Do Sex and Race/Ethnicity Influence CD4 Cell Response in Patients Who Achieve Virologic Suppression during Antiretroviral Therapy?

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To determine whether CD4 cell count response to virus suppression during highly active antiretroviral therapy differs according to sex or race/ethnicity, we analyzed data in our observational cohort study for patients receiving their first antiretroviral regimen who experienced virus suppression by 6 months of therapy. In both univariate and multivariate analyses, women had greater CD4 cell count increases, compared with men, as did patients receiving a regimen that did not include a protease inhibitor. Race/ethnicity was not a factor.

In the United States, the population-based crude mortality rate for women with AIDS is ∼20% higher than that for men with AIDS. Similarly, the mortality rate for Hispanic patients with AIDS is ∼20% higher and that for African American patients with AIDS is ∼50% higher than that for white patients with AIDS [1]. Adjusted population-based data from the United States currently are not available. In both the HIV-uninfected and -infected populations, women have higher CD4 cell counts than men do [2, 3], whereas African Americans in HIV-uninfected populations have not been observed to have higher CD4 cell counts [4]. Given pharmacokinetic, immunologic, and genetic differences by sex and, perhaps, by race/ethnicity, we investigated whether CD4 cell count response to virus suppression during HAART differs by sex or race/ethnicity. Any difference might partially explain the disparity in the survival rate, but there are limited data analyzing only patients who experience virus suppression. A single study of 41 patients found that women had greater CD4 cell count increases than men did in response to virus suppression, but the authors did not adjust for baseline CD4 cell count or examine the effect of race/ethnicity [5]. Differences by sex or race/ethnicity in CD4 cell response to virus suppression might alter the optimal timing of treatment, if suppression can be predicted.

METHODS

The Thomas Street Clinic in Houston, Texas, serves ∼4000 HIV-infected, low-income persons who lack insurance. An ongoing, observational database of >1400 new patients seen from 1998 through 2001 was used to identify patients who were antiretroviral naive (n = 714), treated with HAART (n = 448), had complete baseline virus load and CD4 cell count data available (n = 357), and were monitored for at least 6 months, with virus suppression during HAART experienced at 6 months (n = 100). Baseline values were those obtained on the date of treatment initiation or up to 120 days before initiation (median, 14 days before initiation). Virus suppression at 6 months was defined...
Table 1. Characteristics of 100 patients who experienced virologic suppression during HAART, by sex and race/ethnicity.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sex</th>
<th>Race/ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>(n = 77)</td>
<td>(n = 23)</td>
</tr>
<tr>
<td>Sex</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>100</td>
<td>.02</td>
</tr>
<tr>
<td>White</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>African American</td>
<td>44</td>
<td>70</td>
</tr>
<tr>
<td>Hispanic</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Age, median years (IQR)</td>
<td>38 (34–43)</td>
<td>41 (27–44)</td>
</tr>
<tr>
<td>AIDS-defining illness at baseline</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>CD4 cell count at baseline, median cells ×10⁹/L (IQR)</td>
<td>98 (41–202)</td>
<td>129 (20–344)</td>
</tr>
<tr>
<td>Virus load at baseline, median log copies/mL (IQR)</td>
<td>5.2 (4.6–5.5)</td>
<td>5.2 (4.2–5.5)</td>
</tr>
<tr>
<td>PI-containing therapy</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>CD4 cell count change at 6 months, mean cells ×10⁹/L (SD)</td>
<td>+122 (100)</td>
<td>+180 (127)</td>
</tr>
</tbody>
</table>

NOTE. Data are percentage of subjects, except where noted. HCV, hepatitis C virus; IQR, interquartile range; PI, protease inhibitor.

as an HIV load <400 copies/mL (as determined by RT-PCR) on at least 2 consecutive occasions, the latter of which was 120–240 days after HAART began. Change in CD4 cell count was defined as the difference between the 6-month CD4 cell count (obtained at the same time as the latter undetectable virus load) and the baseline CD4 cell count. HAART was defined as the concomitant receipt of at least 3 antiretrovirals, excluding low-dose ritonavir. Categorical variables were compared with the χ² test. Baseline CD4 cell count, virus load, and age were compared with the Wilcoxon rank sum test. Changes in CD4 cell count were compared by analysis of variance. A multivariate model of change in CD4 cell count was created with analysis of covariance regression, which allows for comparison of continuous data adjusted for categorical and continuous covariates. There were no significant interactions between the covariates and the grouping variables, which indicates that the equal slopes assumption of the analysis of covariance regression modeling was not violated. Statistics were analyzed with SAS software (version 8.01; SAS Institute). The study was approved by the Baylor College of Medicine and Affiliated Hospitals Institutional Review Board and was completed in accordance with the institution’s guidelines for human research.

RESULTS

Of the 100 patients included in the study, 23 were women and 77 were men. Nineteen patients were white, 50 were African American, and 31 were Hispanic. The median baseline CD4 cell count was 105 × 10⁹ cells/L (range, 2 × 10⁹–952 × 10⁹ cells/L; interquartile range [IQR], 37 × 10⁹–293 × 10⁹ cells/L), and the median baseline log₁₀ virus load was 5.2 HIV RNA copies/mL (IQR, 4.6–5.5 HIV RNA copies/mL). Sixty-one patients were treated with a protease inhibitor (PI) (49 regimens included nelfinavir, 5 included indinavir, 4 included ritonavir-boosted indinavir, 1 included ritonavir-saquinavir, 1 included saquinavir, and 1 included amprenavir), and 39 patients used regimens that did not include a PI (26 included efavirenz, 8 included nevirapine, and 5 included abacavir). Characteristics of the patients by sex and race/ethnicity are presented in table 1. Men and women did not differ significantly with regard to baseline CD4 cell count, use of injection drugs, age, proportion with AIDS, proportion coinfected with hepatitis C virus (HCV), baseline virus load, and use of PIs. All the women were non-white (P = .02). In addition, the 3 ethnic groups (white, African American, and Hispanic patients) did not differ significantly with regard to baseline CD4 cell count, use of injection drugs, proportion with AIDS, proportion coinfected with HCV, baseline virus load, and use of PIs. Patients did differ with regard to sex (as above) and age (white patients were the oldest and Hispanic patients were the youngest; P = .04).

CD4 cell count changes (reported in cells × 10⁹/L) were normally distributed and ranged from −94 to +433, with a mean (SD) of +135 (109). The mean (SD) CD4 cell count change was +122 (100) for men and +180 (127) for women, which was a statistically significant difference (P = .02). The mean (SD) CD4 cell count change was +128 (103) for white patients,
Results of the multivariate analysis are presented in figure 1. The model was adjusted for age, presence of an AIDS-defining illness, baseline CD4 cell count, baseline log10 virus load, and use of PIs. Compared with men, women had a mean CD4 cell response that was $66 \times 10^6$ cells/L greater ($P = .01$). African American and Hispanic patients had mean CD4 cell responses that were $18 \times 10^6$ and $23 \times 10^6$ cells/L lower than those for white patients, respectively, but these differences were not significant ($P = .54$ and $P = .48$, respectively). Patients receiving HAART that did not contain a PI had a mean CD4 cell response that was $58 \times 10^6$ cells/L greater than the response of patients receiving a PI ($P < .01$). For each increase in log10 baseline virus load, the mean CD4 cell response increased by $36 \times 10^6$ cells/L ($P = .03$). Age, AIDS, and baseline CD4 cell count were not significant factors. HCV serostatus and use of injection drugs had no significant effects on the overall model or on the other factors in the model, whether added individually or together, and were not retained in the final model.

An analysis that modeled baseline CD4 cell count as a categorical variable (<$100 \times 10^6$, $100 \times 10^6$–$349 \times 10^6$, or $\geq 350 \times 10^6$ cells/L) yielded similar results, as did an analysis that modeled change in CD4 percentage, rather than change in absolute CD4 cell count. Because there were no white women in the study, we performed a multivariate analysis that excluded white men (74% of whom were men who had sex with men) to determine whether the sex difference persisted. Women continued to have a greater mean CD4 cell response than men ($66 \times 10^6$ cells/L; $P = .01$). Women constituted a similar proportion of the patients treated before the year 2000 (19% of 59 patients) or during 2000 and 2001 (29% of 41 patients; $P = .21$). However, only 18% of patients treated during the earlier time period were not receiving a PI, whereas 68% of the patients from the later period were not receiving a PI ($P < .01$). When a term reflecting these time periods was included in the multivariate analysis, it had no important effects on the overall model or the individual regression coefficients. Differences in CD4 cell response might be due to the timing of treatment relative to the baseline laboratory assessment or the duration of treatment before the 6-month laboratory assessment. However, there were no differences in the time from baseline laboratory assessment to the start of HAART (median, 14 days overall) or in the time from the start of HAART to the 6-month laboratory assessment (median, 193 days overall), by sex, race/ethnicity, and PI use.

Of the 257 HAART-treated patients not included in this study, 91 had been monitored for <120 days at the time that data were gathered, and 40 had no laboratory assessment 120–240 days after HAART was started. Of the 126 remaining patients, 36 had 1 virus load value <$400$ HIV RNA copies/mL at 6 months but did not have a second virus load value that met inclusion criteria. Thirty percent of these 126 patients were women, which is not statistically significantly different from the 23% women in the group that experienced virus suppression ($P = .25$). Complete data were available for 116 of these 126 patients, and the mean (SD) change in CD4 cell count was $+136 (120)$ for African American patients, and $+139 (94)$ for Hispanic patients, which was not a statistically significant difference ($P = .93$).

![Figure 1](https://example.com/figure1.png)

**Figure 1.** CD4 cell response to virus suppression among 100 HIV-infected subjects. Data were estimated with an analysis of covariance regression model that was significant ($P = .02$) and were adjusted for age, presence of an AIDS-defining illness at baseline, and baseline CD4 cell count. CD4 cell counts were measured in cells/$10^6$/L ($P = .03$). For each increase in log10 baseline virus load, the CD4 response increased by $36 \times 10^6$ cells/L ($P = .03$). There was no association between change in CD4 cell count and age ($P = .69$), the presence of an AIDS-defining illness at baseline ($P = .17$), or baseline CD4 cell count ($P = .61$). ◆ Mean values; vertical bars, 95% confidence intervals of the mean. Af-Am., African American; PI, protease inhibitor.
+81 (133) \times 10^6 \text{ cells/L}, which was significantly lower than the change among patients who experienced virus suppression \((P < .01)\). The mean CD4 cell count changes for men and women were similar, as were the changes for white, African American, and Hispanic patients. In the multivariate model, sex, race, and use of PI were not significantly associated with CD4 response, whereas baseline CD4 cell count was negatively correlated with CD4 response, and change in log10 virus load was positively correlated with CD4 response.

**DISCUSSION**

Among antiretroviral-naive patients who experienced virus suppression after 6 months of receiving HAART, women had a greater CD4 cell response than men did, even after adjusting for baseline CD4 cell count and virus load. Compared with men, women have a greater risk of rash associated with nevirapine use \([6, 7]\) and of pancreatitis associated with nucleoside analogue use \([8]\). Pharmacokinetic differences by sex, based on different mean body mass indices, nutritional status, or other factors, may explain these increased risks. Pharmacokinetic differences may have resulted in women having higher antiretroviral drug levels, which led to more-profound virus suppression and resulted in a greater increase in CD4 cell count. Data demonstrating an increased CD4 cell response in patients with a greater virologic response to therapy, both in other studies \([9, 10]\) and in the present study, support this hypothesis. Patients’ heights and drug levels are not assessed in the clinic, so data were not available to test this hypothesis. In general, women have higher CD4 cell counts than men do, whether HIV-infected or not \([2, 3]\). The differences in CD4 cell response observed in the present study suggest that women also repopulate their peripheral CD4 cells in response to virus suppression more quickly than men do. Women may have increased peripheral redistribution of memory CD4 cells from lymphoid tissue in response to decreases in virus load induced by HAART \([10]\). An alternate explanation is that thymic output of naive CD4 cells in response to HAART, an important contributor to later CD4 count increases \([11]\), may be greater for women than for men \([12]\).

Race/ethnicity had no effect on CD4 cell count increase in this study. A recent study from Denmark, where patients have free access to care, found that nonwhite patients did not have decreased odds of receiving HAART or achieving virus suppression and had similar CD4 cell count increases \([13]\). Our results are consistent with those observations and suggest that disparities in outcome in the United States are not due to differences in CD4 cell response to virus suppression. In contrast, nonwhite patients likely have decreased access to antiretroviral treatment in the United States, which may be responsible for the disparity \([14]\).

HAART regimens that did not contain a PI conferred a greater CD4 cell response than did HAART regimens that included a PI, even after we adjusted for age, sex, presence of an AIDS-defining illness, and baseline virus load and CD4 cell count. Because all patients in the present study maintained virus loads <400 copies/mL, large differences in adherence are not likely to explain this finding. Nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based therapy may offer more-durable virologic control than single PI–based therapy does, but previous studies that analyzed patients who did and did not experience virus suppression together did not find a difference in CD4 cell response \([15–17]\). An analysis of patients who experienced virus suppression within 8 months after initiating therapy found no difference in CD4 cell increase on the basis of type of therapy received \([18]\). However, the results were not adjusted for baseline CD4 cell count, which differed. Dronda et al. \([19]\) analyzed 288 Spanish patients who experienced virus suppression, 9% of whom were receiving NNRTIs, and reported that PIs produced a superior immune recovery, compared with NNRTIs. Patients in that study primarily received nevirapine, whereas, in the present study, efavirenz, which has been associated with greater CD4 cell count increases than nevirapine \([20]\), was used most commonly. Furthermore, the end point in that analysis was whether a CD4 cell count increase of 100 \times 10^6 \text{ cells/L was achieved, which may obscure factors associated with overall CD4 cell count increase. Thus, differences between that study and the present study in both population and design make comparison difficult. Neither study was designed a priori to compare the 2 classes of drugs.

Consistent with previous results, patients with a greater decrease in virus load had a greater increase in CD4 cell count, independent of other factors \([9, 10]\). That this occurs despite all patients achieving an undetectable virus load is an important observation that suggests that virus load dynamics, as well as ultimate absolute virus load, are important in determining CD4 cell count. Although this observation may suggest that deferral of therapy until a higher virus load is safe, it may be more difficult to achieve virus suppression in persons with higher baseline virus loads \([21]\). In addition, the persons with the highest baseline virus loads in the present study still had lower absolute CD4 cell counts at 6 months, despite greater increases overall, because they started with lower baseline CD4 cell counts.

The data for our study were systematically collected, and the results were confirmed in a number of secondary analyses. Data regarding patients’ heights at the initiation of therapy (needed to calculate body mass index) and blood levels of antiretrovirals were not available, and future studies should gather these data. Other limitations of the present study include its reliance on observational data and small sample size, which limited the power of some of the comparisons. Because the study did not
include any white women, the results may be more generalizable to minority women than to white women.

Our findings do not explain the mortality differences seen in US patients with AIDS by sex and race/ethnicity, but suggest that differing CD4 response to virologic control is not a factor. Although HAART should be initiated at the same CD4 cell count threshold in women as in men [22], some researchers have suggested that women be considered as candidates for receiving HAART at lower virus loads than men [23]. Our data suggest that women who achieve virologic control have the better CD4 cell response to successful HAART at 6 months, which might mitigate any need to start HAART in women at lower virus loads. Because the initial CD4 cell increase in response to HAART predicts longer-term response [24], women who are treated with HAART and who have an optimal virologic response may be poised to have a more favorable clinical course than men are. However, women may have disease progression at higher CD4 cell counts than men do [2], and it is difficult to predict who will achieve virus suppression and who will not. Only larger studies with clinical end points could ascertain whether women are safely able to defer antiretroviral therapy until they reach lower CD4 cell counts than men.

References