AIDS-Defining Neoplasm Prevalence in a Cohort of HIV-Infected Patients, before and after Highly Active Antiretroviral Therapy

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Introduction: Malignant disorders have been linked to the HIV epidemic from its onset. Implementation of highly active antiretroviral therapy (HAART) has resulted in a dramatic reduction in the HIV/AIDS morbidity and mortality. The present study evaluates the neoplasm prevalence before and after the implementation of HAART.

Methods: A cross-sectional study was conducted in 171 HIV-infected adults who were followed in Puerto Rico from May 1992 through December 2005. Neoplasm prevalence was measured, and the difference in AIDS- and non-AIDS-defining neoplasms was analyzed before and after the HAART era. Between-group differences were explored by using χ^2, Fisher exact test, analysis of variance, and student *t* test.

Results: Malignant neoplasms were detected in 171 patients (4.8%). Of these, 51.5% were AIDS-defining neoplasms, and 68% were established before HAART. AIDS-defining neoplasms accounted for 62.4% of those detected before the availability of HAART and 25.9% of those detected after HAART. Except for cervical carcinoma, the prevalence of AIDS-defining neoplasms decreased after HAART. Non-AIDS lymphomas and prostate neoplasms were more frequent after HAART.

Discussion: Our study found a significant reduction of Kaposi sarcoma and AIDS-related lymphoma in the HAART era of the AIDS epidemic. A higher prevalence of non-AIDS-defining lymphomas, prostate carcinoma, and cervical carcinoma was seen in the HAART era. These findings suggest that factors other than severe immunosuppression are involved in the neoplasms' pathogenesis. Preventive strategies that include screening tests, vaccination, and lifestyle modification should be routinely applied in HIV-infected patients. (*Ethn Dis*. 2008;18[Suppl 2]:S2-189–S2-194)

Key Words: HIV Neoplasm Differences after HAART

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Introduction

Malignant disorders have been associated with clinical AIDS since the onset of the HIV epidemic. Kaposi sarcoma and high-grade non-Hodgkin lymphoma (NHL) were included in the first list of AIDS-defining conditions in 1987.[1] Six years later, invasive cervical cancer was included as an additional AIDS diagnostic criterion.[2] AIDS-defining neoplasms are considered an additional manifestation of the disrupted immune system. The introduction of highly active antiretroviral therapy (HAART) in 1996 increased the life expectancy among persons infected with HIV in large part because of an improvement in the immune status of patients and a lowering of the HIV viral load. In Puerto Rico, HAART was routinely given to patients as of 1998, with the same combinations of protease inhibitors, nucleoside reverse transcriptase inhibitors, and nonnucleoside reverse transcriptase inhibitors reported to be highly effective in HIV/AIDS patients. These combinations of drugs partially restore defects in cell-mediated immunity, suppress the HIV viral load, and improve the patient's immunologic and clinical status.[3,4] As a consequence, AIDS-defining illnesses, including Kaposi sarcoma and high-grade NHL, declined considerably after the introduction of these drugs.[4–7] The pathogenesis of invasive cervical carcinoma appears to be more related to papilloma virus infection, and HAART will not decrease its incidence.[8] Eltom et al found a significant decline in the AIDS-related NHL in the general US population between 1996 and 1998, which was mainly attributed to decreased immunologic suppression of HIV/AIDS patients after the implementation of HAART.[9] On the other hand, with the improvement in survival, other co-morbid conditions have played a greater role in the morbidity and mortality of HIV-positive patients. Non-AIDS-defining neoplasms are co-morbid conditions that increase the morbidity, change the therapeutic index, and worsen the mortality profile of patients with HIV infection.[5,10–14]

The prevalence of cancer in men in Puerto Rico for the year 2000 was 300 per 100,000; the highest prevalence was seen in prostate cancer (100 per 100,000), followed by colorectal cancer (40 per 100,000). The cancer prevalence in women was 250 per 100,000, principally related to breast cancer (85 per 10,000) and followed by colorectal cancer (30 per 100.000). The principal causes of cancer deaths were prostate cancer (30 per 100,000) and lung cancer (20 per 100,000) in men and breast cancer (18 per 100,000) and colorectal cancer (11 per 100,000) in women.[15] In this article, we measure and evaluate the prevalence of malignant disorders, including AIDS-related and non-AIDS-related neoplasms in a cohort of HIV-infected persons before and after HAART came into widespread use in Puerto Rico.

Methods

The sample was composed of 171 patients, selected from 3576 adult HIV-

infected patients enrolled in our institution's Retrovirus Research Center cohort from May 1992 through December 2005. Our cohort was composed of adult men and women who were initially seen and followed every six months at the Ramón Ruiz Arnau University Hospital or in the HIV ambulatory clinics of our institution. The cohort was composed of principally indigent persons with an income below the US poverty level; 29% were female, and 52% had injection drug use as the major HIV risk practice.

Once informed consent was obtained, a baseline questionnaire was completed, and appropriate laboratory tests were conducted, including CD4+T lymphocyte count, CD8+T lymphocyte count, HIV viral load, hepatitis C viral load, platelet count, leukocyte and erythrocyte count, and a comprehensive panel test that included albumin, glucose, and creatinine levels. Data collection and laboratory findings were reevaluated and collected every six months. Most of the HIV risk behaviors and sociodemographic data were gathered through personal interviews. The information was complemented with medical record abstraction, in which clinical manifestation of the infection, laboratory data, therapy-related information, and medical complications were abstracted and recorded. Participants were interviewed by an expert case manager who is fluent in Spanish and English, and all information is kept strictly confidential. All of our participants spoke Spanish as their primary language.

The questionnaire included demographic variables, HIV risk factors, clinical manifestations, and mortality information. AIDS-defining illnesses, such as esophageal candidiasis, *Pneumocystis jirovecii* pneumonia, cerebral toxoplasmosis, recurrent bacterial pneumonia, pulmonary tuberculosis, Kaposi sarcoma, high-grade NHL, invasive cervical carcinoma, and wasting syndrome were recorded. Non-AIDS-defining neoplasms were also tabulated and organized into several categories on the basis of the primary organ of tumor origin.

The HAART era was defined as the period when HAART was available for HIV therapy. In Puerto Rico, HAART has been routinely given to all qualified patients since 1998; consequently, we divided the epidemic into two time periods: the pre-HAART era, which ended in 1998, and the HAART era, which began in 1999. The status of participants as of December 2005 was used to measure mortality trends. Mortality data were obtained from a review of the institutional medical records and from the Puerto Rican AIDS surveillance system. In addition, the mortality registry of the Puerto Rican Health Department was reviewed to confirm participants' status. The reported causes of death were tabulated and organized into several categories: 1) system or organ failure (cardiovascular, pulmonary, gastrointestinal, renal, neurologic, and metabolic); and 2) AIDS conditions (Kaposi sarcoma, cerebral toxoplasma, pulmonary tuberculosis [TB], and wasting syndrome). A subgroup of liver conditions that included liver failure (chronic and acute) and cirrhosis was also evaluated.

Statistical Analysis

SPSS (SPSS, Inc., Chicago, Ill) was used to perform univariate and bivariate analyses. Univariate analysis described the frequencies of demographic parameters, risk factors, co-morbidities, mortality rates, and causes of death. Differences between patient groups were analyzed by using the χ^2 or Fisher exact test; analysis of variance and student *t* test were used to evaluate differences in means. Differences in mortality rates and causes of death were evaluated and analyzed. The P value used to determine statistical significance was $<.05$.

RESULTS

General Findings

Of the initial 3576 HIV-infected cohort, 72.5% were men, all were Spanish-speaking Puerto Ricans with a mean educational level below ninth grade, 53.8% were injection drug users (IDUs), and 12% of men reported sex with men as an HIV risk behavior. Of the entire cohort, 171 had a diagnosis of at least one malignant condition established at some point in their lives, which represents a prevalence of 4.8%; 31.5% participants with malignancies were women, 37.4% were IDUs, 46.1% were men who had sex with men, and $<60\%$ had completed ninth grade. Approximately 80% of the participants reported having more than two sex partners in the last year. The malignancy prevalence was higher in men than in women (4.9% vs 4.4%) and in higher in non-IDUs than in IDUs (6.3% vs 3.3%) (data not shown). In those persons with neoplasms, 74.9% were male, 51.5% had AIDS-defining neoplasms, 48.5% had non-AIDS-defining neoplasms, and 79.5% had died as of December 2005 (Table 1). The mean age at neoplasm report was 41.1 ± 11.4 years. As seen in Table 2, persons with AIDS-defining neoplasms in the pre-HAART era were younger, were more often men who had sex with men, and had a higher prevalence of AIDS-related conditions, particularly esophageal candidiasis and wasting syndrome. On the other hand, Table 1 shows that Kaposi sarcoma (39.8%) and cervical invasive carcinoma (23.3%) were the most prevalent AIDS-defining neoplasms in this sample. Breast-ovarian cancer (23.3%), non-AIDS lymphomas (19.3%), and aero-digestive malignancies (5.3%) were the most common non-AIDS defining neoplasms. In 68.5% of participants ($n=117$), the neoplasm was reported before the HAART era, in the remaining 31.5%, it was reported after HAART.

Table 1. Demographic variables, risk factors, AIDS-related antecedents, neoplasm, and death rates among HIV-positive Puerto Ricans before and after the advent of HAART

Parameter	Pre-HAART (*n*=117)	HAART (*n*=54)	Total (*N*=171)
Male (%)	77.8	68.5	74.9
Mean age ±SD	38.8±10.2	46.1±12.4*	41.1±11.4
Injection drug users (%)	42.7	25.9§	37.4
Men who have sex with men (*n*=128) (%)	53.8	27.0*	46.1
Histoplasmosis antecedent %	5.1	3.7	4.7
Esophageal candidiasis antecedent %	29.4	7.4*	22.2
PJP antecedent %	18.8	3.7§	14.0
Recurrent pneumonia antecedent %	11.1	3.7	8.8
Brain toxoplasmosis antecedent %	6.0	1.9	4.7
Wasting syndrome antecedent %	26.5	18.5	24.0
Hepatitis C antecedent %	3.4	14.8*	7.0
AIDS-defining neoplasm %	62.4	25.9*	51.5
Kaposi sarcoma %	52.1	13.0*	39.8
Burkitt lymphoma %	3.4	0.0	2.3
Immunoblastic lymphoma %	2.6	0.0	1.8
Brain lymphoma %	1.0	1.9	1.2
Cervical invasive cancer (*n*=43) %	15.4	35.3	23.3
Non-AIDS-defining neoplasm%	37.6	74.1*	48.5
Aero-digestive %	4.3	7.4	5.3
Colo-rectal %	1.7	3.7	2.3
Liver %	2.6	3.7	2.9
Skin %	1.7	5.6	2.9
Breast/Ovarian (*n*=43) %	26.9	17.6	23.3
Anal %	0.0	1.9	0.6
Lymphoma %	14.5	29.6§	19.3
Leukemia %	1.7	1.9	1.8
Kidney %	0.9	0.0	0.6
Prostate (*n*=128) %	0.0	8.1§	2.3
Mortality by December 2005 %	88.0	61.1*	79.5

HAART = highly active antiretroviral therapy, SD = standard deviation, PJP = *Pneumocystis jiroveccii pneumonia*.
* *P* value <.01 between HAART groups.
§ *P* value <.05 between HAART groups.

Table 2. Demographic variables, risk factors, and AIDS-related co-morbidities by AIDS-defining neoplasms among HIV-positive Puerto Ricans before and after the advent of HAART

Parameter	AIDS neoplasm (*n*=84)	Non-AIDS neoplasm (*n*=87)	Total (*n*=171)
Male %	80.5	69.0	74.9
Age mean (SD)	37.6±9.1	44.9±12.4*	41.1±11.3
Injection drug users %	43.7	31.0	37.4
Men who have sex with men (*n*=128) %	58.6	31.0	46.1
Histoplasmosis antecedent %	8.0	1.2	4.7
Esophageal candidiasis antecedent %	29.9	14.3§	22.2
PJP antecedent %	16.1	11.9	14.0
Recurrent pneumonia antecedent %	12.6	4.8	8.8
Pulmonary tuberculosis antecedent %	3.4	1.2	2.3
Brain toxoplasmosis antecedent %	6.9	2.4	4.7
Wasting syndrome antecedent %	31.0	16.7§	24.0
Hepatitis C antecedent %	8.0	6.0	7.0
Mortality by December 2005 %	81.6	77.4	79.5

* *P* value <.01 between HAART groups.
§ *P* value <.05 between HAART groups.
HAART = highly active antiretroviral therapy, SD = standard deviation, PJP = *Pneumocystis jiroveccii pneumonia*.

Findings by HAART Groups

In Table 1, we show that 68% of the neoplasms were reported in the pre-HAART era. With the exception of the men who have sex with men, no other significant demographic differences were seen between HAART groups. Patients in the pre-HAART group were more frequently IDUs and had a higher prevalence of AIDS-defining conditions than did those in the HAART group. AIDS-defining neoplasms accounted for 62.4% of the malignancies in the pre-HAART group and only 25.9% in the HAART group, this difference was statistically significant. Non-AIDS-defining neoplasms and hepatitis C were significantly higher in the HAART group. Patients in the pre-HAART group had a significantly higher mortality than did those of the HAART group.

We found a significant reduction of Kaposi sarcoma and a reduction or maintenance of the prevalence of high-grade NHL after HAART. Uterine cervical carcinoma had a higher prevalence in the post-HAART group; however, this difference did not reach statistical significance. Conversely, when evaluating the prevalence of non-AIDS neoplasms, we found that with the exception of breast and ovarian neoplasms, the remaining malignancies were more prevalent in the post-HAART group. These differences were significant in non-AIDS-defining lymphomas and in prostate neoplasms. Similar trends were found when evaluating the clinical manifestation and neoplasm prevalence according to sex (Table 3). The differences in the post-HAART group were significantly higher in men than in women. When evaluating men who have sex with men, we found significantly fewer Kaposi sarcomas (71.4% vs 57.1%) after HAART.

Mortality Findings

Of the 171 HIV-infected patients, 136 (79.5%) had died by the study end. As of December 2005, 88.8% of the

pre-HAART group and 61.1% of the HAART group had died (Table 1). The five most prevalent causes of death included pulmonary conditions, non-AIDS neoplasm, Kaposi sarcoma, cardiovascular conditions, and gastrointestinal conditions (Table 4). In general, AIDS-related causes of death were more prevalent in the pre-HAART than in the HAART group. However, only Kaposi sarcoma was significantly more prevalent. Conversely, cardiovascular conditions, gastrointestinal conditions, and non-AIDS neoplasm were more frequently reported as cause of death in the HAART group, although only non-AIDS neoplasm was significantly more prevalent.

Table 3. Age, risk factors, AIDS-related antecedents, neoplasms, and death rates, by sex and HAART group, among HIV-positive Puerto Ricans before and after the advent of HAART

Parameter	Male	Female
	Pre-HAART/HAART (*n*=91/*n*=37)	Pre-HAART/HAART (*n*=26/*n*=17)
Age mean	38.0/47.2*	40.0/43.0
Injection drug users %	46.2/32.4	30.8/11.8
Men who have sex with men (*n*=128)%	53.8/27.0§	na/na
Histoplasmosis antecedent %	5.5/5.4	3.8/0.0
Esophageal candidiasis antecedent %	33.0/8.1*	15.4/5.9
PJP antecedent %	17.6/2.7§	23.1/5.9
Recurrent pneumonia antecedent %	8.8/5.4	19.2/0.0
Brain toxoplasmosis antecedent %	6.6/0.0	3.8/5.9
Wasting syndrome antecedent %	27.5/24.3	23.1/5.9
Hepatitis C antecedent %	4.4/16.2§	0.0/11.2
AIDS defining neoplasm %	69.2/18.9*	38.5/41.2
Kaposi sarcoma %	61.5/18.9*	19.2/0.0
Burkitt lymphoma %	3.3/0.0	3.8/0.0
Immunoblastic lymphoma %	3.3/0.0	0.0/0.0
Brain lymphoma %	1.1/0.0	0.0/5.9
Cervical invasive cancer (*n*=43) %	0.0/0.0	15.4/35.3
Non-AIDS-defining neoplasm %	38.5/81.1*	61.5/58.8
Aero-digestive %	5.5/10.8	0.0/0.0
Colon-rectal %	0.0/5.4	7.7/0.0
Liver %	3.3/5.4	0.0/0.0
Skin %	2.2/5.4	0.0/5.9
Breast/Ovarian (*n*=43) %	0.0/0.0	26.9/17.6
Anal %	0.0/2.7	0.0/0.0
Lymphoma %	15.4/32.4§	11.5/23.5
Leukemia %	1.1/2.7	3.8/0.0
Kidney %	0.0/0.0	3.8/0.0
Prostate (*n*=128) %	0.0/8.1§	0.0/0.0
Mortality by December 2005 %	87.9/70.3§	88.5/41.2*

* *P* value <.01 between HAART groups.
§ *P* value <.05 between HAART groups.
HAART = highly active antiretroviral therapy, PJP = *Pneumocystis jiroveccii pneumonia*.

DISCUSSION

The role of HIV in the process of inducing malignant transformation appears to be an indirect effect of a virus likely related to a disruptive state of the immunoregulation of the body.[16] Most malignancies in the AIDS setting appear to be related to oncogenic virus infections, such as with Epstein-Barr virus, Kaposi sarcoma-associated herpesvirus, and human papillomavirus (HPV).[17] HIV chronically stimulates B lymphocytes, which alters a patient's antitumoral immunity. This effect appears to be synergistic with the oncogenic potential of co-infected viruses. The presence of the HIV virus itself may be capable of inducing malignancies by interacting either directly or indirectly with cell cycling and cell growth or by altering oncogene regulation after genomic integration.[18] Our findings, consistent with previous published data, demonstrate a significant reduction of AIDS-defining neoplasms,[6,8,17,19] with the exception of cervical cancer, after the introduction of HAART. Conversely, during the same time period we found a significant increase in non-AIDS-defining neoplasms, particularly non-AIDS lymphomas and prostate cancer. These findings show how the profile of co-morbidities in HIV-infected persons is becoming more similar to the chronic conditions of an aging population, such as non-AIDS-related neoplasms. Consequently, programs directed to early detection and prevention of these chronic conditions will not only reduce morbidity and mortality but also costs associated with caring for these conditions.

We believe that the introduction of HAART in 1999 in our community is partially responsible for the changes seen in the prevalence of neoplasms. The drug combination used in HAART suppresses the HIV viral load and improves immune restoration, which eventually improves the clinical course of the disease.[3–7] Correcting the immunologic dysfunction has been associated with a dramatic improvement of the morbidity and mortality of persons living with HIV.[3,4,10–14] Previous studies describe a clear relationship between CD4+T cell-count and progressive immunosuppression with the risk of developing Kaposi sarcoma and AIDS-defining lymphoma.[6,8] In scenarios in which the CD4+T cell count can be partially restored by HAART, HIV-related neoplasms should decrease. The increasing trend of cervical cancer in women with HIV is explained by the known causative role of HPV in this tumor and the diminished role of

Table 4. Causes of death among HIV-positive Puerto Ricans before and after the advent of HAART

Cause of death	Pre-HAART (%) (*n*=103)	HAART (%) (*n*=33)	Total (*n*=136)
Cardiovascular conditions	17.5	30.3	20.6
Pulmonary conditions	37.9	33.3	36.8
Gastrointestinal conditions	8.7	12.1	9.6
Hepatic conditions	4.9	6.1	5.1
Renal conditions	5.8	6.1	5.9
Metabolic conditions	2.9	3.8	3.1
Neurologic conditions	3.9	6.1	4.4
Non-AIDS neoplasm	21.4	72.7*	33.8
Brain toxoplasmosis %	5.8	0	4.4
Wasting syndrome %	6.8	3.0	5.9
Kaposi sarcoma %	38.8	6.1*	30.9
Pulmonary tuberculosis %	1.9	0	1.5

* *P* value <.01 between HAART groups.
HAART = highly active antiretroviral therapy.

immunosuppression as a promoter of cervical cancer.[6,8,15] In our study, a higher prevalence of cervical cancer was seen in the HAART era than in the pre-HAART era. Vigorous preventive and therapeutic strategies need to be continued in this high risk-population of patients. Furthermore, primary prevention that includes the HPV vaccine should be encouraged for HIV infected women.

The increasing age in patients with HIV infection has been frequently reported in industrialized countries. In this aging population, non-AIDS malignancies are beginning more relevant. We have seen an increase in non-AIDS-related lymphomas, prostate cancers, aero digestive tumors, skin cancers, and gastrointestinal cancers after HAART in HIV-infected patients. We are uncertain if the prevalence of these tumors in the HIV-infected group is similar to that of the rest of the population. Nevertheless, considering the role of the immune system in controlling malignancy, additional factors may be involved in the pathogenesis of these neoplasms in HIV-infected patients. Tobacco use, alcohol use, diet, and probably co-infections with other viruses may contribute to the malignant transformation. In general, our HIV-positive patients are more likely to smoke and abuse drugs and alcohol than are their HIV-negative counterparts,[20] which may increase their risk for developing malignant neoplasms.[11] Strategies for reducing these risk factors, including effective preventive interventions that increase screening tests; improve dietary habits; and reduce alcohol, tobacco, and drug consumption should be designed for this high-risk population.

As reported by previous authors, our study detected a lower mortality rate in patients in the post-HAART era. The most significant variation of cancer-related death was seen in patients with Kaposi sarcoma. Non-AIDS conditions were more commonly reported as the cause of death in the HAART era. As previously mentioned, HAART's benefits to the immune system should sharply decrease AIDS-related mortality, accompanied by an increase in the frequency of death from non-AIDS conditions, in particular death related to non-AIDS-defining malignant conditions.[11–12]

Our study has several limitations. The sample was selected from a passive surveillance cohort, in which the patients were recruited from the healthcare facility. Patients not seen in the healthcare center for >18 months were considered to be lost to followup, which may have resulted in underreported data. In addition, approximately 22% of the diagnoses of neoplasm were obtained exclusively from death certificate reports; however, all of these patients had complete data collected regarding their HIV infection. The quality of the data collected in the death certificate depends on how accurately and thoroughly the death was reported. In few cases, autopsies were performed to confirm the clinical diagnosis, which may also lead to underreport or overreport. Finally, the study measured and evaluated HAART on the basis of the year in which this type of therapy was introduced in Puerto Rico and may not reflect whether individual patients received the medication. Despite these limitations, the study will help improve the treatment of HIV-infected persons in the HAART era. Additional studies should explore in more detail the full effect of HAART on the HIV/AIDS epidemic in Puerto Rico.

Implications for Improving Health Disparities

The present study was performed in a Hispanic HIV-infected population and reveals an increased prevalence of neoplasms, including cervical and prostate carcinoma. Improvement to preventive strategies are being included per the study recommendations to decrease this health disparity in HIV-infected persons.

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