

# Neurologic Complications of HIV Disease and Their Treatments

Scott Letendre, MD, and Ronald J. Ellis, MD, PhD

*The 2006 Conference on Retroviruses and Opportunistic Infections was marked by a record number of presentations focused on the neurologic complications of HIV infection. Key findings included the identification of the high prevalence of HIV-associated neurocognitive impairment (HNCI) in Western and East Asian populations; biomarkers that may be clinically useful in determining risk and treatment of HNCI, such as neurofilament protein, insulin resistance, leptin, soluble Fas, and total protein levels in cerebrospinal fluid; host genotypes that were associated with HNCI as well as antiretroviral toxic neuropathy; HIV envelope signature positions that were associated with HNCI and reduced CD4 dependence; the importance of combined antiretroviral drug penetration into the central nervous system for control of HIV replication; and an effective treatment for painful sensory neuropathy (capsaicin) and provocative preclinical data on treatments for HNCI (rosiglitazone, glatiramer immunization). Together, these findings heighten concern for persistent neurologic diseases in antiretroviral therapy-treated individuals but provide guidance for their improved identification and treatment.*

## Central Nervous System Complications

### Epidemiology

The use of potent antiretroviral therapy has led to declines in the incidence of the neurologic complications of HIV infection, including HIV-associated neurocognitive impairment (HNCI). Although its incidence has declined, HNCI continues to occur not only in untreated but in treated individuals as well. As HIV-infected individuals live longer, the prevalence of HNCI has risen; different clinical phenotypes have been recognized; and prior associations with biomarkers, such as HIV RNA levels in cerebrospinal fluid (CSF), have weakened. Several presentations at the 13th Conference on Retroviruses and Opportunistic Infections built on these prior observations.

Using a pooled dataset of 7923 seroconvertors enrolled in 22 cohorts

---

Dr Letendre is Assistant Professor in the Department of Medicine, Division of Infectious Diseases, at the University of California San Diego. Dr Ellis is Associate Professor-in-Residence in the Department of Neurosciences at the University of California San Diego.

from Europe, Australia, and Canada (in the Concerted Action on SeroConversion to AIDS and Death in Europe study, or CASCADE), Mussini and colleagues identified 152 subjects who were diagnosed with HNCI (Abstract 351). When stratified by assessment period, the relative risk (RR) of HNCI fell substantially from 1997 to 1999 (RR, .28) and 2000 to 2004 (RR, .19) compared with pre-1997, a finding that is consistent with prior reports. In contrast to this relatively low prevalence of HNCI, a more recent cohort (AIDS Clinical Trials Group [ACTG] 5001) of 1498 antiretroviral therapy-treated individuals demonstrated a high prevalence (43%) of impaired performance on a brief neuropsychologic battery at first testing (Abstract 362). Among the 853 initially unimpaired subjects, 19% subsequently became impaired during the observation period (median 93 weeks). As in these 2 reports, much of the data identifying epidemiologic shifts in HNCI have been derived from Western cohorts. Wright and colleagues sought to identify the prevalence of HNCI in the Asia Pacific NeuroAIDS Consortium (APNAC) cohort (Abstract 366). Of 129 consecutive HIV-infected outpatients from

Indonesia, China, and Malaysia screened with a brief neuropsychologic battery, a surprising 71% had impairment, two thirds of which was mild to moderate and one third severe.

### Clinical Biomarkers

Before the use of combination antiretroviral therapy, the risk of HNCI increased with declining CD4+ cell count. Among antiretroviral-treated individuals, some reports indicate that risk correlates more closely with nadir than with current CD4+ cell count. This shift may reflect incomplete normalization of neuroinflammation following immune reconstitution. The ACTG 5001 analysis confirmed that individuals who had a lower nadir CD4+ cell count (below 200/ $\mu$ L), but not lower current CD4+ cell count, had 23% increased odds of having HNCI. In contrast, Mussini showed that the risk of HNCI increased with declining current CD4+ cell count strata (RR, 4.5 for 200/ $\mu$ L to 349/ $\mu$ L, 11.9 for 100/ $\mu$ L to 199/ $\mu$ L, and 69.0 for 0/ $\mu$ L to 99/ $\mu$ L, compared with those with current CD4+ cell counts of at least 350/ $\mu$ L) but not the nadir CD4+ cell count. This disagreement may be attributable in part to the inclusion in the CASCADE analysis of preantiretroviral therapy-treated subjects, in whom immune reconstitution was probably uncommon. Importantly, neither of these analyses addressed the prevalence of hepatitis C virus (HCV) coinfection, which may be important because numerous studies have now confirmed its association with HNCI and because, in a cohort of 87 HIV-infected individuals reported by Paul and colleagues, HCV coinfection was associated with both worse neuropsychologic performance and lower current CD4+ cell count than HIV infection alone (Abstract 880).

Arendt and colleagues identified

that the relationship between CSF RNA and neuropsychologic performance varied with both antiretroviral use and stage of disease (Abstract 360). For example, in 23 untreated individuals, higher CSF RNA levels correlated with worse global and motor performance regardless of disease stage. In contrast, in 61 treated individuals, higher CSF RNA correlated with worse motor performance, but only in individuals with earlier, not later, disease stage. This reduced predictive ability of CSF RNA is consistent with findings from large published studies and indicates that CSF RNA may still be a useful biomarker in untreated individuals. Shiramizu and colleagues avoided the impact of antiretroviral therapy seen in Western cohorts by measuring HIV RNA and DNA levels in antiretroviral-naive individuals in Thailand (Abstract 352). Consistent with their prior findings from the Hawaii Aging with HIV Cohort, they found that higher HIV DNA levels in circulating leukocytes were associated with the diagnosis of HNCI (HNCI:  $n=12$ , mean  $2.20 \log_{10}$  HIV DNA copies/mL; non-HNCI:  $n=12$ , mean  $0.73 \log_{10}$  HIV DNA copies/mL,  $P=.02$ ). In contrast, HIV RNA levels in plasma did not differ between individuals with and without HNCI.

Investigators at the University of California San Diego (UCSD) sought to better understand the effects of antiretroviral therapy on the relationships between 12 CSF biomarkers and neuropsychologic performance by evaluating 29 individuals before and following a change in antiretroviral therapy (Abstract 346). Antiretroviral therapy variably modified these relationships and this variability depended in part on which biomarker was considered and the duration and effectiveness of antiretroviral therapy. Overall, of the 12 biomarkers measured, 4 (total protein, soluble Fas, urokinase-type plasminogen activator receptor, and interferon inducible protein-10) most consistently correlated with neuropsychologic performance. The relationships between neuropsychologic performance and 2 biomarkers, total protein and soluble Fas, was particu-

larly strong. In a multivariate analysis, for example, higher soluble Fas levels in CSF were associated with worse neuropsychologic performance even after adjusting for duration of antiretroviral therapy and changes in CD4+ cell count and HIV plasma RNA level. Perhaps more importantly, the sensitivity and specificity of a total protein level in CSF above 36 mg/dL for the diagnosis of HNCI in successfully treated individuals were 100% and 78%, respectively, although the small and selected nature of the study may limit the generalizability of this finding. The median duration of antiretroviral therapy in this analysis was 15 weeks but Eden and colleagues determined the effects of a much longer duration of antiretroviral therapy on 2 measures of neuroinflammation (Abstract 355). Despite at least 4 years of effective antiretroviral therapy (plasma HIV RNA below 50 copies/mL), 13 of 16 (81%) HIV-infected treated individuals still had abnormal neopterin levels in CSF. A smaller, but still substantial, proportion of treated individuals (7 of 16 [44%]) had abnormal IgG indices. These abnormalities were not compared with HNCI diagnosis but do support the hypothesis that neuroinflammation can persist despite otherwise effective antiretroviral therapy.

Measurement of these neuroinflammatory and neurotoxic markers requires lumbar puncture and timely sampling, both of which can create challenges in the clinic. An alternative approach to identifying an individual's neuroinflammatory risk is to characterize genes that encode crucial proteins in the immune response. This approach has the additional advantage of avoiding fluctuations in protein expression associated, for example, with antiretroviral therapy use, HIV disease stage, or comorbid conditions. Thus far, published studies have identified that HNCI is associated with polymorphisms in genes encoding MCP-1, its receptor (CCR2), and other inflammation-associated proteins. Pemberton and colleagues characterized several potential susceptibility genes in 56 individuals diagnosed with HNCI and

up to 203 HIV-infected and 204 -uninfected controls (Abstract 343). This analysis identified associations between HNCI and tumor necrosis factor alpha (TNF $\alpha$ )-308 and BAT1 (intron 10). Combining their data with prior reports, the investigators concluded that the currently supported host risk genotype for HNCI is TNF $\alpha$ -308\*(2,2), BAT1 (intron 10)\*(2,x), MCP1\*2578G, and ApoE (4,4).

As suggested by the inclusion of ApoE in this genotype, noninflammatory processes can also increase risk for HNCI. Four studies evaluated relationships between noninflammatory biomarkers and HNCI. Li and colleagues investigated protein nitration, an indicator of nitrosative stress, by measuring 3 nitrotyrosine-modified proteins (3-NT) in 43 CSF samples from individuals enrolled in the North Eastern AIDS Dementia (NEAD) cohort (Abstract 347). Higher 3-NT levels distinguished individuals with active HNCI from those with inactive HNCI, an important clinical distinction. The investigators then used immunoprecipitation and mass spectrometry to identify 9 potential proteins with 3-NT modification, the most important of which seemed to be prostaglandin D2 synthase. In a large and well-designed study, Gisslen and colleagues measured CSF concentrations of the light subunit of the neurofilament protein (NFL), a major structural component of myelinated axons (Abstract 72). CSF NFL levels were higher in individuals with HNCI than in neuroasymptomatic individuals, but did not distinguish them from those who had central nervous system opportunistic infections. CSF NFL levels did distinguish milder and more severe forms of HNCI and intensive sampling of CSF identified that NFL levels declined in parallel with neuropsychologic improvements.

Metabolic complications of HIV disease and its treatments are well recognized. The final 2 biomarker studies investigated links between these metabolic derangements and HNCI. Among 145 individuals enrolled in the Hawaii Aging with HIV Cohort, Valcour and colleagues identified that greater

insulin resistance, as measured by the homeostasis model of assessment, was associated with both milder and more severe forms of HNCI, but only among older individuals (at least 50 years of age; Abstract 349). The relationship between the homeostasis model of assessment and HNCI remained statistically significant even after adjusting for CD4+ cell count, sex, ethnicity, and antiretroviral therapy use, although the effect size was modest. Huang measured leptin in serum and CSF specimens from 84 (42 HIV-infected, 42 HIV-uninfected) men who had undergone comprehensive, standardized neuropsychologic testing (Abstract 73). Leptin may link HIV- and antiretroviral drug-associated lipid disorders since it is produced by peripheral fat cells and penetrates into the brain, where it can regulate appetite and have multiple neuroprotective effects. Among all subjects, lower CSF-to-serum leptin ratios were associated with worse memory and learning performance. This relationship held among the HIV-infected individuals even after adjusting for CD4+ cell count, CSF RNA level, and disease stage.

### Treatment

Antiretroviral therapy can effectively prevent HNCI in many individuals, as evidenced by its reduced incidence, but may not completely treat HNCI once it occurs, as supported by its high prevalence in treated populations. Tozzi and colleagues evaluated the reversibility of HNCI by assessing antiretroviral-associated improvements in 116 affected individuals (Abstract 354). Participants had a mean duration of antiretroviral therapy of 32 months and were assessed up to 6 times with standardized neuropsychologic testing. The investigators observed improvements in neuropsychologic performance at all evaluations (6, 12, 18, 24, 36, and 48 months) but, overall, only 30% of participants were considered to have fully reversible disease. Reversible disease was associated with better education, male sex, less severe impairment at baseline, and greater improvement at the first follow-up, but not age, CDC stage, or either baseline

or change in CD4+ cell count or plasma HIV RNA level.

These findings support initiation of antiretroviral treatment as early in the HNCI disease course as possible. Another hypothesis is that those who are less impaired may be better able to adhere to complex antiretroviral regimens. An analysis from the University of North Carolina of 37 impaired individuals who changed antiretroviral treatment supports this hypothesis, finding that worse neuropsychologic performance before changing therapy (global, verbal memory, attention) predicted worse adherence at 6 months (Abstract 363).

Another explanation for incident or persistent HNCI in successfully treated individuals is poor antiretroviral penetration into the central nervous system, which could allow ongoing HIV replication. Three studies addressed this question by comparing measures of antiretroviral penetration to CSF RNA levels. In a longitudinal study of 101 individuals who initiated new antiretroviral regimens following a baseline assessment (ACTG 736), Marra and colleagues identified that greater antiretroviral penetration, as calculated by summing an ordinal measure of penetration for each drug in the regimen, was associated with greater reductions in CSF RNA ( $r = -.08$ ;  $P = .04$ ), after adjusting for baseline CSF RNA level, change in plasma RNA levels and CD4+ cell count, and antiretroviral experience at baseline (Abstract 361). Letendre and colleagues reported a cross-sectional analysis from the CNS HIV Anti-Retroviral Therapy Effects Research cohort (CHARTER), a North American, 6-center cohort focused on the effects of antiretroviral drugs on the nervous system (Abstract 74). The antiretroviral penetration-effectiveness (P-E) score, a metric similar to the one used in ACTG 736, was compared with CSF RNA levels in 822 CSF-plasma pairs. Overall, higher P-E scores correlated with lower CSF RNA levels ( $r = -.11$ ;  $P = .001$ ) but not plasma RNA levels. P-E scores below 1.5 nearly doubled the odds of having a CSF RNA level above 50 copies/mL (odds ratio [OR], 1.97;  $P < .001$ ). In multivariate

analyses, higher P-E scores remained associated with lower CSF RNA levels even after adjusting for plasma RNA levels, CD4+ cell count, and duration of antiretroviral therapy. The third study derived from another large cohort, the Italian Registry of Investigative NeuroAIDS (IRINA; Abstract 359). Using an approach to categorize antiretroviral penetration similar to those in the ACTG 736 and CHARTER analyses, Giancola and colleagues found that a larger number of penetrating antiretrovirals correlated with lower CSF RNA level ( $r = -.17$ ;  $P < .001$ ; Abstract 359). Similar to the other studies, this association withstood adjustment for other variables and the effect sizes were even larger. Compared with regimens containing no penetrating antiretrovirals, use of 2 (OR, 6.1) or at least 3 (OR, 7.1) penetrating antiretrovirals markedly improved the odds of having a CSF RNA level below 50 copies/mL.

The UCSD approach to categorization of antiretroviral penetration is hierarchical, weighting pharmacokinetic and pharmacodynamic data more heavily than drug characteristics. Atazanavir is an example of the importance of this approach. Atazanavir is 14% unbound to plasma proteins, which should enable penetration into the central nervous system in therapeutic concentrations. Best and colleagues presented findings from the CHARTER group identifying that atazanavir concentrations were actually lower in 76 CSF specimens than expected based on drug characteristics and atazanavir concentrations in matched plasma specimens (Abstract 576). Twenty (26%) CSF specimens were below the assay's limit of detection (5 ng/mL) and 42 (55%) were below 11 ng/mL, a median inhibitory concentration of atazanavir for wild-type HIV. One explanation for these lower-than-expected atazanavir concentrations in the central nervous system may be that many antiretrovirals are substrates for multidrug resistance pumps, such as P-glycoprotein, that are expressed on brain endothelial cells. For example, Marquie-Beck and colleagues presented findings compar-

ing the C3435T polymorphism in *mdr1*, the gene encoding P-glycoprotein, and indinavir concentrations in CSF and plasma from 37 individuals (Abstract 365). Wild-type homozygotes (C/C) had lower indinavir concentrations in CSF ( $P = .02$ ) than wild-type mutants (T/T) and lower indinavir concentrations in plasma, in turn, correlated with higher CSF RNA levels ( $P = .03$ ).

Therapeutic antiretroviral concentrations in plasma in the presence of subtherapeutic antiretroviral concentrations in CSF may lead to discordant resistance between compartments. Two studies addressed the prevalence of discordant resistance in HIV derived from plasma and CSF. Wong and colleagues from the CHARTER group presented data on genotypic resistance derived from 145 CSF-plasma pairs, identifying discordant resistance in 35 (37%; Abstract 75). Among these 35 CSF-plasma pairs, 20 (57%) had more resistance mutations in CSF than plasma and 5 (14%) had resistance mutations present in CSF when only wild-type HIV was identified in plasma. In a smaller analysis, Bush and colleagues identified the discordant resistance mutations in 3 of 7 (43%) CSF-plasma pairs, a prevalence very similar to the larger CHARTER study.

Currently, individuals who have HNCI but do not normalize with antiretroviral therapy have few therapeutic options. Findings from 1 clinical and 3 preclinical studies of approaches designed to address this were presented. The first was an analysis from Schifitto and colleagues of data from ACTG 5090, a randomized, placebo-controlled, multicenter clinical trial of selegiline, a monoamine oxidase-B inhibitor that has antioxidant and proneurotrophic effects (Abstract 364). A total of 128 individuals with HNCI were randomized to 1 of 3 treatment arms and 96 completed 24 weeks of treatment. Selegiline was well tolerated but ineffective, demonstrating no between-arm differences in neuropsychologic performance ( $P = .91$ ). Potula and colleagues from the University of Nebraska presented more hopeful animal data on rosiglitazone, a clinically available peroxisome proliferator-acti-

vated receptor (PPAR)- $\gamma$  agonist that can regulate anti-inflammatory pathways (Abstract 336). Using an established murine model of HIV-1 encephalitis, mice treated with 2 weeks of rosiglitazone had reduced p24+ macrophages in brain tissue (23%) and a substantial reduction in HIV RNA level (15,597 copies/mL), compared with placebo-treated controls (40% and 6921 copies/mL, respectively; both  $P < .05$ ). Even more provocatively, Gorantla and colleagues presented animal data on immunization with glatiramer, a modulator of microglial and T-cell activation (Abstract 335). In severe combined immunodeficiency disease/HIV encephalitis (SCID/HIVE) mice, glatiramer immunization was associated with reductions in microglial and astrocyte-induced inflammation and improved neuronal integrity. In HIV-1/vesicular stomatitis virus-HIV encephalitis (HIV/VSV-HIVE) mice, which have intact adaptive immune responses, glatiramer immunization greatly enhanced control of macrophage-induced inflammation, a mechanism strongly implicated in HIV neuropathogenesis, and restored hippocampal neuroregeneration. From a safety standpoint, the immunizations seemed to be well tolerated by the animals. Finally, Agrawal and Strayer explored the effects of RNA interference on expression of CCR3, a chemokine receptor expressed by neural cells and implicated in neural adaptation of HIV (Abstract 332). Using a panel of small interfering RNAs, they identified R3-526 as the most effective in downregulating CCR3, leading to an almost 80% decrease in CCR3 expression and a 70% decrease in productive HIV infection in microglia.

### Pathogenesis

Several basic studies advanced current knowledge on HIV neuroadaptation and the roles of specific cytokine pathways in neural injury. Building on data identifying position 308 in the V3 loop of gp120 as a possible indicator of neural-adapted HIV, Thomas and colleagues from the Gabuzda lab amplified full-length *env* genes from autopsy brain and lymphoid tissue from 4 patients with HNCI (Abstract 330).

Sequence alignments and viral epidemiology signature pattern analysis confirmed residue 308 as a brain signature position. However, the mechanism by which 308 might be selected was not identified since mutagenesis experiments did not identify that a proline at 308 was associated (1) with improved ability to infect cells in low CD4 or CCR5 conditions or (2) with sensitivity to inhibition by a panel of entry inhibitors. Dunfee and colleagues, also from the Gabuzda lab, presented data on another position, 283, in *env* (Abstract 76), which did seem to be associated with reduced CD4 dependence. To characterize this position, they cloned Env from 2 primary brain isolates that had reduced CD4 dependence and used mutagenesis to identify amino acids that contributed to reduced CD4 dependence and virus replication in macrophages or microglia. These analyses demonstrated that asparagine, rather than consensus threonine, at position 283 in the C2 region of gp120 was associated with reduced CD4 dependence. The investigators also summarized that 5 published studies with matched brain- and lymphoid-derived Env from 31 patients identified that N283 was detected at a 3.5-fold higher frequency in brain-derived Env than lymphoid-derived Env, and that it occurred at a 5-fold higher frequency in brain-derived Env from individuals with HNCI than those without.

These studies provide strong evidence that HIV adaptation to neural cells is an important event in the pathogenesis of HNCI. Two others focused on host factors that may also contribute to it. Carroll-Anziger and colleagues focused on astrocytes, which are critically important in HIV neuropathogenesis but may only support restricted HIV replication (Abstract 339). After stimulating cells with interferon (IFN)- $\gamma$ , HIV replication increased in human fetal astrocytes by 10-fold and in U87MG cells by 3-fold. IFN- $\gamma$  also upregulated expression of CCR3, which is interesting in light of the findings of Agrawal and Strayer (Abstract 332). Astrocytes may also influence HIV disease by producing

SDF-1, a neurotoxic protein that is also the ligand for the HIV coreceptor, CXCR4. Peng and colleagues from the Zheng lab stimulated astrocytes with media from activated macrophages and identified substantial increases in SDF-1 (Abstract 337). In particular, the investigators were able to link production of SDF-1 from astrocytes to interleukin (IL)-1 $\beta$  from activated macrophages by identifying parallel changes in their concentrations and by interfering with astrocyte SDF-1 production by treating macrophages with IL-1Ra and IL-1 $\beta$  small interfering RNAs.

### Peripheral Nervous System Complications

Antiretroviral toxic neuropathy, typically related to exposure to the antiretroviral drugs stavudine or didanosine, represents an important neurologic complication among individuals with HIV infection in the United States and Europe. Additionally, due to the inclusion of these drugs in antiretroviral therapy regimens in the developing world, antiretroviral toxic neuropathy may become a global neurologic problem. Unfortunately, in many cases, neuropathic signs, symptoms, and disability do not disappear after these drugs are stopped. This year's conference featured several presentations bearing on host vulnerability to antiretroviral toxic neuropathy, its clinical course, and new biomarkers and treatments.

In an observational study performed at a single clinical center (Ellis and colleagues, Abstract 368), neuropathic symptoms and signs were prospectively characterized in 2 groups of individuals: one consistently exposed to stavudine or didanosine ("d-drug" exposed, or DDE) over a period of 1 to 5 years ( $n = 252$ ), and another never exposed to d-drugs (NDDE), either prior to or during the clinical follow-up period ( $n = 250$ ). At the initial evaluation, DDE subjects were significantly **less** likely to have symptomatic antiretroviral toxic neuropathy than NDDE subjects. This bias was anticipated, since care providers are likely to switch out a d-drug for an alternative anti-

retroviral agent when neuropathic symptoms develop in an individual who is taking didanosine or stavudine. Among subjects who did not already have antiretroviral toxic neuropathy at baseline, the accumulation of neuropathic symptoms and signs was similar in DDE subjects (359 person-years of follow-up) to that in NDDE subjects (311 person-years of follow-up). Additionally, continued d-drug use did not result in an excess of worsening neuropathic signs or symptoms, even among those already suffering from symptomatic neuropathy at the initial visit. These findings re-emphasize that only a subset of individuals appear susceptible to the development of a dose-limiting neuropathic syndrome with exposure to d-drugs. In the remainder, continued d-drug use appears to be well tolerated.

Kallianpur and colleagues from Vanderbilt took advantage of a unique opportunity to evaluate potential genetic host susceptibility markers associated with the development of antiretroviral toxic neuropathy (Abstract 78). Specifically, in ACTG 384, HIV-infected subjects were randomized to receive an antiretroviral drug regimen that either did or did not include d-drugs (specifically, didanosine plus stavudine versus zidovudine plus lamivudine). The investigators targeted polymorphisms in the hemo-chromatosis (*hfe*) gene that alter intracellular iron disposition, and may thereby affect mitochondrial function. The parent study showed a clear excess of incident neuropathy symptoms among individuals randomized to d-drug—compared with non-d-drug—containing regimens. The incidence of antiretroviral toxic neuropathy was lower in individuals who had 1 of 2 *hfe* polymorphisms (C282Y and H63D), suggesting a protective effect. These polymorphisms were found in only a minority of study participants. In particular, C282Y was rare among African Americans. This study concluded that specific polymorphisms in the *hfe* gene might confer protection from the development of neuropathy with exposure to d-drugs. The putative mechanism by which this genetic marker acts

to reduce susceptibility—through alterations in intracellular iron disposition and mitochondrial function—remains to be demonstrated. A significant limitation of this study is its case definition, which was based on an adverse events scale rather than on a systematic neurologic examination. As previously shown in studies such as NARC007, case ascertainment for neuropathy may be problematic, particularly in multicenter studies.

In another analysis from ACTG 384, Hulgán and colleagues compared the diagnosis of neuropathy to polymorphisms in mitochondrial genes (Abstract 350). In this case, the polymorphisms T4216C and A4917G conferred an increased risk for the development of neuropathy in individuals who were taking d-drugs. Since the same polymorphisms are known to alter amino acid sequence in mitochondrial complex I subunits, the authors inferred that the mechanism by which the polymorphisms confer increased risk involves alterations in mitochondrial oxidative phosphorylation.

Cherry and colleagues reported on associations between another panel of host genetic vulnerability factors and neuropathy (Abstract 344). The cohort examined in this study was somewhat different from those in previous studies, in that it was restricted to individuals who had previously been exposed to stavudine, didanosine, or zalcitabine. Subgroups were defined as individuals who developed neuropathic symptoms or signs on the d-drugs (antiretroviral toxic neuropathy;  $n = 40$ ), and those who did not develop neuropathy despite at least 6 months of exposure to a d-drug (antiretroviral toxic neuropathy resistant;  $n = 28$ ). Polymorphisms in genes encoding 2 inflammatory mediators (TNF $\alpha$ -308 and IL-12B3'UTR) were more frequent among individuals who developed neuropathy during d-drug exposure than among those who did not. The investigators concluded that inflammatory pathways might play a role in the development of neuropathy due to d-drugs. This study was limited by the absence of a comparison group without d-drug exposure, such that relative

risks cannot be assessed either for the development of neuropathy or for the effect of host chemokine polymorphisms on the development of neuropathy.

In an overview session, McArthur presented a review of emerging data on an important new surrogate endpoint for neuropathy in HIV infection: epidermal nerve fiber layer density (ENFL; Abstract 80). The ENFL represents the distal-most end of nerve fibers in the skin that transduce pain and temperature sensation. Recent studies have demonstrated that this layer is deficient in HIV-infected individuals with neuropathy—both primary HIV-associated neuropathy and antiretroviral toxic neuropathy—compared with HIV-infected individuals without neuropathy and with HIV-seronegative individuals. It has been shown that topical capsaicin, the active ingredient in hot chili peppers, dramatically reduces the ENFL at the site of injury. In HIV-seronegative individuals, the ENFL reconstitutes itself over several months, providing clear evidence of peripheral nerve regenerative capac-

ity. This capacity is impaired in individuals with HIV infection. These findings are of considerable interest with respect to the possibility of using ENFL density as a surrogate endpoint in clinical trials of neuroprotective and neuroregenerative agents.

Finally, Simpson and colleagues presented data from a randomized clinical trial of high-dose topical capsaicin dermal patch treatment for painful sensory neuropathy (Abstract 79). Although capsaicin depletes the ENFL, evidence to date suggests that any resulting sensory impairment produces no disability. In the capsaicin dermal patch trial, 307 individuals with painful neuropathy were randomized to receive either a low-concentration capsaicin patch or a high-dose capsaicin patch applied for 30, 60, or 90 minutes. The endpoint was reported pain on a standardized scale. The pooled high-dose capsaicin dermal patch groups experienced pain reduction of 23% lasting up to 12 weeks after a single capsaicin dermal patch application. This compared with only 11% pain reduction in the pooled con-

trol group. Despite transient pain increases during and shortly after capsaicin dermal patch application, tolerability was otherwise quite good. Studies of epidermal nerve fiber reconstitution following capsaicin dermal patch application are ongoing. This represents a novel technique to be added to the existing armamentarium for HIV-associated neuropathic pain, a condition often refractory to treatment.

**Financial Disclosure:** Dr. Letendre has received research support from Abbott, Gilead Sciences, GlaxoSmithKline, and Merck. He has received lecture fees from Abbott and Boehringer-Ingelheim. Dr. Ellis has no financial affiliations with commercial organizations that may have interests related to the content of this article.

**A list of all cited abstracts appears on pages 63 to 70.**

*Top HIV Med.* 2006;14:21-26  
Copyright 2006, International AIDS Society–USA

## Improving the Management of HIV Disease: Web-based CME Conference

### Web casts of IAS–USA courses

#### Free CME credit

The International AIDS Society–USA (IAS–USA) is pleased to introduce the “Web-based CME Conference,” a new online CME activity designed for physicians who are actively involved in HIV disease management. Clinicians can listen to the audio and watch the accompanying slide presentations from the successful and clinically relevant IAS–USA courses in a user-friendly environment.

This long-distance learning CME activity complements the existing IAS–USA regional 1-day advanced-level CME courses on HIV/AIDS-related treatment issues and provides an extra level of convenience. Clinicians who are unable to attend the live regional courses can now view the lectures at their own pace and earn CME credit. This activity has been approved for **AMA PRA Category 1 Credit™**.



Los Angeles, CA: February 23, 2006  
Improving the Management of HIV Disease®  
An Advanced CME Course in HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management

Page: 1 of 1

<p><b>Welcome and Introduction</b> Presenter(s): Ronald T. Mitsuyasu, MD, and Constance A. Benson, MD Status: Available Air Date: 2/23/2006 Air Time: 9:15 AM PST Length: 7 Minutes 39 Seconds</p> <p><b>View: Welcome and Introduction</b></p>		<p><b>Demographic Question-and-Answer</b> Presenter(s): Ronald T. Mitsuyasu, MD, and Constance A. Benson, MD Status: Available Air Date: 2/23/2006 Air Time: 9:00 AM PST Length: 4 Minutes 15 Seconds</p> <p><b>View: Demographic Question-and-Answer</b></p>	
<p><b>Resistance Testing Interpretation</b> Presenter(s): Diane V. Havlir, MD Status: Available Air Date: 2/23/2006 Air Time: 9:10 AM PST Length: 46 Minutes 18 Seconds</p> <p><b>View: Resistance Testing Interpretation</b></p>		<p><b>Cases from the Clinic: Initiating Antiretroviral Therapy and Managing Complicated ART Failure</b> Presenter(s): Constance A. Benson, MD Status: Available Air Date: 2/23/2006 Air Time: 10:20 PM PST Length: 48 Minutes 56 Seconds</p> <p><b>View: Cases from the Clinic: Initiating Antiretroviral Therapy and Managing Complicated ART Failure</b></p>	
<p><b>Drug-Drug Interactions and the Pharmacotherapy of HIV Infection</b> Presenter(s): Courtney V. Fletcher, PharmD Status: Available Air Date: 2/23/2006 Air Time: 11:05 AM PST Length: 35 Minutes 22 Seconds</p> <p><b>View: Drug-Drug Interactions and the Pharmacotherapy of HIV Infection</b></p>		<p><b>Managing Complications of HIV Disease and Antiretroviral Therapy: Case-Based Presentation</b> Presenter(s): Judith A. Aberg, MD Status: Available Air Date: 2/23/2006 Air Time: 11:45 AM PST Length: 34 Minutes 17 Seconds</p> <p><b>View: Managing Complications of HIV Disease and Antiretroviral Therapy: Case-Based Presentation</b></p>	