Determinants of survival in progressive multifocal leukoencephalopathy

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ABSTRACT

Background: We sought to characterize the role of immunologic, virologic, and radiologic determinants of survival in patients with progressive multifocal leukoencephalopathy (PML).

Methods: We recorded the clinical outcome of 60 patients with PML (73% HIV+) who were prospectively evaluated between 2000 and 2007 for the presence of JC virus (JCV)-specific CD8+ cytotoxic T-lymphocytes (CTL) in blood.

Results: Estimated probability of survival at 1 year was 52% for HIV+/PML and 58% for HIV– patients with PML. Patients with PML with detectable CTL within 3 months of diagnosis had a 1-year estimated survival of 73% compared to 46% for those without CTL (hazard ratio [HR] for death = 0.47, 95% confidence interval [CI] 0.13–1.75, $p = 0.26$). Patients with CTL response had an increased likelihood of having contrast enhancement of PML lesions and immune reconstitution inflammatory syndrome (odds ratio 3.7 and 7.8). Estimated 1-year survival was 48% in HIV+ patients with PML with CD4 count $<200/\mu\text{L}$ at PML diagnosis compared to 67% in those with CD4 $>200/\mu\text{L}$ (HR for death 1.41, 95% CI 0.27–7.38, $p = 0.68$). JCV DNA was detected in the urine of 48% and in the blood of 56% of patients with PML, but viremia and viruria were not associated with survival.

Conclusions: The presence of JC virus (JCV)-specific cytotoxic T-lymphocytes (CTL) was associated with a trend toward longer survival in patients with progressive multifocal leukoencephalopathy (PML), which was more pronounced than the impact of CD4 count in HIV+ patients with PML early after diagnosis. Despite the association of contrast enhancement and immune reconstitution inflammatory syndrome with JCV-specific CTL, these cannot be considered as surrogate markers for the prognostic value of the CTL. Strategies aiming at improving the cellular immune response may improve the course of PML. *Neurology*® 2009;73:1551–1558

GLOSSARY

CE = contrast enhancement; **CI** = confidence interval; **CTL** = cytotoxic T-lymphocytes; **HR** = hazard ratio; **IQR** = interquartile range; **IRIS** = immune reconstitution inflammatory syndrome; **JCV** = JC virus; **PBMC** = peripheral blood mononuclear cells; **PML** = progressive multifocal leukoencephalopathy.

Progressive multifocal leukoencephalopathy (PML) is a fatal demyelinating disease of the brain which occurs in immunosuppressed individuals and is caused by JC virus (JCV). There is no cure for PML and survival at 1 year has been reported to be between 38.6% and 56% in HIV+ patients on combination antiretroviral therapy (cART).¹ Our understanding of the factors associated with PML survival remains incomplete. Patients with PML who harbor in their blood JCV-specific CD8⁺ cytotoxic T-lymphocytes (CTL) have a better clinical outcome.² Furthermore, contrast enhancement (CE) of PML lesions on CT or MRI had been associated with a favorable prognosis.³ Whether CE is triggered by components of the immune response is

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unknown. However, recovery of the immune system can also lead to an immune reconstitution inflammatory syndrome (IRIS), which is occasionally a lethal complication of PML in cART-treated HIV+ patients.⁴ In addition, although JCV uses 5HT2a receptors to enter glial cells in vitro,⁵ the effect of 5HT2A receptor blockers on PML outcome is unclear. Finally, while JCV replication in the CNS is always detected in PML, JCV can also be found in the blood of some patients with PML, but the impact of JC viremia on PML survival has not been studied in detail. We therefore sought to correlate immunologic, radiologic, and virologic factors and the use of 5HT2A blockers with PML survival.

METHODS Study population. Sixty patients with virologic, histologic, or clinical-radiologic diagnosis of PML, including 44 HIV+ (73%) and 16 HIV- (27%) patients, were recruited between 2000 and 2007 from inpatient and outpatient populations of the Beth Israel Deaconess Medical Center, the Brigham and Women's Hospital, and Massachusetts General Hospital (MA), the University of Kentucky (KY), Washington University (MO), and the Mount Sinai Medical Center (NY). Twenty HIV+ patients without PML (matched for age and HIV RNA values with HIV+ patients with PML) and 15 healthy individuals served as controls. Blood and urine samples were collected at baseline and, when possible, every 3 months. A criterion of inclusion of patients with PML in this analysis was to have an assay measuring their CTL against JCV in their blood.

Standard protocol approvals, registrations, and patient consents. Approval from an ethical standards committee on human experimentation (institutional or regional) for any experiments using human subjects was received. Written informed consent was obtained from all patients (or guardians of patients) participating in the study (consent for research).

Major histocompatibility complex class I typing. Major histocompatibility complex class I alleles of the study subjects were determined using standard serologic tissue-typing procedures.

Stimulation of peripheral blood mononuclear cells by CTL epitope peptides of JCV. Peripheral blood mononuclear cells (PBMC) were cultured with A*0201-restricted epitopes JCV VP1_{p36}⁶ and VP1_{p100} peptides⁷ for A*0201+ subjects or pools of peptides spanning the entire JCV VP1 protein for HLA A0201- subjects. After 10–14 days of culture, cells were tested for the presence of peptide-specific CTL by tetramer staining or ⁵¹Cr release assay as previously described.²

Quantitative PCR detection of JCV DNA. Quantitative PCR was used to measure JC virus load in the plasma, PBMC, and urine as previously described.⁸

Statistical analysis. Categorical variables were compared using Fisher exact test. The Mann-Whitney *U* test was used to calculate differences between the means of continuous variables. Both tests were 2-tailed and an α of 0.05 was employed. Survival

from the onset of neurologic symptoms of PML was analyzed by time to death using the Kaplan-Meier method and differences among groups were calculated with the log-rank test. Predictors of death events were examined by univariate and multivariable Cox regression models. The association between CTL response and survival was analyzed using CTL as a baseline (first available sample after diagnosis) or a time-updated variable. Multivariable models included the CTL response and covariates showing a significant association with the outcome of interest at univariable analysis. All analyses were performed using the SPSS software package (version 13, SPSS Inc., Chicago, IL).

RESULTS Study group characteristics. The median age of HIV+ patients with PML was 44 years (range 20–69), and it was 60 years (range 40–84) for HIV- patients with PML, 46.5 years (range 32–56) for HIV+, and 33 years (range 24–45) for healthy control subjects. HIV- patients with PML were older than other groups ($p < 0.0001$). The median baseline CD4+ cell count was lower in HIV+ patients with PML (223 cells/ μ L, range 8–957) than in HIV+ patients who did not have PML (347 cells/ μ L, range 15–822, $p = 0.03$). The median plasma HIV RNA level was similar in these 2 groups (1.69 log₁₀ copies/mL, range 1.69–5.70, vs 2.3 log₁₀ copies/mL, range 1.69–5.70, $p = 0.28$).

Characteristics of patients with PML. PML was diagnosed by experienced clinicians and defined by typical clinical and imaging findings and supported by JCV DNA detection in CSF or biopsy. The characteristics of HIV+ and HIV- patients with PML are summarized in the table. The first sample for the JCV-specific CTL assay was obtained within 3 months of PML diagnosis in 29 cases, within 1 year in 39 cases, while the remainder were collected at a later time point.

Estimated survival according to the HIV serostatus of patients with PML. Among 29 patients with PML whose blood sample was collected within 3 months of PML diagnosis, the estimated proportion of surviving at 1 year was 56%. Among these, the 13 HIV- patients with PML had a 1-year survival rate of 58% compared to 52% for the 16 patients in the HIV+ PML group, a difference which was not significant (HR for death [HR] = 1.13, 95% confidence interval (CI) 0.36–3.57, $p = 0.83$) (figure 1).

Estimated survival according to the presence of JCV-specific CD8+ CTL response detected in peripheral blood cells. To determine the impact of the cellular immune response on PML outcome, the 29 HIV+ and HIV- patients with PML who had an assay measuring JCV-specific CTL in their blood within 3 months of diagnosis were divided according to the presence ($n = 12$) or absence ($n = 17$) of these CTL. There was a trend of better 1 year estimated survival

Table	Clinical characteristics of HIV+ and HIV- patients with PML	
	HIV serostatus	
	HIV+ PML (n = 44)	HIV- PML (n = 16)
Median age, y (range)	44 (20-69)	60 (40-84)
Male gender, %	93	44
Ethnicity, %		
Caucasian	70	100
Hispanic	5	
African American	23	
Unknown	2	
Diagnosis, %		
Clinical-radiologic	20	12
Virologic	71	50
Histologic	7	19
Virologic + histologic	2	19
cART therapy at baseline, %	26	—
cART therapy after PML diagnosis, %	86	—
Treatment for PML, %		
Cytarabine	7	0
Alpha-interferon 2b	0	25
5HT2A blockers	18	56
Cidofovir	0	19
Underlying diagnosis for HIV- patients, n		
AML		3
CLL		2
Polycythemia vera		1
Non-Hodgkin lymphoma		1
Dermatomyositis		2
CD8 lymphopenia		2
HCL		1
RA treated with methotrexate		1
Low-grade B-cell lymphoma		1
Hepatitis C		1
CVID		1
Chemotherapy for brain stem glioma		1

PML = progressive multifocal leukoencephalopathy; cART = combination antiretroviral therapy; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; HCL = hairy cell leukemia; RA = rheumatoid arthritis; CVID = common variable immunodeficiency.

in those with detectable CTL (73%) compared to those without (46%) a CTL response (HR for death 0.47, 95% CI 0.13–1.75, $p = 0.26$) (figure 2A).

When this analysis was repeated in the 39 HIV+ and HIV- patients with PML (including the 29 mentioned above) who had an assay measuring JCV-

specific CTL in their blood within 1 year of diagnosis, this trend was accentuated with a 1-year estimated survival in those 18 patients with detectable CTL of 77% compared to 43% in those 21 patients without a CTL response (HR = 0.35, 95% CI 0.11–1.09, $p = 0.07$) (figure 2B).

Since the CTL assay was performed at various time intervals after diagnosis, this could have introduced potential bias associated with better survival. In order to minimize the effect of this bias, we also analyzed the CTL results as a time-updated variable (i.e., each CTL test result contributed to survival until the date of the result of the subsequent assay). Within the whole PML patient group, those with CTL had a HR for death of 0.59 compared to those without CTL (95% CI 0.16–2.13, $p = 0.42$). However, when considering the HIV+ patients with PML only, the detection of a JCV-specific CTL response as a time-updated variable showed a trend toward a decreased risk of death (HR for death 0.32; 95% CI 0.06–1.66, $p = 0.18$). This difference was not present in the HIV- PML group, where the patients with CTL had a HR for death of 1.05 compared to the patients without CTL (95% CI 0.2–5.56, $p = 0.95$).

Association of contrast enhancement of PML lesions on brain MRI with JCV-specific CTL response and survival. Among 22 patients with PML who had MRI and a CTL assay within 3 months of diagnosis, 7 (32%) had CE. All but 1 survived more than 1 year. JCV-specific CTL were detected in 5 of 7 (71%), and the presence of CTL response showed a nonsignificant trend of detecting CE (CTL+ vs CTL-: odds ratio for CE 3.7, 95% CI 0.54–26.04, $p = 0.18$). Patients with PML with CE had a trend toward a better survival at 1 year (83%) compared with those without (39%) (CE + vs CE -: HR for death 0.24, 95% CI 0.03–1.93, $p = 0.18$).

Association of immune reconstitution inflammatory syndrome with JCV-specific CTL response and survival. Among patients tested within 3 months of diagnosis, 8/26 (31%) patients with PML, including 7 HIV+ and 1 HIV-, developed immune reconstitution inflammatory syndrome (IRIS) around the time of evaluation of their cellular immune response. IRIS was defined as an inflammatory reaction within PML lesions occurring after initiation of cART in the setting of a rise of CD4⁺ T-cell count and a decrease of HIV plasma RNA. IRIS was often associated with a worsening of neurologic symptoms. Of all patients with IRIS, 3 (37.5%) survived more than a year and 6 (75%) had detectable JCV-specific CTL. The presence of CTL response was associated with an in-

Figure 1 Estimated survival according to the HIV serostatus of patients with progressive multifocal leukoencephalopathy (PML) enrolled within 3 months of PML diagnosis

Continuous lines denote HIV- serostatus; dashed lines HIV+ serostatus. Differences among groups were calculated with the log-rank test.

creased likelihood of developing IRIS (CTL+ vs CTL-: odds ratio for IRIS 7.8, 95% CI 1.16–52.35, $p = 0.03$). Patients with PML who did or did not develop IRIS had similar 1-year survival rate (54% vs 49%; IRIS+ vs IRIS-: HR for death 0.71, 95% CI 0.19–2.64, $p = 0.61$) (figure 3A).

When this analysis was repeated in patients tested within 1 year from diagnosis, patients with

PML who developed IRIS had a 1-year survival rate of 53% compared to 65% for those who did not develop IRIS (IRIS+ vs IRIS-: HR for death 1.18, 95% CI 0.38–3.63, $p = 0.77$) (figure 3B).

Association of CD4 T-cell counts at the time of PML diagnosis and survival in HIV+ patients with PML. The 16 HIV+ patients with PML with available CD4 counts at the time of PML diagnosis, who were enrolled in the study within 3 months of diagnosis, were divided according to their CD4 count below ($n = 6$) or above ($n = 10$) 200 cells/ μ L. As expected, those with CD4 cell counts below 200 had a trend toward a lower survival rate at 1 year (48%) compared with those with higher CD4 cell counts (67%; HR for death 1.41, 95% CI 0.27–7.38, $p = 0.68$) (figure 4A).

When this analysis was repeated in all the 43 HIV+ patients with PML with available CD4 counts at the time of PML diagnosis divided according to their CD4 count below ($n = 26$) or above ($n = 17$) 200 cells/ μ L, the difference between the 2 groups became significant. Those with CD4 cell count below 200 had a lower survival rate at 1 year (58%) compared with those with higher CD4 cell count (88.5%; crude HR for death 4.46, 95% CI 1.29–5.33, $p = 0.02$) (figure 4B). In a multivariable model, after adjusting for the presence of JCV-specific CTL response, the CD4 cell count was still as strong a predictor of survival (adjusted HR for death 4.16, 95% CI 1.16–14.85, $p = 0.03$).

Estimated survival of patients with PML according to treatment with a 5HT_{2a} receptor blocker after PML diagnosis. Fourteen patients with PML (7 HIV+ and 7 HIV-) were treated with 5HT_{2A} receptor blockers mirtazap-

Figure 2 Estimated survival according to the detection of JCV-specific CD8⁺ cytotoxic T-lymphocytes (CTL) response in blood

(A) Continuous lines denote the presence and dashed lines the absence of JCV-specific CTL response measured by tetrameric HLA-A*0201/JCV VP1_{p36} or VP1_{p100} complexes for A*0201⁺ patients^{6,7} or ⁵¹Cr release assay for HLA A*0201⁺ subjects.² (B) Continuous lines denote the presence and dashed lines the absence of JCV-specific CTL response. Differences among groups were calculated with the log-rank test. PML = progressive multifocal leukoencephalopathy.

Figure 3 Estimated survival of progressive multifocal leukoencephalopathy (PML) according to the occurrence of immune reconstitution inflammatory syndrome (IRIS)

(A) Continuous lines denote the occurrence of IRIS and dashed lines indicate the absence of IRIS in patients with PML. (B) Continuous lines denote the occurrence of IRIS and dashed lines the absence of IRIS in patients with PML. Differences among groups were calculated with the log-rank test. CTL = cytotoxic T-lymphocytes.

ine (Remeron) 15–45 mg at bed time within 1 year after PML diagnosis and did not discontinue the medication until they died or until the end of the observation period. This group was compared with 11 patients with PML (6 HIV+ and 5 HIV-) who were not receiving any other treatment except cART, matched for CD4 count and HIV viral load. The 1-year survival rate was 62% in patients treated with 5HT2A receptor blockers vs 45% in untreated patients, a difference which was not significant (5HT2A+ vs 5HT2A-: HR for death 0.63, 95% CI 0.19–2.07, $p = 0.45$).

Comparison of JCV viremia and viremia in patients with PML and control subjects. There was no association between the presence or absence of JCV DNA in the blood or urine of patients with PML and survival. JCV DNA was detected in the urine of 12/25 (48%) patients with PML, 11/18 (61%) HIV+ patients, and 4/15 (27%) healthy individuals. There was no difference between JC viremia in patients with PML and the 2 control groups, but JC viremia was more frequent in HIV+ patients (61%) compared to healthy individuals (27%; $p = 0.008$). JCV DNA

Figure 4 Estimated survival according to the presence of CD4 T-cell count $<200/\mu\text{L}$ or $>200/\mu\text{L}$ at the time of progressive multifocal leukoencephalopathy (PML) diagnosis in HIV+ patients with PML

(A) Continuous lines denote CD4 count $>200/\mu\text{L}$ and dashed lines CD4 count $<200/\mu\text{L}$ at baseline. (B) Continuous lines denote CD4 count $>200/\mu\text{L}$ while dashed lines CD4 count $<200/\mu\text{L}$ at baseline. Differences among groups were calculated with the log-rank test. CTL = cytotoxic T-lymphocytes.

was not detectable in the blood (plasma or PBMC) of healthy subjects but was detected in 33 of 59 (56%) PML and 6 of 20 (30%) HIV+ control subjects. JCV DNA was more frequent in the plasma of patients with PML (23/59, 39%) than HIV+ control subjects (2/20, 10%; $p = 0.024$). There was a trend for a higher frequency of JCV DNA detection in PBMC as compared with plasma in both groups, including 20/37 (54%) patients with PML and 6/20 (30%) HIV+ controls. There was no difference between median JC viral load in blood from patients with PML (PBMC $1.60 \log_{10}$ copies/ μg of DNA, interquartile range [IQR] 1.13–2.00; plasma $2.98 \log_{10}$ copies/mL, IQR 2.80–3.20) and HIV+ controls (PBMC $1.26 \log_{10}$ copies/ μg of DNA, IQR 1.08–1.71; plasma $3.20 \log_{10}$ copies/mL, IQR 2.80–3.60). The median JC viral load in urine was similar among patients with PML ($3.68 \log_{10}$ copies/mL, IQR 3.42–6.02), HIV+ ($4.97 \log_{10}$ copies/mL, IQR 4.30–7.40), and healthy control subjects ($4.53 \log_{10}$ copies/mL, IQR 3.05–5.93).

DISCUSSION The 52% 1-year survival in our HIV+ PML patient population is comparable with that reported in previous studies.^{9–11} However, the 58% 1-year survival in our HIV– PML group is higher than previously reported. In one review,¹² 80% of patients died within 9 months. In patients with PML with underlying lymphoproliferative disorders,¹³ median survival was 3 months and only 5 (12%) of 42 patients were reported to have a survival exceeding 10 months. The better survival in our population may result from selection bias. In part, the requirement of our patients to give consent for this study may have excluded the most neurologically advanced cases. Also, HIV– patients with PML are a very heterogeneous population and the clinical outcome may vary greatly based on the severity of their underlying condition.

Our results are consistent with and expand those from previous studies on the role of the cellular immune response in PML outcome,^{2,6} since the detection of JCV-specific CTL in blood within 3 months from diagnosis was associated with a trend toward increased survival. However, when the CTL was analyzed as a time-dependent variable, this trend was present in HIV+ individuals only. These results suggest that the beneficial effect of the CTL is predominant in individuals whose immunosuppression may be reversible such as in cART-treated HIV+ patients.

In a small study, CE of PML lesions on MRI was associated with a better outcome.³ Our results suggest that the presence of JCV-specific CTL in PML lesions may trigger local inflammation leading to the

breakdown of the blood–brain barrier and CE. Therefore, the previously detected beneficial effect of CE on PML survival may be due in part to the presence of the CTL. Whether CE may be used as a surrogate marker for the presence of CTL responses deserves further study.

IRIS was also associated with JCV-specific CTL but not with survival. This is consistent with the pathologic descriptions of PML IRIS which feature abundant CD8+ cells in the inflammatory response in the brain.¹⁴ The fact that IRIS can be a lethal complication of PML had also been reported by others.¹⁴ Therefore, other components of the immune response may be implicated in the pathogenesis of IRIS in patients with PML. Of note, although IRIS is commonly thought to be associated with CE of PML lesions on MRI, a recent retrospective analysis indicated that such features occur only in 56.7% of PML/IRIS cases.¹⁵ However, whether all of these cases truly had IRIS has been questioned.¹⁶ It is possible that enhancement is transient in IRIS and may not be present at the time of the MRI. Conversely, CE is often subtle and may also occur independently from the full-blown phenomenon of IRIS.

Consistent with earlier reports, higher baseline CD4 cell count was associated with better survival when considering the entire group of HIV+ patients with PML.^{10,17,18} However, CD4 cell count showed only a weak trend among patients tested within 3 months of PML diagnosis. It is therefore possible that immediately after the development of PML, the presence of memory CTL that can be activated against JCV, and not the absolute number of CD4+ T cells, is the most important predictor of survival of HIV+ patients with PML.

Since JCV uses 5HT2A receptors to enter glial cells, 5HT2A receptor blockers have been given empirically to patients with PML with variable success.^{19,20} Such medications may prevent entry of JCV in uninfected glial cells in the brain, but they are not expected to impede viral replication. Likewise, our results do not suggest that 5HT2A receptor blockers confer an advantage in PML survival. However, the number of subjects in the current study is small, and a randomized controlled trial is necessary to definitively assess the role of these drugs in the management of PML.

The presence of JC viremia or viruria at diagnosis did not have a significant impact on PML survival, as has been previously reported.²¹ JCV excretion in the urine was not correlated with the immunologic status of the subjects. JCV was not detected in the blood of healthy subjects and was higher in plasma of patients with PML vs HIV+ controls.

There are several limitations to this study. Since patients were required to give consent, some of the more advanced cases could not be enrolled and therefore, our population is not entirely representative of the general PML population. In addition, PML is a rare disease and is often mistaken for a stroke or brain tumor, especially in HIV+ patients, which delays the diagnosis. Therefore, only half of our patients with PML were tested within 3 months from diagnosis. Nevertheless, the trend toward improved survival associated with JCV-specific CTL was present in those study subjects enrolled within 3 months of diagnosis, which was accentuated in the larger group of patients tested within 1 year. We had previously shown in a prospective study that the CTL response to JCV is stable in PML survivors for more than a year from disease onset.²

Autologous dendritic cells can efficiently expand JCV-specific T-cell responses in vitro.²² Such methods may constitute a promising approach for PML immunotherapy.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Andrea De Luca and Dr. Mattia Prosperi.

DISCLOSURE

Dr. Marzocchetti reports no disclosures. T. Tompkins holds stock options in BioMarin Pharmaceutical, Inc. Dr. Clifford serves/has served on scientific advisory boards for Biogen Idec, Elan Corporation, Roche, Forest Laboratories, Inc., Genentech, Inc., GlaxoSmithKline, Millennium Pharmaceuticals, Inc., Schering-Plough Corp., Bristol-Myers Squibb, and Genzyme Corporation; received speaker honorarium and funding for travel from GlaxoSmithKline; has received research support from Pfizer Inc., Schering-Plough Corp., Bavarian Nordic, NeurogesX, GlaxoSmithKline, Tibotec Therapeutics, Boehringer Ingelheim, and Gilead Sciences, Inc.; and receives research support from the NIH [U01 NS32228 (PI), U01 AI69495 (PI), NIMH 22005 CHARTER Project (Site PI), NIDA RO3 DA022137 (Co-I), NIMH MH058076 (Site PI), and R21 3857-53187 (PI)]. Dr. Gandhi serves on the editorial board of *Journal Watch Infectious Diseases*, received speaker honorarium from GlaxoSmithKline, received educational support from Gilead Sciences, Inc. and Abbott, and receives research support from Tibotec Therapeutics. Dr. Kesari serves on scientific advisory boards for Bristol-Myers Squibb and Genentech, Inc.; serves on editorial boards for the *Journal of Neuro-Oncology* and the *International Journal of Biomedical Nanoscience and Nanotechnology*; receives royalties from publishing *Cancer Neurology in Clinical Practice* (Humana, 2008); served on a speakers' bureau for Enzon Pharmaceuticals, Inc.; and receives research support from GE Healthcare, the NIH [K08CA124804 (PI)], and the Sontag Foundation. Dr. Berger serves/has served on scientific advisory boards for Millennium Pharmaceuticals, Inc., Bayer Schering Pharma, Merck Serono, Genentech, Inc., Astellas Pharma Inc., and Asphelia Pharmaceuticals; has received speaker honoraria from EMD Serono, Inc., Teva Pharmaceutical Industries Ltd., and Bayer Schering Pharma; and receives research support from Bayer Schering Pharma, EMD Serono, Inc., Biogen Idec, Sanofi-Aventis, Genentech Inc., and UCB. Dr. Simpson has served on scientific advisory boards for Boehringer Ingelheim, Cephalon, Inc., Pfizer Inc., Endo Pharmaceuticals, GlaxoSmithKline, Merz Pharmaceuticals, LLC, MEDA Pharmaceuticals Inc., AlphaPharma Pharmaceuticals LLC, and Biogen Idec; serves on the editorial boards of the *Clinical Journal of Pain* and *AIDS Patient Care*; has served as a consultant to NeurogesX, Eli Lilly and Company, Regeneron Pharmaceuticals Inc., GlaxoSmithKline, Allergan, Inc., Merz Pharmaceuticals, LLC, and Torrey Pines Institute for Molecular Studies; served on speak-

ers' bureaus for Eli Lilly and Company and GlaxoSmithKline; receives research support from NeurogesX, Pfizer Inc., and Allergan, Inc.; and receives research support from the NIH [NINDS R24 MH59724, U01 NS32228 (Co-I) and NIMH 00-AI-0005 (Co-I)]. Dr. Prosperi reports no disclosures. Dr. De Luca has served on scientific advisory boards for Monogram Biosciences, Janssen-Cilag, Tibotec Therapeutics, Gilead Sciences, Inc., and Siemens Healthcare Diagnostics; serves on the editorial board of *Reviews in Antiviral Therapy*; and has received speaker honoraria from GlaxoSmithKline, Abbott, and Boehringer Ingelheim. Dr. Koralnik serves/has served on scientific advisory boards for Roche, GlaxoSmithKline, and Merck Serono; serves on the editorial board of the *Journal of NeuroVirology*; receives royalties from publishing "Topics on the management of HIV and CNS mass lesions and on PML" (*UpToDate*, 2002); has served as a consultant to Bristol-Myers Squibb, Ono Pharmaceutical Co. Ltd., Merck Serono, Roche, GlaxoSmithKline, Alnylam Pharmaceuticals, and Antisense Pharma GmbH; and receives research support from Biogen Idec and the NIH [R01 NS 041198 (PI), R01 NS 047029 (PI), and K24 NS 060950 (PI)].

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