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# TRENDS AND PREDICTORS OF NON AIDS-DEFINING CANCERS IN MEN AND WOMEN WITH HIV-INFECTION. A SINGLE-INSTITUTION RETROSPECTIVE STUDY BEFORE AND AFTER THE INTRODUCTION OF HAART.

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**RUNNING HEAD**: NON AIDS-DEFINING CANCERS IN ADULTS WITH HIV

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**ABSTRACT**

**Background**: The incidence of non-AIDS defining cancers (NADCs) in HIV-positive patients has increased over recent years. Most studies of the risk and spectrum of NADCs are primarily based on male populations and only a few have provided specific information regarding females.

**Methods**: We retrospectively analysed all incident NADCs occurring in a cohort of HIV-positive patients followed up between 1985 and 2011. Incidence rates before and after the introduction of highly active antiretroviral therapy (HAART) were examined using Poisson regression models. Standardised incidence ratios (SIRs) were used to compare the cancer risk of HIV-infected subjects with that of the age- and gender-matched general population as estimated by the Milan Cancer Registry.

**Results**: 5,924 patients (4,382 males and 1,542 females) contributed 50,990 person-years (py) to the follow-up. Among them 144 had new NADC diagnosis. The overall incidence increased from 1.0 case/1,000 py in the pre-HAART period to 4.5 cases/1,000 py in the HAART period ($p < 0.01$). In women, the risks were higher than expected in the case of cancer of the vulva (SIR 69.2), Hodgkin lymphoma (SIR 7.5), anal cancer (SIR 41.2), and lung cancer (SIR 4.8). In men, the risks were higher than expected in the case of anal cancer (SIR 91.5), Hodgkin lymphoma (SIR 13.0), tonsil cancer (SIR 10.9), lung cancer (SIR 2.1), and liver cancer (SIR 7.1).

**Conclusions**: The spectrum and incidence of NADCs in our cohort increased over time. The incidence of NADCs, especially virus- and smoking-associated cancers, was significantly higher than expected in HIV-positive men and women.

**KEY WORDS:**

HIV infection;

Antiretroviral therapy;

Non AIDS-defining cancers

## INTRODUCTION

HIV infection is associated with an increased risk of a range of cancers, including Kaposi's sarcoma, non-Hodgkin lymphoma and cervical cancer, which are considered virus-related and AIDS-defining diseases [1-2]. The advent of highly active antiretroviral therapy (HAART) has significantly changed the natural history of HIV disease by greatly reducing the incidence of AIDS-defining events (including AIDS-defining malignancies), and substantially improving the patients' life expectancy [3-4].

Recent cohort studies have consistently reported an increased risk of non-AIDS-defining cancers (NADCs), whose incidence does not seem to be influenced by HAART [4-8]. A recent meta-analysis by Shiels *et al.* [9] has shown that twice as many NADCs occur in HIV-positive subjects than in the general population, with excess risks in the case of infection-related (liver cancer and Hodgkin lymphoma) and smoking-related cancers (lung, laryngeal and kidney tumours). Moreover, despite the immunoreconstitution induced by HAART, excess NADC mortality has been reported among HIV-1 infected patients [10].

The potential mechanism underlying the increased risk of developing NADCs in the HIV-infected population probably involves complex interactions of multiple known and unknown factors. In addition to aging [11], an effect due to increased life expectancy, other contributing factors are: i) a high prevalence of co-infection with potentially oncogenic viruses (i.e. human papilloma virus, hepatitis B and C viruses), which may be less efficiently controlled by the compromised immune system of HIV-infected patients [12-14]; ii) a high prevalence of high-risk behaviours such as tobacco smoking [15]; and iii) the effects of HIV infection, including direct viral effects [16], and the consequences of immunosuppression, with long-lasting immunosurveillance impairment possibly due to the disruption of various immune repertoires [17]. It has also been speculated that the mutagenic effects of some antiretrovirals may have an adverse effect on the risk of NADCs, but the evidence is so far inconsistent [18].

Most studies of the incidence and spectrum of NADCs give results for both genders combined (with a predominance of men), and only a few have provided specific information concerning the frequency and characteristics of NADCs in women [9]. As there may be gender-related differences in the occurrence of specific NADCs, more data may help to define prevention and management strategies.

We examined the incidence rates and characteristics of NADCs in a cohort of 5,924 HIV-positive men and 1,542 HIV-positive women attending a single HIV Clinical Centre in Milan, Italy.

## METHODS

Since 1985, the clinical data of all HIV-infected patients receiving continuous care at the L. Sacco Department of Clinical Science of the University of Milan have been prospectively entered in a database. Their demographic data and medical history, the mode of transmission, the date of the first positive HIV test, CD4 cell counts, and HIV RNA load (as from 1997) are prospectively updated every three months, and any new medical diagnoses, hospitalisations, pharmaceutical prescriptions, and laboratory and radiographic findings are recorded.

A retrospective analysis was made of the data relating to all of the HIV patients with at least six months' follow-up consecutively enrolled between 1 January 1985 and 31 December 2011. All of the incident cases of pathologically confirmed malignancies not classified as AIDS-defining diseases were identified and considered for the analysis, which included only the first incident NADC.

The Mann-Whitney non-parametric test and Pearson's chi-squared test (or Fisher's exact test, when necessary) were respectively used to compare the continuous and categorical variables in the male and female populations.

Person-years at risk for each HIV-positive subject were calculated from the date of HIV diagnosis to death, the last follow-up visit, or NADC diagnosis (whichever occurred first).

NADC incidence rates were calculated as the number of cases per 1,000 person-years, and Poisson's regression was used to compare the rate in the period 1985-1996 (the pre-HAART era) with that observed in the period 1997-2011 (the HAART era).

The incidence of NADC per 1000 person years of follow up was also analysed by stratifying the patients by current CD4 cell count and current HAART use. The incidence rates were calculated by accruing follow-up periods within the current CD4 cell count strata of <200/μL, 200-500/μ L and >500/μL. Person-years of follow-up were counted from the time of each CD4 determination to the next, and censored when the most recent CD4 cell count was >6 months old.

Univariate and multivariate hazard ratios (HRs) were calculated by means of Cox proportional hazard regression models in order to evaluate the effects of gender, age, risk factor (as fixed covariates), and AIDS diagnosis, nadir CD4 cell counts and the use of HAART (as time-dependent covariates). HAART was defined as the use of at least three antiretroviral agents in accordance with the published guidelines [19].

In order to compare the rates of specific cancers with those observed in the general population, the standardised incidence ratios (SIRs) and 95% confidence intervals (CIs) (Byar's approximation of Poisson's method) were calculated using the number of expected cases based on the general population gender- and age-specific rates for Milan provided by the Milan Cancer Register (MCR) [20]. The area covered by the MCR is the metropolitan area of Milan, which has about 1.3 million inhabitants and includes 29 hospitals coordinated by Milan's local health authority. The MCR has been operative since 1999, and the data are updated to 2006. We are aware that the period covered by the MCR is shorter than the period of our study, but the MCR is the only source of information regarding the incidence of specific cancers in Milan's general population. It is also

important to note that the majority (60%) of the NADC events observed in our cohort were reported during the period covered by the MCR.

## RESULTS

The cohort consisted of 5,924 patients with more than six months of follow-up enrolled between 1 January 1985 and 31 December 2011, who contributed to a total of 50,990 person-years of follow-up; the 1,542 females (26.0%) contributed 14,540 person-years. In the pre-HAART period (1985-1996), 4,453 patients contributed 24,536 person-years; in the HAART period (1997-2011), 3603 patients contributed 26,454 person-years: 59.2% (2,132/3,603) contributed to both periods.

A total of 144 NADCs were diagnosed during the study period: 113 in men (22 in the pre-HAART and 91 in the HAART period), and 31 in women (three in the pre-HAART and 28 in the HAART period). Hodgkin lymphoma (HL) and lung cancer were the most frequent NADCs in both periods. There was a significant expansion in the spectrum of NADCs in the HAART period, including previously unseen cancers, such as anus and liver cancer (hepatocellular carcinoma in almost all cases) in the men, and breast, anus, and vulva cancer in the women (Figure 1).

Table 1 shows the demographic and clinical characteristics of the patients at the time of NADC diagnosis. There were no significant gender differences in baseline characteristics, with the exception of a longer duration of HIV infection (16.0 *vs* 8.0 years; p=0.007) and higher percentage of intravenous drug users among females.

The overall incidence of NADCs was higher during the HAART period in both males (from 1.2 cases/1,000 py [95% CI 0.7-1.8] in the pre-HAART period to 4.9 cases/1,000 py [95% CI 3.9-5.9] in the HAART period) and females (from 0.4 cases/1,000 py [95% CI 0-0.9] to 3.6 cases/1,000 py [95% CI 2.3-5.0].

There was a decrease in the incidence of NADC with the increase in current CD4 counts both in patients on and off HAART that was not statistically significant. When the patients were on HAART, the incidence was 6.3 cases/1,000 py (95% CI 3.1-9.5) in the patients with <200 cells/μL, 3.8 cases/1,000 py (95% CI 2.3-5.4) in the patients with 200-500 cells/μL, and 3.5 cases/1,000 py (95% CI 3.1-5.0) in those with >500 cells/μL; the corresponding figures in the patients off HAART were 4.5 cases/1,000 py (95% CI 2.0-6.9), 2.4 cases/1,000 py (95% CI:1.2-3.7), and 2.0 cases/1,000 py (95% CI: 0.7-3.2).

Univariate analysis showed that the patients who subsequently developed NADCs were older at the time of enrolment (34.6 *vs* 31.0 years; p<0.001) and more frequently males (78.5% *vs* 73.9%, p=0.047). Homosexual males were significantly more represented among the subjects who developed NADCs than among those who did not (22.9% *vs* 19.2%, p=0.028). A higher proportion of patients who developed NADCs had a previous AIDS diagnosis (43.8% *vs* 42.5%; p<0.001), a nadir CD4 cell count of <200 cells/μL (65.3% *vs* 59.7%; p<0.001), and a history of HAART (72.9% *vs* 46.2%; p=0.001). Multivariate analysis showed that age, an AIDS diagnosis and a nadir CD4 count of <200 cells/μL were independently associated with the risk of developing NADC (Table 2).

Table 3 shows the expected cases and corresponding SIRs for all of the NADCs observed during the study period. The SIR for all of the NADCs combined was 1.9 (95% CI 1.5-2.2) in men and 1.5 (95% CI 1-2.2) in women. The observed incidences were higher than expected in the case of anus cancer (SIR=91.5, 95% CI 52.3-148.6 in males; 41.2, 95% CI 4.6-148.8 in females), vulva cancer (SIR=69.2, 95% CI 22.3-161.4), tonsil cancer (SIR=10.9, 95% CI 1.2-39.4 in males), Hodgkin lymphoma (SIR= 13.0, 95% CI 8.5-19.1 in males; 7.5, 95% CI 2.0-19.3 in females), liver (SIR=7.1, 95% CI 4.2-11.2 in males), and lung cancer (SIR= 2.1, 95% CI 1.3-3.4 in males; 4.8, 95% CI 1.3-12.2 in females).

After stratifying the SIRs of possibly human papillomavirus (HPV)-related cancers in the male population by their reported risk factor, the SIR of anal cancer was 160.0 (95% CI

68.9-315.0) among homosexuals and 83.3 (95% CI 26.9-194.5) among the patients who reported being infected as a result of intravenous drug use (IDU).

## DISCUSSION

We assessed the 26-year trends of the frequency and spectrum of NADCs in one of the main reference centres for HIV infection in Italy. Cohort enrolment started at the beginning of the AIDS epidemic and reflects epidemiological trends in Southern Europe, which are characterised by a marked prevalence of intravenous drug users and the significant involvement of women.

The increased incidence and broader spectrum of NADCs in the HAART period is in line with the findings of other studies [4-8]. However, in addition to confirming this trend in males, our study allowed us to find a similar trend in women, who were under-represented or whose risk was not separated from that of men in many previous studies.

There is conflicting evidence as to whether HAART itself has some effect on the risk of developing NADCs [21]. Among patients with NADC diagnosis, 105 (72.9%) had a previous history of antiretroviral treatment, but the use of HAART was not associated with a higher risk of developing NADCs at multivariate analysis, which identified age, a nadir CD4 count of <200 cells/μL, and a previous AIDS diagnosis as predictors of NADCs.

Aging is a known risk factor for a number of cancers, and has been confirmed to be independently associated with NADCs by other studies [6,8].

It has also been widely reported that, unlike AIDS-related malignancies, NADCs are not strictly associated with a high degree of immunodepression at the time of diagnosis [22-23] and, in our study, only 36.1% of the patients had CD4 counts of <200 cells/μL at that time. Furthermore, the hypothesis that a low CD4 cell nadir and current CD4 cell counts have an effect on the risk of NADC is supported by the findings of some recent studies [24, 25] but not confirmed by others [26-27].

In our study, the incidence of NADCs decreased with the increase in current CD4 counts regardless of whether the patients were on HAART or not, but this trend was not statistically significant. However, we cannot exclude the possibility that the retrospective nature of our study, the relatively small number of events, and the difference in the frequency of CD4 cell counts between the pre- and post-HAART periods might have limited our analysis. Conversely, a nadir CD4 cell count of <200 cells/μL was independently associated with a higher risk of developing NADCs. These findings support the hypothesis that immunological recovery in patients with previously severe immunodeficiency may not decrease the risk of NADCs, possibly because the recovery is incomplete. Larger prospective studies are needed to clarify the effects of the time-dependent severity and duration of immunosuppression on the risk of developing NADCs.

Cancers with a known or suspected infectious cause and smoking-related cancers accounted for 75% of the NADCs observed in our cohort. HL was the most frequent, and the excess risk for this cancer was similar to that reported in other studies for both genders [28]. HL is almost always associated with Epstein-Barr virus (EBV) in HIV-infected subjects, and is more frequent in patients with moderate immune suppression [29]; this has raised a number of still unanswered questions concerning the relationship between the degree of immunodeficiency, persistent viral infection and cancer, and it has also been suggested that the immune reconstitution induced by HAART may increase the risk of HL by increasing B cell stimulation and the number of EBV-infected lymphocytes [30].

The patients in our cohort showed a significantly higher incidence of anal carcinoma in comparison with the general population. The risk of anal cancer was especially high in homosexual males, as described in many other studies [9], but was also high in males reporting IDU and women. The women also had a significantly increased risk of vulva carcinoma. There is considerable evidence indicating an association between ano-genital cancers and human papilloma virus (HPV) infections, and HIV-infected subjects are

disproportionately infected with HPV, particularly high-risk HPV strains [12-13]. Moreover, the interactions between HIV and HPV allows for persistence of HPV infection possibly leading to dysplasia and cancer [31]. There is also evidence that HAART does not clear HPV infection, reduce the incidence of precursor ano-genital cancer lesions, or induce the regression of existing high-grade lesions [32-33].

It is worth noting that the HIV-positive males had an excess of tonsil cancer in comparison with the general population, a finding very similar to that reported by Frisch *et al*. [34]. Both tonsil cancers we observed were histopathologically identified as squamous cell tumours. This is interesting because recent data have shown that, together with smoking and alcohol, HPV may play a role in the development of squamous cell carcinomas arising from the lingual and palatine tonsils [35]. A recent study found high-risk HPV genotypes closely associated with cancer in the oral region of 4.5% of HIV-seronegative and 13.7% of HIV-seropositive subjects, and univariate analysis showed that tonsillar HPV infection closely correlated with HIV infection, immunosuppression and sexual behaviour [36].

We found an increasing number of liver cancers (hepatocellular carcinoma in 17 out of 18 cases) and an excess risk among males, but no cases among females. This gender-related disparity in the incidence of liver cancer is similar to that observed in the general population. Liver injury caused by HBV and HCV infections are the major risk factors for HCC, with the vast majority of cases developing in the presence of underlying cirrhosis [38]. Of the 18 patients with a diagnosis of liver cancer, 13 were chronically infected with HCV, two were chronically infected with HBV, one was chronically infected with both, and only two (one with bile duct cancer) had no history of hepatitis virus infection.

Since 1992 (when we started systematically recording information about hepatitis virus serostatus), there has been a high prevalence of HCV (36.4%) and HBV co-infections (9.6%): the prevalence rates were respectively 37.5% and 10.9% in males, and 10.9% and 6.1% in females. Although the information concerning HBV and HCV serostatus is

incomplete for the years preceding 1992, the higher prevalence of HBV and HCV co-infection in males may partially explain the different incidence of liver cancer in the two genders. It is also possible that hormonal factors (i.e. the stimulatory effect of androgen and the protective effect of estrogen) may somehow influence the difference in the risk of liver cancer in HIV-positive men and women, a hypotheisis that is supported by the findings of epidemiological and experimental studies [39].

Lung cancer was significantly more frequent than in the general population among both males and females. It has been reported that cigarette smoking is far more common in HIV-infected subjects than in the general population, and that this contributes to increasing the rates of lung cancer in both men and women [40-41]. Since 1998, when we started systematically recording information about cigarette smoking, 55% of the subjects (54.8% males and 58.2% females) have reported smoking addiction. Although the lack of previous records precluded the inclusion of smoking as a possible correlate of NADC risk in our regression model, these data confirm the high risk of smoking for both men and women, as found in other cohorts [15].

Finally, we observed a relatively modest number of cases of melanoma and did not find any increased risk in comparison with the general population. This is in line with the findings of some other studies [42,43], including a linkage analysis of a large Italian population [44 ], but conflicts with others indicating an increased risk, particularly in men [6,7,45]. The differences in melanoma SIRs between studies may be due to differences in latitude and dissimilarities in the study populations (i.e. HIV risk factors, age, ethnicity/genetics, life style, etc.).

This study has some limitations that have been mentioned above, such as the fact that information concerning viral co-infections and smoking habits was not available for the earlier years of the study period. Moreover, as this was a single-centre study, the relatively

few incident cases of cancer does not allow an analysis of the time trends of site-specific tumours.

Nevertheless, our findings confirm the increasing incidence and broadening spectrum of NADCs, and highlight the need to monitor HIV-infected men and women carefully for their occurrence. In particular, HIV-infected women show an excess risk of virus-related cancers (with the exception of liver cancer) and lung cancer that is similar to that observed in HIV-positive males.

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**FIGURE LEGENDS**

**Figure 1. Distribution of non AIDS-defining cancers during the study period.**

**Table 1. Demographic and clinical characteristics of 144 HIV-infected subjects (113 males and 31 females) at the time of NADC diagnosis.**

| Characteristic | Total N=144 | Females N=31 | Males N=113 |
|---|---|---|---|
| Period of diagnosis, n (%) | | | |
| 1985-1996 | 25 (17.4) | 3 (9.7) | 22 (19.5) |
| 1997-2012 | 119 (82.6) | 28 (90.3) | 91 (80.5) |
| Median age, years (range) | 44 (23-78) | 42 (23-58) | 45 (23-78) |
| Age, n (%): | | | |
| 18-30 | 10 (6.9) | 3 (9.7) | 7 (6.2) |
| 31-40 | 38 (26.4) | 8 (25.8) | 30 (26.5) |
| 41-50 | 59 (41.0) | 17 (54.8) | 42 (37.2) |
| >50 | 37 (25.7) | 3 (9.7) | 34 (30.1) |
| Risk factor, n (%) | | | |
| Heterosexual | 36 (25.0) | 12 (38.7) | 24 (21.2) |
| Homosexual | 33 (22.9) | - | 33 (29.2) |
| Intravenous drug users | 64 (44.4) | 16 (51.6) | 48 (42,5) |
| Other*/unknown | 11 (7.6) | 3 (9.7) | 8 (7.1) |
| Median duration of HIV-infection, years (range) | 9,6 (1-27) | 16,0 (1-23) | 8,0 (1-27) |
| Previous AIDS diagnosis, n (%) | 63 (43.8) | 11 (35.5) | 52 (46.0) |
| CD4 nadir, median cells/$mm^3$ (range) | 115 (1-1185) | 141 (8-467) | 109 (1-1185) |
| Nadir <200 CD4 cells/$mm^3$, n (%) | 94 (65.3) | 23 (74.2) | 71 (62.8) |
| Current CD4 cell count, median cells/$mm^3$ (range) | 286 (2-1659) | 328 (12-948) | 262 (2-1659) |
| Current <200 CD4 cells/$mm^3$, n (%) | 52 (36.1) | 8 (25.8) | 44 (38.9) |
| On HAART, n (%) | 78 (54.2) | 21 (67.7) | 57 (50.4) |
| Median HIV-RNA copies/mL | 132 (49-500000) | 49 (49-127289) | 205 (49-500000) |
| <50 HIV RNA copies /mL, n (%) | 48 (33.3) | 14 (45.2) | 34 (30.1) |

* Other: professional risk and transfusions.

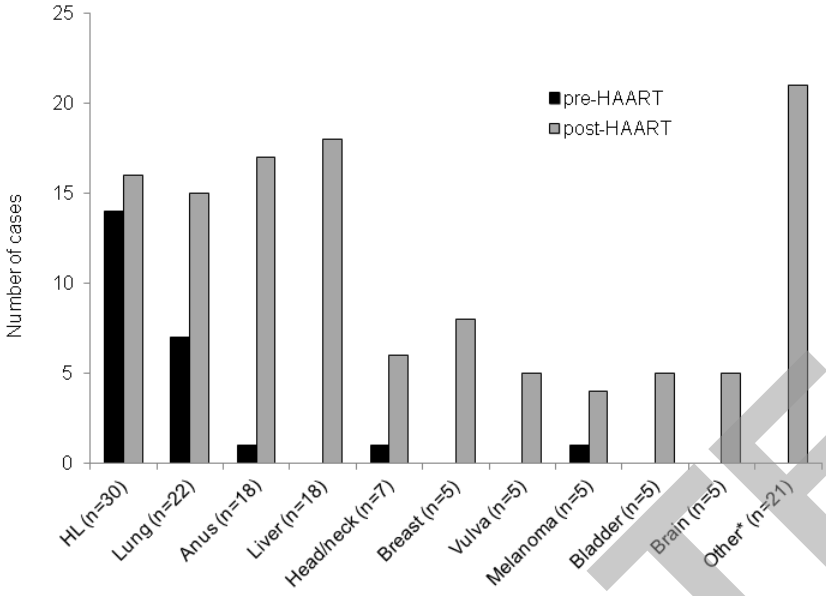
**Table 2. Main characteristics of the patients with and without NADCs and correlates of diagnosis of NADC (Cox proportional hazard regression models).**

| Characteristic | Patients with NADC n=144 (2.4%) | Patients without NADC n=5780 (97.6%) | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | | | HR (95% CI) | p value | HR (95% CI) | p value |
| Mean age at enrolment, years | 34.6 ± 11.8 | 31.0 ± 9.4 | 1.35 (1.26-1.44)[a] | <0.001 | 1.35 (1.24-1.47)[a] | <0.001 |
| Gender, n (%) | | | | | | |
| Women | 31 (21.5) | 1511 (26.1) | 1 | - | 1 | - |
| Men | 113 (78.5) | 4269 (73.9) | 1.50 (1.01-2.23) | 0.047 | 1.14 (0.74-1.76) | 0.547 |
| Risk group, n (%) | | | | | | |
| Heterosexuals | 36 (25.0) | 1501 (26.0) | 1 | - | 1 | - |
| Homosexuals | 33 (22.9) | 1109 (19.2) | 1.70 (1.06-2.73) | 0.028 | 1.40 (0.84-2.31) | 0.196 |
| Intravenous drug users | 64 (44.4) | 2854 (49.4) | 0.80 (0.53-1.21) | 0.286 | 1.29 (0.80-2.08) | 0.295 |
| Other[b] /unknown | 11 (7.6) | 316 (5.5) | 1.63 (0.83-3.20) | 0.159 | 1.38 (0.70-2.72) | 0.357 |
| AIDS before event[c, d], n (%) | 63 (43.8) | 2455 (42.5) | 2.51 (1.76-3.57) | <0.001 | 2.16 (1.52-3.08) | <0.001 |
| HAART before event[c, d], n (%) | 105 (72.9) | 2669 (46.2) | 2.01 (1.33-3.06) | 0.001 | 1.35 (0.87-2.08) | 0.176 |
| Nadir CD4 <200 cells/mmc[c, d], n (%) | 94 (65.3) | 3452 (59.7) | 1.93 (1.34-2.77) | <0.001 | 1.58 (1.10-2.26) | 0.013 |

[a] For every five years older
[b] Other: professional risk, transfusions, vertical transmission
[c] Event: diagnosis of a NADC, death or end of follow-up, whichever occurred first
[d] Time-dependent variable adjusted for age, gender, and risk group

**Table 3. Standardised incidence ratios (SIRs) of NADCs in 1542 women and 4382 men with HIV infection, 1985-2011.**

| Cancer site/type | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | Observed | Expected | SIR | 95% CI | Observed | Expected | SIR | 95% CI |
| Hodgkin lymphoma | 26 | 2.0 | 13.0 | [8.5-19.1] | 4 | 0.5 | 7.5 | [2.0-19.3] |
| Lung | 18 | 8.4 | 2.1 | [1.3-3.4] | 4 | 0.8 | 4.8 | [1.3-12.2] |
| Anus | 16 | 0.2 | 91.5 | [52.3-148.6] | 2 | 0.0 | 41.2 | [4.6-148.8] |
| Vulva | | | | | 5 | 0.1 | 69.2 | [22.3-161.4] |
| Liver | 18 | 2.5 | 7.1 | [4.2-11.2] | 0 | 0.1 | | |
| Colon/rectum | 3 | 6.6 | 0.5 | [0.1-1.3] | 0 | 1.2 | | |
| Stomach | 2 | 2.2 | 0.9 | [0.1-3.3] | 1 | 0.4 | 2.6 | [0-14.2] |
| Larynx | 3 | 1.7 | 1.7 | [0.4-5.1] | 0 | 0.0 | | |
| Tongue | 2 | 0.6 | 3.1 | [0.3-11.1] | 0 | 0.1 | | |
| Breast | 0 | 0.2 | | | 8 | 9.1 | 0.9 | [0.4-1.7] |
| Melanoma | 2 | 4.0 | 0.5 | [0.1-1.8] | 3 | 2.0 | 1.5 | [0.3-4.3] |
| Bone | 1 | 0.4 | 2.5 | [0-13.9] | 1 | 0.1 | 19.0 | [0.2-106.0] |
| Ovary | | | | | 3 | 0.8 | 3.8 | [0.8-11.1] |
| Pancreas | 3 | 1.5 | 2.0 | [0.4-5.9] | 0 | 0.1 | | |
| Kidney | 1 | 2.9 | 0.3 | [0-1.9] | 0 | 0.3 | | |
| Brain | 5 | 2.0 | 2.5 | [0.8-5.9] | 0 | 0.4 | | |
| Testis | 4 | 3.5 | 1.2 | [0.3-2.9] | | | | |
| Thyroid | 2 | 1.5 | 1.4 | [0.2-4.9] | 0 | 1.6 | | |
| Tonsil | 2 | 0.2 | 10.9 | [1.2-39.4] | 0 | 0.0 | | |
| Bladder | 5 | 4.6 | 1.1 | [0.4-2.6] | 0 | 0.3 | | |
| Prostate | 0 | 6.3 | | | | | | |
| Other | 0 | 1.1 | | | 0 | 0.2 | | |
| Any NADC | 113 | 60.9 | 1.9 | [1.5-2.2] | 31 | 20.3 | 1.5 | [1.0-2.2] |




HL= Hodgkin lymphoma
* Testis (n=4), ovary (n=3), colon/rectum (n=3), stomach (n=3), pancreas (n=3), bone (n=2), thyroid (n=2), kidney (n=1)