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 immuno compromised 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 to 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

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\begin{align*}
&\lambda \rightarrow \text{CD4 T cell concentration } X(t) \\
&\delta \rightarrow \text{Viral Load } V(t)
\end{align*}
\]

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

\[
\begin{align*}
\frac{dX}{dt} &= \lambda - d_4 X + p_4 V - \delta V X \\
\frac{dV}{dt} &= p_4 V X (1 - E_{\text{Drug}}) - d_4 V X \\
\lambda(\tau) &= \lambda_0 \times \left( \frac{y(\tau) X(\tau - \gamma)}{0.02 y(-\gamma)} \right)
\end{align*}
\]

The Elsner model [4] 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: \( X_0, \lambda_0, d_4, p_4, c_p, c_4 \), and four for viral load: \( V_0, d_4, V_0, E_{\text{Drug}} \).

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