

# Mechanistic Modelling of Total Body CD4 T-cell Counts from Paediatric HIV Patients Undergoing Planned Treatment Interruption

Eva Germovsek<sup>\*1</sup>, Joanna Lewis<sup>2</sup>, Rollo Hoare<sup>1,2</sup>, Robin Callard<sup>2</sup>, Nigel Klein<sup>1</sup>, Joseph Standing<sup>1</sup>

<sup>1</sup>UCL Institute of Child Health, London, UK; <sup>2</sup> UCL CoMPLEX, London, UK; <sup>\*</sup>eva.germovsek.11@ucl.ac.uk



## Background

T-cell population dynamics in children are influenced by higher thymic output and peripheral T-cell division rates than in adults. CD4 T-cell numbers decline in untreated HIV infection, which can be prevented with antiretroviral therapy (ART). However, paediatric patients sometimes interrupt ART due to various reasons. In the past, complex mechanistic models, describing CD4 cell dynamics, have been tested [1]. These involve measuring and defining many model parameters, which is difficult as only 2% of CD4 cells are in the blood.

## Objectives

The aim is to develop a simpler, but still mechanistic CD4 reconstitution model with fewer parameters than in previously developed models. This way the mechanistic interpretation of the model might improve, as there are fewer parameters to be described.

## Methods

Naïve CD4 concentrations from the PENTA 11 trial [2] were converted to total body naïve CD4 counts and modelled using NONMEM version 7.3 with FOCE method. The data included 29 and 31 HIV patients on continuous and interrupted treatment respectively that had 762 naïve CD4 levels measured. Patients’ mean (range) age at randomization was 9.1 (2.2-15.8) years and their data was collected for up to 5.4 years.

A mechanistic model (Figure 1) with 3 estimated parameters (thymic output, net loss of naïve CD4 cells due to death and proliferation, and initial total body naïve CD4 cell count) was applied to the data.

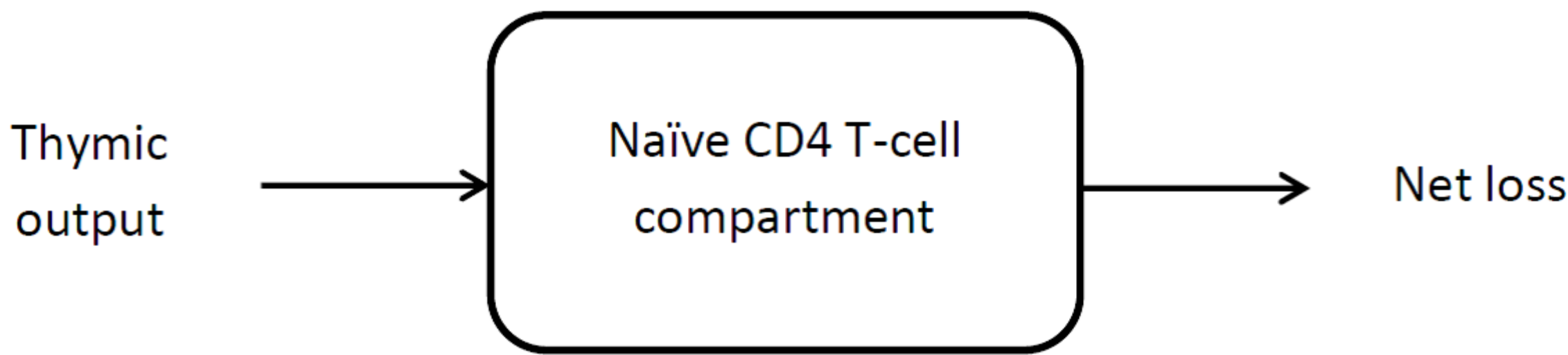


Figure 1: Naïve CD4 T-cell dynamics

Effects of age on input and loss of naïve CD4 cells from the naïve T-cell reservoir were investigated [3], as well as a competition function (Eq. 1) [4] that describes the change in loss with changing cell number. A drug parameter was introduced as a time-varying binary covariate.

$$1 - e^{-A(1)/DQH}, \quad (\text{Eq. 1})$$

where  $A(1)$  is the amount in compartment 1, and  $DQH$  is the characteristic of the total body naïve CD4 cell count describing the response of the net loss to the competition.

## Results

A model that included a function that describes age-related effects on CD4 dynamics and relates them to a healthy child [3, 5]; and also a competition function provided a 6.6 unit drop in OFV ( $p=0.010$ ), compared to a simple 1-compartment model. The competition function parameter ( $DQH$ ) was fixed to  $60,000 \times 10^6$  [4]. Other parameters were estimated (Table 1). Proportional residual error was 23.9%.

Table 1: Results from NONMEM – final parameter estimates

| Parameter                                                  | Mean   | RSE [%] | BSV [%CV] | $\eta$ -shrinkage [%] |
|------------------------------------------------------------|--------|---------|-----------|-----------------------|
| Thymic output as a multiple of that in a healthy child     | 0.119  | 19.7    | 102.9     | 28.7                  |
| Net loss of naïve CD4 cells ( $\text{day}^{-1}$ )          | 0.659  | 11.8    | 108.2     | 36.2                  |
| Initial total body naïve CD4 cell number ( $\times 10^6$ ) | 51,800 | 7.22    | 47.9      | 2.28                  |
| Effect of antiretroviral therapy                           | -0.781 | 4.56    | -         | -                     |

RSE is relative standard error, BSV is between-subject variability.

Goodness-of-fit plots (Figures 2 and 3) and a prediction-corrected VPC (Figure 4) suggest that the model fits to the data well and that there are no major model misspecifications.

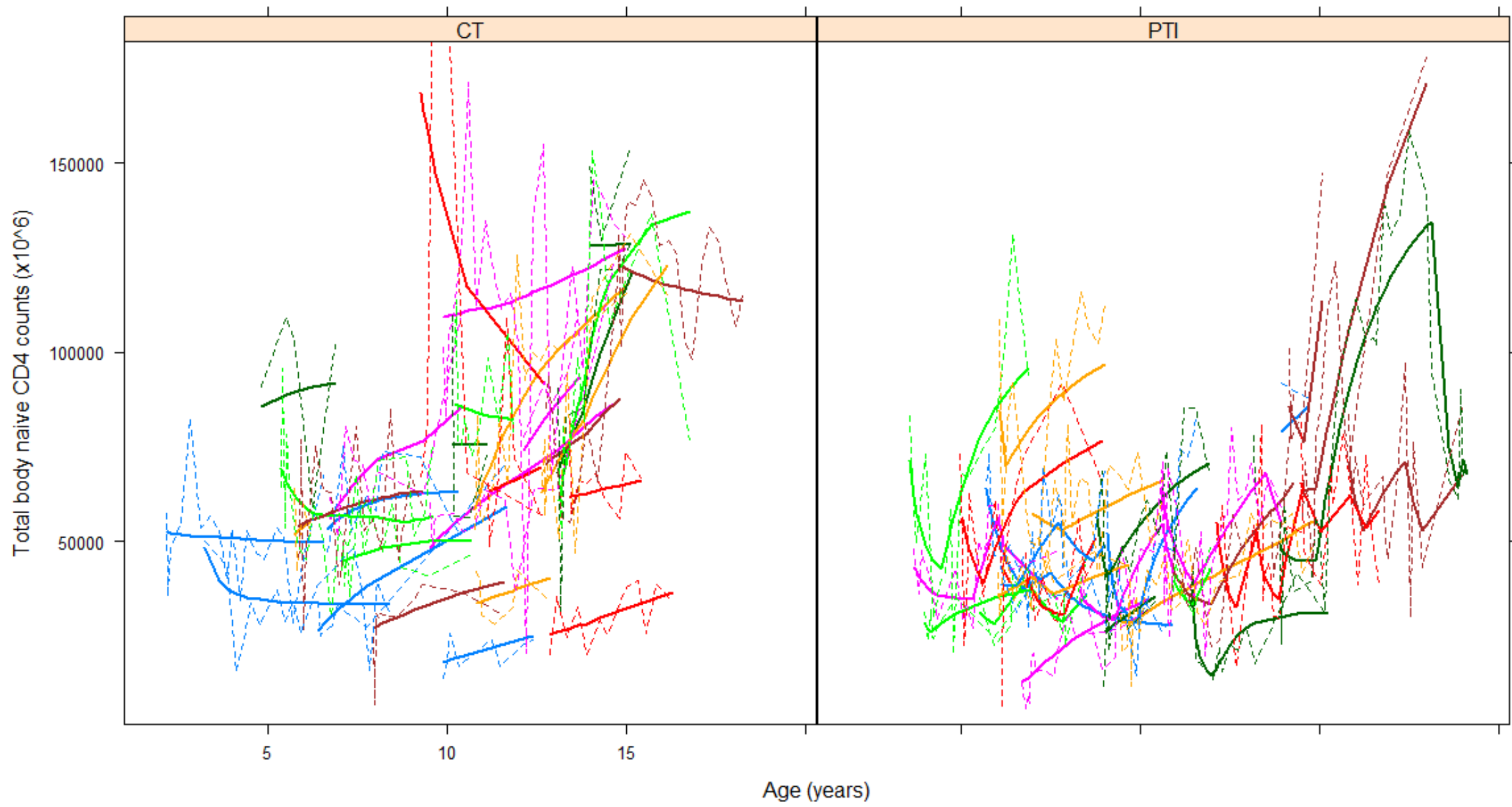


Figure 2: Plots showing goodness-of-fit of the individual predicted total body naïve CD4 counts (solid lines) to the observed data (dashed lines) for HIV patients on continuous (left) and interrupted (right) antiretroviral therapy.

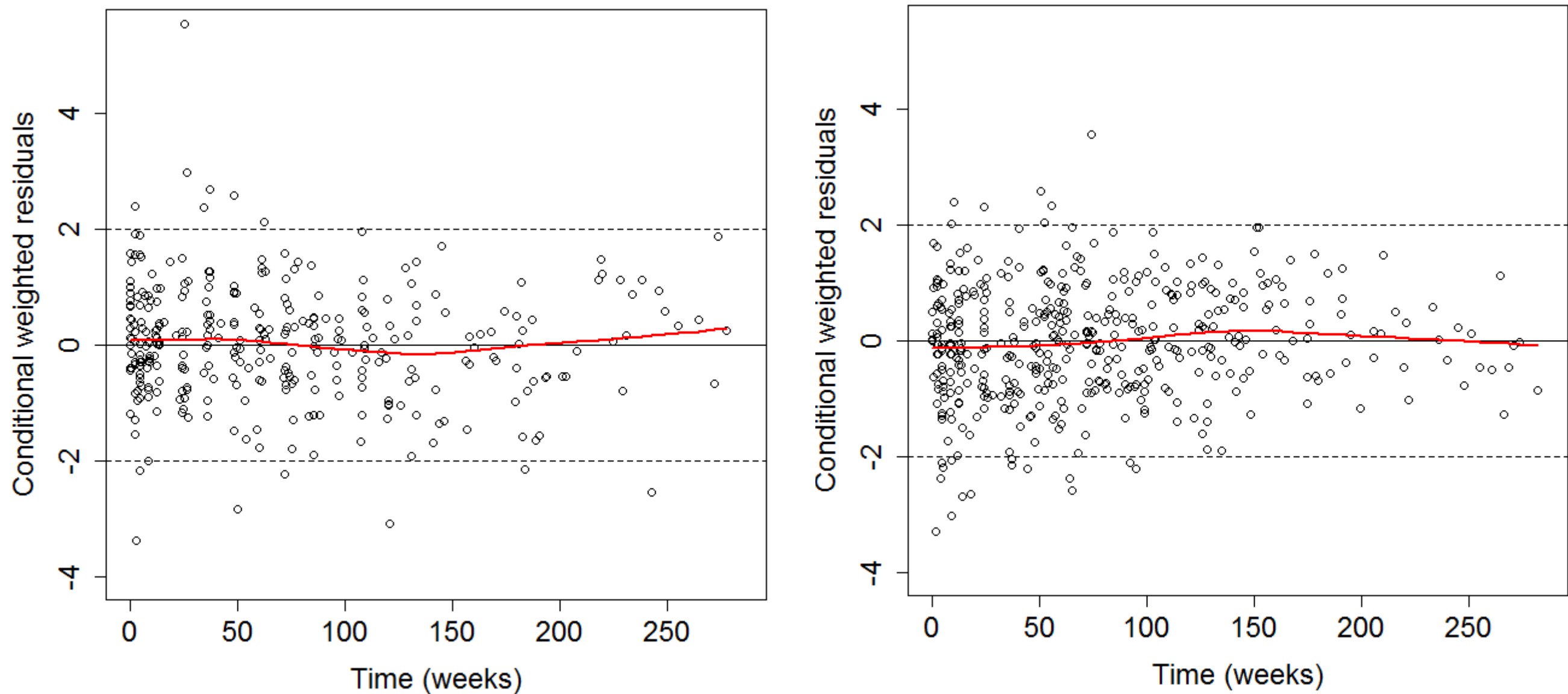


Figure 3: Residual plots of conditional weighted residuals against time in weeks for continuous treatment (left) and interrupted treatment (right) groups. Red line is a lowest line.

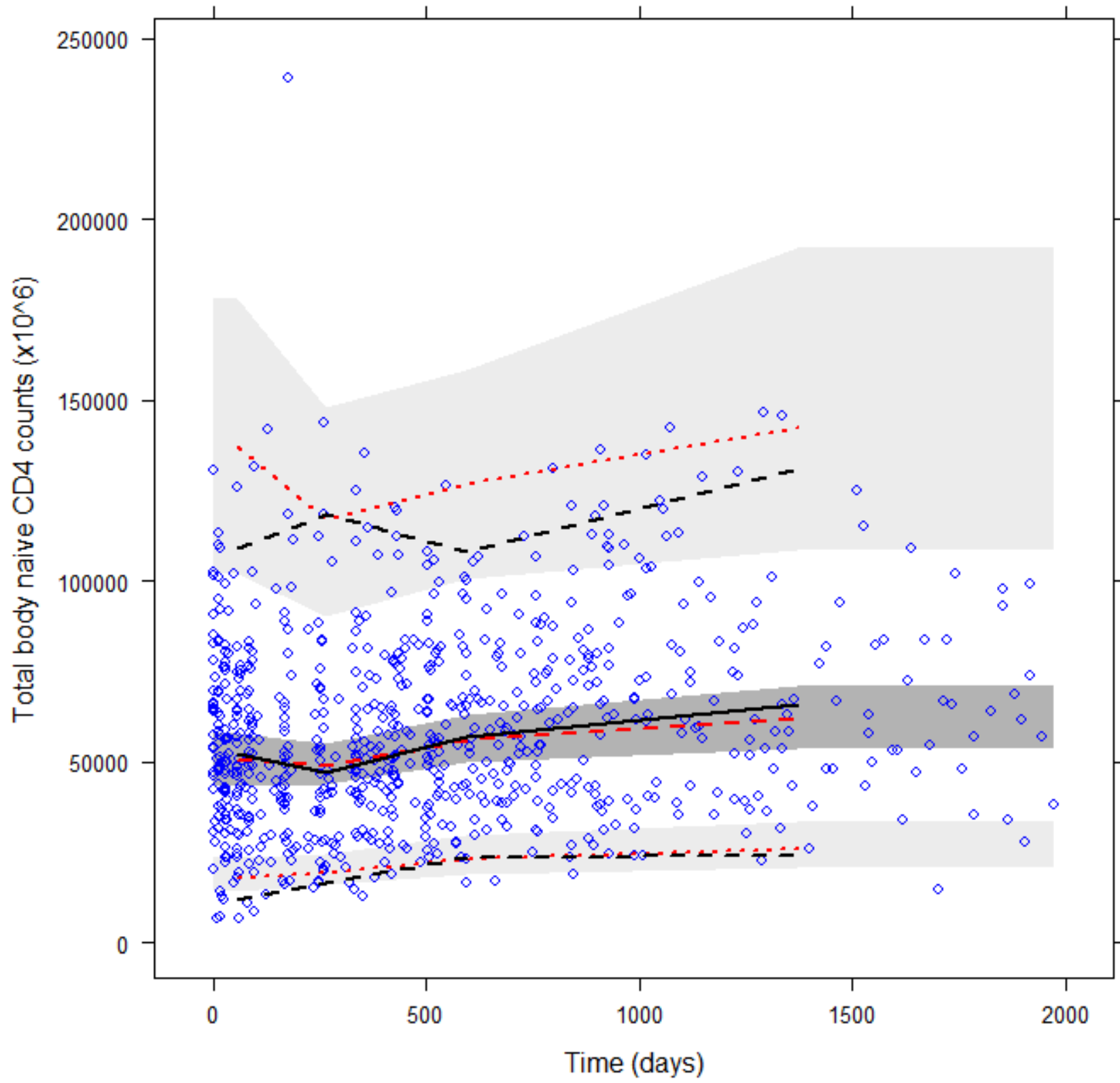


Figure 4: Prediction-corrected visual predictive check performed using 1,000 simulated datasets (from the final model) of the total body naïve CD4 cell counts versus time in days; measured and simulated CD4 T-cell counts were prediction corrected for the differences originating from variations in independent variables; blue dots are observed data points, shaded grey area is a nonparametric 95% confidence interval of the predicted 5th, 50th, and 95th percentiles; black solid line is the median of the observed data; black dashed lines are the 5th and the 95th percentiles of the observed data; corresponding red lines represent the simulated data.

## Conclusions

- A mechanistic model was used to describe CD4 dynamics, with fewer parameters and ordinary differential equations than previously developed models, and might provide more reliable results.
- Provisional results imply that ART reduced the net loss of naïve CD4 cells to 21.9% of the value when off ART.
- Future work will consider including HIV viral load in the model, to further the understanding of the effects of treatment interruption on long-term CD4 reconstitution.

**References**  
1. Lavielle et al., Maximum Likelihood Estimation of Long-Term HIV Dynamic Models and Antiviral Response, Biometrics 2011; 67(1): 250-9  
2. PENTA. Paediatric European Network for Treatment of AIDS: Response to planned treatment interruptions in HIV infection varies across childhood. AIDS. 1996;24(2):231-41.  
3. Bains et al., Quantifying Thymic Export: Combining Models of Naïve T-Cell Proliferation and TCR Excision Circle Dynamics Gives an Explicit Measure of Thymic Output, J Immun. 2009; 183: 4329-36  
4. Hoare et al., A Novel Mechanistic Model for CD4 Lymphocyte Reconstitution Following Paediatric Haematopoietic Stem Cell Transplantation, PAGE 22 (2013) Abstract 2676  
5. Huenecke et al., Age-matched lymphocyte subpopulation reference values in childhood and adolescence: application of exponential regression analysis, Eur J Haematol. 2008; 80(6): 532-39

