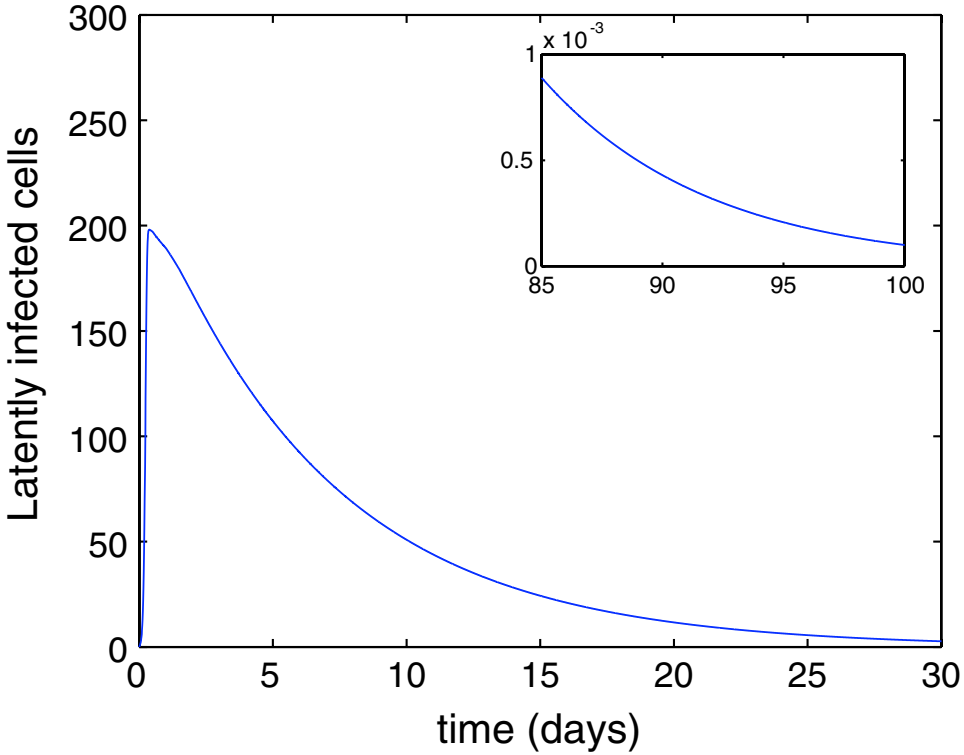




- High viral load, high reservoir of latently infected cells.

Both drugs





- Both viral load and reservoir of latently infected cells are eradicated.

Summary

- The model predicts that latently infected cells can be eradicated by sufficient drugs
- This happens even if they live for maximal time and are wholly unaffected by the drugs
- Except...
- ...we know this doesn’t happen.

The problem with viral elimination

- Viral elimination doesn't occur
- If you stop taking drugs, the virus rebounds
- So what does this mean?

Implications

- We ignored other viral reservoirs
- eg eyes, brain, testicles, follicular dendritic cells, CTLs, etc
- These reservoirs must contribute to sustaining the low-level viral load
- Thus, latently infected cells cannot sustain a viral reservoir on their own.

Conclusion

- Mathematical models are useful for exploring hypothetical questions
- In this case, the hypothesis that latently infected cells are the sole viral reservoir
- If it were, the model predicts complete eradication, which we know doesn't happen
- This occurs even under the most extreme assumptions: that latently infected cells are immune to drugs and live for maximal time
- Thus, other viral reservoirs are critical.

Key reference

- R.J. Smith? and B.D. Aggarwala. Can the viral reservoir of latently infected CD4+ T cells be eradicated with antiretroviral HIV drugs?
  (Journal of Mathematical Biology 2009, 59: 697-715)