# Modelling CD4 T cell reconstitution in HIV-infected children starting ART

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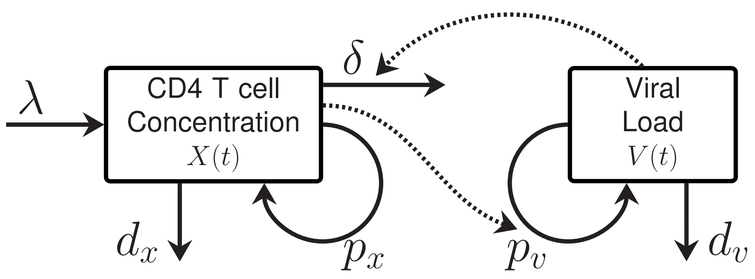
## Introduction

- Antiretroviral therapy (ART) is the standard treatment for adults and children infected with HIV.
- HIV mainly infects CD4 T cells, causing a decline in CD4 T cell concentration. This decline leaves patients immunocompromised and hence vulnerable to opportunistic infections.
- ART suppresses HIV replication, reducing viral load, allowing CD4 T cells to reconstitute. This reconstitution is slow, taking between one a two years.
- Studying immune reconstitution in children is challenging due to the rapidly developing immune system; expected CD4 T cell counts for age decrease three-fold [1].
- This work combines a previously presented model describing CD4 T cell reconstitution following paediatric HSCT [2] with a model for HIV dynamics in adults [3].

## Methods

- The data comprises paired time series of CD4 T cell concentrations and viral loads for up to three years after initiation of ART.
- Datasets come from two clinical trials:
  Dataset A: 66 patients, 721 CD4 counts, 525 viral loads (388 BLQ)
  Dataset B: 1026 patients, 10490 CD4 counts, 2122 viral loads (1223 BLQ).
- The CD4 concentration is modelled directly, without standardisation for age, using mechanistic modelling which takes into account the effects of immune system development.
- Viral dynamics have been adapted to include a term accounting for the decrease of virus loss rate at low viral loads.

### The Model




The equations for the dynamics with time $t$ and age $\tau$ are given by:

$$\frac{\mathrm{d}}{\mathrm{d}t}X = \lambda - d_x\,X + p_x\,X - \delta\,V\,X$$

$$\frac{\mathrm{d}}{\mathrm{d}t}V = p_v\,V\,X\,(1-E_{\mathsf{Drug}}) - d_v\,V\frac{V}{V+V_{50}}$$

$$\lambda(t,\tau) = \lambda_0 \times \left(\frac{y(\tau)\,N(\tau)\,\gamma}{0.02\,\eta(c-\gamma)}\right)$$

$$d_x(\tau,X) = d_0 \times y(\tau) \times \exp\left[c_d\left(\frac{X(t)}{N(\tau)}-1\right)\right]$$

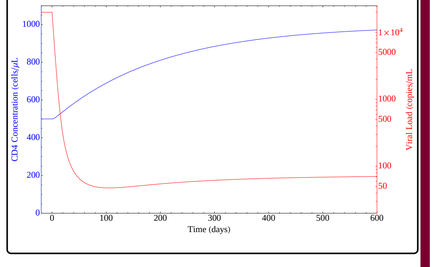
$$p_x(\tau,X) = p_0 \times y(\tau) \times \exp\left[c_p\left(1-\frac{X(t)}{N(\tau)}\right)\right]$$

$$p_v = \frac{d_v\,V_0}{X_0(V_0+V_{50})}, \qquad \delta = \frac{\lambda - d_x\,X_0 + p_x\,X_0}{X_0\,V_0}$$

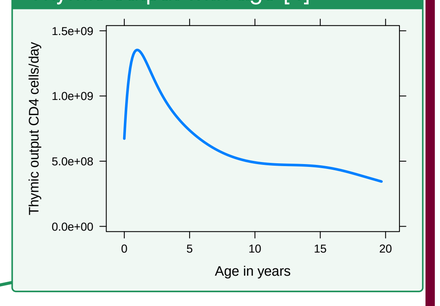
$N(\tau)$ is the expected CD4 T cell concentration of a healthy child with age.
The model has ten parameters to be estimated, six for CD4 concentration: $X_0, \lambda_0, d_0, p_0, c_d, c_p$, and four for viral load: $V_0, d_v, V_{50}, E_{\mathsf{Drug}}$.

The model was fitted to the data using the Importance Sampling algorithm in NONMEM 7.3 and the ADVAN13 subroutine [5].

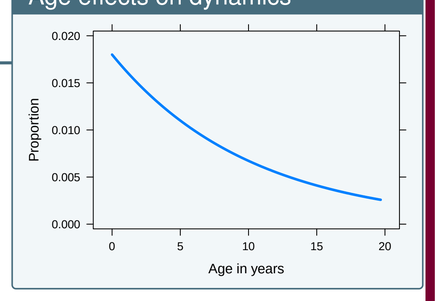
**Sample model output**



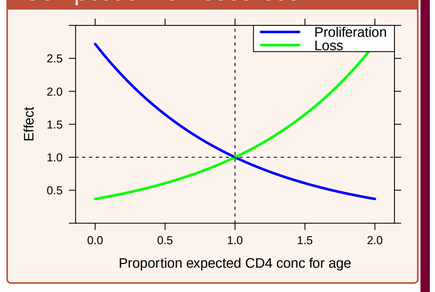

**Thymic output with age [4]**




**Age effects on dynamics**




**Competition for resources**



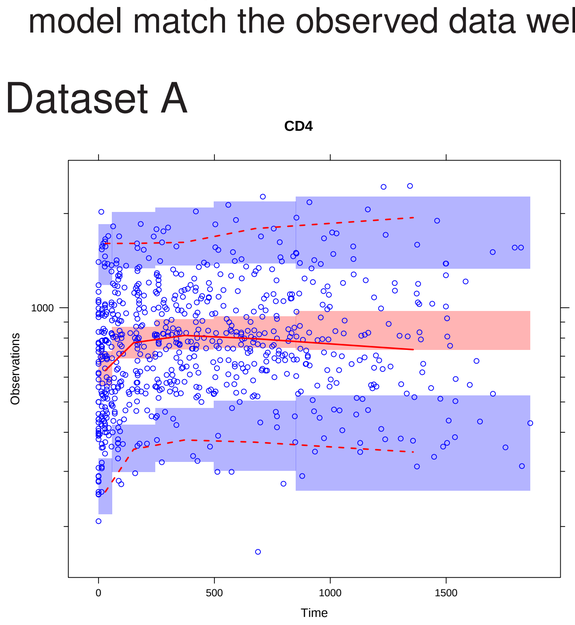

## Results

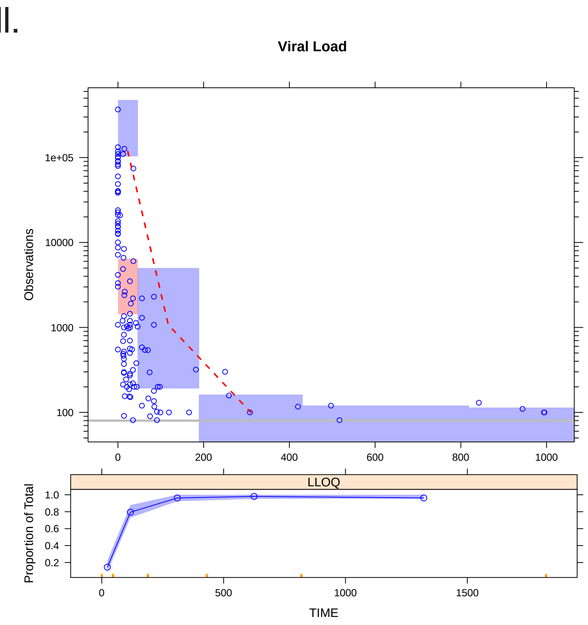
- For Dataset A, all parameters were estimated, with random effects on all parameters, but in Dataset B, $E_{\mathsf{Drug}}$ was fixed to 1.
- Parameter estimates from the model are sensible, with reasonable agreement between the datasets.

| | | Dataset A | | Dataset B | |
|---|---|---|---|---|---|
| Parameter | | Estimate | $\Omega$ | Estimate | $\Omega$ |
| $\lambda_0$ | Proportion of theoretical thymic output [4] (cells/day) | 0.107 | 0.713 | 0.276 | 5.62 |
| $d_0$ | Proportion of expected loss (/day) | 0.496 | 0.509 | 1.49 | 4.52 |
| $p_0$ | Proportion of expected proliferation (/day) | 0.271 | 1.17 | 0.436 | 1.02 |
| $X_0$ | Initial concentration of T cells (cells/$\mu$L) | 569 | 0.183 | 270 | 1.48 |
| $c_d$ | Strength of competition loss | 0.328 | 0.781 | 1.65 | 0.203 |
| $c_p$ | Strength of competition proliferation | 2.06 | 0.460 | 1.11 | 0.558 |
| $V_0$ | Initial viral load (cells/mL) | 21800 | 0.976 | 324000 | 1.96 |
| $d_v$ | Rate of loss for virus cells (/day) | 0.281 | 0.510 | 0.339 | 0.188 |
| $V_{50}$ | Viral load at decrease of cell loss (cells/mL) | 324 | 0.786 | 2180 | 1.39 |
| $E_{\mathsf{Drug}}$ | Effect of drug | 0.898 | 0.326 | 1† | — |
| $\sigma_x$ | Variance of the residual error for CD4 concentration | 0.425 | — | 0.193 | — |
| $\sigma_v$ | Variance of the residual error for viral load | 1.37 | — | 0.967 | — |

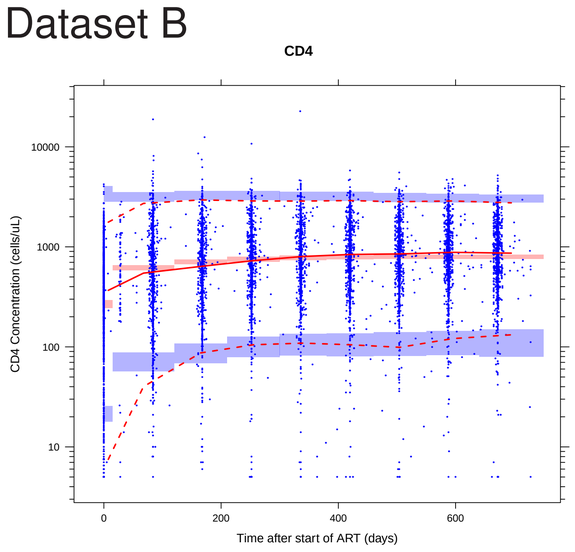
- The visual predictive checks below demonstrate that simulations from the model match the observed data well.

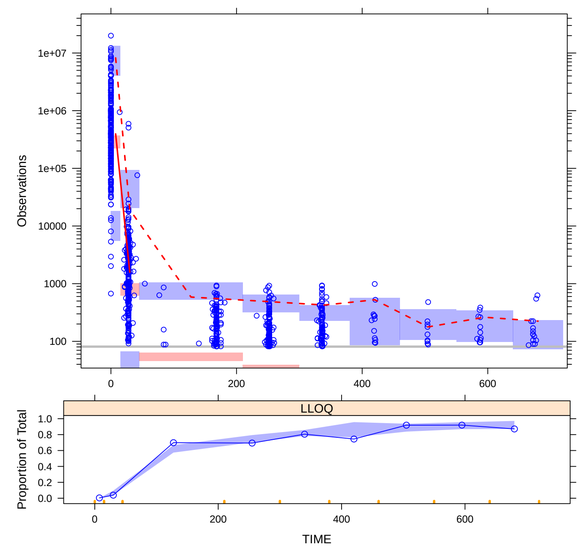
### Dataset A




### Dataset B




## Conclusions

- A model has been developed for CD4 T cell reconstitution and viral load decline for HIV-infected children starting ART
- The model represents the underlying biology of the system, bringing together:
  - The changes in the thymus and dynamics with age
  - Competition for homeostatic signals by CD4 cells in the body
  - Decrease in virus loss rate at low levels of viral load.
- This model has then been successfully fitted to patient data.
- The model has the potential to give insight into the effects of a range of covariates, such as: socio-economic factors, the ART drugs used, or the age of the patient at the start of ART.

## References

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