The use of surrogate markers in the antiretroviral treatment of HIV-1 infection
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CHAPTER 3

CD4 cell counts in seven laboratory workers
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CHAPTER 3

CD4 cell counts in seven laboratory workers

SIR,—Dr Phillips and colleagues report significant declines in absolute CD4 counts with time in most HIV-positive patients with haemophilia and suggest that equations of linear regression between CD4 and increasing duration of HIV seropositivity can be projected to predict when individuals will progress to AIDS. Our experience suggests that biological variables that can influence CD4 counts, such as intercurrent infections, may limit applicability to, for example, homosexual men.

Their model may need to take account of different starting points on the slope—i.e., CD4 count before infection, whether measured or, more probably, estimated. In other words, does the intercept of such a regression line influence the predictive power of the rate of decline of CD4 count with time? Our data on variability of serial CD4 counts in healthy controls suggest that each individual may start from his or her own particular range, but that these ranges vary widely between individuals.

We did 95 CD4 counts on seven laboratory workers between October, 1989, and February, 1991, by whole blood lysis and 'FACSCAN' flow cytometry (the technique used by Phillips et al). Blood was drawn between 09.00 and 10.30 hours and only when donors were free from acute infections. All seven were heterosexual non-smokers at low risk for HIV infection. None reported needlestick injury. In none of them did the CD4 count fall significantly with time.

![Graph showing absolute CD4 counts in seven laboratory workers. Shown as mean (SD) for individuals.](image)

The mean (SD) CD4 count was 860 (316)/μl. Analysis of variance showed that the identity of the laboratory worker made a highly significant contribution to the variance in percentage and absolute CD4 counts (p <0.0001; figure). Student t-tests on log-transformed data revealed significant differences between workers in both absolute and percentage CD4 counts. One had a mean CD4 count of 526/μl, with 45% of counts below 500; another had a mean of 1511/μl, with no results below 500.

If CD4 counts for individuals fluctuate within restricted regions of the normal range, as these results suggest, there are three possible implications for the study of Phillips et al. First, there may be changes in CD4 count around the time of seroconversion which established a new baseline after which declines in CD4 can be interpreted. Second, those with lower baseline CD4 counts may show slower declines of CD4 with time. Third, individuals may show a decline in CD4 count after HIV infection from the baseline value such that the rate of decline is independent of the baseline value. Taking the mean rate of decline in CD4 as 80/μl per year from Phillips et al, the third possibility would suggest that an individual with a baseline CD4 of 550/μl would be expected to progress to
AIDS in 6.25 years, while an individual with the same rate of decline in CD4 but with a baseline of 1150 would progress in 13.75 years. The relative influence of the intercept and the slope of the regression lines in Phillips' study therefore needs to be clarified.

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These letters have been shown to Dr Phillips and colleagues, whose reply follows.-ED. L.

SIR,-Dr Hill and colleagues point out that HIV-seropositive individuals can have a wide variation in CD4 lymphocyte counts and, since the decline of the CD4 count is strongly associated with the development of AIDS, suggests that this factor may explain some of the variation in rates at which HIV-infected patients progress to AIDS. Their hypothesis is likely to depend on whether there is a different rate of decline in CD4 lymphocytes in individuals with lower pre-infection counts compared with those with higher pre-infection counts. Few data are available to answer this question because CD4 counts are seldom measured before HIV infection. The intercept and slope of the regression of CD4 count against time from seroconversion is not a reliable approach since those patients with steeper slopes will tend to have higher intercepts, irrespective of the true association (Spearman rank correlation coefficient =-0.51 [p=0.0001] in our patients). Independent estimates of the two variables are required. However, we have been able to study the association between the intercept and the occurrence of AIDS up to Jan 1, 1990. This analysis shows that patients with a higher intercept for their regression line (with a lower presumed pre-infection CD4 count) were more likely to develop AIDS by Jan 1, 1990, than those with a higher intercept (relative risk 1.6, p=0.03):

<table>
<thead>
<tr>
<th>Intercept (x 10^9/l)</th>
<th>AIDS by Jan 1 1990</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.85</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
</tr>
<tr>
<td>No</td>
<td>21</td>
</tr>
<tr>
<td>≥ 0.85</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
</tr>
<tr>
<td>No</td>
<td>16</td>
</tr>
</tbody>
</table>

Patients with lower pre-infection CD4 counts seem to progress to AIDS more rapidly than those with higher pre-infection counts, as suggested by Hill et al. This finding must be confirmed in other studies. However, the variability between individuals in the rate of decline in CD4 count remains the main determinant of the differences in rates of progression to AIDS.