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AIDS incidence and survival in a hospital-based cohort of asymptomatic HIV seropositive patients in São Paulo, Brazil

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Background In spite of the high incidence of AIDS in Brazil, few studies have tried to evaluate the prognosis of asymptomatic HIV seropositive Brazilian patients.

Methods A hospital outpatient facility-based cohort of HIV seropositive asymptomatic subjects was followed to determine their probability of remaining AIDS-free at 2 and 4 years of follow-up, as well as the one-year estimated cumulative probability of survival for the AIDS incident cases. The cohort was made up of all asymptomatic HIV seropositive subjects referred to the Immunology Branch of a large university hospital in São Paulo, Brazil, between 1985 and June 1997.

Results The cumulative probability of remaining free from AIDS was 79% (± 3.7% SE) at 2 years, and 64.4% (± 5.1% SE) at 4 years after first known positive anti-HIV serology. Women had a marginally significant better probability of remaining AIDS-free after both 2 and 4 years of known seropositivity, as compared with men. There were no significant differences in the prognosis of the infection by age; the only single parameter associated with better prognosis was an initial CD4+ count ⩾350/μl. The probability of survival one year after the diagnosis of AIDS was 78%, and the 50% estimated probability of survival was 19 months. Older patients (aged ⩾35 years) had a better prognosis, as suggested by their longer survival estimates ($P = 0.06$).

Conclusions The probability of survival with AIDS observed in this study was higher than in the few previously published estimates for Brazil. However, since the time frame was so wide, it may not be entirely comparable with earlier studies. Some likely explanations for this possibly better prognosis could include more efficient prophylaxis for opportunistic diseases, as well as an increase in the availability of anti-retroviral drugs. The 8% incidence of AIDS at 2 years observed in this study for those individuals whose initial CD4+ count was ⩾350/ml was close to that found in a large international epidemiological study of seroconverters.

Keywords HIV infection, progression to AIDS, survival with AIDS, Brazil

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Studies on the prognosis of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) are important tools for monitoring the global pandemic. They can provide valuable information about the response of different groups to HIV infection and help estimate future AIDS-related health care needs. Moreover, they may provide baseline parameters to be compared in the future with the survival experience of patients subject to new therapeutic strategies.

Despite their importance, the number of published studies on the survival of AIDS patients in Brazil is very small, and information on the prognosis of HIV seropositive asymptomatic individuals is practically non-existent. The rare prognostic studies that have been published to date were concerned with survival after onset of AIDS. They were conducted either in reference centres, where most patients present some time after the first occurrence of an opportunistic condition and therefore represent prevalent rather than incident AIDS cases,[1] or were based on pooled data from cases reported up to 1989.[2]

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Thus, there are no recent survival estimates that may be useful in a further evaluation of the impact of the approach officially adopted in Brazil in late 1996, which consists of providing all AIDS patients with free-of-charge multiple anti-retroviral therapy.

This study, based in a university hospital outpatient facility, attempted to evaluate prognosis and survival of a relatively small cohort of HIV-positive subjects, followed for up to 9 years. Demographic and immunological characteristics were also analysed, in order to assess their possible influence on survival.

Subjects and Methods

Study population

The study population included all 145 asymptomatic HIV-infected subjects admitted for medical care at the outpatient facilities of the Clinical Immunology service of a university hospital in São Paulo, Brazil (Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo) from 1986 to 1997, and who had at least one follow-up evaluation in the 6-month period following admission. Five subjects were recruited in 1986, five in 1987, six in 1988, four in 1989, 11 in 1990, 19 in 1991, 37 in 1992, 21 in 1993, 21 in 1994, eight in 1995, four in 1996, and four in 1997. Fifteen subjects died during follow-up, 35 were still being followed at the cutoff date (30 June 1997), and 95 were last seen sometime before the closing date. Among the latter, 21 were known to have developed AIDS during the study, while 74 were asymptomatic at their last visit to the clinic. The HIV seropositivity was detected through screening tests performed for blood donation, or at primary health care centres where some of the subjects voluntarily presented for HIV testing. These health care providers then referred the HIV-positive subjects for follow-up; other sources of referral were friends, sexual partners and spouses who were already being followed at the same facilities. The HIV seropositivity was detected by enzyme-linked immunosorbent assays, and confirmed by either Western-blot or immunofluorescence methods. Data collected at admission included risk behaviour for HIV infection, medical history, and baseline haematological, serological and immunological measures, including T lymphocyte sub-population counts. Subjects were evaluated at variable intervals, but not longer than 6 months. At each visit, evidence of a current or past opportunistic disease was sought, a new CD4+ cell count performed, and a follow-up form completed. Treatment and/or prophylaxis of opportunistic diseases were those defined by guidelines and recommendations issued by the Brazilian Ministry of Health at the time of the event. Monotherapy was provided by zidovudine or, rarely, with didanosine or zalcitabine. The latter were more widely employed after 1992, when these drugs became available free of charge. Therapy with multiple drugs, including protease-inhibitors, started officially in November 1996 when the government began to provide the drugs to AIDS patients, as well as to selected HIV-positive non-AIDS subjects.

Primary endpoints of the analysis were the development of AIDS and death. The occurrence of AIDS was defined according to the revised CDC criteria,[3] modified to include pulmonary tuberculosis as an AIDS-defining condition. However, only one patient was diagnosed with AIDS on the basis of the detection of isolated pulmonary tuberculosis.

The cutoff date for the analysis was 30 June 1997.

Table 1 Baseline characteristics of the cohort

Sex n (%)	
Men	105 (72.4%)
Women	40 (27.6%)
Mean age years (range)	35.5 (18–67)
Mean first CD4+ cell count /μl (± SD)	492 (332)
Risk behaviour	
Males n (%)	
Homo/bisexual	69 (65.7%)
Heterosexual	18 (17.1%)
Injecting drug use	15 (14.3%)
Other	3 (2.9%)
Females n (%)	
Heterosexual	28 (70%)
Injecting drug use	6 (15%)
Other	6 (15%)

Statistical analysis

The AIDS-free interval was measured from the first known confirmed HIV-positive serology to the diagnosis of AIDS. Time of seroconversion was unknown for all but three subjects, for whom an approximate seroconversion date was available.

Time to death was measured from the date of the first AIDS-defining event. In addition to hospital records, a search at the municipal office in charge of mortality statistics helped provide information on time and underlying cause of death for four patients. Fischer's exact test was used for categorical variables, and two-tailed t-test for continuous variables. The Kaplan-Meier product-limit method[4] was used to calculate the cumulative probability of AIDS-free interval, as well as that of survival. The log-rank test was used to compare survival curves.

Statistical calculations were performed with the aid of the statistical package Stata.[5]

Results

Baseline characteristics

A total of 145 subjects, 105 men (72.4%) and 40 women (27.6%) were included in the analysis. Their baseline characteristics are shown on Table 1. Mean age for the entire cohort was 35.5 years. Mean first CD4+ count was 492/μl. Homosexual and bisexual activities were the most common risk behaviours in males, while 70% of the women were infected through heterosexual contact. Women were younger than men (mean age 33.1 versus 36.4; $P = 0.04$), and tended to have higher, although not significantly, mean values of first CD4+ counts (552 versus 466/μl; $P = 0.19$).

Progression to AIDS

Mean follow-up was 32.4 months (range 2–106 months). During follow-up, 48 (33.1%) out of the 145 patients developed AIDS, leading to an incidence of the disease of 10.2 per 1000 person-months. Forty-one (85.4 %) out of the 48 incident cases occurred in men, and the remaining seven in women. AIDS incidence was 11.9 per 1000 person-months among males, and 5.5 per 1000 person-months among females.

The probability of remaining AIDS-free for the entire cohort from first positive anti-HIV serology, as estimated by the

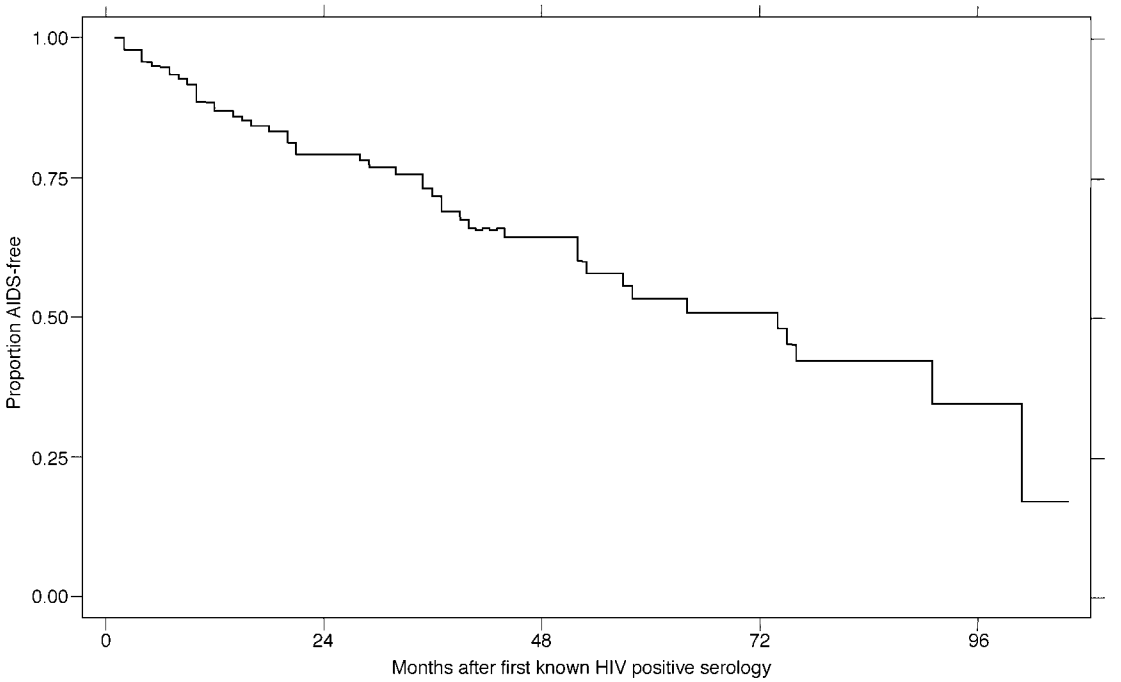

Figure 1 AIDS-free survival curve (Kaplan-Meier estimate) from first known positive serology, of 145 HIV-positive asymptomatic subjects

Kaplan-Meier product-limit method, was (mean ± SE) 79.3 ± 3.7% at 2 years, and 64.4 ± 5.1% at 4 years (Figure 1). Males had a cumulative probability of remaining AIDS-free of 74.6 ± 4.8% at 2 years, and of 57.5 ± 6.0 % at 4 years, compared with females' probabilities of 91.6 ± 4.6% and 87.0 ± 6.2% at the same points in time. As compared by the log-rank test, females' survival estimates were marginally higher than males' ($P = 0.06$). Mean ± SD initial CD4+ cell counts were, respectively, 466 ± 326 for males and 552 ± 347 for females ($P = 0.19$).

The AIDS incidence according to the age groups <35 years (78 subjects), and ⩾35 years (67 subjects) did not differ significantly when their respective curves were compared by the log-rank test ($P = 0.22$); stratification by sex did not change the results ($P = 0.32$). Mean ± SD initial CD4+ cell counts were 500 ± 346 for subjects aged ⩾35 years, compared with 481 ± 324 for subjects <35 years ($P = 0.75$).

Mean CD4+ first counts were significantly higher for those subjects remaining asymptomatic than for those developing an opportunistic disease (583 ± 335 SD versus 306 ± 243 SD; $P < 0.01$). Accordingly, the probability of remaining AIDS-free throughout the study was significantly higher for subjects whose first CD4+ cell count was ⩾350/μl, than for those whose first count was <350/μl (log-rank test: $P = 0.001$) (Table 2).

The most common AIDS-defining opportunistic disease was tuberculosis (all sites combined), which was responsible for nine cases (18.8%), followed by *Pneumocystis carinii* pneumonia (eight cases, or 16.6%) and cerebral toxoplasmosis with six cases (12.5%). Kaposi's sarcoma was the AIDS-defining diagnosis for only two patients, and non-Hodgkin's lymphoma for one.

Forty-one (85.4%) of the 48 AIDS patients in the study received at least one anti-retroviral drug for some time during follow-up. The most widely employed drug was zidovudine (ZDV), which was used by all patients on anti-retrovirals; six of these patients took it in combination with didanosine (DDI). Among the 97 subjects who remained free from AIDS, 36 (33.6%) received an anti-retroviral, either ZDV alone (75%), or in combination with another transcriptase-reverse inhibitor (25%).

Table 2 Cumulative probability of remaining AIDS-free, according to study variables

Variable	% AIDS-free (mean ± SE) at 2 years[a]	% AIDS-free (mean ± SE) at 4 years[a]	*P*-value[b]
Entire cohort	79.0 ± 3.7	64.4 ± 5.1	
Sex			0.06
Men	74.6 ± 4.8	57.5 ± 6.0	
Women	91.6 ± 4.6	87.0 ± 6.2	
Age group (years)			0.22
<35	75.9 ± 5.7	57.9 ± 7.3	
⩾35	82.7 ± 4.8	71.4 ± 6.9	
Initial CD4+ count (μ/l)			0.001
⩾350	92.2 ± 3.3	78.4 ± 6.0	
<350	58.6 ± 7.9	42.6 ± 9.0	

[a] Kaplan-Meier survival estimates.

[b] Log-rank test.

Survival with AIDS

Mean follow-up time after the diagnosis of AIDS for the 48 incident cases was 11.4 months (range 1–60 months). Fifteen (31.3%) patients died, leading to an incidence rate of death of 27.5 per 1000 person-months. Twelve of the 41 male patients died (29.3%), compared with three of the seven women (42.9%). Death rates were 25.2 and 44.1 per 1000 person-months,

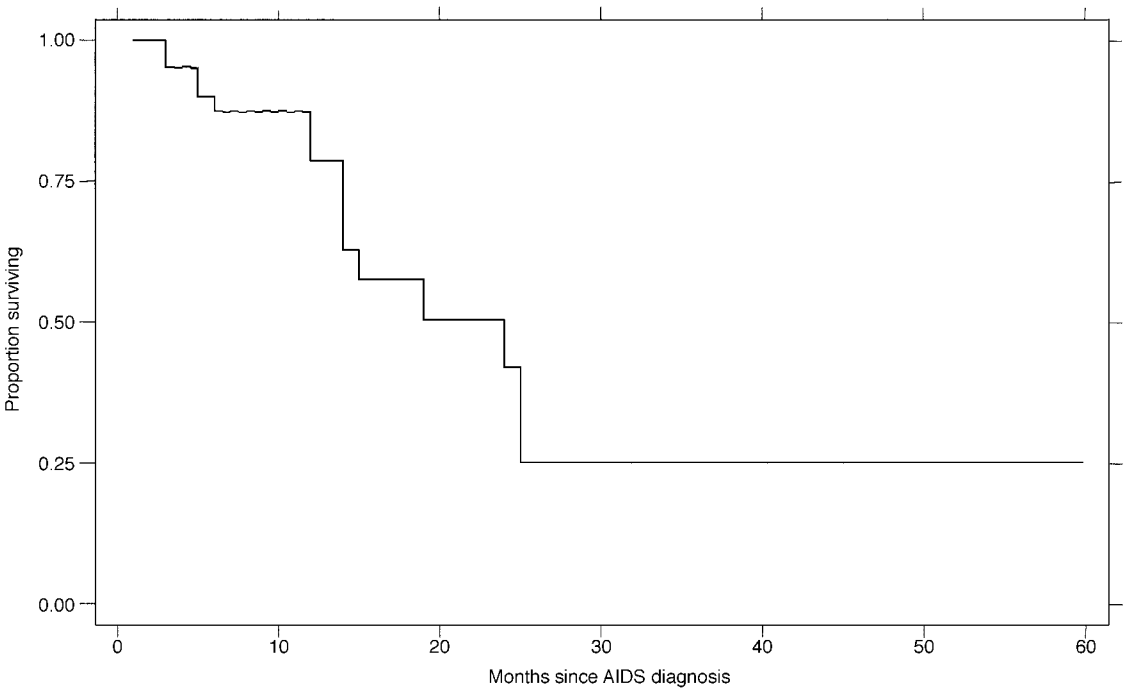

Figure 2 Kaplan-Meier estimates of the survival probability of 48 AIDS incident cases

respectively, for males and females. The most common AIDS-defining diagnosis for patients who died was cryptococcal meningitis (31%).

The cumulative probability of survival (mean ± SE) at one year was 78.6 ± 7.6%. Fifty per cent (±11% SE) estimated probability of survival was 19 months. (Figure 2).

Seven deaths were observed among the 29 patients whose age was ⩾35 years, compared with eight among the 19 younger patients, yielding a marginally significant higher survival probability for older patients (log-rank test: $P = 0.06$).

Incident HIV infection cases

Although the time of infection was not known for the majority of the subjects in this study, for three of them an approximate date of seroconversion was available. These patients were being followed due to their known exposure to HIV, and therefore previous negative anti-HIV serology could be compared with the first positive serology; their approximate date of seroconversion was considered to be the mid-point between the last negative and the first positive tests. The time interval between the last negative and the first positive HIV tests for these patients were 6, 8 and 12 months. Of these three patients, two, both males, remained asymptomatic 61 and 26 months after seroconversion, while the third, a female, developed cryptococcal meningitis 5 years and 4 months after her approximate date of seroconversion, and died 25 months after that diagnosis, despite treatment.

Long-term survival

One patient, a man whose first diagnosis of oesophageal candidiasis was made 60 months before the close of this study, has since remained relatively stable and with few symptoms. His CD4+ cell count was 350/μl of serum in August 1992, and 241 in June 1997, when he had already taken multiple anti-retroviral therapy for the last 8 months.

Discussion

Despite the fact that Brazil is the Latin American country with the highest reported absolute incidence of AIDS,[6] and that the epidemic there dates from the first half of the last decade, no study on the recent survival experience of Brazilian AIDS patients has been published. The few available estimates on AIDS survival in Brazil came from data gathered through 1989[2] and 1991.[1] In the years following the last of those survival estimates prophylaxis and treatment of opportunistic diseases has become more widely available. At the same time first generation anti-retrovirals began to be given, free of charge, first for AIDS patients, and later for asymptomatic HIV-positive subjects meeting some clinical and/or immunological criteria. Thus, it is likely that the prognosis of both non-AIDS HIV-infected subjects, as well as that of AIDS patients might have improved since the publication of the above-mentioned papers. Some indirect evidence can be already inferred from the behaviour of AIDS mortality in males in São Paulo city, which peaked in 1994, levelled-off in 1995, and declined slightly in 1996. However, a declining trend in AIDS incidence has been detected among males since 1993, a fact that could have affected mortality rates.[7,8]

The probability of survival of AIDS patients in the current study was higher than that previously described for Brazilian patients. The 78% estimate for the probability of surviving one

year contrasts with median AIDS survival times of around 5 months found in both previous studies. In addition to better overall provision of prophylaxis and treatment of opportunistic diseases, of anti-retroviral treatment, and also of expertise in the management of the disease in the time since the close of those studies, other reasons, related to differences in methodology, could help explain the apparent improvement in survival. In fact, since the detection of AIDS cases in this study was based on the follow-up of HIV-positive asymptomatic subjects, rather than on AIDS diagnosis reported to a national surveillance system,[2] or on a diagnosis already made elsewhere,[1] this study was more likely to have included truly incident, rather than prevalent, cases. The inclusion of pulmonary tuberculosis as an AIDS-defining disease in this study could have biased the results on prognosis and survival to the better, since it usually occurs at higher CD4+ counts. However, only one patient was diagnosed as an AIDS case solely on the basis of a pulmonary tuberculosis diagnosis, a fact that minimizes the influence of that procedure on the findings of the study. Another plausible explanation may be that the current study was developed exclusively in a university hospital facility, where trained personnel and laboratory resources (e.g. CD4+ cell counts) were available on a routine basis since 1985, unlike most other public facilities devoted to the management of AIDS in Brazil.

Other findings are unique to this work, since no other published paper has dealt with the probability of remaining AIDS-free for Brazilian HIV-infected asymptomatic subjects. The observations in this study were made throughout the evolution of the management of HIV infection and AIDS in Brazil, but ceased before the large-scale introduction of protease inhibitors, which were made available free of charge in November 1996. Therefore its results may be viewed as an approximation of the natural history of HIV infection in Brazil, or at least of what can be inferred from the follow-up of seroprevalent cases. Thus, the observed 21% AIDS incidence at 2 years for the entire group was higher than the 3.2% incidence in homosexuals found in a large international epidemiological study of seroconverters.[9] However, the incidence of the disease was only 8% at 2 years among those subjects in the current study whose initial CD4+ cell count was $\geqslant 350/\mu l$, which suggests that the seroconversion time for these subjects might not be too far back in time from the date of their first known positive anti-HIV serology. In fact, the only variable significantly associated with longer asymptomatic periods in HIV-infected subjects in this study was having an initial CD4+ cell count $\geqslant 350/\mu l$, a finding in agreement with other studies.[10,11]

In this study, sex apparently exerted an influence on the probability of remaining AIDS-free, since women had a marginally significant better survival experience, as well as lower incidences of the disease at both 2 and 4 years. Initial mean CD4+ counts were non-significantly higher among women, which could help explain their higher probability of remaining AIDS-free. Similarly, age did not have a decisive impact on the incidence of AIDS, at least as judged by the cumulative probabilities of <35 year olds compared with those of older subjects.

The most important weaknesses of this observational study are related to the small size of the population under study, which could be responsible for the observed lack of significance of age on the survival of AIDS patients; a cofactor that has been identified in many studies.[12,13] Moreover, some of the survival estimates lacked somewhat in precision as the number of involved patients fell, as reflected by higher standard errors. This is particularly true for the survival probability of AIDS patients at one year, since the error was 7.5%. However, even if the less optimistic estimate was assumed as the 'true' survival probability, it would still be higher than that described in earlier Brazilian studies.

The contributions of this study were to provide both a more updated estimate of survival among Brazilian AIDS patients and the first estimates of prognosis for HIV-infected asymptomatic subjects. The latter was made possible only by the existence, in a university hospital, of an outpatient service established in 1985 and devoted primarily to the follow-up of asymptomatic HIV-positive individuals. Although this practice may not be feasible throughout the country, it should be encouraged in other university-based AIDS-care centres in order to improve not only the understanding of the natural history of AIDS, but also the standards of care.

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