

*Special Contribution*

# Neurologic Complications of HIV Infection: Highlights From the 2013 Conference on Retroviruses and Opportunistic Infections

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*Thirty years into the HIV epidemic, the management and investigation of neurologic complications of HIV disease have evolved from a struggle to understand and treat inexorable disorders to an optimistic effort to address more subtle but often complex conditions in patients surviving long-term with a chronic disease. Although severe forms of HIV encephalitis and HIV-associated dementia, myelopathy, opportunistic infections, and neuropathy are still frequently encountered entities where access to HIV treatment is limited, in settings with sufficient resources, they are predominantly seen in those who present late to care or are unable to maintain consistent antiretroviral adherence. In 2013, practitioners, patients, and investigators can realistically aim for an outstanding quality of life for those living with HIV infection and seek to reduce morbidity associated with milder forms of HIV-associated neurocognitive disorder (HAND). Neurologic presentations at the 20th Conference on Retroviruses and Opportunistic Infections (CROI) reflected this now well-established paradigm shift, focusing on treatment strategies to optimize neurologic and cognitive function, the pathogenesis of HAND in the current era, imaging biomarkers of HAND, the confluence of HIV infection and aging, and characterization of central nervous system HIV reservoirs of infection.*

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Although substantial improvements have occurred in the field, HIV-associated neurocognitive disorder (HAND) still remains prevalent in the potent antiretroviral era. Optimal treatment of HAND, the pathogenesis of HIV in the central nervous system (CNS), and the relevance of a CNS reservoir to the broader topic of systemic HIV eradication are incompletely understood. This article will summarize advances in our understanding of the effects of HIV in the nervous system by highlighting recent findings presented at the 2013 Conference on Retroviruses and Opportunistic Infections (CROI).

## Effects of Antiretroviral Treatment on the CNS and Assessment of Neuropsychologic Performance

A key question relevant to HAND is whether consistent treatment with antiretroviral therapy can protect patients from experiencing progressive neurologic impairment. Several studies investigated the stability of neuropsychologic performance and HAND categories over time in treated subjects. Rourke and colleagues (Abstract 404) examined 375 subjects in the OCS (Ontario HIV Treatment Network Cohort Study) who had plasma

HIV RNA levels suppressed to less than 50 copies/mL on antiretroviral therapy and who were longitudinally assessed for a median of 12 months. During follow-up, they noted that 11% of subjects improved in neurocognitive status (eg, from a diagnosis of asymptomatic neurocognitive impairment [ANI] to normal) and 13% worsened. Similarly, Arendt and colleagues (Abstract 454) examined a cohort of 1439 subjects with HIV infection, with 85% receiving antiretroviral therapy. In this group, 5% met Frascati criteria for ANI, 27% for mild neurocognitive disorder (MND), and 17% for HIV-associated dementia (HAD). This group noted neurocognitive performance decline in almost 10% of subjects in the ANI and MND groups, especially in those older than 50 years of age and those with longer duration of HIV infection. Finally, Lu and colleagues (Abstract 461a) identified a 12.7% rate of cognitive decline during a 4-month period as detected by neuropsychologic testing in a group of 55 adults with long-term HIV infection on stable antiretroviral therapy, with the prevalence of HAND being 25.5% at baseline. The investigators found that the brief HIV Dementia Scale was sensitive to moderate, but not mild, cognitive decline in this group as defined by more detailed neuropsychologic testing. The finding that progressive neurocognitive decline may occur in the context of antiretroviral treatment, with well-controlled viremia, possibly suggests that an active process may progressively damage the CNS despite treatment. One confounding factor in interpreting the significance of a transition

from ANI to MND is that the primary distinction between these 2 forms relies on patient reporting of symptoms of impairment on activities of daily living; if subjects are made aware of an ANI status, this awareness may impact subsequent assessments. Additionally, analysis by treatment status and even treatment adherence needs to be performed in a rigorous manner to determine whether potent antiretroviral therapy can protect the CNS.

The frequency and clinical significance of asymptomatic cerebrospinal fluid (CSF) viral escape in subjects on antiretroviral therapy, where CSF HIV RNA levels are detectable using standard assays in subjects with undetectable plasma viral loads, has been the subject of recent study.<sup>1</sup> Perez-Valero and colleagues (Abstract 402) found CSF viral escape in only 88 of 3304 visits during which paired CSF and plasma samples were obtained for research purposes in HIV-infected subjects on antiretroviral therapy, reflecting detection of CSF viral escape in 60 of 789 subjects tested. The presence of CSF viral escape was not associated with progressive neurologic symptoms but was associated with elevated CSF white blood cells (WBCs) and detectable plasma HIV RNA, though at less than 50 copies/mL. This study does not support an important role for CSF virologic escape detected in the research-related setting with regard to the development of neurologic or cognitive decline. These findings are consistent with an earlier report from CROI 2012 showing that research subjects with 1 identified event of asymptomatic CSF viral escape were not at increased risk of further detectable HIV in the CSF or plasma.<sup>2</sup>

Based on specific biochemical characteristics, certain antiretroviral drugs or regimens have been proposed to have increased effectiveness in the CNS. One characteristic presumed to be important is the level of CNS exposure reached by a given antiretroviral drug, also termed CNS penetration effectiveness (CPE), which has led to the generation of a CPE scoring method to assess potential CNS efficacy of a regimen.<sup>3</sup> Fabbiani and colleagues

(Abstract 405) examined whether the CPE score might be improved by incorporating information about a subject's known resistance genotype. Genotypic information from plasma and the calculated CPE of subjects' regimens were combined to demonstrate that the use of a CPE score corrected for genotypic sensitivity score improved the prediction of neuropsychologic performance in subjects on antiretroviral therapy.

Ellis and colleagues (Abstract 20) presented the findings of their multicenter CIT2 (Cognitive Intervention Trial 2) study, a long-term randomized study to assess whether regimens with high CPE scores might be superior to those with lower CPE scores in improving neuropsychologic performance in persons diagnosed with HAND. As reported, challenges to recruitment in the study resulted in data safety monitoring board recommendations to stop recruitment prior to reaching the proposed enrollment of 120 subjects, based on futility. Furthermore, despite an adaptive randomization design, subjects in the 2 study arms (higher or lower CPE) had statistically significant differences in hepatitis C virus (HCV) status and nadir CD4+ cell count. In an analysis of the 49 subjects with follow-up, no statistically significant differences in neuropsychologic test performance (primary end point) were observed between HIV-infected subjects initiating higher compared with lower CPE regimens. Due to cessation prior to reaching enrollment targets, the study was likely not fully powered to determine whether there is a role for initiating or switching to CNS-targeted antiretroviral therapy in HIV-infected patients with HAND. Whereas the CIT2 study examined the potentially beneficial effects of CNS-targeted therapy, Perez-Valero and colleagues (Abstract 406) examined the possible deleterious impact of HIV monotherapy on the CNS. They found that neither ritonavir-boosted (/r) lopinavir nor darunavir/r as monotherapy was associated with more frequent or severe neurocognitive impairment compared with triple-drug therapy in a large cohort of patients selected for having had more than 1 year of viral suppression

in plasma. However, subjects were not randomized to either regimen, thus it is unclear what biases may have existed for subjects to be eligible for monotherapy versus triple therapy.

Robertson and colleagues (Abstract 410) presented a related study assessing the effect of antiretroviral regimen simplification on neuropsychologic performance. In this study, subjects on stable tenofovir, emtricitabine, plus atazanavir/r were randomized to switch to abacavir, lamivudine, plus unboosted atazanavir or continue tenofovir, emtricitabine, plus atazanavir/r. This large randomized controlled study of 296 subjects, with well-matched groups on stable therapy at baseline, demonstrated no difference in performance over time in either group.

Several studies examined specific individual drugs and their effects in the CNS. Letendre and colleagues (Abstract 178LB) reported consistently high levels of dolutegravir in the CSF in 12 subjects who underwent CSF sampling at weeks 2 and 16 of dolutegravir therapy, with levels exceeding the *in vitro* 50% inhibitory concentration (IC<sub>50</sub>) against wild-type viruses. This group also exhibited rapid reduction of CSF HIV RNA levels after initiation of a regimen containing dolutegravir plus 2 nucleoside analogue reverse transcriptase inhibitors (nRTIs) in treatment-naive subjects. These data suggest that dolutegravir, a new integrase strand transfer inhibitor currently in development with a favorable systemic safety and efficacy profile, may be a potent drug for suppression of HIV in the CNS. Maraviroc has been posited to potentially benefit the CNS by targeting monocyte or macrophage lineage infection due to inhibition of CC chemokine receptor type 5 (CCR5). To investigate this question, Ndhlovu and colleagues (Abstract 403) examined blood and neuropsychologic measures before and after 24-week maraviroc intensification in 11 subjects on virally suppressive antiretroviral therapy (plasma HIV RNA levels < 50 copies/mL for > 6 months). The investigators noted improvements in neuropsychologic test performance over time,

though a control group or placebo group to adequately assess improvements due to practice effect was not included. The investigators saw reduction in total HIV DNA in monocytes—a marker they previously correlated with cognitive impairment—as well as reduction in other measures of systemic immune activation, including soluble (s)CD14 levels and activation of CD8+ T lymphocytes and CD14+CD16+ monocytes. Letendre and colleagues (Abstract 407) also performed a cross-sectional study to assess for potential relationships between exposure to efavirenz and neurocognitive functioning. They found that long-term use of efavirenz was associated with a worsening of neurocognitive functioning compared with use of lopinavir. This study raises further questions about the effects of efavirenz. It remains unknown if the observed poorer performance with efavirenz is due to neurotoxic effects or to lower CPE of efavirenz. This retrospective study could neither randomize nor match individuals. In addition, the efavirenz and lopinavir/r groups differed with regard to duration of therapy, duration of infection prior to initiation of therapy, and possibly their reasons for choosing regimens. It is plausible that efavirenz, given in a triple-drug, once-a-day combination pill, may have been chosen by practitioners because of a perception that subjects might be cognitively impaired and thus need simpler regimens. Further studies are crucial to assess the efficacy of efavirenz in the CNS.

Although most studies focusing on neurologic impairment were predicated on the concept that HAND results from direct HIV effects in the brain, Grima and colleagues (Abstract 452) studied the association between HAND and liver steatosis as a marker of visceral fat in HIV infection. In a study of 129 subjects, more than 90% of whom were on long-term (median, 8 years) antiretroviral therapy, liver steatosis was measured by transient elastography. The investigators found that a statistically significantly higher proportion of subjects with high-grade liver steatosis had neurocognitive impairment as assessed by Frascati criteria. In multivariate

analyses after correcting for other possible cofactors, high-grade steatosis remained independently associated with cognitive impairment. Because high-grade liver steatosis is thought to reflect visceral fat accumulation, this study raises interesting questions regarding whether common metabolic mechanisms might also contribute to HAND. Another connection, as yet unexplored, is the potential impact of hepatic encephalopathy on cognitive performance in individuals with high-grade steatosis that has progressed to cirrhosis.

Finally, to assess the effects of very early acute HIV infection and immediate antiretroviral therapy on the nervous system, Kore and colleagues (Abstract 19) examined neuropsychologic performance in subjects recruited within the first month after HIV infection in Bangkok, Thailand. They found that median performance (an estimated 17 median days after infection) on 4 tests in 36 antiretroviral-naïve subjects with acute HIV was not significantly different from norms derived from age-matched, HIV-infected subjects with similar levels of education and of comparable age. The baseline summarized test performance (composite neuropsychologic test Z score [NPZ4]) modestly correlated with days postinfection and with CSF HIV RNA levels but did not correlate with tests of anxiety or depression. In longitudinal follow-up, improvements in neuropsychologic test performance after acute treatment paralleled changes observed during serial testing at similar intervals in the HIV-uninfected controls. Only motor improvements were seen in HIV-infected patients starting antiretroviral therapy compared with HIV-uninfected controls. During a 6-month period, no difference in neuropsychologic improvement was detected between treatment with a triple-drug, nonnucleoside analogue reverse transcriptase inhibitor (NNRTI)-based regimen and a 5-drug regimen that included maraviroc and raltegravir.

### Neuropathogenesis of HIV Infection

Numerous presentations at the 2013 CROI focused on elucidating the

mechanisms of HIV-related CNS injury, including specific virologic and immunologic substrates of brain injury that might underlie neurologic disorders. Tilghman and colleagues (Abstract 414) sought to assess whether specific viral sequences in blood HIV tyrosine aminotransferase (*tat*) or envelope (*env*) genes were associated with cognitive impairment in 155 subtype-C HIV-infected individuals in India. HIV *tat* and *env* sequences from 56 subjects considered impaired, based on global deficit scores obtained from a detailed neuropsychologic assessment, were analyzed and compared with sequences amplified from 99 HIV-infected unimpaired subjects. Novel signature residues in HIV *tat* were associated with the presence of cognitive impairment. In particular, a structural change in the HIV molecule within the *tat* sequence affected the conformation of a dicysteine motif that has been previously associated with HIV neurotoxicity. Results from this study lend additional support to hypotheses that certain HIV variants may be associated with enhanced neurotoxicity and further our understanding of mechanistic bases of this heightened toxicity. Shikuma and colleagues (Abstract 21) presented another study investigating whether mitochondrial function might associate with neurologic biomarkers in antiretroviral therapy-treated participants enrolled in the cardiovascular substudy of the Hawaii Aging with HIV Cohort (median age, 55 years). They measured markers of mitochondrial function and oxidation, including activity of Complex I (reduced nicotinamide adenine dinucleotide [NADH] dehydrogenase) and Complex IV (cytochrome C oxidase) of the electron transport chain, and mitochondrial-specific 8-oxo-deoxyguanine (mt-8-oxo-dG), a measure of mitochondrial-specific oxidative stress. They observed an association between neuroimaging and neuropsychologic performance and mitochondrial function. These included inverse relationships between Complex I activity and caudate and nucleus accumbens volumes as well as neuropsychologic performance, and between mt-8-oxo-dG and hippocampus

and amygdala volumes. Although results from this study are preliminary, with no HIV-uninfected controls to indicate whether the identified correlations are HIV-specific, these intriguing data suggest a connection between mitochondrial function and measures of brain integrity in HIV infection, an association known to exist in a broad range of neurologic diseases.

Biomarkers of viral burden, inflammation, neuronal injury, amyloid processing, and blood-brain barrier breakdown may not only help detect the presence of neurologic disease but may also reveal neuropathologic mechanisms in HIV disease, especially when combined. To investigate the spectrum of neurologic pathogenesis across distinct stages and conditions of HIV infection, several investigators performed translational studies measuring diverse biomarkers to assess mechanisms of HIV-related brain injury in specific clinical groups. Calcagno and colleagues (Abstract 438) examined neurologic biomarkers in 34 subjects who had no neurocognitive complaints but presented to care with advanced disease (defined as a CD4+ cell count < 100/ $\mu$ L). These antiretroviral-naïve subjects had a median age of 42 years and a median CD4+ cell count of 23/ $\mu$ L. None of the subjects was diagnosed with HAND, based on neuropsychologic testing. Subjects had median CSF HIV RNA levels of 3.8 log<sub>10</sub> copies/mL; showed evidence of elevated total (t)-tau, phosphorylated (p)-tau, and reduced amyloid beta (1-42) in their CSF (9%-15% of subjects); and harbored 12% predicted CXC chemokine receptor type 4 (CXCR4) coreceptor tropism in CSF. Although CSF WBC counts were generally low, likely reflecting the very low systemic CD4+ cell counts, these subjects manifested high levels of intrathecal immunoglobulin synthesis and blood-brain barrier breakdown. However, no appropriately matched controls were included for comparison. Anderson and colleagues (Abstract 437) performed a study of a slightly more heterogeneous subject group with advanced HIV infection (3 of 15 subjects on antiretroviral therapy; CD4+ cell count median, 62/ $\mu$ L),

symptoms of recent neurologic decline, and a high (5 of 15 subjects) prevalence of HAND. They focused on measurement of CSF alpha interferon and found that levels of this marker negatively correlated with performance on a number of tests, most strongly with motor performance. These findings suggest that alpha interferon may be a mediator of HAND in advanced HIV infection. Silke and colleagues (Abstract 430) investigated plasma and CSF inflammatory markers prior to and after initiation of treatment in 60 subjects in Thailand. They found elevated levels of neopterin in plasma and CSF in women with cognitive impairment compared with nonimpaired women and all men. HIV RNA levels declined after 12 months of antiretroviral therapy, but intestinal fatty acid binding protein (iFABP) interleukin-10 and monocyte chemoattractant protein-1 did not diminish with treatment in women as much as in men. Although the cause of these sex differences is as yet unclear, they suggest that immune responses to HIV and treatment may need to be measured independently in women and men to rigorously understand immunopathogenesis in the CNS.

Keating and colleagues (Abstract 432) investigated the patterns of mediators of inflammation and chemotaxis, including interleukin-6, tumor necrosis factor, tissue inhibitor of metalloproteinase-1, and sCD14 and sCD163, among others, detected in the CSF in subjects at distinct stages of HIV infection. They found elevations in certain markers in HIV-infected groups compared with the HIV-uninfected group, beginning at the stage of untreated primary HIV infection (PHI) and persisting through all stages of untreated infection. Several markers were reduced but did not normalize in subjects treated with systemically suppressive antiretroviral therapy. These results suggest a possible utility of these markers for monitoring persistent intrathecal immune activation in the presence of antiretroviral treatment.

Lee and colleagues (Abstract 446) investigated whether HIV controllers who maintain plasma HIV RNA levels below 1000 copies/mL in the absence

of treatment manifest CNS pathology, based on neuroimaging and CSF analyses. Eleven elite controllers (plasma HIV RNA levels below 50 copies/mL) and 6 viremic controllers (plasma HIV RNA levels between 50 copies/mL and 1000 copies/mL) were compared with treated and untreated subjects with chronic HIV infection (CHI) and with HIV-uninfected controls. Despite the fact that HIV controllers overall had median HIV RNA levels in both plasma and CSF of less than 40 copies/mL, they manifested poorer neuropsychologic performance than all other groups, which correlated with lower ratios of the neuronal integrity marker N-acetylacetate/creatinine in the brain. Rates of drug use and alcohol abuse were similar between comparison groups. Further correlation with a broad range of immune activation and neural injury markers might identify mechanisms of this evident neuronal injury in HIV controllers.

### Neuroimaging of HIV

A number of presentations at CROI 2013 focused on the utilization of noninvasive neuroimaging methods to assess HIV reservoirs in the brain. Two major areas of focus were PHI and the impact of cofactors. Ragin and colleagues (Abstract 463) observed changes in white matter integrity (as assessed by diffusion tensor imaging [DTI]) in 16 individuals with PHI compared with 21 HIV-uninfected controls. Changes were greatest within the corpus callosum. Wright and colleagues (Abstract 466) investigated changes in white matter integrity in 62 individuals with PHI, 16 individuals with CHI, and 19 HIV-uninfected controls. No statistically significant differences were seen between the PHI group and HIV-uninfected controls. However, statistically significant differences were seen between the CHI group and either the PHI group or the HIV-uninfected controls. When individuals with PHI and those with CHI were evaluated across the spectrum of duration of infection, progressive changes in DTI metrics were seen with increasing duration of disease. These results suggest that

neuroimaging detects more subtle changes in the brain than neuropsychologic performance assessments (Abstract 19). Grill and colleagues (Abstract 465) showed that levels of CSF tryptophan, a precursor of serotonin and kynurenine, correlated with magnetic resonance spectroscopy (MRS) and CSF markers of inflammation in individuals with CHI but not those with PHI. Finally, Dash and colleagues (Abstract 469) demonstrated in a mouse model that HIV infection leads to changes in MRS over time. In particular, N-acetylaspartate (NAA) and myoinositol (Mi), which are measures of neuronal viability and neuroinflammation, respectively, were altered soon after inoculation with HIV, and these measures continued to worsen with progressive duration of disease. With regard to CHI, a number of variables may influence neuroimaging measures. Using the CHARTER (CNS HIV Antiretroviral Therapy Effects Research) dataset of 263 individuals, Fennema-Notestine and colleagues (Abstract 468) observed that poorer neuronal integrity (as measured by NAA) was seen in individuals with CHI and a history of greater immunosuppression. Heaps and associates (Abstract 467) showed that HIV and HCV have compounding effects on white matter integrity within the corpus callosum. Ortega and colleagues (Abstract 464) investigated the effects of HIV subtype on neuroimaging measures. In their study, DTI was performed in 17 HIV-uninfected controls in the United States, 17 subtype-B HIV-infected individuals in the United States, 17 HIV-uninfected controls in South Africa, and 17 subtype-C HIV-infected individuals in South Africa. HIV infection, regardless of subtype, led to substantial decreases in brain volumetrics, especially within subcortical areas. However, there were no statistically significant differences between the subtype-B HIV- and subtype-C HIV-infected groups.

Finally, Winston and colleagues (Abstract 462) demonstrated that antiretroviral effects on neuroimaging measures may differ depending on when HIV-infected patients ( $n = 22$ )

were examined after administration of therapy. From administration to 48 weeks after receiving therapy, MRS measures improved. However, from 48 weeks to 144 weeks after therapy, many of these improvements were reversed or worsened with medications, suggesting antiretroviral toxicity. In general, these studies suggest that neuroimaging could be considered in future HAND criteria; however, additional longitudinal studies are needed.

### CNS HIV and Aging

By 2015, it is expected that more than 50% of all HIV-infected individuals in the United States will be older than 50 years of age. This rise in the prevalence of older individuals is due both to new infection (approximately 15%) and to patients living longer because of antiretroviral therapy. Older HIV-infected individuals account for approximately 35% of all deaths, with most individuals now dying from non-HIV-related causes.<sup>4</sup> A rapidly growing area of research has begun to concentrate on the effects of HIV and aging on brain function.

The field of HIV and aging in the brain was initially stimulated by results from the Hawaii Aging with HIV Cohort study. The prevalence of HAND was almost 2-fold greater in older ( $> 50$  years old) HIV-infected individuals than in younger (20–39 years old) HIV-infected patients.<sup>5</sup> However, questions remain as to whether this observed increase in the prevalence of HAND is due to a synergistic or additive effect of HIV infection and aging.<sup>6</sup> Goodkin and colleagues (Abstract 439) studied 2278 HIV-infected and 2808 HIV-uninfected individuals from the MACS (Multicenter AIDS Cohort Study). Using a multiple covariate, linear mixed model that controlled for numerous variables, an interaction between age and HIV disease stage was observed, especially within the memory and executive cognitive domains. These findings nicely complement recent results from the CHARTER study. Heaton and colleagues previously demonstrated decreases in global neurocognitive performance with aging

for both HIV-uninfected and HIV-infected individuals in the CHARTER study.<sup>7</sup> However, in the CHARTER data, a greater divergence emerged between the 2 groups at older ( $> 55$  years old) ages.

Numerous etiologies, including genetics, metabolic risk factors, and frailty, could account for the increased prevalence of HAND in older individuals. The original Hawaii Aging with HIV Cohort study demonstrated that older HIV-infected individuals with at least 1 apolipoprotein E4 allele have an increased risk of dementia.<sup>8</sup> Cysique and colleagues (Abstract 442) confirmed this result in a smaller cohort of middle-aged HIV-infected individuals in Australia. In addition, the presence of diabetes and other metabolic risk factors may contribute to HAND in older HIV-infected individuals.<sup>9</sup> Older individuals may be more likely to transition to mild cognitive impairment than younger individuals.

Grant and colleagues (Abstract 440) demonstrated that the VACS (Veterans Aging Cohort Study) Index may not only be a good predictor of future mortality but also of neuropsychologic impairment within the CHARTER cohort. From the MACS cohort, Smith and colleagues (Abstract 444) demonstrated that frail HIV-infected individuals had a greater risk for developing HAND than healthy HIV-infected individuals. Both of these presentations suggest that relatively simple laboratory tests and physical examinations could be added to our existing armamentarium to help predict which HIV-infected individuals are at increased risk of developing HAND.

Additional biomarkers are needed to assist clinicians in evaluating the effects of HIV infection and aging in the brain. Krut and colleagues (Abstract 443) observed independent effects of HIV infection and aging using the CSF biomarker neurofilament light (NFL) protein—a measure of neuronal injury. HIV-infected, untreated subjects had NFL levels equivalent to HIV-uninfected controls who were 19 years older. Although antiretroviral therapy improved NFL levels, CSF values were not completely normalized.

Peterson and colleagues (Abstract 441) confirmed that from a possible panel of CSF measures, NFL was the most sensitive biomarker of HAND. Cysique and colleagues (Abstract 442) studied additional CSF biomarkers to determine whether an Alzheimer's disease profile, as elucidated by the presence of amyloid beta (ie, Ab<sub>42</sub>) or tau, was present in middle-aged individuals with CHI receiving antiretroviral therapy. An Alzheimer's disease profile consisted of 1 of 3 published cutoff criteria: profile 1, t-tau levels greater than 350 ng/L and Ab<sub>42</sub> levels less than 530 ng/L; profile 2, p-tau greater than 60 ng/L and Ab<sub>42</sub> less than 530 ng/L; or profile 3, t-tau greater than 350 ng/L and the ratio of Ab<sub>42</sub> to p-tau less than 6.5. The risk of Alzheimer's disease in HIV-infected patients depended on the profile chosen and varied from 4.5% to 7.4%.

Thomas and colleagues (Abstract 445) studied whether novel neuroimaging measures that use resting-state functional connectivity could assist in discriminating the effects of HIV infection and aging on brain function. A substantial drop-off was seen in functional correlations in HIV-infected individuals more than 40 years old, suggesting a possible synergistic effect at older ages. Additional longitudinal studies are needed to identify the prognostic significance of CSF and neuroimaging biomarkers.

For this field to progress, a number of factors require further consideration, including appropriate controls, possible survivor bias, age at seroconversion, age at initiation of antiretroviral therapy, and duration of infection. The above studies presented at the 20th CROI hold great promise that relatively simple interventions could have a substantial impact on cognition in older HIV-infected patients. Areas to consider include (a) treatment of metabolic risk factors (ie, monitoring glucose levels and hypertension in HIV-infected patients); (b) reduction in comorbid factors (ie, substance abuse, depression, and anxiety); and (c) promotion of healthy behaviors. Many of the above CROI presentations nicely complement work by Foley and

colleagues,<sup>10</sup> who demonstrated that HIV-infected individuals with more cerebrovascular risk factors performed worse on neuropsychologic tests than HIV-uninfected controls. HIV-infected individuals who received treatment for HIV infection and metabolic factors performed better on neuropsychologic testing than HIV-infected patients receiving antiretroviral therapy alone.

### Strategies to Identify and Treat CNS Reservoirs for HIV

HIV eradication and potential approaches to an HIV "cure" were a major focus of clinical and basic presentations at CROI 2013. The question of whether a biologically and clinically significant reservoir exists for HIV within the CNS is crucial to understanding potential sources of resurgent HIV in the absence of antiretroviral treatment. A small number of presentations focused on identifying and accessing this reservoir, including studies of brain tissues in humans and in animal models, research on compartmentalization of HIV between CSF and blood, and strategies to reduce this reservoir.

Several groups examined human autopsy or animal necropsy tissue to seek evidence of HIV infection in CNS tissue. Gelman and colleagues (Abstract 373) investigated the presence of integrated HIV DNA in diverse non-lymphoid body tissues in 5 humans who died with HIV infection. They used an Alu (derived from *Arthrobacter luteus*)-Gag polymerase chain reaction (PCR) method to assess integrated HIV DNA and PCR to measure integrated and nonintegrated *gag/pol* HIV DNA in numerous deep tissues, including spleen, colon, lung, eye, heart, and brain. They identified measurable, though variable, levels of integrated HIV DNA in the brain, especially in cerebral white matter. However, no specific messenger (m)RNA expression pattern was found in subjects with higher levels of integrated HIV DNA in the brain. These findings emphasize the potential need to monitor the deep body tissue compartments in addition to circulating blood and lymphoid

tissues for the presence of latent reservoirs for HIV. These results suggest that methods that can directly assess the brain (especially neuroimaging and CSF studies) should still be considered in order to adequately evaluate HIV reservoirs in the brain.

Identification and monitoring of a brain reservoir for HIV during life is limited by lack of access to brain tissue. One strategy used to circumvent this challenge is to assess CSF, as CSF is produced in the choroid plexus and meninges within the CNS compartment and is in direct communication with the brain. Compartmentalized HIV variants are those uniquely found or enriched within a specific tissue compartment but not in another. The presence of compartmentalized CSF HIV, particularly that which evolves over time independently from variants in the blood, suggests a local reservoir for HIV in the CNS.

To investigate the timing of establishment of compartmentalized HIV, Sturdevant and colleagues (Abstract 23) examined full-length *env* sequences derived from CSF and blood in infants and young children with subtype-C HIV infection and developmental delay at a single time point prior to initiation of antiretroviral therapy. Despite the youth of these subjects and recency of their HIV infection, 28% had CSF viruses defined as compartmentalized based on formal Slatkin-Madison testing for the level of distinct sequences between blood and CSF. Based on visual inspection of phylogenetic trees, an additional 25% of subjects harbored intermediate levels of compartmentalization that the investigators proposed may indicate a transition stage between an equilibrated and compartmentalized state. The slightly older children had a higher proportion of compartmentalized HIV, suggesting that compartmentalization evolved over the course of early infection. Strikingly, they noted that in 2 cases in which subjects were infected with 2 transmitted founder viruses, 1 virus became preferentially sequestered in the CSF and could not be detected in plasma. This study indicates that in children with subtype-C HIV infection

in Malawi, compartmentalization, and thus potentially an HIV reservoir, is established within the first years of infection.

Yuh and colleagues (Abstract 415) showed the feasibility of using 454 deep sequencing methods to assess reverse transcriptase, protease, and *env* sequences in paired longitudinal samples of CSF and blood in adult subjects with early infection. In 5 subjects recruited during PHI and having HIV RNA levels greater than 3000 copies/mL in both plasma and CSF, deep sequencing was successful in all samples and all regions, and all samples demonstrated very low levels of unique variants in CSF and plasma (ie, resistance mutations or polymorphisms in *env*). The biologic and clinical significance of very low-level variants uniquely detected in CSF remains to be seen, but deep sequencing tools may prove valuable in additional assessment of genotypic and phenotypic compartmentalization of HIV in the CNS.

To assess the initial establishment of CNS HIV reservoirs, Spudich and colleagues (Abstract 18) investigated whether founder viruses seen in the CNS compartment are identical to those detected in the periphery in very early acute HIV infection. Ten paired blood plasma and CSF samples with HIV RNA levels greater than 10,000 copies/mL in both specimens and with HIV subtype CR01\_AE in plasma were analyzed with full-genome sequencing. Full length *env* sequences generated by single-genome amplification were phylogenetically compared between compartments and used to determine genetic diversity and estimates of the time to the most recent common ancestor within each compartment. Phylogenetic analysis revealed highly similar sequences between the 2 compartments, and modest differences were noted in genetic diversity between compartments in several cases. One subject had 2 transmitted or founder viruses present in blood but only 1 in CSF, supported by higher within-compartment diversity and a longer time to most recent common ancestor (suggesting divergence of sequences within the donor). Other

subjects actually had higher genetic diversity in the CSF, but nucleotide and amino acid analysis did not reveal a CSF genetic signature. Overall, these findings suggest that there is not a substantial selection or bottleneck for specific HIV virions entering the CNS during the acute stage of infection, and that CSF compartmentalization detected during early or chronic infection likely evolves after initial seeding of the CNS compartment.

In a related study, Campbell and colleagues (Abstract 22) investigated whether natalizumab, a monoclonal antibody against  $\alpha$ 4-integrin known to block trafficking of leukocytes across the blood-brain barrier and also into the gut, could reduce signs of inflammation and viral burden in the brains of rhesus macaques when administered during either acute or chronic simian immunodeficiency virus (SIV) infection. In an accelerated SIV model of neuro-AIDS in CD8+ T lymphocyte-depleted macaques, natalizumab (30 mg/kg) was administered to 6 animals beginning at day 0 of infection. On sacrifice, these animals had no evidence of cell-associated HIV in the brain in contrast to control animals, suggesting that cessation of cellular trafficking with natalizumab during acute SIV infection might prevent establishment of CNS SIV infection. Additionally, when natalizumab was administered to animals during later-stage infection, investigators noted no progression of neuronal injury by neuroimaging markers, reduced inflammatory (CD68+) and HIV p28+ cells, and a lack of further macrophage trafficking to the CNS (and gut) compared with macaques that did not receive natalizumab. The investigators concluded that natalizumab blocks trafficking of HIV to the CNS during acute infection and stabilizes CNS disease during more chronic infection. Whether this occurs primarily through mechanisms of lymphocyte or monocyte trafficking is unknown, because natalizumab blocks trafficking of both these cell types. These findings warrant related studies of neuroimmune modulators in humans but must be approached with caution due to risk of progressive

multifocal leukoencephalopathy in HIV-uninfected patients with multiple sclerosis and inflammatory bowel disease treated with natalizumab.

Ferguson and colleagues (Abstract 434) also examined whether mediation of the inflammatory response to acute HIV infection may affect establishment of a CNS HIV reservoir. They utilized a nonaccelerated SIV macaque model to examine the effects of an HIV vaccine administered during acute infection. In animals that did not receive immunization, astrogliosis and microgliosis of cerebral white matter were observed at 127 days postinfection and progressed through 300 days postinfection. Animals that received an HIV vaccine manifested a lower peak plasma HIV RNA level during acute infection and had reduced neuropathology at identical time points.

Treatment strategies aimed at reaching a CNS sanctuary (ie, a region with reduced exposure to antiretroviral drugs due to their inadequate penetration into the brain compartment) for HIV infection are also relevant to the concept of a local CNS reservoir for HIV. Garrido and colleagues (Abstract 408) explored the use of gold nanoparticles to improve drug delivery to the CNS. They demonstrated that gold nanoparticles entered human lymphocytes and were associated with no reduction in cell viability in flow cytometry experiments. Furthermore, the gold nanoparticles crossed an *in vitro* model of a blood-brain barrier created using human brain microvascular endothelial cells and also reached the brain in mice when injected intravenously. The investigators then attached a derivative of raltegravir to the gold nanoparticles and demonstrated that 5 days of incubation with the conjugated molecules was associated with markedly reduced HIV production in primary peripheral blood mononuclear cells, suggesting that gold nanoparticles linked to antiretroviral drugs may be an avenue for enhanced drug delivery to the CNS.

A key unanswered question regarding the potential for a CNS reservoir is how frequently, if ever, HIV may continue to replicate, let alone evolve, in

the brain in the presence of antiretroviral therapy. Previous reports of symptomatic CNS "escape"<sup>11,12</sup> suggest that in extremely rare cases, HIV produced in the CNS in the context of systemically suppressive antiretroviral therapy may have clinical and biologic consequences. Dahl and colleagues (Abstract 359) initiated a systematic approach to assess whether compartmentalization and viral evolution can occur despite suppressive antiretroviral therapy, using novel methods of single-genome sequencing to derive sequences from the reverse transcriptase gene from large volumes of plasma and CSF. Sixteen amplicons were derived from 11 CSF samples from 5 subjects and compared with pretherapy CSF and plasma samples. Of these, a majority were hypermutants, suggesting replication-incompetent viruses. Pretherapy CSF and plasma sequences showed no compartmentalization, and no changes in sequences were noted in longitudinal sampling on antiretroviral therapy. Further studies should be performed on greater numbers of samples to confirm these findings, which suggest that CSF HIV populations do not evolve in subjects on suppressive antiretroviral therapy. □

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18. Very Early Viral Infection of the Central Nervous System without Evidence of Compartmentalization during Acute HIV-1 Infection (RV254). Serena Spudich, G Kijak, J Ananworanich, M Bose, V Assawadarachai, S Rattamanee, E Sanders-Buell, V Valcour, J Kim, S Tovanabutra, and RV254/SEARCH 010 Study Group.
19. Neuropsychological Performance in Acute HIV: Determinants of Baseline Performance and Effects of Immediate ART. Idil Kore, J Ananworanich, V Valcour, J Fletcher, D Suttichom, P Mangum, L Jagodzinski, J Kim, S Spudich, and RV254/SEARCH 010 Study Group.
20. A Randomized, Controlled Trial of a Central Nervous System-targeted ART Strategy for HIV-associated Neurocognitive Disorders. Ronald Ellis, F Vaida, S Letendre, R Haubrich, R Heaton, A McCutchan, M Cherner, A Umlauf, N Sacktor, and D Clifford.
21. Regional Brain Atrophy Is Associated with Mitochondrial Dysfunction and Elevated Mitochondrial Oxidative Stress in HIV+ Individuals. K Kallianpur, M Gerschenson, T Umaki, D Chow, B Nakamoto, D Libutti, M Lopez, J Taylor, L Marotz, and Cecilia Shikuma.
22. VLA-4 Treatment Blocks Virus Traffic to the Gut and Brain Early, and Stabilizes CNS Injury Late in Infection. Jennifer Campbell, P Auttissier, A MacLean, T Burdo, S Westmoreland, G Gonzalez, E-M Ratai, and K Williams.

23. Central Nervous System Compartmentalization of HIV-1 Subtype C Variants Early and Late in Infection in Young Children. Christa Buckheit Sturdevant, A Dow, C Jabara, S Joseph, G Schnell, N Takamune, M Mallewa, R Heyderman, A Van Rie, and R Swanstrom.

178LB. Distribution and Antiviral Activity in Cerebrospinal Fluid of the Integrase Inhibitor, Dolutegravir: ING116070 Week 16 Results. Scott Letendre, A Mills, K Tashima, D Thomas, S Min, S Chen, I Song, S Piscitelli, and extended ING116070 Study Team.

359. Sequencing of the HIV-1 Population in Cerebrospinal Fluid during Suppressive Therapy. Viktor Dahl, M Gisslen, J Peterson, W Shao, S Spudich, R Price, and S Palmer.

373. Integrated HIV DNA and Associated Histiocyte Marker mRNA in Autopsy Samples of Non-lymphoid Tissue Including the Central Nervous System. Benjamin Gelman, T Chen, J Lisinicchia, and A Rice.

402. Incidence, Risk Factors, and Neurocognitive Impact of Cerebrospinal Fluid Viral Escape: Longitudinal Analysis of the Central Nervous System HIV ART Effects Research and HIV Neurobehavioral Research Program Cohorts. Ignacio Perez-Valero, S Letendre, R Deutsch, R Heaton, D Clifford, J McArthur, S Morgello, B Gelman, A Collier, I Grant, and CHARTER and HNRP Study Groups.

403. Maraviroc Intensification in Virally Suppressed HIV Subjects Leads to Improvement in Neurocognitive Test Performance and Declines in Immune Activation. Lishomwa Ndhlovu, T Umaki, G Chew, M Agsald, K Amina, B Hanks, B Nakamoto, J Barbour, B Shiramizu, and C Shikuma.

404. Rates and Stability of HIV-associated Neurocognitive Disorders among Adults on cART and Suppressed Plasma Viral Load: Prospective Results from the Ontario HIV Treatment Network Cohort Study. Sean Rourke, J Gill, T Bekele, A Carvalhal, J McCombe, A Rachlis, M Atkinson, C Kovacs, T Marcotte, S Letendre, and OCS Cohort Study.

405. Central Nervous System Penetration Effectiveness Score Better Correlates with Cognitive Performance of HIV+ Patients after Accounting for Drug Susceptibility of Plasma Virus. Massimiliano Fabbiani, P Grima, B Milanini, A Mondini, M Colafigli, R Gagliardini, R Cauda, MC Silveri, A De Luca, and S Di Giambenedetto.

406. Protease Inhibitor Mono-therapy Is Not Associated with a Higher Rate or a Different Pattern of Neurocognitive Impairment than Triple Drug Therapy. Ignacio Perez-Valero, A Gonzalez-Baeza, M Estebanez, N Stella-Ascariz, J Mingorance, C Bayon, M Lagarde, F Pulido, A Borobia, J Arribas, and PICASSO Study Group.

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408. Gold Nanoparticles to Improve Drug Delivery to the Central Nervous System. Carolina Garrido, N Dahl, C Simpson, J Bresee, D Feldheim, C Melander, and D Margolis.

410. Similar Cognition Outcomes after 24 Weeks for Tenofovir/Emtricitabine + Atazanavir/Ritonavir-experienced HIV+ Subjects or Those Simplifying to Abacavir/Lamivudine + Atazanavir. Kevin Robertson, P Maruff, D Wohl, L Bhatti, C Small, H Edelstein, H Zhao, D Margolis, L Ross, M Shaefer, for AS-SURE EPZ113734 Study Team.

- 414.** Viral Signatures in HIV-1 Subtype C Tat Are Associated with Neurocognitive Impairment in an Indian Cohort. Myres Tilghman, S Deshpande, J Bhattacharya, M Ghatge, T Marcotte, D Smith, and S Mehendale.
- 415.** Longitudinal Analysis of HIV-1 Cerebrospinal Fluid Compartmentalization in Early Infection Detected by Deep Sequencing. Tiffany Yuh, J Chiarella, B Reese, E St John, B Simen, M Mohiuddin, J Peterson, R Price, M Kozal, and S Spudich.
- 430.** Gender-specific Innate Responses Vary before and after the Initiation of ART in Individuals with Chronic HIV Infection in Thailand. Bonnie Slike, V Valcour, S Krebs, P Sithinamsuwan, P Saengtawan, A Schuetz, J Kim, N Michael, J Ananworanich, M Marovich, and SEARCH 011 Study Team.
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- 434.** Modeling the Development of Chronic Neuroinflammation following Blunting of Primary Viremia through Partial Vaccine Protection. Debbie Ferguson, S Clarke, C Ham, A Das, B Berkhout, A Meiser, S Patterson, N Berry, and N Almond.
- 437.** Cerebrospinal Fluid Interferon-alpha Levels Inversely Correlate with Processing and Motor Speed in HIV+ Subjects with Cognitive Complaints with and without HIV-associated Neurocognitive Disorder. Albert Anderson, J Lennox, D Loring, and W Tyor.
- 438.** Cerebrospinal Fluid Viral and Neurodegenerative Markers in HIV+ Very Late Presenters. Andrea Calcagno, C Atzori, D Imperiale, F Lipani, S Audagnotto, G Orofino, V Ghisetti, G Marietti, G Di Perri, and S Bonora.
- 439.** Older Age and Neurocognitive Function: Multi-center AIDS Cohort Study. Karl Goodkin, E Miller, C Cox, S Reynolds, D Ostrow, O Selnes, E Martin, N Sacktor, and J Becker.
- 440.** Veterans Aging Cohort Study Index Score Is Associated with Neurocognitive and Functional Impairment: A CHARTER Study. D Franklin Jr, R Heaton, S Woods, S Letendre, A Collier, D Clifford, B Gelman, J McArthur, D Simpson, Igor Grant, and CHARTER Group.
- 441.** Changing Cerebrospinal Fluid Concentrations of Neurofilament Light Chain Protein, Tau, and Amyloid Proteins Characterize Evolving Central Nervous System Injury in HIV-1 Infection. Julia Peterson, H Zetterberg, L Hagberg, S Spudich, M Gisslen, and R Price.
- 442.** Prevalence of Cerebrospinal Fluid Alzheimer's Disease-like Profiles in Chronic Middle-aged HIV+ Individuals. L Cysique, J Lamoury, T Hewitt, K Taddei, R Martins, C Chew, P Price, and Bruce Brew.
- 443.** Axonal Disturbance in Neuroasymptomatic Patients off and on Suppressive ART: An Aging Effect of Central Nervous System Infection? Jan Jessen Krut, T Mellberg, R Price, L Hagberg, D Fuchs, L Rosengren, S Nilsson, H Zetterberg, and M Gisslen.
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- 446.** Neurological Characterization of HIV Controllers. Evelyn Lee, J Peterson, R Walter, J Javerbaum, S Deeks, R Price, K Robertson, D Meyerhoff, B Shacklett, and S Spudich.
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- 454.** Progression Rates of Neuro-AIDS and Its Neuropsychological Patterns in the cART Era. Gabriele Arendt, E Orhan, and T Nolting.
- 461a.** Moderate Neurocognitive Decline Can Be Detected over a 4-Month Period Using the HIV Dementia Scale. Grace Lu, L Cysique, K Siefried, B Draper, and B Brew.
- 462.** Dynamics of Changes in Cerebral Metabolites over 144 Weeks in HIV+ Individuals Commencing ART. Alan Winston, R Puls, S Kerr, C Duncombe, P Li, J Gill, R Ramautarsing, S Taylor-Robinson, S Emery, D Cooper, for ALTAIR Study Group.
- 463.** The Brain in Seroconversion: Findings from the Chicago Early HIV Infection Study. Ann Ragin, H Du, Y Gao, S Li, R Mahadevia, C Sammet, Y Wu, and L Epstein.
- 464.** Effects of HIV Clade B and C on Brain Volumetric Measurements. Mario Ortega, J Joska, J Heaps, F Vaida, A Agrawal, R Paul, and B Ances.
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- 467.** Effects of HIV and Hepatitis C Co-infection on White Matter Structural Integrity and White Matter Volumes. Jodi Heaps, P Wright, B Ances, D Clifford, and R Paul.
- 468.** Neuroimaging Correlates of Prior Immunosuppression and Cognitive Status in HIV. Christine Fennema-Notestine, M Taylor, R Notestine, T Wolfson, A Gamst, S Archibald, R Theilmann, R Heaton, C Marra, I Grant, and CHARTER Group.
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