Analysis of T-lymphocyte turnover using a new model for D-glucose labeling

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Background

- HIV infects CD4+ T-cells

- CD4 cells help establish the CD8 response

- Understanding dynamics of turnover is crucial

- There is controversy in the field:
  - results; interpretation of experiments

Experimental Protocol

^{2}H Glucose administration - 7 days

Blood sampling

- every 2 days during glucose infusion

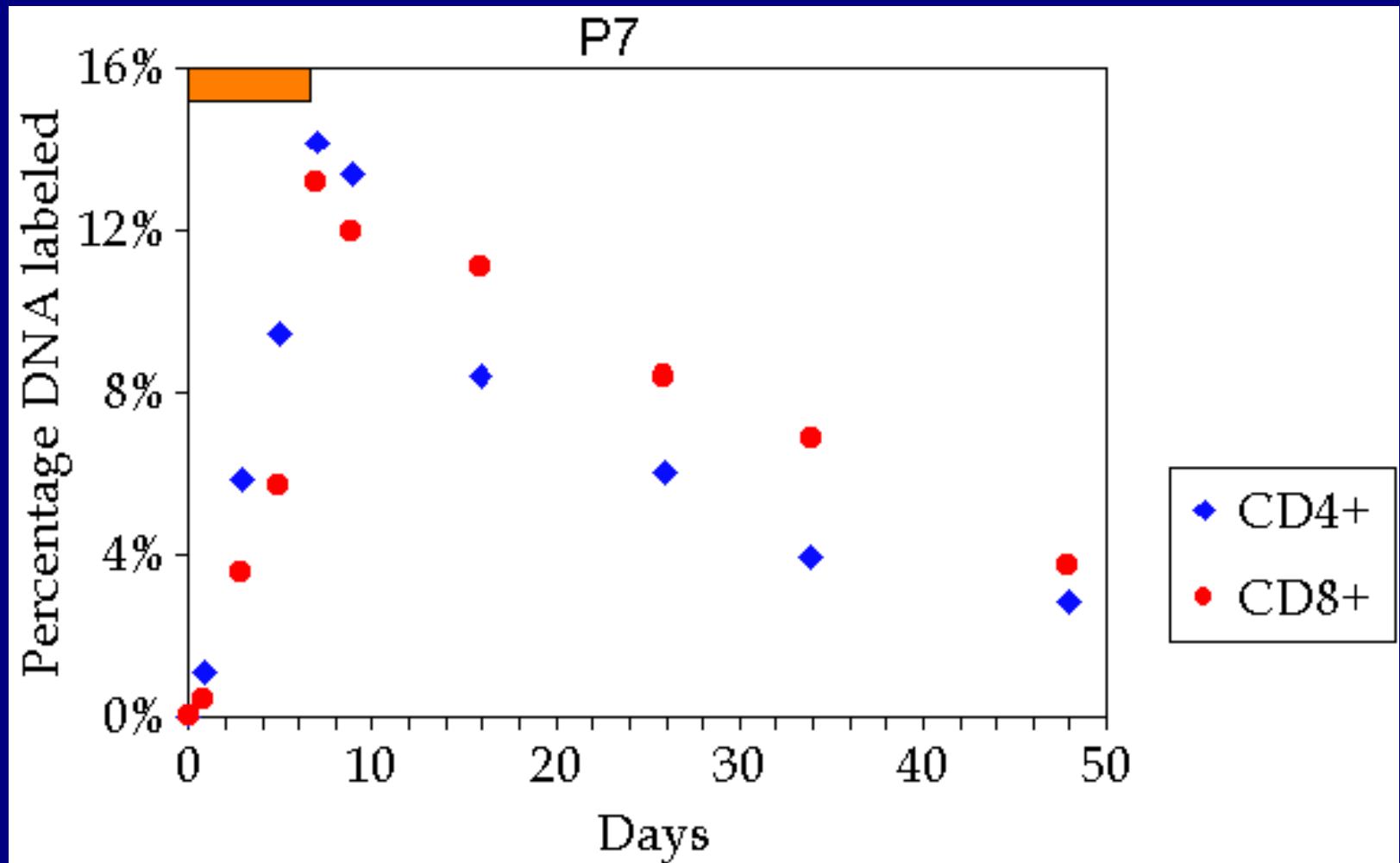- then every week for 5 - 7 weeks

Cell sorting (flow cytometry)

Cell lysis and DNA preparation for gas chromatography-mass spectrometry

Experimental Data

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

Short term ART (N=5)	4 AR for 1 – 2.5 months
Long term ART (N=3)	4 AR for 8 – 12.5 months

Experimental Results

Model I

Labeling of DNA strands

$$U_A \rightarrow U_A + L_A$$

$$L_A \rightarrow L_A + L_A$$

De-labeling of DNA strands

$$U_A \rightarrow U_A + U_A$$

$$L_A \rightarrow L_A + U_A$$
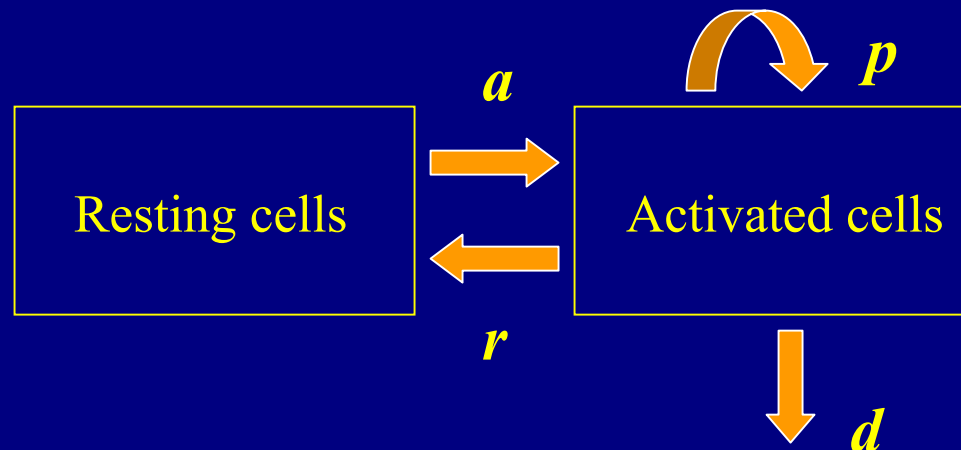
a

p

Resting cells

Activated cells

σ

r

δ

d
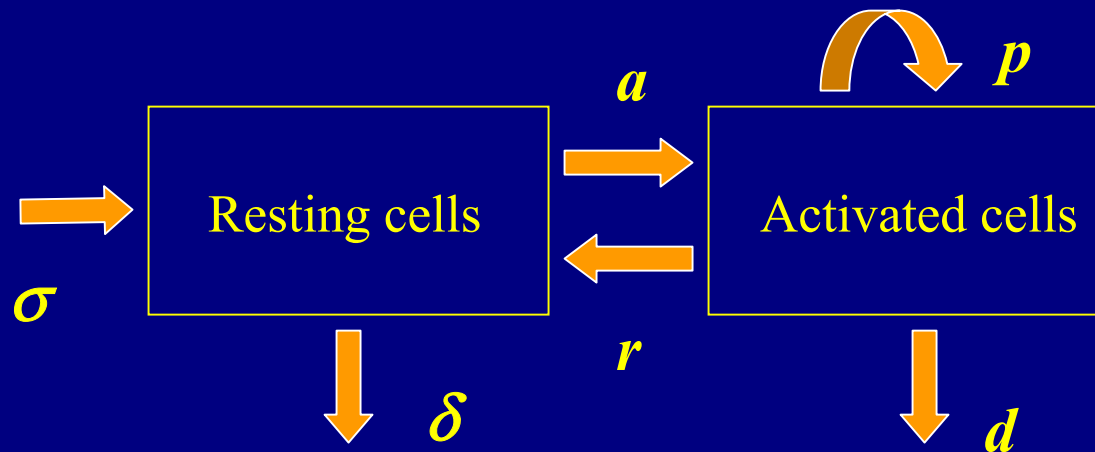
Model II

- In adults thymic source is small: $\sigma = 0$

- Lifespan of resting cells is long: $\delta = 0$
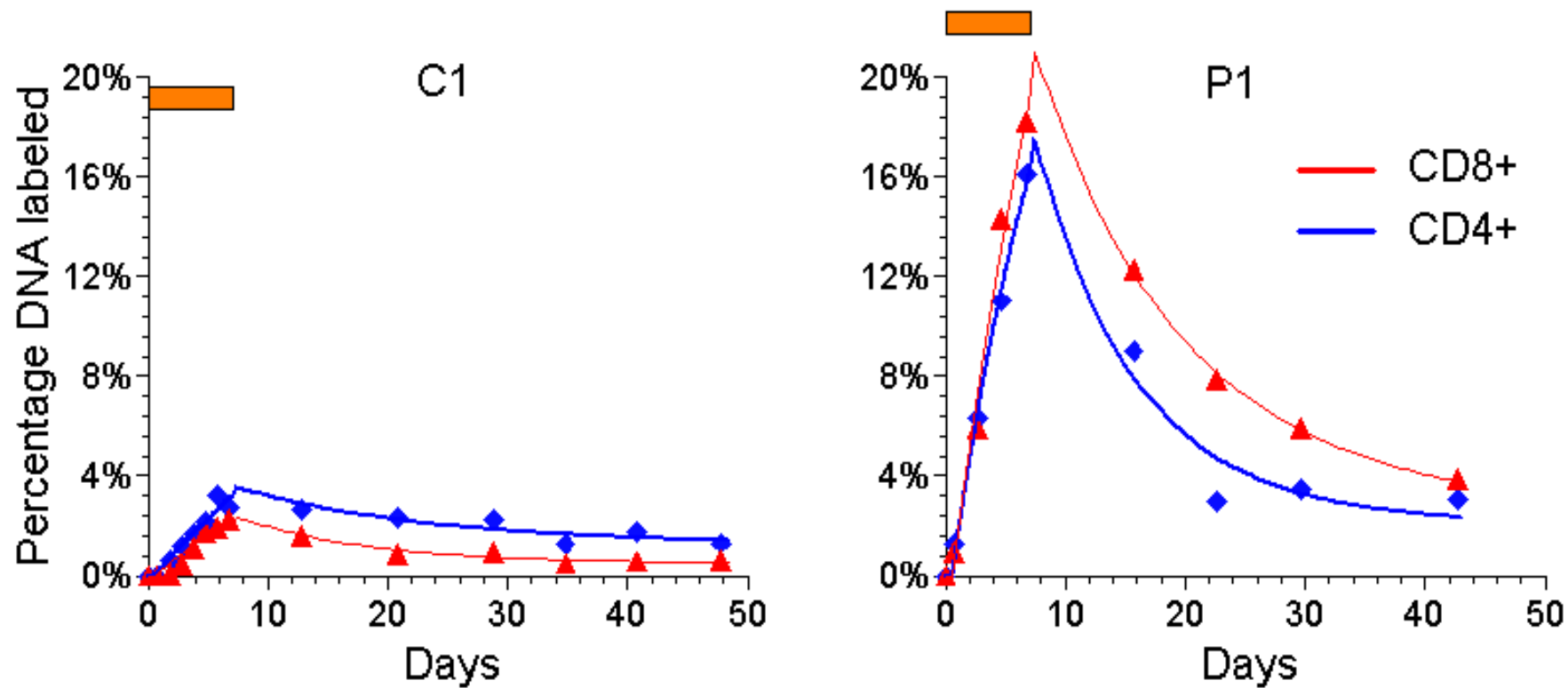
- The fraction of activated cells is $f_A = a/(a+r)$
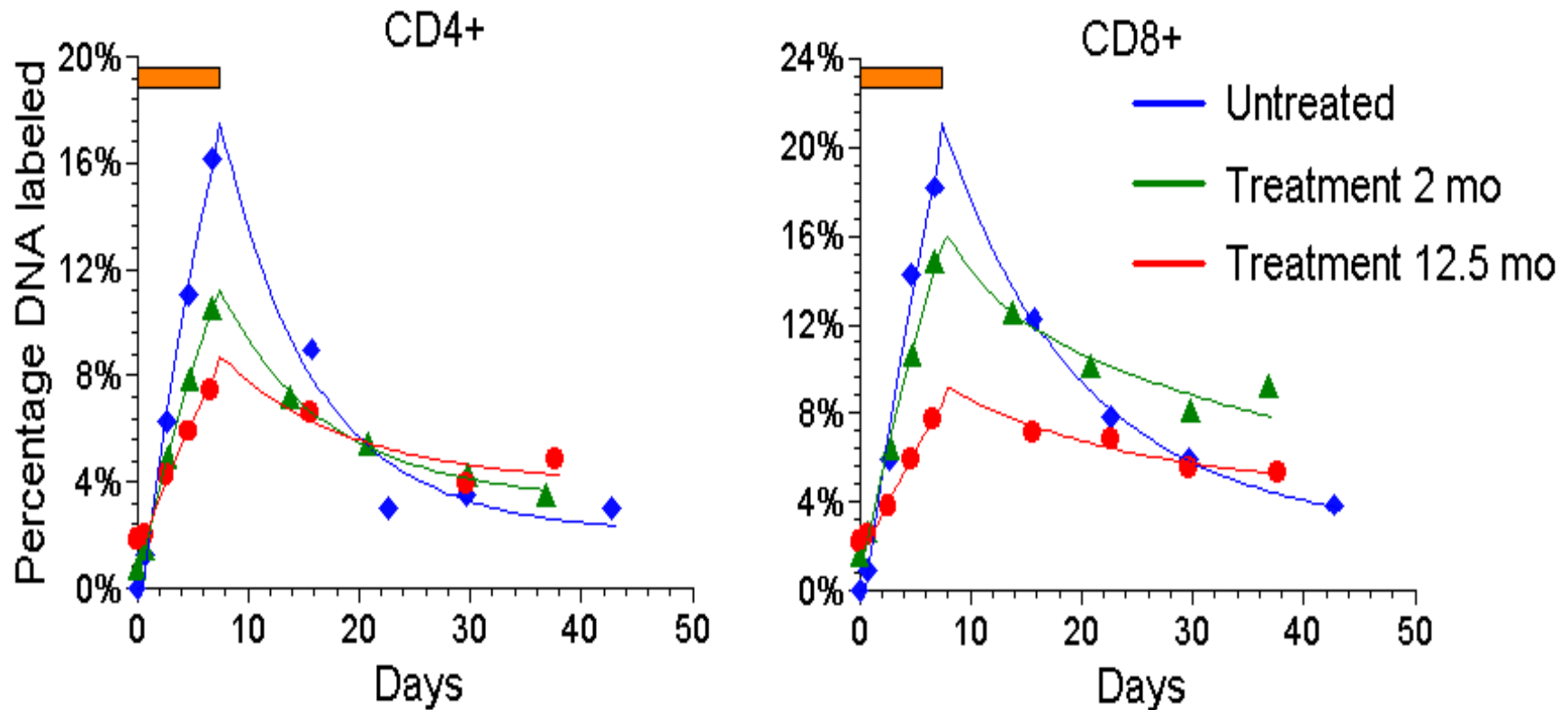
Data Fitting

- Three parameters to fit: d, a and f_A
  - Since at steady state $p=d$

- Non-linear least square method

- Solid line is the theoretical prediction
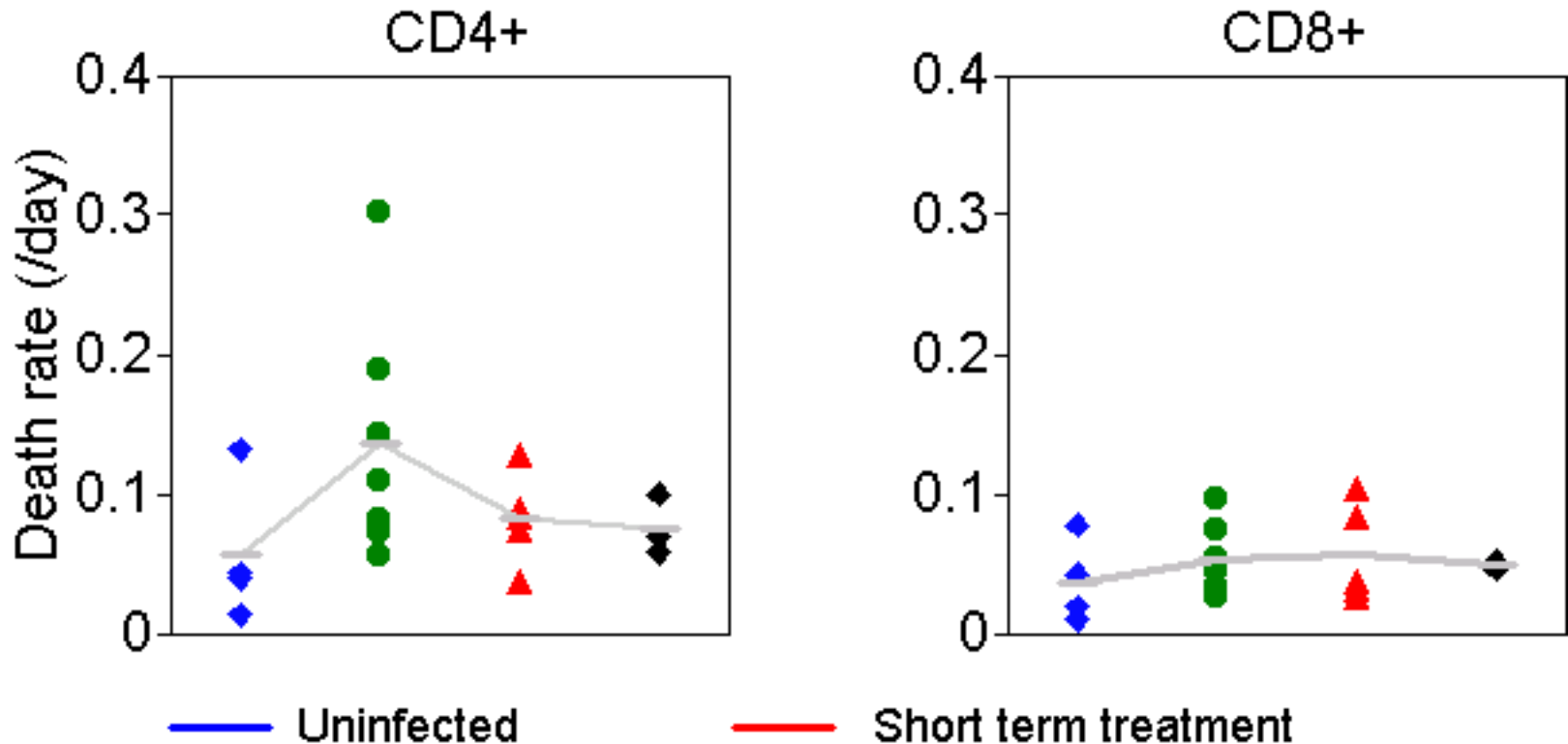
Results: Healthy *vs.* Infected
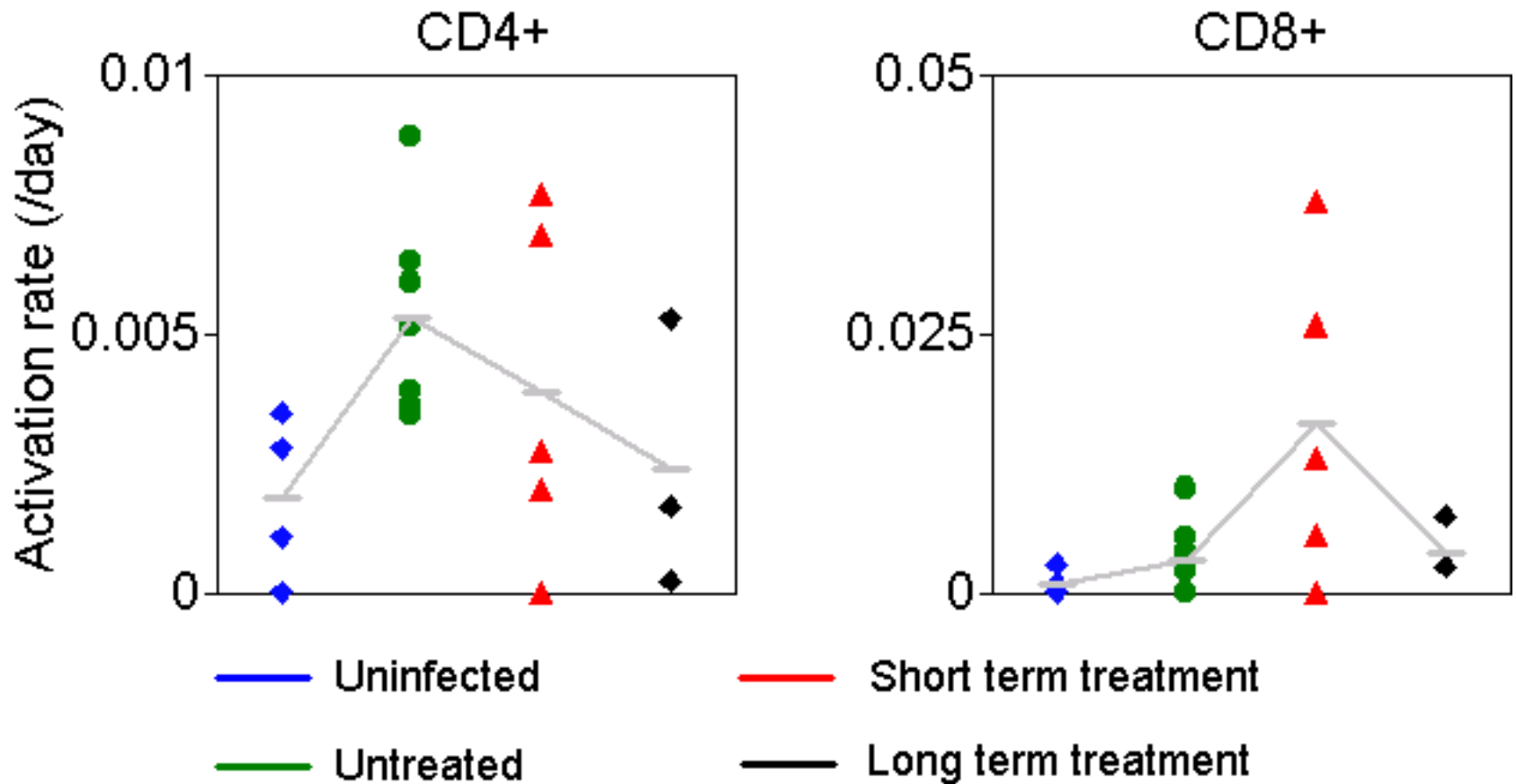
Results: Untreated *vs.* Treated

The model presented is appropriate to fit the data. And the data show the increased turnover in HIV infection.
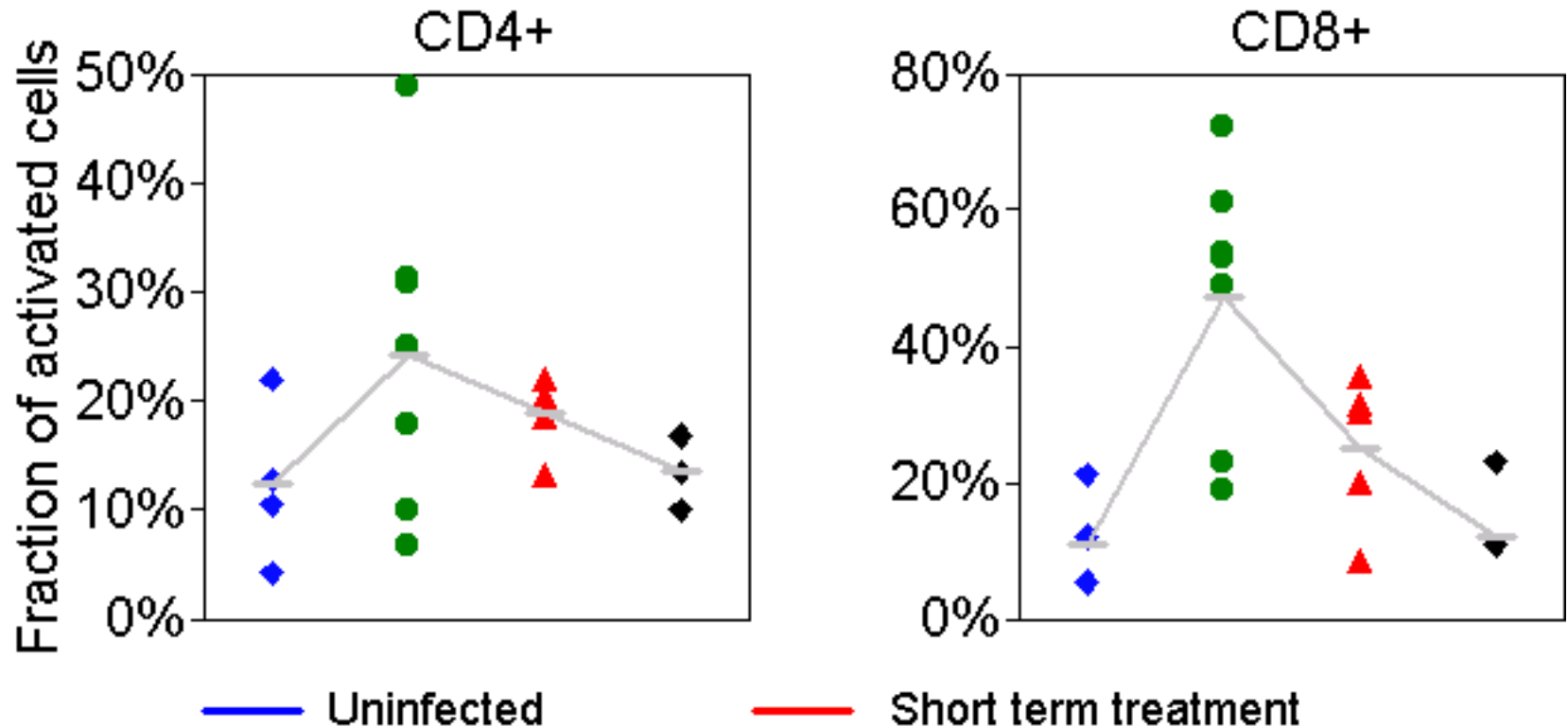
Death Rate of Activated Cells

There is a trend for increased death rate in the CD4+ activated cell population, but no difference in death rates for activated CD8+ cells.

Activation Rate

There is a significant increase in the activation rate of CD4+ cells in HIV infected individuals.
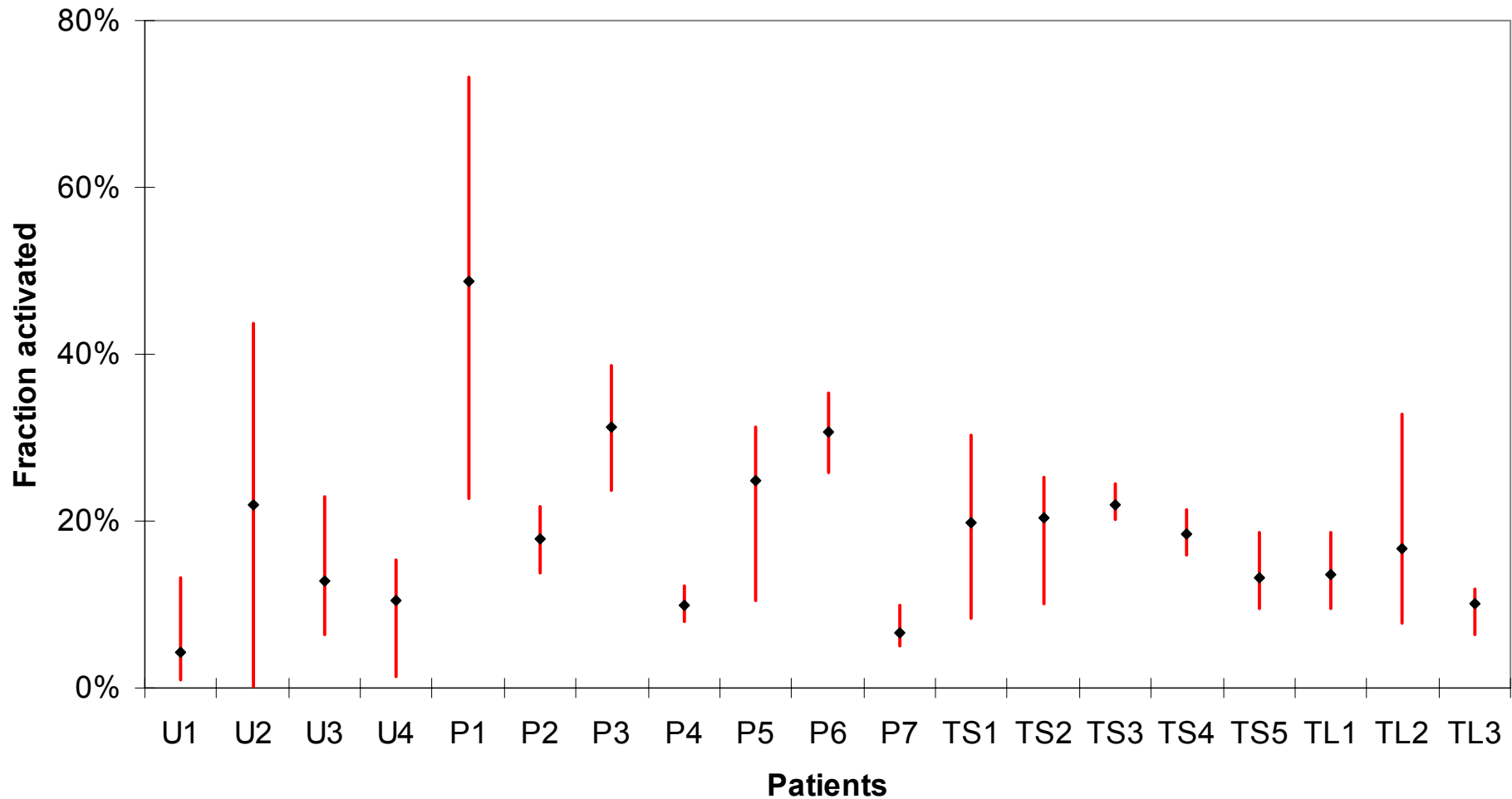
Fraction of Activated Cells

The fraction of activated cells is significantly increased in the CD8+ population of infected individuals, but <u>not</u> in the CD4+ population.

Confidence Intervals for Parameters

CD4+ T-cells (95% CI)

Conclusions I

- Death rate of activated CD4+ T-cells in infected individuals is increased in relation to that of uninfected individuals. Thus, the extra death of CD4+ T-cells may be due to direct killing by HIV.

- The fraction of activated CD4+ T-cells is not increased in infected individuals, but the activation rate is. Thus, it is possible that activated CD4+ die too fast to allow build-up in the fraction of activated cells.

- In CD8+ T-cells the death rate of activated cells is not increased in infected individuals, but the fraction of activated CD8+ is. Thus, overall, the average death rate for the CD8+ T-cell population is also increased.

Conclusions II

- In steady state $p=d$ for activated cells. Thus, the conclusions drawn above for d are also valid for p.

- There are very significant correlations between fraction of activated cells and %Ki67+ cells. Thus, this independent measurement lends support to our results.

- Treatment tends to normalize the abnormal values of the parameters seen in untreated HIV-infected individuals.

- Improved experiments may be necessary to reduce CI.

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