Neurologic Complications of HIV Infection

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The effects of HIV-1 in the nervous system are a topic of avid interest to investigators and clinicians focused on HIV, judging by the large and discriminating audience at the oral sessions and poster presentations relating to neuroscience at the 19th Conference on Retroviruses and Opportunistic Infections. Major areas of investigation at this year's conference included the use of neuropsychological testing and neuroimaging to assess the state of the central nervous system (CNS) and effects of antiretroviral therapy during HIV infection as well as basic and clinical studies of neuropathogenesis of HIV-associated neurocognitive disorder (HAND). Numerous important suggestions emerged during the meeting. Among them was the proposition that earlier initiation of therapy might benefit the CNS. Another was that the relationship between HIV and normal aging remains unclear and warrants further study. Still another was that ongoing abnormalities may persist despite treatment with antiretroviral therapy—including measurable brain microglial activation, detectable cerebrospinal fluid HIV, and progression of neurologic impairment

Introduction—Where Should Priorities Lie?

The neurologic sessions this year at the 19th Conference on Retroviruses and Opportunistic Infections (CROI) focused, as in years past, on understanding the pathogenesis of neurologic impairment in HIV, in particular on HIV-associated neurocognitive disorder (HAND), and on determining the optimal time to initiate treatment for patients with HIV infection to preserve or optimally recover neurologic function. In recent years, the mandate to investigators in Neuro-HIV has been to ascertain the best strategies to address persistent neurologic disease in patients with successful systemic viral suppression on antiretroviral therapy (ART), which assumes that most patients with access to treatment for HIV would choose therapy, resulting in undetectable plasma HIV RNA levels. Ideally, patients with HIV infection would be identified prior to advanced immunosuppression, would have full access to a broad range of ART choices, and would adhere to ART throughout the course of treatment. However, epidemiologic data indicate that it is often difficult to identify HIV infection in its early stages in most communities even in the developed world; at least 34% of patients in the United States have a CD4+ count below 200 cells/μL by the time they are diagnosed with HIV infection.[1] Furthermore, patients in the areas of the world with the highest prevalence of HIV face limited drug choices and numerous barriers to obtaining ART. Data presented at this year's CROI suggest that despite access to treatment, only 24% of HIV-infected patients in the United States have undetectable plasma HIV RNA levels (Skarbinski and colleagues, Abstract 138). These observations raise important questions relevant to the central nervous system (CNS). Is there convincing evidence that earlier diagnosis and treatment might preserve neurologic function? How much viral suppression is enough to preserve the CNS? Will ongoing plasma viremia in treated patients be associated with manifestations of active CNS infection and disorders in treated patients? Finally, investigators are faced with deciding whether we should be targeting our therapies and approaches to the majority of patients—those who are not on ART, do not adhere to ART, or who exhibit clinically consequential resistance—or address the minority of patients with persistent impairment but successful systemic suppression on ART.

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Noninvasive Tools for Investigating Neurologic Status in HIV Infection

Neuropsychological Performance

Methods for assessing neurocognitive status. One of the key challenges in diagnosing and monitoring HAND is the lack of reliable and practical methods of screening for and evaluating neurocognitive impairment. Moore and colleagues (Abstract 499) sought to identify a brief neuropsychologic testing strategy to assess patients for HAND. These investigators administered a comprehensive, 120-minute, 7-domain neuropsychologic battery to 200 HIV-infected US military personnel with few potentially confounding comorbidities, and defined impairment in these subjects as a Global Deficit Score (GDS) of greater than 0.5.[2] The investigators then compared the measurement of impairment by the complete battery with measurements of impairment detected by all possible combinations of 2, 3, and 4 neuropsychologic tests from the overall battery, limiting possible tests such that combinations required fewer than 20 minutes to administer. They identified a 16-minute battery combining 3 neuropsychologic tests with a sensitivity of 86.5% and specificity of 75.5%,

and an 18-minute battery combining 4 tests resulting in a sensitivity of 86.5% and specificity of 87.1%. These batteries may be good substitutes for comprehensive batteries in research settings in which resources and patient fatigue require brief assessments for HAND. Similarly, Smith and colleagues (Abstract 505) reported on the use of the International HIV Dementia Scale (IHDS) as a screening tool for more subtle forms of HAND. Developed as a tool for detection of HIV dementia, the IHDS is a brief bedside or office evaluation method that requires no equipment and includes a motor-speed test, a psychomotor speed test, and a memory-recall test. The investigators compared scores on the IHDS with results of a more comprehensive battery defining HAND according to 2007 Frascati criteria[3] in 106 subjects. They found that using a cutoff score of 11 points or lower, the IHDS had 72% sensitivity and 44% specificity for all forms of HAND, including asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND). Subjects with HAND had a lower IHDS-scale score than did subjects without HAND. The investigators concluded that although the IHDS was developed for detection of dementia, it may be an acceptable brief screening tool for mild categories of HAND. Meyer and colleagues (Abstract 502) examined the interpretation of a 17-neuropsychologic-test battery administered to 100 HIV-uninfected and 221 HIV-infected subjects in Kenya excluding patients with comorbidities expected to confound HAND diagnosis. The investigators found that when the interpretation was applied to test performance of HIV-uninfected subjects, 45% met Frascati criteria for ANI or MND and 6% for HIV-associated dementia (HAD) according to the most liberal definition of domain impairment (1 test per domain > 1 standard deviation [SD] below the mean), whereas these numbers were 14% and 1% when a stricter definition was used (average score for domain > 1 SD below the mean). Rates of ANI and MND were slightly higher in HIV-infected subjects according to the same criteria (68% with 1 test per domain, and 30% with abnormal score for the whole domain), but the rate of HAD was only 0.5% according to all criteria. These findings suggest that at least in the Kenyan population, neuropsychologic-test indications of impairment may be unrelated to HIV and that more rigorous standards should be applied in defining abnormality on testing to reduce false-positive results.

Neurocognitive status in early infection. It remains unresolved as to when neurologic impairment occurs during the course of HIV infection. Many individuals develop dementia after long-standing untreated HIV infection, and recent studies have demonstrated that more subtle impairment characterizes up to 50% of HIV-infected persons remains even in the ART era.[4] Peterson and colleagues (Abstract 80) reported on neurologic performance in 70 subjects recruited during primary HIV infection (median 4 months after HIV transmission) and who were longitudinally followed using an 11-test neuropsychologic battery. At baseline, 42% of subjects performed greater than 1 SD below norm means in more than 2 neuropsychologic domains, meeting Frascati definitions of ANI or MND. Before the initiation of ART, performance improved in most domains over time with repeated testing but declined in the motor domain. In subjects who initiated HIV treatment for reasons independent of the study, motor performance stabilized but did not improve during follow-up. Although these findings suggest that impairment may accrue even in the first year of HIV infection before the initiation of ART, the extent to which these changes are due to HIV rather than concomitant factors remains unknown. Vo and colleagues (Abstract 507) presented data from the Multicenter AIDS Cohort Study (MACS) following subjects who were HIV-uninfected at enrollment but who seroconverted during the course of the study. These investigators evaluated results of a brief battery of neuropsychologic tests from 5 years before seroconversion through 3 years after seroconversion, over a possible 25 years of follow-up by the MACS. They did not observe statistically significant changes in performance in the brief battery before or after seroconversion. Improvement in performance as a result of practice effect from repeated testing, effects of initiation of ART in seroconverters, and the brief nature of the battery may contribute to the differences between the findings of this study and those of Peterson and colleagues. However, the findings of Vo and colleagues also may suggest that HIV itself is not the primary cause of neurologic dysfunction in subjects with recent HIV infection.

Impact of earlier ART on neurocognitive performance. Building on the concept that injury to the CNS may occur early in the course of HIV infection, several studies investigated the effects of earlier initiation of ART on neurologic outcomes. Puthanakit and colleagues (Abstract 24) compared neuropsychological test performance outcomes in 284 Thai and Cambodian HIV-infected children (median 7 years old) in the PREDICT (Prospective Randomized Evaluation of DNA Screening in a Clinical Trial) study who were randomly assigned to immediate ART or therapy deferred until CD4+ percentage fell below 15% or Centers for Disease Control and Prevention (CDC) Category C events occurred. Although children with immediate therapy had higher CD4+ percentages and longer exposure to ART than those who deferred-therapy group at 144 weeks after enrollment, neuropsychologic test performance did not differ between the 2 groups. However, both HIV-infected groups had statistically significantly lower Wechsler Intelligence Scale (IQ) scores than did 164 age-matched HIV-uninfected Thai and Cambodian children, suggesting that either comorbid factors or effects of HIV before the initiation of therapy even in the immediate group had resulted in neurologic injury in these children by the time of evaluation.

Crum-Cianflone and colleagues (Abstract 500) evaluated the rates of neurocognitive impairment, defined as a GDS greater than 0.5, in 200 military personnel with known (within 1.2 years) dates of seroconversion and low

rates of substance use and medical or psychologic factors that might confound neuropsychologic testing. These subjects were assessed with a comprehensive neuropsychologic battery at a fairly early stage of HIV infection, with median nadir CD4+ count 319 cells/μL and median duration of infection of 5 years. A total of 65% of subjects were on ART, initiated at median 1.4 years after HIV diagnosis. The cohort overall had rates of neurocognitive impairment that were not different from those found in 50 HIV-uninfected control subjects assessed with an identical battery. This finding suggests that early intervention for HIV infection might preserve neurocognitive function, although the authors acknowledge that the minimal confounding comorbidities and stable lifestyle context for these subjects might also relate to low levels of impairment in this group. Finally, Marcotte and colleagues (Abstract 485) investigated the neurocognitive outcomes of Maharashtran subjects in Pune, India, with high baseline CD4+ counts (approximately 460 cells/μL) randomly assigned to immediate initiation of ART or to deferred treatment. Improvement from baseline to 1-year follow-up visit was statistically significantly associated with the interaction between poorer baseline neuropsychologic performance and assignment to the immediate treatment group ($P = .02$). These findings suggest that patients with relative neurocognitive impairment in the early stages of HIV might benefit from immediate initiation of ART, even while CD4+ counts are relatively preserved.

Neurocognitive decline in patients with chronic HIV. An area of controversy for clinicians and investigators is whether mild neurologic impairment—defined by reduced performance on neuropsychologic testing but no associated functional impairment—has clinical significance for patients infected with HIV. In the 1555-person CHARTER (CNS HIV Antiretroviral Therapy Effects Research) study, 33% of subjects were considered to have such a condition (defined as ANI by Frascati criteria) at study entry. Grant presented findings (Abstract 77) demonstrating that ANI conferred a risk of progression to symptomatic stages of HAND (MND or HAD) in CHARTER subjects. The researchers evaluated indices of symptoms of neurocognitive impairment, including self-report of symptoms and performance-based assessments, in 226 subjects without impairment and 121 ANI subjects every 6 months for a median time of 45 months. They found that individuals with ANI had an increased relative risk of progressing to symptomatic HAND compared with cognitively normal individuals, 2-times higher if based on self-report and more than 5-times higher if based on performance-based evaluation. These authors made efforts to correct these estimates for potentially confounding factors, including baseline education level and categorization of severity of comorbidities, such as substance abuse. Their findings suggest that mild, asymptomatic, neurologic impairment may reflect an active process that progresses to more substantial impairment in persons with HIV infection. However, since approximately 30% of subjects in the ANI group were not on ART at baseline in the study, it is unclear to what extent ANI subjects with complete systemic viral suppression might experience substantial progression of HAND during continued ART.

Another study from the CHARTER collaborative group (Abstract 474) focused on the related topic of determinants of neurocognitive decline over longitudinal follow-up in a group of 437 HIV-infected subjects mostly on ART. They found that 22.7% of subjects showed decline in performance over time, while 16.5% showed improvement. In a multivariable model, absence of ART, having a low CD4+ count, Hispanic ethnicity, and presence of severe comorbidities were associated with decline in neurocognition. These data are consistent with prior studies suggesting that detectable HIV RNA in plasma plays a continued role in neurologic impairment in the current era.[5-7] The data also suggest that comorbidities rather than HIV alone may contribute to clinical progression.

Brain Imaging Investigations of Neuropathogenesis and Assessment of Neurologic Status

Neuroimaging provides a variety of non-invasive methods to understand the pathophysiologic changes seen with HAND. A large number of presentations at CROI also focused on the use of neuroimaging as a means of investigating HIV neuropathogenesis or as a biomarker of the status of the brain in HIV-infected persons. Presentations highlighted an ever-expanding list of techniques, including morphometry, magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), and positron emission tomography (PET), as methods to investigate the status of the brain in HIV-infected patients, with particular focus on understanding the potential relationship between aging and HIV and the effects of ART.

Volumetrics. Both Becker and colleagues (Abstract 512) and Ortega and colleagues (Abstract 514) studied the effects of HIV and aging using volumetric measurements. Becker and associates performed neuroimaging in 84 HIV-seropositive men and 76 HIV-seronegative men. The investigators observed independent effects of HIV and aging within the gray and white matter and saw no statistically significant relationship. Cardiovascular risk factors were not associated with reductions in brain volume. Further studies that include both male and female HIV-seropositive and -seronegative participants are required. Ortega and colleagues studied 52 HIV-seropositive patients and 26 HIV-seronegative controls. The investigators assessed the effects of ART and aging on brain volumetrics. HIV-seropositive patients, whether on ART or treatment naive, had statistically significant reductions in brain volume within the amygdala, caudate, and corpus callosum compared with HIV-seronegative controls. Both HIV and aging independently caused atrophy in the caudate. These changes gradually occurred after self-reported seroconversion. Further longitudinal studies of primary infected

HIV-seropositive subjects are needed.

A complementary study by Gongvatana and colleagues (Abstract 513) investigated the relationship between observed brain volumetrics and plasma biomarkers (interferon [IFN]-γ, interleukin[IL]-β, IL-6, IL-8, IL-10, IL-16, IL-18, IP-10, monocyte-chemoattractant protein-1 [MCP-1], macrophage inflammatory protein-1-β [MIP-1-β], stromal cell-derived factor-1 [SDF1-α] tumor necrosis factor [TNF-α], and TNF-related apoptosis-inducing ligand [TRAIL]) in 74 HIV-infected participants on ART. As in the above studies, older age was associated with a reduction in brain volume even in HIV-infected subjects with well-controlled plasma viral load. The authors suggest that observed findings may reflect ART toxicity. In addition, higher IFN-γ, MCP-1, and TNF-α were related to increased volumes within the putamen, pallidum, amygdala, and corpus callosum. Higher IL-1, IL-6, IL-16, IL-18, IP-10, MIP-β, and SDF1-α were related to decreased volumes within the putamen, pallidum, thalamus, hippocampus, amygdala, and corpus callosum. Additional studies of HIV-seronegative subjects using imaging and blood biomarkers are needed.

To further study the effects of ART on brain volume, Sammet and colleagues (Abstract 511) used voxel-based morphometry (VBM) to compare gray-matter volume in treated (n = 25) and untreated (n = 25) subjects with primary HIV infection and age–matched HIV-seronegative controls (n = 20). The authors observed a statistically significant reduction in the insular cortex of HIV-seropositive patients on ART compared with HIV-seronegative controls. In addition, treated HIV-seropositive patients had a statistically significant reduction in volume within the anterior cingulate, insular cortex, precuneus, temporal gyrus, and temporal pole compared with treatment-naive HIV-seropositive patients. The authors postulate that the findings may reflect ART toxicity or injury related to immune reconstitution, or both. Further studies should investigate the effects of the degree to which ART penetrates the CNS on brain volume outcomes.

MRS. Cysique and colleagues (Abstract 492) compared metabolic ratios in chronically infected HIV-seropositive patients (n = 90) with HIV-seronegative controls (n = 25). The HIV-seropositive group had higher inflammatory marker levels in frontal white matter and reduced neural integrity in the caudate. No connection was observed between HIV and age. However, duration of HIV infection and presence of cardiovascular risk factors were associated with brain injury in HIV-infected patients. Additional analyses using standard metabolic ratios and correction for multiple comparisons might produce different results.

Young and colleagues (Abstract 79) assessed neuronal and glial changes associated with primary HIV infection. MRS data were obtained from a cohort of individuals with primary HIV infection (n = 53), a chronically HIV-infected cohort (n = 18), and HIV-seronegative controls (n = 19). At baseline, only chronically HIV-infected subjects had a statistically significant decrease in neuronal metabolites compared with individuals with primary HIV infection or HIV-seronegative controls. Within subjects with primary infection who were followed up longitudinally, ratios of choline metabolites associated with inflammation and membrane turnover increased over time before therapy and then stabilized after the initiation of ART. The authors suggested that changes associated with HIV-related injury in the CNS may develop soon after HIV infection, but early initiation of ART may ameliorate some of these changes.

Similar to Young's findings of rising choline/creatine ratios in early infection was a report by Sailasuta and colleagues (Abstract 456) that elevations in brain choline/creatine ratios were characterized in subjects with acute HIV infection compared with HIV-uninfected subjects and improved over time after very early treatment with ART. These studies suggest that both acute and progressive brain inflammation characterizes the earliest stages of HIV infection before the typical initiation of ART.

Navia and colleagues (Abstract 509) demonstrated that neuronal injury was present in chronically HIV-infected participants despite ART. Predictors of decreases in neuronal and glial metabolites included older age, longer duration of infection, and longer exposure to ART. These results suggest a possible connection between neurotoxicity and long-term exposure to ART, but additional studies are needed.

DTI and functional imaging. Wright and colleagues (Abstract 510) assessed the effects of ART on DTI measurements within the corpus callosum. Treatment-naive HIV-infected (n = 21) subjects had statistically significant reductions in DTI parameters compared with HIV-infected patients receiving ART (n = 21) and HIV-seronegative controls (n = 21). Longitudinal analysis of HIV-seropositive patients before and then 3 to 5 months after initiating ART demonstrated a normalization of DTI parameters after starting medications. These results suggest a reduction in inflammation after starting ART. Larger studies of HIV-seropositive patients receiving ART with different degrees of CNS-penetration are needed. In addition, Valcour and colleagues (Abstract 496) demonstrated that impairment evident through neuropsychologic testing correlated with changes in DTI parameters within the corpus callosum of 40 HIV-infected patients.

Thomas and colleagues (Abstract 493) used the recently developed technique of resting-state functional connectivity to map cortical networks within HIV-infected (n = 52) and HIV-infected (n = 52) subjects. Overall, HIV-seropositive subjects had a reduction in functional connections within numerous networks, including the default, salience, and control networks. A cortical signature of HIV might exist that distinguishes it from other neurodegenerative diseases (including Alzheimer's disease). Additional studies of subjects with varying degrees of HAND are required.

PET. Garvey and colleagues (Abstract 78LB) studied the role of neuroinflammation (in particular microglia) within the brains of HIV-infected subjects.

These investigators studied the role of activated microglia using the radiotracer PK 11195 in 7 HIV-infected patients and 9 HIV-seronegative controls. An increase in microglial activation was seen within the corpus callosum, anterior cingulate, and temporal lobes of neuro-asymptomatic HIV-seropositive patients on ART compared with HIV-seronegative controls. These findings warrant additional larger studies to confirm these initial findings, and longitudinal studies to determine when microglial activation is established and how it evolves in relation to ART.

Pathogenesis of HAND

Neuropathogenesis of HAND: Molecular Studies

Limitations in our understanding of the basic neuropathogenesis of HIV prompted some of the investigations presented at this year's conference, where topics included viral tropism and compartmentalization of HIV species in the CNS, potential mechanisms of neurotoxicity of HIV, and host features predisposing patients to the development of dementia.

Virologic studies. Arrildt and colleagues (Abstract 445) studied HIV species derived from cerebrospinal fluid (CSF) in patients with dementia, comparing compartmentalized HIV that was able to infect cells with high CD4 density with HIV that infected cells with low CD4 density. They observed that CD4 density varied in monocyte-derived macrophages and correlated with infectivity, and that macrophage-tropic (M-tropic) viruses appeared to use any CD4 density for entry; in contrast, T-lymphocyte tropism alone, without macrophage tropism, needed high CD4 density.

Studevant and colleagues (Abstract 447) also investigated compartmentalization of HIV-1, reporting the first evidence of compartmentalization of HIV within the CNS in HIV subtype C and in children. The investigators used single-genome amplification to compare CSF and blood samples obtained from 48 children in Malawi aged 4 months to 37 months, infected in utero or during infancy, and detected CNS compartmentalization in 37.5%. Compartmentalization was noted to be more frequent in the older children or those with higher levels of HIV RNA in CSF. The researchers also noted some preliminary evidence of the ability of viruses to use low CD4 density for entry (interpreted as M-tropic viruses) in these env variants from CSF.

Holman and colleagues (Abstract 83) reported on the development of a machine-learning approach to identifying genetic signatures in HIV *env* associated with HAD. Holman and colleagues used 1022 *env* sequences derived from brain tissue from 78 subjects identified through the HIV Brain Sequence Database (http://www.hivbrainseqdb.org/) to develop an iterative approach to recognizing certain amino acid sequences that were associated with HAD. The researchers identified sequences that were associated with HAD or non-HAD status, and they corroborated their findings with *env* sequences derived from 458 CSF samples from 36 additional clinically characterized subjects. The investigators postulated that this approach may be valuable in assessing sequence data from CNS-derived sources in association with neurologic disease and might yield insight into the neurotropism or neurovirulence of specific strains of HIV.

Choi and colleagues (Abstract 450) sequenced HIV-1 *tat* derived from CSF and blood in 60 subjects. They observed that position HXB2 5905 was associated with the CSF and that greater sequence diversity within the CSF was associated with HAND. Further studies specifically on this position and its role in neurotropism may yield insight into mechanisms of HIV compartmentalization in the CNS.

Mechanisms of neuronal injury. Several studies focused on molecular and cellular mechanisms of neuropathogenesis, specifically examining toxic or transmitter molecules that might directly induce or modulate toxic effects in the brain in the setting of HIV infection. Cantres and colleagues (Abstract 459) measured higher levels of lysosomal protease cathepsin B and its inhibitor cystatin B in monocytes in patients with HAD compared with patients with normal cognition or those with ANI, suggesting that the cathepsin B may be an important mediator of neurologic injury in HIV. Gelman and colleagues (Abstract 465) analyzed levels of type 2 dopamine receptor long isoform (DRD2L) and preproenkephalin messenger RNA (mRNA) in autopsy brain specimens from the National NeuroAIDS Tissue Consortium and found that lower levels of DRD2L were associated with better neurocognitive functioning in life. The authors concluded that downregulation of DRD2L in the setting of HIV infection is protective in HAND, and failure to reduce levels is associated with pathogenic effects of the dopamine system in the prefrontal cortex.

Host factors contributing to HAND. Levine and colleagues (Abstract 470) completed a genome-wide association study (GWAS) of 1287 subjects to investigate whether HAND might be linked to certain host genetic features in subjects enrolled in the MACS. The researchers investigated whether the rate of neurocognitive decline, the presence of HAD, or mild to severe neurocognitive impairment based on 2007 Frascati criteria could be linked to any single-nucleotide polymorphisms (SNPs) identified by either the Illumina, Inc. (San Diego, CA) or Affymetrix (Santa Clara, CA) platforms. The researchers did not identify any SNPs that were statistically significantly associated with these phenotypes. Furthermore, they did not validate previously identified candidate alleles as linked to phenotypes of HAND. The authors concluded that their study might not have had adequate subjects to find significant associations and suggest that further studies might be done that integrate their sequence data with those of other large cohort studies.

Neuropathogenesis of HAND: Clinical and Biomarker Studies

Early HIV infection. Paralleling neuroimaging studies of acute and primary

infection, several laboratory studies investigated CNS HIV pathogenesis in the early stages of infection. Morris and colleagues (Abstract 446) studied HIV coreceptor tropism in plasma in 72 subjects beginning at a mean estimated 70 days after HIV exposure and found that 4 of 72 (5.5%) harbored a CXCR4 or dual/mixed tropic (X4/DM) coreceptor phenotype at baseline, and 9 of 72 (12.5%) had an X4/DM coreceptor phenotype during at least 1 follow-up visit. In a generalized estimating equation model, X4/DM tropism was independently associated with HAND based on neuropsychologic testing criteria, though it is unclear whether this association was a causative relationship or a reflection of other differences in the patients with X4/DM coreceptor phenotype. Lee and colleagues (Abstract 457) demonstrated that although undetectable CSF HIV RNA characterizes approximately 15% of treatment-naive subjects in a primary-infection cohort at a median of 3 months after transmission, emergence of CSF HIV RNA levels not different from those in a detectable HIV RNA group occurs by 1 year in subjects remaining off treatment. Furthermore, reduced CSF inflammation associated with undetectable HIV RNA at baseline is not sustained at 1 year, suggesting that mechanisms associated with this reduced HIV burden and associated immune activation in the CNS are likely unique to the earliest stages of HIV.

Chronic HIV infection. In a study investigating neuropathogenesis and use of a laboratory biomarker for HAND during chronic HIV infection, Mellberg and colleagues (Abstract 469) found that a marker of axonal breakdown, CSF neurofilament light chain (NFL), declined in 85 asymptomatic subjects with a median CD4+ count of 190 cells/μL after initiation of ART when treatment naive or off ART for at least 6 months. This finding suggests that low-level CNS injury is ongoing in HIV-infected persons before overt symptoms of cognitive impairment, that this smoldering injury can be reduced by ART, and that NFL may be a useful marker of neurologic injury even in presymptomatic patients.

Numerous clinically oriented studies focused on mechanisms and biomarkers of HAND in the setting of stable ART. Several studies focused on ongoing abnormal activation of cells of the monocyte/macrophage or microglial lineages in the setting of effective ART. As noted above, Garvey and coworkers (Abstract 78LB) demonstrated areas of elevated uptake of a PET ligand targeted to a receptor on the surface of activated microglia in subjects on suppressive ART. Williams presented evidence (Abstract 81) that plasma soluble hemoglobin scavenger receptor (sCD163) may be a marker of persistent inflammation that, in the setting of successful ART, associates with neurologic disease. A total of 34 subjects on suppressive ART were separated into groups classified as impaired or neurocognitively normal as measured by a GDS approach, which emphasizes abnormality. Elevated levels of sCD163 characterized the subjects with a GDS greater than 0.5 and persisted in this group at a second visit on continued therapy, suggesting that processes underlying neurologic impairment in the setting of treatment are associated with immune activation of the monocyte/macrophage lineage and can be measured in the blood.

Several studies also investigated the sources and potential clinical significance of CSF HIV RNA measured in the setting of ART. Letendre and colleagues (Abstract 473) explored the correlates of CSF HIV RNA in patients on ART. They studied paired CSF and blood samples from 413 subjects in the CHARTER study, selected for their being on ART at all visits according to self-report and adherence assessments. In a multivariable model describing predictors of CSF HIV RNA levels in 2207 visits, plasma HIV RNA levels were the strongest predictor, with an odds ratio [OR] of 18.0. Protease inhibitor use was also a statistically significant predictor of detectable HIV RNA in CSF with an OR of 3.3, with CNS penetration–effectiveness (CPE) score having an overall lower effect (OR, 0.7).

Peluso and colleagues (Abstract 489) presented a report on 10 subjects on suppressive ART with either undetectable plasma HIV RNA or very low levels (median HIV RNA, 62 copies/mL) who presented with incident cognitive, balance, and motor symptoms and were found to have detectable CSF HIV RNA levels (median, 3900 copies/mL) and accompanying CSF inflammation and abnormalities on magnetic resonance imaging (MRI) scans. After their regimens were changed to address HIV genotypes associated with resistance detected in CSF and to improve CNS drug exposure based on pharmacologic properties, patients had improvement in clinical symptoms and, when data were available, in CSF parameters. The authors concluded that although the mechanisms of such symptomatic CSF escape are unknown, it is important to test for this condition in certain clinical circumstances since addressing it with treatment strategies might be beneficial for patients. However, Eden and colleagues (Abstract 488) presented evidence that although CSF HIV RNA levels above 50 copies/mL (identified by sampling in research studies in the setting of undetectable plasma HIV RNA) occurred in 25% of asymptomatic subjects during a longitudinal study, there was no evidence of progression of CNS disease or even persistence of CSF escape in longitudinal follow-up in these subjects. Thus, presence of low-level detectable CSF HIV RNA in patients without neurologic symptoms was of unclear significance.

Conclusions

This year's CROI reported substantial scientific contributions from investigators worldwide and reminded us that many important issues regarding the assessment, pathogenesis, and treatment of HIV in the CNS remain unresolved. Key challenges to the field include the lack of consensus on the definitions and significance of milder forms of impairment; the lack of biomarkers for HAND that can be considered with certainty to be specific for the effects of HIV infection; the need for more large-scale,

well-characterized cohort studies to investigate host factors related to disease; and the continued limitations in understanding the biology of HIV infection in the CNS in subjects on suppressive ART. A topic that pervaded sessions throughout this year's CROI but was not directly addressed in the neurology sessions was whether or in what circumstances the CNS compartment needs to be considered a reservoir relevant to HIV cure strategies. Future studies are required to investigate the possible role of the CNS as a viral reservoir that might elude systemic eradication efforts and to understand the potential effects of proposed cure strategies on the nervous system.

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