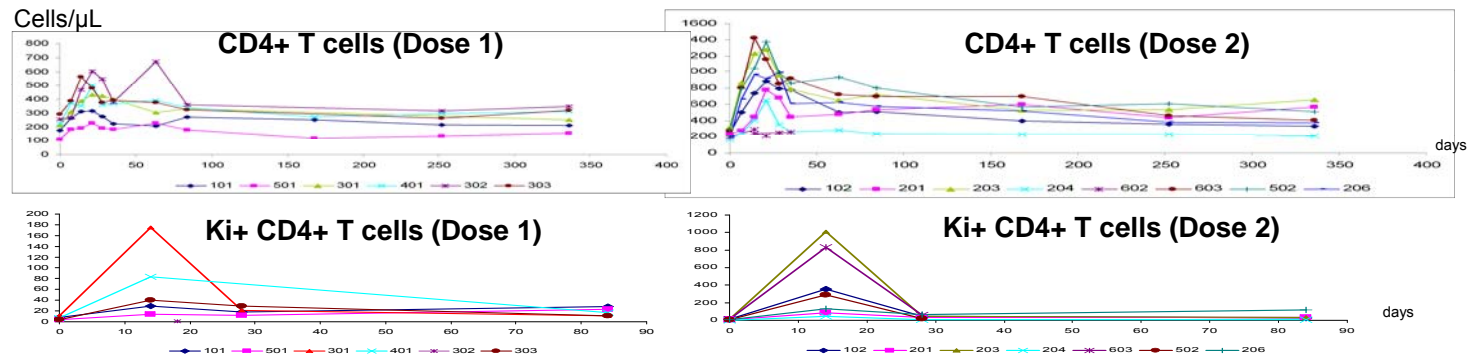


In vivo quantification of the effect of IL-7 on proliferation, survival and production of CD4+T cells: mathematical analysis of one phase I study in HIV-1 infected patients

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Background IL-7 is known to increase intra and extra-thymic proliferation as well as survival of T cells. A phase I study has shown that IL-7 administration in HIV-infected patients leads to an increase of T cells (Y. Levy et al, JCI 2009). However, the relative contribution of production, proliferation and survival to this increase has not been quantified.

Data 13 ART-treated HIV-infected patients whose CD4+ cell counts were between 100 and 400 cells/ μ L and plasma HIV RNA levels were less than 50 copies/ml. Patients received a total of 8 subcutaneous injections of 2 different doses of recombinant human IL-7 (rhIL-7; 3 or 10 μ g/kg, dose 1 and 2, respectively) 3 times/week over a 16-day period. 11 repeated measurements of total CD4+ and Ki67+ positive T cells among CD4+ T cells up to 48 weeks.



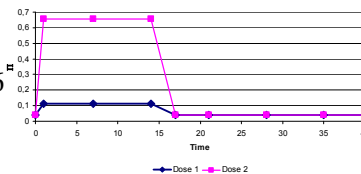
Model The model included two compartments for the CD4+ T Ki 67- (quiescent) cells (Q) and the CD4+ T Ki 67+ (proliferating) cells (P). The effect of IL-7 was modeled by allowing a change of proliferation (π), loss (μ) and/or constant input (λ) of CD4+ T Ki 67- cells (Q) during IL-7 therapy or after. Parameters (μ and λ) were allowed to vary between subjects through random effects. Prior distribution was assumed for ρ . Estimations were performed using a Marquardt algorithm to maximize likelihood (Guedj et al.). Models were compared according to AIC.

$$\frac{dQ}{dt} = \lambda + 2\rho P - \mu_q Q - \pi Q$$

$$\frac{dP}{dt} = \pi Q - \rho P - \mu_p P$$

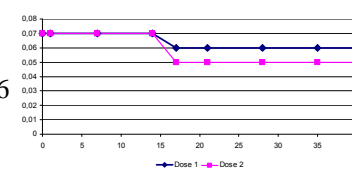
Change in proliferation rate

$$\begin{cases} \tilde{\pi} = \pi_0 & \text{if } t = 0 \text{ or } t > 16 \\ \tilde{\pi} = \pi_1 + \beta \text{ dose}_1 & \text{if } t > 0 \text{ and } t \leq 16 \end{cases}$$



Change in loss rate

$$\begin{cases} \mu_q = \mu_{q0} & \text{if } t \leq 16 \\ \mu_q = \mu_{q1} + \beta \text{ dose}_1 & \text{if } t > 16 \end{cases}$$



Results

Parameter	Estimate	95% CI	Before & after IL7	Before & after IL7	Before IL7	Before IL7	Before IL7	Before IL7
Proliferation & loss	9.3	0.92	Before & after IL7	.04	Before IL7	.07	.18	131
			After IL7 arm 1	.11	After IL7 arm 1	.06	.06	
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			After IL7 grp 1	.11	After IL7 grp 1	.06	.06	
			After IL7 grp 2	.21	After IL7 grp 2	.05	.05	

Conclusion

The quantification of the *in vivo* effect of IL-7 using a mathematical model showed a significant effect on cell loss in addition to peripheral proliferation. The fit of this model was better than one including a change of proliferation only (AIC 131 vs. 151). The increase of peripheral proliferation and the improvement of cell survival seem to be the main mechanisms explaining the increase in CD4+ count in these patients.

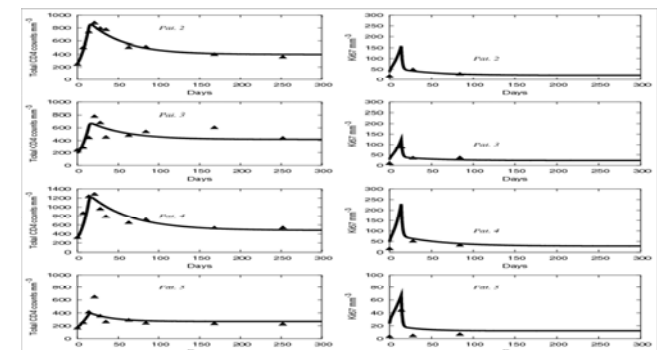


Figure. Fits of CD4+ and CD4+Ki+ T cells for 4 patients.