CD4 counts and the risk of systemic non-Hodgkin's lymphoma in individuals with HIV in the UK

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ABSTRACT

Since the introduction of highly active antiretroviral therapy, there has been a decline in the incidence of non-Hodgkin's lymphoma among HIV-infected individuals. We described trends in the incidence of systemic non-Hodgkin's lymphoma in the UK CHIC Study from 1996-2006 and evaluated the association between immunosuppression and development of systemic non-Hodgkin's lymphoma: 286/23,155 (1.2%) individuals developed an AIDS-defining lymphoma (258 systemic). Younger age, receipt of highly active antiretroviral therapy and later calendar year were all independently associated with a reduced risk of systemic non-Hodgkin's lymphoma. A lower latest CD4 count was strongly associated with systemic non-Hodgkin's lymphoma, in patients who had (RR per $\log_2$(cells/mm^3) higher: 0.62) and had not (0.70) received highly active antiretroviral therapy. Associations with other measures of immunosuppression, including nadir CD4 count, experience and duration of severe immunosuppression, were generally weaker. Earlier highly active antiretroviral therapy initiation and wider access to HIV testing is advocated to reduce the risk of systemic non-Hodgkin's lymphoma.

Key words: non-Hodgkin's lymphoma, HIV, immunosuppression, CD4 count, cohort study.

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Introduction

Registry linkage studies in the pre-highly active antiretroviral therapy (HAART) era found that the incidence of high grade B-cell non-Hodgkin's lymphoma (NHL) in HIV-infected individuals was 60-200 times higher than that in HIV-uninfected persons. The introduction of HAART during the mid-1990s has been associated with a fall in incidence of opportunistic infections and AIDS-associated malignancies.[1,2] The decline in NHL has been attributed to the immune reconstitution produced by HAART[3] but this association remains uncertain. The aim of this study was to investigate the effects of demographic, immunological and treatment-related variables on the incidence of systemic NHL in a large multi-center cohort study.

Design and Methods

The UK Collaborative HIV Cohort (UK CHIC) Study is a collaboration of some of the largest HIV treatment centers in the UK. The dataset contains routinely collected clinical data on all HIV-infected individuals >16 years of age attending one of the centers since 1st January 1996.[4] The dataset used for this analysis contains information on 29,056 individuals from eleven centers (*Online Supplementary Appendix*) until 2006. The UK CHIC Study was approved by a multicenter research ethics committee and by local ethics committees.

Of the 29,056 individuals in the dataset, 5,901 were excluded as they had no prospective CD4 count measurements, their only CD4 counts were after diagnosis of NHL, they had NHL

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prior to or at cohort entry (only 32 patients were diagnosed concomitantly with HIV and NHL). Follow-up was determined from the latest date of 1st January 1996, first clinic attendance or first CD4 count until NHL diagnosis; follow-up on patients without NHL was censored at death/three months after the patient's last CD4 count. Only AIDS-defining NHL were considered; these were grouped as systemic (diffuse large B-cell, immunoblastic, Burkitt's, Burkitt's-like or histological subtype unknown) or primary cerebral NHL (PCL).

All analyses were performed using the statistical package SAS, version 9.1. Univariable Poisson regression identified factors associated with the incidence of systemic NHL. As the number of patients developing PCL was too small for robust analyses, follow-up on patients developing PCL was censored at lymphoma diagnosis. Variables significantly associated with systemic NHL ($p<0.05$) were included in a multivariable model to identify the factors independently associated with systemic lymphoma. In addition to demographic/clinical variables (sex, ethnicity, exposure group, calendar year, age, receipt of HAART, latest HIV RNA), we also considered various measures of immunosuppression, including the nadir and latest CD4 count, whether the patient had experienced severe immunosuppression (≥1 CD4 count <200 cells/mm^3), and the cumulative duration of severe immunosuppression (time with CD4 count <200 cells/mm^3) (as time-updated variables). Whilst all continuous variables were categorized in exploratory analyses, we investigated whether inclusion of each variable as a continuous covariate would be appropriate in multivariable regression models. Thus, the latest CD4 count and viral load and the duration of immunosuppression were included as continuous covariates. In contrast, as few patients on HAART had a nadir CD4 >350 cells/mm^3, the three highest categories of this variable were combined, and the variable was retained as a categorical variable.

HAART was defined as any combination that included a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor, abacavir or enfurvitide (T-20). Whilst our definition of HAART could include patients starting fewer than 3 drugs, 98% of patients in UK CHIC start regimens including ≥3 drugs. Analyses were also performed separately in those who had and had not received HAART (with patients starting HAART contributing to both analyses). Of note, models that include CD4 count nadir together with the latest CD4 count are meaningful only in the context of ART-experienced patients. Sensitivity analyses considered the association between the latest CD4 count and the risk of systemic NHL separately in those with suppressed (≤50 copies/mL) and unsuppressed viral loads.

Results and Discussion

The 23,155 individuals were followed for a total of 120,361 years (median 3.8, range 0.0-11.7). Over this time, 286 (1.2%) developed an AIDS-defining lymphoma (Table 1), of whom 131 (45.8%) have died (median survival: 0.3 (95% CI 0.2-0.4) years). Patients with systemic NHL and PCL were broadly similar in terms of sex, ethnicity, risk group and age (Table 1) but CD4 counts were lower and viral loads higher in those with PCL. The median time between consecutive CD4 counts was 100 days (interquartile range: 77-137) and the median time from the last CD4 count to lymphoma diagnosis was 25 (0-60) days.

In univariable analyses, systemic NHL was more common in homosexual men compared to other individuals

Table 1. Characteristics of patients developing systemic and primary cerebral lymphomas, and those not developing lymphoma, at entry to the study.

			Development of lymphoma		
		N.	Yes - total	Systemic	Primary cerebral lymphoma
Number of patients		25106	286	258	28
Sex:	Male	19010 (75.7)	251 (87.8)	226 (87.6)	25 (89.3)
Ethnicity	White	15026 (59.9)	205 (71.7)	184 (71.3)	21 (75.0)
	Black African	6024 (24.0)	42 (14.7)	37 (14.3)	5 (17.9)
	Other/not known	4056 (16.2)	39 (13.6)	37 (14.3)	2 (7.1)
Risk group	Homo/bisexual	14040 (55.9)	201 (70.3)	180 (69.8)	21 (75.0)
	Heterosexual	8296 (33.0)	57 (19.9)	54 (20.9)	3 (10.7)
	Other/not known	2770 (11.0)	28 (9.8)	24 (9.3)	4 (14.3)
Age (years)	Median (range)	34 (16-83)	37 (18-69)	37 (18-69)	35 (25-56)
CD4 count (cells/mm^3)	Median (range)	312 (0-2827)	216 (0-1486)	225 (0-1486)	74 (0-775)
HIV RNA (log_{10} copies/mL)	Median (range)	4.4 (1.7-7.7)	4.7 (1.7-6.1)	4.7 (1.7-6.1)	5.5 (2.3-5.8)
Use of HAART prior to lymphoma development:		n/a	172 (60.1)	150 (58.1)	22 (78.6)
Median (range) duration of use (years)			1.3 (0.1-8.9)	1.2 (0.1-8.9)	1.5 (0.1-8.6)
Years from HIV diagnosis to lymphoma	Median (range)	n/a	5.3 (0.0-21.2)	5.3 (0.0-21.2)	5.3 (0.1-18.6)
Deaths		1791 (7.1)	131 (45.8)	107 (41.5)	24 (85.7)
Post-lymphoma survival (years)	Median (95% CI)*	n/a	0.28 (0.21-0.38)	0.36 (0.24-0.44)	0.12 (0.06-0.15)

**Obtained from Kaplan-Meier analysis. Table entries are n (%) unless otherwise stated.*

(p=0.02), and in men than women (p=0.002, Table 2). The incidence of systemic NHL increased with age (p=0.01). There were no significant differences in systemic lymphoma rate according to ethnicity (p=0.24), but receipt of HAART (p=0.0001) and later calendar periods (p=0.0001) were both associated with a reduced rate of systemic NHL. Immunosuppression, whether defined by the latest (p=0.0001) or nadir (p=0.0001) CD4 count, ever experiencing severe immunosuppression (p=0.0001) or the duration of severe immunosuppression (p=0.0001), was strongly associated with an increased systemic NHL rate in univariable analyses. Despite this, of the 258 cases of

Table 2. Results from univariable Poisson regression analyses of factors associated with development of systemic lymphomas.

Factor		Systemic lymphomas	PYFU	Incidence rate/ per 1000 PYFU (95% CI)	Rate Ratio (95% CI)	p value
Sex						
	Male	226	92559	2.4 (2.1-2.8)	1	0.002
	Female	32	24130	1.3 (0.9-1.8)	0.55 (0.38-0.81)	
Ethnicity						
	White	184	78133	2.4 (2.0-2.7)	1	0.24
	Black African	37	22571	1.6 (1.1-2.2)	0.74 (0.52-1.06)	
	Other/not known	37	15988	2.3 (1.6-3.1)	0.99 (0.68-1.43)	
Risk group						
	Homo/bisexual	180	72965	2.5 (2.1-2.8)	1	0.02
	Heterosexual	54	32299	1.7 (1.2-2.1)	0.67 (0.49-0.92)	
	Other/not known	24	11426	2.1 (1.3-2.9)	0.72 (0.45-1.15)	
Age (years)						
	16-35	83	45179	1.8 (1.4-2.2)	0.47 (0.28-0.78)	0.01
	36-45	108	48865	2.2 (1.8-2.6)	0.63 (0.39-1.03)	
	46-55	47	17016	2.8 (2.0-3.6)	0.75 (0.44-1.28)	
	>56	20	5630	3.6 (2.0-5.1)	1	
Calendar year						
	1996-1997	62	12915	4.8 (3.6-6.0)	3.33 (2.36-4.68)	0.0001
	1998-2000	71	26527	2.7 (2.1-3.3)	1.73 (1.24-2.42)	
	2001-2003	45	23361	1.9 (1.4-2.5)	1.31 (0.90-1.91)	
	2004-2006	80	53886	1.5 (1.2-1.8)	1	
Any severe immunosuppression*						
	No	81	58112	1.4 (1.1-1.7)	1	0.0001
	Yes	177	58577	3.0 (2.6-3.5)	2.11 (1.61-2.78)	
Duration of severe immunosuppression (years)*						
	0	81	58112	1.4 (1.1-1.7)	1	0.0001
	>0, ≤1	88	28053	3.1 (2.5-3.8)	2.15 (1.57-2.95)	
	>1, ≤2	26	10680	2.4 (1.5-3.4)	1.65 (1.05-2.58)	
	>2, <3	21	6505	3.2 (1.9-4.6)	2.23 (1.35-3.69)	
	>3, ≤4	7	4428	1.6 (0.6-3.3)	1.21 (0.56-2.62)	
	>4	35	8911	3.9 (2.6-5.2)	2.92 (1.95-4.37)	
Latest CD4 count (cells/mm^3)						
	<50	39	3323	11.7 (8.1-15.4)	18.60 (11.06-31.30)	0.0001
	50-199	92	15712	5.9 (4.7-7.1)	8.93 (5.63-14.16)	
	200-349	70	29751	2.4 (1.8-2.9)	3.65 (2.27-5.87)	
	350-499	32	29483	1.1 (0.7-1.5)	1.64 (0.95-2.84)	
	≥500	25	38421	0.7 (0.4-0.9)	1	
Nadir CD4 count (cells/mm^3)						
	<50	69	23787	2.9 (2.2-3.6)	5.20 (2.10-12.92)	0.0001
	50-199	121	39515	3.1 (2.5-3.6)	5.30 (2.16-12.99)	
	200-349	51	29953	1.7 (1.2-2.2)	2.92 (1.16-7.36)	
	350-499	12	13914	0.9 (0.5-1.5)	1.64 (0.58-4.66)	
	>500	5	9521	0.5 (0.2-1.2)	1	
Latest viral load (log_{10} copies/mL)						
	<1.7	51	50581	1.0 (0.7-1.3)	1	0.0001
	1.7-2.7	31	11761	2.8 (1.7-3.6)	2.56 (1.60-4.09)	
	2.7-3.7	22	12106	1.8 (1.1-2.6)	1.87 (1.12-3.12)	
	3.7-4.7	44	20001	2.2 (1.6-2.9)	2.04 (1.33-3.14)	
	4.7-5.7	62	13363	4.6 (3.5-5.8)	4.59 (3.12-6.75)	
	>5.7	9	1139	7.9 (3.6-15.0)	8.50 (4.17-17.35)	
Receipt of HAART						
	No	121	39165	3.1 (2.5-3.6)	1	0.0001
	Yes	137	77525	1.8 (1.5-2.1)	0.57 (0.44-0.73)	

*PYFU: person years of follow-up; CI: confidence interval; HAART: highly active antiretroviral therapy; *Any severe immunosuppression defined as ever having had a CD4 count <200 cells/mm^3; Duration of severe immunosuppression defined as the length of time that an individual has spent with a CD4 count <200 cells/mm^3.*

Table 3. Results from a series of univariable and multivariable Poisson regression analyses showing the relationships between the systemic lymphoma rate, the latest CD4 count, and other measures of advanced HIV infection.

	Patients not receiving HAART			Patients receiving HAART		
	Rate ratio	95% CI	*p* value	Rate ratio	95% CI	*p* value
Unadjusted analyses						
Latest CD4 count (per $\log_2$ higher)	0.67	0.61-0.73	0.0001	0.62	0.57-0.67	0.0001
Nadir CD4 count (cells/mm^3)						
<50	5.74	3.46-9.55	0.0001	2.78	1.59-4.88	0.0004
50-199	4.29	2.84-6.49	0.0001	2.77	1.62-4.72	0.0002
≥200	1	–		1	–	
Any severe immunosuppression*	4.19	2.89-6.06	0.0001	2.63	1.65-4.20	0.0001
Duration of severe immunosuppression (per year)*	1.28	1.18-1.39	0.0001	1.13	1.06-1.20	0.0001
Latest viral load (per $\log_{10}$ copies/mL higher)	1.74	1.33-2.27	0.0001	1.48	1.31-1.66	0.0001
Adjusted analyses+						
Model 1						
Latest CD4 count (per $\log_2$ higher)	0.70	0.63-0.77	0.0001	0.62	0.57-0.68	0.0001
Model 2						
Latest CD4 count (per $\log_2$ higher)	n/a			0.58	0.52-0.64	0.0001
Nadir CD4 count (cells/mm^3)						
<50				0.77	0.39-1.51	0.44
0-199				1.72	1.00-2.97	0.05
≥200				1	–	
Model 3						
Latest CD4 count (per $\log_2$ higher)	0.76	0.68-0.85	0.0001	0.64	0.58-0.70	0.0001
Any severe immunosuppression*	2.05	1.30-3.24	0.002	1.43	0.88-2.35	0.15
Model 4						
Latest CD4 (per $\log_2$ higher)	0.71	0.64-0.79	0.0001	0.62	0.57-0.68	0.0001
Duration of severe immunosuppression (per year)*	1.06	0.94-1.20	0.32	0.99	0.92-1.07	0.83
Model 5						
Latest CD4 (per $\log_2$ higher)	0.73	0.62-0.85	0.0001	0.68	0.61-0.76	0.0001
Latest viral load (per $\log_{10}$ copies/mL higher)	1.38	1.07-1.80	0.01	1.17	1.01-1.36	0.04
Any severe immunosuppression*	1.79	1.04-3.09	0.04	1.47	0.89-2.43	0.13

**Any severe immunosuppression defined as ever having had a CD4 count <200 cells/mm^3; Duration of severe immunosuppression defined as the length of time that an individual has spent with a CD4 count <200 cells/mm^3. + Adjusted for age, calendar year as well as the variables listed in the table.*

systemic NHL, 127 (49%) occurred with a most recent CD4 count of >200 cells/mm^3 (62 (48.8%) were antiretroviral-naïve), and 57 (22%) with a most recent CD4 count of >350 cells/mm^3 (29 (50.9%) were antiretroviral-naïve).

Of the demographic and treatment variables, only older age [RR (95% CI) /5 years older: 1.13 (1.10-1.27), *p*=0.0001], receipt of HAART [0.66 (0.50-0.88), *p*=0.005] and calendar year [compared to 2004-2006, 1996-1997: 3.06 (2.09-4.48); 1998-2000: 1.78 (1.26-2.51); 2001-2003: 1.34 (0.91-1.96), *p*=0.0001] were associated with an increased systemic NHL rate in multivariable analyses.

In univariable analyses (Table 3), all markers of immunosuppression were strongly associated with the risk of systemic NHL both in those receiving and not receiving HAART (Table 3, top). Patients with lower nadir CD4 counts, those who had ever experienced severe immunosuppression and those who had been exposed to severe immunosuppression for longer periods of time were all at higher risk of developing systemic NHL regardless of whether they were receiving HAART, although relative rates were generally closer to unity in those who had received HAART. Furthermore, a higher latest viral load was associated with an increased risk of systemic NHL in both groups of patients. After adjustment for age and calendar year (Table 3, bottom), the latest CD4 count remained strongly associated with the systemic NHL rate in both groups of patients. After adjustment for this variable, however, the association with the nadir CD4 count (in those who had received HAART only), whilst statistically significant, was weaker and did not suggest a higher systemic NHL rate in those with the lowest nadirs. After adjusting for the latest CD4 count, there was no independent relationship between the systemic NHL rate and the duration of severe immunosuppression regardless of HAART exposure. The fact that a patient had experienced severe immunosuppression, however, was independently associated with an increased systemic NHL rate, particularly in those who were not receiving HAART (RR 2.05 [1.30-3.24], *p*=0.002). These associations were similar in mod-

els that additionally included the latest viral load which was significantly associated with the systemic NHL rate. Similar results were obtained after stratifying according to the latest viral load (≤ or > 50 copies/mL) rather than HAART status (*data not shown*).

Our data show that the incidence of systemic NHL has declined over the HAART era, extending the observations in previous publications;[5-12] the continuing decline in incidence may explain some of the differences between this dataset and the recently published Swiss cohort findings.[13] Several studies have found that HAART reduces the incidence of NHL.[2,5,7,14,15] It has been postulated that the mechanism underlying the protective effect of HAART is immune restoration resulting in immunological clearance of EBV and/or EBV-infected memory B-lymphocytes, thought to be the origin of these lymphomas. Indeed HIV patients who develop PCL lack EBV-specific $CD4^+$ T cell-dependent interferon γ production[16] and higher EBV viral loads are associated with both HIV infection and lower CD4 cell counts.[17]

Previous studies have shown that the CD4 count at cohort enrolment[13,18] or at AIDS diagnosis,[19] the nadir CD4[13,18] and latest CD4 count[20] are each associated with an increased risk of NHL. In the present analyses, whilst each measure was associated with an increased NHL risk, the variable most strongly correlated with NHL risk was the latest CD4 cell count. Our findings are similar to those from the CASCADE study in which the latest CD4 cell count was a better predictor of NHL risk than the nadir CD4 count, the time-weighted average CD4 count or the proportion of time with a CD4 cell count $<100/mm^3$.[20] Our finding that almost half of systemic NHL cases were among those with a latest CD4 count of >200 cells/mm^3 and nearly a quarter with a latest count >350 cells/mm^3 supports the recent shift towards earlier initiation of HAART as a means of further reducing the incidence of NHL.[21,22] Additionally, given that a significant proportion of those diagnosed with NHL had low CD4 counts and had not had the opportunity to benefit from HAART, our data support recent strategies to widen HIV testing in order to reduce late diagnosis of HIV infection and optimize the benefits of treatment.[23]

Whilst our cohort tends to over-represent homosexual men, as it expands in size and geographical distribution this effect is declining. As with many large multi-center cohort studies, patients may be lost to follow-up and the CD4 cell count history may be incomplete for others. Our cohort did not have the benefit of central pathological review of systemic NHL and, indeed, many of the data collection tools do not distinguish between these. This may be important since previous studies have suggested that for Burkitt's lymphoma, unlike other systemic lymphomas, risk does not correlate with CD4 count.[19] In addition, compared to other HIV-infected patients with systemic NHL of the diffuse large B-cell type, those with Burkitt's lymphoma are younger, with less advanced HIV disease.[24]

We have confirmed previous findings that the risk of systemic lymphoma has significantly declined in the HAART era and have confirmed that the risk of systemic NHL is most strongly associated with the latest CD4 count rather than the nadir CD4 count or duration of immunosuppression. However, the finding that a significant minority of cases occur at CD4 counts above those at which many individuals are diagnosed with HIV or HAART is generally initiated, supports a shift towards earlier initiation of HAART and wider access to HIV testing.

Authorship and Disclosures

MF and IR designed the research; CAS, TH, LB and ANP performed all analyses, designed the tables and drafted the Methods and Results of the manuscript; MB and MF drafted the Introduction and Discussion sections of the manuscript; JW, CO, RG, PE, MJ, BG, CL, DP, AS, JA, MG and KP contributed to the design of the study, the ongoing collection of data and continued quality control, the interpretation of the results and have provided critical input into the final version of the manuscript prior to submission.

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