Factors associated with death due to HIV/AIDS

Fatores associados ao óbito por HIV/Aids

Factores asociados al fallecimiento por VIH/Sida

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Abstract

Objective: To analyze the factors associated with death in people with HIV/AIDS.

Method: This is an epidemiological and analytical study, carried out from the HIV/AIDS notifications of the state of Mato Grosso do Sul, from 2009 to 2018. Data were analyzed using descriptive statistics, Kaplan-Meier survival analysis and Cox regression.

Results: A total of 8,712 notifications were analyzed, with a survival rate of 86% over the 10 years. Factors associated with death were: males (=1.22; p=0.006), brown skin color (=1.30; p=0.012), eight years or less of study (=1.57; p=0.000), and possible sexual transmission through intercourse with women (=2.72; p=0.000) or with both men and women (=2.24; p=0.002) and use of injectable drugs (=2.57; p=0.016).

Conclusion: Social, cultural and behavioral characteristics may contribute to reduce the survival of people with HIV/AIDS. These factors indicate specificities to be considered in care planning and monitoring of cases, especially with regard to the need for an active search, continuous monitoring, in addition to interventions that involve changes in behavior.

Resumo

Objetivo: Analisar os fatores associados ao óbito em pessoas com HIV/Aids.

Método: Estudo epidemiológico e analítico, realizado a partir das notificações de HIV/Aids do estado de Mato Grosso do Sul, no período de 2009 à 2018. Os dados foram analisados por meio de estatística descritiva, análise de sobrevida via método de Kaplan-Meier e regressão de Cox.

Resultados: Foram analisadas 8.712 notificações, com taxa de sobrevida de 86% ao longo dos 10 anos. Os fatores associados ao óbito foram: sexo masculino (=1,22; p=0,006), cor da pele parda (=1,30; p=0,012), oito anos ou menos de estudo (=1,57; p=0,000), e possível transmissão sexual mediante relação com mulheres (=2,72; p=0,000) ou com ambos – homens e mulheres (=2,24; p=0,002) e utilização de drogas injetáveis (=2,57; p=0,016).

Conclusão: Características sociais, culturais e comportamentais podem contribuir para redução da sobrevida das pessoas com HIV/Aids. Esses fatores sinalizam especificidades a serem consideradas no planejamento assistencial e monitoramento dos casos, em especial no que concerne à necessidade de busca ativa, monitoramento contínuo, além de intervenções que envolvam mudanças de comportamento.

Resumen

Objetivo: Analizar los factores asociados al fallecimiento de personas con VIH/Sida.

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Conflicts of interest: nothing to declare.

Método: Estudio epidemiológico y analítico, realizado a partir de las notificaciones de VIH/Sida en el estado de Mato Grosso do Sul, en el período de 2009 a 2018. El análisis de los datos se realizó por medio de estadística descriptiva, análisis de sobrevida por el método de Kaplan-Meier y de regresión de Cox.

Resultados: Se analizaron 8.712 notificaciones, con un índice de sobrevida del 86 % a lo largo de los 10 años. Los factores asociados al fallecimiento fueron: sexo masculino (=1,22; *p*=0,006), color de piel parda (=1,30; *p*=0,012), ocho años o menos de estudio (=1,57; *p*=0,000), y posible transmisión sexual mediante relación con mujeres (=2,72; *p*=0,000) o con ambos, hombres y mujeres (=2,24; *p*=0,002), y uso de drogas inyectables (=2,57; *p*=0,016).

Conclusión: Características sociales, culturales y de comportamiento pueden contribuir para la reducción de la sobrevida de las personas con VIH/Sida. Esos factores señalan especificidades que se deben considerar en la planificación asistencial y en el monitoreo de los casos, en especial en lo que atañe a la necesidad de la búsqueda activa, el monitoreo continuo e intervenciones que incluyan cambios de comportamiento.

Introduction

In 2019, 41,909 new positive HIV cases, 37,308 AIDS cases and 10,565 deaths were confirmed in Brazil, representing a rate of 4.1 per 100,000 inhabitants.[1] These data demonstrate the magnitude of the epidemic in the country.

It should be noted that advances in HIV infection clinical management allowed it to migrate from a disease with an unfavorable and rapidly fatal prognosis, associated with poor quality of life and high mortality rates, for a chronic condition accompanied by increased survival and improved quality of life. Proof of this is that from 2010 to 2019 a 39% reduction in the rate of HIV mortality was observed in Brazil.[1] It is noteworthy that the country has a public policy that guarantees universal, free and sustainable access to Antiretroviral Therapy (ART), which reduces the chances of death and favors the maintenance of the clinical and biological conditions of People Living with HIV (PLHIV).[2]

This policy values not only the assistance and monitoring of infected people, but also the prevention of new cases through the incorporation of different tools, such as the availability of anonymous HIV testing, male and female condoms, post-exposure prophylaxis, prevention of mother-to-child transmission, harm reduction and pre-exposure prophylaxis.[2] Thus, in addition to advances contributing to increased expectation and quality of life of PLHIV, they reduced the financial costs related to hospitalizations.[3]

In this context, the aging of this population brings other challenges, such as the need to update health professionals, public policies that address chronic non-communicable diseases and HIV seropositivity, the planning of strategies that favor ART compliance, especially because older individuals are more likely to die in the first year of diagnosis, when compared to the younger ones. Moreover, it is even more important to monitor these patients to identify and treat complications inherent to the infection and those related to aging.[4,5]

The identification of risk factors for death of PLHIV could generate subsidies for the creation of strategies to face the barriers of access to treatment, linkage and retention to health services, in addition to the construction of mechanisms to control metabolic, cardiological and neurological changes inherent to aging.[6] Thus, a deeper understanding of the elements and factors associated with death in PLHIV is necessary, in order to support interventions aimed at this population throughout life.

In this perspective, this study seeks to advance the knowledge of the factors that contribute to a higher risk of death and identification of PLHIV profile. Therefore, this study aimed to analyze the factors associated with death in people with HIV/AIDS.

Methods

This is an epidemiological and analytical study, carried out based on data provided by the Health Department of Mato Grosso do Sul coordination, containing information from the HIV/AIDS notification forms, except for the name, referring to the period from 2009 to 2018 It is noteworthy that SINAN data were not used, since only data were available until 2014. All notifications were considered, but those with incomplete data were excluded and the repeated ones were counted only once.

Variables selected for analysis were date of diagnosis, age, sex, skin color, education, probable category of infection (sexual, vertical), injection drug

use, transfusion in hemophiliacs, blood transfusion, accident with sharps, cause and date of death. The age variable was grouped in two ways, in categories with a range of 5 years (10-14; 15-19) in order to identify cases in this population, since it is increasing, while the other categories were grouped every 15 years (20-34; 35-49; 50-64; 65 or more).[10]

The behavior of the continuous random variable, survival time, T ≥ 0, can be expressed through several mathematically equivalent functions, such that, if one of them is specified, the others can be derived. Among them we have the probability density function,

$$f(t) = \lim_{\Delta t \to 0} \frac{P(t \le T \le t + \Delta t)}{\Delta t},$$

defined as the limit of the probability of an individual experiencing the event of interest in the time interval $[t, t+\Delta t]$ per unit of time, such that $f(t) \ge 0$ for all $t \ge 0$. The survival function is determined by $S(t) = P(T \ge t) = 1 - F(t)$ $F(t)$ being the cumulative distribution function, used in practice to describe the different aspects presented by the data set.[7,8]

For the present study, diagnosis and death dates in the State Department of Health database were considered. For those who did not have a date of death, a live patient was considered at the end of the period under analysis.

Empirical estimates of survival function were obtained by the Kaplan-Meier method,[9] through the survfit command from the computer programR survival library.[10] This estimator is also known in literature as a product-limit estimator, and allows the presence of censored observations. Its expression is given by

$$S_{KM}(t) = \prod_{r, t_i < t} \frac{n_i - d_i}{n_i},$$

where t is the longest survival time less than or equal to t, n_i is the number of living individuals up to time t_i and d_i represents the number of HIV/AIDS deaths in time t_i (days). Among the main properties, it is not addicted to large samples, is weakly consistent, converges asymptotically to a Gaussian process, and maximum likelihood estimator of S(t).[7]

The likelihood ratio test was used to select variables. The verification of the significance of param-

eters associated with age group, sex, race, education, exposure category and injectable drug user was performed using the Cox model[11] at a 5% significance level via the coxph command from the survivaldo R library. And, finally, the verification of Cox's proportionality was carried out through the graphic analysis of Schoenfeld residuals.[11] Based on the final adjusted model, the risk estimate was calculated considering a baseline level of comparison.

The project was approved by the Research Ethics Committee of the *Universidade Federal do Mato Grosso do Sul,* with Opinion 3,789,678 and CAAE (*Certificado de Apresentação para Apreciação Ética* - Certificate of Presentation for Ethical Consideration) 23375619.9.0000.0021, meeting the precepts of Brazilian National Health Council Resolution 466/2012.

Results

The number of HIV/AIDS notifications during the study period was 9,158. Of these, one was excluded due to duplicity, 309 due to the absence of the time variable (in days) and 136 due to data inconsistency, which resulted in a final sample of 8,712 notifications. Regarding the population profile, the highest occurrence was observed in males (63.6%), aged between 20 and 49 years (79.3%), white (44.6%) and brown (43.2%) and with eight or fewer years of study (57.11%). Regarding the probable mode of infection, the sexual route was the most frequent (87.9%).

In table 1, it is observed that males ($e^{\hat{\beta}}$=1.22; p=0.006), of brown skin color ($e^{\hat{\beta}}$=1.30; p=0.012), with eight years or less of study ($e^{\hat{\beta}}$=1.57; p=0.000), whose possible sexual transmission was through intercourse with women ($e^{\hat{\beta}}$=2.72; p=0.000) or with both (men and women)($e^{\hat{\beta}}$=2.24; p=0.002), as well as those who use injectable drugs ($e^{\hat{\beta}}$=2.57; p=0.016) have a higher risk of death due to HIV/AIDS at each time unit. It is noteworthy that individuals of yellow skin color presented protection ($e^{\hat{\beta}}$=0.30; p=0.04) in relation to the risk of death (13% less), when compared to those of white skin color (baseline).

Table 1. Survival analysis considering multiple sociodemographic, clinical and behavioral characteristics of people with HIV/AIDS in relation to the death outcome

Variables	n(%)	d%	$e^{\hat{\beta}}$	*p-value
Age group (years)				ns
10-14	25(0.30)	4.00	-	-
15-19	402(4.61)	1.49	-	-
20-34	3906(44.84)	5.99	-	-
35-49	3010(34.55)	11.83	-	-
50-64	1174(13.48)	14.90	-	-
65 and older	195(2.24)	21.03	-	-
Sex				
Male	5549(63.69)	9.71	1.22	0.006
Female	3163(36.61)	8.67	-	-
Skin color/ethnicity				
White	3725(44.69)	7.49	baseline	-
Black	590(7.08)	11.18	-	ns
Yellow	198(2.38)	3.54	0.13	0.040
Brown	3601(43.20)	11.05	1.30	0.012
Indigenous	222(2.66)	14.41	-	ns
Education (years of study)				
More than 8	2870(42.89)	5.89	baseline	-
8 or less	3822(57.11)	12.40	1.57	0.000
Sexual transmission				
Relationship with men	4302(55.56)	7.07	baseline	-
Relationship with women	3112(40.19)	12.79	2.72	0.000
Relationship with both	329(4.25)	8.82	2.24	0.002
Vertical transmission				ns
No	8253(99.04)	9.56	-	-
Yes	80(0.96)	7.50	-	-
Injectable drug use				
No	6175(96.42)	8.49	baseline	-
Yes	229(3.58)	17.90	1.57	0.016
Transfusion in hemophiliacs				ns
No	7377(99.93)	9.26	-	
Yes	5(0.07)	0.00	-	
Blood transfusion				ns
No	6489(99.36)	8.91	-	
Yes	42(0.64)	4.76	-	
Sharp accident				ns
No	6718(99.97)	9.32	-	-
Yes	2(0.03)	0.00	-	-
General	n=8,712	²9.33	-	-

*n=4,923; d=446; 64.1% agreement; ²proportion of deaths, ns: not significant.

Figure 1 shows the graphical representation of the survival curve, which was approximately 86%, of individuals with HIV/AIDS over the 10 years analyzed.

In turn, figure 2 shows the graphical representations of the survival curve by sex, skin color, education, sexual transmission and injectable drug user.

Regardless of the time of analysis, the number of deaths was higher among men when compared to women. Indigenous people showed abrupt declines in the number of deaths over time and pardos had a const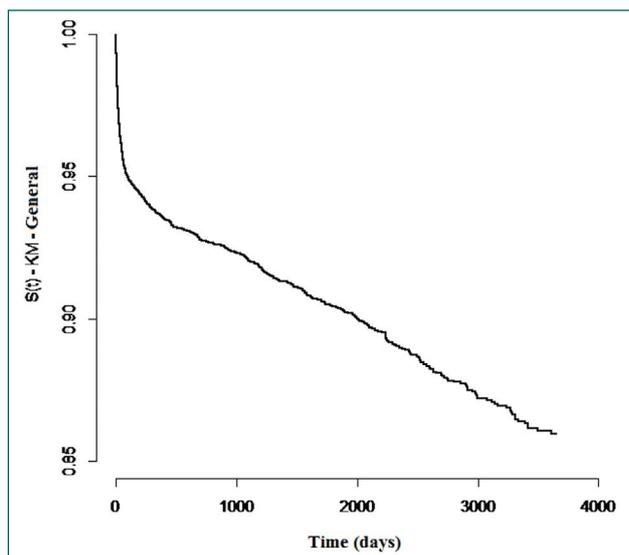ant decline. Individuals with eight years of education or less had a lower survival rate than those with more than eight years of education. Regarding behaviors, individuals who had sexual relations with women presented the survival curve below those who maintained only with men and with both sexes, with a higher chance of death. In turn, injectable drug users present a curve with a sharp drop from the 3,000 days of infection in relation to non-users.

Figure 1. Survival curve (Kaplan-Meier) for life time (days) in people with HIV/AIDS

Discussion

The PLHIV profile in Mato Grosso do Sul is young adults, with a higher proportion of males, low education and the main route of transmission is sexual, a fact not far from other regions of Brazil[3,15,16] and other countries.[13,14]

Regarding the risk of death and survival in relation to sex, in the present study, for any time, the chance of survival for men was lower than for women. Among the factors that may influence this result, gaps related to diagnosis, which sometimes occurs late, and the lower ART compliance in the male population stand out.[15] In this context, it should be noted that the presence of men in health services is, in general, low and factors such as gender relations, work and self-care collaborate with abstention in health services. In order to modify
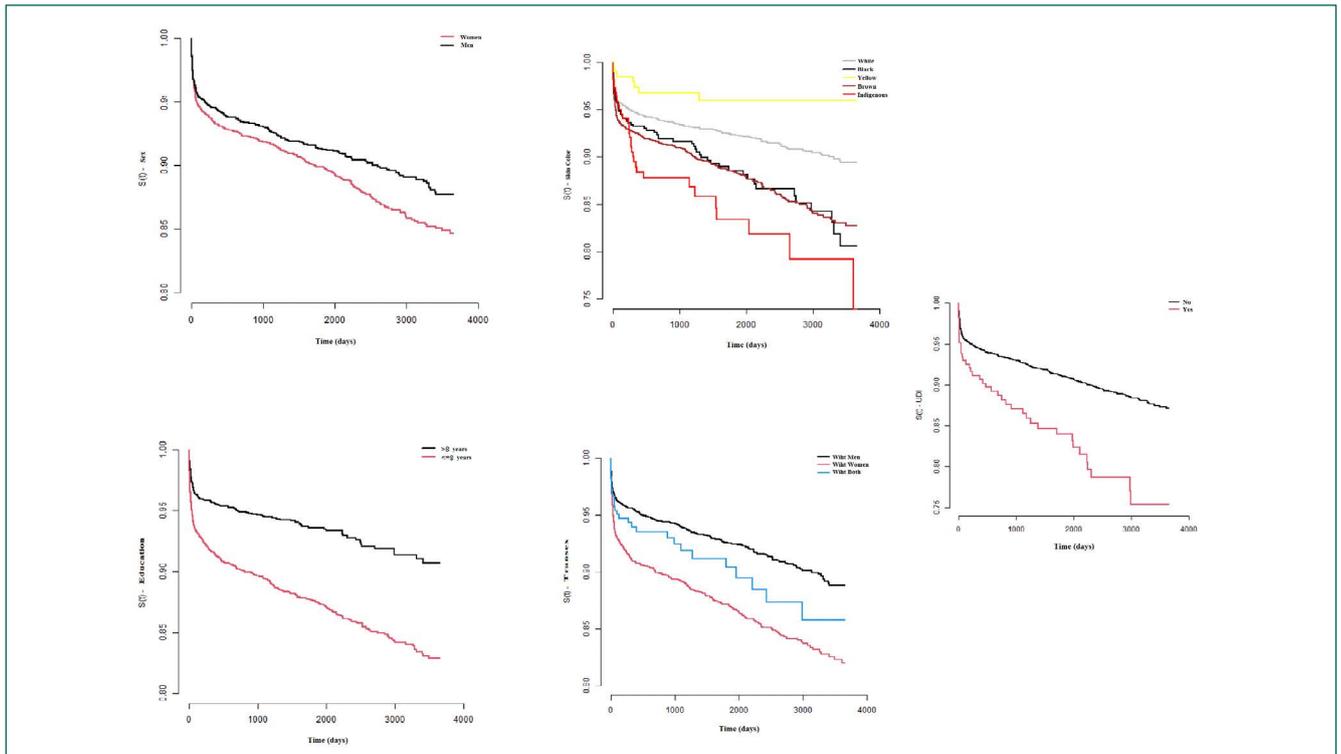
Figure 2. Survival curves of people with HIV/AIDS

this scenario, public policies such as the Brazilian National Policy for Comprehensive Care for Men's Health, proposes strategies that favor the monitoring of their health condition.[16] Thus, early screening and the active search for PLHIV, especially of males, are care actions that need to be reinforced by professionals in services.

It was observed that PLHIV, which self-declared brown, had 30% more chances of death when compared to white. However, it should be noted that the self-declared brown Brazilian population is 46.8%,[17] which may contribute to a higher concentration of infection in these individuals. In turn, studies carried out in Brazil[18] and in the United States[19] found higher infection rates in the black population compared to the white population. It should be noted that the lack of agreement in the ethnic-racial classification in a universal way contributes to disparities.[18] However, it is necessary to consider the population's particularities in relation to race/skin color in the care process, in order to direct the emphasis of follow-up actions. This is because historical issues influence the individual, social and programmatic vulnerability of brown,

black and indigenous people,[20] even with universal access to ART.

In turn, individuals with less than eight years of study had 57% more chances of death. It should be noted that low education is related to the structural conditions of poverty, limited access to health services and low income,[21,22] in addition to contributing to the use of illicit drugs and low compliance with treatment.[23] In this sense, the results showed that using injectable drugs increased the risk of death by approximately 1.6 times in the state, a fact also identified in a population-based study carried out in a city in the United States.[24] Social inequality reflected in the increase in the homeless population and drug users impacts public health and can sometimes compromise access to health services and ART compliance. In view of this, monitoring, the active search for PLHIV drug users, intersectoral interventions that combine housing, case management and behavioral interventions can constitute strategies that increase the survival of these individuals.[24]

The sexual transmission route was predominant, as in other Brazilian locations,[25,26] and those

who had sexual intercourse with women had an approximately 2.8 times greater risk of dying when compared to those who had sexual intercourse with men. It should be noted that the diagnosis of positive anti-HIV serology in women sometimes occurs late, with a high viral load, low CD4+ T lymphocyte count and during pregnancy.[27] Thus, actions aimed at expanding testing in this population are necessary, with a view to early diagnosis and antiretroviral treatment, especially because they use health services more. Corroborating, care actions should consider these factors during planning and implementation, in order to provide opportunities for dialogues involving, for instance, the negotiation of condom use with partners.

Similarly, those who maintain a relationship with both (male and female) also had a higher risk of death. Factors related to the distorted view of HIV and individuals who do not fit into the heteronormative pattern create barriers for seeking testing as well as for hiding information. These conditions influence the phenomenon called internalized homophobia, in which accepted patterns are assumed in relation to those practiced, due to fear of retaliation.[28]

Furthermore, the social stigmas surrounding issues of sexuality and diagnoses of diseases such as AIDS can directly influence the information reported by individuals, which may differ from reality. In view of this, the direction of care and health promotion actions must correspond to the confrontation of prejudice, changes in lifestyle and safe sex practices, in order to reduce the number of new infections and complications of those cases already diagnosed.

Regarding survival, the fact that 86% of PLHIV remained alive over the 10 years under study may be related to the efficiency of ART, a decrease in opportunistic infections and, consequently, in hospitalizations.[18,25] In southern and southeastern Brazil, for instance, inequalities in the survival of PLHIV elucidated the importance of recognizing predictive factors such as education and race/color.[18] In turn, a retrospective cohort study carried out in São Paulo highlighted the positive impact of ART introduction on the survival of PLHIV.[24] In this sense, It

is worth noting that survival can reach more than 10 years in individuals using ART after diagnosis of AIDS. However, the use of medications should be regular, as should the monitoring and follow-up of CD4+ T lymphocyte rates and viral load.[26]

A study carried out in Europe with 35,063 PLHIV showed a decrease in viral load and an increase in CD4+ T lymphocyte rates in individuals on regular use of ART, as well as an increase in survival when compared to those who did not use it regularly.[29] It is noteworthy that Brazil is considered a pioneer country in the free provision of care and treatment for PLHIV, through the universality and completeness of the Unified Health System (*Sistema Único de Saúde*),[30] so that this condition favors the increase in survival of these people.

However, it is worth noting that in addition to ART compliance, other improvements in health care, such as treatment and prophylaxis for opportunistic infections, comorbidity management, improvements in intensive care management, disease screening, and health promotion may also have contributed to longer years lived. In this sense, the importance of studies that make it possible to identify factors associated with mortality is reiterated in order to direct continuous monitoring, sometimes more directed to specific groups, in order to contribute to the significant decline in mortality caused by AIDS.

Given the results, it is suggested to carry out future studies that address the clinical conditions and quality of life of these individuals over the years, in order to improve and direct strategic actions that favor survival.

The present study had as limitations: the use of a secondary database, subject to the incompleteness of the records – especially in relation to the death date outcome as well as the potential failure to update the "evolution of death" field – lack of information inherent to follow-up of patients' treatment and clinical conditions; failure to cross-check the data provided by the State Health Department with those contained in the Notifiable Diseases Information System and in the Mortality Information System; and the isolated analysis of the sexual transmission variable

which should take into account biological sex as well as exposure category, so that study results are not misinterpreted.

Moreover, the results cannot be generalized, since regional characteristics may influence the distribution of cases. However, the findings can trigger reflections on existing public policies and care actions spent on this audience, in addition to directing active search strategies for cases that favor compliance, retention and maintenance of treatment that reflect on survival. In particular, the actions of nurses who are sometimes in charge of Primary Care teams and who need to meet the specific population and address the prevention of disease complications through behavior change.

Conclusion

The factors associated with death in people with HIV/AIDS were being males, brown skin color, eight or less years of education, sexual transmission through relationships with women or with both (men and women) and injectable drug use. Given these findings, it is necessary to apply public policies to combat HIV according to the peculiarities of the state under study. The identification of factors that increase the chances of death offers subsidies for professionals involved in care management and those providing direct assistance to PLHIV, in such a way that they can reorder actions and strategies applied in screening, diagnosis, monitoring and prevention. Furthermore, there is a need for future studies that relate death to factors such as clinical conditions and ART compliance.

Acknowledgments

Collaborations

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