Rev. Inst. Med. trop. S. Paulo
44 (4):179-186, July-August, 2002.

MORBIDITY AND SURVIVAL IN ADVANCED AIDS IN RIO DE JANEIRO, BRAZIL

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SUMMARY

Opportunistic diseases (OD) are the most common cause of death in AIDS patients. To access the incidence of OD and survival in advanced immunodeficiency, we included 79 patients with AIDS treated at Hospital Evandro Chagas (FIOCRUZ) from September 1997 to December 1999 with at least one CD4 count ≤ 100 cells/mm^3. The incidence of OD was analyzed by Poisson's regression, and survival by Kaplan Meier and Cox analysis, considering a retrospective (before CD4 ≤ 100 cells/mm^3) and a prospective (after CD4 ≤ 100 cells/mm^3) period, and controlling for demographic, clinical and laboratory characteristics. The confidence interval estipulated was 95%.

Mean follow-up period was 733 days (CI = 683-782). During the study 9 (11.4%) patients died. Survival from AIDS diagnosis was a mean of 2589 days (CI = 2363-2816) and from the date of the CD4 count CD4 ≤ 100 cells/mm^3 was a mean of 1376 (CI = 1181-1572) days. Incidence of OD was 0.51 pp/y before CD4 ≤ 100 cells/mm^3 and 0.29 pp/y after CD4 ≤ 100 cells/mm^3. A lower number of ODs before CD4 < 100 cells/mm^3 was associated with lower incidence rates after CD4 ≤ 100 cells/mm^3. AIDS diagnosis based on CD4$^+$ counts ≤ 200 cells/mm^3 was associated with lower incidence rates after CD4 ≤ 100 cells/mm^3. Baseline CD4 counts above 50 cells/mm^3 (HR = 0.13) and restoration of baseline CD4$^+$ counts above 100 cells/mm^3 (HR = 0.16) were associated with a lower risk of death. Controling both variables, only restoration of baseline counts was statistically significant (HR = 0.22, p = 0.04).

We found a very low incidence of OD and long survival after CD4 < 100 cells/mm^3. Survival was significantly associated with restoration of baseline CD4 counts above 100 cells/mm^3.

KEYWORDS: AIDS; Morbidity; CD4 counts; Survival.

INTRODUCTION

The introduction of highly active antiretroviral treatment (HAART) has lowered incidence of opportunistic diseases (ODs)[2], prolonged survival[3,23] and reduced AIDS-related hospital admissions[21]. HAART has also had a beneficial effect on individuals with advanced immunosuppression[3]. Little has been done, however, to explore the effects of reconstituting CD4$^+$ cells on OD incidence, especially among patients at an advanced stage of immunodeficiency[16].

Evaluation of the effect of universal distribution of anti-retrovirals free-of-charge in São Paulo revealed a 50% reduction in AIDS-related hospital admission and mortality rates[18]. However, the incidence of AIDS-related events and the factors that may influence survival following this measure have yet to be evaluated in Brazil.

OBJECTIVES

To identify the factors associated with morbidity and survival in AIDS patients treated with HAART at an advanced stage of immunodeficiency, as compared with before CD4 T cell counts dropped below 100 cells/mm^3.

PATIENTS AND METHODS

We conducted a bidirectional cohort study at the Evandro Chagas Hospital Research Centre (Centro de Pesquisa Hospital Evandro Chagas, CPqHEC) of the Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, from September 1, 1997 to December 7, 1999. The CPqHEC is an institution that specializes in treating adults with HIV/AIDS or other infectious diseases, and offers reference on clinical and laboratory services.

Inclusion criteria: adult patients with at least an absolute CD4$^+$ lymphocyte count of ≤ 100 cells/mm^3 in peripheral blood.

Exclusion criteria: individuals monitored for less than 90 days at the end of the study were excluded.

The program PAPES II / Fiocruz supported this work.

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Criterion for defining AIDS and related ODs: the CDC 1993 criterion was adopted[4]. This study however, did not take account of bacterial pneumonias due to the large number of presumptive diagnoses without bacteriological confirmation.

Data gathering: An initial interview was held to obtain retrospective data on diagnoses of AIDS-indicator diseases, as well as prior antiretroviral treatment. Whenever necessary, this information was complemented by consulting medical records. The monthly prospective evaluation recorded diagnoses of AIDS-related ODs, the antiretroviral treatment used and laboratory data such as plasma HIV1-RNA load and $CD4^+$ cell count, which were repeated every four months.

$CD4^+$ T cells were counted by flow cytometry (Epics XL, Coulter Co, FL, USA), using TriTEST CD4 FITC/ CD8 PE/CD3 PerCP monoclonal antibodies (BD Immunocytometry Systems, SJ, CA, USA). Viral load was measured by NucliSens HIV-1 QT (NASBA Diagnostics, Organon Teknika, Holland) in plasma samples. Both exams were assured by the National Network for CD4 and Viral Load Evaluation, from the National Coordination of Sexual Transmitted Diseases and AIDS, Brazilian Ministry of Health.

Statistical analysis: this contemplated two periods: a prospective period, measured in days, from inclusion in the study (date of the first CD4 count below 100 cell/mm^3) through to completion of the project, death of the patient or loss of follow-up; and a retrospective period from the AIDS diagnosis through to the $CD4^+$ cell count of inclusion. OD incidence was analyzed by Poisson regression, and survival by the Kaplan Meier method. The risks associated with the variables were evaluated by Cox regression.

Models were constructed and tested for the incidence of OD (Poisson regression) and survival (Cox proportional harzard model) considering the folowing characteristics: gender, age, the AIDS-defining criterion (OD or CD4 counts $\leq$ 200 cells/mm^3), start of antiretroviral treatment with monotherapy double therapy or HAART, aggregate number of ODs up to inclusion in the study, $CD4^+$ cell count at the moment of inclusion ($\leq$ 50, or >50/ < 100 cells/mm^3), restoration of baseline $CD4^+$ cell count (at the 100 and 200 cells/mm^3 cutoffs) and plasma virus loads over time (< 10,000, < 30,000 and < 100,000 copies/ml). A 95% confidence interval (CI) was stipulated.

Some OD were grouped by relative frequencies and the criterion of severity associated with the diagnosis[13,25] into: Group 1 - tuberculosis; Group 2 - neurotoxoplasmosis, PCP, Isosporiasis, Cryptosporidiasis and Kaposi's sarcoma; Group 3 – DMAC or Cytomegalovirosis and Group 4 - Candidiasis of the esophagus, Cryptococcosis and Histoplasmosis.

The softwares used for analysis were SPSS 8.0 for Windows[22] and EGRET[28].

RESULTS

Characteristics of the Cohort: The study included 79 individuals. Mean age at AIDS diagnosis was 37.9 years (SD = ± 9.19), and median 38 years; age on entry to the study was 39.9 years (SD = ± 9.25), and the median 40 years. Of the patients, 57 (72%) were male and 22 (28%) female. Of the 79 individuals monitored, 9 (11.4%) died from AIDS-related causes. The remaining patients were censored: 66 on completion of the study, 3 for lost follow-up and one for a road accident.

All patients in our study were treated with antiretrovirals. In the retrospective period, 43 (67%) patients had initiated antiretroviral treatment with one drug (monotherapy) and in 21 (33%) of them the initial treatment was the association of two drugs. The drugs available by the Ministry of Health program were nucleoside reverse transcriptase inhibitors (NRTI), zidovudine (AZT), didanosine (ddI), dideoxycytidine (ddC), and lamivudine (3TC). Initial regimens were: AZT in 40 patients (50.6%), ddI in 3 (3.8%), double combination with AZT and ddI in 18 patients (22.8%), AZT and 3TC in 2 patients (2.5%) and AZT and ddC in one patient (1.3%).

During the prospective period, 15 naïve patients were included (19% of the entire cohort). The treatments available at that time were nucleoside reverse transcriptase inhibitors (NRTI), zidovudine, didanosine, dideoxycytidine, lamivudine and stavudine, in addiction to the protease inhibitors (PI) saquinavir, ritonavir, indinavir and nelfinavir. They initiated their treatments with at least a triple combination as follows: AZT and ddI plus ritonavir in one case (1.3%), saquinavir in 2 cases (2.6%), indinavir in 3 cases (3.9%) and nelfinavir in 3 cases (3.9%). 3TC and estavudine added to indinavir in one (1.3%) case, nelfinavir in 1 (1.3%) case and ritonavir-saquinavir in one (1.3%) case. AZT and 3TC plus indinavir in 2 cases (2.6%), ritonavir in one case (1.3%) and ritonavir-saquinavir in one (1.3%) case. The treatment regimens followed varied according to the clinical indication (respecting Brazilian's Guidelines), and a triple therapy was used in almost all patients except in cases requiring rifampicin (n = 6), where the PI was suspended for the 6 months of tuberculosis treatment. Nevirapin a non nucleoside reverse transcriptase inhibitor (NNRT) became available during the prospective period.

Incidence of opportunistic diseases: The overall OD rate for the entire period (from AIDS diagnosis to the end of the study) was 0.39 (CI = 0.31 - 0.47) per person per year (pp/y). A total of 97 ODs occurred, 56 in the retrospective (before CD4 counts $\leq$ 100 cells/mm^3) period and 41 in the prospective (after CD4 counts $\leq$ 100 cells/mm^3) period. Of the 79 patients, 26 (32.9%) never suffered from OD at any time during the natural history of HIV.

PROSPECTIVE PERIOD *(after CD4 counts ≤100 cells/mm^3)*: The incidence rate of OD in the prospective period was 0.29 per person per year (CI = 0.21 - 0.39).

We analysed the incidence rates by frequency of aggregate ODs prior to inclusion in the study (Table 1). OD incidence was thus significantly higher (p = 0.05) among those individuals with an aggregate of more than 2 ODs. We also observed that the incidence rate among the patients with tuberculosis (0.55 pp/year) was nearly twice as high as for those who did not have tuberculosis (0.23 pp/year).

Almost surprisingly, start-up of antiretroviral treatment with triple combinations with PIs (0.54 pp/year) figures as a factor associated with a significant (p = 0.05) greater morbidity in this period in comparison with monotherapic regimens (0.25 pp/year, Table 1).

Incidence rates were controlled for other variables for which the results, although without statistical significance, are given in Table 2.

Table 1

Incidence (Poisson regression) of opportunistic diseases (OD) according to demographic, clinical and laboratory characteristics in advanced immunodeficiency – Significant variables for the prospective (after CD4 counts dropped < 100 cells/mm^3) period

Variable	Category	N	Incidence of OD pp/year	CI	P value
Aggregate number of	1 OD	16	0.34	0.23-0.52	0.05
OD prior to inclusion in	2 OD	10	0.59	0.22-1.60	
the study	3 OD	4	0.78	0.25-2.41	
	4 OD	2	0.73	0.23-2.36	
Tuberculosis diagnosis	Yes	14	0.55	0.21-1.54	0.01
(all participants)	No	65	0.23	0.17-0.34	
initial ARV	Monotherapy	43	0.25	0.04-0.32	0.05
treatment	HAART	15	0.54	0.04-1.43	

N = number; CI= confidence interval; pp/year = per person/year; P values ≤ 0.05 were considered statatiscally significant; ARV = antiretroviral

Table 2

Incidence (Poisson regression) of opportunistic diseases according to demographic, clinical and laboratory characteristics in advanced immunodeficiency – Not significant variables in the prospective period (after CD4 counts < 100cells/mm^3)

Variable	Category	No. of cases	Incidence of OD pp/year	CI	P value
Gender	Male	57	0.26	0.18-0.38	0.26
	Female	22	0.38	0.13-1.05	
Age at inclusion	≤40 years	42	0.29	0.19-0.44	0.95
	>40 years	37	0.29	0.10-0.82	
Aids criteria	CD4<200	44	0.62	0.39-0.97	0.16
	TB	14	0.76	0.22-2.63	
	Protozoan infection	9	0.54	0.14-2.11	
	DMAC or CMV	4	1.13	0.21-5.99	
	Fungal infection	2	2.81	0.61-12.95	
Aids defining OD	TB	14	0.36	0.19-0.70	0.76
	Protozoan infection	9	0.29	0.05-1.55	
	DMAC or CMV	4	0.61	0.08-4.30	
	Fungal infection	6	0.43	0.06-2.71	
CD4 at entry	> 50 cells/mm3	36	0.21	0.07-0.58	0.10
	≤ 50 cells/mm3	43	0.35	0.24-0.51	
Restoration of CD4 counts	No	20	0.41	0.24-0.73	0.17
above 100 cells/mm^3	Yes	59	0.26	0.07-0.89	
Restoration of CD4 counts	No	49	0.27	0.18-0.42	0.66
above 200 cells/mm^3	Yes	30	0.31	0.11-0.89	
Sustained viral load	Yes	22	0.30	0.18-0.51	0.81
Below 10,000 copies	No	57	0.28	0.09-0.91	
Sustained viral load	Yes	30	0.29	0.14-0.40	0.33
Below 30,000 copies	No	49	0.33	0.10-1.05	
Sustained viral load	Yes	47	0.27	0.18-0.42	0.66
Below 100,000 copies	No	32	0.31	0.11-0.89	
TB diagnosis *	Yes	14	0.61	0.22-1.67	0.44
	No	65	0.78	0.53-1.13	

* excluding patients without OD diagnosis; TB = tuberculosis, Protozoan infection = *Pneumocystis*, CNS toxoplasmosis, Fungal infection = *Histoplasma*, *Cryptococcus* and esophageal Candidosis

RETROSPECTIVE PERIOD: The incidence rate of ODs in this period was 0.51 pp/year (CI = 0.39 - 0.66). Higher incidence of ODs was observed in individuals whose AIDS diagnosis was established by OD as compared with diagnosis by $CD4^+ < 200$ cells/mm^3, with a value of p = 0.05 (Table 3).

We determined the incidences of ODs excluding the stratum of patients diagnosed with AIDS by $CD4^+$ counts, and the results indicate that the difference observed in the first analysis is not repeated (p = 0.46).

OVERALL SURVIVAL: Mean survival of the entire cohort from AIDS diagnosis was 2589 days (CI = 2363-2816) equivalent to 7.09 years, and the median was 2916 days (7.98 years).

When $CD4^+$ count used as an inclusion criterion was categorized into ≤ 50 cells/mm^3 (n = 43) and 51 - 100 cells/mm^3 (n = 36), survival was significantly longer (p = 0.03), for those with $CD4^+$ counts > 50 cells/mm^3 (mean = 2650 days, CI = 2512 - 2788, HR = 0.13) than for those with $CD4^+$ counts ≤ 50 cells/mm^3 (mean = 2352, CI = 1956 - 2747).

Survival was also longer for patients whose $CD4^+$ cell counts were restored to > 100/mm^3 during follow-up (n = 59, mean survival = 2769 days; CI = 2583 - 2955), in comparison with those who did not restore (n = 20, mean survival = 1911 days; CI = 1341 - 2481, p = 0.03, HR = 0.16).

Modelling survival to incorporate all the significant variables described above revealed that the effect of $CD4^+$ count at inclusion had become insignificant (HR = 0.24; CI = 0.03 - 2.01, p = 0.19), while the HR for those with restored $CD4^+$ counts was 0.22, and significant (CI = 0.05 - 0.93, p value = 0.04).

We evaluated plasma viral load throughout the study at three cut-off points and observed no differences among the categories evaluated – (a) < 10,000 copies, mean survival = 2663 days (CI = 2261-3064, n = 22) and ≥ 10,000, mean = 2140 days (CI = 1939 - 2348, n = 57); (b) < 30,000, mean = 2635 days (CI = 2294 - 2976, n = 30) and ≥ 30,000, mean = 2136 days (CI = 1910 - 2361); and (c) < 100,000, 2661 days (CI = 2356-2886, n = 32) and ≥ 100,000, mean = 2098 (CI = 1777 - 2418).

Other variables were not statistically significant in survival: AIDS diagnosis by immunological criteria, $CD4^+ < 200$ cells/mm^3 (mean =

Table 3
Incidence (Poisson regression) of opportunistic diseases according to demographic, clinical and laboratory characteristics in advanced immunodeficiency – Significant variables for the retrospective (before CD4 counts dropped < 100 cells/mm^3) period

Variable	Category	N	Incidence of OD pp/year	CI	P value
AIDS criteria	CD4< 200	44	0.13	0.04-0.39	0.05
	TB	17	0.71	0.14-0.39	
	Protozoan infection	12	0.87	0.17-4.45	
	DMAC or CMV	11	1.70	0.24-12.21	
	Fungal infection	12	1.01	0.17-5.87	
TB diagnosis	Yes	14	0.36	0.24-0.54	0.01
(all participants)	No	65	0.76	0.29-1.84	

N = number of cases; pp/year = per person/year; CI = Confidence interval; P values ≤ 0.05 were considered statatiscally significant; TB = Tuberculosis; Protozoan infection = *Pneumocystis*; DMAC = disseminated *Mycobacterium avium* complex; CMV = Cytomegalovirus; Fungal infection = Histoplasmosis, Cryptococcosis and esophageal Candidosis; CI = confidence interval

Table 4
Incidence (Poisson regression) of opportunistic diseases according to demographic, clinical and laboratory characteristics in advanced immunodeficiency – Not significant variables for the retrospective period (before CD4 counts dropped < 100 cells/mm^3)

Variable	Category	No. of cases	Incidence of OD pp/year	CI	P value
Aids defining OD	TB	17	0.71	0.46-1.08	0.46
	Protozoan infection	12	0.87	0.30-2.57	
	DMAC or CMV	11	1.71	0.38-7.61	
	Fungal infection	12	1.01	0.29-3.51	
TB diagnosis	No	65	0.74	0.29-1.87	0.47
* *excluding patients without OD diagnosis*	Yes	14	0.89	0.60-1.34	

TB = tuberculosis, Protozoan infection = *Pneumocystis*, CNS toxoplasmosis; DMAC = disseminated *Mycobacterium avium* complex; CMV = Cytomegalovirus; Fungal infection = *Histoplasma*, *Cryptococcus* and esophageal Candidosis

2466 days, CI = 2086 - 2847) if compared with diagnosis by OD (mean = 2373 days, CI = 2200 - 2547, p = 0.35), prior use of monotherapy (mean = 1276 days, CI = 1168 - 1384) compared with the start of treatment with associations of two or three drugs (mean = 2631 days, CI = 2375 - 2887), in addition to sex and age at AIDS diagnosis.

SURVIVAL DURING THE PROSPECTIVE PERIOD: We described survival and the factors associated with it from the moment when patients were considered severely immunodepressed, at the point their $CD4^+$ count fell below 100 cells/mm^3. Overall mean survival was 1376 days (CI = 1181 - 1572).

Survival was similar among men and women and was neither associated with the age, the AIDS-defining criteria, aggregate diseases prior to inclusion in the study, baseline CD4 counts, viral load or the initial antiretroviral treatment (Table 5).

We found however, longer survival among 59 individuals whose counts were restored to > 100 cells/mm^3 as compared with those whose counts were not restored (Fig. 1). At the 200-cell cut-off point, however, this effect becomes less evident (Table 5).

The model that included the variables restoration of $CD4^+$ cells with a 100-cell cut-off point and counts at time of inclusion in the study with a 50-cell/mm^3 cut-off point indicated that restoration of cells (HR = 0.21, CI = 0.05 - 0.93) continued significant (p = 0.05), while count at start of the study (HR = 0.19, CI = 0.02 - 1.59) lost statistical significance (p = 0.12). The variable determinant of longer survival was restoration of $CD4^+$ count to values > 100 cells/mm^3.

DISCUSSION

Our study started at almost the same time as antiretrovirals became

Table 5
Survival according to demographic, clinical and laboratory characteristics in advanced immunodeficiency (after CD4 dropped below 100 cells/mm^3 - prospective period)

Variable	Category	No. of cases	Mean survival	CI	Log rank p value
Gender	Male	57	1424	1221-1626	0.57
	Female	22	1023	880-1166	
Age at inclusion	≤ 40 years	42	1074	958-1190	0.64
	> 40 years	37	1417	1191-1644	
Aids criteria	CD4 < 200	44	1603	1495-1711	0.16
	OD	35	1180	969-1391	
Aggregate N of OD prior	no OD	47	1606	1495-1711	
to inclusion in the study	1 and 2 OD	26	1112	982-1242	0.11
	3 and 4 OD	6	966	401-1532	
CD4 at entry	> 50 cells/mm3	36	1655	1564-1746	0.09
	≤ 50 cells/mm3	43	1201	1035-1367	
Restoration of CD4 counts	no	20	1489	1298-1680	0.01
above 100 cells/mm^3	yes	59	796	683-908	
Restoration of CD4 counts	no	49	1166		0.10
above 200 cells/mm^3	yes	30	1601		
Sustained viral load	yes	22	1437	1201-1673	0.54
Below 10000 copies	no	57	1018	922-1114	
Sustained viral load	yes	30	1419	1193-1645	0.75
Below 30000 copies	no	49	1022	923-1121	
Sustained viral load	yes	47	0.27	0.18-0.42	0.66
Below 100000 copies	no	32	0.31	0.11-0.89	
Initial ARV treatment	monotherapy	43	1398	1189-1608	0.96
	HAART	15	880	824-935	

N = number, CI = Confidence interval , OD = opportunistic diseases, ARV = antiretroviral, HAART = higly active antiretroviral therapy

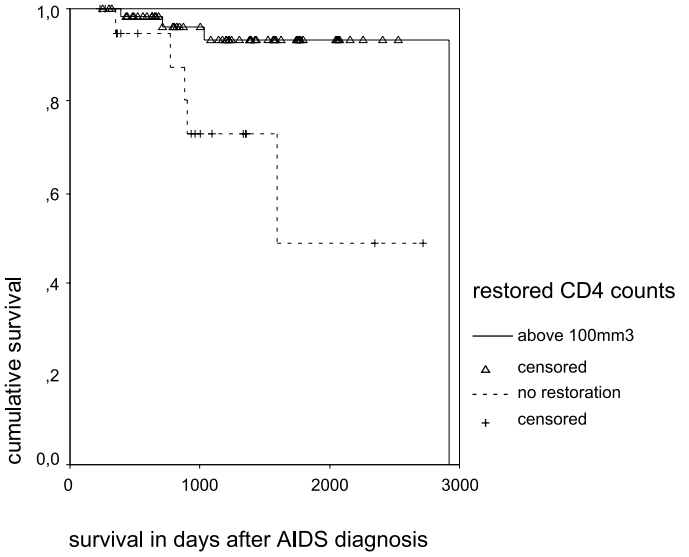

Fig. 1 - Survival (Kaplan Meier) from AIDS diagnosis in patients whose CD4 counts were restored to above 100 cells/mm^3 and those whose counts remained below 100 cells/mm^3

available and as viral load tests were made simultaneously with CD4$^+$ counts[19]. The results of these measures, such as reduced occurrence of ODs and increased survival, were quickly perceived by the researchers involved in our protocol, as by all health workers responsible for caring for those with HIV/AIDS in Brazil[18]. The same has been observed in other parts of the world[5,10, 23].

When survival from AIDS diagnosis was considered, we found a low death rate, given that the deaths only began to occur following inclusion in the study at a time when the individuals were already at an advanced stage of immunodeficiency, and treated with HAART.

The median survival time for the whole cohort, from AIDS diagnosis up until the end of the study, was 7.09 years. This is an extremely long period when compared with other studies in Brazil, where the period between AIDS diagnosis and death varied from 4.9 months to 9.15 months[9,12]. In another more recent Brazilian study, which differentiated by gender, survival of 20 months was observed for men and 11 months for women[26]. Even studies prior to the introduction of PIs in Europe and the United States encountered post-AIDS survival shorter than our results, viz. Australia, 14.4 months[13] and 15 months[7], San Francisco 12.5 months[11], Denmark 13.0 months[24] and New York, 13.7 months[1].

In addition to the effect of HAART, the criteria for inclusion in our study may have led to a selection bias towards individuals who had already survived with AIDS for a reasonably long time before inclusion in our cohort. Also, the CPqHEC is a centre specializing in research and treatment for individuals with HIV/AIDS, where adhesion to proposed appointments and treatments is good, and where these individuals receive multidisciplinary care and are treated free of charge, not just for HIV, but also for associated ODs.

From 1997 onwards, some authors showed a decline in AIDS-related mortality, which was attributed to antiretroviral therapy with protease inhibitors[5,10] and longer survival times, thus similar to our results[14].

In the prospective period of the study (after CD4 counts < 100 cells/mm^3), the incidence rate of opportunistic diseases (0.29 pp/y) was almost half that observed in the retrospective period (before CD4 counts < 100 cells/mm^3 = 0.51 pp/y), which we consider the opposite of what one might expect on the basis that advanced immunodeficiency should be associated with higher rates. We attribute this finding to the use of HAART during the prospective period. Other authors also describe a decrease in morbidity associated with the use of PIs in several countries[10,17,23].

Our study showed no significant difference in OD incidence and survival among women and men under or over 40 years old. Although some studies have evaluated the role of age and gender in the prognosis for morbidity and mortality from ODs[10,23], and no association has been established between these two factors, CHAISSON *et al.* argues that this finding in other studies reflects differences in access to health services and not in demographic features[5]. One recent study, which evaluated survival among men and women, showed shorter survival times among women that were not explained by differences in access to health services, and pointed to a lower CD8$^+$ cell counts among women as being the main factor implicated[26].

In the cases we studied, the AIDS diagnosis by disease was significantly ($p < 0.05$) associated with greater morbidity from OD in the retrospective period as compared with diagnosis by CD4$^+$ < 200 cells/mm^3. In 1999, LEDERGERBER *et al.* also showed a risk of disease 2.5 times higher in patients whose AIDS diagnosis was established by OD[10]. However, survival does not appear to be influenced by these factors in our study, given that these events preceded inclusion in the protocol by several years, and lose force over time.

Although the results presented show a strong relationship between the aggregate quantity of OD during the retrospective period and morbidity during the prospective period, no significant differences in survival was detected.

In the pre-HAART era, some studies suggested that the higher aggregate number of ODs in the course of AIDS was associated with higher risk of death[20], while others observed that the prognosis for patients with other associated ODs was not necessarily worse than for those with a single disease[13]. More recent studies show that the severity associated with each individual OD continues to influence the prognosis over time[10], in addition to determining greater risk of incidence of other ODs[8]. However, these studies did not evaluate aggregate OD, because the patients were included in those studies at an early stage of HIV infection and thus without any significant aggregate of OD.

Baseline CD4$^+$ cell count showed a strong association with survival, which was not shown with morbidity. Many authors have evaluated the role of CD4$^+$ cell counts in the prognosis of death[5,10], but few have tested the factors associated with ODs incidence.

The very low incidence of ODs and the small number of participants, as compared with other cohorts in multicentre studies, may have contributed to this association not being detected in our study.

We also evaluated the effect of reconstitution of the immune system by categorizing individuals whose CD4$^+$ cells were or were not restored to levels of > 100 cells/mm^3, again finding a strong association with

survival, but not with morbidity. We evaluated restoration of the immune system at another cut-off point ($CD4^+ > 200$ cells/mm^3) to determine, as other authors have done[5], whether the effect would be stronger at higher $CD4^+$ levels, but observed no statistically significant differences in morbidity at this cut-off point.

No differences were observed in OD rates or in survival according to viral load at the 10,000-copy, 30,000-copy or 100,000-copy cut-off points. Other studies to evaluate the value viral have shown that ODs have been associated with higher viral loads and with progression to other ODs[10].

In the cases we studied, the use of monotherapy was associated with lower OD rates than triple therapy. Our including individuals with at least one $CD4^+$ cell count ≤ 100 cells/mm^3 resulted in a selection bias towards individuals who had survived for a long time with severe immunodeficiency on monotherapy or double therapy. Meanwhile, patients included in our study who initially used triple treatments (15%) were diagnosed as AIDS cases by disease, already with severe immunodeficiency (CD4 counts below 100 mm^3) and most of the times with other OD diagnoses which led to an association, at the time of inclusion in the study, between the start of HAART and ODs morbidity.

When we evaluated the effect of these treatments in survival, we observed that although a trend to survive longer was observed among those who used double or triple treatment as the initial regimen, this difference was not statistically significant.

Antiretroviral treatment has been evaluated in other studies, and its protective role has been very clearly demonstrated in studies of large numbers of cases, which noted a relationship between intensification of the treatment (inclusion of PIs) and improved prognosis[2,17].

In conclusion, our study observed a reduction in OD incidence after CD4 counts dropped below 100 mm^3, time almost all patients were under HAART. We also observe the protective role of reconstituting CD4 cells in survival. These effects were associated with the use of highly active antiretroviral treatment jointly with the prophylaxis for OD such as *Pneumocystis carinii* pneumonia (PCP) neurotoxoplasmosis and tuberculosis which is routine practice at our Centre.

RESUMO

Morbidade e sobrevida em AIDS avançada no Rio de Janeiro, Brasil

As doenças oportunistas (DO) são a causa mais comum de morte em pacientes com AIDS. Para acessar a incidência de DO e a sobrevida na imunodeficiência avançada, foram incluídos 79 pacientes com AIDS tratados no Hospital Evandro Chagas (FIOCRUZ) no período de Setembro de 1997 a Dezembro de 1999, com ao menos uma contagem de células CD4 ≤ 100/mm^3. A incidência de DO foi analisada pela regressão de Poisson e a sobrevida pela analise de Kaplan Meier e Cox, considerando um período retrospectivo (anterior à contagem de CD4 ≤ 100 cels/mm^3) e um prospectivo (após a contagem de CD4 ≤ 100 cels/mm^3) e controlando-se características demográficas clínicas e laboratoriais. O intervalo de confiança estipulado foi o de 95%.

O período médio de acompanhamento foi de 733 dias (IC = 683 - 782). Durante o estudo, nove (11,4%) pacientes morreram. A sobrevida a partir do diagnóstico de AIDS foi em média de 2589 dias (IC = 2363 - 2816) e da data da contagem de CD4 ≤ 100 cels/mm^3 foi em média de 1376 dias (IC = 1181 - 1572). A incidência de DO foi de 0,51 pp/ano no período pré-CD4 ≤ 100 cels/mm^3 e 0,29 pp/ano no período pós-CD4 ≤ 100 cels/mm^3. Um menor número de DO acumuladas no período pré-CD4 ≤ 100 cels/mm^3 foi associado com taxas de incidência menores no período pós-CD4 ≤ 100 cels/mm^3. O diagnóstico de AIDS baseado em contagem de $CD4^+$ ≤ 200 cels/mm^3 foi associado com menores taxas de incidência durante o período pós-CD4 ≤ 100 cels/mm^3. As contagens basais de células CD4 acima de 50 cel/mm^3 (HR = 0,16) foram associadas a um menor risco de morte assim como a restauração da contagem basal acima de 100 cels/mm^3 (HR = 0,16). Controlando-se ambas, somente a restauração da contagem basal manteve sua significância estatística (HR = 0,22, p = 0,04)

Encontramos uma baixa incidência de DO durante o período pós-CD4 ≤ 100 cels/mm^3 e uma sobrevida longa após CD4 ≤ 100 cels/mm^3. A sobrevida foi significativamente associada com a restauração das contagens de CD4 basais.

ACKNOWLEDGEMENT

We thank to the Day-Hospital team for the special dedication: Liane Braga da Silveira, Luci Alves, Solange Alves da Cruz, Sonilde Mello Fasolo and Marcia Regina Lyra da Silva.

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Received: 5 February 2002
Accepted: 27 June 2002