Encephalopathy

Evaluation of Human Immunodeficiency Virus (HIV) Type 1 RNA Levels in Cerebrospinal Fluid and Viral Resistance to Zidovudine in Children with HIV Encephalopathy

Shizuko Sei, Sean K. Stewart, Maureen Farley, Brigitta U. Mueller, James R. Lane, Merlin L. Robb, Pim Brouwers, and Philip A. Pizzo

Pediatric Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda; SRA Technologies, Inc., and Department of Retroviral Research, Walter Reed Army Institute of Research, Rockville, Maryland

The amount of human immunodeficiency virus (HIV) type 1 RNA and the presence of a codon 215 mutation indicative of zidovudine resistance were evaluated in cerebrospinal fluid (CSF) and plasma obtained from HIV-1-infected children. The level of HIV-1 RNA in CSF was highest in children with severe encephalopathy \( (n = 25; \text{median}, 430 \text{ copies/mL}; \text{range}, 0-2.2 \times 10^5 \text{ copies/mL}) \) followed by the moderately encephalopathic \( (n = 7; \text{median}, 330; \text{range}, 0-1130) \) and nonencephalopathic groups \( (n = 9; \text{median}, 0; \text{range}, 0-566) \). There was no correlation between CSF and plasma HIV-1 RNA levels. Five of 7 children with the codon 215 mutation in CSF had a progression of encephalopathy, while all 8 children with wild type codon 215 had improved or stable disease during zidovudine treatment \( (P = .007) \). These findings suggest that increased viral replication and emergence of drug-resistant HIV-1 variants within the central nervous system may play a role in progression of HIV encephalopathy.

Human immunodeficiency virus (HIV) type 1–associated encephalopathy, or HIV encephalopathy, is a syndrome that includes motor and cognitive dysfunction, seen especially in patients with advanced HIV disease \([1-3]\). These HIV-1–induced neurologic consequences may be more frequent in children, few of whom have other confounding central nervous system (CNS) opportunistic conditions compared with adult patients with AIDS \([4, 5]\). HIV-1 has been detected in brain tissues and cerebrospinal fluid (CSF) obtained from patients with AIDS, especially those with HIV encephalopathy \([6-9]\). Although the precise mechanisms remain uncertain, mounting evidence suggests that active HIV-1 infection of macrophages or microglia within the CNS may induce neurovirulent conditions, resulting in neurologic disturbance and neuronal death \([10-12]\).

Administration of zidovudine has been shown to be beneficial in treating persons with HIV encephalopathy \([13-16]\). Dramatic improvement in performance scores and brain computed tomographic (CT) findings has been demonstrated in HIV-encephalopathic children who received zidovudine \([17-19]\). While the concentration of zidovudine in CSF is \( \sim 25\% \) of the plasma concentration under steady-state conditions \([20]\), other nucleoside reverse transcriptase inhibitors have a lower CNS penetration \([21, 22]\), and this may account in part for the variable neurologic responses in patients treated with such agents \([23]\). Even though zidovudine may effectively reverse or improve neurologic symptoms of HIV encephalopathy, its effect can be transient \([24, 25]\). The onset of CNS symptoms may be a part of progressive HIV disease that can be associated with an increasing virus burden in peripheral blood \([26]\). It is, however, unclear whether the level of viral replication within CNS is also up-regulated in patients with HIV encephalopathy.

In the current study, we evaluated the amount of HIV-1 RNA and presence of the mutation conferring viral resistance to zidovudine in CSF and plasma obtained from HIV-1–infected children with or without encephalopathy. We also examined whether the presence of zidovudine-resistant HIV-1 in CSF affected the neurologic outcome during treatment with zidovudine.

Methods

Patients and clinical specimens. Lumbar punctures were done in selected children referred to the Pediatric Branch, National Cancer Institute, between October 1990 and September 1995, to determine their eligibility for various clinical protocols or as a part of follow-up studies associated with protocols. Patients with acute onset of neurologic symptoms, who required CSF examination, were excluded from this study. The state of the immune function at the time of lumbar puncture was classified according to the CDC classification system \([27]\).

CSF was collected under a normal sterile procedure, and an aliquot was sent for routine laboratory testing. The cellular component was removed from the remaining CSF by centrifugation at 900 g for 15 min, and CSF was stored at \(-70^\circ\text{C} \) until used for viral RNA analyses and evaluation of HIV-1 p24 antigen level. Plasma samples were processed from anticoagulated whole blood specimens obtained within 1 week of lumbar punctures (within 24
Evidence of HIV encephalopathy was assessed by clinical history, age-appropriate comprehensive neuropsychometric test, and brain CT. The median time of the tests in relation to lumbar puncture was 6 days (6 days before lumbar puncture; range, -86 to +6). The age-appropriate comprehensive neuropsychometric tests used in this study included the Bayley scales of infant development for infants ranging in age from 2 to 30 months [28], the McCarthy scales of children’s abilities for children 30 months to 6 years of age [29], and the Wechsler intelligence scale for children—revised for children older than 6 years [30]. These tests generate a composite score of general cognitive functioning based on the child’s performance in various domains. The scores are normalized to facilitate a comparison among different age groups [31]. Based on the neuropsychometric scores, each patient’s CNS status at the time of lumbar puncture was classified as either severely encephalopathic (composite score <70), moderately encephalopathic (70 ≤ composite score <85, or composite score ≥85 but significant decline of >15 points from the previous testing), or no encephalopathy (composite score ≥85). In a cohort of patients, the follow-up neuropsychometric testing was done ~6 months after the lumbar puncture using the same test instrument. Changes of neurocognitive function were documented as an improvement (increase of >7 points), no change (increase or decline of <7 points), or a worsening performance (decline of >7 points).

Brain CT scans were evaluated for the presence and severity of brain atrophy (both ventricular and sulcal enlargement), calcifications, and white matter abnormalities using a previously described analog rating scale method [32]. None of the patients studied had abnormal brain lesions indicative of opportunistic infection or neuroplastic processes.

### Quantitation of viral RNA and HIV-1 p24 antigen.

Viral RNA was extracted from pelleted virus obtained by ultracentrifugation of CSF or plasma at 44,000 g for 1 h at 4°C and subjected to reverse transcription (RT) as previously described [33]. The RT mixture (cDNA) was subjected to 30 cycles of gene amplification by polymerase chain reaction (PCR) using a DNA thermal cycler (Perkin-Elmer Cetus, Norwalk, CT) in the PCR working buffer containing 50 mM KCl, 10 mM TRIS HCl, 3 mM MgCl₂, 0.5 μM oligonucleotide primer pair, 200 μM dATP, dGTP, dTTP, and dCTP, and 2.5 U of Taq polymerase. Oligonucleotide primer pairs used in this study included SK38/39 for HIV-1 PCR and RAG 3/4 for exogenously added RNA used as a control for RT-PCR [33]. The amplification products generated by SK 38/39 were visualized by solution hybridization with a [3P]-labeled probe, SK 19, analyzed on an 8% polyacrylamide gel. The image on the gel was analyzed by Phosphorimager (Molecular Dynamics, Sunnyvale, CA). The PCR products amplified with RAG 3/4 were subjected to agarose gel electrophoresis and stained with ethidium bromide. The copy number of HIV-1 genome in a given sample was determined from the standard curve constructed from reference DNA preparations with known copy numbers of HIV-1 DNA that were included in each PCR experiment as described [33, 34].

HIV-1 p24 antigen levels in selected CSF samples were determined by commercially available ELISA kit (Coulter Immunology, Hialeah, FL).

### Results

Forty-one children, ranging in age from 6 months to 12 years (median, 2.2 years), who acquired HIV-1 infection vertically (n = 36) or via blood products (n = 5), were studied. The immune function at the time of lumbar puncture was considered “severely suppressed” in 34 of 41 patients according to CDC immune classification [27] (table 1). Neurologic condition was classified on the basis of neuropsychometric scores as noted above. Twenty-five of 41 children were considered severely encephalopathic, 7 as moderately encephalopathic, and 9 as normal (no encephalopathy) (table 1).

Twenty-nine of 41 patients had been receiving zidovudine, as a single drug (n = 21) or in combination (n = 8), for >6 weeks at the time of the lumbar puncture. Eight of 9 patients who were receiving other antiretroviral regimens at the time of lumbar puncture had previously received zidovudine orally for various periods of time (5 weeks to 2 years; median, 9.5 months). The interval from the last exposure to zidovudine ranged from 2 months to 3 years (median, 7 months) in these 8 children. Three patients were naive to any antiretroviral treatment (table 1).

A total of 47 CSF samples were examined. All 41 patients had at least 1 CSF specimen available for the analyses. Addi-
Figure 1. Comparison of HIV-1 RNA levels in CSF (A) and plasma (B) among severely encephalopathic, moderately encephalopathic, and nonencephalopathic groups. Levels of HIV-1 RNA in CSF were much higher in severely encephalopathic children followed by moderately encephalopathic and nonencephalopathic children (P = .007), whereas the plasma HIV-1 RNA levels did not show a significant difference (P = .09).

Table 1. Clinical characteristics of HIV-1–infected children at the time of lumbar puncture.

<table>
<thead>
<tr>
<th>Encephalopathy</th>
<th>Severe (n = 25)</th>
<th>Moderate (n = 7)</th>
<th>No encephalopathy (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median/range (years)</td>
<td>2.2/0.5 - 11.2</td>
<td>2.4/1.4 - 7.8</td>
<td>4.3/1.2 - 12.8</td>
</tr>
<tr>
<td>Absolute CD4 T cell count (*/mm³)</td>
<td>86</td>
<td>172</td>
<td>42</td>
</tr>
<tr>
<td>CD4 T cell %</td>
<td>6</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>CDC immune category</td>
<td>No evidence of suppression</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Moderate suppression</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Severe suppression</td>
<td>21</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Antiretroviral regimen</td>
<td>Zidovudine (&gt;6 weeks) as single or combination therapy</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Other regimen*</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-naive</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE. Unless indicated, data are no. of subjects.
* E.g., didanosine, zalcitabine.

Comparison of CSF HIV-1 RNA Levels by Various Factors

CNS condition. HIV-1 RNA was detected in CSF from 29 of 32 children with encephalopathy (severe and moderate combined) compared with 2 of 9 patients with no encephalopathy (P < .001, Fisher’s exact test). HIV-1 RNA copy numbers in CSF were significantly higher in severely encephalopathic children followed by moderately encephalopathic and nonencephalopathic children (P = .007, Kruskal-Wallis test) (figure 1A). In contrast, there was no significant difference in the plasma HIV-1 RNA levels among groups (P = .09, Kruskal-Wallis test) (figure 1B), nor was there significant correlation between CSF and plasma HIV-1 RNA levels (r = .19, P = .31). The levels of HIV-1 RNA in CSF were compared with severity of CNS dysfunction in encephalopathic children. HIV-1 RNA copy numbers in CSF were not significantly different between severely encephalopathic versus moderately encephalopathic children (figure 1A), although all 5 children who had >10⁴ copies/mL HIV-1 RNA in CSF were severely encephalopathic and had a greater degree of brain atrophy assessed by CT [32] compared with encephalopathic children with <10⁴ copies/mL HIV-1 RNA in CSF (mean atrophy score ± SD: 64.0 ± 16.4 vs. 34.9 ± 20.9; P = .008, Mann-Whitney test) (Brouwers P, et al., unpublished data).

CD4 cell count. The majority of children (34/41) had severely suppressed immune function at the time of lumbar puncture. No significant correlation was found between the level of HIV-1 RNA in CSF or plasma and immune status assessed by CD4 cell count or percentage or CDC immune category [27] in the cohort of patients evaluated in this study.
**CSF profiles**  All of the CSF specimens were examined for total cell count and protein and glucose levels. CSF total cell count ranged from 0 to 22/mm³ (mean ± SD, 3.1 ± 5), predominantly lymphocytes and histiocytes, with protein of 19–56 mg/dL (mean ± SD, 25 ± 8.9) and glucose of 39–73 mg/dL (mean ± SD, 53.7 ± 7.6). One CSF sample from a child with severe encephalopathy contained 22 cells/mm³ (5% segmented neutrophils, 58% lymphocytes, 3% histiocytes, 9% reactive lymphocytes) with 30 mg/dL protein and 39 mg/dL glucose. The CSF samples with >1000 HIV-1 RNA copies/mL had higher total cell counts and higher protein concentrations and a lower level of glucose compared with the CSF specimens with <1000 HIV-1 RNA copies/mL (mean ± SD: 6.1 ± 7.3 vs. 2.0 ± 3.3 cells/mm³, 32.3 ± 12.4 vs. 22.1 ± 5.0 mg/dL, 47.4 ± 7.7 vs. 56.0 ± 6.3 mg/dL with P = .05, .017, and .012, respectively) regardless of the clinical CNS condition.

Sufficient quantities of CSF were available for HIV-1 p24 antigen testing in 17 samples. Five of 17 samples tested positive for p24 antigen and appeared to contain a higher number of HIV-1 RNA copies than found in samples negative for p24 antigen (n = 12; data not shown; P < .04, Mann-Whitney test). Eleven of the 12 CSF samples negative for p24 antigen had detectable levels of HIV-1 RNA.

There was no correlation between the duration of CSF storage at −70°C and the levels of HIV-1 RNA in CSF.

**Antiretroviral regimen.**  Of 29 children who had been receiving zidovudine as a single drug or in combination with other antiretroviral agents at the time of the lumbar puncture, 3 were receiving continuous intravenous infusion of zidovudine as a single regimen given at 480 mg/m²/day. The remaining 26 were receiving orally administered zidovudine, with doses of 60–180 mg/m² c/d every 6 h. The other 12 children were either receiving single didanosine (n = 8) or zalcitabine (n = 1) therapy or were treatment-naïve (n = 3). The levels of HIV-1 RNA in CSF were significantly lower in children treated with zidovudine (zidovudine group) than those who were not receiving zidovudine (no-zidovudine group [including 3 treatment-naïve children]) (geometric mean ± SD: 57 ± 25 vs. 1943 ± 12 copies/mL for the zidovudine group vs. the no-zidovudine group, P < .005, Mann-Whitney test), while there was no significant difference in plasma HIV-1 RNA levels between groups (1.63 × 10⁵ ± 14 vs. 5.34 × 10⁴ ± 8 copies/mL for the zidovudine group vs. the no-zidovudine group, respectively, P = .24, Mann-Whitney test). The similar difference in CSF HIV-1 RNA was observed even when nonecephalopathic children were excluded from the comparison (192 ± 14 vs. 1943 ± 12 copies/mL for the zidovudine group vs. the no-zidovudine group, P = .04, Mann-Whitney test), despite the fact that zidovudine-treated children appeared to have higher levels of HIV-1 RNA in plasma (6.86 × 10⁵ ± 10 vs. 5.34 × 10⁴ ± 8 copies/mL for the zidovudine group vs. the no-zidovudine group, excluding nonecephalopathic children, P = .02, Mann-Whitney test). The dose of zidovudine did not have a significant impact on the level of HIV-1 RNA in CSF.

**Zidovudine Resistance and Neurologic Outcome**

Presence of codon 215–mutant HIV-1 variants was assessed by the nested PCR using viral RNA obtained from CSF and plasma in 32 children. The viral pol gene could be successfully amplified in 23 initial CSF samples and in 24 plasma specimens. Of these CSF and plasma specimens, 15 pairs were obtained from the same persons. The presence of mutant codon 215 corresponded between CSF and plasma in all 15 paired specimens (follow-up specimens not included, see below; P = .002, Fisher’s exact test). The use of zidovudine at the time of lumbar puncture was significantly associated with the presence of codon 215–mutant HIV-1 variant in plasma (P = .03, Fisher’s exact test) (table 2). CSF showed a similar but less significant trend (P = .07, Fisher’s exact test) (table 2). The detection frequency of mutant HIV-1 in CSF was comparable between severely and moderately encephalopathic children.

The presence of the codon 215 mutation and the subsequent neurologic changes were compared in 15 of 22 children with encephalopathy who had follow-up assessments done ~6 months after the lumbar puncture. Thirteen of the 15 children had neuropsychometric function retested with the same instrument. Two other children, who died before reaching the 6-month follow-up visit, had clinical evidence of deterioration or improvement. Two of the 15 children were previously untreated patients and were placed on orally administered zidovudine treatment. The other 13 patients, who had been receiving oral zidovudine, were switched to a continuous infusion of zidovudine after the lumbar puncture because of declining neuropsychometric testing scores despite oral treatment with zidovudine. Nested PCR demonstrated that 7 of the 9 children who had improved neuropsychometric testing scores had wild type co-

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**Table 2.** Viral pol gene codon 215 mutation in CSF and plasma specimens and antiretroviral agent(s) at the time of lumbar puncture in HIV-1 infected children.

<table>
<thead>
<tr>
<th>Zidovudine resistance (codon 215 analysis)</th>
<th>Zidovudine*</th>
<th>Other†</th>
<th>No prior treatment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CSF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Mutant type</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>6</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td><strong>Plasma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Mutant type</td>
<td>11</td>
<td>4</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>9</td>
<td>2</td>
<td>24</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. of subjects.

*Single drug or in combination.

†Didanosine or zalcitabine. All patients in this category had received orally administered zidovudine for various periods before being switched to other antiretroviral agents.
and 2 had mutant type (suggestive of zidovudine-resistant variants). All 5 children who showed evidence of neurologic deterioration with further declining testing scores or clinical progression had the codon 215 mutant in CSF, and 1 other patient who had stable CNS status had wild type. Thus, the progression of encephalopathy during zidovudine treatment, regardless of its route of administration, was significantly associated with the presence of mutant codon 215 in CSF specimens ($P = .007$, Fisher’s exact test).

**Follow-Up CSF Evaluation in Selected Patients**

Second CSF specimens were obtained from 6 children with severe encephalopathy after 6–16 months of treatment with continuous infusion of zidovudine. Paired plasma samples were available from 5 of the 6 patients. The downward trend in HIV-1 RNA copy numbers in CSF ($-2.176$ to $-0.192 \log_{10}$) was found in 4 patients, 3 of whom had increases in neuropsychometric testing scores of 6–20. However, there was no direct correlation between the degree of HIV-1 RNA reduction and improvement in the scores. Two other children who had an upward trend in HIV-1 RNA in CSF, $0.33$ and $2.049 \log_{10}$, had small increases in test scores and no changes, respectively. Log changes in number of HIV-1 RNA copies in plasma appeared to correlate with those in CSF although it did not reach statistical significance, probably because of the small number of patients examined (data not shown). Mutational analysis at codon 215 in the first and second paired CSF and plasma specimens showed consistent results in all but 1 patient. This patient, who was treatment-naive, initially had wild type in both CSF and plasma but was found to have mutant codon 215 virus in CSF while maintaining wild type in plasma at the second lumbar puncture 6 months later. The second neuropsychometric testing did not show a significant improvement (only a small upward trend of up to 6 points) in this case.

**Discussion**

The pathogenesis of HIV encephalopathy has been the subject of intense research since the syndrome was first recognized more than a decade ago [39]. Although the HIV-1 genome can be identified in the brains of HIV-encephalopathic patients, the role of HIV-1 infection itself remains unclear. We have previously shown that the amounts of provirus found in brain tissues of HIV-encephalopathic patients are much higher than in brains of nonencephalopathic AIDS patients, while the levels of proviral DNA in lymph nodes and spleen may be comparable in patients with and without evidence of encephalopathy [36]. Moreover, the provirus found in brains from HIV-encephalopathic patients contained pol gene mutations that could potentially confer resistance to the drugs they had been receiving [36]. The data suggested that resistance to antiviral drugs could permit active viral replication within the CNS, contributing to the development of HIV-induced neurologic manifestations. However, these observations were based on measurement of HIV-1 provirus rather than RNA and therefore did not directly demonstrate an active state of viral replication.

In the current study, we showed that HIV-1 RNA is more frequently detected in CSF from children who had abnormal CNS function than from those who did not. Although we could not definitively exclude the presence of other confounding opportunistic infections in most cases, the clinical and laboratory profile of these encephalopathic patients is consistent with HIV-1–induced CNS dysfunction (HIV encephalopathy). It is notable that there was no significant difference in the level of plasma HIV-1 RNA between encephalopathic versus nonencephalopathic children. This is consistent with our previous observation [36] and suggests that the virus turnover within the CNS may be independent of that in peripheral blood, at least at the late stage of the disease.

Although the children with the highest CSF HIV-1 RNA copy numbers ($>10^4 \text{mL}^{-1}$) had severe neurocognitive deficits and cortical atrophy, there was no statistically significant difference in HIV-1 RNA levels in CSF between severely encephalopathic and moderately encephalopathic children, nor was there a direct relationship between neurocognitive testing scores and HIV-1 RNA copy numbers in CSF. These data strongly suggest that the presence of active viral replication may be crucial for development of HIV encephalopathy, but the quantity of the virus per se may not be a sole determining factor for subsequent pathophysiologic changes in brain. It has been suggested that the neuron damage or depletion occurring in HIV encephalopathy is caused by neurotoxic factors rather than reflecting direct killing of neurons by HIV-1. The predominant targets of HIV-1 infection within the CNS are macrophages and microglia, while very little infection is noted in neurons, astrocytes, and oligodendrocytes. Indeed, potential neurotoxicity by virus-encoded proteins [40] or cytokines and other cell-derived proteins, including tumor necrosis factor-α [41], arachidonic metabolites [42], nitric oxide [43], quinolinic acid [44], or platelet-activating factor [45], has been extensively investigated in vitro or in vivo. It is also possible that some of the virus strains may be more neurovirulent than others or that there may be differential host susceptibilities to viral infection within the CNS. These neurotoxic factors, neurovirulent viral phenotype, and/or host susceptibilities may have contributed to the severe degree of CNS dysfunction in children who were severely encephalopathic but had low levels of HIV-1 RNA in CSF.

In this study, lower HIV-1 RNA copy numbers in CSF were observed with zidovudine compared with other dideoxynucleoside analogues (didanosine or zalcitabine) or no treatment, while there was no difference in plasma HIV-1 RNA levels. This may be related to the differential CNS penetration profiles between zidovudine and other dideoxynucleoside agents. Poor CNS penetration by certain antiretroviral agents may fail to impede viral replication in the CNS, even though the replication is suppressed in the systemic circulation. If the achievable drug
concentration in CNS is suboptimal, resistant virus may emerge in the CNS sooner than in peripheral blood. Thus, it is possible that the dynamics of viral replication can be separated between the CNS versus the systemic compartment, depending on the selection of antiretroviral regimen.

We demonstrated that the presence of the codon 215 mutation in CSF and plasma was associated with poor neurologic outcome with zidovudine treatment. Although the presence of other mutations within the pol region was not evaluated in our study, it is highly possible that children who had the codon 215 mutation harbored zidovudine-resistant HIV-1 strains, since this is one of the most common mutations associated with resistance to zidovudine [38]. The progression of neurologic manifestations in these children, therefore, may have resulted from poorly controlled viral replication by zidovudine. These data may stress the importance of an effective suppression of viral replication within CNS compartment, especially because the neurotoxic factors induced in HIV-1 infection are still unidentified and may be multifactorial. As newer families of antiretroviral agents become available to treat HIV-1–infected persons, detailed studies of CNS penetration combined with the longitudinal monitoring of both immune system and CNS function will help elucidate the neuropathogenesis of HIV-1 disease and may lead to new approaches to treating patients with HIV encephalopathy.

Acknowledgments

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References