Estimation of parameters in viral dynamics models

Viral decay after treatment and infected cell turnover rates

Perelson et.al. Science 1996

Model equations for Pre-treatment viral dynamics

$$\begin{aligned} \frac{dT^*}{dt} &= kTV - \delta T^* \\ \frac{dV}{dt} &= N\delta T^* - cV \end{aligned}$$

- T^* is the population of infected cells
- V is the population of (infectious) viral RNA
- T is the population of uninfected cells - remains constant

Prior to treatment - assume system is in steady state

Analysis can be conducted in some cases without this assumption

Treatment perturbs this steady state allowing decay rates to be estimated

- Treatment with protease inhibitors does not halt the production of viral RNA, but stops virion formation so that viral RNA produced after treatment is non-infectious.
- Treatment "perturbs" viral steady state by halting production of infectious virus.
- Using measurements of **viral loads** after treatment, viral clearance and **infected cell** turnover rates are estimated using a model.
- The model provides the relationship between viral loads and infected cell turnover rate.

Model equations for Pre-treatment viral dynamics

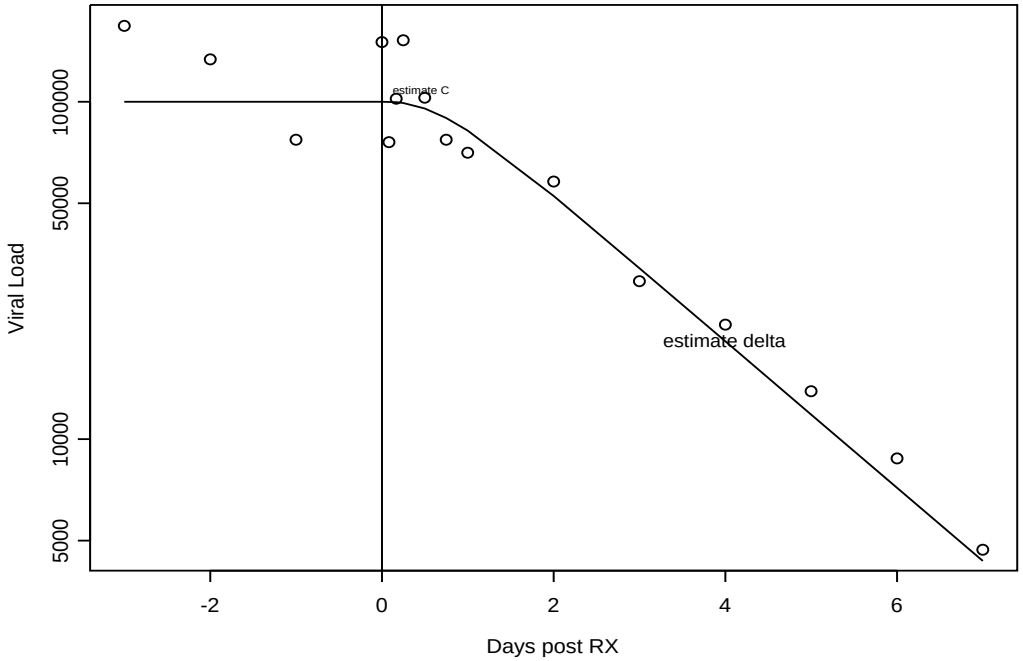
$$\begin{aligned} \frac{dT^*}{dt} &= kTV_I - \delta T^* \\ \frac{dV_I}{dt} &= N\delta T^* - cV_I \end{aligned}$$

Model equations for viral decay after treatment

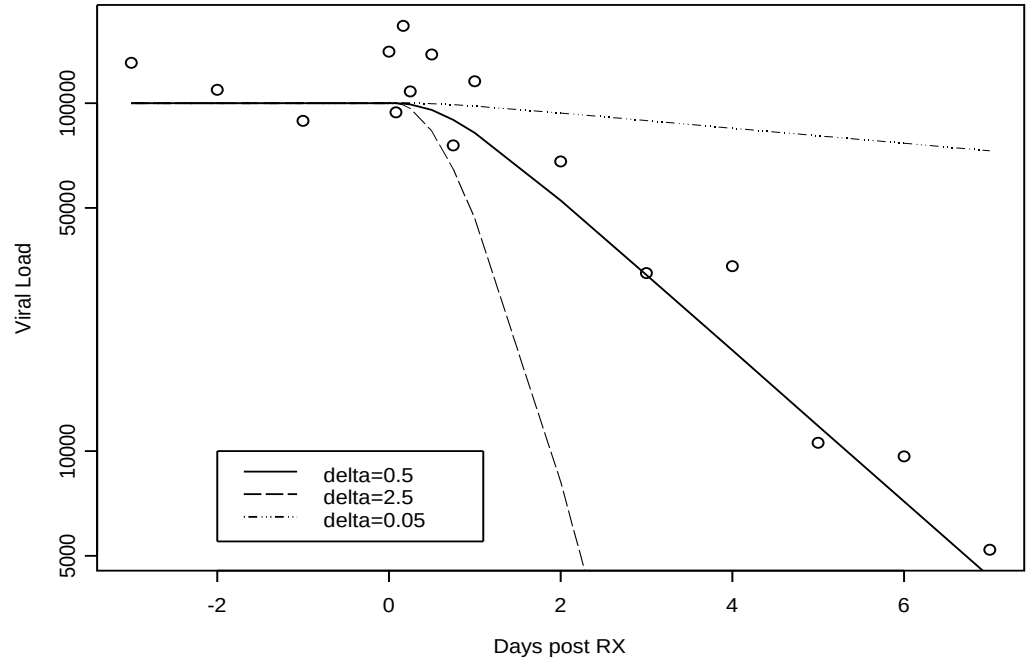
$$\begin{aligned} \frac{dT^*}{dt} &= kTV_I - \delta T^* \\ \frac{dV_I}{dt} &= -cV_I \\ \frac{dV_{NI}}{dt} &= N\delta T^* - cV_{NI} \end{aligned}$$

- T^* is the population of infected cells
- V_I (V_{NI}) is the population of infectious (non-infectious) virus
- $V = V_I + V_{NI}$ is the total **observed** viral load

Example: simulated viral load up to 7 days post treatment



Decay rates CANNOT be estimated from steady state data



Conclusions based on estimation of viral clearance and infected cell turnover.

- Estimates of δ (infected cell turnover rate) and c (viral RNA clearance rate) showed that infected cells and viral RNA are turning over rapidly and continuously during the long latent stage of HIV infection prior to AIDS
- Previously, it was thought that HIV was relatively inactive during the latent stage prior to development of AIDS
- Estimates of number of viral particles produced per day have been obtained using these estimates and explain why HIV escapes immune response and can easily becomes resistant to suboptimal treatment.
- Homework Find something very unusual in the presentation of the results in Perelson Science 1996 paper.

Adjustment to single infected cell compartment model

- As data from longer periods of time post treatment became available it becomes apparent that the initial model did not accurately describe the data.
- Data collected up to 2 months post infection suggest **bi-phasic** decay.
- A new model with two infected cell compartments is proposed:
  - One compartment of infected cells is short-lived, Activated CD4 lymphocytes?
  - Second compartment is longer-lived, tissue macrophages, virus bound to dendritic cells, etc?

Bi-phasic viral decay, more than one infected cell compartment produces virus

Perelson et.al. Nature 1997

Pre-Treatment

$$\begin{aligned}
\frac{dX}{dt} &= k_T TV - \delta X \\
\frac{dY}{dt} &= k_M MV - \mu Y \\
\frac{dV}{dt} &= p_x X + p_y Y - cV
\end{aligned}$$

- T (M) is the population of uninfected short (long) lived cells
- X is the population of short lived infected cells
- Y is the population of longer lived infected cells
- V is cell free viral RNA
- $mu << \delta$

Bi-phasic viral decay, more than one infected cell compartment produces virus

Perelson et.al. Nature 1997

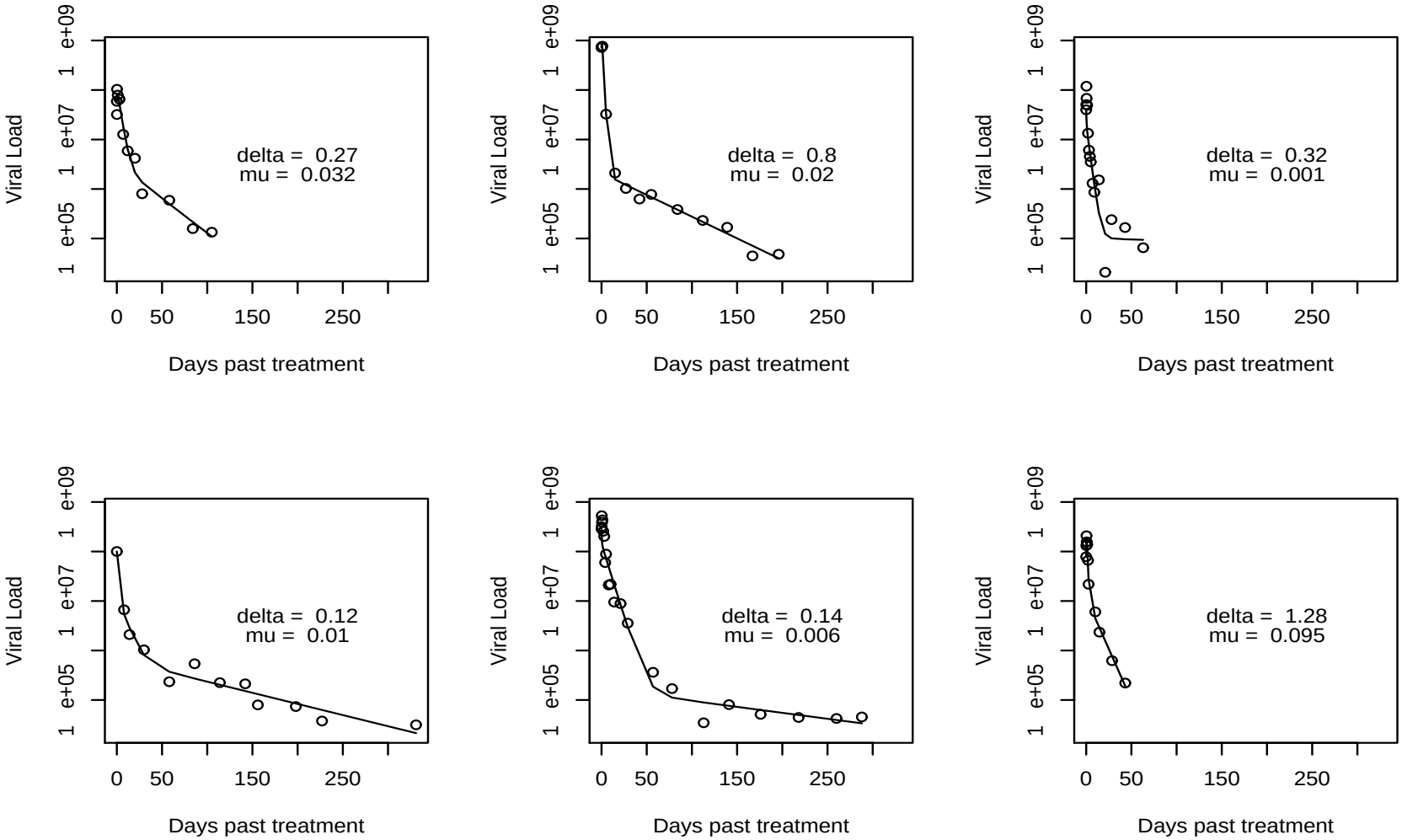
Post-Treatment

$$\begin{aligned}
\frac{dX}{dt} &= k_T TV - \delta X \\
\frac{dY}{dt} &= k_M MV - \mu Y \\
\frac{dV}{dt} &= p_x X + p_y Y - cV
\end{aligned}$$

- T (M) is the population of uninfected short (long) lived cells
- X is the population of short lived infected cells
- Y is the population of longer lived infected cells
- V is cell free viral RNA
- $mu << \delta$

Viral decay after treatment in children

Constant decay model



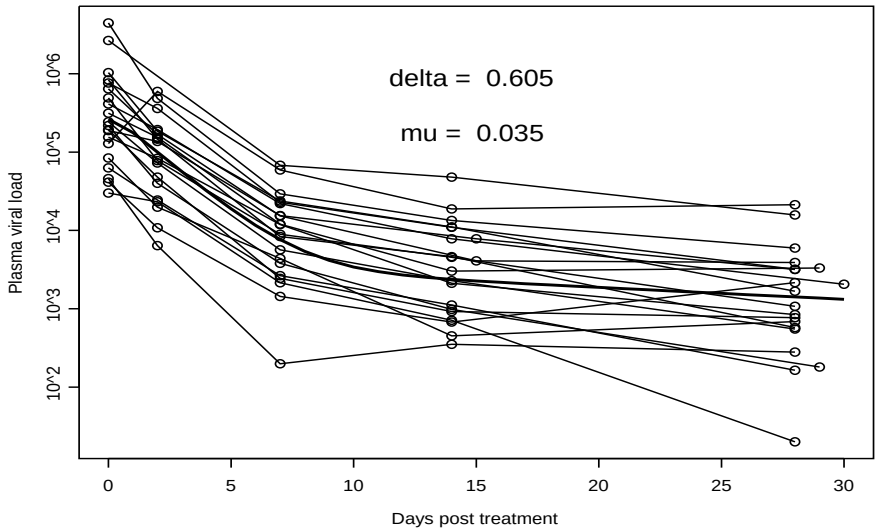
Conclusions based on Constant Decay model

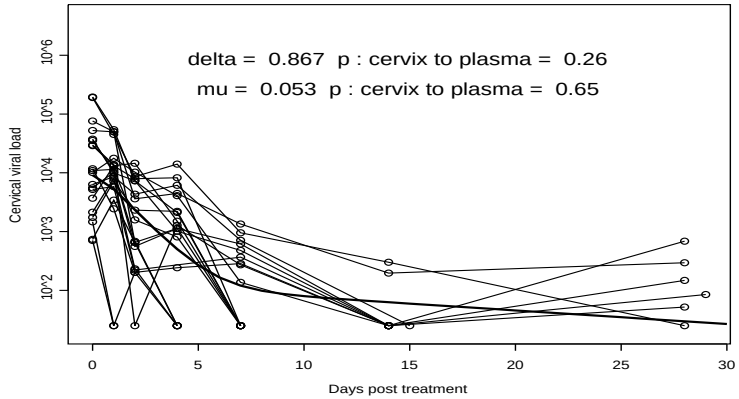
- Estimates of δ and μ using plasma viral load are obtained and used to estimate time on treatment of approximately 2 years to eradicate virus
- Second phase rates, μ significantly different than zero in most children.
- The model provides a relationship between the rates of interest, δ and μ and the observed viral load data.

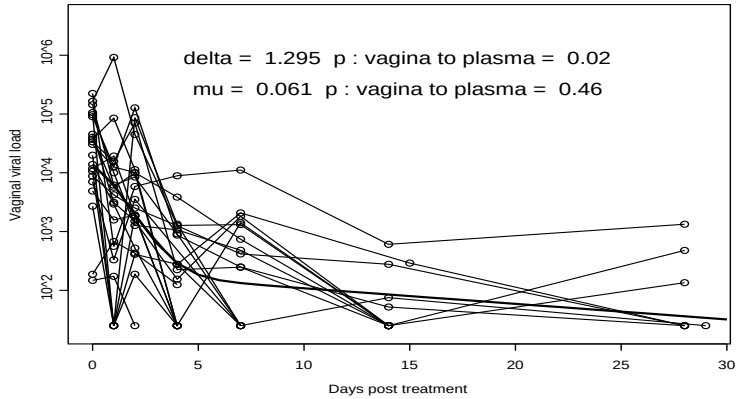
Is the decay of infected cells the same in plasma and female genital tract?

Vaginal, cervical, and plasma viral loads from 21 women collected after RX start

Susan Graham, Scott McClelland, Julie Overbaugh CROI 2006







- First phase decay δ (of productively infected cells) is significantly faster in the vaginal compartment than in the plasma compartment.

Alternative to the constant decay model

Holte et.al. JAIDS 2006

Density Dependant Decay Model

$$\begin{aligned}
\frac{dX}{dt} &= -\delta X \\
\frac{dY}{dt} &= -\mu Y \\
\frac{dV}{dt} &= p_x X + p_y Y - cV
\end{aligned}$$

- X is the population of short lived infected cells
- Y is the population of longer lived infected cells
- V is cell free viral RNA

Alternative to the constant decay model

Holte et.al. JAIDS 2006

Density Dependant Decay Model

$$\begin{aligned} \frac{dX}{dt} &= -\delta X^{\mathbf{r}} \\ \frac{dY}{dt} &= -\mu Y^{\mathbf{r}} \\ \frac{dV}{dt} &= p_x X + p_y Y - cV \end{aligned}$$

- X is the population of short lived infected cells
- Y is the population of longer lived infected cells
- V is cell free viral RNA

Null hypothesis: Constant decay model is correct, $\mathbf{r = 1}$

Alternative to the constant decay model

Holte et.al. JAIDS 2006

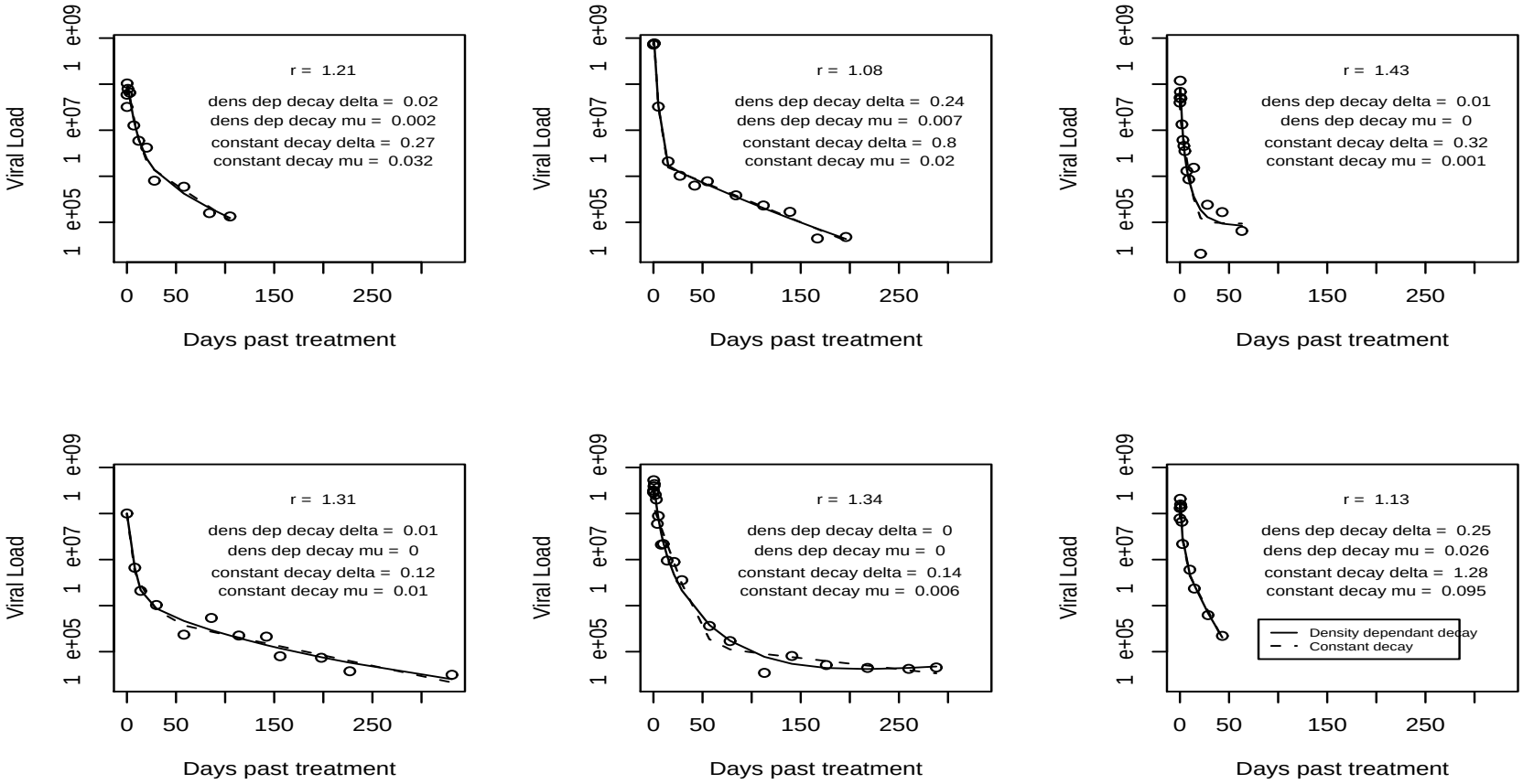
Density Dependant Decay Model

$$\begin{aligned}
\frac{dX}{dt} &= -\delta X^{\mathbf{r}-1} X \\
\frac{dY}{dt} &= -\mu Y^{\mathbf{r}-1} Y \\
\frac{dV}{dt} &= p_x X + p_y Y - cV
\end{aligned}$$

- X is the population of short lived infected cells
- Y is the population of longer lived infected cells
- V is cell free viral RNA

Null hypothesis: Constant decay model is correct, $\mathbf{r = 1}$

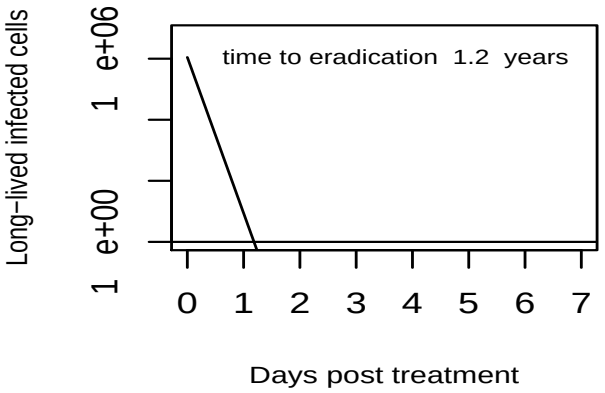
Density Dependant Decay model results

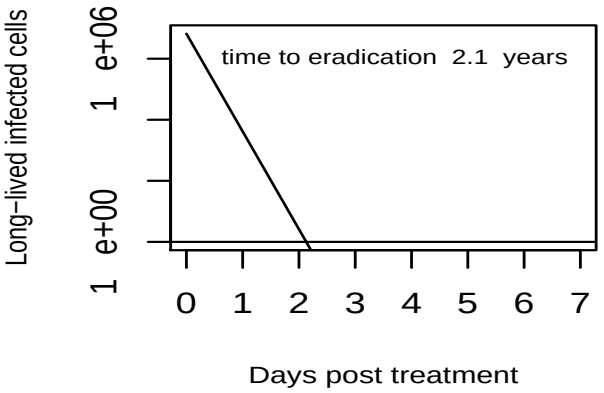


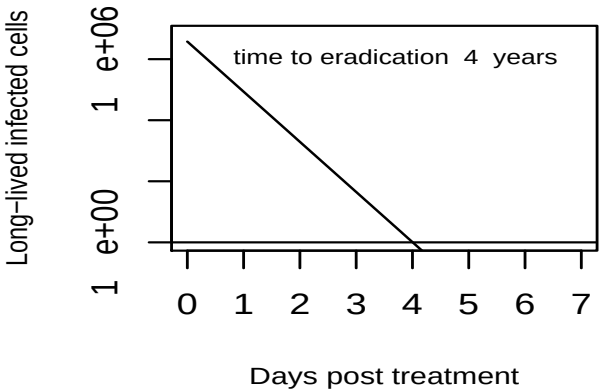
Density Dependant Decay model results - Continued

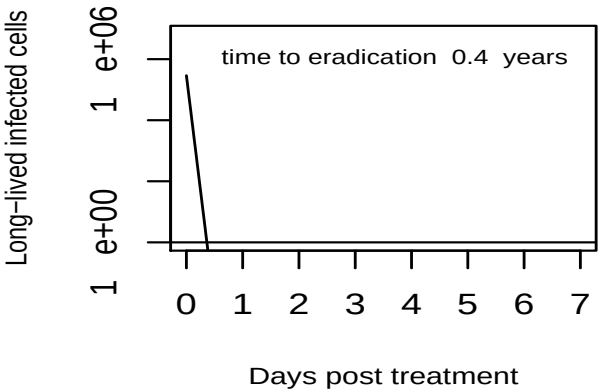
- The parameter r is significantly greater than 1 for all but one child suggesting that that the constant decay model is not appropriate for the observed data.
- Estimated second phase decay, μ, is significantly different than 0 for all children using the constant decay model, but only for one child using the density dependant decay model.
- Very different conclusions about the long term dynamics of viral load after treatment depending on which model is used for prediction and inference.

Density dependant vs constant decay model - time to eradication

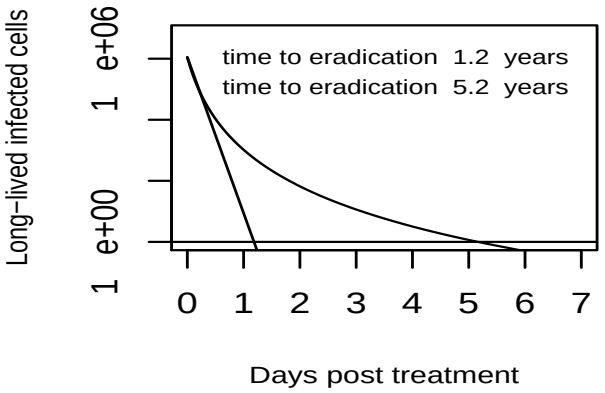


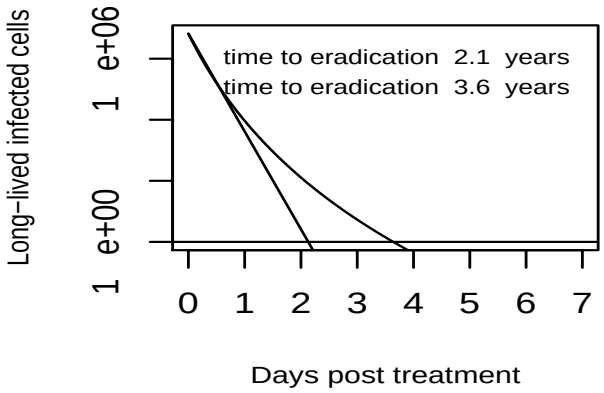


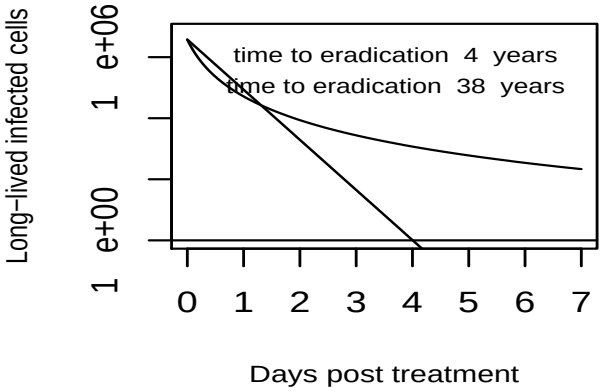


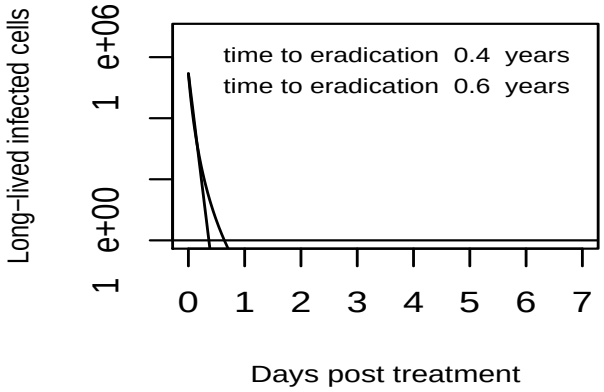


Density dependant vs constant decay model - time to eradication

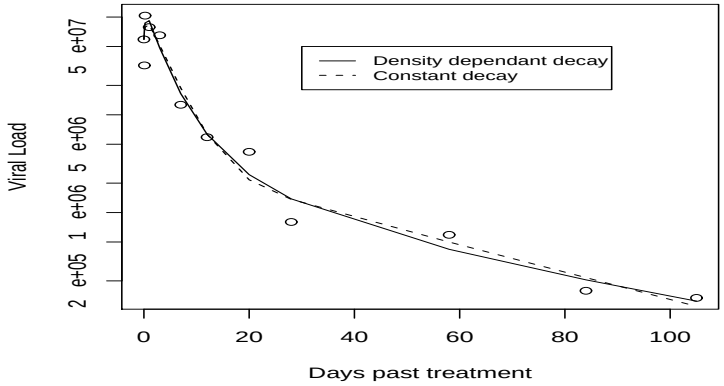






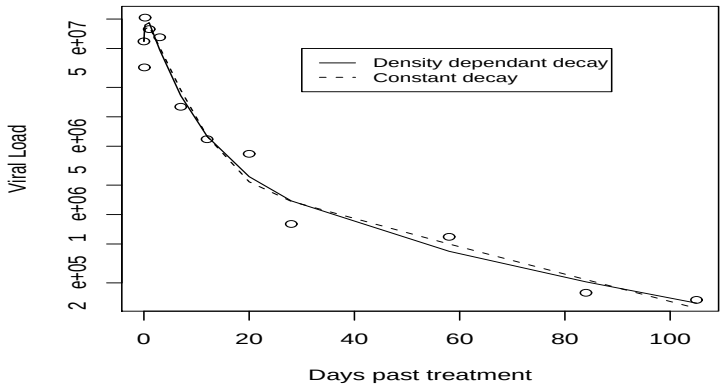


Conclusions based on models for viral decay after treatment



- Using models to make predictions is subject to the dangers of the potential for incorrect mathematical models....

Conclusions based on models for viral decay after treatment



- Using models to make predictions is subject to the dangers of the potential for incorrect mathematical models....
- ... in addition to extrapolating beyond the range of observed data

When/why should mathematical models be used in HIV research?

- Can and should be used to generate conjectures and predictions that can be tested in laboratory or clinical populations
- Can and should be used to estimate dynamic parameters which have prognostic value.
  - Viral set point after infection is prognostic for disease outcome, Mellors et.al Annals Int. Med. 1997.
  - Similar studies for infected cell decay rates would be useful.
- Can be used to explore time varying phenomena within a fixed interval of time. Care is needed when interpreting the results
- When modelling results are treated as just that: Modelling results. To be differentiated from observed data.

Summary

- Viral dynamics models have been used successfully to describe disease mechanisms.
- Caution is needed in interpretation of model predictions since models can be incorrect and extrapolation is always risky.
- Ongoing collaboration between modelers and clinicians and lab scientists is essential.
- Viral dynamics research and modelling needs to be more transparent.
- Viral dynamics studies and analysis require the same rigorous design and analysis as any other type of study.