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Negative influence of age on CD4$^+$ cell recovery after highly active antiretroviral therapy in naïve HIV-1-infected patients with severe immunodeficiency

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Summary *Objective:* To study the effect of age on several outcomes among 187 antiretroviral-naive infected patients who started highly active antiretroviral therapy (HAART) with $\leq$200 CD4$^+$/μl.
Methods: We carried out a retrospective study to determine the hazard ratio (HR) to reach an outcome in patients who experienced a change from the baseline in CD4$^+$ counts of at least +100, +200, +300, +400 and +500 cells/μl at any moment during the follow-up and the odds ratio (OR) of achieving and maintaining a CD4$^+$ value above a certain setpoint during at least 6, 12 or 18 months.
Results: The adjusted HR for an increase of +400 CD4$^+$/μl and +500 CD4$^+$/μl were 1.3 (95% CI: 1.1; 1.5) and 1.3 (95% CI: 1.1; 1.6) times slower for each additional 5 years of age at baseline. In addition, for every 5 years of extra age, the adjusted OR to achieve an absolute CD4$^+$ cell count >500/μl at 6, 12 and 18 months after the initiation of HAART were 2.2 (95% CI: 1.5; 3.2), 1.8 (95% CI: 1.2; 2.6), and 1.8 (95% CI: 1.2; 2.9) times less likely, respectively. We also found that patients $\geq$45 years old had worse complete CD4$^+$ recovery (CD4$^+$ > 500 cells/μl) than patients <45 years old.

Abbreviations: ADCs, AIDS defining conditions; AIDS, acquired immune deficiency syndrome; CD4$^+$, CD4$^+$ T-cell count; CDC, Centers for Disease Control and Prevention; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus type 1; HIV-VL, suppression of plasma HIV-1 viral load; HR, hazard ratio; NNRTI, non-nucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor.

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Conclusion: The CD4+ recovery after HAART is a prolonged and continuous process which extends for several years. Age at baseline is inversely correlated with the magnitude and speed of CD4+ recovery among HIV-1 infected patients.

Introduction

Highly active antiretroviral therapy (HAART) for treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection has improved steadily since the advent of combination therapy in 1996. In fact, Centers for Diseases Control and Prevention (CDC) has reported that the age of patients in the developed countries was increasing during this last decade.[1]

Nowadays, many patients starting HAART achieve suppression of plasma HIV-1 viral load (HIV-VL) to below detection limits and experience an immunologic enhancement evidenced by increased CD4+T cell count (CD4+).[2,3] The recovery of CD4+ after effective HAART is a 2-phase process with a rapid initial rise in the first few months, primarily due to increases in memory T cells, followed by a slow, steady increase in naive T-cell counts that can continue for years with sustained suppressive HAART.[4] As HAART became available, a minimal beneficial effect on immunological outcome has been reported in older subjects compared to younger ones. Both the intensity and the speed of immunological responses might be reduced in elderly subjects. However, a few reports have shown a similar immunological outcome in both older and younger HIV-positive subjects. Interestingly, older age did not seem to significantly affect the long-term virologic outcome of HAART among treated subjects.[5]

The thymus is the primary source of new naive T cells and it atrophies with age.[6] For that reason, patient's age at HAART initiation could influence CD4+ recovery; and the effects of HAART may differ between young and old HIV-1-infected patients.[7] This is an important issue because an increasing number of older individuals are now living on HAART.[8] In this study, we analyze the influence of age on several clinical, immunological, and virological outcomes in naïve HIV-1-infected patients who started HAART with severe immunodeficiency.

Materials and methods

Patients and HAART

We carried out a retrospective study on 187 HIV-1 infected patients on HAART from the Hospital Gregorio Marañón (Madrid, Spain) who belonged to a cohort that has been followed according to standardized procedures according to published guidelines. Following HAART, patients were monitored every 3–6 months with determination of lymphocyte subsets and HIV-VL. This study was approved by the Institutional Ethics Committee.

From a total of 1400 patients who initiated a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) based HAART between 1996 and 2004, 206 were ART-naïve (patients not exposed to NRTI or NNRTI previously) and had a CD4+ <200/μl. From these 206 patients, we selected 187 who had a follow-up of at least 6 months after the initiation of HAART. We excluded those 19 HIV patients because a long follow-up (at least 6 months) was not available so evaluation of a significant increase of CD4+ was not viable.

Clinical and laboratory markers data

Data were collected by chart and database review with a standard questionnaire in order to obtain baseline data such as age, sex, HIV risk group, Centers for Disease Control and Prevention (CDC) clinical category, methadone use, baseline CD4+ cells and HIV-VL, hepatitis C virus (HCV) and hepatitis B virus (HBV) serology, type of HAART; HIV-VL, CD4+, new Acquired Immune Deficiency Syndrome (AIDS) defining conditions (ADCs) and deaths during follow-up. The cutoff of HIV-VL below the detection limit was <200 copies/ml. We considered a failure of HAART when one patient showed 2 or more values of viral load >400 copies/ml.

Statistical analysis

Initiation of HAART was defined as the first time they took three or more antiretroviral drugs that included at least 2 NRTI plus one unboosted or boosted PI or one NNRTI. Subsequent changes of HAART were ignored in terms of statistical analysis. We considered several outcome variables including death, AIDS, achievement of a HIV-VL below the detection limits and CD4+ recovery (absolute values and change from baseline in CD4+ counts). The CD4+ recovery and viral load control were referred to achieving at least an increase or determined value at any time during follow-up. For this purpose, the patients were followed up every 3 months.

We determined the hazard ratio (HR) by multivariate Cox regression analysis to reach an outcome as the patients that experienced a change from baseline in CD4+ counts of at least 100, 200, 300, 400 and 500 cells/μl at any moment during the follow-up and the odds ratio (OR) of achieving and maintaining a CD4+ above a certain setpoint during at least 6 months (for patients with at least 12 months of follow-up), 12 months (for patients with at least 18 months of follow-up) or 18 months (patients with at least 24 months of follow-up).

In these analyses, the dependent variable was the occurrence of an outcome variable and the independent variable was age (×5 years). This analysis was adjusted by baseline characteristics (CDC C clinical category, CD4+, HIV-VL, HCV coinfection, and PI based HAART). All tests were two-tailed with P values <0.05 considered significant. Statistical analysis was performed by SPSS 12.0 software (SPSS Inc., Chicago, IL, USA).