Neurologic Complications of HIV Disease and Their Treatment

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Substantial work on the peripheral and central nervous system complications of HIV was presented at the 16th Conference on Retroviruses and Opportunistic Infections. Six studies of more than 4500 volunteers identified that distal sensory polyneuropathy remains common, ranging from 19% to 66%, with variation based on disease stage, type of antiretroviral therapy, age, and height. Eight studies of more than 2500 volunteers identified that neurocognitive disorders are also common, ranging from 25% to 69%, with variation based on stage of disease, antiretroviral use, diabetes mellitus, and coinfection with hepatitis viruses. Therapy-focused studies identified that resistance testing of cerebrospinal fluid (CSF)-derived HIV may improve management of people with HIV-associated neurologic complications, that poorly penetrating antiretroviral therapy is associated with persistent low-level HIV RNA in CSF, and that efavirenz concentrations in CSF are low but in the therapeutic range in most individuals. Neuroimaging reports identified that people living with HIV had abnormal findings on magnetic resonance imaging (gray matter atrophy, abnormal white matter), magnetic resonance spectroscopy (lower neuronal metabolites), and blood-oxygen-level dependent functional magnetic resonance imaging (lower cerebral blood flow). Other important findings on the basic neuroscience of HIV and diagnosis and management of neurologic opportunistic infections are discussed.

HIV-Associated Peripheral Neuropathy

Neuropathy Remains Common

Changes in the epidemic may affect the occurrence and severity of distal sensory polyneuropathy (DSPN) in people living with HIV or AIDS. Many of the potentially influential changes link to the use of combination antiretroviral therapy, including the substantial immune recovery that can occur, the advancing age of people whose survival has been extended by antiretroviral therapy, and declines in the use of neurotoxic nucleoside analogue reverse transcriptase inhibitors (nRTIs) (eg, the dideoxynucleoside analogues, stavudine and didanosine, sometimes referred to as "d-drugs"). Two complementary posters evaluated the changes in several putative risk factors for DSPN and their impact on its diagnosis and severity.

Ellis and colleagues reported on findings in the CHARTER (Central Nervous System [CNS] HIV Antiretroviral Therapy Effects Research) cohort, comprising 1539 HIV-infected individuals who enrolled in a prospective, observational study at 6 US sites (Abstract 461). DSPN was defined as having at least 1 clinical sign in a symmetric, bilateral pattern on neurologic examination; signs included diminished distal vibratory and pin sensation and reduced ankle reflexes. Correlates of DSPN and neuropathic pain evaluated in univariate and multivariate analyses were age, antiretroviral therapy and d-drug use, HIV disease markers (plasma viral load, the lowest CD4+ cell count [the lowest reported or measured "CD4+ nadir"], and extent of immune recovery [estimated by the difference between the current and nadir CD4+ cell counts]), hepatitis C virus (HCV) serostatus, substance use disorders (alcohol, opiates), and recent nonprescription opiate use. Pain and its effect on quality of life were assessed using the Medical Outcomes Survey for HIV (MOS-HIV). Fifty-seven percent of the patients had at least 1 abnormal clinical sign of DSPN, and 28% had 2 or more signs. Of those with at least 1 sign, 335 (38%) reported neuropathic pain, which was statistically significantly associated with reduced quality of life as measured by the MOS-HIV. Statistically significant risk factors for objective evidence of DSPN in multivariate analyses were older age, lower CD4+ nadir, current antiretroviral therapy use, past d-drug use, and a history of opiate abuse or dependence. Subjective neuropathic pain was predicted by prior d-drug use and lower CD4+ nadir.

The CHARTER study's findings on the burden of DSPN in a cohort of mostly antiretroviral-experienced individuals were complemented by an analysis from the ALLRT (AIDS Clinical Trials Group [ACTG] Longitudinal Linked Randomized Trials) cohort. Evans and colleagues studied 2135 antiretroviral-naive participants observed longitudinally for up to 7 years (Abstract 462). All volunteers initiated a new antiretroviral regimen, and approximately 90% of them had achieved undetectable viral loads after 48 weeks of therapy. Thirty percent of participants had at least 1 abnormal neuropathy sign on clinical examination at week 48. The frequency of abnormal signs increased to 41% among those who were observed for 8 years, even though d-drug use declined during

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the period of observation. Importantly, concurrent rates of symptomatic DSPN were 3% and 5%, indicating that most DSPN in this study was asymptomatic. Statistically significant risk factors for DSPN in multivariate models were older age, d-drug use during the period of observation, higher pretreatment viral loads in plasma, and lower pretreatment CD4+ cell counts in blood.

These 2 studies assessed 2 large and distinct cohorts, but their findings were consistent: DSPN remains common and is associated with older age and d-drug use. The consistent, strong association of DSPN with more advanced immunosuppression, even among those with successful virologic suppression from antiretroviral therapy, suggests that earlier introduction of antiretroviral therapy may protect patients from neuropathic disability and improve quality of life. As more effective and less toxic therapies are developed, this goal becomes increasingly achievable.

Other Risk Factors for Neuropathy

Recent Conferences on Retroviruses and Opportunistic Infections have included reports on genetic susceptibility factors for the neurologic complications of HIV disease. Prominent among these factors have been polymorphisms that increase the likelihood of developing painful neuropathy with the use of neurotoxic d-drugs. In light of the continuing use of stavudine and didanosine in resource-limited settings, such polymorphisms may be particularly important in sub-Saharan Africa, India, China, and elsewhere. Canter and colleagues approached this issue by performing a subanalysis of genetic risk factors for symptomatic neuropathy in non-Hispanic black participants exposed to zidovudine/lamivudine or stavudine/didanosine in clinical trial ACTG 384 (Abstract 160). These investigators sequenced the coding region of each participant's mitochondrial DNA and determined subhaplogroups based on published algorithms. Peripheral neuropathy was more likely to develop in individuals with African subhaplogroup L1c (9/16 patients, or 56%) than in those with other subhaplogroups (42/140 patients, or 30%; P = .048). In multivariate analyses, older age, randomization to the stavudine/didanosine group, and subhaplogroup L1c were each predictors for incident, symptomatic DSPN, even after adjustment for sex, pretreatment CD4+ cell count and HIV RNA level, and randomization to nelfinavir.

DSPN occurs more commonly in the legs than the arms, and one explanation for this is that longer nerves are more susceptible to injury. Because of this, DSPN may develop more frequently in taller patients than in shorter ones. Cherry and colleagues tested this hypothesis by examining the association between neuropathy risk and several simple clinical indicators, including height (Abstract 161). In a mixed cohort of 100 Australians, 98 Malaysians, and 96 Indonesians receiving antiretroviral therapy who did not have DSPN at baseline, the investigators screened for new-onset DSPN. In addition to stavudine exposure, taller height and older age were independently associated with the risk of incident DSPN. The DSPN risk increased from 20% in younger, shorter patients to 33% in younger, taller patients, 38% in older, shorter patients, and 66% in those older than 40 years and taller than 170 cm who received stavudine. These data suggest that older, taller patients may be prioritized to receive nonstavudine-containing antiretroviral regimens in resource-limited settings.

The metabolic syndrome includes hyperlipidemia, insulin resistance, hypertension, and inflammation and has been linked to the vascular disease that can occur with aging. HIV infection and antiretroviral therapy each appear to increase the risk of metabolic syndrome. Because components of the metabolic syndrome are known to also increase the risk of polyneuropathy, some investigators have speculated that the metabolic syndrome may be among the factors leading to persistent DSPN in individuals treated with antiretroviral therapy.

Ances and colleagues evaluated this possibility in a subgroup of 130 patients from the CHARTER cohort who had fasting measurements of blood levels of glucose and triglycerides (Abstract 463). For these analyses, the metabolic syndrome was defined as having 3 or more of the following 5 risk factors: (1) high body mass index (BMI > 30 kg/m^2), (2) hypertriglyceridemia (≥ 150 mg/dL), (3) low concentration of high-density lipoprotein (HDL) cholesterol (< 40 mg/dL for men and < 50 mg/dL for women), (4) hypertension (systolic ≥ 130 mm Hg, diastolic ≥ 85 mm Hg) or use of antihypertensive medication, (5) hyperglycemia (≥ 110 mg/dL) or use of antidiabetic medication. Although almost one-third of participants met criteria for the metabolic syndrome and more than half had DSPN, the 2 disorders were not associated. Among the metabolic syndrome components, only hypertriglyceridemia was associated with DSPN. In a separate analysis of the larger cohort, diabetes mellitus, although uncommon, was associated with an increased frequency of DSPN.

The role of HCV infection in neuropathy has been a matter of controversy for several years. Cherry and colleagues took advantage of unique cohorts comprising a total of 503 patients of diverse ethnic backgrounds in Melbourne, Australia; Jakarta, Indonesia; Kuala Lumpur, Malaysia; and Baltimore, Maryland, who had HCV seroprevalences ranging from 10% to 61% (Abstract 466). When results of all cohorts were combined, no association was found between HCV serostatus and symptomatic DSPN (P = .8). In fact, HCV infection was associated with a slightly reduced risk of DSPN at the Melbourne site. Adjusting for exposure to neurotoxic d-drugs did not alter these findings. Notably, in the CHARTER cohort, DSPN was more prevalent among HCV-seropositive individuals, but this relationship was not statistically significant in a multivariate model. Taken together, the findings of these studies suggest that HCV infection is not a major risk factor for DSPN in coinfected individuals. Table 1 summarizes the major findings of this group of abstracts.

Treatment of Neuropathy

Existing treatments for painful neuropathy are only symptomatic, and inves-

tigators have long sought treatments that would enhance peripheral nerve regeneration and restore function, in addition to relieving pain. The type of DSPN that is linked to the neurotoxicity of d-drugs—as opposed to the DSPN that occurs in people living with HIV who have never taken d-drugs—probably results from mitochondrial "poisoning." Although the use of d-drugs has declined in North America and Europe because of the availability of alternatives, they are still widely prescribed in resource-limited settings because low-cost generic versions are available.

Cherry and colleagues reported on a neuroprotective treatment for d-drug-associated DSPN, coenzyme Q10 (CoQ10; ubiquinone) (Abstract 447). CoQ10 is a component of the electron transport chain in mitochondria and participates in aerobic cellular respiration, which generates the vast majority of the body's energy in the form of adenosine triphosphate. These investigators studied an in vitro model of d-drug neurotoxicity using fetal rat dorsal root ganglia exposed to d-drugs with or without CoQ10 in a novel water-soluble formulation. Neurite growth was relatively preserved in the CoQ10-treated samples, despite the presence of d-drug. Furthermore, CoQ10 did not interfere with the antiviral activity of d-drugs. Although CoQ10 is currently too expensive for widespread use in resource-limited settings, these data support continued investigation of CoQ10 and related compounds as a potential management strategy for patients with possible nRTI-induced neuropathy.

One proposed mechanism of neurotoxicity causing DSPN in HIV infection is abnormal activation by the virus of CC chemokine receptor 5 (CCR5) receptors on sensory neurons, triggering apoptotic cellular pathways. Yeh and colleagues considered whether treatment with the investigational CCR5 antagonist vicriviroc might result in reduced frequency of DSPN or improvement in signs or symptoms in those with DSPN (Abstract 486). They studied 118 antiretroviral therapy–experienced patients with advanced HIV disease, 90 of whom underwent randomization to receive 1 of 3 dose levels of vicriviroc plus background antiretroviral therapy and 28 of whom underwent randomization to receive placebo plus background antiretroviral therapy. Approximately two-thirds of each group had abnormal signs of neuropathy; many were symptomatic. After 24 weeks of treatment, there was no difference in the prevalence of DSPN or symptomatic neuropathy in any of the treatment groups. The authors caution, though, that the relatively small numbers of enrolled subjects limited the study's power to demonstrate an effect on DSPN.

Basic Neuroscience of HIV

Basic neuroscience abstracts fell into 5 broad thematic categories that reflect growing trends in the field. The first and largest group encompassed the theme of neuroprotection. Ensuring adequate protection of the brain from the deleterious effects of HIV has become an important focus of investigational treatments, especially as modern cohort studies demonstrate that many individuals living with HIV have mild to moderate cognitive impairment despite good virologic responses to antiretroviral therapy.

Table **1.** Summary of Studies Evaluating HIV-Associated Distal Sensory Polyneuropathy (DSPN)

Abstract No. Authors	Location	Sample Size	Prevalence	Correlates
Abstract 461 Ellis et al	United States	1539	57% ≥ 1 sign 28% ≥ 2 signs 38% symptomatic	Older age, lower CD4+ nadir, history of d-drug use, current antiretroviral therapy use, history of opiate use
Abstract 462 Evans et al	United States	2135	30% ≥ 1 sign at 48 weeks 41% ≥ 1 sign at 8 years 5% symptomatic	Older age, history of d-drug use, higher pre–antiretroviral therapy plasma viral load, lower pre–antiretroviral therapy CD4+ count
Abstract 160 Canter et al	United States	230	Up to 56% DSPN	Mitochondrial haplogroup, older age, d-drug use
Abstract 161 Cherry et al	Australia, Indonesia, Malaysia	37	Up to 66% DSPN	Taller height, older age, d-drug use
Abstract 463 Ances et al	United States	130	55% DSPN	Fasting hypertriglyceridemia, diabetes mellitus
Abstract 466 Cherry et al	Australia, Indonesia, Malaysia, United States	503	Up to 62% DSPN	Varied by site (Kuala Lumpur, 19%; Baltimore, 62%), not hepatitis C virus infection

D-drug indicates the dideoxynucleoside analogue–containing drugs stavudine and didanosine.

A number of researchers are investigating protection of the brain in the presence of low-grade HIV replication and immune responses in the brain. For instance, Zhang and colleagues reported on a research collaboration between the University of Massachusetts and Bristol-Myers Squibb, identifying that HIV attachment inhibitors prevented neuronal viral Env-mediated toxicity in neuronally differentiated SH-SY5Y and B2-M17 cell lines, whereas CCR5 inhibitors did not display the same neuroprotection (Abstract 448). The investigators used a variety of virus particles (including Env from a patient with HIV-associated dementia [HAD], and particles deficient in *pol*, reverse transcriptase, *vif*, and *vpr*) and identified reduced apoptosis with the inhibitors, although only 1 marker, annexin V staining, was used. These promising findings should be confirmed with other apoptosis markers and performed in primary human neuronal tissue culture and an animal model.

The second theme was the role of the immune system in neurodegeneration. Zhu and colleagues have continued their work on the consequences of cleavage of stromal cell-derived factor 1α (SDF-1α, also called CXC chemokine ligand 12 [CXCL12]) into a neurotoxic peptide that binds CXC chemokine receptor R3 (CXCR3) (Abstract 449). They noted that CXCR3 was upregulated in neurons in HIV or feline immunodeficiency virus (FIV) disease, which was accompanied by suppression of autophagy, reduced neuronal viability, and neurobehavioral abnormalities. Interestingly, the investigators noted that didanosine may have neuroprotective properties independent of its effects on HIV replication because it seemed to prevent activation of CXCR3 and its consequent inhibition of autophagy.

Maingat and colleagues assessed the impact of the systemic immune response on neurodegeneration by exposing specific pathogen-free cats infected with a neurovirulent strain of FIV to repeated lipopolysaccharide (LPS) exposure (Abstract 457). LPS activates the innate immune system, and repeated LPS administration can induce tolerance or nonactivation of this immune response. The investigators found that repeated LPS administration reduced CD3+ cell infiltration into the brain and improved neurobehavioral performance. The importance of this observation is that selective modulation of the systemic innate immune system could affect cognition. In a similar vein, Yao and colleagues investigated the neuroprotective properties of CC chemokine ligand 2 (CCL2; also called monocyte chemotactic protein-1, [MCP-1]), which they demonstrated involved activation of the kinase Akt and nuclear factor κB (Akt/NF-κB) pathway (Abstract 451). This is in keeping with other work demonstrating that HIV neuroprotection is mediated via activation of Akt.

The third theme focused on HIV virology in the nervous system. Schnell and colleagues reported their cross-sectional and longitudinal analyses using single genome amplification of cerebrospinal fluid (CSF)- and blood-derived HIV, expanding their prior work that identified that the degree of compartmentalization was associated with neurocognitive impairment (Abstract 158).[1] In the reported analysis, 4 volunteers who had no neurocognitive symptoms had mixing of *env* sequences between CSF and blood, although some similar sequences tended to cluster in 1 compartment or the other. Eight volunteers with HAD, the severe form of HIV-associated neurocognitive disorder (HAND), had much more distinct partitioning between CSF and blood sequences, consistent with prior reports.[2-4] In volunteers with advanced immunosuppression, CSF-derived sequences appeared to be more closely related to each other than were blood-derived sequences, indicating amplification from a smaller number of clones in the nervous system.

The study's particularly provocative findings were based on changes in sequences over time preceding incident HAD, identifying that CSF-derived HIV sequences from up to 2 years before the diagnosis of HAD were present when HAD was diagnosed, consistent with restricted evolution of HIV in the CNS. When combined with their findings that some sequences in blood appeared to derive from CSF, these findings raise the possibility that "signature" sequences for HAD may be detectable in blood before the onset of HAD. If so, this could provide a valuable clinical tool for making a diagnosis in individuals who might be at risk of virus-driven HAND (as opposed to host-driven HAND).

Pasutti and colleagues provided additional evidence of limited expression of HIV in the brain by comparing genetic diversity of HIV DNA and RNA from the brains and spleens of 9 people who died with HIV or AIDS (Abstract 159). C2-V3 sequences were compartmentalized in all subjects and, within the brain, DNA and RNA sequences were phylogenetically distinct in most (8 of 9) cases. DNA diversity in brain was greater than RNA diversity in brain, and the genetic distances from the most recent common ancestor were shorter for brain-derived sequences than for spleen-derived sequences. Together, these data support the idea that only a subset of the viruses that infect the CNS are expressed, possibly reflecting CNS-specific constraints on viral fitness.[5-7]

The fourth theme was other mechanisms of HIV-associated neurotoxicity. Kandanearatchi and colleagues presented continuing work on the role of the kynurenine pathway, which involves the production of the excitotoxin quinolinic acid (Abstract 454). The current work identifies that quinolinic acid results in up-regulation of CCR5 expression, which can increase susceptibility to HIV infection, lead to damage of neuronal and glial cells, and is independent of the damage proposed to occur by quinolinic acid at *N*-methyl-D-aspartate (NMDA) receptors. Yang and colleagues presented work on NMDA receptor-mediated excitotoxicity, identifying that soluble factors produced by macrophages were associated with activation of extrasynaptic NMDA receptors with resultant neuronal injury (Abstract 453).

The fifth theme was new models for HIV-associated neurotoxicity. Pardo and colleagues reported work with adult human organotypic cerebral cortex cultures (Abstract 446). This

culture model is as close to the clinical in vivo situation as yet obtained. One important, potential drawback is that the tissue is obtained from surgical lobectomies, which are typically performed because of antiepileptic drug-resistant pathology in the temporal lobe. The nature of the underlying pathology raises concerns regarding its impact on the function of the tissue in culture. Gorantla and colleagues refined an existing mouse model using HIV-infected NOD/*scid*-IL-2Rg^{null} mice with human hematopoietic CD34+ stem cells (Abstract 456). This mouse model manifested hallmarks of human HIV-associated central nervous system disease, and the authors proposed that it would be useful to model virologic, immunologic, and pathologic manifestations of HIV disease.

HIV-Associated Neurocognitive Disorders

The widespread use of antiretroviral therapy has led to a decline in the more severe neurologic complications of HIV, such as HAD, but people living with HIV continue to experience mild and moderately severe forms of nervous system disease. The updated definition of HAND has helped standardize reports from different regions of the world. This diagnostic approach defines asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND) as impairment in cognitive functioning that involves at least 2 domains and is documented by performance that is at least 1.0 standard deviation below the mean for age-education-appropriate normative values on standardized neuropsychologic tests.[8] MND and ANI are distinguished by their impact on everyday functioning, with impairment occurring in MND but not in ANI. Implicit in the definition is the requirement to test or observe at least 5 cognitive domains through comprehensive testing using standardized neuropsychologic tests.

Heaton and colleagues reported many of the primary findings of the CHARTER cohort (Abstract 154). The 1555 volunteers in this observational study were mostly middle-aged (mean, 43 years), nonwhite (61%) men (77%) who had received a diagnosis of AIDS (63%) by CD4+ counts below 200 cells/µL. The mean CD4+ count at the time of assessment was 420 cells/µL, with 83% of values above 200 cells/µL. Consistent with this, a substantial majority (71%) was taking antiretroviral therapy, whereas about half of the remainder (14%) had discontinued antiretroviral therapy and the rest had never taken it (15%). Even though most subjects were taking effective antiretroviral therapy and had substantial immune recovery, a majority (53%) had impaired neuropsychologic performance compared with healthy controls. Among those who had impaired global performance, more than half performed poorly on tasks of learning, executive functioning, recall, and working memory.

Compared with the report on the University of California San Diego HIV Neurobehavioral Research Center cohort in 1995,[9] the proportion of impaired individuals among those who had US Centers for Disease Control and Prevention (CDC) stage C disease had declined, but the proportions of impaired individuals among those with CDC stages A or B disease had remained stable or increased. Following the updated nosology guidelines, the investigators carefully assessed comorbid conditions, such as history of severe head injury, severe or intractable epilepsy or psychiatric disease, and severe or ongoing substance use disorders, and they categorized volunteers into those who seemed to be affected or unaffected by these conditions. The majority (84%) did not seem to be severely affected by these comorbidities and, in this group, 47% still met criteria for neurocognitive impairment (compared with 84% of the remaining 238 whose performance was affected by these conditions). Neurocognitive impairment was associated with lower nadir CD4+ cell counts, detectable HIV RNA levels in blood, and the use of antiretroviral therapy. In particular, volunteers whose CD4+ counts had never dropped below 200 cells/µL and who currently had HIV RNA levels in blood below 50 copies/mL performed better than other volunteers, strongly arguing that earlier, effective antiretroviral therapy prevents or treats HAND.

Important and confirmatory findings of the impact of HIV on the brain were reported from other countries. In an analysis of data from 107 volunteers of the French Neuradapt cohort, Vassallo and colleagues reported that 25% of participants were diagnosed with HAND (ANI, 11%; MND, 10%; HAD, 4%), which requires impairment in at least 2 cognitive abilities, and an additional 44% had impairment in 1 cognitive domain, even though most volunteers in this study were antiretroviral therapy–treated (86%), middle-aged (mean, 44 years) men (77%) who did not have HCV coinfection (78%) (Abstract 464). Most were successfully treated, with viral loads in blood that were below 40 copies/mL and a mean CD4+ count of 527 cells/µL. Univariate analyses identified associations between any neurocognitive impairment and HCV seropositivity or antidepressants (used by 8% of the cohort). Multivariate analysis identified that HCV coinfection was the only independent risk factor for abnormal neuropsychologic performance.

Another analysis from France identified links between cognitive impairment and hepatitis B virus (HBV) coinfection instead of HCV coinfection (Abstract 474). Bonnet and colleagues assessed 230 volunteers who had similar demographic and disease characteristics to the other cohorts detailed above and were enrolled in the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) CO3 Aquitaine cohort. This analysis focused on the diagnosis of MND, identifying the condition in 24% of the cohort, which is substantially higher than the prevalence identified in the CHARTER cohort (10%). This difference is important because MND is, by definition, associated with impaired daily functioning. In a multivariate analysis, MND was associated with older age (10% increased odds for each year), AIDS (2.4-fold increased odds), and HBV surface antigenemia (4.0-fold increased odds) as well as lower levels of education and current unemployment.

The difference between the impact of HCV and HBV in these analyses from

Nice and Bordeaux raises important points. First, even though HCV can infect glial cells, the primary target cells of each virus are hepatocytes. Therefore, the consolidating explanation for the observed difference in the findings is that these viruses primarily injure the brain via their impact on the liver (eg, via subclinical hepatic encephalopathy) or perhaps via persistent immune activation. Second, even though many comorbid conditions can injure the brain, the ones that impact a particular population are strongly determined by the prevalence of those conditions in the local population. In the United States, where active HBV disease is uncommon relative to high-prevalence regions of the world, the impact of HBV coinfection on neuropsychologic performance in population analyses is negligible. In other regions where active HBV disease is more common, it may be a more influential determinant of clinically apparent brain injury.

The link identified between older age and worse neuropsychologic performance confirms prior observations.[10] Because antiretroviral therapy has improved survival, an expanding population has lived with the disease for many years. As this group reaches their 40s and 50s, their risk of cognitive impairment may be substantially higher than for people who do not have HIV. Candidate mechanisms that might affect the aging, HIV-infected brain include accelerated neurodegeneration of the type that can occur with normal aging, disorders of amyloid (similar to Alzheimer's disease), or vascular injury that can occur with metabolic disorders such as insulin resistance and dyslipidemias.

Dulioust and colleagues presented the results of a neurologic substudy of the Sigma cohort, which cross-sectionally assessed 37 antiretroviral therapy–treated individuals who were 60 years of age or older (Abstract 459). Most (36/37 patients) had suppressed HIV RNA levels in blood below 50 copies/mL with antiretroviral therapy, had a median nadir CD4+ count of 113 cells/μL, and had substantial immune recovery (median current CD4+ count, 522 cells/μL). Brief neuropsychologic testing identified that more than half (19/37 patients, 51%) of the older individuals in this study were impaired and that the pattern of impairment was subcortical and typical of HAND. A substantial proportion of participants also had cardiovascular risk factors (25/37 patients, 68%) such as hypertension and dyslipidemia, but they were not more likely to have impaired neuropsychologic performance.

The role of metabolic abnormalities, such as dyslipidemia or insulin resistance, was also examined in a substudy of CHARTER that was presented by McCutchan and colleagues (Abstract 458). Measurements of fasting glucose, insulin, and lipid levels were added to the comprehensive CHARTER assessments in 145 volunteers. Forty-five individuals (31%) in this subgroup had HAND, and these individuals also had higher body mass indices (27 vs 25, respectively; $P = .07$), lower HDL-cholesterol levels (43 vs 50 mg/dL, respectively; $P < .05$), higher triglyceride levels (184 vs 136 mg/dL, respectively; $P < .05$), and a greater prevalence of type II diabetes mellitus (17% vs 4%, respectively; $P < .05$), but not higher levels of fasting glucose, insulin, or a measure of insulin resistance (homeostasis model assessment for insulin resistance). Multivariate analysis identified that only diabetes mellitus was associated with worse neuropsychologic performance (odds ratio [OR] = 7.6; $P < .01$). One explanation for why this finding may differ from those of Dulioust and colleagues is that the Sigma group did not include individuals who had diabetes mellitus.

In addition to comorbid conditions, like infection with HCV or HBV, and host factors, like aging and metabolic disorders, the impact of HIV disease on the brain can be influenced by viral factors. Abstracts from prior Conferences on Retroviruses and Opportunistic Infections have identified specific mutations that are present in the brains of people dying with HAD and that these mutations can be associated with reduced dependence on CD4 for cell entry. Other investigators have found in vitro evidence that the subtypes of HIV may differ in their impact on the brain. This work has focused primarily on subtype C, but data presented at this year's conference focused on subtype F.

Romania has a unique population of young adults who were parenterally infected with subtype F HIV as infants and have been living for approximately 2 decades. Duiculescu and colleagues evaluated volunteers from this population who received care in Bucharest (Abstract 477). In a retrospective analysis of the 110 children (76 boys, 34 girls) with a mean age of 11.1 years at the beginning of the follow-up, HIV encephalopathy (HIVE) accounted for 20% of AIDS-defining illnesses before the availability of combination antiretroviral therapy and 18.8% afterward ($P > .10$).

HIV RNA levels measured in CSF from 19 children with HIVE were higher than those who did not have neurologic disorders ($P < .05$). In fact, HIV RNA levels in CSF were higher than those in blood in 12 of the 19 children with HIVE. Computerized tomography revealed that brain atrophy was the most frequent finding (84%), and magnetic resonance imaging (MRI) revealed white matter lesions in two-thirds. In a prospective evaluation of a subgroup of 43 young adults, 26 (60%) received a diagnosis of HAND: 16 (37%) had mild impairment, 4 (9%) had moderate impairment, and 6 (14%) were severely impaired. These data demonstrate the high prevalence of HAND in this unique Romanian cohort and do not support that the neurovirulence of subtype F HIV differs from that of subtype B.

Two studies reported on data from continents other than North America and Europe. Robertson and colleagues used a brief neuropsychologic testing battery and medical examination to determine the prevalence of HAND in volunteers in ACTG 5199 from countries within Africa (Malawi, Zimbabwe), Asia (India, Thailand), and South America (Brazil, Peru) (Abstract 485). They identified that 29% had at least 1 neurologic abnormality, including 6% with MND, 1% with HAD, 10% with "diffuse CNS disease," and 6% with "focal CNS disease."

Ruel and colleagues evaluated neurocognitive function in African children, a group that has been understudied in recent years (Abstract 920). The

investigators evaluated 96 HIV-infected and 122 HIV-uninfected children from Kampala, Uganda, who were aged 3 years to 12 years and enrolled in the CHAMP (Children with HIV and Malaria Project). All HIV-seropositive children had CD4+ counts that exceeded 250 cells/μL (median, 714 cells/μL) and 15% (median, 26%), with a median HIV RNA level of 52,500 copies/mL in blood.

Despite this relatively early disease, HIV-infected children who were between 3 years and 5 years old performed worse than HIV-uninfected children in 3 of 5 measures in the Mullen Early Learning Scales, an indication of developmental delay. Older HIV-seropositive children (6-12 years) also performed worse in 14 of 15 measures in the Kaufman Assessment Battery for Children-2 and in all 8 measures in the Bruininks and Oseretsky Test of Motor Proficiency-2. Worse performance was associated with higher HIV RNA levels in blood but not CD4+ counts. Although malaria is a focus of the research, this particular analysis did not address the impact of asymptomatic or minimally symptomatic malaria on performance.

The study has important implications because, as the investigators indicate, few clinics have the resources to assess children for developmental delay and, in the absence of testing, the children in this study would not be eligible to receive antiretroviral therapy based on current World Health Organization guidelines. Because HAND is not always completely reversible in adults, these findings argue for testing and early treatment of HIV-infected children with developmental delay or cognitive impairment.

From the US National NeuroAIDS Tissue Consortium, Everall and colleagues reported on the pathologic findings from brain tissue of 589 people who had died with HIV or AIDS (Abstract 155). One hundred nine (17%) cases exhibited evidence of typical HIV-related brain pathology (HBP; HIV encephalitis, HIV leukoencephalopathy, or microglial nodules). HBP was not more common when typical opportunistic conditions (eg, cryptococcal meningitis, toxoplasmic encephalitis) were present (19% of cases), with the exception of cerebral lymphoma, which occurred in 10% of cases that had HBP compared with 4% of cases without HBP ($P = .026$).

Even though most brains did not have typical HBP, most (78%) were not normal. One hundred fifteen (20%) had evidence of a noninfectious pathology, and another 69 (12%) had minimal abnormalities that were not typical for another diagnosis. Volunteers who died with evidence of HBP were less likely to be taking antiretroviral therapy before death and had lower nadir CD4+ counts and higher HIV RNA levels in blood before death. Substantial proportions of individuals had HAND (88%) or major depressive disorder (60%) during their lives, but neither condition was associated with typical HBP. Instead, HAND, particularly HAD, was associated with type II Alzheimer gliosis ($P = .027$). Overall, these findings indicate that the prevalence of HBP has remained stable or decreased since the widespread use of combination antiretroviral therapy but, despite this, other forms of brain pathology were common and few people died with normal-appearing brains. Table 2 summarizes the major findings of this group of abstracts.

Fatigue is a common symptom reported by HIV-infected individuals. Schifitto and colleagues found that 64% of participants of ACTG 5090 reported fatigue (Abstract 479). They found no statistically significant differences between fatigued and nonfatigued participants with regard to HIV RNA level in CSF or blood, CD4+ count, or performance on neuropsychologic tests. A subset of participants (n = 44) underwent magnetic resonance spectroscopy (MRS) imaging, identifying lower levels of the cellular energy marker creatine in the basal ganglia of fatigued participants. Based on these findings, alterations in energy metabolism in the brain may be responsible for the fatigue that afflicts a large proportion of people living with HIV.

Antiretroviral Therapy and the Nervous System

Penetration of antiretroviral drugs into the nervous system has been an important focus of research in recent years, identifying that drugs that better penetrate into the CNS result in greater reductions of HIV RNA levels in CSF and greater improvements in neuropsychologic performance. Such research is limited by the inability to directly measure antiretroviral concentrations in brain tissue in humans and by the absence of pharmacokinetic data in CSF for many antiretroviral drugs. Direct measurement of antiretroviral drug concentrations in brain tissue may best be accomplished in animal studies, but human studies reported at the conference extended work in the field by measuring drug concentrations in CSF and improving current assessment tools.

In a substudy of CHARTER, Best and colleagues measured efavirenz and emtricitabine concentrations in CSF (Abstract 702). Efavirenz concentrations have been measured previously in CSF,[11,12] but the results were inconsistent, with 1 study finding low levels of efavirenz in CSF and the other finding none. Best and colleagues initially found efavirenz to be undetectable in CSF also but used an extraction method (with methyl *tert*-butyl ether) to lower the sensitivity of the assay by an order of magnitude. Once they did so, they found that efavirenz concentrations were 0.5% of those in blood and exceeded the median inhibitory concentration in most of the 80 CSF specimens assayed. Emtricitabine was much easier to detect in CSF (43% of the concentration in blood) and exceeded the median inhibitory concentration in all 21 CSF specimens assayed. These results may explain the inconsistency in the published findings on efavirenz concentrations in CSF (ie, additional steps are necessary in the laboratory to measure the low concentrations of efavirenz present in CSF) and identify that emtricitabine may be an excellent choice for controlling HIV in the nervous system.

In another substudy of CHARTER, Letendre and colleagues used a modified version of a commercial nucleic acid sequence-based amplification assay to more sensitively measure HIV RNA levels in CSF from 300 individuals whose

Table 2. Summary of Studies Evaluating HIV-Associated Neurocognitive Disorders (HAND) and other Central Nervous System Disorders

Abstract No. Authors	Location	Sample Size	Prevalence	Correlates
Abstract 154 Heaton et al	United States	1555	53% global neuropsychologic impairment	Lower nadir CD4+ counts, detectable HIV RNA in blood, current antiretroviral therapy use
Abstract 464 Vassallo et al	France	107	69% HAND or neuropsychologic deficit	Hepatitis C virus coinfection
Abstract 474 Bonnet et al	France	230	25% mild neurocognitive disorder	Older age, AIDS, active hepatitis B virus disease
Abstract 458 McCutchan et al	United States	145	31% HAND	Diabetes mellitus, higher body mass index and triglycerides, lower high-density lipoprotein cholesterol
Abstract 459 Dulioust et al	France	37	51% HAND	Not cardiovascular risk factors
Abstract 477 Duiculescu et al	Romania	43	60% HAND	Higher HIV RNA in cerebrospinal fluid
Abstract 485 Robertson et al	Various	293	29% neurologic abnormalities	
Abstract 920 Ruel et al	Uganda	218	HIV-infected performed worse in most measures	
Abstract 155 Everall et al	United States	589	17% typical HIV brain pathology, 78% at least 1 central nervous system abnormality	Antiretroviral therapy nonuse, lower nadir CD4+ counts, higher HIV RNA levels in blood

HIV RNA levels were below 50 copies/mL when measured by a commercial reverse transcriptase-polymerase chain reaction assay (Abstract 484b). Forty-one percent (122) had HIV RNA levels between 2 copies/mL and 50 copies/mL in CSF, and these individuals used antiretroviral regimens that had worse estimates of penetration into the central nervous system (CNS penetration-effectiveness [CPE] scores < 1.5; 64% vs 51%, respectively; OR, 1.7; $P = .03$). The more sensitive assay was also performed in 100 matched blood plasma specimens from these 122 individuals, identifying that 26% had no detectable HIV RNA in blood, even though HIV was present in CSF. These individuals performed much worse on neuropsychologic testing (d = 0.71; $P = .006$) than did those who had detectable HIV RNA in both fluids. These findings indicate that a substantial proportion of effectively treated individuals have low-level HIV in CSF and that this is associated with worse antiretroviral drug penetration characteristics and worse neuropsychologic performance, suggesting that this measure may reflect ongoing viral-induced injury of the nervous system. These findings also support that a more sensitive viral load assay may have clinical value.

Canestri and colleagues also presented data supporting that antiretroviral therapy is not effective in the nervous system in all treated individuals and that this can lead to neurologic abnormalities (Abstract 484a). The group identified 10 individuals who were on stable antiretroviral therapy for a median of 14 months but had a new onset of acute or subacute neurologic abnormalities such as symptoms of neurocognitive impairment, psychosis, and nervous system inflammation. Even though HIV RNA levels were below 500 copies/mL in blood in all subjects and below the quantitation limit of the assay in 7, HIV RNA levels in CSF averaged 952 copies/mL and were more than 1 $\log_{10}$ copies/mL higher than in blood. Resistance testing was performed using HIV from CSF, and antiretroviral therapy was modified based on these results as well as estimates of antiretroviral drug penetration into the CNS (CPE scores). Treatment modification resulted in clinical improvement in all subjects and declines in HIV RNA levels in CSF below quantitation in 7. These data reinforce that antiretroviral therapy can fail primarily in the CNS and identify a clinical approach that improves the effectiveness of treatment when this occurs.

Cross-sectional analyses of data can be biased because they cannot accurately account for interindividual differenc-

es in time-dependent data such as duration of antiretroviral therapy, immune deterioration or recovery, and fluctuations in neuropsychologic performance. Longitudinal analyses can eliminate many of the biases inherent in cross-sectional analyses. Tate and colleagues used comprehensive, computerized neuropsychologic testing at 1 timepoint and the prior year's clinical records to calculate slopes of change in CD4+ cell counts and transitions between detectable and undetectable HIV RNA levels in blood (Abstract 476). Better performance in tasks assessing attention and executive functioning was predicted by increasing CD4+ cell counts over the prior year and transitions from detectable to undetectable HIV RNA levels in blood, consistent with use of effective antiretroviral therapy during that period. Although computerized testing can be flawed and the authors do not report global performance, this relatively small analysis (n = 81) reinforces the value of longitudinal data in understanding complex relationships between disease markers and brain health.

Few studies have reported on the cognitive benefits of antiretroviral therapy in regions outside Europe, North America, and Australia. After antiretroviral therapy was initiated in volunteers of ACTG 5199 (based in Africa, Asia, and South America), Robertson and colleagues identified statistically significant improvements in neuropsychologic functioning even after controlling for baseline performance, age, education, sex, CD4+ cell count, and HIV RNA levels in blood (Abstract 485). Of note, neuropsychologic response to antiretroviral therapy varied by country, suggesting important differences between treatment and regional differences such as HIV subtype, host characteristics, and comorbidities.

One challenge to understanding the impact of antiretroviral therapy on the brain is the rapidly expanding number of drugs available to patients and prescribers. A recent class of antiretroviral drugs, CCR5 antagonists, was designed to interfere with the use of this cell-entry receptor by HIV. Two drugs in this category are either currently available (maraviroc) or in development (vicriviroc), and physicochemical data indicate that both may penetrate into the CNS in therapeutic concentrations. The expression of CCR5 and of the other common coreceptor of HIV, CXC chemokine receptor R4 (CXCR4), varies by cell type. HIV strains that infect macrophages and microglia, the cells that are productively infected in the brain, are more likely to use CCR5 than CXCR4. The combination of preferential use of CCR5 in the brain and good penetration of CCR5 antagonists suggests that this class of drugs could play an important role in treatment of the HIV-infected nervous system.

This conclusion would be further supported if coreceptor usage assays indicated differences between HIV derived from the CSF and HIV from the blood. Spudich and colleagues compared coreceptor usage and replication capacity in 18 chronically HIV-infected individuals using a commercial tropism assay. They demonstrated that CCR5 usage was similar by HIV derived from CSF and from blood but, when CXCR4 was used by blood-derived HIV, the relative usage by CSF-derived virus was less (P = .022) (Abstract 469). They also demonstrated that HIV derived from blood had higher estimated replication capacity than HIV derived from CSF (P = .0017). The compartmentalization they observed in coreceptor usage, however, supports the idea that CCR5 antagonists may retain activity in the nervous system even when they fail in blood.

Neuroimaging of the Brain

An expanding role for neuroimaging in the neurocognitive complications of HIV was identified by findings from studies that used 3 techniques: structural MRI with morphometry, MRS, and functional MRI. Brain morphometry measures were assessed from a subset of the CHARTER cohort, identifying that lower volumes of cortical gray matter and larger volumes of abnormal white matter were associated with impaired neuropsychologic performance (Abstract 154). Data from the HIV Neuroimaging Consortium also identified that HIV-infected individuals had reduced brain volumes, whether evaluated as overall volumes or regional volumes, such as from the cortical (eg, parietal, temporal, and frontal cortex) or subcortical (eg, basal ganglia) regions (Abstract 480). Within certain brain regions, such as the corpus callosum, HIV-infected subjects who had the apolipoprotein E allele *ApoE4* had greater atrophy than HIV-infected subjects without this allele did (Abstract 460). These structural neuroimaging results confirm prior studies[13,14] and indicate that, in the current era, HIV is associated with loss of cortical and subcortical gray matter as well as white matter.

The HIV Neuroimaging Consortium also reported on the relationships between HIV and regional metabolite concentrations as analyzed by MRS (Abstract 156). HIV-infected individuals who were taking antiretroviral therapy had higher levels of inflammatory metabolites (myoinositol-to-creatine ratio) in the frontal gray matter, frontal white matter, and basal ganglia. Subjects who had HAND had lower levels of neuronal metabolites (*N*-acetyl aspartate-to-creatine ratio), especially in the basal ganglia. Interestingly, neuronal injury in the basal ganglia was also associated with a measure of fatigue, which afflicts many people living with HIV, as discussed above (Abstract 479). Navia and colleagues posited a multistage in vivo model of brain injury, in which early HIV disease is associated with inflammatory changes throughout the brain and leads to neuronal injury and subsequent clinically evident neurocognitive impairment.

The impact of aging in people living with HIV was demonstrated by functional MRI. A cohort of HIV-infected and -uninfected individuals ranging from 20 years to 63 years old identified that HIV and older age were each associated with lower cerebral blood flow. Overall, HIV-infected individuals had cerebral blood flow similar to HIV-uninfected individuals who were 15 years to 20 years older. These results have important implications for the clinical management of HIV-infected individuals because an increasing proportion is older than 50 years. Although these noninvasive neuroimaging results are

novel and enable better understanding of the basic pathophysiology of HIV in the brain, they have not yet assisted in clinical guidelines for diagnosing HAND (Abstract 181). Because of the relatively high costs and relatively limited availability of many of these techniques, these modalities may not be available in the clinical setting for many years.

Opportunistic Infections of the Nervous System

Progressive Multifocal Leukoencephalopathy

Interest in progressive multifocal leukoencephalopathy (PML) has increased in the wider scientific community as the disease has been identified in immunosuppressed individuals who are not infected with HIV but are treated with immune modulators such as natalizumab, an integrin inhibitor that reduces migration of activated immune cells into the CNS. Infection with JC virus (JCV), the causative agent of PML, is highly prevalent throughout the world, and reactivation of the virus during immunosuppression can lead to PML. Among people living with HIV, however, susceptibility to PML remains poorly understood.

Although antiretroviral therapy has generally improved the prognosis of PML in those with HIV, nearly all patients deteriorate neurologically and ultimately die despite immune recovery with antiretroviral therapy. To better understand interindividual differences in survival in people with PML, Khanna and colleagues studied 29 individuals with PML from the Swiss HIV Cohort Study, 18 of whom survived for longer than 1 year and 11 for less than 1 year (Abstract 794). They measured T-cell and humoral immunity against JCV using laboratory assays on cryopreserved cell and plasma samples at times before and after diagnosis. The principal finding was that longer durations of survival were associated with greater JCV-specific T-cell and antibody responses before the onset of PML compared with such responses either in patients who had shorter durations of survival or in CD4+-count-matched, HIV-infected individuals who did not have PML. These data indicate that better immune responses to JCV lead to better survival in people with PML, suggesting that enhancing immune responses, perhaps by vaccination, may improve survival.

Understanding the mechanisms by which reactivating JCV gains access to CNS tissues might lead to effective treatments to prevent PML or limit its progression. Chapagain and Nerurkar studied a potential mechanism of JCV migration involving initial infection of human brain microvascular endothelial cells, which form part of the blood-brain barrier (Abstract 793). This research showed that neuraminidase, which blocks specific sialic acids on endothelial cell surfaces, could prevent migration of JCV across an in vitro blood-brain barrier model. These findings suggest that addition of a sialic acid blocker to antiretroviral therapy might serve as a specific treatment for PML.

Cryptococcal Meningitis

Parkes-Ratanshi and colleagues compared prophylaxis for cryptococcal meningitis (CM) and candidal infections with fluconazole 200 mg thrice weekly in a large, community-based, randomized clinical trial enrolling antiretroviral therapy–naive Ugandans with CD4+ counts below 200 cells/μL (Abstract 32). Only 1 case of CM occurred in 760 fluconazole recipients compared with 18 CM cases in 759 placebo recipients (hazard ratio [HR], 0.05; $P < .001$); rates of candidal esophagitis (HR, 0.14; $P < .001$) and vaginitis (HR, 0.15; $P < .001$) were also reduced. Importantly, though, all-cause mortality did not differ between the groups (98 vs 100 deaths; $P > .10$).

Diagnosis of chronic meningitis in HIV patients in resource-limited settings requires differentiation of CM from tuberculous meningitis (TbM), but laboratory support for culture and even cryptococcal antigen detection is not widely available. When clinical profiles were compared in 112 CM and 46 TbM Malawian patients, high CSF pressure and low CSF glucose level supported a diagnosis of CM, and fever, neck stiffness, and lower Glasgow Coma Scale scores supported a diagnosis of TbM (Abstract 791). The investigators derived a potentially useful diagnostic index by multiple regression that distinguished CM and TbM with a sensitivity of 83% and specificity of 79% among HIV-infected individuals. CM was associated with higher opening pressure on lumbar puncture (OR, 0.99; $P = .015$) and lower leukocyte counts in CSF (OR, 1.0028; $P = .027$), and TbM was associated with fever (OR, 8.86; $P = .002$), neck stiffness (OR, 3.11; $P = .028$), and lower Glasgow Coma Scale scores (OR, 0.79; $P = .001$). Although the best sensitivity produced by a classification regression tree analysis of the algorithm was 57%, these findings still provide important guidance for distinguishing CM and TbM in resource-limited settings particularly when Gram and India ink stains may not be available.

To determine the optimal timing of antiretroviral therapy initiation in people with CM, Makadzange and colleagues compared early (within 72 hours) and late (after 10 weeks) treatment with stavudine, lamivudine, and nevirapine in a randomized clinical trial in Harare, Zimbabwe (Abstract 36cLB). Overall mortality rates were high (62%) and were substantially higher in the early (23/26 patients, or 82%) than in the late (8/28 patients, or 37%) treatment group; death occurred much earlier in the early treatment group (median, 5 weeks vs 39 weeks, respectively; HR, 2.4; $P < .03$). This striking difference in mortality appears to contradict conclusions of another, similar study in resource-limited settings in which a subgroup of CM patients survived longer when antiretroviral therapy was started early.[15]

In resource-limited settings, high-dose fluconazole (greater than 800 mg/day) could provide a simple, inexpensive alternative to amphotericin-based regimens for the first 2 weeks of therapy for CM. The potentially increased efficacy of doses greater than 800 mg per day in CM has been demonstrated by the recent finding of increased fungicidal activity against CSF cryptococci

of oral fluconazole at 1200 mg per day compared with 800 mg per day.[16]

Supporting this concept, serum and CSF levels of fluconazole were measured in 78 HIV-infected Thai patients receiving amphotericin in combination with 800 mg, 400 mg, or no fluconazole daily for induction therapy of CM (Abstract 792). CSF levels of fluconazole approached those in serum and nearly doubled in those receiving 800 mg per day compared with 400 mg per day. Higher levels in blood and CSF at day 14 were associated with improved clinical outcomes (alive, culture negative, and neurologically improved) at day 70. Thus, higher concentrations of fluconazole from larger doses seem to improve clinical outcomes.

Immune restoration inflammatory syndrome (IRIS) in CM was documented in 38 of 75 (51%) patients after a median of 6 weeks of treatment with antiretroviral therapy in a prospective study in Uganda (Abstract 774). Twenty-seven cytokines were measured serially in serum by multiplex bead-based immunoassays. Concentrations of many analytes differed between those who had been diagnosed with IRIS and those who had not (higher in IRIS: interleukin [IL]-6, IL-17, tumor necrosis factor-alpha, and granulocyte macrophage colony-stimulating factor; lower in IRIS: IL-8 and interferon-inducible protein-10). Higher levels of IL-6 were the most common correlate of IRIS. Nineteen subjects had high levels of C-reactive protein in blood (above 32 mg/L) and, among this subgroup, 14 (74%) had IRIS and 10 (53%) died, suggesting that this widely available inflammatory indicator may be a practical serum biomarker for high risk of IRIS in CM.

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