Paper # H1890

Influence of Age in HIV-Infection Outcomes among Antiretroviral-Naive Patients with Severe Immunodeficiency during Highly Active Antiretroviral Therapy

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OBJETIVE

Patient age at HAART initiation could influence CD4+ recovery and the effects of HAART may differ between young and elder HIV-infected patients. This is an important issue because an increasing number of middle-aged and older individuals are now living with HIV owing to HAART that prolongs survival on the one hand and to late diagnosis of patients living with occult HIV infection on the other hand. In this study, we analyze the influence of age on several clinical, immunological, and virological outcomes in naïve HIV-1-infected patients that started HAART with severe immunodeficiency.

PATIENS AND METHODS

Patients and HAART

The patients for this study came from the HIV outpatient clinic of the Hospital Gregorio Marañón (Madrid, Spain). From a total of 1400 patients that initiated a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) based HAART between 1996 and 2004, 206 were ART-naïve and had a CD4+ < 200/uL. From these 206 patients, we selected the 187 who had a follow-up of at least 6 months after the initiation of HAART including the determination of T-lymphocyte subsets and VL. After the initiation of HAART, patients were monitored every 3 - 6 months with determination of lymphocyte subsets and VL. During the study period, the selection of HAART regimens and changes in therapy were done according to well-established treatment guidelines. This study was approved by the Institutional Ethics Committee.

Clinical and laboratory markers data

Data were collected by chart or database review with a standard questionnaire in order to extract information including baseline data such as age, sex, HIV risk group, Centers for Disease Control and Prevention (CDC) clinical category, methadone use, baseline CD4+ and VL, HCV and HBV serology, and type of HAART. We recorded follow-up information including responses of VL and CD4+, new AIDS defining conditions (ADCs) and deaths.

Statistical analysis

Initiation of HAART was defined as the first time they took three or more antiretroviral drugs that include PI and/or NNRTI. Subsequent changes of HAART were ignored in terms of statistical analysis. We considered several outcome variables including death, AIDS, achievement of a VL below the detection limits and CD4+ recovery. We determined the relative risk (RR) to reach an outcome by multivariate Cox regression analysis 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 theses analysis, the dependent variable was the occurrence of an outcome variables and the independent variable was age (x10 years). This analysis was adjusted by baseline characteristics (CDC C clinical category, CD4+, VL, HCV infection, and PI based HAART).

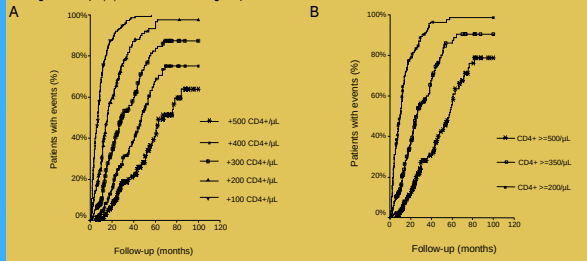
All tests were two-tailed with P-values <0.05 considered significant. Statistical analysis was performed by SPSS 12.0 software (SPSS INC, Chicago, IL, USA).

Table 1. Clinical, immunologic, and virologic characteristics of the HIV-1-infected patients at baseline.

Baseline characteristics	Values
No. HIV-1 patients	187
Male sex	155 (82.9)
Age (years)	39.5 (34.0; 44.7)
HCV infection	79 (42.2)
HIV transmission category	
Intravenous drug use (ADVP)	89 (43.2)
Heterosexual	52 (25.2)
Homosexual	44 (21.4)
ADVP/Homosexual	2 (1.0)
Other	19 (9.2)
Clinical category (CDC)[b]	
A	55 (29.4)
B	17 (9.1)
C	115 (61.5)
HIV markers	
CD4+ T cells/μL	56 (20; 116)
Log_{10} VL (copies/mL)	5.28 (4.85; 5.61)
Antiretroviral therapy	
First HAART regimen at baseline	
HAART protocols	
2 NRTI + 1 PI	72 (38.5)
2 NRTI + 1 NNRTI	44 (23.5)
2 NRTI + 2 PI	45 (24.1)
3 NRTI + 1 NNRTI	12 (6.4)
Others	14 (7.5)

Values are expressed as median (percentile 25; percentile 75) and absolute count (percentage). HCV: Hepatitis C virus. HIV-1: Human immunodeficiency virus type 1. VL: viral load. HAART: highly active antiretroviral therapy. NRTI: nucleoside analogue HIV reverse transcriptase inhibitor. NNRTI: non-nucleoside analogue HIV reverse transcriptase inhibitor. PI: protease inhibitor. VL: viral load. CDC: Center for Disease Control and Prevention.

Figure 1. Evolution of HIV-infected patients on HAART. (A): Patients with an increase of $CD4^+$ T-cells during follow-up. (B): Patients achieving a specific value of $CD4^+$ T-cells.



CONCLUSION

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

Sources of financial support: Fundación para la Investigación Sanitaria (FIS) del Ministerio de Sanidad y Consumo (PI040883, PI052479, PI052472, PI052411), Red Temática Cooperativa de investigación en SIDA (RIS G03/173) of FIS.

RESULTS

Characteristics of the HIV-infected patients

As mentioned before, a total of 187 ART-naïve patients who initiated HAART with a CD4+ < 200/Ul were included in this study. The demographics and HIV-related characteristics are shown in Table 1. In brief, 82.9% were male and their median age was 39.5 years. HIV infection was acquired by intravenous drug use in 43.2% and by sexual route in 46.5%, 61.5% had had a prior AIDS-defining condition, the median CD4+ was 56 cells/μL and the median VL was 5.28 log10 copies/mL.

The initial HAART regimen was based on unboosted PI in 38.5%, NNRTI in 23.5%, boosted-PI in 24.1% and other regimens in 13.9%. After 2 years on HAART, 42.7% patients were maintained in their initial regimen, 29.4% were on second line HAART, and 20.7% had more than two line HAART.

Evolution of virological events

One hundred and forty (74.9%), 124 (66.3%), and 109 (58.3%) patients achieved and maintained a VL below the limit of quantification during at least 6, 12 and 18 months respectively. Moreover, we did not find an effect of age on control VL (data not shown). However, the adjusted HR to achieve a VL below the limit of quantification was 0.84 (CI95%: 0.72; 0.95) times slower per each 10 years of additional age and 1.69 (CI95%: 1.23; 2.32) times slower for HCV coinfected patients.

Evolution of immunological events

The number of patients that experienced an increase in the CD4+ following HAART of at least 100, 200, 300, 400 and 500 cells/uL was 180 (96.3%), 146 (78.1%), 115 (61.5%), 83 (44.4%), and 57 (30.5%), respectively (Figure 1A). The number of patients that achieved an absolute CD4+ above 200, 350, and 500 cells/uL was 165 (88.2%), 122 (65.2%), and 80 (42.8%) (Figure 1B).

We found that the baseline CD4+ was the most important variable to predict a small or moderate CD4+ recovery. The adjusted HR to achieve a CD4+ >350/μL and to achieve a CD4+ >200 CD4+/μL was 1.30 (CI95%: 1.09; 1.55) and 1.39 (CI95%: 1.19; 1.61) times faster per each additional 50 CD4+/μL at baseline.

However, we found that age (x10 years) was associated with large increases in CD4+ (Figure 2A). The adjusted HR for an increase of ≥ 400 CD4+/μL and ≥ 500 CD4+/μL was 1.7 and 1.6 respectively; and to achieve values of CD4+ >500 cells/μL was 1.4. We also found that age (x10 years) was the most important factor to achieve an absolute CD4+ >500/μL at least 6, 12, and 18 months after the initiation of HAART; and to achieve an absolute CD4+ >350/μL at least 18 months after the initiation of HAART (Figure 2B). The adjusted OR to achieve an absolute CD4+ >500/μL at 6, 12 and 18 months after the initiation of HAART was 4.6, 3.2, and 3.4 times less likely per 10 years of extra age, respectively. Furthermore, the adjusted OR to achieve an absolute CD4+ >350/μL 18 months after the initiation of HAART was 1.9 times less likely for 10 years of extra age (Figure 2B).

Figure 2. Summary of effect of age on $CD4^+$ recovery. (A): Hazard ratio (HR) to achieve CD4+ recovery outcome (times slow for 10 years of age extra). (B): Odds ratio (OR) to achieve values of $CD4^+$ >200, >350 and >500 cells/μL at least 6, 12, and 18 months (less likelihood for 10 years of age extra)