Neurologic Complications of HIV Disease and Their Treatment

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Important new information regarding neurologic complications of HIV disease was presented at the 2007 Conference on Retroviruses and Opportunistic Infections. In addition to presentations on pathogenesis and treatment of neurologic complications, the conference included findings that have implications for the management of HIV disease outside the nervous system. Key findings included that the distribution of antiretrovirals into the central nervous system may influence the effectiveness of treatment outside this protected compartment; that postponing initiation of therapy until blood CD4+ counts fall to 300 cells/μL may increase the risk for HIV-associated neurocognitive impairment but interruption of antiretroviral therapy in individuals with high CD4+ counts may have neuropsychologic benefits; that substantial changes, including macrophage activation and neuronal injury can occur shortly after HIV transmission; that HIV can influence neural progenitor cells to decrease neuronal differentiation; that newer neuroimaging technologies, such as diffusion tensor imaging and blood oxygen level-dependent functional magnetic resonance imaging can identify important effects of HIV on the brain such as alterations in cerebral oxygen consumption; that serotonin reuptake inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors may reduce HIV RNA levels in cerebral spinal fluid; and that erythropoietin and the non-immunosuppressive immunophilin ligand, GPI-1046, may improve HIV-associated injury of peripheral nerves. The conference also included an important focus on JC virus encephalitis (also known as progressive multifocal leukoencephalopathy).

Reports with Implications for Systemic Disease

Important new information regarding neurologic complications of HIV disease was presented at the 2007 Conference on Retroviruses and Opportunistic Infections. Reports on host and viral influences on pathogenesis, treatment of neurologic complications, newer neuroimaging methods, peripheral neuropathy, and JC virus encephalitis (JCV-E), also known as progressive multifocal leukoencephalopathy (PML), were included, as well as findings that have implications for the management of HIV disease outside the nervous system. Two studies examined the relationship between characteristics associated with antiretroviral distribution into the central nervous system (CNS) and HIV RNA levels in plasma. The relevant hypothesis for each of these analyses was that characteristics favoring better distribution of antiretroviral drugs throughout the body, including the nervous system, would lead to better control of HIV replication in plasma because (a) better distribution of antiretrovirals is associated with suppression of HIV RNA in cerebrospinal fluid (CSF)[1] and (b) reductions of HIV RNA in CSF are associated with reductions of HIV RNA in plasma.[2]

In the AIDS Clinical Trials Group (ACTG) 736 study, serial veni- and lumbar punctures (LP) were performed in 101 HIV-infected individuals before and after a change in antiretroviral therapy (Abstract 382b). The study confirmed that antiretroviral therapy regimens that contained a greater number of drugs with better distribution characteristics were more likely to suppress HIV RNA levels in CSF (odds ratio [OR], 5.0; P = .05). Notably, these same regimens were more likely to suppress HIV RNA levels in plasma as well (OR, 2.6; P = .03). The investigators also identified that previously untreated individuals were more likely to suppress HIV RNA in CSF and plasma (OR, 2.9; P = .02). Together, these findings extend the commonly held notion that the first regimen is the most likely to successfully reduce viral replication. Selection of an initial regimen that includes antiretroviral drugs with better distribution characteristics may further improve the chances for success.

An analysis from the Italian Cohort Naive Antiretrovirals Group (ICoNA) provided data complementary to these findings by analyzing the relationship between antiretroviral distribution characteristics and durability of the treatment response in plasma (Abstract 382a). This large cohort study assessed previously untreated individuals before and after initiating combination antiretroviral therapy. The investigators identified 2785 individuals who started antiretroviral therapy between 1997 and 2006 (the median number of individuals were enrolled in 2000) and who had suppressed HIV RNA levels below 80 copies/mL. This group identified those who experienced rebound replication (defined as 2 consecutive HIV RNA values above 400 copies/mL), calculated the rate of rebound per 100 person-years of follow up, and determined the relationships of this measure with CD4+ cell counts and the CNS Penetration-Effectiveness (CPE) score.[1] They found that lower CPE scores (a reflection of worse distribution characteristics) seemed to be associated with higher rates of rebound among individuals

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with CD4+ counts below 200 cells/μL. In a multivariate Poisson regression analysis that adjusted for 11 cofactors, individuals with CD4+ counts below 200 cells/μL who took regimens with lower CPE scores trended toward a higher risk of rebound (adjusted relative risk [RR], 0.04; 95% confidence interval [CI], 0.01-1.61). Among individuals with CD4+ counts above 350 cells/μL, however, higher CPE scores were associated with a higher rate of rebound (adjusted RR, 4.54; 95% CI; 1.30-15.89). The observed relationships should be confirmed and their mechanisms explained but the data stand as provocative evidence that antiretroviral distribution may influence the durability of treatment response, perhaps for the better in some but for the worse in others.

Current guidelines recommend that the decision to initiate antiretroviral therapy in asymptomatic persons be individualized when the CD4+ count falls between 200 and 350 cells/μL.[3] The decision to start therapy typically involves discussion with the patient regarding the different treatment options available, dosing preferences, toxicities, adherence, and drug resistance. Reducing the risk of brain injury, however, is typically not included in these discussions. Although potent combination antiretroviral therapy has generally reduced the incidence of HIV-associated neurocognitive impairment (HNCI), few studies have quantified the impact of postponing therapy on it. If initiating therapy at CD4+ counts above 300 cells/μL had benefits for the nervous system, it would be another important consideration for patients. Muñoz-Moreno and colleagues attempted to answer this question by comparing the prevalence of HNCI with the CD4+ counts at which individuals first initiated antiretroviral therapy (Abstract 383). The analysis was small (n = 64) and descriptive but the investigators identified that fewer individuals had impaired neuropsychologic (NP) performance when antiretroviral therapy was initiated at higher CD4+ counts (>300 cells/μL, 56%; ≤300 cells/μL, 64%; >250 cells/μL, 53%; ≤250 cells/μL, 67%; >200 cells/μL, 53%; ≤200 cells/μL, 73%). This finding is consistent with larger studies that have identified associations between higher HNCI prevalence and lower CD4+ count nadirs and argues that patients should be counseled that delaying therapy may increase their risk for HIV-associated brain injury.

Treatment interruption is no longer routinely recommended since it increases the risk of HIV disease progression and death. Despite this, many individuals continue to interrupt therapy for a variety of reasons, including toxicities (eg, dyslipidemias, hepatitis) and psychosocial factors. Because stopping antiretroviral therapy results in rebounds in HIV replication and loss of CD4+ cells, it may also carry a potential risk for neurocognitive decline. Arguing against this, however, were data from ACTG 5170 study that indicate that stopping therapy may actually have NP benefits (Abstract 113). Robertson and colleagues prospectively studied individuals before and after treatment interruption as well as some individuals who reinitiated antiretroviral therapy. These individuals had generally not experienced advanced immunosuppression (median CD4+ nadir, 436 cells/μL) and had received antiretroviral therapy for a median of 4.5 years. Using a brief NP testing battery, changes in performance were evaluated at baseline and at 4 time points up to 96 weeks after antiretroviral therapy was stopped. The investigators saw small but statistically significant neurocognitive improvements at each follow-up evaluation. Because efavirenz is associated with CNS side effects, the investigators stratified the analyses by efavirenz use. Improvements in NP performance did not differ between those who did or did not use efavirenz. To determine if improvements over time were related to practice (improved performance resulting from familiarity with testing instruments) the investigators specifically evaluated improvement after the third testing session, after which the benefits of practice are minimal. Even after the third testing, NP performance continued to improve. In comparison, a subgroup of 46 individuals restarted antiretroviral therapy before week 26 and had no statistically significant deterioration or improvement in NP performance. Taken together with the findings of Muñoz-Moreno, delaying antiretroviral therapy until CD4+ counts fall below 300 cells/μL may increase risk for HIV-associated CNS injury but initiating antiretroviral therapy at CD4+ counts closer to 500 cells/μL may increase risk for antiretroviral therapy-associated CNS injury. These conclusions, however, should be confirmed before they influence treatment decisions.

Two other abstracts had treatment-related implications. To reduce the cost and toxicity of antiretroviral therapy, clinical investigators studied the use of potent, single-agent therapy (SAT), typically a ritonavir-boosted protease inhibitor (PI), such as atazanavir or lopinavir. PIs are usually extensively bound to plasma proteins, and only the unbound fraction is available for distribution to protected compartments. This practice thus raises concern regarding effectiveness in the CNS.

Yeh and colleagues provided evidence that SAT with lopinavir/ritonavir controlled HIV replication in the CSF of most individuals (Abstract 381). Only 12 individuals were included in this analysis; they enrolled in the parent study of SAT, Integrated Minority AIDS Network Incorporated-2 (IMANI-2), had plasma HIV RNA levels below 75 copies/mL after 24 weeks of therapy, and consented to LP. Among the 11 persons in the analysis (1 was excluded because of a traumatic LP), 10 (91%) had HIV RNA levels in CSF below 50 copies/mL. One individual, however, had up to 747 copies/mL of HIV RNA in CSF despite having the highest CSF lopinavir concentrations in the group and no evidence of mutations associated with reduced susceptibility to lopinavir in CSF. This individual had very high levels of monocyte chemotactic protein-1 (MCP-1) in CSF, a potently chemotactic protein that is associated with the CNS complications of HIV, arguing that this individual was predisposed to having a greater migration of replication-competent lymphocytes and monocytes into the CNS. The clini-

cal consequences of these elevated HIV RNA levels and MCP-1 levels are undetermined.

Clapham and others previously identified that HIV may adapt to the nervous system by increasing tropism for macrophages, in part by evolving an envelope that enables entry of cells that express only low levels of CD4 or CCR5. When adaptation occurs, it may have implications for the ability of 2 investigational classes of antiretrovirals, both monoclonal antibodies to CD4 and CCR5 antagonists, to control replication in the CNS. The investigators prepared pseudovirions from 10 brain- and 9 lymph node-derived envelopes by cotransfecting 293T cells with env + pSVIIIenv and env – pNL4.3 vectors, and then performed neutralization and inhibition experiments with a variety of proteins. They identified that better macrophage tropism was associated with reduced sensitivity to inhibition by CD4 monoclonal antibody. In addition, pseudovirions generated using the brain tissue of 2 individuals were more sensitive to TAK779 (a CCR5 antagonist) and b12 (an antibody for the CD4 binding site). No increased or decreased susceptibility to these or other inhibitors was seen for the other pseudovirions (Abstract 170).

Central Nervous System Complications

Host Pathogenesis

Many theories have been posited to explain vulnerability to CNS complications of HIV disease. These theories include elements attributable to the host (eg, production of inflammatory proteins, mediators of oxidative stress, and excitotoxic glutamate) and to the virus (eg, neuroadaptation and production of neurotoxic viral proteins). By better understanding pathogenesis, we hope to identify at-risk individuals and prevent neurologic complications from occurring. Once they occur, however, the goal is to understand mechanisms of recovery to enable selection of the best treatments. Investigations of neural progenitor cells (NPCs) may provide important insights into HIV neuropathogenesis.

The production of new neurons, or neurogenesis, is increased during neurodegenerative disorders. Stimulation of neurogenesis is being explored as a potential therapy for a variety of neurodegenerative disorders. The effects of HIV infection on NPCs are not known. Peng and colleagues studied human monocyte-derived macrophages (MDMs) infected with HIV-1 macrophage-tropic HIV strains or immune-activated with lipopolysaccharide (LPS) (Abstract 353). HIV-1-infected MDMs activated by LPS released soluble factors that substantially increased NPC proliferation. Despite overall increases in proliferation of NPCs, neuronal differentiation was inhibited and astrocyte differentiation was increased. Thus, the combined effects of HIV infection and immune stimulation in this model would be reduced neurogenesis and increased gliosis, which is consistent with the neuropathologic findings of HNCI. If applicable to humans, these data suggest that inhibiting the effects of HIV on neurogenesis may help to ameliorate brain injury in HIV infection.

Measurements of host biomarkers can play numerous roles in understanding and treating neuroAIDS, including identifying new pathways for in vitro investigation, providing confirmatory evidence of laboratory observations, identifying at-risk individuals, and monitoring therapy.[5] Studies performed primarily before the era of potent antiretroviral therapy validated several biomarkers that were associated with risk, including neopterin, beta-2-microglobulin, and MCP-1. None of these have consistently been associated with neuroAIDS in more recent studies, so there is a pressing need for new biomarker investigations of treated, impaired individuals.

Three studies used different approaches to identify relationships between host biomarkers and neurologic outcomes. Researchers from the Universities of Nebraska and Puerto Rico used an elegant but complex and labor-intensive proteomics approach to identify differential protein expression between neurologically symptomatic and asymptomatic individuals (Abstract 388). The investigators used 3 primary methods to accomplish this. First, they used 2-dimensional electrophoresis with differential gel electrophoresis (DIGE) technology to identify protein differences between the CSF of individuals with HNCI and those without it. Once these experiments identified proteins that differed between the groups, the second step was to use liquid chromatography and tandem mass spectrometry along with specialized software to identify the proteins. Once they identified the differential proteins, they used Western blot to confirm the presence of the protein in 1 group of specimens and its absence in the other group. This approach identified 90 protein spots with statistically significant differential expression. Fifty-two of these were selected for further analysis and this yielded high confidence identification of 19 proteins, including complement C3, gelsolin, vitamin D binding protein, procollagen C endopeptidase enhancer, clusterin, cystatin C, and neuronal cell adhesion molecule.

As demonstrated in these experiments, CSF from well-characterized research volunteers can be a very useful tool for understanding neuroAIDS. Since volumes of CSF are typically very limited and biomarker concentrations are often lower than in serum or plasma, sensitive assays that use only small volumes of CSF can be very valuable tools. A bead-based immunoassay system has these characteristics along with the substantial added ability to measure numerous analytes at once. Researchers from the United States, Sweden, and Italy used this system to simultaneously measure 29 proteins in CSF and blood specimens from 72 HIV-seropositive individuals without neurologic symptoms, 43 with AIDS dementia complex (ADC), 15 with early HIV infection, and 20 HIV-seronegative controls (Abstract 387). The team confirmed associations between ADC and MCP-1 and identified that another chemokine previously associated with ADC, interferon-inducible protein (IP)-10, was associated only with HIV serostatus but not ADC. They also identified associations between ADC

and 2 other proteins, interleukin-6 and interleukin-1 receptor antagonists in CSF. Interleukins have previously been linked to ADC[6,7] but this study provides a more recent validation of these findings and identifies that the bead-based immunoassay system may be a useful tool for future discovery and hypothesis-driven investigations.

The third study, from the CNS Antiretroviral Therapy Effects Research (CHARTER) study, measured 2 chemokines, MCP-1 and stromal cell-derived factor-1 (SDF-1), in CSF using routine plate-based immunoassays (Abstract 370). This analysis was distinctive in comparing chemokine concentrations in CSF with findings from morphometric analyses of magnetic resonance imaging (MRI) of the brain to build hypotheses about their relationship to NP performance. Higher MCP-1 levels were associated with greater volumes of abnormal white matter and higher SDF-1 levels were associated with greater volumes of cortical grey matter. These findings suggested that the 2 chemokines had opposing effects on cognition. When levels of these chemokines were compared with NP performance, this hypothesis was confirmed: Higher MCP-1 and lower SDF-1 levels were associated with worse NP performance. The association of MCP-1 with HNCI is well known, but the observation that SDF-1 may modify this effect is new.

Several other neuroimaging studies investigated links between HIV disease and brain injury. Similar to the CHARTER study, Tate and colleagues also evaluated white matter. Instead of morphometric methods, they used diffusion tensor imaging (DTI) to compare the fiber tract integrity of HIV-infected individuals with HIV-seronegative controls (Abstract 117). The control group had the highest fractional anisotropy (FA) and lowest mean diffusivity (MD) values (indicating maintenance of white matter integrity), although HIV-seropositive individuals with CD4+ counts above 350 cells/μL had intermediate FA and MD values, and those HIV-seropositive individuals with CD4+ counts below 350 cells/μL had the worst FA and MD values (indicating disruption of white matter tracts). DTI differences were most pronounced in the anterior regions of the corpus callosum with changes in FA and MD values being associated with neuropsychological measures of motor speed, semantic fluency, and free memory recall. DTI may thus have possible utility in studying the structural impact of HIV within the brain.

Ances and colleagues used single voxel magnetic resonance spectroscopy (MRS) to measure N-acetyl aspartate, choline, and creatine, as well as 2 novel markers– lactate, a marker of inflammation and anaerobic glycolysis, and lipid, an indicator of cell membrane turnover due to oxidative stress within the lenticular nuclei of the basal ganglia of individuals with HNCI and HIV-seronegative controls (Abstract 116). The groups did not differ in lenticular nuclei volume, N-acetyl aspartate and creatine, or choline and creatine. In contrast, the lactate/creatine ratio was significantly higher in individuals with HNCI and the ratio of the sum of lipid and lactate to creatine was significantly higher among all HIV-seropositive groups than in seronegative controls. The study identifies that HIV-associated inflammation and oxidative stress can be detected by measurement of lactate and lipids using MRS.

A second study from Ances and colleagues assessed HIV-infected individuals using blood oxygenation level-dependent functional MRI (BOLD-fMRI) (Abstract 377). Participants viewed a fixed number pattern in the center of a screen that corresponded to finger taps on a 4-button box within a 3-Tesla scanner. Changes in cerebral blood flow and cerebral metabolic rate of oxygen consumption (CMRO2) were studied within the lenticular nuclei of the basal ganglia of HIV-seropositive patients and seronegative controls. Both early and chronically HIV-infected individuals who had normal NP performance each had greater functional changes in cerebral blood flow and CMRO2 than seronegative controls, suggesting that even neurocognitively normal individuals may have derangements in presynaptic recycling of glutamate. Spudich and colleagues also studied individuals with early HIV infection using MRS (Abstract 115). N-acetyl aspartate, a marker of neuronal integrity, was significantly decreased in individuals with early infection compared with seronegative controls. Consistent with this observation, the researchers also identified that some individuals with early HIV infection, particularly those with neurologic symptoms, had elevated levels in CSF of biomarkers reflecting neuronal injury (total tau and neurofilament-light). An imaging marker of inflammation, choline, was increased and correlated with elevations of inflammatory biomarkers in CSF, such as neopterin. Together, these neuroimaging studies support that inflammation and injury of the brain occurs early in the course of HIV disease and before the onset of advanced immunosuppression.

HIV Pathogenesis

A number of reports focused on differences in HIV between individuals who experience neurologic complications and those who do not. Three of these focused on evidence of quantitative differences in HIV replication. In the same series of analyses of early HIV infection mentioned in the previous section, Spudich and colleagues also reported on HIV RNA levels in CSF in 42 individuals, identifying that they were substantially elevated with a median of 1700 copies/mL (Abstract 115). A quarter of individuals had levels exceeding 63,096 copies/mL, a very high value for CSF. Correlational analyses supported that these high values were linked to high plasma HIV RNA levels (increasing by 0.85 $\log_{10}$ copies/mL for each 1-$\log_{10}$ increase in plasma; $P < .001$) and to high leukocyte counts in CSF ($P < .01$). The high quality of their case definition data enabled the investigators to identify slow declines of HIV RNA levels in CSF of only 0.04 $\log_{10}$ copies/mL for each 10 days postexposure, suggesting that injury attributable to this substantial early replication of HIV in the CNS may be slow to resolve.

Several studies have demonstrated that higher HIV RNA levels in CSF, but not in plasma, were associated with

increased risk for current HNCI[8-10] and predicted risk for future HNCI.[11] Most of these studies, however, were performed in Western populations that were likely infected with clade B HIV, and before the widespread use of combination antiretroviral therapy. More recent studies have not as strongly linked evidence of greater HIV replication within the nervous system to neurologic outcomes,[12] possibly because effective antiretroviral therapy reduces HIV RNA levels in CSF below the quantitation limit of current commercial assays. Since ongoing, low-level HIV replication may be responsible for the high prevalence of HNCI in treatment-experienced individuals, different approaches are needed to better understand the contribution of HIV to brain injury in this population.

Shiramizu and colleagues used one approach to address this challenge: measurement of HIV DNA in peripheral blood mononuclear cells (PBMCs) (Abstract 114). This group has previously reported on the association between higher HIV DNA in PBMCs and HNCI,[13,14] but in this analysis, higher HIV DNA levels were present even in cognitively impaired, treatment-experienced individuals and only true in a subset of activated monocytes and macrophages (CD14+ and CD16+) that have been linked to HIV neuropathogenesis,[15] integrating complementary elements of 2 models of HIV neuropathogenesis.

Another approach to detecting ongoing HIV replication in treatment-experienced individuals is to use a more sensitive assay for HIV quantification in CSF. Using this approach, 1 recent study showed that 8 of 13 (62%) antiretroviral therapy-experienced subjects had more than 2 copies/mL of plasma HIV RNA but none surpassed this level in CSF.[16] In contrast, a second study showed that a minority of subjects (13 of 47, or 28%) taking successful antiretroviral therapy had more than 2.5 copies/mL of HIV RNA in CSF.[2] At the conference, the CHARTER Group identified that 62 of 125 (49.6%) CSF specimens that had less than 50 copies/mL of HIV RNA when assayed with an ultrasensitive assay still had detectable HIV RNA levels when assayed using a modified HIV-1 assay that had sensitivity levels of 2.5 copies/mL of HIV RNA (Abstract 369). Among a clinically relevant subgroup of 40 individuals who had fewer than 50 copies/mL of HIV RNA in both plasma and CSF, 17 (42%) still had detectable HIV RNA in CSF and, importantly, this was associated with poorer estimated antiretroviral distribution (median CPE score 1.5 vs 2.0; $P = .01$). These findings support the conclusion that the high prevalence of HNCI in treatment-experienced populations may be attributable to ongoing, low-level replication and that this may be due to poor distribution of antiretroviral drugs into the CNS.

Much of the clinical research in neuroAIDS to date has been performed in North American, European, and Australian populations, most of which are infected with clade B virus. Other clades, such as clade C, however, account for most of the HIV infections worldwide and some laboratory data suggest that they may be less neuropathogenic. For example, clade C virions may not replicate as well in microglia or brain macrophages.[17,18] Infection with clade C may lead to differing cellular expression of proteins or toxins.[19] Proteins encoded by clade C virus may have differing properties from those encoded by clade B.[20]

Most of the laboratory findings to date have focused on events outside the nervous system. This is important because recent data indicate that East Asian,[21] South Asian,[22,23] and African[24,25] populations have high, not low, prevalences of cognitive impairment. Jialin Zheng and colleagues performed experiments to investigate differences in neurotoxic glutamate production from MDMs infected with strains of either clade B and clade C (Abstract 354). Infection of MDMs with clinical clade B isolates was associated with greater production of glutamate than infection with clinical clade C isolates. Inter-clade differences in glutamate production were linked to inter-clade differences in reverse transcriptase activity. Conditioned media from MDM cultures were incubated with primary rat neuronal cultures, identifying that the observed differences in glutamate production were associated with inter-clade differences in neurotoxicity, ie, media from clade B-infected MDMs were associated with greater neuronal injury than those from clade C-infected MDMs. These results stand in contrast to existing clinical observations but may indicate that even though prevalences of cognitive syndromes are similar in clade B- and clade C-infected populations, the underlying mechanisms by which the brain is injured may differ, which has important implications for the treatment of neuroAIDS in international settings.

Treatment

The underlying premise of optimizing distribution of antiretroviral drugs into protected compartments is that improving control of HIV has benefits for the host. Recent efforts have focused on selecting the antiretroviral drugs to which the host's virus is susceptible and that also have the best distribution characteristics. Another approach is to improve distribution by redesigning antiretroviral formulations to target particular tissues. This has been attempted in the past by use of liposomal forms of antiretrovirals.[26-30] Bosket and colleagues developed and evaluated another delivery system in a mouse model. Experimental HIV encephalitis was first induced in severe combined immune-deficient mice by injecting their brains with HIV-infected macrophages. The investigators then used MRI to inject supermagnetic iron oxide nanoparticles as a tag to track monocytes as they crossed the blood-brain barrier. Some of the mice were also administered macrophages laden with indinavir nanoparticles. The investigators were able to demonstrate in vivo migration of macrophages to brain tissue, and also measured indinavir levels of 10 to 15 nanomolar 5 days after a single intravenous injection, a level that exceeds the median inhibitory concentration (IC_{50}) for wild-type virus. The brains of nanoparticle-treated mice also showed reduced p24 staining, suggesting improvements in HIV encephalitis. This approach would

be even more impressive if it could improve delivery of antiretroviral drugs that penetrate more poorly than indinavir, which has the best distribution to the CNS among the PI class.[31]

Another approach to treating the CNS would be to reduce migration of HIV-producing cells across the blood-brain barrier. Effective antiretroviral therapy typically reduces replication but may be incompletely effective and does not target specific cell types such as the CD14+ and CD16+ monocytes that have been linked to HNCI.[15,31] Williams and colleagues reasoned that depletion of these highly activated cells would reduce their migration across the blood-brain barrier, reduce delivery of HIV and toxic inflammatory products to the CNS, and ultimately limit brain injury (Abstract 364). To test this theory, they administered to simian immunodeficiency virus (SIV)-infected rhesus macaques a polyamine biosynthesis inhibitor, PA-001 that selectively kills CD14+ and CD16+ monocytes. Escalating doses resulted in near complete depletion of CD14+ and CD16+ monocytes by 16 days of treatment. No inflammation was histologically detected in the CNS and treated animals did not develop SIV encephalitis, in contrast to untreated animals. Gastrointestinal toxicity did occur at higher doses (400 mg/m^2) but lower doses (250 mg/m^2) were still effective and were not associated with gastrointestinal toxicity.

These experimental treatments may provide important options to afflicted individuals in the future but effective therapies are still needed. Clinical trials thus far have not provided consistently effective adjunctive therapies for HNCI[32] but some drugs that have been approved by the US Food and Drug Administration for other indications and are already used in the HIV-infected population may have secondary benefits for the CNS. For example, lithium may protect neurons by modulating glycogen synthase kinase-3 beta,[33] certain serotonin reuptake inhibitors (SRIs) can reduce HIV replication by uncertain mechanisms,[34] and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), may reduce HIV replication via numerous mechanisms including reduction of chemokine receptor-containing membrane lipid rafts,[35-37] adhesion molecule expression,[38] and Rho guanosine triphosphatase activity.[39] Since SRIs and statins are commonly used in clinic populations, the CHARTER Group examined the impact of their use on HIV RNA levels in CSF and performance on NP testing (Abstract 384). SRI users were less likely to have HIV RNA levels above 50 copies/mL in CSF (29% vs 37% in non-SRI users; OR, 0.69; P = .05). This association was most evident for 3 of the 7 SRIs (citalopram, sertraline, and trazodone; combined 25% vs 38% in non-SRI users; OR, 0.56; P = .01) and was limited to those not taking concomitant antiretroviral therapy (61% vs 83%; OR, 0.31; P = .01). Users of these 3 SRIs also performed better on NP tests (median global deficit score, 0.37 vs 0.47; P = .04). Statin users were also less likely to have HIV RNA levels in CSF above 50 copies/mL (16% vs 37%; P < .001), but in contrast to SRIs, statins showed the strongest association in those using antiretroviral therapy (2% vs 18%; P < .001) and statin use was not associated with better NP performance. These data support a role for SRIs and perhaps statins in the treatment of HNCI but these observations require confirmation and the mechanisms of their effects need to be more clearly identified before the adoption of their use in clinical practice.

Selected Other Topics

Distal Sensory Polyneuropathy

Contrary to popular belief, peripheral nerves are dynamic, plastic structures that may undergo both injury and regeneration. Most current treatment of polyneuropathy in HIV infection is focused on symptom relief, neglecting the underlying neuropathogenesis and permitting potential continued damage to peripheral nerves. Jack and colleagues studied an in vivo model relevant to HIV infection in humans (Abstract 363). Transgenic mice expressing HIV viral envelope protein, gp120, under the control of a glial fibrillary acidic protein promoter were administered oral didanosine. This reliably produced a reduction in intraepidermal unmyelinated small sensory fibers in the foot pads of the mice. By administering either recombinant human erythropoietin (rhEPO) or the non-immunosuppressive immunophilin ligand, GPI-1046, the investigators were able to partially block the neuropathic effects seen in the animal model. These findings are of interest because assessments of intraepidermal nerve fiber layer density in humans are currently being studied for their potential clinical utility in diagnosis and monitoring polyneuropathies that have a small fiber component, which includes HIV distal sensory polyneuropathy (DSPN). A clinical trial of rhEPO administration in humans with DSPN is also underway.

JC Virus Encephalitis

David M. Clifford delivered a state-of-the-art talk on JCV-E, or PML. He reviewed the evidence indicating that JCV-E continues to cause substantial morbidity and mortality among people living with HIV, even though combination antiretroviral therapy has improved its prognosis. Unfortunately, 50% of patients still die within 6 months of onset.

Two studies provided evidence that survival of persons diagnosed with JCV-E could be improved. Gasnault and colleagues reported preliminary results of individuals with JCV-E who were treated under protocol Agence Nationale de Recherches Sur le Sida (ANRS) 125, which provided intensified antiretroviral therapy regimens within 90 days of diagnosis (Abstract 379). The 6-month cumulative probability of survival was 77% (95% CI, 63%-95%), supporting that early, intensive antiretroviral therapy may greatly benefit persons with JCV-E. Survival was associated with recovery of anti-JCV CD4+ memory T cell responses, detection of anti-JCV interferon-gamma producing CD8+ T cell effectors, and reduction of JCV DNA in CSF to levels below detection.

Published studies have reported that interferon alfa treatment can delay progression and prolong survival

of individuals with JCV-E,[40] although it may provide little added benefit when combined with potent antiretroviral therapy.[41] Verma and colleagues used in vitro methods to identify 1 reason for lack of interferon benefit: Interferon beta may more potently inhibit JCV replication than does interferon alfa (Abstract 359). To demonstrate this, they infected primary human fetal glial cells with JCV, incubated the infected cells with interferon alfa and interferon beta, and measured T antigen DNA, mRNA transcripts, and interferon-stimulated gene mRNA transcripts. Interferon beta reduced JCV replication more effectively than interferon alfa and the inhibition was reversed with anti-interferon antibodies. These findings argue that people with JCV-E may benefit by combining more intensive antiretroviral therapy along with interferon beta.

Neurosyphilis

Syphilis and neurosyphilis are frequent comorbidities in HIV-infected individuals. The success of antitreponemal therapy is conventionally evaluated by performing serial LPs to determine if CSF leukocyte counts are reduced after treatment. Having a method to assess treatment success in neurosyphilis that does not require repeated LPs would simplify the management of this condition and potentially increase patient adherence to therapy. Marra and colleagues evaluated one such approach (Abstract 372). In 68 HIV-infected subjects with CSF leukocyte counts above 20 cells/µL who received treatment for a first episode of neurosyphilis, CSF Venereal Disease Research Laboratory (VDRL) test was reactive in 29 (43%). Normalization of the serum Rapid Plasma Reagin test (RPR) was associated with reduction of the CSF leukocyte count to below 20 cells/µL. After 7 months of treatment, RPR normalization correctly predicted CSF normalization 88% of the time and, after 13 months of treatment, RPR normalization correctly predicted CSF normalization 96% of the time.

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Additional References

1. **Letendre S**, Capparelli E, Best B, et al. Better antiretroviral penetration into the central nervous system is associated with lower CSF viral load. [Abstract 74.] 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006; Denver, CO.

2. **Spudich S**, Lollo N, Liegler T, Deeks SG, Price RW. Treatment benefit on cerebrospinal fluid HIV-1 levels in the setting of systemic virological suppression and failure. *J Infect Dis.* 2006;194:1686-1696.

3. **Hammer SM**, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. *JAMA.* 2006;296:827-843.

4. **Letendre S**, Marquie-Beck J, Singh KK, et al. The monocyte chemotactic protein-1 -2578G allele is associated with elevated MCP-1 concentrations in cerebrospinal fluid. *J Neuroimmunol.* 2004;157:193-196.

5. **McArthur JC**, Letendre SL. Is the glass three-quarters full or one-quarter empty? *J Infect Dis.* 2007;194:1628-1696.

6. **Gallo P**, Frei K, Rordorf C, Lazdins J, Tavolato B, Fontana A. Human immunodeficiency virus type 1 (HIV-1) infection of the central nervous system: an evaluation of cytokines in cerebrospinal fluid. *J Neuroimmunol.* 1989;23:109-116.

7. **Perrella O**, Carrieri PB, Guarnaccia D, Soscia M. Cerebrospinal fluid cytokines in AIDS dementia complex. *J Neurol.* 1992;239:387-389.

8. **Brew BJ**, Pemberton L, Cunningham P, Law MG. Levels of human immunodeficiency virus type 1 RNA in cerebrospinal fluid correlate with AIDS dementia stage. *J Infect Dis.* 1997;175:963-966.

9. **Ellis RJ**, Hsia K, Spector SA, et al. Cerebrospinal fluid human immunodeficiency virus type 1 RNA levels are elevated in neurocognitively impaired individuals with acquired immunodeficiency syndrome. HIV Neurobehavioral Research Center Group. *Ann Neurol.* 1997;42:679-688.

10. **McArthur JC**, McClernon DR, Cronin MF, et al. Relationship between human immunodeficiency virus-associated dementia and viral load in cerebrospinal fluid and brain. *Ann Neurol.* 1997;42:689-698.

11. **Ellis RJ**, Moore DJ, Childers ME, et al. Progression to neuropsychological impairment in human immunodeficiency virus infection predicted by elevated cerebrospinal fluid levels of human immunodeficiency virus RNA. *Arch Neurol.* 2002;59:923-928.

12. **Sevigny JJ**, Albert SM, McDermott MP, et al. Evaluation of HIV RNA and markers of immune activation as predictors of HIV-associated dementia. *Neurology.* 2004;63:2084-2090.

13. **Shiramizu B**, Gartner S, Williams A, et al. Circulating proviral HIV DNA and HIV-associated dementia. *AIDS.* 2005;19:45-52.

14. **Shiramizu B**, Ratto-Kim S, Sithinamsuwan P, et al. HIV DNA and dementia in treatment-naive HIV-1-infected individuals in Bangkok, Thailand. *Int J Med Sci.* 2006;4:13-18.

15. **Pulliam L**, Gascon R, Stubblebine M, McGuire D, McGrath MS. Unique monocyte subset in patients with AIDS dementia. *Lancet.* 1997;349:692-695.

16. **Yilmaz A**, Svennerholm B, Hagberg L, Gisslen M. Cerebrospinal fluid viral loads reach less than 2 copies/ml in HIV-1-infected patients with effective antiretroviral therapy. *Antivir Ther.* 2006;11:833-837.

17. **Centlivre M**, Sommer P, Michel M, et al. HIV-1 clade promoters strongly influence spatial and temporal dynamics of viral replication in vivo. *J Clin Invest.* 2005;115:348-358.

18. **Victoria JG**, Lee DJ, McDougall BR, Robinson WE. Replication kinetics for divergent type 1 human immunodeficiency viruses using quantitative SYBR green I real-time polymerase chain reaction. *AIDS Res Hum Retroviruses.* 2003;19:865-874.

19. **Solis M**, Wilkinson P, Romieu R, Hernandez E, Wainberg MA, Hiscott J. Gene expression profiling of the host response to HIV-1 B, C, or A/E infection in monocyte-derived dendritic cells. *Virology.* 2006;352:86-99.

20. **Ranga U**, Shankarappa R, Siddappa NB, et al. Tat protein of human immunodeficiency virus type 1 subtype C strains is a defective chemokine. *J Virol.* 2004;78:2586-2590.

21. **Wright E**, Brew B, Lal L, et al. Neurocognitive impairment, symptomatic peripheral neuropathy, and depression in HIV-infected outpatients within the Asia Pacific Region: findings of the APNAC study. [Abstract 366.] 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006; Denver, CO.

22. **Riedel D**, Ghate M, Nene M, et al. Screen-

ing for human immunodeficiency virus (HIV) dementia in an HIV clade C-infected population in India. *J Neurovirol.* 2006;12:34-38.

23. **Yepthomi T**, Paul R, Vallabhaneni S, et al. Neurocognitive consequences of HIV in southern India: a preliminary study of clade C virus. *J Int Neuropsychol Soc.* 2006;12:424-430.

24. **Modi G**, Hari K, Modi M, Mochan A. The frequency and profile of neurology in black South African HIV infected (clade C) patients - A hospital-based prospective audit. *J Neurol Sci.* 2007;254:60-64.

25. **Wong MH**, Roberson K, Nakasujja N, et al. Frequency of and risk factors for HIV dementia in an HIV clinic in sub-Saharan Africa. *Neurology.* 2007;68:350-355.

26. **Phillips NC**, Tsoukas C. Liposomal encapsulation of azidothymidine results in decreased hematopoietic toxicity and enhanced activity against murine acquired immunodeficiency syndrome. *Blood.* 1992;79:1137-1143.

27. **Kim S**, Scheerer S, Geyer MA, Howell SB. Direct cerebrospinal fluid delivery of an antiretroviral agent using multivesicular liposomes. *J Infect Dis.* 1990;162:750-752.

28. **Steim JM**, Camaioni Neto C, Sarin PS, Sun DK, Sehgal RK, Turcotte JG. Lipid conjugates of antiretroviral agents. I. Azidothymidine-monophosphate-diglyceride: anti-HIV activity, physical properties, and interaction with plasma proteins. *Biochem Biophys Res Commun.* 1990;171:451-457.

29. **Garg M**, Asthana A, Agashe HB, Agrawal GP, Jain NK. Stavudine-loaded mannosylated liposomes: in-vitro anti-HIV-I activity, tissue distribution and pharmacokinetics. *J Pharm Pharmacol.* 2006;58:605-616.

30. **Oussoren C**, Magnani M, Fraternale A, et al. Liposomes as carriers of the antiretroviral agent dideoxycytidine-5'-triphosphate. *Int J Pharm.* 1999;180:261-270.

31. **Letendre SL**, Capparelli EV, Ellis RJ, McCuthan JA. Indinavir population pharmacokinetics in plasma and cerebrospinal fluid. The HIV Neurobehavioral Research Center Group. *Antimicrob Agents Chemother.* 2000;44:2173-2175.

32. **McArthur JC**, Haughey N, Gartner S, et al. Human immunodeficiency virus-associated dementia: an evolving disease. *J Neurovirol.* 2003;9:205-221.

33. **Letendre SL**, Woods SP, Ellis RJ, et al. Lithium improves HIV-associated neurocognitive impairment. *AIDS.* 2006;20:1885-1888.

34. **Kristiansen JE**, Hansen JB. Inhibition of HIV replication by neuroleptic agents and their potential use in HIV infected patients with AIDS related dementia. *Int J Antimicrob Agents.* 2000;14:209-213.

35. **Goebel J**, Logan B, Forrest K, Mieczkowski A, Roszman TL, Willis KM. Atorvastatin affects interleukin-2 signaling by altering the lipid raft enrichment of the interleukin-2 receptor beta chain. *J Investig Med.* 2005;53:322-328.

36. **Hillyard DZ**, Nutt CD, Thomson J, et al. Statins inhibit NK cell cytotoxicity by membrane raft depletion rather than inhibition of isoprenylation. *Atherosclerosis.* 2007;191:319-325.

37. **Popik W**, Alce TM, Au WC. Human immunodeficiency virus type 1 uses lipid raft-colocalized CD4 and chemokine receptors for productive entry into CD4(+) T cells. *J Virol.* 2002;76:4709-4722.

38. **Gilbert C**, Bergeron M, Methot S, Giguere JF, Tremblay MJ. Statins could be used to control replication of some viruses, including HIV-1. *Viral Immunol.* 2005;18:474-489.

39. **del Real G**, Jimenez-Baranda S, Mira E, et al. Statins inhibit HIV-1 infection by down-regulating Rho activity. *J Exp Med.* 2004;200:541-547.

40. **Huang SS**, Skolasky RL, Dal Pan GJ, Royal W, McArthur JC. Survival prolongation in HIV-associated progressive multifocal leukoencephalopathy treated with alpha-interferon: an observational study. *J Neurovirol.* 1998;4:324-332.

41. **Geschwind MD**, Skolasky RI, Royal WS, McArthur JC. The relative contributions of HAART and alpha-interferon for therapy of progressive multifocal leukoencephalopathy in AIDS. *J Neurovirol.* 2007;7:353-357.

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