Non-Hodgkin lymphoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy

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Objective: To assess the long-term effect of HAART on non-Hodgkin lymphoma (NHL) incidence in people with HIV (PHIV).

Design: Follow-up of the Swiss HIV Cohort Study (SHCS).

Methods: Between 1984 and 2006, 12 959 PHIV contributed a total of 75 222 person-years (py), of which 36 787 were spent under HAART. Among these PHIV, 429 NHL cases were identified from the SHCS dataset and/or by record linkage with Swiss Cantonal Cancer Registries. Age- and gender-standardized incidence was calculated and Cox regression was used to estimate hazard ratios (HR).

Results: NHL incidence reached 13.6 per 1000 py in 1993–1995 and declined to 1.8 in 2002–2006. HAART use was associated with a decline in NHL incidence [HR = 0.26; 95% confidence interval (CI), 0.20–0.33], and this decline was greater for primary brain lymphomas than other NHL. Among non-HAART users, being a man having sex with men, being 35 years of age or older, or, most notably, having low CD4 cell counts at study enrolment (HR = 12.26 for < 50 versus ≥ 350 cells/μl; 95% CI, 8.31–18.07) were significant predictors of NHL onset. Among HAART users, only age was significantly associated with NHL risk. The HR for NHL declined steeply in the first months after HAART initiation (HR = 0.46; 95% CI, 0.27–0.77) and was 0.12 (95% CI, 0.05–0.25) 7 to10 years afterwards.

Conclusions: HAART greatly reduced the incidence of NHL in PHIV, and the influence of CD4 cell count on NHL risk. The beneficial effect remained strong up to 10 years after HAART initiation.

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Introduction

Following the advent and widespread use of HAART, a decrease in HIV-associated morbidity and mortality was observed [1,2] including that due to non-Hodgkin lymphoma (NHL) [3–9]. Most studies of NHL so far, however, have used calendar period (e.g., before or after 1996 or 1997) as a proxy of HAART use [10], or have included relatively small numbers of NHL diagnosed after HAART initiation [2,8,11].

We therefore evaluated the long-term effect of HAART and its impact on known risk factors for NHL using data from the Swiss HIV Cohort Study (SHCS), a large prospective cohort with detailed follow-up information, including CD4 cell count and HAART use.

Materials and methods

The SHCS is an ongoing study that has been enrolling people infected with HIV (PHIV) over 16 years of age since 1988, with some retrospective enrolment going back to 1984, from seven large hospitals in Switzerland (www.shcs.ch). After written informed consent is obtained, detailed demographic, lifestyle, and clinical information is collected. Follow-up visits take place every 6 months and all AIDS-defining events, including NHL diagnosis and death, are recorded. The present study included PHIV enrolled up to 30 September 2005, and information recorded in the SHCS database up to 31 March 2006. PHIV were excluded from the present study if they: (1) did not have information on date of birth, gender or HIV-transmission category ($n = 103$); (2) were diagnosed with NHL at enrolment or earlier ($n = 96$); (3) had no follow-up visits ($n = 682$).

The majority of remaining NHL cases ($n = 365$) were identified from the SHCS database, but record linkage with eight Swiss Cantonal Cancer Registries [12] allowed for the identification of 64 additional NHL cases. Histological confirmation was mentioned in the majority of NHL cases, but histological subtype was often not available, or was reported using different classification systems [12]. Only primary brain lymphoma (PBL) could be systematically distinguished from other NHLs, and therefore, in the present study, results were reported for PBL and other NHL only. HAART was defined as a combination of at least three drugs, including a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. CD4 cell counts at enrolment in the SHCS, and at, or within 6 months prior to, HAART initiation and NHL diagnosis were retrieved. Antiretroviral treatment 1 month prior to NHL diagnosis was also retrieved.

For each subject, person-years (py) at risk were calculated between enrolment and NHL diagnosis, death, or last follow-up visit, whichever occurred first. Incidence rates per 1000 py were standardized for gender and age based on the enrolled population in the overall study period, using the direct method [13]. Ninety-five percent confidence intervals (CI) of incidence were computed according to the Poisson distribution [13]. The effect of various risk factors on NHL onset was assessed using hazard ratios (HR), estimated by means of the Cox proportional hazard model [14], and adjusted for SHCS centre, gender, age (in 5-year groups), and, when mentioned, CD4 count at enrolment (< 50, 50–99, 100–199, 200–349, ≥ 350 cells/μl, and unknown). Calendar period, HAART use, and time since HAART initiation were introduced as time-dependent variables. Person-years of HAART use can include periods where treatment was interrupted.

This study was approved by the local ethical committees of the collaborating clinics and of the International Agency for Research on Cancer.

Results

The present study included 12 959 PHIV among whom 429 NHL cases were identified (incidence = 5.5 per 1000 py; 95% CI, 5.0–6.1). NHL incidence reached a peak of 13.6 per 1000 in 1993–1995 and declined thereafter down to 1.8 in 2002–2006. The number of intravenous drug users enrolled has decreased over the years, whereas the number of heterosexuals has increased, especially among women (www.shcs.ch). Eighteen percent of patients had AIDS at enrolment, and 23.5% developed it afterwards. Among people who developed AIDS during follow-up, NHL was the AIDS-defining illness in 201 (5.2%) (data not shown).

A large proportion (48.7%) of the person-years available derived from HAART users and Table 1 shows the incidence and HR of NHL by various characteristics separately in non-users and users of HAART. Incidence of NHL decreased from 8.8 per 1000 py in non-users to 1.9 per 1000 py in users, and the HR for users versus non-users was 0.26 (95% CI, 0.20–0.33). Among non-users of HAART, significantly increased HR for NHL were found among men (HR versus women = 1.94; 95% CI, 1.43–2.61), older individuals (HR $\geq$ 45 versus

Table 1. Incidence rates and hazard ratios (HR) of non-Hodgkin lymphoma (NHL) overall, and by selected characteristics and use of HAART.

	Non-users of HAART[a]				HAART users[a]			
	NHL	py	Incidence/1000 py[b] (95% CI)	HR (95% CI)[c]	NHL	py	Incidence/1000 py[b] (95% CI)	HR (95% CI)[c]
Overall	333	38735	8.8 (7.9–9.8)	1[d]	96	36787	1.9 (1.6–2.4)	0.26 (0.20–0.33)
Gender								
Female[d]	54	12047	4.3 (3.2–5.6)	1	18	10748	1.1 (0.7–1.8)	1
Male	279	26688	10.6 (9.4–11.9)	1.94 (1.43–2.61)	78	26039	2.3 (1.8–2.8)	1.41 (0.84–2.39)
Age at enrolment (years)								
<35[d]	188	28120	4.4 (3.8–5.0)	1	32	20520	1.9 (1.3–2.7)	1
35–44	77	7352	9.1 (7.1–11.3)	1.39 (1.06–1.82)	31	10586	1.9 (1.3–2.7)	1.75 (1.06–2.88)
≥ 45	68	3263	16.5 (12.8–21.0)	2.71 (2.04–3.60)	33	5682	4.4 (3.0–6.2)	3.39 (2.07–5.56)
HIV-transmission category								
Intravenous drug users[d]	89	16793	4.9 (3.9–6.0)	1	24	9458	1.7 (1.1–2.6)	1
Heterosexuals and other	77	10260	8.3 (6.6–10.4)	1.36 (0.98–1.88)	29	13844	1.6 (1.1–2.3)	0.60 (0.33–1.07)
Men having sex with men	167	11682	9.5 (8.1–11.0)	1.81 (1.36–2.42)	43	13485	1.6 (1.2–2.1)	0.75 (0.43–1.32)
CD4 cell count at enrolment (cells/μl)[e]								
≥ 350[d]	85	21188	4.3 (3.5–5.4)	1	34	15509	1.7 (1.2–2.3)	1
200–350	57	6284	9.5 (7.2–12.3)	2.28 (1.62–3.20)	19	8582	2.2 (1.3–3.5)	0.88 (0.50–1.55)
100–199	47	2927	16.9 (12.4–22.5)	4.08 (2.82–5.90)	16	5434	1.5 (0.9–2.4)	1.10 (0.60–2.01)
50–99	39	1140	35.9 (25.5–49.1)	9.42 (6.28–14.11)	13	2437	3.0 (1.6–5.2)	1.91 (0.99–3.67)
<50	49	1253	39.0 (28.9–51.6)	12.26 (8.31–18.07)	11	3340	2.0 (1.0–3.6)	1.21 (0.61–2.43)

CI, confidence interval; py, person-years.
[a]The same person can contribute person-years to both 'Non-users' and 'Users' of HAART.
[b]Rates are standardized (direct method) on age and/or gender based on all SHCS patients.
[c]Adjusted for centre, age, and gender, as appropriate.
[d]Reference category.
[e]A total of 1197 patients (including 7426 py, and 59 NHL) were excluded as information on CD4 cell count was missing.

<35 years $= 2.71$; 95% CI, 2.04–3.60), and men having sex with men (HR versus intravenous drug users $= 1.81$; 95% CI, 1.36–2.42). The associations of NHL risk with gender and HIV-transmission category were greatly attenuated and became non-statistically significant among HAART users, whereas the direct association with age did not change. The greatest difference between users and non-users was found in respect to the influence of CD4 cell count at study enrolment on NHL risk. Among non-users, NHL rates increased steeply with decreasing CD4 cell count from 4.3 per 1000 py in PHIV with ≥ 350 cells/μl to 39.0 per 1000 py in PHIV with <50 cells/μl (HR $= 12.26$; 95% CI, 8.31–18.07). Among users, the association between CD4 cell count and NHL risk was not statistically significant (HR for CD4 <50 versus ≥ 350 cells/μl $= 1.21$; 95% CI,: 0.61–2.43; Table 1). When we evaluated the relationship between NHL risk and CD4 cell count at HAART initiation, findings were similar to those for CD4 cell count at study enrolment (HR for <50 versus ≥ 350 cells/μl $= 1.66$; 95% CI, 0.84–3.27; data not shown).

Figure 1 shows that among HAART users, compared to non-users, there was not only a decrease in the number of NHL cases, but a marked shift towards higher CD4 cell count at cancer diagnosis.

The decline in PBL after 1995 was stronger than for other NHL, i.e., PBL represented 31.6% of NHL before 1996, but only 13.3% in 1999–2006 (Table 2). Among non-users of HAART, the relationship between NHL risk and the degree of immunosuppression at study enrolment was stronger for PBL (HR for <50 versus ≥ 200 cells/μl $=$ 28.58; 95% CI, 15.36–53.18) than for other NHL (HR $= 5.02$; 95% CI, 3.13–8.06). Among users, neither the risk of PBL nor of other NHL was significantly associated with CD4 cell count, although the small number of PBL cases led to HR with very broad CI (Table 2).

Figure 2 shows HR for NHL in different periods after HAART initiation compared to non-users. The risk of NHL was already halved in the first 5 months of use and continued to decline thereafter (HR after 36–59 months $=$ 0.10; 95% CI, 0.06–0.17). The reduction in NHL risk persisted unchanged up to 84–119 months after HAART initiation (HR $= 0.12$; 95% CI, 0.05–0.25).

Of the 96 HAART users who developed NHL, 75 (78.1%) were still receiving HAART 1 month before cancer diagnosis. Regimens included a protease inhibitor in 50, a non-nucleoside reverse transcriptase inhibitor in 12, and both types of drugs in 13 PHIV. Of the 21 individuals who developed NHL while no longer on HAART, five were taking at least one, and 16 were taking no antiretroviral drug 1 month before NHL diagnosis.

Discussion

Our present study includes the largest number of NHL cases and person-years of HAART use ever evaluated in PHIV. Many studies have been conducted to determine

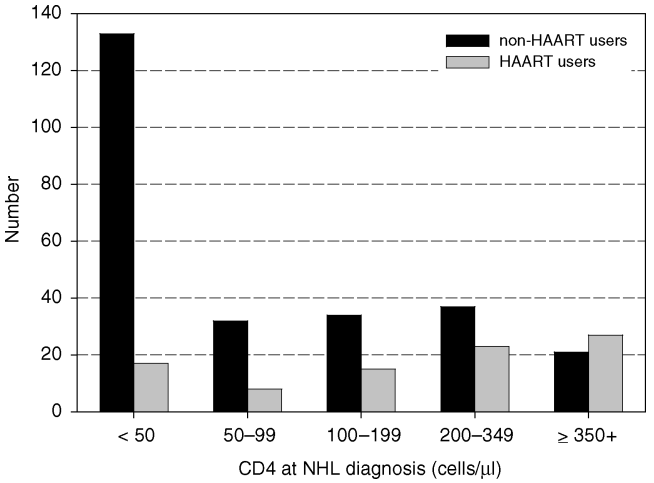

Fig. 1. Distribution of 347[a] non-Hodgkin lymphomas (NHL) by use of HAART and CD4 cell count at NHL diagnosis. [a]CD4 cell count at diagnosis was not available for 82 NHLs.

whether the use of HAART has led to a change in NHL incidence among PHIV, similar to the striking decline seen in Kaposi's sarcoma. While some early studies did not report a decrease in NHL incidence up to the late 1990s [2,5,15–17], clear evidence of the beneficial effect of HAART on NHL incidence emerged soon after [3,4,9,11].

Record linkage studies of AIDS and cancer registries found that the relative risk of NHL among PHIV or people with AIDS, compared to the general population, approximately halved in Europe and the United States after the advent of HAART, although it remained greater than 20 [10,12,18]. HAART has also narrowed the gap in survival between NHL patients with and without HIV infection [19,20].

In the SHCS, NHL incidence reached 13.6 per 1000 py in 1993–1995 and then declined to less than 2 per 1000 py in the HAART era. HAART also diminished the variation in NHL risk by host characteristics. Among non-users, significantly increased NHL risks were found in men, individuals older than 45 years, men having sex

Table 2. Incidence rates and hazard ratios (HR) of primary brain lymphoma and other non-Hodgkin lymphoma (NHL) overall, by year of diagnosis, and by CD4 cell count at enrolment and use of HAART and NHL type.

		Primary brain lymphoma			Other NHL		
	py	Cases	Incidence/1000 py[a] (95% CI)	HR (95% CI)[b]	Cases	Incidence/1000 py[a] (95% CI)	HR (95% CI)[b]
Overall	75522	104	1.4 (1.1–1.7)	–	325	4.2 (3.7–4.6)	–
Year of diagnosis							
1984–1992[c]	14235	36	2.8 (2.0–3.9)	1	86	7.0 (5.6–8.6)	1
1993–1995	10660	47	4.5 (3.3–6.0)	1.54 (0.96–2.45)	94	9.1 (7.4–11.2)	1.43 (1.05–1.94)
1996–1998	12435	9	1.0 (0.5–2.0)	0.17 (0.07–0.40)	67	5.3 (4.1–6.7)	0.79 (0.56–1.11)
1999–2006	38193	12	0.3 (0.1–0.5)	0.07 (0.03–0.17)	78	1.6 (1.2–1.9)	0.25 (0.17–0.36)
HAART[d,e]							
Non-users							
CD4 cell count at enrolment (cells/μl)							
≥ 200[c]	27472	24	0.9 (0.6–1.4)	1	118	4.6 (3.8–5.5)	1
50–199	4067	30	6.9 (4.6–9.8)	8.47 (4.84–14.84)	56	13.9 (10.5–18.0)	3.13 (2.23–4.37)
< 50	1253	25	17.1 (11.1–25.3)	28.58 (15.36–53.18)	24	21.9 (14.0–32.7)	5.02 (3.13–8.06)
Users							
CD4 cell count at enrolment (cells/μl)							
≥ 200[c]	24092	6	0.2 (0.1–0.5)	1	47	1.6 (1.2–2.1)	1
50–199	7871	3	0.2 (0.0–0.7)	1.55 (0.38–6.43)	26	1.8 (1.2–2.6)	1.40 (0.86–2.28)
< 50	3340	2	0.3 (0.0–1.0)	2.53 (0.48–13.35)	9	1.8 (0.8–3.3)	1.14 (0.56–2.36)

CI, confidence interval; py, person-years.
[a]Rates are standardized (direct method) on age and/or gender based on all SHCS patients.
[b]Adjusted for centre, age and gender.
[c]Reference category.
[d]The same person can contribute person-years to both 'Non-users' and 'Users'.
[e]1197 patients (including 7426 py, 14 primary brain lymphoma and 45 other NHL) were excluded as information on CD4 cell count was missing.

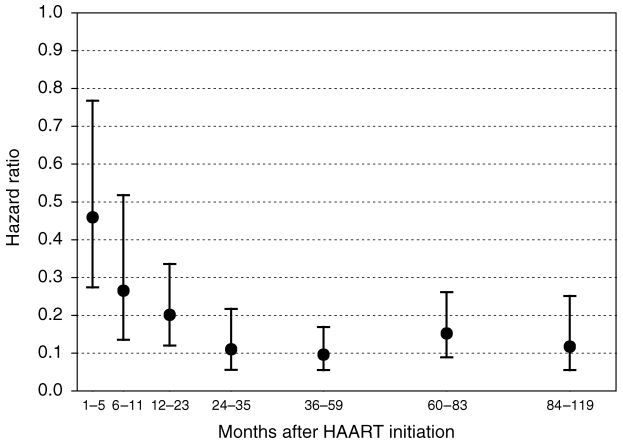

Fig. 2. Hazard ratio[a,b] of non-Hodgkin lymphoma in patients receiving HAART by months after HAART initiation[c], adjusted for centre, age, gender, and CD4 cell count at enrolment. [a]Vertical bars represent 95% confidence intervals. [b]Reference category was defined as non-HAART users. [c]Follow-up was censored at 10 years (119 months) after HAART initiation.

with men and severely immunodepressed individuals. All these associations, except the one with age, were greatly reduced among users. The near complete disappearance of the association between CD4 cell count at enrolment or at initiation of antiretroviral treatment and NHL risk supports the strong efficacy of HAART regardless of the degree of immune impairment when follow-up or treatment begins. In fact, HAART diminished NHL incidence by approximately 60% among PHIV whose CD4 cell count at enrolment was ≥ 350 cells/μl, but by nearly 20-fold among those whose count was < 50 cells/μl. Thus, although it was already clear that HAART prevents NHL through improvement of immune status [20], this study shows that HAART avoids the majority of NHL, even among the most severely immunosuppressed individuals.

The availability of follow-up data until 2006 in the SHCS allowed us, for the first time, to estimate the persistence of the effect of HAART on the prevention of NHL up to 10 years after treatment initiation. While we confirmed that NHL risk is already halved in the first months of treatment, we found that the HR further declined during the first 3 years, and did not show signs of increasing again for at least 10 years.

PBL was nearly as frequent (17.1 per 1000 py) as other NHL (21.9 per 1000 py) in non-users whose CD4 cell count was < 50 cells/μl. By 1999, or among HAART users, PBL had become extremely rare (≤ 0.3 per 1000 py), as has been reported in studies from the United States [10,21].

Weaknesses of our present study include the lack of information on year of seroconversion, and the lack of NHL histology, which obliged us to combine all NHL other than PBL. Furthermore, we did not include information on adherence to HAART. Our computation of person-years of HAART use, therefore, includes periods where use was interrupted, and so treatment efficacy may be underestimated [22]. Indeed, we found that 22% of NHL in HAART users arose in persons who were no longer on HAART at cancer diagnosis. Our findings do reflect, however, the effectiveness of up to 10 years of HAART use to reduce NHL incidence in a cohort that is well representative of the general population of PHIV in Switzerland, as, since the beginning of the epidemic, 49% of PHIV and 68% of people with AIDS in Switzerland have been enrolled in the SHCS (www.shcs.ch).

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