Influence of Age on CD4 Cell Recovery in Human Immunodeficiency Virus–Infected Patients Receiving Highly Active Antiretroviral Therapy: Evidence from the EuroSIDA Study

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Highly active antiretroviral therapy (HAART) is usually responsible for controlled human immunodeficiency virus (HIV) replication and a rise in CD4 cells. However, quantitative CD4 cell reconstitution is heterogeneous. In addition to other predictors of response to HAART, host factors could contribute to this heterogeneity. The thymus could play an important role in CD4 cell restoration while the patient is receiving HAART to this heterogeneity. The thymus could play an important role in CD4 cell reconstitution heterogeneous. In addition to other pre–established functions, the thymus could play an important role in CD4 cell restoration in the patient is receiving HAART.

Influence of Age on the CD4 Cell Response to Highly Active Antiretroviral Therapy (HAART) was examined in 1956 patients (median age, 37.2 years) in the EuroSIDA study. Median initial CD4 cell count was $192 \times 10^4$ cells/L, follow-up was 31 months, and time to maximum CD4 cell response was 20 months. Age groups were not different for baseline CD4 cell count, baseline human immunodeficiency virus RNA load, or treatment history. CD4 cell increase, stratified by age quartiles, differed during months 3–36 of HAART ($P = .023$). Maximum CD4 cell increase from start of HAART differed by age group ($P = .0003$), as did maximum CD4 cell count ($P = 10^{-10}$). Multivariate analysis confirmed the inverse relationship between age and maximum CD4 cell response ($P = .023$). Time to a CD4 increase of $>200 \times 10^4$ cells/L was shorter for patients in the younger age groups ($P = 10^{-26}$), as confirmed by multivariate analysis ($P = 10^{-26}$). Younger age may favor CD4 cell restoration because of preserved thymic function.

Patients and Methods

Patients. EuroSIDA is a prospective cohort study of patients with HIV infection in 52 centers across Europe and Israel [5]. Each center provided data on consecutive outpatients until a predetermined number was enrolled. Three waves of enrollment constituted the EuroSIDA I cohort (started May 1994, 3120 patients), the EuroSIDA II cohort (started December 1995, 1367 patients), and the EuroSIDA III cohort (started April 1997, 2846 patients). Information from up to 11, 8, and 5 follow-up visits was available for cohorts I, II, and III, respectively. The present analysis included all follow-up visits to February 2000.

EuroSIDA study patients had $\leq 500 \times 10^4$ CD4 cells/L in the 4 months before enrollment in the study and were $\geq 16$ years old at enrollment. Information was collected from patient case notes onto a standardized collection form at baseline and every 6 months. At each visit, the most recent weight and hemoglobin level and all CD4 cell count and virus load measurements since the last follow-up were requested. Dates of starting and stopping each antiretroviral drug and prophylaxis against opportunistic infections were recorded. Dates of diagnosis of AIDS-defining diseases, as defined by the Centers for Disease Control and Prevention (CDC) 1993
clinical guidelines [6], were recorded. Members of the coordinating office visited all centers to ensure correct patient selection and accurate data collection.

Statistical methods. This study included all EuroSIDA patients who started a HAART regimen of 2 nucleoside reverse-transcriptase inhibitors plus either 1 or 2 protease inhibitor(s) (PIs) or a nonnucleoside reverse-transcriptase inhibitor (NNRTI) during follow-up, who had CD4 cell counts measured in the 3 months before starting HAART and at least once after, and who had ≥12 months of follow-up after starting HAART. Patients were split into 4 age groups according to the age quartiles at the start of HAART. Statistical comparisons between age groups and baseline data or demographic data were done by Wilcoxon or χ² tests. Changes in CD4 cell count after starting HAART were estimated by linear interpolation at 3 monthly intervals until <100 patients remained in any age group. For analysis of peak CD4 lymphocyte response, values for CD4 cell count were log transformed, and univariate and multivariate linear regression analyses were used to determine the factors related to peak CD4 cell increase.

Variables included in the univariate analysis were demographic (sex, race, risk factor for HIV infection, and region of Europe), clinical and biologic (CD4 disease stage, CD4 cell count at HAART initiation, and CD4 cell nadir), and therapeutic (date of start of HAART, treatment-naive status, PI- or NNRTI-based regimen, whether the regimen included a double-PI association, number of new drugs started, and time on treatment to achieve maximum response). The multivariate analysis included variables significant in the univariate analysis. An additional analysis was adjusted for plasma virus load at HAART initiation for patients for whom this information was available. We used Kaplan-Meier survival curves to assess the time to an increase in CD4 cell count of >200 × 10⁶ cells/L. We used Cox proportional hazards models to determine factors associated with this CD4 cell increase. The same variables as above were entered for univariate analysis. Any variable significant in univariate analysis at P < .1 was included in the multivariate models: One model was based on these variables; another was also adjusted for the most recent available value for plasma virus load. All models were stratified by center. All statistical analyses were performed on an intent-to-treat basis, and no adjustments were made for patients stopping or changing regimens. All analyses were performed with SAS software (version 6.12; SAS Institute). P < .05 was considered significant.

Results

Characteristics of patients and treatment history. In total, 1956 patients (median age, 37.2 years; interquartile range [IQR], 32.7–44.5 years) fulfilled inclusion criteria. There were no significant differences among age quartiles in terms of CD4 nadir (median, 142 × 10⁶ cells/L; IQR, 60–234 × 10⁶ cells/L; P = .18), CD4 cell count at start of HAART (median, 192 × 10⁶ cells/L; IQR, 88–305 × 10⁶ cells/L; P = .33), time from CD4 cell nadir to HAART initiation (median, 7 months; IQR, 2–16 months; P = .18), date of HAART initiation (median, March 1997; IQR, September 1996–September 1997; P = .065), length of follow-up (median, 31 months; IQR, 24–36 months; P = .19), number of CD4 cell measurements while on HAART (median, 10; IQR, 7–13; P = .41), or interval between measurements (median, 3 months; IQR, 2–4 months; P = .91). A total of 1344 (68.7%) patients had plasma virus load measured before or at the start of HAART. These measurements were not distributed differently by age group (P = .80). Baseline plasma virus load did not differ by age quartile (median, 4.28 log₁₀ RNA copies/mL; IQR, 3.48–4.94 log₁₀ RNA copies/mL; P = .53); 135 patients had initial virus loads of <2.7 log₁₀ copies/mL (no difference between age groups; P = .08). All patients had ≥1 virus load measurement after starting HAART.

Of the subjects, 261 (13.3%) were antiretroviral naive, 371 (19.0%) started a regimen of ≥4 antiretrovirals, 123 (6.3%) started an NNRTI-based regimen, 101 (5.2%) started HAART with 2 PIs, and 779 (39.8%) started 1 antiretroviral drug they had never taken before, 573 (29.3%) started 2 new drugs, and 604 (30.9%) started ≥3 new drugs. There were no significant differences between age quartiles in the distribution of these variables. There were also no differences in terms of individual drugs used in the 4 age groups (data not shown).

CD4 cell response to HAART. The median increase in CD4 lymphocytes after initiation of HAART at 3 monthly intervals was estimated and stratified by age group. At each time point from 3 to 36 months, younger age groups had significantly greater median CD4 cell increases (P = .023).

For each patient we determined the maximum CD4 cell count and maximum CD4 cell gain after starting HAART. Older patients had poorer responses for these variables: In the 4 groups, median maximum CD4 cell counts (by increasing age quartile) were 500, 448, 430, and cells/L (no difference between age groups; P = .80); 135 patients had initial virus loads of <2.7 log₁₀ copies/mL (no difference between age groups; P = .08). All patients had ≥1 virus load measurement after starting HAART.

An increase of >200 × 10⁶ CD4 cells/L was observed in 1109 patients (56.7%). Kaplan-Meier curves (figure 1) indicate that...
Discussion

Quantitative CD4 cell response to HAART is variable and not fully explained. Among possible genetic factors, the heterozygous state for the Δ32 deletion in the CCR-5 HIV coreceptor gene was recently shown to favorably influence response to treatment [7], and several predictors of virologic successful response to HAART have been described [8, 9]. These predictors were confirmed in this study in terms of CD4 cell recovery. In our study, time on treatment was strongly correlated with the CD4 cell response in all age groups. However, younger age was still associated both with a higher absolute CD4 cell gain and a shorter time to maximum response independent of baseline CD4 cell and plasma HIV RNA levels and of other variables that influence CD4 cell response, whereas therapeutic regimens did not differ between age groups. The median age in our study was 37.2 years, and older age has predicted good virologic response to HAART, possibly because of more-favorable socioeconomic conditions [9]. Therefore, differences in CD4 cell response reaching statistical significance inside the relatively narrow age range of this study appear to be all the more relevant.

Older age at seroconversion unfavorably influences the course of untreated HIV infection [10], which may reflect the more pronounced inability of an aging immune system to counterbalance CD4 cell loss. The favorable impact of younger age

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<th>Analysis, age group (years)</th>
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<th>95% Confidence interval</th>
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NOTE. Model 1 was adjusted for factors significant in univariate analyses at P<.1; the model was adjusted for exposure group, clinical status (AIDS, yes or no), treatment history and intensity of HAART regimen, no. of new antiretroviral drugs started, date of starting HAART, CD4 cell count at start of HAART, and CD4 lymphocyte count nadir. Model 2 was adjusted for the same factors as those in model 1, as well as for the most recent virus load measurement and for reaching a virus load of <2.7 log_{10} copies/mL as a time-dependent variable.
on quantitative CD4 T cell recovery while a patient is receiving HAART is a new finding and could reflect the state of thymic function. Indeed, CD4 cell recovery after intensive chemotherapy and hematopoietic stem cell transplantation is inversely correlated with age and is thymus dependent [11, 12]. In treated HIV infection, CD4 cell recovery is biphasic and involves first memory cells and then naive cells.

The first rapid phase probably depends on cell redistribution from lymphoid tissue and may also result to some degree from cell proliferation in the periphery [13, 14]. HAART seems to restore normal T cell production rate and half-life within the first 3 months [15] of treatment. The second phase is slower, and the question of whether these cells originate from thymopoiesis has been addressed. First, the number of naive CD4 cells in blood has been correlated with the size of the thymus in untreated HIV-positive adults [1]. Furthermore, the extent of naive CD4 cell recovery on treatment in adults and children [3, 4] and the correction of T cell half-life [15] may be associated with an increase in thymic volume. Finally, by using T cell receptor rearrangement excision circles (TRECs) as a quantification method for cells produced by the thymus, Douek et al. [2] showed that such cells persist in adulthood and slowly decrease with age in healthy subjects but are absent in athymic persons. In addition, they showed that the number of TRECs in naive CD4 T cells increases in HAART-exposed HIV patients with undetectable plasma virus load [2]. HAART also normalizes the function of progenitor cells in HIV infection and thus might allow de novo production of T lymphocytes [16]. Therefore, we suggest that the favorable influence of younger age on CD4 cell recovery while a patient is receiving HAART may be explained by more-effective thymic function.

The present findings confirm that renewal of CD4 cells is a long-term process and demonstrate that age is inversely correlated with the magnitude and speed of CD4 cell recovery in actively treated HIV infection. These are additional arguments for the involvement of renewed thymopoiesis in CD4 cell reconstitution.

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References