CD4 and total lymphocyte counts as predictors of HIV disease progression

F.A. POST, R. WOOD and G. MAARTENS

From the Department of Medicine, University of Cape Town Medical School, Cape Town, South Africa

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Summary

CD4+ T-lymphocyte (CD4) counts are a standard laboratory marker of disease progression in HIV infection, but expense precludes their use in large parts of the world. Total lymphocyte counts (TLC), in contrast, are widely available. We compared CD4 and TLC counts as predictors of developing AIDS or death in 831 HIV-positive out-patients (582 males and 249 females with both homosexual (males, n=316) and heterosexual (n=515) transmission patterns. The first CD4 count <200/µl and first TLC <1250/µl predicted similar (p=0.52) survival, irrespective of clinical stage. For each clinical stage, a significant difference in progression to AIDS and mortality was predicted by TLC above or below 1250/µl (p<0.03). Survival and progression to AIDS occurred at similar rates in patients with a TLC <1250/µl or a CD4 count <200/µl (p=0.1), and patients with a TLC >1250/µl or a CD4 count >200/µl (p<0.5). A TLC <1250/µl preceded the development of Pneumocystis carinii pneumonia or cerebral toxoplasmosis in 76% of patients. In this longitudinal study, TLC and CD4 counts were equal predictors of disease progression. A TLC <1250/µl could be considered an indication for commencing cotrimoxazole prophylaxis.

Introduction

HIV infection can be monitored by laboratory1,2 and clinical3,4 markers of disease progression. The CD4+ T-lymphocyte (CD4) count is considered the best laboratory marker of progression of HIV infection,1 but lacks uniform reproducibility,2 is a crude predictor of HIV disease progression when taken by itself,3 and, because of expense, has limited availability in both resource-poor and developed countries.7

In the absence of CD4+ T-lymphocyte counts, the use of total lymphocyte counts (TLC) has been advocated to predict CD4 count8 and to stage HIV disease.6,9 The use of the TLC as predictor of CD4+ T-lymphocyte count is limited by the presence of CD4+ T-lymphopenia in up to 30% of non-lymphopenic patients.8 However, a low TLC was found to predict progression to clinical AIDS.2,10 This longitudinal study compared total lymphocyte count with CD4 count as predictor of developing AIDS and death in lymphopenic and non-lymphopenic HIV-positive patients.

Methods

Computer-based medical records of Somerset and Groote Schuur Hospital HIV clinics, two principal Western Cape HIV out-patient clinics, were analysed. Patients had been staged clinically (retrospectively from 1984 to 1991, prospectively from 1992 onwards) at each visit according to the WHO clinical staging system,8 in which stage 4 is equivalent to the 1987 Centres for Diseases Control (CDC) definition of AIDS.11 Paired CD4 and TLC values (n=1965) were available in 831 patients. CD4 counts were determined by flow cytometry and total

Address correspondence to Dr R. Wood, Department of Medicine, University of Cape Town Medical School, Anzio Road, Observatory 7925, Cape Town, South Africa

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lymphocyte counts by automated blood cell counter. Lymphopenia was defined as a TLC <1250/μl.

Survival was expressed as the Kaplan-Meier estimate of cumulative probability of survival, and was calculated in months from the index visit (first visit at which CD4 or TLC occurred in the defined range) to the date of death (not censored) or last visit (censored). Similarly, AIDS-free survival was calculated from the index visit to the date of initial AIDS diagnosis/death (not censored) or last visit (censored).

Survival curves were created for various degrees of lymphopenia (increments of 250 lymphocytes) and compared for closest fit to the curves of a CD4 count below 200/μl. Optimal match of the survival curve of a CD4 count <200/μl was achieved by a TLC <1250/μl. Probability of AIDS-free and overall survival was therefore determined for each clinical stage and a TLC above or below 1250/μl or a CD4 count above or below 200/μl. Statgraphics version 6.0 was used to create Kaplan-Meier plots and the log-rank test used to establish statistical difference between survival curves.

**Results**

Patients of the two HIV clinics represented both homosexual (n = 316) and heterosexual (n = 515) transmission pattern, male (n = 582) and female (n = 249) sex, and the three local population groups (Whites n = 280, Blacks n = 339, and mixed-race n = 212). Intravenous drug abuse and haemophilia did not occur as risk factors for HIV infection in our patients.

A CD4 count <200/μl occurred in 81% (547/675) of total lymphocyte counts <1250/μl, and a CD4 count >200/μl was present in 80% (1032/1290) of TLC >1250/μl. A total lymphocyte count <1250/μl was 68% sensitive and 89% specific for a CD4 count <200/μl. A TLC >1250/μl or a CD4 count >200/μl predicted the absence of clinical AIDS in 90% and 94% of patients, respectively. Survival of patients of any clinical stage whose total lymphocyte count had declined below 1250/μl was similar to the survival of patients with a first CD4 count below 200/μl (Figure 1). Survival of patients (n = 132) with a first TLC below 750/μl was not statistically different (p = 0.37) from patients (n = 146) who had a CD4 count below 50/μl (45% at 1 year and 20% at 2 years). In lymphopenic patients (TLC <1250/μl) as well as patients with a CD4 count <200/μl, clinical stage was a major determinant of mortality (Figure 2a,b). Progression to AIDS and death occurred at significantly (p <0.03) higher rates in lymphopenic patients than in non-lymphopenic (TLC >1250/μl) patients (Table 1). Mortality and progression to AIDS were not significantly different (p >0.5) between patients of similar clinical stage and a TLC <1250/μl or a CD4 count <200/μl (Figure 2a-d), nor between patients with a TLC >1250/μl and patients with a CD4 count >200/μl (p >0.1, data not shown).

**Discussion**

The CD4+ T-lymphocyte count is considered the best laboratory marker of progression of HIV infection, and serial CD4 count determinations are commonly used to monitor the degree of HIV-induced immunosuppression. Low CD4 counts are indicative of decreased cellular immunity, and are associated with increased risk of developing AIDS or death. In the absence of CD4 counts, the use of total lymphocyte counts has been advocated to predict CD4 count and to stage HIV disease. The usefulness of the total lymphocyte count is best evaluated by direct comparison with CD4 count as predictor of end-points such as AIDS and death. This study found CD4 and TLC to be equal predictors of progression of HIV infection. The routine use of total lymphocyte counts rather than CD4 counts would substantially...

![Figure 1](image-url)
Figure 2. Overall survival and AIDS-free survival for patients with CD4 counts $<200/\mu l$ and total lymphocyte counts $<1250/\mu l$. $p$ values represent log-rank comparison of survival curves.

### Table 1
One-year Kaplan-Meier estimate of progression to clinical AIDS (WHO stage 1–3) and death (WHO stage 4), stratified by a total lymphocyte count (TLC) above or below 1250/μl

<table>
<thead>
<tr>
<th></th>
<th>One-year progression to AIDS</th>
<th>One-year mortality (Stage 4)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Stage 1</td>
<td>Stage 2</td>
</tr>
<tr>
<td>TLC $&gt;1250/\mu l$</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>TLC $&lt;1250/\mu l$</td>
<td>14%</td>
<td>12%</td>
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</tbody>
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reduce the costs associated with managing HIV infection.

The WHO staging system incorporates the use of TLC < 1000, 1000–2000 and > 2000/μl to replace few of whom had severe lymphopenia, a TLC above CD4 counts < 200, 200–500 and > 500/μl in its laboratory axis.8 In Rwandan HIV-positive women, few of whom had severe lymphopenia, a TLC above or below 2000/μl had no prognostic value.12 Our results suggest that a TLC of 1250 rather than 1000/μl should be the equivalent of a CD4 count of 200/μl, and that the presence of a TLC above or below 1250/μl is associated with a significant difference in rates of progression of HIV infection.

In two previous studies, patients of various WHO clinical and/or laboratory stages were rearranged into four ‘modified stages’, and survival was determined for each ‘modified stage’.4,12 In our patients, TLC (and CD4 counts) added independent, prognostically meaningful information to the WHO clinical stage (Table 1). The stratification of patients by WHO clinical stage and absence or presence of lymphopenia is easily performed and practical for the management of HIV infection in resource-poor countries.

In advanced HIV infection, the total lymphocyte count declines as a result of progressive depletion of CD4 + T-lymphocytes, CD8 + T-lymphocytes and B-lymphocytes.13 CD8 + T-lymphopenia was found to be an independent predictor of mortality,14 and the decrease in B-cells may further contribute to the immunodeficient state associated with advanced HIV infection. In our patients, severe lymphopenia (TLC < 750/μl) predicted poor survival regardless of clinical stage, and might reflect a high susceptibility to opportunistic infections. In one study, systemic Mycobacterium avium complex infection was restricted to patients with severe lymphopenia (mean 540/μl).15 Cotrimoxazole is effective prophylaxis against toxoplasmosis, PCP and bacterial infections, and is recommended for all patients with CD4 counts < 200/μl.16 Although PCP is less common in Africa, toxoplasmosis and bacterial infections are major causes of mortality.17 As lymphopenia preceded the development of PCP or toxoplasmosis in 76% of our patients, a TLC < 1250/μl could be considered a criterion for instituting cotrimoxazole prophylaxis.

A TLC > 1250/μl was only 4% less sensitive than a CD4 count > 200/μl as a predictor of the absence of clinical AIDS. Using lymphopenia rather than CD4 T-lymphopenia as a criterion for commencing cotrimoxazole prophylaxis may thus select a slightly smaller group of patients at risk for developing PCP. Although we have shown the total lymphocyte count to be equal to the CD4 count for overall prognosis, its usefulness in individual patients as a criterion for commencing prophylaxis needs to be studied prospectively.

References