Human immunodeficiency virus and cancer. A population of HIV-infected patients at Hospital de Santa Maria and predictors of cancer

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Abstract

Background Cancer has become a growing burden on morbidity and mortality in human immunodeficiency virus (HIV)-infected individuals in the era of highly active antiretroviral therapy (HAART). The objectives of this study were to determine the rates and cancer predictors of a population of HIV-infected individuals and to draw some recommendations for cancer screening in these patients.

Methods This retrospective case-control study describes malignant cancers diagnosed in HIV-infected subjects at Hospital de Santa Maria and assesses cancer predictors in HIV-infected subjects using HIV-infected controls without cancer. A total of 225 patients were included in this study: 25 cancer cases and 200 controls. Eight HIV-infected controls without cancer diagnosis were selected for each cancer case. Besides cancer's date of diagnosis and its histological type, we also recorded demographic data, medical history and HIV-related information. Cancers were grouped as AIDS-defining cancers (ADCs), and non-ADCs. Non-ADCs were further categorized as being infection related (NADC-IR) and unrelated (NADC-IUR).

Results The majority of cancer cases were diagnosed in male patients (84%). The mean age of patients was higher in NADCs, mostly in NADCs-IUR, where almost half (43%) were infected with type 2 HIV. About half (52%) of cancer cases were ADCs (32% Kaposi sarcoma, 16% non-Hodgkin's lymphoma, and 4% cervical cancer). The most common NADCs were: lung, skin and hepatocellular carcinoma (8% each). In univariate analyses, immunosuppression, HBV coinfection, smoking and alcoholism were associated with ADCs. In multivariate analysis, alcoholism and higher HIV viral load remained independent predictors of ADCs. Longer duration of HIV infection, type 2 HIV and a longer history of HAART were associated with NADCs, in univariate analyses.

Conclusions Besides the evident multifactorial etiology, in this study ADCs appeared to be associated with immunosuppression, while NADCs seemed to be correlated by other oncogenic mechanisms such as chronic inflammation. Based on this study, cancer screening should be performed in these patients in Portugal.

Keywords: HIV, AIDS, malignancy, early detection of cancer.

Introduction

Human immunodeficiency virus (HIV) infection is correlated with an augmented

incidence of specific types of cancer, namely Kaposi sarcoma, non-Hodgkin's lymphoma and cervical cancer, all associated with profound immunosuppression and/or chronic infection by oncogenic virus. These malignancies were classified in 1993 as AIDS-defining cancers (ADCs) by the Centers for Disease Control and Prevention (CDC). The use of highly active antiretroviral therapy (HAART) has dramatically transformed the causes of hospitalization and death among HIV-infected patients, mainly reducing AIDS-associated causes, i.e. ADCs, with a simultaneous increase of cardiovascular pathologies and non-AIDS-defining cancers (NADCs), which are major causes of mortality in the HAART era.¹ NADCs went from being

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responsible for 1% of the deaths in people with HIV in the pre-HAART era to 13% in the HAART era.²

Noteworthy is the increased occurrence of NADCs, like Hodgkin's lymphoma and lung, liver and anal cancers.^{2,3} This can be explained by the prolonged survival, overall ageing of the HIV-infected population and the decreasing mortality associated to opportunistic infections.⁴ The high prevalence of risk factors commonly present in Europe and North America plays a role as contributing factor, as is the case for smoking (associated with lung, neck, head and bladder cancers), alcoholism (related to liver, head and neck cancers) and chronic infections by oncogenic viruses (i.e. hepatocellular carcinoma, anal and cervical cancers, which are linked to hepatitis B (HBV) or C virus (HCV) and human papillomavirus (HPV), respectively).⁵ The etiology of NADCs is most likely multifactorial.⁶

In Portugal, between January 1 and December 31, 2010, 2,325 new cases of HIV infection were registered, with a cumulative total of 39,347 notifications;⁷ ranking, in terms of incidence, second of 53 European countries, immediately after Estonia.⁸ About 1,000 patients die each year with AIDS in Portugal.⁹

Then again, the treatment of HIV-infected patients with cancer is often complicated by comorbid diseases, cumulative toxicity, potential drug-drug interactions, chemotherapy enhanced immunosuppression, a predilection for severe radiation adverse effects and the controversial fact that these patients make poor surgical candidates.⁶ The prognosis of HIV-infected cancer patients is typically worse than that of uninfected cancer patients, which can be explained by the more advanced stage of cancer at diagnosis, rapid progression, frequent metastases, high rate of relapse, poor therapeutic response and AIDS-related mortality.^{5,6}

Therefore, it is crucial that governments take an *avant-garde* vision and prioritize cancer through national cancer control plans, concentrate on public health infrastructures and ensure adequate support for patients under cancer prevention and control.¹⁰

Objectives

The objectives of this case-control study were to assess the frequencies and cancer predictors of a population of HIV-infected patients at Hospital de Santa Maria, Lisbon, and to make a series of recommendations for cancer screening in these patients, in Portugal.

Methods

This is a retrospective case-control study of two samples, selected from a population of 400 HIV-infected patients followed by the same physician, at the Outpatient Clinic, in the Department of Infectious Diseases, at Hospital de Santa Maria, Centro Hospitalar Lisboa Norte. This department follows a total of 3,000 patients on a regular basis, originating not only from North to South of Portugal but also from the Azores and Madeira Islands, as well as from some other European countries (such as Spain, Switzerland, United Kingdom, Ukraine and others) and from African countries with Portuguese as an official language (PALOP). This study has been approved by the Ethics Committee of Hospital de Santa Maria, and by Professor Francisco Antunes, Director of the Department of Infectious Diseases, Hospital de Santa Maria.

Population, selection and exclusion criteria and study periods

Data for 225 patients were collected from medical records: 25 patients made up the case-study population and the remaining 200 subjects constituted the control population. The sample size was calculated taking into account a 5% sampling error, a 95% confidence interval and a total population followed by the same physician that included 400 patients. A sample of 197 patients was obtained; this number was rounded to 200 in order to enable a proportion of eight controls for each of the 25 cancer cases. Cancer cases were identified through a consultation of 400 medical records. The date of cancer diagnosis was established consistently with the anatomical-pathological report or, in its absence, coincidently with the imaging studies' results. Only the first cancer diagnosis was included in the study population, whereas benign neoplasms,

cancer cases with date of diagnosis prior to HIV infection or without control data compatible with the time of cancer diagnosis, were excluded. Two cases of cancer could not be included due to the inability to consult the medical records, which can be explained by the death of those patients and consequent closure of their medical records. For controls, selection of patients was determined using the *randbetween* function in *Microsoft Office Excel 2007*[®] and data were collected at the time of the corresponding clinic visit, preferably in the same month, or in the previous or following month of the time of the cancer diagnosis. Pairing of the eight controls with each cancer case was also randomized as previously described. The collection of variables' data was performed between August 24 and October 12, 2011.

Definitions

Cases were divided into ADCs and NADCs. A subset of NADCs with a known infectious cause were further categorized as infection related (IR).^{3,11} these were anal and oral HPV-related squamous cell carcinomas, hepatocellular carcinoma associated with HBV and/or HCV infection and stomach *Helicobacter pylori*-related carcinoma. The remaining malignancies were categorized as NADCs – infection unrelated (IUR). The mean duration of HIV infection corresponded to the average time, in years, since the first HIV positive test until the date of cancer diagnosis. The mean duration of the follow-up coincided with the average time, in years, since the first immunosuppression appointment until the date of cancer diagnosis. Assessment of HBV coinfection implied collecting data related to hepatitis B surface antigen (HBsAg), antibodies (anti-HBs) and antibodies to hepatitis B core antigen (anti-HBc). HBV coinfection was defined as a positive serological test for HBsAg and anti-HBc for over six months, while patients with history of vaccination, positive anti-HBs with >10 mIU/mL, negative HBsAg and negative anti-HBc were considered as being immune due to vaccination. Coinfection with HCV was considered positive or negative according to the detection of HCV antibodies (anti-HCV) or HCV viremia. For the HIV viral load, we used

two parallel analytical techniques: a Real-Time PCR and Versant k-PCR TaqMan (Roche) which show sensitivities of <37 and <40 copies/mL, respectively. Viral load was considered unknown for cases and controls with the date of cancer diagnosis before 1996, due to the unavailability of these tests at the time. The concept of HAART was considered to be the use of three or more antiretroviral drugs. “Always” describes the uninterrupted use of HAART until the date of cancer diagnosis.

Variables

The data were entered into two databases accounting, each of them, for the cases and controls. The following data were obtained by reviewing the medical records of both cases and controls: gender, age, race, place of birth, HIV infection diagnosis and first appointment dates, HIV type and mode of transmission, smoking, alcoholism, HBV and HCV coinfection, nadir CD4, CD4 and CD8 counts, HIV viral load and use of HAART. For cancer cases additional data were collected, including the date of malignancy diagnosis and its histological type. All variables were recorded at the time of the cancer diagnosis.

Statistical analysis

The coded data were processed by using *Statistical Package for Social Sciences* (SPSS) version 17.0. Predictor analysis was performed for all variables. Statistical analysis included descriptive univariate and multivariate analysis. After univariate analysis and selection of factors with statistical significance, the multivariate analysis was conducted by binary logistic regression. Variables significantly associated with a risk of developing cancer in the univariate analysis ($p < 0.05$), were included in the multivariate logistic regression model. Odds ratios were calculated using the Chi-square test.

Results

A total of 225 patients were included in this study: 25 cancer cases and 200 controls. The majority of ADCs (10 of the 13 cases) were diagnosed between 1993 and 2005 and three cases, in the pre-HAART era. All NADC cases were diagnosed in the HAART era and from

2003 to 2010 (except for one). Approximately half of all cases corresponded to ADCs (n=13, 52%) (figure 1), 61% (n=8) of which were Kaposi's sarcoma, 31% (n=4) were non-Hodgkin lymphomas and 8% (n=1) were invasive cervical carcinomas. All patients with non-Hodgkin lymphoma (n=4) and almost all patients with Kaposi's sarcoma (seven out of eight) were male.

ADC AIDS-defining cancer; NADC non-AIDS-defining cancer; NADC-IR non-AIDS-defining cancer-infection related; NADC-IUR non-AIDS-defining cancer-infection unrelated.

Figure 1. Flow diagram showing the distribution of cancer cases divided by AIDS-defining cancers (ADCs) and non-AIDS-defining cancers (NADCs) and further categorized as non-AIDS-defining cancers infection unrelated (NADCs-IUR) and non-AIDS-defining cancers infection related (NADCs-IR).

From the 12 NADC cases, which accounted for 48% of all malignancies, seven cases (28% of all malignancies) and five cases (20% of all malignancies) were NADCs-IUR and NADCs-IR, respectively (figure 1). Skin and lung carcinomas were the most common NADCs-IUR (29% each). In turn, hepatocellular carcinoma (40%) was the most commonly found NADC-IR. Almost all patients with NADCs-IUR (five out of seven) and all patients with NADCs-IR (five out of five) were male (table I).

The demographic, epidemiological, clinical, analytical and therapeutic variables of cases and controls are summarized in table II. The majority of cancer cases were diagnosed in male patients

(21 out of 25, 84%) and the mean age was 41 years (standard deviation – SD: 6.7) for ADCs cases, 57 years (SD: 12.6) for NADC-IUR cases and 45 years (SD: 6.9) for NADC-IR cases, when compared to 41 years (SD: 9.9) for controls. Most patients with ADCs were Caucasians (n=12, 92%), compared to the majority of patients with NADCs-IUR and -IR that were of African descent (n=4, 43% and n=3, 40%, respectively). A large percentage of ADC cases, NADC-IR cases and controls (n=10, 77%; n=4, 80% and n=170, 85%, respectively) were Portuguese, whereas almost half (n=3, 43%) of the NADC-IUR cases were PALOPs.

Regarding the mean duration of HIV infection, NADC-IR cases showed a greater number of years (10 years, SD: 5.3), followed by NADC-IUR cases and controls with nine (SD: 4.7) and eight years (SD: 8.5) respectively, and finally ADC cases with seven years (SD: 5.3). The NADC-IUR and NADC-IR cases also had a longer mean follow-up duration of ten years (both SD: 5.1), compared to controls with seven years (SD: 5.1). Most patients with ADCs, NADCs-IR and controls (n=11, 85%; n=4, 80% and n=187, 93% respectively) were carriers of type 1 HIV, unlike those with NADCs-IUR where almost half (n=3, 43%) were infected with type 2 HIV. As mode of HIV transmission, 39% (n=5) of ADC cases had a history of injecting drug use, while 71% (n=5) of NADC-IUR cases were men who have sex with men (MSM). Finally, NADC-IR cases and controls presented heterosexual contacts as predominant mode of HIV transmission (n=3, 60%, and n=74, 37%, respectively). The percentage of smoking was significantly higher in ADC cases (n=11, 85%), NADCs-IR and NADCs-IUR (n=4, 80% and n=5, 71%, respectively), compared with 45% (n=90) in controls. The percentage of alcoholism was also higher in ADC cases (n=8, 61%), compared with 15% (n=29) of controls.

Most patients with NADCs-IR were coinfecting with HBV and HCV (n=1, 20% and n=3, 60%, respectively) and so were patients with ADCs (n=2, 15% and n=6, 46%, respectively), compared to controls (n=16, 8% and n=65, 33%, respectively).

Type of malignancy	Male		Female		Total	
	no.	%	no.	%	no.	%
AIDS-defining cancers (ADCs)						
• Cervix	0	0	1	8.3	1	7.7
• Non-Hodgkin lymphoma	4	36.4	0	0	4	30.8
• Kaposi sarcoma	7	63.6	1	91.7	8	61.5
Subtotal	11	100.0	2	100.0	13	100.0
Non-AIDS-defining cancers (NADCs)						
Infection unrelated (IUR)						
Breast	0	0	1	50.0	1	14.3
• Ovarian	0	0	1	50.0	1	14.3
• Skin (non-melanoma)	2	40.0	0	0	2	28.55
• Prostate	1	20.0	0	0	1	14.32
• Lung	2	40.0	0	0	2	28.55
Subtotal	5	100.0	2	100.0	7	100.0
Non-AIDS-defining cancers (NADCs)						
Infection related (IR)						
Hepatocellular carcinoma	2	40.0	0	0	2	40.0
Anal squamous cell	1	20.0	0	0	1	20.0
• HPV-related oral squamous cell	1	20.0	0	0	1	20.0
• Stomach	1	20.0	0	0	1	20.0
Subtotal	5	100.0	0	0	5	100.0
Grand total	21		4		25	

ADC AIDS-defining cancer; HPV human papillomavirus; NADC non-AIDS-defining cancer; NADC-IR non-AIDS-defining cancer-infection related; NADC-IUR non-AIDS-defining cancer-infection unrelated.

Table I. Malignancies divided by AIDS-defining cancers (ADCs) and non-AIDS-defining cancers (NADCs) and summarized by gender, from a sample of 25 HIV-infected patients.

Most patients with NADCs-IUR and NADC-IR (n=6, 86% and n=4, 80%, respectively) had a CD4 cell count above 350 cells/cmm compared to 82% (n=164) of controls. In contrast, 39% (n=5) of ADC cases presented a CD4 cell count of less than 100 cells/cmm.

Thus, the mean CD4 cell count was lower in ADC cases (278 cells/cmm, SD: 286.6) and NADC-IR cases (571 cells/cmm, SD: 327.6), compared to controls (631 cells/cmm, SD:

330.9). HIV viral load above 75,000 copies/mL was only found in ADC and NADC-IR cases (n=4, 38% and n=1, 20%, respectively). Approximately 39% (n=5) of ADC cases had never received HAART, compared to 17% (n=34) of controls. On the contrary, 100% (n=5) of NADC-IR cases and 86% (n=6) of NADC-IUR cases had always received HAART, compared to 68% (n=136) of controls.

Variable	ADC		NADC-IUR		NADC-IR		Controls		Total
	n=13	5.8%	n=7	3.1%	n=5	2.2%	n=200	88.9%	n=225
Gender									
• Male	11	84.6	5	71.4	5	100.0	143	71.5	164
• Female	2	15.4	2	28.6	0	0	57	28.5	61
Mean age (SD) ^a	40.92	(6.664)	56.57	(12.634)	44.8	(6.907)	41.19	(9.854)	41.73 (10.1)
Race									
• Caucasian	12	92.3	4	57.1	3	60.0	178	89.0	197
• African descent	1	7.7	3	42.9	2	40.0	22	11.0	28
Place of birth^b									
• Portuguese	10	76.9	4	57.1	4	80.0	170	85.0	188
• European	1	7.7	0	0	0	0	4	2.0	5
• PALOP	2	15.4	3	42.9	1	20.0	25	12.5	31
• Others	0	0	0	0	0	0	1	0.5	1

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Variable	(continued from previous page)								
	ADC		NADC-IUR		NADC-IR		Controls		Total
	n=13	5.8%	n=7	3.1%	n=5	2.2%	n=200	88.9%	n=225
Mean duration of HIV infection, years (SD)	7.0	(5.292)	9.0	(4.69)	9.8	(5.31)	8.4	(8.466)	8.37 (8.148)
Mean duration of follow-up, years (SD)	4.77	(5.134)	10.43	(5.127)	9.6	(5.128)	6.7	(5.031)	6.77 (5.089)
HIV type									
• 1	11	84.6	4	57.1	4	80.0	187	93.5	206
• 2	2	15.4	3	42.9	1	20.0	13	6.5	19
HIV transmission									
• MSM	4	30.8	5	71.4	0	0	51	25.5	60
• Heterosexual	2	15.4	1	14.3	3	60.0	74	37.0	80
• Bisexual	1	7.65	0	0	0	0	14	7.0	15
• Injecting drug user	5	38.5	1	14.3	2	40.0	60	30.0	68
• Others ^c	1	7.65	0	0	0	0	1	0.5	2
Smoking ^d									
• Yes	11	84.6	5	71.4	4	80.0	90	45.0	110
• No	2	15.4	2	28.6	1	20.0	88	44.0	93
• Unknown ^c	0	0	0	0	0	0	22	11.0	22
Alcoholism ^d									
• Yes	8	61.5	2	28.6	2	40.0	29	14.5	41
• No	5	38.5	5	71.4	3	60.0	145	72.5	158
• Unknown ^c	0	0	0	0	0	0	26	13.0	26
HBV coinfection ^f									
• Positive	2	15.4	1	14.3	1	20.0	16	8.0	20
• Negative	11	84.6	6	85.7	4	80.0	180	90.0	201
• Unknown ^c	0	0	0	0	0	0	4	2.0	4
HCV coinfection ^f									
• Positive	6	46.2	1	14.3	3	60.0	65	32.5	75
• Negative	7	53.8	6	85.7	2	40.0	134	67.0	149
• Unknown ^c	0	0	0	0	0	0	1	0.5	1
CD4 cell count, cells/cmm ^a									
• ≤100	5	38.5	0	0	0	0	5	3.0	10
• 101-200	2	15.4	0	0	0	0	8	4.0	11
• 201-350	1	7.6	1	14.3	1	20.0	23	11.0	26
• >350	5	38.5	6	85.7	4	80.0	164	82.0	178
• Unknown ^c	0	0	0	0	0	0	0	0	0
Mean CD4 cell count, cells/cmm (SD) ^a	277.78	(286.57)	722.43	(414.71)	571.4	(327.58)	631.01	(330.89)	612.1 (339.7)
CD4/CD8 ratio % ^a									
• 0-24	7	53.8	1	14.3	0	0	22	11.0	30
• 25-49	4	30.8	1	14.3	1	20.0	51	22.5	57
• ≥50	2	15.4	5	71.4	4	80.0	127	66.5	137
Nadir CD4 cell count, cells/cmm ^a									
• <200	9	69.2	4	57.1	3	60.0	80	40.0	96
• 200-499	4	30.8	1	14.3	2	40.0	95	48.0	102
• ≥500	0	0	2	28.6	0	0	24	11.0	26
• Unknown ^c	0	0	0	0	0	0	1	1.0	1
HIV-RNA copies/mL ^a									
• <400	2	15.4	4	57.1	4	80.0	147	73.5	157
• 400-75,000	4	30.8	2	28.6	0	0	28	14.0	34
• >75,000	5	38.4	0	0	1	20.0	0	0	6
• Unknown ^c	2	15.4	1	14.3	0	0	25	12.5	28
HAART									
• Always ^g	8	61.5	6	85.7	5	100.0	136	68.0	155
• Never	5	38.5	1	14.3	0	0	34	17.0	40
• Interrupted	0	0	0	0	0	0	30	15.0	30
• Unknown ^c	0	0	0	0	0	0	0	0	0

^aSimilar to the other data, these variables have also been collected at the moment of cancer diagnosis.

^bRegarding the patients' place of birth, the category "European" includes all European countries except for Portugal. The category "PALOP" refers to African countries with Portuguese as an official language (Angola, Cape Verde, Guinea-Bissau, Mozambique and

Sao Tome and Principe) and the "Others" category includes all the countries not included in the above categories, such as Zaire and Brazil.

^cConcerning the mode of HIV transmission, the "Others" category includes the concepts of transsexual, vertical transmission, by blood transfusion, transplantation and transmission to hemophiliacs.

^dThe presence of smoking or alcohol abuse was categorized into "Yes", "No" or "Unknown" due to the unavailability of information on the medical records that could allow a quantification.

^eThe term "Unknown", used for characterizing some of the variables, included all data that were not found by reviewing the medical records.

^fHBV coinfection was defined as a positive serological test for HBsAg and anti-HBc for over six months, while coinfection with HCV was considered positive or negative according to the detection of HCV antibodies (anti-HCV) or viremia.

^g"Always" describes the uninterrupted use of HAART until the date of cancer diagnosis.

ADC AIDS-defining cancer; **HAART** highly active antiretroviral therapy; **HBsAg** hepatitis B virus surface antigen; **HBV** hepatitis B virus; **HCV** hepatitis C virus; **HIV** human immunodeficiency virus; **MSM** men who have sex with men; **NADC** non-AIDS-defining cancer; **NADC-IR** non-AIDS-defining cancer-infection related; **NADC-IUR** non-AIDS-defining cancer-infection unrelated; **PALOP** African countries with Portuguese as an official language; **RNA** ribonucleic acid; **SD** standard deviation.

Table II. Demographic, epidemiological, clinical, analytical and therapeutic variables at the time of cancer diagnosis for cases and controls.

Predictors of AIDS-defining cancers (ADCs)

In univariate analysis, a shorter mean duration of HIV infection (OR: 0.21, 95% CI: 0.07-0.65, $p<0.01$), smoking and alcoholism (OR: 0.15, 95% CI: 0.03-0.69, $p=0.01$ and OR: 0.11, 95% CI: 0.03-0.35, $p<0.01$, respectively), coinfection with HBV (OR: 0.05, 95% CI: 0.02-0.19, $p<0.01$), CD4 cell count ≤ 100 cells/cmm (OR: 0.04, 95% CI: 0.00-0.17, $p<0.01$), CD4/CD8 ratio $<25\%$ (OR: 0.11, 95% CI: 0.03-0.34, $p<0.01$), nadir CD4 cell count <200

cells/cmm (OR: 0.30, 95% CI: 0.09-0.99, $p=0.04$) and HIV RNA $>75,000$ copies/mL (OR: 259.5, 95% CI: 13.2-50.82, $p<0.01$) were more frequently associated with ADCs. Other modes of HIV transmission had a borderline significance (OR: 16.6, 95% CI: 0.98-281.7, $p=0.05$). In multivariate analysis, alcoholism (OR: 0.15, 95% CI: 0.35-0.89, $p<0.01$) and HIV viral load $>75,000$ copies/mL (OR: 0.15, 95% CI: 0.23-0.97, $p=0.014$) remained as independent predictors of ADCs (table III).

Factor	Controls n=200	Cases n=13	Univariate		p	Multivariate		p
			OR	95%CI		OR	95%CI	
Mean duration of HIV infection, years (SD)	8.4 (8.466)	7 (5.292)	0.21	0.07-0.65	$p<0.01$			
HIV transmission								
• MSM	51	4	0.30	0.38-4.40	0.67			
• Heterosexual	74	2	0.31	0.07-1.44	0.13			
• Bisexual	14	1	1.11	0.13-9.14	0.92			
• Injecting drug user								
•	60	5	1.46	0.46-4.64	0.52			
•								
• Others ^a	1	1	16.6	0.98-281.7	0.05			
Smoking ^b								
• Yes	90	11	0.15	0.03-0.69	0.01			
• No	88	2	4.32	0.93-20.00	0.049			
• Unknown ^c	22	0	3.40	0.20-59.22	0.40			
Alcoholism ^b								
• Yes	29	8	0.11	0.03-0.35	$p<0.01$	0.15	0.35-0.89	$p<0.01$
• No	145	5	4.22	1.32-13.45	0.02	0.67	0.54-1.14	0.67
• Unknown ^c	26	0	4.10	0.24-71.04	0.33			
HBV coinfection ^d								
• Positive	16	2	0.05	0.02-0.19	$p<0.01$			
• Negative	180	11	1.64	0.34-7.91	0.54			
• Unknown ^c	4	0	0.62	0.03-12.09	0.75			

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Factor	Controls n=200	Cases n=13	Univariate		p	(continued from previous page)		
			OR	95%CI		Multivariate		p
CD4 cell count, cells /cmm								
• ≤100	5	5	0.04	0.00-0.17	p<0.01			
• 101-200	8	2	0.23	0.04-1.21	0.08			
• 201-350	23	1	1.56	0.19-12.55	0.68			
• >350	164	5	7.29	2.25-23.58	p<0.01			
• Unknown ^c	0	0	---	---	---			
CD4/CD8 ratio %								
• 0-24	22	7	0.11	0.03-0.34	p<0.01			
• 25-49	51	4	0.77	0.23-2.61	0.67			
• ≥50	127	2	9.57	0.06-44.36	p<0.01			
Nadir CD4 cell count, cells/cmm								
• <200	80	9	0.30	0.09-0.99	0.04			
• 200-499	95	4	2.03	0.61-6.83	0.25			
• ≥500	24	0	3.75	0.22-65.06	0.36			
• Unknown ^c	1	0	0.20	0.01-5.22	0.36			
HIV-RNA copies/mL								
• <400	147	2	0.07	0.01-0.31	p<0.01	0.15	0.23-0.87	0.014
• 400-75,000	28	4	2.73	0.79-9.47	0.11			
• >75,000	0	5	259.5	13.2-50.82	p<0.01	0.15	0.23-0.97	0.014
• Unknown ^c	25	2	1.27	0.27-6.08	0.76			

^aConcerning the mode of HIV transmission, the "Others" category includes the concepts of transsexual, vertical transmission, by blood transfusion, transplantation and transmission to hemophiliacs.

^bThe presence of smoking or alcohol abuse was categorized into "Yes", "No" or "Unknown" due to the unavailability of information on the medical records that could allow a quantification.

^cThe term "Unknown", used for characterizing some of the variables, included all data that were not found by reviewing the medical records.

^dHBV coinfection was defined as a positive serological test for HBsAg and anti-HBc for over six months, while coinfection with HCV was considered positive or negative according to the detection of HCV antibodies (anti-HCV) or its viremia.

Note: Bold is used for emphasis of statically significant variables (p<0.05) in the univariate analysis. The designated p<0.01 is used for underlining more statistically significant results than those previously mentioned.

95%CI 95% confidence interval; HBsAg hepatitis B virus surface antigen; HBV hepatitis B virus; HIV human immunodeficiency virus; MSM men who have sex with men; OR odds ratio; RNA ribonucleic acid; SD standard deviation.

Table III. Factors associated with AIDS-defining cancers (ADCs), from a sample of 13 HIV-infected patients.

Predictors of non-AIDS-defining cancers (NADCs)

Caucasian and African descent patients (OR: 5.78, 95% CI: 1.69-19.78 and OR: 0.17, 95% CI: 0.05-0.59, respectively, both p<.01), longer mean duration of HIV infection (OR: 0.15, 95% CI: 0.05-0.43, p<0.01), type 1 and 2 HIV (OR: 7.19, 95% CI: 1.91-27.07 and OR: 0.14, 95% CI: 0.04-0.52, respectively, both p<0.01), higher mean CD4 cell count (OR: 1.81, 95% CI: 1.57-2.09, p<0.001), HIV viral load above 75,000 copies/mL (OR: 0.02, 95% CI: 0.00-0.50, p=0.02) and with a longer history of HAART (OR: 0.05, 95% CI: 0.01-0.37, p<0.01) were factors associated with NADCs, in univariate analysis. PALOP as a place of birth and smoking

showed borderline significances (both p=0.05). None of the above-mentioned factors remained as an independent NADC predictor in the multivariate model (table IV).

In the logistic regression analyzes limited to NADCs-IUR, Caucasian and African descent patients (OR: 6.07, 95% CI: 1.27-28.91, p=0.02 and OR: 0.16, 95% CI: 0.03-0.79, p=0.02, respectively), PALOP as a place of birth (OR: 0.19, 95% CI: 0.04-0.90, p=0.04), longer mean duration of HIV infection (OR: 0.15, 95% CI: 0.05-0.43, p<0.01), type 1 and 2 HIV (OR: 10.79, 95% CI: 2.18-53.39, p<0.01 and OR: 0.09, 95% CI: 0.02-0.46, p<0.01, respectively), MSM as mode of HIV transmission (OR: 7.30, 95% CI:

1.37-38.82, $p=0.02$) and higher mean CD4 cell count (OR: 2.17, 95% CI: 1.88-5.51, $p<0.001$) were factors more frequently associated with NADCs-IUR, in univariate analysis. In

multivariate analysis, only type 1 HIV (OR: 0.04, 95% CI: 0.004-0.30, $p=0.002$) remained as independent predictor of NADCs-IUR (table V).

Factor	Controls n=200	Cases n=12	Univariate		p	Multivariate		
			OR	95%CI		OR	95%CI	p
Race								
• Caucasian	178	7	5.78	1.69-19.78	$p<0.01$	0.31	0.07-1.39	0.13
• African descent	22	5	0.17	0.05-0.59	$p<0.01$			
Place of birth ^a								
• Portuguese	170	8	2.83	0.81-10.00	0.11			
• European	4	0	0.57	0.03-11.24	0.71			
• PALOP	25	4	0.29	0.08-1.02	0.05			
• Others	1	0	0.19	0.01-4.85	0.31			
Mean duration of HIV infection, years (SD)	8.4 (8.466)	9.33 (4.735)	0.15	0.05-0.43	$p<0.01$			
HIV type								
• 1	187	8	7.19	1.91-27.07	$p<0.01$	0.28	0.06-1.39	0.12
• 2	13	4	0.14	0.04-0.52	$p<0.01$			
Smoking ^b								
• Yes	90	9	0.27	0.07-1.04	0.05			
• No	88	3	2.36	0.62-8.97	0.21			
• Unknown ^c	22	0	3.15	0.18-55.06	0.43			
Mean CD4 cell count, cells/cmm (SD)	631.01 (330.89)	659.5 (372.67)	1.81	1.57-2.09	$p<0.001$			
HIV-RNA copies/mL								
• <400	147	8	1.39	0.40-4.80	0.61			
• 400-75,000	28	2	0.81	0.17-3.91	0.80			
• >75,000	0	1	0.02	0.00-0.50	0.02			
• Unknown ^c	25	1	1.57	0.19-12.70	0.67			
HAART								
• Always ^d	68	11	0.05	0.01-0.37	$p<0.01$			
• Never	17	1	1.02	0.12-8.4	0.98			
• Interrupted	15	0	2.09	0.12-36.99	0.62			
• Unknown ^c	0	0	-	-	-			

^aRegarding the patients' place of birth, the category "European" includes all European countries except for Portugal. The category "PALOP" refers to African countries with Portuguese as an official language (Angola, Cape Verde, Guinea-Bissau, Mozambique and Sao Tome and Principe) and the "Others" category includes all the countries not included in the above categories, such as Zaire and Brazil.

^bThe presence of smoking was categorized into "Yes", "No" or "Unknown" due to the unavailability of information on the medical records that could allow a quantification.

^cThe term "Unknown", used for characterizing some of the variables, included all data that were not found by reviewing the medical records.

^d"Always" describes the uninterrupted use of HAART until the date of cancer diagnosis.

Note: Bold is used for emphasis of statically significant variables ($p<0.05$) in the univariate analysis. The designated $p<0.01$ is used for underlining more statistically significant results than those previously mentioned and $p<0.001$, for "highly" statistically significant results.

95%CI 95% confidence interval; HAART highly active antiretroviral therapy; HIV human immunodeficiency virus; OR odds ratio; PALOP African countries with Portuguese as an official language; RNA ribonucleic acid; SD standard deviation.

Table IV. Factors associated with non-AIDS-defining cancers (NADCs) (all), from a sample of 12 HIV-infected patients.

Factor	Controls n=200	Cases n=7	Univariate		p	Multivariate		p
			OR	95%CI		OR	95%CI	
Race								
• Caucasian	178	4	6.07	1.27-28.91	0.02			
• African descent	22	3	0.16	0.03-0.79	0.02			
Place of birth ^a								
• Portuguese	170	4	4.25	0.91-19.95	0.07			
• European	4	0	0.34	0.02-6.98	0.49			
• PALOP	25	3	0.19	0.04-0.90	0.04			
• Others	1	0	0.11	0.01-3.01	0.19			
Mean duration of HIV infection, years (SD)	8.4 (8.466)	9 (4.69)	0.15	0.05-0.43	p<0.01			
HIV type								
• 1	187	4	10.79	2.18-53.39	p<0.01	0.04	0.004-0.30	0.002
• 2	13	3	0.09	0.02-0.46	p<0.01			
HIV transmission								
• MSM	51	5	7.30	1.37-38.82	0.02	4.89	0.49-48.05	0.17
• Heterosexual	74	1	0.28	0.03-2.40	0.25			
• Bisexual	14	0	0.86	0.05-15.76	0.92			
• Injecting drug user	60	1	0.39	0.05-3.30	0.39			
• Others ^b	1	0	8.87	0.33-236.3	0.19			
Mean CD4 cell count, cells/cmm (SD)	631.01 (330.89)	722.43 (414.71)	2.17	1.88-5.51	p<0.001			

^aRegarding the patients' place of birth, the category "European" includes all European countries except for Portugal. The category "PALOP" refers to African countries with Portuguese as an official language (Angola, Cape Verde, Guinea-Bissau, Mozambique and Sao Tome and Principe) and the "Others" category includes all the countries not included in the above categories, such as Zaire and Brazil.

^bConcerning the mode of HIV transmission, the "Others" category includes the concepts of transsexual, vertical transmission, by blood transfusion, transplantation and transmission to hemophiliacs.

Note: Bold is used for emphasis of statically significant variables (p<0.05) in the univariate analysis. The designated p<0.01 is used for underlining more statistically significant results than those previously mentioned and p<0.001, for "highly" statistically significant results.

95%CI 95% confidence interval; HIV human immunodeficiency virus; MSM men who have sex with men; OR odds ratio; PALOP African countries with Portuguese as an official language; RNA ribonucleic acid; SD standard deviation.

Table V. Factors associated with non-AIDS-defining cancers infection unrelated (NADCs-IUR), from a sample of seven HIV-infected patients.

Factor	Controls n=200	Cases n=5	Univariate		p	Multivariate		p
			OR	95% CI		OR	95%CI	
Mean duration of HIV infection, years (SD)	8.4 (8.466)	9.8 (5.31)	0.11	0.04-0.34	p<0.01			
Mean CD4 cell count, cells/cmm (SD)	631.01 (330.89)	571.4 (327.58)	2.40	2.05-2.80	p<0.001			
HIV-RNA copies/mL								
• <400	147	4	0.69	0.08-6.34	0.75			
• 400-75,000	28	0	1.82	0.10-33.77	0.69			
• >75,000	0	1	0.01	0.00-0.21	p<0.001			
• Unknown*	25	0	1.60	0.09-29.78	0.75			

*The term "Unknown", used for characterizing some of the variables, included all data that were not found by reviewing the medical records.

Note: Bold is used for emphasis of statically significant variables (p<0.05) in the univariate analysis. The designated p<0.01 is used for underlining more statistically significant results than those previously mentioned and p<0.001, for "highly" statistically significant results.

95%CI 95% confidence interval; HIV human immunodeficiency virus; OR odds ratio; RNA ribonucleic acid; SD standard deviation.

Table VI. Factors associated with non-AIDS-defining cancers infection related (NADCs-IR), from a sample of five HIV-infected patients.

In univariate analysis, longer mean duration of HIV infection (OR: 0.11, 95% CI: 0.04-0.34, $p<0.01$), lower mean CD4 cell count (OR: 2.40, 95% CI: 2.05-2.80, $p<0.001$) and HIV viral load higher than 75,000 copies/mL (OR: 0.01, 95% CI: 0.00-0.21, $p<0.001$) were factors more frequently associated with NADCs-IR. None of the above factors remained significant in multivariate analysis (table VI).

Discussion

In this retrospective case-control study, approximately half ($n=13$, 52%) of cancer cases were identified as ADCs. The other malignancies consisted of NADCs-IUR ($n=7$, 28%) and NADCs-IR ($n=5$, 20%). Kaposi's sarcoma was the most frequent of ADC malignancies and in males, while the four cancer cases in females included: Kaposi's sarcoma, cervical, breast and ovarian carcinomas. Skin and lung cancers were the most common NADCs-IUR, while hepatocellular carcinoma was the most frequently found NADC-IR.

Controls

The demographics and mode of HIV transmission of controls were in agreement with the available data for the Portuguese population. Of the 39,347 HIV-infected cases reported in Portugal until December 31, 2010, 39.9% (30% in this study) corresponded to injecting drug users, while 42.1% (37% in this study) had heterosexual contacts. Nowadays, heterosexual contacts (60%) account for higher rates of transmission than injecting drug use (14.4%), which means that the initial trend of HIV infection in Portugal changed in 2010.⁷

ADCs

One of the interesting findings of this study was the number of Kaposi's sarcoma diagnoses, much higher than expected, accounting for approximately one third ($n=8$) of all malignancies, out of which one third ($n=3$) of these patients had never received HAART and another one third ($n=3$) were injecting drug users.

NADCs

The increased incidence of NADCs has been widely described in the literature.¹³⁻¹⁷ NADCs that reportedly occur at a higher rate among HIV-infected patients compared to general population include anal cancer (80-fold increase), Hodgkin's lymphoma (17-fold), melanoma (six-fold), lung carcinoma (three-fold), hepatocellular carcinoma, vaginal, oropharyngeal and colorectal cancers, and leukemia.^{3,18} In this study, skin and lung cancers were the most commonly found NADCs-IUR. On the other hand, hepatocellular carcinoma was the most frequent NADC-IR. Hepatocellular carcinoma is the most frequent NADC-IR observed in the literature and it is expected to continue having an importance within the HIV-infected population, particularly in the context of HBV and HCV coinfection.¹⁹ In this study, all cases of hepatocellular carcinoma ($n=2$) presented with HCV coinfection and one case also had HBV coinfection. Although a statistically significant association was not established between HBV or HCV coinfection and NADCs-IR, this could be explained not only by the low number of cancer cases, but also due to the inclusion of other cancers (NADCs-IR) in the statistical analysis, whose primary risk factors are not HBV or HCV infection. A separate statistical analysis for hepatocarcinoma was not performed due to the small sample size.

Key-predictors associated with ADCs and NADCs

The key-predictors associated with ADCs were smoking, alcoholism, HBV coinfection, higher HIV viral load and lower CD4 cell count, CD4/CD8 ratio and nadir CD4 cell count. Alcoholism and a higher HIV viral load remained independent predictors of ADCs in the multivariate analysis. Regarding NADCs, longer duration of HIV infection, type 2 HIV, higher mean CD4 cell count and a longer history of HAART were the most significantly associated factors. More significantly associated with NADCs-IUR were an increased duration of HIV infection and type 2 HIV. Finally, a longer duration of HIV infection, a lower mean CD4

cell count and a higher HIV viral load were more frequently associated with NADCs-IR.

An interesting finding of this study included the association of older age, type 2 HIV, longer duration of HIV infection, higher mean CD4 cell count and history of HAART with NADCs. Primarily, it is interesting to note the enormous ethnic diversity and the consequent prevalence of type 2 HIV, diagnosed not only in the Infectious Diseases Department of Hospital de Santa Maria, but also in Portugal, corresponding to 3.1% of HIV infections.⁷ Secondly, these data lead to suspect that because of the more indolent progression of type 2 HIV infection, with lower viremia and higher CD4 cell count than those seen with type 1 HIV infection, other oncogenic mechanisms besides immunosuppression (such as chronic inflammation) may play an important role in the tumorigenesis of NADCs. Moreover, HIV infection has been reported to inhibit tumor suppressor genes, to induce genetic instability, increase the susceptibility of tissues to the effects of carcinogens and lead to endothelial cell abnormalities, including elaboration of angiogenic factors, which could facilitate tumor growth.² Additionally, the increased inflammation mediated by HIV infection, which has been also linked to an increased risk for cardiovascular disease, may persist even after the initiation of effective antiretroviral therapy (ART). Certain inflammatory markers have been shown to decrease after ART initiation, regardless of regimen, (as opposed to changes in other markers, which varied by regimen). A decrease in tumor necrosis factor (TNF) receptors and adhesion molecules after ART initiation has also been noted, being considered an indicator of a generally positive effect of ART on inflammation.²⁰ Furthermore, the association between a longer history of HAART and NADCs can be interpreted as the use of HAART appearing to have a protective effect on ADCs but not on NADCs. Certain researchers have already expressed some concerns about the possible long-term mutagenic effects of antiretroviral drugs.^{21,22} Others have actually demonstrated increases in the incidence of Hodgkin lymphoma,^{23,24} anal carcinoma^{13,23,27} and hepatocellular carcinoma²³ during the HAART

era, suggesting that those cancers and other NADCs may not be strongly associated with immune reconstitution provided by antiretroviral medication.

In my study, immunosuppression was associated with ADCs, similar to data from other studies.^{17,25,23} An association between immunosuppression and NADCs-IR was also established. Several studies in the HAART era^{17,25,26} have failed to find an association between CD4 cell count and NADCs, even though the latest data²⁴ show an association between immunosuppression and an increased risk of incidence of certain NADCs, but not all. In this study, a longer mean duration of HIV infection was also related to NADCs (all) and, separately, to NADCs-IUR and NADCs-IR, which is consistent with field literature.¹⁵

Smoking was not associated with NADCs-IUR, even if borderline significant association was observed with all NADCs and lung carcinoma had been one of the most frequent malignancies in this group. Again, this is justified by the inclusion of malignancies in this group, in which smoking is not the primary risk factor. Interestingly, a statistically significant association between ADCs and alcoholism was observed, as an independent predictor in the multivariate analysis, as well as an association of those malignancies with smoking and HBV coinfection. These findings may reflect risk behaviors from these patients, namely unprotected sexual contacts and injecting drug use (mode of HIV transmission most commonly found in ADC cases, 39%), predisposing them to sexually transmitted viral infections, alcoholism and/or smoking.

Limitations

This study has a series of limitations inherent to the retrospective case-control study design. First, potential conflicting data can be explained by variations on population demographics, stage of HIV infection and access to health services. Second, this study presents a comparatively low number of female patients and poor data about smoking and alcohol consumption. Third, the low number of NADC cases was insufficient to

examine patients' characteristics and factors associated with specific cancers, which surely camouflaged risk factors for certain cancers, as was the case with smoking and lung cancer. In addition, the two types of groups established for NADCs are debatable. Included in the list of NADCs were malignancies where only a small proportion was related to infections. However, a

statistical analysis was also performed for all NADCs, as well as for NADCs-IUR and NADCs-IR, separately. In general, the results of this study were consistent with those presented by field literature. Finally, given the freedom on accessing and reviewing all medical records, it is unlikely that any malignancy has been underreported.

Malignancy	Patients' age	Procedure	Evidence of benefit	Interval	Remarks
Cervix	Women ≥20 years old	Gynecological genital examination, swab and cytology	Decrease of mortality	1 year	In Portugal, cytology is recommended in HIV-negative women 25 to 60 years old ^a
Breast	Women 50-69 years old	Mammography	Decrease of mortality	2 years	According to the Portuguese recommendations in HIV-negative women ^a
Anal	Men and women with receptive anal intercourse	Inspection of anus and genitals, digital rectal examination (DRE); on conspicuous findings: high resolution anoscopy and proctoscopy	Unknown, but recommended by some experts; swab with cytology insufficiently validated	1 year	Not yet recommended for HIV-negative patients in Portugal
Skin	Men and women ≥35 years old	Skin cancer screening	Controversial	-	-
Colorectal	Men and women ≥45 years	Stool examination for occult blood and colonoscopy	Decrease of mortality in HIV-negative patients	5-10 years	In Portugal, stool examination for occult blood is recommended in HIV-negative men and women 50 to 74 years old; for low risk HIV-negative patients, a single colonoscopy is recommended, between 50 and 60 years ^b
Prostate	Men >45 years	DRE, prostate specific antigen (PSA) test	Controversial	1 year	In Portugal, only DRE is recommended in HIV-negative patients; PSA test is not recommended for non-risk HIV-negative patients ^c

^aTaking into account the National Plan of Oncologic Diseases Prevention and Control 2007/2010 (PNPCDO).

^bAccording to the Portuguese Society of Digestive Endoscopy.

^cTaking into account the recommendations of the Center for Preventive Activities of the Portuguese Association of General Practitioners (APMCG).

Table VII. Possible recommendations for cancer screening in HIV-infected patients in Portugal, adapted from the model of Hensel M et al.²⁸ and taking into account the November 2009 guidelines of the European AIDS Clinical Society.

Conclusion

It becomes paramount to regularly monitor HIV-infected patients, especially those with higher viremia and risk behaviors such as alcoholism, but also with longer duration of HIV infection, immunosuppression, HBV or HCV coinfection and smoking, because these factors appear to have a statistically significant association with cancer.

Alcohol abstinence and a close control of viremia in these patients are advisable. Older patients, with longer duration of HIV infection and longer history of HAART appeared to be

more predisposed to develop certain malignancies, particularly NADCs.

Despite an evident multifactorial etiology, while ADCs were significantly associated with immunosuppression, NADCs appeared to be related to other oncogenic mechanisms such as chronic inflammation. Thus, in accordance with my findings and also with data from field literature,²⁸ the implementation of cancer surveillance plans in the HIV-infected population is worthwhile.

The screening for cervical, breast, prostate, anal, skin, colorectal cancer and others

carcinomas become imperative for these patients (table VII). Therefore, this brings about the need to perform prospective studies into the effectiveness and cost-benefit of these early cancer detection strategies in Portugal.

Conflicts of interest None to declare.

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