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Trends in AIDS-Defining and Non-AIDS-Defining Malignancies among HIV-Infected Patients: 1989–2002

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In a comparison of rates of acquired immunodeficiency syndrome (AIDS)-defining malignancies (ADMs) for 1989–1996 versus 1997–2002, we found a decrease in ADMs (rate ratio, 0.31; $P < .0001$) and a significant increase in non-AIDS-defining malignancies (non-ADMs; rate ratio, 10.87; $P < .0002$). The mean CD4 cell count was lower among patients with ADMs than among those with non-ADMs. A longer duration of survival during highly active antiretroviral therapy might explain the increasing incidence of non-ADMs.

Since the early days of the AIDS epidemic, HIV-infected patients have had an increased propensity to develop malignancies [1–4]. In the HAART era, the spectrum of neoplasias in HIV-infected patients has been changing, with a decrease in the rate of AIDS-defining malignancies (ADMs). However, the rate of non-AIDS-defining malignancies (non-ADMs) is reported to be unchanged [5–7]. An increase in the incidence of non-ADM has even been predicted, given the increased duration of survival among HIV-infected patients [8], but this has not been observed in most studies [5, 9, 10].

Methods. A prospective, computerized database of information on HIV-infected adults (known as the Studies of HIV/AIDS Longitudinal Outcome Metrics [SHALOM] cohort), which is followed at the University of Alabama at Birmingham HIV Clinic (Birmingham, AL), was used to identify patients with ADMs and non-ADMs diagnosed during the period of January 1989 through August 2002. Demographic, laboratory, and treatment data were analyzed. HAART was defined as an

antiretroviral regimen that contained ≥ 1 protease inhibitor or 1 nonnucleoside reverse-transcriptase inhibitor.

The time from the first clinic visit to the date of cancer diagnosis (for patients with cancer) or to the date in the database on which the person was last known to be alive (for patients without cancer) was calculated in person-years. Incidence rates are presented as the number of cases per 1000 person-years. Rate ratios (RRs) and the corresponding 95% CIs were calculated, comparing the incidence rates from 1989–1996 (the pre-HAART era) with the incidence rates from 1997–2002.

Comparisons of categorical variables were performed using the χ^2 test, and comparisons of continuous variables were performed using the Wilcoxon rank sum test. Cancer rates were not adjusted for age, race, or sex, because the population served by our clinic did not significantly change during the period of observation.

Results. From September 1989 through August 2002, a total of 2882 patients were observed at the University of Alabama at Birmingham HIV Outpatient Clinic. For the analysis of cancer incidences among these patients, 2 time periods were chosen to represent the period before the availability and widespread use of HAART (the pre-HAART era; 1989–1996) and the period during which use of HAART was widespread (the HAART era; 1997–2002). A total of 2882 patients were studied, comprising 7452 person-years of follow-up (2994 person-years of follow-up for 1989–1996 and 4458 person-years of follow-up for 1997–2002).

There were a total of 227 incident cases of malignancies diagnosed. Among them were 178 ADMs (109 cases of Kaposi sarcoma, 64 cases of non-Hodgkin lymphoma, and 5 cases of invasive cervical cancer) and 60 non-ADMs (including 11 cases of Hodgkin disease, 18 cases of skin cancer, 9 cases of invasive anal cancer, 13 cases of colon cancer, 3 cases of lung cancer, 2 cases of breast cancer, 1 case of lung cancer, 1 case of kidney cancer, and 1 case of head and neck cancer). Most cases of skin cancer were basal cell carcinoma (16 of 18 cases), with 1 case of squamous cell cancer and 1 case of Merkel cell carcinoma. The descriptive statistics for patients with cancer and those without cancer are presented in table 1.

When comparing subjects who had ADMs with those who had non-ADMs, we found no difference in the median age at diagnosis of cancer (36.0 vs. 37.0 years), male sex (93.1% vs. 90.0%), white race (73.4% vs. 68.3%), or mode of acquisition of HIV infection (86.0% vs. 81.3% were men who have sex with men) (table 2).

In the overall study population, 63.0% of the patients were

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Table 1. Characteristics of HIV-infected patients with cancer and those without cancer.

Characteristic	All patients (n = 2882)	Patients with cancer (n = 227)	Patients without cancer (n = 2655)	P ^a
White race	59.5	72.3	58.4	<.0001
Male sex	80.2	92.1	79.2	<.0001
Man who has sex with men	68.4	85.4	66.9	<.0001
Injection drug user	13.6	17.4	13.3	.1
Receipt of HAART ^b	63.0	30.7	66.2	<.0001
Nadir CD4 cell count during follow-up, median cells/ μ L	116.0	36.0	129.0	<.0001
Age ^c				
Median, in years	35.0	36.0	34.0	.0002
20–34 years	49.7	42.7	50.3	
35–54 years	46.6	51.1	46.2	
\geq 55 years	3.7	6.2	3.5	.01

NOTE. Data are percentage of patients, unless otherwise indicated.

^a Comparison of patients with cancer and those without cancer.

^b Percentage of patients receiving HAART at any time during the year preceding diagnosis of cancer.

^c Age recorded at clinic enrollment.

receiving HAART during part or all of the follow-up period, and the median nadir CD4 cell count was 116.0 cells/ μ L. Patients with cancer were less likely to be receiving HAART in the year preceding diagnosis of cancer than were patients without cancer (30.7% vs. 66.2%; $P < .0001$) (table 1). In the cohort

of patients with cancer, patients with ADMs had a lower mean nadir CD4 cell count (22 vs. 78 cells/ μ L; $P = .02$) and a much lower mean CD4 cell count at the time of cancer diagnosis (38 vs. 277 cells/ μ L; $P < .0001$), compared with those who had non-ADM. Patients with ADMs were less likely than those with

Table 2. Characteristics of HIV-infected patients with cancer.

Characteristic	Cancer type			P ^a
	All (n = 227)	ADM (n = 178)	Non-ADM (n = 49)	
White race	72.3	73.4	68.3	.5
Male sex	92.1	93.1	90.0	.6
Man who has sex with men	85.4	86.0	81.3	.4
Injection drug user	17.4	20.5	10.0	.1
Receipt of HAART ^b	30.7	20.0	58.2	<.0001
Duration of HAART, median days ^c	309.5	71.5	437.0	.0007
Nadir CD4 cell count during follow-up, median cells/ μ L	36.0	22.0	78.0	.0002
CD4 cell count before diagnosis of cancer, median cells/ μ L ^d	93.0	37.5	276.5	<.0001
Age ^e				
Median, in years	36.0	36.0	37.0	.05
20–34 years	42.7	45.7	33.3	
35–54 years	51.1	49.1	58.3	
\geq 55 years	6.2	5.2	8.3	.2

NOTE. Data are percentage of patients, unless otherwise indicated. ADM, AIDS-defining malignancy.

^a Comparison of patients with ADMs and those with non-ADM.

^b Percentage of patients receiving HAART at any time during the year preceding cancer diagnosis.

^c Median total number of days receiving HAART prior to cancer diagnosis.

^d CD4 cell count within 90 days before cancer diagnosis.

^e Age recorded at clinic enrollment.

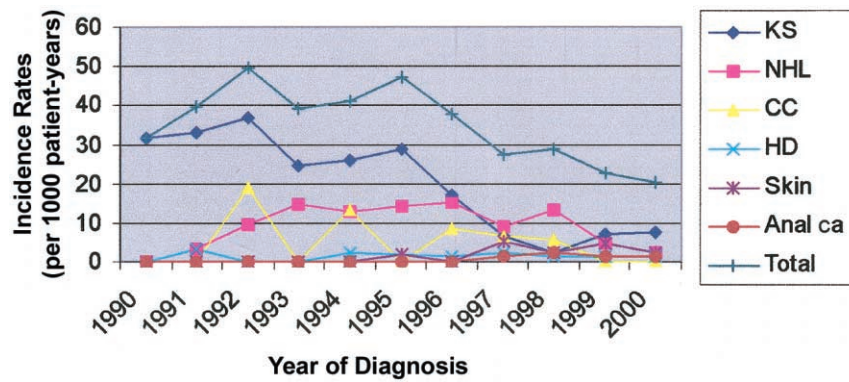


Figure 1. Trends in the incidence of cancer among HIV-infected patients. Anal ca, anal cancer; CC, cervical cancer; HD, Hodgkin disease; KS, Kaposi sarcoma; NHL, non-Hodgkin lymphoma; Skin, skin cancer.

non-ADMs to be receiving HAART at the time of cancer diagnosis (20% vs. 58%; $P < .0001$) and had an overall lower median duration of HAART before cancer diagnosis (71.5 days [range, 0–1708 days] vs. 437 days [range, 0–1485 days]; $P = .004$) (table 2).

There was a gradual decrease in the overall cancer incidence from 77.05 cases per 1000 patient-years in 1989 to 12.45 cases per 1000 patient-years in 2002 (figure 1) and from 42.45 cases per 1000 patient-years in the 1989–1996 period to 21.14 cases per 1000 patient-years in 1997–2002 (RR, 0.53; 95% CI, 0.41–0.69) (table 3). The incidence of ADM decreased from 39.91 cases per 1000 patient-years in 1989–1996 to 11.33 cases per 1000 patient-years in 1997–2002 (RR, 0.31; 95% CI, 0.22–0.42). Conversely, the incidence of non-ADM increased from 3.27 cases per 1000 patient-years to 10.87 cases per 1000 patient-years (RR, 3.32; 95% CI, 1.69–6.55).

From 1989–1996 to 1997–2002, among patients with ADM, there was a significant decrease in the incidence of Kaposi sarcoma (from 27.82 to 5.41 cases per 1000 patient-years; RR,

0.19; 95% CI, 0.12–0.30) and non-Hodgkin lymphoma (from 11.09 to 6.40 cases per 1000 patient-years; RR, 0.58; 95% CI, 0.35–0.94). There was no significant change in the incidence of cervical cancer (RR, 0.32; 95% CI, 0.05–1.89).

Among the most common non-ADM, there was a significant increase from 1989–1996 to 1997–2002 in the incidence of skin cancer (from 0.33 to 3.64 cases per 1000 patient-years; RR, 11.18; 95% CI, 1.5–84.0). There were no cases of anal cancer during the period of 1989–1996, and there were 9 cases during the period of 1997–2002 (incidence, 1.49 cases per 1000 patient-years). There was no significant change in the rate of Hodgkin disease, and there was a trend toward an increased incidence of colon cancer (from 0.65 to 2.34 cases per 1000 patient-years; RR, 3.60; 95% CI, 0.8–16.3).

Discussion. Unlike ADM, no association has been found between advancing immunosuppression and the development of non-ADM, with the exception of Hodgkin disease [3, 11, 12]. The pathogenesis of these malignancies is likely to be multifactorial, with other viral infections (such as human papilloma

Table 3. Trends in malignancies among HIV-infected patients.

Type of cancer	Annual incidence (no. of cases) ^a		RR (95% CI)	P
	1989–1996	1997–2002		
AIDS-defining malignancy	39.91 (121)	11.33 (57)	0.31 (0.22–0.42)	<.0001
Non-Hodgkin lymphoma	11.09 (34)	6.40 (30)	0.58 (0.35–0.94)	.03
Kaposi sarcoma	27.82 (84)	5.41 (25)	0.19 (0.12–0.30)	<.0001
Cervical cancer	6.36 (3)	2.01 (2)	0.32 (0.05–1.89)	.2
Non-AIDS-defining	3.27 (10)	10.87 (50)	3.32 (1.69–6.55)	.0002
Hodgkin disease	1.31 (4)	1.49 (7)	1.14 (0.33–3.89)	.8
Skin cancer	0.33 (1)	3.64 (17)	11.18 (1.49–84.04)	.003
Anal cancer	0.00 (0)	1.49 (9)	NA	
Colon cancer	0.65 (2)	2.34 (11)	3.60 (0.8–16.3)	.07

NOTE. NA, not available.

^a No. of cases per 1000 patient-years.

virus [HPV] and Epstein-Barr virus infections) or other high-risk exposures associated with HIV infection playing a vital role.

Patients with non-ADM had a significantly higher median absolute CD4 cell count at the time of diagnosis of cancer than did those with ADM (276.5 vs. 37.5 cells/ μ L), but the differences in nadir CD4 cell count between the 2 groups were much less marked (78 vs. 22 cells/ μ L). These findings and those of other published reports [3] suggest that patients with a history of profound immunosuppression may no longer be at increased risk of developing ADM if they experience an immunologic response to HAART.

Our findings, consistent with previously published data [5, 12, 13], demonstrated significant reductions in the incidence of Kaposi sarcoma and of non-Hodgkin lymphoma but not in the incidence of cervical cancer. Conversely, we found an overall increase in the incidence of non-ADM—specifically, skin and anal cancer. Although many previously published studies have not found a significant change in the incidence of these malignancies between the pre-HAART and HAART eras [5, 10–12], recent studies have noted a trend towards an increasing incidence of non-ADM [14]. To date, no associations between the patients' CD4 cell count and the risk of acquiring a non-ADM have been found [10, 12]. These findings suggest that prolonged exposure to HAART and the attendant reconstitution of the immune system might not decrease but may, in fact, increase the risk of non-ADM.

With regard to anogenital malignancies, although we saw no change in the rates of cervical cancer, we did note a significant increase in the number of diagnoses of invasive anal cancer between the pre-HAART era and the HAART era (0 vs. 7 cases). The disparity between these trends may be explained by the strict adherence to cervical cancer screening guidelines, including at least annual Papanicolaou (Pap) smears, in a single clinic setting. If anal cancer rates continue to increase, similar preventive measures (e.g., anal Pap smears) may be warranted.

Our study demonstrated a significant increase in the number of skin cancer diagnoses between the pre-HAART era and the HAART era. The large majority of the skin cancers were basal cell carcinomas, consistent with findings from Lobo et al. [15]. Skin carcinomas are the most common malignant conditions in transplant recipients [16, 17]. Their incidence is associated with the level and duration of immunosuppression [17] and is strongly associated with HPV infection [18]. As in transplant recipients, persistent HPV infection might lead to a progressive increase in cases of anogenital and skin cancer in HIV-infected persons [19].

Finally, we observed a trend toward an increased incidence of colon cancer. This was not explained by increased screening, because the policies on colon cancer screening had not changed

in our clinic and the number of colonoscopies performed had not increased.

Limitations of our study include the relatively small size of our cohort and the fact that it was drawn from a single site that may have had specific demographic characteristics, limiting the generalizability of our results. However, the advantages include a uniformity in the means of data collection and an extended follow-up period of up to 13 years. The median age of patients and the percentage of men who have sex with men did not significantly change between the pre-HAART and post-HAART periods. A change in demographic characteristics is therefore unlikely to explain the trends. Background age-adjusted skin, colorectal, and anal cancer rates remained constant in Alabama (1, 49, and 1.3 cases per 100,000 patient-years, respectively) during the observation period [20]. Finally, the trends in ADM in our cohort were consistent with those found in other studies, suggesting validity and generalizability of the non-ADM trends as well.

In summary, these data depict the cancer epidemiology in a single HIV cohort spanning 13 years and 2 distinct time periods (the pre-HAART era and the HAART era). They confirm a decrease in the rate of ADM and signal an increase in the rate of non-ADM, especially of skin cancer and anal cancer. These trends are clinically significant and may warrant evaluation of specific screening interventions, particularly given the expectation of improved survival in this group.

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Potential conflict of interest. All authors. No conflict.

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