ORIGINAL ARTICLE

HIV-1/AIDS Neuropathology in a Canadian Teaching Centre

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ABSTRACT: ***Background:*** The nervous system is a major target of HIV-1 infection and site of many complications of AIDS. Most of our knowledge pertaining to the range and frequency of neuropathology in HIV-1/AIDS is from large centres outside Canada in different social and health care settings. The goal of the present study was to describe HIV-1/AIDS-associated neuropathology before and during the era of highly active antiretroviral therapy at a Canadian teaching centre. ***Methods:*** The records of the Department of Pathology, London Health Sciences Centre were electronically searched for cases of HIV-1/AIDS that came to postmortem examination since 1985. The clinical records and pathological materials were reviewed. ***Results:*** Sixteen autopsies of HIV-1/AIDS were identified. All patients were male. Fourteen contracted HIV-1 through high risk homosexual activity, one through the transfusion of blood products and one through intravenous drug use. Three patients (19%) had pre-mortem evidence of HIV-1 associated dementia. At autopsy, 12 of the 16 cases had neuropathological findings and the most common diagnoses were HIV-1 encephalitis, progressive multifocal leukoencephalopathy, toxoplasmosis, and primary CNS lymphoma. ***Conclusions:*** High risk homosexual activity was a more prominent factor in acquiring AIDS in cases coming to postmortem examination compared with previous reports from most larger urban centres outside Canada where injection drug use and high risk heterosexual activity factored prominently. The incidence of HIV-1 associated dementia was similar to that reported previously. This study confirms the heavy burden and wide spectrum of disease experienced by the nervous system in HIV-1/AIDS.

RÉSUMÉ: Neuropathologie due au VIH-1/SIDAdans une institution canadienne d'enseignement. ***Introduction***: Le système nerveux est une cible majeure de l'infection par le VIH-1 et le siège de plusieurs complications du SIDA. La plupart de nos connaissances sur la diversité et la fréquence des complications neuropathologiques dans l'infection par le VIH-1/SIDAproviennent de grands centres de l'extérieur du Canada, dans un contexte social et de soins de santé différents des nôtres. Le but de cette étude était de décrire la neuropathologie associée à l'infection par le VIH-1/SIDA avant et pendant l'ère de la thérapie antirétrovirale hautement active (HAART) dans une institution canadienne d'enseignement. ***Méthodes***: Les cas de VIH-1/SIDAayant eu une autopsie depuis 1985 ont été identifiés par une recherche électronique de dossiers du département d'anatomopathologie du London Health Sciences Centre. Les dossiers cliniques et les spécimens anatomopathologiques ont été révisés. ***Résultats***: Seize dossiers de patients atteints d'infection par le VIH-1/SIDAayant eu une autopsie, ont été identifiés. Tous les patients étaient des hommes. Quatorze d'entre eux avaient été infectés lors d'activités homosexuelles à haut risque, un lors d'une transfusion de produits sanguins et un par injection intraveineuse de drogue. Trois patients (19%) avaient des signes de démence associée au VIH-1 avant leur décès. À l'autopsie, 12 des 16 cas avaient des lésions neuropathologiques et les diagnostics les plus fréquents étaient les suivants: encéphalite à VIH-1, leuco-encéphalopathie multifocale progressive, toxoplasmose et lymphome primaire du système nerveux central. ***Conclusions***: L'activité homosexuelle à haut risque était un facteur plus important de transmission du SIDAchez les cas ayant eu une autopsie dans notre milieu que chez les cas publiés provenant de la plupart des grands centres urbains de l'extérieur du Canada où l'utilisation de drogues intraveineuses et l'activité hétérosexuelle à haut risque étaient les facteurs dominants. L'incidence de la démence associée à l'infection par le VIH-1 était semblable à celle rapportée antérieurement. Cette étude confirme la lourdeur et la diversité de la maladie au niveau du système nerveux dans l'infection par le VIH-1/SIDA.

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The brain continues to be a common site of HIV-1-related infectious and neoplastic complications.[1,2] Common neuropathological findings include HIV-1 encephalitis, HIV-1 leukoencephalopathy, progressive multifocal leukoencephalopathy (PML), cytomegalovirus (CMV) encephalitis, cryptococcosis (Crypt), cerebral toxoplasmosis (TOXO) and primary central nervous system lymphoma (PCNSL). HIV-1 associated dementia (HAD) is independent of opportunistic infections or neoplasms but is associated with HIV-1 encephalitis and higher brain viral burden.[3,4]

The demographic features and various neuropathological manifestations of HIV-1 infection show considerable variability between large urban centres in the United States and Europe. This variability may be attributable to a number of factors

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including social structure, mode of infection and health care accessibility. Previous studies have revealed variations in the frequency, risk factors, HIV-1 related complications and neuropathological diagnoses.[5-10] Relevant risk factors and mode of infection can vary widely. For example, in a comparative international postmortem study of six large cities,[11] the percentages of patients contracting the virus through intravenous drug use (IDU) in each city ranged from 1% in Budapest to 67% in Newark. Health care standards and accessibility can also be strikingly variable. In Canada, universal access to health care may introduce more uniformity of delivery and follow-up. The management of AIDS and the prophylaxis, identification and treatment of complications is undertaken with an understanding of the full range of disease potential. However, a more accurate understanding of disease frequency in a given setting will further benefit such efforts and make the delivery of health care better suited to individual communities.

In order to develop a better understanding of the nervous system disease in the Southwestern Ontario AIDS population, we examined the clinical and pathology records of all HIV-1 positive patients that came to autopsy at the London Health Sciences Centre (LHSC) from 1985 to 2002.

Southwestern Ontario, which includes 15 municipalities (Figure 1), is the catchment area for LHSC. According to the 1996 Census, Southwestern Ontario has a population of almost 1.5 million, representing 13% of the population of Ontario. The City of London represents approximately 23% of this population. The St. Joseph's Health Care London, HIV Care Program provides tertiary care to patients with HIV/AIDS in London and Southwestern Ontario. Roughly 56% of the patients treated by the HIV Care Program since 1991 resided in the city of London, while the remainder lived in surrounding communities. Whether or not the urban/rural composition of a clinic population would affect the findings of such a study is uncertain. Unfortunately, similar postmortem studies have not commented on urban/rural patient ratios.

Two hundred and fifty-five London clinic patients with HIV-1/AIDS have died since 1991, resulting in an autopsy rate of 6.3% during this time period. The autopsy rate has been 23.3% since 1998 when closer collaborative ties were developed with the London HIV Care Program and the Pittsburgh HIV-1/AIDS Brain Bank. This autopsy rate compares favorably with previous studies on this topic[12,13] although we recognize that even current autopsy rates represent a small and potentially biased sampling of the total HIV-1/AIDS population at this centre.

Figure 1: *Map of Southwestern Ontario to show referral area for the St. Joseph's Health Care London, HIVCare Clinic.*

MATERIALS AND METHODS

The archives of the Department of Pathology, LHSC, were electronically searched to identify all autopsied cases of HIV-1/AIDS. The search identified 16 cases between 1985 and 2002 distributed as follows: one in 1991, two in 1992, one in 1993, one in 1996, three in 1998, three in 1999, three in 2000, and two in 2002. Clinical records were examined from LHSC and from the affiliated HIVCare Clinic to tabulate the following variables: age, sex, mode of infection, time since first positive HIV-1 serology test, date of death, and the incidence of HAD and other neurological complications. HIV-1 associated dementia was diagnosed by clinic physicians on the basis of a mental status exam in a patient with no other identifiable source of dementia. Pathology reports and glass slides were examined for the presence or absence of several diagnostic categories including: HIV-1 encephalitis/HIV-1 leukoencephalopathy, PML, CMV encephalitis, TOXO, Crypt, PCNSL, and HAD. Patients were classified as having AIDS based on the 1993 revised CDC HIV classification system and expanded AIDS surveillance definition for adolescents and adults. Clinical records of all patients who died since 1991 were examined for demographic details of the Southwestern Ontario HIV-1/AIDS population dying during the period of this study. Clinical and pathological data obtained from our study was subsequently compared to similar studies from other centres.[5,9,12,14-16]

At autopsy, brains were fixed in 20% formalin for 7-10 days. The brains were sampled widely to include neocortex (frontal, temporal, parietal, occipital), hippocampus, deep white matter, basal ganglia, brainstem and cerebellum. Paraffin sections were stained routinely with hematoxylin and eosin. Special stains were applied as necessary, including Gomori's methenamine silver, gram, periodic acid Schiff, Ziehl-Nielsen, Fite acid-fast and Giemsa stains. Immunohistochemistry was performed for a

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Table 1: Demographic characterization and prevalence of HAD and of various HIV-1/AIDS related neuropathologies among the Southwestern Ontario cohort of patients.

	Patient	Age at death	Time since first positive serology test for HIV-1 (months)	AIDS defining illness	CD4	Prevalence of various neuropathologies						HAD	Treatment	
						TOXO	PML	AE	PCNSL	HIVE/ HIVL	HIV immuno		Duration of HAART (months)	Off HAART P.T.D. (months)
post-HAART era	1	43	60	KS	65 cells/ul					★	pos	★	40	18
	2	33	1.5	MAC	no data						neg		0.5	0
	3	37	138	PNEU	600 cells/ul						neg		15	0.5
	4	44	157	PCP	<10 cells/ul					★	pos	★	36	15.5
	5	60	1.5	PML	8 cells/ul		★				neg		1.5	0
	6	35	117	HE	88 cells/ul		★		★	★	pos	★	1	5
	7	43	104	TOXO	140 cells/ul					★	neg		2	24
	8	59	*	none	n/a						neg		0	n/a
	9	56	*	none	n/a						neg		0	n/a
	10	67	156	PCNSL	170 cells/ul		★		★		neg		32	2
	11	44	132	none	288 cells/ul			★			equivocal		0	n/a
pre-HAART era	12	39	120	MAC	20 cells/ul					★	pos		n/a	n/a
	13	34	5.5	PNEU	30 cells/ul		★			★	pos		n/a	n/a
	14	45	*	TOXO	n/a	★					neg		n/a	n/a
	15	49	1.5	TOXO	no data	★				★	neg		n/a	n/a
	16	46	0.5	TOXO	no data	★				★	pos		n/a	n/a

TB=Tuberculosis meningitis; PNEU=Strepococcus pneumoniae pneumonia; PCP=Pneumocystis Carini pneumonia; TOXO=Toxoplasmosis; PML=Progressive multifocal leukoencephalopathy; AE=Aspergillus encephalitis; PCNSL=primary CNS lymphoma; MAC=Mycobacterium avium-intracellulare complex; HIVE=HIV-1 encephalitis; HAART=highly active antiretroviral treatment; KS=Kaposi's sarcoma; HIVL=HIV-1 leukoencephalopathy; HE=HIV-1 encephalopathy; HAD=HIV-1 associated dementia; HIV immuno=HIV immunohistochemistry (p24); CD4 refers to the last recorded CD4 count within one year of death; P.T.D.=prior to death; n/a=not applicable.

* these patients were only diagnosed as HIV-1 infected at postmortem exam.

number of viral antigens as follows: CMV (SIGNET, monoclonal, 1:100, 1 hour), herpes simplex virus 1 (Dako, polyclonal, 1:40, 1 hour), herpes simplex virus 2 (Dako, polyclonal, 1:50, 1 hour), varicella-zoster virus (Novocastra, monoclonal, 1:50, 1 hour) and HIV-1 p24 (Dako, monoclonal, 1:50, overnight). Briefly, following deparaffinization, slides were blocked in 3% H_2O_2. Slides were incubated with respective primary antibodies as above at room temperature. Slides were incubated with appropriate biotinylated secondary antibodies and developed with diamino benzidine or 3-amino-9-ethylcarbazole.

Results

The salient neuropathological findings are summarized in Table 1. The most frequent neuropathological manifestation was HIV-1 encephalitis/HIV-1 leukoencephalopathy occurring in eight of 16 patients. Other diagnoses encountered were PML, PCNSL and TOXO occurring in four, two and three of the patients respectively, one patient with a presumed coincidental astrocytoma (patient #3) and one patient with fungal encephalitis (Figure 2). As is not uncommon in the setting of AIDS, multiple neuropathological diagnoses were made in some individuals with one patient having three of the above diagnoses (patient #6). The HIV-1 antigen p24 was detected by immunohistochemistry in five cases, all of which displayed evidence of HIV-1 encephalitis/HIV-1 leukoencephaolpathy. The prevalence of various neuropathologies within each of 12 other centres is compared in Table 2. Although our sample size is small, relative to the larger centres, the proportion of cases of HIV-1 encephalitis and PML was higher in this group of patients while none of the Southwestern Ontario cases had CMV encephalitis.

Table 3 provides a charting of demographic variables to allow a comparison with previous studies from larger centres. In London Ontario, all of the patients were male (compared with as low as 65% in Newark and 74% in the Bronx) with an average age of 46 years ranging from 33 to 67 years (compared with average of 39 in other large autopsy studies). Furthermore, the average duration of infection was approximately 6.4 years for the patients that were aware of their HIV-1 infected status prior to death (Table 1). Thirteen of the 16 patients had AIDS (Table 1). Three patients were identified as HIV-1 positive following death. The prevalent risk factor of HIV-1 exposure in the London Ontario population was high risk sex with males. This was the

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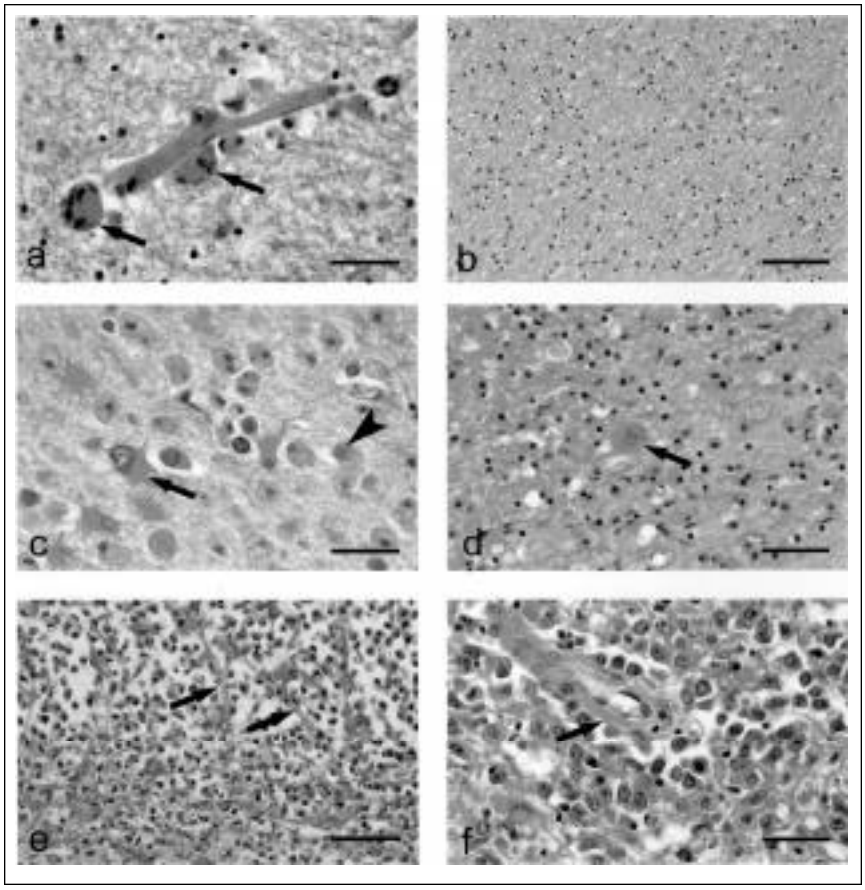

Figure 2: *Photomicrographs of HIV-1/AIDS Neuropathology*
a) HIVE with multinucleated giant cell formation (arrows), bar = 50μm
b) HIVL showing white matter pallor and vacuolation, bar = 100μm
c) PML lesion with atypical astrocytes (arrow) and intranuclear viral inclusions with smudgey/ground glass nuclear change (arrowhead), bar = 50μm
d) Cerebral toxoplasmosis with toxoplasma bradyzoite (arrow), bar = 50μm
e) Cerebral aspergillus abscess showing septate, acute-angle branching fungal hyphae (arrows), bar = 50μm
f) Primary CNS lymphoma infiltrate of neoplastic lymphocytes, with dark pleomorphic nuclei and negligable cytoplasm, around a cerebral vessel (arrow), bar = 50μm

mode of infection for all but two patients; patient #12 acquired the virus through transfusion with infected blood products, and patient #1 acquired the virus through IDU. Moreover, none of the cases in this autopsy series acquired HIV-1 through high risk heterosexual activity.

Comparison of the demographic details of the 16 autopsied cases with those of all clinic deaths in the same period showed that the autopsy set was reasonably representative of the total. The total population treated by the HIV Care program consisted of 92% males. The average age at death was 39. The percentages of patients reporting various risk factors for acquiring HIV-1 consisted of 70% men who have sex with men, 11% IDU, 14% high risk heterosexual behavior, 10% through infected blood products, and 2% through vertical transmission. It is noteworthy that 10% of the patients reported multiple risk factors.

Discussion

Since 1996, patients with HIV-1/AIDS in Southwestern Ontario were prescribed highly active anti-retroviral treatment, which consists of a combination of three or more nucleoside reverse transcriptase inhibitors and/or protease inhibitors or non-nucleoside reverse transcriptase inhibitors. In some instances these were discontinued due to failure to control viral load or were not initiated in patients near death at the time of discovery of HIV-1 positivity. These clinical circumstances and the observed CD4 counts are as expected for a postmortem study of this nature.

Progressive multifocal leukoencephalopathy was a less frequent complication in the first decade of the AIDS epidemic, but this opportunistic infection had increased dramatically by the mid ’90s.[17] This study supports this trend with PML being a common finding among Southwestern Ontario patients after the

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Table 2. Prevalence of various HIV-1/AIDS related neuropathologies in thirteen centres. Parentheses are indicative of the frequency in the given region.

Centre of study: numberof cases	Prevalence of various neuropathologies					
	PML	**Crypt**	**CMVE**	**TOXO**	**PCNSL**	**HIVE/HIVL**
Baltimore: n=303[5]	10 (3%)	26 (9%)	55 (19%)	22 (7%)	30 (10%)	72 (24%)
Newark: n=119[5]	2 (2%)	15 (13%)	6 (5%)	15 (13%)	3 (3%)	15 (13%)
Edinburgh: n=117 [5]	3 (4%)	0	11 (14%)	7 (9%)	13 (16%)	36 (44%)
London, ENG: n=290[5]	14 (5%)	3 (1%)	52 (18%)	27 (10%)	32 (11%)	63 (22%)
Paris: n=243[5]	26 (11%)	9 (4%)	40 (17%)	94 (39%)	33 (14%)	73 (30%)
Budapest: n=72[5]	3 (4%)	3 (4%)	14 (19%)	9 (12%)	10 (14%)	28 (39%)
Inner-City Bronx: n=252[9]	n/a	17 (7%)	23 (9%)	28 (11%)	13 (5%)	n/a
Vancouver: n=39[12]	1 (3%)	2 (5%)	9 (23%)	7 (18%)	11 (28%)	17 (44%)
Brazil: n=22[16]	n/a	3 (14%)	n/a	4 (18%)	2 (9%)	4 (18%)
Switzerland: n=135[13]	9 (7%)	5 (4%)	14 (10%)	35 (26%)	4 (3%)	21 (16%)
Los Angeles: n=89[14]	6 (7%)	11 (12%)	14 (16%)	6 (7%)	3 (3%)	n/a
Japan: n=15[15]	1 (7%)	0	3 (20%)	1 (7%)	2 (13%)	4 (27%)
London, ON: n=16	4 (25%)	0	0	3 (19%)	2 (13%)	8 (50%)

PML=Progressive multifocal leukoencephalopathy; Crypt=Cryptococcosis; CMVE=Cytomegalovirus encephalitis; TOXO=Toxoplasmosis; PCNSL=primary CNS lymphoma; HIVE=HIV-1 encephalitis; HIVL=HIV-1 leukoencephalopathy; n/a, not available.

Table 3. Demographic characteristics and high risk behavior of HIV-1 infected autopsies examined in thirteen regions. Parentheses indicate the frequency in a given region.

	Demographics					Risk factor				
Centre of study: n (number of autopsies)	Time period of study	Gender male	Mean age at death male	female	both	MSM	blood products	IDU	Hetero-sexual	Other/ undeter-mined
Baltimore: n=303[5]	1983-1993	270 (89%)	39	40	39	173 (57%)	11 (3%)	83 (27%)	8 (3%)	28 (9%)
Newark: n=119[5]	1983-1993	77 (65%)	38	34	37	8 (7%)	1 (2%)	78 (67%)	11 (10%)	17 (13%)
Edinburgh: n=117[5]	1983-1993	97 (83%)	33	29	32	29 (25%)	4 (3%)	74 (63%)	3 (3%)	7 (6%)
London, ENG: n=290[5]	1983-1993	281 (97%)	40	33	40	202 (70%)	24 (8%)	13 (5%)	12 (4%)	39 (13%)
Paris: n=243[5]	1983-1993	217 (89%)	41	36	40	117 (48%)	23 (9%)	45 (19%)	26 (11%)	28 (12%)
Budapest: n=72[5]	1983-1993	68 (94%)	40	41	40	53 (74%)	12 (16%)	1 (1%)	2 (3%)	4 (6%)
Inner-City Bronx: n=252[9]	1982-1995	187 (74%)	n/a	n/a	39	35 (14%)	5 (2%)	123 (49%)	47 (19%)	31 (12%)
Vancouver: n=39[12]	1984-1991	37 (95%)	38	25	38	n/a	n/a	n/a	n/a	n/a
Brazil: n=22[16]	n/a	22 (100%)	36		36	19 (86%)	1 (5%)	1 (5%)	0	1 (5%)
Switzerland: n=135[13]	1981-1987	117 (87%)	n/a	n/a	38	89 (66%)	2 (1%)	26 (19%)	19 (14%)	1 (1%)
Los Angeles: n=89[14]	n/a	87 (98%)	n/a	n/a	40	79 (89%)	2 (2%)	11 (12%)	2 (2%)	7 (8%)
Japan: n=15[15]	1985-1999	15 (100%)	41		41	7 (47%)	7 (47%)	0	0	1 (7%)
London, ON: n=16	1985-2002	16 (100%)	46		46	14 (88%)	1 (6%)	1 (6%)	0	0

MSM=men who have sex with men; IDU=intravenous drug use; n/a=not available.

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introduction of highly active anti-retroviral treatment (HAART).

Previous studies had identified HIV-1 encephalitis as the most prevalent postmortem neuropathological diagnosis[11] and this is also corroborated by the present study. It has been suggested that IDU patients were twice as likely to manifest HIV-1 encephalitis than those who acquired the virus through homosexual behavior.[18] However, despite having only one reported case of IDU in our series, HIV-1 encephalitis remains a common form of neuropathology. As noted by other authors, multinucleated giant cells are an insensitive marker of HIV-1 encephalitis. Of the eight patients exhibiting HIV-1 encephalitis/HIV-1 leukoencephalopathy in our study, only five had multinucleated giant cells. Intravenous drug use has been linked to a higher incidence of HAD,[18] but the small size of our series precludes an analysis of this factor in the present study.

Our study is composed of a relatively small number of cases, therefore we were cautious not to overgeneralize the results. Further research is needed in order to substantiate the trends described over time and in a larger set of patients. Similarly, HAART usage among the Southwestern Ontario cohort of patients was variable. Our study is unique in that it was the only study described in this review, with the exception of the Japanese study, that described patients in both the pre and post-HAART eras. However, only four patients in our cohort were on HAART for greater than one year, two of whom were off the medications for more than one year prior to death.

Current HAART protocols have an uncertain impact on the future of HAD. Evidence has been presented to suggest that the incidence of HAD is lower since the availability of HAART[19-21] while other studies were less optimistic.[22] Some experts have noted a change in time course towards greater chronicity and a trend of increasing prevalence of HAD among patients with relatively preserved CD4 counts.[23,24] Furthermore with HAART resistance the potential exists for an increased incidence of HAD.[22] The present study shows no trend towards a lower incidence of HIV-1 encephalitis or HIV-1 associated dementia with the availability of HAART. In fact, all three cases of HAD in our cohort occurred after the implementation of HAART. We suggest that it is premature to draw conclusions about the long-term effect of HAART on the incidence and prevalence of HAD.

The spectrum of neuropathological disease was wide, as noted in previous studies, with PML being a relatively common and CMV encephalitis a less common neuropathological finding at our centre to date. The latter is consistent with the observation that since the introduction of HAART in 1996, death from, and the incidence of, CMV and *Mycobacterium avium-intracellulare* complex has decreased.[1,2] Cases with multiple neuropathological diagnoses are not uncommon in AIDS and several of the present cases confirm this.

No appreciable trends in the prevalence of PML, PCNSL, or HIV-1 encephalitis/HIV-1 leukoencephalopathy were noted when comparing cases that were recently determined to be HIV-1 infected (within six months of death) to those with more longstanding evidence of HIV-1/AIDS. Conversely, the prevalence of TOXO was restricted to those cases identified as being HIV-1 infected within six months of death. More importantly, these cases came to autopsy before the introduction of HAART and toxoplasma prophylaxis. It should be pointed out that patient #11 had several sources of immunocompromise (cancer, radiation therapy, corticosteroid therapy and HIV-1) and as a result the fungal encephalitis cannot be definitively ascribed to HIV-1.

High risk homosexual activity was the most prominent risk factor in the present study. The relatively low prevalence of IDU may be due to the size of city or other social and health care factors (poverty, overcrowding, education, universal health care, access to needle exchange programs), however the relationship between such factors and the prevalence of IDU is uncertain.[25-34] The gender composition of our patients is not unexpected in a North American setting. All of the cases in the present study were male, compared with a range of 65-95% in other North American reports.[5,12,14] The mean age at death in our autopsy series is slightly greater than that of other centres.

Nervous system disease in HIV-1 continues to be an important determinant of health and provision of health care for these patients. The identification of demographic trends and disease incidences in individual centres is relevant to these concerns and reveals considerable differences between centres that may be influenced by a number of social factors. These findings contribute information towards the optimization of social, educational and health care measures in individual centres caring for patients with HIV-1/AIDS.

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