Original article

Survival of patients with AIDS and association with level of education level and race/skin color in South and Southeast Brazil: a cohort study, 1998-1999*

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Abstract

Objective: to analyze the survival of people with AIDS and association with schooling and race/skin color. **Methods:** this was a retrospective cohort study of people diagnosed with AIDS between 1998 and 1999, in the South and Southeast regions of Brazil. We used survival analysis (Kaplan-Meier method), stratified by schooling and race/skin color and multivariate analysis was performed using Cox regression. **Results:** the study included 2,091 people who had survived at 60 months, with 65% survival among White participants and 62% among Black/brown participants. Irregular use of antiretroviral (HR=11.2 – 95%CI8.8;14.2), and age ≥60 years (HR=2.5 – 95%CI1.4;4.4) were related to lower survival; schooling >8 years (HR=0.4 – 95%CI0.3;0.6) and being female (HR=0.6 – 95%CI0.5;0.8) were positively related to survival; those with less schooling had lower survival. **Conclusion:** lower schooling levels overlap race/skin color differences in relation to survival; these inequalities explain the differences found, despite the policies on universal access to antiretroviral.

Keywords: Acquired Immunodeficiency Syndrome; Survival; Survival Analysis; Educational Status; Ethnicity and Health.

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Introduction

Socio-economic conditions have been predictors of the heterogeneity of the risk of becoming ill and dying from different causes, both in Brazil and in other parts of the world.[1] Premature death is more frequent among Indigenous and Black Brazilians, whereby socio-economic differences extending over successive generations can explain health inequalities.[2] The human immunodeficiency virus (HIV) epidemic is also distributed in an heterogeneous manner in Brazil and interferes with the quality of life and survival of people with HIV.[3]

With effect from the 1980s, when Brazil's first AIDS case was identified, this disease has spread in different age groups, in both sexes and throughout all the Brazilian states. Notwithstanding, the epidemic has undergone changes over the years in Brazil's five regions, spreading to municipalities distant from large metropolitan areas, in addition to a proportional increase of cases among low-income and poorly educated people.[3]

> *Discrepancies have been registered in access to antiretroviral treatment and patient survival throughout the country.*

Furthermore, discrepancies have been registered in access to antiretroviral treatment and patient survival throughout the country. One of the most evident determinants of this heterogeneity is social inequality and its structural character. It is not only with regard to the profile of the AIDS pandemic, but also in relation to the identification of groups in which the disease has evolved unfavorably.[4]

Individuals of lower socio-economic status are at greater risk of contracting opportunistic infections or suffering from other complications, owing to their nutritional status, living and housing conditions and obstacles to accessing health services, antiretroviral treatment and primary and secondary prevention measures. This in turn hinders the timely treatment of episodes of the disease and adherence to clinical follow-up.[5,6] Burch et al.[6] have drawn attention to the need for studies of association between socioeconomic conditions and AIDS prognosis in regions where there is free of charge access to health care and specific medication.

Slavery was a historical context of Brazil's past that brought evidence that a person's race/ skin color is associated with social and economic inequality.[7] Knowledge about the relationship between AIDS mortality and socio-economic and racial status is of extreme importance for analyzing the role of health services in view of guaranteed citizen rights, regardless of sex, race/skin color or social standing.[8] Controversy exists as to Black/brown people, especially those with HIV, accessing health services and the Brazilian National Health System (SUS).[3,9] Late access to clinical follow-up and treatment, influenced by everyday barriers and institutional racism, may result in delayed patient care and, consequently, a worsened prognosis of the disease.[9]

Distinct analyses, according to different periods of the epidemic, have enabled the history of AIDS in Brazil to be described right from the outset[10] as well as in relation to the decades that followed,[3,11] including the scaling up of prevention, patient care and access to medication. It is important to revisit the path taken by the epidemic in past decades, using population-based data, in order to record the impact of scaling up access to prevention and care services.

Patient survival and universal access to antiretroviral therapy (ART) have been addressed by a variety of Brazilian researchers, including with regard to socioeconomic differences. There is, however, a scarcity of research focusing on the association between reported race/skin color and the evolution of HIV infection.[12] The objective of this study was to analyze the survival of people with AIDS aged 13 and over, living in Brazil's Southern and Southeastern regions, and its association with level of education and race/skin color.

Methods

This was a retrospective cohort study based on a sample of medical records of patients with AIDS aged 13 or over, living in South and Southeast Brazil, diagnosed between 1998 and 1999, who were followed for ten years.

The criterion for inclusion in the study was being an AIDS case confirmed in 1998 and 1999 by means of: CD4 T-cell count (below 350/mm³, regardless of

symptoms); and the Rio de Janeiro/Caracas criteria and the modified Centers for Disease Control and Prevention criteria. Death was not taken to be a criterion for inclusion in this study.

Out of the total of cases reported in the two regions in 1998 and 1999, the following were excluded: (i) patients living in municipalities with fewer than 40 reported cases in the period (18% of the total); (ii) those who were diagnosed for the first time as having AIDS in the same week they died; (iii) cases reported by unknown reporting units and (iv) cases having a diagnosis date later than the date of death or the date on which the case was reported.[3]

We used cluster sampling in two stages: municipalities, or clusters of municipalities; and patients. Primary sampling units were selected randomly with probability proportional to the number of reported cases. Municipalities that did not report the minimum number of cases were grouped together with other larger municipalities. The sampling fractions were 1/13.4 for the Southeastern region and 1/6.9 for the Southern region. Eighteen primary sampling units were randomly selected in the Southeast and ten in the South. During a second stage of this process, 123 people were randomly selected in the Southeast and 128 in the South. The data we collected were weighted, and the significance of each patient, obtained through the inverse sampling fraction for the region to which they belonged, in order to compensate for the different selection probabilities used in the regions. The sampling fractions were as follows:[3]

$$f = \frac{18 \times N_i}{29{,}600} \times \frac{123}{N_i} = \frac{1}{13{,}639} \quad \text{for the Southeastern region}$$

$$f = \frac{10 \times N_i}{8{,}797} \times \frac{128}{N_i} = \frac{1}{6{,}873} \quad \text{for the Southern region}$$

N_i =number of AIDS cases in the municipality (or cluster of municipalities)

These fractions enabled statistical examination of significant differences of 5 and 9 month mean survival between groups to be compared in each region. In the final sample we used unequal division by strata (regions), with the aim of reducing differences between their sampling fractions.

In this study the dependent variable was patient survival time, calculated with effect from date of AIDS diagnosis up to date of death (failure), and from the date of diagnosis to the date of the last appointment attended at the health service – or abandonment of clinical follow-up (censoring) and the end of the study (planned censoring).

The independent variables collected were: sex, age range (in years: 13-25, 26-39, 40-59 and 60 and over), reported race/skin color (Black, brown, White, Indigenous, yellow); schooling (in years of study: 0-4, 5-8 and >8) and HIV exposure category, all reported at the time of diagnosis; regular ART use, taken to be when there were records of the patient getting medication at health services for an uninterrupted period of more than six months; and care provided by the multidisciplinary team, comprised not only of a physician and a nurse, but also a psychologist, a dentist, a social worker, a psychiatrist, a physiotherapist, a nutritionist, an occupational therapist and/or other professionals available in the cities studied.

AIDS cases were retrieved from the Ministry of Health's Notifiable Diseases Information System (SINAN), while the database was built using sociodemographic, epidemiological and clinical information retrieved from the medical records of patients having clinical follow-up at HIV/AIDS reference services in the selected cities.[3]

We obtained the absolute and relative frequencies of the independent variables, for each region, according to schooling and reported race/skin color. We performed univariate analysis of the cumulative probabilities of patient survival for the different levels of education and reported race/skin color.

The lethality coefficient in the population studied was estimated by taking deaths as the numerator and the total number of individuals at the beginning of the cohorts as the denominator. We used Pearson's Chi-square test of association and Fisher's exact test, when necessary, with a 5% significance level in order to compare proportions between levels of education and reported race/skin color.

After checking the proportionality of the selected variables, using a Log-Log graph, we analyzed the survival curves using the Kaplan-Meier method and the Log Rank, Breslow and Tarone-Ware tests (in order to check proportionality between curves at the beginning, middle and end of the time segment,

respectively),[13] using a 5% significance level and cumulative survival probability expressed in months for each variable of interest.

We used the Mantel Haenszel method to calculate the hazard ratio (HR) when analyzing survival. Following the univariate analysis, we performed stepwise adjustment of the Cox multiple regression model or proportional hazards model using a 95% confidence interval. We used the premise that the HR for an independent variable would be proportional over time, thus permitting simultaneous inclusion of several covariables in the multiple model of survival time.[13]

In order to avoid confounding factors, we removed all "No information" categories, i.e. whenever there was no information registered on the medical records for any of the variables studied, for all survival comparison and analysis tests performed. When calculating survival according to reported race/skin color, we compared White individuals with Black/brown individuals and excluded all other categories owing to the small number of individuals in them.

We used Microsoft Excel 2016 and IBM SPSS Statistics 21 for Windows to perform the statistical analysis.

The study project was approved by the Research Ethics Committee of the São Paulo State Health Department STI and AIDS Reference and Training Center – Protocol No. 15/05, dated June 20th 2005. It was also approved by the Campinas State University (Unicamp) Research Ethics Committee – Opinion No. 1.338.512, dated November 26th 2015.

Results

After exclusions, we were left with 29,600 AIDS cases for the Southeastern region and 8,797 for the Southern region. From these we obtained 2,214 patients in 90 municipalities in the Southeastern region and 1,280 patients in 33 municipalities in the Southern region. The sample size was 1,484 medical records of people with AIDS for the Southeastern region and 898 for the Southern region, according to the resident population in the same age group diagnosed as having AIDS, resulting in a final sample of 2,091 AIDS cases aged 13 or over.

Cumulative survival over 108 months was lower in patients aged 60 years or more (36.6%; p<0.001), individuals with up to four years of schooling (59.9%), individuals with Black and brown skin color (56.3%) and males (60.9%) (Table 1). A higher percentage of deaths was found in people exposed to HIV via blood (47.0%) and those using antiretroviral therapy inconsistently (78,2%).

Patients with up to four years of schooling had lower survival in the 60 months following AIDS diagnosis when compared to individuals with other levels of schooling (Figure 1). When schooling was stratified, survival was similar between people with White skin color and those with Black/brown skin color, although it was always lower among those with less schooling.

There were proportionally more males (81,5%), people with White skin color (72.8%) and individuals to whom HIV was transmitted sexually (82.8%) among those with more than eight years of schooling. In all levels of schooling, more 80% of individuals regularly took antiretroviral drugs and among those with most schooling ARV use was above 90.0%. Individuals with up to four years of schooling had greater access to other health professionals apart from doctors and nurses (72.9%) (Table 2).

Cumulative survival at 60 months and at the end of the study was 71% and 60% among people with sexual exposure and schooling between zero and four years, 83% and 71% for those with five to eight year of schooling, and 82% and 69% for those with more than eight years of schooling (Figure 2). This difference between the survival curves is shown by the result (p<0.001) of the Log Rank (Mantel-Cox), Breslow and Tarone-Ware proportionality verification tests. In the blood exposure category, which covered injecting drug use, hemophilia, history of blood transfusion and working with biological material, survival proportionality was statistically similar between the schooling categories, as proven by the results of the Log Rank (Mantel-Cox) (p=0.159), Breslow (p=0.122) and Tarone-Ware (p=0.133) tests.

The variables positively associated with longer survival were: female sex (HR=0.62 – 95%CI0.5;0.8), compared to males; and 5-8 years of schooling (HR=0.6 – 95%CI0.5;0.8) and >8 years of schooling (HR=0.4 – 95%CI0.3;0.6) (Table 3), when compared to 0-4 years of schooling. The variables associated with lower survival were: irregular ART use (HR=11.2 – 95%CI8.8;14.2); and being in the 60 and over age group (HR=2.5 – 95%CI1.4;4.4).

Table 1 – Cumulative survival during 108 months of follow-up, according to AIDS case sociodemographic, epidemiological and treatment/care variables in the South and Southeast regions of Brazil, 1998-2009

Variable	Total (n=2,091)		Death (n=753)		Cumulative survival	P value[a]
	n	%	n	%	%	
Sex						
Male	1,357	64.9	530	70.4	60.9	
Female	734	35.1	223	29.6	69.6	<0.001
Age group (in years)						
13-25	232	11.1	73	9.7	68.5	
26-39	1,210	57.9	432	57.4	64.3	
40-59	608	29.1	222	29.5	63.5	
≥60	41	2.0	26	3.5	36.6	<0.001
Schooling (in years of study)						
0-4	1,177	56.3	472	62.7	59.9	
5-8	383	18.3	102	13.5	73.4	
>8	151	7.2	31	4.1	79.5	
No information	380	18.2	148	19.7	61.1	<0.001
Reported race/skin color						
White	1,095	52.4	388	51.5	64.6	
Black/brown	419	20.0	183	24.3	56.3	
Yellow/indigenous	8	0.4	2	0.3	75.0	
No information	569	27.2	180	23.9	68.4	<0.001
HIV transmission category[b]						
Sexual	1,388	66.4	419	55.6	69.8	
Blood	440	21.0	207	27.5	53.0	
No information	263	12.6	127	16.9	51.7	<0.001
Use of antiretroviral therapy						
Yes	1,808	86.5	542	72.0	70.0	
No	170	8.1	133	17.7	21.8	
No information	113	5.4	78	10.4	31.0	<0.001
Other health professionals[c]						
Yes	1,404	67.1	465	61.8	66.9	
No	687	32.9	288	38.2	58.1	<0.001
Region						
Southeast	1,309	62.6	459	61.0	64.9	
South	782	37.4	294	39.0	62.4	0.246

a) P value of Pearson's chi-square test and Fisher's exact test Fisher (for categories of variables with n≤5).
b) HIV: human immunodeficiency virus.
c) Other health professionals to whom AIDS patients had access, in addition to a doctor and a nurse: psychologist, dentist, social worker, psychiatrist, physiotherapist, nutritionist, occupational therapist and/or other professionals available in the cities studied.
Note:
Chi-square for reported race/skin color was calculated by comparing the White and Black/brown groups.

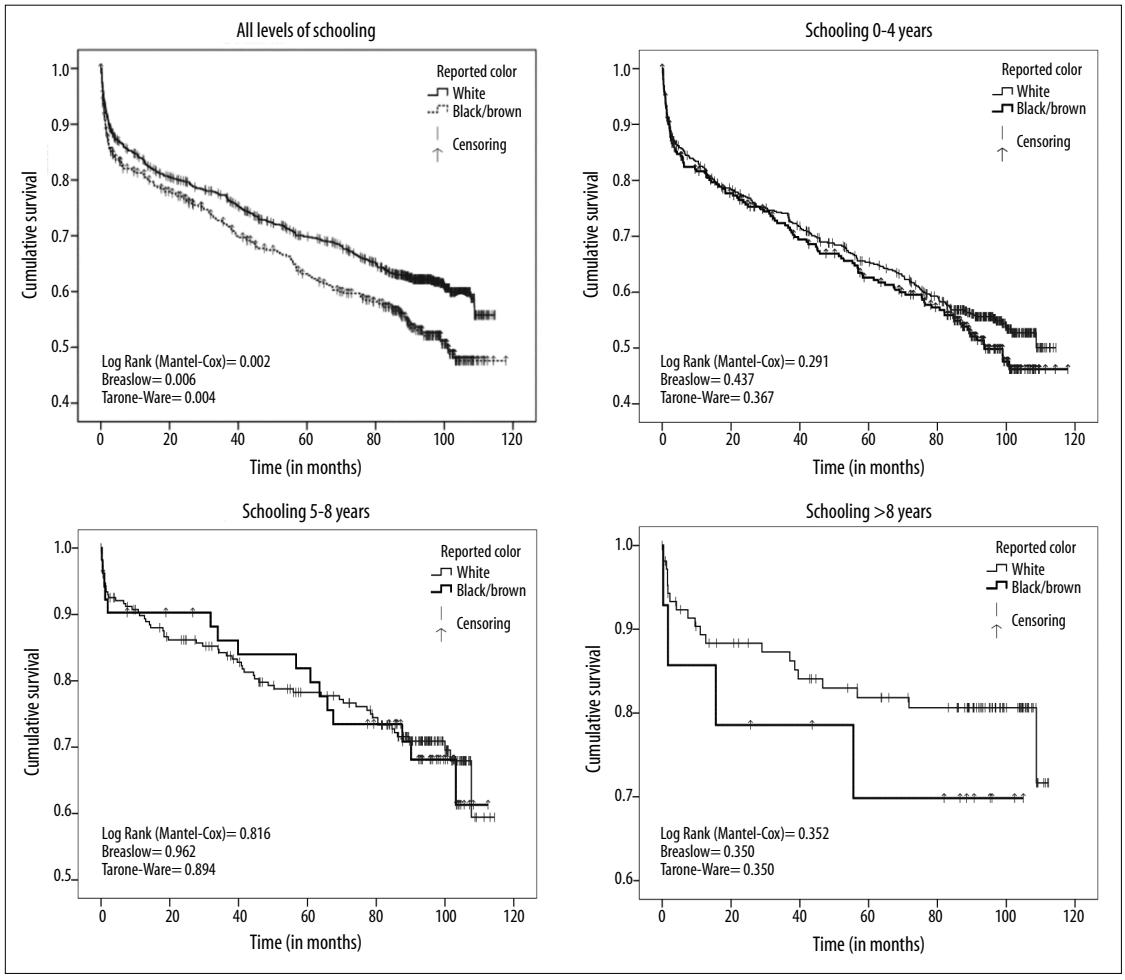

Figure 1 – Survival curves according to race/skin color, stratified by schooling (in years of study) of people living with AIDS in the South and Southeast Regions of Brazil, 1998-2009

After adjustment via the multiple model, mean survival for the Southeastern region was 84.2 months (95%CI81.4;87.1), and 80.3 months for the Southern region (95%CI77.1;83.5). Cumulative survival at 60 months occurred in 54% of individuals with fewer than four years of schooling, and in 71% at the end of the period. Eighty-two percent of patients with five to eight years of schooling and 86% of those with more than eight years of schooling survived at 60 months in the Southeastern region. Among Southern region patients with up to four years of schooling 69% survived the first 60 months and 54% had survived at the end of the study. Seventy-nine percent of patients with between five and eight years of schooling survived 60 months as did 86% of those with more than eight years of schooling (data not shown in figures or tables).

Discussion

Our study identified 72% survival among people with White skin color and 70% among those with Black/brown skin in the 120-month period. Survival was associated with greater probability of death among people with up to four years of schooling. In both exposure categories, survival among those with less schooling was also lower, owing to differences in the distribution of the sociodemographic, epidemiological, clinical and health service use variables. One of the study's main limitations is its retrospective approach based on the use of secondary data from medical records that are not always filled out properly. On the other hand, population-based information

Table 2 – AIDS case distribution, according to schooling (in years of study) and sociodemographic variables, exposure category and use of health services, in the South and Southeast regions of Brazil, 1998-2009

Variable	Schooling (in years of study)								P value[a]
	0-4 (n=1,177)		5-8 (n=383)		>8 (n=151)		No information (n=380)		
	n	%	n	%	n	%	n	%	
Sex									
Male	729	61.9	261	68.1	123	81.5	244	64.2	
Female	448	38.1	122	31.9	28	18.5	136	35.8	<0.001
Reported race/skin color									
White	592	50.3	234	61.1	110	72.8	159	41.8	
Black/brown	274	23.3	53	13.8	14	9.3	78	20.5	
Indigenous/yellow	5	0.4	1	0.3	1	0.7	1	0.3	
Unknown	306	26.0	95	24.8	26	17.2	142	37.4	<0.001
Age group (in years)									
13-25	150	12.7	40	10.4	5	3.3	37	9.7	
26-39	695	59.0	237	61.9	75	49.7	203	53.4	
40-59	311	26.4	98	25.6	68	45.0	131	34.5	
≥60	21	1.8	8	2.1	3	2.0	9	2.4	<0.001
HIV transmission category[b]									
Sexual	779	66.2	285	74.4	125	82.8	199	52.4	
Blood	310	26.3	67	17.5	8	5.3	55	14.5	
Unknown	88	7.5	31	8.1	18	11.9	126	33.2	<0.001
Use of antiretroviral therapy									
Yes	1,020	86.7	346	90.3	137	90.7	305	80.3	
No	84	7.1	24	6.3	9	6.0	53	13.9	
Unknown	73	6.2	13	3.4	5	3.3	22	5.8	<0.001
Other health professionals[c]									
Yes	858	72.9	271	70.8	89	58.9	186	48.9	
No	319	27.1	112	29.2	62	41.1	194	51.1	<0.001
Region									
Southeast	672	57.1	220	57.4	89	58.9	328	86.3	
South	505	42.9	163	42.6	62	41.1	52	13.7	<0.001

a) P value of Pearson's chi-square test.
b) HIV: human immunodeficiency virus.
c) Other health professionals to whom AIDS patients had access, in addition to a doctor and a nurse: psychologist, dentist, social worker, psychiatrist, physiotherapist, nutritionist, occupational therapist and/or other professionals available in the cities studied.
Note:
Chi-square for reported race/skin color was calculated by comparing the White and Black/brown groups.

derived from a sample of total reported AIDS cases living in Southern and Southeastern Brazil provides estimates of survival from a sample that is representative of AIDS patients living in these two regions, in addition to providing indicators for the period of the epidemic following the beginning of ART use in Brazil.

The main findings of the study cannot be generalized for the current reality of patients with AIDS in the regions studied, nor for other Brazilian populations and regions. Its data relate to the period 1998-1999, when ART was just beginning and when drug regimens were less efficacious than they currently are. Nevertheless the results enable a view of the

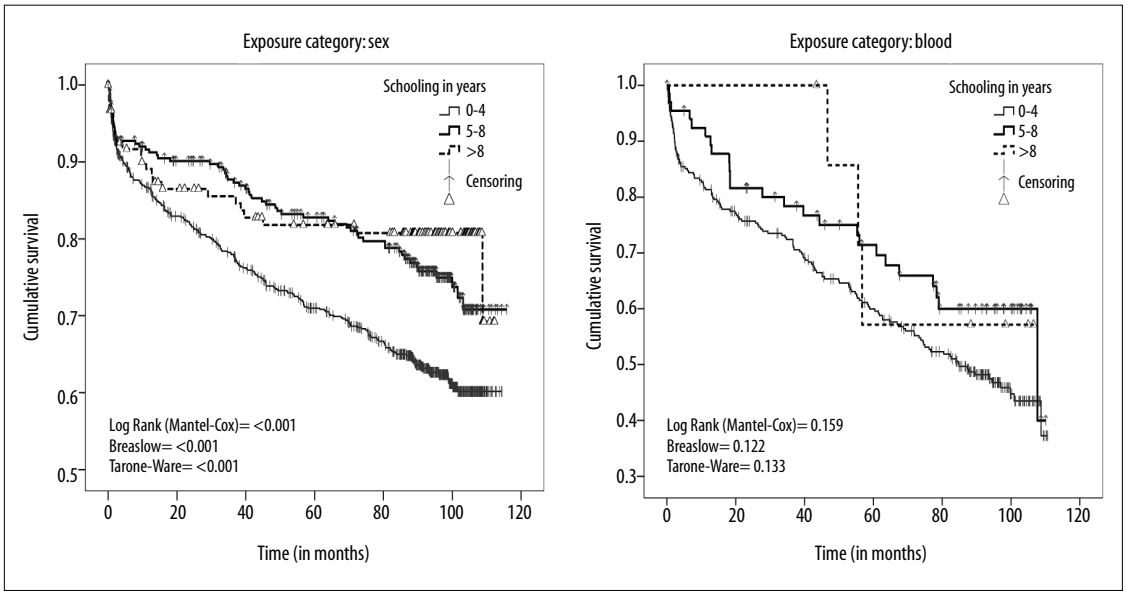

Figure 2 – Survival curves by exposure type, adjusted for schooling (in years of study), of people living with AIDS in the South and Southeast regions of Brazil, 1998-2009

relationship between survival and socio-economic, health and time aspects in people living with AIDS.

Estimates of AIDS patient survival reveal increased time in Brazil's most populous regions, as demonstrated by the indicators of other representative historical cohort studies.[3,10,11]

Given the high proportions of people using antiretroviral therapy regularly, there is evidence of relevant impact on the survival of AIDS patients in diverse age ranges, thus reducing the incidence of opportunist infections and hospitalizations in Brazil, as in various parts of the world.[3,14-16] However, this impact is not homogenous among the population. In particular, adherence to treatment and regular use of medication are determining factors for controlling viral load and increasing CD4 T lymphocytes,[17] as well as for a better prognosis.[18]

With regard to schooling and race/skin color, it is recognized that differences in socio-economic conditions are worthy of special interest in the case of AIDS. Given the efforts of current State policies, particularly those of the Department of STI, HIV/AIDS and Viral Hepatitis Surveillance, Prevention and Control, for universal access to care and treatment, it is expected thus reducing disparities among more vulnerable groups.[19]

Low schooling is associated with poorer living, housing and eating conditions, unsatisfactory transport and access to health services, in addition to social discrimination.[20] In several regions of Brazil, survival and ART adherence have been associated with lower schooling.[3,15,16] We used schooling in this study as a proxy variable for people's socio-economic status, both because of the availability of this information on medical records and also because of its use in other studies.[2,3,11]

Our results in relation to race/skin color are similar to those of a study conducted in the United States (USA), where mortality associated with AIDS is significantly higher among Black and Hispanic people,[21] despite survival having become similar between different ethnic groups in the USA following the advent of ART.[22] Lower perception of risk[23] and higher rates of HIV prevalence have been identified in individuals who refer to themselves as being Black/brown,[24] as well as greater mortality associated with ethnic groups in the first decades of the epidemic.[25] Although other studies may not have found association between ethnicity and AIDS mortality, they have identified lower adherence to ART in Black/brown individuals in the post-HAART period.[26] However consensus does not exist as to ethnic-racial classification in Brazil,[27] information on reported race/ skin color has been used to infer characteristics of populations that may be more vulnerable.[8]

Table 3 – Hazard ratio (HR) and 95% confidence interval (95%CI) of variables associated with survival of people living with AIDS, with both crude analysis and analysis adjusted using Cox regression, in the South and Southeast regions of Brazil, 1998-2009

Variable	Univariate			Multiple		
	HR	95%CI	Valor p	HR	95%CI	P value
Sex						
Male	1.00	–		1.00	–	
Female	0.71	0.61;0.83	<0.001	0.62	0.51;0.75	0.013
Age group (in years)						
13-25	1.00	–		1.00	–	
26-39	1.12	0.87;1.43		1.18	0.87;1.60	
40-59	1.19	0.91;1.54		1.35	0.98;1.87	
≥60	2.82	1.78;4.44	<0.001	2.48	1.41;4.39	0.017
Reported race/skin color						
White	1.00	–		1.00	–	
Black/brown	1.32	1.10;1.57	<0.001	1.20	0.99;1.47	0.074
Schooling (in years of study)						
0-4	1.00	–		1.00	–	
5-8	0.61	0.49;0.75		0.61	0.49;0.77	
>8	0.46	0.32;0.67	<0.001	0.44	0.30;0.65	0.014
HIV transmission category[a]						
Sexual	1.00	–		1.00	–	
Blood	1.77	1.49;2.10	<0.001	1.23	0.99;1.52	0.066
Use of antiretroviral therapy						
Yes	1.00	–		1.00	–	
No	11.56	9.41;14.19	<0.001	11.23	8.85;14.25	0.012
Other health professionals[b]						
Yes	1.00	–		1.00	–	
No	1.58	1.36;1.83	<0.001	1.20	0.99;1.46	0.068
Region						
Southeast	1.00	–		1.00	–	
South	0.99	0.86;1.16	<0.001	0.99	0.84;1.18	0.964

a) HIV: human immunodeficiency virus.
b) Other health professionals to whom AIDS patients had access, in addition to a doctor and a nurse: psychologist, dentist, social worker, psychiatrist, physiotherapist, nutritionist, occupational therapist and/or other professionals available in the cities studied.

We found inequalities in survival of people living with AIDS in this cohort of people resident in Brazil's two most populous regions. Schooling was a predictor of lower survival, overlapping the differences between the groups of reported race/skin color. Even in the light of public policies on comprehensive health care and universal access to antiretroviral therapy, nevertheless inequalities in survival remain among AIDS patients in Brazil.

Authors' contributions

All the authors took part in the conception of the study, data analysis and interpretation, writing and critically reviewing the intellectual contents of the manuscript. They have approved the final version and take on responsibility for all aspects of this paper, including the guarantee of its accuracy and integrity.

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