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AIDS Incidence and Mortality in a Hospital-Based Cohort of HIV-1–Seropositive Patients Receiving Highly Active Antiretroviral Therapy in São Paulo, Brazil

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ABSTRACT

Brazilian AIDS and HIV-1–seropositive patients have had free access to highly active antiretroviral therapy (HAART) since November 1996. Although secondary data based on official mortality statistics indicate a sharp decrease in AIDS mortality, few if any studies tried to estimate the prognosis for patients with HIV who have been followed from the beginning of the HAART era. An observational study, with retrospective and prospective components, was done in 233 adult HIV-1–infected subjects who were recruited in the last 10 years at the outpatient sector of the Secondary Immunodeficiencies Clinic of the Department of Dermatology, Hospital das Clinicas da FMUSP, Sao Paulo, Brazil. The definition of AIDS followed the guidelines issued by the Centers for Disease Control (CDC) in 1987. One hundred sixty patients were asymptomatic, 46 had AIDS, 24 had AIDS-related complex, and 3 presented with acute infection at study entry. Twenty-nine (18%) of the asymptomatic subjects developed AIDS during follow-up, with 5 (3%) deaths. Among the 46 AIDS cases at entry, 7 (17%) died during follow-up. Thus, a total of 12 people (5.2%) died of AIDS in this cohort over a mean follow-up of 5.2 years and 24 people were lost to follow-up (10.3%). Ninety percent of the survivors were on combined therapy (82% with 3 or more drugs, and 8% with 2 drugs), while 10% were not taking antiretrovirals. People with AIDS at entry were 5 times more likely to die during this period compared to patients who were asymptomatic at entry ($p = 0.006$). Women showed better outcomes than men, reflecting differences in $CD4^+$ T-cell counts at study entry. All but 1 patient progressed to AIDS during the pre-HAART era (before 1996). In spite of its recent decline, mortality from AIDS-related conditions remains an important public health issue.

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INTRODUCTION

BRAZIL has the highest cumulative incidence of AIDS in Latin America,[1] with more than 200,000 cases reported in the last 20 years of the epidemic.[2] Although the spread of HIV infection has recently been slowed, it is estimated that more than 500,000 Brazilians are currently infected with HIV, most of them unaware of their serologic status.[3]

In the last 10 years, the Brazilian federal government has set up a national AIDS program for the diagnosis, monitoring, and treatment of patients with HIV/AIDS. This program has received worldwide recognition as a standard for HIV/AIDS care. The main feature of this successful initiative is free antiretroviral drug availability in the public health service sector.[4,5] Until now, however, few data have been reported relating the effect of this policy on the incidence of AIDS and AIDS-related mortality. In a previous study, we reported the incidence of, and mortality from, AIDS in a cohort of asymptomatic HIV-positive subjects from São Paulo in the pre-highly active antiretroviral therapy (HAART) era.[6] Thus, in the current study, our aim was again to estimate incidence and mortality in asymptomatic HIV-positive subjects from São Paulo, the city with the highest number of AIDS cases in Brazil, in order to evaluate the influence of the free availability of antiretroviral treatment on these parameters.

MATERIAL AND METHODS

The study population included 233 HIV-1–infected subjects who were enrolled on a cohort aimed to describe the natural history of HIV infection in São Paulo, a study conducted at the outpatient service of the Secondary Immunodeficiencies Clinic of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. The first cases were recruited in October 1987 and the last in December 2000. Patients were seen in the clinic at time intervals not longer than 6 months, usually less. Cut-off date for the current analysis was February 15, 2002.

Demographic and clinical data were obtained from clinical charts or direct interview and the Ethical Committee of Hospital das Clínicas, University of Sao Paulo (HC-FMUSP) approved the study protocol.

Definitions and statistical methods

AIDS-defining events were determined according to guidelines issued by the Centers for Disease Control and Prevention (CDC) in 1987.[7] Differences in patient characteristics or laboratory values of asymptomatic and AIDS patient groups at entry were tested for statistical significance with Yates' corrected χ^2 for proportions or the nonparametric Kruskal-Wallis for continuous variables. Follow-up time was defined from the date of entry into the cohort until the occurrence of an AIDS-defining event, or patients were censored on the date of their most recent $CD4^+$ T-cell count. Incidence of AIDS-defining events was calculated as the number of events per person-years of follow-up for all strata. Risk ratios and their 95% confidence intervals were calculated using Epi Info (version 6.04c; CDC, Atlanta, GA). Survival curves for the time to AIDS-defining events for the 160 asymptomatic patients at entry were calculated by the Kaplan-Meier product-limit method using Stata software (versions 5.0, Stata Corporation, College Station, TX).[8] The log-rank statistic was calculated to test for equality of survivor functions.

RESULTS

The characteristics of the patients included in the study are shown in Table 1. One hundred fifty-seven (67%) patients were men, and 76 were women (33%). One hundred sixty patients were asymptomatic, 46 had AIDS, 24 had AIDS-related complex (ARC), and 3 had primary acute HIV infection. Proportions of male gender, mean age, mode of transmission, pretreatment T $CD4^+$ count and pretreatment plasma HIV RNA levels are also shown in Table 1.

For most of the following analysis, the patients with ARC (24) and those presenting with acute retroviral syndrome (3) were excluded. Thus, 46 patients with AIDS and 160 HIV-infected asymptomatic subjects were analyzed

Table 1. Characteristics at Baseline and Follow-Up of Two Hundred Six HIV-1–Infected Patients Classified according to the CDC Classification (1987)

Characteristics at entry	*Asymptomatic* n = *160 (78%)*	*AIDS* n = *46 (22%)*	p *value*
Gender: n (%)			
Female	54 (34)	12 (26)	0.9
Male	106 (66)	34 (74)	
Age: mean years ± SD	36 ± 9	38 ± 7	1.0
Risk: n (%)			
Homo/bisexual men	76 (47)	22 (48)	0.9
Heterosexual	54 (34)	11 (24)	
Intravenous drug users	8 (5)	6 (13)	
Unknown, others	22 (14)	7 (15)	
$CD4^+$ T cells/mm^3 at entry: *n* (%)			
< 200	27 (30)	33 (72)	0.04
> 200	133 (22)	13 (28)	
$CD4^+$ T cells/mm^3 (median ± range)			
Entry	477 ± 308	183 ± 196	0.7
Prior to initiation of HAART	294 ± 283	160 ± 147	0.8
Current (last available)	514 ± 310	290 ± 232	
Plasma HIV RNA, Log_{10} s/mL (median ± range)			
Prior to initiation of HAART	4.53 ± 0.8	4.75 ± 1.2	NS
Last measurement	3.26 ± 1.38	3.8 ± 1.4	
AIDS-defining events[a]	29 (18%)	—	
AIDS deaths *n* (%)	5 (3%)	7 (15%)	0.006
HAART efficacy, *n* (%) of VL < 400 copies/mL	51 (32%)	10 (22%)	0.25

[a]AIDS-defining events (according to CDC) that occurred among HIV-1–infected individuals who started as asymptomatic: 6, oroesophagus moniliasis; 4, pulmonary and extrapulmonary tuberculosis; 3, disseminated herpes zoster; 2, *P. carinii* pneumonia (PCP); 1, encephalitis toxoplasmosis; 1, chronic diarrhea by *Cryptosporidium* sp.; 1, cerebral cryptococcis.

HAART, highly active antiretroviral therapy; VL, viral load.

here. The self-reported route of HIV transmission included 98 (47%) men who had sex with men, 65 (32%) patients who reported heterosexual contact, 14 (7%) intravenous drug users (IDU), and 29 (14%) patients who reported unknown or no risk factor. *Pneumocystis carinii* pneumonia prophylaxis was given to all patients who presented $CD4^+$ T-cell counts below 200 cells/mm^3, and zidovudine (AZT) or didanosine (DDI) monotherapy was given to 37% of the individuals in this cohort. The diagnoses of AIDS-defining illnesses are shown in Table 1. Patients with $CD4^+$ T-cell-count lower than 200 cells/mm^3 experienced a greater incidence of AIDS-defining events than those with more than 200 cells/mm^3 at entry (odds ratio [OR]: 4.12; 95% confidence interval [CI]: 2.16–7.9).

Among the 46 patients with AIDS at entry, 7 (15%) died during follow-up compared to 5 (3%) deaths among the 160 symptomatic at-entry subjects (OR: 5.56 95% IC: 1.46–21.51, $p = 0.006$). A total of 12 people died of AIDS in this cohort, and 24 people were lost to follow-up. Mean follow-up time was 52 months. The last available information on HAART indicated that 42 patients were receiving three or more drugs, including one or more protease inhibitors, 2 were given double therapy, and 2 cases did not receive any drug. Their mean age were 38 years, and 74% were males. Mean $CD4^+$ T-cell counts were 183 ± 196/mm^3, 160 ± 147, and 290 ± 232, at study entry, pre-anti-retroviral therapy (ART) treatment, and post-ART, respectively. Ten patients attained a plasma viral load (VL) of less than 400 copies per milliliter after 36 months of therapy in this group, indicating an efficacy of HAART of 22%.

Mean age of the 160 asymptomatic HIV-1–infected carriers at entry was 36 years; 66% were males. Twenty-nine (18.1%) developed AIDS-defining events during follow-up (last case in December 1999), with 5 (3%) deaths in this group, and 20 cases were lost to follow-up after an average of 44 months of ART. Fifty-one (32%)

TABLE 2. CHARACTERISTICS AT BASELINE AND FOLLOW-UP OF TWO HUNDRED THIRTY-ONE HIV-1–INFECTED PATIENTS, ACCORDING TO $CD4^+$ CELL COUNT AT STUDY ENTRY

Characteristics at entry	*< 200* (n = *66*)	*> 200* (n = *165*)	p *value*
Gender: n (%)			
Female	15 (23)	60 (36)	0.9
Male	51 (77)	105 (64)	
Age: mean years ± SD	37 ± 9	38 ± 7	1.0
Risk: n (%)			
Homo/bisexual men	29 (44)	78 (47)	0.9
Heterosexual	16 (24)	58 (35)	
IV drug users	7 (11)	5 (04)	
Unknown, others	14 (21)	24 (14)	
$CD4^+$ T cells/mm^3 (median ± SD)			
Entry	94 ± 56	532 ± 278	0.7
Prior to initiation of HAART	116 ± 104	314 ± 180	0.8
Currently (last available)	320 ± 208	527 ± 312	
Gain of $CD4^+$ T cells	+210	+175	
Plasma HIV RNA, Log_{10} s/mL (median ± SD)			
Prior to initiation of HAART	4.80 ± 1.0	4.44 ± 1.0	NS
Last visit	3.40 ± 1.53	3.80 ± 1.4	
Drop in viral load (last-first visit)	−1.63 ± 1.93	−1.30 ± 1.54	
AIDS-defining events	37 (56%)	39 (27%)	< 0.0005
AIDS deaths *n* (%)	7 (3%)	6 (15%)	0.006
HAART efficacy, *n* (%) VL < 400 copies/mL	25 (38%)	45 (27%)	0.25
Type of ART			
None	1	35	
Two	9	21	
Three or more drugs	56	107	

NS, not significant.

of them achieved a VL of less than 400 copies per milliliter in their last available measurement.

When the cohort is classified according to the $CD4^+$ T-cell count at study entry, patients with less than 200 cells/mm^3 ($n = 66$) and more than 200 cells/mm^3 ($n = 165$) presented an incidence of 37 (56%) and 39 (24%) AIDS-defining events, respectively. The ART efficacy, defined as a VL of less than 400 copies per milliliter was 38% ($n = 25$) for the CD4 < 200 group, with a mean decrease in viral load of −1.63 log, and 27% ($n = 45$) for the group with a CD4 higher than 200, with a mean decrease of VL of −1.93 log. Seven (15%) and six (4%) deaths occurred in the CD4 < 200 and CD4 > 200 groups, respectively (Table 2).

Causes of death

During follow-up, two patients died of non-Hodgkin's lymphoma, two of tuberculosis of the central nervous system, one of lactic acidosis, one of chronic hepatitis C and liver failure, one of septicemia from an unknown agent, one of disseminated cytomegalovirus infection, one of non-*Pneumocystis carinii* interstitial pneumonia, and one of chronic diarrhea. For two patients the causes of death were unknown.

Progression to AIDS

During follow-up, 29 (18.1%) of the 160 asymptomatic patients developed AIDS, leading to an incidence of the disease of 3.84 per

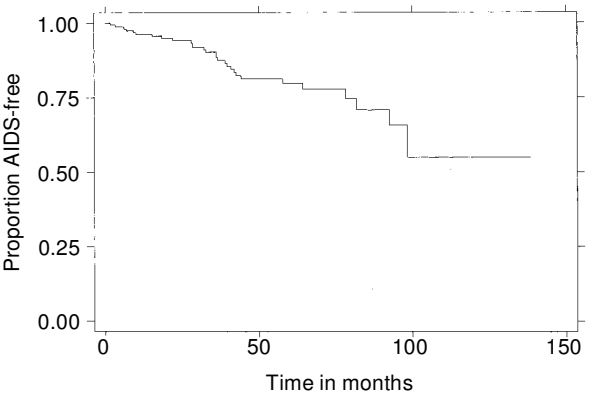

FIG. 1. AIDS-free survival curve (Kaplan-Meier estimates) of 160 asymptomatic HIV-seropositive patients.

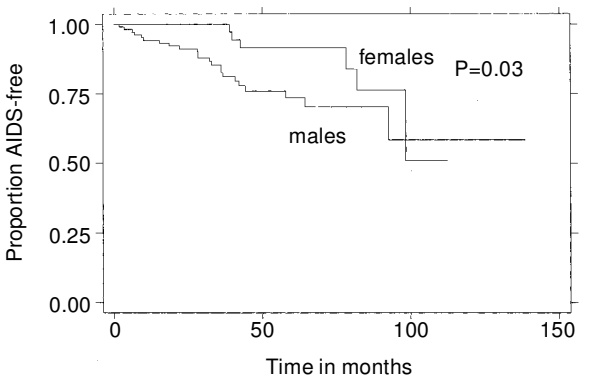

FIG. 2. AIDS-free survival curve (Kaplan-Meier survival estimates) of 160 asymptomatic HIV-1–seropositive patients.

1000 person-months, and the mean follow-up was 47.2 months (range, 2–138 months). Twenty-three of the 29 incident cases occurred in men, and the remaining 6 in women. AIDS incidence was 4.91 per 1000 person-months among males, and 2.1 per 1000 person-months among females. The probability of remaining AIDS-free for the entire cohort from the first positive anti-HIV serology was (mean ± standard error [SE]) 94.1% ± 1.9% at two years, 81.2% ± 3.7% at four years, and 77.7% ± 4.3% at 6 years of follow-up, respectively (Fig. 1). Males had a cumulative probability of remaining AIDS-free of 70.1% ± 6% at 6 years, compared to females' probability of 91.5% ± 4.7% at the same point in time. As compared by the log-rank test, females' probability estimates of remaining AIDS-free were significantly higher than males' ($p = 0.03$) (Fig. 2). Mean CD4 cells count at entry were significantly higher among females ($p = 0.02$) (Table 3).

DISCUSSION

Overall, 5.6% of our HIV-1–infected patients died in the last 5 years. As expected, people with AIDS at entry were 5 times more likely to die during this period than asymptomatic subjects at entry. AIDS incidence among asymptomatic subjects was 18.1%. The majority progressed to AIDS during the pre-HAART era, before 1997. Only one case progressed to AIDS after 1997 when HAART became widely available in Brazil.

Patients with a $CD4^+$ T-cell count below 200 cells/mm^3 at entry showed a similar RNA VL response to HAART compared to with those with a $CD4^+$ T-cell count above 200 cells/mm^3. Recent reports have shown that the virologic response to HAART is independent of the CD4 count at entry.[8,9] However, risk of death from AIDS was significantly higher among the CD4 < 200 group, showing that even when there is no apparent benefit in terms of virologic success (VL < 400 copies per milliliter), HAART seems to improve survival in this group. Some investigators argue that even when there is active replication of the virus in the host, the fitness of the escaped virus population is decreased under HAART pressure.[10]

The $CD4^+$ T cells increased after HAART by an average of 210 cells/mm^3 for the CD4 < 200 group and by 175 cells/mm^3 for the CD4 > 200 group. These results are similar to those reported for several observational cohort studies in the United States and Europe.[11] Women in this cohort showed a higher CD4 T cell counts at study entry and less AIDS progression than men.

Although some deaths were caused by usual opportunistic infections, others were related to HAART complications or neoplasms. Thus, clinicians should be aware that although the risk of serious opportunistic infections is currently lower than in the past, patients now face the threat of potentially severe complications caused by the therapy itself.

The probability of remaining AIDS-free,

TABLE 3. CUMULATIVE PROBABILITY OF REMAINING AIDS-FREE, ACCORDING TO GENDER

	%AIDS-free (mean ± SE) at			
Variable	*2 years*	*4 years*	*6 years*	p-*value*
Entire cohort	94.1 ± 1.9	81.2 ± 3.7	77.7 ± 4.3	
Gender				0.03
Men	91.2 ± 2.8	75.9 ± 4.9	70.1 ± 6.0	
Women	100.0	91.5 ± 4.7	91.5 ± 4.7	

when AIDS is defined according to the CDC classification of 1987 was much higher in the current study than in our previous report from a similar cohort followed from 1985 to 1997, that is, in the pre-HAART era in Brazil.[6] In the latter study, the probability of remaining AIDS-free at 2 and 4 years was 79% and 64%, respectively,[6] compared to 94% and 81% in the current study. The better prognosis of HIV infection observed in the present study might have been because of the use of antiretrovirals for many asymptomatic patients at risk for opportunistic diseases, as established on the guidelines of the National Brazilian AIDS Program.[4,5]

However, it is not possible to exclude that earlier and more frequent diagnosis of HIV infection, a consequence itself of a better medical care delivered to AIDS patients in recent years, could have also played a part in the improved prognosis seen in this study.

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