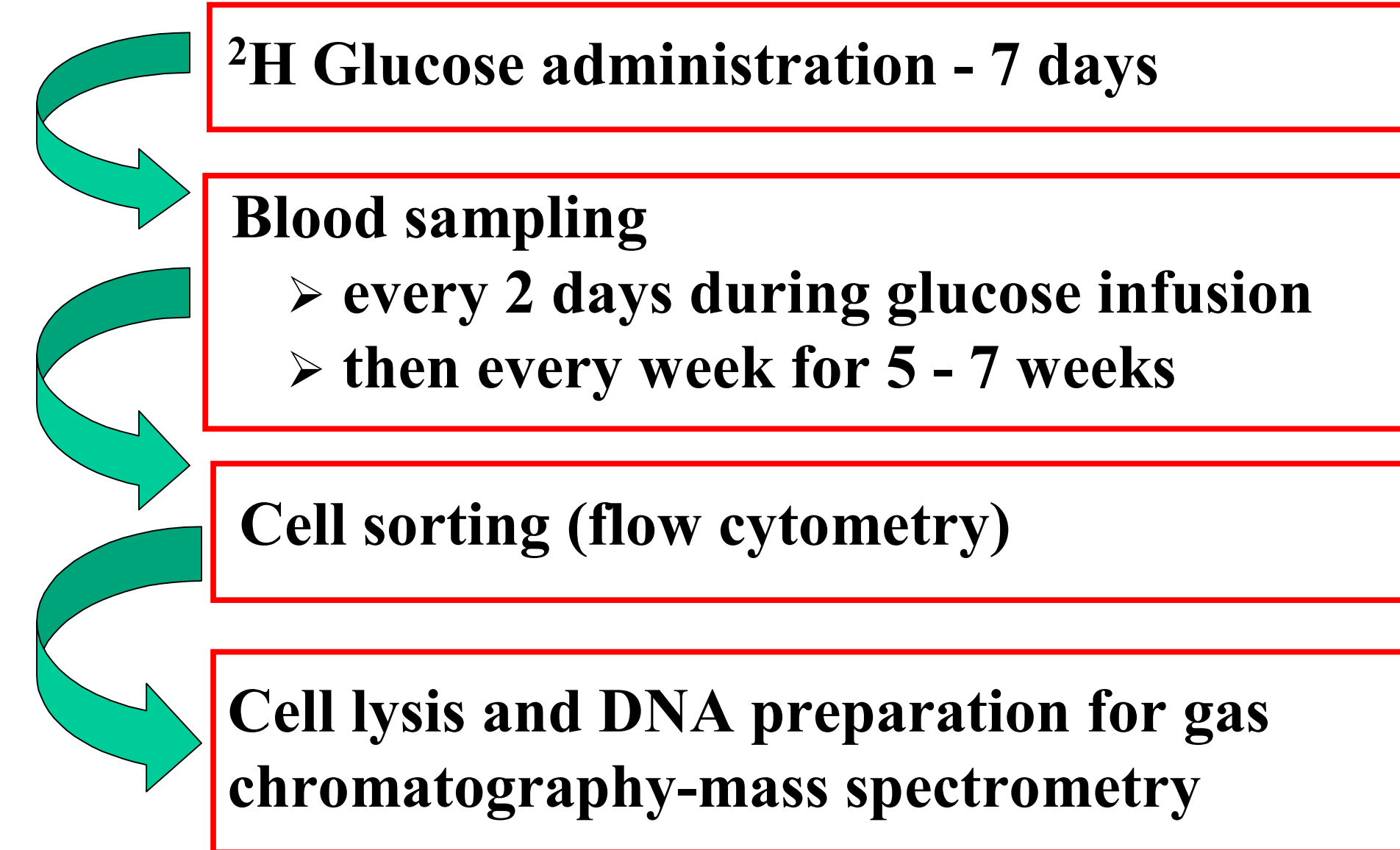




EXPERIMENT

Protocol

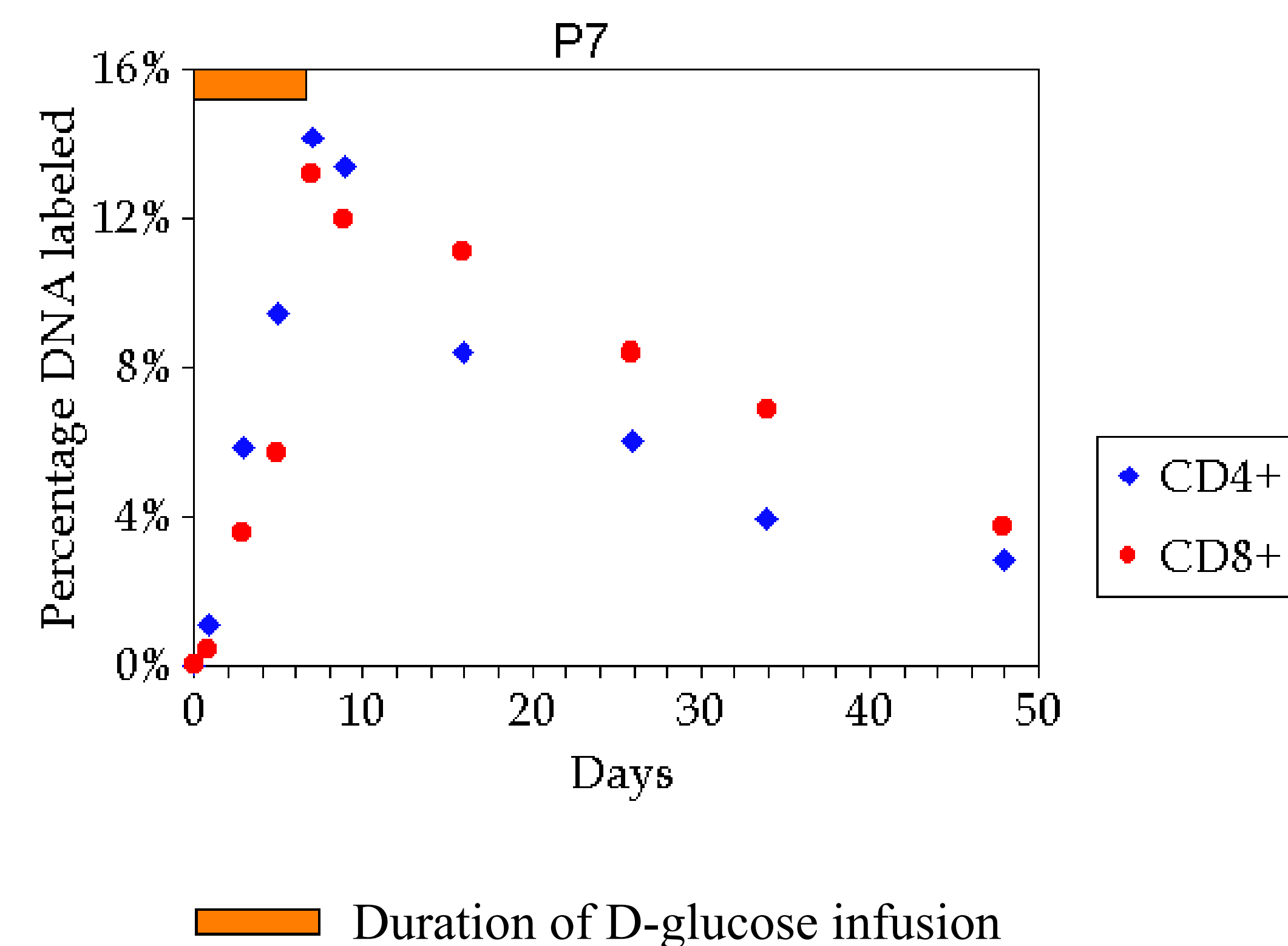


Data

	Controls	Infected
N	4	7
	Mean	
Age (years)	30.0	32.6
CD4+ (μl^{-1})	1076	388
CD8+ (μl^{-1})	603	816
Viral copies (ml^{-1})	–	131,491

From the 7 HIV+, some started treatment and returned	
Short term ART (N=5)	4 drugs for 1 – 2.5 months
Long term ART (N=3)	4 drugs for 8 – 12.5 months

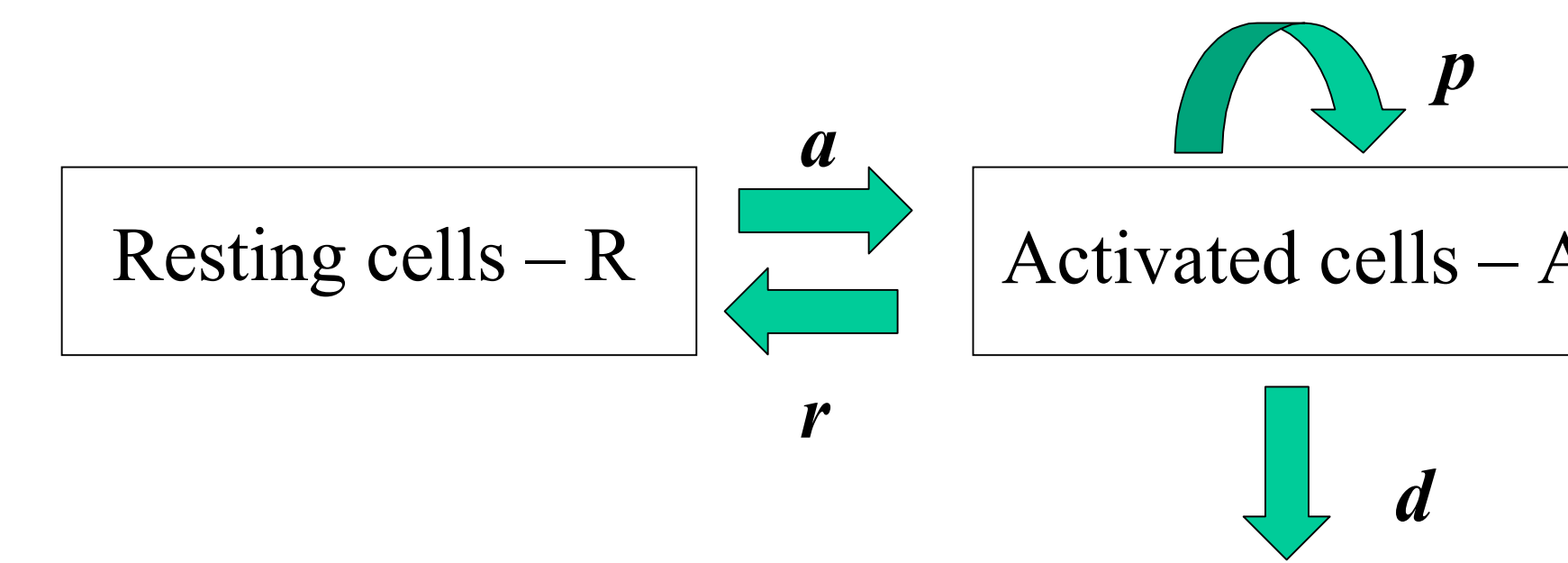
Results



MODEL

Motivation

- ✓ Previous models considered homogeneous populations of T cells, but some of these are resting and can not be labeled.
- ✓ Thus, the source term in those previous models corresponds here to activation from the resting population.
- ✓ This new model allows the study of the dynamics of T-cell activation in HIV-1 infection.

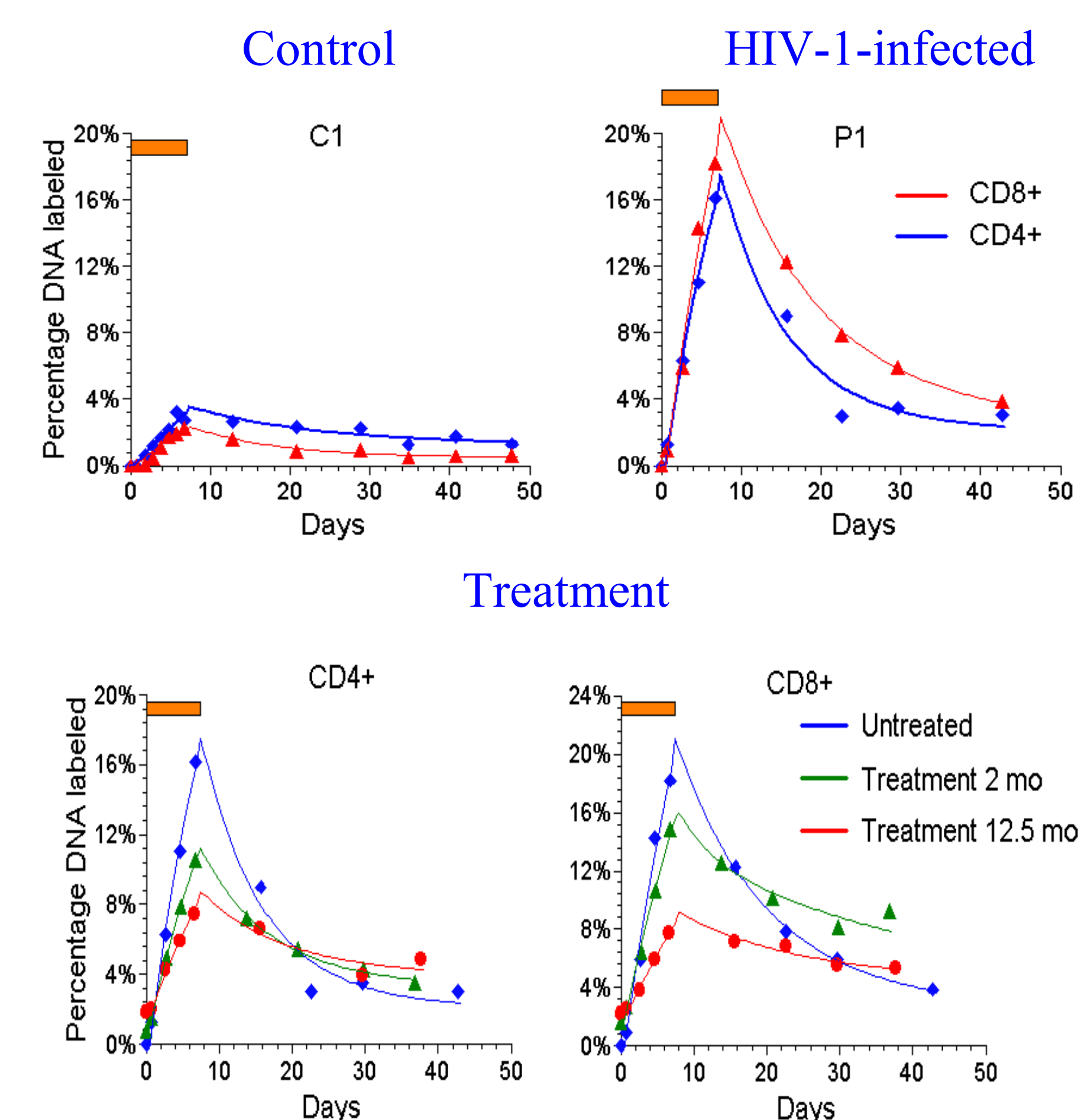


Labeling equations

$$\begin{aligned} \frac{dU_R}{dt} &= -aU_R + rU_A \\ \frac{dL_R}{dt} &= -aL_R + rL_A \\ \frac{dU_A}{dt} &= -(d+r)U_A + aU_R \\ \frac{dL_A}{dt} &= (p-d-r)U_A + nU_A + aL_R \end{aligned}$$

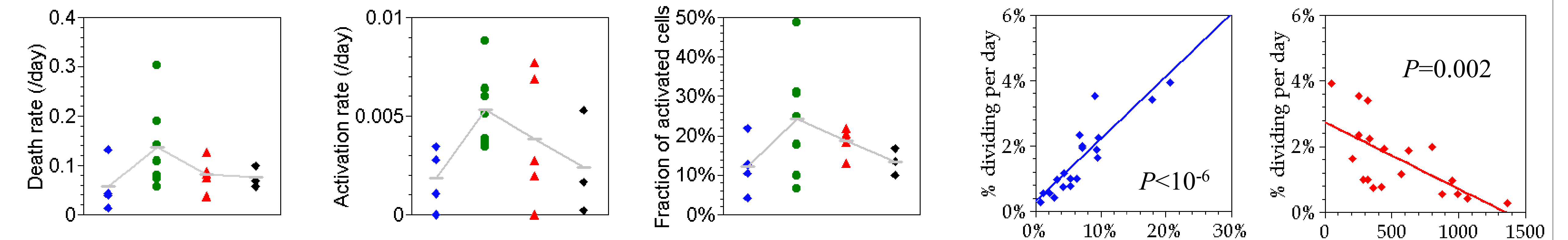
- ✓ Proliferation during this period only changes the amount of labeled DNA (L_A).
- ✓ At steady state (constant T-cell numbers) $p=d$
- ✓ Fraction of activated cells: $f_A = A/(R+A) = a/(a+r)$
- ✓ Average fraction of cells dividing per day: pf_A
- ✓ For the de-labeling period the equations are symmetric, changing U with L.

Data fits

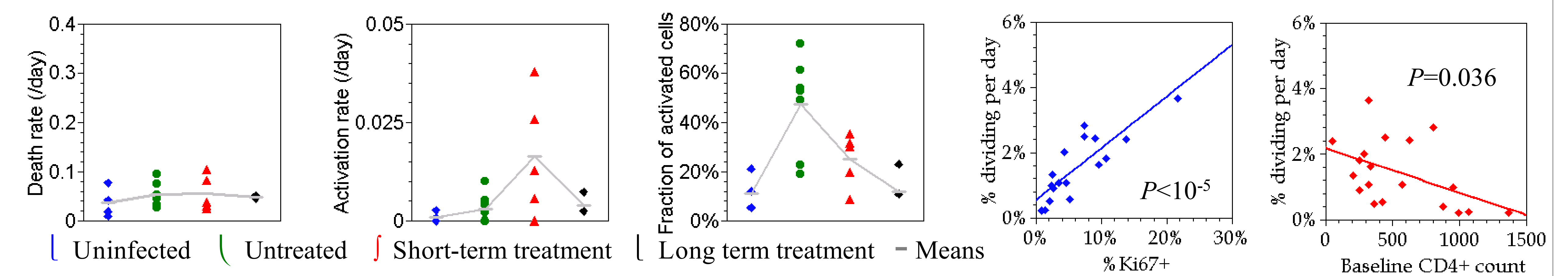


RESULTS

Activated CD4+ T-cells



Activated CD8+ T-cells



- ✓ In the activated cell population, the death rate of CD4+ T cells in HIV-1-infected individuals is increased vs. healthy subjects (medians 0.11/day vs. 0.04/day, $P=0.07$), but in CD8+ T-cells this rate is not statistically different (medians 0.03/day vs. 0.05/day, $P=0.32$).
- ✓ The activation rate is increased for CD4+ T cells of infected patients vs. healthy individuals (medians 0.0051/day vs. 0.0019/day, $P=0.012$), but such an increase is not seen in the CD8+ T-cell population ($P=0.13$).
- ✓ The fraction of CD4+ activated cells is not increased in infected individuals ($P=0.23$), but that of activated CD8+ T-cells is ($P=0.01$).
- ✓ The estimated fraction of dividing T-cells (CD4+ or CD8+) correlates with independent measurements of the percentage of Ki67+ cells, and correlates inversely with baseline CD4+ T-cell count.
- ✓ The fraction of activated CD8+ T-cells is significantly larger than the fraction of activated CD4+ T-cells in infected individuals ($P=0.047$), but not in healthy controls ($P>0.5$).

CONCLUSIONS

- ✓ This new model fits the data, showing that in HIV-1 infection, CD4+ T-cell proliferation, death and activation rates are increased. These rates decrease after short-term HAART, and tend to normalize after long-term HAART.
- ✓ The death rate of activated CD8+ T-cells is not increased in HIV infection, but the fraction of activated cells is. Overall this means that the average death and proliferation rates are also increased in the CD8+ T-cell population of infected individuals.
- ✓ The findings for the death rates of CD4+ vs. CD8+ T-cells are consistent with a virus-induced component (cytopathic or immune mediated) in the death of CD4+ T cells.
- ✓ The fraction of activated CD4+ T-cells is not significantly increased in infected individuals, indicating that activated CD4+ T-cells die too fast to allow any build-up in this fraction, even though they are being activated faster than in uninfected subjects.
- ✓ Our results are compatible with previous estimates of proliferation and death rates of T-lymphocytes in HIV infection (by BrdU and D-glucose), and also with previous estimates of the percentage of activated cells by HLA-DR and CD38 measurements.