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Predictors of CD4+ cell count response and of adverse outcome among HIV-infected patients receiving highly active antiretroviral therapy in a public hospital in Peru

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Summary
Objectives: Our aim was to investigate CD4+ cell recovery and adverse outcome after highly active antiretroviral therapy (HAART) under the Peruvian National Program for HIV.
Methods: A prospective, observational study was conducted between May 2004 and September 2005. Data were collected from records of patients receiving HAART at a public hospital under the Peruvian National Program for HIV. Predictors of CD4+ cell count recovery and adverse outcome were analyzed by multiple regression.
Results: Three hundred and twenty-six patients were included in the study. The mean increase in CD4+ cell count at six months was 114 cells/μl (95% confidence interval: 103—126). Patients with a lower CD4+ cell count at baseline and those starting HAART with a didanosine-based regimen had a higher increase in CD4+ cell count at six months. Patients starting HAART with a stavudine-based regimen had a lower increase in CD4+ cell count at six months. World Health Organization clinical stage IV at diagnosis of HIV infection, a low body weight at baseline, and starting HAART with a stavudine-based regimen were independently associated with an adverse outcome.
Conclusions: The CD4+ cell response to HAART under the Peruvian National Program for HIV was comparable with reports from other countries. However, the fact that advanced clinical disease predicted adverse outcome emphasizes the need for earlier access to HAART.

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Introduction

Since the introduction of highly active antiretroviral therapy (HAART) ten years ago, HIV-related morbidity and mortality have decreased substantially in the industrialized world.[1–4] However, global HIV-related mortality has continued to rise. By 2000, more than 90% of HIV cases and deaths occurred in developing countries where less than 10% of people living with HIV/AIDS had access to HAART.[5,6] In 2002, the Global Fund to Fight AIDS, Tuberculosis and Malaria was launched, and has approved nearly 450 grants in 136 countries.[7]

New evidence supports the implementation of national programs, suggesting lower mortality rates in settings where HAART is provided free of charge.[8] Up until May 2007, 28 941 cases of HIV and 19 828 cases of AIDS had been reported to the Peruvian Ministry of Health.[9] The HIV epidemic in Peru is still considered a 'concentrated epidemic'[10] given that it predominantly affects high-risk groups and occurs in less than 1% of the general population;[11,12] however, 68% of all AIDS cases are concentrated in Lima.[9]

Free access to HAART became available with the inauguration of the Peruvian National Program (NP) in May 2004 with the financial aid of the Global Fund. Peruvian HIV patients are often diagnosed at an advanced stage of the disease,[13] with CD4+ cell counts below 100 cells/μl and with irregular exposure to antiretroviral therapy (ART). Both advanced disease and previous exposure to ART (which has been linked with ART resistance)[14] have been associated with reduced treatment efficacy.[15,16] However, in several developing countries where patients start HAART at an advanced stage of immune suppression, consistent short-term rises in CD4+ counts have been reported.[17,18] Information on the CD4+ cell response during HAART under the Peruvian NP is very limited and of extreme relevance as it will guide further decision-making in the program. Our aim was to study predictors for CD4+ cell recovery and adverse outcome in patients after 6 months of HAART under the Peruvian NP.

Methods

Setting

The Infectious Disease Clinic at the Hospital Nacional Cayetano Heredia (HNCH) in collaboration with the Instituto de Medicina Tropical Alexander von Humboldt (IMTAvH) of the Universidad Peruana Cayetano Heredia (UPCH), is a national referral center for HIV diagnosis and management. It receives more than 5000 HIV-related outpatient visits and diagnoses approximately 400 HIV cases per year.[19] Currently 5892 patients receive HAART subsidized by the NP; our institution cares for 18% them. According to the Ministry of Health, in order to start HAART within the NP, patients should be: (1) symptomatic or (2) asymptomatic with a CD4+ cell count below 200 cells/μl or a plasma viral load above 55 000 copies/mm^3.

The NP coordinates appointments for baseline and follow-up CD4+ cell count and viral load measurements at the laboratories of the Peruvian National Institute of Health, although only half of our patients have viral load results available.[19] The NP provides fixed doses of generic antiretroviral drugs, given their lower cost. Four nucleoside analogue reverse transcriptase inhibitors (NRTI; zidovudine (AZT), didanosine (ddI), stavudine (d4T), and lamivudine (3TC)), two non-nucleoside analogue reverse transcriptase inhibitors (NNRTI; nevirapine (NVP) and efavirenz (EFV)), and two protease inhibitors (PI; lopinavir/ritonavir and indinavir) are available. NP guidelines recommend AZT + 3TC + NVP as the first-line regimen.[20] If the first-line regimen is contraindicated due to a high risk of toxicity, previous treatment failure, or by an expert panel decision, other regimens can be used.

Study population

HIV-infected individuals who received antiretroviral therapy at HNCH and who were $\geq$18 years of age, had started HAART within the NP between May 2004 and September 2005, and who had not been receiving any antiretroviral drug by other means when they started HAART within the NP, were eligible for this study. However, previous use of an antiretroviral drug was not an exclusion criterion. Patients were excluded if they were transferred to another health service within the first six months of treatment. To evaluate CD4 + cell increase and associated factors, we excluded all patients who did not have CD4+ cell counts at baseline and at six months. We also analyzed the determinants of an adverse outcome, which we defined as: (1) dying, (2) not achieving any increase in the absolute number of CD4+ lymphocytes after six months of HAART, or (3) abandoning treatment within the first six months.

Procedures

Medical records, laboratory results, and patient treatment files were retrieved and reviewed by the IMTAvH research group. We registered the following variables: sex, age, World Health Organization (WHO) clinical stage at diagnosis of HIV infection, ART use before enrolment in the NP, baseline CD4+ cell count, weight, hematocrit, and first ART regimen prescribed within the NP. Clinical and laboratory values measured up to 6 months before and 14 days after the date of enrolment were considered as baseline values. For those with more than one measurement during this period, the one closest to the date of HAART prescription was chosen. For CD4+ cell count monitoring, measurements between 5 and 7 months after enrolment were considered as the 6th month value. CD4+ cell counts were determined by either a FACSCalibur^{TM} flow cytometer instrument (Becton Dickinson and Company, Franklin Lakes, New Jersey, USA) or a FACSCount^{TM} flow cytometer instrument (Becton Dickinson); the former is used at the Peruvian National Institute of Health and the latter is used at the IMTAvH for research and service purposes.

Statistical analysis

We computed the mean and 95% confidence interval (CI) of the increase in CD4+ lymphocytes after six months of HAART. To evaluate the effect of the baseline factors on this increase, we used bivariate correlation and Student's *t*-tests. All factors with significant results ($p < 0.05$) were then included in a multiple linear regression model. Through backward elimination, the factors that did not contribute significantly to the prediction of the increase in CD4+ cell

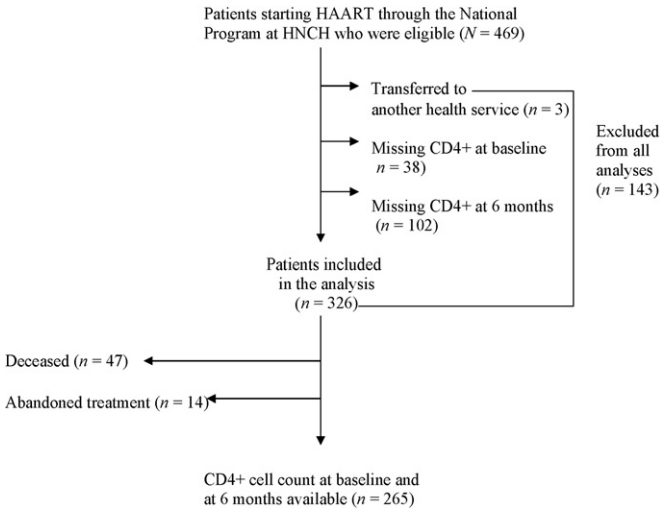

Figure 1 Flow chart showing the number of eligible subjects, and the number of subjects included in the CD4+ cell increase and adverse outcome analyses.

counts were removed. In a further analysis, we identified baseline factors associated with adverse outcome. Chi-square, Fisher's exact, and Student's *t*-tests were used for bivariate evaluations. Crude odds ratios (OR) and 95% CI were also determined. Factors with $p < 0.2$ on univariate analysis were included in a logistic regression analysis. Data were stored in Microsoft Access and analyzed with SPSS for Windows version 13.0 (SPSS, Inc., Chicago, IL, USA).

Ethical considerations

The study was approved by the Institutional Review Board at the Universidad Peruana Cayetano Heredia.

Results

Of the 469 patients who were eligible, 326 (70%) were included in the study. Of these, 47 (14%) died, 14 (4%) abandoned treatment, and 265 (81%) had baseline and follow-up CD4+ cell counts (Figure 1). The remaining 143 patients (30%) were excluded from all analyses: three patients because they were transferred to another health service, 38 due to missing CD4+ cell counts at baseline, and 102 due to missing CD4+ cell counts at six months (Figure 1).

Patient characteristics

The majority (71%) of the 326 patients included in one or both of the analyses were men (Table 1). The mean age was 36 years (standard deviation (SD): 10 years). The median baseline CD4+ cell count was 78 cells/μl (interquartile range (IQR): 139). Of the 326 study patients, 292 (90%) started on an NNRTI-based regimen (93% with NVP and 7% with EFV). The remaining patients started with a PI-based regimen. Among the included patients, the proportion of men was 71% (230/326) compared to 61% (87/143) among the subjects excluded from all analyses. This difference was of borderline significance ($p = 0.05$); there were no other differences between the study patients and the excluded subjects (Table 1).

Factors associated with CD4+ cell count increase

Two hundred sixty-five patients had baseline and follow-up values of CD4+ cell counts, and 215 (81%) of these had a CD4+ cell count below 200 cells/μl. After six months, 98 of them (46%) reached a CD4+ cell count of 200 cells/μl or more. The mean increase was 114 cells/μl (95% CI: 103—126). On bivariate analysis we observed that those who started HAART in the

Table 1 Baseline characteristics of patients included in and excluded from the study

Characteristic [a]	Patients included (*N* = 326)	Patients excluded (*N* = 143)	*p*-Value
Male sex, *n* (%)	230 (71)	87 (61)	0.05 [b]
Age in years, mean (SD)	36 (10)	35 (9)	0.3 [c]
WHO clinical stage IV at diagnosis of HIV infection, *n* (%)	223 (68)	101 (71)	0.7 [b]
ART experienced, *n* (%)	91 (28)	51 (36)	0.1 [b]
Weight in kg, mean (SD)	57 (11)	58 (10)	0.4 [c]
Hematocrit %, mean (SD)	34 (6)	35 (5)	0.6 [c]
CD4+ cell count, median (IQR)	78 (139)	78 (129)	0.6 [d]
Drugs in first regimen of the national program, *n* (%)			
Nevirapine	278 (85)	120 (84)	0.8 [b]
Efavirenz	23 (7)	10 (7)	1.0 [b]
Zidovudine	260 (80)	113 (79)	1.0 [b]
Lamivudine	320 (98)	141 (99)	1.0 [e]
Didanosine	36 (11)	16 (11)	1.0 [b]
Stavudine	28 (9)	17 (12)	0.3 [b]
Protease inhibitor	32 (10)	13 (9)	0.9 [b]

SD, standard deviation; IQR, interquartile range; ART, antiretroviral therapy.
[a] At the time of enrolment in the national program, unless otherwise indicated.
[b] Chi-square test, continuity correction.
[c] Student's *t*-test.
[d] Mann—Whitney U-test.
[e] Fisher's exact test.

Table 2 Multivariate analysis for predictors of CD4+ count increase ($N = 265$)

Explanatory variables in the final model[a]	B	Standard error	Significance	Tolerance
Constant	141.7	8.2	<0.001	
Baseline CD4+ cell count	−0.2	0.05	<0.001	0.89
Stavudine-containing regimen	−54.9	22.9	0.02	0.91
Didanosine-containing regimen	53.6	20.7	0.01	0.97

B = unstandardized regression coefficient.
[a] The initial model contained five explanatory variables: baseline CD4+ cell count, previous use of antiretrovirals, stavudine-containing regimen, didanosine-containing regimen, and hematocrit (R^2: 0.15 and adjusted R^2: 0.13). Through backward selection, hematocrit and previous use of antiretrovirals were removed (final R^2: 0.15 and adjusted R^2: 0.14).

NP with lower CD4+ cell counts had a larger increase (Spearman correlation coefficient: $p = 0.01$). Patients with a low baseline hematocrit also showed a larger increase in CD4+ cell counts (Pearson correlation coefficient: $p = 0.04$). Those who had been exposed to ART before their enrolment in the NP had a mean increase of 93 cells/μl compared to 123 cells/μl among treatment-naïve subjects (Student's t-test: $p = 0.04$). Patients starting a didanosine-based regimen had a mean increase of 150 cells/μl compared to 110 cells/μl among patients who received other regimens (Student's t-test: $p < 0.05$). On the other hand, subjects starting with a stavudine-containing regimen had a smaller increase in CD4+ cell counts (mean 41 cells/μl compared to 121 cells/μl among patients starting on a regimen without stavudine; Student's t-test: $p = 0.02$). We found no significant association between mean increase in CD4+ cell count and sex, age, WHO stage at diagnosis, weight, and the use of any of the other antiretroviral drugs in the first treatment regimen. On multiple linear regression analysis, the association with baseline CD4+ cell count, didanosine, and stavudine remained significant. The model based on these three variables explained 14% of the variation in CD4+ cell increase (Table 2).

Factors associated with an adverse outcome

Of all the patients included in the study, 28% met the criteria for an adverse outcome (47 died, 14 abandoned treatment, and 28 had a decrease in CD4+ cell count). The bivariate analysis showed that baseline weight, hematocrit, and WHO clinical stage IV at the time of diagnosis of HIV infection were significantly associated with an adverse outcome (Table 3). Starting an AZT- or d4T-based treatment regimen was also associated with an adverse outcome. On multiple logistic regression analysis, the following factors remained significantly associated with an adverse outcome: WHO clinical stage IV at diagnosis of HIV infection (adjusted OR 2.8, 95% CI: 1.2—6.4), low baseline weight (adjusted OR 0.96 per kg increase in baseline weight, 95% CI: 0.93—0.99), and starting a stavudine-based regimen (adjusted OR 4.9, 95% CI: 1.9—12.5).

Table 3 Bivariate and multivariate analysis for predictors of adverse outcome

Characteristic[a]	Treatment success ($N = 237$)	Treatment failure ($N = 89$)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Male sex, n (%)	170 (72)	60 (67)	0.8 (0.5—1.4)	—
Age in years, mean (SD)	35.5 (9.9)	35.9 (8.9)	1.00 (0.98—1.03)	—
WHO clinical stage IV at diagnosis of HIV infection, n (%)	154 (65)	69 (78)	1.9 (1.1—3.3)	2.8 (1.2—6.4)
ART experienced, n (%)	65 (27)	26 (29)	1.1 (0.6—1.9)	—
Weight in kg, mean (SD)	58.4 (11.1)	53.3 (11.3)	0.96 (0.94—0.98)	0.96 (0.93—0.99)
Hematocrit %, mean (SD)	34.9 (5.5)	32.7 (7.0)	0.94 (0.90—0.98)	—
Baseline CD4+ cell count <100, n (%)	131 (55)	53 (66)[c]	1.6 (0.9—2.7)	—
Drugs in first regimen of the national program, n (%)				
Nevirapine	203 (86)	75 (84)	0.9 (0.5—1.8)	—
Efavirenz	18 (8)	5 (6)	0.7 (0.3—2.0)	—
Zidovudine	199 (84)	61 (69)	0.4 (0.2—0.7)	—
Lamivudine	232 (98)	88 (99)	1.9 (0.2—16.5)	—
Didanosine	22 (9)	14 (16)	1.8 (0.9—3.7)	—
Stavudine	14 (6)	14 (16)	3.0 (1.4—6.5)	4.9 (1.9—12.5)
Protease inhibitor	22 (9)	10 (11)	1.2 (0.6—2.7)	—

OR, odds ratio; CI, confidence interval; SD, standard deviation; ART, antiretroviral therapy.
[a] At the time of enrolment in the national program, unless otherwise indicated.
[b] Multiple logistic regression analysis, backward stepwise approach. Variables entered on step 1: weight, WHO stage, hematocrit, baseline CD4+ count, stavudine, zidovudine, and didanosine. Nagelkerke R^2: 0.15.
[c] Baseline CD4+ cell counts were missing in nine subjects with treatment failure.

In a further analysis of the 28 patients who started with a stavudine-based regimen, there were no significant differences in baseline characteristics compared to the patients who started with other regimens (data not shown). Seventeen of these patients had anemia at the start of HAART, and eleven patients weighed less than 60 kg and might have received a higher dose of stavudine for their body weight. The most frequent drugs in the stavudine-based regimen were lamivudine and nevirapine (16/28), followed by lamivudine and lopinavir/ritonavir (7/28), lamivudine and efavirenz (2/28), and three patients took an individualized PI-based regimen. Four out of the 22 patients who survived six months after starting HAART had their treatment regimen changed within this period.

Discussion

This study shows that a good immunological response can be achieved after 6 months of HAART under the Peruvian NP. The mean increase in CD4+ count was higher than 100 cells/μl. Larger rises were observed in patients who started HAART with lower CD4+ cell counts. We also observed that a didanosine-based regimen was associated with a greater increase in CD4+ cell count. Patients who started a stavudine-based regimen had a smaller increase in CD4+ cell count. Also, when we took an adverse outcome as the endpoint, there was an association with stavudine-containing regimens. A low body weight at baseline and WHO clinical stage IV at the time of HIV diagnosis were independently linked to an adverse outcome.

The immunological response we found is consistent with mean CD4+ rises of 65—143 cells/μl described in other settings.[2,15,17,18,21—25] In a report on patients from 11 countries who attended HIV/AIDS programs conducted by Doctors Without Borders/Médecins Sans Frontières (MSF), who started HAART at advanced stages of disease (median CD4+ cell counts 89 cells/μl) and received a generic fixed dose combination (d4T, 3TC, NVP), the median increase after six months of HAART was 102 cells/μl.[21] Furthermore, a recent meta-analysis on the efficacy of HAART programs in resource-poor settings showed rises in CD4+ counts between 74 and 288 cells/μl.[26] Our patients had low CD4+ counts before starting HAART. However, the inverse correlation between the baseline CD4+ cell count and its increase at 6 months demonstrates that patients at higher risk of disease progression can rapidly recover their immune function after initiating HAART.[15] A good immunological response to HAART is associated with a good prognosis despite poor pre-treatment values. The most remarkable increase in CD4+ cell counts has been described between the first and the third month after starting HAART; the overall increase achieved thereafter is smaller.[27—30]

A stavudine-based regimen was associated with a lower increase in CD4+ cell count and with an adverse outcome; this is in contrast to several clinical trials that have not found regimens containing zidovudine to be superior to stavudine with regard to immunological or virological response.[31—37] We reviewed the complete clinical files of the 28 patients who started HAART with a stavudine-containing regimen but were unable to explain, based on the clinical information, why an adverse outcome was so frequent in this group.

Advanced stage HIV disease at diagnosis was associated with an adverse outcome, i.e., patients with a late diagnosis had a higher death rate, a lower immunological response, or a higher rate of treatment abandonment in the first six months of HAART. This is in accordance with observations in other settings.[2,18,21,38] In a community health center in Cape Town, advanced WHO clinical stage at diagnosis was associated with mortality within 4 months of starting HAART.[38] There was no association with later mortality.

In a large study comparing data from low- and high-income countries, similar immunological and virological responses after 6 months of starting HAART were found, but in the same period, mortality during treatment was substantially higher in patients from low-income settings.[8]

We found an association between low baseline CD4+ counts and an adverse outcome in the univariate analysis but the factor did not remain significant in the multivariate analysis. Nevertheless, several studies report that low baseline CD4+ counts are associated with death or poor outcome.[2,7,21,38] A low baseline weight was an independent predictor of an adverse outcome in our study, which is in agreement with other observational studies where patients with a body mass index under 18 kg/m^2 had a two-fold increased risk of dying.[21] Our model did not find differences in immune response to HAART with respect to age, which contrasts with other observations, even in similar populations.[22,29,39,40]

This study has several limitations. We could not include some pre-treatment characteristic factors known to affect CD4+ increase, such as viral load and co-existing opportunistic infections, because these data were available only for a small number of patients. In addition, the information on previous use of ART was not based on clinical records but on patient interview, which may have affected its reliability. Finally, 30% of the population was not included in the analysis because CD4+ counts were lacking either at baseline or at six-month follow-up.

In conclusion, the immunological response to HAART under the Peruvian NP was found to be comparable with reports from industrialized countries. The fact that advanced clinical disease predicts an adverse outcome as outlined by this and other studies, clearly emphasizes the need for earlier access to HAART in order to optimize the response to therapy.

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