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Prevalence of defining malignancies in adult patients with HIV/AIDS in the National Cancer Institute of Colombia. 2007-2014

Prevalencia de neoplasias en pacientes adultos con VIH/sida del Instituto Nacional de Cancerología de Colombia. 2007-2014

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| Abstract |

Introduction: The widespread use of antiretroviral therapy has increased the survival rates of patients infected with human immunodeficiency virus (HIV) and, in consequence, the prevalence of both defining and non-defining cancers. In Colombia, information in this regard is unknown.

Objective: To determine the prevalence of defining malignancies in adult patients with HIV treated at the National Cancer Institute over a seven-year period.

Materials and methods: Descriptive study involving adult patients diagnosed with HIV and cancer. Sociodemographic variables, CD4 count, viral load and antiretroviral therapy were analyzed by establishing association measures with the presence of defining malignancies.

Results: 139 patients with confirmed HIV and cancer diagnosis were found; 84.2% were men. The age range was between 18 and 71 years, with a mean of 41.3±10.9 years. Defining cancers corresponded to 65.5% of the cases, the most frequent being non-Hodgkin lymphoma. The remaining percentage corresponded to non-defining cancers, mainly anal cancer and Hodgkin's lymphoma.

Conclusion: Despite the global trend, the population studied here shows predominance of defining cancers, which, like HIV, continue to be detected at a late stage.

Keywords: HIV; Acquired Immunodeficiency Syndrome; Malignances; Highly Active Antiretroviral Therapy; Colombia (MeSH).

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| Resumen |

Introducción. El uso de la terapia antirretroviral ha aumentado la supervivencia de los pacientes con virus de inmunodeficiencia humana (VIH) y, como consecuencia, la prevalencia de cánceres definitorios y no definitorios. En Colombia no se conoce información al respecto.

Objetivo. Determinar la prevalencia de neoplasias definitorias en pacientes adultos con VIH del Instituto Nacional de Cancerología en un período de 7 años.

Materiales y métodos. Se realizó un estudio descriptivo que incluyó pacientes adultos con diagnóstico de VIH y cáncer. Se analizaron variables sociodemográficas, conteo de CD4, carga viral y tratamiento antirretroviral. Se establecieron medidas de asociación entre las últimas tres variables y la aparición de neoplasias definitorias.

Resultados. Se estudiaron 139 pacientes con diagnóstico de VIH y cáncer, 84.2% de los cuales eran hombres. El rango de edad osciló entre 18 y 71 años con una media de 41.3±10.9 años. Las neoplasias definitorias se presentaron en 65.5% de los casos; la más frecuente fue el linfoma no Hodgkin. El porcentaje restante correspondió a neoplasias no definitorias, en su mayoría, cáncer anal y linfoma de Hodgkin.

Conclusión. Pese a la tendencia mundial, en la población evaluada hay preponderancia de neoplasias definitorias, las cuales —al igual que el VIH— siguen detectándose de forma tardía.

Palabras clave: VIH; Síndrome de inmunodeficiencia adquirida; Neoplasias; Terapia antirretroviral altamente activa; Colombia (DeCS).

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Introduction

The world witnessed an HIV/AIDS epidemic for four decades, after the first case was reported back in the 1980s. Numbers are not encouraging; according to the report issued by the Joint United Nations Program on HIV/AIDS (UNAIDS) in 2014, 35 million people were infected around the world, with an incidence of 2.1 million new cases a year, in other words, about 6 000 new infections a day (1). In Colombia, the virus has a prevalence of 0.5-0.9% of the total population according to Unicef and UNAIDS reports (2). This, along with an average of 35% decrease in mortality rates observed during the past ten years, has caused an increase of the prevalence not only in relation to the number of new cases, but also to greater survival of infected individuals (1).

Regarding the association of HIV with cancer, between 6% and 49% of patients with retroviral infection develop some neoplasm during the course of the disease (3-5). Although a greater risk can be observed, there is no clarity about the direct pathophysiological role of the virus in the large group of tumors detected in this group of patients. Possible theories have considered the immunosuppressive role of the virus, coinfection with other oncogenic potential viruses such as Epstein Barr or hepatitis C, and the presence of common risk factors between both diseases (3,6,7).

Non-Hodgkin's lymphoma, Kaposi's sarcoma, and invasive cervical cancer report the highest relative risks, which are considered as the defining features of acquired human immunodeficiency syndrome (AIDS) (8). These neoplasms are usually observed in more than 70% of the cases worldwide (4,5). However, after the widespread introduction of the highly active anti-retroviral therapy (HAART) in the mid-1990s, a change in the distribution of neoplasms in this group of patients could be seen, in other words, the frequency of non-defining malignancies increased (6,9,10).

Considering the lack of studies on this condition in Colombia, this study intends to establish the prevalence of defining malignancies in adult patients with HIV/AIDS treated at the National Cancer Institute of Colombia (INC in Spanish) —national cancer reference center in the country— over a seven-year period. In addition, an evaluation was also performed on the association between the onset of defining neoplasms and the use of antiretroviral treatment, viral load and CD4 in the included patients. If the prevalence of defining malignancies in this group of patients is known, a hypothesis about the diagnostic opportunity of HIV/AIDS and the coverage of antiretroviral treatment in this population could be considered.

Materials and methods

Definition of study subjects

The study population included INC patients attended in the institution between 2007 and 2014, of legal age, with a confirmed HIV/AIDS diagnosis, whether or not they were taking antiretroviral therapy, a diagnosis of one or more solid organ or hematological malignancies confirmed by pathology, with or without specific treatment for them. Patients with benign neoplasms, in whom a malignant component was ruled out by pathology, were excluded.

Study design and stages

An observational, analytical, cross-sectional study was performed, in which patients were selected from the databases of the Epidemiological Research, Public Health, Systems and Clinical Laboratory groups, as well as from the data of consultations and inter-service consultations of the Infectious Diseases Group in the same institution between 2007 and 2014. This period was chosen since, as of June 2007, the clinical and laboratory reports of INC patients were available in the Systems, Applications & Products in Data Processing (SAP) software; this way, an adequate collection of information was guaranteed.

After obtaining a unified list, in April 2014, a review of the medical records was initiated, following approval (institutional registration INC-C410-3610-679) from the institutional Ethics Committees of the Faculty of Medicine of Universidad Nacional de Colombia and the INC. Then, the socio-demographic variables of the population were measured and the diagnoses were verified.

During the research, the INC Research Area Group supported the review of quality and veracity of the data provided in the registration forms. Furthermore, an adequate transcription of the information was verified in the database before the statistical analysis.

Definitions

The stage of retroviral infection was determined based on CD4 count, viral load and AIDS defining illnesses in each patient according to the 2008 classification issued by the Disease Control and Prevention Centers (CDC in Spanish) (11):

Stage 1: Non-defining condition, CD4>500 cells or CD4>29%.
Stage 2: Non-defining condition, CD4=200-499 cells or CD4=14-28%.
Stage 3: AIDS-defining condition regardless of CD4, CD4<200 cells or CD4<14% counts.
Stage 4: No information on CD4 count or AIDS defining conditions.

To establish the stage of the neoplasms, the medical records of the treating services were analyzed. These records were classified as defining and non-defining, taking into account the official definition of AIDS published by the CDC in 1992, which considers non-Hodgkin's lymphoma, Kaposi's sarcoma and invasive cervical cancer as defining malignancies (12).

Statistical analysis

A sample size of 126 patients was calculated with an expected difference between defining and non-defining malignancies of 20-

25% (4.9), 95% confidence interval (CI), and 7% accuracy around the estimator. A database was constructed based on the different variables, which served for conducting different analyzes using the statistical software R (R Core Team, New Zealand). A descriptive analysis was completed using means and standard deviations for numerical variables, and percentages for categorical variables. A 95% CI was calculated to establish the frequency estimators (prevalence of defining malignancies).

Taking into account the contingency tables, the Fisher's exact test was used to assess the association between the onset of defining malignancies and low CD4 count, high viral load and absence of antiretroviral treatment, which, according to the literature, happen to be associated with their development (4,13). Statistical significance levels of 5% with two-tailed hypotheses were used for this test.

Results

During the initial search in the databases of the participating services, 176 potential patients were identified. 37 patients were excluded since three were under 18 years of age, 12 did not have a confirmatory or negative test, seven had incomplete medical records, and 15 had a confirmed diagnosis of retroviral infection but cancer was ruled out during their stay in the institution due to the presence of benign neoplasms or opportunistic infections that mimicked malignant neoplasms.

In total, 139 patients that met the inclusion criteria and completed the data collection form were found. Of these, 84.2% were men (n=117) and 15.8% were women (n=22) whose ages ranged from 18 to 71 years, with an average of 41.3±10.9. Other characteristics of the population are summarized in Table 1.

Table 1. Socio-demographic characteristics of HIV and cancer patients of INC 2007-2014.

Variable		Frequency (n=139)	Percentage
Sex	Male	117	84.2%
	Female	22	15.8%
Schooling	None	1	0.7%
	Complete Primary school	17	12.2%
	Incomplete Primary school	8	5.8%
	Complete high school	24	17.3%
	Incomplete high school	17	12.2%
	Technical	8	5.8%
	University	26	18.7%
	Not reported	38	27.3%
Civil status	Single	82	58.9%
	Married	15	10.8%
	Widower	3	2.2%
	Separated	12	8.6%
	Common-law marriage	24	17.3%
	Not reported	3	2.2%

Source: Own elaboration based on the data obtained in the study.

Likewise, other important variables for the diagnosis and follow-up of HIV and cancer were recorded for a complete characterization of the study population. Opportunistic infections were found in 35.9% of patients (n=50), the most frequent being *Pneumocystis jirovecii* pneumonia, followed by cryptococcosis, tuberculosis and esophageal candidiasis. These infections were found individually, combined with each other or with other high frequency infections in this population group such as herpes zoster.

Sex preference was only reported in 64.7% of the cases, being the man-man relationship the most frequent (18.7% of the patients). With respect to HIV infection, 86.3% of patients had continuous access to antiretroviral therapy, and the most frequent combination was protease inhibitors with nucleoside analogues (35.3% of subjects). Data on CD4 count, viral load and stage of retroviral infection are summarized in Table 2.

Table 2. Characteristics of retroviral infection in patients with HIV and cancer at INC 2007-2014.

Variable		Frequency (n=139)	Percentage
CD4 count	<200 cells	45	32.3%
	201-350 cells	29	21.0%
	351-499 cells	11	7.9%
	>500 cells	12	8.6%
	Not reported	42	30.2%
Viral load	Undetectable	54	38.8%
	1 000-250 000 copies	25	18.0%
	250 001-1 000 000 copies	6	4.3%
	>1 000 000 copies	4	2.9%
	Not reported	50	36.0%
Stage of retroviral infection by HIV*	Stage 1	6	4.3%
	Stage 2	16	11.5%
	Stage 3	108	77.7%
	Stage 4	9	6.5%

*According to Schneider *et al.* (11).
Source: Own elaboration based on the data obtained in the study.

Solid neoplasms predominated in 60.4% of the cases studied. At the time of inclusion, 12.2% of patients (n=17) were stage I, 10.8% (n=15) stage II and 45.3% (n=64) stages III and IV. For the remaining 31.7% (n=43), the stage was not recorded or the neoplasm was not stable. Although a high percentage of neoplasm diagnoses in advanced stages were observed, only three patients died within 30 days after diagnosis. 42.4% of subjects received anti-neoplastic chemotherapy (n=59), and the rest received combination therapy (23%), palliative care (18.7%), surgery (9.4%), antiretrovirals (4.3%) and radiotherapy (2.2%).

According to the main objective of this study, AIDS-defining malignancies were found in 91 patients, which correspond to 65.5% of the total sample (95%CI: 57.2-73.3). Non-Hodgkin's lymphoma was the predominant defining malignancy (n=46), followed by Kaposi's sarcoma (n=42) and invasive cervix cancer (n=3). Non-defining malignancies were found in 34.5% of the subjects (n=48), and the most frequent were anal cancer (n=7), Hodgkin's lymphoma (n=7) and non-invasive cervix cancer (n=6). The distribution of other neoplasms of this type was homogenous, and no hepatocellular carcinoma or lung cancer cases were reported in this series of patients (Figure 1).

Regarding HIV and cancer diagnosis, 56.8% of the patients were first diagnosed with the retroviral infection and then with the neoplasm. Diagnosis was simultaneous in 22.3% of the cases, cancer was first diagnosed in 16.6% (n=23), and data were incomplete in 4.3% (n=6). The initiation of HAART before cancer diagnosis occurred in 17.3% of the patients, was simultaneous in 14.4%, and subsequent in 18.7%. In 13.7% of cases, no antiretroviral management was initiated during institutional follow-up, and the remaining 35.9% (n=50) did not record the date of any of the two events, which prevented establishing a correlation.

Finally, Fisher's exact test evaluated the association between the presence of defining malignancies and the CD4 count, viral load and antiretroviral treatment variables. A statistically significant association was found only in CD4 count (p=0.034). There was a marginal correlation with the detectable or undetectable viral load (p=0.074), which may be influenced by the sample size (Table 3).

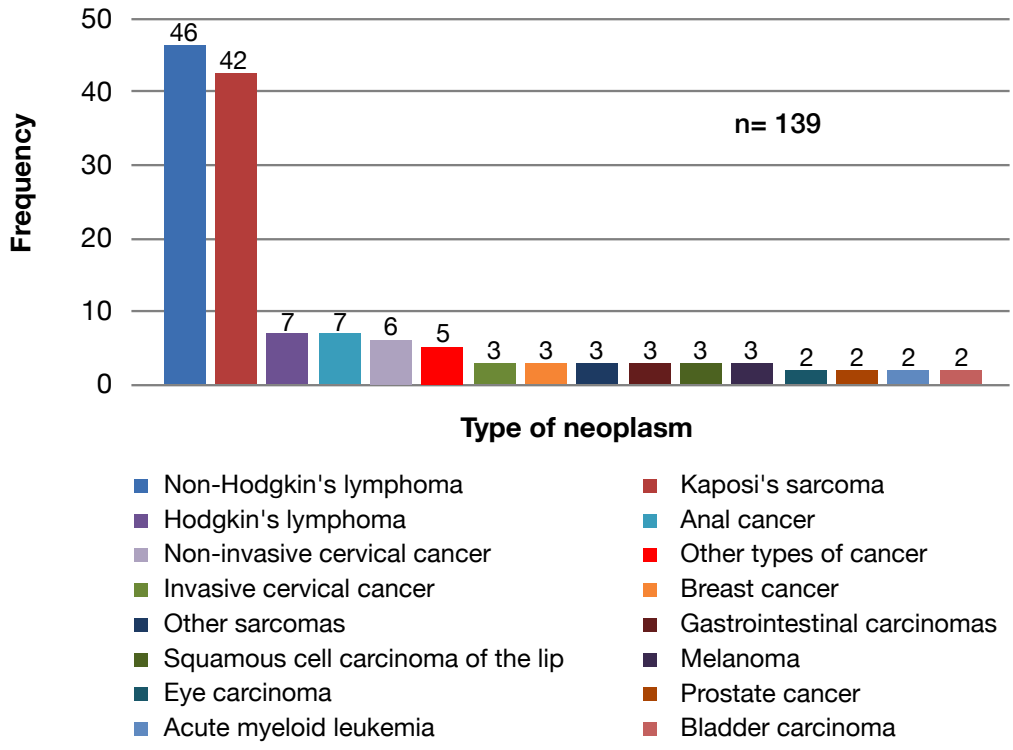

Figure 1. Distribution of neoplasms in the population of patients with HIV and cancer at INC 2007-2014.
Source: Own elaboration based on the data obtained in the study.

Table 3. Association between the development of defining malignancies and the CD4 count, viral load and antiretroviral treatment variables.

Type of neoplasm	CD4 count *†		Viral load ‡		Antiretroviral treatment	
	<350	>350	Detectable	Undetectable	Yes	No
Defining	53	11	29	26	81	10
Non-defining	21	12	25	9	39	9

* Fisher's exact test p=0.045.
† Patients without reported CD4 count = 42
‡ Patients without reported viral load = 50
Source: Own elaboration based on the data obtained in the study.

Discussion

The adult population treated at INC and recorded between 2007 and 2014 included 139 patients with HIV and cancer, of which 65.5% had AIDS defining malignancies as well. These results are similar to those found by Bedimo *et al.* (4), where 78% of cases had defining malignancies, and by Shiels *et al.* (14) who sub-analyzed the pre-HAART period and found that 64% of the cases had defining malignancies. However, these data have a lower percentage than the findings of Allardice *et al.* (5), who found 138 out of 162 patients with AIDS-defining malignancies (85.1%), and Fink *et al.* (15), who reported a prevalence of 82% of this type of cancer in the study population. The latter is the only work in Latin America with a population similar to the present study.

Such discrepancies are expected given the particular characteristics of the population, since INC, as a national reference center for cancer, selects patients after they have been evaluated and intervened in other institutions with a lower level of complexity. In addition, this study is descriptive and includes patients diagnosed with HIV before and after extensive use of HAART, thus it is not possible to establish changes in the epidemiological pattern of neoplasms related to this therapy since the 1990's. This prevents direct comparison with other international cohorts, but leaves open the possibility of further studies that show the chronological evolution of neoplasms in relation to the use of HAART. Currently, it can only be concluded that this population seems to behave similarly to others around the world before HAART. Differences should be further assessed in studies with a larger population.

Regarding sociodemographic characteristics, it is important to highlight the predominance of the male sex (84.2%), which coincides with the reports by national health entities (16) and other international studies (14). The age range of the patients was broad: three patients were older than 65 years, and working-age population was predominant, affecting not only their quality of life but also their social performance. The mean age was 41.3 years, similar to the findings of Shiels *et al.* (14) in the U.S. population, who reported that the diagnosis of both diseases occurs around age 38.

With reference to the variables for the diagnosis and follow-up of retroviral infection, HIV was mostly diagnosed at stage III, which implies that more than 76% of patients had CD4 counts lower than 200 or some AIDS-defining disease by the time of the study (11). This may occur due to failures in early detection or diagnoses at advanced stages of infection (4,17), considering that most patients of INC are referred from other cancer institutions with an initial diagnosis of retroviral infection for treatment and follow-up. This hypothesis is supported by the finding of more than 50% of subjects with an HIV diagnosis prior to cancer diagnosis.

Other relevant data on infection follow-up include viral load and treatment coverage. The viral load has a high underreporting rate (35.5%) despite its great impact on the follow-up of HIV-infected patients. This is one of the limitations of this study, because the lack

of this data prevents objectively determining the virologic response to antiretroviral treatment. Moreover, HAART coverage in this study was 86.3%, a positive figure compared to the 30% reported by the Ministry of Social Protection in 2012 (18).

Specifically for cancer, the diagnosis was made at advanced stages (stages III and IV) in 45.3% of the cases, which could be caused by two factors. First, late diagnosis could be related to a low suspicion index in patients with non-specific symptoms and findings in imaging studies. In some HIV patients, neoplasms are not detected early because of the absence of guiding symptoms or because they are mistaken for opportunistic infections (19). In this study, 15 of the HIV patients detected in the initial search were excluded from the study because opportunistic infections were found during follow-up and cancer was ruled out. Secondly, patients admitted at INC are carefully selected and admitted with more advanced neoplasms.

Regarding cancer, the most frequent type of neoplasm was non-Hodgkin's lymphoma, followed closely by Kaposi's sarcoma and, less frequently, by invasive cervical cancer. These data are similar to those reported by Allardice *et al.* (5) in Scottish population, who found 2 574 HIV-infected patients between 1981 and 1996, of which 6.3% developed some neoplasm, non-Hodgkin's lymphoma being the most frequent (n=82). These results differ from the American populations, where Kaposi's sarcoma predominates (4,9,15). As mentioned above, the only known Latin American study was made by Fink *et al.* (15), who found 406 patients with HIV and cancer, in which Kaposi's sarcoma predominated with 225 cases (15).

In line with national and international studies, the most frequent non-AIDS defining malignancies are Hodgkin's lymphoma and anal cancer (4,9,15,20). As in cervical cancer, early detection through anal cytology in high-risk population could be a public health strategy for this population group. On the other hand, this study did not find hepatocellular carcinoma or lung cancer cases, which are the next more frequent neoplasms according to the existing literature (5,14,21).

Consistent with the findings of other studies (4,13,17,22-24), establishing non-causal associations between defining malignancies and low CD4 count, high viral load and no antiretroviral treatment was intended. When excluding unreported data, association was only found at the limit of the statistical significance between a higher viral load and the development of defining neoplasms. The lack of association with the other variables may be related to a lower number of patients compared to the American and European series, which opens the possibility for further research.

This work has some limitations, which include its retrospective character considering that the records are made by different health professionals and, as mentioned before, the under-registration of some data that may compromise interpretation. Similarly, the number of patients included is low in relation to other studies reviewed. In spite of this, according to the methodological design, the minimum number of patients was achieved for an adequate inference of the results. Finally, since this is a cross-sectional study, it was not possible to establish causality between the onset of HIV and cancer. These limitations are common in other studies with a similar design, and should be considered when generating strategies for quality research.

In conclusion, a predominance of defining malignancies was observed in the group of patients with HIV and cancer at INC, as reported by other studies worldwide in the pre-HAART period. The HIV infection diagnosis continues to be made at late stages; thus, strengthening strategies for early detection of HIV in the population is strongly advised. In view of the impact that the association between HIV and cancer may have in the short term for the health system, more studies with a larger population should be carried out to generate a national picture of this correlation.

Conflict of interests

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