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The effect of HAART and calendar period on Kaposi's sarcoma and non-Hodgkin lymphoma: Results of a match between an AIDS and cancer registry

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Abstract

Objectives—To assess the impact of HAART use on AIDS-defining KS and NHL among adults with AIDS.

Design—Registry linkage study.

Methods—Adults diagnosed with AIDS from 1990 to 2000 in the San Francisco AIDS case registry were matched with cancer cases diagnosed from 1985 to 2002 in the California Cancer Registry. Multivariate Cox proportional hazards models were used to evaluate the risk and survival of AIDS-related KS, systemic NHL, and primary CNS lymphoma.

Results—Of the 14,183 adults with AIDS, 3028 were diagnosed with KS, 776 with systemic NHL, and 254 with CNS NHL. After adjustment for potential confounders, more recent calendar period and use of HAART were significantly associated with a decreased risk of KS while HAART use but not calendar period were significantly associated with systemic and CNS NHL. In adjusted analysis of KS survival time, there was strong evidence of a reduced risk of death associated with HAART use and more recent calendar period. In contrast, in adjusted analyses of systemic NHL survival time, HAART use was not associated with improved survival time; however, calendar period was associated with longer survival. In adjusted analysis of CNS NHL survival time, only cancer treatment was associated with a longer survival time.

Conclusions—After controlling for calendar period and other confounders, use of HAART decreased the risk of KS, systemic NHL, and CNS NHL. Use of HAART also increased KS survival time but not NHL survival time.

Keywords

AIDS; HAART; KS; NHL; risk factors; survival

INTRODUCTION

In the 1970's, the increasing use of immune suppressive drugs for organ transplantation led to the discovery that the risk of certain cancers was elevated in transplant recipients [1, 2]. A

decade later, scientists recognized that the risk of certain cancers was also elevated in people with severe immunodeficiency due to HIV infection. As a result, the Centers for Disease Control and Prevention (CDC) added Kaposi's sarcoma (KS), non-Hodgkin lymphoma (NHL), and invasive cervical cancer to the AIDS case definition in 1981, 1985, and 1993, respectively [3–5].

In the mid-1990s, the advent and use of highly active antiretroviral therapy (HAART) led to a dramatic reduction in AIDS-related morbidity and mortality among people with HIV infection [6, 7]. New drugs and therapies have also been developed specifically for KS and AIDS-related lymphomas [8–10]. The addition of these therapies combined with use of HAART has subsequently contributed to further improvements in the health and overall survival of individuals with HIV/AIDS [11, 12]. However the use of ever-improving HAART regimens and improved prevention and treatment of opportunistic infections, has also led to an increasing percentage of malignancy-related deaths in AIDS patients [13]. The juxtaposition of these two phenomena, better prevention and treatment of disease and longer life expectancy and risk of cancer, was the impetus for our investigation of the contributing factors for the risk and survival of AIDS-related KS and NHL in the era of HAART.

Previous studies linking AIDS and cancer registry data have not been able to assess the impact of individual level HAART use on AIDS defining cancers. Instead, previous linkage studies have used calendar period as an indirect measure of the impact of HAART on cancer [14–18]. In this investigation, we assessed the impact of individual level HAART use on the risk and survival of AIDS-defining KS, systemic NHL, and primary CNS lymphoma among adults with AIDS in San Francisco.

METHODS

Study population

AIDS surveillance in San Francisco is conducted through both active and passive reporting and AIDS case reporting is estimated to be between 95 and 98% complete [19]. Reporting activities include staff visits to hospitals, clinics, and physician offices. Additionally, suspected cases are identified through laboratory and pathology reports and are confirmed through medical record review. Other case finding activities include monthly local and yearly national death registry surveillance and reports from other health departments and medical providers. The date antiretroviral therapy began, type of therapy used, and CD4 test results are recorded from medical records at the time of initial case report and every 12 to 18 months thereafter.

The California Cancer Registry (CCR) is a statewide, population-based registry that has collected cancer incidence and mortality information for all cancers except basal and squamous cell skin and *in situ* cervical cancers. The CCR utilizes standardized data collection and quality control procedures, and has consistently met the highest standards of the North America Association of Central Cancer Registries (NAACCR) for data quality and completeness [20].

For this study, adult AIDS cases (ages 16–86 years old) diagnosed between 1990–2000 in the AIDS case registry were matched with cancer cases diagnosed between 1985–2002 in the CCR using the probabilistic data linkage program AutoMatch, version 4.2 [21]. At the time of the match, the CCR database contained 100 percent of the expected number of cancers for diagnosis years 1988–2000. Additionally, records for cases diagnosed 1985–1987 in the Greater Bay Area Cancer Registry (GBACR) Surveillance, Epidemiology, and End Results (SEER) region were included in this linkage. The GBACR became a SEER region in 1973 and includes Region 1 (Monterey, San Benito, Santa Clara, and Santa Cruz

counties) and Region 8 (San Francisco, Alameda, Contra Costa, Marin, and San Mateo counties) of the California Cancer Registry [22]. Completeness of cases from 1985–1987 for the GBACR is considered to be 100 percent. Name, social security number, date of birth, sex, race/ethnicity, and date of death were used to match cases in the AIDS and cancer registries. To verify possible matches, ‘also known as’ names, addresses, and phonetic spelling of names were also used. When there was a discrepancy in cancer diagnosis dates between registries, the first report of a given cancer was chosen. Cancers were classified using the Surveillance, Epidemiology and End Results (SEER) site recoding scheme, which is based on ICD-O-2 and ICD-O-3, with Kaposi’s sarcoma and mesothelioma definitions added to the cancer categories [23]. To minimize the possibility that an AIDS-defining cancer occurred prior to HIV infection, in this analysis we only included AIDS-defining cancers that occurred within five years of the initial AIDS diagnosis or anytime thereafter as has been done in previous registry linkage studies [24–28].

The University of California Committee on Human Research reviewed and approved this study protocol.

Statistical methods

Contingency table analyses (chi-square) were conducted to compare the distribution of participant characteristics by year of AIDS diagnosis. Cox proportional hazards models were used to evaluate the effect of individual level HAART use on the risk and survival of AIDS-related KS, systemic NHL, and primary CNS lymphoma. Persons missing HAART start dates were excluded from these analyses. Individuals diagnosed with both KS and NHL were evaluated in both the KS-specific and NHL-specific models. In our analysis, we adjusted for age (per decade), race/ethnicity, AIDS risk group, gender, calendar year, HAART use and HAART era (January 1, 1996 or later) using the forward stepwise procedure. The significance level for the stepwise model was $p < 0.10$. For the cancer risk analyses, time zero was defined as 5 years before the initial AIDS diagnosis, as has been done in prior registry linkage studies [24–31], and the censor date was December 31 2002. Calendar year, age, HAART use and HAART era were treated as time-varying covariates. Information about HAART use was obtained from medical records. HAART was defined as combination therapy which included a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. HAART was further defined as a three-category time-varying covariate taking into account both the availability of HAART and the amount of HAART use. The three categories were 1) no HAART use, 2) HAART use for less than 6 months and 3) HAART use for 6 months or more. Calendar time was defined as categorical time-varying covariate corresponding to the availability and improvement in HAART regimens. The categories were 1) the pre-HAART years 1990–1995 (the reference group), 2) the early HAART years 1996–1998, 3) the years following FDA approval of abacavir 1999–2000, and for the survival analyses only 4) the years following FDA approval of tenofovir 2001–2007.

Survival time was calculated from date of cancer diagnosis to date of death or, if alive, censored at December 31, 2007 (the last date for which complete death data was available from the U.S. National Death Index), whichever occurred first. Additional covariates in these analyses included CD4+ cell count at time of cancer diagnosis (the closest CD4+ cell count within three months [before or after] cancer diagnosis date), cancer stage of disease (categorized as localized, regional, distant, and unstaged or missing) and cancer treatment. For the survival analyses, tests of proportionality of hazards for the covariates revealed a lack of proportionality for cancer treatment in each of these models. Therefore, we stratified by cancer treatment to address the proportionality assumption in these models. No other meaningful violations of the proportionality assumption were found. All statistical analyses were performed using SASR software version 9.2 [32].

We excluded cases who were non-San Francisco residents at time of AIDS diagnoses ($n=2080$), cases who were lost to follow up prior to January 1996 since we were unable to ascertain information regarding use of HAART ($n=505$), cases who did not have a chart review ($n=852$), and cases whose only chart review was at the time of AIDS diagnoses ($n=32$). We searched the cancer registry for the 5 years prior to the first AIDS diagnosis and if we found the cancer registry had an earlier date of diagnosis for KS or NHL, the earliest diagnosis date was used in the analysis ($n=249$).

RESULTS

There were 17,709 adults diagnosed with AIDS between 1990 and 2000. Of these, 3469 were eliminated from the analyses because their medical chart review information was either missing or likely to be incomplete. Eight were eliminated because their cancer diagnosis was more than 60 months before their AIDS diagnosis and 49 were eliminated because their cancers were either unspecified or occurred before 1990.

Of the remaining 14,183 persons with AIDS, 3875 (27%) had an AIDS-defining cancer diagnosis. Among this group, the most common AIDS-related cancer diagnoses was KS ($n=3028$, 79%) followed by systemic NHL ($n=776$, 20%), CNS NHL ($n=254$, 7%) and cervical cancer ($n=6$, <1%). Of the 14,183 AIDS cases, 6,578 (46%) had received HAART therapy and 329 (5%) received HAART prior to the HAART era. Table 1 shows case characteristics by AIDS diagnosis in three time periods: 1) before January 1996, 2) January 1 1996 to December 31 1998 and 3) January 1 1999 to December 31 2000. White men who have sex with men accounted for the majority of all AIDS cases in each time period. However, those diagnosed with AIDS after January 1996 were significantly more likely to be non-white, female, and injection drug users ($p<0.001$). In addition, those diagnosed with AIDS after the introduction of HAART were significantly more likely to have a CD4 count <200 at AIDS diagnosis, less likely to have had an AIDS-related cancer diagnosis and more likely to have used HAART prior to AIDS diagnosis ($p<0.001$).

In both the pre-HAART (1990–1995) and HAART (1996–2000) time periods, the most common NHL subtype among non-users of HAART were CNS lymphomas (26% and 51%, respectively) (Table 2). Among HAART users and in both the pre-HAART and HAART time periods, the most common NHL subtype was diffuse large cell (35% and 37%, respectively).

Cancer Risk

Table 3 shows the adjusted proportional hazard analysis of cancer risk and the association between HAART use and HAART availability. After adjusting for age, sex, race/ethnicity, HIV risk group, calendar year and being in the HAART era, the risk of developing KS, systemic NHL, and primary CNS lymphoma was significantly reduced among persons who had ever used HAART (adjusted relative hazard [RH] for KS=0.81, 95% confidence interval (CI) 0.68–0.96; adjusted RH for systemic NHL=0.63, 95% CI 0.47–0.83; and adjusted RH for primary CNS lymphoma=0.22, 95% CI 0.13–0.36). The risk of KS was also significantly reduced in the HAART era (adjusted RH=0.67, 95% CI 0.57–0.80). However, after controlling for HAART use, age, gender, race/ethnicity, HIV risk group, and calendar year, risks of systemic NHL and primary CNS lymphoma were not found to be statistically significant during the HAART era (adjusted RH=0.79, 95% CI 0.58–1.07, adjusted RH=1.22, 95% CI 0.76–1.95 respectively).

Cancer mortality

Kaposi's sarcoma—The adjusted proportional hazards survival analyses for KS are shown in Table 4. After adjustment, factors associated with a shorter KS survival time included older decade of age (RH 1.07 95% CI 1.02–1.13), regional and distant stage of cancer compared to localized (RH=1.64 95% CI 1.05–2.56 and RH=1.20 95% CI 1.05–1.38, respectively), CD4 count at cancer diagnosis <200 (RH=2.55 95% CI 1.92–3.39) and CD4 data missing (RH=2.52 95% CI 1.91–3.34) compared to CD4 >350. Factors associated with a longer KS survival time included HAART use for 6 or more months (RH=0.37 95% CI 0.31–0.45) compared to no HAART use, calendar period 1996–1998 (RH=0.58 95% CI 0.51–0.67), calendar period 1999–2000 (RH=0.44 95% CI 0.34–0.56) and calendar period 2001–2007 (RH=0.28 95% CI 0.21–0.39) compared to 1990–1995, an initial AIDS diagnosis of KS (RH=0.49 95% CI 0.44–0.53) compared to a non-KS diagnosis, and cancer treatment (RH=0.78 95% CI 0.71–0.85 and cancer treatment missing (RH=0.77 95% CI 0.68–0.86) compared to no cancer treatment.

When the adjusted analyses were stratified by cancer treatment (Table 5), KS survival time was significantly improved among those in both strata who used HAART for 6 months or more and for calendar periods 1996–1998, 1999–2000, and 2001–2007.

Systemic NHL—In the adjusted model, survival time following a diagnosis of systemic NHL was significantly improved for calendar periods 1996–1998 (RH=0.61 CI 0.48–0.79), 1999–2000 (RH=0.51 CI 0.34–0.77), and 2001–2007 (RH=0.46 CI 0.30–0.70) as compared to the calendar period 1990–1995 (Table 4). Survival time for systemic NHL was also significantly improved for AIDS patients initially diagnosed with NHL (RH=0.55 CI 0.46–0.65), compared to those with other AIDS diagnoses, and for those receiving cancer treatment (RH=0.57 CI 0.46–0.70), compared to those with no cancer treatment. Decreased systemic NHL survival time was significantly associated with older decade of age (RH=1.11 CI 1.02–1.21) and distant stage of cancer compared to localized (RH=1.43 CI 1.16–1.77).

When the adjusted analyses were stratified by cancer treatment, survival time following a diagnosis of systemic NHL was significantly improved for those receiving cancer treatment and for calendar periods 1996–1998, 1999–2000, and 2001–2007 (Table 5). HAART use was not a significant predictor of survival time either for those receiving or not receiving cancer treatment. For those not receiving treatment, calendar period was not significantly associated with systemic NHL survival time.

CNS NHL—For primary CNS NHL, receiving cancer treatment was associated with an increased survival time in the adjusted model (RH 0.53 CI 0.38–0.72) (Table 4). None of the other covariates were associated with improved survival time. When the adjusted analyses were stratified by cancer treatment, neither HAART use nor calendar period were associated with CNS NHL survival time (Table 5).

DISCUSSION

Our analysis is unique and has much strength. Foremost, by using the San Francisco AIDS registry data, we are able to directly assess the impact of HAART use and immunodeficiency (CD4 cell count) on AIDS-related NHL and KS risk and survival time. The San Francisco AIDS registry data ascertainment protocols include multiple chart reviews for AIDS cases and include extensive information about HIV/AIDS treatments including HAART use, not only at the time of AIDS diagnosis, but also periodically until death or loss to follow-up. The San Francisco AIDS registry also collects information about subsequent AIDS diagnoses. In addition, the match with the CCR would have picked up any previously unreported cases of NHL and KS that were identified by the cancer registry as

well as providing information on cancer treatment. Finally, the San Francisco AIDS registry and the California Cancer registry are population based and are therefore representative of the entire city of San Francisco.

We found that more recent calendar period and use of HAART were significantly and independently associated with a decreased risk of KS and that HAART use, but not calendar period, was significantly associated with a decreased risk of systemic NHL and CNS NHL. Although previous studies have found a reduced risk of KS since the introduction of HAART [16, 18, 33, 34] and among HAART users [34], we are unaware of any studies that have simultaneously evaluated the independent associations of both calendar time and use of HAART on cancer risk. Similarly, while several prior studies have found a reduced risk of NHL associated with calendar period [18, 35–38] and use of HAART [39, 40], to our knowledge only one study evaluated both calendar period and use of HAART on risk of NHL and the effects of calendar period were mixed [40].

Several factors may contribute to the different impact of calendar period on risk for KS and NHL, including changes in health related behaviors to decrease exposure to human herpes virus type 8 (HHV-8, the etiologic agent for KS) and increased use of antiviral drugs that have anti-herpetic properties. Nevertheless, we observed that the beneficial effect of HAART use on reducing the risk of both KS and NHL is very strong, especially in reducing the risk of CNS NHL.

In evaluation of risk factors for KS survival time, we found strong evidence of a reduced risk of death associated with HAART use (> 6 months of use) and a gradient of risk associated with calendar period (the more recent the calendar period the lower the risk of death). These findings were observed for both those who did and did not received cancer treatment. While this confirmed what other studies have found regarding HAART use [12] and calendar period on improving KS survival time [41, 42], our results are unique in being able to evaluate the independent effect of cancer treatment, HAART use, and calendar period on KS survival.

In contrast, in adjusted analyses we did not find HAART use to be associated with systemic NHL survival time although the relative hazards were reduced and it is possible that with a larger number of systemic NHL cases the hazards would reach statistical significance. We did, however, find strong evidence for a reduced risk associated with calendar period but in stratified analyses this was found to be true only for those who received cancer treatment. Again, other studies have found improved systemic NHL survival for calendar period [36, 43] or use of HAART [44] but none have assessed the independent effect of cancer treatment, HAART use, and calendar period.

Previous studies have found improved CNS NHL survival for more recent calendar period [43] or use of HAART [45]. In our adjusted analysis of CNS NHL survival time, only cancer treatment was associated with a longer survival time. However, patients who did not receive cancer treatment may also have been sicker or have had more advanced cancer than the patients who received such treatment; thus, we cannot fully attribute longer survival time to treatment per se. In addition, those persons receiving HAART and who receive cancer treatment may have better access to health care than those not receiving treatment, and this difference may lead to longer survival time.

A few limitations should also be noted about this paper. First, we analyzed data from the first 12 years of the HAART era and, along with improved formularies for HAART, the long-term effects of HAART may not have fully manifested themselves. For instance, we may see an even more drastic reduction in the risk of AIDS-related KS and NHL and an increase in cancer survival as time goes on. Second, in San Francisco, the AIDS epidemic

has been concentrated in the population of men who have sex with men and our results may not be generalizable to other risk groups. Also, because of the number of women in our analyses is relatively small, we were unable to assess cervical cancer risk and survival. Third, our ascertainment of HAART use depends on medical chart abstraction and it is possible that HAART use is underreported in some cases or misclassified among people who have not been compliant with their prescribed treatments. Fourth, the cancer registry data on cancer treatment may be incomplete as it only ascertains treatment that is initiated in the first four months following the initial diagnosis. Lastly, there may be other temporal effects or cancer co-factors contributing to a change in risk of HIV-related cancers in the era of HAART that we have not controlled for such as viral infections, screening and treatment practices for cancer or changes in behaviors.

In summary, our study is one of the first linking individual HAART use to population based cancer and AIDS registry data. Our results therefore distinguish between the impact of actual HAART use rather than relying on an ecological approach using calendar times marking the pre-HAART and HAART era. Thus, the reduced risk and improved survival for KS and NHL associated with both HAART use and calendar period should be reassuring for people with HIV infection. However, it will be important to continue to monitor the effects of continued HAART use on the risk and survival of AIDS-related KS and NHL, as well as monitor changes in tumor biology. Close monitoring of such epidemiologic trends is necessary to implement appropriate cancer prevention, screening, and treatment for people with HIV infection.

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Table 1

Characteristics of 14,183 patients diagnosed with AIDS from 1990 to 2000 in San Francisco, CA, by calendar period of initial AIDS diagnosis.

	AIDS diagnosed before 1996		AIDS diagnosed 1996–1998		AIDS diagnosed 1999–2000	
	N = 10,956	%	N = 2,235	%	N = 992	%
Age at AIDS diagnosis*						
<35 years	3,558	32	679	30	272	27
35–45 years	4,823	44	944	42	425	43
>45 years	2,575	24	612	27	295	30
Race/ethnicity*						
African American	1,425	13	434	19	195	20
Latino	1,191	11	296	13	164	17
White	7,931	72	1,402	63	576	58
Other	409	4	103	5	57	5
Gender*						
Male	10,543	96	2,078	93	905	91
Female	413	4	157	7	87	9
Risk Group*						
MSM (includes MSM IDU)	9,840	90	1,828	82	783	79
IDU	852	8	319	14	159	16
Other Risk	264	2	88	4	50	5
CD4 at AIDS diagnosis*						
CD4>350	535	5	148	7	84	8
CD4 200–350	1,644	15	340	15	143	14
CD4<200	6,890	63	1,592	71	720	73
Missing	1,887	17	155	7	45	5
AIDS-related cancer* †						
No	7,477	68	1,936	87	895	90
Yes	3,479	32	299	13	97	10
HAART use prior to AIDS*						

	AIDS diagnosed before 1996		AIDS diagnosed 1996–1998		AIDS diagnosed 1999–2000	
	N = 10,956	%	N = 2,235	%	N = 992	%
None or at the same time as AIDS	10,936	>99	1,950	87	731	74
1–6 months	9	<1	122	5	51	5
>6 months	11	<1	163	7	210	21

HAART=highly active antiretroviral therapy; IDU= injection drug users; MSM=men who have sex with men.

* Chi-square test $p<0.001$.

[†] Includes 6 cases of invasive cervical cancer

Table 2

Distribution of NHL subtypes by HAART era and HAART use among 1030 people with AIDS-defining NHL during 1990–2000 in San Francisco, CA.

NHL Subtype	Lymphomas diagnosed 1990–1995		Lymphomas diagnosed 1996–2000 (HAART Era)	
	No HAART use N (Col %)	HAART use N (Col %)	No HAART use N (Col %)	HAART use N (Col %)
CNS NHL (all types)	171 (26)	4 (8)	43 (51)	36 (16)
Diffuse large cell	163 (24)	17 (35)	17 (20)	84 (37)
Immunoblastic	126 (19)	15 (31)	7 (8)	30 (13)
Burkitt's lymphoma	56(8)	4 (8)	6 (7)	29 (13)
NHL, other type	152 (23)	9 (18)	12 (14)	49 (21)
Column Total	668 (100)	49 (100)	85 (100)	228 (100)

CNS=central nervous system; HAART=highly active antiretroviral therapy; NHL=non-Hodgkin lymphoma.

Adjusted Cox proportional hazard analysis of cancer risk and the association with HAART use and HAART availability among 14,183 people diagnosed with AIDS during 1990–2000 in San Francisco, CA.

Table 3

Cancer Type	HAART use RH*	95% CI	P-value	HAART era RH**	95% CI	P-value
KS	0.81	0.68–0.96	0.02	0.67	0.57–0.80	<0.0001
Systemic NHL	0.63	0.47–0.83	0.001	0.79	0.58–1.07	0.12
CNS NHL	0.22	0.13–0.36	<0.0001	1.22	0.76–1.95	0.41

CI=Confidence Interval; CNS=central nervous system; HAART=highly active antiretroviral therapy; KS=Kaposi's sarcoma; NHL=non-Hodgkin lymphoma; RH = Relative Hazard.

* Adjusted for current age, race/ethnicity, HIV risk group, sex, calendar year, and HAART era.

** Adjusted for current age, race/ethnicity, HIV risk group, sex, calendar year, HAART use.

Table 4

Adjusted Cox proportional hazard models for risk of death among people diagnosed with KS, systemic NHL, and CNS NHL 1990–2000 in San Francisco, CA.

Characteristic	Kaposi's sarcoma N=3028			System NHL (excluding CNS) N=776			CNS NHL N=254		
	N (%)	Adjusted RH (95% CI)	P -value	N (%)	Adjusted RH (95% CI)	P -value	N (%)	Adjusted RH (95% CI)	P -value
Decade of age at cancer diagnosis	3028 (100)	1.07 (1.02–1.13)	0.01	776 (100)	1.11 (1.02–1.21)	0.02	254 (100)		
Sex									
Male	3020 (>99)			755 (97)	1.00	-	245 (96)		
Female	8 (<1)			21 (3)	0.60 (0.34–1.04)	0.07	9 (4)		
Race/ethnicity									
White	2345 (78)			594 (76)			173 (68)		
Hispanic	348 (11)			99 (13)			47 (19)		
Black	236 (8)			66 (9)			28 (11)		
Other	99 (3)			17 (2)			6 (2)		
Risk									
Other Risk	19 (1)			14 (2)			8 (4)		
IDU	63 (2)			48 (6)			19 (7)		
MSM (includes MSM IDU)	2946 (97)			714 (92)			227 (89)		
HAART									
No use		1.00	-		1.00	-		1.00	-
< 6 months use		0.83 (0.66–1.05)	0.12		0.83 (0.54–1.29)	0.41		0.80 (0.42–1.50)	0.49
≥ 6 months use		0.37 (0.31–0.45)	<0.01		0.78 (0.57–1.06)	0.11		0.60 (0.31–1.15)	0.12
Calendar Time									
1990–1995		1.00	-		1.00	-		1.00	-
1996–1998		0.58 (0.51–0.67)	<0.01		0.61 (0.48–0.79)	0.0001		1.09 (0.79–1.52)	0.60
1999–2000		0.44 (0.34–0.56)	<0.01		0.51 (0.34–0.77)	0.001			
2001–2007		0.28 (0.21–0.39)	<0.01		0.46 (0.30–0.70)	0.0004			
1999–2007*								0.65 (0.33–1.29)	0.22
Initial AIDS diagnosis**									
No	2034 (67)	1.00	-	544 (70)	1.00	-	227 (89)		

Characteristic	Kaposi's sarcoma N=3028			Systemic NHL (excluding CNS) N=776			CNS NHL N=254		
	N (%)	Adjusted RH (95% CI)	P-value	N (%)	Adjusted RH (95% CI)	P-value	N (%)	Adjusted RH (95% CI)	P-value
Yes	994 (33)	0.49 (0.44-0.53)	<0.01	232 (30)	0.55 (0.46-0.65)	<0.01	27 (11)		
Stage of cancer									
Localized	314 (10)	1.00	-	281 (36)	1.00	-	170(67)		
Regional	23 (1)	1.64 (1.05-2.56)	0.03	95 (12)	0.93 (0.67-1.30)	0.16	7 (3)		
Distant	822 (27)	1.20 (1.05-1.38)	0.008	178 (23)	1.43 (1.16-1.77)	0.0009	31 (12)		
Unstaged/missing	1869 (62)	0.92 (0.80-1.06)	0.24	222 (29)	0.75 (0.54-1.05)	0.09	46 (18)		
CD4 count at cancer diagnosis									
>350	147 (5)	1.00	-	136 (17)			4 (2)		
200-350	1288 (43)	1.32 (0.94-1.87)	0.11	67 (9)					
<200	1485 (49)	2.55 (1.92-3.39)	<0.01	438 (56)					
<=350*							102 (40)		
Missing		2.52 (1.91-3.34)	<0.01	135 (17)			148 (58)		
Cancer treatment									
No cancer treatment	894 (29)	1.00	-	140 (18)	1.00	-	58 (23)	1.00	-
Any cancer treatment	1416 (47)	0.78 (0.71-0.85)	<0.01	563 (73)	0.57 (0.46-0.70)	<0.01	163 (64)	0.53 (0.38-0.72)	<0.01
Info missing	718 (24)	0.77 (0.68-0.86)	<0.01	73 (9)	0.84 (0.57-1.23)	0.37	33 (13)	0.70 (0.45-1.10)	0.12

CI=Confidence Interval; CNS=central nervous system; HAART=highly active antiretroviral therapy; IDU=injection drug users; KS=Kaposi's sarcoma; MSM=men who have sex with men; NHL=non-Hodgkin lymphoma; RH = Relative Hazard.

* Category collapsed for CNS NHL analyses due to small sample size.

** Initial AIDS diagnosis: KS for KS model, systemic NHL for systemic NHL model, and CNS NHL for CNS NHL model.

Table 5

Adjusted Cox Proportional Hazard model for KS, systemic NHL, and CNS NHL survival time, stratified by cancer treatment.

	Adjusted RH (95% CI)	P-value	Adjusted RH (95% CI)	P-value
<u>Kaposi's sarcoma</u>	No cancer treatment[*] N=894; 770 deaths		Received cancer treatment[*] N=1,416; 1230 deaths	
HAART				
No use	1.00 (reference)	-	1.00 (reference)	-
< 6 months use	1.01 (0.66–1.55)	0.97	0.86 (0.61–1.21)	0.38
≥6 months use	0.54 (0.38–0.76)	0.0004	0.37 (0.29–0.48)	<0.0001
Calendar Time				
1990–1995	1.00 (reference)	-	1.00 (reference)	-
1996–1998	0.55 (0.44–0.76)	<0.0001	0.66 (0.54–0.81)	<0.0001
1999–2000	0.38 (0.24–0.61)	<0.0001	0.56 (0.38–0.81)	0.002
2001–2007	0.22 (0.12–0.39)	<0.0001	0.34 (0.21–0.56)	<0.0001
<u>Systemic NHL</u>	No cancer treatment^{**} N=140; 128 deaths		Cancer treatment^{**} N=563; 484 deaths	
HAART				
No use	1.00 (reference)	-	1.00 (reference)	-
< 6 months use	1.28 (0.42–3.86)	0.67	0.83 (0.49–1.39)	0.47
≥6 months use	0.58 (0.27–1.25)	0.16	0.79 (0.54–1.16)	0.25
Calendar Time				
1990–1995	1.00 (reference)	-	1.00 (reference)	-
1996–1998	1.15 (0.69–1.91)	0.60	0.53 (0.39–0.72)	<0.0001
1999–2000	1.42 (0.58–3.47)	0.44	0.44 (0.27–0.71)	0.0008
2001–2007	0.34 (0.04–3.03)	0.34	0.41 (0.24–0.68)	0.0006
<u>CNS NHL</u>	No cancer treatment N=58; 56 deaths		Cancer treatment N=163; 158 deaths	
HAART				
No use	1.00 (reference)	-	1.00 (reference)	-
< 6 months use	0.50 (0.10–2.48)	0.40	0.90 (0.45–1.80)	0.77
≥6 months use	0.56 (0.12–2.53)	0.45	0.47 (0.22–1.05)	0.06
Calendar Time				
1990–1995	1.00 (reference)	-	1.00 (reference)	-
1996–1998	2.04 (0.90–4.63)	0.09	1.06 (0.72–1.58)	0.76
1999–2007	0.67 (0.15–3.06)	0.60	0.90 (0.40–1.99)	0.79

CI=Confidence Interval; CNS=central nervous system; HAART=highly active antiretroviral therapy; NHL=non-Hodgkin lymphoma; RH = Relative Hazard.

* Adjusted for cancer stage, CD4+ cell count at KS diagnosis, initial AIDS diagnosis, and age.

** Adjusted for cancer stage, initial AIDS diagnosis, age, and sex.