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Continuing declines in some but not all HIV-associated cancers in Australia after widespread use of antiretroviral therapy

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Abstract

Objective—To describe changes in cancer incidence in people with HIV in Australia since the introduction of highly active antiretroviral therapy (HAART).

Design—Population-based, retrospective cohort study of people with HIV (n = 20 232) using data linkage between national registers of HIV/AIDS and cancer in 1982–2004.

Methods—Age-adjusted and sex-adjusted incidence rate ratios with 95% confidence intervals were calculated to compare site-specific cancer incidence during the early (1996–1999) and late (2000–2004) HAART periods with that prior to HAART (1982–1995). Five-year age-specific, sex-specific, calendar year-specific, and state-specific standardized incidence ratios with 95% confidence interval were also calculated for each period.

Results—Incidence of Kaposi sarcoma and non-Hodgkin lymphoma declined significantly ($P_{trend} < 0.001$). Incidence of Hodgkin lymphoma was significantly higher during the early-HAART period (incidence rate ratio 2.34, 95% confidence interval 1.19–4.63) but declined thereafter ($P_{diff} = 0.014$). Incidence of anal cancer was unchanged ($P_{trend} = 0.451$) and remained raised more than 30-fold. Incidence declined significantly for melanoma ($P_{trend} = 0.041$) and prostate cancer ($P_{trend} = 0.026$), and, during the late-HAART period, was lower than in the general population for both cancers. Incidence of colorectal cancer was consistently lower than in the general population.

Conclusion—Incidence of Kaposi sarcoma and non-Hodgkin lymphoma has continued to decline among people with HIV in Australia, though it remains very substantially elevated. Incidence of Hodgkin lymphoma may now also be declining. Incidence of anal cancer has remained stable, and it is now the third most common cancer in HIV-infected Australians. Reasons for the reduced incidence of colorectal and prostate cancer, and more recently of melanoma, are unclear.

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Keywords

cancer; cohort studies; HAART; HIV; infection

Introduction

A broad range of cancers occurs at increased rates in people with HIV infection, most being cancers for which there is a known or suspected infectious cause [1]. Since the advent of HAART, a dramatic decline in the risk of AIDS-defining cancers, Kaposi sarcoma and non-Hodgkin lymphoma (NHL), has been consistently observed in cohort data [2-6]. Whether the risk of other cancers has also declined is less clear as there are fewer data on trends in cancer incidence in more recent years [2,4,5]. In Australia, previous reports of cancer risk in people with HIV have included follow-up only until 1999 [7].

There was rapid uptake of HAART in Australia in the late 1990s, since which time 70–80% of HIV-positive respondents in community-based surveys have reported HAART use [8]. Since 2000, the median $CD4^+$ T-cell count of HAART-treated patients enrolled in the Australian HIV Observational Database has been around 500 cells/μl [9]. Rates of HIV-associated disease in Australia are therefore likely to reflect those of a highly treated population. This article investigates changes in site-specific cancer incidence since the introduction of HAART, in a nationwide, population-based cohort of adults with HIV in Australia.

Methods

Study cohort

The study cohort included all adults (aged 16–80 years) with HIV in Australia in 1982–2004 (n = 20 232), as notified to the Australian National HIV/AIDS Registries. AIDS has been a notifiable condition in all states and territories of Australia since 1984, and testing for HIV antibody became widely available in early 1985.

Cancer data collection

Incident cancers were ascertained using probabilistic data linkage with the Australian National Cancer Statistics Clearing House (NCSCH), which contains data on all incident invasive cancers diagnosed in Australian residents since 1 January 1982, excepting nonmelanoma skin cancer [10]. Diagnoses of in-situ cancers are not recorded. Data linkage was based on a customized, researcher-defined algorithm, and specific clerical review rules, following the approach used in previous linkages [7,11]. Briefly, records were linked on name code (first two letters of the first and last name), sex, date of birth, and date of death (if deceased). A match was accepted if there was exact concordance in these fields. Inexact matches (n = 463 of 2844 total matches, 16%) were only accepted if supported by consistency between records in the state/territory and postcode of residence.

For each matched record, the date of diagnosis and ICDO-3 and ICD10 codes were obtained. General population cancer rates were also obtained. Approval for the study was granted by all Australian jurisdictional health departments and relevant institutional review boards.

Statistical analysis

AIDS-defining cancers—Consistent with previous Australian studies [12], analysis of AIDS-defining cancers was restricted to people with a known date of HIV diagnosis during the analysis period (n = 17 175, 85%). People notified only with AIDS were not included.

Follow-up was prospectively defined and commenced at the date of HIV diagnosis until the date of cancer diagnosis, 80 years of age, death, or 31 December 2004.

Other cancers—For all other cancers, person-years were accumulated until the date of cancer diagnosis, 80 years of age, death, or 31 December 2004. Follow-up commenced either from the date of HIV diagnosis (n = 14 013, 69%) or 5 years prior to AIDS if the date of HIV diagnosis was unknown (n = 1218, 6%) or preceded AIDS diagnosis by less than 5 years (n = 5001, 25%). Previous analyses in this cohort have shown that calculated rates of cancer in the 5-year period prior to AIDS are similar to those in people with HIV infection before AIDS diagnosis [13]. For all persons for whom follow-up was retrospectively defined, person-years were survival-adjusted to account for the effect on cancer incidence of the proportion of people who may have developed cancer and died prior to AIDS. Specifically, person-years were adjusted by applying the appropriate all-age, sex-specific cancer survival rates covering each yearly interval up to 5 years prior to AIDS. Australian National (1982–1997) [14] or South Australian (1977–1998) [15] population-based survival rates were used, these being the most comprehensive available at the time of analysis.

Cancer incidence—Incidence (per 100 000 person-years) was calculated for each type of cancer. Cancers were classified using ICD10, with the exception of Kaposi sarcoma and lymphoid and hematopoietic neoplasms, which were classified using ICDO-3 morphology codes. Kaposi sarcoma was defined by the code 9140; cases with the code 8000 (unknown morphology, n = 3) were accepted provided Kaposi sarcoma was indicated on the National AIDS Registry. Lymphoid and hematopoietic neoplasms were classified according to current guidelines [16]. Multiple myeloma (ICDO-3 9731–9734) was examined separately.

Cancer incidence was calculated across three time periods broadly representative of HAART availability in Australia, 1982–1995 (pre-HAART), 1996–1999 (early-HAART), and 2000–2004 (late-HAART). Individual-level data on HAART use were not recorded.

For cancers, or groups of cancers (oral cavity and oropharynx, colorectal) with at least 10 cases after HAART, standardized incidence ratios (SIRs) with 95% exact confidence intervals (CIs) were computed comparing the number of observed cases in each period with that expected based on the application of 5-year age-specific, sex-specific, state/territory-specific, and calendar-year-specific general population cancer incidence rates, assuming a Poisson distribution [17]. The exception was for Kaposi sarcoma, for which 1982 population rates were applied because of the impact of AIDS-related Kaposi sarcoma in later years.

Comparison of SIRs across calendar periods may be confounded by differences in the underlying age–sex structure of the cohort over time. Therefore, for each cancer, incidence rate ratios (IRRs) with 95% CIs were calculated comparing incidence during the early-HAART and late-HAART periods relative to that pre-HAART, after adjustment for current age (time dependent, single years) and sex. Age was modelled as a continuous variable for all cancers with the exception of Hodgkin lymphoma, for which it was also modelled categorically (<35, 35–59, 60+ years), based on the bimodal distribution of age-specific rates in the Australian general population (1982–2004).

For descriptive purposes, cancers were tabulated as infection-related or noninfection-related, as defined by the International Agency for Research on Cancer [18].

All analyses were performed using Stata version 10 (StataCorp LP, College Station, Texas, USA).

Results

AIDS-defining cancers

The study cohort for the analysis of AIDS-defining cancers included 17 175 people with a known date of HIV diagnosis during the analysis period (see Table 1). In total, there were 135 179 person-years (mean 7.9) of follow-up, including 48 271 person-years (mean 4.7) of follow-up pre-HAART, and 33 031 person-years (mean 3.2) and 53 877 person-years (mean 4.1) during the early-HAART and late-HAART periods, respectively.

SIRs and multivariate IRRs are presented in Tables 2 and 3, respectively. SIRs for Kaposi sarcoma ($n = 929$) were substantially raised, though declined markedly across HAART periods. In multivariate analysis controlling for current age and sex, a significant decline in incidence was observed across periods ($P_{trend} < 0.001$), and incidence was significantly lower in the late-HAART compared with early-HAART period ($P_{diff} < 0.001$). SIRs for NHL ($n = 661$) also declined greatly. In multivariate analysis, a significant decline in incidence was observed across periods ($P_{trend} < 0.001$) and from the early-HAART to late-HAART periods ($P_{diff} < 0.001$). Of NHL subtypes, a significant decline in incidence was observed for diffuse large B-cell lymphoma (DLBL, $n = 325$; $P_{trend} < 0.001$) but not for Burkitt lymphoma ($n = 32$; $P_{trend} = 0.776$) or primary central nervous system (CNS) lymphoma ($n = 38$; $P_{trend} = 0.553$).

There were insufficient cases of invasive cervical cancer ($n = 1$ case among 9806 person-years of follow-up among females with HIV) to allow analysis.

Other cancers

The study cohort for the analysis of all other cancers included 20 232 people (Table 1). There were 80 155 person-years (mean 5.8) during the pre-HAART period and 37 700 person-years (mean 3.3) and 58 462 person-years (mean 4.2) during the early-HAART and late-HAART periods, respectively.

Infection-related cancers—There were 45 cases of Hodgkin lymphoma, of which mixed cellularity was the most commonly specified subtype ($n = 15$ of 28 cases for which subtype was specified). SIRs were significantly raised across all periods. In multivariate analysis adjusted for categories of age (<35, 35–59, 60+ years), there was no significant change in incidence ($P_{trend} = 0.804$). However, incidence was significantly higher during the early-HAART period than the late-HAART period ($P_{diff} = 0.014$). Results were similar when age was modelled as a continuous variable (data not shown).

There were 41 cases of anal cancer, of which 38 (93%) were squamous cell carcinoma. SIRs were at least 30-fold across all HAART periods, and no trend in incidence was observed in multivariate analysis ($P_{trend} = 0.451$). Almost all cases occurred in males ($n = 40$); the SIR during the late-HAART period for males was 34.22 (95% CI 20.60–53.44) and was 39.61 (95% CI 23.47–62.60) for those males reporting HIV exposure through homosexual or bisexual contact.

There were 11 cases of liver cancer, all of which occurred in the post-HAART period. SIRs were significantly raised during both the early-HAART and late-HAART periods. Multivariate analyses were not performed as there were no cases during the period prior to HAART.

Noninfection-related cancers—There were 53 cases of cutaneous melanoma. Most ($n =$ 21 of 28 cases for which morphology was specified) were superficial spreading melanoma, and over half of all cases affected the trunk. SIRs were not significantly raised during the pre-HAART and early-HAART periods, and in the late-HAART period, the SIR was significantly

decreased. A significant decline in incidence was observed across periods in multivariate analysis (P_{trend} = 0.041).

SIRs for prostate (n = 24) and colorectal (n = 17; 10 colon, seven rectum) cancers were either not raised or were significantly decreased. For prostate cancer, a significant decline in incidence was observed across periods in multivariate analysis (P_{trend}= 0.026).

No significant trends in incidence were noted for cancers of the oral cavity and oropharynx, lip, lung, or leukaemia.

Discussion

Nonuniform trends in the incidence of specific cancer types were observed in people with HIV in Australia since the introduction of HAART. Among those cancers occurring at greatly increased rates in the pre-HAART period, three distinct patterns emerged. First, for Kaposi sarcoma and NHL, incidence declined dramatically and continued to decline in the late-HAART period, though it remained substantially elevated. Second, for Hodgkin lymphoma, incidence increased during the early-HAART period but later declined. Third, for anal cancer, there was no change in incidence over time. For two cancers not increased in the pre-HAART period, melanoma and prostate cancer, incidence declined significantly and by the late-HAART period, was lower than in the general population. For colorectal cancer, incidence was consistently lower than in the general population. There was no significant trend for all other cancer types examined.

A dramatic and continuing reduction in incidence of Kaposi sarcoma and NHL since the introduction of HAART has been well described [2-4,6], though a recent plateau in incidence of Kaposi sarcoma was reported in one study [19]. Incidence of both cancers is rapidly reduced following HAART initiation [19,20] and is strongly inversely correlated with $CD4^+$ T-cell count [3,6,21]. Both are associated with gamma herpesvirus infection: Kaposi sarcoma with human herpesvirus type 8 in all cases and NHL with Epstein–Barr virus (EBV) in more than 50% of HIV-associated cases [22]. Clearly, for both these cancers, current functional immunity is central to pathogenesis. The continuing decline in their incidence raises the question of whether it may be reduced to normal with earlier or more effective HAART.

Among NHL subtypes, a significant decline in incidence was observed for DLBL but not for Burkitt lymphoma. The unchanging incidence of Burkitt lymphoma, noted by others [6,23], likely reflects its less-frequent association with EBV infection and absence of a relationship with the level of immunodeficiency [24]. That incidence of CNS lymphoma did not decline was unexpected. This may be an artefact of underascertainment of histopathologically verified AIDS-associated CNS lymphoma in Australia in the pre-HAART period, in which the majority of cases in earlier years were diagnosed on radiological and clinical grounds alone [25] and may not have been registered as cancer.

A number of studies have suggested that incidence of Hodgkin lymphoma has remained stable [3,26] or increased in the post-HAART era [4] or with HAART use [5]. An association between Hodgkin lymphoma incidence and moderate levels of immunodeficiency has been suggested by some [26] but not all [27] studies. Our finding of a peak in incidence in the early-HAART period would be consistent with a cohort which passed through a phase of moderate immunodeficiency post-HAART. It is acknowledged that the interpretation of Hodgkin lymphoma incidence trends is complicated by its bimodal age distribution and that the increase in incidence observed post-HAART may reflect cohort ageing [27]. However, appropriate age adjustment, using categories of age reflecting the two age peaks of Hodgkin lymphoma, did not substantially alter our results.

Anal cancer incidence has remained stable in people with HIV in Australia, and, by the late-HAART period, it was the third most common type of cancer in this cohort. In other studies, stable [3,23] or increasing incidence [2,4] has been described. No studies have reported declining incidence. Anal cancer is causally associated with anal infection by high-risk subtypes of human papillomavirus (HPV) [28]. Immunodeficiency is associated with a higher prevalence of anal HPV infection and with precursor anal squamous lesions. However, whether the restoration of cellular immunity post-HAARTaffects risk of invasive anal cancer is unclear [29].

A significant decline in melanoma incidence was observed. Melanoma risk is strongly related to immunodeficiency in immunosuppressed transplant recipients [30]. Eruption of dysplastic melanocytic nevi has been documented soon after both HIV infection and solid organ transplantation, and fading of nevi on reduction of immunosuppression has been reported [31]. Curiously, incidence of melanoma was significantly lower than in the general population during the late-HAART period. Although the risk of melanoma is slightly raised overall in people with HIV [1], most studies reporting data in the post-HAART period have not observed excess risk [5,23].

Prostate cancer incidence was the same, or lower, than for the general population and declined significantly after HAART. For reasons unclear, reduced prostate cancer risk has been repeatedly documented in HIV-infected men [3,23]. Lower rates of prostate cancer screening and complications of HIV infection including lower androgen levels [32] and diabetes mellitus [33], each believed to be associated with reduced prostate cancer risk, may be possible explanations. In addition, there has been a single report of an inhibitory effect of protease inhibitors on prostate cancer cell lines [34]. Incidence of colorectal cancer was consistently reduced relative to that in the general population, providing some evidence against an obvious infectious cause.

This study had several strengths, including the use of national, population-based registries of both people with HIV and cancer and the long period of follow-up, an average of 8 years per person. Most prior registry-based studies did not involve nationwide data, and follow-up was commonly truncated after 2–5 years. As comparison of SIRs over time may be confounded by cohort ageing, interpretation of trends in cancer risk before and after HAART was verified through the use of age-adjusted, within-cohort analyses.

Some limitations include the size of the cohort, and therefore, limited statistical power with which to detect significant associations for rare cancers. Cancer ascertainment will have been affected by the accuracy of the data linkage algorithm, though it was based on a previously validated algorithm with 99% sensitivity and 100% specificity in identifying cases of AIDS-related NHL on the New South Wales cancer registry [35]. Bias may have been introduced through heightened medical surveillance for cancer, though the absence of increased risk for screen-detected cancer argues against substantial surveillance bias. The method of adjustment for survival after cancer diagnosis was approximate and could have resulted in either underestimation or overestimation of the expected numbers of cancers. Patient-level data on HAART use were not available, and, therefore, estimation of the effect of HAART was based on calendar-periods.

In an era of improving efficacy and wider availability of HAART, the pattern of cancer occurrence in people with HIV continues to change. For Kaposi sarcoma and NHL, continuing declines in incidence are being observed, though it remains very markedly increased relative to the general population. For Hodgkin lymphoma, this article provides evidence of a possible decline in incidence. Anal cancer has increased in prominence, being the third most common type of cancer in our cohort. Reasons for the declining incidence of prostate cancer, and

continually low incidence of colorectal cancer, are largely unclear. The variation in cancer trends likely reflects the different role of immune function and infection in the pathogenesis of individual cancers. Large-scale cohort studies with patient-level data on current $CD4^+$ T-cell count and HAART use have the potential to greatly inform the management of long-term cancer risk in this population.

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References

1. 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. [PubMed: 17617273]
2. Crum-Cianflone N, Hullsiek KH, Marconi V, Weintrob A, Ganesan A, Barthel RV, et al. Trends in the incidence of cancers among HIV-infected persons and the impact of antiretroviral therapy: a 20-year cohort study. AIDS 2009;23:41–50. [PubMed: 19050385]
3. Engels E, Biggar R, Hall H, Cross H, Crutchfield A, Finch J, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer 2008;123:187–194. [PubMed: 18435450]
4. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, et al. 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. [PubMed: 18490686]
5. Powles T, Robinson D, Stebbing J, Shamash J, Nelson M, Gazzard B, et al. Highly active antiretroviral therapy and the incidence of non-AIDS-defining cancers in people with HIV infection. J Clin Oncol 2009;27:884–890. [PubMed: 19114688]
6. Biggar RJ, Chaturvedi AK, Goedert JJ, Engels EA. AIDS-related cancer and severity of immunosuppression in persons with AIDS. J Natl Cancer Inst 2007;99:962–972. [PubMed: 17565153]
7. 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. [PubMed: 12004274]
8. Falster K, Gelgor L, Shaik A, Zablotska I, Prestage G, Grierson J, et al. Trends in antiretroviral treatment use and treatment response in three Australian states in the first decade of combination antiretroviral treatment. Sexual Health 2008;5:141–154. [PubMed: 18588779]
9. Australian HIV Observational Database (AHOD). AHOD Annual Report. Sydney, Australia: 2008.
10. Australian Institute of Health and Welfare (AIHW) and Australasian Association of Cancer Registries (AACR). Cancer in Australia: an overview, 2008. Canberra, Australia: AIHW; 2008. AIHW Cat. No. CAN 42. Cancer Series No. 46

11. Grulich AE, Wan X, Law MG, Coates M, Kaldor JM. Risk of cancer in people with AIDS. AIDS 1999;13:839–843. [PubMed: 10357384]
12. Grulich AE, Li Y, McDonald AM, Correll PK, Law MG, Kaldor JM. Decreasing rates of Kaposi's sarcoma and non-Hodgkin's lymphoma in the era of potent combination antiretroviral therapy. AIDS 2001;15:629–633. [PubMed: 11317001]
13. Li Y, Law M, McDonald A, Correll P, Kaldor JM, Grulich AE. Estimation of risk of cancers before occurrence of acquired immunodeficiency syndrome in persons infected with human immunodeficiency virus. Am J Epidemiol 2002;155:153–158. [PubMed: 11790679]
14. Australian Institute of Health and Welfare (AIHW) & Australasian Association of Cancer Registries (AACR). Cancer survival in Australia, 2001. Part 2: Statistical tables. Canberra, Australia: AIHW; 2001. AIHW Cat. No. CAN 14. Cancer Series No. 19
15. South Australian Cancer Registry. Epidemiology of Cancer in South Australia 1977–1998. Adelaide, Australia: South Australian Cancer Registry; 2000.
16. Jaffe, ES.; Harris, NL.; Stein, H.; Vardiman, J., editors. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2001. World Health Organization Classification of Tumours.
17. Breslow, NE.; Day, NE. Volume II: The design and analysis of cohort studies. IARC Scientific Publications No. 82. Lyon, France: Oxford University Press; 1987. Statistical methods in cancer research.
18. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, Ghissassi FE, et al. A review of human carcinogens: Part B – biological agents. Lancet Oncol 2009;10:321–322. [PubMed: 19350698]
19. Franceschi S, Maso LD, Rickenbach M, Polesel J, Hirschel B, Cavassini M, et al. Kaposi sarcoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. Br J Cancer 2008;99:800–804. [PubMed: 18665172]
20. Polesel J, Clifford GM, Rickenbach M, Dal Maso L, Battegay M, Bouchardy C, et al. Non-Hodgkin lymphoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. AIDS 2008;22:301–306. [PubMed: 18097233]
21. Bower M, Fisher M, Hill T, Reeves I, Walsh J, Orkin C, et al. CD4 counts and the risk of systemic non-Hodgkin's lymphoma in individuals with HIV in the UK. Haematologica 2009;94:875–880. [PubMed: 19336735]
22. International Agency for Research on Cancer (IARC). IARC Monographs on the evaluation of carcinogenic risks to humans: Epstein–Barr Virus and Kaposi's Sarcoma herpesvirus/human herpesvirus 8. Lyon, France: IARC Press; 1997.
23. Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, et al. Trends in cancer risk among people with AIDS in the United States 1980–2002. AIDS 2006;20:1645–1654. [PubMed: 16868446]
24. Engels EA. Infectious agents as causes of non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 2007;16:401–404. [PubMed: 17337646]
25. Newell M, Hoy J, Cooper S, DeGraaff B, Grulich AE, Bryant M, et al. Human immunodeficiency virus-related primary central nervous system lymphoma: factors influencing survival in 111 patients. Cancer 2004;100:2627–2636. [PubMed: 15197806]
26. Biggar RJ, Jaffe ES, Goedert JJ, Chaturvedi A, Pfeiffer R, Engels EA, et al. Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. Blood 2006;108:3786–3791. [PubMed: 16917006]
27. Clifford GM, Rickenbach M, Lise M, Dal Maso L, Battegay M, Bohlius J, et al. Hodgkin lymphoma in the Swiss HIV Cohort Study. Blood 2009;113:5737–5742. [PubMed: 19336755]
28. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans: human papillomaviruses. Lyon, France: IARC Press; 2007.
29. Palefsky J. Human papillomavirus-related tumors in HIV. Curr Opin Oncol 2006;18:463–468. [PubMed: 16894294]
30. Vajdic CM, van Leeuwen MT, Webster AC, McCredie MRE, Stewart JH, Chapman JR, et al. Cutaneous melanoma is related to immune suppression in kidney transplant recipients. Cancer Epidemiol Biomarkers Prev 2009;18:2297–2303. [PubMed: 19622722]
31. Zattra E, Fortina AB, Bordignon M, Piaserico S, Alaibac M. Immunosuppression and melanocyte proliferation. Melanoma Res 2009;19:63–68. [PubMed: 19194340]

32. Crum NF, Furtek KJ, Olson PE, Amling CL, Wallace MR. A review of hypogonadism and erectile dysfunction among HIV-infected men during the pre and post-HAART eras: diagnosis, pathogenesis, and management. AIDS Patient Care STDs 2005;19:655–671. [PubMed: 16232050]

33. Grinspoon S. Diabetes mellitus, cardiovascular risk, and HIV disease. Circulation 2009;119:770–772. [PubMed: 19221228]

34. Pajonk F, Himmelsbach J, Riess K, Sommer A, McBride WH. The human immunodeficiency virus (HIV)-1 protease inhibitor saquinavir inhibits proteasome function and causes apoptosis and radiosensitization in non-HIV-associated human cancer cells. Cancer Res 2002;62:5230–5235. [PubMed: 12234989]

35. Grulich AE, Wan X, Coates M, Day P, Kaldor JM. Validation of a nonidentifying method of linking cancer and AIDS register data. J Epidemiol Biostat 1996;1:207–212.

Table 1

Characteristics of cohorts for analysis of AIDS-defining and other cancers.

	Cohort for analysis of AIDS-defining cancers		Cohort for analysis of other cancers	
Characteristic	***n* (%)**	**PY (mean)**	***n* (%)**	**PY (mean)**
Total	17 175 (100)	135 179 (7.9)	20 232 (100)	176 317 (8.7)
HIV/AIDS				
HIV, prior to AIDS	17 175 (100)	111 390 (6.5)	20 232 (100)	143 679 (7.1)
AIDS	6520 (38)	23 789 (3.6)	9427 (47)	32 637 (3.5)
Sex				
Male patient	15 755 (92)	125 372 (8.0)	18 794 (93)	165 262 (8.8)
Female patient	1420 (8)	9806 (6.9)	1437 (7)	11 055 (7.7)
Calendar period[a]				
1982–1995	10 181 (59)	48 271 (4.7)	13 703 (68)	80 155 (5.8)
1996–1999	10 281 (60)	33 031 (3.2)	11 580 (57)	37 700 (3.3)
2000–2004	13 277 (77)	53 877 (4.1)	14 019 (70)	58 462 (4.1)
HIV exposure				
Male homosexual/bisexual[b]	13 075 (76)	106 378 (8.1)	15 847 (78)	141 314 (8.9)
Heterosexual only	1583 (9)	10 409 (6.6)	1640 (8)	12 359 (7.5)
Injection drug use	675 (4)	5710 (8.5)	820 (4)	7545 (9.2)
Other	1842 (11)	12 682 (6.9)	1925 (10)	15 099 (7.8)

PY, person-years.

[a] Time-dependent.

[b] Can include injection-drug use.

Table 2

Standardized incidence ratios for cancer in HIV/AIDS in Australia, by calendar period.

	1982–1995 (Pre-HAART)			1996–1999 (Early-HAART)			2000–2004 (late-HAART)		
Cancer site[a]	**Obs**	**SIR**	**95% CI**	**Obs**	**SIR**	**95% CI**	**Obs**	**SIR**	**95% CI**
Infection-related									
KS (HHV-8)	678	38 239	35 415–41 229	158	9970	8476–11 651	93	2701	2180–3309
NHL (EBV)	370	75.71	68.19–83.83	170	36.88	31.51–42.86	121	12.65	10.49–15.11
DLBL	160	107.33	91.35–125.31	96	68.32	55.34–83.43	69	26.23	20.41–33.19
Burkitt lymphoma	9	142.38	65.11–270.28	8	131.01	56.56–258.14	15	67.63	37.85–111.54
Other	169	50.70	43.35–58.95	104	33.09	27.03–40.09	84	12.51	9.98–15.48
CNS lymphoma	11	302.71	151.11–541.64	11	229.66	114.65–410.93	16	99.97	57.14–162.35
Hodgkin lymphoma (EBV)	16	7.99	4.57–12.98	18	17.27	10.24–27.30	11	7.37	3.68–13.18
Anus (HPV)	13	42.24	22.49–72.23	9	36.41	16.65–69.12	19	32.11	19.33–50.14
Oral cavity, oropharynx (HPV)	5	1.89	0.61–4.41	10	1.58	0.76–2.91	7	1.65	0.66–3.39
Liver (HBV/HCV)	0	–	0.00–4.01	4	4.78	1.30–12.24	7	2.96	1.19–6.10
Other cancers increased in incidence in immunodeficient populations									
Lip	9	2.22	1.02–4.21	5	2.07	0.67–4.82	4	1.08	0.29–2.77
Lung	14	1.47	0.80–2.46	8	1.24	0.54–2.45	15	1.10	0.62–1.82
Melanoma	27	1.09	0.72–1.58	11	0.72	0.36–1.29	15	0.54	0.30–0.89
Leukaemia	9	3.53	1.61–6.70	4	2.06	0.56–5.27	9	1.91	0.87–3.62
Cancers not increased in incidence in immunodeficient populations									
Colorectal	6	0.44	0.16–0.96	3	0.31	0.06–0.89	8	0.38	0.16–0.75
Prostate	10	1.19	0.57–2.18	6	0.63	0.23–1.38	8	0.27	0.11–0.52

Note: Calculated for cancers with at least 10 cases in total after HAART, with the exception of lip cancer. Analyses for KS and NHL based on cohort with known dates of HIV diagnosis (n = 17 175); analyses for all other cancers based on full cohort (n = 20 232). SIRs adjusted for survival in patients with retrospectively defined date of HIV diagnosis. Abbreviations: CI, confidence interval; EBV, Epstein–Barr virus; Exp, expected; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV-8, human herpesvirus 8; HPV, human papillomavirus; KS, Kaposi sarcoma; NHL, non-Hodgkin lymphoma; Obs, observed; SIR, standardized incidence ratio.

[a]ICD10/O-3 codes: KS 9140, 8000 if KS on AIDS Registry; NHL 9591, 9596, 9670–9729, 9820–9837, 9940, 9948 and 9590 if ICD10 C82-C85; DLBL 9680, 9684, 9678, 9679; Burkitt 9687, 9826; CNS lymphoma, NHL with C70-C72 topography; Hodgkin lymphoma 9650–9667; anus C21; oral cavity, oropharynx C01–C10, excl. C07–C08; liver C22; lip C00; melanoma C43; leukaemia 9800–9989, excl. 9820–9837, 9940, 9948; trachea, bronchus and lung C33–34; colorectal C18 –C20; prostate C61.

Table 3

Incidence rate ratios for cancer in HIV/AIDS in Australia, by calendar period.

	1982–1995 (pre-HAART)	1996–1999 (early-HAART)		2000–2004 (late-HAART)			
Cancer site[a]	***n* (ref)**	***n***	**IRR (95% CI)**[b]	***n***	**IRR (95% CI)**[b]	P_{trend}[‡]	P_{diff}[‖]
Infected-related							
KS (HHV-8)	678	158	0.33 (0.28–0.39)	93	0.11 (0.09–0.14)	<0.001	<0.001
NHL (EBV)	370	170	0.60 (0.50–0.72)	121	0.24 (0.19–0.29)	<0.001	<0.001
DLBL	160	96	0.78 (0.60–1.00)	69	0.31 (0.23–0.41)	<0.001	<0.001
Burkitt lymphoma	9	8	1.12 (0.43–2.92)	15	1.14 (0.49–2.66)	0.776	0.975
Other	169	104	0.80 (0.62–1.02)	84	0.35 (0.27–0.46)	<0.001	<0.001
CNS lymphoma	11	11	1.46 (0.63–3.39)	16	1.29 (0.58–2.87)	0.553	0.763
Hodgkin lymphoma (EBV)	16	18	2.34 (1.19–4.63)	11	0.91 (0.42–2.01)	0.804	0.014
Anus (HPV)	13	9	1.17 (0.50–2.75)	19	1.32 (0.64–2.73)	0.451	0.763
Oral cavity, oropharynx (HPV)	5	3	0.89 (0.21–3.74)	7	1.00 (0.31–3.24)	0.986	0.863
Liver (HBV/HCV)	–	4	–	7	–	–	
Other cancers increased in incidence in immunodeficient populations							
Lip	9	5	0.92 (0.31–2.77)	4	0.38 (0.11–1.26)	0.119	0.189
Lung	14	8	0.84 (0.35–2.01)	15	0.77 (0.37–1.63)	0.505	0.852
Melanoma	27	11	0.70 (0.35–1.42)	15	0.51 (0.27–0.98)	0.041	0.432
Leukemia	9	4	0.80 (0.24–2.61)	9	1.03 (0.39–2.67)	0.958	0.674
Cancers not increased in incidence in immunodeficient populations							
Colorectal	6	3	0.70 (0.17–2.82)	8	0.86 (0.29–2.51)	0.804	0.771
Prostate	10	6	0.69 (0.25–1.91)	8	0.35 (0.14–0.89)	0.026	0.236

Note: Calculated for cancers with at least 10 cases in total after HAART, with the exception of lip cancer. Analyses for KS and NHL based on cohort with known dates of HIV diagnosis (n = 17 175); analyses for all other cancers based on full cohort (n = 20 232). IRRs adjusted for survival in patients with retrospectively defined date of HIV diagnosis. Abbreviations: CI, confidence interval; EBV, Epstein–Barr virus; Exp, expected; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV-8, human herpesvirus 8; HPV, human papillomavirus; IRR, incidence rate ratio; KS, Kaposi sarcoma; NHL, non-Hodgkin lymphoma; Obs, observed.

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[b] Adjusted for current age (single years; Hodgkin lymphoma ages <35, 35–59, 60+ years) and sex (excepting Hodgkin lymphoma, and cancers of the anus, oral cavity and lip due to insufficient cases in female patients).

‡ *P* value for test for trend across periods.

‖ *P* value for test for difference between early-HAART and late-HAART periods.