Neurologic Complications of HIV Disease and Their Treatment

Scott Letendre, MD, J. Allen McCutchan, MD, MSc, and Ronald J. Ellis, MD, PhD

New data were presented at the 15th Conference on Retroviruses and Opportunistic Infections that further support the importance of considering the neuroeffectiveness of antiretroviral drugs when designing treatment regimens. Two studies linked antiretroviral therapy that had estimates of better neuroeffectiveness with better global neuropsychologic outcomes in life. A third study linked estimates of better antiretroviral therapy neuroeffectiveness, particularly nonnucleoside analogue reverse transcriptase inhibitors, with a lower prevalence of HIV-associated brain pathology at death. Additional findings presented at the conference focused on the correlates of HIV-associated neurocognitive disorders (HAND) and peripheral neuropathy. Supporting the concept that viral factors influence the pathogenesis of HAND, high frequencies of HAND were identified in people infected with HIV subtype D and in people infected with subtype B and having brain-specific mutations in V3 of gp160*. Supporting the importance of host correlates of HAND, important data from a macaque study identified a strong link between a major histocompatibility complex class I allele,* Mane-A*10*, and simian immunodeficiency virus encephalitis. Supporting the importance of comorbidities in determining risk for HAND, high levels of lipopolysaccharide in blood, likely derived from the HIV-injured intestine and bacterial translocation, were linked to HAND. Coinfections with JC virus or* Treponema pallidum *were topics of other presentations, identifying a prognostic marker for PML (better CD8+ cytotoxic T-lymphocyte responses were associated with survival) and a diagnostic one for neurosyphilis (CXCL13 levels in CSF).*

Neuroeffectiveness of Antiretroviral Drugs

The effectiveness of antiretroviral drugs in the nervous system has been the subject of debate since the observation that zidovudine may more consistently benefit people with AIDS dementia than didanosine.[1,2] Animal studies continue to support that some antiretroviral drugs do not treat HIV in the nervous system as well as they do outside the nervous system. At this year's conference, Annamalai and colleagues studied the effects of antiretroviral therapy on SIV in brain and lymphoid tissue in an accelerated rhesus macaque model of simian immunodeficiency virus (SIV) encephalitis (Abstract 386). The investigators compared HIV levels measured by real-time polymerase chain reaction (RT-PCR) in untreated macaques to those that had been treated with the combination of the investigational drug PSI-5400 (a racemic mixture of emtricitabine), and tenofovir for 28 days. In treated animals, HIV levels were significantly lower in all lymphoid tissues (spleen, bone marrow, lymph nodes) but in only 1 (frontal cortex) of 4 brain regions (frontal cortex, putamen, hippocampus, and brainstem). Potential explanations for these tissue-specific differences include the limited neuroeffectiveness of tenofovir (and perhaps PSI-5400) and the longer half-life of the principal target cells in the brain (macrophages) than in lymphoid tissues (lymphocytes).

Human data supporting the limited neuroeffectiveness of tenofovir in the nervous system were presented by Best and colleagues (Abstract 131). Tenofovir concentrations were measured in body fluids from 187 volunteers of the CHARTER (Central Nervous System HIV Antiretroviral Therapy Effects Research) study, identifying that the concentrations in cerebral spinal fluid (CSF) were low (median 5.5 ng/mL, interquartile range 2.7-11.3 ng/mL) and averaged only 5% of the concentrations in blood plasma. Compare these concentrations with the higher concentrations of 2 nucleoside analogue reverse transcriptase inhibitors (nRTIs), abacavir (median concentration in CSF, 128 ng/mL; mean CSF-to-plasma ratio, 36%)[3] and lamivudine (median concentration in CSF, 470 nM; mean CSF-to-plasma ratio, 15%).[4] In the tenofovir analysis, two-thirds of CSF specimens had concentrations below 7 ng/mL, and 30% of these specimens had HIV RNA levels in CSF above 50 copies/mL. In the one-third of CSF specimens that had tenofovir concentrations above 7 ng/mL, only 5% had HIV RNA levels above 50 copies/mL (P = .02 for the comparison between the 2 groups). Together, these data support that the neuroeffectiveness of tenofovir is limited and may be inferior to abacavir or lamivudine, although a direct comparison is needed to confidently reach this conclusion.

Data such as these support development of strategies for selection of neuroeffective regimens in the clinic. Strategies that might have clinical utility have used pharmacokinetic and other data to rank individual drugs and regimens for their likely neuroeffectiveness. Such strategies are particularly useful for clinicians in managing their patients who have common neurologic complications, such as HIV-associated neurocognitive disorders (HAND), pro-

Dr Letendre is Associate Professor in the Department of Medicine, Division of Infectious Diseases, at the University of California San Diego (UCSD). Dr McCutchan is Professor in Residence in the Department of Medicine, Division of Infectious Diseases, at UCSD. Dr Ellis is Associate Professor in the Department of Neurosciences at UCSD.

gressive multifocal leukoencephalopathy (PML), or cryptococcal meningitis.

One strategy was previously validated by demonstrating that higher regimen estimates of neuroeffectiveness were associated with lower HIV RNA levels in CSF.[5] At this year's conference, investigators from the National Institute of Infectious Diseases (Rome) further validated this CNS penetration-effectiveness (CPE) ranking approach, also known as CHARTER ranks, by comparing it with another system they had used in previously published analyses. In this observational study of 185 HIV-infected volunteers, neuropsychologic test batteries were administered before antiretroviral therapy initiation and at follow-up (Abstract 391). Results using the 2 ranking systems were compared with changes in normatively adjusted neuropsychologic summary scores from baseline to the last observation. Half (50%) of the subjects had impaired neuropsychologic performance at baseline. Higher CPE rank, consistent with greater neuroeffectiveness, correlated with greater improvements in neuropsychologic performance. In contrast, higher estimates of neuroeffectiveness with the alternative ranking approach did not show such correlation.

These findings were confirmed by another longitudinal study (Abstract 68). In this analysis of volunteers with HAND, Letendre and colleagues also identified that higher CPE rank was associated with greater improvement in neuropsychologic performance. Of note, application of the CHARTER ranking system to the treatment of people with HAND is being tested in an ongoing, National Institutes of Health–funded, prospective, randomized clinical trial.[6]

The importance of considering the neuroeffectiveness of antiretroviral therapy was highlighted by 2 other studies. Everall and colleagues (Abstract 67) presented data from 374 volunteers who enrolled in the National NeuroAIDS Tissue Consortium (NNTC) before dying with HIV and AIDS. Neuropathologists from NNTC examined brain tissue obtained at autopsy, identifying that 76 (20%) had evidence of HIV-associated brain pathology, defined as evidence of HIV leukoencephalopathy or HIV micro-glial nodular encephalitis. Those who had HIV-associated brain pathology at autopsy had more advanced immunosuppression (lower current and nadir plasma CD4+ cell counts) and higher plasma HIV RNA levels before death and, consistent with these findings, were less likely to report use of antiretroviral therapy during the antemortem observation period. This analysis used a variation of the CPE ranking approach, summing the CPE ranks for all antiretroviral drugs reported during the antemortem observation period rather than for a single regimen. Estimates of greater cumulative neuroeffectiveness (ie, higher CPE ranks) were associated with a lower likelihood of HBP at autopsy ($P = .03$).

An interesting additional finding was that volunteers who reported use of a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) during the antemortem observation period had a substantially lower likelihood of HIV-associated brain pathology at autopsy (NNRTI-containing regimen, 12%, vs protease inhibitor [PI]-containing regimen without an NNRTI, 22%, vs no antiretroviral therapy, 28%; $P = .03$). The neuroeffectiveness of NNRTIs, like nevirapine, is supported by this analysis of nearly 400 people, but the current analysis does not distinguish whether the observed associations might be attributable to other factors linked to NNRTI use, like less antiretroviral experience, better antiretroviral adherence, or the theoretically reduced neuropathogenicity of some drug resistance mutations in the brain.

The idea that some drug resistance mutations are less neuropathogenic than others was supported by data presented by Hightower and colleagues (Abstract 394). This analysis builds on the observations that some antiretroviral resistance mutations result in reduced replication capacity and may be associated with lower viral loads and decreased virulence (eg, see references[7-9]). In this study of 94 volunteers, drug resistance mutations were detectable in 48 (51%), and the most common resistance-associated mutations were 184V/I (20%) and K103N (15%). Drug resistance, particularly M184V/I, was associated with lower HIV RNA levels in CSF (2.6 vs 3.3 $\log_{10}$ copies/mL, $P = .009$)—but not in plasma—and better neuropsychologic performance, particularly among those who had definite normal or definite impaired performance ($P = .05$). This analysis also identified that higher HIV RNA levels in CSF were associated with worse neuropsychologic performance but only among those who did not have drug resistance mutations, providing a possible explanation for the weakening of this relationship in the combination antiretroviral therapy era (eg, see reference[10]).

Using data from the FHDH (French Hospital Database on HIV) cohort, Gasnault and colleagues showed that the benefits of neuroeffective antiretroviral therapy may not be limited to the neurologic complications of HIV alone but may also improve survival in those who have CNS opportunistic diseases (Abstract 385). In a retrospective analysis of more than 1400 individuals, they found that survival after a PML diagnosis improved dramatically in the combination antiretroviral therapy era as compared with earlier treatment periods.

Only 20% of individuals who were diagnosed with PML between 1992 and 1995 survived 1 year. In comparison, 54% of individuals survived 1 year for the other 3 treatment periods (1996-1998, 1999-2002, 2003-2004). Survival was lowest among those who did not take antiretroviral therapy. Among those who did take antiretroviral therapy, regimens with better estimated neuroeffectiveness (CPE ranks of at least 1.5) had a 6-fold lower risk of death even after adjusting for other potentially influential demographic factors, such as age, AIDS diagnosis before PML diagnosis, nadir plasma CD4+ cell count, sex, and HIV transmission risk factor.

These results suggest that control of HIV replication in the CNS plays a role in recovery from PML. A limitation of this study was its failure to account for the number and potency of antiretroviral drugs in patients' regimens; this information would provide some assurance that the effects were the result of potency in the CNS specifically, rather than simply overall systemic efficacy or immune recovery. For instance, Gasnault

also demonstrated a survival benefit (77% at 6 months) in an interim analysis of 26 individuals who enrolled in a trial of intensified antiretroviral therapy (tenofovir-emtricitabine-efavirenz-lopinavir-ritonavir-enfuvirtide) for PML that was reported at the 2007 conference.[11] Although the study regimen selected for this trial included drugs that are more (lopinavir-ritonavir, emtricitabine) and less (tenofovir, efavirenz, enfuvirtide) neuroeffective, survival was linked to recovery of JC virus (JCV)–specific immune responses, emphasizing that recovery from PML probably requires both viral and host factors.

A contrasting viewpoint to the idea that some antiretroviral drugs are neuroprotective is that some may directly or indirectly injure the brain. Data from Husstedt and colleagues support direct injury by some antiretroviral drugs, namely the dideoxy-nRTIs (DDNs) didanosine, stavudine, and zalcitabine (Abstract 389). The toxic effects of these drugs on the brain have long been suspected based on their link to peripheral neuropathy (eg, see reference[12]) and to a neuromuscular weakness syndrome (stavudine[13]).

In a retrospective, cross-sectional analysis, data from 60 individuals taking antiretroviral therapy that included DDNs (mean duration, 19 months) were compared with those of controls taking antiretroviral therapy without DDNs. Use of DDNs was associated with prolonged event-related potentials (P3 component, 448 milliseconds, vs 431 milliseconds; $P < .02$) and a higher prevalence of impaired neuropsychologic performance ($P < .009$). These findings need to be confirmed in longitudinal and interventional studies but, if confirmed, would have important implications for the use of DDNs, which continue to be commonly used in resource-limited settings.

Favoring the concept of indirect injury of the brain by antiretroviral therapy, Letendre and colleagues presented data supporting that an intended consequence of effective antiretroviral therapy, immune recovery, might injure the brain under certain circumstances, such as when individuals have preexisting HAND (Abstract 68). In this analysis, 25 individuals with HAND initiated a new antiretroviral therapy regimen and were observed for 24 weeks. Nearly all subjects (88%) had improved neuropsychologic performance by 24 weeks, but the extent of improvement varied widely between individuals (change in the Global Deficit Score, median, −0.53, interquartile range, −0.79 to −0.19). The neuropsychologic performance of 15 (60%) normalized by 24 weeks. Those who improved the least (or not at all) had lower nadir blood CD4+ cell counts and higher HIV RNA levels in CSF before treatment and greater increases in blood CD8+ cell counts during treatment (linear regression model, r^2, 0.48; $P = .0001$).

This combination of lower CD4+ cell counts before treatment, higher antigen levels within the CNS, and greater expansion of CD8+ cells, which can home to and injure the nervous system,[14] suggests that recovery from HAND may be limited by a neuroimmune process directed at HIV antigens that is similar to the immune reconstitution inflammatory syndrome (IRIS, eg, see references[15,16]). Thus, antiretroviral therapy might be a double-edged sword that can either benefit or injure the brain depending on clinical circumstances.

A combination of viral, host, and comorbid factors is thought to contribute to HAND. For instance, highly neurotropic HIV isolates can be isolated from brain tissue from individuals dying of HAND, and these isolates replicate with reduced dependence on CD4[17] and enhanced macrophage tropism.[18] Host factors, such as variability in the chemokine CCL2, have also been linked to the risk of HAND.[19,20] Comorbidities are a third important determinant of risk and include disparate conditions such as coinfection with other pathogens (eg, hepatitis C virus [HCV][21]), use of recreational stimulants (eg, methamphetamine[22]) and advancing age.[23]

Susceptibility to NeuroAIDS: HIV Correlates

The importance of the HIV envelope in HAND was supported by work from Pillai and colleagues from the CHARTER Group. To validate their previous finding that a serine at position 5 of the V3 loop of HIV-1 *gp160* (N300S) was associated with HAND,[24] the investigators used clonal RNA sequencing of *C2-V3 env* to identify this mutation in matched CSF and blood plasma specimens from 39 volunteers, 19 of whom had HAND. As hypothesized, the N300S mutation was more common in volunteers who had HAND ($P < .032$) than in those without HAND. The positive predictive value of this mutation for the presence of HAND was high (86%), although the sensitivity was low (33.3%). Thus, the investigators confirmed their prior finding in an independent cohort, but the poor sensitivity in this analysis argues against the clinical utility of this mutation for identifying presence or risk of HAND.

HIV enters macrophages and microglia, its major target cells in the brain, primarily via CCR5.[25] Consistent with this, several studies have identified that brain-derived HIV isolates from people dying of AIDS-related complications are more likely than not to use CCR5[26] and be macrophage-tropic even when isolates from tissues outside the nervous system, such as the spleen, used CXCR4 and replicated in T-cell lines.[27]

Dual-mixed HIV strains have only been infrequently isolated from brain tissue so Gray and colleagues characterized isolates from 2 individuals (1 with HAND, 1 with CNS lymphoma) to better understand how they influence the HIV neuropathogenesis (Abstract 397). Even though the envelope proteins derived from brain were dual-mixed, they had greater fusogenicity with CCR5. In contrast, matched dual-mixed envelope proteins from spleen or blood had greater fusogenicity with CXCR4. The investigators identified that all clones from brain tissue of the individual dying with HAND were missing an asparagine residue at position 11 in the V3 loop (R306S), but that it was conserved in spleen clones. They then mutated the brain-derived clones to 306R and the spleen-derived clones to 306S, demonstrating reduced CCR5-mediated fusion of the brain clones and reduced CXCR4-mediated

fusion of the spleen clones, which supported the importance of this mutation in determining coreceptor usage in compartmentalized brain isolates. Together, these findings support that dual-mixed HIV isolates still predominantly use CCR5 in the brain, which has implications for the neuroeffectiveness of CCR5 inhibitors like maraviroc and vicriviroc even when dual-mixed HIV is present in blood.

In addition to *env*, other HIV genes, such as *tat*, have been implicated in neuropathogenesis. Most of the investigations supporting the role of HIV genes derive from the United States and Europe, where subtype-B HIV infections predominate, but non-subtype-B infections are more common in the rest of the world. The genetic differences between HIV clades may influence neuropathogenicity.[28] Three studies at this year's conference assessed the potential influence of viral diversity on HIV neurologic complications.

Sacktor and colleagues studied HIV-infected individuals in Uganda, where HIV clades A, C, and D are common (Abstract 404b). Sixty antiretroviral therapy–naive, HIV-seropositive individuals from Kampala who had blood CD4+ counts below 200 cells/μL were evaluated. Subtype assignments were generated by sequence analysis based on portions of *gag* and *gp41*. Evaluations included a neurological examination, an 8-part neuropsychologic test battery, and assessments of daily function. A higher proportion of subjects infected with HIV subtype D met study criteria for dementia (8/9, 89%), compared with only 24% (7/33) of those infected with subtype A. This difference was not explained by group differences in age, education, sex, blood CD4+ cell counts, or plasma HIV RNA levels. The mechanism by which subtype D may confer greater neurovirulence is yet to be determined. A strength of this study was that all patients were from the same geographic region, reducing the impact of factors other than subtype that could lead to observed differences in HIV-associated neurologic disease.

Robertson and colleagues reported the baseline findings of a multisite, international study performed in Brazil, India, Malawi, Peru, South Africa, Thailand, and Zimbabwe (Abstract 388), the most widely representative assessment of neurocognitive complications of HIV in international settings to date. Before initiation of antiretroviral therapy, subjects underwent a structured neurologic examination and a brief neuropsychologic assessment that focused on motor performance.

In contrast to studies using more comprehensive neuropsychologic assessments, these screening tests revealed a low prevalence of HIV dementia (2 cases, 0.2%) and minor neurocognitive disorder (19 cases, 2.2%) among the 860 enrolled patients. In contrast, 87 subjects (10%) had evidence of peripheral neuropathy. Of note, neurocognitive test performance varied substantially between countries, which might be explained by many factors, including host genetics, cultural customs, opportunistic infections, coinfections, substance use, HIV subtypes, or variation in test administration.

In a third international study, Valcour and colleagues performed 2 analyses of data from Thai volunteers infected with the AE circulating recombinant form (CRF, or CRF01_AE) of HIV (Abstract 387). First, in a cross-sectional analysis of data from the SEARCH 005 study, 36% (8/22) of a cohort with undetectable plasma HIV RNA levels who were nested in the 2NN clinical trial,[29] had mildly impaired global neuropsychologic performance. Second, in a prospective, treatment trial (SEARCH 001),[30] antiretroviral therapy was administered to 30 volunteers, half of whom had HAND. Even though HIV RNA levels were reduced below detection, those who had HAND continued to perform worse at 6 months (P = .08) and 12 (P = .17) months, confirming the limited effectiveness of combination antiretroviral therapy in individuals infected with CRF01_AE.

Susceptibility to NeuroAIDS: Host Correlates

Genetic variants that influence the phenotype of CNS disease in humans are well known, particularly in neuroimmunology. For example, multiple sclerosis is associated with certain susceptible major histocompatibility complex (MHC) haplotypes. The MHC is present in many species, and the human form is termed the human leukocyte antigen (HLA) system. This group of genes resides on chromosome 6 and encodes cell-surface antigen-presenting proteins and other genes. The major HLA antigens are essential elements in immune function and are broadly categorized as either class I or class II. Class I antigens (A, B, and C) present peptides from inside the cell (including viral peptides), and class II antigens (DR, DP, and DQ) present phagocytosed antigens from outside of the cell to T cells. Previous analyses have identified that MHC class II expression was elevated in the brains of individuals dying with HIV encephalitis[31] and was restricted to macrophages and microglia, the primary target cells of HIV in the brain.

In this context, Mankowski and colleagues reported an HLA haplotype that may specifically affect CNS retroviral disease (Abstract 72). They studied an accelerated simian immunodeficiency virus (SIV) encephalitis model in pigtailed macaques. This animal model is characterized by a shortened asymptomatic interval and an increased incidence of CNS disease compared with other SIV models. In 60 macaques, an MHC allele, *Mane-A*10*, seemed to protect animals from SIV encephalitis (24% vs 67%; odds ratio, 6.0; P = .003) but was unrelated to plasma SIV RNA levels or blood CD4+ cell counts, suggesting that protection from CNS disease was not related to slower immune disease progression but rather to a CNS-specific action of the allele. This concept was supported when lower levels of SIV RNA, activated (CD68+) macrophages, and amyloid precursor proteins were identified in the brains of macaques that had the protective *Mane-A*10* allele than in the control animals.

Migration of lymphocytes and macrophages is an important component of the host response to HIV in the nervous system and can lead to persistent immune-mediated injury despite apparent control of HIV in blood by antiretroviral therapy. Even though CD8+

T cells, such as effector memory and cytotoxic T cells, play important roles in control of HIV in the brain and other organs, they can also cause injury to host tissues, particularly in the context of antiretroviral therapy–induced immune recovery.

Two studies provided supportive evidence of the importance of CD8+ T cells in the nervous system by surface-phenotyping cells from CSF. Sadagopal and colleagues (Abstract 396a) assessed the frequency of HIV-specific CD8+ T cells and their maturation phenotypes (CD45RO, CD57, and CCR7) using 9-color flow cytometry in 7 volunteers who had very low levels of HIV replication in plasma and very slowly progressive HIV disease ("immune controllers"). The frequencies of HIV-specific CD8+ T cells in CSF averaged 2.4-fold greater than in blood ($P = .0004$). The CSF cells were also expanded with phytohemagglutinin and evaluated for frequency of HIV-specific T cells by flow cytometry and for interferon gamma production to HLA-class I–restricted optimal peptides by enzyme-linked immunosorbent spot assay. Expanded cells from CSF responded to a greater number of HIV-specific HLA class I–restricted optimal peptides ($P = .036$) and at higher frequencies than expanded cells from blood ($P = .012$). The enrichment of HIV-specific CD8+ T cells in CSF relative to blood in these individuals, who were immunocompetent and had low levels of HIV RNA in CSF and no neurocognitive symptoms, argues that these cells are important for control of HIV in the CNS. These findings, however, also reinforce concerns that the expansion of CD8+ T cells after initiation of antiretroviral therapy may lead to a robust immune response to HIV antigens in the brain with resulting injury.

In a second study, Spudich and colleagues (Abstract 411) compared activation markers of blood and CSF T cells obtained from individuals recently infected with HIV with those who were chronically infected. The investigators identified high levels of CD8+ T-cell activation in cells from CSF, but the relationship with HIV RNA levels varied by disease stage. Consistent with the idea that CD8+ T cells help control HIV in the CNS, volunteers who had early HIV infection and high levels of activated CD8+ T cells in CSF had low levels of HIV RNA in CSF. In contrast, volunteers who had chronic HIV infection and high levels of activated CD8+ T cells in CSF had high levels of HIV RNA in CSF, suggesting that the T cells were homing to the CNS in response to HIV antigens but were ineffective in controlling replication. Together, the findings from these 2 studies suggest that CD8+ T cells help control HIV replication in the nervous system in early disease, but when HIV disease advances to later stages, the frequency and activation of these cells increase in the nervous system, possibly tipping the scales in favor of injury rather than control.

Susceptibility to NeuroAIDS: Comorbidities

Recent findings indicate that the majority of all CD4+ T lymphocytes are lost during acute HIV infection, with mucosal compartments being most severely affected. The frequency of infection is very high in gut CD4+ T cells and is associated with increased gut permeability and microbial translocation, which is evident as circulating lipopolysaccharide (LPS).[32] Higher LPS levels in blood correlate with CD8+ T-cell activation[33] and so may help drive HIV disease progression. Because LPS can also damage the blood-brain barrier and increase monocyte trafficking into the nervous system, Ancuta and colleagues studied its effect in 119 HIV-seropositive volunteers, 82 of whom had neurocognitive impairment (Abstract 69). They found that plasma levels of LPS were higher in subjects who had HIV-associated dementia (> 79 pg/mL; odds ratio, 3.8; $P = .007$) but not milder forms of HAND and that this association remained statistically significant even after adjusting for CD4+ cell counts and plasma HIV RNA levels. Thus, immune activation stemming from HIV-mediated injury of the gut and microbial translocation may be an important determinant of risk for progression to both AIDS and neuroAIDS.

Ancuta and colleagues also identified that plasma LPS levels were higher in individuals coinfected with HCV, supporting that this may be another mechanism by which this common comorbidity may injure the brain. Two studies supported the continued importance of HCV coinfection as a risk factor for HAND. Letendre and colleagues presented data from 401 volunteers in Anhui, China, in collaboration with Peking University and the National Center for AIDS/STD Control and Prevention in China (Abstract 413). In this cohort of former plasma donors, the prevalence of HCV seropositivity was high (46% if HIV-seropositive, 26% if HIV-seronegative) even though none of the volunteers used injection recreational drugs. Among all subjects, those who had impaired neuropsychologic performance were much more likely to be HCV coinfected (50% vs 31%, $P < .001$). Among those who were HIV-seropositive, HCV and AIDS were independently associated with HAND (50% of those who had both conditions also had HAND). Thus, in former plasma donors in China, HCV may be an even more important comorbidity predisposing HIV-seropositive individuals to brain injury than it is in the United States and Europe.

Fishman and colleagues presented important new evidence that HCV can adapt to cells in the CNS compartment (Abstract 414). They found that HCV was present in brain tissue from 7 of 13 viremic patients (54%), as determined by 5'-untranslated-region and *E1*-envelope-gene analysis. They also identified that *N*-linked glycosylation sites were mutated in the consensus brain sequences of 4 patients and that these differed from sequences obtained from plasma and liver. Quasispecies analysis revealed that several mutations present in clones from more than 1 brain region, such as the A113G mutation found in 10% of cerebellum and medulla amplicons, were absent from amplicons derived from liver and plasma. These findings further support the idea that the brain injury evident on neuropsychologic testing and neuroimaging of HCV-seropositive individuals may be attrib-

utable, at least in part, to infection of glial cells, rather than merely a consequence of liver disease and systemic inflammation.

Peripheral Neuropathy

Neuropathic pain is a frequent neurologic problem affecting HIV-infected patients. Unfortunately, successful virologic suppression and immune restoration with antiretroviral therapy does not necessarily reverse or ameliorate this disabling condition. To complicate matters, some antiretroviral drugs, such as the DDNs, can also damage peripheral nerves. This toxicity of DDNs is well recognized, but recent epidemiologic and in vitro data have also linked PIs to neuropathy. Ellis and colleagues in the CHARTER study group assessed this association in 1159 HIV-infected subjects enrolled in a large, prospective, observational, multicenter North American study (Abstract 393). Over half (58%) met criteria for HIV-associated distal sensory polyneuropathy (DSPN) by neurologic examination, and most (58%) of those with clinical examination findings indicating DSPN also had distressing sensory symptoms. Subjects were grouped into categories according to past and current exposure to any antiretroviral drugs and to PIs. Disease indicators such as nadir blood CD4+ cell count, plasma viral load, and duration of HIV infection, as well as advancing age and exposure to DDNs, were compared with DSPN in multivariate models.

In univariate analyses, both past and current PI exposure did increase the risk of DSPN. After adjusting for previously validated concomitant risk factors in multivariate models, however, the investigators found that PI exposure did not confer an increased risk of DSPN over that in subjects who had never used antiretroviral therapy. Neither duration of PI use nor exposure to individual PI drugs was associated with DSPN in multivariate models. These data suggest that the independent risk attributable to PIs, if any, is very small. This risk must be weighed against the important role of PIs in modern antiretroviral therapy regimens.

Other Neurologic Infections

Cryptococcal Meningitis

Two abstracts examined the role of antiretroviral therapy in prognosis of cryptococcal meningitis and of quantitation of serum cryptococcal antigen in diagnosis and prognosis of cryptococcal meningitis. Bisson and colleagues reviewed patients with first episodes of cryptococcal meningitis in Botswana to examine the effects of prior antiretroviral therapy on outcomes of cryptococcal meningitis therapy (Abstract 1010). Of 92 treated patients, 26 had received antiretroviral therapy for an average of about 3 months before their cryptococcal meningitis diagnosis. All patients were induced with amphotericin B (1 mg/kg/day) for 2 weeks, followed by consolidation with fluconazole 400 mg per day, followed by prophylaxis with 200 mg per day.

In-hospital mortality was lower (8% vs 21%) in those who took prior antiretroviral therapy than in all others. This difference was statistically significant in an age- and sex-adjusted analysis (odds ratio, 0.19; $P = .05$). This and another study from South Africa[34] showed that antiretroviral therapy at the time of a first admission with cryptococcal meningitis is associated with lower risk of death during antifungal therapy. Fear of inducing IRIS-related complications of cryptococcal meningitis should not be a barrier to beginning antiretroviral therapy before development of an opportunistic infection. Although early initiation of antiretroviral therapy in cryptococcal meningitis patients who are not on antiretroviral therapy was not directly assessed by the study, these findings and the results of a randomized clinical trial (Abstract 142) argue in its favor.

In a retrospective review of 42 cases of cryptococcal disease over 7 years, Kandel and colleagues examined the predictive value of serum titers of cryptococcal antigen (sCrAg) in the initial diagnosis and prognosis of cryptococcal complications (Abstract 1011). Median titers of sCrAg were markedly higher in those with cryptococcal meningitis than in those with other complications (1:512 vs 1:16, respectively). Over half (11 of 21) who met criteria for cryptococcal meningitis had 1 or more complications of death (2), intracranial hypertension (9), prolonged alteration of consciousness (3), or persistent hydrocephalus (1). Thus, adverse prognosis from cryptococcal meningitis was also associated with higher sCrAg titer. Patients with sCrAg titers of at least 1:2048 presenting with initial symptomatic cryptococcal infection have at least a 70% chance of developing complicated cryptococcal meningitis. If lumbar puncture must be delayed in such patients, regimens adequate for treating cryptococcal meningitis should still be used.

Progressive Multifocal Leukoencephalopathy

Two abstracts examined determinants of prognosis in PML. To develop biomarkers of PML prognosis, Marzocchetti compared 73 HIV-seropositive, PML-positive patients with 20 HIV-seropositive, PML-negative matched controls and 23 HIV-seronegative, PML-positive and 15 HIV-seronegative, PML-negative unmatched controls (Abstract 71). Concentrations of JCV DNA in peripheral blood mononuclear cells, plasma, and urine were measured by PCR-based assays, and CD8 + cytotoxic T-lymphocyte (CTL) responses against JCV VP1 protein were assessed by tetramer staining in HLA *A*0201*-positive persons and by chromium release assays in others. Survival was better in HIV-seropositive (77%) than in HIV-seronegative (60%) PML patients. In PML patients, JCV was detectable more frequently in plasma (56% vs 30%) and urine (61% vs 27%) than in matched HIV-seropositive controls, but JCV titers were similar. In HIV-seropositive, PML-positive patients, those who had detectable CTL responses within 1 year of diagnosis had markedly better survival than those who did not (83% vs 33%). Survival was also better in those with higher blood CD4+ counts at PML diagnosis (> 200 cells/μL, 92%, vs < 200 cells/μL, 70%).

Two studies highlighted manifestations of PML in the cerebellum. The

first described features of "unmasked" PML, that is, PML diagnosed within 6 months of starting antiretroviral therapy. Because IRIS usually occurs in the first months after starting antiretroviral therapy, it might play a role in cases of PML that occur during that period. In the first study, Sidhu and McCutchan examined records of 20 HIV-seropositive PML patients whose PML was diagnosed between 1996 and 2006 to assess the relationship of PML onset and potent antiretroviral therapy (Abstract 417). Unmasked PML was seen in 8 (40%) patients and was diagnosed a median of 80 days (range, 47-140 days) after starting antiretroviral therapy.

In comparison, PML was diagnosed in 6 patients before they started antiretroviral therapy, and the remaining 6 had undergone antiretroviral therapy for more than 6 months before receiving the PML diagnosis. Among the 8 cases of unmasked PML, disease was confined to the posterior fossa (cerebellum and peduncles) in 4, 3 of whom had cranial nerve palsies involving cranial nerves VI and VII. Only 3 of 8 had enhancement on magnetic resonance imaging, all improved, and 5 of 8 survived for more than 400 days (the 3 others were lost to follow-up at 10, 16, and 69 days). Unmasked PML does not require evidence of severe IRIS, as manifested by enhancement on magnetic resonance imaging, and appears to have a relatively good prognosis. Reasons for its unusually common localization to the posterior fossa (7% in another large pre–antiretroviral-therapy-PML case series and 50% in this series) are unclear.

A second study stems from a recently described,[35] progressive cerebellar disease of HIV-infected patients called JCV granule cell neuronopathy. This syndrome is distinct from PML, which commonly affects cerebral white matter. To determine the prevalence of JCV in granule cell neurons (GCNs) in HIV-seropositive patients, brains from 44 patients with HIV and PML and 44 controls with HIV but not PML were examined by Wuthrich and colleagues using immunohistochemical and immunofluorescence methods (Abstract 418). A substantial proportion of the HIV-seropositive, PML-positive patients (72%) had detectable JCV in their GCNs compared with HIV-seropositive, PML-negative controls (0 of 44). The JCV VP1 protein, which is associated with productive infection, was found infrequently, supporting the presence of a latent or abortive JCV infection of GCNs. Because JCV infection of GCN occurred only in the context of PML in this series, the analysis does not support that this syndrome occurs independently of PML. However, restricted infection of GCNs may provide important insights into the initiation and progression of this debilitating disorder.

CNS Syphilis

The number of B cells is higher in the CSF of HIV-seropositive patients with neurosyphilis than in HIV-seronegative patients with neurosyphilis[36] or HIV-seropositive patients with uncomplicated syphilis.[37] To build on these observations, Marra and colleagues examined levels of CD19+ B cells and the B-cell chemokine CXCL13 in the CSF of 180 HIV-seropositive individuals who had either syphilis or neurosyphilis (Abstract 407). Levels of CSF CXCL13 and B cells were elevated in neurosyphilis, and their levels were highly correlated (r^2, 0.69). Using a more inclusive definition of neurosyphilis (CSF VDRL-test-positive or CSF leukocyte level above 20/μL), the investigators found that higher levels of CSF CXCL13 (odds ratio, 15.5; $P < .001$) or CD19+ B cells (odds ratio, 12.8; $P < .001$) were each strongly associated with neurosyphilis, even after adjusting for antiretroviral therapy use. Although these data confirm the importance of B cells in treponemal neuropathogenesis, they also identify that measurement of CXCL13, which can be performed using a currently available commercial immunoassay, may be an important new diagnostic test for neurosyphilis.

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