

# Survival of adult AIDS patients in a reference hospital of a metropolitan area in Brazil

## Sobrevivência de pacientes adultos com Aids em hospital de referência no Nordeste brasileiro

Maria F Guerreiro<sup>a</sup>, Ligia RS Kerr-Pontes<sup>b</sup>, Rosa S Mota<sup>c</sup>, Marcondes C França Jr.<sup>d</sup>, Fábio FTávora<sup>d</sup> e Iusta Caminha<sup>d</sup>

<sup>a</sup>Núcleo de Vigilância Epidemiológica e Controle de Doenças e Agravos, Secretaria Municipal de Desenvolvimento Social. Fortaleza, CE, Brasil. <sup>b</sup>Departamento de Saúde Comunitária, Universidade Federal do Ceará (UFC). Fortaleza, CE, Brasil. <sup>c</sup>Departamento de Matemática e Estatística (UFC). Fortaleza, CE, Brasil. <sup>d</sup>Faculdade de Medicina (UFC). Fortaleza, CE, Brasil

### Keywords

Acquired immunodeficiency syndrome, drug therapy. Survival. Antiviral agents. Socioeconomic factors. Educational status. Antiretroviral therapy.

### Abstract

#### Objective

To evaluate the influence of sociodemographic, clinical, and epidemiological factors in AIDS patients survival in a reference hospital.

#### Methods

A sample of 502 adult AIDS patients out of 1,494 AIDS cases registered in a hospital in Fortaleza, Brazil, was investigated between 1986 and 1998. Sixteen cases were excluded due to death at the moment of the AIDS diagnosis and 486 were analyzed in the study. Socioeconomic and clinical epidemiological were the variables studied. Statistical analysis was conducted using the Kaplan-Meier survival analysis and the Cox proportional hazards model.

#### Results

Three hundred and sixty two out of the 486 patients studied took at least one antiretroviral drug and their survival was ten times longer than those who did not take any drug (746 and 79 days, respectively,  $p < 0.001$ ). Patients who took two nucleoside reverse transcriptase inhibitors (NRTI) plus protease inhibitor were found to have higher survival rates ( $p < 0.001$ ). The risk of dying in the first year was significantly lower for patients who took NRTI and a protease inhibitor compared to those who took only NRTI. In addition, this risk was much lower from the second year on (0.10; 95%CI: 0.42-0.23). The risk of dying in the first year was significantly higher for less educated patients (15.58; 95%CI: 6.64-36.58) and those who had two or more systemic diseases (3.03; 95%CI: 1.74-5.25). After the first year post-diagnosis, there was no risk difference for these factors.

#### Conclusions

Higher education revealed to exert a significant influence in the first-year survival. Antiretroviral drugs had a greater impact in the survival from the second year on. A more aggressive antiretroviral therapy started earlier could benefit those patients.

### Resumo

#### Objetivo

Avaliar, em um hospital de referência, a influência de fatores sociodemográficos e clínico-epidemiológicos na sobrevivência de pacientes com Aids.

#### Métodos

Foi estudada uma amostra de 486 adultos com Aids atendidos em hospital de

### Descritores

Síndrome de imunodeficiência adquirida, quimioterapia. Sobrevivência. Antivirais. Fatores socioeconômicos. Escolaridade. Terapia anti-retroviral.

### Correspondence to:

Ligia RS Kerr Pontes  
Rua Bento Albuquerque, 1300 apto 701, Papicu  
60190-080 Fortaleza, CE, Brasil  
E-mail: ligia@ufc.com.br

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*referência no Ceará, entre 1986 e 1998. Foram avaliadas as variáveis socioeconômicas e clínico-epidemiológicas. A análise foi realizada pelo método Kaplan-Meier e por regressão de Cox.*

#### **Resultados**

*Dos 486 pacientes estudados, 362 utilizaram pelo menos uma droga anti-retroviral e tiveram sobrevida dez vezes maior que os que não a utilizaram (746 e 79 dias, respectivamente;  $p < 0,001$ ). O risco de morrer, no primeiro ano, foi significativamente menor (0,25; IC95%: 0,12-0,50) para os que fizeram uso de dois inibidores de transcriptase reversa ou HAART e menor a partir do segundo ano (0,10; IC95%: 0,42-0,23) em relação aos que não os usaram. Indivíduos sem nível universitário (15,58; IC95%: 6,64-36,58) e que apresentaram duas ou mais doenças sistêmicas (3,03; IC95%: 1,74-5,25) tiveram risco significativamente maior de morrer no primeiro ano. Após o primeiro ano, não se observou diferença.*

#### **Conclusão**

*O melhor nível socioeconômico, medido indiretamente pela escolaridade, demonstrou grande influência na sobrevivência no primeiro ano. As drogas anti-retrovirais tiveram mais impacto na sobrevivência a partir do segundo ano, assim como igualaram o risco de morrer de pacientes com duas ou mais doenças sistêmicas àqueles que não tiveram nenhuma no mesmo período. Concluiu-se que uma introdução mais precoce e mais agressiva dos anti-retrovirais poderia beneficiar os pacientes.*

Most literature studies on AIDS patient survival report cases in developed countries.<sup>14,15</sup> A decreasing mortality rate in relation to total cases has been registered in Brazil every year despite the scarcity of studies,<sup>2,6</sup> especially in the northeast region, that would allow measuring the impact of antiretroviral drugs and other variables on patient survival. In addition, new diagnostic techniques, such as CD4<sup>+</sup> count and viral load, have been employed recently in an attempt to improve the patient's prognosis with the introduction of antiretroviral treatments timely. Since 1991, antiretroviral drugs are available at no cost to all patients in Brazil.

Fortaleza, the capital of the state of Ceará, is one of the largest cities in the northeast region. The AIDS epidemic in this city has shown a trend towards an increasing number of cases since it was first recognized in 1983. A predominance of homosexual/bisexual transmission and a steady rise in incidence among heterosexual individuals, chiefly among women, have been evidenced. This disease profile differs from that of other regions in Brazil, especially the southeast region where most cases are concentrated. There have been registered a significant number of AIDS cases among intravenous drug users and a marked decrease in male-to-female ratio.

Studies relating social demographic and clinical epidemiological factors to the survival of AIDS patients have not yet been conducted in the state. Hence, the present study intends to evaluate the impact of these variables on patient survival in the region.

## **METHODS**

### **Population and variables studied**

Between 1986 and April 1998, 1,734 AIDS cases were diagnosed in adults in the city of Fortaleza, of which 1,494 (86.2%) were referred to the state hospital, a reference center of AIDS treatment.

A random sample of 502 adult AIDS patients was made up in alphabetical order. Sixteen individuals diagnosed at death as having AIDS (3.18%) were excluded, remaining 486 in the study. Of these, 362 patients received antiretroviral therapy and 124 did not.

The variables studied to assess a potential relationship with patient survival were:

- a) *Social demographics*: sex; age at diagnosis (<30, 30-34, 35-39, and  $\geq 40$  years); educational level (illiterate, elementary, high school, university); place of origin (capital or interior of the state); and socioeconomic status assessed indirectly through city area of residence. Socioeconomic status variable was defined according to: educational level of the head of the family (less than 4 years of schooling; 4 to 7 years of schooling; and 8 or more years of schooling); *per capita* income (up to half minimum salary; half to one; one to two; two to five; five to fifteen; fifteen to twenty; and above twenty minimum salaries); proportion of residences with water supply; inadequate sewage system and residences with no garbage collection. Scores 1 to 10 were

attributed to these variables, then added and classified as high, medium and low according to the patient's area of residence.

- b) *Clinical epidemiological*: probable form of transmission (homosexual/bisexual, heterosexual, or blood); CD4<sup>+</sup> counts (CD4<sup>+</sup>  $\geq 100 \times 10^6/L$ , first count after AIDS diagnosis); early hemoglobin level ( $\geq 11$  g/dl and  $< 11$  g/dl); characteristic opportunistic diseases (Kaposi's sarcoma, *Pneumocystis carinii* pneumonitis, tuberculosis, other diseases); early presence of systemic diseases (only one disease, two or more at the time of diagnosis); use of antiretroviral drugs (reverse transcriptase inhibitors + protease inhibitors or zidovudine alone); and diagnostic criteria (Caracas criteria<sup>9</sup> versus CDC criteria<sup>1</sup>). See under Discussion the possible influence of diagnostic criteria in the survival analysis.

### Statistical analyses

Survival time corresponded to the number of days elapsed between AIDS diagnosis and death or the number of days elapsed between diagnosis and the last visit to the hospital for those lost to follow up or those who were alive at the end of the study.

The impact of the variables on patient survival was analyzed using Kaplan-Meier survival analysis method, and any possible statistical differences between the subgroups were evaluated using the log-rank test. Individuals who died before the completion of the study were considered as "failures" (n=279), and those who remained alive or were lost during the study period were assigned as "censored" (n=207). For assessing the performance of predictive factors, multivariate analysis was carried out using the Cox proportional hazards model. The Stata<sup>TM</sup> version 6.0 software was used for the entire analysis.

The proportional hazard assumption was analyzed by testing the probable interaction of variables with time in the regression model and graphically using the ln (-ln) survival curve.

### RESULTS

The median survival for patients receiving at least one drug compared to those who were not under any medication was approximately 10 times higher (746 and 79 days, respectively;  $p < 0.001$ ).

Assuming that only patients receiving antiretroviral drugs would be of greater significance since their survival has been dramatically increased after the emergence of drugs to fight AIDS, it was decided to

include in the study only these cases (362 patients: 183=failures and 179=censored).

Male-to-female case distribution in the cohorts was of approximately 6.3:1 (Table). There was no statistically significant difference between median survivals of male and female patients ( $p=0.43$ ).

As to the transmission category, study patients were mainly homosexuals/bisexuals (52.0%), heterosexuals (33.1%), and 14.8% were infected through blood (intravenous drug users, hemophiliacs or transfused). The median survival was not significantly different for any of these categories ( $p=0.21$ ).

There was no difference in the median survival among different age groups ( $p=0.46$ ); patients with different AIDS-characteristic diseases ( $p=0.38$ ); patients who had one or more systemic diseases ( $p=0.78$ ); patients who had CD4<sup>+</sup> counts  $\geq 100 \times 10^6/L$  ( $p=0.12$ ); patients who were diagnosed according to different criteria ( $p=0.38$ ); patients who lived in the capital ( $p=0.11$ ); or between patients who lived in areas with different socioeconomic status ( $p=0.06$ ).

To assess the possible effects of other confounding survival variables the study period was divided in two segments: patients diagnosed before 1995 and after 1995. Survival was only assessed in patients receiving at least one antiretroviral drug. Patients diagnosed after 1995 showed to have higher survival rates. However, after adjusting for therapy (reverse transcriptase inhibitor + protease inhibitor vs. reverse transcriptase inhibitor), only the therapy effect remained significant. Furthermore, it was found that the two period segments were significantly related to therapy ( $p < 0.001$ ), therefore, only the variable therapy was kept in the model and the two period segments were discarded.

Patients who received a combined therapy of reverse transcriptase inhibitors and protease inhibitors had survival rates significantly greater than those receiving only one or more reverse transcriptase inhibitors ( $p < 0.001$ ), and those who had hemoglobin levels of 11 g/dl or more at the time of diagnosis ( $p < 0.001$ ).

Patients with two or more systemic diseases at the time of diagnosis had a greater risk of death in the first year compared to those who had no, or only one, systemic disease (1.7; 95%CI: 1.1-2.9). Hemoglobin levels equal to or greater than 11 g/dL reduced the fatality risk of patients with more than one-year survival. On the other hand, patients receiving zidovudine or stavudine combined with other drug of similar effect (didanosine, zalcitabine, lamivudine)

had a higher risk of dying in all cohorts (5.6; 95%CI: 3.3-9.7) in the first year (4.4; 95%CI: 2.2-8.8), and more pronouncedly in the second year (8.1; 95%CI: 3.4-19.2) when compared to those receiving a combination therapy (reverse transcriptase inhibitor + protease inhibitor).

CD4<sup>+</sup> counts have been available in the public service since July 1997 but the number of AIDS patients who have access to this service in the hospital today is still limited. The assessment of CD4<sup>+</sup> together with other significant variables resulted in great instability

in the statistical model. For that, the impact of CD4<sup>+</sup> on the survival was analyzed in a separate model which included the patient's drug therapy and his/her CD4<sup>+</sup> count ( $\geq 100 \times 10^6/L$  and  $CD4^+ < 100 \times 10^6/L$ ). CD4<sup>+</sup> counts were found to be a confounding effect of the treatment, and patients with  $CD4^+ \geq 100 \times 10^6/L$  had a significantly higher survival (0.42; 95%CI: 0.20-0.86). In addition, the fatality risk for patients receiving one or more reverse transcriptase inhibitors associated with other antiretroviral drugs (protease inhibitors) did not differ in the first year (0.26; 95%CI: 0.03-2.14), and was significantly lower (0.06; 95%CI: 0.02-0.19)

**Table** - AIDS patients attended to a hospital of Ceará, according to the variables studied and the survival time, during the period 1986-1998.

Variables	N individuals	Median survival time (days)*	P (value)**
Coorte	362	746	
Sex			0.43
Male	313	742	
Female	49	1.231	
Age (years)			0.46
<30	115	675	0.37
30-34	93	800	0.51
35-39	72	844	0.23
40 or +	82	663	0.37
Education level***			0.30
High	53	1.068	
Low	264	708	
Social-economic status of the City zone of origin (see Note)			0.06
High	90	497	0.02
Medium	142	778	0.34
Low	86	915	0.22
Origin			0.11
Capital	324	729	
Interior of State	38	831	
Risk group			0.21
Homosexual/Bisexual	182	815	0.37
Heterosexual	116	743	0.70
Blood products	52	651	0.08
1 <sup>a</sup> AIDS-defining disease****			0.38
TB alone	31	1.231	0.32
PCP alone	38	550	0.17
KS alone	13	562	0.48
Others	280	763	0.53
1 <sup>a</sup> systemic disease			0.78
No disease	118	675	0.83
One only	152	828	0.50
Two or more	68	708	0.58
Anti-retroviral use*****			<0.001
RTI + PI	130		<0.001
RTI	122	684	0.06
AZT	105	311	<0.001
Hemoglobin level (g/dl)			<0.001
$\geq 11$	190	991	
<11	157	459	
CD4 <sup>+</sup> count			0.12
$\geq 100 \times 10^6/l$	100		
<100 x 10 <sup>6</sup> /l	67	1.068	

\*Cumulative survival median.

\*\*Log-rank Test (1<sup>st</sup> column compares all the subgroups of each variable, 2<sup>nd</sup> column compares each of the sub3groups with the rest, together).

\*\*\*Educational level: high = University education, low = less than University education.

\*\*\*\*Tb = Tuberculosis ; PCP = *Pneumocystis carinii* pneumonitis; KS = Kaposi's sarcoma, Others = other diseases, excluding those cited.

\*\*\*\*\*RTI = Reverse Transcriptase Inhibitor (zidovudin, didanosin, zalcitabin, lamivudin, estavudin)

PI = Protease Inhibitor (indinavir, saquinavir)

**Note** - Social-economic condition of the residential city zone = considered: per capita income in minimum salaries + education level + water supply, inadequate drainage and garbage collection facilities. The variable social-economic condition of the area where the patient lived was defined according to: the educational level of the head of the family (less than 4 years of schooling, 4 to 7 years of school education and 8 or more years of studies); the per capita income (up to half of the minimum salary, half to one, one to two, two to five, five to fifteen, fifteen to twenty and above twenty minimum salaries); proportion of residences with water supply; inadequate drainage system and residences without garbage collection [28]. For these variables, scores of 1 to 10 were attributed, added and classified as high, medium and low, in reference to the origin of the city zone of each patient. All the data were from the "Fundação Instituto Brasileiro de Geografia e Estatística (IBGE)", 1991.

in the second year for those who were not on protease inhibitors, when corrected for the CD4<sup>+</sup> counts respectively, for the entire study period.

AIDS treatment, education level and presence of two or more systemic diseases did not satisfy the proportional hazards assumption of Cox model. For that reason, an analysis of the hazard ratio was conducted for two different periods: the first year after diagnosis and from the second year on.

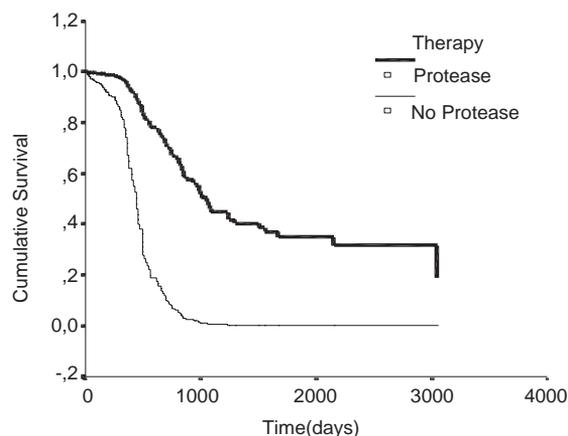
The risk of death in the first year after diagnosis for those receiving reverse transcriptase inhibitors combined with protease inhibitors was significantly lower compared to that of those who did not receive these drugs in combination (0.25; 95%CI: 0.12-0.50). From the second year on, an even lower risk was observed (0.10; 95%CI: 0.42-0.23).

Also, the risk of death in the first year was found to be significantly higher for those who were university educated (15.58; 95%CI: 6.64 -36.58) and who had two or more systemic diseases (3.03; 95%CI: 1.74-5.25) at the time of diagnosis. However, after the first year, no difference was observed in the fatality risk for any of these groups (0.61; 95%CI: 0.36-1.04 and 0.79; 95%CI: 0.47-1.33, respectively).

The adjusted survival rate for the entire period studied was greater for patients receiving combination therapy (reverse transcriptase inhibitor + protease inhibitor), for those university educated and with up to one systemic disease at the time of diagnosis (Figures 1, 2, and 3).

## DISCUSSION

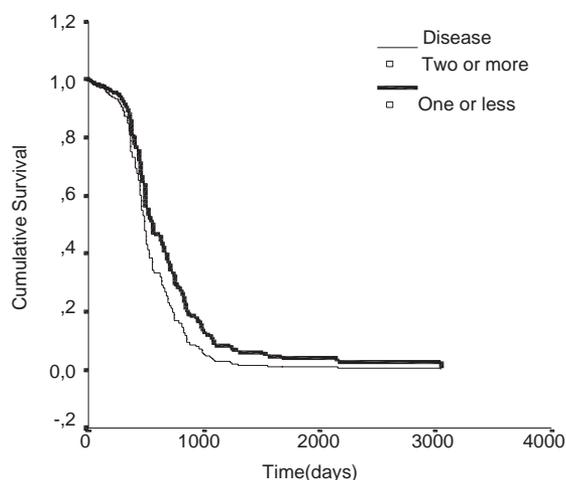
Among the variables that had a significant impact on survival rates, the most predominant ones were:



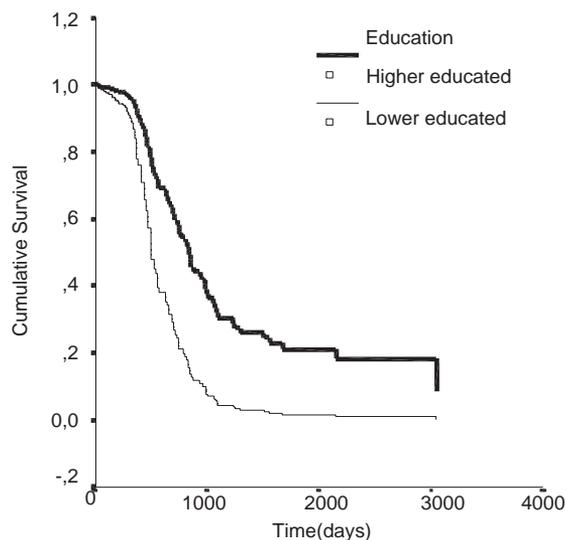
No Protease = Reverse Transcriptase Inhibitors with no Protease  
**Figure 1** - Survival of AIDS patients under anti-retroviral therapy, 1986-1998.

therapy regimen, CD4<sup>+</sup> count, education status, and presence of systemic diseases.

Antiretroviral drugs had a significant impact on the survival of AIDS patients admitted to the state reference hospital. At some points in the disease course, antiretroviral drug therapy was shown to be the best survival predictor.<sup>3,7</sup> It was found that antiretroviral therapy had a greater impact from the second year onwards. This occurrence could have some explanations. According to the Brazilian Consensus for Antiretroviral Therapy for HIV-infected adults and adolescents, the introduction of antiviral treatment depends on a variety of factors, such as viral load and CD4<sup>+</sup> counts.<sup>8</sup> As a result, the entire diagnostic process of AIDS patients takes a relatively long time and



Two or more systemic diseases  
Not more than one systemic disease  
**Figure 2** - Survival of AIDS patients with systemic disease, 1986-1998.



High education level = University education.  
Low education level = Less than university education.  
**Figure 3** - Survival of AIDS patients, according to the educational level, 1986-1998.

requires setting up the antiretroviral therapy regimen as part of the patient's routine hospital care.

Another explanation could be that, as an AIDS opportunistic infection, pulmonary tuberculosis affects 30.9% of the diagnosed cases, and it is characterized as an AIDS-defining disease. Disseminated tuberculosis associated with pulmonary tuberculosis occurs in 6.4% of the cases. To treat these patients, there is a need to modify the antiretroviral therapeutic regimen and delay its start to avoid drug interactions between the two courses of therapy, which could compromise their clinical progress due to a delay in introducing protease inhibitors. Thus, extensive diagnostic procedures and treatment delay, and the often concomitant occurrence of tuberculosis could explain the greater impact on survival from the second year onwards.

The presence of more than one systemic disease had also an effect on the first-year survival. Those patients diagnosed as having two or more systemic diseases had a much greater likelihood of dying than those who had no systemic disease or only one, probably due to greater compromise of their immune systems. However, such difference is not observed from the second year onwards. For those patients with more serious concurrent infections, a more rigorous antiretroviral therapy regimen is immediately established, while those who have less advanced symptoms are put on more conservative therapeutic schemes. Such practice may be contributing to even out risks for survival of those patients having two or more systemic diseases in the second year and those having no more than one systemic disease.

Patient's education status was used as an indirect indicator of socioeconomic status, as only a small percentage succeed in getting university education in Brazil. In Ceará and its capital Fortaleza, only 0.6% and 1.7% of the population, respectively, get to the university.<sup>4</sup> Considering the first-year period of the study, it was observed that the risk of dying for those who did not have university education was much higher than that for those who had university education. A plausible explanation would be the fact that, in the first year of diagnosis, the disease exerts a greater impact on the lives of less educated patients due to their poor socioeconomic conditions. From the second year onwards, equal access to antiretroviral therapy allied to similar compliance problems would make both groups alike concerning biological aspects, thus balancing out their risks. Some studies revealed that continuous drug compliance is essential to avoid viral resistance, which is somewhat difficult to achieve with the current

treatment schemes. In addition, the impact of prolonged treatment on the quality of life should be considered carefully.<sup>13</sup>

Other variables found to be significant for survival in other nationwide and worldwide cohort studies were not found to have considerable effects on survival rates of the current study cohorts. There were no significant differences in survival rates of the age groups studied, which is consistent with Seage et al's findings in Boston.<sup>15</sup> However, other studies have also suggested that individuals from older age groups tend to show lower survival rates.<sup>2,14</sup>

Among the potential modes of virus exposure, there were no differences in survival rates in the present study. Similar results were reported in the US,<sup>15</sup> although European studies revealed differences in survival rates among groups with different viral exposures.<sup>5,11</sup>

Typical AIDS infections such as tuberculosis, *Pneumocystis carinii* pneumonitis, Kaposi's sarcoma, and others were evaluated separately and when compared against each other, no statistically significant difference in survival rates was observed. Similarly, no difference was found in survival related to the first AIDS manifestation in Ireland. Other study showed significant differences in survival related to the first AIDS-defining disease.<sup>10</sup> Patients who developed tuberculosis as their first AIDS opportunistic diseases revealed survival rates significantly higher than those who did not have the disease.<sup>12</sup>

Diagnostic criteria could influence Aids survival studies since there were several versions in the 1980s (different versions of CDC criteria), which more conservative compared to those of the 1990s (the Caracas or Rio de Janeiro criteria), more well-suited to Brazilian patients. The most recent criteria elicit a better prognosis and can be theoretically more adequate to diagnose Aids at an earlier stage. Survival of the whole patients was significantly greater among those who took any medication. However, the survival improvement could be not only attributed to the treatment but it seems to reflect also changes in the diagnostic criteria. Patient who took no medication were also the ones diagnosed according to the 1980's criteria, since AZT was introduced to these patients only in the beginning of the 1990s (only two patients took AZT in November 1989). In further analysis, only patients who took any medication were kept in the study, and therefore the diagnostic criteria did not influence the study results because starting from 1990 all AIDS diagnoses followed the new criteria.

In conclusion, this study revealed that antiretroviral drugs had a significant impact on the increased survival of AIDS patients. The same impact was seen for higher education status and the presence of no more than one systemic disease. It was also observed that these variables had differing impact on the first-year and second-year survival rates. Better outcomes due to antiretroviral therapy found from the second year onwards may suggest that diagnostic procedures and the cessation of drug treatment especially because of frequent tuberculosis diagnosis are prematurely reducing the possible benefits on patient survival. A revision of the more conservative antiretroviral

therapy procedures for patients who do not present two or more systemic diseases in the first year after diagnosis has to be considered since their fatality risk from the second year post-diagnosis onwards is balancing out to that of those who had serious diseases, and these patients could benefit from a more aggressive treatment. There is a need of further studies including a larger number of patients for whom there are CD4<sup>+</sup> counts and viral load data in order to study the effects of the variables found to have significant impact on survival in the present study. Current cohorts of AIDS patients should also be studied as regards of their treatment compliance since this could influence these patients' survival.

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