Hodgkin lymphoma in the Swiss HIV Cohort Study

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Hodgkin lymphoma (HL) risk is elevated among persons infected with HIV (PHIV) and has been suggested to have increased in the era of combined antiretroviral therapy (cART). Among 14 606 PHIV followed more than 20 years in the Swiss HIV Cohort Study (SHCS), determinants of HL were investigated using 2 different approaches, namely, a cohort and nested case-control study, estimating hazard ratios (HRs) and matched odds ratios, respectively. Forty-seven incident HL cases occurred during 84 611 person-years of SHCS follow-up. HL risk was significantly higher among men having sex with men (HR vs intravenous drug users = 2.44, 95% confidence interval [CI], 1.13-5.24) but did not vary by calendar period (HR for 2002-2007 vs 1995 or earlier = 0.65, 95% CI, 0.29-1.44) or cART use (HR vs nonusers = 1.02, 95% CI, 0.53-1.94). HL risk tended to increase with declining CD4$^+$ cell counts, but these differences were not significant. A lower CD4$^+$/CD8$^+$ ratio at SHCS enrollment or 1 to 2 years before HL diagnosis, however, was significantly associated with increased HL risk. In conclusion, HL risk does not appear to be increasing in recent years or among PHIV using cART in Switzerland, and there was no evidence that HL risk should be increased in the setting of improved immunity. (Blood. 2009;113:5737-5742)

Introduction

Persons infected with HIV (PHIV) are at significantly increased risk of Hodgkin lymphoma (HL),[1] with standardized incidence ratios (SIRs) 5- to 30-fold higher than the general population.[2-14] SIRs for HL are significantly elevated in all strata of gender and HIV-transmission category.[2-4,6,10,14] The relationship between HL risk and degree of immunodeficiency is, however, clearly less strong than those for AIDS-defining cancers Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL). Some epidemiologic data have suggested that HL risk may be higher among PHIV at moderate than at severe levels of immunodeficiency[15] and hence in the setting of improved immunity because of combined antiretroviral therapy (cART).[2] Some biologic support to this possibility came from the observation that a complex inflammatory microenvironment, including CD4$^+$ T cells, seems to be essential for the survival of HL (Reed-Sternberg) cells.[16,17]

Some studies,[10-12,18] although not all,[14] have indeed reported a higher SIR for HL among PHIV (in comparison to the general population) in the period since the introduction of cART in 1996. Furthermore, in a previous report from the Swiss HIV Cohort Study (SHCS), the SIR for HL appeared higher among cART users than nonusers.[2]

Hence, we took advantage of the more than 20 years of follow-up data available from the SHCS to assess the incidence of and risk factors for HL in PHIV, with a particular aim to address the uncertain role of immunodeficiency and cART use on HL onset.

Methods

The SHCS is an ongoing study that has been enrolling PHIVs since 1984 from 7 large hospitals in Switzerland and affiliated regional hospitals and private practitioners (www.shcs.ch). Detailed information on disease, laboratory tests, and HIV-related treatments is collected at enrollment and at each 6-month follow-up visit. The present study included 14 606 PHIV enrolled and followed up in the SHCS database up to May 2007.

A total of 77 HL cases were identified in SHCS participants, of which 66 were identified from the SHCS database, and 11 were identified through record linkage with 8 Swiss Cantonal Cancer Registries.[2] Of these, 23 prevalent cases occurred before, or within 1 month of, SHCS enrollment and 7 were diagnosed more than 6 months after the last SHCS follow-up date, leaving 47 eligible incident cases occurring during active SHCS follow-up (median follow-up from SHCS enrollment to HL diagnosis = 5 years; interquartile range, 2-9 years).

Confirmation of histologic subtype was available for 37 (78.9%) of the 47 HL cases, including 18 mixed cellularity (ICD-O code 96523), 11 nodular sclerosis (96633), 6 lymphocyte depleted (96533), and 2 nodular sclerosis with lymphocyte predominance (96653, 96613).

Markers of immunodeficiency, including total lymphocyte, CD4$^+$ and CD8$^+$ cell counts, as well as CD4$^+$ and CD8$^+$ percentages (as percentage of total lymphocytes), were retrieved from available measurements routinely recorded in the SHCS database. For the calculation of incidence rates and HRs ("Statistical analysis"), PHIVs were classified by these markers at SHCS enrollment.

To assess markers of immunodeficiency at time periods closer to HL diagnosis, a complementary nested case-control analysis was also undertaken. For each of the 47 HL cases, a maximum of 10 control subjects were

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Table 1. Crude incidence rates and HR of HL overall, and by selected characteristics of PHIV enrolled in the SHCS

	Person-years	HL	Crude incidence, per 100 000 person-years (95% CI)	HR (95% CI)*
Overall	84 611	47	55.5 (40.8-73.9)	
Age, y†				
34 or younger	31 699	14	44.2 (24.1-74.3)	1
35-44	33 328	21	63.0 (38.9-96.5)	1.19 (0.58-2.42)
45 or older	19 584	12	61.3 (31.5-107)	1.01 (0.44-2.32)
HIV-transmission category				
IDUs	27 444	10	36.4 (17.4-67.3)	1
Heterosexuals/other	28 408	13	45.8 (24.3-78.5)	1.33 (0.58-3.08)
MSM	28 759	24	83.5 (53.4-124)	2.44 (1.13-5.24)
Calendar period†				
1995 or earlier	23 839	15	62.9 (35.1-104)	1
1996-2000	22 611	11	48.7 (24.1-87.4)	0.66 (0.29-1.49)
2001-2007	38 161	21	55.0 (34.0-84.3)	0.65 (0.29-1.44)
AIDS history†				
No	65 242	33	50.6 (34.8-71.1)	1
Yes	19 368	14	72.3 (39.4-122)	1.27 (0.67-2.43)
cART use†				
No	39 560	20	50.6 (30.8-78.2)	1
Yes	45 051	27	59.9 (39.5-87.3)	1.02 (0.53-1.94)

*Adjusted for age and HIV-transmission category, when appropriate.

†Time-dependent variable; the same person can contribute person-years to more than one category.

matched at random from eligible SHCS participants with at least the same length of follow-up in the SHCS. Matching criteria were: (1) SHCS center; (2) gender; (3) age group at SHCS enrollment (< 24, 25-34, 35-44, 45-54, ≥ 55 years); (4) calendar period at enrollment (1985-1989, 1990-1992, 1993-1995, 1996-1998, 1999-2001); and (5) HIV-transmission category (men having sex with men [MSM], intravenous drug users [IDUs], and heterosexual/other). Markers of immunodeficiency were extracted from the SHCS database at 2 time periods (1-2 years and < 1 year) before the reference date, defined for cases as that of HL diagnosis, and for controls as that occurring after a similar length of follow-up in the SHCS as the matched case before HL diagnosis.

cART use was defined as the prescription of at least 3 antiretroviral drugs, including a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor or 3 nucleosides, including abacavir. Only persons who had used cART for more than 1 month were classified as users. Person-years of cART use can include periods when treatment was interrupted.

The SHCS has been approved by the ethical committees of all the collaborating clinics, and the present analysis was additionally approved by the scientific committee of the SHCS and the ethics committee of the International Agency for Research on Cancer. Written informed consent was obtained from all SHCS participants in accordance with the Declaration of Helsinki.

Statistical analysis

For each participant, person-years at risk were calculated from SHCS enrollment to HL diagnosis, death, or 6 months after the last SHCS follow-up visit (6 months being the average time between SHCS visits), whichever occurred first. Crude incidence rates and 95% confidence intervals (CIs) of incidence were computed according to the Poisson distribution.[19] The effects of various risk factors on HL onset were assessed using hazard ratios (HRs) and corresponding 95% CIs, estimated by the Cox proportional hazard model,[20] adjusted for age at SHCS enrollment (≤ 34, 35-44, ≥ 45 years) and HIV-transmission category (MSM, IDUs and heterosexual/other). Age, calendar period, cART use, and history of AIDS diagnosis were introduced as time-dependent variables in the model, that is, the same person could contribute person-years to more than one category.

For the case-control study, logistic regression, conditioned on matching variables, was used to calculate odds ratios (ORs) and corresponding 95% CIs.

The $CD4^+/CD8^+$ ratio was calculated as a ratio of the absolute $CD4^+$ and $CD8^+$ cell counts. Tests for trends in markers of immunodeficiency were performed by dividing $CD4^+$ and $CD8^+$ cell counts into categories of 100 cells/μL, total lymphocytes into categories of 500 cells/μL, and $CD4^+$ percentages, $CD8^+$ percentages, and $CD4^+/CD8^+$ ratios into categories of 10%, and fitting them into the HR and OR models as continuous variables.

Results

A total of 47 incident HL cases occurred during 84 611 person-years of SHCS follow-up, equivalent to a crude incidence rate of 55.5 cases per 100 000 person-years (Table 1). There was no significant effect of age on HL risk. MSM showed significantly higher HL incidence than IDUs (HR = 2.44, 95% CI, 1.13-5.24). After adjustment for HIV-transmission category, HL incidence was not significantly different between males and females (HR = 1.01, 95% CI, 0.44-2.32, data not shown). HL risk did not differ significantly by calendar period (HR for 2001-2007 vs 1995 or earlier = 0.65, 95% CI, 0.29-1.44). Neither was there any evidence for a significant association between HL incidence and a history of AIDS (HR = 1.27, 95% CI, 0.67-2.43) or use of cART (HR for users vs nonusers = 1.02, 95% CI, 0.53-1.94; Table 1).

No significant differences in HL incidence between calendar periods (1996-2007 vs 1995 or earlier) or between users and nonusers of cART were observed also in stratified analyses by HIV-transmission category (Table 2). In all strata, however, crude HL incidence tended to be higher among MSM than other HIV-transmission categories (Table 2). HL incidence did not increase with duration of cART use (HR for > 5 years' vs ≤ 5 years' use = 0.68, 95% CI, 0.27-1.74; data not shown).

Table 3 shows the effects of markers of immunodeficiency at SHCS enrollment on HL incidence. There were no significant associations with HL incidence for categories of total lymphocyte count, $CD4^+$ cell count, $CD8^+$ cell count, or $CD4^+/CD8^+$ ratio at SHCS enrollment. There was, however, some suggestion of increasing HL incidence at lower $CD4^+$ cell counts (HR for ≤ 199 μL vs ≥ 500 μL = 1.81, 95% CI, 0.76-4.29) and at lower $CD4^+/CD8^+$ ratios (HR for $< 25\%$ vs $\geq 50\%$ = 1.97, 95% CI, 0.93-4.20). Although unavailable for a sizeable number of PHIV (n = 4564, predominantly those enrolled in the SHCS during the

Table 2. Crude incidence rates and HR of HL by HIV-transmission category, cART use, and calendar period

	MSM				Other			
	Person-years	HL	Crude incidence per 100 000 person-years (95% CI)	HR*	Person-years	HL	Crude incidence per 100 000 person-years (95% CI)	HR*
Calendar period†								
1995 or earlier	7674	8	104 (44.5-206)	1	16,164	7	43.3 (17.2-89.7)	1
1996-2007	21 085	16	75.9 (43.3-124)	0.58 (0.22-1.52)	39,687	16	40.3 (23.0-65.6)	0.89 (0.32-2.48)
cART use†								
No	12 237	11	89.9 (44.6-161)	1	27,322	9	32.9 (14.9-62.8)	1
Yes	16 522	13	78.7 (41.7-135)	0.72 (0.29-1.78)	28,529	14	49.1 (26.7-82.6)	1.62 (0.64-4.08)

*Adjusted for age.
†Time-dependent variable; the same person can contribute person-years to more than one category.

1980s), relative measures of $CD4^+$ counts (HR for $< 14\%$ vs $\geq 26\% = 4.01$, 95% CI, 1.42-11.3) and $CD8^+$ counts (HR for $< 50\%$ vs $\geq 60\% = 0.40$, 95% CI, 0.15-1.05), expressed as percentages of total lymphocytes, were associated with HL incidence, albeit in opposite directions. When expressed as continuous variables, lower $CD4^+/CD8^+$ ratio (HR per 10% decrease = 1.13, 95% CI, 1.02-1.23), lower $CD4^+$ percentage (HR per 10% decrease = 1.63, 95% CI, 1.27-1.99), and higher $CD8^+$ percentage (HR per 10% decrease = 0.68, 95% CI, 0.39-0.97) were significantly associated with increased HL incidence.

The aforementioned markers of immunodeficiency were also compared between the 47 incident HL cases and 444 correspondingly matched controls using a nested case-control approach. When measured at 1 to 2 years before HL diagnosis, ORs for HL by

Table 3. Crude incidence rates and HR of HL, by markers of immunodeficiency at enrollment in the SHCS

	Person-years	HL	Crude incidence per 100 000 person-years (95% CI)	HR (95% CI)*
Total lymphocyte count, cells/μL				
2000 or more	24 436	17	69.6 (40.4-112)	1
1000-1999	38 887	16	41.1 (23.5-67.0)	0.59 (0.30-1.16)
0-999	12 505	9	72.0 (32.6-137)	1.09 (0.48-2.48)
Unknown	8783	5		
Per 500/μL decrease				0.99 (0.85-1.13)
$CD4^+$ cell count, cells/μL				
500 or more	25 979	10	38.5 (18.3-71.1)	1
200-499	31 900	20	62.7 (38.2-97.0)	1.67 (0.78-3.58)
50-199	13 376	7	52.3 (20.7-108)	1.81 (0.76-4.29)
0-49	5116	5	97.7 (30.8-230)	
Unknown	8240	5		
Per 100/μL decrease				1.08 (0.97-1.20)
$CD8^+$ cell count, cells/μL				
1000 or more	25 004	16	64.0 (36.5-104)	1
500-999	35 164	17	48.4 (28.1-77.6)	0.74 (0.37-1.46)
0-499	15 247	9	59.0 (26.8-113)	0.94 (0.42-2.14)
Unknown	9196	5		
Per 100 cells/μL decrease				0.97 (0.93-1.01)
$CD4^+/CD8^+$ ratio, %				
50 or more	33 077	14	42.3 (23.1-71.2)	1
25-49	22 959	13	56.6 (30.0-97.1)	1.41 (0.66-3.01)
0-24	19 325	15	77.6 (43.3-128)	1.97 (0.93-4.20)
Unknown	9250	5		
Per 10% decrease				1.13 (1.02-1.23)
$CD4^+$ percentage				
26 or more	20 602	5	24.3 (7.7-57.1)	1
14-25	20 373	10	49.1 (23.4-90.6)	2.04 (0.69-5.97)
0-13	14 518	14	96.4 (52.5-162)	4.01 (1.42-11.3)
Unknown	29 117	18		
Per 10% decrease				1.63 (1.27-1.99)
$CD8^+$ percentage				
60 or more	19 107	14	73.3 (39.9-123)	1
50-59	15 057	9	59.8 (27.1-114)	0.85 (0.37-1.98)
0-49	21 147	6	28.4 (10.2-62.2)	0.40 (0.15-1.05)
Unknown	29 298	18		
Per 10% decrease				0.68 (0.39-0.97)

*Adjusted for age and HIV-transmission category, when appropriate.

Table 4. Nested case/control study: OR of HL, by markers of immunodeficiency at 2 different time periods before diagnosis

	1-2 years before HL					Within 1 year before HL				
	HL		Matched controls			HL		Matched controls		
	n	(%)	n	(%)	OR* (95% CI)	n	(%)	n	(%)	OR* (95% CI)
Overall	47		444			47		444		
Total lymphocyte count, cells/μL										
2000 or more	14	(36.8)	128	(39.3)	1	3	(7.3)	132	(34.6)	1
1000-1999	21	(55.3)	163	(50.0)	1.10 (0.53-2.31)	21	(51.2)	197	(51.6)	5.81 (1.68-20.1)
0-999	3	(7.9)	35	(10.7)	0.71 (0.18-2.78)	17	(41.5)	53	(13.9)	21.0 (5.44-81.0)
Unknown	9		118			6		62		
Per 500/μL decrease					0.96 (0.78-1.19)					1.91 (1.43-2.56)
CD4⁺ cell count, cells/μL										
500 or more	13	(34.2)	126	(38.1)	1	3	(7.3)	136	(35.3)	1
200-499	17	(44.7)	151	(45.6)	1.10 (0.52-2.36)	14	(34.2)	177	(46.0)	3.65 (1.02-9.55)
50-199	8	(21.1)	47	(14.2)	1.24 (0.45-3.44)	18	(43.9)	50	(13.0)	18.0 (5.06-63.7)
0-49	0	(0.0)	7	(2.1)		6	(14.6)	22	(5.7)	
Unknown	9		113			6		59		
Per 100/μL decrease					1.08 (0.94-1.25)					1.65 (1.33-2.03)
CD8⁺ cell count, cells/μL										
1000 or more	16	(42.1)	122	(36.9)	1	5	(12.2)	133	(34.7)	1
500-999	15	(39.5)	158	(47.7)	0.73 (0.35-1.52)	17	(41.5)	192	(50.1)	2.66 (0.96-7.41)
0-499	7	(18.4)	48	(14.5)	1.09 (0.41-2.89)	19	(46.3)	58	(15.2)	11.1 (3.69-33.6)
Unknown	9		116			6		61		
Per 100/μL decrease					0.96 (0.91-1.02)					1.21 (1.09-1.34)
CD4⁺/CD8⁺ ratio, %										
50 or more	13	(34.2)	151	(46.0)	1	16	(39.0)	167	(43.6)	1
25-49	11	(29.0)	111	(33.8)	1.20 (0.52-2.79)	13	(31.7)	133	(34.7)	0.96 (0.44-2.08)
0-24	14	(36.8)	66	(20.1)	2.44 (1.05-5.70)	12	(29.3)	83	(21.7)	1.47 (0.65-3.31)
Unknown	9		116			6		61		
Per 10% decrease					1.07 (0.96-1.19)					1.03 (0.94-1.13)
CD4⁺ percentage										
26 or more	11	(32.4)	117	(40.6)	1	12	(30.8)	146	(41.8)	1
14-25	13	(38.2)	124	(43.1)	1.14 (0.50-2.59)	15	(38.5)	143	(41.0)	1.28 (0.58-2.83)
0-13	10	(29.4)	47	(16.3)	2.07 (0.81-5.31)	12	(30.8)	60	(17.2)	2.16 (0.89-5.26)
Unknown	13		156			8		95		
Per 10% decrease					1.37 (0.96-1.96)					1.57 (1.11-2.21)
CD8⁺ percentage										
60 or more	12	(35.3)	74	(25.9)	1	15	(39.5)	90	(26.8)	1
50-59	8	(23.5)	70	(24.5)	0.74 (0.26-1.39)	7	(18.4)	99	(29.5)	0.40 (0.15-1.08)
0-49	14	(41.2)	142	(49.7)	0.60 (0.26-1.39)	16	(42.1)	147	(43.8)	0.64 (0.30-1.38)
Unknown	13		158			9		108		
Per 10% decrease					0.80 (0.61-1.06)					0.92 (0.71-1.19)

*Conditioned upon matching variables.

markers of immunodeficiency were similar to estimates based on markers at SHCS enrollment (Table 4). Thus, neither total lymphocyte nor $CD4^+$ nor $CD8^+$ cell counts were significantly associated with HL risk at 1 to 2 years before HL diagnosis, but a decreased $CD4^+/CD8^+$ ratio was (OR for $< 25\%$ vs $\geq 50\% = 2.44$, 95% CI, 1.05-5.70). $CD4^+$ percentage (OR for $< 14\%$ vs $\geq 26\% = 2.07$, 95% CI, 0.81-5.31) and $CD8^+$ percentage (OR for $< 50\%$ vs $\geq 60\% = 0.60$, 95% CI, 0.26-1.39) at 1 to 2 years before HL diagnosis were still associated with HL risk in opposite directions, but these differences were no longer significant.

In contrast, when measured within the year before HL diagnosis, HL was strongly associated with lower total lymphocyte count (OR for ≤ 999 μL vs ≥ 2000 μL $= 21.0$, 95% CI, 5.44-81.0), lower $CD4^+$ cell count (OR for ≤ 199 μL vs ≥ 500 μL $= 18.0$, 95% CI, 5.06-63.7), and lower $CD8^+$ cell count (OR for ≤ 499 μL vs ≥ 1000 μL $= 11.1$, 95% CI, 3.69-33.6) because of a severe drop in absolute counts of all types of lymphocytes among HL cases, but not among their corresponding controls. When measured within the year before HL diagnosis, $CD4^+/CD8^+$ ratio and $CD8^+$ percentage were not significantly associated with HL risk. $CD4^+$ percentage was, however, but only as a continuous variable (OR per 10% decrease $= 1.57$, 95% CI, 1.11-2.21).

Discussion

We[2] and others[3-12,14,18] have shown that the risk of HL in PHIVs is significantly higher than in the general population. However, this is the first study, to our knowledge, to focus on the association of cART use and markers of immunodeficiency with HL risk in a large cohort of PHIV.

Most HL cases arising during active SHCS follow-up corresponded to the mixed cellularity (49%) or lymphocyte-depleted (16%) forms, which are those most strongly associated with Epstein-Barr virus (EBV).[21] This distribution is similar to that in previous reports of HL arising in PHIV,[15,22,23] but not those in the general population where the nodular sclerosis form predominates.[24,25] We could not demonstrate any significant association between age and HL risk, perhaps partly because of the lack of

power to stratify by different histologic subtypes, which are known to have different age-specific patterns in the general population.[26]

HIV-transmission category was associated with HL risk, with the relative risk among MSM being twice that among IDUs and intermediate among heterosexual/others. Similar elevated risks among MSM have recently been reported for NHL in the SHCS[27] and elsewhere.[14,18] The explanation of these findings is unclear but may include more severe competing mortality in IDUs than in MSM.

We previously reported from the SHCS,[2] albeit tentatively, that SIRs for HL relative to the general population were increased in cART users (SIR = 36.2, 95% CI, 16.4-68.9) compared with nonusers (SIR = 11.4, 95% CI, 5.2-21.7), and similar studies from France[10] and the United States[11,12,18] reported increases in SIRs between the pre-cART (1995 or earlier) and post-cART (1996 or later) periods. However, the present comparison of incidence rates internal to the SHCS revealed no such increases. Analysis of the French cohort using HL incidence rates[28] rather than SIRs[10] revealed a similar disappearance of the increase by calendar period.

This apparent discrepancy, depending on whether external (SIRs) or internal (HRs) comparisons are used, is noteworthy. It seems that the interpretation of changing SIRs for HL over time have been greatly complicated by the convergence of 2 phenomena: (1) a substantial increase in the mean age of PHIV since the introduction of cART (from 34.2 years in the period before 1996 to 42.8 years in 2002-2007 in the SHCS), and (2) the unique bimodal nature of HL age-specific incidence in the general population, which, in Switzerland and elsewhere, is dominated by nodular sclerosis HL[26] and drops between ages 10 to 30 and 30 to 60 years, increasing again thereafter.[29] This highlights the dangers of directly comparing SIRs over time in cohorts where shifts in age distribution are taking place.

Absolute $CD4^+$ cell counts do not seem to explain the relationship between HIV-related immunodeficiency and HL as well as they do for KS and NHL. The finding that cART had little effect on HL is another clear difference with respect to KS[30] and NHL.[27] Equally, a history of AIDS diagnosis, which has often been used as proxy of immunodeficiency, did not significantly predict HL risk, as also shown previously.[3,28] Nevertheless, HL risk did tend to increase with lowering $CD4^+$ cell counts, as has recently been shown also for PHIV in France,[28] even if this difference was not statistically significant in the SHCS. This is contrary to what was reported in an AIDS registry linkage study in the United States, where, after restricting to a subset of HL cases diagnosed between 4 and 27 months after AIDS diagnosis (of note, 70% of HL cases in the SHCS occurred in the absence of AIDS) and with available $CD4^+$ cell counts at AIDS, Biggar et al proposed that HL risk decreased at $CD4^+$ cell counts less than 200 cells/μL.[15]

We were concerned that the effect of $CD4^+$ cell count at SHCS enrollment on HL risk might have been masked because of changes in this measure during follow-up, particularly with respect to the immune reconstitution offered by cART. Thus, we designed a nested case-control approach, complementary to the cohort analysis, to look at markers of immunodeficiency at time periods closer to HL diagnosis. Using this approach, we were able to confirm the absence of a reduced HL risk at $CD4^+$ cell counts less than 200 cells/μL, even when measured 1 to 2 years before HL diagnosis.

Within the year before HL diagnosis, however, we observed a severe drop in lymphocyte counts among HL cases so that low $CD4^+$ or $CD8^+$ cell counts became a strong late marker of HL. Indeed, lymphocytopenia, because of sequestration of lymphocytes at the tumor site, is a well known symptom of HL arising in the absence of HIV infection,[24] highlighting the problem of interpreting $CD4^+$ cell counts directly preceding HL onset.

The finding that the $CD4^+/CD8^+$ ratio was the most promising early immunologic marker of HL risk was unexpected and was reflected by the fact that $CD4^+$ and $CD8^+$ measured as percentages of all lymphocytes at SHCS enrollment were also associated with HL in opposite directions. These effects were still observed at 1 to 2 years before HL diagnosis, but not close to HL onset. Although this appears to be the first report of the importance of a balance of $CD4^+$ and $CD8^+$ cells in peripheral blood in relation to onset of HL (or any other cancer) in PHIV, a striking inversion of $CD4^+/CD8^+$ ratio has been previously shown in the inflammatory infiltrate of HIV-related HL lesions.[31]

These findings merit some interpretation in light of what is known about the immunology of EBV, given its heavy implication in HIV-related HL.[21] Immune surveillance of EBV infection is thought to be primarily controlled by EBV-specific $CD8^+$ T cells.[32] Given the accumulating evidence of the contribution of specific $CD4^+$ T cells in controlling viral infections (reviewed by Kaech et al[33]), it is probable that that $CD4^+$ T cells are also needed for the expansion of EBV-specific $CD8^+$ T cells and the quality of their long-term function. Indeed, a depletion in EBV-specific $CD4^+$ T-cell effector function and/or help for $CD8^+$ T cells has already been suggested as an immunologic basis for NHL[34] and primary brain lymphoma in PHIV,[35] which are also caused by EBV. Thus, although our study relied purely on routinely collected laboratory data and included no virus-specific immunologic endpoints, it is possible that our findings reflect the effects of an imbalance in the pool of EBV-specific $CD4^+$ and/or $CD8^+$ cells on the risk of developing HL in PHIV.

The SHCS has many strengths, including the size, duration, and regularity of follow-up and comprehensiveness of clinical and laboratory information. Approximately half of PHIV in Switzerland have been enrolled in the SHCS, and both sexes and different risk categories are well represented. Additional strengths were the supplementation of cancer diagnoses through linkage with cancer registries,[2] which allowed the knowledge of histologic subtype for a majority of HL patients, or at least the accurate exclusion of NHL. The principal weakness of the study was that the relatively small number of HL patients still limited the possibilities of stratified analyses, in particular with respect to the histologic subtypes of HL, which, in the general population at least, are known to differ in their epidemiology.[21]

In conclusion, despite previous fears, HL risk does not appear to be increasing in recent years or among PHIVs using cART. Furthermore, although the association of HL with immunodeficiency, as measured by $CD4^+$ cell count, is clearly not the same as for KS or NHL, we could not find evidence that HL risk should be increased in the setting of improving $CD4^+$ cell counts.

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Authorship

Contribution: G.M.C. and S.F. conceived the study and drafted the manuscript; M.R. was responsible for management of the clinical databases of the Swiss HIV Cohort and liaison with the SHCS centers and Scientific Board; M.L. and L.D.M. were responsible for the linkage of the Swiss HIV Cohort with the cantonal cancer registries as well as data managerial and statistical issues; G.J., A.B., and S.E. are representatives of the individual cantonal cancer registries that were responsible for the data linkage exercise and collection of additional information on cancer cases; and M.B., J.B., E.B.E.A., and U.K. are experts on the clinical, immunologic, and/or epidemiologic aspects, respectively, of EBV infection and lymphoma development in the Swiss HIV Cohort, and gave important scientific input to the conception, analysis, and interpretation of the study. All authors read and gave feedback on the final version of the manuscript.

Appendix

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