

# HIV-related non-Hodgkin's lymphoma in Calgary

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**OBJECTIVE:** To determine the incidence of human immunodeficiency virus (HIV) associated non-Hodgkin's lymphoma (NHL) in a cohort of patients from a distinct geographic region (southern Alberta). The type and location of NHL as well as how it affected the survival of these patients was examined.

**PATIENTS AND METHODS:** The Southern Alberta HIV Clinic in Calgary serves all of southern Alberta, which has an estimated population of one million. The clinic has provided primary care for 1086 patients from January 1983 to August 1995. Data were obtained by reviewing the clinic's database and patients' charts.

**RESULTS:** Over a 12-year period, 39 cases of NHL were diagnosed in a group of 1086 HIV-infected patients. Presentation of NHL was at an extranodal site in all but four cases, with the most common sites being the bowel and central nervous system. The mean CD4 count on presentation with NHL was  $143.4 \pm 37.4 \times 10^6/L$  (range 1 to  $1219 \times 10^6/L$ ). Mean survival was  $1.25 \pm 0.25$  years with a range from 0 (diagnosed on autopsy) to 6.45 years. Patients with a CD4 count of less than  $200 \times 10^6/L$  and/or diagnosed with an AIDS-defining illness before development of NHL had significantly reduced survival (0.85 years versus 2.48 years,  $P < 0.02$  and 0.57 years versus 2.09 years,  $P < 0.001$ , respectively). Patients who presented with NHL involving either nodes alone or central nervous system had significantly decreased survival (0.28 years and 0.29 years, respectively,  $P < 0.05$ ). Patients with NHL involving the gastrointestinal tract had a longer mean survival than those with NHL elsewhere ( $P < 0.05$ ). All but seven cases received therapy for NHL including chemotherapy, radiotherapy, surgery or combined therapy. Fifteen patients (47% of treated) achieved a complete response that led to improved survival ( $P < 0.01$ ). Patients tolerated surgery, chemotherapy and radiotherapy well and no deaths were due to NHL therapy.

**CONCLUSIONS:** These data suggest that development of NHL in HIV is associated with reduced survival, and that survival is predominantly determined by CD4 count and site of involvement at the time of diagnosis of NHL.

Key Words: Human immunodeficiency virus, Non-Hodgkin's lymphoma

## Lymphome non hodgkinien associé au VIH, à Calgary

**OBJECTIF :** Déterminer l'incidence du lymphome non hodgkinien (LNH) associé au virus de l'immunodéficience humaine (VIH) auprès d'une cohorte de patients provenant d'une région géographique distincte (sud de l'Alberta). Le type et la localisation du LNH et la façon dont il a influé sur la survie de ces patients ont été examinés.

**PATIENTS ET MÉTHODE :** Une clinique VIH du sud de l'Alberta, située à Calgary, dessert tout le sud de la province dont la population est estimée à un million de personnes. La clinique a offert les soins de premiers recours à 1 086 patients entre janvier 1983 et août 1995. Les données ont été obtenues au moyen d'un repérage, à partir de la base de données de la clinique et des dossiers des patients.

**RÉSULTATS :** Sur une période de 12 ans, 39 cas de LNH ont été diagnostiqués dans un groupe de 1 086 patients infectés par le VIH. Le LNH s'est installé hors des ganglions dans tous les cas, sauf quatre, les sièges les plus courants de la mala-

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die étant l'intestin et le système nerveux central. La numération moyenne des CD4 au moment de la présentation du LNH était de  $143,4 \pm 37,4 \times 10^6/L$  (variation de 1 à  $1\,219 \times 10^6/L$ ). La survie moyenne a été de  $1,25 \pm 0,25$  an, variant de 0 (diagnostiqué à l'autopsie) à 6,45 ans. Les patients dont la numération des CD4 était inférieure à  $200 \times 10^6/L$  et/ou qui souffraient d'une maladie liée au diagnostic du SIDA, avant l'installation du LNH ont présenté une survie significativement moindre (0,85 an contre 2,48 ans,  $P < 0,02$  et 0,57 an contre 2,09 ans,  $P < 0,001$ , respectivement). Les patients qui se présentaient avec un LNH caractérisé par une atteinte uniquement ganglionnaire ou une atteinte du système nerveux central présentaient une survie significativement moindre (0,28 an et 0,29 an respectivement,  $P < 0,05$ ). Les patients dont le LNH mettait en jeu les voies digestives présentaient une survie moyenne plus longue que ceux dont le LNH s'était manifesté autrement ( $P < 0,05$ ). Tous les cas sauf sept ont reçu un traitement pour LNH, y compris la chimiothérapie, la radiothérapie, la chirurgie ou le traitement associatif. Quinze patients (47 % des patients traités) sont parvenus à une réponse complète, qui a contribué à l'amélioration de la survie ( $P < 0,01$ ). Les patients ont bien toléré la chirurgie, la chimiothérapie et la radiothérapie. Aucun décès n'a été attribuable au traitement du LNH.

**CONCLUSIONS :** Ces données suggèrent que l'installation du LNH en présence du VIH est associée à une survie réduite et que la survie est principalement déterminée par la numération des CD4 et par la localisation de l'atteinte au moment où le diagnostic de LNH est posé.

**H**uman immunodeficiency virus (HIV) infection is associated with an increased risk of developing certain malignancies such as Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) (1-8). Since 1983 the incidence of NHL in the United States has increased dramatically among men in the age range of 20 to 49 years. It has been estimated that between 8% and 27% of all cases of NHL in the United States will be a consequence of HIV infection (9). With the development of antiretroviral therapies and improved prevention and treatment of opportunistic infections, patients with HIV infection are now living longer, placing them at greater risk of developing an HIV-associated malignancy. It has been suggested that NHL may become the main limiting factor for the survival of patients with long-standing HIV infection (10). One study estimated that approximately 45% of HIV-infected individuals will develop lymphoma within 36 months of starting antiretroviral therapy (10).

The purpose of this study was to collect a cohort of HIV-infected individuals, from a distinct geographic region (southern Alberta), and to determine the incidence of HIV-associated NHL and how the development of NHL affected these people. The type and site of the NHL and the degree of immunosuppression (CD4 count) at presentation were also assessed. Several modalities were used in the treatment of NHL in this study, including chemotherapy, radiotherapy and surgery. The ability of these patients to tolerate and respond to NHL therapy was noted.

#### PATIENTS AND METHODS

The Southern Alberta HIV Clinic in Calgary (SAC) serves all of southern Alberta, which has an estimated population of one million. Approximately 94% of all HIV-positive patients from this area attend SAC or its satellite clinic. From January 1, 1983 to August 31, 1995, SAC provided primary care for 1086 HIV-infected individuals. Data were obtained by reviewing the clinic's database and patients' charts.

Life tables were constructed and analyzed using the SPSS program (Statistical Package for the Social Sciences Inc, Illinois), and differences between groups were compared according to the method of Lee and Desu (11). Student's two-tailed t test was used for comparison of continuous variables.

#### RESULTS

Of 1086 patients, 35% met the 1992 Centers for Disease Control and Prevention definition of AIDS (12). Males made up 92% of the SAC population. The most prevalent risk factors in males were homosexual contact (73%), high risk heterosexual contact (9%), intravenous drug use (5%) and hemophilia (2%) (1% had no recognized risk factors). The most prevalent risk factors in females were high risk heterosexual contact (68%) followed by being the recipient of blood products (21%) and intravenous drug use (6%) (5% had no recognized risk factors).

Thirty-nine cases of NHL were diagnosed in 38 individuals (3.4% of all SAC patients and 8.5% of all AIDS patients). One patient who presented with Burkitt's lymphoma (cured with chemotherapy) developed a high grade lymphoma three years later that was histologically distinct from the previous lymphoma. Due to the retrospective nature of this study it is possible that some cases of NHL were missed since autopsies were not obtained on all patients. There were four patients with lesions that appeared radiographically to be lymphoma; however, these patients refused further investigations and autopsy. Of these patients, three had central nervous system (CNS) lesions and one had a lung lesion. Only patients with histologically proven NHL were included in this study.

There were 37 cases of high grade lymphoma and two cases of intermediate grade lymphoma. In all but four patients, presentation was at an extranodal site. Thus, 35 (89.7%) of the cases presented as stage IV disease and all patients with nodal presentation had stage III disease by the Ann Arbor Staging Classification (13). The most frequent sites of involvement were the gastrointestinal (GI) tract (13 cases) and the CNS (eight cases) (Table 1). Three patients had bony lesions (sternum, scapula, ribs, femur). Eight of 39 cases (20.5%) presented with NHL at multiple sites (Table 1). Three of 39 (7.7%) cases of NHL had coexisting KS, which was similar to the incidence of KS in the general SAC population (9.1%) (Table 1).

Thirty-seven of 38 patients with HIV-related NHL were males. Thirty-two of 37 (86.5%) reported homosexual contact as their main HIV risk factor. Two of 32 also used intravenous drugs. The mean age of patients who developed NHL was  $41.9 \pm 1.6$  years, range 26.5 to 67.9 years. Patients with CNS NHL were significantly ( $P < 0.05$ ) younger ( $33.8 \pm 1.7$  years)

**TABLE 1**  
**The Southern Alberta HIV Clinic cohort of HIV-associated non-Hodgkin's lymphoma**

Patient	Sites	CD4 count	Therapy	Survival (years)
1	Sternum	190	MACOP-B	4.0
2	Bowel*	45	Surgery, CHOP	1.2
3	Bowel <sup>†</sup>	n/a	Surgery, MOPP	6.5
4	CNS, testicle <sup>†</sup>	115	MACOP-B, radiotherapy	0.3
5	Liver <sup>†</sup>	421	MACOP-B	3.1
6a	Bowel (Burkitts)	1219	CHOP	3.8
6b	Bowel*	744	CHOP	0.7
7	CNS* <sup>†</sup>	15	Nil <sup>‡</sup>	0.1
8	Skull, scapula*	18	MACOP-B	1.3
9	Bowel	138	MACOP-B	5.1
10	Kidney* <sup>§</sup> ¶	18	Surgery, prednisone, VP16, novantrone, vincristine	0.9
11	Nasopharynx, lung* <sup>†</sup>	9	MACOP-B, radiotherapy	1.4
12	Nodes, kidney, liver, CNS*	n/a	MACOP-B	0.7
13	Palate*	25	Surgery	1.2
14	Bowel	266	Surgery	0.8**
15	Bone marrow*	4	Nil (refused)	0.6
16	CNS*	54	Radiotherapy <sup>‡</sup>	0.1
17	Bowel*	7	MACOP-B	0.8
18	Spleen, liver, nodes <sup>†</sup>	42	MACOP-B	0.3
19	Bowel	236	CHOP	>2.8
20	Spleen	297	VACOP-B	>3.2
21	Nodes, rib, femur	276	Nil (refused)	1.2
22	Palate	156	Surgery	>2.5
23	Bowel*	120	Surgery, CHOP	0.7
24	Vagina <sup>†</sup>	88	Radiotherapy	1.5
25	CNS, nodes* <sup>†§</sup>	5	CNOP	0.5
26	Nodes*	1	Radiotherapy	0.5
27	Nodes*	30	Cyclophosphamide	0.2
28	Bowel*	42	Nil (refused)	0.5
29	Liver*	42	Nil	0.1
30	Liver, kidneys	32	Diagnosed on autopsy	0.0
31	Nodes	80	CHOP	>0.3
32	CNS*	35	Radiotherapy	>0.3
33	Nodes* <sup>§</sup>	66	CHOP	>0.2
34	CNS	24	CHOP	>0.2
35	CNS* <sup>†</sup>	125	Nil	0.3
36	Bowel	160	CHOP	>0.4
37	Bowel* <sup>†</sup>	110	Nil <sup>‡</sup>	0.1
38	Bowel <sup>†</sup>	49	Surgery	0.4

\*Preceding AIDS-defining illness; <sup>†</sup>Cause of death directly due to non-Hodgkin's lymphoma; <sup>‡</sup>Died before initiation of chemotherapy; <sup>§</sup>Kaposi's sarcoma; ¶This case has been described previously (reference 27); \*\*Moved, lost to follow-up. CHOP Cyclophosphamide, doxorubicin, vincristine, prednisone; CNOP Cyclophosphamide, novantrone, vincristine, prednisone; CNS Central nervous system; HIV Human immunodeficiency virus; MACOP-B Methotrexate, doxorubicin, cyclophosphamide, vincristine, bleomycin, prednisone; MOPP Nitrogen mustard, vincristine, prednisone, procarbazine; n/a Not applicable; VACOP-B Etoposide, adriamycin, cyclophosphamide, vincristine, prednisone, bleomycin; VP16 Etoposide

than those who developed NHL of the bowel (40.3±2.0 years) or sites other than the CNS (44.0±1.8 years). The mean CD4 count of those in the SAC cohort with NHL was 143.4±37.4×10<sup>6</sup>/L (range 1 to 1219×10<sup>6</sup>/L). Patients who developed NHL of the CNS had lower CD4 counts than patients

with NHL involving sites other than the CNS (53.2±16.9 versus 164.7±45.5, P<0.03) (Table 1).

As of August 31, 1995, eight of 38 patients were alive. Survival ranged from 0 (diagnosed on autopsy) to 6.45 years. The mean survival of patients with HIV-associated NHL was

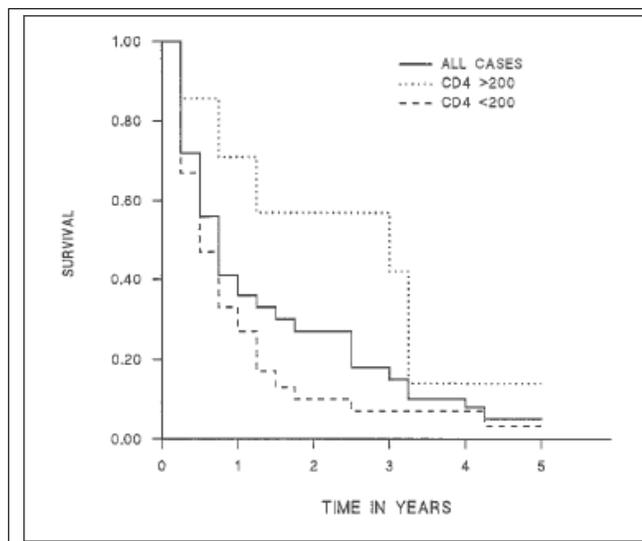


Figure 1) Life table analysis for 37 cases. Patients with a CD4 count  $<200 \times 10^6/L$  had reduced survival ( $P < 0.03$ ). CD4 counts were not available for two patients (see Table 1)

$1.25 \pm 0.25$  years (median survival 0.76 years) (Figure 1). Patients with CD4 counts greater than  $200 \times 10^6/L$  at the time of diagnosis of NHL survived significantly longer than those with CD4 counts less than  $200 \times 10^6/L$  ( $2.48 \pm 0.46$  years versus  $0.85 \pm 0.20$  years,  $P < 0.02$ ) (Figure 1).

Eleven of 30 deaths were directly due to NHL, and those who died of NHL were of similar age and had similar CD4 counts to those with NHL who died of other causes. Patients who died of NHL had similar mean survival but shorter median survival than those who did not die of NHL (0.36 versus 0.73 year median survival,  $P < 0.05$ ). Patients who died of NHL were more likely to have CNS NHL (36% versus 15%) or multiple sites of involvement (36% versus 18%) compared with those who did not die of NHL (Table 1).

Patients who presented with NHL involving the CNS, multiple sites or nodes alone had significantly decreased survival ( $0.28 \pm 0.06$  years,  $P < 0.001$ ;  $0.70 \pm 0.05$  years,  $P < 0.05$ ; and  $0.29 \pm 0.7$  years,  $P < 0.04$ , respectively) compared with patients with NHL involving other areas. Patients with NHL involving the GI tract survived longer than those with NHL involvement outside of the GI tract ( $1.96 \pm 0.5$  years versus  $0.95 \pm 0.2$  years,  $P < 0.05$ ). Patients with NHL involving the GI tract had higher CD4 counts than patients with extraintestinal NHL; however, these differences were not significant ( $260.9 \pm 108.5$  versus  $93.6 \pm 21.2 \times 10^6/L$ ,  $P = 0.16$ ). The CD4 counts of patients with NHL involving nodes only or multiple sites were not significantly different from those of patients with involvement at other sites.

Twenty-one patients were diagnosed with an AIDS-defining illness before the diagnosis of NHL. As might be expected, these patients had significantly reduced survival compared with those who did not have a prior AIDS-defining illness ( $0.57 \pm 0.09$  years versus  $2.09 \pm 0.46$  years,  $P < 0.001$ , respectively). When survival was calculated from the date of either the AIDS-defining illness or NHL, patients with a preceding AIDS-defining illness survived  $1.41 \pm 0.17$  years

compared with those with NHL as their AIDS-defining illness ( $2.09 \pm 0.46$  years,  $P = 0.17$ ). It should be noted that the CD4 counts of patients with a preceding AIDS-defining illness were significantly lower ( $P < 0.02$ ) upon diagnosis of NHL than those for patients with NHL as their AIDS-defining illness ( $40.5 \pm 9.0$  and  $220.3 \pm 77.3 \times 10^6/L$ , respectively).

Age at the time of diagnosis of HIV has been found to influence survival. When the population of the SAC cohort with NHL was divided into those older or younger than 50 years, there was no difference in survival ( $1.31 \pm 0.50$  years and  $1.23 \pm 0.28$  years, respectively). Patients older than 50 years and those younger than 50 years responded similarly to NHL therapy (complete response rates 50.0% versus 48.0%). There was no difference in incidence of therapy-related side effects between these groups. Patients older than 50 years had similar CD4 counts, at the time of diagnosis of NHL, to those younger than 50 years ( $126.0 \pm 44.2$  versus  $148.1 \pm 46.4 \times 10^6/L$ ). Among patients with HIV-associated NHL younger than 50 years, 10.0% had coexisting KS and 26.7% had NHL involving the CNS. Contrary to this, there were no cases of KS in association with NHL or NHL involving the CNS in patients above the age of 50 years. Those older than 50 years who developed NHL of the GI tract generally had reduced survival compared with younger patients with GI NHL (mean survival  $0.83 \pm 0.29$  years versus  $2.18 \pm 0.67$ ,  $P < 0.10$ ). Patients older than 50 years had a decreased incidence of an AIDS-defining illness before diagnosis of NHL compared with younger patients (37.5% versus 60%). When data excluding patients with NHL of the CNS or only data from patients with a preceding AIDS-defining illness were examined, again there was no difference in survival in patients older than 50 years and those younger.

Thirty-two of 39 cases of NHL were treated with chemotherapy, surgery, radiotherapy or combination therapy (Table 1). Chemotherapy, radiotherapy and surgery were well tolerated. In four of 18 cases, chemotherapy was modified due to thrombocytopenia and/or neutropenia. Seven patients received no therapy. Of these individuals, one died before the initiation of therapy, NHL was diagnosed on autopsy in one patient and five refused therapy. Complete response, as defined by no evidence of disease six months following therapy, was achieved in 15 of 32 cases. Six of these patients survived more than three years. Three patients died less than six months following therapy but were disease-free at that time, and three patients were less than six months post-therapy at the close of this study. There were two documented cases of relapse of NHL after no evidence of disease was present for more than one year. Therapy and type of therapy did not significantly affect survival. However, the efficacy of therapies could not be accurately assessed due to the retrospective design of this study.

Patients who achieved a complete response to therapy survived longer than those who failed to achieve a complete response ( $2.52 \pm 0.44$  years versus  $0.42 \pm 0.10$  years, respectively,  $P < 0.01$ ). Patients who achieved a complete response were of similar age but had significantly higher ( $P < 0.04$ ) CD4 counts than those who did not have a complete response

( $259.57 \pm 87.91$  and  $56.13 \pm 11.30 \times 10^6/L$ , respectively). Eleven of 17 patients who failed to achieve a complete response had NHL involvement of the CNS and/or at multiple sites.

In 32 of 39 (82.1%) cases, patients were on antiretroviral therapy at the time of diagnosis of NHL. The mean duration of antiretroviral therapy before the development of NHL could not be accurately determined from the available records.

## DISCUSSION

The incidence of HIV-associated NHL is increasing in the United States and Europe, and this increase will likely continue as patients with HIV live longer (8,10). In the SAC population, 3.4% of HIV-positive patients developed NHL, similar to other studies and approximately 60 times greater than in the general public (8,14).

The predilection of HIV-associated NHL to present at an extranodal location has been documented in this and other studies (2-6,10,13,15,16). In the SAC cohort 89.7% of patients presented with NHL at an extranodal site. GI tract involvement occurred in 33.3% of the SAC cohort with NHL, which is in keeping with other studies (2,4,5,13,17).

High grade lymphoma accounts for less than 10% of NHL in the HIV-negative population compared with the 94.8% in this study, which is higher than most previous reports (2-5). A more modest increase in high grade NHL has been noted in other immunosuppressed states such as organ transplantation (18). The reason for this increased incidence of high grade NHL in HIV is not known. It has been postulated that HIV may play an indirect role in the pathogenesis of NHL. However, the HIV genome is usually absent in HIV-associated NHL tissue (7,8). The rate of NHL does not generally vary with the risk factor for acquiring HIV infection, but the incidence of both KS and NHL is lower in hemophiliacs infected with HIV than in HIV-positive homosexuals (14,19). Interestingly, an increased risk of developing NHL has been found in patients with KS, herpes simplex virus co-infection and a low neutrophil count (20). In the present study, there was no difference in the rate of KS between the patients with NHL and the rest of the HIV-infected patients.

In the present study the mean survival from the diagnosis of NHL was 1.25 years with a median survival of 0.76 years. How NHL alone affected survival could not be determined in this study. Survival of AIDS patients is closely linked to the degree of immunosuppression at the time of diagnosis (21-24). It is difficult to estimate accurately the predicted survival of the SAC cohort with NHL, independent of diagnosis of NHL. Several studies have looked at CD4 as a predictor of survival, and one such study found the median survival of patients with a CD4 count of 100 to 199 to be 68 months in a group of HIV-infected hemophiliacs (22). In a general population of HIV-infected males, a median survival of patients with a CD4 count from 100 to 200 was found to be 20.3 months (21). These estimates are well above the 0.76-year median survival found in this study, suggesting that NHL markedly reduced survival in the SAC cohort. Several studies that have shown that NHL in HIV is an indicator of poor prognosis (2-6,8,10,21,23,25). Only one of these studies performed a Cox regression analysis

to look independently at the role of development of NHL on survival and found that these patients had reduced survival (21). The median survival for patients with HIV-associated NHL has generally been reported to be between three and nine months, similar to what was found in the present study (2-5,15,21,25,26).

The initial AIDS-defining illness has been shown to influence survival (21). Most notably, the AIDS-defining illnesses – HIV encephalopathy, cytomegalovirus (CMV) infection, mycobacteriosis and NHL – have been associated with decreased survival (21). In the SAC cohort with NHL, there was no difference in survival between patients who had NHL as their AIDS-defining illness and those who had another AIDS-defining illness when taken from the date of the initial AIDS-defining illness. When survival was measured from the date of diagnosis of NHL, patients with a preceding AIDS-defining illness had significantly reduced survival. The development of more than one AIDS-defining illness has also been found to be associated with decreased survival (21) and this was confirmed in the present study. In the SAC cohort, those with a previous AIDS-defining illness before the diagnosis of NHL had significantly lower CD4 counts and this may have played a role in their decreased survival. However, one study has shown that the development of certain AIDS-defining illnesses including NHL, HIV encephalopathy, CMV and/or two or more AIDS-defining illnesses reduced survival independent of CD4 count (21).

Patients with HIV-associated NHL of the CNS have been found to have markedly decreased survival compared with patients with NHL at other sites; thus, survival figures can be biased by the proportion of such patients within a study (10,25,26). In the SAC cohort, 20.5% had CNS NHL, similar to several other studies (2-5,25,26). In the SAC cohort, those with NHL of the CNS appeared to represent a distinct subgroup of patients. They were significantly younger, had significantly lower CD4 counts and had significantly reduced survival compared with those with NHL at other sites. Reduced survival and lower CD4 counts in CNS NHL have been noted previously; however, there have not been reports of a tendency for CNS NHL to occur in younger individuals (2-5,25,26).

In a large study of all new adolescent and adult cases of AIDS diagnosed in Australia from 1991 to 1994 ( $n=3204$ ) it was found that age less than 50 years at the time of diagnosis of AIDS was associated with longer survival (21). When the SAC population with NHL was divided into those greater or less than 50 years of age, there was no difference in survival or response to therapy. However, the sample size of this study has limited power to detect small differences in subgroups.

A complete response was seen in 15 of 32 patients (46.9%) who received NHL therapy, consistent with several other studies (3,16,25,27). One of the highest response rates was reported by Bermudez et al (26), in which 64% of patients had a complete response to MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, bleomycin, prednisone). This was one of the chemotherapy regimens in the present study. Due to the retrospective nature of this study the efficacy of differing therapies could not be assessed.

This study suggests that NHL occurs in approximately 3% of the HIV population of southern Alberta and is associated with reduced survival. The main features that appeared to influence survival of those with HIV-associated NHL were the severity of immune suppression; previous AIDS-defining illnesses; and the site of NHL involvement. With improved survival of HIV-infected individuals it is essential that we gain a better understanding of HIV-associated NHL with aims of developing improved treatment strategies and further prolonging survival.

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