

Nonparametric local linear mixed-effects modeling for the time profile of rate of change and the correlation between the rates of change of two markers.

The longitudinal curves for variable $y_i(t_{ij})$ are

$$y_{ij} = f(t_{ij}) + u_i(t_{ij}) + e_{ij},$$

for subject i at observation time t_{ij} , where $f(t_{ij})$ is the population trend, $f(t_{ij}) + u_i(t_{ij})$ is the subject specific trend at subject i with $u_i(t_{ij})$ the random deviation of subject i from the population trend, e_{ij} is the random error. Since we do not know the parametric forms of function f or u_i , at each time t , we locally approximate them via linear approximations

$$f(t_{ij}) \approx f(t) + f'(t)(t_{ij}-t);$$

$$u_i(t_{ij}) \approx u_i(t) + u_i'(t)(t_{ij}-t);$$

where $f'(t)$ and $u_i'(t)$ are the derivative functions and represent the growth rate. The longitudinal curves around time t are locally approximated by straight lines via the local linear mixed-effects model,

$$Y_{ij} = \alpha_0 + \alpha_1(t_{ij} - t) + a_{0i} + a_{1i}(t_{ij} - t) + e_{ij}.$$

Estimate of α_0 thus gives the estimate of $f(t)$, α_1 the estimate of $f'(t)$, a_{0i} the estimate of $u_i(t)$ and a_{1i} the estimate of $u_i'(t)$. Thus, the population rate of change at t is estimated by α_1 , and that within subject i by $\alpha_1 + a_{1i}$. Repeating the above local linear approximation for t over the observation period, we obtain the time profile of the rates of change for all subjects. Details about the nonparametric local linear mixed-effects model and its estimation are in reference 24.

If there are two variables $y_{1, ij}$ and $y_{2, ij}$ and we are interested in how the rate of change in one variable is associated with the rate of change in the other, we can simultaneously apply the nonparametric local linear mixed-effects modeling to both variables and evaluate the correlation.

At each time t , we jointly fit the models

$$y_{1, ij} = \alpha_0 + \alpha_1(t_{ij} - t) + a_{0i} + a_{1i}(t_{ij} - t) + e_{1,ij}$$

$$y_{2, ij} = \beta_0 + \beta_1(t_{ij} - t) + b_{0i} + b_{1i}(t_{ij} - t) + e_{2,ij}$$

The correlation between the rates of change of the two variables at time t is estimated by the correlation between $\alpha_1 + a_{1i}$ and $\beta_1 + b_{1i}$. Repeating the above joint modeling and correlation estimation over different time, we obtain the time profile for the correlation between the rates of change of two markers. Further details about correlation estimation from joint models are in references 24 and 25 of the main manuscript.

Figure S1. Correlation of serum IL-7 levels with age at M0 in the HC group, HIV+ (n=43), and subgroup of HIV+ who initiated ART (n=30)

The association between age and serum IL-7 levels in HIV+ at M0 is shown in HC (A), all HIV+ patients (B), and those HIV+ patients who later initiated ART (C).

Figure S2. Numbers of cycling CD4+, CD8+ and CD3+ T-cell subsets

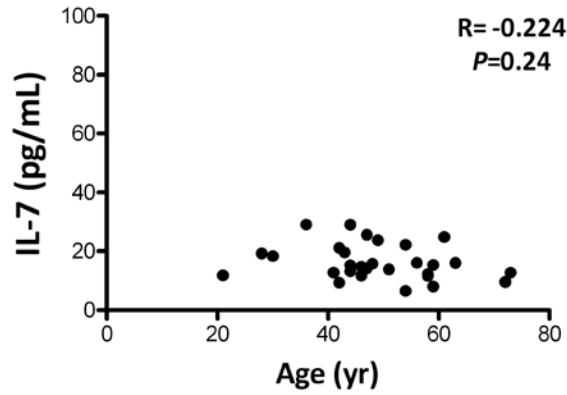
The total number of cycling CD4+ (A), CD8+ (B), CD3+ (C), CD4+CD127+ (D), CD8+CD127+ (E), CD3+CD127+ (F), CD4+CD127- (G), CD8+CD127- (H), CD3+CD127- (I) T cells/ μ L is shown in the group of HIV+ patients (n=30) who were followed longitudinally from M0 to M24. Circles (black) represent median values and bars indicate IQR. Grey dashed lines indicate healthy control (HC) median values. P values (grey) at the top of the graphs represent unpaired comparison between HC and HIV+ at each time point and P values (black) above the IQR bars indicate paired comparison of HIV+ patients at each time point during the therapy to the pre-therapy level (M0). Significant P values <0.01 are reported, one star (*) indicates $0.01 > P > 0.001$, two stars (**) indicate $0.001 \geq P \geq 0.0001$, and P values <0.0001 are denoted by three stars (***).

Figure S3. Recovery of CD4⁺ and CD8⁺ memory T cells/ μ L subsets

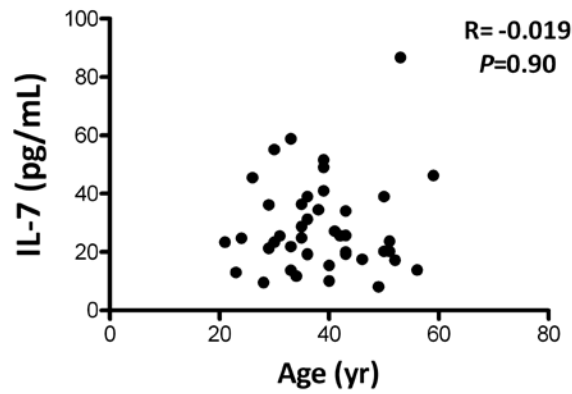
The number of CD4⁺ and CD8⁺ naïve (A&B), central memory (C&D), effector memory (E&F), and effectors (G&H) is shown in the group of HIV⁺ patients (n=30) who were followed longitudinally from M0 to M24. Circles (black) represent median values and bars indicate IQR. Grey dashed lines indicate healthy control (HC) median values. *P* values (grey) at the top of the graphs represent unpaired comparison between HC and HIV⁺ at each time point and *P* values (black) above the IQR bars indicate paired comparison of HIV⁺ patients at each time point during the therapy to the pre-therapy level (M0). Significant *P* values <0.01 are reported, one star (*) indicates 0.01>*P*>0.001, two stars (**) indicate 0.001≥*P*≥0.0001, and *P* values <0.0001 are denoted by three stars (***). Naïve cells were defined as CD27⁺CD45RO⁻, central memory as CD27⁺CD45RO⁺, effector memory as CD27⁻CD45RO⁺, and effectors as CD27⁻CD45RO⁻.

Figure S1

A. Healthy control



B. All HIV+ (n=43)



C. HIV+ with subsequent ART (n=30)

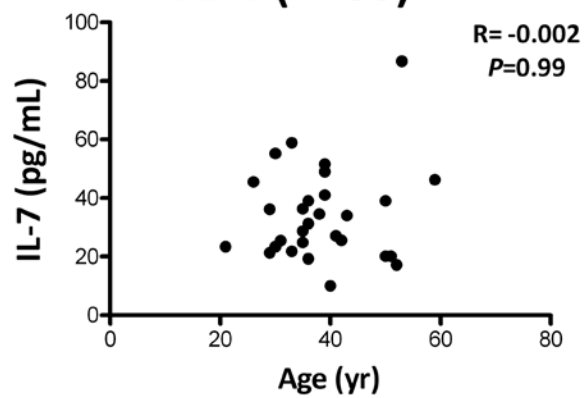


Figure S2

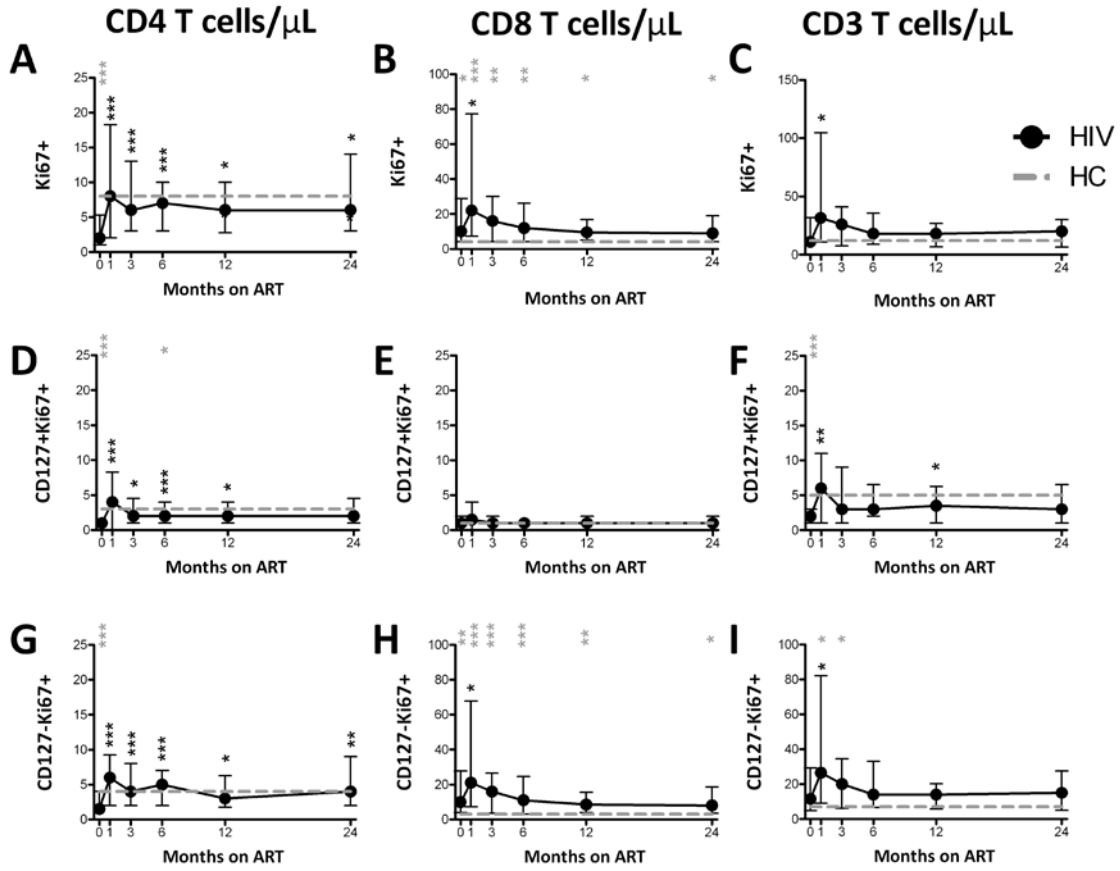


Figure S3

