

AIDS-Related Malignancies: State of the Art and Therapeutic Challenges

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ABSTRACT

Despite the impact of combination antiretroviral therapy (cART) on HIV-related mortality, malignancy remains an important cause of death in the current era. Although the advent of cART has resulted in reductions in the incidence of Kaposi's sarcoma and non-Hodgkin's lymphoma, non-AIDS-defining malignancies present an increased risk for HIV-infected patients, characterized by some common clinical features, generally with a more aggressive behavior and a more advanced disease at diagnosis, which is responsible for poorer patient outcomes. Specific therapeutic recommendations are lacking for these new nonopportunistic malignancies, such as Hodgkin's lymphoma, anal cancer, lung cancer, hepatocarcinoma, and many others. Antiretroviral agents have a propensity for causing drug interactions as a result of their ability to either inhibit or induce the cytochrome P450 (CYP) enzyme system. Because many antineoplastic drugs are also metabolized by the CYP system, coadministration with cART could result in either drug accumulation with increased toxicity, or decreased efficacy of one or both classes of drugs. Further research delineating the combined safety and pharmacokinetics of antiretrovirals and antineoplastic therapy is necessary. Special considerations of these AIDS-related and non-AIDS-related malignancies and their clinical and therapeutic aspects constitute the subject of this review.

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INTRODUCTION

HIV and malignancies have been linked since 1981 when the first description of Kaposi's sarcoma (KS) was reported in young, white homosexual men who exhibited concomitant severe immunosuppression, a condition subsequently referred to as AIDS. In addition to this original AIDS-defining cancer, other malignancies such as non-Hodgkin's lymphoma (NHL) and invasive cervical cancer were found with an unprecedented incidence in HIV-infected immunosuppressed individuals and were included as AIDS-defining tumors.¹ The combination antiretroviral therapy (cART) era, which started in 1996 with the introduction of protease inhibitors as a novel class of anti-HIV drugs, has deeply modified not only the morbidity and the mortality related to HIV disease but also the spectrum of the different malignancies reported in HIV-infected patients. If indeed the incidence of AIDS-related malignancies have decreased over time, others tumors, referred to as non-AIDS-defining malignancies, have emerged²: Hodgkin's lymphoma (HL), invasive anal carcinoma, lung cancer, skin cancers, and hepatocarcinoma have become a new challenge for HIV-treating clinicians.

Improved survival of patients with HIV infection may have contributed somewhat to this increas-

ing incidence; however, survival alone cannot entirely explain the increase in cancer rates. The pathogenesis of these tumors seems highly variable: most are related to oncogenic viruses, others are related to environmental factors such as smoking and sun exposure. There are more and more arguments suggesting that all tumors are more frequent in HIV-infected individuals compared with the general population. A recent large meta-analysis by Grulich et al³ in HIV-infected patients and immunosuppressed transplantation patients suggests that the higher risk of cancers owing to infectious causes in these populations can be attributed to the immunodeficiency.

Therapeutic management of malignancies, in the context of HIV disease, remains a challenge: how to best prevent and treat malignancies without compromising the control of HIV replication? Special considerations of AIDS-related and non-AIDS-related malignancies and their clinical and therapeutic aspects constitute the subject matter of this review.

EPIDEMIOLOGY

The relationship of HIV infection and the resulting immune suppression with non-AIDS defining cancers has been addressed in several cohort and record

linkage studies before 1996 and since the advent of cART.³⁻¹¹ In this review, we focus on studies exploring the risk of AIDS-defining and non-AIDS-defining cancers in patients infected with HIV or AIDS relative to the general population in the cART era. In these studies, standardized incidence ratios (SIRs) were estimated. This method compares the observed number of cases arising in a group under investigation (patients with HIV infection) with the number expected to occur on the basis of general population rates.¹⁰ When comparing the results of the different studies, one must keep in mind that their results may differ because of differences in the relative proportion of patients from the various risk groups (men who have sex with men, intravenous drug users, heterosexual patients, others) and because of the level of immune suppression, which is likely to be more profound in patients with AIDS than in patients with HIV infection alone.

Three studies reported results for the cART era and evolution between the cART era and the previous period: Clifford et al¹¹ in HIV-infected patients in Switzerland, Engels et al¹² in AIDS patients in the United States, and Herida et al² in HIV-infected patients in France.

Among AIDS-defining cancers, NHL and KS incidences have decreased dramatically in the cART era (from 1996), leading to a decrease in SIRs. In contrast, the SIR for cervical cancer has remained stable over time, with no clear impact from cART. The risk of these three cancers, however, is still high compared with that in the general population (Table 1).^{2,11,12}

Overall, for non-AIDS-defining cancers, the three studies are consistent, with an estimated SIR ranging between 2 and 3 (3.1, 95% CI, 2.4 to 4.1¹¹; 1.7, 95% CI, 1.6 to 1.9¹²; and 1.9, 95% CI, 1.7 to 2.1²), stable over time, with contrasting results depending on cancer type.¹² The SIR for HL has increased in the cART era compared with the previous period consistently across studies. For other non-AIDS-defining cancers, there is no clear impact of cART on SIRs. Patients with HIV are also at increased risk of lung cancer, partly because of higher exposure to tobacco,¹³ of liver cancer, mainly because of chronic hepatitis B and/or hepatitis C virus coinfection, and of anal cancer, linked with human papillomavirus (HPV) infection.

In a recent meta-analysis,³ including seven studies of people with HIV/AIDS (unfortunately not differentiating the pre cART and the cART era) and five studies of individuals who underwent organ transplantation, there was an increased risk of the same cancers in both

populations relative to the general population, most of these with a known infectious cause (NHL, HL, Kaposi's, liver, cervix, anal), the exception being lung cancer.

In 2005 in France,¹⁴ one third of deaths in patients infected with HIV were from malignancies; 42% were AIDS-defining and 58% were non-AIDS-defining malignancies. A recent article by Biggar et al¹⁵ described the survival after cancer diagnosis in persons with AIDS in New York City. Between 1996 and 2000, the 24-month survival rate in patients with AIDS was 58% for KS, 41% for systemic NHL, 29% for primary brain NHL, 64% for cervical cancer; 10% for lung cancer, 55% for HL, and 76% for anal cancer. No data were reported for liver cancer. The risk of death in cancer patients with AIDS was significantly higher than in cancer patients without AIDS for all cancers tested, except anal cancer. These results show that cancer in patients with AIDS tends to be more severe and/or less often cured.

AIDS-DEFINING MALIGNANCIES

KS

Although the incidence has dramatically decreased in the cART era, KS remains the second most frequent tumor observed in HIV-infected patients.¹⁶ Within the French Hospital Database on HIV Infection (FHDH), the incidence of KS fell from 32 per 1,000 person-years in 1993 to 1994 to 3 per 1,000 person-years after 1999, remaining stable up to 2006.¹⁷ The risk of visceral KS decreased more than the risk of cutaneous KS (> 50% and < 30%, respectively). Currently in Western countries, men having sex with men and patients from sub-Saharan origin represent the two main populations at risk for KS.

KS-associated herpesvirus, also referred to as human herpesvirus 8 (HHV8), was reported in 1994 by Chang et al¹⁸ from KS tissue in an HIV-infected patient. Other malignant disorders such as multicentric Castleman's disease, primary effusion lymphoma, and solid/extracavitary lymphomas have been shown to be directly associated with HHV8.

HIV-infected individuals have a high prevalence of coinfection with HHV8.¹⁹ HHV8 coinfection is associated with an elevated KS risk. In addition, immunosuppression and HIV viral replication strongly predict KS.^{19,20} Maurer et al,²¹ however, recently reported a

Table 1. Standardized Incidence Ratios for AIDS-Defining and Non-AIDS-Defining Cancers Evaluated in Recent Studies

Study	AIDS-Defining Cancers			Non-AIDS-Defining Cancer			
	Non-Hodgkin's Lymphoma	Kaposi's Sarcoma	Invasive Cervical Cancer	Hodgkin's Lymphoma	Lung Cancer	Anal Cancer	Liver Cancer
Clifford et al ^{11*}							
SIR	24.2	25.3	0.0	36.2	2.8	50.4	6.4
95% CI	15.0 to 37.1	10.8 to 50.1		16.4 to 68.9	0.9 to 6.5	9.5 to 149	0.6 to 23.7
Engels et al ^{12†}							
SIR	22.6	3640	5.3	13.6	2.6	19.6	3.3
95% CI	20.8 to 24.6	3330 to 3980	3.6 to 7.6	10.6 to 17.1	2.1 to 3.1	14.2 to 26.4	2.0 to 5.1
Herida et al ^{2‡}							
SIR				31.7	2.1		
95% CI				25.8 to 38.5	1.7 to 2.6		

Abbreviation: SIR, standardized incidence ratio.

*In combination antiretroviral therapy users.

†In patients with AIDS in 1996 through 2002.

‡In patients with HIV in 1996 through 1999.

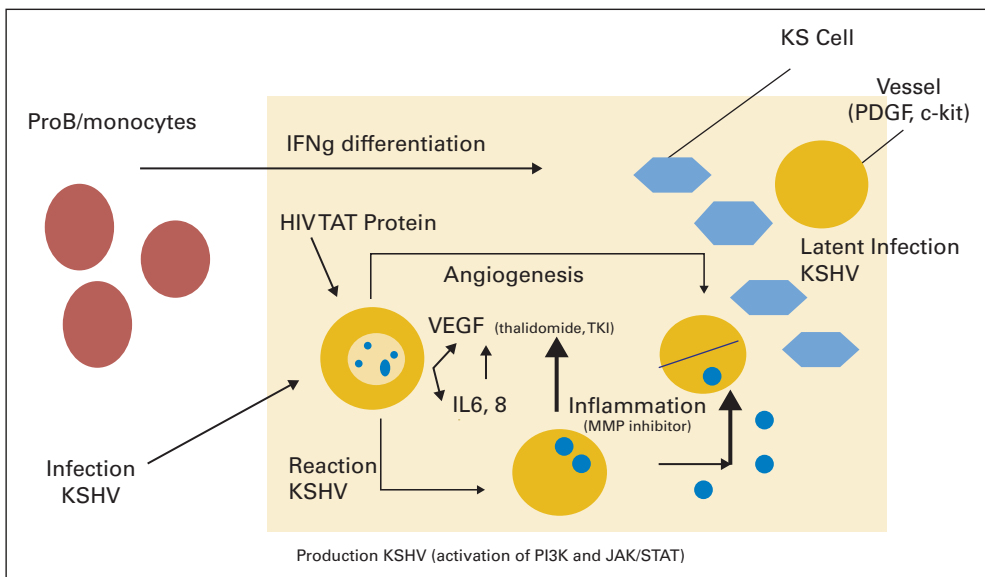


Fig 1. Molecular targeted therapies in AIDS-defining malignancies. ProB, precursor lymphocyte B; KS, Kaposi's sarcoma; PDGF, platelet-derived growth factor; IFN, interferon; TAT, transactivating protein HIV-tat; KSHV, Kaposi's sarcoma-associated herpesvirus; VEGF, vascular endothelial growth factor; IL, interleukin; MMP, matrix metalloproteinase. Tat was first identified as a regulatory protein essential in the HIV viral cycle due to its ability to dramatically increase HIV gene expression.

cluster of cases of persistent HIV-associated KS in patients with moderately low CD4 count and a controlled viral load under cART. This phenomenon may increase in frequency as the HIV-infected population ages, and careful monitoring is recommended for this group of patients.²² Quantification of HHV8 viremia has not been shown to be of value, neither in the diagnosis of KS in HIV-infected patients nor in clinical monitoring of patients.²³

AIDS-related KS is most commonly staged according to the AIDS Clinical Trials Group classification system, which originally (pre cART) characterized patients into good- or poor-risk groups based on tumor burden, immune function as measured by CD4⁺ T-lymphocyte count, and the presence of systemic illness.²⁴ In the cART era, the combination of tumor burden and systemic illness adequately identified patients with an unfavorable prognosis.²⁵

cART has provided a great benefit in the regression in the size and number of existing KS lesions.^{22,26} In patients with limited cutaneous lesions and HIV viremia, an effective cART regimen may represent the first step of therapy for KS. As virus replication is progressively suppressed and immune restoration begins, KS lesions typically start to decrease in size and may disappear completely after a few weeks or months.

Systemic cytotoxic chemotherapy is warranted in patients with advanced (visceral lesions usually observed in patients with untreated HIV infection) or rapidly progressive disease. The decision to initiate systemic chemotherapy is based not only on the extent of KS, but also on other parameters, such as patient performance status, end organ function, degree of immunosuppression, and concomitant medications.²⁶ Large randomized studies have established liposomal anthracyclines (liposomal doxorubicin 20 mg/m² every 3 weeks, liposomal daunorubicin 40 mg/m² every 2 weeks) as first-line chemotherapeutic agents with favorable response rates and durations compared with combination chemotherapy regimens (bleomycin plus vincristine with or without doxorubicin).²⁶⁻²⁹ Paclitaxel has shown striking efficacy, even for patients with anthracycline-resistant disease, with response rates ranging from 60% to 70% in phase II studies.^{30,31} The higher toxicity and the need for a 3-hour infusion, however, make paclitaxel less attractive than pegylated liposomal doxorubicin as ini-

tial systemic treatment. Moreover, dose reductions of paclitaxel may be required because of drug interactions.³² Although clinical experience with docetaxel is more limited than that of paclitaxel, small studies suggest that this alternate taxane can produce meaningful responses.^{33,34} For patients who have attained appropriate immune reconstitution with cART therapy but have residual cutaneous KS, systemic interferon alfa can also be considered, with response rates of 20% to 40% and a high rate of side effects.³⁵

Recent advances in the understanding of KS pathogenesis via the infection of endothelial cells by HHV8 have led to the development of new targeted agents, such as metalloproteinase inhibitors (Col-3), angiogenesis inhibitors (thalidomide, fumagillin), tyrosine kinase inhibitors (imatinib mesylate, c-kit, and platelet-derived growth factor inhibitor), and mammalian target of rapamycin inhibitors (Fig 1).^{22,26}

NHL

Worldwide, NHL is the most common AIDS-defining malignancy and one of the most frequent causes of mortality in patients with HIV, even in patients with immunologic and virologic response to cART.³⁶ Within the FHDH, the incidence of systemic NHL has decreased between 1993 and 1994 and between 1997 and 1998, from 8.6 per 1,000 to 4.3 per 1,000 person-years, respectively ($P < 10^{-30}$)³⁷; the incidence was 2.8 per 1,000 person-years in 2006.³⁸ This decline was also observed in Europe and the United States, but the risk of NHL is still quite high in HIV-infected patients (SIR > 20).^{11,12} The incidence of primary CNS AIDS-related lymphoma has dramatically decreased since cART.³⁷

Most cases are high-grade, aggressive lymphomas, according to the WHO classification.^{39,40} The CD4 cell count is predictive of the development of NHL, and immune reconstitution with cART may lead to a decrease in the incidence of NHL.^{37,41,42} In addition, HIV plasma RNA is also an important prognosis factor. For example, in a recent cohort study, the cART benefit in viral replication control has been shown to be independently associated with improved survival in patients with lymphoma treated for 2 years.⁴³

In terms of therapy considerations, thanks to cART, disease can be managed with standard-dose regimens (mainly cyclophosphamide, vincristine, prednisone, doxorubicin, and methotrexate for Burkitt's lymphoma and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] for the others) adapted to the pathologic subtype without much increased toxicity.⁴¹ In the post highly active antiretroviral therapy (HAART) era, the prognostic factors are mainly those of the International Prognostic Index (lactate dehydrogenase above normal, Ann Arbor stage III to IV, altered performance status of 2 to 4). The question is still debated, however, concerning the use of cART concomitantly or just after chemotherapy. In any case, the use of hematopoietic growth factors may prevent chemotherapy dose reduction and hematologic complications (with the essential inclusion of opportunistic infection prophylaxis, especially against toxoplasmosis and *Pneumocystis jiroveci*). It is recommended that zidovudine is avoided because of its myelosuppressive effects. Patients can be treated with a full-dose cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based regimen, with or without rituximab, or with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.⁴⁴⁻⁴⁶ Recent data have emphasized doubts regarding the safety of R-CHOP combination therapy in patients with HIV. Kaplan et al⁴⁷ reported that, in the AIDS Malignancies Consortium trial 010, 15 of the 16 infectious deaths occurred in the rituximab arm. Conversely, in the Boue et al⁴⁶ study, most of the deaths were related to lymphoma progression. These different results may be due to the different levels of CD4 cell counts between the two studies, although a recently presented German study did not detect an increased mortality from infection in HIV severely immunosuppressed patients with lymphoma treated with rituximab.⁴⁸ Larger-scale studies are warranted to validate the feasibility of an intensive approach in AIDS NHL and especially the role of stem-cell transplantation for patients with high risk or relapsed NHL.⁴⁹

In the Boue et al study,⁴⁶ R-CHOP showed efficacy for patients with HIV-associated B-cell lymphoma, yielding a 77% complete response rate and a 75% 2-year overall survival rate. The main study results in terms of overall survival for patients with AIDS NHL treated with chemotherapy plus rituximab are listed in Table 2.^{46,47,50,51} Additionally, in a recent French study, the 5-year overall survival rate was 45% in 200 post-cART patients versus 24% in 165 pre-cART patients (E.O., personal data). These findings suggest that patients with NHL must be treated the same as HIV-uninfected patients to reach a similar median survival.^{41,52} This is the case for St Jude patients with stage IV Burkitt's lymphoma in whom it has been recently shown that the

same intensive chemotherapy for HIV-negative patients gives the best results.⁵³

As for primary lymphoma of the brain, cerebral radiation (CR) combined with corticosteroids remains a standard approach, with or without high-dose methotrexate-based protocols. Its success dramatically improved when combined with continuing cART therapy (132 days v 33 days, respectively, for patients with CR v patients receiving neither CR nor HAART).⁵⁴

Cervical Cancer

In the HIV setting, it is well known that women are at increased risk for cervical carcinoma, so since 1993, the United States Centers for Disease Control has decided to include HIV-infected women with cervical cancer in the symptomatic definition of AIDS. Clifford et al¹¹ found a statistically significant elevated incidence of invasive cervical cancer for HIV-infected women (SIR = 8.0; 95% CI, 2.9 to 17.4). No cases were observed, however, among cART users. In women with AIDS in the United States, the risk of cervical cancer did not change significantly between 1990 and 1995 and 1996 to 2002 (SIRs of 4.2 and 5.3, respectively).¹² In a French prospective study, enrolling 1,124 HIV-infected women, the incidence rate of invasive cervical cancer was 1.1 cases per 1,000 person-years (95% CI, 0.0 to 2.2), which was 10 times higher than that of the French general population (incidence crude rate of 0.14 per 1,000 person years).⁵⁵

Immunosuppression and HPV coinfection play a major role on the pathogenesis of the disease.⁵⁶ To date, approximately 40 distinct HPV types are known to infect the genital tract. High-risk types, including HPV16, HPV18, HPV45, and HPV31, are those that are commonly detected in invasive cervical cancers. Persistent infections with high-risk types, such as HPV16, have been shown to be a major determinant of cervical cancer.⁵⁶ The use of cART seems to have no effect on patient outcome (and seems to bring about no decline in incidence).⁵⁷ There is a significantly increased incidence and stage of cervical intraepithelial neoplasia in HIV-infected patients, which emphasizes the role of screening programs in such a population.⁵⁸

HIV-infected women with cervical neoplasia have several specific features: advanced disease at diagnosis, high recurrence rate of the disease, and frequent unusual cytotoxic toxicities.⁵⁹ Depending on the disease status, the recommendations of management for cervical carcinoma in women infected with HIV are the same as those for the general population requiring specific considerations, especially between cART and cytotoxic interactions. HIV-infected patients with cervical cancer are more likely to die as a result of cancer than of HIV-related diseases, which is why it is very important to emphasize the cervical cancer screening programs to reduce incidence and mortality rates in the HPV/HIV infection setting.⁶⁰

Table 2. Chemotherapy Combined With Rituximab for Patients With AIDS NHL

First Author	Schedule	Sample Size	CR (%)	2-Year OS (%)
Boué, 2006 ⁴⁶	R-CHOP	61	77	75
Kaplan, 2005 ⁴⁷	R-CHOP	99	58	55
Spina, 2005 ⁵⁰	R-CDE	74	70	64
Ribera, 2008 ⁵¹	R-CHOP	81	69	56

Abbreviations: NHL, non-Hodgkin's lymphoma; CR, complete response; OS, overall survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CDE, rituximab, cyclophosphamide, doxorubicin, and etoposide.

NON-AIDS-DEFINING MALIGNANCIES

A recent study by Bonnet⁶¹ showed that prolonged immunosuppression with CD4 count less than 500/ μ L is associated with a higher risk of non-AIDS cancers, whereas both HIV viral replication and immunosuppression are linked to AIDS-defining cancers. Many questions about this new growing issue of non-AIDS-defining malignancies in HIV remain without answer at this time. It is unclear why malignancies in HIV-infected patients have a more aggressive behavior than in the general population. Despite the increased incidence of non-AIDS

malignancies, it is still unclear what the optimal cancer surveillance of patients should be.

HL

Risks relative to the general population are increased and range from five- to 25-fold,^{11,12,38,62} with an increase in incidence of this disease in the cART era. This might be explained because the risk of HL peaks when CD4 counts range from 150 to 199 CD4 cells/ μ L, as recently reported by Biggar et al,⁶² and the overall effect of cART is to increase the CD4 count level in the HIV-infected population. A potential mechanism was evoked by Levine⁶³ emphasizing the role of the Reed Sternberg (RS) cells producing a myriad of growth factors that increased the influx of CD4 cell and inflammatory cells, which, in turn, provide proliferation signals for the RS tumoral cells. One can imagine that in the case of severe immunosuppression, leading to a nonfavorable milieu, the progression of the RS tumoral cells can be compromised.⁶³

HIV-infected patients are more likely than non-HIV-infected patients to present with an unfavorable histologic subtype (mixed cellularity and lymphocyte-depleted generally observed in the second peak of incidence in older HIV-negative patients, whereas the nodular sclerosing subtype predominates in young adults without HIV/AIDS), "B" symptoms, advanced-stage disease, or extranodal disease. HL in HIV-infected patients is Epstein-Barr virus-associated in almost all cases, in contrast to what observed in the general population, in which this association is only observed in 20% to 50% according to histologic type and age at diagnosis.⁶⁴ Bone marrow involvement is common and can be found in more than 50% of patients in certain series⁶⁵ and may be the initial feature at diagnosis in 20% of cases, so that medullary biopsy is obligatory. The classical prognostic criteria of the general population, such as stage, bulky disease, bone marrow involvement, and high lactate dehydrogenase level, are applicable in the HIV setting, along with low CD4 cell count and prior AIDS diagnosis.

The optimal therapy for HIV HL has not yet been defined. Although cART combined with conventional chemotherapy regimens has yielded a strong effect on outcome and survival in patients with HIV (2-year survival rate of 45% in the pre-cART v 62% in the post-cART period; $P = .03$),^{49,66} the median survival remains poorer than in the general population. The standard chemotherapy regimen is doxorubicin, bleomycin, vinblastine, and dacarbazine, although mechlorethamine, vincristine, cyclophosphamide, and prednisone/doxorubicin, bleomycin, and vinblastine is a possible alternative.^{67,68} Initial experience suggests that antiretrovirals can be used concomitantly even with dose-intense regimens, including bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone.⁶⁹ The use of concurrent cART with the Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone, and involved-field radiation for initial bulky disease) was associated with a high complete response rate (81%), albeit at the cost of considerable myelosuppression and neurotoxicity.⁷⁰ This treatment has produced better survival than standard treatments.⁷⁰

Anal Cancer

The incidence of anal cancer has dramatically increased in patients with HIV, and, like cervical cancer, it is strongly associated with oncogenic subtypes of HPV. Clifford et al found a statistically significant elevated incidence of anal cancer in HIV-infected persons (SIR =

50.4; Table 1) with no clear difference between cART users and non-users.¹¹ In patients with AIDS in the United States, the risk of anal cancer did not change significantly between 1990 and 1995 and 1996 to 2002 (SIRs of 20.7 and 19.6, respectively).¹² In the FHDH, the overall incidence rates of anal cancer were 10.5 per 100,000 person-years (95% CI, 4 to 17 per 100,000 person-years) from January 1992 to March 1996, 18.4 per 100,000 person-years (95% CI, 10 to 27 per 100,000 person-years) from April 1996 to December 1998, and 39.6 per 100,000 person-years (95% CI, 32 to 47 per 100,000 person-years) from January 1999 to December 2004.⁷¹

Like cervical cancer, anal cancer is preventable through identification and treatment of high-grade intraepithelial lesions.⁷² Recently in a cross-sectional study, Abramowitz et al⁷³ showed that 23% of 473 HIV-infected patients had histologically confirmed anal HPV-related lesions (36% of homosexual men, 15% of heterosexual men, and 11% of women). In this report, such as in other series,^{71,74} a critical point is that even though homosexual and bisexual men with HIV are at increased risk for persistent HPV infection and HPV-associated anal cancer, nonhomosexual men and women with HIV are also at risk. In Goldie et al,⁷⁴ screening homosexual and bisexual HIV-infected patients with anal Papanicolaou tests provided a substantial clinical benefit with a cost comparable to that of the other existing screening prevention programs, whereas in other groups, cost-effectiveness studies are needed.

Chemoradiotherapy (fluorouracil and mitomycin or cisplatin) has become the reference treatment in localized invasive anal cancer, yielding 55% to 75% survival rates and objective responses in 70% to 95% of the patients, with preservation of the anal sphincter at 5 years in 60% to 90% of the cases, irrespective of the stage.^{75,76} Few prospective data are available on the therapeutic response in HIV-positive patients, except for the recent results from a large study describing HIV-associated anal cancer and its outcomes in the HAART era.⁷⁷ This study, as others,^{16,78} has found that survival was similar between HIV-infected and HIV-uninfected individuals with squamous cell anal carcinoma, with 2-year survival rates at 77% for HIV-infected patients compared with 75% for HIV-uninfected patients.

It is clear that when monitoring HIV-infected patients in a prevention setting, a Papanicolaou smear, anoscopy, and anal biopsy remain necessary to diagnose intraepithelial anal lesions or true invasive cancers.⁷² In addition, any person diagnosed with anal cancer, especially if male and younger than 70 years, must be evaluated for HIV infection.

Lung Cancer

Lung cancer has an increased incidence in patients with HIV, at a younger age and mainly in smokers as compared with the general population.⁷⁹⁻⁸⁵ In the Clifford et al study,¹¹ they reported cases of lung cancer in cART users who were smokers. It is well known that patients with HIV are more often smokers than their counterparts in the general population. For lung cancer, the results of three studies^{2,11,12} were consistent with SIRs ranging between 2 and 3 and remaining stable overtime (Table 1). HIV-infected patients often present with specific features: younger age at diagnosis; advanced stage of disease at diagnosis, compromising the use of optimal strategies such as surgery; and adenocarcinoma as the most frequent histologic subtype in certain series.⁸⁰⁻⁸² As for management, no specific recommendations exist; surgery remains the treatment of choice for localized disease. In several small series of patients (10

to 36 patients), median overall survival ranged from 3 to 8 months in HIV-infected patients with lung carcinoma (Table 3).^{79,81-85} The most important point is to work on tobacco prevention and tobacco cessation programs.

Other Non-AIDS-Defining Cancers

Possibly as a result of the lengthening of life expectancy of patients with HIV, other malignancies have been reported in this patient population. These include nonmelanomatous skin cancer, especially basal carcinoma marked by atypical (and often multiple) locations at diagnosis, mainly on the trunk, occurring in the younger population, and generally have an increased risk of recurrence, more treatment complications, and poorer outcome.⁶⁰ Patients must be treated as though they were HIV uninfected. Considering hepatocarcinoma, Clifford et al¹¹ found a statistically significant elevated incidence for HIV-infected persons (SIR = 7.0; Table 1) with no clear difference between cART users and nonusers. In this study, The SIR for liver cancer was higher in intravenous drug users compared with other risk categories (homosexual or bisexual men). In both studies,^{11,12} the SIRs were stable overtime. Hepatitis B and C virus coinfection is the most plausible explanation for the elevated SIRs. Optimal treatment for these patients can be similar to that of their counterparts in the general population, even for transplantation.⁸⁶

Other solid tumors described in patients with HIV are conjunctival cancer (particularly in Africa), sarcoma, melanoma, and germ cell tumors. Most of these tumors (except for germ cell tumors) present with unusual features, advanced disease at diagnosis, and, so far, aggressive outcome. For breast cancer risk, it was significantly reduced in the pre-HAART era. However, it increased significantly between 1980 and 2002, approaching the risk of the general population.⁸⁷ Non-AIDS-defining hematopoietic neoplasms other than HL reported in the literature are plasma-cell disorders, myeloma, and leukemia, for which additional work is required to ascertain their associations with immune deficiency and the optimal therapeutic strategies.

cART AND CHEMOTHERAPY INTERACTIONS

Patients who receive the combination of cancer chemotherapy and cART may achieve better response rates and higher rates of survival

than patients who receive antineoplastic therapy alone. The likelihood of drug interactions with combined therapy, however, is high (Table 4),⁸⁸ because protease inhibitors and non-nucleoside reverse transcriptase inhibitors are substrates and potent inhibitors or inducers of the cytochrome P450 (CYP) system.⁸⁹ Because many antineoplastic drugs are also metabolized by the CYP system,⁹⁰ coadministration with cART could result in either drug accumulation and possible toxicity or decreased efficacy of one or both classes of drugs. Few data describe the pharmacokinetic interactions between antineoplastic drugs and antiretrovirals.

Paclitaxel and docetaxel are both metabolized by the CYP system, although differences exist in the nature of the isoenzymes involved (for docetaxel, metabolism is exclusively mediated by the CYP3A4 pathway). Several case reports describe severe paclitaxel-related toxicity when used in combination with cART.^{32,91} A case report exists for a woman receiving nelfinavir-based cART who was treated with docetaxel and trastuzumab for metastatic breast cancer; she experienced respiratory distress and fatal febrile neutropenia.⁹² Although other confounding factors may have been present, these cases serve as reminders of the vigilant monitoring necessary when taxanes and cART are coadministered.

Similarly, vinca alkaloids are substrates of CYP3A4. A significantly higher rate of grade to 4 neuropathy was observed in patients with AIDS-related NHL receiving CHOP plus cART compared with patients receiving CHOP alone.⁴⁴ Life-threatening interactions between antiretroviral therapy and vinblastine were described.^{93,94}

Other cytotoxic agents, such as epipodophyllotoxins (etoposide and teniposide), camptothecins (irinotecan and topotecan), and alkylating agents (cyclophosphamide and ifosfamide), commonly used in the treatment of AIDS-related malignancies, are susceptible to interact with cART by their CYP3A4-mediated metabolism.⁸⁸ Existing data regarding the metabolic fate of the anthracyclines doxorubicin and daunorubicin suggest that clinically detrimental interactions should not be expected with coadministered with cART because the CYP system was not the main route of metabolism.⁸⁸ Toffoli et al⁹⁵ showed that cART therapy has no significant effect on doxorubicin pharmacokinetics. Similarly, the pharmacokinetics of liposomal daunorubicin were not modified by cART in 23 patients with AIDS-related KS.⁹⁶

Antiretroviral-mediated modulation of P-glycoprotein (Pgp) may provide another mechanism whereby the pharmacokinetics of

Table 3. Characteristics of HIV-Infected Patients With Lung Cancer in Different Trials

Characteristic	Spano et al, 2004 ⁷⁹		Tirelli et al, 1986 ⁸¹		Karp et al, 1993 ⁸⁴		Sridhar et al, 1992 ⁸³		Vyzula et al, 1996 ⁸²		Alshafie et al, 1997 ⁸⁵	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. of patients	22		36		7		19		16		11	
Median age, years	45		38		38		48		44.5		50	
CD4 ⁺ < 200/ μ L		9		28		—		53		54		30
Adenocarcinoma	8	36.5	14	39	7	100	5	31	8	50	5	46
Squamous cell carcinoma	11	50.0	12	33	0		6	37	3	19	4	36
Small-cell lung carcinoma	1	4.5	5	14	0		1	6	2	12	0	
Large-cell carcinoma	1	4.5	5	14	0		2	13	3	19	1	9
Other	1	4.5	—		0		2	13	—		1	9
Stage III or IV	16	75	26	84	7	100	15	79	13	81	10	90
Median survival, months	7		5		1		3		8		< 2	

Table 4. Antineoplastic Agents Modulating or Metabolized by Cytochrome P450 Enzymes and Interaction With Antiviral Drugs

Anticancer Therapy	Primary Isoforms That Mediate Biotransformation	Interaction With NNRTI Drugs	Interaction With PI Drugs*
Alkylating agents			
Cyclophosphamide	3A4, 2B6, 2D6	↑	—
Ifosfamide	3A4	↑	↓
Lomustine	3A4	↑	↓
Anthracyclines			
Doxorubicin	3A4	—	↓
Mitoxantrone	3A4	—	↓
Camptothecins			
Irinotecan	3A4	↓	↑
Topotecan	3A4	↑	—
Epipophyllotoxins			
Etoposide	3A4	↓	↑
Taxanes			
Docetaxel	3A4	↓	↑↑
Paclitaxel	3A4, 2C8	↓	↑
Vinca alkaloids			
Vincristine	3A4	↓	↑

NOTE. Symbol definitions are as follows: ↑, interaction increases concentration of active metabolite; ↓, interaction decreases concentration of active metabolite; —, potential for interaction appears to be minimal.

Abbreviations: NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

*Effects may be more pronounced with ritonavir.

anticancer agents can be altered. In vitro studies demonstrated that protease inhibitors could also interfere with the activity of Pgp or multidrug resistance proteins,⁹⁷ which are involved in cellular efflux of a broad range of drugs.⁹⁸ In a small study of three patients with AIDS-related KS receiving concomitant cART and pegylated doxorubicin, a transient increase in the expression of Pgp was detected in the peripheral-blood lymphocytes of patients 24 hours after the end of

administration.⁹⁹ Therefore, the potential for additional interactions via modulation of this transporter also exists.

In conclusion, the emerging reports of malignancies, especially of non-AIDS-defining malignancies, represent a new challenge in the care of patients with HIV infection. Some features remain common, such as younger age at diagnosis and the generally aggressive behavior of the tumors. These malignancies obviously have multifactorial risk elements that are either environmental or stem from lifestyle behavior (smoking) or oncogenic viruses or incomplete immune restoration with cART. Optimal treatment protocols, similar to those recommended in non-HIV infected patients, should be adhered to; however, drug-drug interactions may be a concern. Many efforts must be addressed, including optimal prevention strategies, frequency of screening, and monitoring of patients.

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The author(s) indicated no potential conflicts of interest.

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