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Neurologic Complications of HIV Disease and Their Treatment

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Abstract

Findings on the nervous system complications of HIV disease and their impact on people living with HIV continue to accumulate. New reports at the 17th Conference on Retroviruses and Opportunistic Infections this year confirmed that HIV-associated neurocognitive disorders (HAND) are common, even among effectively treated individuals. Risk of HAND correlated with nadir CD4⁺ cell counts and with cerebrospinal fluid (CSF) viral loads that were at least as high as plasma viral loads. Other new data regarding risk factors for HAND implicated vascular disease, apolipoprotein E and mannose binding lectin genotypes, reduced resting cerebral blood flow, and HIV mutants that cause macrophages to shed the HIV gp120 protein. Two analyses linked worse neurocognitive performance to use of efavirenz, raising concerns about neurotoxicity. Analyses comparing differences in estimated distribution of antiretroviral drugs into the central nervous system (CNS) to neurocognitive outcomes using the 2008 version of the CNS penetration-effectiveness (CPE) ranking system did not support a hypothesis of neurotoxicity but did have mixed results, some supporting a benefit and some supporting no effect. Of note, a revised version of the CPE ranking system was presented that was more strongly associated with CSF viral loads than the 2008 version. Reports also estimated that primary CSF virologic failure occurs in 3% to 10% of treated individuals, although the clinical consequences of this remain uncertain. New data on common coinfections in people with HIV identified that a specific strain of *Treponema pallidum* may be more neurovirulent than other strains, that hepatitis C virus Core protein may be neurotoxic, and that hepatitis B virus may replicate in the nervous system. The extensive data presented will inform new research and clinical decisions in the coming year.

Introduction

Research on the central and peripheral neurologic complications of HIV infection continues to expand, answering some important questions but raising new ones as well. New reports on the correlates of neurocognitive impairment should help clinicians identify at-risk patients. A newly revised central nervous system (CNS) penetration-effectiveness (CPE) ranking

system was presented that is more strongly associated with cerebrospinal fluid (CSF) viral loads than the older approach. Also, the frequency of primary CSF virologic failure was estimated, neurovirulent HIV mutations were identified, and a new animal model for HIV-associated sensory neuropathy was described. Summaries of these and other reports are presented below in 5 sections: Central Nervous System Complications, Pathogenesis and Biomarkers of Nervous System Disease, Brain Imaging, HIV-Associated Peripheral Neuropathy, and Other Infections of the Nervous System.

Central Nervous System Complications

Reports from North America and Europe

Work presented at prior conferences has shown that HIV-associated neurocognitive disorders (HAND) continue to be common, even among many people taking effective antiretroviral therapy with immune recovery (eg, Heaton et al¹). Several explanations for these findings are possible, and one is that brain injury acquired during advanced immunosuppression might be only partially reversible with antiretroviral therapy. Because HAND is more common in people with advanced immune suppression, its incidence or severity might be reduced when antiretroviral therapy is initiated at higher CD4+ cell counts. If initiation of antiretroviral therapy at higher CD4+ cell counts prevents HAND, this would be an important added benefit because HAND is associated with unemployment, worse quality-of-life, reduced antiretroviral therapy adherence, and earlier death.

To examine whether earlier initiation of antiretroviral therapy might be associated with lower risk of HAND, Ellis and colleagues evaluated the relationship between the lowest reported or observed CD4+ cell count (ie, the nadir) and neurocognitive impairment in 1525 individuals enrolled in the CHARTER (CNS HIV Antiretroviral Therapy Effects Research) cohort, a prospective, multicenter study that incorporated comprehensive neurocognitive and medical assessments (Abstract 429). Neurocognitive impairment and HAND diagnoses were defined according to the Frascati criteria,² and comorbid conditions contributing to impairment were evaluated by a single, experienced neuropsychologist. Just over half of this mostly antiretroviral therapy–experienced cohort was neurocognitively impaired, in most cases at mild to moderate levels.

The principal findings were that participants who had a nadir CD4+ cell count below 50/mL had the greatest risk of neurocognitive impairment (222 of 387 patients; 57.4%) and, compared with this reference group, the odds of impairment diminished at successively higher nadir CD4+ cell count strata, with the lowest risk in those with nadir CD4+ cell counts above 350/mL (130 of 287 patients; 45.3%). In the subgroup of individuals who were taking antiretroviral therapy and had plasma HIV RNA levels below 50 copies/mL, this difference was even greater (60.5% vs 45.6%). When analyzed as a continuous predictor, a graded decrease in neurocognitive impairment risk was observed across the entire range of nadir CD4+ cell counts. The influence of nadir CD4+ cell count on neurocognitive impairment was similar in multivariable analyses adjusting for demographic and clinical covariates that might affect neurocognitive performance, including age, duration of HIV infection, and suppression of plasma viral loads from antiretroviral therapy.

Another possible explanation for persisting HAND among effectively treated individuals (ie, with suppressed plasma viral loads) is limited distribution of these drugs into the CNS. Several presentations compared estimated distribution of antiretroviral therapy into the CNS to CSF viral loads, neurocognitive performance, or neuroimaging findings. Letendre and colleagues presented cross-sectional CSF and plasma viral load data from 1221 individuals enrolled in the CHARTER cohort (Abstract 172). Eight hundred forty-two of these individuals were taking antiretroviral therapy, and 135 (16%) had a CSF HIV RNA level above 50 copies/mL (ie, detectable). Multivariable analysis identified that detectable CSF viral loads were associated with higher plasma viral loads, current CD4+ cell counts below 200/mL, estimates of lower antiretroviral therapy distribution into the CNS using a revised version of the CPE ranking system (CPE 2010; Table 1), worse adherence (taking fewer than 95% of doses in the 4 days preceding assessment), and non-white ethnicity. This revised version of the CPE ranking method incorporated data from recent pharmacokinetic and pharmacodynamic analyses and was more strongly associated with CSF viral loads than the older CPE 2008 method.³

A report from the 16th conference in 2009 described 10 neurologically symptomatic individuals, all of whom had viral loads higher in CSF than in plasma.⁴ This report did not include a denominator, making it impossible to estimate the frequency of primary CSF virologic failure (ie, detectable viral loads in CSF but not in plasma while taking antiretroviral drugs) in a clinic population. In the cross-sectional CHARTER analysis, this frequency was determined by identifying the proportion of neurocognitively symptomatic and asymptomatic persons who were taking antiretroviral therapy and had plasma HIV RNA levels that were suppressed below 50 copies/mL: 14 of 463 CHARTER participants (3%) had CSF HIV RNA levels above 50 copies/mL (Abstract 172). In another cross-sectional analysis focused specifically on CSF virologic failure, Edén and colleagues identified that 7 of 67 (10.4%) neurocognitively asymptomatic individuals who were taking antiretroviral therapy and had plasma HIV RNA levels suppressed below 50 copies/mL also had CSF HIV RNA levels above 50 copies/mL (Abstract 432), confirming that primary CSF virologic failure may be relatively infrequent. Cross-sectional studies, however, are inherently limited in their ability to accurately estimate population event frequencies, particularly uncommon ones.

Longitudinal designs can typically better estimate event frequencies, although most cohort studies sample participants relatively infrequently (eg, every 6 or 12 months). In a longitudinal analysis of 346 CHARTER participants who were taking antiretroviral therapy and whose CSF HIV RNA levels were suppressed below 50 copies/mL at their first visit, 67 (19%) persons experienced failure (defined as CSF HIV RNA level > 50 copies/mL) after a median of 9.3 months. Shorter times to loss of viral response (TLOVRs) in CSF were associated with baseline CD4+ cell counts below 200/mL, younger age, and worse neurocognitive performance (Abstract 430).

Two statistical interactions were also present in this analysis: older people taking antiretroviral drugs with estimates of better penetration had longer TLOVRs in CSF than did other participants, and black people who had impaired neurocognitive performance had shorter TLOVRs in CSF than did other participants. Of note, neither of these interactions

was present in a parallel analysis of TLOVR in plasma among persons whose plasma viral loads were suppressed at their first visit. Because the effects were present in the CSF analysis but not in the plasma analysis, they may reflect conditions specific to control of HIV in the nervous system. An important limitation of this analysis is that it did not observe initiation of antiretroviral therapy in any of the participants (ie, all participants were already taking antiretroviral drugs by the time of their first visit).

Several other abstracts reported new findings on the frequency and correlates of HAND. Starace and colleagues reported data from 45 virally suppressed individuals to determine if “neuroactive” antiretroviral drug regimens (defined as those with a CPE 2008 rank ≥ 2) were associated with better neurocognitive performance (Abstract 433). They administered the Cotugno Mini Battery, a set of 6 neuro-psychologic tests of verbal memory span, auditory verbal learning, verbal fluency, executive function, speeded information processing, and walking ability. Overall, 31 of 45 (69%) participants had HAND, with 26 having asymptomatic neurocognitive impairment and 5 having minor neurocognitive disorder (MND). Those taking neuroactive antiretroviral drugs were less likely to have HAND and had better performance on 3 of the 6 administered tests (verbal memory span, verbal fluency, speeded information processing). Of note, performance on the other 3 tests also was better in the neuroactive antiretroviral therapy group, although the differences did not reach statistical significance.

Garvey and colleagues reported results of a retrospective review of a much larger sample (nearly 20,000 persons) who initiated antiretroviral therapy between 1996 and 2007 and enrolled in the multicenter UK CHIC (United Kingdom Collaborative HIV Cohort) project (Abstract 427). In this analysis, the investigators determined the correlates of severe CNS disorders and mortality. A total of 224 individuals developed a severe CNS disorder during the observation period; these included disorders that commonly afflict people with AIDS, such as cryptococcosis, toxoplasma, JC virus infection, and HIV encephalopathy. For the purposes of this analysis, all severe CNS disorders were grouped together. In this longitudinal study, the initial and most recent CPE 2008 ranks for the antiretroviral regimens were evaluated, and the investigators grouped regimens into categories that differed substantially in size (ranking < 1 , 1560 [7.9%]; ranking 1–1.5, 8444 [42.6%]; ranking 2–2.5, 9386 [47.3%]; ranking > 2.5 , 438 [2.2%]).

The investigators identified that subjects in the 2 minority CPE 2008 groups (rankings < 1 or > 2.5) were more likely than others to develop a severe CNS disorder over approximately 5 years of observation, although these groups also had lower CD4+ cell counts than the majority groups. Multivariable analysis identified associations between the occurrence of severe CNS disorders and lower baseline or current CD4+ cell counts, higher plasma HIV RNA levels, shorter durations of antiretroviral therapy, and heterosexual risk behavior—but not CPE 2008 category. Among these correlates, the association with heterosexual activity (relative risk, 3.2 compared with men who have sex with men) is unexpected and deserves further epidemiologic investigation to determine why persons who engage in unprotected heterosexual activity may be at risk. An even more important finding may have resulted from the multivariable mortality analysis: very low or very high CPE 2008 ranks were associated with higher mortality. This analysis did not account for the number of

antiretroviral drugs in each regimen, an important limitation because highly treatment-experienced individuals who take more than 3 antiretroviral drugs will have higher CPE 2008 ranks and may have a poor prognosis. Despite this, these findings add to existing data supporting that antiretroviral drug penetration may influence survival.^{5,6}

Although these findings add to evidence supporting the potential benefits of better penetrating antiretroviral therapy, not all studies agree. For example, Muñoz-Moreno and colleagues did not find an association between estimates of antiretroviral therapy penetration into the CNS and neurocognitive performance (Abstract 416). These investigators used a classification and regression tree approach to analyze data from a single clinic population of 172 individuals. Among the 142 antiretroviral therapy-experienced individuals, neurocognitive impairment was associated with shorter duration of the current antiretroviral therapy regimen (< 32.2 months), longer duration since initiation of antiretroviral therapy (> 13.5 years), older age (> 32 years of age), and higher peak plasma HIV RNA level (highest ever > 4.8 log₁₀ copies/mL) but not with estimate of worse antiretroviral therapy penetration into the CNS using the CPE 2008 method.

Ciccarelli and colleagues also did not find an association between estimates of worse antiretroviral therapy penetration and impaired neurocognitive performance (Abstract 417). This study assessed 136 consecutive clinic patients using a comprehensive neurocognitive test battery. Antiretroviral therapy penetration into the CNS was again estimated using the CPE 2008 method (< 1.5 vs = 1.5). The 70 individuals who had impaired neurocognitive performance in this study were not more likely to take “worse-penetrating” antiretroviral therapy regimens, but they were more likely to take efavirenz (odds ratio [OR], 5.37; *P* = .004). Although this finding raises concerns about long-term efavirenz neurotoxicity, no abstracts reported associations linking better antiretroviral therapy penetration to worse neurocognitive performance, which would have been evidence of neurotoxicity across a broader spectrum of antiretroviral drugs.

The report by Winston and colleagues highlighted the challenge of interpreting associations between estimates of antiretroviral therapy penetration, possible neurotoxicity, and imaging or neurocognitive outcomes (Abstract 434). This multicenter project, the ALTAIR (Alternative Antiretroviral Strategies: a Comparison of Three Initial Regimens) study, randomly assigned 30 participants to 1 of 3 open-label regimens (tenofovir/emtricitabine/efavirenz [CPE 2008 = 1.0]; tenofovir/emtricitabine plus atazanavir/ritonavir [CPE 2008 = 1.0]; or tenofovir/emtricitabine plus zidovudine plus abacavir [CPE 2008 = 2.5]). All subjects were neurocognitively asymptomatic at initiation of antiretroviral therapy and were longitudinally assessed using computerized neurocognitive testing and proton magnetic resonance spectroscopy (MRS).

After 48 weeks, persons receiving tenofovir/emtricitabine plus zidovudine plus abacavir had better performance than those taking tenofovir/emtricitabine/efavirenz on tests of 2 cognitive abilities, speed-of-information processing and executive functioning. In contrast to the neurocognitive differences, people taking tenofovir/emtricitabine/efavirenz had changes considered beneficial on MRS, with increases in *N*-acetyl aspartate (NAA) to creatine (Cr) ratios (a neuronal indicator) and declines in myoinositol (MI) to Cr ratios (an inflammation

indicator). Although the pretreatment asymptomatic status of the participants of this study is an important limitation, this combination of findings supports that efavirenz-containing regimens may better lead to normalization of the HIV-infected nervous system (via improvements in both neuronal and neuroinflammatory indicators) but, despite this, may still lead to worse neurocognitive performance.

To better understand the possible neurotoxicity of antiretroviral treatment, Liner and colleagues exposed fetal rat cortical neuronal cultures to increasing concentrations (from 0.01 to 300 $\mu\text{g/mL}$) of 15 individual antiretroviral drugs and 6 antiretroviral drug combinations over 1 week (Abstract 435). Neuronal pathology and cell death were assessed by microtubule-associated protein 2 staining, calcium signaling in response to glutamate, and mitochondrial membrane potential using fluorescent microscopy. Based on the findings, the investigators constructed concentration-effect curves and calculated median toxic concentrations for each drug. The investigators identified that the median toxic concentrations of several antiretroviral drugs fell within the range of concentrations reported in plasma or CSF with standard clinical dosing, including for abacavir, amprenavir, atazanavir, didanosine, efavirenz, lamivudine, nevirapine, tenofovir, and zidovudine.

These findings implicate nearly all currently used antiretroviral drugs as potentially neurotoxic to fetal rat cortical neurons, making the findings difficult to apply to clinical decision making, but they also lay the groundwork for additional analyses and reinforce the concept of a therapeutic window in the nervous system. The therapeutic window concept would dictate that antiretroviral drug concentrations be sufficiently high to reliably inhibit HIV replication but not so high that they put patients at risk of neuronal injury. This concept is also supported by the analysis by Garvey and colleagues (Abstract 427) that identified that severe CNS disorders were more common in the approximately 10% of persons who were taking antiretroviral regimens that had either very low or very high CPE 2008 ranks, although this association was only statistically significant in univariate analyses. Defining the upper and lower limits of the nervous system therapeutic window will be challenging and may require therapeutic drug monitoring, at least in individuals who have neurocognitive impairment that does not resolve with antiretroviral therapy.

A non-mutually exclusive alternative to optimizing antiretroviral therapy penetration into the CNS for treatment of HAND, a strategy being investigated in controlled clinical trials, is intensification of antiretroviral therapy regimens with additional antiretroviral drugs. Yilmaz and colleagues explored the effect of antiretroviral therapy intensification on residual, low-level CSF viral loads and CSF immune activation biomarkers (eg, neopterin, β_2 -microglobulin) (Abstract 431). They assessed 10 individuals who were taking at least 3 antiretroviral drugs and had HIV RNA levels suppressed below 50 copies/mL in CSF and in plasma but detectable levels in CSF using an assay with a detection limit of 2 copies/mL. All participants added to their existing regimen 1 of 3 antiretroviral drugs, either 1 of 2 “good” penetrators (maraviroc or lopinavir/ritonavir) or 1 “poor” penetrator (enfuvirtide). The findings during 8 weeks of antiretroviral therapy intensification and an additional 16 weeks of observation failed to demonstrate consistent decreases (or increases) in low-level viral loads or levels of immune activation biomarkers regardless of whether a “good” or “poor” penetrating antiretroviral drug was added to the existing regimen. Because no neurocognitive

assessments were presented, no conclusions could be reached about whether adding antiretroviral drugs to an existing regimen leads to clinical change, either improvement or worsening.

Reports from Resource-Limited Settings

Depression is common in patients with HIV infection in high-resource settings in the United States and Europe and is associated with delayed initiation of, poorer adherence to, and lower rates of HIV suppression with antiretroviral therapy compared with patients without a mental illness. Patients who have their depression treated, however, are equally likely to initiate antiretroviral therapy as patients without a mental illness and have improved antiretroviral therapy adherence, providing a strong rationale for identifying and treating depression. To date, research on the correlates and consequences of depression in HIV-infected patients in resource-limited settings (RLS) has been sparse. Four studies addressed aspects of these issues in sub-Saharan Africa.

The first study identified that depression was common among 1268 adults living in Botswana (Abstract 1010). Nearly one-third of men (31.4%) and one-fourth of women (25.3%) met criteria for depression on the Hopkins Symptoms Checklist for Depression. Risk of depression in men was associated with being unmarried and not living with a partner, rural residence, worse health status, more frequent visits to health care practitioners, intergenerational sex (sex with women >10 years younger), and fear of HIV or AIDS stigma. For women, the associated risk factors were lower education, higher income, and lack of control of sexual decision making. Although this project was designed to estimate depression prevalence in the general population, it implies that depression could affect clinical care of the substantial subgroup of people living with HIV infection in Botswana.

This inference from Botswana was applied in an analysis of 412 persons observed for 2 years in the Ugandan AIDS Rural Treatment Outcomes (UARTO) cohort (Abstract 1011). Adherence, as judged by self-report of number of missed doses per month and number of interrupted days per month, was remarkably high (92.6%), with 87% achieving plasma virologic suppression (< 50 copies/mL). Depression as measured by the Hopkins Symptoms Checklist for Depression contributed to poor adherence and failure of HIV suppression. Other contributors to poor adherence were male sex, younger age, being unmarried, lower socioeconomic status, distance to clinic, tobacco and alcohol use, and shorter duration of treatment. In a separate report from the same cohort, severe food insecurity was also associated with symptoms of depression in women but not men (Abstract 1012).

The effects of depression and excessive alcohol use on adherence were examined in HIV-infected Nigerian patients either receiving antiretroviral therapy (n=222) or untreated (n=177) (Abstract 1013). The Alcohol Use Disorders Identification Test assessed alcohol use, and the Center for Epidemiological Studies Depression Scale measured depression. Untreated patients were more likely to use alcohol excessively and be depressed. In multivariable analyses, depression was associated with low socioeconomic status and failure to disclose HIV serostatus to anyone. Depression, but not excessive alcohol use, was associated with worse adherence, as measured by medication refill rates.

Another topic that gained greater exposure was the long-term impact of HIV infection on children. Compared with norms for HIV-seronegative children (0 – 6 years old), HIV-infected children in Uganda were more likely to have derangements in visual reception and receptive and expressive language (Abstract 860). Despite the introduction of antiretroviral therapy, however, no statistically significant improvement was seen in neurocognitive scores, raising concerns about the irreversibility of these deficits. Supporting that these early deficits are reversible, however, was a multicenter study of older children (7 – 16 years old) in the United States and Puerto Rico that did not observe overall differences in neurocognitive performance scores compared with those of HIV-seronegative control subjects (Abstract 861). In this analysis, children with a history of advanced immune suppression were more likely to have neurocognitive deficits. Thus, similar to supportive findings in adults, earlier initiation of antiretroviral therapy in children may better maintain CD4+ cell counts and reduce the risk of neurocognitive impairment. Many of these studies evaluating CNS disorders are summarized in Table 2.

Pathogenesis and Biomarkers of Nervous System Disease

HIV Characteristics

A major question in HIV neurology research is whether neurovirulence differs between viral subtypes of HIV-1. Subtype-D HIV has been implicated as being more neurovirulent than other subtypes in adults, based in part on clinical data showing a difference in the frequency of HAND reported in Ugandan adults: 8 of 9 persons (89%) with subtype-D HIV had HAND compared with 7 of 33 (24%) persons with subtype-A HIV.⁷ Because subtype-D HIV is also associated with more rapid immune disease progression, and advanced disease in turn is associated with HAND, distinguishing the impact of subtype-D HIV infection on the immune and nervous systems is an important focus for future research.

The impact of subtype-D HIV on the developing brain has not been previously reported but was expected to be similar to the relationship observed in adults. In a cross-sectional study of 102 Ugandan treatment-naive children aged 6 years to 12 years (Abstract 175), HIV subtype was determined by a real-time polymerase chain reaction assay with subtype-specific probes in 5 regions (*gag*, *pol*, *vpu*, *env*, or *gp41*). Based on consistent subtypes from at least 2 regions, 37 children had subtype-A HIV, 24 had subtype D, and 9 had recombinant subtypes (32 were indeterminate), a distribution similar to adults in Kampala.

Those with subtype-A HIV infections had higher plasma viral loads but no other demographic or disease-related differences. In contrast to the data for adults, children with subtype-A HIV had worse—not better—scores on neurocognitive tests of sequential processing ($P = .04$), simultaneous processing ($P = .04$), and learning ($P = .03$) than did children who had subtype D, but they did not have worse planning and reasoning, attention, or motor task scores. None of these differences persisted, however, after adjusting for the difference in plasma viral loads in the primary analysis. In a subanalysis of children whose subtype determination included the *env* region ($n = 53$), however, the differences between sequential and simultaneous processing did remain statistically significant after adjusting for plasma viral loads as well as other demographic and social characteristics. Thus, in the small number of children examined with a limited number of neurocognitive tests, the expected

order of neurovirulence in HIV clades A and D was reversed compared with adults. Although this finding may be related to differences in HIV replication between groups, the subanalysis indicates that it is not.

Neurotropic or neurovirulent strains of subtype-B HIV have been identified in a number of studies, although no consensus has emerged about the genetics of these strains and the mechanism by which HIV adapts to and injures the brain. Brain-derived HIV strains are more likely to be macrophage-tropic, to use CC chemokine receptor 5 (CCR5) for entry into macrophages, to cause fusion of cells to form syncytia, and to promote neuronal apoptosis. A new phenotypic characteristic of neurotropic strains that may contribute to brain damage, shedding of soluble gp120, and its genetic correlates were investigated in brain tissue from people dying with HIV-associated dementia (HAD), the most severe form of HAND (Abstract 176). Two mutations in the beta-3 strand of the bridging sheet between the V1 and V2 regions of HIV *gp120* (D197 and T200) were found to be associated with neurotropism (T200) and HAD (both D197 and T200). In vitro studies of brain-derived HIV strains into which these envelope mutations were introduced showed that these mutations contributed to increased infection of macrophages and greater shedding of soluble gp120 from a transfected human embryonic kidney cell line (293T).

Because soluble gp120 can cause neuronal apoptosis, this characteristic may contribute to the neurovirulence of these variants. Together, the combination of reduced CD4 dependence and increased shedding of gp120 may identify particularly neurotropic and neurovirulent viruses that could greatly increase risk of HAND. The frequency of these mutations and their characteristics in living HIV-infected individuals, however, remain unknown.

Possible clinical evidence of neuro-adaptation was presented from a study comparing CSF viral loads to neurocognitive performance in 379 untreated individuals (Abstract 172). Higher CSF viral loads were associated with higher plasma viral loads, lower current and nadir CD4+ cell counts, and older age. Higher CSF viral loads were not associated with worse neurocognitive performance; however, the 14% of individuals who had CSF viral loads at least as high as their plasma viral loads (a putative indicator of neuroadapted HIV) had substantially worse neurocognitive performance (Cohen's $d = 0.65$; $P = .001$), even after adjusting for age, nadir CD4+ cell count, and other measures reflecting disease severity and comorbid conditions. No genotype data were presented, however, to support the hypothesis that individuals who have very high relative CSF viral loads are more likely to have compartmentalized HIV.

Host Characteristics

The role of vascular disease, either coronary or cerebral, in the development of HAND is unclear. Vascular disease could provide a mechanism that explains the impact of accelerated aging and the metabolic syndrome on the persisting high prevalence of HAND in antiretroviral therapy-treated individuals. In the neurologic substudy of the SMART (Strategies for Management of Antiretroviral Therapy) study, 292 HIV-infected participants with CD4+ cell counts greater than 350/mL underwent 5 neurocognitive tests before and 6 months after starting antiretroviral therapy (Abstract 415). Although only 3% of participants had evidence of coronary vascular disease, 3 vascular disease-related risk factors (history of

coronary vascular disease, use of antihypertensive drugs, and elevated total cholesterol levels) increased the risk of impairment at baseline. The ORs for neurocognitive impairment were increased by coronary vascular disease history (OR, 6.1; $P = .02$) and total cholesterol (OR, 1.1 per 10 m/mL, $P = .05$) but not by use of antihypertensive drugs (OR, 1.6; $P = .40$). In this study, none of the HIV disease- or antiretroviral therapy-related risk factors predicted impairment, including AIDS, current or nadir CD4+ cell count, plasma viral load, or CPE 2008 rank. These participants differed from those previously reported as having several vascular disease-related, but no HIV-related, risk factors for neurocognitive impairment. Although the relatively early disease stage of these participants may account for this inconsistency, these findings indicate that the impairment of at least some patients is either mediated by or has risk factors in common with vascular disease.

Two host proteins, apolipoprotein E and mannose binding lectin, may provide links between risks of vascular disease and HAND. An analysis based on a cohort study of 203 HIV-infected individuals in Anhui province, China, identified that the 21% of individuals who had at least 1 *APOE* epsilon4 allele had 3-fold increased odds of having neurocognitive impairment at their first assessment (Abstract 414). This association held in multivariable analyses that adjusted for disease and treatment characteristics. Polymorphisms in the *MBL2* gene were not associated with neurocognitive impairment at the first testing but did predict neurocognitive decline over 12 months. Specifically, the neurocognitive performance of the 12% of participants who had the *MBL2* O/O genotype was more likely to decline over 12 months than for the 49% of participants who had the A/A genotype (OR = 3.6; $P = .004$). Of note, neurocognitive performance was not associated with polymorphisms or copy number variants in several other genes previously implicated in risk of AIDS or HAND, including *CCR2*, *CCR5*, *MCP-1*, and *CCL3L1*.

Cross and colleagues evaluated the unfolded protein response (UPR) in HIV-infected macrophages (Abstract 407). The UPR is a cellular adaptation to stressors such as heat shock and glucose deprivation that prevents congestion of the endoplasmic reticulum with nonfunctional, misfolded proteins. Infected macrophages constitute a reservoir of infection in the CNS and other tissues in antiretroviral therapy-treated individuals. Also, macrophages generate soluble, excitatory neurotoxins that may contribute to neuronal injury and neurocognitive impairment. The investigators showed that HIV, by modulating the UPR pathway, helps keep macrophages alive while they efficiently replicate virus. They also showed that it was possible to manipulate UPR function using various drugs, thereby inhibiting HIV replication. These findings raise the possibility of reducing the macrophage reservoir and blocking macrophage neurotoxicity by pharmacologic interventions directed at UPR pathways.

Brain Imaging

The role of neuroimaging in understanding the pathogenesis and clinical management of HAND continues to expand. Four techniques that were prominently displayed included morphometry, MRS, diffusion tensor imaging (DTI), and arterial spin labeling. Brain morphometric measures were assessed as part of the Neuradapt study (Abstract 400). Within a cohort of 169 HIV-infected subjects, people with HAND had larger subcortical (eg,

putamen, thalamus, and globus pallidus) volumes than did either HIV-infected, unimpaired individuals or HIV-seronegative control subjects. These larger structural volumes were associated with increases in the MRS measure of the choline (Cho) to Cr ratio, a marker of inflammation, suggesting that HAND may continue because of persistent immune activation, which may in turn be caused by persistent low-level HIV replication.

The observed morphometric increases are similar to those from a prior study⁸ but differ from others^{9,10} in which decreases in volume were seen with HIV infection. In a cross-sectional multicenter study, investigators observed statistically significantly lower values for all MRS measures including ratios for NAA to Cho, MI to Cr, and Cho to Cr in asymptomatic HIV-infected individuals about to start antiretroviral therapy (Abstract 403). Observed reductions in inflammatory ratios (MI to Cr and Cho to Cr) are contrary to a published report¹¹ and could result from the earlier stage of the disease of the participants in the conference report.

The conference also highlighted an increasingly popular neuroimaging method, DTI. This technique measures the restricted diffusion of water within the brain in order to visualize neural fiber tracts. Two studies investigated the effects of HIV infection and other comorbid conditions on DTI measures. Structural changes were observed within the caudate (eg, a decrease in fractional anisotropy and an increase in mean diffusivity) in HIV-infected individuals with metabolic syndrome compared with those without metabolic syndrome (Abstract 401), identifying a macromechanism by which metabolic syndrome may lead to HAND (ie, disruption of neural fiber tracts).

Another analysis compared DTI findings of people with HIV mono-infection with those in people with HIV and hepatitis C virus (HCV) coinfection in a cohort, most of whom were taking antiretroviral therapy (Abstract 402). Coinfected individuals performed worse on brief neurocognitive testing but did not have worse fractional anisotropy or mean diffusivity measures with DTI, suggesting that HCV infection may injure the brain via a mechanism not evident with detailed imaging of neural fiber tracts. These reports suggest that DTI may help investigators distinguish the effects of comorbid conditions from the effects of HIV infection on brain pathology. However, larger, controlled studies are needed to fully evaluate the role of DTI and other modalities.

New data on the emerging method of arterial spin labeling were also shown. In a cross-sectional analysis, a statistically significant decrease in resting cerebral blood flow was seen in untreated HIV-infected individuals compared with antiretroviral therapy-treated, HIV-infected individuals and with HIV-seronegative control subjects (Abstract 171). Although treated individuals had better cerebral blood flow than untreated individuals, antiretroviral therapy did not seem to completely normalize cerebral blood flow, identifying another mechanism that might account for persistent HAND in treated individuals (ie, persistently abnormal cerebral blood flow). In a smaller longitudinal component, untreated HIV-infected individuals who initiated antiretroviral therapy had an improvement in resting cerebral blood flow. These results support a role for arterial spin labeling measurements of cerebral blood flow to evaluate the effectiveness of antiretroviral therapy in the nervous system. Once again, however, larger, controlled studies are needed because this technique is still in its infancy.

HIV-Associated Peripheral Neuropathy

Painful HIV sensory neuropathy (HIV-SN) continues to be a common problem despite successful virologic suppression with antiretroviral therapy. Taller individuals are more susceptible than shorter ones,¹² a phenomenon believed to result from the dependency of longer distal nerve segments on metabolic support from sensory nerve cell bodies in the dorsal root ganglion near the spinal cord. Mitochondria are distributed along the length of axons and are particularly important for energy production in these very long cell components. Mitochondria also play important roles in the management of oxidative stress that can occur with HIV infection and other conditions.

Axonal mitochondria are assembled in the sensory neuron cell body and transported down the axon in a relatively slow process that results in distal mitochondria being considerably “older” than those in the cell body. Lehman and colleagues evaluated a common 5-kilobase deletion mutation of mitochondrial DNA as a marker of mitochondrial “aging” along the length of the axon (Abstract 412). They found that sural nerves of HIV-infected individuals who died with neuropathy (provided by the National NeuroAIDS Tissue Consortium) had higher levels of mitochondrial deletion mutations than did sural nerves of HIV-seronegative control subjects or HIV-infected individuals who died without neuropathy. Deletion mutations were more common in distal nerve segments than in the dorsal root ganglia of the same patients. The investigators also found evidence of mitochondrial dysfunction and abnormal oxidative stress in the sensory nerves of SIV-infected macaques treated with antiretroviral therapy.

Among the major risk factors for painful HIV-SN are low CD4+ cell count, older age, and exposure to certain nucleoside analogue reverse transcriptase inhibitors like stavudine and didanosine. Injury to small unmyelinated nerve fibers leads to pain, and previous studies have demonstrated that reductions in epidermal nerve fiber density (ENFD) can serve as measures to assess this damage. However, ENFD has not been systematically evaluated in neuropathy-free HIV-infected subjects not yet exposed to antiretroviral therapy.

Shikuma and colleagues evaluated baseline cross-sectional data from 87 antiretroviral therapy-naïve Thai subjects in the SEARCH 003 (Southeast Asia Research Collaboration With Hawaii 003) clinical trial (Abstract 173). All subjects were free of HIV-SN as demonstrated by physical examination. Superficial skin biopsies from the proximal thigh and distal leg were assessed for unmyelinated nerve fibers according to an established method (protein gene product [PGP] 9.5 immunostaining). Mitochondrial functional integrity was assessed in peripheral blood mononuclear cells (PBMCs) from these same individuals by immunoassay for oxidative phosphorylation markers.

In these Thai subjects (average age, 36 years; mean CD4+ cell count, 153/ μ L; mean plasma HIV RNA level, 4.9 log₁₀ copies/mL) the average ENFD values (fibers/mm of epidermis) were unexpectedly higher than published age-matched population normative values from the United States, both for both proximal thigh and distal leg. Nevertheless, in the Thai subjects, lower distal ENFD was associated with being older and taller and with having a lower CD4+ cell count and higher viral load. PBMC oxidative phosphorylation protein or activity level

did not correlate with ENFD value in the subgroup of 38 individuals in whom these assessments were performed.

These findings suggest that, in addition to height and age, race or ethnicity may also substantially affect the density of small, unmyelinated pain nerve fibers. They also imply that nerve damage exists even in antiretroviral therapy-naïve subjects with no signs or symptoms of neuropathy and that this damage is related to advanced HIV immunosuppression. Because the mitochondrial functional assays were performed in PBMCs rather than peripheral nerve tissue, they do not clearly exclude a role of mitochondrial dysfunction in HIV-SN.

An important limitation in research on HIV-SN is that no large-animal model is widely available to investigate this condition. Mankowski and colleagues attempted to address this important shortcoming by looking to SIV infection in macaques as a model for HIV-SN (Abstract 174). They collected samples of skin from distal leg as well as sural nerves and lumbar dorsal root ganglia from animals at asymptomatic and terminal stages of SIV infection. ENFD was measured by staining for the nerve marker PGP 9.5. Inflammatory responses in dorsal root ganglia were evaluated by immunostaining for macrophage activation.

Similar to HIV-infected humans, SIV-infected macaques showed loss of epidermal nerve fibers and infiltration of macrophages into the dorsal root ganglion. Dorsal root ganglia also showed neuronal loss and SIV replication in macrophages. Pain-sensing C-fiber conduction velocities in sural nerves were reduced, and these changes correlated strongly with the extent of dorsal root ganglia macrophage infiltration. These similarities between sensory neuropathies induced by SIV and those by HIV suggest that macaques may provide a valid large-animal model for HIV-SN, which in turn should lead to new research into pathogenesis and new treatments to prevent or ameliorate HIV-SN.

Other Infections of the Nervous System

Syphilis

HIV infection is associated with an increased risk of syphilis and appears to increase the risk of symptomatic CNS disease, but identification of characteristics of *Treponema pallidum* that could influence neurovirulence has remained elusive. Molecular methods were used to type *T pallidum* from 79 persons with syphilis in the Seattle area from 1999 to 2008 to describe the epidemiology and clinical phenotypes of *T pallidum* strains (Abstract 177). After amplification of *T pallidum* DNA from organisms isolated from either blood or CSF, strain type was determined using 3 methods: number of repeats in the acidic repeat protein gene, restriction fragment length polymorphism analysis of *T pallidum* subfamily II repeat protein genes, and sequence analysis of an 84-base-pair region of the *tp0548* gene. Of 79 individuals studied, 76 were men, 66 were HIV-infected, 73 had early-stage (primary, secondary, or early latent) syphilis, and 9 had late-stage syphilis or syphilis of unknown duration. By serologic criteria (positive CSF VDRL test result), 18 (23%) had neurosyphilis.

Six *T pallidum* strains were identified among the 79 patients (types 4, 9, 10, 12, 13, and 20). One strain was particularly associated with neurosyphilis: strain 9 had a 36% rate of neurosyphilis compared with 8% in other strains combined. Both a previously established marker of neurosyphilis (rapid plasma reagin titer 1:32; OR = 2.2) and strain 9 (OR = 8.6) contributed to a model for discriminating neurosyphilis, suggesting that strain typing could contribute to diagnosis of this condition. Extension of this study to other geographic regions and further study of strain 9 for factors associated with neuroinvasion promise to expand the understanding of neurosyphilis.

Hepatitis B Virus

HIV and HCV have been shown to adapt to the nervous system, but no such data exist for hepatitis B virus (HBV). Duiculescu and colleagues investigated the presence and compartmentalization of HBV in the CSF of individuals with chronic HIV-HBV coinfection (Abstract 428). They did so by measuring HBV DNA in CSF from 18 patients with detectable plasma HBV DNA and, in a subgroup of 5, by characterizing anti-HBV drug resistance-associated mutations using a reverse hybridization line probe assay. Eleven of the 18 individuals (61%) had detectable HBV DNA in CSF at levels approximately 2 log₁₀ IU/mL lower than in plasma (mean 4.1 vs 6.0 log₁₀ IU/mL).

Interestingly, HBV DNA levels correlated with HIV RNA levels in both fluids, suggesting a role for active HBV replication in regulation of HIV replication (or vice versa). Of 7 patients with undetectable plasma HIV RNA while taking lamivudine-containing antiretroviral therapy, none had detectable HBV DNA in CSF. Analysis of genetic variation between plasma and CSF HBV identified concordant profiles in 2 but discordance in the other 3. Of the 3 with discordance, 2 had HBV drug resistance-associated mutations present in CSF that were not present in plasma, suggesting that the nervous system might serve as either a source of or a refuge for HBV drug-resistant mutants. These data are sparse, however, and further investigations are needed to confirm these findings and to determine their clinical implications.

Hepatitis C Virus

Many published reports have identified that HCV can infect glial cells, can compartmentalize in the nervous system, and can worsen neurocognitive performance and neuroimaging findings. Few studies, however, have investigated whether HCV-encoded proteins are neurotoxic, similar to the effects of HIV-encoded Env and Tat. Vivithanaporn and colleagues hypothesized that HCV-encoded Core protein would be neurotoxic and investigated its effects on human fetal neurons with or without Core-treated human glia (Abstract 410). Building on their findings on the neurotoxicity of HIV-encoded Vpr,^{13,14} they also concurrently exposed cultures to Vpr.

They found that Core protein reduced expression of 2 markers of neuronal viability, beta-tubulin and lipidated LC3-II, and that it induced expression of proinflammatory cytokines or chemokines in microglia and astrocytes. The Core protein's neurotoxicity was potentiated by the presence of Vpr protein. The investigators also studied the in vivo impact of Core protein in Vpr-transgenic mice by administering intrastriatal stereotactic implants of HCV Core.

Core protein–treated mice showed evidence of pathologic behavior (worse ipsiversive rotary behavior after implantation) and, at necropsy, had evidence of fewer neurons and more microglia, further supporting that HCV infection of the brain can induce neuroinflammation and neuronal injury and that these effects may be additive to those of HIV infection.

Summary

As more data accumulate on the presence and treatment of the neurocognitive disorders associated with HIV disease, several trends are increasingly clear. First, advanced HIV disease confers an increased risk of neurocognitive impairment that may be either partially irreversible or only partially treatable with the antiretroviral therapy regimens commonly in use. Second, better-penetrating antiretroviral therapy better reduces HIV in the nervous system, but HIV suppression below the detection range of commercial assays does not guarantee full cognitive recovery. Third, certain antiretroviral drugs may have long-term neurotoxicity, but nearly all existing data support that better-penetrating antiretroviral therapy per se is not neurotoxic. Fourth, primary CSF virologic failure does occur but seems to be an infrequent event that can either be symptomatic or asymptomatic.

Together, these findings argue for new research into (1) strategies to prevent the neurocognitive complications of HIV infection, including new diagnostic methods to identify asymptomatic patients who are at risk, (2) new diagnostic methods to distinguish reversible from irreversible disease, (3) clinical strategies to distinguish neurocognitive symptoms attributable to HIV infection and persistent immune activation from antiretroviral therapy neurotoxicity or comorbid conditions, and (4) more effective therapeutic strategies once disease occurs.

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Table 1

Revised Central Nervous System Penetration-Effectiveness Ranking

Antiretroviral Drug Class	4	3	2	1
Nucleoside analogue reverse transcriptase inhibitors	Zidovudine	Abacavir	Didanosine	Tenofovir
		Emtricitabine	Lamivudine	Zalcitabine
			Stavudine	
Nonnucleoside analogue reverse transcriptase inhibitors	Nevirapine	Delavirdine	Etravirine	
		Efavirenz		
Protease inhibitors	Indinavir/ritonavir	Darunavir/ritonavir	Atazanavir	Nelfinavir
		Fosamprenavir/ritonavir	Atazanavir/ritonavir	Ritonavir
		Indinavir	Fosamprenavir	Saquinavir
		Lopinavir/ritonavir		Saquinavir/ritonavir
				Tipranavir/ritonavir
Entry/fusion inhibitors		Maraviroc		Enfuvirtide
Integrase strand transfer inhibitors		Raltegravir		

Note: Larger numbers reflect estimates of better penetration or effectiveness in the central nervous system (eg, a ranking of 4 indicates the best penetration or effectiveness). Based on data from Abstract 172.

Table 2

Summary of Studies Evaluating HIV-Associated Neurocognitive Disorders (HAND) and Other Central Nervous System Disorders

Abstract No. Authors	Location	Sample Size	Findings	Correlates of Findings
Abstract 429 Ellis et al	USA	1525	52% global neurocognitive impairment	Lower nadir CD4+ cell count
Abstract 172 Letendre et al	USA	1221	51% global neurocognitive impairment	CSF viral load plasma viral load
Abstract 432 Edén et al	Sweden	67	Neurocognitively asymptomatic cohort	Primary CSF failure occurred in 10.4%
Abstract 430 Letendre et al	USA	346	53% global neurocognitive impairment	Worse neurocognitive performance associated with shorter times to loss of viral response in CSF and plasma
Abstract 433 Starace et al	Italy	45	69% HAND	Lower CPE 2008 rank
Abstract 427 Garvey et al	UK	19,828	224 severe CNS disorders; 1256 deaths	Lower CPE 2008 rank associated with death, not severe CNS disorders
Abstract 416 Muñoz-Moreno et al	Spain	172	60% HAND	Shorter duration of current antiretroviral therapy; longer duration of total antiretroviral therapy; older age; highest ever plasma viral load; not lower CPE 2008 rank
Abstract 417 Ciccarella et al	Italy	136	52% global neurocognitive impairment	Efavirenz use; not lower CPE 2008 rank; lower nadir CD4+ cell count
Abstract 434 Winston et al	England, Canada, China, Thailand	30	Neurocognitively asymptomatic before randomization	Efavirenz associated with less neurocognitive improvement but higher NAA:Cr and lower MI:Cr ratios on MRS
Abstract 860 Brahmabatt et al	Uganda	187	HIV-seropositive children performed worse	<i>0–6 years</i> : visual reception; receptive language; expressive language <i>7–14 years</i> : sequential processing; expressive language
Abstract 861 Smith et al	North America	461	HIV-seropositive children performed worse	CDC C class HIV diagnosis
Abstract 1011 Bangsberg et al	Uganda	456 (combined)	Depression: more common in women	Worse adherence; treatment failure; food insecurity
Abstract 1012 Tsai et al				
Abstract 1013 Farley et al	Nigeria	399	Depression: 13% (CES-D 16)	Lack of antiretroviral therapy; lower socio-economic status; failure to disclose HIV serostatus

CDC indicates Centers for Disease Control and Prevention; CES-D, Center for Epidemiological Studies Depression Scale; CPE 2008, central nervous system penetration-effectiveness ranking system³; CSF, cerebrospinal fluid; MI:Cr, myoinositol to creatine ratio; MRS, magnetic resonance spectroscopy; NAA:Cr, *N*-acetyl aspartate to creatine ratio.