Decreasing rates of Kaposi's sarcoma and non-Hodgkin's lymphoma in the era of potent combination anti-retroviral therapy

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Objective: To describe the changing incidence of Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) in people with HIV in Australia during the time period of introduction of potent combination anti-retroviral therapy.

Design: A national, population-based linkage study of cancer and HIV registration data.

Methods: We calculated person-year rates of KS and NHL in people after reporting of HIV diagnosis. Trends in cancer incidence rates were examined, based on four time periods defined by the availability of specific anti-retroviral therapies.

Results: Linkage identified 206 cases of KS and 235 cases of NHL in 8108 people reported with HIV infection. There was an increasing trend in NHL incidence rates over the four time periods (*P* for trend, 0.012), but incidence for the period since the availability of the new therapies was significantly lower than that for the period immediately prior (incidence rate ratio 0.58; 95% confidence interval, 0.36–0.92). Incidence of KS had been decreasing prior to the new therapies and declined further since their widespread use (*P* for trend, 0.045).

Conclusions: Population-based incidence rates of AIDS related KS and NHL have decreased since the widespread use of potent anti-retroviral therapies in Australia. NHL incidence decreased less than KS, and NHL is now the most common AIDS-associated cancer in Australia.
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Introduction

The use of potent anti-retroviral combination therapy has led to declines in the incidence of most opportunistic infections, and of Kaposi's sarcoma (KS), in people with HIV. However, the pattern for HIV-related non-Hodgkin's lymphoma (NHL) is less clear, with conflicting results from available studies [1–7]. It has been speculated that the effect of the new therapies on NHL incidence is less than for other AIDS-related illnesses, because malignant transformation in NHL may not be influenced by therapy-induced recovery in specific immunity [6].

In Australia, there has been nationwide registration of cancer and notification of HIV diagnosis since 1985. In

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addition, people with newly acquired HIV infection, defined as an HIV diagnosis within 12 months of a negative HIV test, or a clinical diagnosis of HIV seroconversion illness, have been registered since 1991 [8]. We performed a population-based linkage study of HIV and cancer registers to examine trends in incidence rates of NHL and KS in people with HIV in Australia.

Methods

We performed linkage for all those individuals who had sufficient identifiers on the national HIV database (first two letters of first and last name, date of birth, and sex) to enable linkage with the national cancer register. Our linkage procedure, formerly used with the AIDS register in the state of New South Wales, has been described previously [9].

Incidence rates of KS and NHL were calculated using person-years methods. For each of these cancers, person-years at risk were calculated from the date of HIV diagnosis to the date of cancer diagnosis, death, or end of period of available cancer data (from 1995 to 1998 depending on jurisdiction), whichever occurred first. In addition, standardized incidence ratios (SIR) were calculated based on age-, sex-, and state-specific incidence rates of KS and NHL. For NHL, as HIV-associated disease accounts for a small minority of total cases, SIR were calculated based on the year of follow up. For KS, as the great majority of cases in Australia occur in people with HIV, SIR were calculated using rates from 1975–1979, prior to the AIDS epidemic, as standard.

To analyse time trends, incidence rate ratios (IRR) and standardized incidence rate ratios (SIRR) were calculated over four pre-defined time periods, based on therapeutic practices in Australia [10], relative to the first period. Period one (prior to July 1990) was selected as the time period when zidovudine monotherapy was standard practice. Period 2 (July 1990 to June 1994) was a period in which sequential antiretroviral monotherapy was used. In period 3 (July 1994 to June 1996) dual therapy with two anti-retroviral nucleoside analogues was standard therapy, and in period 4 (from July 1996) potent triple combination therapy became standard of care. By 1997, it was estimated that around 60% of people diagnosed with HIV in Australia were receiving at least three antiretroviral agents [11].

IRR and SIRR were calculated separately in HIV seroconverters and in all those registered with HIV infection. For those who were not seroconverters, it was possible that changes over time in immune status at HIV diagnosis might have affected trends in cancer rates, so for those who had a recorded CD4 cell count at HIV diagnosis, IRR and SIRR were adjusted for CD4 cell count (< 200, 200–499, $\geqslant 500 \times 10^6$/l) at HIV diagnosis. For KS, it was possible that differences over time were due to differences in the proportion of people with HIV reporting homosexual contact, so time trend analyses restricted to men reporting homosexual contact were also performed. Confidence intervals and time trends were estimated using Poisson regression.

Results

By August 1999, 46% (8108) of people registered with HIV, and 75% (1101) of people registered with newly acquired HIV infection had sufficient identifiers for linkage to be performed. The percentage of people registered with HIV who had sufficient identifiers for linkage increased over the four time periods (32%, 57%, 85% and 94%), and the proportion who reported homosexual contact as their HIV risk behaviour decreased (73%, 72%, 70% and 63%).

Two hundred and six cases of KS and 235 cases of NHL were recorded in 8108 people registered with HIV infection. The ratio of incidence rates of KS to NHL steadily declined over the period of this study. Prior to July 1990, incidence rates of KS were twice as high as those of NHL. After this period, more cases of NHL than KS were registered, and the ratio of KS to NHL incidence rates fell to 0.44 after July 1996.

For KS, rates had been declining since period 2, and there was a significant decline in rates over the four periods ($P = 0.045$). An identical pattern was seen when the analysis was restricted to men who reported homosexual contact ($P = 0.028$). For NHL, there was a significant increase over the four time periods ($P = 0.012$), but incidence rates in period 4 were significantly lower than in period 3 (IRR, 0.58; 95% confidence interval, 0.36–0.92; see Table 1 and Fig. 1). CD4 cell count at HIV diagnosis was available for 2410 persons (29.7%). Six hundred and seventy-nine (28%) had a CD4 cell count $< 200 \times 10^6$/l, 819 (34%) had a CD4 cell count of $200–499 \times 10^6$/l, and 912 (38%) had a CD4 cell count of $\geqslant 500 \times 10^6$/l. Median CD4 cell count at HIV diagnosis decreased from 496×10^6/l in period 1 to 360×10^6/l in period 3, and then increased to 393×10^6/l in period 4. Adjusting for CD4 cell count at HIV diagnosis did not affect time trends and patterns of SIRR were essentially identical (data not presented).

There were 13 cases of KS and 22 cases of NHL in 1101 seroconverters during follow-up. There was a

Table 1. Time trends in KS and NHL in all people with HIV diagnosis, in all people with HIV diagnosis registered with a CD4 cell count at HIV diagnosis (adjusted for CD4 cell count), and in HIV seroconverters only.

Cancer type	Time period	n[a]	Person-years	Incidence/1000 person-years[b] (95% CI)	Incidence rate ratio (95% CI)	*P* trend[c]
Kaposi's sarcoma						
All people with HIV (n = 8108)						
	Prior to July 1990	44	9563	4.6 (3.4–6.2)	1.00	
	July 1990–June 1994	97	15552	6.2 (5.1–7.6)	1.36 (0.95–1.94)	
	July 1994–June 1996	55	10623	5.2 (4.0–6.7)	1.13 (0.76–1.67)	
	June 1996–December 1998	10	5321	1.9 (1.0–3.5)	0.41 (0.21–0.81)	0.045
All people with HIV with CD4 cell count at HIV diagnosis (n = 2410), adjusted for CD4 cell count						
	Prior to July 1994	14	2759	5.1 (3.0–8.6)	1.00	
	July 1994–June 1996	21	2700	7.8 (5.1–11.9)	1.38 (0.70–2.71)	
	June 1996–December 1998	4	1579	2.5 (1.0–6.7)	0.44 (0.15–1.34)	0.298
People registered with newly acquired HIV (n = 1101)						
	Prior to July 1994	9	2100	4.3 (2.2–8.2)	1.00	
	July 1994–June 1996	4	1475	2.7 (1.0–7.2)	0.63 (0.19–2.05)	
	June 1996–December 1998	0	661	0.0 (–)	0.00 (–)	0.096
Non-Hodgkin's lymphoma						
All people with HIV (n = 8108)						
	Prior to July 1990	22	9600	2.3 (1.5–3.5)	1.00	
	July 1990–June 1994	110	15628	7.0 (5.8–8.5)	3.07 (1.94–4.85)	
	July 1994–June 1996	80	10656	7.5 (6.0–9.3)	3.28 (2.04–5.25)	
	June 1996–December 1998	23	5318	4.3 (2.9–6.5)	1.89 (1.05–3.39)	0.012
All people with HIV with CD4 cell count at HIV diagnosis (n = 2410), adjusted for CD4 cell count						
	Prior to July 1994	19	2779	6.8 (4.4–10.7)	1.00	
	July 1994–June 1996	21	2716	7.7 (5.0–11.9)	1.03 (0.55–1.92)	
	June 1996–December 1998	8	1578	5.1 (2.5–10.1)	0.67 (0.29–1.54)	0.413
People registered with newly acquired HIV (n = 1101)						
	Prior to July 1994	11	2103	5.2 (2.9–9.4)	1.00	
	July 1994–June 1996	9	1473	6.1 (3.2–11.7)	1.17 (0.48–2.82)	
	June 1996–December 1998	2	660	3.0 (0.8–12.1)	0.58 (0.13–2.61)	0.662

[a]Number of observed cases. [b]Incidence per 1000 person-years. [c] *P* for linear trend across time periods. CI, Confidence interval.

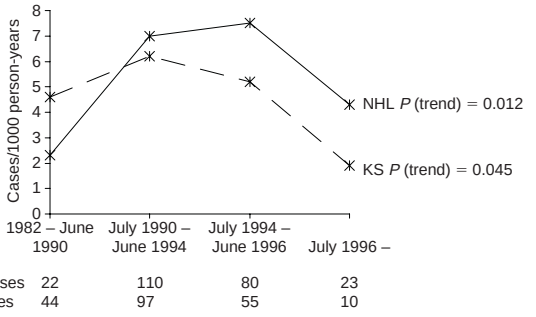

Fig. 1. Time trends in KS and NHL incidence in people diagnosed with HIV in Australia, 1982–1998.

non-significant decreasing trend in IRR for both KS ($P = 0.096$) and for NHL ($P = 0.662$). For both cancers, incidence rates were lowest in the period after July 1996, although this did not reach statistical significance.

Discussion

This study finds decreasing incidence rates of both NHL and KS in people with HIV since the introduction of potent anti-retroviral therapies. For NHL, incidence had been increasing prior to 1996, and this increase masked the decrease since the introduction of the new HIV therapies when long-term trends were considered. The increase in NHL incidence in the early epidemic, which was also seen for KS, may have been related to increasing immune deficiency of the cohort. This study also confirms at a population level the previously described decreases in the incidence of KS during the 1990s. This decrease began before the introduction of the new therapies. KS has decreased in incidence by far more than NHL, so that NHL is now the most common AIDS-associated cancer in Australia.

Analysis of time trends in incidence rates of AIDS-associated cancers in cohort studies has been hampered because of the relative rarity of these conditions. Population-based linkage studies based on HIV registers can overcome this problem. This study comprises 46% of all diagnosed cases of HIV infection in Australia, and 63% of all cases diagnosed during the 1990s. In considering time trends in AIDS-related cancers that might be related to the new HIV therapies, it is important to consider trends in other important risk factors, such as degree of immune deficiency. Although CD4 cell count at HIV diagnosis varied over the time period considered, controlling for this variable made no difference to the trends reported. However, it must be acknowledged that CD4 cell count at HIV diagnosis only partially characterizes the immune status of the cohort. Trends in the same direction were also seen in seroconverters, although these trends were not significant. We have shown previously that only 68% of people with AIDS diagnosed with KS are registered with this cancer in New South Wales, compared with 91% of NHL [9,12], but there are no data on whether cancer registration in people with HIV may have changed over time. Even allowing for a large degree of under-registration of KS, it appears that NHL has been the most commonly diagnosed AIDS defining cancer in people with HIV in Australia since the mid 1990s.

Previous cohort studies in people receiving the new HIV therapies have reported decreases [1,3], no significant change [2,4,6], and increases [5] in the occurrence of NHL. The largest study found decreases in rates of primary brain NHL but no trend in other subtypes [7]. We did not have data on NHL subtype. It may be that the discrepant trends we have described, with an increase in overall NHL incidence up to the time of the availability of the new therapies followed by a decrease, may explain the inconsistency of previous reported time trends. Only when we compared post June 1996 rates with the time period immediately prior, rather than a wider time period, did we find a significant reduction in NHL incidence. The only study to have reported increasing rates of NHL examined trends between 1985 and 1997, and reported a non-significant reduction in rates in the last 2 years of the study [5].

Epidemiological studies have indicated that the incidence of KS was probably decreasing, albeit slowly, prior to the introduction of combination anti-retroviral therapy [1,2,13], and our data add support to this finding. Thus the magnitude of the reduction in KS incidence rates over a long time period over-estimates the effect of the new therapies. The decrease was not due to the declining proportion of cases of HIV in men reporting homosexual contact.

It is unclear why rates of NHL appear to be decreasing more slowly than other AIDS-associated illnesses, but there are at least three possible explanations. First, unlike KS, NHL does not appear to be due to a specific infective agent, so partial immune restoration may be less effective in prevention. Second, NHL occurs at a less severe degree of immune deficiency than most other AIDS-associated illnesses. Third, there is evidence that chronic stimulation of the immune system is a risk factor for AIDS-related NHL, and potent combination antiretroviral therapy may be only partially effective at reversing this immune stimulation [14,15].

In summary, the era of potent combination antiretroviral therapy has been associated with an acceleration in already declining incidence rates of KS in people with

HIV, and a decline in incidence rates of NHL. The magnitude of reduction in NHL rates has not been as great as the reduction in rates of KS, and of most other opportunistic infections in people with AIDS, so it is likely that NHL will comprise an increasing proportion of AIDS-associated illnesses.

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