

# A homeostatic model for CD4 count recovery in HIV-infected children starting antiretroviral therapy

Joanna Lewis<sup>1,2</sup>, Joseph F. Standing<sup>2</sup>, A. Sarah Walker<sup>3</sup>, Nigel Klein<sup>2</sup> and Robin Callard<sup>1,2</sup>

<sup>1</sup>UCL CoMPLEX, London WC1E 6BT <sup>2</sup>Immunology and Infectious Diseases, UCL Institute of Child Health, London WC1N 1EH <sup>3</sup>MRC Clinical Trials Unit, London WC2B 6NH



## Introduction

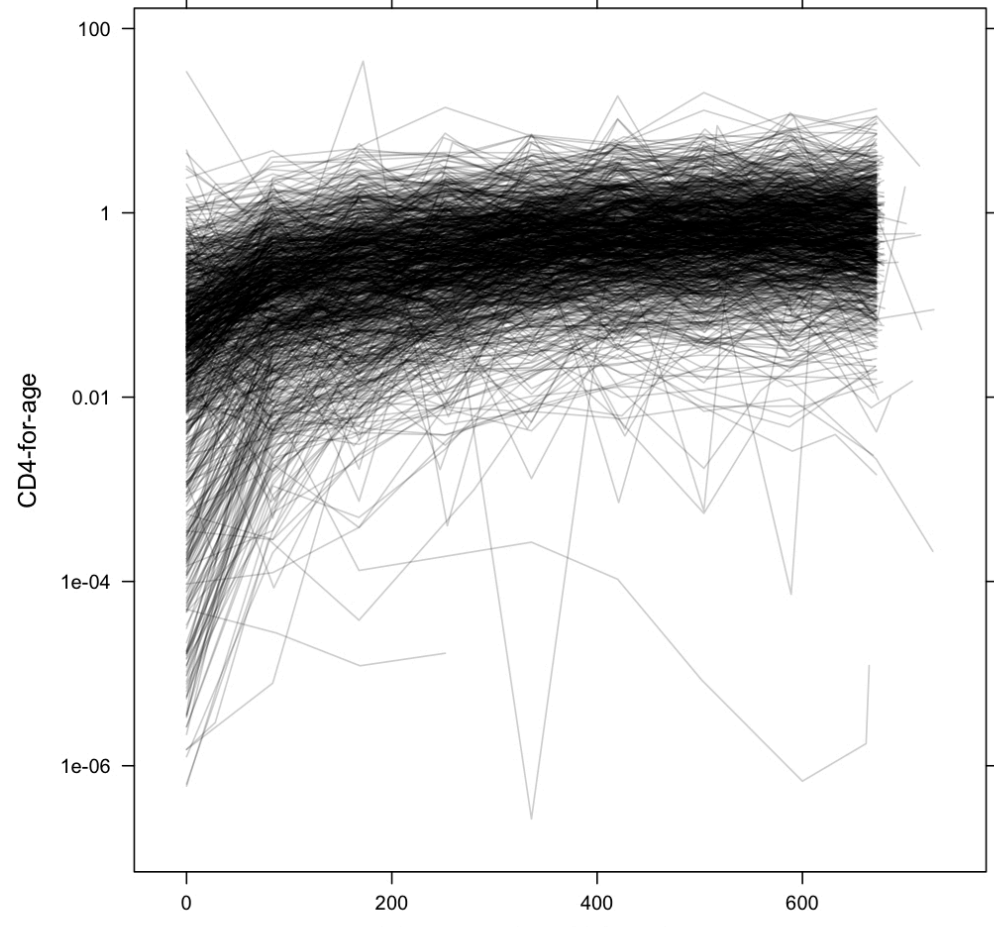
A two-compartment model of CD4 memory T-cell homeostasis has already provided a compelling explanation of the slow decline in CD4 count during chronic HIV infection, as a set-point modified by changing population dynamics<sup>1</sup>.

We aimed:

- to construct a similar model for CD4 recovery in HIV-infected children starting antiretroviral therapy (ART).
- to apply the model in a mixed-effects framework, to describe between-child differences in CD4 recovery profiles.
- to understand the processes contributing to CD4 recovery in children.
- to investigate developmental, immunological and other factors associated with differences in CD4 response and incomplete reconstitution of the CD4 T-cell pool.

## Data

- 9166 CD4 counts from the ARROW clinical trial<sup>2</sup>.
- Truncated at 2 years.
- 914 HIV-infected children who showed typical, asymptotic CD4 reconstitution on ART.
- CD4 counts adjusted for age by dividing by the count expected in a healthy child<sup>3</sup> (CD4-for-age).
- Median (IQR) pre-ART age: 5.6 (2.3, 8.9) years, CD4 count: 342(165, 643) cells  $\mu\text{L}^{-1}$ , CD4-for-age: 0.26 (0.14, 0.41).
- Percentage of cells expressing markers of cell division (Ki67) and activation (HLA-DR) was available at 952 timepoints, in 148 (16%) children (aged 3.9 (2.1, 9.5) years).



## Model

- Two-compartment model, described using ODEs
- Nonlinear mixed-effects models
- Lognormal distributions for random effects
- Fitted with FOCE in NONMEM 7

$$\begin{aligned} \dot{x} &= \theta - a(x) - \delta_x(x) \\ \dot{y} &= a(x) - r - \delta_y(y) \end{aligned}$$

$x(0) = (1-F)T_0$   
 $y(0) = FT_0$

$\delta_x(x) = \delta_0 e^{\sigma x}$   
 $\delta_y(y) = \mu y$

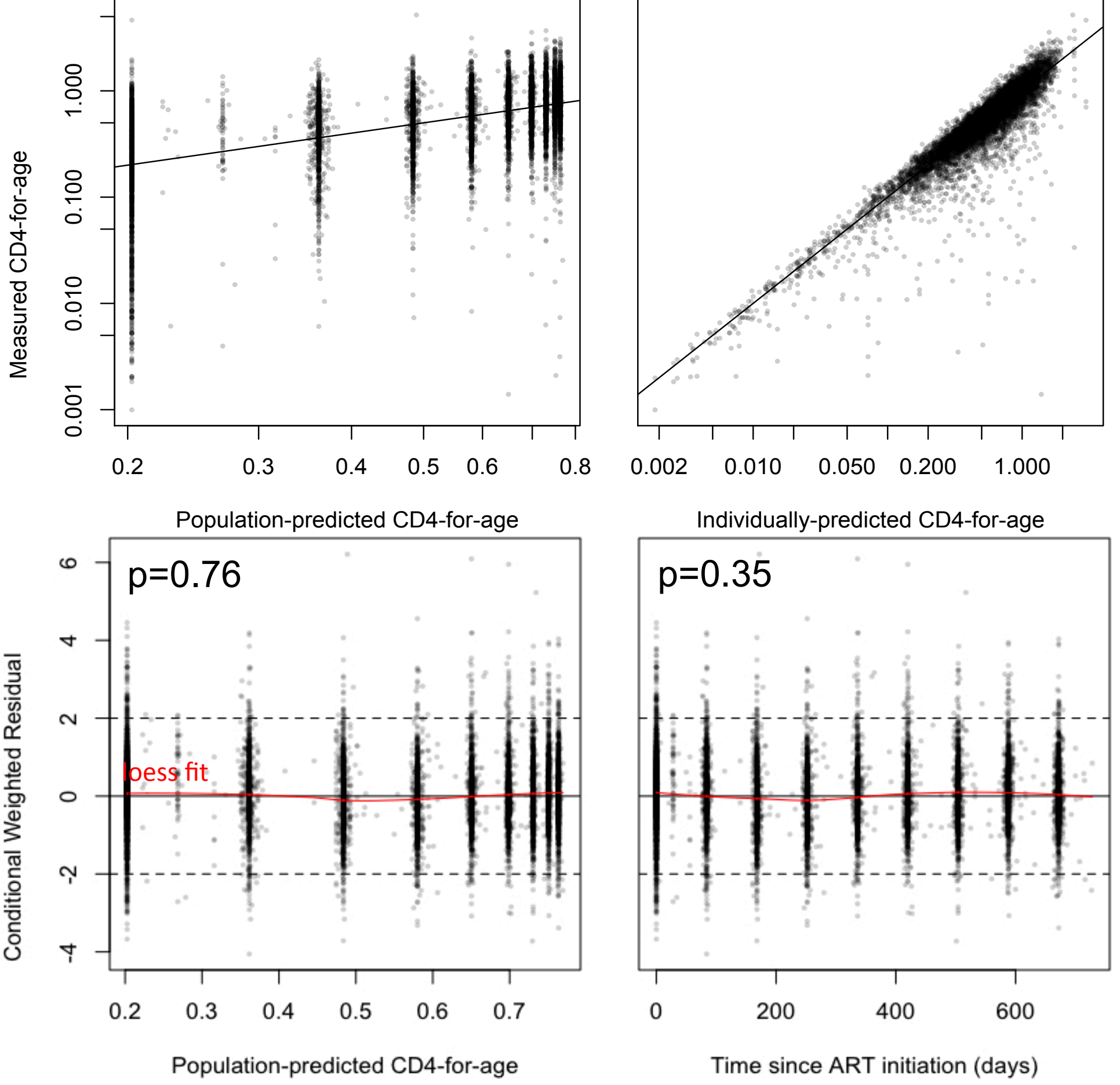
**Fixed (value)**

- $\epsilon$  (1 cells<sup>-1</sup>)
- $\sigma$  (1 cells<sup>-1</sup>)
- $q$  (15 cells<sup>-1</sup> day<sup>-1</sup>)
- $r$  (2 day<sup>-1</sup>)
- $F$  (0.1)

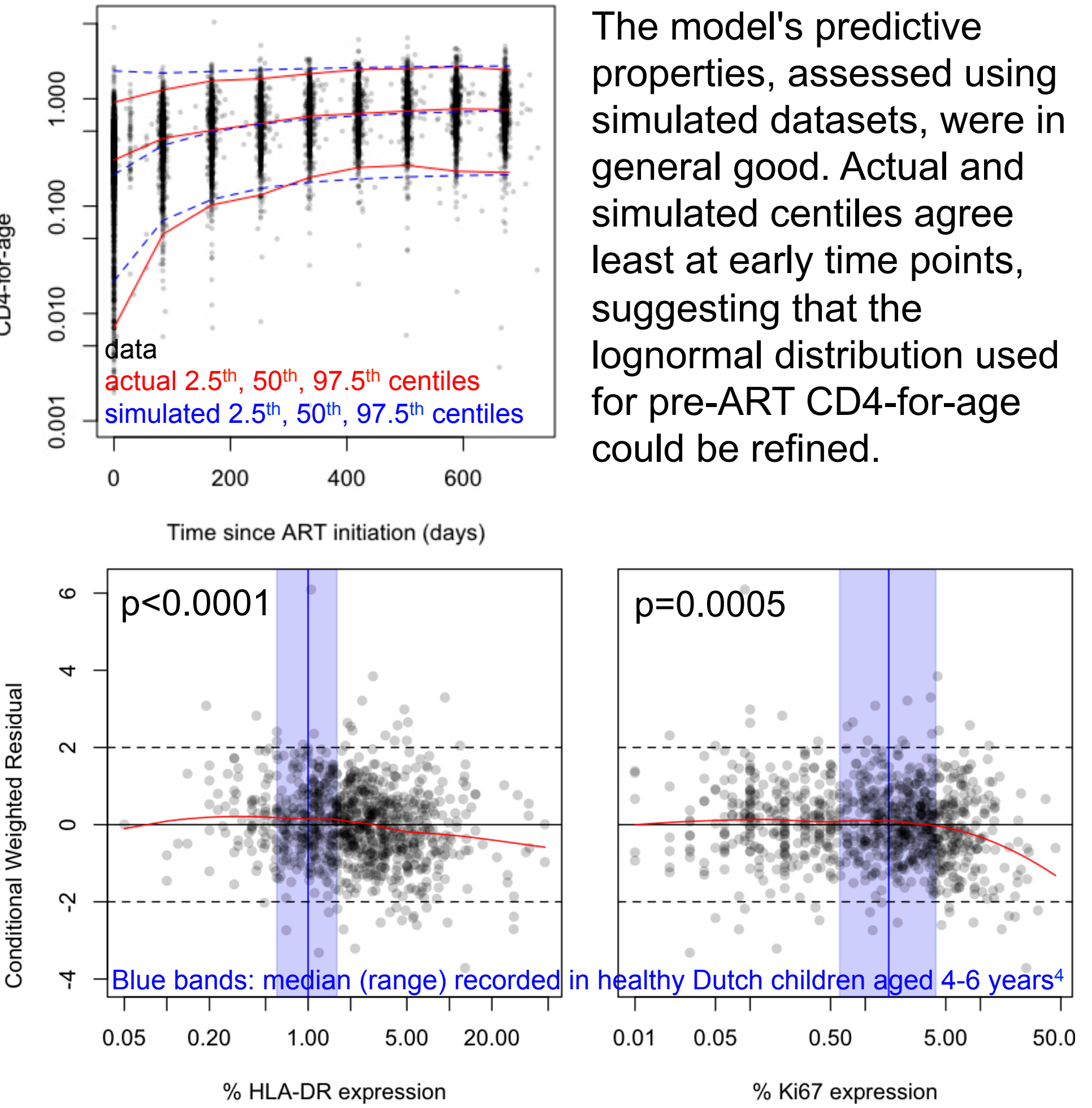
**Fitted (fixed and random effects)**

- $a_0$  (activation to divide)
- $\delta_0$  (resting cell death)
- $\theta$  (thymic production)
- $T_0$  (pre-ART CD4-for-age)

## Model fit and residuals



Diagnostic plots illustrated the model's good fit to the data. The "tail" of poorly-predicted low CD4s-for-age could represent children with especially low CD4 counts due to pathological T-cell dynamics poorly described by the model.



The model's predictive properties, assessed using simulated datasets, were in general good. Actual and simulated centiles agree least at early time points, suggesting that the lognormal distribution used for pre-ART CD4-for-age could be refined.

Blue bands: median (range) recorded in healthy Dutch children aged 4-6 years<sup>4</sup>

The model was a poorer fit where higher activation (HLA-DR) and division (Ki67) markers had been recorded, suggesting that qualitatively different population dynamics may be at work in patients with significant bystander activation of T-cells.

## Population predictions

- Two sets of dynamics are apparent: fast redistribution from the dividing to the resting pool, followed by slower transfer with recovery of cell numbers.
- Death rates in both compartments grow as the compartment size recovers.
- Activation rate falls as resting cell numbers increase.
- Thymic production is faster than T-cell production by peripheral division throughout.
- More cells are lost from the resting than the dividing pool because of its greater size.
- The number of cells lost by death from the dividing pool is low at all times, but increases slightly as the dividing pool grows with recovery
- Recovery is mainly a result of growth of the resting population because of its much larger size, but the dividing pool plays a crucial role - illustrated by the falling proportion of cells which are in division.
- In the long term, around 0.07% of cells are in division.

## Individual predictions

- The random effects in the model successfully capture between-child differences in CD4-for-age recovery trajectories.
- The model is appropriate for children with a range of ages and pre-ART CD4 counts.

## Population parameters

Fixed-effects parameters agreed well with literature values:

| Parameter                                              | Estimate (std error)             | Literature value    |
|--------------------------------------------------------|----------------------------------|---------------------|
| $a_0$ (activation to divide; day <sup>-1</sup> )       | $(3.01 \pm 0.11) \times 10^{-3}$ | 0.002 <sup>4</sup>  |
| $\delta_0$ (resting cell death; day <sup>-1</sup> )    | $(1.59 \pm 0.15) \times 10^{-3}$ | ~0.001 <sup>5</sup> |
| $\theta$ (thymic production; cells day <sup>-1</sup> ) | $(1.67 \pm 0.67) \times 10^{-3}$ | ~0.001 <sup>6</sup> |
| $T_0$ (pre-ART CD4-for-age; cells)                     | $0.203 \pm 0.007$                | 0.2 <sup>7</sup>    |

## Individual parameters

Older children had faster cell activation, increased death of resting cells and poorer thymic activity.

Children with poor recovery had low thymic output, faster stimulation of T-cells to divide and increased death of resting cells. All three processes are therefore candidate causes for low long-term CD4-for-age.

Ki67 expression (a marker of cell division) at ART initiation was higher in children with faster activation to divide and faster death of resting cells. It also predicted low pre-ART CD4-for-age, perhaps because children with low CD4 counts compensate with increased homeostatic proliferation.

## Conclusions

1. A homeostatic model of T-cell dynamics can be used to understand CD4 T-cell dynamics and recovery in HIV-infected children starting ART.
2. Faster T-cell death, faster activation to divide and lower thymic output are all candidate causes for incomplete T-cell reconstitution in children.
3. Children starting ART at older ages have higher thymic output, relative to expected level in a healthy child.
4. We found correlations between random effects and markers of T-cell activation and division, suggesting that between-child differences in recovery are related to altered T-cell homeostasis.

We thank the children, carers and staff from all the centres participating in the ARROW trial, and the ARROW Trial Steering Committee for access to data. Drugs were provided by ViiV healthcare/GlaxoSmithKline.

1. Yates A et al. *PLoS Medicine* **4** (2007)
2. ARROW Trial Team. *Lancet* **381** (2013)
3. Huenecke S et al. *Eur J Haematol* **80** (2008)
4. Ribeiro R et al. *PNAS* **99** (2002)
5. de Boer R et al. *J R Soc Inter* **9** (2012)
6. Bains I et al. *Blood* **113** (2009)
7. Picat M-Q et al. (under review)