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Review

Progressive multifocal leukoencephalopathy: the evolution of a disease once considered rare

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Progressive multifocal leukoencephalopathy, a formerly rare disease that chiefly occurred in persons with underlying lymphoma and chronic lymphocytic leukemia, is now seen with increasing frequency in the era of acquired immunodeficiency syndrome. Progressive multifocal leukoencephalopathy is currently estimated to arise in 5% of all human immunodeficiency virus-infected individuals. The clinical features of the disorder in patients with acquired immunodeficiency syndrome do not appear to be significantly different from progressive multifocal leukoencephalopathy occurring in association with other immunosuppressive disorders. Radiographically, the appearance of HIV dementia on magnetic resonance imaging is sometimes confused with that of progressive multifocal leukoencephalopathy. Among the characteristics that are helpful in distinguishing between the two disorders are the presence of focal findings, the rate of disease progression, the specific magnetic resonance imaging attributes, including the location of the lesions, and certain cerebrospinal fluid parameters, including surrogate markers for human immunodeficiency virus dementia and the presence of myelin basic protein. The remarkable increase in the burden of progressive multifocal leukoencephalopathy has provided a vital impetus for its study, particularly with respect to diagnosis and therapy. Establishing an unequivocal diagnosis of progressive multifocal leukoencephalopathy currently requires brain biopsy. The application of polymerase chain reaction for JC virus amplification to cerebrospinal fluid samples suggests that it may provide an alternative means of diagnosis. Recent *in vitro* studies of cytosine arabinoside and camptothecin suggest that they, or similar agents, may prove useful in the treatment of this illness and well-designed clinical trials are underway.

Keywords: progressive multifocal leukoencephalopathy; AIDS; viral infection; demyelination; brain

Introduction

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system that results from infection of oligodendrocytes with JC virus (JCV), a papovavirus (Richards, 1988). Perhaps the first description of this illness was by the German pathologist Hallervorden (1930) in a monograph titled 'Eignnartige und nicht rubriziebare Prozess' ("Unique and Non-Classifiable Processes") published in 1930. He described two patients, one with tuberculosis and the other without recognized underlying systemic disease, who exhibited multifocal neurological symptoms associated with discrete areas of demyelination and bizarre enlarged astrocytes (Hallervorden, 1930). However, PML was not crystallized as a distinct entity until 1958 when Aström, Mancall and Richardson identified the disorder on the basis of its unique pathological features of demyelination, abnormal oligodendroglial nuclei and giant astrocytes (Aström *et al*, 1958). However, PML was not crystallized as a distinct entity until 1958 when Aström, Mancall and Richardson identified the disorder on the basis of its unique pathological features of demyelination, abnormal oligodendroglial nuclei and giant astrocytes (Aström *et al*, 1958). In 1965, viral particles morphologically typical of the papovaviruses were detected by electron micro-

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scopic studies in the brains of patients dying of PML (ZuRhein and Chou, 1965) and, in 1971, JCV (named after the initials of the patient from whom it was first isolated) was cultivated and identified (Padgete *et al*, 1971).

Until the acquired immunodeficiency syndrome (AIDS) epidemic, experience with this disease was limited. A comprehensive review of PML published in 1984 found only 230 reported cases (Brooks and Walker, 1984). Within 1 year of the initial description of AIDS in 1981, PML was recognized as an associated disorder (Gottlieb *et al*, 1981; Masur *et al*, 1981; Siegal *et al*, 1981; Miller *et al*, 1982; Bedri *et al*, 1983). Current estimates suggest that approximately 4% – 5% of all human immunodeficiency virus (HIV)-infected individuals will develop PML (Berger *et al*, 1987). This formerly rare disease, once regarded as a clinical curiosity by most neurologists, has lately become remarkably common.

Advances in the understanding of the pathogenesis of this disease have improved in the past two decades chiefly for two reasons. First, there has been a marked increase of the incidence of PML due to AIDS, consequently providing more opportunity to study the disease. Second, there has been development of highly sensitive molecular techniques which allow detection of very few copies of a viral genome including advances in *in situ* hybridization and amplification of viral genomes using PCR, polymerase chain reaction (Arthur *et al*, 1989; Houff *et al*, 1989; Telenti *et al*, 1990; Weber *et al*, 1990; Henson *et al*, 1991; Lynch and Frisque, 1991; Tyornatore *et al*, 1992).

Epidemiology

Between the ages of 1 and 5 years, approximately 10% of children demonstrate antibody to JCV and by age 10, 40 – 60% of the population does so (Taguchi *et al*, 1982; Walker and Padgett, 1983a; Walker and Padgett, 1983b). By middle adulthood 80–90% have IgG antibodies against JC virus and seroconversion rates have exceeded 90% in some urban areas (Walker and Padgett, 1983a). To date, no disease has been convincingly associated with acute infection, although Blake and colleagues have reported a 13-year-old girl with meningoencephalitis attributed to acute JCV infection (Blake *et al*, 1992). The acute infection in this patient was identified by a rise of IgM titers to JCV and not by viral isolation (Blake *et al*, 1992). Although the overwhelming majority of people have antibodies to JCV by adulthood indicating prior exposure to the virus, the occurrence of PML in the absence of cellular immunodeficiency is quite extraordinary. Indeed, it is but a small minority of persons with underlying impairment of cellular immunodeficiency who ultimately develop disease suggesting that the presence of JCV and immunodeficiency is not by itself a sufficient condition for the development of the disorder.

Prior to the AIDS epidemic, the male to female ratio of PML approximated 1:1. The AIDS epidemic transformed this ratio to 5:1 by 1987 (Holman *et al*, 1991), however, it is likely that the changing pattern of infection with increasing numbers of women affected by AIDS as opposed to homosexual men will return this ratio towards parity. Furthermore, instead of affecting chiefly elderly individuals (Brooks and Walker, 1984) as was observed in studies prior to AIDS, PML has become a disease of the young and middle age populations affected by AIDS. The greatest incidence is in individuals between the ages of 20 and 50 years (Holman *et al*, 1991). PML is rarely observed in immunosuppressed children, perhaps chiefly the result of the lower percentages of children who have been exposed to JCV. However, despite its rarity in this age group, it has been described in both HIV-infected children (Henson *et al*, 1991a,b; Berger *et al*, 1992a) and those with other underlying causes of immunodeficiency (Katz *et al*, 1994).

The spread of JCV is postulated to be by respiratory means (Shah, 1990). The high prevalence of antibodies in the adult population and the rarity of PML in children supports the contention that PML is the consequence of reactivation of JCV in individuals who have become immunosuppressed. Additionally, high titers of IgM antibody specific for JCV would be anticipated in patients with PML if it were the result of acute infection. However, antibody studies reveal that the sera of only one of 21 patients with PML had IgM specific for JCV, whereas, 20 of 21 had IgG antibody specific for JCV (Padgett and Walker, 1983a). Some investigators have argued that the latter study does not exclude the possibility of PML resulting from acute JCV infection as many of these patients were studied late in the course of their disease (Gibson *et al*, 1981).

Underlying illnesses

The first three patients described by Aström, Mancall and Richardson in their seminal description of PML had either chronic lymphocytic leukemia or lymphoma and, until the early part of the last decade, the vast majority of the patients with PML had lymphoproliferative disorders as the underlying cause of their immunosuppression (Aström *et al*, 1958). Lymphoproliferative diseases remained the most common underlying illness for the development of PML until the AIDS epidemic and, in some communities where the incidence of AIDS is small, are still the likeliest underlying disorders.

In a review of 69 pathologically confirmed cases and 40 virologically and pathologically confirmed cases of PML performed in 1984 (Brooks and Walker, 1984), Brooks and Walker found that the most common underlying illnesses were lympho-

proliferative diseases, accounting for 62.2% of the cases. Hodgkin's disease, chronic lymphocytic leukemia and lymphosarcoma were the most common disorders in this category in descending order of frequency (Brooks and Walker, 1984). Myeloproliferative disorders accounted for 6.5%, carcinoma for 2.2%, immune deficiency states for 16.1% (AIDS was classified in this category and represented only 3% of the total number of cases), granulomatous and inflammatory diseases, such as sarcoid, tuberculosis and Whipple's disease for 7.4% and there was no identified underlying illness for 5.2% (Brooks and Walker, 1984).

PML occurring in association with AIDS was reported within 1 year of the initial recognition of AIDS in 1981 (Gottlieb *et al*, 1981; Masur *et al*, 1981; Siegal *et al*, 1981; Miller *et al*, 1982). Since then, this formerly rare disease has become remarkably common. AIDS has been estimated to be the underlying disease for PML in 55% to more than 85% of all current cases (Major *et al*, 1992). Based on reporting of AIDS to the Centers for Disease Control (CDC) between 1981 and June 1990, 971 of 135,644 (0.72%) individuals with AIDS were reported to have PML (Holman *et al*, 1991). This is likely an underestimate since inclusion in the CDC AIDS reporting system required pathologic confirmation of the PML. A study of PML among patients with AIDS in the San Francisco Bay area estimated a prevalence of PML of 0.3% (Gillespie *et al*, 1991). The findings of these investigators suggested that PML in HIV-infected patients was underestimated by as much as 50% (Gillespie *et al*, 1991). The intrinsic nature of mortality data, inaccurate diagnosis, and incomplete reporting may affect these estimates. Other types of studies suggest that the incidence of PML in AIDS cases is substantially higher than that reported by the CDC with estimates of 1–5% in clinical studies and as high as 10% in pathological series (Krupp *et al*, 1985; Stoner *et al*, 1986; Berger *et al*, 1987; Kure *et al*, 1991; Kuchelmeister *et al*, 1993; Whiteman *et al*, 1993). In one large, retrospective, hospital-based, clinical study (Berger *et al*, 1987), PML occurred in approximately 4% of patients hospitalized with AIDS. In a combined series of seven neuropathological studies comprising a total of 926 patients with AIDS (Kure *et al*, 1991), 4.0% had PML. Similarly, a neuropathology series from Switzerland detected PML in more than 7% of their patients dying with AIDS (Lang *et al*, 1989). A pathological study performed on 548 consecutive, unselected autopsies between 1983 and 1991 of patients with AIDS by the Broward County (Florida) Medical Examiner revealed that 29 (5.3%) had PML confirmed at autopsy (Whiteman *et al*, 1993). Yet another recent neuropathologic review based on autopsies between 1985 and 1992, found 21 (9.8%) cases of PML in 215 individuals dying with AIDS (Kuchelmeister *et al*, 1993). The authors acknowledge that the unusually high estimate is probably skewed given the numerous referral cases from outside the study center (Kuchelmeister *et al*, 1993). Although these estimates may be susceptible to selection bias, there clearly appears to be an increasing frequency with which PML has been observed since the inception of the AIDS epidemic.

Perhaps the most severe states of prolonged cellular immunodeficiency other than AIDS accompany renal and other organ transplanation. Despite the anecdotal case reports of PML associated with organ transplant, two recent reviews do not mention PML as a complication (Harmon, 1991; Yoshimura and Oka, 1990) and in a study of 36 long term survivors of renal transplantation, PML was not observed (Divakar *et al*, 1991). In one study of 21 patients who were pre-selected because of the development of neurologic complications following bone marrow transplantation, only one patient had PML (Diener *et al*, 1991). At University of Miami/Jackson Memorial Hospital Medical Center approximately 100 patients undergo renal transplant and 50 patients undergo other major organ transplants yearly. We have observed no cases of clinically suspected or pathologically confirmed PML among this group in the last 3 years. PML may also occur in the setting of other chronic and autoimmune diseases such as tuberculosis, systemic lupus erythematosus, and sarcoidosis (Brooks and Walker, 1984; Gullota *et al*, 1992; Kaye *et al*, 1992).

Pathology

Macroscopically, the cardinal feature of PML is demyelination. Demyelination may, on rare occasion, be unifocal, but typically occurs as a multifocal process. These lesions may occur in any location in the white matter, however, they have a predilection for the parieto-occipital regions. Not infrequently lesions involve gray matter (von Eisiedel *et al*, 1993) and are also found involving cerebellum, brainstem and, exceptionally, the spinal cord (Bauer *et al*, 1969; Kuchelmeister *et al*, 1993; von Einsiedel *et al*, 1993). In an autopsy series of 21 cases, 17 cases showed PML foci in infratentorial structures — 13 cases in cerebellum, 13 cases in brainstem, and 10 cases in both regions (Kuchelmeister *et al*, 1993). The lesions range in size from 1 mm to several centimeters (Aström *et al*, 1958; Richardson, 1970); larger lesions are not infrequently the result of coalescence of multiple smaller lesions.

The histopathological hallmarks of PML are a triad (Aström *et al*, 1958; Richardson, 1970) of multifocal demyelination, hyperchromatic, enlarged oligodendroglial nuclei (Figure 1) and enlarged bizarre astrocytes with lobulated hyperchromatic nuclei (Figure 2). The latter may be seen to undergo mitosis and appear to be quite malignant. *In situ* hybridization for JCV antigen allows for detection of

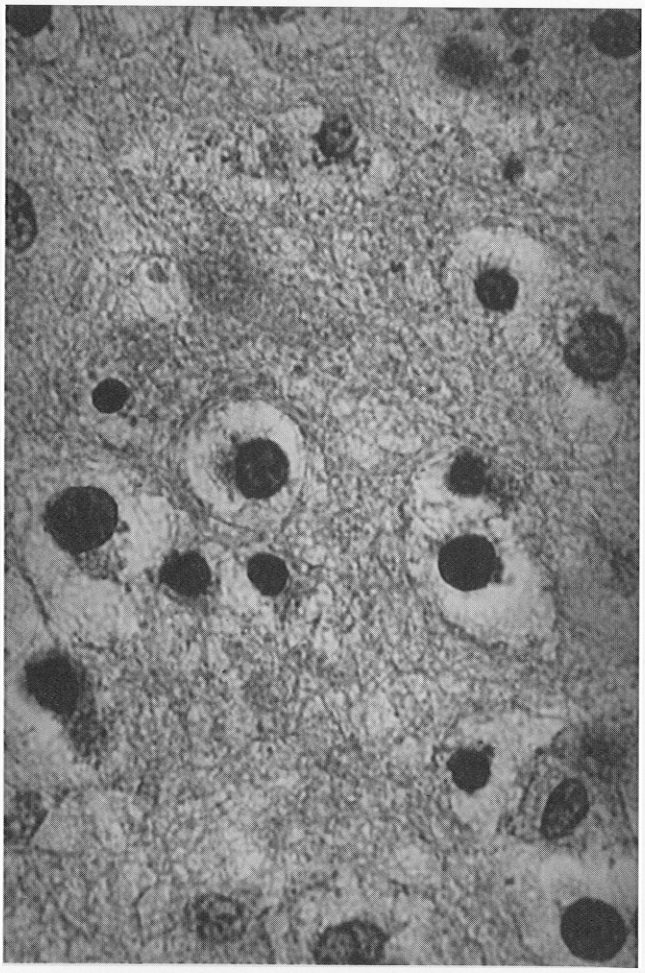

Figure 1 Multiple dense, enlarged oligodendroglial nuclei in a region of demyelination.

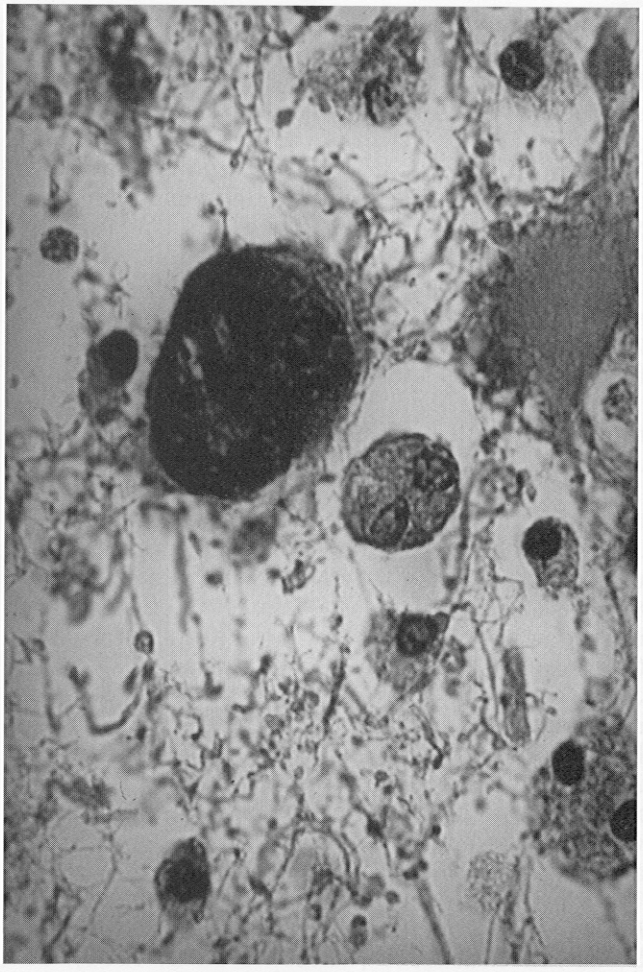

Figure 2 Enlarged, bizarre astrocyte from region of demyelination.

the virion in the infected cells. Electron microscopic examination will reveal the JC virus in the nucleus of the oligodendroglial cells. These virions measure 28 to 45 nm in diameter and appear singly or in dense crystalline arrays (ZuRhein and Chou, 1965; ZuRhein, 1967). Less frequently, the virions are detected in reactive astrocytes and they are uncommonly observed in macrophages that are engaged in removing the affected oligodendrocytes (Mazlo and Herndon, 1977; Mazlo and Taviska, 1982). Recently, Boldorini *et al* reported the subcellular distribution of virions with particular attention to cells usually not involved by papovavirus infection (Boldorini *et al*, 1993). Interestingly in five of eight cases virions were found in the nucleus and cytoplasm (two cases) or cytoplasm only (three cases) of neurons (Boldorini *et al,* 1993). This finding could have implications in the interpretation of cortical signs and symptoms of PML patients. The virions are generally not seen in the large bizarre astrocytes (Mazlo and Taviska, 1982).

Even though neuropathologic findings of PML do not reveal fundamental differences between cases with AIDS and non-AIDS PML, the former group more frequently tends to present with extensive lesions having particularly destructive, necrotizing character (Schmidbauer *et al*, 1990; Kuchelmeister *et al*, 1993). Some investigators (Kuchelmeister *et al*, 1993) have suggested that AIDS-associated PML may present more frequently with infratentorial lesions than non-AIDS PML cases, although others have not found a substantial difference (von Einsiedel *et al*, 1993).

Clinical disease

The clinical hallmark of PML is the presence of focal neurological disease associated with radiographic evidence of white matter disease in the absence of mass effect. Emphasis needs to be placed on the focal features of this disease, particularly those that are apparent on clinical examination. The

Table 1 Comparison of the initial neurologic manifestations of progressive multifocal leukoencephalopathy in patients with and without AIDS. A summary of three clinical series

Manifestation	*AIDS-related PML*				*Non AIDS-related*
	Berger et al, 1987 no. (n=25)	*von Einsiedel et al, 1993 no. (n=15)*	*total=40 no.*	*%*	*Brook et al, 1984 % (n=107)*
Cognitive deficits	6	6	12	30.0	36.1
Dementia	0	5	5	12.5	11.6
Mono- or hemiparesis	12	9	21	52.5	33.3
Sensory deficits	2	1	3	7.5	5.8
Visual deficits	6	3	9	22.5	33.3
Homonymous hemianopsia	2	1	3	7.5	23.2
Visual loss and cortical loss	4	2	6	15.0	10.1
Speech deficits	4	8	12	30.0	17.3
Limb incoordination	7	6	13	32.5	13.0
Headache	4	1	5	12.5	7.2
Vertigo	2	1	3	7.5	4.3
Seizures	0	3	3	7.5	5.8

[a] % of cases in pathologically confirmed cases

most common presentations include weakness, visual deficits and cognitive abnormalities, each occurring as a heralding manifestation in approximately one-third of patients (Brooks and Walker, 1984). Table 1 summarizes the initial neurologic manifestations in three clinical series of patients with PML unrelated to AIDS (Brooks and Walker, 1984) and AIDS-related PML (Berger *et al*, 1987; von Eisiedel *et al*, 1993). Weakness is typically a hemiparesis, but monoparesis, hemiplegia, and quadriparesis may be observed with progression of disease. At the time of diagnosis, weakness is present in more than 80% of patients (Arthur *et al*, 1989). Other motor disturbances are also observed. Limb and trunk ataxia resulting most often from cerebellar involvement is detected in as many as 10%. Nearly one third of patients have cerebellar signs at the time of diagnosis (von Einsiedel *et al*, 1993; Brooks and Walker, 1984). On occasion, the ataxia may be the result of severe impairment in position sense rather than be the result of cerebellar disease. Extrapyramidal disease, at least at onset, is rare but bradykinesia and rigidity may be detected in a substantial minority of patients with advanced disease (Richardson, 1970; Richardson, 1974). Dystonia and severe dysarthria have also been observed as a consequence of lesions in the basal ganglia (Singer *et al*, 1993). Not unexpectedly, lesions due to PML in the basal ganglia are chiefly a reflection of involvement of medullated fibers coursing through this region rather than involvement of the deep gray matter (Whiteman *et al*, 1993). The presentation of the AIDS patient with PML does not appear to be substantially different from that of patients with PML complicating other immunosuppressive conditions except perhaps for a higher frequency of focal motor deficits, dysarthria and limb incoordination (Table 1) (Krupp *et al*, 1985; Berger *et al*, 1987). The latter two may be a reflection of a greater frequency of infratentorial lesions in AIDS-related PML (Table 1).

Neuro-ophthalmic symptoms occur in 50% of patients with PML and are the presenting manifestation in 30%–45% (Brooks and Walker, 1984; Bachman, 1993). The most common visual deficits are homonymous hemianopsia or quadrantanopsia due to lesions of the optic radiations. Cortical blindness is present at the time of diagnosis in 5–8% and may eventuate with progression of the disease (Brooks and Walker, 1984). Other ophthalmic manifestations include visual agnosia, alexia without agraphia, Balint's syndrome and, on rare occasion, ocular motor abnormalities; the latter, as a result of demyelinating lesions in the brainstem. Although optic nerve atrophy has been reported as a consequence of PML (Brooks and Walker, 1984), it has never been confirmed histopathologically. In several reported cases, coexistent diseases could explain the optic nerve involvement (Headington and Umiker, 1962; Bachman, 1993).

The spectrum of cognitive changes observed is quite broad. Unlike the slowly evolving, global dementia of HIV-associated dementia complex (HIV dementia), the mental impairments of PML are often more rapidly advancing and typically occur in conjunction with focal neurological deficits (see below). Among the abnormalities seen are personality and behavioral changes, poor attention, motor impersistence, memory impairment, dyslexia, dyscalculia, and the alien hand syndrome. A global dementia occurring in the absence of focal neurological disease is rarely the presenting manifestation of PML (Brooks and Walker, 1984; von Einsiedel *et al*, 1993). Disturbances of language that may be observed include both dysarthria and aphasia. Aphasia occurs in up to 10% of patients with

PML (Brooks and Walker, 1984).

Other clinical manifestations that are observed less frequently are sensory disturbances, headache, vertigo and seizures (Brooks and Walker, 1984; Berger *et al*, 1987; von Einsiedel *et al*, 1993). Seizures may be seen and have been attributed to lesions that affect cortical gray matter (von Einsiedal *et al*, 1993). Although von Einsiedel and colleagues suggest that AIDS-related PML cases present more frequently with seizures, hemiparesis and dysarthria than non-AIDS associated PML, one needs to be cautious about the interpretation of this data which is based mainly on autopsy results and clustering of reports with small sample sizes.

Prognosis

In AIDS patients, as in those with other underlying diseases, PML usually progresses inexorably to death within a mean of 4 months (Brooks and Walker, 1984; Berger *et al*, 1987). More than 80% succumb within 1 year from the time of diagnosis (Brooks and Walker, 1984; Berger *et al*, 1987; Kuchelmeister *et al*, 1993; von Einsiedel, 1993). However, on rare occasion, individuals with PML experience both clinical and radiographic recovery, including full neurological recovery, in the absence of specific therapeutic intervention (Berger and Mucke, 1988). In our own experience eight pathologically confirmed AIDS patients with PML have exhibited both neurological recovery and survival in excess of 1 year. These patients present approximately 7% of the total number of patients seen to date with PML complicating AIDS. In general, when compared to the group of patients with a typical course of PML, the individuals with neurological improvement and prolonged survival more often had PML as the initial manifestation of AIDS, were systemically healthier and had a higher CD4 T-lymphocyte counts. Additionally, brainstem disease was not observed in this group. The explanation for their benign clinical course remains a conundrum and could not be attributed to any specific therapeutic intervention. One of those patients remained neurologically well 8 years after the initial diagnosis of PML despite the subsequent development of tuberculosis pericarditis and lymphoma (Berger and Mucke, 1988) and another previously described (Berger and Mucke, 1988) had no evidence of demyelination or PML at autopsy nearly 3 years after her initial biopsy revealing PML.

Radiographic imaging

The diagnosis of PML is strongly supported by radiographic imaging, but currently confirmation requires brain biopsy. Computed tomography (CT) of the brain reveals hypodense lesions of the affected white matter (Figure 3) that generally do not enhance with contrast and exhibit no mass effect.

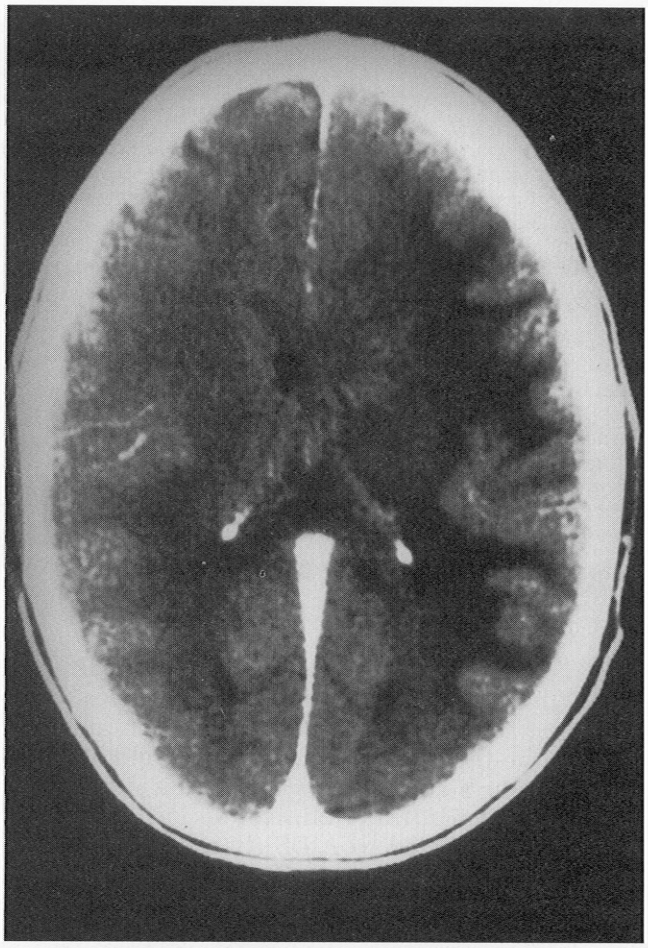

Figure 3 Computed tomographic image of the brain reveals extensive hypodense lesion of the left cerebral hemisphere (photograph courtesy of Dr Justin McArthur, Baltimore, Maryland).

These lesions may have a 'scalloped' appearance as a result of the subcortical arcuate fibers lying directly beneath the cortex (Whiteman *et al*, 1993). With a higher sensitivity magnetic resonance imaging (MRI) shows patchy or confluent hyperintense lesions on T2-weighted images in the affected regions (Figure 4). As with CT scan, contrast enhancement is an exception, however, contrast enhancement has been observed with both brain imaging techniques in approximately 5–10% of pathologically confirmed cases of PML (Whiteman *et al*, 1993). The enhancement observed is typically faint and peripheral. The lesions of PML have a predilection for the parieto-occipital lobes but may occur virtually anywhere. A review of 47 cases of biopsy or autopsy-proven PML, found involvement of the basal ganglia, external capsule and posterior fossa structures (cerebellum and brainstem) (Whiteman *et al*, 1993) (Figure 5). One third of patients had involvement of the posterior fossa structures and in 5–10% of patients the disease activity was isolated to these structures (Whiteman

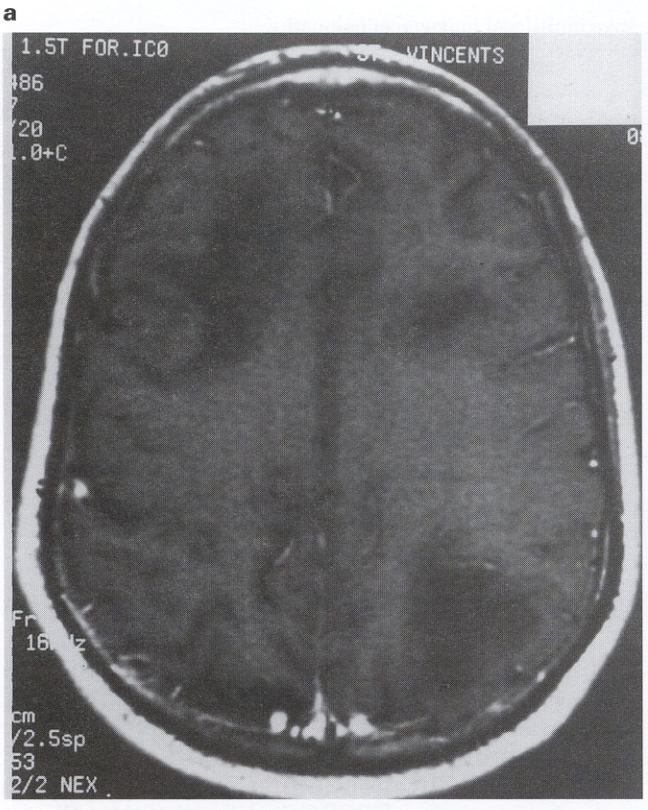

Figure 4 (a) Cranial MRI (T1-weighted image) showing hypointense signal abnormalities of the white matter of both frontal lobes and the left occipital lobe. (b) Cranial MRI (T2-weighted image) showing hyperintense signal abnormalities in the white matter of the corresponding areas.

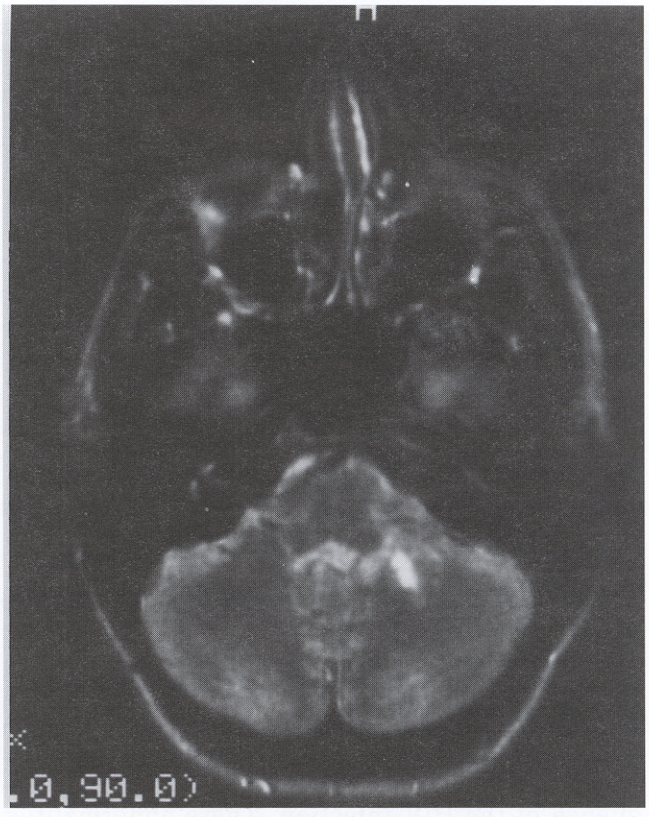

Figure 5 Cranial magnetic resonance image (T2-weighted image) showing a subtle hyperintense signal abnormality extending from the left middle cerebellar peduncle into the left cerebellar hemisphere.

et al, 1993).

Other diseases may cause white matter disease, especially in association with HIV infection. The demyelination observed with HIV dementia may be radiographically indistinguishable from that of PML. Clinically, however, PML is associated with focal neurological disease and is more rapidly progressive. Radiographic distinctions include a greater propensity of PML lesions to involve the subcortical white matter, its hypointensity on T1WI images, its rare enhancement and more frequent occurrence of infratentorial lesions (Whiteman *et al*, 1993). Cytomegalovirus (CMV) may also cause demyelinating lesions. Typically these lesions are located in the periventricular white matter and centrum semiovale, and subependymal enhancement is observed (Sze and Zimmermann, 1988; Bowen and Post, 1991). MRI images similar to those seen in PML can have been recently described in a patient with dementia and extrapyramidal secondary to systemic lupus erythematosus (Kaye *et al*, 1992).

Cerebrospinal fluid and other studies

With the exception of polymerase chain reaction (PCR) performed on cerebrospinal fluid (CSF) for

Table 2 JC virus detection by PCR in cerebrospinal fluid from progressive multifocal leukoencephalopathy

Groups	*No. / total*				
	Moret et al, 1993	*Gibson, 1993*	*Weber et al, 1994*	*McGuire et al, 1994*	*Aksamit et al, 1994*
PML					
AIDS	9/9	10/13	23/28	24/26[a]	11/23
Other	—	—	—	—	20/28
Total	9/9	10/13	23/28	24/26[a]	31/51
Controls					
AIDS	0/3	0/41	0/82	10/114	1/170
Other	0/5	—	—	1/16[b]	0/249
Total	0/8	0/41	0/82	11/130	1/419
Sensitivity (%)	100	76	82	92	61
Specificity (%)	100	100	100	92	99

[a] Defined as HIV infected patients
[b] Positive sample was from a patient with chronic lymphocytic leukemia and unexplained hemiparesis

the presence of JCV, other studies applied to CSF are nondiagnostic. The routine studies performed on CSF are usually normal in the absence of HIV infection (Brooks and Walker, 1984; Berger *et al*, 1987; von Einsiedel *et al*, 1993). In patients with PML complicating HIV infection, the CSF abnormalities typically reflect those observed as a consequence of the HIV infection. These abnormalities may include a mononuclear pleocytosis (≤ 20 cells cu mm^{-1}), elevated protein (≤ 65 mg dl^{-1}) and borderline low glucose (Navia *et al*, 1986a; Marshall *et al*, 1988). PML in the absence of AIDS may be associated with a slight elevation in the CSF protein, a mild lymphocytic pleocytosis and the presence of myelin basic protein (Brooks and Walker, 1984; Berger *et al*, 1987).

Until recently confirmation of PML relied exclusively on typical histopathologic changes and detection of JC virus in brain samples from biopsies or at autopsy. JCV can be detected by electron microscopy or isolated in cell cultures, viral antigens detected by immunocytochemistry, and viral DNA detected by *in situ* hybridization or PCR (ZuRhein and Chou, 1965; Padgett *et al*, 1971; Tornatore *et al*, 1992; Moret *et al*, 1993). By electron microscopy using negative staining technique papova-like particles were observed in two of three CSF samples from patients with clinical and neuroradiologic evidence of PML and not in 12 controls with AIDS (Orefice *et al*, 1993).

The recent application of PCR to CSF samples is promising in establishing the diagnosis premortem with less invasive procedures than brain biopsy (Weber *et al*, 1994). Two earlier encouraging reports were able to detect JCV DNA with 100% specificity in more than three-fourths of CSF samples from patients with PML (Gibson *et al*, 1993; Moret *et al*, 1993). Gibson and colleagues detected JCV DNA in 10 of 13 CSF samples from patients with previously confirmed PML, while no amplification was obtained in 42 CSF samples from patients without PML (Gibson *et al*, 1993). In a second study, CSF samples from 12 AIDS patients were examined by PCR. All nine samples from patients with PML diagnosis amplified JCV DNA products, but five controls and three AIDS patients without PML did not show amplification (Moret *et al*, 1993). These and other reports of PCR amplification in CSF for the diagnosis of PML are summarized in Table 2. Based on a series of 110 CSF samples, 28 PML cases and 82 controls, Weber *et al* reported 82% sensitivity and 100% specificity for diagnosis of PML with PCR (Weber *et al*, 1994). Yet another large cohort, 156 individual CSF samples, revealed a 92% sensitivity and specificity (McGuire *et al*, 1994). With an overall sensitivity of 61%, Aksamit *et al* reported a specificity above 99% in a large sample size, 470 CSF samples (Aksamit and Kost, 1994). False positive samples might depend on the stage of the disease or on technical variation, such as set of primers and amount of CSF analyzed (Gibson *et al*, 1993; Moret *et al*, 1993; Weber *et al*, 1994). Despite these variations and the limited clinical experience with this technique, PCR is likely to prove a sensitive and highly specific diagnostic tool for confirming PML. If its promise is upheld with larger, more intensive studies, it will doubtlessly reduce the need for brain biopsy to establish the diagnosis.

Serum antibodies are not helpful in establishing the diagnosis, since 80% or more of the population show seropositivity to antibodies against JC virus by adulthood (Taguchi *et al*, 1982). The electroencephalogram may show focal slowing, but, like other studies, is also non-diagnostic.

Differential diagnosis

The large increase in the incidence of PML in the last decade has been due to the AIDS epidemic, and therefore the majority of PML cases will present in

AIDS patients. With increasing frequency, clinicians find themselves confronted by HIV-infected patients with cognitive impairment and a cranial MRI showing 'hyperintense signal abnormalities on T2 weighted image (T2WI) characteristic of PML' due to the HIV dementia (AIDS dementia complex). It is the presence of these white matter lesions detected on MRI that frequently leads to the incorrect diagnosis of PML. HIV dementia may be the initial manifestation of AIDS in up to 3% of adult AIDS patients (Janssen *et al*, 1992; McArthur *et al*, 1993), has an estimated annual incidence of close to 7%, and will affect one third or more of AIDS patients before their death (McArthur *et al*, 1993).

Cardinal features include an insidiously progressive psychomotor slowing, impaired memory and apathy (Price and Brew, 1988; McArthur *et al*, 1993). Early complaints of forgetfulness, difficulty concentrating and manipulating complex tasks, problems reading, general slowness, headache, and fatigue are classic. Because of the advanced degree of immunosuppression, AIDS patients with HIV dementia or PML generally exhibit similar constitutional features, including wasting, global alopecia, oral thrush and hairy leukoplakia, seborrheic dermatitis and generalized lymphadenopathy. The patient with HIV dementia commonly has slow mental processing (bradyphrenia), abnormalities of saccadic and pursuit eye movements, diminished facial expression, low-volume, poorly articulated speech, impaired coordination and balance, postural tremor, poor dexterity and a slow clumsy gait. Unlike PML, focal neurological findings are uncharacteristic and suggest an alternative diagnosis. CSF examination is most valuable in eliminating the possibility of other disorders. Pathological examination reveals brain atrophy and meningeal fibrosis. The most common histopathological feature of this illness is white matter pallor, associated with an astrocytic reaction chiefly distributed perivascularly in periventricular and central white matter (Navia *et al*, 1986b). There is no evidence of myelin breakdown or loss of myelin basic protein. Multinucleate giant cells secondary to virus-induced macrophage fusion is the pathologic hallmark of the disease (Sharer, 1992). Other pathological features include microglial nodules, diffuse astrocytosis, and perivascular mononuclear inflammation (Navia *et al*, 1986b).

In HIV dementia, the most commonly reported abnormality on CT of the brain is cerebral atrophy, however, low density white matter abnormalities are also frequently observed. CT scan is quite helpful in ruling out focal mass lesions as a cause of a patient's altered mental status (Berger *et al*, 1994). On MRI, large areas of white matter lesions are observed diffused over a large area, typically in the centrum semiovale and periventricular white matter (Olsen *et al*, 1988; Post *et al*, 1988). Less commonly, localized involvement with ill-defined margins (patchy) or small foci less than 1 cm in diameter (punctate) are observed (Olsen *et al*, 1988). These white matter abnormalities are frequently mistaken for PML and the history, clinical findings and, to a lesser extent, CSF parameters are quite helpful in distinguishing between the two disorders (Table 3) (Griffin *et al*, 1991; Royal *et al*, 1994). The clinician needs to be mindful that these conditions are not mutually exclusive and that both conditions may coexist in the same patient.

HIV dementia and PML are not the only disorders of white matter occurring in AIDS in the absence of mass producing lesions. Incidental white matter abnormalities are not uncommonly observed in HIV-infected individuals and do not appear to have any clinical significance (McArthur *et al*, 1990). Among the disorders in the radiographic differential diagnosis an acute, diffuse, rapidly fatal leukoencephalopathy has been reported. Others include (1) an HIV-associated granulomatous angi-

Table 3 Distinguishing HIV dementia from progressive multiple leukoencephalopathy (PML)

Characteristics	*HIV Dementia*	*PML*
Clinical		
Dementia	Prominent	Rare
Progression	Usually slow (months)	Usually rapid (weeks)
Focal neurological findings	Unusual	Characteristic
Radiographic		
Subcortical involvement	Infrequent	Characteristic
Intensity on T1 weighted image	Isointense	Hypointense
Enhancement	No	Faint and peripheral (5-10%)
Infratentorial lesions	No	Often (30% or more)
Cerebrospinal fluid		
Surrogate markers	Commonly increased	No correlation with disease
p24 antigen	Commonly increased	No correlation with disease
Myelin basic protein	Negative	May be present
JCV PCR amplification	Negative	Often positive (60% or more)

Table 4 Proposed therapies for PML

Nucleoside analogues
Cytosine arabinoside
Adenine arabinoside
Iododeoxyuridine
Zidovudine
Immunomodulatory agents
Alpha interferon
Beta interferon
Transfer factor
Levamisole
Tilorone
Others
DNA Torpoisomerase I inhibitors
Corticosteroids
Herapin
Antisense oligonucleotides (proposed)

itis; (2) a multifocal necrotizing leukoencephalopathy with a predilection for the pons; (3) a relapsing and remitting neurological illness clinically indistinguishable from multiple sclerosis; and (4) CMV ventriculoencephalitis and other viral opportunistic infections (Olsen *et al*, 1988; Post *et al*, 1988).

Treatment

Unequivocally effective therapy of PML has remained elusive, whether specific antiviral therapy directed at the JC virus or attempts to enhance cellular immunity. A variety of treatment regimens have been proposed on the basis of anecdotal reports and small series (Table 4). No randomized, double-blind therapeutic regimen has yet been completed and the observation that PML may remain stable for long periods of time or even remit in the rare patient (Stam, 1966; Kepes *et al*, 1975; Padgett and Walker, 1983b; Price *et al*, 1988; Sima *et al*, 1983; Berger and Mucke, 1988; Embrey *et al*, 1988) highlights the inadequacies of anecdotal reports suggesting the value of a specific therapy. The rarity of PML prior to the AIDS epidemic precluded practical therapeutic trials.

Nucleoside analogues by interfering with the synthesis of viral DNA have proven effective in the treatment of some viral diseases. Several nucleoside analogues have been tried in the treatment of PML with varying degrees of anecdotal success. Early experience with cytosine arabinoside (ARA-C, cytarabine), a drug chiefly used in the treatment of myeloproliferative disorders, has been mixed (Castleman *et al*, 1972; Bauer *et al*, 1973; Conomy *et al*, 1974; Marriott *et al*, 1975). Rapid and sustained improvement in neurological symptoms were reported by Bauer and colleagues (Bauer *et al*, 1973) with ARA-C administered intravenously as 60 mg m^{-2} day^{-1} and intrathecally as 10 mg m^{-2}. The patient described by Marriott *et al* (1975) showed more delayed, but similarly sustained improvement following ARA-C 2 mg kg^{-1} day^{-1} on 5 consecutive days every 3 weeks. Similar anecdotal reports of various degrees of improvement have been reported by others (Conomy *et al*, 1974; Buckman and Wiltshaw, 1976; Rockwell *et al*, 1976; Peters *et al*, 1980; O'Riordan *et al*, 1990; Portegies *et al*, 1991). These regimens employed either intrathecal and/or intravenous administration of ARA-C. The clinical observations regarding the potential efficacy of ARA-C in PML is supported by the recently acquired *in vitro* data on human fetal brain tissue infected with JCV. Major and colleagues have determined that cytosine b-D arabinofuranoside at a concentration of 25 μg ml^{-1} of culture effectively suppresses JC virus replication (Major *et al*, 1992).

Enthusiasm for the use of ARA-C in PML should be tempered by its toxicity profile and the lack of a consistent salutory effect. A study of intrathecal ARA-C administered as 10 mg m^{-2} daily for 3 days with repeat dosing at variable intervals in 26 AIDS patients with PML revealed a salutory effect of 60% that was sustained in 50% for up to 2 years and was transient (less than 6 months) in the remainder (Britton *et al*, 1992). However, some case reports suggest a total lack of efficacy of cytosine arabinoside administered either solely intravenously (Castleman *et al*, 1972; Smith *et al*, 1982) or in combination with intrathecal therapy (Van Horn *et al*, 1978). Currently, there is a large collaborative effort orchestrated through the National Institutes of Health AIDS Clinical Trials Group comparing high dose antiretroviral therapy alone or in combination with either intravenous or intrathecal ARA-C in treating PML. The results of this study will be instrumental in determining the value of ARA-C in the treatment of PML.

Other nucleoside analogues do not appear to have the same success of ARA-C in the treatment of PML. Wolinsky and colleagues (Wolinsky *et al*, 1976) noted the failure of a 14 day course of adenosine arabinoside (ARA-A; vidarabine), 20 mg kg^{-1} day^{-1} in two patients with PML. Similar failures of adenosine arabinoside therapy in the treatment of PML have also been described (Raud *et al*, 1977; Walker, 1978). Tarsy *et al* (Tarsy *et al*, 1973) had no success with a combination of prednisone and intrathecal idoxuridine (5-iodo-2'-deoxyuridine) 2 mg kg^{-1} h^{-12}. Kerr and colleagues' studies have demonstrated the efficacy of the antineoplastic drug camptothecin, a DNA topoisomerase I inhibitor in blocking JCV replication *in vitro* by means of pulsed doses employed in amounts that were non-toxic to cells (Kerr *et al*, 1993).

Because of their antiviral activity, presumably the result of their ability to stimulate natural killer (NK) cells (Tyring *et al*, 1988), interferons have been proposed as potential therapeutic agents in the treatment of PML. Alpha interferon has established efficacy in the treatment of other papovavirus-related

diseases (Weck *et al*, 1988). In an open label trial of the safety and efficacy of recombinant α-interferon 2A administered as 3 million units subcutaneously daily with a gradual increment (typically by 3 million units every third day) in the treatment of HIV-associated PML, two of 17 patients had survival extending greater than 1 year (Berger *et al*, 1992b). No patient had a dramatic reversal in neurological function. In one patient, combined therapy of intravenous adenine arabinoside and β-interferon (Tashiro *et al*, 1987) showed no efficacy. However, intrathecal β-interferon 1 million units weekly for a total of 19 weeks and, thereafter, monthly was associated with modest improvement in her clinical picture and magnetic resonance imaging (Tashiro *et al*, 1987).

The rationale for the use of low dose heparin sulfate as an adjunct in the treatment of PML is based on the model of the pathogenesis of PML proposed by Houff and Major (Houff *et al*, 1988) which postulates that PML is the result of activated JCV infected B lymphocytes crossing the blood–brain barrier (BBB) and initiating new areas of neuroglial infection throughout the course of the disease. Heparin sulfate has been shown to prevent activated lymphocytes from crossing the BBB in animal models by stripping the lymphocyte glycoprotein cell surface receptors for cerebrovascular endothelial cells. By the time of diagnosis, the virus is well established in the brain, therefore, this therapy is unlikely to be of any value in established disease, but may be useful as a means of prophylaxis in high risk patients, if their hypothesis is correct.

Other agents either alone or in combination with nucleoside analogues have been tried in treatment of PML. No value has been demonstrated with corticosteroid therapy alone or in conjunction with other agents (Tarsy *et al*, 1973; Van Horn *et al*, 1978). In theory, recovery of the underlying immunological disorder should be associated with recovery from PML and that has been observed on rare occasion in individuals who have recovered from the illness or condition that had resulted in immunosuppression. A stabilization of the neurological deficits in a patient treated with tilorone, an immune enhancer (Selhorst *et al*, 1978), is tempered by the converse observation (Dawson, 1982) which noted no improvement following the cessation of immunosuppressive therapy in a patient with PML and myasthenia gravis. A recent report (Conway *et al*, 1990) suggests that PML occurring in association with HIV infection may respond to zidovudine. A dramatic improvement followed the administration of zidovudine 200 mg every 4 h and worsening followed a reduction in dose to 200 mg every 8 h. A return to prior higher zidovudine doses resulted in neurological stability (Conway *et al*, 1990). Zidovudine may effect levels of the *tat* protein that have been demonstrated to transactivate JCV (Tada *et al*, 1990). In our experience, zidovudine use in AIDS-associated PML, even in high doses (≥ 1000 mg day^{-1}) has been devoid of significant benefit. There is limited experience with the other antiretroviral agents.

Another form of potential therapy is the use of antisense oligonucleotides. These molecules can be designed to bind selectively to a target region of messenger RNA and prevent its translation into protein. The development and trials of such agents for PML await further investigation.

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