The Changing Pattern of HIV Neuropathology in the HAART Era

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Abstract. Highly active antiretroviral treatment (HAART), which has been available for most AIDS patients in France since 1996, has resulted in a dramatic improvement of the progression of the disease. From the survey of our series of 343 brains with acquired immunodeficiency syndrome (AIDS) from patients who died between 1985 and 2002, we found both quantitative and qualitative changes in the pattern of human immunodeficiency virus (HIV) neuropathology. Quantitatively, despite a dramatic decrease in the number of autopsies, brain involvement remained a major cause of death. There was an overall decrease in incidence of cerebral toxoplasmosis, cytomegalovirus encephalitis (CMVE), and HIV encephalitis (HIVE), for which successful treatment is available. This contrasted with the unchanged incidence of progressive multifocal leukoencephalopathy (PML) and malignant non-Hodgkin lymphomas (MNHL). However, when looking closer at the 3 last years, the incidence of diseases affecting patients with severe immunodepression (CMVE, PML, and MNHL) decreased between 2000 and 2002, whereas infections occurring in patients with milder immunodeficiency, toxoplasmosis, varicella-zoster encephalitis (VZVE), or herpes simplex virus encephalitis (HSV) became more frequent. In addition, we found uncommon types of brain infection such as BK virus encephalitis or general paresis. Finally, we described new variants of HIVE: severe leukoencephalopathy with intense perivascular macrophage and lymphocyte infiltration, possibly due to an exaggerated response from a newly reconstituted immune system, and chronic “burnt out” forms of HIVE as VZVE, toxoplasmosis, or PML, possibly associated with prolonged survival, in which neither inflammation nor organisms could be detected. These findings are compared with those reported in other neuropathological studies from different developed countries.

Key Words: Acquired immunodeficiency syndrome (AIDS); Central nervous system; Highly active antiretroviral treatment (HAART); Human immunodeficiency virus (HIV); Neuropathology.

INTRODUCTION

Introduction of highly active antiretroviral therapy (HAART, or combined antiretroviral therapy including protease inhibitors) has resulted in a dramatic improvement of the course and prognosis of HIV-related disorders, as confirmed by many clinical studies. In most developed countries, where treatment is widely available, it has dramatically reduced morbidity and mortality (1) in HIV infected patients, as well as improved their quality of life. HIV infection tends to become a chronic disease, and recent epidemiological studies show that AIDS-defining events are no longer the major causes of death in HIV-infected patients who now die more frequently from hepatitis B- or C-associated cirrhosis, non-HIV-related malignancies, cardiovascular events, suicide, overdose, or treatment related fatalities (2). However, despite the fact that their overall incidence and prevalence has decreased spectacularly after the introduction of HAART, neurological complications still remain an important cause of death and disability in AIDS (2–4), although their relative incidence as their course and clinical presentation have been modified.

The most dramatic benefit of HAART is the restoration of a functional immune system that affords protection against opportunistic infections (5). Indeed, clinical epidemiological studies have shown a marked decrease in the incidence of the main cerebral opportunistic infections, such as toxoplasmosis (4) or cryptococcal meningitis (6), for which successful treatment is available and prolonged survival of patients with neurological complications related to the immunodeficiency syndrome and considered incurable to date, particularly primary cerebral malignant non-Hodgkin’s lymphomas (PCMNHL) (7) and progressive multifocal leukoencephalopathy (PML) (8–10). However, neurological deficit and cognitive disorders can still persist or progress in some patients with treatable infections, and there may be no clinical neurological improvement despite prolonged survival in some patients receiving HAART, particularly those with PML (10).

On the other hand, the impact of HAART on HIV-associated cognitive disorders, which represents one of the most disabling complications of the disease, is not as clear or promising. Some dysfunctions in patients receiving HAART may be reversible, as suggested by
recent reports of improved neuropsychological performance (11, 12), and return to normality of brain metabolite levels on proton MRS (13). However, other studies suggest that this treatment might have a more limited impact on HIVD than on other AIDS defining illnesses (14). The increasing incidence of HIV-dementia in patients with relatively high CD4 counts (15) and the persistence and deterioration of the cognitive disorders in some patients, particularly in those with severe dementia despite treatment (14, 16), remain puzzling findings.

Whereas HAART changed the course of neurological complications of HIV infection, new issues have emerged concerning viral persistence (17), viral resistance, drug toxicity and access to the CNS (18), and restoration of the immune response (19). Presently, a satisfactory answer to these questions cannot be provided, partly because of the lack of neuropathological studies. Indeed, the spectacular improvement in patient survival has brought about a dramatic decrease in autopsies of these patients. Whereas the decreased mortality is good news for patients, the decreasing number of autopsies makes it difficult to evaluate the effects of treatment. Moreover, existing autopsy (20–22) or biopsy (23) studies of patients treated with HAART are nonsystematic and deal with patients submitted to different schedules of treatment in different countries and different time periods. These studies make overall comparisons of the incidence of the neurological complications of AIDS before and during the HAART era, but do not accurately reflect what happens during successful treatment, since the proportion of treated cases and the treatment modalities are highly variable.

In order to answer these issues more accurately we reviewed our autopsy series of AIDS patients who died between January 1985 and December 2002 at the Henri Mondor and Raymond Poincaré Hospitals (24–26). Of a total of 343 patients examined, 23 had died between January 1997 and December 2002, following the introduction of HAART, which had been available for all patients in France since 1996. The value of this relatively small series is that it represents a prospective study and that all had received HAART, at least during the last 3 months of their life. Analysis and comparison with the other studies of similar group of patients (20–23) show quantitative and qualitative changes in the pattern of HIV neuropathology.

**TABLE**

Neuropathological Findings in 23 AIDS Patients Who Died Between 1997 and 2002*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV encephalitis</td>
<td>4</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>3</td>
</tr>
<tr>
<td>Malignant non-Hodgkin lymphoma</td>
<td>3</td>
</tr>
<tr>
<td>CMV encephalitis</td>
<td>2</td>
</tr>
<tr>
<td>VZV encephalitis</td>
<td>4</td>
</tr>
<tr>
<td>HSV encephalitis</td>
<td>2</td>
</tr>
<tr>
<td>PML</td>
<td>4</td>
</tr>
<tr>
<td>General paresis of the insane</td>
<td>1</td>
</tr>
<tr>
<td>BK virus encephalitis</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>2</td>
</tr>
<tr>
<td>Nonspecific changes</td>
<td>2</td>
</tr>
</tbody>
</table>

(1 acute, 3 “burnt out”)

(1 acute, 2 chronic)

(1 “burnt out”)

(1 associated with VZVE, 1 with CMVE)

(1 “burnt out”)

* The total number of lesions is greater than 23 because more than 1 lesion may be found in the same patient.
Quantitative Changes in the Pattern of HIV Neuropathology after the Introduction of HAART

Not unexpectedly, and in keeping with general clinical and pathological experience of other Western countries, there has been a spectacular decrease in the total number of autopsies of AIDS patients. Figure 1, which represents the annual number of autopsy cases in our series, shows that following the spread of the AIDS epidemic between 1985 and 1991, there was a small decrease in the total number of autopsies per year, probably related to prevention and initial antiretroviral treatments; however, since 1996, when HAART became widely available in France, this decrease became dramatic. As illustrated in the Table, which takes into account the neuropathological changes in the 23 AIDS patients who died between 1997 and 2002, brain involvement remained a common cause of death. This is consistent with general autopsy findings.

Fig. 3. Variation of the incidence of the main neurological complications of AIDS.

Fig. 4. Annual number of autopsy cases of HIVE.
Fig. 5. Severe demyelinating leukoencephalopathy with infiltration of lymphocytes. 

- **a:** Coronal section of the cerebral hemispheres at the level of the head of caudate showing mild subcortical atrophy and slight grey discoloration of the white matter; no obvious myelin loss is seen.
- **b:** Myelin staining reveals mild myelin pallor, particularly obvious in the deeper white matter. Luxol fast blue/cresyl violet.
- **c:** Deep white matter of the left hemisphere. Acute myelin loss with vacuolization and intense perivascular infiltration of mononuclear cells. H&E, ×50.
- **d:** Cortico-subcortical junction. Incipient demyelination with vacuolization, reactive astrocytosis, and intense perivascular infiltration by macrophages. H&E, ×200.
- **e:** Multinucleated giant cell
showing that the brain is the second most frequently affected organ in HIV infection after the lung (19, 20), and is becoming the most frequently affected since the introduction of HAART (21). This supports the view that neurological complications still represent a major cause of disability and death in AIDS patients (2, 4). On the other hand, as already highlighted by Jellinger et al (20) and Masliah et al (21), the incidence of nonspecific or nonlethal CNS changes in patients who died from extracerebral causes is increasing. Three of the last 4 cases listed in the Table had hepatitis B or C, which represents a cause of increasing morbidity and death in HIV infected patients (2), particularly drug addicts (22), and 2 of them had hepatitis-related cirrhosis with clinical and pathological features of hepatic encephalopathy.

The change of incidence of the main neurological complications of AIDS according to the time of occurrence and type of treatment becomes apparent when one compares the pre-HAART period (including that during which multiple therapies became available, i.e. from 1985 through 1999) (26) with the 3 last years (2000–2002), when patients received HAART immediately after being found HIV-positive, usually before severe immunosuppression or patent AIDS-defining illness had occurred.

During the first period, there was an overall decrease of infections (cerebral toxoplasmosis, cytomegalovirus encephalitis [CMVE], and HIV encephalitis [HIVE]) for which successful treatment is available, whereas the incidence of PML and PCMNHL was unchanged. Acute cerebral toxoplasmosis (Figs. 2, 3b), the most frequent neurological complication of AIDS in France during the early years of the epidemic, decreased following the introduction of antitoxoplasmosis treatment. At first, acute lesions were replaced by chronic lesions (scars); however, after the advent of effective prophylaxis, the latter also decreased. CMV infection of the CNS constantly increased with longer survival (Fig. 3d), but following the introduction of effective treatment, its incidence somehow decreased. The incidence of PML increased in the early years, due to longer survival, and remained stable thereafter (Fig. 3e). Not unexpectedly, the number PCMNHL increased steadily (Fig. 3f).

In contrast, during the last 3 years the incidence of diseases affecting patients with severe immunodeficiency decreased due to the preservation or restoration of immunity in treated patients. This is obvious for CMVE (27), new cases of which did not appear after 1999 (Fig. 3d). Similarly, the incidence of PCMNHL decreased after 1999 with no autopsy cases in 2001 and 2002 (Fig. 3f).

This is in keeping with recent epidemiological surveys indicating a significantly decreased incidence of non–Hodgkin lymphomas, particularly primary cerebral lymphomas associated with prolonged survival of the patients after the introduction of HAART (7, 28, 29). The situation is not so clear for PML, which is not always associated with very severe immunodeficiency (30). Interestingly, 2 of the 3 patients who died during the last period had long-lasting infection (Fig. 3e) consistent with the clinical observation that HAART significantly improves the survival of patients with AIDS-related PML (8–10) and 1 brain had almost completely “burnt out” lesions. In contrast, infections occurring in patients with milder immunodeficiency became more frequent. Having completely disappeared between 1997 and 1999, toxoplasmosis is now reappearing both as chronic and acute lethal forms (Figs. 2, 3b). Varicella-zoster virus encephalitis, formerly considered a rare complication of AIDS and classically affecting patients with milder immunodeficiency (31), is dramatically increasing (Fig. 3c). Herpes simplex virus encephalitis (HSVE), an exceptionally rare occurrence in HIV infection (32) and developing in mildly immunodeficient patients, was found in 2 cases. In 1 case it was associated with CMV encephalitis and in the other with VZV encephalitis, confirming previous observations that concomitant herpes virus infections of the CNS are a characteristic feature of AIDS (33, 34). The incidence of HIVE (Figs. 3a, 4), which had increased in the early years due to prolonged patient survival, has decreased significantly since the introduction of AZT (35); however, it remained frequent. Following the introduction of HAART, we did not observe a single case with HIVE between 1997 and 1999. However, in the last 3 years, HIVE reappeared either as rare acute forms, possibly the result of viral resistance and treatment limitations due to toxicity or lack of compliance with the treatment, or as new “burnt out forms.” Actually, despite the small number of cases, the prevalence of HIVE is obviously increasing (Fig. 3a).

Comparable findings have been reported by others. The Italian study, which examined brain biopsies removed between 1991 and 1998 (23), observed a decrease of CNS lymphomas, stabilization of toxoplasmic lesions that had decreased during the pre-HAART period, and a slight increase of PML. With regard to autopsy material,
Fig. 6. a–d: “Burnt out” VZV multifocal encephalitis. a: Medial part of the right parietal lobe. Presence of multiple necrotic and demyelinated lesions involving predominantly the cortico-subcortical regions. Klüver-Barrera stain. b: Mesial right temporal lobe showing a characteristic “target-like” lesion at the cortico-subcortical junction. Klüver-Barrera stain. c: Same lesion as in...
an Austrian study of patients who died between 1984 and 1999 (20) also showed a decrease in CNS lymphomas, PML and CMV encephalitis, and an increase in VZV and HIV encephalitis in the years 1996 to 1999. In the series from San Diego obtained from 1982 to 1998 (21), the authors did not find clear changes in the overall trend of the different complications after the introduction of HAART; however, there was a constant decrease in CNS lymphomas and opportunistic infections, and a steady high rate (25%) of HIV encephalitis. In an autopsy series from New York City, including 394 cases collected between 1979 and 2000 (22), 281 of which underwent neuropathological examination, the authors did not find any change in the frequency of CNS infections over time. However, in keeping with epidemiological studies (2), they emphasize a shift in death-related pathologies from opportunistic conditions to those unrelated to the direct effects of HIV.

**Qualitative Changes in the Pattern of HIV Neuropathology after the Introduction of HAART**

**Uncommon Types of Brain Infection:** The proportion of uncommon types of brain infection that have escaped diagnosis and treatment or have been diagnosed following review is increasing, probably because the classical neurological complications in AIDS have received more attention. This may be one explanation for the striking increase in observations of VZV and HSV encephalitis. We had the opportunity to examine 1 case of BK virus encephalitis (36), for which there is no treatment available and only 2 neuropathologically documented cases having been reported previously (37, 38), and 1 case of general paresis of the insane (GPI). Although neurosyphilis is not uncommon in patients with AIDS, those who are more likely to progress to symptomatic neurosyphilis show an accelerated disease course and fail to respond to treatment (39), GPI has seldom been reported and was not documented pathologically (40).

**Severe Demyelinating Leukoencephalopathy with Infiltration of Lymphocytes:** New forms of the classical complications of HIV infection have also appeared. A new type of severe leukoencephalopathy with intense perivascular infiltration by HIV-gp41 immunoreactive monocytes/macrophages and lymphocytes associated with widespread myelin loss, axonal injury, microgliosis, and astrogliosis was described by Langford et al (41) in 7 patients who failed HAART.

One of the authors (FS) had the opportunity to examine a comparable case, a 46-year-old Nigerian man who presented with altered consciousness, cognitive deficit, confusion, right-sided spatial neglect, dysphasia, dysarthria, myoclonus, and possible right-sided weakness. Oral hairy leuokplakia, inguinal lymphadenopathy, and mild anemia were also noted. An MRI showed multifocal changes involving both grey and white matter, suggesting a diagnosis of encephalitis. Testing for HIV infection proved positive and the CD4 count was 50. Retrospectively, a viral disease consistent with seroconversion was noted 7 years ago. Three months later, despite good virological response to HAART, the patient became comatose, requiring intubation and ventilation and remained in this condition until his death, which occurred 6 months after the onset of the illness.

At neuropathological examination there was extensive and symmetrical myelin loss (Fig. 5a, b) with axonal damage and reactive astrocitosis and intense perivascular infiltration by macrophages, a number of which were laden with hemosiderin and lipids (Fig. 5c, d). Occasional HIV-p24-positive macrophages, microglial cells, and multinucleated giant cells were present in the perivascular infiltrates (Fig. 5f) and also within brain parenchyma (Fig. 5e). Immunocytochemistry for CD3 showed diffuse presence of T lymphocytes, both around the vessels and within the cerebral parenchyma (Fig. 5g).

Although the pathogenesis of the lesions is unclear, one plausible explanation is an immune reconstitution-related tissue injury (41). Such a type of injury resulting from an overzealous response of a newly reconstituted immune system to HIV antigens already present when therapy was initiated (42) has previously been described for cryptococcal meningitis (43) and CMV retinitis (44). Inflammatory reaction has also been reported in PML after HAART (45). This mechanism may also have some bearing with that involved in the diffuse infiltrative lymphocytic syndrome, which represents a systemic host-determined and antigen-driven response to HIV (46). It is associated with expression of HIV protein and HIV genome in tissues (47) and frequently involves the peripheral nerve (48).
**Chronic “Burnt Out” Forms of CNS Infection:** Due to prolonged survival, original “burnt out” forms of treatable infections, including HIV encephalitis, VZV encephalitis, or toxoplasmosis, in which no inflammation and no infectious agent could be detected, became more frequent. These “burnt out” lesions may have some connection with the nonspecific, focal, white matter changes requiring brain biopsy observed by Ammassari et al (23) with increasing frequency. In some cases, these “scar lesions” were found in clinically and biologically cured patients who had died from other causes, as previously reported for toxoplasmosis (49). Such cases should become more frequent as the patient’s survival increases and most complications of AIDS benefit from efficient therapy.

We had the opportunity to observe a case of “burnt out” VZV multifocal encephalitis and ventriculitis (49) in a 46-year-old homosexual man found to be HIV-positive and with a history of resolved thoracic herpes zoster 3 years later. Subsequently, he suffered from carbon monoxide (CO) intoxication and was treated by hyperbaric oxygen with no improvement of his neurological status. CD4 count was 4 and HIV viral load was 102,000 copies/ml. MRI showed multiple necrotic lesions in the temporal and parietal cortex associated with ventriculitis, very suggestive of VZV infection of the brain. This was confirmed by VZV polymerase chain reaction (PCR) in CSF. He was treated with high doses of acyclovir and HAART. This treatment resulted in increased CD4 count, decreased viral load, and negative PCR for VZV in the CSF. However, his neurological status did not improve and he died from aspiration bronchopneumonia.

Neuropathological examination showed Grinker’s myelinopathy, a delayed complication of CO poisoning as the probable cause of persisting encephalopathy. There were also lesions characteristic of VZV multifocal encephalitis in the parietal and temporal (Fig. 6b) cortico-subcortical regions. They had a typical “target” appearance with a necrotic center, a rim of myelin pallor, and a halo of edema (Fig. 6c). However, at microscopy the peripheral rim was just necrotic with macrophages (Fig. 6d). There was not characteristic astrocytic reaction, inflammation, or intranuclear inclusion bodies and VZV immunocytochemistry was negative. Similarly, the periventricular necrosis contained only macrophages, with no inflammation, inclusion bodies, or positive immunostaining for VZV.

In other instances, despite efficient treatment as revealed by biological tests, imaging, and eventually neuropathology, the disease continued to progress clinically and often radiologically. This is becoming a recurring issue in patients with severe extensive multifocal toxoplasmosis in whom, despite efficient treatment for toxoplasmosis and HIV infection, there is progressive demyelination and deterioration of the mental status (Prof. Y. Cordioliiani, personal communication). It seems that when treatment is administered too late, irreversible cerebral destruction occurs with secondary progressive Wallerian degeneration.

This may be illustrated by the case of a 49-year-old female intravenous drug user who presented with intellectual decline, asthenia, and headaches. This led to the diagnosis of multiple toxoplasma abscesses and HIV seropositivity, for which she received antitoxoplasmosis treatment and HAART. As a result, the CD4 had increased, the viral load had decreased, and there was also radiological evidence of decreased size of the toxoplasma abscesses. However there was no obvious improvement of the neurological signs and she suffered several seizures. The main concern of the physicians was the occurrence of white matter changes that continued to progress despite treatment (Fig. 6e). A brain biopsy performed in order to eliminate an associated HIV encephalitis or PML was noncontributory. Her mental status progressively worsened and she died from aspiration bronchopneumonia.

At postmortem, many disseminated chronic toxoplasma abscesses completely devoid of inflammation and parasite-free, even by immunocytochemistry, were found. In addition, there was extensive myelin pallor of the deep...
white matter, together with severe, ongoing, progressive Wallerian degeneration around and at a distance from the necrotic “burnt out” abscesses (Fig. 6f, g).

We also observed 3 cases of “burnt out” HIVE in which cognitive disorders persisted and even worsened despite efficient HAART. In those patients, it seemed that whereas productive HIV infection of the CNS had been cured by HAART, it did not prevent the irreversible secondary lesions, including diffuse poliodystrophy with neuronal loss and leukoencephalopathy, which were sufficient to explain the progressive worsening of the patient’s neuropsychological status.

One notable case (26) was a 69-year-old Senegalese man diagnosed HIV-positive. Three years later he presented with intellectual impairment and gait disturbances. CD4 count was 313/mm$^3$ but his viral load was extremely high (>500,000 copies/ml), and p24 was positive in CSF. MRI showed cerebral atrophy and multifocal high signal intensity in the deep white matter, suggestive of HIVE (Fig. 7a). He received HAART. Three months later his laboratory parameters had improved (CD4: 455/mm$^3$, viral load negative and p24 negative in CSF), and on MRI the deep white matter showed diffuse low signal intensity, more similar to the HIV leukoencephalopathy than HIVE type (Fig. 7b). Despite mild improvement of his gait, his intellectual status progressively deteriorated and he died from bronchopneumonia 6 months after the onset of the symptoms.

Neuropathological examination confirmed marked cerebral atrophy and myelin pallor of the deep white matter (Fig. 7c). Histology showed diffuse poliodystrophy with neuronal loss, frequent apoptotic neurons, astrocytosis, and mild microglial activation. There was myelin pallor of the deep white matter with marked astrocytosis at the cortico-subcortical junction and a few activated microglial cells and perivascular macrophage. There were no microglial nodules, no multinucleated giant cells, no inflammation, and negative p24 immunostaining. No additional AIDS-related neuropathology was detected.

**Prolonged PML with Necrotic Almost Completely “Burnt Out” Lesions:** Finally, although PML cannot be considered a treatable opportunistic complication of AIDS, we observed necrotic, almost completely “burnt out” lesions in a patient treated by HAART and with a long-lasting disease.

A 37-year-old heterosexual female who did not use drugs was diagnosed HIV-positive in 1995 when she was pregnant. Because of resistance to most antiretroviral drugs except ddI and because of drug-induced polyneuropathy, antiretroviral treatment was interrupted in March 2000. In July 2001, she presented with fatigue, headaches, and gait disturbance. Neurological examination revealed an isolated static and kinetic cerebellar syndrome. MRI showed high signal intensities, without contrast enhancement or mass effect, in the left cerebellar hemisphere and left half of the pons. Her CD4 count was 0/mm$^3$ and viral load was >500,000 copies/ml. HAART was started. In January 2002, her laboratory parameters had improved (CD4: 300/mm$^3$, viral load: undetectable) and MRI showed comparable cerebellar images and mild extension of the pontine lesions to the right. Subsequent MRIs showed stabilization of the lesions, which remained unchanged thereafter, as did the patient’s status. In October 2002, she presented with profuse diarrhea, wasting, and profound deterioration of her general status and died.

Neuropathological examination showed necrotic changes involving the white matter of the left cerebellar hemisphere (Fig. 7d) associated with demyelinated lesions in the lateral middle cerebellar peduncle, right cerebellar hemisphere, and pons (Fig. 7e). On the left hemisphere there was complete disappearance of the white matter of the folia that formed a cavity containing small numbers of macrophages, or, occasionally, bizarre astrocytes (Fig. 7f). There was marked loss of Purkinje cells with empty baskets and apoptotic changes in some of the remaining cells. Axonal swelling (torpedoes) was frequently seen in the granular layer. In the vermis the white matter was replaced by abundant lipid-laden macrophages and, in the right cerebellar hemisphere, only limited demyelinating foci containing lipid laden macrophages were present (Fig. 7g). There was no inflammation and astrocytosis was reduced to the presence of rare bizarre astrocytes and microglial activation to the presence of lipid-laden macrophages. There was no oligodendroglial inclusion and in situ hybridization (ISH) for JC virus only showed mild positivity in the nuclei of occasional bizarre astrocytes (Fig. 7h). In the pons the changes seemed more active, including numerous lipid-laden macrophages and frequent bizarre astrocytes. There were also rare inclusion-bearing oligodendrocytes positively stained by ISH for JC virus. Immunocytochemistry for SV40 cross-reacting for JC virus was invariably negative.

PML with necrotic white matter changes has already been reported in AIDS patients (51), particularly in case of co-infection by HIV and JC virus (52). On the other hand, “burnt out” lesions (in which inflammation is absent and JC virus can be identified only by ISH) associated with classical PML lesions remote from these foci were not uncommon in long-lasting disease, particularly in non-AIDS patients (52). It seems likely that HAART-induced restoration of immune functions and prolonged survival slowed down the activity of JC virus infection and allowed PML changes to progress to a chronic state. In our case, one may also speculate that a possible HIV co-infection at the origin of the necrotic changes was cured by HAART. However, the latter was started too late to prevent irreversible destruction of the cerebellar white
matter and consequent Purkinje cell loss. This observation is in keeping with clinical findings of prolonged survival without neurological improvement in patients with AIDS-related progressive multifocal leukoencephalopathy on potent combined antiretroviral therapy (10).

In conclusion, it is now apparent that the introduction of HAART has dramatically modified the course and prognosis of HIV infection. Although the neurological complications remain a major cause of disability and death in AIDS patients, they involve a relatively small number of patients. Neuropathological studies tend to show changes in the respective incidence—as well as in the neuropathological appearance—of the different neurological complications of AIDS, and suggest that many of the latter might still be improved by a better knowledge of their etiopathogenetic mechanisms and consequent progress in the type and schedule of treatment. However these encouraging results are limited to developed countries where multi-therapies are widely available. In the rest of the world where more than 90% of AIDS cases live and die, patient survival is so short that neurological disorders, because they are late complication of HIV infection, do not represent a significant health issue. It is therefore crucial that further research continues both for a better understanding of the mechanisms of neurodegeneration in AIDS and the impact of multi-therapies and for wider prevention and treatment of HIV infection.

REFERENCES