Exploratory Analysis of Age on Longitudinal CD4+ T-Cell Reconstitution in HIV-Infected Patients Using a Semi-mechanistic Model

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Objectives: To interrogate the effect of chronological age on CD4+ T-cell (CD4+) recovery in HIV-suppressed subjects under antiretroviral therapy, considering thymus output, naïve T-cell death and immune activation.

Methods: Model parameters were obtained from the literature. CD4+ data from two published studies were digitized for parameter optimization and model validation: 978 subjects (median age: 36 years) followed for 144 weeks1 and 95 subjects (median age: 41 years) followed for up to 15 years2. Model development was conducted in Berkeley Madonna and Phoenix WinNonlin 6.4, with simulation and data visualization in R. The effects of age were explored on three CD4+ dynamic parameters, and CD4+ count plateaus from 20 to 80 years for each scenario were calculated.

Results: Total CD4+ were split into two compartments, naïve CD4+ and memory CD4+ cells. Generation of naïve CD4+ was zero-order. The conversion between and death rate of both cell populations were first-order, and proliferation was capacity-limited. Rate constant of naïve CD4+ conversion and memory cells death were optimized using reference 1, with other parameters fixed to literature values (converted into years). Simulations from the final model well correlated with observed data ($R^2 = 0.9517$). Age effects were described using exponential models for thymus output and naïve CD4+ death rate, and linear for immune activation. Decreased thymus output with age drove the change of CD4+ plateau. Increased activation and extended naïve CD4+ with age were shown to play minimal roles.

Conclusions: A semi-mechanistic model to describe longitudinal CD4+ reconstitution in mid-aged HIV-suppressed subjects was established. Based on simulation, age on thymus output has the largest effect on plateau CD4+ counts, revealing the decreased thymus output with aging is the major factor of impaired CD4+ reconstitution. This study supports the negative effect of aging on CD4+ T-cell recovery in HIV-suppressed patients.

References:
2. X. Zhang et al, HIV Clinical Trials, 14(2) 61-7, 2013