

# Towards a Viral Kinetic Model for Cytomegalovirus Infections

Ben K. Margetts, Judith Breuer, Nigel Klein, & Joseph F. Standing  
UCL CoMPLEX, UCL Institute of Child Health, & Great Ormond Street Hospital



## Introduction

Cytomegalovirus (CMV) infections are a significant cause of morbidity and mortality in immunocompromised paediatric patients. At Great Ormond Street Hospital, we have a large body of these patients, and so understanding the replication dynamics of this virus is important to control these infections as they present.

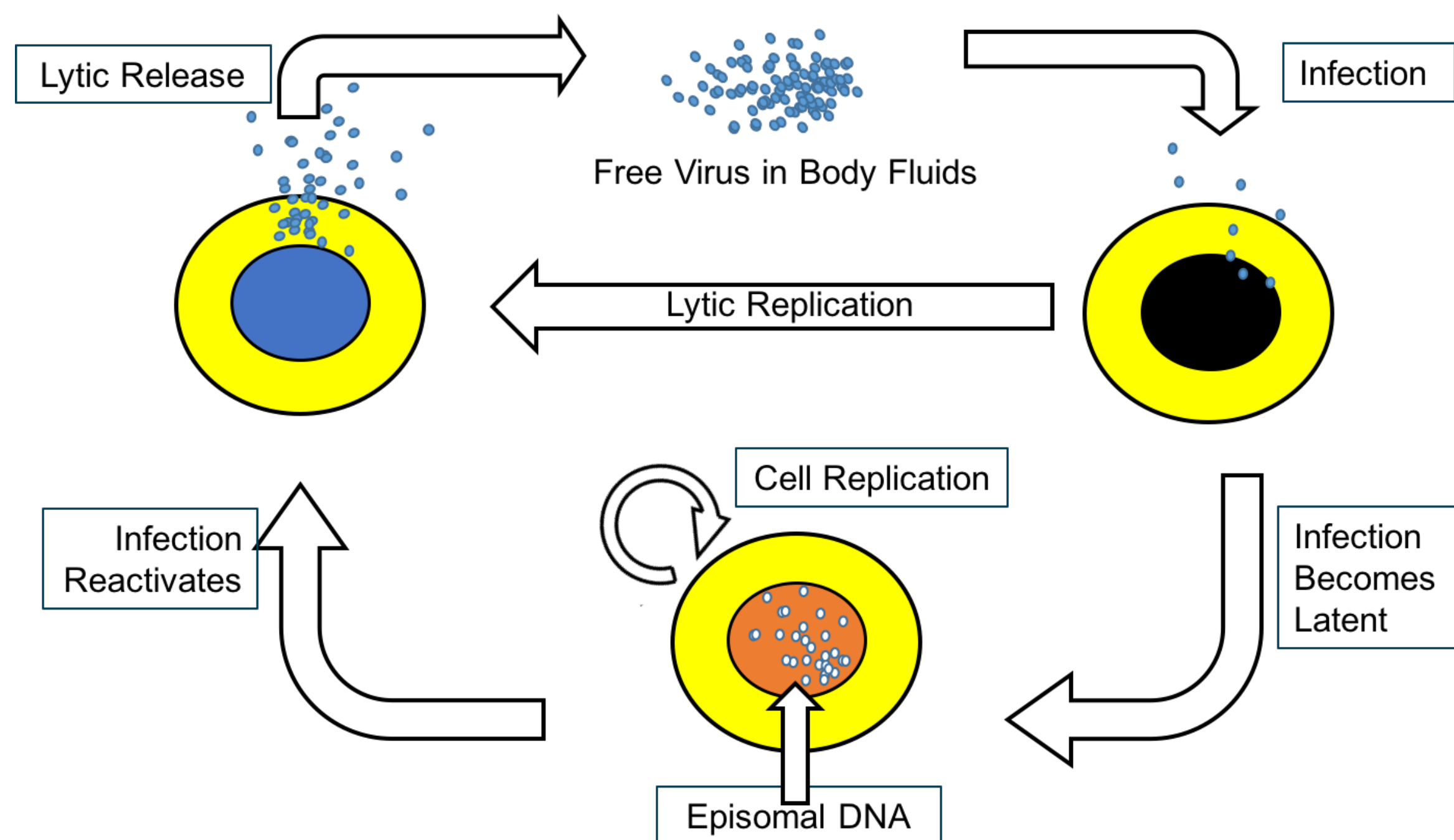


Figure 1. Cytomegalovirus Replication Mechanisms

Antiviral agents act exclusively on the replication pathway of the virus, and so when treating the infection, we rely heavily on the immune response to clear free virions. This is complicated by the acquisition of drug resistance mutations, which are rapidly spread through the viral population through drug selection pressure and a fast turn-over rate.

## Nonlinear Mixed Effects Model

A nonlinear mixed effects model was fitted to these data. This incorporated a statistical model, describing the inter and intra-individual variability in the data, alongside an ordinary differential equation (ODE) model, describing the biological system driving the viral kinetics. The model used a combination of estimated parameters, and parameters that were derived from the clinical data, predicting the change in viral load over time. Random effects were placed on all estimated parameters ( $\alpha, \delta, I, c$ ).

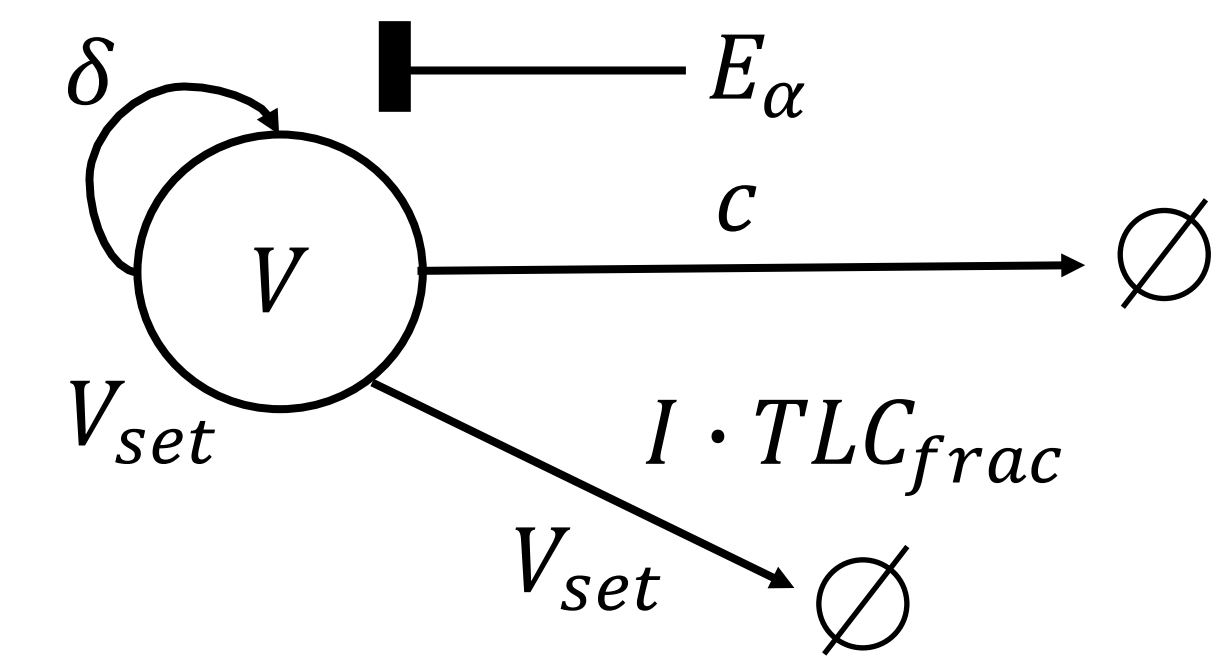


Figure 2. Cytomegalovirus ODE Model Structure

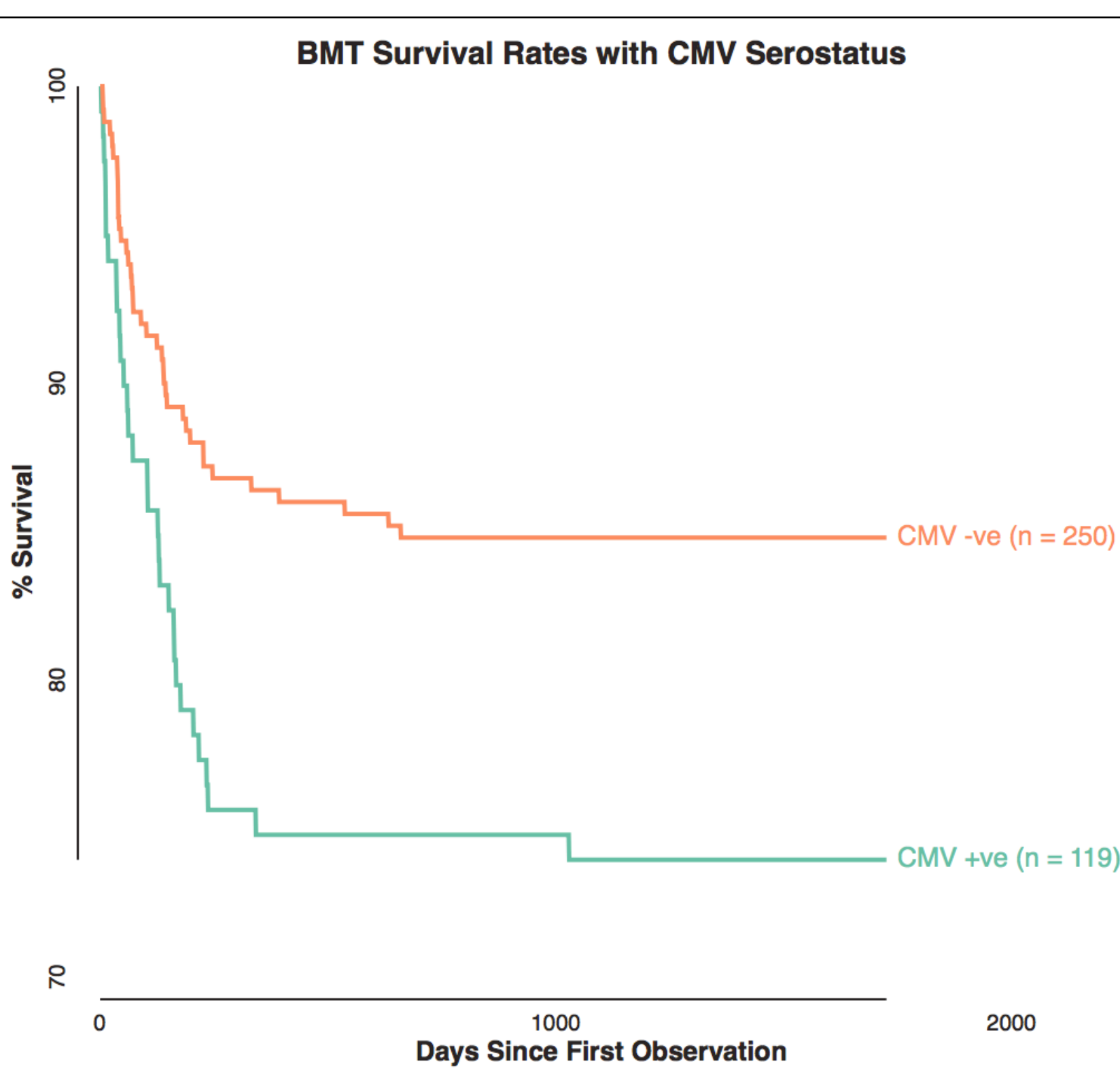
Data-Derived Parameter	Description
$E$	Presence or Absence of Drug
$V_{set}$	Scalar - Maximum Viral Load
$TLC_{frac}$	Fraction of Lower Bound of Total Lymphocyte Count Reference Range
$V_0$	Initial Viral Load

Estimated Parameter	Description
$\alpha$	Antiviral Efficacy
$V$	Free Virus
$\delta$	Replication Rate
$I$	Immune Efficacy
$c$	Clearance

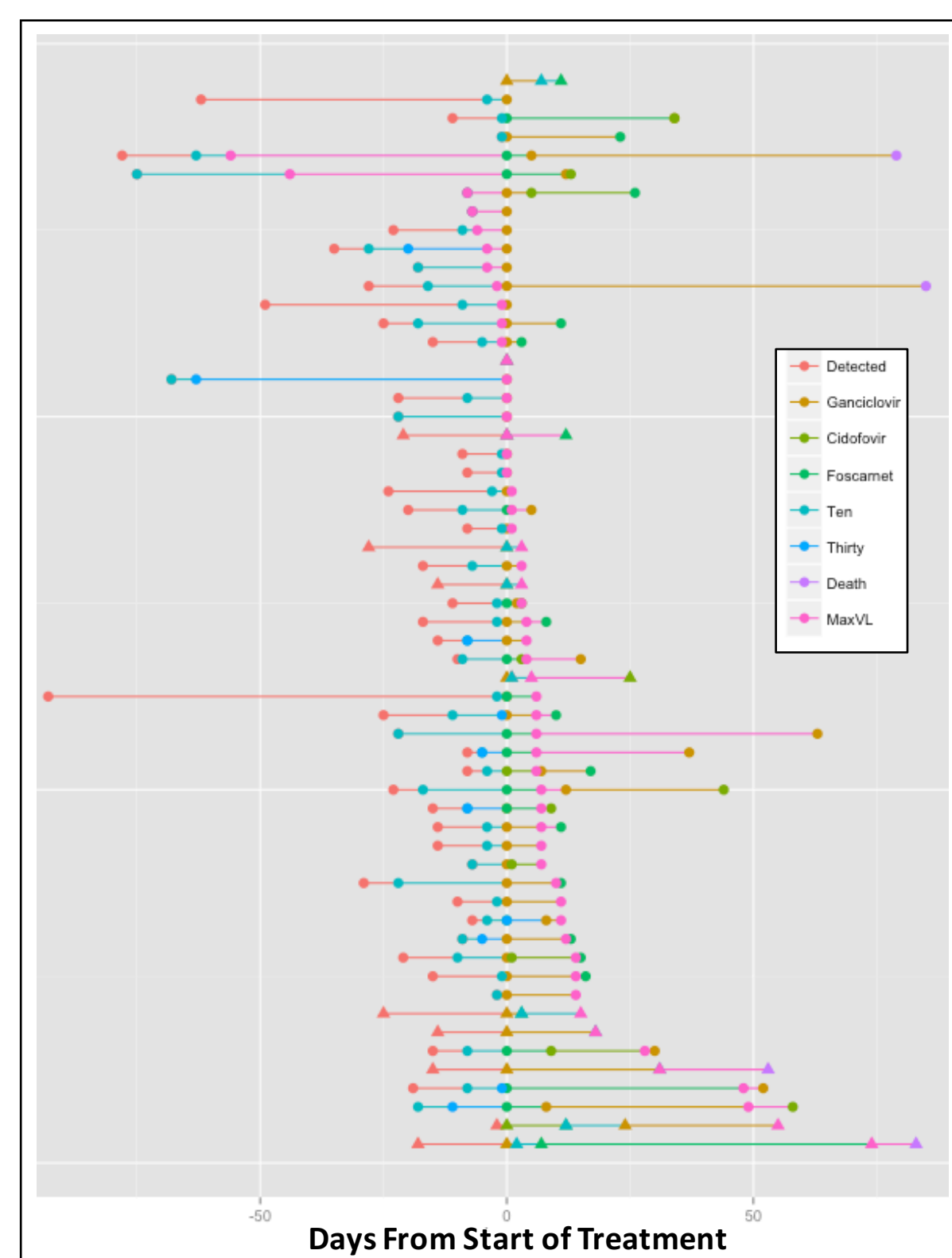
## Available Data

Clinical data from 335 bone marrow transplant patients from 2010-2014 were studied. 86 of these patients were found to have exhibited a serious ( $>10^3$  copies/mL) CMV infection during the course of their recovery.

BMT Survival Curves

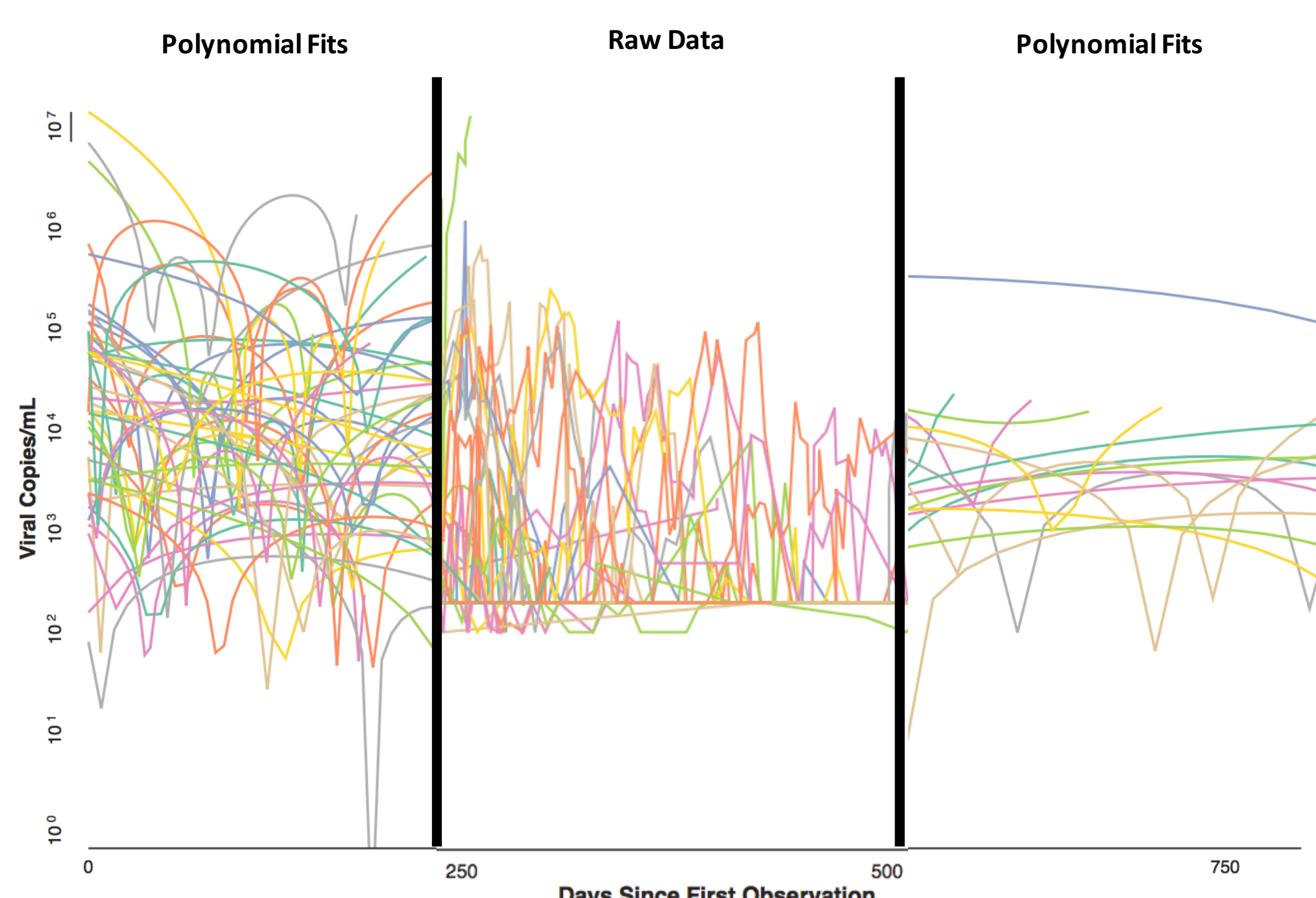


Example CMV Patient Timelines



Alongside the viral load qPCR data, total lymphocyte counts (TLC), lymphocyte subset counts (LSS), drug administration data, and clinical notes were made available for each patient. The viral kinetics appeared to follow a traditional reactivation cycle, as can be seen below.

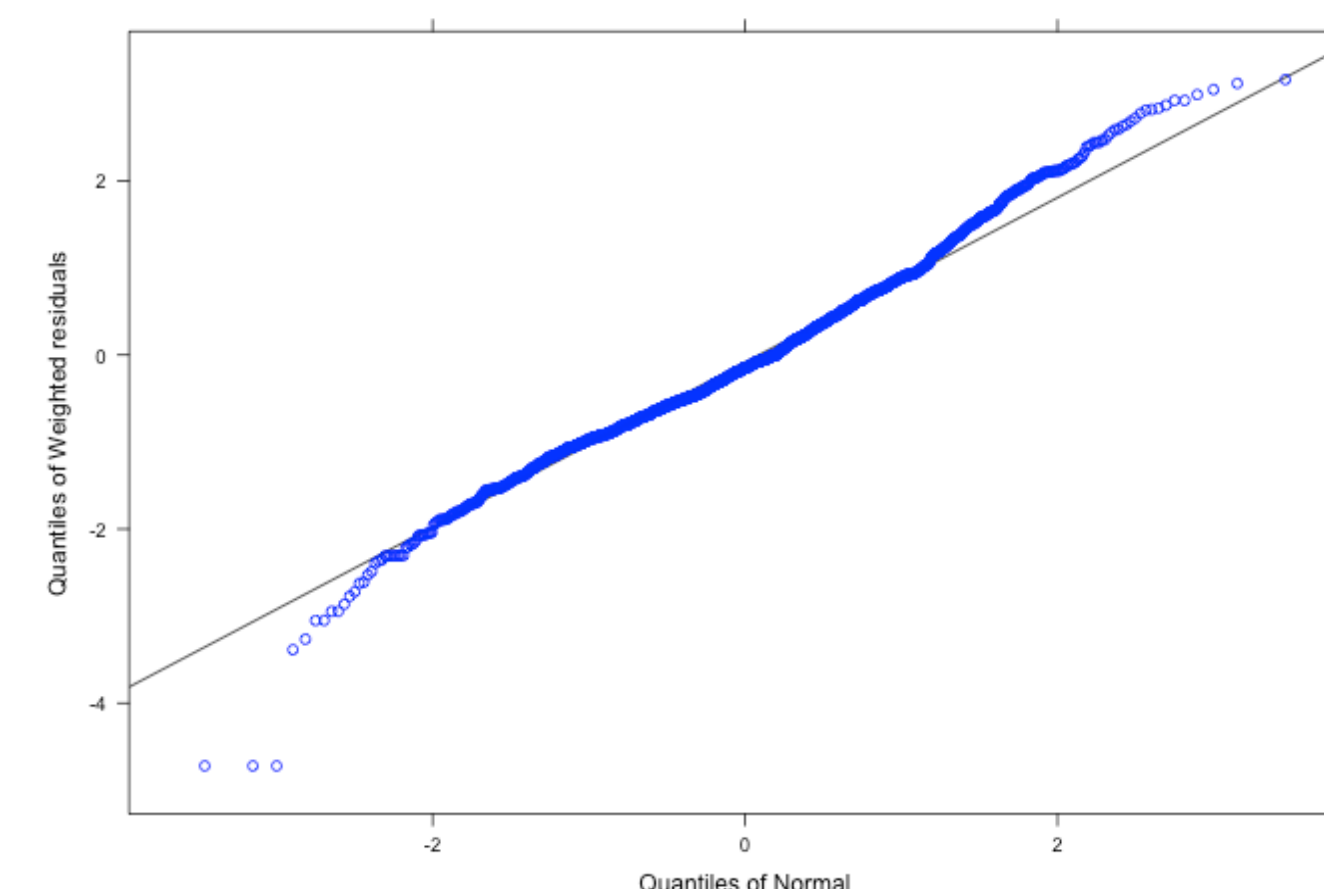
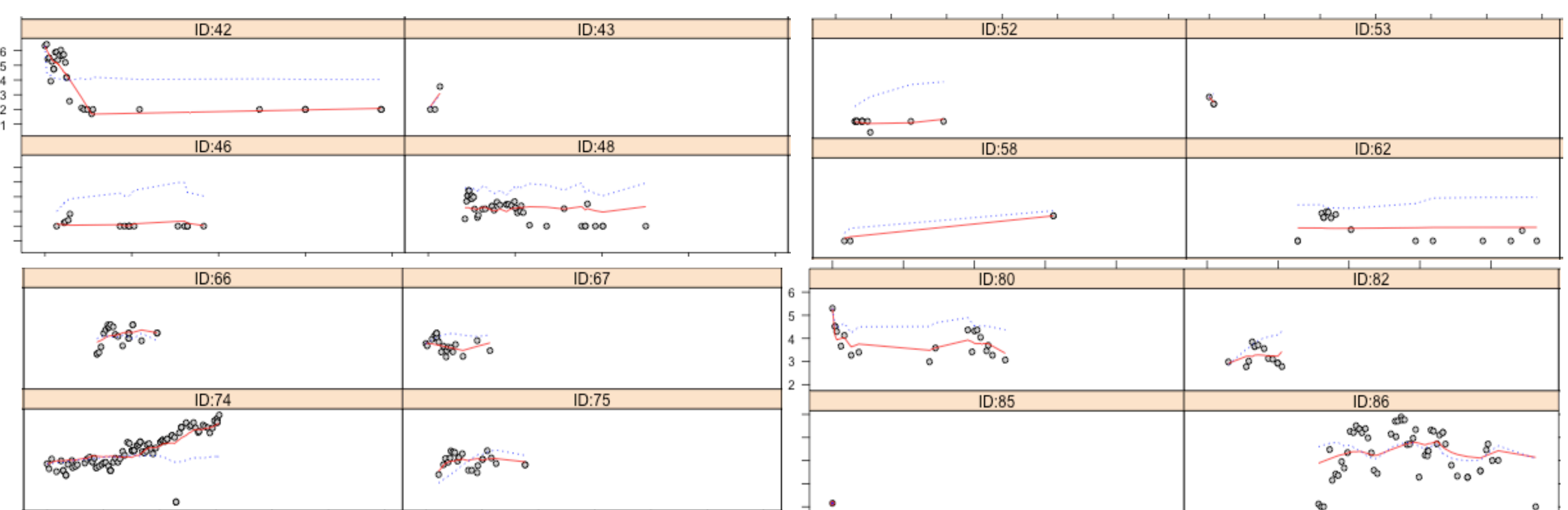
CMV Viral Loads Over Time



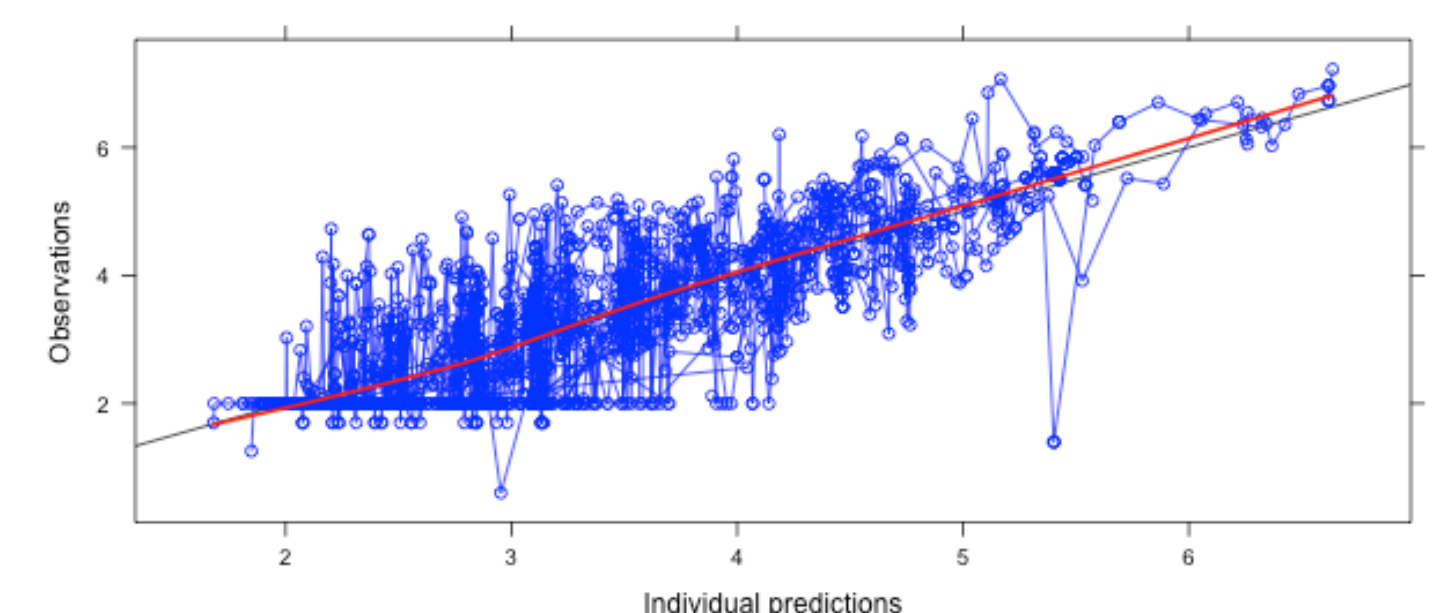
## Results

As can be seen below, the model appears to capture the general trends of the viral infection, but fails to adequately account for some sharp increases and decreases in viral load, suggesting that another mechanism may be driving these changes.

Patient Observations vs. Predictions ( $\log_{10}$  Copies/mL)



Q-Q Plot of Weighted Residuals vs. Expected Normal



Total Observations vs Predictions

## Future Work & Conclusion

We have created a basic NLME viral kinetic model of CMV, driven by patient data. The model predicts general trends, but fails to predict sharp changes in viral load. Our next steps will be to build a latency compartment, that produces sharp bursts of viral reactivation as the immune response fluctuates in efficacy. We believe that this, along with a detailed model of immune response, may help improve the predictive ability of the model, and account for the variance seen in this population.

## References:

- 1) Beal SL, Sheiner LB *et al.* NONMEM Users Guides. 1989-2013.
- 2) Mueller, Nicolas J. "Cytomegalovirus: Why Viral Dynamics Matter." *EBioMedicine* 2.7 (2015): 631.