To the Editor—We were interested to read the recent article by Li and colleagues [1] in which they consider CD4+ T-cell reconstitution in human immuno-deficiency virus (HIV)-infected adults who are starting antiretroviral therapy (ART). They report an association...
Figure 1. A, Schematic of the mathematical model (1) used to fit CD4+ T-cell trajectories. Initial restoration slope is given by the ratio $B/\tau$, where $B$ is the total long-term improvement in CD4-for-age, and $\tau$ is the time taken for a proportion $1 - 1/e \approx 0.63$ of this improvement to occur. B and C, Initial restoration slope may be increased (in these examples, doubled) by either larger $B$ (doubled to $2B$ in panel B) or smaller $\tau$ (halved to $\tau/2$ in panel C). D–F, Individual parameter values from a mixed-effects fit of log[(CD4+ T-cell count)/(expected count in healthy child of the same age)] to the nonlinear function in model (1). At the time of antiretroviral therapy initiation, the 122 children studied (of whom 46% were boys) had a median age of 4.88 years (interquartile range [IQR], 2.11–9.31 years), a median CD4+ T-cell count of 492 cells/μL (IQR, 163–740 cells/μL), a median CD4-for-age of −1.39 (IQR, −2.00 to −0.83), and coexpression of CD45RA and CD31 on a median 36% of CD4+ T cells (IQR, 20%–50% of CD4+ T cells). Abbreviation: CD31%, percentage of CD4+ T cells coexpressing CD45RA and CD31.
between faster initial recovery of the CD4+ T-cell count and higher percentage of CD31+ T cells, often described as recent thymic emigrants. On this basis, they suggest that thymic exhaustion may underlie poor long-term recovery of the CD4+ T-cell count. We conducted a similar analysis in children and found the opposite effect: children with a high CD31+ T-cell percentage showed slower initial recovery of the CD4+ T-cell count. The higher and more variable thymic output among children [2] may be responsible for this contrast.

In the model of CD4+ T-cell count reconstitution presented by Li et al [1], (where \( t \) is time since ART initiation), the initial restoration slope is given by the ratio \( B/r \) (Figure 1A). A steeper restoration slope (corresponding to a faster initial reconstitution) can therefore be the result of either a larger \( B \) (ie, greater long-term improvement in CD4+ T-cell count from pre-ART levels; Figure 1B) or a reduced \( r \) (ie, faster proportional rate of CD4+ T-cell recovery; Figure 1C). In a simple model of T-cell homeostasis [3], the exponent \( r \) quantifies only density-dependent processes such as peripheral expansion and T-cell death [4], whereas \( B \) depends also on thymic output, as well as on direct effects of viral load and long-term damage to T-cell dynamics and the lymphoid system.

We were interested to learn whether Li and colleagues’ findings in adults also applied to children, given the differences in thymic activity between the groups. We used data from a large study of HIV-infected children who were starting ART in Uganda as part of the ARROW clinical trial. To account for healthy, age-related declines in CD4+ T-cell count, we modeled \( \log(\text{CD4+ T-cell count}/\text{expected CD4+ T-cell count in a healthy child of the same age}) \) (hereafter, “CD4-for-age”) throughout [5]. A total of 122 children had CD4-for-age trajectories that could be fitted individually, using the model presented by Li et al. We used a mixed-effects model based on model (1) for these 122 children. This approach is similar to that of Li and colleagues in that an individual curve is fitted to each patient’s time course, but our model differs insofar as it accounts for the hierarchical structure of the data. Statistical analysis was performed using R [6] and the nlme package [7]. Following the example presented by Li et al, we plotted the CD31+ T-cell percentage against the initial restoration slope and found an opposite association in children from the ARROW trial, compared with that reported for adults by Li and colleagues; whereas the CD4+ T-cell count recovery in adults with a higher baseline CD31+ T-cell percentage had a faster initial slope \( (r = 0.843; P < .001) \) [1], the CD4+ T-cell count recovery in children with a high baseline CD31+ T-cell percentage had a slower initial slope \( (r = -0.47; P < .0001) \; \text{Figure 1D}. \)

To better understand this contrast between adults and children, we examined separately the correlations between CD31+ T-cell percentage and the parameters \( B \) and \( r \). We found a strong negative correlation between \( B \) and CD31+ T-cell percentage \( (r = -0.48; P < .0001) \; \text{Figure 1E}. \). Because there is also a strong negative correlation between \( A \) (pre-ART CD4-for-age) and \( B \) \( (r = -0.85; P < .0001) \) (data not shown), we suggest that CD31+ T-cell percentage in children indicates high thymic activity, which generates a high pre-ART CD4-for-age and needs only a small increase to reach its long-term level. We found no correlation between CD31+ T-cell percentage and \( \tau \) \( (r = -0.043; P = .64) \; \text{Figure 1F}. \). In individuals for whom thymic output is the main factor affecting CD31+ T-cell percentage, this finding agrees with our assertion that \( \tau \) is not affected by thymic output. We suggest that, in adults, a population in which thymic output is lower and less variable, CD31+ T-cell percentage may be more dependent on peripheral T-cell division and death than on thymic activity and, therefore, may have a weaker correlation with \( B \). HIV-induced abnormalities in the density-dependent processes may then have a stronger effect on the association between CD31+ T-cell percentage and initial restoration slope. Thus, the shift away from thymic toward peripheral T-cell production may lead to the opposing correlations being observed. A more detailed analysis of the flow cytometry data might shed light on the specific mechanisms involved.

Given the distinct mechanistic meanings of the parameters \( B \) and \( \tau \) in model (1), we would be very interested to see figures analogous to Figure 1D–F for adult patients, to evaluate the hypothesis described above. If the observation by Li and colleagues is found to stem predominantly from a lower \( \tau \)—that is, from altered peripheral expansion and death—in individuals with a high CD31+ T-cell percentage, it would be necessary to reconsider their conclusion that incomplete recovery of CD4+ T-cell count is a result of thymic exhaustion.

**Notes**

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