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REVIEW

Non-acquired immunodeficiency syndrome definings malignancies among human immunodeficiency virus-positive subjects: Epidemiology and outcome after two decades of HAART era

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Abstract

Highly active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV) infection has been widely available in industrialized countries since 1996; its widespread use determined a dramatic decline in acquired immunodeficiency syndrome (AIDS)-related mortality, and consequently, a significant decrease of AIDS-defining cancers. However the increased mean age of HIV-infected patients, prolonged exposure to environmental and lifestyle cancer risk factors, and coinfection with oncogenic viruses contributed to the emergence of other malignancies that are considered non-AIDS-defining cancers (NADCs) as a relevant fraction of morbidity and mortality among HIV-infected people twenty years after HAART introduction. The role of immunosuppression in the pathogenesis of NADCs is not well defined, and future researches should investigate the etiology of NADCs. In the last years there is a growing evidence that intensive chemotherapy regimens and radiotherapy could be safely administrated to HIV-positive patients while continuing HAART. This requires a multidisciplinary approach and a close co-operation of oncologists and HIV-physicians in order to best manage compliance of patients to treatment and to face drug-related side effects. Here we review the main epidemiological features, risk factors and clinical behavior of the more common NADCs, such as lung cancer, hepatocellular carcinoma, colorectal cancer and anal cancer, Hodgkin's lymphoma and some cutaneous malignancies, focusing also on the current therapeutic approaches and preventive screening strategies.

Key words: Human immunodeficiency virus infection; Malignancy; Highly active antiretroviral therapy; Non-acquired immunodeficiency syndrome-defining cancers

Core tip: Since the introduction of highly active antiretroviral therapy (HAART) the incidence of acquired immunodeficiency syndrome (AIDS)-defining diseases has declined. This has resulted in a significant improvement in survival of human immunodeficiency virus (HIV)-infected patients. However the incidence of non-AIDS defining cancers (NADCs) did not decrease, and this determines now a relevant burden of mortality among HIV-positive patients. The availability of an even more effective HAART along with chemotherapy and radiotherapy regimens suitable also for HIV-patients could improve the outcome of these patients in the setting of NADCs. Screening interventions to detect precancerous lesions are also of paramount importance in order to decrease mortality of NADCs.

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INTRODUCTION

The early studies among patients receiving transplantation forty years ago showed that Kaposi sarcoma and lymphomas were diagnosed with an high incidence in this immunocompromised population. This findings were confirmed twenty years later when Kaposi sarcoma and some types of lymphoma presented a strong association with an advanced stage of human immunodeficiency virus (HIV)-related acquired immunodeficiency syndrome[1,2]. These malignancies have been classified as acquired immunodeficiency syndrome (AIDS)-defining cancers (ADCs) by Center for Diseases Control and Prevention since 1993[3].

With the introduction of combination antiretroviral therapy there has been a dramatic decrease of the incidence of AIDS-related morbidity and mortality in HIV-positive patients[4-7]. The HAART has also improved the short and medium-term survival in HIV-infected patients with ADCs[8]. As a consequence of the restored immune function, the incidence of AIDS-defining cancers has significantly declined, and the prognosis markedly improved. The HAART showed to modify positively the clinical outcome of Kaposi sarcoma, a typical AIDS-defining cancer, and it represents now a cornerstone for the treatment of all stages of this neoplasm[9]. *In vitro* and *in vivo* studies performed on mice deprived of thymus showed that HAART, and in particular protease inhibitors class, has a direct antitumoral activity. Even the risk of developing non-Hodgking lymphoma was reduced markedly after HAART introduction: Besson *et al*[10] showed in a large French population of HIV-infected patients that the incidence fell sharply between 1993-1994 and 1997-1998 from 86 per 10000 in the 1993-1994 to 42.9 per 10000 person-years. Similarly, another American study among 537 with AIDS-related NHL documented that the annual average incidence of NHL decreased from 29.6 per 1000 person-years in the pre-HAART period (1988-1995) to 6.5 per 1000 person-years in the post-HAART era (1996-2000). The more pronounced changes were observed among the group of diffuse large B-cells lymphomas, with a dramatic decrease of incidence of primary cerebral and of high grade hymmunoblastic lymphomas[11], that are linked to Epstein-Barr virus (EBV) latent co-infection[12].

In contrast with the positive impact of HAART on the incidence of AIDS-defining infectious and malignant diseases, HIV-positive patients remain at increased risk of non-AIDS-related mortality and morbidity, including cardiovascular disease, neuro-behavioral disease and cancers. NADCs have gradually emerged as a major fraction of the overall cancer burden[13,14]. Trends in all-cause mortality emerged from the Data collection on Adverse events of anti-HIV Drugs (D:A:D) study showed a significant decrease from 17.5 per 1000 person-years in 1999-2000 to 9.1 in 2009-11. A similar decrease in the same period was seen for the mortality rate of AIDS-defining conditions (5.9 to 2.0), liver (2.7 to 0.9) and cardiovascular diseases (1.8 to 0.9), whereas NADCs increased from 1.6 per 1000 persons-years in 1999-2000 to 2.1 in 2009-2011[15]. Some large cohort studies, and data derived from linkages among the AIDS and cancer registries, revealed that the risk of developing solid tumors and non-AIDS defining lymphomas was two to three-fold higher than in the general population[16,17]. In the meantime the overall mortality associated with NADCs increased from < 1% in pre-HAART era to 13% after HAART introduction[18]. This changing scenario could be explained by the influence of some demographic features of HIV-positive population such as the advancing age, the role of behavioral risk factors like smoking and alcohol consumption, and chronic coinfection with other viral pathogens (EBV, HCV, HBV and Human Papilloma virus)[19]. There was not demonstrated a clear relationship between immunosuppression and development of NADCs. While some studies showed that a low nadir of CD4 cell count is predictive of a increased risk of developing NADCs[20-22], Engels *et al*[23] did not find a correlation between advanced immunosuppression and the risk of developing NADCs.

Here we focus on the epidemiological and clinical features of the most common NADCs among HIV-positive individuals. We also briefly review their therapeutic approach and the outcome after twenty years of HAART.

LUNG CANCER

Lung cancer was showed to be the most frequent NADCs occurring in HIV-positive people and, it stands as the leading cause of cancer-related deaths among HIV-

positive people in a large United States population-based registry[24]. Two meta-analysis estimated that the risk of lung cancer in HIV-infected people was more than two-fold higher than in the general population[25,26], and the risk is relevant for all main lung cancer subtypes (squamous cell carcinoma, adenocarcinoma and small cell carcinoma). Male sex is more affected, and the mean age when diagnosis of lung cancer occurs is about 15 years lower than in HIV-negative people[27].

Cigarette smoking is the most important risk factor for developing lung cancer and the prevalence of tobacco use among HIV-positive people is higher than in the general population, ranging from 40% to 70% compared to 20% observed among HIV-negative people[28-30]. When considering the role of tobacco in lung carcinogenesis smoking cessation recommendations and interventions represent a critical part in the routine clinical encounter in this high-risk population.

Immunosuppression caused by HIV infection results in chronic activation, disfunction of immune system, and chronic inflammation, all likely promoting carcinogenesis in HIV-infected individuals. Nonetheless the relationship between a low T CD4 cells count, the duration of immuno-suppression and the risk of developing lung cancer is not well understood[31]. A large American cohort study of 37294 HIV-infected people showed that HIV infection appears a risk factor for lung cancer even after controlling for other confounding variables, but it did not find an association of lung cancer with low T CD4 cells count[32]. It has been reported that HIV-infected people present more frequently an advanced stage of lung cancer and the outcome is poorer if compared with the general population[33]. However these observations have recently been challenged. One epidemiological study evaluating 322 HIV-positive patients with non-small cell lung cancer showed no difference in stage at cancer diagnosis if compared with 71976 HIV-negative controls, and the median survival was similar between two groups with early stage of disease. In addition the survival of HIV-positive patients with an early stage disease, who underwent surgical resection was similar to that of control group (50 mo *vs* 58 mo; $P = 0.88$)[34].

Non-small cell lung malignancies covers more than 80% of lung cancers among HIV-positive subjects, and the adenocarcinoma is the more frequent histological type, mirroring the current epidemiological trend in the general population[35-37].

Due to the lack of randomized trials and guidelines the choice of appropriate therapy for HIV-infected patients with lung cancer tends to vary based upon patient's clinical conditions and the degree of immunosuppression. Toxicity, poor tolerability and potential of interaction between chemotherapy and HAART are concerns limiting systemic cancer therapy in HIV-positive patients[38,39]. In a retrospective multicenter Italian study of 68 consecutive cases of lung cancer diagnosed in HIV-positive patients, clinical presentation and treatment outcome in the pre-HAART and post-HAART era were compared. The overall median age was 43.5 years and all but one patients (67 out of 68 patients) were heavy smokers. Overall in 58 patients (85.3%) a non-small cell lung cancer was diagnosed, and among these adenocarcinoma was the predominant histological type. Chemotherapy was much more frequent among post-HAART patients, of whom 27 were treated (79.4%) *vs* 16 (48%) in the pre-HAART group ($P = 0.04$). The authors also showed that the overall survival rate was significantly better for the post-HAART group (3.8 mo in the pre-HAART period *vs* 7 mo in the post-HAART period, $P = 0.01$)[40]. Recently The Intergroupe Francophone de Cancerologie Thoracique has initiated a phase II trial of carboplatin plus pemetrexed in HIV-infected patients with advanced NSCLC (NCT01296113). In the United States, an AIDS Malignancy Consortium trial is evaluating the carboplatin/paclitaxel regimen in HIV-infected patients with advanced solid tumors, including lung cancers (AMC-078, NCT01296113). These studies could provide a better knowledge on treatment options and clinical outcome of HIV-positive patients with lung cancer.

COLORECTAL CANCER

Among the NADCs, colorectal cancer (CRC) has been identified as one of the tumors with an increasing in incidence in the HIV population[21]. In a prospective cohort study of 2882 patients with HIV infection the annual incidence of CRC was reported to increase from 0.65 per 1000 patients-years in the pre-HAART era to 2.34 per 1000 patient-years between 1997 and 2002[41]. As a consequence of increased life expectancy of HIV-positive people due to the efficacy of HAART, many people are living long enough to develop CRC. Clinical presentation, treatment and survival of HIV-positive patients affected by CRC were described by the Italian Cooperative Group AIDS and Tumours, where 27 cases of HIV-positive CRC patients were matched with 54 HIV-negative controls retrieved from a national database. HIV-positive patients developed CRC at an earlier age and the disease was more advanced than in the general population. The authors showed also that at the time of diagnosis most of patients had ad advance disease stage and an overall poor outcome, with a probability of survival at 4 years of 15% and 49% for HIV-positive and HIV-negative patients respectively. However it was also noted that chemotherapy was well tolerated in all patients, and in the HAART era there were neither opportunistic infections nor chemotherapy-related deaths[42]. Berretta *et al*[43] also showed that liver metastases due to CRC could be treated with surgical resection, along with chemotherapy, without discontinuing HAART. CRC is a condition that could easily identified at an early stage by screening colonoscopy since many lesions are preceded by premalignant adenomas and could be removed by endoscopy procedures. These observations are supported by the results of a screening colonoscopy study that evaluated the prevalence of neoplastic lesions. Future researches should address the role of screening in the HIV-positive population for CRC in order to improve

early diagnosis and survival[44].

HEPATOCELLULAR CARCINOMA

HIV-infected subjects are at greater risk of developing and dying of hepatocellular carcinoma (HCC). In the HAART era, the incidence of this malignancy was 10 to 36 new cases per 100000 HIV-infected people per year, corresponding to 3-fold to 6-fold excess risk if compared with the general population[13,45].

The high incidence of HCC among HIV-infected patients was also recently documented in a multicenter Italian cohort including 13388 HIV-positive patients enrolled since 1998, where liver cancer ranked as the most frequent NADC[46].

The main risk factors for development of HCC are viral hepatitis and alcohol abuse. The chronic evolution of HBV infection in the liver and the progression to cirrhosis of HCV-related chronic hepatitis are more frequent in HIV-positive individuals than in the HIV-negative people. Moreover HIV-induced immunosuppression may accelerate liver fibrosis and increase the risk to develop HCC[47]. Moreover hepatocytes apoptosis seems to be promoted by upregulation of tumor necrosis factor (TNF) by the HIV surface protein gp120[48].

Another factor that could worsen the liver damage is the antiretroviral therapy which is known to have some direct hepatotoxic effects[49]. These factors could explain the increased incidence of HCC observed in HIV-positive patients, four to seven folds higher than in the general population[50].

An Italian multicenter cohort study comparing 104 HIV-positive patients and 484 uninfected controls with HCC, showed that HIV-infected patients were significantly younger at HCC diagnosis, and they present more commonly HBV or HCV co-infection. The survival was poorer in the HIV-positive patients even though in these patients HCC was more frequently diagnosed at an early stage. However the subgroup of HIV-positive patients receiving HAART and with an undetectable HIV viral load had a better outcome than patients with an higher plasmatic HIV RNA[51]. In this study, even thought the treatment rates were similar between HIV-positive and HIV-negative patients, the overall survival rate was worse in the HIV-positive group, maybe due the fact that in these patients retreatment of an HCC recurrence was considered in a lower number of cases.

Localized therapies such as surgical resection, ethanol injection and radiofrequency ablation should be considered for patients with solitary or small number of HCC lesions[52]. Encouraging data on feasibility of liver transplantation (LT) were showed by Vibert *et al*[53]. Overall survival and relapse rate were not significantly different among HIV-positive patients with HCC compared to HIV-negative control group. This data were recently confirmed by Di Benedetto *et al*[54], who recently compared the outcome of 30 HIV-positive patients who underwent LT with 125 HIV-negative patients: at 1 year and 3 years post LT overall survival (77% at 1 years and 65% at 3 years among HIV-infected *vs* 86.4% and 70% among HIV-negative patients) was similar between the two groups. Therefore HIV-infected patients should be offered the same LT options for HCC treatment that are provided for HIV-uninfected subjects. Prevention of HCC should be addressed to reduce the burden of some risk factors; counselling for alcohol avoidance and promotion of HBV vaccination are important elements of primary prevention. Hepatic ultrasonography and alpha fetoprotein measurement every 6 mo are also essential diagnostic tools for early diagnosis of HCC. Among patients with high risk of developing HCC, such as advanced liver cirrhosis, computed tomography and magnetic resonance imaging are useful to detect hepatic lesions < 3 cm[55]. Recently, with the advent of the new direct-acting antiviral agents, HCV treatment has rapidly changed with a dramatic improvement of cure rates; therefore, eradication of HCV is a more feasible target even in the difficult-to-treat HIV-positive population[56].

HODGKIN'S LYMPHOMA

In immunosuppressed patients, Hodgkin's lymphoma (HD) occurs more frequently than in the general population of the same age, and some epidemiological studies showed that HIV-infected people have a 10-fold higher risk of developing HL than HIV-negative subjects[16,57,58]. HIV-associated HD displays several peculiarities when compared with HD in the general population, such as an unusual aggressive behavior and an overall poor prognosis. More specifically HIV-HL is characterized by the high incidence of more aggressive histological subtypes, mixed cellularity (MC) and lymphocyte depletion (LD), that appears specifically related to advanced immune compromise in HIV-infected patients. A high frequency of EBV association has been shown in HL (80%-100%) tissues from HIV-HL, which indicates that EBV does represent an important factor involved in the pathogenesis of HIV-HL. There are evidences that the EBV-encoded latent membrane protein 1 (LMP1), which is expressed in the majority of HIV-HL, may play a role in the pathogenesis of this lymphoma[59,60]. At the time of HL diagnosis many HIV-positive patients present an advanced stage of disease and systemic "B" symptoms such as fever, night sweats, and/or weight loss > 10% of the normal body weight. Among 290 patients with HIV-HL, an advanced stage of this malignancy was observed in 79% of patients; extranodal involvement was reported in 59% of patients, with bone marrow, spleen and liver involved in 38, 30 and 17 patients respectively. The authors of this study found that the following parameters were associated with a better survival: MC subtype, the absence of extranodal involvement, the absence of "B" symptoms, and prior use of HAART[61]. In a similar study performed in Spain among 104 patients with HIV-HL the complete remission rate was significantly higher in HAART group (91% *vs* 70%, $P = 0.023$)[62]. After the first prospective multi-institutional study performed by

AIDS Clinical Trial Group (ACTG), which used the ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine), more intensive chemotherapy regimens including BEACOPP (bleomycine, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), Stanford V (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone), and VEBEP (epirubicine, bleomycin, vinorelbine, cyclophosphamide and prednisone) with radiotherapy have been proposed, and a complete remission (CR) rate > 60% has been obtained[63-66]. Combined administration of HAART and chemotherapy showed to reduce the risk of opportunistic infections, relapses and to improve the CR rate. Moreover the use of high dose chemotherapy and autologous stem cell transplantation (ASCT) seems to be the gold standard as salvage treatment for relapsing or progressing HL in HIV-positive patients[67,68].

ANAL CANCER

Anal carcinoma is an uncommon malignancy in the general population, but it stands as one of the leading NADCs among HIV-positive patients since the HAART introduction[69-71]. In the Swiss HIV Cohort Study a 30-fold higher rate of anal cancer was showed in comparison to the HIV-uninfected subjects[45].

Anal cancer affects primarily men who have sex with men (MSM), with a mean age of 45-50[72]. Squamous cell carcinoma is the most common histological type and it arises from precursor high-grade anal intraepithelial lesions (AIN) within the anal canal[73]. Some high risk types of Human papillomavirus (hr-HPV), especially HPV-16, play a pivotal role in the pathogenesis of anal squamous cell carcinoma (ASCC), and in HIV-positive patients the prevalence of hr-HPV infection was estimated to be three to five fold higher than in the general population[74]. Sexual transmission of HPV through anal intercourse explains the high rate of ASCC diagnosed in HIV-positive MSM subjects[75].

A lower T CD4 cell count has been associated with a reduced clearance of anal HPV infection, and the development of precancerous lesions, such as low grade AIN. The improved survival of at risk HIV-positive patients could also allow the progression of early precancerous lesions to invasive anal cancer. Concurrent chemotherapy and radiotherapy is the first line treatment of anal cancer, and this approach could be safely used for HIV patients. Intensity-modulated radiation therapy has recently proposed to achieve high doses of radiations and reduce dermatological and gastrointestinal toxicity[76,77]. Screening interventions targeted to high risk group, like HIV-infected MSM, are based primarily on anal Pap smear and high-resolution anoscopy. The latter one proved to be cost-effective in the early detection of precancerous anal lesions, which would allow to treat them with minimally invasive localized therapies[78]. Vaccination against hr-HPV has proved to be effective for preventing anal cancer precancerous lesions in women[79]. Further studies are warranted to evaluate if this approach could have similar positive results among high risk HIV-infected patients, such as MSM.

CUTANEOUS MALIGNANCIES

Multiple studies demonstrated that immunosuppressed patients have an increased risk of cutaneous malignancies, and it seems to be most pronounced in solid-organ transplants recipients, who have a 65 to 250 times increased risk as compared to general population[80,81].

Since the early phase of HIV epidemic, Kaposi sarcoma was the most common malignancy with cutaneous involvement[2], whereas the incidence and risk factors associated with cutaneous non-ADCs (NADCs) among HIV-infected persons are less defined. In a large American cohort of 4490 HIV-positive patients retrieved from 1986 to 2006, there were 254 (5.7%) patients who developed skin cancers, and basal cell carcinoma (BCC) was the most frequent non-ADCs, with a ratio of BCC to squamous cell carcinoma (SCC) of 6:1, that differs from transplant recipients who develop SCC in the majority of cases[82]. Similarly in the period between 1985 and 2002 analyzed by an afore-mentioned Swiss study, BCC were more frequent than SCC, and the overall incidence of nonmelanomatous skin cancer was three-fold higher than in the general population (Standardized Incidence Ratio, SIRs = 3.2, 95%CI: 2.2-4.5) in this large national cohort study[83]. More recently the same authors showed that the SIRs of non-melanomatous skin cancers increased between the pre- and early-HAART period, but not between the early- and late-HAART period[45]. In a recent meta-analysis that analyzed 13 studies in the post-HAART and 8 in the pre-HAART era, also the risk of melanoma was showed to be increased among HIV/AIDS population[84]. Even if KS was the most frequent cutaneous cancer, its incidence significantly decreased after 1995, while the age-adjusted incidence rates of cutaneous NADCs remained stable[82]. The factors associated with the development of cutaneous NADCs in this study were aging and the withe/non-Hispanic race, similarly to what has been showed in other HIV-positive cohort and in the general population[85,86]. The development of cutaneous NADCs was also showed to be not related to the CD4+ T lymphocites count and receipt of HAART, but HIV-infected subjects are characterized by an high likelihood of developing subsequent cutaneous malignancies at novel sites. In the afore-mentioned study of Crum-Cianflone *et al*[82], 24% of the participants, who initially presented with a BCC, developed a subsequent BCC, and 8% developed a second type of cutaneous cancer.

These findings were confirmed by another large prospective cohort study which enrolled patients diagnosed with non-melanoma skin cancers, with a median follow-up of 7.3 years. This study showed that the overall 5-years recurrence rates after treatment in HIV-positive patients was 13.8%, and 2.9% in HIV-uninfected patients respectively (HR = 3.1; P = 0.005)[87]. The high rate of recurrences suggests that HIV-infected individuals with an initial cutaneous NADC should be carefully followed up for both recurrent disease and the development of novel

cutaneous malignancies. In the last decade some cases of Merkel cell carcinoma (MCC) in HIV-infected people were observed[88], and the risk of acquiring MCC was reported, if compared with the general population, to be 13-fold higher in this population by Engels *et al*[89].

Merkel cell carcinoma (MCC) is an uncommon, highly malignant, primary neuroendocrine tumour of the skin, that usually has its origin in the head, neck or extremities of elderly patients.

In 2008 a polyomavirus (Merkel cell polyomavirus, MCPyV) was reported to be a likely causative agent for the majority of MCCs[90,91]; this has been subsequently well established by multiple international groups[92].

Its clinical behavior is very aggressive and tendency to local recurrence, regional lymph nodes involvement and distant metastases are very high. Thus this tumor has to be regarded not as a localized skin cancer but as a systemic disease. We previously reported on an HIV-infected patient who developed a MCC with the only involvement of inguinal lymph node without evidence of primary skin localization[93]. We decided to administer to the patient, after surgical resection, postoperative radiotherapy and adjuvant combination chemotherapy with carboplatin and etoposide, according to paradigms established for small-cell lung cancer[94]. We did not document significant chemotherapy-related toxicities and the patient did not withdraw concomitant HAART. Even thought immunosuppressed patients with MCC were showed to have a poorer survival as compared to immune competent people[95], our patient did not experience a disease recurrence six years after the time of MCC diagnosis. A good performance status and a stable control of HIV infection with an effective HAART regimen should encourage clinicians to consider, for patients with MCC, systemic chemotherapy and adjuvant radiation in order to avoid regional and distant relapses of this cancer.

OTHERS

Only some retrospective studies and small case series are available to depict the distinct epidemiological and clinical features of other malignancies. In the early HAART period Sutton *et al*[96], showed that the estimated risk of acute myeloid leukaemia was twice if compared with the general population. The authors also showed that intensive chemotherapy proved to be effective to achieve completed remission of acute myeloid leukemia in 11 out of 15 HIV-positive patients. A low T CD4 lymphocytes count, regardless of karyotype, emerged as a predictor of a poor prognosis and short overall survival[97,98].

The incidence of cancers of the mouth and the pharynx, documented among HIV-positive people enrolled in the Swiss cohort from 1985 to 2002, was four-fold higher than in the general population (standardized incidence ratio, SIR = 4.1; 95%CI: 2.1-7.4), and this could be related to the smoking behavior since this was reported in 72% of the overall cohort of HIV-positive patients[83]. On the other hand the prostate cancer incidence rate was showed to be lower in HIV-positive people compared with HIV-uninfected men, even after adjusting for cancer risk factors[99,100].

In a study-linkage performed during 2003-2005 in 12 regions of United States with a population-based cancer ascertainment, Goedert *et al*[101] described the cancer profile of women diagnosed with AIDS. The incidence of breast (SIR = 0.69; 95%CI: 0.62-0.77) and uterine corpus cancers (SIR = 0.57; 95%CI: 0.39-0.81), but not of ovary cancer (SIR = 1.05; 95%CI: 0.75-1.42) was significantly lower than in the general population. The low risk of breast cancer among HIV-infected people could reflect the impairment of endogenous sexual hormone levels, and the ability of HIV to infect, replicate in, and to impair proliferation of breast cells. Breast cancer screening should be performed according to current relevant guidelines for the general population[52].

There is now a general agreement that HIV-positive patients who ensure a good adherence to an effective HAART regimen, and who are not affected by opportunistic infections, should be considered for the same anti-neoplastic treatment protocols for NADCs as in the general population, with a close monitoring of drug toxicity and interactions.

CONCLUSION

There is now a growing evidence that malignancies, whether they are strictly related to advanced stages of HIV infection, or not related to HIV-induced immunosuppression, are one of the main causes of death in the HIV-positive subjects. The effectiveness and tolerability of modern HAART regimens contributed to increase expectancy of life of these patients. Their progressive aging, the role of behavioral risks, such as smoking and alcohol intake, and other viral co-infections could negatively affect NADCs epidemic. In the other hand the availability of HAART and the better mean performance status of HIV-positive patients in the last decade, when compared with these in the pre-HAART era, gave clinicians the opportunity to treat NADCs with more effective chemotherapy regimens and to improve the long term survival. Further studies are needed to evaluate the best therapeutic approaches to NADCs and the impact of targeted cancer screening interventions among HIV-positive individuals.

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