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Measurement of Naive CD4 Cells Reliably Predicts Potential for Immune Reconstitution in HIV

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Abstract

Background—Pathogenesis studies show that naive CD4 cells are preferentially depleted in lymphoid tissues during HIV infection, and studies of advanced patients suggest levels of naive CD4 cells in blood correlate to total CD4 cells after starting antiretroviral therapy (ARV). We hypothesized that measuring naive CD4 cells in blood in people at earlier stages of disease would identify those at highest risk for poor CD4 reconstitution who may benefit from earlier initiation of ARV.

Methods and Findings—We identified 348 patients from multiple AIDS Clinical Trials Group studies who were ARV naive, had a CD4 count between 200 and 500 cells per microliter, a measure of pretreatment-naive CD4 percent, and serial follow-up measures of CD4 count and plasma HIV RNA after starting ARV. We used logistic regression to model the ability of naive CD4 percent to predict 100 and 200 CD4 cell increases after 24 months of therapy. After controlling for baseline viral load and demographic variables, baseline naive but not total CD4 cell count strongly predicted CD4 cell increases. Lower baseline naive CD4 percent was associated with greater time spent at lower CD4 T-cell counts after initiating ARV.

Conclusions—Measurement of naive CD4 percent in patients can identify those least likely to reconstitute immunity, who may benefit from earlier ARV treatment.

Keywords

early therapy; immune reconstitution; naive CD4 T cells

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INTRODUCTION

Current guidelines for initiation of antiretroviral therapy (ARV) suggest it be started when peripheral blood (PB) CD4 T cells decrease to below 350 cells per microliter^{1,2} when plasma HIV RNA is high or when major symptoms associated with an AIDS-defining illness are present. This strategy focuses on preventing disease progression.

There are no validated markers to differentiate those who will have a more robust CD4 response to ARV from those who will not. Pathogenesis-based studies have shown that viral replication in lymphatic tissues (LTs) causes inflammation and scarring that is associated with impaired reconstitution of CD4 T cells in LTs and PB.^{3–5} The subset most affected are naive CD4 T cells,⁶ and pretreatment levels of naive CD4 T cells have been shown to correlate to the rise in CD4 T cells with ARV.^{7–9} We, therefore, reasoned that it should be possible to use naive CD4 T cells in PB as a surrogate marker for damage to LTs and identify people most likely to benefit from earlier initiation of therapy. We studied patients whose PB CD4 T-cell count was in the range where most patients consider initiating ARV, that is, 200–500 cells per microliter and show that the size of the PB-naive CD4 population was the strongest predictor of treatment associated changes in PB total CD4 count, even more so than total CD4 count.

METHODS

We collected data from patients in AIDS Clinical Trials Group treatment studies 384, 388, A5014, A5095, and A5001.^{10–15} We studied all patients who were ARV naive, had pretreatment measurements of baseline PB-naive (CD45RA+/62L+) CD4 T cells and serial measurements of CD4 T-cell counts and plasma HIV RNA (HIV-1 Monitor assay 1.0 or 1.5) through 24 months, and had baseline CD4 T-cell counts 200–500 cells per microliter. A follow-up CD4 measurement was selected for each 4-month interval; patients selected for analysis were further required to have at least 4 postbaseline measurements including 1 in the second year after initiation of ARV. All regimens met the standard for HAART.

Our goal was to model the ability of naive CD4 percent in PB to predict clinically significant changes in PB CD4 T cells defined as a confirmed 100 or 200 cell increase in the first 24 months of ARV. A Confirmed increase was defined as 2 consecutive measures showing a 100 or 200 cell increase over baseline. We used an analysis cohort (n = 348) for the predictive model and tested the model's validity in a separate confirmation cohort (n = 100), randomly selected from the largest contributing study (AIDS Clinical Trials Group 384). We used sex, age, race/ethnicity, baseline CD4 T-cell count, plasma HIV RNA, and protease inhibitor versus nonnucleoside reverse transcriptase inhibitor regimen as predictive variables in addition to naive CD4 percent in logistic regression models. We further examined the effect of baseline naive CD4 percent to predict postbaseline CD4 T-cell counts above a clinically relevant threshold, using a generalized estimating equations (GEE) model.

RESULTS

We identified 348 persons who had 24 months of follow-up and baseline measures of naive CD4 percent. Most were male (87%), and the median age was 36 years. The median CD4 T-cell count at ARV initiation was 321 cells per microliter (interquartile range: 264–398 cells/ μ L). Overall, 278 of 348 individuals (80%) had a confirmed 100-cell increase and 192 of 348 (55%) a confirmed 200-cell increase in 24 months after initiation of ARV. Persons with higher measures of naive CD4 T cells at baseline had proportionately greater increases in PB CD4 T cells (Fig. 1). We used regression analysis to determine if PB-naive CD4 T cells can predict ARV-associated changes in PB CD4 T cells and included in the model baseline CD4 T-cell count and plasma HIV RNA. Baseline naive CD4 percent was highly significant for predicting

both 100 and 200 CD4 T-cell increases ($P < 0.001$). Baseline viral load (VL) was also highly significant for predicting 100-cell increases ($P < 0.001$) but did not reach significance for 200-cell increases ($P = 0.07$). Importantly, baseline PB CD4 did not predict 100-cell and 200-cell increases in PB CD4 T-cell count after 24 months of ARV in this population ($P = 0.59$ and 0.66 , respectively, from multivariate models including baseline VL and naive CD4 percent; $P = 0.39$ and $P = 0.28$ in univariate models). Thus, baseline CD4 and VL were not as reliable as naive CD4 percent at predicting immune reconstitution. Similar results were seen in 306 subjects with good virologic suppression over months 4–24. In additional modeling, age did not significantly predict 200-cell increases but was significant for predicting 100-cell increases in both univariate ($P = 0.004$) in multivariable models ($P = 0.026$). Thus, in agreement with previous studies, age did correlate to a statistically significant increase in CD4 T-cell count but did not correlate to levels of reconstitution that would bring PB CD4 T-cell counts closer to a normal level. No other factors evaluated (sex, race/ethnicity, protease inhibitor versus non-nucleoside reverse transcriptase inhibitor regimen) were additionally significant ($P > 0.05$). The positive effect of higher baseline naive CD4 percent remained consistent when models were evaluated among 139 subjects with baseline CD4 350–500 and for 213 subjects with baseline CD4 300–500.

We next constructed models for 100 and 200 CD4 T-cell increases and confirmed the models using a subset of patients set aside for this purpose (Table 1). Predictions of the model were generally confirmed in a subset of patients reserved to validate the model. For patients with naive CD4 percent at the 25th percentile (which corresponded with a naive CD4 percent of 25%), the probabilities of 100-cell and 200-cell increases were 0.75 and 0.49, respectively. Thus, to achieve a 200-cell increase in PB CD4 T-cell count after 24 months of ARV, the probability is <50% if the naive CD4 percent was at (or below) 25%.

Recent studies have shown that time spent at lower CD4 T-cell counts is associated with higher rates of opportunistic infection and mortality. We compared the proportional amount of time spent with CD4 T cells >350 and 500 cells per microliter when stratified by naive CD4 T-cell measures at baseline (Fig. 2). Higher baseline naive CD4 percent significantly predicted the likelihood that a postbaseline CD4 T-cell count was >350 cells per microliter ($P = 0.001$), in a GEE model that also adjusted for baseline CD4 T-cell count ($P < 0.001$), $\log_{10}$ HIV RNA ($P = 0.12$), and age ($P = 0.13$). In a similar multivariate model, baseline naive CD4 percent was also highly predictive for T-cell counts >500 cells per microliter during follow-up ($P < 0.001$).

DISCUSSION

We demonstrate that measuring naive CD4 T cells in PB can identify individuals in the chronic stage of disease who are most likely to achieve significant CD4 T-cell reconstitution from ARV and experience a greater proportion of time with less risk of morbidity and mortality. Naive CD4 percent was significantly better than PB CD4 or HIV RNA for predicting magnitude of CD4 cell rise. We focused on individuals with PB CD4 T cells between 200 and 500 cells per microliter, the range where most would consider initiating ARV and noted, moreover, that findings remained consistent when analyses were limited to subsets with the highest baseline CD4 cell counts (350–500, 300–500). The Data Collection on Adverse Events (D:A:D) and Flexible Initial Retrovirus Suppressive Therapies Trial (FIRST) studies showed the risk of non-AIDS-related morbidity and mortality among patients treated with ARV were more likely to occur at lower CD4 T-cell counts.^{16,17} We showed that patients most likely to have diminished CD4 immune reconstitution with ARV are those with smaller populations of naive CD4 T cells when ARV is begun.

These data have important clinical implications for timing of ARV as individuals with lower naive CD4 cells might better preserve the existing CD4 population and those with higher levels of PB-naive CD4 T cells might shift the risk/benefit ratio toward a decision to delay treatment.

The idea of using a measure of PB-naive CD4 T cells as a threshold marker to identify those least and most likely to reconstitute PB CD4 T cells was suggested by recent pathogenesis-based studies that demonstrate naive CD4 T cells are preferentially depleted in LTs^{6,18} and by clinical trials illustrating the predictive ability of PB-naive cells for CD4 cell reconstitution after 6 months of ARV.⁹ The present study considerably expands the latter work and extends observations to a 2-year treatment period. Early after initiation of ARV, effector memory cells are the first to repopulate the PB pool, likely reflecting, in part, redistribution of cells from tissues sites, whereas late reconstitution is mainly from naive CD4 T cells.¹⁹ This demonstrates that overall CD4 T-cell reconstitution is dependent on the integrity of the naive CD4 T-cell population in LTs and may be the underlying mechanism for decreased mortality seen in those who initiate ARV with higher CD4 counts compared with those deferring ARV until CD4 counts are lower.^{20,21} This is important because naive CD4 cells are the critical reservoir supplying the central memory and ultimately effector memory population of CD4 T cells.

In conclusion, we show that patients with relatively high measures of naive CD4 T cells are less likely to have failure of immune reconstitution with ARV and will spend relatively less time at risk for opportunistic infection or mortality from any cause. In particular, we demonstrate that this measure could be used to delineate patients at higher PB CD4 T-cell counts who are less likely to reconstitute immunity, which could be problematic if ARV treatment is delayed until the patient has lower CD4 T-cell counts. Conversely, this measure might also identify those who could expect higher levels of immune reconstitution even when treatment is delayed. Large prospective studies should be undertaken to more precisely define the role of measurement of naive CD4 T cells in the management of HIV infection.

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FIGURE 1.

Proportion of subjects with ≥ 100 and ≥ 200 CD4⁺ T-cell increase after 24 months of potent ARV stratified by baseline naive CD4 percent (n = 348).

FIGURE 2.

Percentage of time during 24 months of follow-up during which participants had a CD4 T-cell count above 350, 500, or 750 cells per cubic millimeter.

TABLE 1

Probability of a 100 and 200 CD4 T-Cell Increase After 24 Months on Potent ARV in the Analysis Cohort Compared With the Confirmation Cohort Stratified by Naive CD4 Percent

Naive CD4 Percent (Quartile)	≥100 Cell Increase		≥200 Cell Increase	
	Analysis Cohort n = 348 [*]	Confirmation Cohort n = 100 [†]	Analysis Cohort n = 348 [*]	Confirmation Cohort n = 100 [‡]
25% (25th percentile)	0.75	0.76	0.49	0.44
36% (median)	0.81	0.82	0.56	0.74 [‡]
46% (75th percentile)	0.85	0.88	0.62	0.59

* Predicted probabilities based on logistic regression model containing only naive CD4 percent.

[†] Observed probabilities for subjects grouped by naive CD4 percentages, <30% (observed median = 23%), 30%–39% (observed median = 36%), > 40% (observed median = 50%).

[‡] 0.62, using a wider range, naive CD4 percent: 20%–50%.