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Neuropathology and general autopsy findings in AIDS during the last 15 years

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Abstract A retrospective study of 450 consecutive AIDS autopsy cases (397 males, 53 females; mean age at death 38.4 years) in Vienna, Austria, between 1984 and 1999 compares the central nervous system (CNS) findings in three cohorts: 1984–1992 (190 cases), 1993–1995 (162 cases) and 1996–1999 (98 cases, after introduction of triple antiretroviral therapy) and the relationship of CNS findings to systemic AIDS pathology in the latter two cohorts. In these two groups, following involvement of the lung (85% and 75%, respectively), the brain continued to be the second most frequently involved organ (decrease from 80% to 60%, respectively). Extracerebral protozoal (*Pneumocystis carinii*, toxoplasmosis), *Mycobacterium avium* complex, viral [e.g., cytomegalovirus (CMV)], multiple opportunistic organ and CNS infections, and Kaposi sarcoma significantly decreased over time. There was less decrease in fungal infections, while bacterial organ and CNS infections (except for mycobacteriosis), lymphomas, HIV-associated CNS lesions (around 30%), non HIV-associated changes (vascular, metabolic, etc.) and negative CNS findings (10–11%) remained unchanged. Nonspecific CNS changes (e.g., meningeal fibrosis) increased. Extracerebral pathology in subjects with advanced HIV-related CNS lesions showed more frequent but decreasing systemic bacterial and CMV infections than those with negative or nonspecific neuropathology, while other opportunistic and multiple organ infections and lymphomas showed no differences between both groups. In a cohort of drug abusers, HIV encephalitis, progressive multifocal leukoencephalopathy, bacterial infections, hepatic encephalopathy, and negative CNS findings were more frequent than in non-users who showed increased incidence of CMV, toxoplasmosis, or other opportunistic CNS infections, and nonspecific CNS findings; the frequency of lymphomas was similar in both drug abusers and non-users. Similar to a recent autopsy study from San Diego, these data suggest that despite the beneficial effects of modern antiretroviral combination therapy, involvement of the brain in AIDS subjects continues to be a frequent autopsy finding, while the increased incidence of HIV encephalitis in our small cohort of drug users was less than observed in other recent autopsy studies.

Key words AIDS · Extracerebral pathology · Central nervous system lesions · Opportunistic infections

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Introduction

During the last years, changing patterns of both organ and systemic pathology and central nervous system (CNS) findings have been observed in subjects with AIDS [24, 30, 35, 39, 53, 54] which, at least in part, appears to be related to the effects of highly active antiretroviral therapy (HAART) [9, 13, 14, 14a, 17, 19, 40, 41, 47, 55]. Whereas until 1986, 75% of autopsies of AIDS patients showed single infections, particularly *Pneumocystis carinii* pneumonia (PCP) [53], since 1987, 72% of autopsies presented with multiple infection agents including PCP, *Mycobacterium avium* complex (MAC), cytomegalovirus (CMV), and various fungal agents [30]. After the introduction of antiretroviral combination therapy, death from PCP, bacterial sepsis, CMV, MAC infections, and toxoplasmosis declined, whereas mortality from fungal infections, tuber-

culosis, HIV encephalopathy, and other causes increased; the distribution of organ involvement by major opportunistic infections and neoplasms has remained virtually the same throughout the years [30, 53]. The death rate from non-Hodgkin's lymphomas (NHL) and Kaposi's sarcoma (KS) has remained high, the latter being more frequent in patients with a history of intravenous (IV) drug abuse [53]. Recently, Masliah et al. [39], in a retrospective study of 390 AIDS autopsy cases (from 1982 to 1998) in San Diego, California, reported a decreased frequency of CMV, PCP, and MAC, whereas bacterial infections increased and the incidence of fungal infections remained unchanged over time. NHL showed an upward trend, while the frequency of KS remained unchanged. Following involvement of the lung (84%), the brain continued to be the second most frequently affected organ (63%), followed by the adrenal glands (44%). Whereas alterations of the brain by opportunistic infections and NHL showed a downward trend, HIV encephalitis continued to be detected in around 25% of the cases. In other autopsy series, it ranged from 0% to 55% (average 25–35%) [10, 11, 12, 18, 27, 28, 30, 32, 33, 34, 38, 39, 43, 48, 51], with highest incidence (56–59%) in drug abusers [7, 8, 38]. In the San Diego series, cases with early HIV brain pathology (e.g., lymphocytic meningitis) showed minimal systemic pathology, whereas those with advanced HIV-related neuropathology or no CNS involvement revealed significant organ pathology with opportunistic infections and neoplasms. These trends remained largely unchanged throughout the total period [39]. This study suggests that despite the beneficial effects of antiretroviral and anti-opportunistic infection therapy, involvement of the brain continues to be a frequent autopsy finding accompanied by variable extracerebral pathology.

The present report presents the results of a retrospective study of 450 consecutive autopsies of AIDS patients in Vienna, Austria, between 1984 and 1999, comparing the CNS findings in three cohorts: 190 cases from 1984 to 1992 (previously published in part [18, 54]); 162 cases from 1993 to 1995; and 98 cases from 1996 (when the modern triple antiretroviral therapy including protease inhibitors [13, 19, 26] was introduced) to 1999. For the latter two series, the frequency of organ pathology and its relationship to CNS pathology is also reviewed.

Material and methods

Results are based on a consecutive unselected autopsy series of 450 patients (448 adults and 2 children), all HIV-1 seropositive and meeting the diagnostic criteria for AIDS according to the Centers for Disease Control definitions [23], who died in one of two specialized departments in Vienna, Austria, between January1984 and December 1999. In each of these cases, a complete autopsy was performed. In the two series spanning the period 1993 and 1999, tissue blocks from most parenchymal organs were examined histologically using routine staining and immunohistochemical methods. For the previous series (1984–1992), data for histological examination of parenchymal organs were not available for all cases and, therefore, were not included.

Gross and microscopic examination of the brain was performed in all cases; for technical reasons, the spinal cord was available only in a small number of cases. Tissue blocks were sampled from 10 to 15 different brain areas and from macroscopically suspected regions. Paraffin sections (4 μm) were stained with hematoxylin-eosin, cresyl violet, and Klüver-Barrera. Special stains included Giemsa, Gram, Grocott, periodic acid-Schiff, and Ziehl-Neelson. For immunohistochemistry, monoclonal antibodies against CMV, HIV 8p4 and p 24 (Dakopatts, Glostrup, Denmark), herpes simplex virus I (Dakopatts), *Toxoplasma gondii* (Virion, Rüschlikon, Switzerland), and glial fibrillary acidic protein (GFAP; Dakopatts), and for characterization of lymphomas, monoclonal antibodies against B cells (L-26) and T cells (UCHL-1) (both Dakopatts), were used with a biotinylated streptavidin method. For detection of CMV, in situ hybridization was performed using a biotinylated c-DNA oligoprobe for CMV (Enzo Diagnostics, New York, USA).

Results

Of the 450 patients investigated, 397 were male and 53 female with an increased male:female ratio in the 1996–1999 cohort (69:29). The mean age at death was 38.4 ± 1.2 years and ranged from 4 to 77 years with the lowest mean (36 years) in the 1996–1999 cohort (Fig. 1). Risk factors for AIDS included homosexuality/bisexuality in

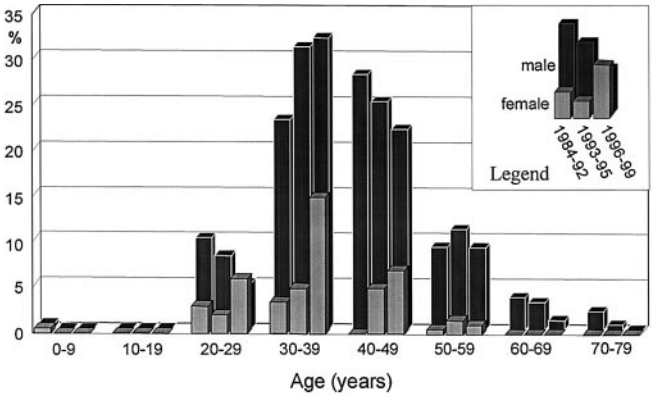

Fig. 1 Age distribution in the present autopsy series of AIDS patients

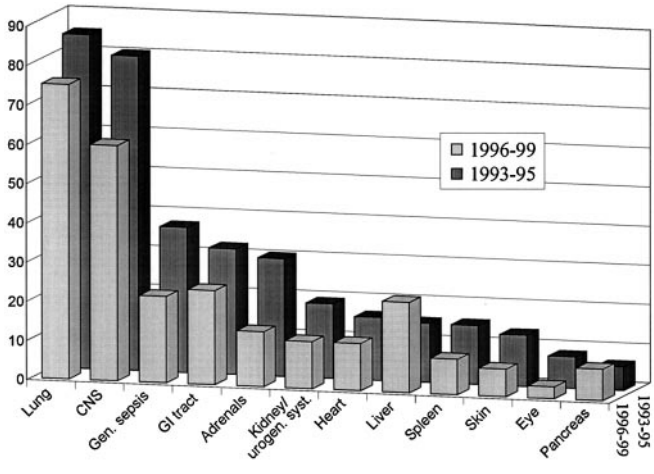

Fig. 2 Organ infections in 160 autopsy cases of AIDS (1993–1999)

almost 80%, IV drug abuse (14%; which increased to 20% in the last cohort), and both homosexuality and IV drug abuse (around 1%); heterosexual transmission was assumed in around 15%, 6 patients had received HIV-contaminated blood transfusions, and 2 children aged 3 and 4 years, respectively, were from HIV-positive parents.

General autopsy findings

The major systemic autopsy findings of the case series 1993–1995 and 1996–1999 are summarized in Fig. 2 and Table 1. The most frequently involved organ was the lung (85% and 75%, respectively), followed by the CNS (showing a decrease in lesion frequency from 80% to 60%). Involvement of other parenchymal organs also decreased, e.g., viral, in particular CMV, infections (from 44% to 35%), bacterial sepsis (from 35% to 22%), KS (from 19% to10%), and fungal infections (from 33% to 25%), whereas tuberculosis slightly increased (5% to 7%). There was decreasing involvement of gastrointestinal (GI) tract (31% to 20%), adrenals (29% to 12%), kidney/urogenital organs (18% to 9%), spleen, skin, heart and eye, with a mild increase in liver and pancreas involvement. Whereas the frequency of protozoal infection (PCN from 15% to 5.5%; toxoplasmosis from 10% to 2%) decreased by two-thirds, and multiple organ infections (from 60% to 39%) and KS (from 19% to 10%) were also significantly decreased, the incidence of bacterial extracerebral infections (except for MAC infections which decreased from 16% to 10%) and malignant lymphomas showed no significant change.

Table 1 Major extracerebral infections (tumors) in 260 autopsy cases of AIDS (1993–1999). Values are given in % (*GI* gastrointestinal)

Type of lesion	1993–1995 (n = 162)	1996–1999 (n = 98)
Bacteria	**71.1**	**66.0**
Staphylo-, Streptococcus	49.3	50.0
Mycobacterium avium	16.2	10.0
Nocardia asteroides	3.1	1.0
Others (*Pseudomonas aeruginose*, etc.)	2.5	6.0
Mycobacterium tuberculosis	5.0	7.0
Protozoa	**25.6**	**8.5**
Pneumocystis carinii	15	5.5
Toxoplasma gondii	10	2.0
Trematodes (*Leishmania*)	0.6	1.0
Fungi	**32.7**	**25.5**
Candida albicans	18.0	18.0
Cryptococcus neoformans	7.3	5.5
Histoplasma capsulatum	1.2	0
Aspergillus	6.2	2.0
Viruses	**52.0**	**35.4**
Cytomegalovirus	44.0	34.4
Retinitis	6.8	3.0
Adrenal glands	34.3	11.0
GI tract	18.0	3.0
Lungs	20.0	7.0
Generalized	8.1	4.0
Herpes simplex	6.2	1.0
Varicella-zoster	1.8	
Tumors	**26.0**	**20.0**
Focal/systemic lymphoma	6.2	7.0
Kaposi sarcoma	19.2	10.0
Other malignancies	0.6	2.0
Double infections	**31.5**	**20.0**
Multiple infections	**28.7**	**19.0**

Table 2 Neuropathological findings in 450 autopsy cases of AIDS (1984–1999) (*PML* progressive multifocal leukoencephalopathy)

Type of lesion (percent)	1984–1992	1993–1995	1996–1999
HIV-associated	**28.7**	**38.0**	**30.0**
HIV encephalitis	11.5	5.6	8.0
HIV leukoencephalopathy	2.6	6.2	5.0
HIV encephalitis + leukoencephalopathy	2.0	2.0	2.0
Vacuolar leukoencephalopathy	1.0	1.8	5.0
Lymphocytic meningitis	2.2	2.4	5.0
Diffuse glial poliodystrophy	8.4	20.0	5.0
Cerebral vasculitis	1.0	–	–
Opportunistic infections	**63.7**	**67.4**	**34.0**
Toxoplasmosis	24.0	20.4	8.0
Cytomegalovirus	17.4	20.0	11.0
PML	5.7	8.7	5.0
Candida albicans	4.2	1.2	1.0
Cryptococcosis	3.1	4.4	4.0
Aspergillus fumicatus	1.5	1.0	–
HSV encephalitis	0.5	–	–
Varicella-zoster encephalitis	–	1.2	2.0
Micronodular encephalitis (agent?)	3.1	8.1	–
Bacterial infections[a]	4.2	2.4	3.0
Tumors	**7.9**	**13.6**	**9.0**
Lymphoma, primary	6.3	11.2	6.0
Lymphoma, secondary	1.1	2.4	3.0
Kaposi sarcoma, secondary	0.5	–	–
Other lesions	**17.6**	**20.1**	**27.0**
Infarcts, anoxia	6.3	5.6	6.0
Hemorrhages	2.5	1.2	4.0
Metabolic[b]	2.2	3.7	1.0
Cerebral edema	3.3	1.0	6.0
Nonspecific[c]	3.3	8.6	10.0
No lesions	**11.0**	**4.4**	**10.0**
Combined infections/lymphoma			
Double	18.0	17.0	11.0
Triple or multiple	3.6	3.1	–
No. of cases	**190**	**162**	**98**
Males	175	144	69
Females	15	18	29

[a] Purulent meningitis, brain abscess, bacterial encephalitis
[b] Central pontine myelinolysis, hepatic encephalopathy (Wernicke encephalopathy, etc.)
[c] Meningeal fibrosis, Pseudo-Fahr, cerebellar atrophy, etc.

Neuropathology findings

The neuropathological findings of the three autopsy cohorts are summarized in Table 2. Overall, HIV-associated CNS lesions represented 32.2%; with 28.7%, 38.0%, and 30.0% in the different cohorts, respectively. HIV encephalitis and/or leukoencephalopathy, at approximately 16% (range 13.8–18%), was highest in the 1984–1992 series. Opportunistic bacterial, fungal, and parasitic infections of the CNS decreased from 36% (1984–1992) to 16% (1996–1999), and viral infections from 34.3% (1993–1995) to 13% (1996–1999); the total percentage of opportunistic infections including micronodular encephalitis without detectable causative agent was 64% and 67%, respectively, in the first two cohorts with a significant reduction to 31% in the 1996–1999 cohort. CMV infection of the CNS, not seen in our material between 1984–1988, did not show significant differences in its distribution pattern – ventriculitis or ventriculo-encephalitis, necrotic encephalitis or micronodular encephalitis between the case series 1988–1994 (around 25% each [54]) and 1993–1995, whereas in the 1996–1999 series practically no micronodular CMV encephalitis was observed. CNS toxoplasmosis, in the first autopsy series (1984–1992) frequently presenting as acute disseminated or "necrotizing" encephalitis [32, 44] and less frequently as old necrotic lesions or recurrent encephalitis (relation about 50%:30%:10%), was often associated with other opportunistic CNS infections. In the 1993–1995 series it showed almost equal distribution of acute and old CNS lesions, while in the last cohort, old necrotic or scar lesions outnumbered acute toxoplasmic encephalitis by 6:2. The incidence of multiple concomitant CNS lesions due to different infectious agents and/or tumors consistently decreased with time from 21% to 11%. The CNS involvement by primary or secondary NHL remained fairly constant, between 8% and 13%, while other changes (e.g., vascular, metabolic, etc.) and nonspecific lesions e.g., meningeal fibrosis (increase from 3.3% to 10%) increased from 17.6% to 27%. However, the percentage of patients in which no pathological CNS changes were found also remained fairly constant between 1984–1992 (11%) and 1996–1999 (10%).

A comparison of neuropathological findings in 25 drug abusers (18 males, 7 females) and 75 non-drug users, mainly homosexual men (n = 62) and 13 females of the HAART series is given in Fig. 3. While HIV encephalitis, progressive multifocal leukoencephalopathy (PML), bacterial CNS infections, diffuse glial poliodystrophy, and nonspecific CNS changes were more frequent in drug abusers, CMV encephalitis, toxoplasmosis, and other opportunistic CNS infections were more frequent in non-drug users. Of the non-drug users 23% showed no neuropathology as compared to 15% of drug users. The frequency of primary or secondary CNS lymphomas was almost equal in both groups.

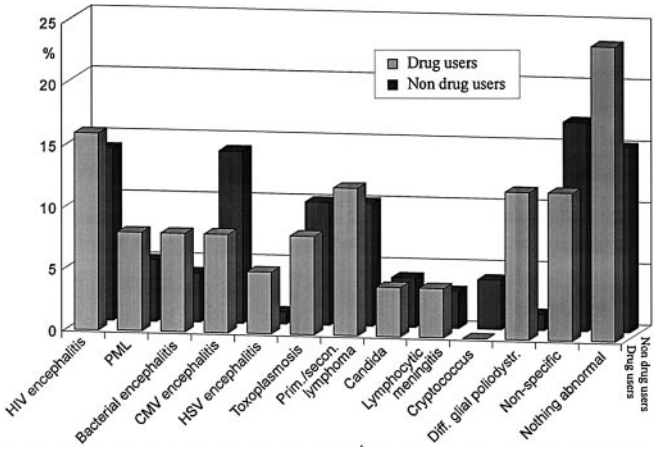

Fig. 3 Comparison of neuropathologic findings in 25 drug users and 75 non-drug users of the autopsy series 1996–1999 (*PML* progressive multifocal leukoencephalopathy, *CMV* cytomegalovirus, *HSV* herpes simplex virus, *Diff*. Diffuse, *poliodystr*. poliodystrophy)

Relationship between general autopsy and neuropathology findings

Evaluation of CMV infections was performed for two autopsy series, one series of 235 patients between 1988 and

Table 3 Relationship between systemic and CNS involvement by CMV infection

Lesion pattern	1988–1994 (n = 235)	1995–1999 (n = 140)
Systemic CMV	88/235 (37%)	31/140 (22%)
Extracerebral	49/235 (22%)	30/140 (21.3%)
Extracerebral + CNS	32/235 (13.6%)	27/140 (19%)
Multiple extracerebral + CNS	22/36 (60%)	5/7 (71%)
Isolated extracerebral + CNS	10/45 (20.4%)	6/16 (37%)
Isolated CNS	7/88 (8%)	1/31 (3%)

Table 4 Relationship between extracerebral and CNS involvement in 260 autopsy cases of AIDS (1993–1999) (*Extracer*. extracerebral)

Type of lesion	1993–1996 (n = 162)			1996–1999 (n = 98)		
	Extra-cer.	CNS	%	Extra-cer.	CNS	%
Malignant lymphoma	7	4	57	8	3	38
Bacterial infections	50	4	8	40	4	10
CMV, generalized	8	7	89	2	2	100
CMV, retinitis	7	4	57	3	1	33
CMV, adrenal gland	19	4	21	10	3	30
CMV, GI tract	4	1	25	2	1	50
CMV, isolated CNS	–	3	–	–	1	–
Toxoplasmosis	20	24	–	2	8	–
Cryptococcus neoformans	5	6	–	2	0	0
Aspergillus fumicatus	1	0	0	2	0	0
Candida albicans	4	0	0	8	1	12

1994 published previously [54] and 140 cases between 1996 and 1999 (Table 3). The incidence of systemic CMV infection decreased from 37% to 22%, and that of isolated CMV infection of the CNS from 8% to 3%, while the frequency of extracerebral disseminated CMV infections remained constant, and combined involvement of parenchymal organs and CNS slightly increased. The relationship between the extracerebral and CNS involvements by CMV and other opportunistic infections as well as by lymphomas between the autopsy series of 1993–1995 and 1996–1999 is summarized in Table 4. Whereas there was a decrease in secondary CNS affections by lymphomas and toxoplasmosis, there were no considerable differences in the secondary CNS involvement seen with other opportunistic infections.

Table 5 Systemic pathology in cases with HIV-related neuropathology

Type of lesion	1993–1995 (n = 14)		1996–1999 (n = 15)	
	n	%	n	%
Bacterial infections lung	11	78	9	60
Bacterial sepsis	2	14	3	20
Candida sepsis	1	7	3	20
Aspergillus	1	7	1	7
CMV infection organs	3	21	4	26
Pneumocystis carinii	2	14		
Toxoplasmosis	1	7		
Kaposi sarcoma	1	7	3	20
Pancreatitis	0	–	3	20
Hepatitis C	0	0	2	13
Tuberculosis	0	–	1	7
Organ lymphoma/carcinoma	0	–	2	14
Cryptococcosis	1	7	0	0
Double infections/lesions	3	21	7	47
Triple infections/lesions	3	21	0	–

Table 6 Systemic pathology in HIV-associated cases with no or nonspecific neuropathology

Type of lesion	1993–1995 (n = 22)		1996–1999 (n = 30)	
	n	%	n	%
Bacterial infections lung	5	23	12	40
Bacterial sepsis	5	23	7	23
Fungal pneumonia	1	5	1	3
Candidiasis	2	9	4	13
CMV infection organs	5	23	4	13
Pneumocystis carinii	2	9	3	10
Tuberculosis	2	9	2	7
Kaposi sarcoma	7	32	2	7
Systemic/organ lymphoma	1	5	1	3
Cryptococcosis	1	5	0	–
Hepatitis C	0	–	4	13
Double infections/lesions	4	18	12	40
Triple infections/lesions	1	5	2	7

Extracerebral systemic pathology in cases with HIV-related neuropathology and in those with no or nonspecific CNS lesions are listed in Tables 5 and 6. In subjects with advanced HIV-related neuropathology, during the HAART era, bacterial infections slightly decreased, whereas other opportunistic and double infections increased (Table 5). In a small number of cases with early brain pathology, e.g., lymphocytic meningitis (five cases each in both cohorts) tuberculosis was seen in one case each, bacterial pneumonia in four cases each, associated with fungal infections in two cases of the HAART series. In AIDS patients with no or nonspecific CNS lesions, the frequency of bacterial and many other opportunistic organ infections as well of extracerebral lymphomas remained unchanged, but the incidence of double or multiple opportunistic infections increased (Table 6).

Discussion

In most autopsy series of AIDS patients, including our own, the lung/respiratory tract was the most frequently involved organ with an incidence of 60–96% [1, 22, 25, 39, 45, 56], followed by the CNS (60–93%) [2, 4, 5, 11, 16, 18, 27, 30, 33, 38, 39, 48, 59], and the GI tract and/or adrenal glands [24, 39, 49]. Among CNS lesions, HIV-related pathology ranged from 0% to 63% with an average of 25–30%, followed by combined opportunistic infections (20–95%) toxoplasmosis (3–54%), CMV encephalitis (7–34%), cryptococcus (1–14%), PML (2–10%), and primary CNS-NHL (PCNSL) (0–23%; average 6–7.6%), while negative or minor nonspecific CNS findings were reported in 2–37% [2, 4, 5, 10, 11, 12, 18, 20, 28, 35, 38, 39, 42, 43, 46, 51, 56]. The introduction of antiretroviral combination therapy caused considerable changes in the patterns of extracerebral and CNS pathologies, in particular a significant decline in PCP [9, 14, 24, 30, 35, 39, 52, 53, 55], reduced incidence of opportunistic GI disease [41] and, in some autopsy series, decrease in toxoplasmic and CMV encephalitis, and mycobacteriosis [2, 39]. In general, however, bacterial and other opportunistic organ infections remained unchanged or even increased in frequency over time [24, 30, 35, 38]. The incidence of multiple organ and CNS opportunistic infections and of HIV-related CNS pathologies (encephalitis, etc.) has increased during the last years, probably due to prolonged survival of AIDS patients, the appearance of drug-resistant pathogens, IVdrug abuse, and the severity of systemic disease [6, 15, 24, 36, 39, 54]. Although a decrease in CMV replication in human HIV-infected subjects was observed after the introduction of HAART [47], in several autopsy series including our own, CMV infection remains one of the most common causes of death [24, 39] and has become the most frequent single opportunistic infection of the CNS [54]. While a slight increase in clinical AIDS dementia complex [17] and of PML have been reported during the last few years [2], the incidence of HIV encephalitis under antiretroviral therapy in some autopsy series either initially declined [6, 15, 36, 48] or remained practi-

cally unchanged over time ([39], and own series) or, in patients with longer survival, even increased [30]. PCNSL, in contrast to systemic/organ NHL, showed either an upward trend [39] or even a significant increase over time [2, 24], which was not confirmed in our series.

The present study shows similar changes in the pattern of organ pathology and CNS findings over a period of 15 years. Following involvement of the lung/respiratory tract declining from 85% to 75%, the brain continues to be the second most frequently affected organ with decreasing frequency from 80% to 60%, followed by general sepsis (35–22%), and involvement of GI tract and adrenals, kidney/urogenital tract, heart, spleen and liver, etc. In general, there was a decline in organ infections, except for liver and pancreas. Extracerebral viral (mainly CMV), protozoal (PCP and toxoplasmosis), and multiple infections, KS and, to a lesser extent, mycobacteriosis and fungal infections decreased, while other bacterial infections and organ NHL remained unchanged. This is in line with data from other recent autopsy series suggesting that the continued decrease of PCP and toxoplasmosis frequency in autopsy material might be related to HAART [24, 30, 39, 53]. While the incidence of KS in our cohort was higher than in other autopsy series [50], that of extracerebral NHL was similar or even lower [29, 50]. Whereas HIV-related CNS pathology (28–38%) with HIV encephalitis in 14–18% remained unchanged over time, an almost 50% decline in opportunistic CNS infections, except for bacterial encephalitis, PML, and cryptococcosis, was even more obvious than in other recent autopsy series [24, 30, 39, 53]. In line with a significant decrease in multiple organ infections, multiple CNS infections also decreased by almost 50%, whereas CNS involvement by primary and secondary lymphomas, varying in frequency between the three cohorts, remained unchanged between the first and last ones. While in earlier periods, CNS toxoplasmosis, often associated with extracerebral involvement, presented as acute disseminated or necrotic encephalitis, in the recent cohort, old necrotic lesions or scars outnumbered the – probably cured – organ lesions. On the other hand, the relationship between extracerebral and CNS CMV infection remained fairly constant over time, but micronodular encephalitis practically disappeared. Consistent with other recent studies, the present data show that, in spite of aggressive therapy, organ and CNS infections by various and multiple agents remain important causes of death. While the percentage of negative CNS findings remaining unchanged over time (10–11%) was much lower than in other autopsy series [39], other (metabolic, vascular, nonspecific) CNS lesions increased over time (from 17.6% to 27%), possibly due to prolonged survival, increase in meningeal fibrosis as sequela of cured meningitis, or increased hepatic involvement in IV drug abusers.

Differences have been reported in the lesion patterns of organs and CNS between HIV-positive drug abusers and homo/heterosexual AIDS patients: in drug users, tuberculosis, mycobacteriosis, histoplasmosis, and HIV encephalitis are more frequent, while CMV, PCNSL, and invasive candidiasis are less prominent [7, 8, 30, 35, 37, 38, 39]. Our small cohort of drug abusers, mainly from the period of modern antiretroviral therapy, showed slightly more frequent HIV encephalitis and PML, bacterial CNS infections, and diffuse glial poliodystrophy (hepatic encephalopathy), but less frequent CNS toxoplasmosis, CMV and opportunistic CNS fungal infections, whereas the frequency of primary and secondary NHL was almost equal to that in non-drug users.

Masliah et al. [39], in their 15-year autopsy series compared the effects of systemic pathology over time on the AIDS-related CNS alterations. In cases with no CNS changes and in those with late AIDS-related CNS lesions, systemic opportunistic infections were much more frequent and either decreased over time or, as combined infections and neoplasm, did not vary significantly over time compared to the group of early HIV infection of the CNS [3, 21], which showed only rare systemic opportunistic infections and neoplasms without variation over time. These results were only in part confirmed in our small cohort, where only cases with full-blown HIV-related neuropathology showed more frequent systemic bacterial and CMV infections decreasing over time, while all the other organ infections and neoplasms showed no significant differences between both groups. Our cohort of early HIV-associated CNS pathology (e.g., lymphocytic meningitis) was too small to provide relevant data on its relations to systemic pathology, although this has been shown to be a valuable approach to determining the stage of HIV involvement of the CNS [28].

In conclusion, the present and other recent autopsy studies have shown that despite beneficial effects of modern antiretroviral combination therapy, involvement of the brain and multiple opportunistic organ infections continue to be frequent causes of death in AIDS patients, and that there are differences in the lesion patterns between subjects with HIV-associated CNS pathology and those with negative or non-specific CNS findings as well as between IV drug abusers and non drug users, although the frequency of HIV encephalitis in both groups of our series was less than observed in other recent autopsy studies.

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Note added in proof Recently d'Arminio Monforte et al. reported a 95% reduction of the risk for CNS-AIDS after HAART es compared to untreated patients [14a].