Effect of sociodemographic, clinical-prophylactic and therapeutic procedures on survival of AIDS patients assisted in a Brazilian outpatient clinic

Efeitos de fatores sociodemográficos, clínico-profiláticos e terapêuticos na sobrevida de pacientes com aids acompanhados em uma unidade ambulatorial brasileira

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Abstract

The Brazilian AIDS Program offers free and universal access to antiretroviral therapy. This study investigates the influence of sociodemographic, clinical-prophylactic and therapeutic factors on survival, after AIDS diagnosis, in an open cohort of 1,420 patients assisted in a university hospital in the city of Rio de Janeiro (1995 – 2002). Kaplan-Meier and Cox proportional hazards models were used to estimate the effect of variables in the three dimensions studied. The overall survival time of the upper quartile was 24 months (CI95%= 20.5-27.5), increasing from 14 months, in 1995, to 46 months, in 1998. We found a protective effect of heterosexual behavior against death that could be attributed to the increasing female-to-male sex ratio in the cohort, which coincided with the time of therapy introduction. Low schooling, hospital admission and lack of follow-up were identified as risk factors for death; PCP and Toxoplasmosis prophylaxis were protective. The number of attempts required to consolidate the antiretroviral therapy showed no significant effect on survival. The full model, which includes the number of antiretroviral drugs in the regimen, confirmed the triple therapy as the best regimen. This study brings important information for designing guidelines to deal with different aspects related to the practical management of patients and their behavior, thus contributing to the success of the program of free access to antiretroviral therapy implemented in Brazil.

Key words: Epidemiological studies. Cohort studies. Proportional risk models. Non-parametric methods. Survival analysis. Anti–HIV agents. Fatal outcome. Survival rate. Hospital mortality. Brazil

Resumo

O programa Brasileiro de DST/AIDS oferece acesso livre e universal à terapia anti-retroviral. Este estudo investiga a influência dos fatores sociodemográficos, clínico-profiláticos e terapêuticos na sobrevida, após o diagnóstico de AIDS, em uma coorte aberta de 1.420 pacientes atendida em hospital universitário na Cidade do Rio de Janeiro (1995-2002). Kaplan-Meier e modelo de risco proporcional de Cox foram usados para estimar os efeitos das variáveis nas três dimensões estudadas. O tempo de sobrevida global no quartil superior foi de 24 meses (IC95%= 20,5-27,5), aumentando de 14 meses, em 1995, para 46 meses, em 1998. Encontrou-se um efeito protetor do comportamento heterossexual contra o risco de morte que pode ser atribuído à proporção crescente de mulheres na coorte, que coincide com a introdução da terapia. Baixa escolaridade, admissão hospitalar e ausência de seguimento nas consultas foram fatores de risco, enquanto a profilaxia para PCP e para toxoplasmose foram protetoras. O número de tentativas requeridas para consolidar a terapia anti-retroviral mostrou não ter efeito significativo na sobrevida. O modelo completo, incluído o número de drogas anti-retrovirais do esquema, confirmou a tripla terapia como o melhor esquema. Este estudo traz importantes informações para definir orientações que lidem com diferentes aspectos relacionados com o manuseio prático de pacientes e seus comportamentos, desta forma contribuindo para o sucesso do livre acesso à terapia anti-retroviral no controle da AIDS.

Palavras-chave: Estudos epidemiológicos. Estudos de coortes. Modelos de riscos proporcionais. Métodos não paramétricos. Análise de sobrevivência. Agentes anti –HIV. Evolução fatal. Taxa de sobrevivência. Mortalidade hospitalar. Brasil .

Introduction

The Brazilian HIV/AIDS epidemic is a countrywide phenomenon[1], affecting all segments of the population, especially people with low schooling, who often present higher risk sexual behaviors[2]. Since the development of highly effective antiretroviral (ARV) drugs, an improvement in the clinical course of the disease has been observed, with reduction in the incidence and severity of opportunistic infections. Survival analyses carried out in Brazil[3-6] and in other Western countries[7-10] have shown substantial increase in survival time and quality of life, strongly associated with ARV therapy, especially when combined in Highly Active Antiretroviral Therapy (HAART).

Since 1998, the Brazilian AIDS Control Program offers free and universal access to ARV drugs[11] distributed by authorized health services. The success of this program depends both on its coverage (providing wide access) and on individual compliance and response to therapy. Many individual characteristics may contribute to the latter: income, schooling, other therapeutic measures, and intervening variables, such as the long duration of treatment, which affects the probability of success or failure of the drug therapy. The estimation of the effect of such variables can improve the understanding of the impact of the national program on the survival and quality of life of HIV patients in Brazil.

In this study, we investigated the influence of sociodemographic, clinical-prophylactic and therapeutic factors on the post-AIDS survival of a retrospective cohort in a university hospital of the city of Rio de Janeiro, from 1995 to 2002.

Methods

Data comes from the medical records of a cohort of patients, assisted in the Outpatient Service of the Immunology Clinic of a university hospital in the city of Rio de Janeiro, aged 14 or older. We included all 1,538 patients diagnosed with AIDS[12] from 1995 to

2002. Cases with survival times smaller than 1 month (118), a time span not sufficient for evaluating some aspects of the clinical practice, were excluded. The final sample comprised 1,420 cases.

Survival time was defined as the time between the diagnosis of AIDS and death or exclusion caused either by the end of the study period, death not related to AIDS or withdrawal from the clinic. The latter was defined as the absence of any kind of medical record during the whole year of 2002. Possible non-informed deaths were investigated in the Mortality Information System, using name, date of birth and mother's name as search keywords. We searched all deaths certificates that occurred in Rio de Janeiro, between 1995 and 2002, ages 14 to 75, caused by AIDS, cardio respiratory disease, and undetermined and external causes[13] (1995 ICD-9, chapters III, VII, VIII, XVI, and XVII; and ICD-10, chapters I, IX, X, XVIII and XX)[14-15]. Twelve cases with survival time greater than 100 months were excluded at this point in order to avoid bias introduced by a long survival time.

Survival curves and summary statistics (median and upper quartile survival time), were estimated using the Kaplan-Meier (KM) method. The use of the upper quartile (P75), instead of the median, was necessary because of the low mortality rate associated with some strata, especially after the introduction of free access to ARV drugs. Peto and log-rank tests were calculated to compare estimated survival curves[16]. The former test is more sensitive to differences in the first section of the survival curves while the latter is more sensitive to differences in their final section.

We used the Cox proportional hazard model[17] to estimate hazard ratios for a set of sociodemographic, clinical-prophylactic and therapeutic covariates (HR), adjusted by treatment. Clinical status at inclusion in the cohort was evaluated based on the type of diagnosis: clinical or laboratorial. Covariates were included hierarchically in three steps[18], according to their dimension. First, variables of the sociodemographic dimension were included, followed by those in the clinical-prophylactic dimension and last, the therapeutic dimension. Within each dimension, the inclusion of variables followed a forward process, where the effects of covariates were tested one by one and all together. Covariates that showed a significant effect on survival ($p<0.05$) were maintained in the model. We also maintained some non-significant variables in the model, due to their well-known association with survival (age, for example). To evaluate model fit we used the likelihood ratio.

After selecting the sociodemographic variables (Model 1), the same procedures were repeated for the clinical-prophylactic set of variables (Model 2) and the therapeutic set (Model 3), always keeping the previously selected variables in the new model. This approach is based on the reasoning that there is a hierarchical chain of causal determination, where the closer links of this chain correspond to the therapeutic dimension while the farthest link corresponds to the sociodemographic dimension. This statistical procedure not only permits considering the competitive effect of a set of variables belonging to the same dimension, but changes in the effect of some variables caused by the inclusion of other dimensions are also expected.

Sociodemographic covariates were: age (continuous variable), sex, schooling (dichotomized on < 8 years and ≥ 8 years) and categories of exposure, classified in 4 groups: men who have sex with men (MSM), heterosexual behavior, injecting drug users (IDU), blood and blood product transfusion recipients (blood).

Clinical-prophylactic variables were: year of the first consultation, type of AIDS diagnosis, classified as immunological (CD4 counts < 200 cells/mm3) or clinical (AIDS defining illnesses), characteristics of patients' follow up (regular outpatient clinic with no hospital admission, at least one hospital admission and only one consultation) and use of Pneumocystis Carinii Pneumonia (PCP) and Toxoplasmosis prophylaxis.

Two variables were chosen to summarize ARV therapy for each patient: 1) the

number of drugs used in the first regimen that lasted at least two months (1st ARV therapy), cathegorized in 0, 1, 2 and ≥ 3 ARV drugs. This time lag was chosen because patients often try many drug combinations before adapting to one regimen, and two months is the minimum time required for a physician to evaluate the adequacy of therapy for a specific patient; 2) *the number of attempts before stabilizing a drug regimen*, categorized as 1, 2, 3 attempts. With this variable, we seek to evaluate if this initial trial-and-error process has an impact on survival.

Schoenfeld residuals were used to test the proportional risk assumption[19]. We used the open source statistics package R[20] to perform all statistical analyses. This study received the approval of the research ethics committee in the hospital and had no financial support.

Results

Median survival times, estimated only for 1995 and 1996, were 35 and 68 months respectively. Probability of surviving 1 or 2 years, for those starting in 1995, was 74% and 56% and, in 1996, 81% and 67%, respectively. Only 1.4% of the patients died from causes not related to AIDS, and 25% died of immunodeficiency. Among censored patients, more than half were alive and censored due to the end of the study.

Kaplan-Meier survival analysis is presented in Table 1. Females survived longer than males. Mean age at inclusion in the cohort was 35.2 years in 1996, and 37.6 years in 2002. Most patients were in the 30 to 39 year-old interval (43.3%). Survival was significantly longer for patients with 8 or more years of schooling. Considering the transmission categories recorded, the shortest survival was found for IDU, and the longest for patients with heterosexual behavior as the only known risk factor. Survival of percentile 75 increased from 14 months, for those diagnosed in 1995, to 46 months in 1998. As more than 75% of the patients survived longer than 5 years (from 1999 to 2002), calculation of the confidence interval was unfeasible. Survival was three times longer when the criteria for AIDS diagnosis were immunological. Hospital admissions are associated with shorter survival times and no follow-up consultations to even smaller ones. Prophylaxis for PCP and Toxoplasmosis (p-value for Log rank = 0.007 and for Peto = 0.005) were considered protective. The number of attempts before stabilizing the 1st ARV therapy varied from one (71.7%) to 8. This variable presented no effect on survival.

In this cohort, 553 (38.9%) patients did not use ARV drugs or never achieved the 1st ARV therapy criterion. The remainder either used one (12.3%), two (25.4%) or three or more ARV drugs (23.4%). Survival increased dramatically due to the inclusion of more drugs (Table 1). The survival probability at 24 months more than doubled as the number of ARV employed in the treatment increased, going from 40% for those with no ARV, to 75.4% for those with one, 90.2% for those with 2 ARV drugs, and 94.3%, for those with ≥ 3 ARV drugs. KM survival estimates for 2 and ≥ 3 ARV drugs showed a significant difference. Nucleoside analogues alone and in combination are the most common antiretroviral regimens used for treatment (37%), followed by a 2 nucleoside and protease inhibitor (PI) combination (15%), 2 nucleoside and non-nucleoside combination (8%). A small fraction of cases (1%) used all 3 ARV classes together.

Table 2 presents the death hazard ratios (HR) estimated by the three models. In Model 1, schooling and transmission categories showed a statistical level of significance and were kept in the model. Age was maintained as well due to its undeniable effect on survival. An increase of 44% in risk was observed in patients with less than 8 years of education, when compared with those with ≥ 8 years. Heterosexual behavior presented a protective effect, with a hazard ratio of 0.65, when compared with the MSM category. Blood transmission, either by injecting drugs or contaminated blood products, showed no detectable effect (Table 2). Gender, when adjusted for age, years of education and the transmission category showed no statistical

Table 1 – Frequency distribution and Kaplan Meier survival analysis of AIDS cases. Rio de Janeiro/Brazil. 1995-2002.
Tabela 1 *– Distribuição de freqüência e análise de sobrevida Kaplan Meier de casos de Aids. Rio de Janeiro/Brasil. 1995-2002.*

		Distribution		Kaplan Meier (months)		Logrank	Peto
Variables	Categories	N	%	Percentile 75	CI 95%	p-value	p- value
Gender	Male	950	66.9	23	19.3-26.7	0.027	0.044
	female	470	33.1	28	16.6-39.4		
Age	≤ 29	359	25,4	26	14.8-37.2	0.191	0.241
	30 to 39	612	24.5	25	18.1-31.9		
	≥ 40	443	43.3	22	17.8-26.2		
Schooling	≥ 8 years	736	62.5	29	10.4-17.6	0.012	0.013
	< 8 years	441	37.5	21	14.4-23.6		
Exposure categories	MHSM	539	44.8	24	19.5-28.5	0.042	0.050
	Heterosexual	513	42.6	40	22.2-57.8		
	IDU	58	4.8	19	11.9-26.2		
	Blood	94	7.8	34	13.6-54.4		
Year of 1st consultation	1995	253	17.8	14	10.4-17.6	<0.000	<0.000
	1996	292	20.6	19	14.4-23.6		
	1997	259	18.2	26	19.1-32.9*		
	1998	187	13.2	46	*		
	1999	118	8.3	–	–		
	2000	68	4.8	–	–		
	2001	105	7.4	–	–		
	2002	138	9.7	–	–		
Diagnosis Criteria	CD4	346	24.4	67	*	<0.000	<0.000
	Clinical	1074	75.6	20	17.0-23.0		
Type of care	Outpatient	1002	70.8	35	25.1-44.9	<0.000	<0.000
	Hospitalization	306	21.6	18	14.4-23.6		
	1 consultation	107	7.6	7	19.1-32.9		
PPC Prophylaxis	No	640	45.1	16	12.3-19.7	0.129	0.076
	Yes	780	54.9	35	25.5-44.5		
Number of treatment attempts	1 attempt	622	71.7	61	41.6-80.4	0.709	0.630
	2 attempt	163	18.8	61	41.3-80.7		
	≥ 3 attempts	82	9.5	67	38.7-95.3		
Number of ARV drugs	no ARV	553	38.9	6	4.6-7.4	<0.000	<0.000
	1 ARV	174	12.3	25	16.0-34.0		
	2 ARV	361	25.4	–	–		
	≥ 3 ARV	332	23.4	–	–		
Outcome	Aids death	357	25.1	–	–	–	–
	non-Aids death	20	1.4				
	end of study l	571	40.2				
	oss of follow-up	472	33.2				

* impossible to calculate * *impossível de calcular*

Table 2 - Hazard Ratios of Death (HR) and 95% Confidence Intervals from the Cox Model by set of socio-demographic, clinical-prophylactic and therapeutic covariates.
Tabela 2 - *Índices Arriscados de Morte (HA) e Intervalos de Confiança de 95% do Modelo de Cox por um conjunto de covariantes sociodemográficas, clínico-profiláticas e terapêuticas.*

Variables	Model 1 (HR)	Model 2 (HR)	Model 3 (HR)
RC: ≤ 29- years			
Age	1.01	1.01	1.02
	(0.99-1.03)	(0.99-1.03)	(1.01-1.03)
RC: ≥ 8 years schooling			
< 8 years schooling	1.44	1.35	1.1
	(1.10-1.88)	(1.03-1.76)	(0.83-1.40)
RC: MSM			
Heterosexual behavior	0.65	0.67	0.75
	(0.49-0.86)	(0.50-0.89)	(0.56-1.0)
IDU	0.91	1	1.17
	(0.52-1.62)	(0.56-1.78)	(0.66-2.10)
Blood	0.83	0.81	0.94
	(0.51-1.35)	(0.50-1.33)	(0.60-1.55)
RC: immunological AIDS			
Clinical AIDS	-	2.034	1.299
	-	(1.35-3.06)	(0.86-1.97)
RC: ROC			
Hospital Admittance	-	1.677	1.537
	-	(1.25-2.25)	(1.14-2.07)
Only one consultation	-	3.929	1.592
	-	(2.61-5.90)	(1.05-2.40)
RC: no prophylaxis			
PCP (prophylaxis)		0.69	0.93
	-	(0.52-0.90)	(0.70-1.22)
RC: no ARV therapy			
one ARV therapy	-	-	0.346
	-	-	(0.24-0.51)
two ARV therapy	-	-	0.123
	-	-	(0.08-0.18)
≥ 3 ARV therapy	-	-	0.084
	-	-	(0.05-0.14)
LR (loglik)	-1477.63	-1439.28	-1353.22
d. f.	5	9	12
n	1047	1047	1050
p-value	0.000	0.000	0.000

Loglik: Log likelihood - d .f.: degree of freedom- Likelihood ratio: LR- Sample number: n – Reference category: RC - men who have sex with men (MSM) - regular outpatient clinic with no hospital admission: ROC

significance. Interactions were tested and presented no effect.

In model 2, the clinical AIDS diagnosis doubled the risk when compared with the immunological diagnosis. The HR of patients who had only one medical consultation was 3.93 times greater than the regular patients of the clinic. Admission to hospital wards increased the risk by 67%. PCP prophylaxis was protective (HR=0.69). Toxoplasmosis prophylaxis lost significance when adjusted by the PCP prophylaxis (HR=0.71; CI 95%= 0.52-1.10). The effects of sociodemographic variables were almost the same or slightly reduced, when compared to Model 1.

Regarding the number of ARV drugs used, the expected protective effects were observed: 65%, 88% and 92%, respectively for one, two and three/more drugs. Sociodemographic variables (except age) and PCP prophylaxis lost statistical significance in this model, as expected, because of the strong effect and the proximal role of ARV drugs on survival. An increase of the HR for age was observed: each additional year of life increased the relative risk by approximately 2%. The risk of the covariate number of ARV drugs was not constant over time, as detected by the analysis of the Schoenfeld residuals. Therefore, estimates obtained for this variable have to be carefully considered and precision is overestimated.

Discussion

The origin of the medical registration of our data set, primarily used for care purposes, not research, implies in the possibility of problems in the reliability of the variables used. However, as we crosschecked clinical information with laboratory, pathology and radiographic results, we believe that all information related to those aspects presents good quality. The same resource could not be used to assess patient adherence to treatment, as medical records systematically lacked this information. Nevertheless, the best way to improve registration is to use it, as it is especially important to train young health professionals in a university environment.

The hospital delivers specialized care for people living in any neighborhood of the city of Rio de Janeiro, as well as to those living in cities located in the outskirts of Rio de Janeiro's metropolitan area. Although our study subjects are not representative of the Brazilian AIDS population, there is no reason to suspect they are different in respect to clinical and sociodemographic conditions of the spectrum of AIDS patients in Rio de Janeiro.

Comparing our results to another Brazilian study[6] we found that the 1995 and 1996 median survival estimates were greater. This difference can be due to the minimum observation time criterion adopted in each study (30 days and 7 days, respectively). Another possible source of difference is the origin of the population, respectively, hospital and population-based. Finally, comparisons to other studies were impaired due to the lack of median survival time estimates. In Australia, Dore et al.[21] observed a median survival time, between 1996 and 2000, of 39.6 months based on population data from the national surveillance system, while in our cohort, 60% of patients were alive after 61 months. Although the median and percentile 60 are not strictly comparable, the improved survival of 20 months or more could not only be attributed to the universality of drugs access after 1996 in Brazil, but also to the improvement in the access to social benefits and in the skill and dedication of the hospital health worker staffs.

The protective effect of heterosexual behavior, present both in men and women, in relation to MSM could be ascribed to the increasing female-to-male ratio that coincided with the introduction of HAART. The shorter survival time observed for those with low schooling may be explained by difficulties in the physical access to medical units, in understanding the prescription, and consequent impaired adherence.

AIDS cases diagnosed based on CD4 counts presented longer survival, probably because they were detected earlier in the disease process, with a smaller degree of

immune impairment and higher probability of immune reconstitution with ARV therapy.

The main objective of analyzing *the number of attempts before stabilizing a drug regimen* was to evaluate if this possible maladjustment to the therapeutic regimen would impact patient survival time. In this case, not finding any effect, no matter the number of attempts, was an important result, and will ease the doctors' task of individualizing the best treatment for each patient. Likewise, it reinforces the need of discovering the drug combination with minimum side effects.

This study clearly shows that ARV treatment substantially altered the clinical course of HIV infection, reducing its mortality. Furthermore, it confirms the survival benefits of the triple/more therapy compared with double therapy, as observed in previous studies[10,22]. Finally, this study endorses the Brazilian guidelines for antiretroviral treatment[23] recommendation, which advises prescribing the triple drug regimen.

Conclusion

The increase in survival along the years, observed in this study, brings new challenges to the care of AIDS patients, including many other aspects of medical and social care of the HIV disease, in addition to drug combination. In Brazil, thousands of people use ARV drugs, and as the therapeutic guidelines (efficacy, compliance, side effects and resistance to drugs) develop, all other components (education, prevention and epidemiological surveillance) of the national AIDS programs need more attention[11]. This cohort can bring useful information to the practical management of patients as well as to the knowledge of the behavior of this population, thus contributing to the success of free access to ARV therapy in the control of AIDS in Brazil.

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