

Prevalence of Kaposi's sarcoma in patients with AIDS and associated factors, São Paulo-SP, Brazil, 2003-2010*

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Abstract

Objective: to estimate the prevalence of Kaposi's sarcoma (KS) in patients with AIDS and identify the associated factors to the occurrence of this neoplasm. **Methods:** this is a cross-sectional study with notification data from two AIDS reference centers in São Paulo-SP, Brazil, from January, 2003 to March, 2010; probabilistic linkage and multiple logistic regression methods were applied. **Results:** among 3,557 AIDS cases, 213 (6%) presented KS; 95.3% of them occurred in males; male sex (OR=3.1; 95%CI=1.4;6.6), age at the AIDS diagnosis >28 years old (OR=1.6; 95%CI=1.0;2.6), MSM (OR=3.2; 95%CI=2.0;4.9), prior use of HAART (OR=0.4; 95%CI=0.3;0.5), AIDS diagnosis between 2007-2010 (OR=0.3; 95%CI=0.2;0.4), and CD4+ T-cell counting under 200cells/mm³ (OR=16.0; 95%CI=6.0;42.7) and 200-500cells/mm³ (OR=2.5; 95%CI=1.1;6.4) were associated to the occurrence of KS. **Conclusion:** KS has a high prevalence in São Paulo-SP; strategies for early HIV diagnosis may reduce this prevalence.

Keywords: Acquired Immunodeficiency Syndrome; Kaposi's Sarcoma; Highly Active Antiretroviral Therapy; Epidemiology, Descriptive.

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Introduction

Kaposi's sarcoma (KS) is a mesenchymal tumor, caused by herpes virus type 8 (HHV-8), and a characteristic neoplasm of acquired immunodeficiency syndrome (AIDS). After the emergence of AIDS in 1980, a more aggressive form of the disease, more common among homosexual or bisexual men and associated with the human immunodeficiency virus (HIV), was documented. It was soon recognized as an epidemic form of KS,¹ which had a big impact on the Public Health due to its high magnitude and mortality. KS was the first opportunistic infection recognized in association with HIV and is still the most common neoplasm related to AIDS.^{1,2}

The introduction of highly active antiretroviral therapy (HAART) helped to strengthen the immune system of people infected with HIV and lowered the risk of these people to develop KS. Nevertheless, KS is still considered the most prevalent tumor among this population.^{3,4}

Kaposi's sarcoma was the first opportunistic infection recognized in association with HIV and is still the most common neoplasm related to AIDS.

Although HAART does not interfere directly with the replication of HHV-8, cases of regression of KS-AIDS lesion have been observed frequently after the use of HAART in combination with chemotherapy or radiotherapy,⁵ though the mechanism by which HAART leads to the regression of KS remains controversial.^{2,3} The incidence of KS has substantially declined due to HAART,⁴ in the same way that KS-AIDS became less aggressive when compared to KS among individuals with no antiretroviral treatment.^{6,7}

In Brazil, from 1996 to 2010 – already in the post-HAART era –, the incidence of KS was still 2.5 times higher than in the United States of America (USA), and it remains as the most common neoplasm in HIV carriers.⁸

The aim of this study was to estimate the prevalence of Kaposi's sarcoma in patients with AIDS and identify the factors associated with the occurrence of this neoplasm.

Methods

This is a cross-sectional study based on data of patients with AIDS under follow-up at two AIDS reference centers, from January 2003 to March 2010.

Both centers offer specialized care in AIDS in the municipality of São Paulo-SP, each with approximately 5,000 patients followed-up for HIV/AIDS. São Paulo-SP is the largest municipality in Brazil, and had 11.3 million inhabitants, according to 2010 census.⁹ It is the capital of São Paulo State and the main financial, corporate and commercial center in South America. From 1980 to 2014, 86,112 AIDS cases were reported in the municipality, representing a detection rate of 18.6 per 100,000 inhabitants/year at the end of the period, with 41,704 individuals living with HIV,¹⁰ to whom the municipality offers free treatment since 2014, regardless of the CD4+ T-cell count in the laboratory result of the patient.

The study population consisted of patients aged 13 years old or over with AIDS, registered on the Information System for Notifiable Diseases (Sinan), and being followed-up in those centers, in the period of the study.

We defined AIDS cases as 'every individual infected with HIV who had at least one disease indicative of AIDS, and/or CD4+ T-cell count below 350 cells/mm³, regardless of the presence of other causes of immunodeficiency'.

During the study period, the Brazilian Ministry of Health proposed several changes for AIDS cases definition: 1) Centers for Disease Control and Prevention (CDC)/USA criterion; 2) Rio de Janeiro-Caracas criterion; 3) death exceptional criterion; and 4) adapted CDC criterion. In this study, each of these changes was followed, according to their period of validity. Exposure categories for HIV transmission and treatment regimens were classified according to the criteria of the Brazilian Ministry of Health.

Although a presumptive diagnosis of KS is often based on medical history and appearance of skin lesions,¹¹ only cases confirmed by biopsy were considered.

The data sources used in the research were: (i) São Paulo Integrated AIDS Database (BIPAIDS), created from the linkage between the deaths database of the State System for Data Analysis (SEADE) and the database of the Information System for Notifiable Diseases (Sinan-AIDS) of São Paulo State Program for STD/AIDS; (ii) Laboratory Tests Control System (SISCEL); and (iii) Drug Logistics Control System (SICLOM), of the Ministry of Health.

ReLinkII software, version 3.1, performed the linkage between the databases. The databases were

linked through the probabilistic method. Routines were used for standardization of common fields that would be used to relate and identify duplicate records between the bases. True pairs were classified through the blocking of variables consisting of first and last name, sex, date of birth and mother's name, in order to optimize the comparison between records. The application of algorithms to an approximate comparison of strings aimed to identify possible phonetic and typographical errors. The calculation of scores that summarize the overall level of agreement between records of the same pair was established; we also set thresholds for the classification of pairs of records into true pairs, non-pairs and doubtful pairs. A manual review of doubtful pairs was made aiming to classify them as true pairs or non-pairs and to check for duplicate records in files. These data were individually checked to confirm the coinfection.

In order to complete the ignored information, additional data were collected from patients' medical records.

The independent variables of the study were:

- a) Sociodemographic characteristics
 - Sex (male; female);
 - Age (in years: 13 to 19; 20 to 29; 30 to 39; 40 to 49; 50 to 59; 60 to 69; 70 to 79);
 - Education level (in years of schooling: ≤ 8 ; 9 to 12; ≥ 13 ; none);
 - Ethnicity/skin color (white, black, brown, Asian, indigenous);
- b) Behavioral characteristics
 - Exposure category (heterosexual, men who have sex with men – MSM –, injectable drug users; other);
- c) Clinical and laboratory characteristics
 - KS (yes; no);
 - Use of HAART prior to the diagnosis of KS (yes; no);
 - CD4+ T-cell count (< 200 cells/mm³; 200 to 500cells/mm³; > 500 cells/mm³); and
 - period of AIDS diagnosis (2003 to 2006; 2007 to 2010)

The CD4+ T-cell count at the time of diagnosis of AIDS was considered for the analysis.

KS was the event chosen as the dependent variable. Sociodemographic, behavioral, clinical and laboratory characteristics were regarded as independent variables of interest. The associated factors were analyzed in blocks through the multiple logistic regression model, and all variables with a significance level of $p < 0.15$ were considered eligible to be included in the model. The test based on the likelihood ratio was used every time

a new variable was included, and, if the significance of the new model was higher than 0.05, the variable was excluded.

Epi Info™ software, version 3.4.3, was used to complement data entry, and STATA, version 10.0 was used for modeling.

The study was approved by the Ethics Research Committees of the Reference and Training Center in STD/AIDS (RTC-DST/AIDS) – Protocol No. 555.248, dated March 11th, 2014 – and of the Institute of Infectious Diseases Emilio Ribas (IDERI) – Protocol No. 618.177, dated April 9th, 2014.

Results

The study population consisted of 3,557 AIDS cases, of which 213 (6.0%) had KS.

The epidemiological, demographic, and clinical and laboratory characteristics of patients with AIDS and Kaposi's sarcoma are presented in Table 1.

There was a predominance of males in the total number of AIDS cases (73.3%) and in almost all cases of KS (95.3%). The diagnosis of AIDS was predominant at the age of 30 to 39 years old (39.6%), the same age group that presented the highest proportion of KS cases (37.1%).

Cases of AIDS – 38.6% (1,372/3,557) – and of KS – 55.9% (119/213) – occurred more often in individuals with nine or more years of schooling. About two-thirds of them (62.8%) reported being white; and this proportion rose to 68.5% among the cases of KS.

The largest proportion of patients with AIDS was of heterosexual individuals (39.3%); however, among the cases of KS, the highest proportion was represented by MSM (62.9%).

More than half of patients with AIDS reported prior use of HAART (53.8%), whereas only 39.4% of individuals with KS were undergoing this therapy.

Most patients with AIDS (70.8%) had a CD4+ T-cell count between 200 and 500cells/mm³; in the cases of KS, the proportion of CD4+ T-cells at this range was of 65.3%.

Comparing the periods of 2003-2006 and 2007-2010, there was a higher number of diagnosis of AIDS in the second period (2,277 *versus* 1,280), although the highest number of cases of KS were diagnosed in the first period (123 *versus* 90).

In the crude analysis, presented in Table 2, the following variables were associated with the progression

Table 1 – Sociodemographic, behavioral and clinical laboratory characteristics of patients with AIDS treated at the Reference and Training Center for STD/AIDS and at the Institute of Infectious Diseases Emilio Ribas, São Paulo-SP, 2003-2010

Characteristics	Kaposi's sarcoma						p ^a
	Yes (n=213)		No (n=3,344)		Total (n=3,557)		
	n	%	n	%	n	%	
Sex							<0.001
Male	203	95.3	2,406	71.9	2,609	73.3	
Female	10	4.7	938	28.1	948	26.7	
Age group (at the time of AIDS diagnosis, in years)							0.559
13-19	1	0.5	55	1.6	56	1.6	
20-29	45	21.1	669	20.0	714	20.1	
30-39	79	37.1	1,331	39.8	1,410	39.6	
40-49	63	29.6	945	28.3	1,008	28.3	
50-59	22	10.3	265	7.9	287	8.1	
60-69	2	0.9	65	1.9	67	1.9	
70-79	1	0.5	14	0.4	15	0.4	
Education level (in years of schooling)							<0.001
≤8	63	29.6	1,211	36.2	1,274	35.8	
9-12	53	24.9	447	13.4	500	14.1	
≥13	66	31.0	806	24.1	872	24.5	
None	–	–	22	0.7	22	0.6	
Ignored	31	14.6	858	25.7	889	25.0	
Self-reported ethnicity/skin color							0.006
White	146	68.5	2,087	62.4	2,233	62.8	
Black	33	15.5	374	11.2	407	11.4	
Brown	21	9.9	417	12.5	438	12.3	
Asian	1	0.5	25	0.7	26	0.7	
Indigenous	–	–	3	0.1	3	0.1	
Ignored	12	5.6	438	13.1	450	12.7	
Exposure Category							<0.001
Heterosexual	36	16.9	1,361	40.7	1,397	39.3	
Men who have sex with men	134	62.9	1,165	34.8	1,299	36.5	
Injectable Drug User	7	3.3	213	6.4	220	6.2	
Other	–	–	20	0.6	20	0.6	
Ignored	36	16.9	585	17.5	621	17.5	
Prior use of HAART^b							<0.001
No	129	60.6	1,514	45.3	1,643	46.2	
Yes	84	39.4	1,830	54.7	1,914	53.8	
CD4+ T-cell count (at the time of AIDS diagnosis)							<0.001
> 500cells/mm ³	7	3.3	418	12.5	425	11.9	
200-500cells/mm ³	139	65.3	2,381	71.2	2,520	70.8	
<200cells/mm ³	67	31.5	545	16.3	612	17.2	
Period of AIDS diagnosis							<0.001
2003-2006	123	57.7	1,157	34.6	1,280	36.0	
2007-2010	90	42.3	2,187	65.4	2,277	64.0	
Total	213	100.0	3,344	100.0	3,557	100.0	

a) Fisher's exact test

b) HAART: Highly active antiretroviral therapy

to KS: male sex (OR=7.9; 95%CI=4.2; 15.0); age under 28 years old at the time of AIDS diagnosis (OR=1.3; 95%CI= 0.9; 2.0); up to 8 years of schooling (OR=1.6; 95%CI=1.1; 2.2) and 9 to 12 years of schooling (OR=2.3; 95%CI=1.5; 3.3) ; MSM (OR=4.3; 95%CI=3.0; 6.3); prior use of HAART (OR=0.5; 95%CI=0.4; 0.7); CD4+ T-cell count at the time of diagnosis of AIDS between 200 and 500cells/mm³ (OR=3.5; 95%CI=1.6; 7.5) and below 200cells/mm³ (OR = 7.3; 95%CI=3.3; 16.1); and period of AIDS diagnosis from 2007 to 2010 (OR = 0.4; 95%CI=0.3; 0.5).

Table 2 also shows the multiple logistic regression model, which identified the following associated factors: male sex (OR=3.1; 95%CI=1.4; 6.6); age under 28 years old at the time of AIDS diagnosis (OR=1.6; 95%CI=1.0;2.6); MSM (OR=3.2; 95%CI=2.0; 4.9); prior use of HAART (OR=0.4; 95%CI=0.3; 0.5); CD4+ T-cell count at the time of AIDS diagnosis between 200 and 500cells/mm³ (OR=2.5; 95%CI=1.1; 6.4) and below 200 cells/mm³ (OR=16.0; 95%CI=6.0;42.7); and period of AIDS diagnosis from 2007 to 2010 (OR=0.3; 95%CI=0.2;0.4).

Table 2 – Crude and adjusted analysis of factors associated with Kaposi's sarcoma in patients with AIDS treated at the Reference and Training Center for STD/AIDS and the Institute of Infectious Diseases Emilio Ribas, São Paulo-SP, 2003-2010

Variable	Kaposi's sarcoma			OR _{cr} ^a	IC _{95%} (OR _{cr} ^a)	p ^c	OR _{adj} ^b	IC _{95%} (OR _{adj} ^b)	p ^c
	N Total	n	%						
Sex						<0.001			<0.001
Female	948	10	1.1	1.0	–		1.0	–	
Male	2,609	203	7.8	7.9	4.2; 15.0		3.1	1.4; 6.6	
Age group (at the time of AIDS diagnosis, in years)						0.140			0.045
≤28	635	30	4.7	1.0	–		1.0	–	
> 28	2,922	183	6.3	1.3	0.9; 2.0		1.6	1.0; 2.6	
Education level (in years of schooling)						0.004			
≥13	872	66	7.6	1.0	–		–	–	–
9-12	500	53	10.6	2.3	1.5; 3.3		–	–	–
≤8	1,274	63	4.9	1.6	1.1; 2.2		–	–	–
Self-reported ethnicity/skin color						0.002			
White	2,233	146	6.5	1.0	–		–	–	–
Black/brown	845	54	6.4	0.9	0.7; 1.3		–	–	–
Other	29	1	3.4	0.5	0.1; 3.4		–	–	–
Exposure Category						0.048			0.032
Heterosexual	1,397	36	2.6	1.0	–		1.0	–	
Men who have sex with men	1,299	134	10.3	4.3	3.0; 6.3		3.2	2.0; 4.9	
Injectable Drug User	220	7	3.2	1.2	0.5; 2.8		–	–	
Prior use of HAART^d						<0.001			<0.001
No	1,643	129	7.9	1.0	–		1.0	–	
Yes	1,914	84	4.4	0.5	0.4; 0.7		0.4	0.3; 0.5	
CD4+ T-cell count (at the time of AIDS diagnosis)						<0.001			<0.001
> 500cells/mm ³	425	7	1.6	1.0	–		1.0	–	
200-500cells/mm ³	2,520	139	5.5	3.5	1.6; 7.5		2.5	1.1; 6.4	
<200cells/mm ³	612	67	10.9	7.3	3.3; 16.1		16.0	6.0; 42.7	
Period of AIDS diagnosis						<0.001			<0.001
2003-2006	1,280	123	9.6	1.0	–		1.0	–	
2007-2010	2,277	90	4.0	0.4	0.3; 0.5		0.3	0.2; 0.4	

a) OR_{cr}: crude odds ratio

b) OR_{adj}: adjusted odds ratio

c) Wald test

d) HAART: Highly active antiretroviral therapy

Discussion

The findings of this study indicate that, despite the therapeutic arsenal available in Brazil and the free access to treatment for people with HIV, KS is still highly prevalent (about 1 in 20 cases) among individuals with AIDS in São Paulo-SP, showing a strong association with sex, age, MSM, prior use of HAART, period of AIDS diagnosis and low CD4+ T-cell count. Early diagnosis of HIV infection and use of HAART were identified as the main protective factors against KS.

The prevalence found was much higher than the one shown by the data of national registers, among which 3,103 cases of KS/AIDS were reported in the same period,¹¹ corresponding to 1.5% of all reported AIDS cases.¹² Other studies conducted in Brazil have estimated prevalences of 9.1% and 17.1% of KS in people with AIDS in the municipality of Rio de Janeiro-RJ (2009) and in São Paulo State (2010), respectively.^{13,14}

Prevalence of KS in individuals with AIDS has been observed in other countries, ranging from 7 to 32% in Africa (2005 to 2011),^{15,16} 22.6% in Cuba (1998-2002)¹⁷ and 1.0% in Spain (1997-2008).¹⁸

Although it was described in 1872, in its classic form, KS achieved global clinical importance as an opportunistic disease since the first reports of the AIDS epidemic. Nowadays, despite advances in the diagnosis and HAART, KS remains the most common neoplasm in HIV-infected individuals,^{1,2} and is an AIDS-defining illness. Up to 2008, in the United States, and 2009, in Australia, KS was the second most common neoplasm associated with AIDS, even after the HAART era, which began in 1996.^{19,20}

In Brazil, KS is predominant among men (95.3%). As observed in other studies, men who have sex with men were identified as the predominant group, being approximately three times more likely to contract the disease when compared to heterosexuals, which corroborates data from a study that showed an association of KS with homosexual and bisexual males.²¹

KS risk found in this study was three times higher for men, which is similar to a South African study²² conducted from 2004 to 2010. Despite the higher risk for men, women with AIDS should not be neglected in relation to Kaposi's sarcoma: a study conducted in Italy²³ showed that KS is more aggressive and involves greater risk of death in women than in men, with higher proportion of visceral diseases, particularly in

pulmonary involvement. This disease, when spread out among women, is usually mistaken with lung infection. Perhaps this mistake occurs due to the low suspicion of KS in women with AIDS.²⁴

In the present study, KS was associated with age over 28 years, a finding consistent with other researches that correlated this variable with the outcome.¹⁹ In the pre-HAART era, KS was not consistently related to age or ethnicity/ skin color, but in the USA, Beral et al identified, in the 1981-1989 period, that the proportion of KS increased in the age group of 35 to 40 years.¹

KS was predominant in white individuals, although this variable did not reveal statistical association. In the USA, from 1995 to 2008, with regard to adolescents and young adults with AIDS, the incidence was higher in black people and Hispanics, when compared to white individuals.²⁵

In this study, the prior use of HAART proved to be a protective factor against the development of KS, in agreement with other studies, according to which the use of HAART leads to a significant reduction in the incidence of Kaposi's sarcoma,^{21,26} in addition to extending the survival of patients with KS, with an 80% reduction in the risk of death.²⁷

Two periods of AIDS diagnosis were compared (2003-2006 and 2007-2010), and we observed a reduction in the number of KS cases in the most recent period, despite the increase in the number of AIDS cases in the same period, probably due to the increased adherence to antiretroviral drugs.

KS still prevails as the most frequent neoplasm in patients with AIDS living in São Paulo,¹⁴ although it showed a lower prevalence in the reported cases in the state,²⁷ from 4.6% from 1990 to 1995 to 1.6% from 2001 to 2005 – a possible effect of HAART, in line with decreases observed in the USA and Europe.^{28,29}

A strong association between KS and CD4+ T-cell count was identified in this study, with a risk 16 times higher when the count was below 200cells/mm³. Frequently, the development of KS in people living with HIV is correlated with low levels of CD4+ T-cell, confirming the results of a study conducted in Brazil⁸ and also the findings from researches conducted in other countries, such as South Africa²² and Malawi,¹⁵ in which CD4+ T-cell count below 150cells/mm³ was associated with higher mortality; in the USA, low levels of CD4+ T-cell was found to be associated with a risk of death 4 times higher;²⁶ in France³⁰ the risk of KS doubled when related to CD4+ T-cell count between

350 and 499 cells/mm³; and in Italy,²¹ the highest risk of contracting KS was associated with a CD4+ T-cell count below 200 cells/mm³.

Different findings were reported by Lima et al²⁷ in Brazil and by Nguyen et al⁵ in the United States, in which there was no association between KS and low CD4+ T-cell counts; however, 83% of that sample had CD4+ T-cell count below 200 cells/mm³.

A limitation found in this study was the difficulty to identify the time sequence of the exposure of interest in relation to the effect (Kaposi's sarcoma). The lack of an evaluation of individual adherence to antiretroviral drugs was another limitation. Likewise, the staging of KS was not known, which hampered the verification of differences between cases exclusively cutaneous and those with visceral involvement.

Albeit these limitations, this study allowed us to determine the prevalence and factors associated with KS among patients with AIDS treated at two specialized centers in Brazil's largest city. The potential for transmission of HIV and HHV-8 through unprotected sex reinforces the need for health education actions, to promote safe sex

practices. In Brazil, where free condoms are available, the main question to address is the reduction of barriers against the access to these means for prevention of HIV and Herpes virus infections. Moreover, universal access to antiretroviral therapy by the Brazilian National Health System (SUS) and the early diagnosis and treatment enable the immunity system compatible with life in those people who have HIV infection, remaining the challenge of treatment adherence to prevent Kaposi's sarcoma.

Authors' Contributions

Toscano ALCC and Tancredi MV contributed to the conception and design of the study, analysis and interpretation of data, discussion of results and drafting of the article. Pinto VM, Pimentel SR, Silva TSB, Ito SMA, Golub J and Silva MH contributed to the study design, analysis and interpretation of data, discussion of results and critical proofreading of the article. All authors have approved the final version of the manuscript and declared to be responsible for all aspects of the study, ensuring its accuracy and integrity.

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