The Pattern of Non-AIDS-defining Cancers in the HIV Population: Epidemiology, Risk Factors and Prognosis. A Review

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Abstract: The advent of highly active antiretroviral therapy (HAART) has significantly reduced the incidence of AIDS events, including AIDS-defining malignancies. Nevertheless, several cohort studies conducted in the post-HAART period have reported an increasing risk of non-AIDS-defining cancers (NADC).

Overall, the potential mechanisms leading to an increased risk of developing NADCs probably involve multiple known and unknown factors. In addition to ageing, chronic inflammation and ongoing immune system dysregulation, other contributing factors are co-infection with potentially oncogenic viruses (HBV, HCV, HPV, EBV) and high-risk behaviours such as tobacco smoking.

As a consequence of these risk factors, high standardized incidence ratios have been consistently reported, mainly in cohort studies regarding smoking-related cancers (lung cancer, but also pharyngeal and kidney cancer), due to the far more common cigarette smoking habit in the HIV population. Also in the setting of infection-related malignancies, the high frequency of liver cancer, as a consequence of HBV and HCV co-infection is well known. Similarly, HPV infection accounts for the higher risk of anal cancer. On the same line, Hodgkin lymphoma is more frequent in the HIV population, due to the dysregulation and proliferation of EBV-infected lymphocytes.

Several studies addressed the direct relationship between immunosuppression and cancer progression, showing that subjects with HIV infection experience higher cancer-specific mortality, as compared to the general population, independently of cancer stage or cancer treatment.

In the HIV population, for many NADCs, the prognosis is still worse as compared to the general population. However, an improvement has been reported over the last decades, mainly thanks to more available and adequate treatment chances.

Keywords: HIV, AIDS, NADCs, cancer incidence, cancer mortality, HAART.

1. INTRODUCTION

During the last two decades, the introduction of highly active antiretroviral therapy (HAART) led to a decreasing incidence of AIDS-related morbidity and mortality in subjects living with HIV infection in developed countries, and to a dramatic change in the epidemiologic correlates in this population [1]. In particular, cohort studies reported the progressive aging of subjects with HIV infection and an increase in the proportion of non-AIDS-related comorbidities, such as hepatitis B and C, cardiovascular diseases, neuro-behavioral disease, iatrogenic disorders, and (primarily) malignant disease [2, 3].

The burden of this phenomenon was even more evident in recent years, emerging as a dramatic shift in causes of death. Before HAART was in use, non-AIDS-defining cancers (NADC) accounted for less than 1% of all causes of death, whereas AIDS-defining conditions, including AIDS-defining malignancies (ADM), represented the most frequent cause of death in the HIV population [4, 5]. Early after the introduction of HAART, the proportion of non AIDS-related solid tumors increased steadily over time, as a cause of death among HIV-infected patients [6, 7]. Collecting data from all French hospital wards involved in the management of HIV infection, a study published in 2001 found that the overall mortality associated with NADCs increased from <1% in pre-HAART era to 12.4% after HAART introduction [8]. Another study, performed by the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) on more than 46,000 subjects receiving antiretrovirals from 1995 to 2009, estimated that 9.8% of deaths were due to cancer. The fraction of deaths due to NADCs was 7.1%, while only 2.6% were attributable to AIDS-defining cancers [9]. More recent studies showed higher proportional mortality...
ratios, associating more than 10% of all deaths with NADCs [10].

Nonetheless, this change may be mainly due to the HAART-associated decrease in the incidence of AIDS-defining malignancies, which seemed a more influential driver than the increase in the incidence of non AIDS-related malignancies. Considering the first decade of the Post-HAART era, Data collection on Adverse events of anti-HIV Drugs (D:A:D) study reported a significantly decreasing trend in overall mortality (from 17.5 per 1000 person-years in 1999-2000 to 9.1 in 2009-11) and in mortality due to AIDS-defining conditions (rate decreasing from 5.9 to 2.0). On the other hand, mortality due to NADCs slightly increased from 1.6 to 2.1 per 1000 persons-years [11].

This trend in mortality rates was sustained by a parallel increase in the incidence of non AIDS-defining comorbidities, and particularly in NADCs. Recent cohort studies consistently reported an increased risk of NADCs, whose incidence did not seem affected by HAART and consequent immune reconstitution [10-12].

This may be due to several interacting factors, such as aging and the long-lasting effects of HIV infection. The main driver may be the disruption of various immune repertoire involved in immune surveillance against cancer [13, 14]. Moreover, several studies explored the prevalence of high-risk behaviors, such as tobacco smoking and the possible exposition to co-infection with potentially oncogenic viruses, namely hepatitis B and C viruses (HBV and HCV), human papillomavirus (HPV) and Epstein-Barr virus (EBV) [15]. Other factors were proposed, such as a possible direct role of HIV and a supposed mutagenic effect of some antiretrovirals, but the evidence is currently inconsistent [16].

In this review, we evaluated risk factors and incidence rates of NADCs, the global burden of NADCs and of specific cancers in different clinical settings (Table 1). Risk factors associated with NADCs were also evaluated in the HIV population (Table 2) and prognosis parameters were compared to those observed in the general population (Table 3). We also focused on the main NADCs with higher incidence ratios as compared to the general population, namely lung cancer, anal carcinoma, hepatocellular carcinoma and Hodgkin lymphoma.

2. INCIDENCE RATES OF ALL NADCs

Two meta-analyses, including record linkage cohort studies of AIDS and cancer registries, estimated that, in the post-HAART era, the risk of developing solid tumors and non-AIDS defining lymphomas was two to three-fold higher than in the general population [13, 17].

The meta-analysis by Shieles et al. combined data from 18 studies, aiming at estimating the relative incidence of specific non-AIDS cancers between HIV infected individuals and the general population [17]. This study confirmed that HIV patients had twice the risk of non-AIDS cancers than the general population. Standardized Incidence Ratios (SIRs) for all non-AIDS cancers were higher in men than in women, and in those with than without AIDS, even if no substantial difference was observed by the HAART era. Among a total of 4,797 NADC cases, the most frequently observed non-AIDS cancer type was lung cancer (17.6%), followed by Hodgkin lymphoma (n=13.4%), anal cancer (5.3%) and liver cancer (3.5%). In particular, many infection-associated cancers were more frequent among HIV patients, including cancers of the anus (SIR=28), oropharynx (SIR=19), liver (SIR=5.6), stomach (SIR=1.7), and Hodgkin lymphoma (SIR=11). The incidence rates of cigarette smoking-associated cancers were also higher among HIV-infected individuals, as in lung (SIR=2.6), kidney (SIR=1.7) and laryngeal cancers (SIR=1.5). Additionally, some cancers showed a lower incidence in HIV-infected subjects than in the general population: substantially lower rates of the breast (SIR=0.74) and prostate (SIR=0.69) cancers were reported [17].

All cohort studies exploring temporal trends of NADCs in the HIV population showed at least a stable incidence over time [18, 20], and most research reported increasing NADC frequency, from the pre-HAART to the post-HAART period [14, 19, 21-23].

Indeed, among HIV subjects, the risk of NADCs varied by geographical and clinical conditions and differed by immune and clinical variables (mainly antiretroviral treatment in use and CD4 cell recovery), and socio-demographic features, such as advancing age and prevalence of behavioral risk factors (like smoking and alcohol consumption). Other epidemiologic features of study populations, such as the frequency of chronic co-infection with other viral pathogens (HBV, HCV, HPV and EBV), may explain the different incidence rates reported in different geographical areas [7, 15, 24].

In the US HIV/AIDS Cancer Match Study, people living with HIV had 21% higher risk of all NADCs combined, compared with the general population, with higher incidence rates in the post-HAART era. Between 1991 and 2005, the estimated number of NADCs increased by approximately threefold over time [25]. In a study performed in British Columbia, HIV subjects had an SIR of 2.05 for NADCs development as compared to the general population. During the observation period (1996-2008), 2.95% of patients developed an NADC [26].

An Italian retrospective cohort study (MASTER cohort), conducted from 1986 to 2012, compared the global incidence of NADCs in 16,268 HIV-infected subjects to the Italian general population, using incidence rates from the Italian Cancer Registries. No significant difference was observed and an SIR of 0.9 was reported, both before and after 1998 [27]. On the other hand, a mono-centric Italian study, conducted in the Milan metropolitan area between 1985 and 2011, reported an SIR of 1.9 in men and 1.5 in women for all NADCs. Moreover, incidence significantly increased from 1.0 case/1000 person-years (PY) in the pre-HAART period to 4.5 cases/1000 PY in the post-HAART period [14].

In these study populations, the types of NADCs most commonly reported were generally homogeneous among different studies [17-24]. Interestingly, evaluating NADCs in people with HIV/AIDS and in transplant recipients, a recent meta-analysis showed that several cancers occurred at a similar increased incidence in both populations. Many of them had a known or suspected infectious cause [13].
Table 1. Non-AIDS-defining cancers risk factors (RF) in subjects living with HIV infection.

<table>
<thead>
<tr>
<th>Risk Factor (RF)</th>
<th>Prevalence of RF in Subjects with HIV Compared to the General Population</th>
<th>Specific NADCs Associated with RF</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV replication</td>
<td>Exclusively in HIV-infected</td>
<td>Supposed correlation with lung, liver and HPV-related cancers</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Much more frequent</td>
<td>Possible for lung and virus-related cancers</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td>Much more frequent</td>
<td>Lung, head and neck, kidney and bladder cancers</td>
</tr>
<tr>
<td>EBV</td>
<td>More frequent</td>
<td>Hodgkin lymphoma, head and neck carcinoma, gastric adeno-carcinoma</td>
</tr>
<tr>
<td>HPV</td>
<td>More frequent</td>
<td>Cervical and anal cancer, head and neck carcinoma</td>
</tr>
<tr>
<td>HBV and HCV</td>
<td>More frequent</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Probably more frequent</td>
<td>Hepatocellular carcinoma, gastroenteric cancers</td>
</tr>
<tr>
<td>Denutrition/lower body mass index</td>
<td>More frequent in AIDS</td>
<td>Possible association with any NADC</td>
</tr>
</tbody>
</table>

Table 2. Non-AIDS-defining-cancers in people with HIV infection according to two meta-analysis and some Nation-wide cohorts: standardized incidence ratios of selected and any NADCs.

<table>
<thead>
<tr>
<th>Standardized Incidence Ratios (95% Confidence Intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meta-analysis</strong></td>
</tr>
<tr>
<td>Grulich E. et al. [13]</td>
</tr>
<tr>
<td>Lung cancer</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
</tr>
<tr>
<td>Anal cancer</td>
</tr>
<tr>
<td>Any NADC</td>
</tr>
</tbody>
</table>

Table 3. Prognosis of non-AIDS-defining cancers with higher standardized incidence ratios according to recent cohort studies and clinical series, in HIV-positive and HIV-negative subjects.

<table>
<thead>
<tr>
<th>Median Overall Survival, % of Subjects Alive (Years of Observation)</th>
<th>Complete Response after Therapy (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV Positive</strong></td>
<td><strong>HIV Negative</strong></td>
<td><strong>HIV Positive</strong></td>
</tr>
<tr>
<td>LNG cancer</td>
<td>10-15 (1)</td>
<td>20-50 (1)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>78-81 (5)</td>
<td>80-88 (5)</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>22-82 (1)</td>
<td>33-86 (1)</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>39-85 (5)</td>
<td>65-84 (5)</td>
</tr>
</tbody>
</table>

In low-income countries and developing areas, the epidemiology of NADCs in HIV population was likely different from high-income countries. Regrettably, most developing countries lack population-based cancer registry data that would allow an assessment of the burden of cancer in specific groups, such as HIV-infected individuals.

However, where information was available, a recent rise in cases of NADCs was observed, likely due to the recent availability of HAART in less developed regions of the world [28, 29]. A study conducted in Sao Paulo, among people with AIDS, showed similar patterns to those observed in developed countries: all NADCs increased significantly since the mid-2000s, driven by the significant upward trends of anal and lung cancers (annual increase of 24.6% and 15.9% respectively) [29].

3. RISK FACTORS

3.1. Immunodeficiency

The strong association between lower CD4 count and increased AIDS-related malignancies risk is well proven [30].
On the other hand, the hypothesis that both low nadir CD4 cell counts and current CD4 cell counts may play a role in NADC development is supported by some studies [14, 31-33] but not by others [34-36]. Some studies using static CD4 measures (baseline or nadir values) did not observe such a relationship [34-36]. On the other hand, analyses using time-updated CD4 measures reported an inverse association between recent CD4 count and risk of any NADC and of some specific cancer types [32, 33]. However, some reports also highlighted a significant association between NADC risk and nadir CD4 cell counts. The rationale for this relationship may be the baseline disruption of immunological cancer-fighting repertoires, which may not be restored even when CD4 counts increased with antiretroviral therapy [14, 26, 37]. Interestingly, as a possible marker of ongoing immune system deterioration, the exposure to low CD4 counts (e.g. less than 200 cells/μl) was found independently associated with increased NADC, with a higher impact than updated CD4 cell counts [38].

Indeed, it is well known that HIV-associated immunodeficiency allows the progression of other infectious diseases, including those caused by oncogenic viruses. Thus, it may play a role in the pathogenesis of infection-related NADCs, through two main mechanisms: the uncontrolled spread of viruses and the impaired immune surveillance of malignant cells [39, 40]. On the other hand, even the augmented risk of infection-unrelated NADCs may be related to a possibly impaired immune surveillance of malignant cells [37, 38].

The observed association between lower CD4 levels and NADC development further supports the need for HAART utilization at any stage of HIV infection, as it may be protective thanks to immune-restoration. Consistently, some recent studies supported the early introduction of antiretroviral treatment also for their protective role against NADCs [41-43]. The TEMPRANO ANRS 12136 Study Group evaluated the efficacy of antiretroviral introduction immediately after HIV diagnosis, associated with preventive 6-month therapy with isoniazid. As compared to deferred HAART initiation, this therapeutic strategy was associated with lower rates of severe illnesses. In particular, NADCs showed lower prevalence in subjects receiving immediate HAART, although the small number of cancer cases prevented from drawing significant conclusions [41].

Consistently, in the Strategic Timing of Antiretroviral Treatment (START) study, immediate antiretroviral treatment initiation was proven to reduce the risk of HIV-related conditions and cancer, as compared to the deferred treatment strategy [42]. This finding was confirmed both for infection-related and infection-unrelated malignancies [43]. The authors concluded that this benefit may be attributable to several HAART-related factors, such as virological suppression, immune restoration, better control of co-infections, and reduction in the pro-inflammatory pattern of HIV infection [43]. Nonetheless, other studies are needed to better understand the mechanisms involved in the role of HAART in reducing the risk of NADCs.

### 3.2. The Direct Role of HIV-1

HIV itself may have an independent effect on carcinogenesis. Some studies reported an association between ongoing viral replication and cancer risk, although it was unclear if a significant independent association was real, even after allowing for all possible confounders [44]. Some in vitro studies also indicated that HIV itself may have direct pro-oncogenic effects, via Tat and Vpr proteins: the HIV Tat gene was responsible for the expression and modulation of certain proto-oncogenes (c-myc, c-fos, and p53) in malignant cells [45]. The potential mechanisms were not fully clarified, involving the alteration of cell cycle regulation, the downregulation of tumor suppressor genes, the inhibition of telomerase activity, and the impairment of DNA repair function [45]. In the setting of cancer development, the induction of tumor angiogenesis was reported to be enhanced in HIV infected cells, through a lymphangiogenic factor, the matrix protein p17, encoded by HIV [46].

However, in the evolution of NADCs, the role of HIV itself is likely minor, as compared with the impact of other risk factors, such as tobacco use, co-infections and immune system deterioration. Nonetheless, some research found that a longer time with undetectable HIV RNA exerted a protective role against NADCs, highlighting the strong relationship among the immune system, HIV control and NADC development [47].

### 3.3. Antiretroviral Therapy Toxicity

Most available studies failed to prove a direct association between antiretroviral therapy and cancer risk [16, 48, 49]. Indeed, a potential carcinogenic effect of specific compounds or drug classes was suggested [50-52], but the beneficial effects of antiretroviral therapy on HIV replication, immune function, and inflammation largely exceeded the downside of its potential toxicity [48].

Some attention was paid to the potential toxic effects of older drugs, such as zidovudine, but also to antiretrovirals in current use for both treatment-experienced and naive patients [50]. For example, the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz was associated with increased risk of Hodgkin lymphoma in one study [51], although this finding was not confirmed by more recent studies [48, 52, 53]. In vitro evaluations even suggested a potential anti-neoplastic effect of efavirenz, with specific toxicity toward cancer cell cultures [49].

In observational studies, the use of protease inhibitors (PI) was found to be an independent predictor of anal cancer as compared to NNRTI-based therapy [52, 53]; in these studies, the effect of confounding factors could not be excluded, as longer PI exposure was observed among males having sex with males (MSM) and little information was available on sexual habits, such as unprotected anal intercourse. However, the association between PI use and NADCs was confirmed after anal cancer was excluded from the analysis [53]. Nonetheless, the higher risk of cancer in subjects treated with PI-based antiretroviral regimens was evaluated in other studies and excluded at least for other NADCs, such as lung cancer [16]. The integrase inhibitor raltegravir was found to induce host DNA rearrangements, but no evidence of a clinical effect is available [54]. A recent study, conducted in the EuroSIDA cohort, found no evidence for an increased NADC risk associated with raltegravir-based antiretroviral therapy, as compared to a historical cohort of patients adding
any other new antiretroviral drug to their initial regimen [55].

Finally, CCR5 inhibitors were hypothesized to reduce immunological surveillance of malignant cells, even though their potential toxicity was not proven [56].

3.4. Viral Co-infections

Viral hepatitises, besides alcohol abuse, are the main risk factors for the development of hepatocellular cancer (HCC) [57-59]. The evolution of chronic HBV infection was more frequent in HIV subjects than in the general population [57]. In subjects with HIV-HBV co-infection, HCC pathogenesis showed peculiar characteristics, with a higher frequency of mutations in the precore or core region of HBV, associated with higher HBV-DNA levels [57]. Although it was unclear if a higher viral replication was associated to a higher risk of HCC development, it could reinforce other mechanisms typical of HIV infection, such as an accelerated liver fibrosis and increased rate of hepatocytes apoptosis, promoted by upregulation of tumor necrosis factor (TNF) [58].

Moreover, higher levels of intra-hepatic HCV-RNA, detected in HIV-positive patients as compared to HCV mono-infected subjects, were associated with higher risk of inflammation and progression to cirrhosis [59].

A high frequency of EBV detection (almost 80%) was reported in tissues obtained from HIV-positive patients affected by Hodgkin lymphoma, one of the most frequent NADCs occurring in HIV population [60]. This observation suggested that EBV had a role in the pathogenesis of Hodgkin lymphoma. Moreover, some evidence emerged that the mechanism involved in the development of HIV-related Hodgkin lymphoma involved the EBV-encoded latent membrane protein 1 (LMP1), expressed in most of these patients [61].

It is also well known the pivotal role of HPV in the pathogenesis of anal squamous cell carcinoma (ASCC): high risk types of HPV (hr-HPV) are involved, especially HPV-16 [62]. Noteworthy, in HIV-infected patients the prevalence estimates of hr-HPV infection were higher than in the general population [63, 64]. For example, in a study including MSM, 28% of HIV patients were also infected by HPV-16 in the anal canal [63]. Consistently, in a study of women at high risk for HIV, evaluating medical and behavioral risk factors, the prevalence of anal HPV infection was 1.8 times higher in HIV-positive than in HIV-negative women [64].

Several interactions between HIV and HPV were evaluated, and HIV was positively correlated to persistent HPV infection, thus favoring the development of dysplasia and cancer [65]. Moreover, some HPV genotypes, more frequent in HIV-seropositive than in HIV-seronegative subjects, were closely associated with cancer in the oral region: these hr-HPV genotypes were largely reported in the development of squamous cell carcinomas arising from the lingual and palatine tonsils [66].

As regards HAART, no evidence is currently available that it may play a role in the clearance of HPV infection, in the control of precursor anogenital cancer lesions or in the possible regression of previous high-grade lesions [67]. Moreover, the role of HPV vaccination was not supported by a trial on the prevention of new anal HPV infections and on the outcomes of high-grade anal lesions, conducted in HIV-infected adults [68].

3.5. Behavioral Risk Factors

As reported in several areas and clinical settings, cigarette smoking was more prevalent in HIV-infected individuals than in the general population [15, 69, 70]. One study reported that around 60% of subjects living with HIV/AIDS in New York State were current smokers, three times more than the estimated prevalence in the general population [69]. In a cohort of HIV-infected subjects, living in the metropolitan area of Milan (Italy), from 1998 to 2011, a similar prevalence of tobacco smoking was reported (55%) [14]. A survey conducted in the USA reported a declining estimated prevalence of smoking in subjects with HIV infection, in the 2009-2014 period (from 38% to 34%); despite this decline, cigarette smoking was still higher in this group than in the general population [70].

The SIR of smoking-related cancers (lung, kidney, laryngeal and stomach cancers) was higher among women than men with HIV infection [17]. This evidence may be explained by the relative increase in smoking among HIV-infected women compared to HIV-infected men. However, data only compared cigarette smoking between men and women: more studies are needed to compare smoking frequency and risk in other subgroups.

Closely related to HPV infection, unsafe sexual behaviors were associated with NADC risk [71].

Moreover, in a large cohort study, a higher risk of NADCs was observed in HIV subjects with altered body mass index (both lower than 18.5 and higher 30 Kg/m²), confirming findings from the general population for BMI-related NADCs, such as esophagus, pancreas, colon and rectum cancers [72].

3.6. Inflammation and Ageing

Inflammation is enhanced by the immune dysregulation induced by HIV replication, leading to an increased risk of comorbidities in a context described as premature ageing. In the HIV population, this process may induce an earlier development of NADCs, although it was demonstrated only a slight effect for some NADCs, namely lung cancer, anal cancer, myeloma, pharynx and kidney cancers [73]. However, given the strong relationship between oncogenesis and inflammation, in the HIV population, some clinical trials evaluated the possible association between cancer and plasma levels of interleukin-6 (IL-6), C-reactive protein (CRP), D-dimer, a fibrin-degradation product, and other inflammatory markers [74, 75]. One study enrolled 5,000 HIV-infected patients in the control arms of three randomized trials [75]. Even after adjustment for other inflammation markers, higher baseline levels of IL-6 were independently associated with higher cancer risk, both for infection-related and infection-unrelated malignancies [75]. These findings suggested that a reduction of inflammatory and coagulation biomarker levels, in particular, IL-6, may be a useful indicator of reduction in the general pro-inflammatory milieu, with the possible consequent decrease of inflammation-related oncogenic risk.
The possible carcinogenetic role of T-cell activation, enhanced inflammatory or coagulation pathways, may justify the use of adjunctive anti-inflammatory or anti-thrombotic therapies in the setting of HIV infection. An AIDS Clinical Trial Group observational study investigated the use of statins and its possible association with a decrease in non-AIDS-defining events: statin use was associated with a 57% reduction in NADC risk, while no significant benefit was reported for cardiovascular events [76]. After this study, it was hypothesized that statins have cholesterol-independent, anti-inflammatory properties and may be included in a wider prevention strategy against NADCs.

Finally, a beneficial role of antiretroviral therapy in the reduction of NADC occurrence was shown in recent studies, evaluating the effects of early HAART on NADC risk [42, 43, 77]. The protective role of HAART on cancer risk may be due to the combined effects on the modulation of the inflammatory patterns, immune recovery, and the control of HIV and other viruses replication.

4. PROGNOSIS

In recent years, some international cohort studies described cancer prognosis and mortality after diagnosis in the setting of HIV-infected subjects. A trend toward an improvement in overall survival (OS) was generally observed, even though a total mortality difference still persisted between HIV positive and negative subjects [78, 79]. It should be noted, however, that survival estimates in clinical series tended to be more favorable than survival in population-based series [80].

Moreover, international studies found relevant differences in mortality rates between HIV subjects living in different European and North American clinical settings, due to various factors, including behavioral characteristics and comorbidities, such as HCV infection [78-81].

An Italian study evaluated 5-year survival for all cancers in HIV patients, comparing prognosis periods and reporting that survival improved from 12% in 1986-1995 to 41% in 1996-2005 [78]. Corresponding hazard ratios (HRs) of death among HIV-infected individuals versus the general population decreased from 5.1 (95% confidence interval, CI: 4.3 to 6.1) to 2.9 (95% CI: 2.6 to 3.3). Overall HRs were 2.5 (95% CI: 2.1 to 3.1) for all NADCs and 5.9 (95% CI: 3.1 to 11.2) for Hodgkin lymphoma. A 3-fold survival difference was reported for cancers of the stomach, liver, anus, lung, brain, and the most aggressive lymphoma subtypes [78].

In almost all reports, a key determinant of NADC prognosis among HIV-infected patients was the lack of access to both antiretroviral and antiblastic chemotherapy [78-80]. According to a study performed by Suneja et al. in the USA, comparing treatment uptake in HIV-infected and uninfected cancer patients, the main predictors of treatment lack among HIV patients included higher and unknown stages, intravenous drug use and older age (45-64 years) [82]. Another study conducted in the USA found that prostate cancer and Hodgkin lymphoma were treated differently in HIV-infected as compared to HIV-uninfected people [83]. The persisting, although narrowing, gap in cancer survival indicates the need for enhanced therapeutic approaches, to give HIV patients the same survival opportunity observed in the general population. Furthermore, a special effort should be dedicated to the improvement of cancer prevention and screening programs.

Cancer survival among people with HIV infection was usually described in developed countries, whereas little information is available from developing countries [84, 85]. In a study conducted in Sao Paulo, Brazil, based on a probabilistic record linkage between the Cancer and the AIDS Registry, the overall survival after diagnosis of any NADC was lower in people with than without AIDS [84]. The disparity was mainly observed in the first year after cancer diagnosis, and was attributed to the persisting lack of national guidelines for the management of malignancies in HIV-infected people in Brazil. Especially in resource-limited settings, therapeutic chances may be limited for subjects with HIV infection, which is often an exclusion criterion in randomized controlled trials [85].

5. EPIDEMIOLOGY OF SPECIFIC NADCS

5.1. Lung Cancer

Lung cancer is one of the most frequent NADCs occurring in subjects living with HIV. In fact, besides its high prevalence in the general population, lung cancer is well known for an even more frequent occurrence in subjects with HIV infection: SIRs higher than 2 have been reported by almost all studies comparing incidence rates between HIV-infected people and the general population [86]. According to a large American population-based registry, lung cancer is also the most frequent cancer-related cause of death among people with HIV infection [87]. Interestingly, most subjects are asymptomatic when diagnosed with lung cancer, and the mean age at diagnosis is between 45 and 50 years, 5 to 10 years lower than in the general population [88].

The risk excess is considerable for all the main subtypes of lung cancer (adenocarcinoma, squamous cell carcinoma and small cell carcinoma). More than 80% of all lung cancers observed among HIV-positive subjects were non-small cell histological subtypes: in particular adenocarcinoma was the most frequent type, as well as in the general population [89].

The relationship between lung cancer and smoking is well known: the relevant impact of this risk factor may overcome other possible secondary causes, as almost 60% of subjects with HIV infection were smokers, according to some surveys conducted in high-resource countries [69-70]. Nevertheless, a meta-analysis evaluating the incidence of NADCs in transplant recipients and in HIV infected individuals found that SIRs for tobacco-related cancers were not significantly higher in the HIV/AIDS cohorts [13, 90]. This evidence was not consistent with the hypothesis that tobacco smoke was the key determinant of lung cancer in subjects with HIV infection, considering the huge difference in smoking rates in these two populations. In fact, tobacco smoking was as frequent in kidney transplant recipients as in the general population, whereas it was twice as frequent in people with HIV/AIDS [69]. Moreover, in a retrospective cohort study including more than 5,000 HIV-infected subjects, a higher risk of lung cancer was observed as compared to the
general population (SIR 2.5), even after adjusting for tobacco smoking [33]. The role of HIV as a possible causal factor of lung cancer is still controversial. Although viral sequences were absent in neoplastic cells, a possible effect of HIV was hypothesized, as it was proven the role of HIV-1 Tat protein in the modulation of proto-oncogene expression in bronchoalveolar carcinoma cell lines [45].

The ageing of the HIV population is also an important cofactor for lung cancer risk, while the role of immune system deterioration is still not entirely clear [91]. Indeed, it was hypothesized that the impact of HIV on the immune system may lead to reduced tumor surveillance also in the setting of lung cancer, with higher SIRs in patients with lower CD4 counts and in subjects with AIDS [30, 92].

Mortality rates were higher among HIV-positive patients, both treated and untreated, than in the general population [93, 94]. At least in part, this was probably due to treatment disparities between the two groups, only partially motivated by the evidence of higher risk of chemotherapy toxicity and surgical procedures [94, 95]. As for the general population, unfavorable prognostic factors of lung cancer were more advanced stages, poor performance status, and lack of therapy against the disease [96]. Antiretroviral therapy showed a positive impact on survival rates [97].

5.2. Hepatocellular Carcinoma

After the introduction of HAART, HCC incidence was observed in different cohorts, with rates ranging from 10 to 36 new cases per 100,000 HIV-infected people per year [86, 91, 98]. The corresponding HCC risk was 3- to 6-fold higher in HIV than in general population [86].

As for other NADCs, HCC incidence increased after the introduction of HAART, along with the ageing of the HIV population. Nonetheless, some recent data obtained by the US HIV/AIDS Cancer Match Study suggest a possible changing scenario, at least in the American epidemiological trends: while HCC cases increased from 1991 to 2005 among subjects with HIV infection [25], a reduction in the standardized incidence ratio has been observed in a more recent evaluation of the same cohort, focusing on the post-HAART period and evaluating the period from 1996 to 2012 [99].

It is well known that subjects with HIV infection are at higher risk for HBV and HCV infections as compared with the general population [57-59], and HCV and HBV represent the main risk factors for HCC worldwide. Besides them, in most studies, concomitant HIV infection per se and lower CD4 cell counts were also independently associated with increased risk for HCC, regardless of HAART era [40].

This was consistent with the observation that HIV-induced immunosuppression and immune activation, caused by microbial translocation in the gut, increased the risk of HCC through an acceleration of liver fibrosis process [100]. Moreover, hepatocytes apoptosis may be promoted by the upregulation of TNF by the HIV surface protein gp120 [58]. In many cohorts of subjects with HIV infection, another factor that could worsen liver damage was the abuse of alcohol and other substances with direct hepatotoxic effects [101].

HCC was one of the main causes of death for people with AIDS between 1999 and 2006 [102]. Prognostic factors impacting on survival were the re-treatment options at HCC recurrence, and tumor characteristics. HIV-infected subjects did not show relevant prognostic differences when compared to the general population [103]. Indeed, although liver transplantation represents one of the possible therapeutic option also for HIV-infected HCC patients, direct drug-drug interactions and the immune deterioration in the context of anti-rejection immunosuppressive treatments are concerns and pose challenging questions [104].

5.3. Anal Carcinoma

Incidence rates of anal cancer are reported between 15 to 24 cases per 100,000 HIV-infected people per year among HIV-infected persons in the USA and Europe [86, 98]. Whereas anal carcinoma is uncommon in the general population, it is one of the most common NADCs among HIV-positive patients, with reported excess risk ranging from 20- to 50-fold in cohort studies [86, 99]. The mean age at presentation is 45-50 years and it is more frequently observed in MSMs, in men reporting intravenous drug use and women [105].

As previously noted, the main cause of anal carcinoma is HPV acquired through sexual transmission, mainly involving HPV-16 [62-64]. The most common histological type is squamous cell carcinoma, arising from precursor high-grade anal intraepithelial lesions (AIN) [106]. Indeed, the oncogenic mechanisms leading to this specific cancer are not confirmed yet. Despite the suggestion that HPV oncogenic mechanisms are similar in cervix and anus, biological models of anal carcinogenesis are still unclear [107]. The role of immune deficiency was hypothesized, as anal carcinoma risk was associated with the cumulative duration of low CD4 count in the period preceding the evolution from AIN to cancer [108]. This evidence suggested that cancer progression may be linked to previous immune disruption, leading to the development of an oncogenic process even in the context of an ongoing immune reconstitution. On the other hand, SIRs for anal cancer in HIV subjects decreased over time, with the more efficient control of HIV replication; this suggested a possible role of the antiretroviral treatment in suppressing the effect of HIV infection on HPV carcinogenesis [99]. Moreover, it was observed that lower HIV viral load was associated with a reduced risk of anal cancer [109].

In HIV-infected patients with invasive anal carcinoma, the prognosis improved steadily during the last decades, reducing the gap with the uninfected population [110]. Recent comparisons showed similar toxicity rates between HIV-positive and negative patients, and similar trends with regards to progression-free, colostomy-free and cancer-specific survival [110, 111]. Moreover, HAART improved the tolerability to concurrent radiation and chemotherapy, including cisplatin plus 5-fluorouracil. Other significant predictors of survival were age, sex, the evidence of metastasis at diagnosis, and lower comorbidity status [112].

5.4. Hodgkin Lymphoma

In immunosuppressed patients, Hodgkin lymphoma occurs more frequently than in the general population. In HIV subjects, the incidence rate of Hodgkin lymphoma is 22-82 new cases per 100,000 per year, corresponding to a 10-
20-fold excess risk in comparison with the general population [17, 86].

Noteworthy, incidence rates for Hodgkin lymphoma among subjects with HIV infection decreased by 4% per year between 1996 and 2010, according to the US HIV/AIDS Cancer Match Study [99]. Moreover, the SIR for Hodgkin lymphoma declined at a rate of 3% annually since 1996. In a study conducted among US veterans, lower HIV-RNA viral load was associated with lower risk of Hodgkin lymphoma, demonstrating the beneficial effect of prolonged control of HIV viral load in the prevention of this NADC [113].

Hodgkin lymphoma is associated with EBV in most HIV-patients [114]. On the other hand, the relationship between an ongoing viral infection and immune system deterioration is still poorly understood: inconsistent data emerged from cohort studies, and peculiar pathological findings were observed, such as the sequestration of lymphocytes at the tumor site, in the context of Hodgkin lymphoma [60, 115]. In particular, in the Swiss HIV Cohort Study, increased Hodgkin lymphoma risk was associated with lower CD4/CD8 ratio, suggesting a possible beneficial effect of the immune system restoration [115]. On the contrary, some clinical observations seemed to confirm the hypothesis that a moderate immune activation or reconstitution after HAART introduction may increase B-cell stimulation, the burden of EBV–infected lymphocytes and the consequent risk of Hodgkin lymphoma development [116].

The role of concomitant antiretroviral treatment was clearly demonstrated in the context of Hodgkin lymphoma chemotherapy. In fact, while standard Adriamycin/ Bleomycin/ Vinblastin/ Dacarbazine treatment, without antiretroviral treatment obtained low complete response (CR) and OS rates [117], the current strategy combining the use of antiretrovirals and chemotherapy allowed significant improvement in CR, OS and event-free survival rates [118]. This achievement was reached with the strategy applied in the general population: chemotherapy, radiotherapy if appropriate, possibly second line approaches (high-dose chemotherapy and autologous stem cell transplantation), strategies to support the immunological recovery (e.g. granulocyte-colony stimulating factor), and appropriate prophylactic and therapeutic measures against opportunistic infections [119]. Particular attention deserves the possible emergence of drug-drug interactions with antiretrovirals, potentially involved in the increase of neurological and cardiologic toxicities induced by chemotherapy: this contingency frequently leads to a switch to antiretrovirals with lower potential interactions and careful monitoring of dose-related toxicities [120].

5.5. Other NADCs

Several studies reported a high incidence of cutaneous malignancies in immunosuppressed patients [13, 36, 121]. This excess risk was higher in solid-organ transplants recipients (SIRs > 60 in comparison with the general population), that also had a higher frequency of squamous cell carcinoma (SCC) [13, 122]. On the contrary, in HIV positive patients, the most frequent skin NADC was basal cell carcinoma (BCC), with a ratio of BCC to SCC of 6:1 [121].

In a study performed after the introduction of HAART, a significantly higher risk of developing acute myeloid leukaemia was reported, with an incidence rate twice as high as in the general population. In this study, in most subjects, a complete remission was obtained using an intensive chemotherapy regimen [123]. More recent morbidity and mortality reports observed lower incidence of leukemia, at least partially explained by the better immunological conditions of patients in these cohorts. In fact, low CD4 cell count affects the risk of leukemia and the prognosis of this NADC [124].

The incidence of mouth and pharynx cancers was 4-fold higher than in the general population, in a study conducted in the Swiss cohort from 1985 to 2002 [36]. This could be due to the high frequency of tobacco smoking, as well as to the impact of HPV co-infection [66].

According to a study performed by Goedert et al. in the USA, the pattern of women cancers incidence was significantly different in HIV than in general population: lower incidences of breast (SIR 0.69) and uterine corpus cancers (SIR 0.57), but not of ovary cancer (SIR 1.05) were reported [125]. As regards the lower incidence of breast cancer in HIV infected women, a possible explanation was the impairment of endogenous sexual hormone levels, and the ability of HIV to infect breast cells and reduce their proliferation [125]. Nevertheless, no variation in breast cancer screening was suggested: indeed, between 1980 and 2002 this risk increased in HIV women, approaching that of the general population. The authors concluded that the breast cancer deficit reflected direct or indirect effects of HIV and that HAART introduction contributed to reduced them.

Changes in hormone levels were hypothesized to play a protective role also against prostate cancer, as the incidence of this malignancy was lower among HIV-infected men as compared to the general population [17, 31].

Interestingly, different geographical areas may show the emergence of specific NADCs patterns, not observed and described so far, such as the high frequency of stomach cancer in a cohort of Asian people living with HIV infection [126]. Even though the cohort was not representative for the whole Asian continent, this finding confirms the heterogeneity of NADC geographical distribution.

CONCLUSION

Several data emerging from international cohort studies recently revealed the relevant impact of NADCs on people living with HIV worldwide, suggesting their possible increasing role in the future [127]. This trend will have a deep impact on morbidity and mortality rates, but also on the perception of health and quality of life in this population [7-10]. Indeed, although increased life expectancy was achieved in the last decades, narrowing the gap with the general population, the incidence of NADCs was not affected by the immune reconstitution achieved in subjects currently treated for HIV infection [9-11].

As several interacting factors should be taken into account to explain the persistence of NADC risk, further research is needed to better understand underlying pathological mechanisms and possible solutions, for example exploring the correlates of the premature ageing of HIV population, such as inflammation and deterioration of immune surveillance against cancer [73].
High-risk behaviors (e.g. tobacco smoking) and co-infections with potentially oncogenic viruses (more frequent in the HIV population) have a well-documented role and should be the targets of specific public health programs [128].

A direct role of HIV and the mutagenic effect of some antiretrovirals were also proposed as possible risk factors, but more epidemiological evidence is needed to prove their impact on NADC incidence. On the contrary, robust evidence is available about the beneficial impact of an early antiretroviral introduction on the risk of developing NADCs [42, 43, 77].

Whatever the cause of NADC occurrence in the setting of HIV infection, the increasing incidence of some cancers deserves special attention by HIV clinicians. In particular, special attention must be paid to the screening and early diagnosis of some of the most frequent NADCs, especially considering the ageing of HIV population [129, 130]. These good clinical practices are well defined and reported in international guidelines for the screening of liver and anal cancers, whereas they should be implemented in the field of lung cancer and Hodgkin lymphoma, to provide early diagnosis [131].

With regard to some specific NADCs, if all treatment options are guaranteed to HIV infected patients, overall survival is similar in HIV and general population [110, 119]. This evidence emphasizes the need to extend treatment options to all subjects living with HIV infection, allowing a careful and multidisciplinary evaluation of the oncologic comorbidity.

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