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Recreational amphetamine use and risk of HIV-related non-Hodgkin lymphoma

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Abstract

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The results of many laboratory studies suggest that amphetamine use may lead to altered immune function and cytokine expression, both of which are implicated in HIV-related lymphomagenesis. We examined the hypothesis that use of amphetamines modifies risk of non-Hodgkin lymphoma (NHL) in HIV-infected men in the Multicenter AIDS Cohort Study. Data on amphetamine use were collected every six months during the follow-up period between 1984 and 2002. A total of 171 NHL cases were diagnosed from the 19,250 person-years accrued. Multivariable Cox models were used to estimate the effects of baseline exposures, time-varying recent exposures, and three years lagged exposures on risk of NHL adjusting for potential confounders such as demographics, use of other substances, and risky sexual behaviors. We found that weekly or more frequent use of amphetamines was associated with an increased risk of NHL, with hazard ratios of 1.75 (95% CI = 0.81–3.77) for use at baseline, 4.73 (1.41–15.81) for recent use, and 3.05 (1.19–7.82) for three years prior use. Similar associations were observed when we separately examined systemic NHL and diffuse large B-cell lymphoma. Given these observations, the impact of amphetamines on lymphomagenesis among HIV-infected populations should be assessed more thoroughly.

Keywords

Amphetamines; Recreational drug use; Non-Hodgkin lymphoma; HIV infection; Homosexual men

Introduction

HIV-related non-Hodgkin lymphoma (NHL) has been a significant cause of morbidity and mortality throughout the HIV epidemic [1, 2]. Although the introduction of highly active antiretroviral therapy (HAART) has dramatically reduced the incidence of primary cerebral lymphoma, the decline in systemic NHL has only been modest [3–5]. A study examining US national cancer incidence between 1980 and 2002 showed that persons with HIV/AIDS continue to have a significantly elevated risk of NHL (standardized incidence ratio = 22) in the era of HAART [6].

Amphetamine is a commonly used substance among populations at increased risk for acquiring HIV (e.g., homosexual men and intravenous drug users) [7–9]. In laboratory studies, amphetamines suppress T cell function and proliferation in mouse models and *in vitro*, as well as skew cytokine secretion in a Th2 direction [10–14]. Th2 cytokines such as IL-10 are direct B cell-stimulatory factors whose overproduction could enhance B cell activation. It has been suggested that NHL pathogenesis in HIV-infected individuals involves loss of immunoregulation due to compromised T-cell function and chronic B-cell hyperactivation driven by chronic exposure to infectious agents and to B-cell stimulatory cytokines [15, 16].

Therefore, these laboratory findings suggest that use of amphetamines in HIV-infected persons might affect NHL pathogenesis in multiple ways.

However, few epidemiologic studies have examined the effect of amphetamine use on HIV-related NHL. An earlier case–control study based on 84 NHL cases diagnosed between 1984 and 1993 in the Multicenter AIDS Cohort Study (MACS) did not find a clear association between NHL case status and use of amphetamines [17]. Another case–control study found that lifetime amphetamine use was associated with reduced risk of NHL in HIV-infected men [18]. Both of these studies examined baseline substance use only, and did not address the possible adverse effect for heavy/frequent use of amphetamines on incidence of NHL. Using a prospective study design, we investigated the hypothesis that use of amphetamines, particularly frequent use of these substances, affects the risk of developing NHL in HIV-

infected men, using data from the MACS. We conducted survival analyses taking advantage of the repeated exposure measurements in the MACS.

Materials and methods

Study population

The MACS, started in 1984, is an ongoing cohort study of the natural and treated histories of HIV-1 infection in men who have sex with men (MSM) [19, 20]. Data collection centers are located in Chicago IL, Baltimore MD/Washington DC, Pittsburgh PA, and Los Angeles CA. The study had three recruitment periods: (1) April 1984 to March 1985, when 4,954 predominately white men were enrolled; (2) April 1987 to September 1991, when 668 ethnically more diverse men were enrolled; and (3) October 2001 to August 2003, when 1,350 men, primarily African-American and Latino, were enrolled. Men were recruited through public service announcements in media, presentations to homosexual organizations, recruitment by earlier participants, and visits to gay bars and baths. The present study was based on men in the first and second recruitment periods. The men in the MACS are followed at approximately six-month intervals. At each study visit, participants complete an interviewer-administered questionnaire and a physical examination. The interview requests information on demographic characteristics, sexual and substance use behaviors, and medical history. Blood is collected at each visit to obtain virologic, serologic, immunologic and other laboratory measurements, and for a repository of serum, plasma, and peripheral blood mononuclear cells.

Outcomes

Cancer diagnosis was enquired regularly to study participants at each study visit. For a reported cancer diagnosis, medical records were obtained and reviewed by MACS study staff to confirm reports of these conditions. When a cancer diagnosis was confirmed, information on date of diagnosis, site, histology, diagnosis method, and the availability of biopsy were recorded and entered into the database. If the subject developed more then one cancer, information on the first three cancer diagnoses were collected in the study. We identified NHL by the International Classification for Disease-Oncology version 1 (ICD-O-1) topography and morphology codes, available in the MACS database since the beginning of MACS in the 1980s. NHL was identified by morphology codes 959x–964x, 969x, and 975x for this analysis. NHL of the central nervous system (CNS) was identified with topography codes 191–192. NHL that did not occur in CNS was defined as systemic NHL.

In 2006, all NHL cases in MACS were recoded and assigned an ICD-O-3 code. ICD-O-3 was then used to identify NHL subtypes. Within systemic NHL, the diffuse large B-cell lymphoma (DLBCL) subtype was identified using ICD-O-3 histology code 9678–9680 and 9684, while Burkitt's lymphoma was identified using code 9687 and 9826.

Variables

Use of amphetamines was first modeled as a binary variable (any use vs. no use since last visit). To assess if there was a threshold effect and to examine the dose–response relationship, amphetamine use was further classified as no use (reference), monthly or less frequent use, or weekly or more frequent use. A test for linear trend was conducted by treating amphetamine use as a continuous variable with the following coding: 0 if no use, 12 if monthly or less frequent use, and 52 if weekly or more frequent use. The following variables were explored as potential confounders: age, education, study center, alcohol use (non-drinker, ≤2 times per week, >2 times per week), tobacco smoking (non-smoker, <1 pack per day, ≥1 pack per day), use of other substances (i.e., each of marijuana, cocaine, and

amyl nitrite was classified as “no use,” “monthly or less frequent use,” or “weekly or more frequent use”), number of male sexual partners since the last study visit (<6, ≥6, 6 is the 75th percentile in the entire study cohort), receptive anal intercourse (RA) and condom use since the last study visit (no RA, RA with condom use at all times, RA with inconsistent or no condom use), use of antiretroviral therapy (single, dual, or HAART), and CD4 cell count (continuous). Given that antiretroviral treatments did not become widely available until 1987, individuals were assumed to have received no therapy from visits 1 to 5 (1984–1986). We used the CD4 cell count obtained at the previous visit to control for the potential confounding effect of this variable on use of amphetamines. This ensured that the CD4 cell count included in the models preceded the substance use reported in the current visit.

Statistical analysis

Analyses were based on persons who were HIV seropositive at the time of study enrollment (seroprevalent) and those who subsequently acquired HIV (seroconverted). Persons who had only one HIV-positive study visit were excluded from the analysis. Since the vast majority (94%) of the NHL cases were of white race, we restricted our analysis to white men.

To understand the correlates for use of amphetamines in this cohort of HIV-positive homosexual men, we used logistic regression to examine the associations between amphetamine use and potential confounding factors at the time of study enrollment. We performed survival analysis using Cox proportional hazards models to examine the associations between use of amphetamines and risk of NHL. Follow-up started at the first HIV seropositive visit, and ended at either the time of NHL diagnosis or the last NHL-free visit. For persons diagnosed with NHL at the time of death, the time of NHL development was estimated as the mid-point between the time of the last study visit and the time of death. Potential confounders that suggested an association with NHL in the crude analysis (p-value <0.10) were adjusted for in the multivariable model, i.e., age, tobacco and alcohol use, use of other substances (marijuana, cocaine, and amyl nitrites), number of male sexual partners, receptive anal intercourse and condom use, antiretroviral treatment, and CD4 cell count.

We conducted two separate analyses: (1) using exposure at baseline, i.e., first seropositive visit (time fixed), and (2) using recent exposure from one prior study visit, defined as the visit before the study visit under analysis (time-varying). Information on amphetamine use was not specifically elicited between visits 16–21 (October 1991–September 1994). Therefore, these visits were excluded from the analysis using recent exposure. Previous studies suggested that pathogenesis of HIV-related NHL begins three years, or even longer, before its clinical diagnosis [16, 21–23]. Therefore, to further explore the effect of amphetamine use in the most relevant exposure period, we conducted an exploratory lagged analysis that assumed an average induction time of three years for HIV-related NHL. In this analysis, we used the exposure status for all covariates from at least three years prior in this time-varying analysis.

Since different NHL subtypes (e.g., systemic vs. CNS, DLBCL vs. Burkitt's lymphoma) may have different etiologies, we performed an analysis restricted to systemic lymphoma and DLBCL because these lymphomas are more relevant in the post-HAART era and there were too few lymphomas of other subtypes to be studied separately. Because use of amphetamines is expected to be correlated with use of other substances and with unsafe sex [24, 25], the following informal diagnostic methods were used to assess the presence of multicollinearity [26]: (1) examination of the statistical associations between these variables; (2) removing use of marijuana, cocaine, amyl nitrite, as well as unsafe sex variables one at a time to see if large changes (e.g., >20%) in the estimated regression coefficients for amphetamine resulted; and (3) examination of whether there was a non-significant coefficient for an important predictor, such as CD4 cell count. The proportional hazards

assumption was examined by testing the significance of interaction terms between the use of amphetamines and categorical variables for follow-up time periods. All analyses were conducted using SAS statistical software version 9 (Statistical Analyses System Inc, Cary, NC, USA).

Results

The analyses included 1,788 men infected with HIV at study entry and 461 men who subsequently became HIV seropositive. These 2,249 men provided 19,250 HIV seropositive person-visits during 1984–2002. The characteristics of the study population are shown in Table 1. Use of amphetamines was associated with younger age, lower education, tobacco smoking, alcohol drinking, use of other substances, numbers of male sexual partners, and risky sexual behaviors, i.e., inconsistent or no use of condoms. One hundred and seventy-one NHL cases were diagnosed during the study period, of which 54 occurred in CNS and 117 were systemic lymphomas. Among the systemic lymphomas, 58 were of DLBCL subtype, 20 were Burkitt's lymphoma, five were of other subtypes, and 32 had no subtype information (histology was NOS).

In the analysis of baseline exposure, a positive association between NHL and frequent use of amphetamines (weekly or more frequent, hazard ratio (HR) = 1.75, 95% CI = 0.81–3.77) was suggested, although the confidence intervals included 1 (Table 2). In the time-varying exposure analyses, recent frequent amphetamine use was associated with a significantly increased NHL risk: HR for weekly or more frequent use = 4.73 (1.41–15.81). In the exploratory analysis for three years lagged exposure, frequent use of amphetamines was again associated with increased risk of NHL: HR = 3.05 (1.19–7.82). When we separately examined systemic NHL and DLBCL, similar associations for amphetamine use were observed in all analyses (Table 2).

The regression coefficient and variance estimates for amphetamine use were not sensitive to the inclusion or exclusion of the variables of other substance use or sexual practices, suggesting that multicollinearity was unlikely to have significantly affected the validity of our results. Use of marijuana, cocaine, and amyl nitrites was not found to be clearly associated with risk of NHL. We did not find violations for the proportional hazards assumption in these models.

Discussion

We found that weekly or more frequent use of amphetamines was associated with an elevated risk of overall NHL and systemic NHL in HIV-infected homosexual men. This contrasts with the findings of Holly and Lele [18] who reported that lifetime amphetamine/methamphetamine use was associated with reduced risk of NHL in HIV-infected men in a case–control study based on 263 NHL cases and 97 controls. This discrepancy could be due to different substance use behaviors by the two study populations. Holly and Lele [18] categorized baseline lifetime amphetamine/methamphetamine use as 1–19 times and 20 times or greater. While lifetime amphetamine use of 1–19 times likely represents a very low level of use, the average use for persons who used amphetamines 20 times or greater may still be much lower than that for men who report at least weekly use. In our study, baseline use of amphetamines monthly or less frequently was not associated with risk of NHL (HR = 0.89 (0.57–1.38) and 0.72 (0.41–1.25) for systemic NHL). Therefore, if a possible threshold effect is present, studies may fail to identify the association if relative high levels of exposure could not be examined.

Two case–control studies examined the association between use of amphetamines and non-HIV-related NHL. Nelson and colleagues [27] examined amphetamine use for up to 16+ times in lifetime in 184 male NHL cases and 184 age-, sex- and race-matched controls. They did not observe any significant association between this level of amphetamine use and NHL in the multivariable analyses. Doody et al. [28] examined the impact of medical amphetamine use by conducting medical chart review. They reported an odds ratio of 2.2 (1.1–4.8) for health plan members who were prescribed amphetamines at least five years before the diagnosis of the malignancy, and a dose–response relationship with increasing number of prescription notes. However, amphetamines were largely prescribed for weight control in this study (61% of notations). Since overweight/obesity has been linked to risk of NHL [29–32], these results might have been affected by confounding by indication. To our knowledge, the present study is the first to examine the effect of high frequency of amphetamine use on risk of NHL. There is a clear need of more cohort studies with improved control of confounding and exposure measurement to elucidate the association between use of amphetamines and risk of NHL in both HIV-infected and HIV-uninfected populations.

Biologically plausible mechanisms for the positive association between amphetamine use and risk of NHL have been reported by laboratory studies. These include a potential suppressive effect of amphetamines on T lymphocytes, and biasing of cytokine secretion toward Th2 cytokine. The association between frequent amphetamine use and DLBCL, which are not uniformly EBV-positive cancers, suggests that immunomodulatory effects other than loss of immunosurveillance to EBV, e.g., B cell hyperactivation, may be one pathogenic mechanism in HIV infected amphetamine users. However, marijuana and cocaine have also been shown to skew cytokine secretion in a Th2 direction and to suppress cell-mediated immunity [33–37], but use of these drugs was not associated with risk of NHL in the present study, even at high frequency of use. Therefore, if the observed association for amphetamines is truly unbiased, it may depend on other biologic effects of amphetamines that are not shared with marijuana and cocaine. At present, evidence of the immunomodulatory effects of amphetamines in vivo is mostly based on animal models, rather than clinical or epidemiological data, which are sparse. An amphetamine derivative, methylenedioxymethamphetamine (MDMA), has been shown in double-blind human studies to alter several in vitro measures of immune function, including reduced numbers of circulating CD4 T cells, reduced mitogen-induced T-cell proliferation, Th2 cytokine biasing, and increased circulating natural killer cells [38–41]. However, the long-term effects of amphetamine use on the human immune system and on malignancy outcomes remain largely unknown and require further investigation.

Elevation of B-cell activation markers in HIV-infected men who developed NHL has been observed at least three years prior to the clinical onset of disease [16, 21, 23]. These results suggest that the pathogenesis of HIV-related NHL could be as long as three or more years. Our findings from the three-year lagged analyses are consistent with this notion. In these analyses, three years prior use of amphetamines was associated with NHL risk, indicating a possible role of amphetamines in early lymphomagenesis should the association be causal. Furthermore, the strong association with recent frequent use of amphetamine suggests that amphetamines might also play a role in promoting lymphoma progression to clinical onset of the disease.

Our study has several potential limitations. First, the number of cases exposed to amphetamines was low, thus limiting our ability to estimate risk precisely. Consequently, our results should be interpreted with caution and need to be confirmed in larger prospective studies with a high prevalence of amphetamine use, e.g., intravenous drug users. Second, we could not rule out the possibility of residual confounding by poorer adherence to

antiretroviral therapy associated with use of amphetamines. However, the lack of clear associations between frequent use of the other substances, which is also linked to less compliance to antiretroviral treatment [42–44], suggests that the association for amphetamines is unlikely to be entirely explained by residual confounding. Furthermore, we did not have enough cases to examine selected NHL subtypes that might have a different etiology (e.g., Burkitt's lymphoma). Finally, MACS did not conduct centralized pathology review for cancer cases. As a result, the possibility of misclassification for NHL diagnosis and histology subtype could not be excluded. Despite these limitations, our study has the substantial strengths of a longitudinal design and detailed exposure/confounder measurements that allowed assessment for dose-response relationship and lagged exposures, as well as adjustment for a number of potential confounders. Given our present observation that frequent use of amphetamines was associated with an increased risk of HIV-related NHL, the potential carcinogenic effect of amphetamines in HIV-infected as well as uninfected populations should be more thoroughly assessed.

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Table 1

Characteristics of the 2,249 HIV-infected white men at baseline[a] and during follow-up, 1984–2002

	Subjects (n = 2,249) (Baseline[a] characteristics) Number (%)[b]	Person-years (n = 19,250)
Age (years)	32.8 (28.5/37.9)[c]	
Education		
Less then college degree	1046 (46.5)	
College degree or higher	1178 (52.4)	
Use of amphetamines in the past six months		
None	1576 (70.1)	16050 (83.4)
Monthly or less frequent	527 (23.4)	2036 (10.6)
Weekly or more frequent	85 (3.8)	404 (2.1)
Use of marijuana in the past six months		
None	573 (25.5)	8806 (45.7)
Monthly or less frequent	934 (41.5)	5708 (29.7)
Weekly or more frequent	735 (32.7)	4495 (23.4)
Use of cocaine in the past six months		
None	1297 (57.7)	14859 (77.2)
Monthly or less frequent	863 (38.4)	3591 (18.7)
Weekly or more frequent	83 (3.7)	565 (2.9)
Use of amyl nitrites in the past six months		
None	626 (27.8)	10956 (56.9)
Monthly or less frequent	969 (43.1)	5217 (27.1)
Weekly or more frequent	85 (3.8)	2828 (14.7)
Tobacco Smoking in the past six months		
No	1327 (59.0)	12621 (65.6)
<1 pack per day	338 (15.0)	2615 (13.6)
≥1 pack per day	575 (25.6)	3972 (20.6)
Alcohol drinking in the past six months		
No	176 (7.8)	1637 (8.5)
≤2 times/week	1157 (51.4)	10157 (52.8)
>2 times/week	900 (40.0)	6030 (31.3)
Number of male sexual partners in the past six months		
<6	1106 (49.2)	14214 (73.8)
≥6	1140 (50.7)	4660 (24.2)
Receptive anal sex (RA) in the past six months		
No	341 (15.2)	8691 (45.1)
RA with use of condoms at all times	235 (10.4)	4409 (22.9)
RA with inconsistent or no use of condom	1647 (73.2)	5672 (29.5)
Baseline CD4 lymphocyte count (/μl)	578 (422/770)[c]	

[a] Baseline defined as the first HIV seropositive study visit

[b] Percent may not add up to 100% due to missing values

[c] Median (25/75 percentile)

Table 2

Multivariable Cox proportional hazards models on time to NHL in relation to use of amphetamines (1) at baseline[a], (2) as recent exposure, and (3) from three years prior

Frequency of amphetamine use	No. of exposed NHL (baseline/recent/lagged exposure)	Baseline[a] exposures		Recent exposures (Approximately 6 months prior)		Lagged exposures (At least three years prior)	
		HR (95% CI)	*p*-trend	HR (95% CI)	*p*-trend	HR (95% CI)	*p*-trend
Overall NHL							
No use	127/151/108	1		1		1	
Any use	40/10/16	0.94 (0.62–1.41)		1.46 (0.63–3.37)		1.36 (0.75–2.44)	
Monthly or less frequent	32/5/11	0.89 (0.57–1.38)	0.25	0.96 (0.34–2.77)	0.03	1.05 (0.52–2.11)	0.03
Weekly or more frequent	8/5/5	1.75 (0.81–3.77)		4.73 (1.41–15.81)		3.05 (1.19–7.82)	
Systemic NHL							
No use	87/103/67	1		1		1	
Any use	27/8/15	0.89 (0.54–1.45)		1.49 (0.56–3.98)		2.11 (1.11–4.09)	
Monthly or less frequent	19/3/10	0.72 (0.41–1.25)	0.10	0.69 (0.16–2.95)	0.01	1.56 (0.73–3.35)	<0.01
Weekly or more frequent	8/5/5	2.31 (1.04–5.15)		6.39 (1.85–22.11)		4.32 (1.63–11.42)	
Diffuse large B-cell lymphoma							
No use	46/50/40	1		1		1	
Any use	12/4/10	1.07 (0.43–2.62)		1.58 (0.34–7.28)		2.59 (0.89–8.01)	
Monthly or less frequent	8/2/7	0.58 (0.19–1.80)	0.01	0.89 (0.11–6.96)	0.16	1.89 (0.49–7.25)	0.03
Weekly or more frequent	4/2/3	4.21 (1.30–13.61)		4.86 (0.60–39.71)		5.34 (1.09–26.23)	

Models adjusted for age, tobacco smoking, alcohol use, use of marijuana, cocaine and amyl nitrites, number of male sexual partners, receptive anal intercourse, antiretroviral therapy (not in baseline model), and CD4 cell count

[a]Baseline defined as the first HIV seropositive study visit