Clinical presentation and outcome of non-AIDS defining cancers, in HIV-infected patients in the ART-era: the Italian Cooperative Group on AIDS and tumors activity

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Abstract. – The advent of antiretroviral therapy (ART) has markedly extended the survival rates of patients with human immunodeficiency virus (HIV), leading to suppression even though not eradication of HIV. In HIV infected patients, cancer has become a growing problem, representing the first cause of death. A large number of worldwide studies have shown that HIV infection raises the risk of many non-AIDS defining cancers (NADCs), including squamous cell carcinoma of the anus (SCCA), testis cancer, lung cancer, cancer of the colon and rectum (CRC), skin (basal cell skin carcinoma and melanoma), Hodgkin disease (HD) and hepatocellular carcinoma (HCC). Generally in HIV positive patients NADCs are more aggressive and in advanced stage disease than in the general population. In the ART era, however, the outcome of HIV positive patients is more similar as in the general population. Only about lung cancer the outcome seems different between HIV positive and HIV negative patients.

The aim of this article is to provide an update on NADCs within the activity of the Italian Cooperative Group on AIDS and Tumors (GICAT) to identify clinical prognostic and predicting factors in patients with HIV infection included in the GICAT.

Key Words:
  HIV, Cancer, Treatment, NADCs, Chemotherapy. Clinical aspects.

Introduction

The advent of the antiretroviral therapy (ART) has markedly extended the survival rates of patients with HIV. HIV infected people have experienced a significant improvement in immunity and increase in life expectancy[1]. However, patients taking otherwise effective antiretroviral drugs remain at increased risk of non-AIDS-related mortality and morbidity, including cardiovascular disease, neurocognitive disease, neuroendocrine dysfunctions and cancer[1].

As a consequence of improved immune function, the incidence of AIDS-defining cancers (ADCs), such as Kaposi's sarcoma, non-Hodgkin's lymphoma (NHL) and invasive cervical cancer, has significantly declined[2-5]. On the contrary, non-AIDS defining cancers (NADCs) have gradually emerged as a major fraction of the overall cancer burden[6]. These NADCs include hepatocellular carcinoma (HCC), anal cancer, lung cancer, colorectal cancer (CRC), gastrointestinal cancer (GI), breast cancer and Hodgkin's lymphoma (HL)[7-11].

It is known that cancer risk is higher in HIV infected people compared to the general population[6], but the reasons are still partially unknown. Some of the increased risk may be explained by a high prevalence of cancer risk factors, such as smoking, alcohol consumption, human papilloma virus (HPV) infection and HCV infection among HIV infected people[12]. The role of immunosuppression in the development of NADCs is controversial: Patel et al[13], for instance, found that the risk of developing CRC was significantly increased in the presence of a low nadir CD4 cell count; on the contrary, in other papers no association between the degree of immunosuppression

and the development of NADCs has been described[14,15]. The use of ART was associated with lower rates of NADCs in a study by Burgi et al[16], whereas the standardized incidence ratio (SIR) for NADCs was reported not to be decreased in the post-ART era among patients enrolled in the Swiss cohort study[17].

In HIV positive patients, cancer represents the first cause of death. A large number of worldwide studies have shown that in HIV positive patient the NADCs are usually characterized by a higher grade, more aggressive clinical course, more rapid progression, advanced stages at cancer diagnosis and shorter survival compared with HIV negative individuals[4,18,19]. Longer duration of HIV infection and history of repeated opportunistic infections are also considered as relevant risk factors for of NADCs[4].

Here we report the case loade on NADCs treated within the Italian Cooperative Group on AIDS and Tumors (GICAT).

Patients and Methods

The GICAT has studied malignancies in HIV positive patients since 1986. For the aim of these studies a validated questionnaire was sent out on behalf of GICAT and through its completion by the participating centers the following data were collected: demographic features, HIV risk factors, cigarette smoking habits, exposure to environmental carcinogens, HIV viral load, immunological and clinical features at the time of diagnosis, histological type and clinical stage of the tumor, antiretroviral therapy history, type of chemotherapy, response, survival and cause of death.

Anal Cancer

Anal squamous cell carcinoma (ASCC) is an uncommon cancer in the general population, whereas it represents an important source of morbidity and mortality in HIV infected subjects[10,20,21]. Two meta-analyses have established a 30-fold increased risk for anal cancer among HIV positive people in comparison with the general population[22,23]. ASCC arises from precursor high-grade anal intraepithelial lesions (AIN) within the anal canal[24]. Infection with high-risk types of human papillomavirus (hr-HPV), especially HPV-16, causes more than 80% of cases of ASCC. Due to sexual transmission of HPV

through anal intercourse, the risk is particularly higher in HIV infected men-who-have-sex-with-men (MSM) (46/100,000 per year % 5/100,000 per year of HIV negative men)[10].

Data on ASCC in HIV positive patients are limited and the majority of the studies are small case series. Thus, the statistical power to evaluate survival differences between HIV positive and HIV negative persons is often inadequate. Recently, the GICAT reported on a retrospective study on the clinical presentation and outcome of HIV positive patients with ASCC. Data on 65 patients were collected. All patients had histologically confirmed ASCC. Fifty-three (81.5%) patients were male, and 24 patients (37%) were older than 45 years, according to data in literature where the risk of ASCC in the general population is more common in females and increases with age[25]. Probably HIV infection is likely to facilitate persistence of HPV infection of the anal region and to increase the risk of anal squamous intraepithelial lesion[26]. The majority of patients (40%) were MSM, while 25% and 27% were drug users and heterosexual, respectively. Forty-three patients (66.1%) were diagnosed with HIV before 1996. Thirty-five patients (54%) had CD4 positive cells count > 200/mm^3 and 28 patients (43%) had viral load > 50 cp/ml at the time of ASCC diagnosis. The median time difference between HIV and ASCC diagnosis was 120 months (range 10-282 months). Sixty-one patients (96.8%) received ART at ASCC diagnosis. Thirty-two patients (49.2%) and 5 patients (7.7%) had clinical stage II-III and IV at diagnosis, respectively. We observed a predominance of advanced disease at the time of diagnosis in HIV positive patients compared to general population where ASCC is predominantly a loco-regional disease and rarely metastatic at the time of diagnosis. This evidence is probably a result of the effect of HIV infection and immune-suppression on the natural history of anal HPV infection[20]. Fifty-two patients (80%) had performance status (PS) 0-1 at the time of ASCC diagnosis. Twenty-seven patients (41.5%) underwent surgery with curative intent. Sixty-one percent of stage 1 ASCC patients benefit of local excision. Thirty-five patients (53.9%) were given combined modality therapy (CMT) consisting of pelvic radiotherapy with concurrent chemotherapy. Twenty-two patients (33.8%) had side effects during CMT. No grade 3-4 hematological or extra-hematological effects were observed in our patients. We did not find a significant correlation between low CD4

positive cells count (< 200/mm^3) and an increase in toxicity due to CMT (p = 0.6011). These results are in contrast with some studies in the literature that focused on the poorer therapy tolerability of HIV infected patients with ASCC compared with the general population due to unforeseeable interactions of chemotherapy with ART. In fact, protease inhibitors and non-nucleoside reverse transcriptase inhibitors are substrates and potent inhibitors or inducers of the cytochrome P450 (CYP) system. The co-administration of anti neoplastic drugs and ART could result in either drug accumulation and possible toxicity or decreased efficacy of one or both classes of drugs[27]. Among responders, 37 patients (60%) had a complete response (CR) and 16 patients (24.6%) a partial response (PR).

Seven patients (10.8%) had progressive disease (PD) and 1 patient (1.5%) showed stable disease (SD). Thirty patients (46.2%) have relapsed disease with average time of eight months (1-75). At anal cancer relapse, 23 patients (35.3%) did not receive any therapy; 12 patients (40%) underwent surgery alone; 5 patients (16.7%) received chemotherapy alone; 1 patient (3.33%) underwent radiotherapy alone; 4 patients (13.3%) received palliative surgery and 3 patients (10%) underwent radiotherapy plus chemotherapy or surgery plus radiotherapy. We did not observed any significant difference between the stage of ASCC at diagnosis (early stage *vs.* locally advanced and/or metastatic) and the time to relapse ($\chi^2$2 log-rank test = 2.29, p = 0.32). No significant difference occurred between the initial treatment modality (chemotherapy *vs.* radiotherapy *vs.* chemotherapy plus radiotherapy) and the time to relapse ($\chi^2$2 log-rank test = 2.48, p = 0.29). Instead, we observed a significant difference between patients with CR or PR compared with patients with SD o PD and the time to relapse ($\chi^2$2 log-rank test = 7.77, p = 0.05). Median survival was 106 months and the probability of survival at 5 years was 51%. Twenty-six patients (40%) died: 20 patients (76.9%) for disease progression; 1 patient (3.9%) for HIV infection progression, and 5 patients (19.2%) for other complications. Median survivals were 52 months and 13 months for stage II-III and IV, respectively. Median survival was not achieved for stage I ($p \leq$ 0.0001). Five year overall survival rate by stage distribution was: stage I (88%), stage II-III (41%), stage IV. We obtained these data throughout the use of best treatment modalities for stage, with CMT for more advanced stage and local surgery for earlier stages, as commonly used in general population. Notably, before the introduction of ART, HIV positive patients with ASCC, treated with CMT, had a poorer outcome than the general population. In the ART era, the 5 year overall survival of HIV positive patients with ASCC has improved and is reported to be similar to the one of the general population. In conclusion, in the ART era the prevalence of HPV infection and the risk for ASCC is increasing and may increase even further. This evidence depends on certain factors including especially longer life expectancy in HIV infected patients in ART era[20]. According to literature data we observed predominance of advanced disease at the time of diagnosis in HIV positive patients with ASCC compared to general population. Furthermore, our data have shown a comparable outcome in HIV infected patients as in general population. This may be explained by the fact that our patients with ASCC were subjected to standard treatment plus ART with good efficacy and acceptable toxicity. Despite the retrospective nature of analysis, the absence of patient strict criteria of inclusion/exclusion, our data on HIV positive patients with ASCC, compared both to general population and to small reports on HIV positive patients present in the literature, are promising[25].

Lung Cancer

Lung cancer represents the most frequently occurring NADC in HIV infected people[6,14]. Several reports have shown increased rates of lung cancer in HIV infected patients as compared with uninfected patients. In a recent meta-analysis of seven studies, globally considering 44,172 people with HIV/AIDS, of whom 1,297 diagnosed with lung cancer, Grulich et al[22] estimated an overall HIV-associated lung cancer risk of 2.7 (95% Confidence Interval (CI) 1.9-3.9). Analogously, the risk for lung cancer associated with HIV infection was estimated to be increased 2.6-fold (95% CI 2.1-3.1) in another meta-analysis of Shields et al[23]. The risk of lung cancer in the setting of HIV infection is elevated for all major lung cancer subtypes (adenocarcinoma, squamous cell carcinoma and small cell carcinoma) and has not been significantly modified by the introduction of ART: Engels et al[14] reported that the relative risk (RR) of lung cancer occurring during the pre-ART era (2.5 (95% CI 1.9-3.3)) was similar to that described in the early (3.3 (95% CI 2.9-3.8)) and recent ART era (2.6 (95% CI 2.1-3.1)).

The increased incidence of lung cancer may be related to following factors: the prolonged life expectancy of HIV positive patients during the ART era, the longer period of immune suppression of these patients and in particular the excess number of cigarettes they smoke[28].

In fact, among HIV infected individuals smoking rates range from 35% to 70%, compared to approximately 20% in the general US population[29,30]. Furthermore, no data suggests that the introduction of ART into clinical practice may account for the increased incidence of lung cancer by itself, and probably the failure to identify a risk for lung cancer in pre-ART cohorts is related to short overall survival. We reported data on the impact of ART on natural history of lung cancer in HIV positive patients, comparing patients with HIV-lung cancer treated in the pre-ART era versus the ART era. The rationale was that the improvement in clinical conditions, which was experienced after ART became available, might lead to a more extensive treatment of lung cancer in these patients and perhaps to prolonged survival. We regard lung cancer in HIV patients as a model to study because of the assumed increasing incidence of this disease in HIV positive individuals as a result of the prolonged survival induced by ART and the frequent smoking habit[31,32]. Between November 1986 and March 2003, 68 patients were diagnosed as having lung cancer and HIV infection, of whom 34 (50%) in the era before the introduction of ART into clinical practice (1986-1997) and the remaining 34 (50%) after it became available (1997-2003). HIV patients with lung cancer were mostly males (87%) and smokers. The overall median age was 43.5 years, 40.4 and 46.7 years for the pre- and post-ART groups, respectively. HIV infected patients are still quite young, which may explain why lung cancer occurs at a younger age as compared to HIV negative lung cancer patients. Risk factors for HIV infection were intravenous drug use (68% *vs.* 50%), followed by MSM transmission (17% *vs.* 29.9%) in pre-ART era and ART-era respectively; and other factors (20.5%). Data about the viral load at the time when lung cancer was diagnosed are available only for the post-ART group of patients; in most cases, namely 20 out of 34 (58.8%), it was undetectable, while in the remaining 14 a median value of 38,020 cp/mL (95-400,000) was detected. Median CD4 count did not differ significantly in both groups, with 278 cells/µl (range 12-987) in the pre-ART cohort *vs.* 339 cells/µl

(range 4-761) in the post-ART group. These data show that lung cancer is more common in association with acceptable immune competence than in the more advanced stages of HIV infection. As already pointed out by other investigators[33], this might suggest that the immune function plays less of a role in the pathogenesis of lung cancer than in Kaposi's sarcoma or non-Hodgkin's lymphomas. The adenocarcinoma subtype of NSCLC prevails in young patients affected by lung cancer. As for staging, stages III and IV were the most common, with 79% and 91%, and 4% and 31% in the pre- and post-ART settings, respectively. ECOG PS ≥ 2 was significantly more frequent in the pre-ART than in the post-ART cohorts, with 15 out of 34 (44%) and 10 out of 34 (29%) respectively, ($p = 0.02$). Sixteen pre-ART (47%) and 27 (79.4%) post-ART patients had chemotherapy, either alone or combined with radiotherapy; the difference is significative ($p = 0.04$). In the pre-ART group, 10 out of 16 patients (62.5%) were treated with cisplatin, mostly associated with etoposide; 6 out of 16 patients (37.5%) were given platin-free mono- or polichemotherapy based on either cyclophosphamide, anthracyclines or etoposide. During the post-ART era, 13 out of 27 patients (48.1%) received a platinum-based association, mostly including gemcitabine; 10 out of 27 patients (37%) were given a platin-free association, namely vinorelbine and gemcitabine, and 4 out of 27 patients (14.8%) were administered a single-agent regimen, namely vinorelbine or etoposide or gemcitabine. The median number of chemotherapy cycles was 3 for the pre-ART group[18,19,34-37] *vs.* 2.71-6 for the post-ART group. Treatment toxicity was never serious: the greatest hematological toxicity was G3 in 15% and 25% of the patients in the pre- and post-ART groups, respectively. No non-hematological toxicity greater than 2 and no chemotherapy-related deaths were recorded. Chemotherapy was much more frequent among post-ART patients, of whom 27 were treated (79.4%) *vs.* 16 (48%) in the pre-ART group, $p = 0.04$. In our opinion, this may be due to the improved clinical features of the patients at the time of diagnosis, to the results of the 1995 meta-analysis and to a growing amount of papers confirming that the association of chemotherapy and antiretroviral therapy is feasible and safe[38]. The OS rate was significantly better for the post-ART group, 3.8 months *vs.* 7 months, $p = 0.01$. However, the cause of death was comparable between both groups, with lung tumor as the leading

cause. We believe that these results may be attributed to a concomitant synergistic effect by ART and chemotherapy. When the cause of death was lung cancer, OS was significantly better for the post-ART patients with 7 months *vs.* 4.1 months in the pre-ART group ($p = 0.02$). There is a direct correlation between a better OS in the post-ART group of patients affected by lung cancer and a higher performance status score at the time of diagnosis; nevertheless, our study shows indirectly that chemotherapy has at least a non detrimental effect on the survival rate for these patients. It demonstrates that the association of chemotherapy and ART is feasible, as already stated, and supports its protective effect, which co-induces a significative improvement in the overall survival[39]. Our study shows that lung cancer does have an impact on the OS of HIV positive patients suffering from this neoplasia; for this reason, we strongly advice that patients with advanced lung cancer and HIV be treated in accord with the standard policy for HIV negative patients, that is that they receive an adequate number of platin based combination cycles and/or radiotherapy.

Colorectal Cancer

Colorectal cancer (CRC) is the second cause of cancer death in Western Countries. The spectrum of cancers may further develop because of HIV positive patients' longer survival in the ART era, particularly NADCs[4]. NADCs are usually characterized by a higher grade, more aggressive clinical course, more rapid progression, advanced stage and shorter survival compared with HIV negative individuals[18]. Data on the incidence and natural history of CRC in HIV infected people are limited; in particular, there are few data about presentation, clinical course, treatment, response to therapy, and survival of CRC in a series of HIV infected patients.

CRC has been identified as one of the tumors that may be increasing in incidence in the HIV population[13]. In fact, the annual incidence of CRC increased from 0.65 per 1000 patient/years in the pre-ART era to 2.34 per 1000 patient/years between 1997 and 2002[40,41]. Patel et al[13] reported an increased incidence of CRC in the HIV setting, whereas large reviews of matched cancer and AIDS registries do not show the same results[18,42,43]. The evidence probably depends on the longer life expectancy of HIV positive patients due to ART applied in clinical practice.

Considering that HIV is now a chronic disease,

many patients are living long enough to develop CRC; however, few studies have evaluated the incidence of CRC in HIV positive cohorts and the majority of them have excluded that the risk of CRC is increased among HIV infected people[15,44,45]. A major limitation is the lack of data regarding rates of CRC screening in the HIV population[46]. In fact, Reinhold et al. found that HIV positive patients were less likely to undergo any CRC screening examination (flexible sigmoidoscopy, fecal occult blood test, air contrast barium enema) than uninfected subjects[47]. As a consequence, reduced screening may have led to an underestimated incidence of CRC in the HIV population-based studies published so far.

Available data[19,35,48,49] suggest that HIV infected patients with CRC present with more advanced disease and at a younger age than individuals without HIV91. Within the GICAT we have compared the clinical presentation and outcome of 27 HIV positive patients and 54 age- and sex-matched controls with CRC, concluding that HIV positive patients had a poorer PS, an unfavorable Dukes' stage, a higher grading and shorter survival than uninfected subjects[35].

Moreover, we have demonstrated that the concomitant use of chemotherapy and ART is safe and feasible; the efficacy and the results obtained are similar to those in the general population[19,48,50,51]. Another aspect reported within the GICAT activity is the role of surgery in this particular setting of patients with metastatic CRC. Also in this area of interest we have demonstrated that the surgery for metastatic disease (only liver disease) is feasible and safe[52]. Clearly, the multidisciplinary approach represents the goal to obtain good results in terms of efficacy and safety.

Considering that CRC is especially amenable to screening, as premalignant adenomas exhibit a slow progression to malignancy and are often visibly identifiable and treatable via colonoscopy, future research should specifically address the issue of screening for HIV infected subjects, in order to determine the appropriate age to start screening, the frequency of screening and the most cost-effective screening technique for this subgroup of subjects.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver, and according to the World Health Organization report, the fourth most common cause of death. The risk for HCC is sevenfold higher in HIV positive patients

than in the general population. Since the introduction of ART, no incidence of HCC has been observed, unlike for other HIV-associated cancers. In HIV patients co infected with HCV or HBV the risk for developing HCC is common and significantly higher, as a result of chronic viral hepatitis. Little is still known about the interactions between HIV and HBV and/or HCV over the long term: HIV co-infection seems to accelerate disease progression and to reduce the efficacy of anti-HCV and anti HBV therapies. However, it is unclear whether HIV infection directly increases the likelihood of HCC in patients with viral hepatitis. In addition to potential indirect effects of HCC risk through improvements in immune reconstitution and survival, ART is known to have some direct hepatotoxic effects, especially among HIV positive patients chronically infected with HBV or HCV[36].

As for the impact of HIV itself on liver tumorigenesis, studies performed in mice have reported a potential oncogenic role for HIV Tat gene[53]. However, in humans there is no evidence for a direct role of HIV on HCC development: in a large retrospective study, Giordano et al[54] showed that HCC rates were not higher in HIV mono infected patients than in general population; in a retrospective cohort study on US veterans, HIV positive people were reported to have a higher risk to develop HCC than HIV negative ones, but HIV status was not independently associated with cancer after adjusting for HCV and alcohol abuse. Anyway, HIV-induced immunosuppression may accelerate liver fibrosis and exacerbate the risk to develop HCC[55]. Gp120 may modulate human hepatic stellate cells (HSCs) phenotype in a profibrogenic way and upregulate tumor necrosis factor (TNF)-related pathways, making hepatocytes more susceptible to apoptosis[56]. In contrast with potential indirect effects on HCC risk through improvement in immune reconstitution and survival, ART is known to have some direct hepatotoxic effects, especially among HIV infected patients chronically infected with HBV or HCV[57].

In addition to the elevated risk for developing HCC, individuals with HIV infection may have higher HCC-related morbidity and mortality. Some studies showed that HIV-HCV co infected patients develop liver cirrhosis faster than HCV mono infected individuals, and that in these patients, HCC is more aggressive[58-61].

In 2011, within the GICAT activity, we reported the largest case survey on clinical characteristics of HIV positive patients with HCC. We compared 104 HIV infected and 484 uninfected patients, evaluating HCC tumor characteristics, therapeutic approaches, patient survival time from HCC diagnosis and clinical prognostic predictors. We found that HIV positive patients were significantly younger than uninfected ones at HCC diagnosis and were co infected with HBC or HCV in the great majority of cases. CD4 cell count at diagnosis was not independently associated with survival; on the contrary, patients receiving ART and with undetectable HIV RNA at diagnosis had a better prognosis than untreated subjects or subjects with higher HIV viral load. Of interest, even though in HIV infected patients HCC was diagnosed mostly at an early stage (66% at Barcelona Clinic Liver Cancer (BCLC) stage A or B) and then amenable for potentially curative approaches, the median survival time was significantly shorter than that observed in the HIV negative counterpart (35 *vs.* 59 months). A more aggressive biological behavior for HCC in the setting of HIV infection may be advocated as a potential explanation, but it should be taken into account that these data may be significantly biased by the difficulty to accurately define when HBV or HCV infection was acquired[36].

Regarding of treatment approach, we demonstrated that both curative of palliative therapies are feasible and safe[62-67]. In the palliative treatment setting, we have reported the behavior on concomitant use of sorafenib and ART demonstrating that the results, in terms of efficacy and safety, are similar to those of the general population[68].

In conclusion, prevention and early diagnosis are key points for the management of HCC, but, at present, there are no universal guidelines, especially when occurring in HIV positive patients[7]. Primary prevention should promote alcohol avoidance and HBV vaccination; secondary prevention is based on the use of ultrasonography and alpha-fetoprotein measurement every six months.

Pancreatic Cancer

Pancreatic cancer (PC) is the fourth and fifth most common cause of cancer-related death among men in United States and in Europe, respectively. Few data are available on patients with PC. Within the GICAT we have reported data on 16 patients HIV positive with PC[11]. We matched these patients (ratio 1:2) with 32 HIV negative patients affected by PC, based on sex

and year of cancer diagnosis. All patients had histologically confirmed pancreatic adenocarcinoma. Our series is the first reported on clinical characteristics, HIV related data, treatment and survival data of PC in HIV positive patients. We can summarize our results as follows. First, at PC diagnosis HIV positive patients were significantly younger ($p = 0.009$), with a median age of 49 years, than the control group (59.5 years) and the general population (75 years)[69]. This fact could be in part explained by an earlier exposure to well known risk factors such as cigarette smoking and alcohol intake in HIV positive patients compared to HIV negative patients. Second, there was a predominance of males in HIV positive patients in contrast with the data reported in the literature where the incidence is equal in both sexes[70]. Third, at multivariate analysis, HIV positive patients compared to HIV negative patients had a higher risk of an unfavorable performance status (PS ≥ 2) (OR = 8.50; 95% CI: 1.23-58.54). In HIV positive patients this unfavorable PS was probably associated only in part to HIV-related immunodepression. Notably, the majority of our patients had their HIV infection under control as assessed by 11 patients (68.8%) with CD4 positive cells count >200/mm³ and 7 patients (58.3%) with viral load <50 cp/ml, respectively, at PC diagnosis. However, 37.5% of our HIV positive PC patients shared HCV co-infection, 3 patients (18.7%) had HBV co-infection and 2 patients (12.5%) had an HBV-HCV co-infection. Moreover, the majority of HIV positive patients were drug users (56.3%). There is a clear role of co-infections and related diseases, along with an earlier exposure to well-known risk factors for metabolic diseases and tumors (i.e. cigarette smoking and alcohol consumption) and an increased number of co-morbidities that could explain the unfavorable PS in HIV positive population. Fourth, we have observed a clear predominance of HIV positive patients with metastatic disease (81.2%), compared to the control group where the majority of patients shared a I-III stage (according to TNM). However, a higher risk of an advanced TNM stage at PC diagnosis for HIV positive patients (OR = 6.33; 95% CI: 1.50-26.73) was significant at univariate analysis but lacked statistical significance at multivariate analysis (OR = 2.14; 95% CI: 0.33-13.88; $p = 0.42$). Similar to our control group, it is estimated that 50% of PC patients in general population presents metastatic disease, another 35% presents with locally advanced, surgically unresectable disease and about

15% presents a potentially resectable tumor[71,72]. A higher metastatic presentation in our HIV positive patients is, maybe, a consequence of the poor awareness about data on malignancies as important causes of morbidity and mortality in HIV positive patients in the ART era[4,13]. Fifth, due to their metastatic presentation at diagnosis and their unfavorable PS, 7 HIV positive patients (43.7%) underwent surgery, with only 1 case treated with standard surgery, whereas in the control group the majority of patients (81.3%) underwent surgery and, among them, 16 patients were treated with standard surgery. Nevertheless, these are the first data reported in the literature on clinical characteristics, HIV-related data, treatment and survival of PC in HIV positive patients. Moreover, these clinical data, along with the epidemiologic data, force us to: 1) recognize HIV positive patients as a particular category of subjects at cancer risk 2) treat, when indicated, co-morbidities and co-infections 3) implement, in clinical practice, systematic screening for tobacco smoking and alcohol abuse 4) reserve also to HIV positive patients the best cancer treatment modalities used in the general population. In fact, although limited in number, our data show that in ART era, HIV positive patients may receive chemotherapy and/or radiotherapy with an acceptable toxicity.

Hodgkin's Lymphoma

HIV-associated Hodgkin's lymphoma (HIV-HL) displays some peculiarities when compared with HL of the general population. First, in the pre-cART era, HIV-HL exhibited an unusually aggressive clinical behavior and was associated with a poor prognosis[73]. Second, the pathologic spectrum of HIV-HL differs markedly from that of HL in the general population[74,75]. In particular, the mixed cellularity (MC) subtype predominates among HIV-HL[74]. Finally, despite advances in chemotherapy and supportive care, optimal treatment is still a matter of controversy.

In immune-suppressed patients, HL occurs more frequently than in the general population of the same age and gender. A summary of epidemiological studies assessing the HL risk in HIV positive people is given in Table I[17,76-90].

Overall, HIV infected persons have a tenfold higher risk of developing HL than HIV negative persons. The increase in the risk was shown to be more pronounced in HIV infected individuals with moderate immune suppression and, noteworthy, is in sharp contrast with the pattern ob-

Table I. Main results reported from epidemiological studies on HL risk among HIV-infected individuals.

First author (publication year)	Study period	Country	Main results
Biggar (1987)	1973-1984	United States	Analysis of changes in the risk of malignancies from 1973 to 1978 through 1984 in never married men (a surrogate group of MSM men) in high- or low-risk areas for AIDS. A non significant (p = 0.13) excess risk for HL was noted
Hessol (1992)	1978-1989	United States	Coh ort study of 6,704 HIV positive MSM. This was the first study to demonstrate a statistically significant excess risk for HL in HIV positive persons (RR = 5.0, 95% CI: 2.0-10.3)
Serraino (1993)	1985-1992	Italy	Clinical case series to compare the distributions of HL types between HIV positive and HIV negative persons. A fourfold increase of the mixed cellularity type and a 12-fold increase of the lymphocyte depletion type found in HIV-positives
Serraino (1997)	1985-1995	Italy	Cohort study of 1,255 HIV positive persons with known date of seroconversion. First observation, based on only three observed cases, of an excess HL risk of nearly tenfold (95% CI: 8-111) in Europe
Franceschi (1998)	1985-1993	Italy	Record linkage of the National AIDS registry with population- based cancer registries. The increased HL risk was confirmed (RR = 8.9, 95% CI: 4.4-16.0) by means of a higher number of observed HL cases
International Collaboration on HIV and Cancer (2000)	1985-1999	Australia, Europe, United States	Cancer incidence data collected from 23 studies that followed up 47,936 persons with HIV infection. One of the first and largest evaluations of the impact of ART on the spectrum of HIV associated cancers. With regard to HL, this meta-analysis found no difference in incidence rates before (1992-1996) or after (1997-1999) the use of ART (RR = 0.8, 95% CI: 0.3-1.9)
Gruilich (2002)	1985-1999	Australia	This record linkage study of HIV, AIDS, and cancer registries confirmed, in Australia, the excess risk for HL (RR = 7.8, 95% CI: 4.4-13.0) previously noted in the United States and Europe.
Dal Maso (2003)	1985-1998	Italy	Update of the record linkage study between the national AIDS registry and population- based cancer registries. After 5 years, the relative risk for HL nearly doubled (RR = 16.2, 95% CI: 11.8-21.7).
Herida (2003)	1992-1999	France	Evaluation of HL risk of 77,025 HIV positive persons during pre- and post ART periods, as compared to the general population of France of the same age and sex. HL risk seemed higher in the post ART (RR = 31.7) period than in the pre ART one (RR = 22.8).
Clifford (2005)	1985-2003	Switzerland	Record linkage between the Swiss HIV Cohort and cancer registries. As seen in France, the findings of the study pointed to a higher risk for HL in HIV positive persons treated with ART (RR = 36.2), as compared to those who were never treated (RR = 11.4)
Biggar (2006)	1991-2002	United States	The study focused on the relationship between degree of immune suppression and risk of HL. The findings indicated that incidence rates increased with increasing number of CD4 positive cells in HIV positive persons treated with ART.
Serraino (2007)	1985-2005	France, Italy	Cohort study of 8,074 HIV positive persons: the risk of HL did not significantly vary between those treated (RR = 9.4) or not treated (RR = 11.1) with ART before HL occurrence
Engels (2008)	1991-2002	United States	Record linkage study of 57,350 HIV infected persons with cancer registries. Whereas the incidence of KS and of NHL declined over time, that of HL increased (RR = 2.7, 95% CI: 1.0-7.1, 1996-2002% 1991-1995). The study findings pointed to a shift in the spectrum of cancers associated with HIV infection determined by ART

Table continued

Table I. *(continued).* Main results reported from epidemiological studies on HL risk among HIV-infected individuals.

First author (publication year)	Study period	Country	Main results
Powels (2009)	1983-2007	London, UK	Chelsea and Westminster HIV cohort (n = 11,112); standardized incidence ratios (SIRs) calculated using general population incidence data; significant increase in the HL risk (SIRs) across time periods from 4.5 (1983-1995) to 11.1 (1996-2001) to 32.4 (2002-2007)
Seaberg (2010)	1984-2007	United States	Multicenter AIDS Cohort study (n = 6,949), compared with SEER data; SIR for HL 7.3
Franceschi (2010)	1985-2007	Switzerland	Swiss HIV Cohort Study (n = 9,429); SIR for HL increased from 9.2 (1985-1996) to 21.0 (1997-2001) to 28.1 (2002-2006)

HL: Hodgkin's lymphoma; MSM: men-who-have-sex-with-men; ART: antiretroviral therapy; KS: Kaposi's sarcoma; NHL: non-Hodgkin's lymphoma.

served for KS or NHL[86]. However, another study indicated that the risk of HL declined as the most recent CD4 count increased[91]. Further, compared with patients with CD4 count greater than 500 cells per μL, the rate ratio for HL ranged from 1.2 (95% CI 0.7-2.2) for CD4 counts 350-455 cells per μL to 7.7 (3.9-15.2) for counts 50-99 cells per μL in the French Hospital Database on HIV cohort[55]. Another cohort study also showed that the risk of HL was highest at 50-99 per μL CD4 cells[92]. By contrast, another prospective cohort study from London demonstrated that cART was associated with an increased risk of HL (SIR 2.67; 95% CI, 1.19-6.02)[4]. Thus, as the overall effect of cART is to increase the CD4 count level, it was speculated that, with severe immune suppression, the cellular background surrounding the RS cells might be altered. A potential mechanism emphasizes the role of the RS cells producing several growth factors that increased the influx of CD4 cells and inflammatory cells, which, in turn, provide proliferation signals for the RS neoplastic cells. In the case of severe immune suppression, leading to an unfavorable milieu, the progression of the RS neoplastic cells may be compromised[93-95]. In addition, HIV-HL is EBV associated in approximately 90% of cases, in contrast to what is observed in the general population, in which this association is only observed in 20-50% according to histological type and age at diagnosis[96]. Usurpation of physiologically relevant pathways by EBV-encoded latent membrane protein 1 (LMP1) may lead to the simultaneous or sequential activation of signaling pathways involved in the promotion of cell activation, growth, and survival, contributing, thus, to most of the features of HIV-HL. Whether this change

affects its categorization as HL or whether it delays HL development is unknown.

HIV-HL displays different pathological features compared to those of HL in HIV negative patients[74]. In fact, HIV-HL is characterized by the high incidence of unfavorable histological subtypes such as MC and LD[74,75].

Similarly to that observed in HIV-NHL, one of the most peculiar features of HIV-HL is the widespread extent of the disease at presentation and the frequency of systemic B symptoms. At the time of diagnosis, 70-96% of the patients have B symptoms and 66-92% has advanced stages of disease with frequent involvement of extra nodal sites, the most common being bone marrow (23-50%), liver (10-40%), and spleen (20-25%)[75,97-100]. HIV-HL tends to develop as an earlier manifestation of HIV infection with median CD4+ cell counts ranging from 185 to 306/μL[75,97-100].

The widespread use of cART has resulted in substantial improvement in the survival of patients with HIV infection and HL, due to the reduction of the occurrence of opportunistic infections and to the opportunity to allow more aggressive chemotherapy[101-104].

Within the GICAT, we have collected data on 290 patients with HIV-HL[105]. Two hundred and eighty-one patients (87%) were males, and the median age was 34 years (range 19-72 years), and 69% of patients were intravenous drug users. The median CD4 cell count was 240/μL (range 4-1,100/μL), and 57% of patients had a detectable HIV viral load. MC was diagnosed in 53% of cases, followed by NS in 24% and LD in 14%. Advanced stages of disease were observed in 79% of patients and 76% had B symp-

toms. The overall extra nodal involvement was 59% with bone marrow, spleen, and liver involved in 38, 30, and 17%, respectively. With the aim to evaluate the impact of ART on clinical presentation and outcome of our patients, we split the series into two subgroups: in the first group, we included those patients who received cART since 6 months before the onset of HL (84 patients); in the second group, we included those patients who never received ART before the diagnosis of HL or less than 6 months (206 patients). Briefly, in comparison to those who never experienced ART, patients in ART before the onset of HL are older and have less B symptoms and a higher leukocyte and neutrophil count and hemoglobin level. The following parameters were associated with a better overall survival (OS): MC subtype, the absence of extra nodal involvement, the absence of B symptoms, and prior use of ART. Interestingly, three parameters were associated with a better time to treatment failure: a normal value of alkaline phosphates, prior exposure to ART, and an international prognostic score (IPS) less than 3[105]. Table II summarizes these data.

Similar studies were carried out in France, Germany, and Spain[102-104,106]. Overall, no differences were found between groups at baseline, but complete remission (CR) and overall survival rates were significantly higher in ART groups. In the Spanish study, factors independently associated with CR were a CD4 cell count >100 cells/µL and the use of ART; CR was the only factor independently associated with OS[106]. Due to the low incidence of HIV-HL, no randomized controlled trials have been conducted in this setting, and standard therapy for HIV-HL has not clearly been defined. However, results from recent studies provide some evidence on how optimal treatment approaches for HIV-HL may look like. Because most patients have advanced stage disease, combination chemotherapy regimens were usually administered. As the widespread use of ART allows the use of more aggressive chemotherapeutic regimens, the Stanford V regimen – consisting of short-term chemotherapy (12 weeks) with adjuvant radiotherapy – was given in a prospective phase II study within the European Intergroup Study HL-HIV[107]. From May 1997 to October 2001, 59 consecutive patients were treated. Stanford V was well tolerated, and 69% of the patients completed treatment with no dose reduction or delayed chemotherapy administration. The most important dose-limiting side effects were bone marrow toxicity and neurotoxicity. Eighty-one percent of the patients achieved a CR, and after a median follow-up of 17 months, 33/59 (56%) patients were alive and disease-free. The estimated 5-year OS, disease-free survival (DFS), and freedom from progression (FFP) were 59%, 68%, and 60%, respectively. The FFP probability was significantly ($p = 0.002$) higher among patients with an IPS of < 2 than in those with IPS > 2, and the percentage of

Table II. Clinical differences in 290 patients with HIV-HL according to prior ART exposure.

Characteristics	Prior-ART 84 patients (%)	ART naïve 206 patients (%)	*p*-value
Risk group			
Intravenous drug users	45	72	
Heterosexual contacts	30	13	
MSM contacts	25	14	0.0002
Age, years			
<30	5	47	
31-40	46	40	
>41	49	13	<0.0001
B symptoms	68	80	0.03
White blood cells			
<4,000	30	51	
>4,000	70	49	0.002
Neutrophil count			
<2,500	33	54	
>2,500	67	46	0.002
Hemoglobin level			
<10.5	35	49	
>10.5	65	51	0.03

MSM: men-who-have-sex-with-men.

FFP at 2 years were 83% and 41%, respectively. Similarly, the OS probability was significantly different ($p = 0.0004$), and the percentage of survival at 3 years were 76% and 33%, respectively, for IPS < 2 and IPS > 2[113]. Within the GICAT, 71 patients were included in a prospective phase II study aiming to evaluate the feasibility and activity of a novel regimen including epirubicin, bleomycin, vinorelbine, cyclophosphamide, and prednisone (VEBEP regimen). Seventy percent of patients had advanced stages of disease, and 45% had an IPS >2. The CR was 67%, and 2-year OS, DFS, and event free survival (EFS) were 69%, 86%, and 52%, respectively[108]. Unfortunately no data are reported on cancer related fatigue[109].

In summary, the outcome of patients with HIV-HL has improved with better combined antineoplastic and antiretroviral approaches. The main important challenges for the next years are (a) to validate the role of PET scan both in the staging and in the evaluation of response, (b) to better understand the interactions between chemotherapy and antiretroviral therapy in order to reduce the toxicity of both approaches, (c) to evaluate the use of new drugs (i.e., brentuximab vedotin) in this setting, and (d) to evaluate the long-term toxicity of the treatment in cured patients.

Conclusions

In the ART era, HIV positive people are living longer and therefore are aging. Considering that the incidence of most malignancies increases with age, they have more opportunities to develop cancer. In addition to prolonged survival, the NADC epidemic may be significantly influenced by behavioral risk factors, such as intravenous drug use and smoking, and ART.

Within the activity of the GICAT we have demonstrated that the multidisciplinary approach in this particular setting of patients is the right way to obtain good and safe results. Moreover, NADCs represent a new oncologic challenge due to the aging of these patients[110].

Unfortunately, many questions regarding the relationship between HIV and NADCs are still left unanswered. Future research should focus on the etiology of NADCs, in order to shed light on the pathogenesis of cancer and ultimately to work for prevention; moreover, additional studies should evaluate the best therapeutic approaches to NADCs and the impact of cancer screening interventions among HIV infected people, in an effort to diagnose cancer at an earlier stage.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Pinzone MR, Fiorica F, Di Rosa M, Malaguarnera G, Malaguarnera L, Cacopardo B, Zanghì G, Nunnari G. Non-AIDS-defining cancer s among HIV-infected people. Eur Rev Med Pharmacol Sci 2012; 16: 1377-1388.

2) Simard EP, Engels EA. Cancer as a cause of death among people with AIDS in the United States. Clin Infect Dis 2010; 51: 957-962.

3) Martellotta F, Berretta M, Vaccher E, Schioppa O, Zanet E, Tirelli U. AIDS-related Kaposi's sarcoma: state of the art and therapeutic strategies. Curr HIV Res 2009; 7: 634-638.

4) Berretta M, Cinelli R, Martellotta F, Spina M, Vaccher E, Tirelli U. Therapeutic approaches to AIDS related malignancies. Oncogene 2003; 22: 6646-6659.

5) Nasti G, Martellotta F, Berretta M, Mena M, Fasan M, Di Perri G, Talamini R, Pagano G, Montroni M, Cinelli R, Vaccher E, D'Arminio Monforte A, Tirelli U; GICAT; ICONA. Impact of highly active antiretroviral therapy on the presenting features and outcome of patients with acquired immunodeficiency syndrome-related Kaposi sarcoma. Cancer 2003; 98: 2440-2446.

6) Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, Biggar RJ; HIV/AIDS Cancer Match Study. Trends in cancer risk among people with AIDS in the United States 1980-2002. AIDS 2006; 20: 1645-1654.

7) Nunnari G, Berretta M, Pinzone MR, Di Rosa M, Berretta S, Cunsolo G, Malaguarnera M, Cosentino S, De Paoli P, Schnell JM, Cacopardo B. Hepatocellular carcinoma in HIV positive patients. Eur Rev Med Pharmacol Sci 2012; 16: 1257-1270.

8) Mani D, Haigentz M, Aboulafia DM. Lung Cancer in HIV Infection. Clinical Lung Cancer 2012; 13: 6-13.

9) Carbone A, Gloghini A, Vaccher E, De Paoli P. Lymphomas and other cancers in HIV-infected patients WCRJ 2014; 1: e291.

10) Fontana Del Vecchio R, Pinzone MR, Cacopardo B, Nunnari G. Anal cancer in HIV-positive patients WCRJ 2014; 1: e405.

11) Zanet E, Berretta M, Di Benedetto F, Simonelli C, Bearz A, Morra A, Bonanno S, Berretta S, Tirelli U. Pancreatic cancer in HIV-positive patients: a clinical case-control study. Pancreas 2012; 41: 1331-1335.

12) SILVERBERG MJ, CHAO C, LEYDEN WA, XU L, HORBERG MA, CHAO CR, TOWNER WJ, HURLEY LB, QUESENBERRY CP JR, KLEIN DB. HIV infection and the risk of cancers with and without a known infectious cause. AIDS 2009; 23: 2337-2345.

13) PATEL P, HANSON DL, SULLIVAN PS, NOVAK RM, MOORMAN AC, TONG TC, HOLMBERG SD, BROOKS JT; Adult and Adolescent Spectrum of Disease Project and HIV Outpatient Study Investigators. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med 2008; 148: 728-736.

14) ENGELS EA, BROCK MV, CHEN J, HOOKER CM, GILLISON M, MOORE RD. Elevated incidence of lung cancer among HIV-infected Individuals. J Clin Oncol 2006; 24: 1383-1388.

15) MARTELLOTTA F, SCHIOPPA O, CACOPARDO B, FISICHELLA R, TIRELLI U. Current status and perspectives of AIDS-related Kaposis's sarcoma in the c-ART era WCRJ 2014; 1: e393.

16) BURGI A, BRODINE S, WEGNER S, MILAZZO M, WALLACE MR, SPOONER K, BLAZES DL, AGAN BK, ARMSTRONG A, FRASER S, CRUM NF. Incidence and risk factors for the occurrence of non-AIDS-defining cancers among human immunodeficiency virus-infected individuals. Cancer 2005; 104: 1505-1511.

17) CLIFFORD GM, POLESEL J, RICKENBACH M, DAL MASO L, STEFFEN I, LEDERGERBER B, RAUCH A, PROBST-HENSCH NM, BOUCHARDY C, LEVI F, FRANCESCHI S; SWISS HIV COHORT. Cancer Risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst 2005; 97: 425-432.

18) COOLEY TP. Non-AIDS-defining cancer in HIV infected people. Hematol Oncol Clin N Am 2003; 17: 889-899.

19) BERRETTA M, DI BENEDETTO F, BEARZ A, SIMONELLI C, MARTELLOTTA F, DEL BEN C, BERRETTA S, SPINA M, TIRELLI U. FOLFOX-4 Regimen with concomitant HAART in metastatic colorectal cancer HIV-infected patients: a report of five cases and review of the literature. Cancer Invest 2008; 26: 610-614.

20) ZANET E, BERRETTA M, MARTELLOTTA F, CACOPARDO B, FISICHELLA R, TAVIO M, BERRETTA S, TIRELLI U. Anal cancer: focus on HIV-positive patients in the HAART era. Curr HIV Res 2011; 9: 70-81.

21) D'SOUZA G, WILEY DJ, LI X, CHMIEL JS, MARGOLICK JB, CRANSTON RD, JACOBSON LP. Incidence and epidemiology of anal cancer in the multicenter AIDS cohort study. J Acquir Immune Defic Syndr 2008; 48: 491-499.

22) GRULICH AE, VAN LEEUWEN MT, FALSTER MO, VAJDIC CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 2007; 370: 59-67.

23) SHIELS MS, COLE SR, KIRK GD, POOLE C. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. J Acquir Immune Defic Syndr 2009; 52: 611-622.

24) WATSON AJ, SMITH BB, WHITEHEAD MR, SYKES PH, FRIZELLE FA. Malignant progression of anal intra-epithelial neoplasia. ANZ J Surg 2006; 76: 715-717.

25) MARTELLOTTA F, BERRETTA M, CACOPARDO B, FISICHELLA R, SCHIOPPA O, ZANGHÌ A, SPARTÀ D, CAPPELLANI A, TALAMINI R, IZZI I, RIDOLFO A, TORRESIN A, FIORICA F, TIRELLI U. Clinical presentation and autcome of squamous cell carcinoma of the anus in HIV-infected patients in the HAART-era: a GICAT experience. Eur Rew Med Pharmacol Sci 2012; 16: 1283-1291.

26) MAGGARD MA, BEANES SR, KO CY. Anal canal cancer: a population based reappraisal. Dis Colon Rectum 2003; 46: 1517-1523.

27) DI FRANCIA R, DI PAOLO M, VALENTE D, CACOPARDO B, CILENTI L. Pharmacogenetic based drug-drug interactions between Highly Active Antiretroviral Therapy (HAART) and antiblastic chemotherapy WCRJ 2014; 1: e386.

28) BEARZ A, VACCHER E, TALAMINI R, BERRETTA M, TIRELLI U. Comment on lung cancer in the Swiss HIV Cohort Study: role of smoking, immunodeficiency and pulmonary infection. Br J Cancer 2012; 106: 1899-1900.

29) BURKHALTER JE, SPRINGER CM, CHHABRA R, OSTROFF JS, RAPKIN BD. Tobacco use and readiness to quit smoking in low-income HIV-infected persons. Nicotine Tob Res 2005; 7: 511-522.

30) CENTERS FOR DISEASE CONTROL AND PREVENTION. Vital Signs: Current Cigarette Smoking Among Adults Aged-18 Years–United States, 2009. MMWR 2010; 59: 1135-1140.

31) DAL MASO L, POLESEL J, SERRAINO D, FRANCESCHI S. Lung cancer in persons with AIDS in Italy, 1985-1988 HIV. AIDS 2003; 17: 2117-2119.

32) TIRELLI U, SPINA M, SANDRI S, SERRAINO D, GOBITTI C, FASAN M, SINICCO A, GARAVELLI P, RIDOLFO AL, VACCHER E. Lung carcinoma in 36 patients with human immunodeficiency virus infection. The Italian Cooperative Group on AIDS and Tumors. Cancer 2000; 88: 563-569.

33) POWLES T, NELSON M, BOWLER M. HIV-related lung cancer--a growing concern? Int J STD AIDS 2003; 14: 647-651.

34) BEARZ A, VACCHER E, MARTELLOTTA F, SPINA M, TALAMINI R, LLESHI A, CACOPARDO B, NUNNARI G, BERRETTA M, TIRELLI U; Italian Cooperative Group on AIDS and Tumors. Lung cancer in HIV positive patients: the GICAT experience. Eur Rev Med Pharmacol Sci 2014; 18: 500-508.

35) BERRETTA M, CAPPELLANI A, DI BENEDETTO F, LLESHI A, TALAMINI R, CANZONIERI V, ZANET E, BEARZ A, NASTI G, LACCHIN T, BERRETTA S, FISICHELLA R, BALESTRERI L, TORRESIN A, IZZI I, ORTOLANI P, TIRELLI U. Clinical presentation and outcome of colorectal cancer in HIV-positive patients: a clinical case-control study. Onkologie 2009; 32: 319-324.

36) BERRETTA M, GARLASSI E, CACOPARDO B, CAPPELLANI A, GUARALDI G, COCCHI S, DE PAOLI P, LLESHI A, IZZI I, TORRESIN A, DI GANGI P, PIETRANGELO A, FERRARI M,

BEARZ A, BERRETTA S, NASTI G, DI BENEDETTO F, BALESTRERI L, TIRELLI U, VENTURA P. Hepatocellular carcinoma in HIV-infected patients: check early; treat hard. Oncologist 2011; 16: 1258-1269.

37) BEARZ A, GARASSINO I, CAVINA R, FAVARETTO A, BOCCALON M, TALAMINI R, BERRETTA M, SPAZZAPAN S, SIMONELLI C, SANTORO A, TIRELLI U. Pemetrexed single agent in previously treated non-small cell lung cancer: a multi-institutional observational study.. Lung Cancer 2008; 60: 240-245..

38) SOCINSKI M. The role of chemotherapy in the treatment of unresectable stage III and IV non small cell lung cancer. Respir Care Clin N Am 2003; 9: 207-236.

39) BEARZ A, LLESHI A, PERIN T, FRATINO L, VENTURINI S, GIACALONE A, SARTOR I, BERRETTA M, SULFARO S, TIRELLI U. Small cell lung cancer in a elderly patient: efficacy of somatostatin analog treatment. A case report. Onkologie 2011; 34: 117-120.

40) BEDIMO R, CHEN RY, ACCORT NA, RAPER JL, LINN C, ALLISON JJ, DUBAY J, SAAG MS, HOESLEY CJ. Trends in AIDS-defining and non-AIDS-defining malignancies among HIV-infected patients: 1989-2002. Clin Infect Dis. 2004; 39: 1380-1384.

41) BONNET F, LEWDEN C, MAY T, HERIPRET L, JOUGLA E, BEVILACQUA S, COSTAGLIOLA D, SALMON D, CHÊNE G, MORLAT P. Malignancy-related causes of death in human immunodeficiency virus-infected patients in the era of highly active antiretroviral therapy. Cancer 2004; 101: 317-324.

42) LEVINE AM. AIDS-related malignancies: the emerging epidemic. J Natl Cancer Inst 1993; 85: 1382-1397.

43) JEMAL A, SIEGEL R, XU J, WARD E. Cancer statistics, 2010. CA Cancer J Clin 2010; 60: 277-300.

44) YEGUEZ JF, MARTINEZ SA, SANDS DR, SANDS LR, HELLINGER MD. Colorectal malignancies in HIV positive patients. Am Surg 2003; 69: 981-987.

45) CHAPMAN C, ABOULAFIA DM, DEZUBE BJ, PANTANOWITZ L. Human Immunodeficiency Virus–associated adenocarcinoma of the colon: clinicopathologic findings and outcome. Clin Colorectal Cancer 2009; 8: 215-219.

46) BERRETTA M, TIRELLI U. Colorectal cancer screening in HIV-infected patients 50 years of age and older: missed opportunities for prevention. Am J Gastroenterol 2006; 101: 907.

47) REINHOLD JP, MOON M, TENNER CT, POLES MA, BINI EJ. Colorectal cancer screening in HIV-infected patients 50 years of age and older: missed opportunities for prevention. Am J Gastroenterol 2005; 100: 1805-1812.

48) BERRETTA M, LLESHI A, CAPPELLANI A, BEARZ A, SPINA M, TALAMINI R, CACOPARDO B, NUNNARI G, MONTESARCHIO V, IZZI I, LANZAFAME M, NASTI G, BASILE F, BERRETTA S, FISICHELLA R, SCHIANTARELLI CC, GARLASSI E, RIDOLFO A, GUELLA L, TIRELLI U. Oxaliplatin based chemotherapy and concomitant highly active anti-retroviral therapy in the treatment of 24 patients with colorectal cancer and HIV infection. Curr HIV Res 2010; 8: 218-222.

49) BINI EJ, GREEN B, POLES MA. Screening colonoscopy for the detection of neoplastic lesions in asymptomatic HIV-infected subjects. Gut 2009; 58: 1129-1134.

50) BERRETTA M, MARTELLOTTA F, SIMONELLI C, DI BENEDETTO F, DE RUVO N, DRIGO A, BEARZ A, SPINA M, ZANET E, BERRETTA S, TIRELLI U. Cetuximab/targeted chemotherapy in an HIV-positive patient with metastatic colorectal cancer in the HAART era: a case report. J Chemother 2007; 19: 343-346.

51) BERRETTA M, LLESHI A, ZANET E, BEARZ A, SIMONELLI C, FISICHELLA R, NASTI G, BERRETTA S, TIRELLI U. Bevacizumab plus irinotecan-, fluorouracil-, and leucovorin-based chemotherapy with concomitant HAART in an HIV-positive patient with metastatic colorectal cancer. Onkologie 2008; 31: 394-397.

52) BERRETTA M, DI BENEDETTO F, SIMONELLI C, BEARZ A, BERRETTA S, MAUGERI D, TIRELLI U. Multidisciplinary approach in a HIV/HCV-positive patient with liver metastases by colorectal cancer in the HAART era. Ann Oncol 2006; 17: 1333-1334.

53) ALTAVILLA G, CAPUTO A, LANFREDI M, PIOLA C, BARBANTI-BRODANO G, CORALLINI A. Enhancement of chemical hepatocarcinogenesis by the HIV-1 tat gene. Am J Pathol 2000; 157: 1081-1089.

54) GIORDANO TP, KRAMER JR, SOUCHEK J, RICHARDSON P, EL-SERAG HB. Cirrhosis and hepatocellular carcinoma in HIV-infected veterans with and without the hepatitis C virus: a cohort study, 1992-2001. Arch Intern Med 2004; 164: 2349-2354.

55) GUIGUET M, BOUE F, CADRANEL J, LANG JM, ROSENTHAL E, COSTAGLIOLA D; Clinical Epidemiology Group of the FHDH-ANRS CO4 cohort. Clinical epidemiology group of the FHDH-ANRS CO4 cohort. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDHANRS CO4): a prospective cohort study. Lancet Oncol 2009; 10: 1152-1159.

56) BABU CK, SUWANSRINON K, BREN GD, BADLEY AD, RIZZA SA. HIV induces TRAIL sensitivity in hepatocytes. PLoS One 2009; 4: e4623.

57) Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. JAMA 2000; 283: 74-80.

58) PINEDA JA, ROMERO-GÓMEZ M, DÍAZ-GARCÍA F, GIRÓN-GONZÁLEZ JA, MONTERO JL, TORRE-CISNEROS J, ANDRADE RJ, GONZÁLEZ-SERRANO M, AGUILAR J, AGUILAR-GUISADO M, NAVARRO JM, SALMERÓN J, CABALLERO-GRANADO FJ, GARCÍA-GARCÍA JA; Grupo Andaluz para el Estudio de las Enfermedades Infecciosas; Grupo Andaluz para el Estudio del Hígado. HIV coinfection shortens the survival of patients with hepatitis C-virus-related decmpensated cirrhosis. Hepatology 2005; 41: 779-789.

59) PUOTI M, BRUNO R, SORIANO V, DONATO F, GAETA GB, QUINZAN GP, PRECONE D, GELATTI U, ASENSI V, VACCHER E; HIV HCC Cooperative Italian-Spanish Group. Hepatocellular carcinoma in HIV-infected patients: Epidemiological features, clinical presentation and outcome. AIDS 2004; 18: 2285-2293.

60) Brau N, Fox RK, Xiao P, Marks K, Naqvi Z, Taylor LE, Trikha A, Sherman M, Sulkowski MS, Dieterich DT, Rigsby MO, Wright TL, Hernandez MD, Jain MK, Khatri GK, Sterling RK, Bonacini M, Martyn CA, Aytaman A, Llovet JM, Brown ST, Bini EJ; North American Liver Cancer in HIV Study Group. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a US-Canadian multicenter study. J Hepatol 2007; 47: 527-537.

61) Garcia-Samaniego J, Rodriguez M, Berenguer J, Rodríguez-Rosado R, Carbó J, Asensi V, Soriano V. Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. Am J Gastroenterol 2001; 96: 179-183.

62) Di Benedetto F, Di Sandro S, De Ruvo N, Berretta M, Montalti R, Guerrini GP, Ballarin R, De Blasiis MG, Spaggiari M, Smerieri N, Iemmolo RM, Guaraldi G, Gerunda GE. Human immunodeficiency virus and liver transplantation: our point of view. Transplant Proc 2008; 40: 1965-1971.

63) Di Benedetto F, De Ruvo N, Berretta M, Masetti M, Montalti R, Di Sandro S, Ballarin R, Codeluppi M, Guaraldi G, Gerunda GE. Hepatocellular carcinoma in HIV patients treated by liver transplantation. Eur J Surg Oncol 2008; 34: 422-427.

64) Di Benedetto F, De Ruvo N, Berretta M, Masetti M, Montalti R, Di Sandro S, Quintini C, Codeluppi M, Tirelli U, Gerunda GE. Don't deny liver transplantation to HIV patients with hepatocellular carcinoma in the highly active antiretroviral therapy era. J Clin Oncol. 2006 10; 24: e26-27.

65) Tavio M, Grossi P, Baccarani U, Scudeller L, Pea F, Berretta M, Adani G, Vivarelli M, Riva A, Tirelli U, Bresadola V, Viale P, Risaliti A. HIV-infected patients and liver transplantation: who, when and why. Curr HIV Res 2011; 9: 120-127.

66) Berretta M, Zanet E, Di Benedetto F, Simonelli C, Bearz A, Morra A, Bonanno S, Berretta S, Tirelli U. Unusual presentation of metastatic hepatocellular carcinoma in an HIV/HCV coinfected patient: case report and review of the literature. Tumori 2008; 94: 589-591.

67) Ursino S, Greco C, Cartei F, Colosimo C, Stefanelli A, Cacopardo B, Berretta M, Fiorica F. Radiotherapy and hepatocellular carcinoma: update and review of the literature. Eur Rev Med Pharmacol Sci 2012; 16: 1599-604.

68) Berretta M, Di Benedetto F, Dal Maso L, Cacopardo B, Nasti G, Facchini G, Bearz A, Spina M, Garlassi E, De Re V, Fiorica F, Lleshi A, Tirelli U. Sorafenib for the treatment of unresectable hepatocellular carcinoma in HIV-positive patients. Anticancer Drugs 2013; 24: 212-218.

69) Ahlgren JD. Epidemiology and risk factors in pancreatic cancer. Semin Oncol. 1996; 23: 241-250

70) Jemal A, Siegel R, Ward E, Winchester DP. Cancer statistics, 2009. CA Cancer J Clin 2009; 59: 225-249.

71) Sener SF, Fremgen A, Menck HR, Winchester DP. Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985-1995, using the National Cancer Database. J Am Coll Surg 1999; 189: 1-7.

72) Yeo TP, Hruban RH, Leach SD, et al. Pancreatic cancer. Curr Probl Cancer 2002; 26: 176-275.

73) Errante D, Gabarre J, Ridolfo AL, Rossi G, Nosari AM, Gisselbrecht C, Kerneis Y, Mazzetti F, Vaccher E, Talamini R, Carbone A, Tirelli U. Hodgkin's disease in 35 patients with HIV infection: an experience with epirubicin, bleomycin, vinblastine and prednisone chemotherapy in combination with antiretroviral therapy and primary use of G-CSF. Ann Oncol 1999; 10: 189-195.

74) Grogg KL, Miller RF, Dogan A. HIV infection and lymphoma. J Clin Pathol 2007; 60: 1365-1372.

75) Tirelli U, Errante D, Dolcetti R, Gloghini A, Serraino D, Vaccher E, Franceschi S, Boiocchi M, Carbone A. Hodgkin's disease and human immunodeficiency virus infection: clinicopathologic and virologic features of 114 patients from the Italian Cooperative Group on AIDS and tumors. J Clin Oncol 1995; 13: 1758-1767.

76) Powles T, Robinson D, Stebbing J, Melbye M. Highly active antiretroviral therapy and the incidence of non-AIDS- defining cancers in people with HIV infection. J Clin Oncol 2009; 27: 884-890.

77) Biggar RJ, Horm J, Goedert JJ, Melbye M. Cancer in a group at risk of acquired immunodeficiency syndrome (AIDS) through 1984. Am J Epidemiol 1987; 126: 578-586.

78) Hessol NA, Katz MH, Liu JY, Buchbinder SP, Rubino CJ, Holmberg SD. Increased incidence of Hodgkin disease in homosexual men with HIV infection. Ann Intern Med 1992; 117: 309-311.

79) Serraino D, Carbone A, Franceschi S, Tirelli U. Increased frequency of lymphocyte depletion and mixed cellularity subtypes of Hodgkin disease in HIV-infected patients. Italian Cooperative Group on AIDS and Tumours. Eur J Cancer 1993; 29A: 1948-1950.

80) Serraino D, Pezzotti P, Dorrucci M, Alliegro MB, Sinicco A, Rezza G. Cancer incidence in a cohort of human immunodeficiency virus seroconverters. HIV Italian Seroconverters Study Group. Cancer 1997; 79: 1004-1008.

81) Franceschi S, Dal Maso L, Arniani S, Crosignani P, Vercelli M, Simonato L, Falcini F, Zanetti R, Barchielli A, Serraino D, Rezza G. Risk of cancer other than Kaposi sarcoma and non-Hodgkin's lymphoma in persons with AIDS in Italy. Cancer and AIDS Registry Linkage Study. Br J Cancer 1998; 78: 966-970.

82) International Collaboration on HIV and Cancer. Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virusinfectedadults. J Natl Cancer Inst 2000; 92: 1823-1830.

83) Grulich AE, Li Y, McDonald A, Correll PK, Law MG, Kaldor JM. Rates of non-AIDS-defining cancers in people with HIV infection before and after AIDS diagnosis. AIDS 2002; 16: 1155-1161.

84) Dal Maso L, Franceschi S, Polesel J, Braga C, Piselli P, Crocetti E, Falcini F, Guzzinati S, Zanetti R, Vercelli M, Rezza G; Cancer and AIDS Registy Linkage Study. Risk of cancer in persons with AIDS in Italy, 1985-1998. Br J Cancer 2003; 89: 94-100.

85) Herida M, Mary-Krause M, Kaphan R, Cadranel J, Poizot-Martin I, Rabaud C, Plaisance N, Tissot-Dupont H, Boue F, Lang JM, Costagliola D. Incidence of non AIDS-defining cancers before and during the highly active antiretroviral therapy era in a cohort of human immunodeficiency virus-infected patients. J Clin Oncol 2003; 21: 3447-3453.

86) Biggar RJ, Jaffe ES, Goedert JJ, Chaturvedi A, Pfeiffer R, Engels EA. Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. Blood 2006; 108: 3786-3791.

87) Serraino D, Piselli P, Busnach G, Burra P, Citterio F, Arbustini E, Baccarani U, De Juli E, Pozzetto U, Bellelli S, Polesel J, Pradier C, Dal Maso L, Angeletti C, Carrieri MP, Rezza G, Franceschi S; Immunosuppression and Cancer Study Group. Risk of cancer following immunosuppression in organ transplant recipients and in HIV-positive individuals in southern Europe. Eur J Cancer 2007; 43: 2117-2123.

88) Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, Grigg R, Hylton T, Pawlish KS, McNeel TS, Goedert JJ. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer 2008; 123: 187-194.

89) Seaberg EC, Wiley D, Martínez-Maza O, Chmiel JS, Kingsley L, Tang Y, Margolick JB, Jacobson LP; Multicenter AIDS Cohort Study (MACS). Cancer incidence in the Multicenter AIDS Cohort Study before and during the HAART era: 1984-2007. Cancer 2010; 116: 5507-5516.

90) Franceschi S, Lise M, Clifford GM, Rickenbach M, Levi F, Maspoli M, Bouchardy C, Dehler S, Jundt G, Ess S, Bordoni A, Konzelmann I, Frick H, Dal Maso L, Elzi L, Furrer H, Calmy A, Cavassini M, Ledergerber B, Keiser O; Swiss HIV Cohort Study. Changing patterns of cancer incidence in the early and late-HAART periods: the Swiss HIV Cohort Study. Br J Cancer 2010; 103: 416-422.

91) Bohlius J, Schmidlin K, Boué F, Fätkenheuer G, May M, Caro-Murillo AM, Mocroft A, Bonnet F, Clifford G, Paparizos V, Miro JM, Obel N, Prins M, Chêne G, Egger M; Collaboration of Observational HIV Epidemiological Research Europe. HIV related Hodgkin lymphoma in the era of combination antiretroviral therapy: incidence and evolution of CD4+ -cell lymphocytes. Blood 2011; 117: 6100-6108.

92) Lanky E, Rosenberg PS, Fily F Lascaux AS, Martinez V, Partisani M, Poizot-Martin I, Rouveix E, Engels EA, Costagliola D, Goedert JJ; FHDH-ANRS CO4. HIV associated Hodgkin lymphoma during the first months on combination antiretroviral therapy. Blood 2011; 118: 44-49.

93) Levine AM. Hodgkin lymphoma: to the HAART of the matter. Blood 2006; 108: 3630.

94) Gloghini A, Carbone A. Why would the incidence of HIV-associated Hodgkin lymphoma increase in the setting of improved immunity? Int J Cancer 2007; 120: 2753-2754.

95) Carbone A, Cabras A, Gloghini A. HIV associated Hodgkin's lymphoma. Antiapoptotic pathways and mechanisms for immune escape by tumor cells in the setting of improved immunity. Int J Biol Markers 2007; 22: 161-163.

96) Dolcetti R, Boiocchi M, Gloghini A, Carbone A. Pathogenetic and histogenetic features of HIVassociated Hodgkin's disease. Eur J Cancer 2001; 37: 1276-1287.

97) Hentrich M, Berger M, Wyen C, Siehl J, Rockstroh JK, Müller M, Fätkenheuer G, Seidel E, Nickelsen M, Wolf T, Rieke A, Schürmann D, Schmidmaier R, Planker M, Alt J, Mosthaf F, Engert A, Arasteh K, Hoffmann C. Stage adapted treatment of human immunodeficiency virus associated Hodgkin lymphoma: results of a prospective multicenter study. J Clin Oncol 2012; 30: 4117-4123.

98) Landrieu JM, Roithmann S, Tourani JM, Levy R, Desablens B, le Maignan C, Gastaut JA, Brice P, Raphael M, Taillan B. Hodgkin's disease during HIV-1 infection: the French registry experience. Ann Oncol 1993; 4: 635-641.

99) Rubio R. Disease associated with human immunodeficiency virus infection. A clinical study of 46 cases. Cancer 1994; 73: 2400-2407.

100) Montoto S, Shaw K, Okosun J, Gandhi S, Fields P, Wilson A, Shanyinde M, Cwynarski K, Marcus R, de Vos J, Young AM, Tenant-Flowers M, Orkin C, Johnson M, Chilton D, Gribben JG, Bower M. HIV status does not influence outcome in patients with classical Hodgkin lymphoma treated with chemotherapy using doxorubicin, bleomycin, vinblastine, and dacarbazine in the highly active antiretroviral therapy era. J Clin Oncol 2012; 30: 4111-4116.

101) Ribera J-M, Navarro JT, Oriol A, López-Guillermo A, Sureda A, Abella E, Hernández-Rivas JA, Xicoy B, Grau J, Batlle M, Feliu E. Prognostic impact of highly active antiretroviral therapy in HIV-related Hodgkin's disease. AIDS 2002; 16: 1973-1976.

102) Gérard L, Galicier L, Boulanger E, Quint L, Lebrette MG, Mortier E, Meignin V, Oksenhendler E. Improved survival in HIV-related Hodgkin's lymphoma since the introduction of highly active antiretroviral therapy. AIDS 2003; 17: 81-87.

103) Hoffmann C, Chow KU, Faetkenheuer G, Stellbrink HJ, van Lunzen J, Jaeger H, Stoehr A, Plettenberg A, Wasmuth JC, Rockstroh J, Mosthaf F, Horst HA, Brodt HR. Strong impact of highly active antiretroviral therapy HIV-associated Hodgkin disease. Br J Haematol 2004; 125: 455-462.

104) Hentrich M, Maretta L, Chow KU, Bogner JR, Schürmann D, Neuhoff P, Jäger H, Reichelt D, Vogel M, Ruhnke M, Oette M, Weiss R, Rockstroh J, Arasteh K, Mitrou P. Highly active antiretroviral therapy (HAART) improves survival in HIV-associated Hodgkin's disease: results of a multicenter study. Ann Oncol 2006; 17: 914-919.

105) CHIMIENTI E, SPINA M, GASTALDI R ET AL. Clinical characteristics and outcome of 290 patients (pts) with Hodgkin's disease and HIV infection (HD-HIV) in pre and HAART (highly active antiretroviral therapy) era. Ann Oncol 2008; 19: iv136, abstract 168.

106) BERENGUER J, MIRALLES P, RIBERA JM RUBIO R, VALENCIA E, MAHILLO B, PINTADO V, PALACIOS R, MONTES ML, TÉLLEZ MJ, LA CRUZ J, TORRE-CISNEROS J, RODRÍGUEZ-ARRONDO F, SEPÚLVEDA MA, GUTIÉRREZ F, PERALTA G, BOIX V. Characteristics and outcome of AIDS related Hodgkinlymphoma before and after the introduction of highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2008; 47: 422-428.

107) SPINA M, GABARRE J, ROSSI G, FASAN M, SCHIANTARELLI C, NIGRA E, MENA M, ANTINORI A, AMMASSARI A, TA-LAMINI R, VACCHER E, DI GENNARO G, TIRELLI U. Stanford V and concomitant HAART in 59 patients with Hodgkin's disease and HIV infection. Blood 2002; 100: 1984-1988.

108) SPINA M, ROSSI G, ANTINORI A, ET AL. VEBEP regimen and highly active antiretroviral therapy (HAART) in patients (pts) with HD and HIV infection (HD-HIV). Ann Oncol 2008; 19: iv152, abstract 227.

109) GIACALONE A, SPINA M, BERRETTA M, TIRELLI U. Two types of fatigue in cancer patients. Br J Cancer 2012; 106: 424.

110) BERRETTA M, DI FRANCIA R, TIRELLI U. Editorial: The new oncologic challenges in the 3rd millennium. WCRJ 2014; 1: e133.