CD4⁺ Cell Count Increase Predicts Clinical Benefits in Patients with Advanced HIV Disease and Persistent Viremia after 1 Year of Combination Antiretroviral Therapy

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The relationship between 12-month CD4⁺ cell count response and clinical outcome (AIDS-defining event or death) in a subset of 228 patients with a human immunodeficiency virus load >400 copies/mL despite receiving combination antiretroviral therapy as part of a larger randomized trial was defined by use of Cox models. The 12-month CD4⁺ cell count responses were divided into 5 categories, ranging from decrease or no change (29% of patients) to a ≥100-cell/mm³ increase (27% of patients). There was a lower risk of clinical progression for each incremental increase in CD4⁺ cell count response. A 25-cell/mm³ increase in CD4⁺ cell count was associated with a 21% reduction in the risk of an AIDS-defining event or death (P < .0001).

Despite the indisputable impact of combination antiretroviral therapy (cART) on HIV-related morbidity and mortality, a durable virologic response is not attained in all treated patients. Virologic failure is observed in 50%–60% of patients within 2 years of initiation of cART, thereby risking immunologic deterioration and disease progression, including the development of AIDS or death [1–3]. However, discordant CD4⁺ cell count responses in which sustained increases in CD4⁺ cell counts occur despite incomplete virologic suppression have been described [4–9]. Patients with discordant CD4⁺ cell count responses to cART have shown rates of disease progression and death similar to those observed in patients with full virologic suppression [8]. The exact mechanism whereby recovery of CD4⁺ cell counts occurs in the presence of persistent viremia has not been fully elucidated, although a reduction in HIV-associated T cell apoptosis and a decrease in viral replication capacity have been proposed as possible explanations [6, 10–12].

In most studies, an increase in CD4⁺ cell count of at least 50 cells/mm³ has been arbitrarily selected as being representative of the beneficial immunologic response to cART; however, this definition has not been prospectively evaluated. Similarly, although increases in CD4⁺ cell count after 6 months of cART have been associated with a favorable clinical outcome regardless of virologic response, the magnitude of the CD4⁺ cell count increase that is necessary to confer this clinical benefit has not been determined [8, 9]. We report here on the relationship between 12-month CD4⁺ cell count response and clinical outcome in an HIV-infected population who started cART and had persistent viremia at month 12 of treatment.

Patients, materials, and methods. The study population was derived from patients participating in a randomized clinical trial comparing treatment with either nelfinavir- or ritonavir-based cART [13]. Patients enrolled in this trial were ≥13 years of age, had CD4⁺ cell counts ≤200 cells/mm³, were protease inhibitor (PI) naive (with the exception of possible prior use of unboosted saquinavir hard gel capsules), and provided informed consent for participation. A total of 775 patients were enrolled from 40 centers across the United States and Canada. After randomization, patients were seen for visits at months 1 and 4 of the study and every 4 months thereafter, until study termination.

For inclusion in the present analysis, patients were required to meet the following criteria: (1) they had to have previous antiretroviral experience; (2) they had to have a plasma viral load (VL) >400 copies/mL (by Roche Amplicor HIV-1 Monitor assay) at month 12 of treatment; (3) they had to be alive and had not experienced an AIDS-defining event during the first 12 months after randomization; and (4) they had to have had CD4⁺ cell counts and plasma VL measurements recorded at baseline and at 12 months of follow-up.

The outcome of interest in this analysis was the relationship
between various grades of CD4+ cell count response after 12 months of cART and clinical outcome. Twelve months after the start of treatment selected as the time point for assessment, because the virologic and immunologic response to a new antiretroviral regimen would have occurred by this time. The observed CD4+ cell count response at month 12 was divided into the following 5 categories: (1) a decrease or no change in CD4+ cell count (the reference group); (2) an increase of 1–24 cells/mm3; (3) an increase of 25–49 cells/mm3; (4) an increase of 50–99 cells/mm3; and (5) an increase of ≥100 cells/mm3. The end point of interest was the first occurrence of an AIDS-defining event or death (whichever occurred first) after the first 12 months of cART. A central end-point review committee who were blinded to treatment group reviewed all clinical events.

Baseline characteristics were summarized as medians and interquartile ranges (IQRs) for continuous variables and as proportions for categorical variables and were compared among patients in the 5 categories by the Wilcoxon rank sum test and the χ2 test, respectively. Progression to an AIDS-defining event or death was examined according to the 4 CD4+ cell count categories after 12 months of cART in comparison with the reference group by time-to-event methods (Kaplan-Meier curves and the Cox proportional hazards model). Time to an event was calculated from the date of the 12-month visit to the first occurrence of an AIDS-defining event or death; observations were censored at study termination or the date on which a patient was lost to follow-up. Adjusted Cox regression analyses were stratified by country (United States and Canada) and included the following covariates for adjustment: age, previous AIDS diagnosis, baseline CD4+ cell count, baseline log10 VL, previous PI exposure, and 12-month VL response. In addition, a Cox regression analysis was performed with 12-month CD4+ cell count response as a continuous variable in the final model. For this analysis, the hazard ratio (HR) was determined for each 25-cell/mm3 increase. Statistical analyses were performed by use of SAS software (version 8.2; SAS Institute).

Results. Of the 775 patients originally randomized, 610 participated in a substudy in which VL and CD4+ cell count data were collected. Of these, 150 patients were antiretroviral naive at baseline and were excluded from the analysis. Another 147 patients were excluded because they either had experienced a clinical end point before 12 months (n = 39) or were missing VL or CD4+ cell count results at either baseline or month 12 (n = 108). Of the remaining 313 patients, 228 had a VL >400 copies/mL at 12 months and were the subjects of the present analysis. Baseline characteristics of the cohort are shown in table 1.

A decrease or no change in CD4+ cell count at month 12 relative to baseline was observed in 65 (29%) and 2 (1%) patients, respectively; these patients composed the reference group. Of the remaining patients, 34 (15%), 26 (11%), 39 (17%), and 62 (27%) had increases in CD4+ cell count of 1–24, 25–49, 50–99, and ≥100 cells/mm3 by 12 months, respectively. Overall, the median changes in VL at 1, 4, 8, and 12 months were −1.08, −0.57, −0.20, and −0.14 log10 copies/mL, respectively. The 12-month VL changes for each CD4+ cell count response category are shown in table 1. Sixty-two patients (27%) achieved at least 1 VL ≤400 copies/mL during the first year.

After month 12, patients were followed for a median of 40 months (IQR, 29–45 months). A total of 81 patients (35.5%) developed AIDS (n = 50) or died (n = 51) during follow-up, with 20 patients reaching both end points [13]. A further 18 patients (7.9%) were lost to follow-up. The most common AIDS-defining events were esophageal candidiasis (19 cases) and Pneumocystis jiroveci pneumonia (15 cases).

Kaplan-Meier curves describing the risk of progression to AIDS or death in each subgroup of patients are shown in figure 1. The cumulative percentages of patients who developed AIDS or died during the first 2 years of follow-up were 17.9%, 29.4%, 3.9%, 2.6%, and 1.6% in patients with a decrease or no change in CD4+ cell count or with increases of 1–24, 25–49, 50–99, and ≥100 cells/mm3, respectively (figure 1). After 3 years of follow-up, these percentages were 39.2%, 47.1%, 19.7%, 13.1%, and 6.6%, respectively (figure 1). For comparison, among the 85 patients with a VL ≤400 copies/mL at 12 months who were consequently excluded from the main analysis, the cumulative percentage progressing to AIDS or death after 2 and 3 years of follow-up were 3.5% and 9.5%, respectively.

Unadjusted and adjusted analyses investigating the relationship between 12-month CD4+ cell count response and subsequent AIDS-defining illness or death yielded similar results. There was a lower risk of clinical progression relative to the reference group for each incremental increase in CD4+ cell count response. The adjusted HRs decreased from 0.83 (95% confidence interval [CI], 0.45–1.55; P = .57) for those with an increase of 1–24 cells/mm3, to 0.47 (95% CI, 0.22–1.00; P = .05) for those with an increase of 25–49 cells/mm3, to 0.31 (95% CI, 0.15–0.67; P = .003) for those with an increase of 50–99 cells/mm3, and to 0.23 (95% CI, 0.11–0.50; P < .0002) for those with an increase of ≥100 cells/mm3. When 12-month CD4+ cell count response was analyzed as a continuous predictor of an AIDS-defining event or death after 12 months, the adjusted HR was 0.79 (95% CI, 0.71–0.88; P < .0001) for each increase of 25 cells/mm3. In this multivariate model, the following covariates were significantly associated with an AIDS-defining event or death: baseline log10 VL (HR, 2.39 for each greater 1 log10, P < .0001), age (HR, 1.44 for each 10 years older; P = .009), previous use of saquinavir (HR, 1.62; P = .04), baseline CD4+ cell count (HR, 0.82 for each 25 cells/mm3 lower; P = .006), and VL decrease through 12 months of follow-up (HR, 0.58 for each decrease of 1 log10; P = .002).

Discussion. For HIV-infected patients, the primary goal of
Table 1. Characteristics of the patients, according to 12-month CD4+ cell count response.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients</th>
<th>Decrease or no change</th>
<th>CD4+ cell count increase, cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 228)</td>
<td>(n = 67)</td>
<td>1–24 (n = 34) 25–49 (n = 26) 50–99 (n = 39) ≥100 (n = 62) P</td>
</tr>
<tr>
<td>Age, years</td>
<td>38 (33, 44)</td>
<td>38 (33, 44)</td>
<td>38 (33, 44) 41 (32, 46) 39 (33, 44) 37 (32, 41) .81</td>
</tr>
<tr>
<td>Male, %</td>
<td>84.6</td>
<td>79.1</td>
<td>82.4 88.5 94.9 83.9 .25</td>
</tr>
<tr>
<td>AIDS diagnosis, %</td>
<td>49.6</td>
<td>43.3</td>
<td>50.0 42.3 56.4 54.8 .56</td>
</tr>
<tr>
<td>Baseline VL, log_{10} copies/mL</td>
<td>4.9 (4.2, 5.5)</td>
<td>4.7 (4.0, 5.2)</td>
<td>5.2 (4.4, 5.6) 4.8 (4.1, 5.4) 4.8 (4.3, 5.6) 5.2 (4.3, 5.6) .14</td>
</tr>
<tr>
<td>Baseline CD4+ cell count, cells/mm³</td>
<td>46 (20, 84)</td>
<td>74 (30, 107)</td>
<td>31 (8, 46) 64 (30, 91) 44 (24, 72) 40 (18, 77) &lt;.001</td>
</tr>
<tr>
<td>Previous antiretrovirals received, no.</td>
<td>3 (2, 4)</td>
<td>3 (2, 4)</td>
<td>3 (2, 5) 3 (2, 3) 3 (2, 4) 3 (2, 4) .78</td>
</tr>
<tr>
<td>Previous saquinavir use, %</td>
<td>34.2</td>
<td>37.3</td>
<td>41.2 34.6 35.9 25.8 .54</td>
</tr>
<tr>
<td>Ritonavir, a %</td>
<td>49.1</td>
<td>52.2</td>
<td>58.8 38.5 33.3 54.8 .12</td>
</tr>
<tr>
<td>Change in VL between baseline and 12 months, log_{10} copies/mL</td>
<td>−0.1 (−0.9, 0.3)</td>
<td>0.2 (−0.3, 0.7)</td>
<td>0.0 (−0.8, 0.5) 0.0 (−0.4, 0.2) −0.3 (−1.0, 0.2) −0.8 (−1.4, 0.0) &lt;.0001</td>
</tr>
</tbody>
</table>

**NOTE.** Data are median (interquartile range) of values, unless otherwise noted. P values are for differences among the 5 CD4+ cell count groups. VL, viral load.

a Represents the percentage of patients randomized to the ritonavir arm; the remaining patients were randomized to the nelfinavir arm.
cART is to attain a VL below the limit of detection of the currently available technology (<50 copies/mL) [14]. However, this goal is not always realistically attainable in antiretroviral-experienced patients, because of the presence of mutations that confer drug resistance. For such patients, the goals of therapy are often modified to focus on immunologic maintenance or recovery and delayed disease progression. Several studies have supported this approach as being feasible for periods of up to 5 years and have found immunologic recovery to be correlated with improved clinical outcomes even in the presence of detectable viremia [14, 15]. However, to our knowledge, no study has yet quantified the clinical benefit associated with this discordant immunologic response according to the magnitude of the immunologic recovery observed.

In the present cohort of 228 HIV-infected patients with advanced immunosuppression who started a PI-containing cART regimen, an incremental decrease in the risk of clinical progression with increasing 12-month CD4\(^+\) cell count responses was observed despite persistent viremia. Thus, our results indicate that, in cases where complete VL suppression does not occur, the CD4\(^+\) cell count response is a very important predictor of clinical outcome and that patients with discordant responses to cART may still experience a favorable clinical outcome during the next first few years of therapy.

Our findings have important implications for the management of antiretroviral-experienced patients. First, for patients in whom complete virologic suppression is unlikely or has not occurred, emphasis should be placed on monitoring and maximizing CD4\(^+\) cell count increases. Second, our data provide support for maintaining patients with discordant responses on their current regimen as long as CD4\(^+\) cell count recovery is maintained, thereby waiting for new agents with which to construct a potent regimen composed of as many virologically active drugs as possible. Although this strategy risks the continued accumulation of antiretroviral resistance–conferring mutations over time, recent data suggesting that patients can continue to benefit from virologically failing regimens for up to 5 years may indicate that, at least in the short term, the benefits of maintaining a discordant response outweigh the risks [14]. Still, until these strategies can be directly compared in a clinical trial, patients with feasible antiretroviral options should consider switching to a regimen containing as many active antiretroviral drugs as possible, regardless of their CD4\(^+\) cell count response to the failing regimen [14].

There are a few limitations to our investigation. To be included in the present analysis, patients must have had a CD4\(^+\) cell count and a VL measurement 12 months after starting cART. Patients who died, developed an AIDS-defining illness, or were lost to follow-up during the first 12 months of enrollment were not included. Restricting ourselves to this cohort may have resulted in an underestimation of AIDS-defining illnesses or death. Our definition of virologic failure was a VL >400 copies/mL at 12 months, and so patients who potentially achieved viral suppression or a partial virologic response at some time point were included. Our patient population had advanced HIV disease, which affects the generalizability of our results. Furthermore, the antiretroviral agents currently in use are different from those used in this study.

Figure 1. Kaplan-Meier curves of progression to an AIDS-defining event or death after 12 months of combination antiretroviral therapy, according to 12-month CD4\(^+\) cell count response. HR, hazard ratio.
In summary, our analysis found a significant, graded association between CD4+ cell count increase after 12 months and risk of progression to AIDS or death in patients with persistent viremia. This finding could help to guide clinical decision making with regard to the use of antiretroviral therapy for patients with advanced HIV disease and few treatment options.

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References