Human Immunodeficiency Virus–Associated Dementia: Review of Pathogenesis, Prophylaxis, and Treatment Studies of Zidovudine Therapy

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Human immunodeficiency virus (HIV)–associated dementia (HIVD) has been reported in up to 15% of HIV-infected adult patients. Although the pathogenesis of HIVD remains unclear, HIV probably plays an important role in the syndrome, as evidenced by the correlation between cerebrospinal fluid (CSF) HIV load and neuropsychological functioning. Although a large number of antiretrovirals are used to treat HIVD, zidovudine is the best studied. Zidovudine therapy has been associated with reduced levels of HIV RNA in CSF, fewer HIV-related changes in brain tissue at autopsy, and time-limited improvements in neurological function among AIDS and HIVD patients.

More recent studies have investigated the penetration into CSF of other antiretrovirals, including protease inhibitors, and the clinical efficacy of abacavir in the treatment of dementia. HIV encephalopathy may occur in 30%–60% of children with AIDS and causes significant disability. Zidovudine has been associated with improved neuropsychological functioning in children with progressive encephalopathy, but optimum dosing levels, duration of effect, and prophylactic potential remain to be demonstrated.

Neurological complications are among the most frequent and detrimental of the problems that affect HIV-infected patients [1]. Both children and adults can have such complications at any stage of the illness [1], with 40%–70% of all HIV-infected persons developing symptomatic neurological disorders at some point [2]. Pharmacotherapies now available not only allow HIV patients to live longer but also have changed the constellation and sequence of complications most commonly associated with AIDS. Thus, occurrence of Pneumocystis carinii pneumonia and other opportunistic infections is often delayed, whereas neurological disorders increasingly appear as the initial AIDS manifestation [3].

In addition to secondary infectious or neoplastic neurological complications resulting from immunosuppression, several primary neurological disorders may be associated with HIV-1. Among these are myelopathy, myopathy, and distal sensory polyneuropathy [2]. Disabling cognitive, behavioral, and motor impairment, termed HIV-associated dementia (HIVD) in adults and HIV encephalopathy in children, is one of the most devastating and enigmatic of the primary HIV neurological complications. (HIVD also is sometimes called AIDS dementia complex [ADC], multinucleate giant cell encephalitis, or HIV-1-associated cognitive/motor complex [2]. For simplicity, all are referred to here as HIVD.) This article summarizes the epidemiology, clinical features, pathogenesis, and treatment of HIVD in adults and children.

HIV Dementia (HIVD) in Adults

Epidemiology

In the United States, neurological disease is recorded for as many as 100,000 HIV-infected patients each year [2]. Reports suggest an incidence of HIVD of 7% per year among survivors in the first 2 years of the disease, with 15% of the cohort developing dementia before death [4]. The actual occurrence may be higher than these figures indicate, because many cases of HIVD may not be diagnosed when other life-threatening illnesses are present [2]. In fact, some autopsy series show neuropathologic abnormalities in as many as 80% of AIDS patients [5]. It appears that the incidence of HIVD may have fallen in recent years with the advent of highly active antiretroviral therapy, although epidemiological data are not yet available to support this impression.

Although HIVD occasionally is an AIDS-defining illness [2, 6], it usually develops late in the disease after the patient has been diagnosed with other AIDS-related illnesses and when CD4+ lymphocyte counts have declined to <200/mm³ [7]. A prospective study of 492 homosexual men with AIDS identified risk factors associated with more rapid development of dementia and documented median survival times for those developing vs. those not developing HIVD [4]. Primary risk factors for rapid development of HIVD included...
decreased hemoglobin levels in the year before AIDS was diagnosed, low body mass index in the 1–6 months before AIDS, self-reported constitutional symptoms 7–12 months before AIDS, older age at initial AIDS diagnosis, and Kaposi’s sarcoma as the initial AIDS-related diagnosis. Multivariate analyses identified decreased hemoglobin level in the 1–6 months before the AIDS diagnosis as the most significant predictor of dementia (relative hazard = 0.60 for each additional 2 g/dL \( P = .03 \)). Neither demographic characteristics, AIDS-defining illness, zidovudine use before AIDS, nor CD4+ lymphocyte count before AIDS was an important predictor in this cohort. Importantly, patients who developed HIVD had shorter median survival times than did those who did not develop the complication: 6.0 months among demented patients vs. 7.8 months among nondemented patients after a second AIDS-defining illness \( (P = .075) \) [4].

**Clinical Features of HIVD**

HIVD is largely a diagnosis of exclusion, with early signs and symptoms that may be difficult to recognize [2]. Clinical symptoms fall into three categories: cognitive, behavioral, and motor [8, 9]. Cognitive symptoms include impaired short-term memory and concentration, increased distractibility, mental slowing, and loss of flexibility and spontaneity. Personality change, apathy, withdrawal, irritability, and depression often characterize behavioral changes. Motor symptoms may be evidenced by fine-motor clumsiness or slowness, tremor, and leg weakness.

Results of neurological examination often are normal or nearly so in patients with early HIVD [9]. In some patients, cognitive impairment may be detected with the Luria hand test or word reversal tests. A series of neuropsychological tests measuring several domains of cognitive function are being assessed by investigators within the AIDS Clinical Trials Group (ACTG) of the U.S. National Institute of Allergy and Infectious Diseases. There may be impairment of smooth eye pursuits or saccadic movements, while slow or clumsy movements may be detected by tests involving finger tapping or alternating wrist movements. There also may be mild hyperreflexia and difficulty with tandem gait. As the disease progresses, major intellectual and motor impairments become evident, and in the later stages, patients enter a conscious but vegetative state. To grade the severity of HIVD symptoms, a system based on functional performance has been developed and has been used widely in clinical trials (table 1) [10]. Scoring ranges from 0 (normal) and 0.5 (subclinical neurocognitive symptoms) to 4 (nearly vegetative and mute).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical features</th>
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<tbody>
<tr>
<td>0 (normal)</td>
<td>Normal mental and motor function</td>
</tr>
<tr>
<td>0.5 (equivocal/subclinical)</td>
<td>Absent, minimal, or equivocal symptoms without impairment of work or capacity to perform ADL; mild signs (snout response, slowed ocular or extremity movements) may be present; gait and strength are normal</td>
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<td>1 (mild)</td>
<td>Able to perform all but the more demanding aspects of work or ADL, but with unequivocal evidence (signs or symptoms that may include performance on neuropsychological testing) of functional intellectual or motor impairment; can walk without assistance</td>
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<tr>
<td>2 (moderate)</td>
<td>Able to perform basic activities of self-care but cannot work or maintain the more demanding aspects of daily life; ambulatory, but may require a single prop</td>
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<tr>
<td>3 (severe)</td>
<td>Major intellectual incapacity (cannot follow news or personal events, cannot sustain complex conversation, considerable slowing of all output) or motor disability (cannot walk unassisted, requiring walker or personal support, usually with slowing and clumsiness of arms as well)</td>
</tr>
<tr>
<td>4 (end-stage)</td>
<td>Nearly vegetative; intellectual and social comprehension and output are at a rudimentary level; nearly or absolutely mute; paraparetic or paraplegic with urinary and fecal incontinence</td>
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</table>

**Table 1. Staging of HIV dementia on the basis of functional performance.**

NOTE. ADL = activities of daily living. From [10].

other infections [2]. CSF abnormalities often seen include mild mononuclear cell pleocytosis (counts usually of <50 cells/mm³, seen in one-fifth of patients), elevated total immunoglobulin fraction, increased total protein concentration (usually to <200 mg/dL, seen in two-thirds of patients), oligoclonal bands, and intrathecal synthesis of IgG antibody to HIV [11]. In later stages of the disease, markers of immune activation in CSF, including \( \beta_2 \)-microglobulin, neopterin, and quinolinate, generally are elevated [2]. Finally, detection of HIV-1 p24 antigen in CSF, which is independent of such antigen in serum, is correlated with HIVD [12].

Radiological studies (brain CT, MRI) are needed to exclude other infections or neoplasms and to identify cerebral atrophy and changes in white matter. Primary neuroradiological features of HIVD include global cerebral atrophy, proportionate ventricular enlargement, symmetrical abnormalities of the white matter (leukoencephalopathy), and vascular mineralization in children [2] (figure 1). There appears to be a correlation between the amount of cerebral atrophy seen on magnetic imaging of the brain and severity of dementia [14]. Current studies are investigating the utility of magnetic resonance spectroscopy in the diagnosis of HIVD.
Neuropathologic Findings

Characteristic changes in the brains of persons with HIVD can exist singly or overlap. The most common finding is cerebral atrophy with resultant ventricular enlargement, widened sulci, and loss of white matter (as indicated by symmetrical hyperintensities on T2-weighted MRI) [6] (figure 2). Neuropathologic findings generally reveal the following.

HIV-1 encephalitis. Distinct pockets of inflammatory cells, such as microglia, macrophages, and multinucleated giant cells formed by fusion of microglia and macrophages, are found in white and deep grey matter as well as in the cortex [15]. Although these findings are specific for the diagnosis of HIVD, they are present in only 50% of demented patients.

HIV leukoencephalopathy. HIV leukoencephalopathy is characterized by diffuse damage to white matter or myelin attenuation, astrogliosis, macrophages, and multinucleated giant cells—without distinct pockets of inflammation. Myelin pallor in young children may be difficult to distinguish because of their incomplete myelination [15].

Diffuse poliodystrophy. Reactive astrogliosis and microglial activation in cerebral gray matter may possibly be associated with neuron loss or dendritic damage. Severe cases may also evidence spongiform changes [15].

Vascular calcification of the basal ganglia and possibly the centrum semiovale is often present in pediatric AIDS. In fact, it may be found either with or without notable HIV-1 encephalitis. In contrast, inflammatory changes are more common in the spinal cord in pediatric patients, whereas vacuolar myelopathy is seen less often. However, corticospinal tract degeneration may also be found in pediatric HIV-1 infection [15].

Theories on Pathogenesis

The pathogenesis of HIVD remains unclear, and it is not known whether HIV plays a primary or secondary role in prompting CNS deterioration [16, 17]. Historically, HIV antigen and HIV-1 DNA have been demonstrated in the brains of patients with HIVD. These are predominantly localized in lymphoreticular cells, including monocytes/macrophages and endothelial cells; it appears to be these cells, rather than neurons or glial cells, that are infected [2].

In general, the severity of certain pathological findings correlates with clinical state [18, 19]. There is no convincing evidence of neuronal HIV infection [2]. β2-microglobulin and neopterin levels in CSF and CD4+ cell counts have been found to be predictive markers for the development of HIVD [20]. A
number of indirect factors may contribute to the pathogenesis of HIVD, including cytokines (e.g., TNF), parts of HIV itself (gp41, gp120, Tat, Rev, Nef), and excitatory amino acids (e.g., quinolinic acid). Portegies et al. [12] found that although HIV-1 antigen expression in CSF accompanied neurological deterioration, it was not a good predictor of dementia, because it was not detectable before such deterioration was clinically evident. Newer data, based on assays of CSF for HIV RNA and tests of virus load in CSF, show a better correlation between HIV RNA levels in CSF and the severity of dementia.

McArthur et al. [21] reported that in patients with advanced disease (CD4+ cell counts of <200 cells/mm³), virus loads in CSF and brain were correlated, indicating that virus burden in CSF may be a valid marker for virus burden in the brain. Additionally, patients with dementia had significantly elevated virus load in CSF compared with that in nondemented subjects. Ellis et al. [22] reported a similar pattern in patients with advanced HIV disease. The major issue concerning HIV RNA in CSF, however, remains how well it correlates with response to therapy.

In light of this evidence, numerous indirect mechanisms for HIV’s effect on the brain have been suggested. Cytokines, particularly TNF-α and interleukins, elaborated by infiltrating macrophages and microglia, serve as cofactors for dementia in a number of other models [23]. These cytokines may be causative factors of both the vacuolar myelopathy and sensory neuropathy seen in HIVD [2].

White matter pallor, rather than resulting from demyelination, may be a consequence of HIV-1 induced alterations in the blood-brain barrier [24].

gp120, an HIV surface antigen, can cause neuronal death in the presence of microglial cells. This antigen has been related to the opening of calcium channels in neuronal membranes [25].

Possible amplification of HIV’s effects by interactions between HIV-infected monocytes and astrocytes has been suggested [2]. These interactions might release neurotoxic factors and enhance glial proliferation.

Activation of N-methyl-D-aspartate (NMDA) receptors may be the final common pathway in HIVD, as it is in other neurodegenerative processes [26–28]. In vitro studies show that gp120 neurotoxicity can be blocked by NMDA antagonists [29].

Chemokines are proteins involved in the trafficking of cells and their interaction with receptors. Several chemokines, including CCR-5 and CXCR4 for neurons, provide another mechanism by which HIV may interact with endothelial cells and neurons [30].

**Treatment**

Although the pathophysiology of HIVD is still unclear, HIV probably plays an important role in the syndrome. Thus, the ability of therapeutic agents to penetrate the blood-brain barrier becomes a key consideration in the choice of therapy [31]. Among the major nucleoside reverse transcriptase inhibitors, penetration of brain tissue has been reported to be ~20% with zidovudine, ~30% with stavudine, and ~2%–4% with didanosine [32]. No studies concerning the penetration of brain tissue by lamivudine are available; however, zidovudine is the most lipophilic nucleoside analogue. To date, zidovudine and lamivudine have shown the highest ratios of CSF drug concentration to IC₅₀ (the minimum drug concentration that produces ≥50% inhibition of HIV activity), although early studies indicate that indinavir and nevirapine also are promising. Insufficient data exist to evaluate the protease inhibitors and non-nucleoside reverse transcriptase inhibitors with respect to penetration.

Hydroxyurea (an agent used variously to treat cancer and sickle cell disease [33]) penetrates the blood-brain barrier well, with concentrations in brain of ~25% of concentrations in plasma [34].
The addition of hydroxyurea to didanosine-containing regimens has been shown to enhance the in vitro anti-HIV activity of didanosine [35]. Whereas didanosine targets viral protein, hydroxyurea targets cellular protein, which is less vulnerable to development of resistance. Hydroxyurea appears to lower cellular levels of dATP, rendering DNA synthesis more susceptible to didanosine, a dATP competitor [36]. In general, information concerning the ability of various therapeutic agents to cross the blood-brain barrier is incomplete; however, in vitro blood-brain barrier permeability to such agents recently has been reported, in descending order, as follows: nevirapine; didanosine, stavudine, zalcitabine, and zidovudine; indinavir; and saquinavir [37]. Abacavir also appears to have good penetration [38]. Combining drugs does not substantially improve permeability [31]. On the basis of studies in humans, the ordering of the ratio of drug concentration in CSF to that in plasma for nucleoside antiretrovirals appears to be as follows, in descending order: zidovudine, stavudine, abacavir, didanosine, lamivudine, zalcitabine. The ratio for the nonnucleoside reverse transcriptase inhibitor nevirapine falls approximately midway in this continuum, while those for delavirdine and efavirenz fall below that for zalcitabine [31]. As a class, protease inhibitors are highly protein-bound and do not cross the endothelial barrier well, although indinavir, the least protein-bound, has the greatest potential for free drug to cross the blood-brain barrier [39]. Preliminary data suggest that protease inhibitors, when used in combination therapies, may improve or stabilize the neurological condition of some patients [40, 41]. Ferrando et al. [42] followed neuropsychometric performance in cohorts of patients receiving and not receiving highly active antiretroviral therapy and found that those receiving highly active antiretroviral therapy had significantly better performance on several measures.

Additional information concerning the movement of zidovudine into CSF was provided by a study that measured levels of zidovudine in CSF by means of an implanted spinal catheter; the area under the curve for drug in CSF to drug in plasma was reported to be 75% [43]. Although levels of protease inhibitors in CSF and brain are believed to be generally quite low because the inhibitors are highly protein-bound (60% for indinavir and 98% for saquinavir and ritonavir) [31], there is some evidence that their use may result in regression of abnormalities in CSF to that in plasma for nucleoside antiretrovirals appears to be as follows, in descending order: zidovudine, stavudine, abacavir, didanosine, lamivudine, zalcitabine. The ratio for the nonnucleoside reverse transcriptase inhibitor nevirapine falls approximately midway in this continuum, while those for delavirdine and efavirenz fall below that for zalcitabine [31]. As a class, protease inhibitors are highly protein-bound and do not cross the endothelial barrier well, although indinavir, the least protein-bound, has the greatest potential for free drug to cross the blood-brain barrier [39]. Preliminary data suggest that protease inhibitors, when used in combination therapies, may improve or stabilize the neurological condition of some patients [40, 41]. Ferrando et al. [42] followed neuropsychometric performance in cohorts of patients receiving and not receiving highly active antiretroviral therapy and found that those receiving highly active antiretroviral therapy had significantly better performance on several measures.

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Although their precise mechanism(s) of action has yet to be defined, there is evidence that antiretrovirals decrease levels of p24 antigen in CSF, an indirect marker for virus load [46–48]. Royal et al. [47] found that patients with HIVD who reported taking antiretroviral medication had p24 antigen in CSF less frequently and at lower concentrations than did those who did not take such drugs. A retrospective study of a consecutive series of 196 AIDS patients in The Netherlands from 1982 to 1988 found significant declines in both HIVD and the presence of p24 antigen in CSF among those treated with zidovudine [46]. Heyes et al. [49] studied quinolinic acid (a potential neurotoxin that is an NMDA receptor agonist) in CSF in 11 HIV-1-infected patients. After treatment with zidovudine for at least 4 weeks, patients exhibited an 11-fold reduction in quinolinic acid levels in CSF and improved neurological status, as indicated by scores in neuropsychological tests and reduced severity of HIVD [49].

Given the difficulties in mounting long-term trials of dementia, several recent studies have focused on the ability of antiretroviral agents to reduce levels of HIV RNA in CSF. Foudraine et al. [50] reported that the combination of stavudine and lamivudine was as effective as zidovudine plus lamivudine in reducing HIV RNA levels in CSF. Collier et al. [51] reported that virus was undetectable in CSF from 9 of 10 patients treated with indinavir in addition to background therapy.

Over the past 10 years, there have been numerous studies of the effects of antiretroviral agents on HIVD. Given zidovudine’s longevity and widespread use among HIV-infected patients, it is not surprising that the most complete information based on the results of clinical trials in humans is available for zidovudine [48]. Preliminary studies of the efficacy of newer antiretrovirals are, however, beginning to be published. For example, a recent controlled study of abacavir added to “best background antiretroviral therapy” revealed that no significant additional neuropsychological improvement was provided by abacavir compared with placebo [52]. These results are not particularly surprising, because the patients included generally had advanced disease, and many had recently had protease inhibitors added to their treatment regimens.

The following summarizes results of studies of the effect of zidovudine on HIVD in adults with respect to clinical efficacy, dosage, duration of effectiveness, and prophylactic effect (table 2) [4, 46, 53–66]. Results of autopsy studies of the use of zidovudine for HIV encephalitis follow. Studies of combination therapies that included zidovudine generally are not reviewed because it is often difficult to separate the effects of the individual agents in these reports.

Studies of clinical efficacy. In a 1987 study, Yarchoan et al. [53] followed four patients (two with HIVD, one with HIVD and peripheral neuropathy, and one with paraplegia) taking zidovudine. In three cases, zidovudine at 1,500 mg/day was
Table 2. Studies of zidovudine in adults with HIV dementia.

<table>
<thead>
<tr>
<th>Type of study, reference</th>
<th>n</th>
<th>Study design</th>
<th>Duration</th>
<th>Diagnosis</th>
<th>Daily AZT dose</th>
<th>HIVD-related outcomes</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Studied of clinical efficacy</td>
<td></td>
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</tr>
<tr>
<td>Yarchoan et al. [53]</td>
<td>4</td>
<td>Case reports</td>
<td>Unknown</td>
<td>2, HIVD; 1, HIVD plus neuropathy; 1, paraplegia</td>
<td>1,500 mg orally (n = 3); 5 mg/kg iv q4h (n = 1)</td>
<td>Cognition; motor skills</td>
<td>3 patients with HIVD showed improvement; 1 patient with paraplegia did not</td>
</tr>
<tr>
<td>Schmitt et al. [54]</td>
<td>262</td>
<td>R, DB, PC trial</td>
<td>Planned for 24 w; ended at 16 w</td>
<td>150, AIDS; 112, ARC</td>
<td>1,500 mg (n = 134); placebo (n = 128)</td>
<td>Affect; cognition; motor skills</td>
<td>Significant improvement in AZT group in cognition and motor areas; no difference in affect; study ended early because of decreased mortality in AZT group</td>
</tr>
<tr>
<td>Portegies et al. [55]</td>
<td>40</td>
<td>Retrospective</td>
<td>1–32 mo</td>
<td>HIVD</td>
<td>400–1,200 mg (n = 10); no AZT (n = 20); unknown (n = 10)</td>
<td>Cognition; motor skills</td>
<td>3 patients receiving AZT showed marked improvement for 16–32 mo; 2 patients receiving AZT showed slight improvement</td>
</tr>
<tr>
<td>Nordic Medical Research Council [56]</td>
<td>474</td>
<td>R, DB, MC trial</td>
<td>Median, 19 mo</td>
<td>AIDS (n = 126); HIV symptoms (n = 248); low CD4+ cell count (n = 100)</td>
<td>400 mg (n = 160); 800 mg (n = 158); 1,200 mg (n = 156)</td>
<td>Quality of life</td>
<td>Fewer cases of HIVD at higher doses (P &lt; .06); no difference in quality of life measures</td>
</tr>
<tr>
<td>Sidtis et al. [57]</td>
<td>40</td>
<td>R, DB, PC, MC trial</td>
<td>64 w</td>
<td>HIVD</td>
<td>1,000 mg (n = 12); 2,000 mg (n = 12); placebo (n = 15)</td>
<td>Cognitive; motor skills</td>
<td>Averaged across tests, found significant improvement in 2,000 mg group vs. placebo; 1,000 mg group intermediate</td>
</tr>
<tr>
<td>Tozzi et al. [58]</td>
<td>30</td>
<td>Open</td>
<td>12 mo</td>
<td>HIVD</td>
<td>500 mg (n = 13); 750 mg (n = 8); 1,000 mg (n = 9)</td>
<td>Cognitive; motor skills</td>
<td>73% showed some improvement within 3 mo and 83% after 6 mo; AZT dose not correlated with response; 8 patients had neurological deterioration after 6–12 mo of treatment</td>
</tr>
<tr>
<td>Brouwers et al. [59]</td>
<td>38</td>
<td>R trial</td>
<td>12 w</td>
<td>CNS compromised, 21 (12, HIVD); normal, 17</td>
<td>Simultaneous vs. alternating AZT and ddI; alternating doses: 600 mg of AZT, 500 mg of ddI</td>
<td>Cognitive; motor skills</td>
<td>Improvement seen in both groups; no overall difference between groups</td>
</tr>
<tr>
<td>Studied of duration of effect*</td>
<td></td>
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<tr>
<td>Reinvang et al. [60]</td>
<td>11</td>
<td>Open</td>
<td>12 mo</td>
<td>HIVD (n = 6); AIDS (n = 5)</td>
<td>800–2,000 mg AZT: 24 with AIDS; no AZT: 9 with AIDS; 16 with HIV infection</td>
<td>Cognitive</td>
<td>Improvement in HIVD group after 4–6 mo of treatment; deterioration after 9–12 mo</td>
</tr>
<tr>
<td>Karlsen et al. [61]</td>
<td>49</td>
<td>Open</td>
<td>30.3 mo</td>
<td>AIDS (n = 33); HIV (n = 16)</td>
<td>AZT: 24 with AIDS; no AZT: 9 with AIDS; 16 with HIV infection</td>
<td>Cognitive; motor skills</td>
<td>Improvement in AIDS group receiving AZT at 6 months; decline in functioning at 12 months in AZT group</td>
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<tr>
<td>Studied of prophylactic effect</td>
<td></td>
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<tr>
<td>Portegies et al. [46]</td>
<td>196</td>
<td>Retrospective</td>
<td>6 y</td>
<td>AIDS and neurological symptoms</td>
<td>AZT (n = 89); no AZT (n = 107)</td>
<td>Diagnosis of HIVD; p24 antigen in CSF</td>
<td>Decreased incidence of HIVD paralleled increased use of AZT; significantly fewer patients treated with AZT had HIVD (P &lt; .0001) or p24 antigen in CSF (P = .0002)</td>
</tr>
<tr>
<td>Volberding et al. [62]</td>
<td>1,338</td>
<td>R, DB, PC trial</td>
<td>Mean, 55 w</td>
<td>Asymptomatic HIV; no HIVD</td>
<td>500 mg (n = 453); 1,500 mg (n = 457); placebo (n = 428)</td>
<td>Development of HIVD</td>
<td>HIVD developed in 2 patients in placebo group, 1 patient in 1,500 mg group, 0 patients in 500 mg group</td>
</tr>
</tbody>
</table>
administered orally, while one patient received the drug via iv infusion. Neurophysiological tests, including nerve conduction studies and positron emission tomography, as well as tests of cognition and motor skills, were conducted before and during administration of zidovudine. The authors reported that the condition of the three patients with HIVD improved while that of the patient with paraplegia did not. Notably, paraplegia is a symptom more commonly associated with myelopathy than with HIVD.

A randomized, double-blind trial of zidovudine (1,500 mg/day, n = 134) vs. placebo (n = 128) included 150 patients with AIDS and 112 patients with AIDS-related complex [54]. The study was planned for 24 weeks but was discontinued after 16 weeks when significantly decreased mortality in the zidovudine group was detected. Among neuropsychological outcomes, cognition (attention and memory) and motor skills were found to be significantly improved at both weeks 8 and 16 among patients receiving zidovudine (P < .05) and especially among AIDS patients receiving the drug. No overall significant difference in affect was detected between patients in the zidovudine and placebo groups. Although findings are limited by the short duration of the study, the authors concluded that zidovudine can reduce HIV-associated neuropsychological abnormalities.

Records of 536 HIV-infected patients with neurological symptoms were retrospectively reviewed at the Academic Medical Centre in Amsterdam between 1982 and 1992 [55]. Forty patients met U.S. Centers for Disease Control and Prevention criteria for HIVD, and 39 of these were not taking zidovudine at the time of diagnosis. Twenty of the 40 never received zidovudine, 10 received zidovudine at unreported stages of the disease, and 10 began receiving the drug at dosages of 400–1,200 mg/day after being diagnosed with HIVD. Of these latter 10, 3 showed marked improvement with respect to cognition and motor skills (by at least one HIVD stage), with improvement lasting for 16, 24, and 32 months; 2 additional patients in this group showed slight improvement. Although the authors concluded that zidovudine may improve symptoms in patients with HIVD, the retrospective design, small sample size, and variable dosage of zidovudine limit the generalizability of the results.

In summary, although there are limitations in trial designs, the results of these early studies suggest that zidovudine can result in significant improvements in cognition and motor skills in some patients with HIVD. The dosage of zidovudine needed to attain these effects has been the subject of additional research.

**Studies of dosage.** The Nordic Medical Research Council’s HIV Therapy Group conducted a randomized, double-blind, parallel-group, multicenter trial comparing the outcomes of 474 patients with AIDS (n = 126), HIV-related symptoms (n = 248), or low CD4+ cell counts (n = 100) who received daily doses of either 400 mg (n = 160), 800 mg (n = 158), or 1,200 mg (n = 156) of zidovudine for a median of 19 months [56]. The quality of life was evaluated monthly by both the patient and the physician; laboratory and clinical evaluations also were done monthly. Although HIVD was not a primary outcome variable, fewer cases of HIVD were diagnosed among
patients receiving higher dosages of zidovudine (8%, 6%, and 3% for dosages of 400 mg/day, 800 mg/day, and 1,200 mg/day, respectively; \( P = .06 \)). No significant differences among groups were demonstrated in quality of life assessed by either physicians or patients. Because the incidences of anemia and leukopenia were dose-related, the authors concluded that zidovudine should be limited to daily doses of between 400 mg and 600 mg in AIDS patients, in spite of the difference in the incidence of dementia as noted above.

The ACTG conducted a randomized, double-blind, placebo-controlled, multicenter trial of zidovudine treatment of HIVD [57]. Forty patients were randomly assigned to receive either 1,000 mg (\( n = 12 \)) or 2,000 mg (\( n = 13 \)) of zidovudine or placebo (\( n = 15 \)) and were followed for an average of 64 weeks. Neuropsychological tests were done at baseline and every 4 weeks. When the data were averaged across tests, patients taking zidovudine were found to have significant improvement in symptoms at 16 weeks compared with those in patients taking placebo (\( P = .046 \)). With respect to pairwise comparisons, however, only the comparison between the groups receiving zidovudine at 2,000 mg/day and placebo was significant, with an intermediate level of improvement noted in the group receiving 1,000 mg/day. Patients from the placebo group who were re-randomized to one of the two zidovudine groups (\( n = 12 \)) showed significant improvement across neuropsychological tests between weeks 16 and 32 (\( P < .01 \)); substantial loss to follow-up during the final 32 weeks of the study limited analyses. Although the authors concluded that zidovudine treatment benefits patients with HIVD, the study was limited by its small sample size, high dropout rate, and failure to demonstrate a clear optimal dose of zidovudine.

An open study of 30 consecutive patients with HIVD focused on the effect of long-term zidovudine treatment on severity of dementia [58]. The sample was stratified by baseline hemato logic status and absolute neutrophil count, and patients were assigned to receive one of three daily zidovudine doses: 500 mg (\( n = 13 \)), 750 mg (\( n = 8 \)), or 1,000 mg (\( n = 9 \)). Reversal to a less severe HIVD category, as determined by use of Price and Brew’s staging system, was observed after 1, 3, 6, 9, and 12 months for 15, 22, 25, 19, and 14 patients, respectively. Overall, 73% of patients showed some improvement within 3 months and 83% after 6 months of treatment. Although zidovudine dose was not correlated with response, among the eight patients having neurological deterioration after 6–12 months of drug therapy, five were receiving the lowest dosage of zidovudine (500 mg daily). Reduced dosages of zidovudine were administered to eight patients who developed hematologic toxicity after an average of 4.5 months of treatment and to an additional five patients who developed bone marrow toxicity after an average of 5 months of treatment. Despite the fact that the study was limited by its lack of a control group and by its small sample size, the authors concluded that use of zidovudine was associated with a reversal of neurological dysfunction in patients with HIVD.

The effect of treatment with alternating vs. simultaneous regimens of zidovudine and didanosine on the cognitive and motor skills of patients with symptomatic HIV infections was studied in a randomized, unblinded trial that evaluated 38 patients [59]. Twenty-one patients (12 with HIVD) exhibited CNS symptoms. Patients in the simultaneous treatment group received 300 mg of zidovudine and 250 mg of didanosine daily for 12 weeks; both doses were approximately half of that usually recommended. Remaining patients alternated between 600 mg of zidovudine daily for 3 weeks or 500 mg of didanosine daily for 3 weeks. Significant improvement in neuropsychological function, particularly memory and attention, was seen with both therapeutic regimens (\( P < .01 \)), and patients with CNS symptoms at the beginning of the trial showed the most improvement. The authors concluded that combination regimens of zidovudine and didanosine reduce HIV-induced CNS symptoms, while noting that the small sample and relatively low dosages of drugs administered limited the generalizability of results.

In summary, although there does appear to be a dose-response effect with zidovudine, the optimum dosage of the drug in patients with or at risk for HIVD is not clearly demonstrated by these studies. Controlled trials are needed to evaluate the relative effects of various drug dosages, particularly in the lower-dose regimens conventionally used in current practice.

Studies of duration of effect. The duration of treatment effect with zidovudine therapy was evaluated as part of more comprehensive studies by Portegies et al. [55] and Tozzi et al. [58]. In the former, a retrospective study of 40 patients with HIVD, 5 of the 10 patients who began zidovudine treatment after HIVD was diagnosed showed improvement in symptoms, with 3 showing notable improvement that lasted for 16, 24, and 32 months. Similarly, Tozzi et al. observed that 8 (31%) of the 26 patients who showed some improvement in neuropsychological functioning had clinical relapses after 6–12 months of treatment.

Reinvang et al. [60] conducted a small, open study of 11 AIDS patients (6 with HIVD) being treated with zidovudine in doses ranging from 800 mg to 2,000 mg daily. Overall, cognitive functioning improved during the first 4–6 months of the trial, although the trend was only “weakly significant.” This improvement was not evident at the second follow-up after 9–12 months of treatment. On the basis of these findings, the authors expressed doubt concerning the long-term benefits of zidovudine in the treatment of AIDS patients with HIVD. It is notable, however, that the power of the study to detect differences was low, given the small sample and the fact that a wide range of dosages of zidovudine was administered.

In a continuation of this study, 33 AIDS patients and 16 asymptomatic HIV-positive patients were followed for an av-
verage of 30.3 months [61]. No asymptomatic patient received zidovudine, while 24 of the 33 AIDS patients took the drug. Zidovudine-treated AIDS patients showed significantly greater improvement on neuropsychological tests administered 6 months after baseline than did either AIDS patients not treated with zidovudine or asymptomatic patients who did not receive the antiretroviral treatment (P < .05). By 12 months, however, the mean performance of zidovudine-treated AIDS patients had declined in all areas, and significantly so in verbal abilities (P < .05). The authors concluded that the effect of zidovudine appears to be transient, even though neither analyses of data for the full follow-up period nor dosages of zidovudine were provided.

Taken together, these studies suggest that the benefits of zidovudine are time-limited. This tentative conclusion awaits confirmation by the results of prospective, randomized, placebo-controlled trials of the duration of effects of various dosages of zidovudine as well as its interactions with other antiretrovirals used in combination therapies.

Studies of prophylactic effect. There have been several studies of the possible prophylactic effect of zidovudine that used development of HIVD as the primary outcome variable. A retrospective study of a consecutive series of AIDS patients evaluated the incidence of HIVD and the presence of HIV-1 p24 antigen in CSF in relation to zidovudine treatment [46]. This research capitalized on the fact that zidovudine was not available in The Netherlands before May 1987 but was used routinely for patients with severe HIV infection after that time. Of the 196 AIDS patients with neurological symptoms seen at the AIDS unit at the Academic Medical Centre in Amsterdam between 1982 and 1988, 40 (20%) had HIVD and 89 (45%) received zidovudine. The incidence of HIVD decreased as the use of zidovudine increased: the proportion of patients using the drug was 26% at the end of June 1987 and 84% at the end of 1988, while the incidence of HIVD was 21% in the last half of 1985, 53% in the first half of 1987, 10% in the second half of 1987, and 3% in 1988. Compared with patients who did not take zidovudine, significantly fewer of those who took the drug developed HIVD (38 [36%] of 107 vs. 2 [2.3%] of 89; P < .0001) or had p24 antigen in their CSF (16 [26%] of 61 vs. 0 of 37; P = .0002). The authors concluded that the introduction of zidovudine in The Netherlands was accompanied by a “striking decline” in HIVD. They speculated that zidovudine may prevent HIVD by inhibiting reactivation of viral replication. It is important to note that although the authors state that the same diagnostic criteria for HIVD were used throughout the study, other parameters, such as concomitant drug therapy or earlier detection of disease, may have changed over time and affected the results of this retrospective study.

The ACTG conducted a randomized, double-blind, placebo-controlled trial of the prophylactic effect of zidovudine [62]. The sample included 1,338 HIV-positive subjects with CD4+ cell counts of <500/mm³ and normal neuropsychiatric functioning. Patients received either placebo (n = 428) or 500 mg (n = 453) or 1,500 mg (n = 457) of zidovudine daily and were followed for an average of 55 weeks. Measures included the drug’s ability to forestall a variety of complications, including HIVD, in HIV-infected patients. HIVD developed in two patients in the placebo group, one in the group receiving 1,500 mg of zidovudine, and none in the group receiving 500 mg of zidovudine. Rates of anemia and neutropenia were significantly higher in the group receiving 1,500 mg of zidovudine than in either the placebo group or the group receiving 500 mg of zidovudine (P < .0001). The authors concluded that zidovudine is safe and effective in this group of patients, although the rates of development of HIVD were too low in all groups to quantify a protective effect of zidovudine.

The effect of early vs. late administration of zidovudine has been the focus of two studies [63, 64]. The Veterans Affairs Cooperative Study Group on AIDS Treatment compared outcomes in symptomatic HIV-positive patients with no HIVD who received daily doses of 1,500 mg of zidovudine either early (n = 170; i.e., for the entire study period) or late (n = 168; i.e., after the patient’s CD4+ cell count was <200/mm³) in infection [63]. HIVD was identified in six patients in the late-therapy group but in none of those receiving early therapy (statistical significance not reported). Leukopenia and anemia occurred at similar rates in both the early and late groups (82% vs. 77% for leukopenia and 20% vs. 16% for anemia). The authors concluded that use of zidovudine deserves consideration in both symptomatic and asymptomatic HIV-positive patients with low CD4+ cell counts.

In the other study of the timing of zidovudine therapy, the Concorde Coordinating Committee randomly assigned 1,749 asymptomatic HIV-positive patients to receive 1,000 mg of zidovudine daily early (n = 877; i.e., from the time of randomization) or to have treatment deferred (n = 872) [64]. Of those deferred, 418 patients eventually received zidovudine at the onset of AIDS-related complex or AIDS or the development of a persistently low CD4+ cell count. Patients were followed for a median of 3.3 years, during which HIVD was the AIDS-defining illness in six patients of the early-zidovudine group and in seven of the deferred-zidovudine group. Anemia and neutropenia developed earlier in the early-therapy group. The authors concluded that these results did not support the early use of zidovudine for HIV-infected persons who were free of symptoms.

A prospective, open study followed nearly 500 homosexual men with AIDS for up to 7 years [4]. Zidovudine dosage was variable but averaged <600 mg daily. Although 15% of those studied developed dementia before death, use of zidovudine either before or after AIDS developed did not predict the occurrence of HIVD. (Pre-AIDS hemoglobin level was the most significant predictor of HIVD.) The authors suggested that although zidovudine appears to delay the development of AIDS, any additional protective effects against HIVD might be
reduced once AIDS develops. They also noted, however, that the average dosage of zidovudine in this study may have been too low to provide prophylaxis.

The Multicenter AIDS Cohort Study, an ongoing, longitudinal study, described trends in the incidence of HIV-related neurological disorders in four metropolitan areas in the United States: Baltimore-Washington, Chicago, Pittsburgh, and Los Angeles [65]. Information concerning HIVD and sensory neuropathy was analyzed for 2,641 men who were HIV-1-seropositive. The incidence of HIVD did not change significantly between 1988 and 1992 in this sample, and no protective effect of antiretroviral use could be inferred. These results do not confirm the decline in HIVD reported by Portegies et al. [46]; however, because the major decrease in The Netherlands occurred before 1988, the time frame of the Multicenter AIDS Cohort Study (1988–1992) may have resulted in its missing any effect of zidovudine on the incidence of HIVD in these U.S. cities.

Finally, Baldeweg et al. [66] retrospectively reviewed records of 141 HIV-infected men who had received care for a median of 1 year at HIV outpatient clinics. The sample was stratified according to current (n = 67) vs. not current (n = 74) zidovudine use and to whether the patient had asymptomatic HIV (n = 60), symptomatic HIV (n = 51), or AIDS (n = 30). At a median zidovudine dose of 500 mg, lower neuropsychological functioning was associated with stage of HIV infection; overall, no effect of current zidovudine use on neuropsychological functioning was found. Among symptomatic HIV-infected and AIDS patients, significantly fewer of those currently taking zidovudine exhibited abnormalities detectable by electroencephalography (P < .05). Of the 98 men who had used zidovudine either for <1 month (short-term group, n = 61) or for ≥1 year (long-term group, n = 37), patients with long-term zidovudine use with either symptomatic HIV infection or AIDS had significantly higher scores on tests of cognition than did those in corresponding short-term groups (P < .01). The authors concluded that long-term zidovudine therapy may reduce neurological, neuropsychological, and electrophysiological abnormalities, thereby decreasing the risk for HIVD. The study is limited, however, by its natural history design, which does not support an assessment of cause and effect, and its exclusion of women.

Taken together, these studies suggest that zidovudine may forestall the development of HIVD in some patients, particularly when zidovudine is used before symptoms are evident [63]. Large, prospective clinical trials that include both symptomatic and asymptomatic patients treated at various stages of illness are required to adequately address this question.

**Autopsy studies.** Results of autopsy studies of HIV encephalitis support the efficacy of zidovudine (table 3) [18, 67–70]. Vago et al. [67] evaluated autopsy results for 202 patients who died at the Clinic of Infectious Diseases, Sacco Hospital, in Milan between 1984 and 1990. Overall, 82 patients had taken zidovudine in doses of 600–1,000 mg daily orally for 1–30 months. The incidences of multinucleated giant cells, HIV leukoencephalopathy, and a history of severe dementia were significantly lower in the zidovudine group (P ≤ .05). HIV encephalitis and HIV encephalitis plus HIV leukoencephalopathy were found less frequently in the zidovudine group, but the differences were not significant. The effects of zidovudine were time- and dose-related, with the maximum effect in patients treated for 6–12 months and at cumulative doses of >200 g. These results are similar to those of an autopsy study in the United States of 56 patients who died of AIDS [18]. Among the 40 who had HIVD, significantly fewer of those treated with antiretroviral medication for >12 months (n = 10) exhibited multinucleated giant cells and/or diffuse myelin pallor than did those who had used the drugs for shorter time frames (n = 14) or not at all (n = 16) (P ≤ .05).

Several studies evaluated the effect of taking zidovudine until shortly before the patient’s death. Gray et al. [68] examined the CNS of 192 patients dying of AIDS between 1982 and 1992. The prevalences of both multinucleated giant cells and HIV encephalitis plus HIV leukoencephalopathy were significantly lower among patients who took zidovudine for >3 months and until shortly before death (n = 72) than among patients not treated with zidovudine (n = 97) (P ≤ .01). The fact that the prevalence of markers of HIV activity in the brain was intermediate for the group who discontinued zidovudine treatment at least 1 month before death (n = 23) led the authors to conclude that discontinuing zidovudine may increase the risk of HIV encephalitis. Maehlen et al. [69] compared outcomes among four groups of patients: those who had never taken zidovudine (n = 50) and those who took zidovudine for >2 months and stopped treatment at ≤1 month (n = 29) vs. at 2–6 months (n = 23) vs. at >6 months (n = 26) before death. The incidence of multinucleated giant cells was inversely related to the length of time since zidovudine treatment was discontinued (percentage with multinucleated giant cells of 7%, 30%, and 35% if zidovudine was discontinued at ≤1 month, 2–6 months, and >6 months before death, respectively) but was less closely associated with the presence of either diffuse white matter damage or microglial nodules. The authors concluded that zidovudine reduced the risk of brain lesions only if treatment was continued until the patient was near death. Finally, Bell et al. [70] evaluated autopsy results for 66 patients who died of AIDS and correlated use of zidovudine with HIV encephalitis and with pre-death neurophysiological and neuropsychological tests. Zidovudine use, particularly when it was used within 1 year of death, was significantly associated with lower risks of HIV encephalitis (P < .01) and of cognitive impairment (P < .05). The effect on HIV encephalitis remained, even when adjusted for the lifetime dosage of zidovudine.
Results of evaluations of epidemiological surveys, clinical trials, CSF assays, and autopsy studies lead to several conclusions concerning the use of antiretrovirals, particularly zidovudine, in the prevention and treatment of HIVD among adults.

Although the pathophysiology of HIVD remains to be fully explicated, the reduction in HIV or its attendant markers in CSF probably should be an important goal of therapy. In this regard, antiretroviral therapy has been found to be associated with decreased levels of HIV-1 p24 antigen in CSF [46, 47, 49]. Although direct assays of HIV RNA in CSF have only recently been used, several groups have reported reductions in HIV load in CSF concomitant with antiretroviral therapy [46, 47, 49].

Postmortem studies have confirmed that patients treated with zidovudine, especially for 1 year and until shortly before death, have fewer HIV-related changes in brain tissue, that is, a lower prevalence of multinucleated giant cells and of HIV encephalitis and HIV leukoencephalopathy, than do comparable patients who were not treated with zidovudine or whose therapeutic time frames were dissimilar [18, 67–70].

Table 3. Autopsy studies of zidovudine treatment among adults who died of AIDS.

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Study time frame</th>
<th>Dosage and duration of AZT use</th>
<th>Outcomes measured</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vago et al.</td>
<td>202</td>
<td>1984–1990</td>
<td>600–1,000 mg daily for 1–30 mo (n = 82); no AZT (n = 120)</td>
<td>MGCs; HIVE; HIVE + HIV; history of dementia</td>
<td>MGCs and HIVL significantly lower in AZT group (P &lt; .02); HIVE and HIVL less frequent in AZT group (NS); severe dementia significantly less frequent in AZT group (P &lt; .03); effects of AZT time- and dose-related, with maximum effect in patients treated for 6–12 mo and at cumulative doses of &gt;200 g</td>
</tr>
<tr>
<td>Glass et al.</td>
<td>56 (40 with HIVD)</td>
<td>Not reported</td>
<td>No antiretroviral, or use for &lt;3 mo (n = 16); antiretroviral for 3–12 mo (n = 14); antiretroviral for &gt;12 mo (n = 10)</td>
<td>MGCs; diffuse myelin pallor; microglial nodules; perivascular cuffs</td>
<td>Use of antiretroviral for &gt;12 mo significantly associated with fewer MGCs and less diffuse myelin pallor (P &lt; .05)</td>
</tr>
<tr>
<td>Gray et al.</td>
<td>192</td>
<td>1982–1992</td>
<td>No AZT (n = 97); AZT discontinued &gt;1 mo before death (n = 23); AZT taken for &gt;3 mo and till death (n = 72)</td>
<td>HIVE/HIVL; MGCs</td>
<td>Prevalence of MGCs and of HIVE + HIVL significantly lower in AZT-till-death group than in no-AZT group (P &lt; .01); discontinuing AZT may increase risk of HIVE</td>
</tr>
<tr>
<td>Maehlen et al.</td>
<td>128</td>
<td>1983–1994</td>
<td>No AZT (n = 50); AZT (usually 600 mg/d) for &gt;2 mo and terminated ≤1 mo (n = 29), 2–6 mo (n = 23), or &gt;6 mo (n = 26) before death</td>
<td>MGCs; diffuse damage of white matter; microglial noduli</td>
<td>Incidence of MGCs inversely related to whether AZT was taken until patient was close to death; AZT reduced risk of brain lesions only if continued until near death</td>
</tr>
<tr>
<td>Bell et al.</td>
<td>66</td>
<td>1990–?</td>
<td>Never or &lt;6 w; &gt;6 w but stopped &gt;1 y before death; &gt;6 w and used within 1 y of death (n’s not reported)</td>
<td>HIVE; cognitive impairment (neurophysiological and neuropsychological tests)</td>
<td>AZT use, particularly when used within 1 y of death, associated with lower risk of HIVE (P &lt; .01); association remained when adjusted for lifetime dose of AZT; AZT use also associated with reduced risk of cognitive impairment (P &lt; .05)</td>
</tr>
</tbody>
</table>

NOTE. AZT = zidovudine; HIVE = HIV encephalitis; HIVL = HIV leukoencephalopathy; MGCs = multinucleated giant cells.

Summary

Results of evaluations of epidemiological surveys, clinical trials, CSF assays, and autopsy studies lead to several conclusions concerning the use of antiretrovirals, particularly zidovudine, in the prevention and treatment of HIVD among adults. Although the pathophysiology of HIVD remains to be fully explicated, the reduction in HIV or its attendant markers in CSF probably should be an important goal of therapy. In this regard, antiretroviral therapy has been found to be associated with decreased levels of HIV-1 p24 antigen in CSF [46, 47, 49]. Although direct assays of HIV RNA in CSF have only recently been used, several groups have reported reductions in HIV load in CSF concomitant with antiretroviral therapy [50, 51]. The clinical relevance of HIV load in CSF remains unclear, although preliminary observations suggest that an increase in level of HIV RNA in CSF correlates with a decline in cognitive status [21, 22].

Postmortem studies have confirmed that patients treated with zidovudine, especially for >1 year and until shortly before death, have fewer HIV-related changes in brain tissue, that is, a lower prevalence of multinucleated giant cells and of HIV encephalitis and HIV leukoencephalopathy, than do comparable patients who were not treated with zidovudine or whose therapeutic time frames were dissimilar [18, 67–70].
In The Netherlands, the incidence of HIVD declined sharply following the introduction of zidovudine [46]. In addition, several studies directly linked the use of zidovudine with improved neuropathologic functioning, particularly with improvements in cognition and motor skills, among patients with AIDS and HIVD [46, 53–55, 65]. Such improvements, however, appear to be time-limited, generally becoming evident in the first 4–6 months of treatment but reverting toward baseline within 6–12 months [55, 58, 60, 61]. The optimum dosage of zidovudine has not been clearly demonstrated, although maximum response may occur at 1,000–2,000 mg/day [57]. Finally, zidovudine therapy, especially among asymptomatic HIV-infected patients and particularly at higher dosages, may have a prophylactic effect against HIVD [63]. Future studies must assess the effect of other antiretroviral agents as well as of therapies aimed at indirect pathophysiological factors (e.g., cytokines, excitotoxins, channel abnormalities) in the prophylaxis and treatment of HIVD.

**HIV Encephalopathy in Children**

**Epidemiology, Clinical Features, and Pathogenesis**

Neurological disease is the initial presenting condition in ≤5% of adult patients with HIV infection but in up to 18% of children and adolescents [19]. Overall, estimates of the incidence of HIV encephalopathy among children with AIDS range from 30% to 60% [15, 19, 71], while as many as 88% of children with symptomatic HIV disease exhibit CNS abnormalities [72].

Among adults, HIV is transmitted between individuals primarily by horizontal methods—by sexual contact or behaviors related to drug use. In contrast, more than three-quarters of cases among children are transmitted vertically (perinatally) [19, 73]. CNS infection may occur early in fetal development, and infection at these early stages may explain why symptoms of HIV encephalopathy tend to develop more rapidly in children than in adults [19, 73].

The neurological course of HIV encephalopathy in children generally falls into one of three categories: subacute progressive, plateau progressive, and static [73]. In subacute progressive encephalopathy (PE), children at first develop slowly but normally; then, social, language, and motor skills begin to be lost. Acquired microcephaly may indicate slowed brain growth, and HIV-1 p24 antigen may be detected in CSF. Children demonstrating plateau PE also develop initially at a slow but normal pace; then there is a decline in the rate of developmental progress, with little or no further acquisition of skills. Acquired microcephaly again is present, but CSF usually is negative for HIV-1 p24 antigen. Finally, a minority of children (~25%) have static encephalopathy. These children are late to acquire motor and language skills, are cognitively impaired, and acquire skills slowly. Brain scans and CSF evaluations generally are normal. As with adult HIVD, the pathogenesis of childhood HIV encephalopathy is uncertain. Severity of pathological findings usually correlates with clinical status, but in some children with evidence of PE at autopsy, there is no evidence of significant replication of HIV-1 or of inflammatory changes in the CNS [74]. Children with HIV encephalitis also demonstrate the unusual pathological feature of calcifications and vascular mineralizations in the brain [75]. It has been suggested that increased viral replication and emergence of drug-resistant HIV variants within the CNS may affect the development of PE [76].

**Treatment**

As in adults, there is evidence that zidovudine decreases levels of HIV-1 p24 antigen in CSF of children with PE [77, 78]. McKinney et al. [78] measured levels of p24 antigen in CSF of 51 children between 3 months and 12 years of age. Eighteen (35%) were positive for the antigen at baseline. After 6 months of treatment with zidovudine, eight patients who had tested positive at baseline underwent follow-up CSF testing; all eight showed a decrease in p24 antigen concentrations, and six (75%) tested negative for the antigen. Sixteen of the 33 patients who were negative at baseline had lumbar punctures after 6 months of zidovudine treatment; one then tested positive for p24 antigen. Laverda et al. [77] performed immunologic and virological studies on the CSF of 15 HIV-infected children (4 with PE) before and at least 6 months after treatment with 600 mg/(m² · d) [77]. Substantial declines from baseline were observed in levels of IL-6, IL-1β, and p24 antigen in CSF.

Several studies have evaluated the clinical efficacy of zidovudine treatment of PE (table 4) [78–83].

**Studies of efficacy.** In a phase I clinical trial, Pizzo et al. [79] evaluated changes in cognitive and adaptive functioning after 6 months of zidovudine therapy among 13 children ages 6 months to 12 years with symptoms of AIDS. Eight of the children had clinical evidence of encephalopathy before receiving drug therapy. Zidovudine was administered iv in dosages of 0.5, 0.9, 1.4, or 1.8 mg/(kg · h) depending on time of study entry. Development of neutopenia was common and dose-related. Significant improvement was found in cognitive scores for children with and without PE at presentation at all dosage levels (P < .01). Improvements were noted quickly, within 3–4 weeks of initiation of therapy, at all dosage levels and generally were steady and maintained throughout the follow-up period. In an extension of this study, the 13 children were reevaluated after 12 months of zidovudine therapy [80]. Gains noted at 6 months in both cognitive functioning and adaptive behavior were largely maintained in children with and without PE. Although these studies were small and used an open-label design, the authors concluded that zidovudine can benefit children with symptomatic HIV infection, including those with encephalopathy.

An open-label study of the efficacy of zidovudine at 180 mg/m² orally q6h was conducted among 88 children aged 3...
months through 12 years with either AIDS or advanced HIV disease [78]. Cognitive functioning was tested at baseline and 6 months later among 55 of these children, including 39 with PE. Overall, 23 patients (42%) had increases of ≥8 points on test scores; 10 had increases of ≥15 points. Although children <30 months of age showed significant cognitive improvement ($P < .01$), older children did not. Anemia or neutropenia was reported in 61% of patients; most of these conditions were treated by transfusion, reduced zidovudine dosage, or both. The conclusion would have been strengthened had scores been compared on tests for children with vs. without PE.

Contrasting results were obtained in a study of 54 children ages 2 months to 12 years with HIV infection (4 with PE) included in an open, 1-year protocol examining the effects of oral zidovudine on neurodevelopmental functioning [81]. No significant changes in cognitive functioning were found after 12 months of zidovudine treatment.

Wolters et al. [82] included 25 children (ages 1–12 years) with symptomatic HIV infection (13 with PE) in an open, 6-month study of the effect of zidovudine on cognition, adaptive behavior, and motor skills. Twelve children received zidovudine orally, while 13 received the drug by continuous infusion; medication dosages were not reported. With the exception of motor skills, significant improvements were seen in all neurodevelopmental areas measured between baseline and final testing after 6 months of zidovudine treatment ($P = .01$). Although children with PE had lower scores at baseline, no difference was found in levels of improvement between the groups with and without PE. Route of administration also was not found to affect the magnitude of improvement. The authors concluded that zidovudine administered either orally or by continuous infusion is associated with improvements in cognition and adaptive behavior in children. The generalizability of the results is limited, however, by the small sample size and lack of a control group.

### Studies of dosage

Few studies of optimum dosage levels of zidovudine in children have been conducted. Pizzo et al. [79] concluded that the optimum iv zidovudine dosage ranges from 0.9 to 1.4 mg/(kg · h) on the basis of their findings that there were no significant differences in improvement in cognitive scores in children receiving either 0.5, 0.9, 1.4, or 1.8 mg/(kg · h) but that adverse effects (primarily neutropenia) were more frequent and severe with the higher dosages.

### Table 4. Studies of zidovudine in HIV-infected children with progressive encephalopathy.

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Study design</th>
<th>Mean duration</th>
<th>Diagnosis, patient age range</th>
<th>AZT dose</th>
<th>PE-related outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pizzo et al. [79]</td>
<td>13</td>
<td>Open</td>
<td>6 mo</td>
<td>Symptomatic HIV, 8 with PE; 6 mo–12 y</td>
<td>0.5, 0.9, 1.4, and 1.8 mg/(kg · h) continuous iv</td>
<td>Cognitive; adaptive behavior</td>
<td>Significant improvement in cognitive scores for all children after 6 mo of AZT ($P &lt; .01$); improvement at all dosages, in those with and without PE; most adverse effects at ≥1.4 mg/(kg · h)</td>
</tr>
<tr>
<td>Brouwers et al [80] (continuation of [79])</td>
<td>13</td>
<td>Open</td>
<td>1 y</td>
<td>Symptomatic HIV, 8 with PE; 6 mo–12 y</td>
<td>0.5, 0.9, 1.4, and 1.8 mg/(kg · h) continuous iv</td>
<td>Cognitive; adaptive behavior</td>
<td>Significantly improved cognitive and adaptive behavior scores at 6 mo ($P &lt; .01$); gain largely maintained at 12 mo</td>
</tr>
<tr>
<td>McKinney et al. [78]</td>
<td>55</td>
<td>Open</td>
<td>6 mo</td>
<td>AIDS or advanced HIV disease, 39 with PE; 3 mo–12 y</td>
<td>180 mg/m² p.o. q6h</td>
<td>Cognitive</td>
<td>42% had increases of ≥8 points on test scores; children &lt;30 mo old showed significant cognitive improvement ($P &lt; .02$) but older children did not</td>
</tr>
<tr>
<td>Nozyce et al. [81]</td>
<td>54</td>
<td>Open</td>
<td>1 y</td>
<td>HIV, 4 with PE; 2 mo–12 y</td>
<td>180 mg/m² p.o. q6h</td>
<td>Cognitive</td>
<td>No significant change in cognitive function over 12 mo</td>
</tr>
<tr>
<td>Wolters et al. [82]</td>
<td>25</td>
<td>Open</td>
<td>6 mo</td>
<td>Symptomatic HIV, 13 with PE; 1–12 y</td>
<td>Continuous iv ($n = 13$); p.o. ($n = 12$); does not stated</td>
<td>Cognitive; adaptive behavior; motor skills</td>
<td>Significantly improved ($P &lt; .01$) in all areas except motor skills after 6 mo of treatment; no difference in improvement between children with and without PE or between routes of administration</td>
</tr>
<tr>
<td>Brady et al. [83]</td>
<td>424</td>
<td>R, DB</td>
<td>39 mo</td>
<td>HIV with mild–moderate symptoms, no PE; 3 mo–12 y</td>
<td>90 vs. 180 mg/m² p.o. q6h</td>
<td>Development of PE; cognitive</td>
<td>No significant differences between dosage groups in development of PE, cognitive functioning, or survival</td>
</tr>
</tbody>
</table>

NOTE. All studies were studies of efficacy except [83], which was a study of dosage, and [79], which was both. AZT = zidovudine; DB = double-blind; PE = progressive encephalopathy; R = randomized. Reprinted with permission from The Annals of Pharmacotherapy [1].
were most common in those receiving zidovudine in dosages of 1.4 and 1.8 mg/(kg \cdot h). Because the research was designed to address questions of efficacy and not of dosage, however, this conclusion should be confirmed in additional trials.

Brady et al. [83] conducted a large (n = 424), randomized, double-blind clinical trial of the effects of two oral doses of zidovudine (90 vs. 180 mg/m² q6h) on cognitive functioning. Children included were 3 months to 12 years of age, were HIV-infected, and exhibited mild to moderate symptoms. No patient had PE. Follow-up continued for an average of 39 months, with neuropsychological testing done at 6-month intervals. No significant differences were found between treatment groups at any time point with respect to development of PE, cognitive functioning, or survival. Overall, 39% of patients had at least one episode of grade 3 or greater hematologic toxicity. There was no difference between treatment groups in the rate of such toxicity, although fewer patients receiving low-dose zidovudine developed neutropenia. The authors concluded that in children with mild to moderate HIV disease, the recommended oral dosage of zidovudine should be 90 mg/m² q6h.

Summary

Fewer studies have been conducted of the efficacy and optimal dosing of zidovudine in children than in adults. In these young patients, duration of effect and the potential of zidovudine use for prophylaxis for PE remain to be determined. Overall, zidovudine appears to improve neuropsychological functioning in children infected with HIV [78–80, 82]. Such improvement has been demonstrated in children with and without PE and by use of both oral and iv routes of administration. Currently, controlled trials that follow children for a sufficient period and use neuropsychological, neuroimaging, and virological (in plasma and CSF) end points are needed to establish treatment parameters for zidovudine and combination regimens in this population.

Conclusions

HIVD in adults and PE in children are devastating complications of HIV infection. The prognosis for patients who develop these conditions is uniformly poor and, as the conditions progress, the clinical symptoms that characterize HIVD and PE become increasingly incapacitating.

On the basis of current data, zidovudine is one of the drugs that should be considered as part of combination regimens designed to manage HIVD and PE. In both adults and children, zidovudine use has been associated with decreases in p24 antigen and HIV load in CSF and with improvements in neuropsychological functioning. The length of clinical response varies among individuals but appears to decline after 6–12 months of zidovudine use. Although dose-response relation-

ships have been demonstrated in adults, optimal dosages of zidovudine in adults and children have not been established, and it is not clear when in the course of the infection drug therapy should begin. It is important to note that virtually all patients with HIVD or PE will receive zidovudine in combination with protease inhibitors and/or nonnucleoside reverse transcriptor inhibitors or as part of promising protocols of highly active antiretroviral therapy [84, 85]. Although characteristics of several newer antiretroviral agents and combinations of agents, including their ability to cross the blood-brain barrier, provide some promise in the treatment of HIVD, there are minimal clinical data as yet available to guide their use.

The use of zidovudine is not without attendant problems. Myelosuppression, with anemia and leukopenia, is a prominent side effect [86, 87]. At least in adults, however, instances of significant myelosuppression resulting in anemia and leukopenia generally do not require the discontinuation of zidovudine therapy, because these conditions can be managed with hematopoietic growth factors or transfusions [87–89].

In conclusion, a review of the neurological literature suggests that maintenance treatment of patients with combinations of antiretroviral drugs that include CNS-penetrant agents, such as zidovudine, appears to be a strategy consonant with enhanced quality of life in long-term survivors. Well-designed clinical trials are needed to refine how such therapies should be implemented and to compare their relative efficacies and safety profiles. It is critically important to include neuropsychological end points and to examine a variety of CSF parameters in primary antiretroviral trials to determine the neurological safety and efficacy of these agents.

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References

