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Topics in Antiviral Medicine™

A publication of the IAS–USA

Perspectives CME

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Topics in Antiviral Medicine™

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The IAS–USA offers this state-of-the-art activity as part of a nationwide CME effort for physicians on the evolving challenges of managing HIV disease.

Learning Objectives

On completion of this activity, the learner will be able to:

- Describe important new data on neurologic complications in HIV infection presented at the 20th Conference on Retroviruses and Opportunistic Infections (CROI)
- Discuss the impact of antiretroviral treatment as prevention and how such a strategy may be implemented
- Describe the incidence of and potential contributors to HIV-associated neurocognitive disorder (HAND) among aging HIV-infected patients
- Discuss the risks for and treatment of osteoporosis and vitamin D deficiency in HIV-infected patients

Intended Audience

This enduring material is designed for physicians who are actively involved in the medical care of people with HIV infection, specifically those who:

- Have a solid, working knowledge of HIV disease management
- Provide comprehensive or specialty care for patients with HIV infection
- Are currently active in HIV research

This activity is also relevant for other practitioners, including nurse practitioners, nurses, physician assistants, pharmacists, and others.

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Improving the Management of HIV Disease®

The annual full-day advanced CME courses continue to focus on cutting-edge, scientifically rigorous issues presented by leading experts in the field, providing the latest insights and data on the full spectrum of HIV- and AIDS-related treatment issues.

New York, New York
Friday, October 18, 2013
The New York Academy of Medicine
Cochairs: Roy M. Gulick, MD, MPH,
Scott M. Hammer, MD

Hepatitis C Virus Infection: Looking Beyond the Interferon Alfa Era

The full-day advanced CME course is designed for clinicians who are experts in the complexities of antiretroviral management and who are well positioned to join their hepatology and gastroenterology colleagues in providing care for hepatitis C virus (HCV)-infected patients, in what has become an exciting new era in HCV care.

Atlanta, Georgia
Tuesday, September 24, 2013
Georgia Tech Global Learning Center
Cochairs: Susanna Naggie, MD,
Michael S. Saag, MD

Chicago, Illinois
Tuesday, October 8, 2013
Gleacher Center
Cochairs: Kenneth E. Sherman, MD, PhD,
Donald M. Jensen, MD

Evolving Strategies in Hepatitis C Virus Management

Part of the IAS–USA focus on the management of HCV infection, these half-day, small-group, intensive CME workshops are presented by leading experts in the field. Attendance is limited to 35 practitioners, so early registration is encouraged.

Raleigh-Durham, North Carolina
Tuesday, September 17, 2013
Raleigh Marriott City Center

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Friday, October 11, 2013
Hyatt Regency Miami

Boston, Massachusetts
Tuesday, October 15, 2013
Omni Parker House

New Orleans, Louisiana
Wednesday, October 23, 2013
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Special Contribution

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

Serena S. Spudich, MD, and Beau M. Ances, MD, PhD

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.

Keywords: *HIV, neurology, dementia, neuropathy, HIV-associated neurocognitive disorder, HAND, neuroimaging, central nervous system*

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

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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.[1] 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.[2]

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.[3] 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_{50}) 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-naive 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/μL). These antiretroviral-naive subjects had a median age of 42 years and a median CD4+ cell count of 23/μL. None of the subjects was diagnosed with HAND, based on neuropsychologic testing. Subjects had median CSF HIV RNA levels of 3.8 $\log_{10}$ 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/μL), symptoms of recent neurologic decline, and a high (5 of 15 subjects) prevalence of HAD. 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/creatine 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.[4] 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.[5] 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.[6] 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.[7] 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.[8] 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.[9] 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_{42}) 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_{42} levels less than 530 ng/L; profile 2, p-tau greater than 60 ng/L and Ab_{42} less than 530 ng/L; or profile 3, t-tau greater than 350 ng/L and the ratio of Ab_{42} 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,[10] 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 nonlymphoid 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-Maddison 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 α4-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"[11,12] 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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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.

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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 Autissier, 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.

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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 Agsalda, K Amina, N Hanks, B Nakamoto, J Barbour, B Shiramizu, and C Shikuma.

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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.

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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.

432. Elevated Cerebrospinal Fluid Inflammatory Biomarkers across the Spectrum of HIV Disease Progression. Sheila Keating, J Peterson, M Gisslen, J Heitman, S Wu, S Spudich, P Norris, and R Price.

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.

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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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445. HIV and Aging: New Graph Theoretical Models of rs-fcMRI Neuropathophysiology. Jewell Thomas, M Brier, and B Ances.

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.

452. High Grade Liver Steatosis and Cognitive Impairment in HIV+ Patients. Pierfrancesco Grima, M Fabbiani, A Mondi, A D'Avino, S Limiti, M Colafigli, B Milanini, E Baldonero, R Cauda, and S Di Giambenedetto.

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.

465. Altered Tryptophan Metabolism Correlates with Intrathecal Inflammation and Cerebral Metabolites Detected by Magnetic Resonance Spectroscopy in Primary HIV Infection. Marie Grill, J Peterson, E Lee, R Walter, D Fuchs, L Hagberg, D Meyerhoff, R Price, and S Spudich.

466. Effects of Primary and Chronic HIV Infection on White Matter Integrity Using Diffusion Tensor Imaging. Patrick Wright, R Fernandez, D Meyerhoff, R Price, K Robertson, E Lee, J Rutlin, J Shimony, S Spudich, and B Ances.

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.

469. Diffusion Tensor Imaging Uncovers Specific Brain Microstructural Deficits during Chronic HIV-1 Infection of Humanized Mice. Prasanta Dash, J Knibbe, T Gutti, E Makarov, D Baber, S Gorantla, L Poluektova, H Gendelman, and M Boska.

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Sexually Transmitted Infections in the HIV-Infected Patient

Linda M. Gorgos, MD, MSc

Osteomalacia and Osteoporosis in the HIV-Infected Patient

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HIV and Pain

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Common Drug Interactions in Patients Receiving Antiretroviral Therapy

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Perspective

Treatment as Prevention: Toward an AIDS-Free Generation

In British Columbia, Canada, intensive efforts have been made to implement and maintain a treatment-as-prevention strategy among the HIV-infected population. Acceleration of antiretroviral therapy coverage has resulted in a substantial increase in the median CD4+ cell count at which treatment is initiated and a dramatic decline in community plasma HIV RNA levels. This has resulted in a reduction in diagnoses of new cases of HIV infection, including among injection drug users. Proportions of individuals with viral suppression have steadily increased and the expansion of antiretroviral therapy coverage has not been associated with increased levels of HIV resistance. Further, adoption of routine HIV testing in acute care settings has been very well accepted and has captured new cases at a rate of 5 per 1000 tests outside of high-risk populations, offering an additional strategy for identifying and linking at least some individuals with undiagnosed HIV infection to care. Deriving optimal individual and social health outcomes in HIV infection requires improvement in every element of the cascade of care. This article summarizes a presentation by Julio S. G. Montaner, MD, at the IAS–USA continuing education program held in San Francisco, California, in March 2013.

Keywords: *HIV, AIDS, treatment, prevention, community viral load, routine HIV testing*

In British Columbia, Canada, as in other relatively resource-rich locales, there was a dramatic decline in death rate from HIV disease and an increase in life expectancy following the advent, in 1996, of potent antiretroviral therapy. At the same time it was seen that whereas new cases of HIV infection decreased between 1996 and 1999, the rate of new cases of syphilis increased. It was thus hypothesized that effective antiretroviral therapy was producing a secondary benefit in terms of reducing HIV transmission.

This hypothesis, of a secondary preventive effect of antiretroviral therapy, was supported by the observation that the number of infants born with HIV infection in Canada decreased dramatically after 1996, in the absence of a decrease in the number of infants exposed to HIV-infected mothers, as a result of the introduction of effective antiretroviral therapy during pregnancy. During the past 7 years, only 2 children in British Columbia have been born with HIV infection. In both cases, HIV infection in the mother was not identified prior to birth, because the mother was not engaged in health care.

In 2006, a case was made for expanding access to antiretroviral therapy in order to curb the growth of the HIV epidemic.[1] This was based on the premise that antiretroviral therapy stops HIV replication; as a result, viral load drops to undetectable levels in both plasma and sexual fluids, which can result in long-term remission and, secondarily, lead to a sharp reduction in HIV transmission. Some residual replication can occur when viral load is reduced to undetectable levels, but it is unclear what impact this has on the preventive benefit of antiretroviral therapy.

Extensive efforts have been made in British Columbia to support a treatment-as-prevention strategy, including expanding and accelerating HIV testing and supporting and facilitating access to antiretroviral therapy, as a means to improve patient-centered outcomes (ie, prevention of morbidity and mortality) and societal outcomes (ie, prevention of HIV transmission).

Antiretroviral Therapy Outcomes Among Injection Drug Users in Vancouver, Canada

Reducing HIV transmission among injection drug users (IDUs) poses particular problems, largely because IDUs may frequently share needles (sometimes several times per day). As a result, there has been concern that IDUs may be exposed to some cell-associated HIV that may decrease the effectiveness of treatment as prevention.

The Downtown Eastside neighborhood of Vancouver—a highly marginalized district that is one of the poorest in Canada—is an area where injection

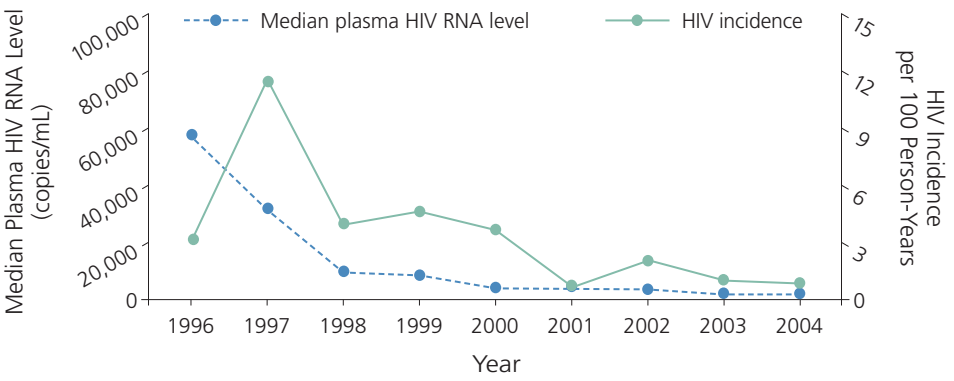

Figure 1. Longitudinal community plasma HIV RNA levels and incidence of HIV infection among a cohort of injection drug users in inner city Vancouver, Canada. Adapted from Wood et al.[2]

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drug use is heavily concentrated. As part of a prospective epidemiologic cohort study in this district, Dr Montaner and colleagues collected blood samples from residents for approximately a decade, allowing them to monitor plasma HIV RNA concentrations in the community as a sentinel exercise. After 1996, with the introduction of potent antiretroviral therapy, median plasma HIV RNA levels in the community were sharply reduced. As shown in Figure 1, this reduction was mirrored by a reduction in HIV incidence rate.[2]

Similar findings were observed in the ALIVE (AIDS Linked to the Intravenous Experience) cohort in Baltimore, Maryland. Starting in 1997, HIV incidence decreased by 74% for each $\log_{10}$ copy/mL decline in community HIV RNA level. In a separate model, the data showed that within the IDU cohort, HIV incidence decreased by 5% for each 1% increase in antiretroviral therapy coverage.[3]

Underscoring these observations are the findings of the HPTN (HIV Prevention Trials Network) 052 study of HIV-serodiscordant couples. The study, conducted predominantly among heterosexual couples, showed that immediate (compared with delayed) antiretroviral therapy was associated with a 96.3% reduction in HIV transmission, irrespective of whether the index member of the couple was a man or a woman.[4] The study also showed that immediate treatment was associated with an individual-level benefit in terms of reducing the incidence of a combined end point of morbidity and mortality, defined a priori, indicating that the strategy of immediate antiretroviral therapy is associated with a benefit to the individual as well as to the public.

The only event of HIV seroconversion observed in the immediate-treatment group was ultimately shown to have occurred around the time of treatment initiation. Such observations strongly suggest that in settings in which HIV-infected individuals have effective viral suppression, transmission risk can be virtually eliminated.

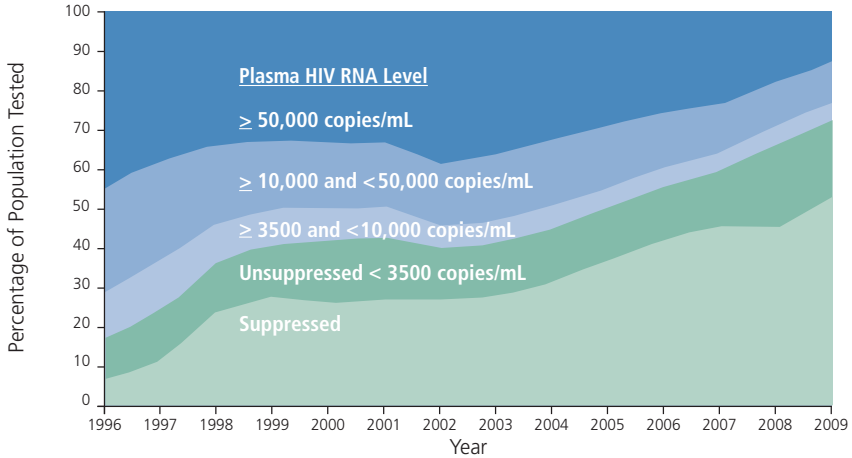
Increasing Antiretroviral Therapy Coverage in British Columbia

The expansion of antiretroviral therapy coverage in British Columbia has occurred in 3 phases within the context of evolving treatment guidelines. The first phase, between the summer of 1996 and the summer of 2000, was marked by a steep increase in participation in antiretroviral therapy following the introduction of triple-drug therapy. From the summer of 2000 through the end of 2003, there was little growth in the number of patients receiving antiretroviral therapy. Changes in treatment guidelines and the conviction that treatment was contributing to more than just improvement in individual health outcomes inspired a campaign to accelerate access to antiretroviral therapy, resulting in another steep increase in the number of patients receiving antiretroviral therapy beginning in 2004.

Since 2004, the median CD4+ cell count at the start of antiretroviral therapy in British Columbia has increased from below 200/μL to above 350/μL as of 2011 (the last year for which full data are available). The proportion of patients starting therapy at CD4+ cell counts less than 200/μL has steadily decreased over the last several years. This achievement has required persistent outreach efforts to diagnose infected individuals and to engage and maintain them in care. The incidence of AIDS had been reduced by 80% since the pre–potent antiretroviral therapy era and further declined between 2004 and 2010. Finally, the frequency of all-cause mortality among HIV-infected persons, which had been reduced by more than 90% with the potent antiretroviral therapy era, also declined over the past several years during the campaign to accelerate access to antiretroviral therapy.

There has been concern in some quarters that expanding coverage of antiretroviral therapy may increasingly involve patients with additional comorbidities or social challenges and that this may result in decreased adherence rates and potentially lead to increased prevalence of resistance to antiretroviral drugs.[5,6] This has not been seen in British Columbia, where the proportion of individuals with suppression of plasma HIV RNA level to below 50 copies/mL has been at 90% or higher since 2007. Levels of antiretroviral resistance, including single- and multi-drug resistance, have decreased with the increasing level of viral suppression in the community.

The overall improvement in community viral load as a result of the antiretroviral therapy expansion effort can be seen in Figure 2.[7] This figure



	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Denominator	2882	3864	4227	4440	4627	4895	5090	5302	5569	5744	5877	6159	6334	6596
Actively on antiretroviral therapy	837	1960	2597	2994	3079	3120	3211	3356	3585	3913	4255	4654	5123	5413
No. of plasma HIV RNA tests	4896	10,803	12,930	14,117	15,888	17,673	19,663	21,259	22,677	23,110	23,815	24,897	26,009	26,818

Figure 2. Plasma HIV RNA levels over time of all HIV-infected individuals tested in British Columbia, Canada, irrespective of whether they ever received antiretroviral therapy. Adapted with permission from Nosyk et al.[7]

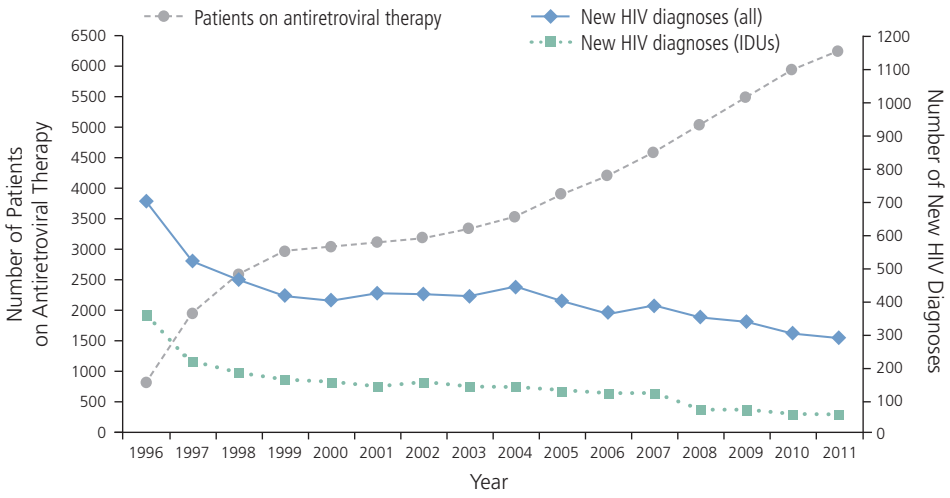


Figure 3. Changes in incidence of new diagnoses of HIV infection among injection drug users (IDUs) and in non-IDUs in British Columbia, Canada. Adapted from Montaner et al.[8]

shows the HIV RNA levels of individuals diagnosed with HIV infection in British Columbia, irrespective of whether they have ever been on antiretroviral therapy. The proportion of those with undetectable HIV RNA has increased over time, approaching 50% in 2009, along with the number of HIV-infected persons engaged in care and the number receiving antiretroviral therapy. In 2009, nearly 27,000 viral load measurements were performed on 6596 patients, 5413 of whom were on antiretroviral therapy. As shown in Figure 3, the improvement in community viral load has been accompanied by substantial reductions in new diagnoses of HIV infection among IDUs and non-IDUs.[8] The number of diagnoses of HIV infection has continued to decline in recent years. There were 301 new cases in British Columbia in 2010, 289 new cases in 2011, and 248 new cases in 2012. This progress has been achieved at a time when rates of hepatitis C virus infection have remained stable and those for syphilis, gonorrhea, or chlamydial infections have increased in the province.

HIV Testing

Further reduction of HIV transmission requires, first and foremost, enhancement of HIV testing. It is estimated that 20% of HIV-infected individuals are unaware of their infection and that more than half of new infections are attributable to this group. Numerous options are available for point-of-care testing, and there is no excuse for not implementing such strategies.

A program of routine testing in emergency departments or internal medicine wards was implemented in 3 hospitals in British Columbia with very distinct demographics. The program included only individuals with no prior HIV diagnoses and no known risk factors or indications for HIV testing. Preliminary results demonstrate that overall, there was 94% patient acceptance of the HIV screening test, with approximately 5 positive results per 1000 HIV screening tests found in this population that had no suspicion of HIV infection. The Centers for Disease Control and Prevention (CDC) has estimated that such screening is highly cost-effective in settings where rates are higher than 1 positive result per 1000 screening tests. Based on these findings, British Columbia has implemented this strategy of screening in acute care settings province-wide and hopes to see a marked reduction in the proportion of HIV-infected individuals who remain undiagnosed and unconnected to care.

HIV Treatment

For the treatment-as-prevention strategy to work optimally, treatment must begin early. The IAS–USA was the first to support more liberal guidelines encouraging early treatment, including treatment for HIV-serodiscordant couples, which it encouraged ahead of the completion of the HPTN 052 study results.[9] The recommendations of the US Department of Health and Human Services (DHHS) and, more recently, the World Health Organization (WHO) have moved in the same direction.[10,11]

Cascade of HIV Care

Increased HIV testing and guidelines encouraging earlier access to antiretroviral therapy are not sufficient for a successful treatment-as-prevention strategy. It is also necessary to strengthen the cascade of care, from diagnosis,

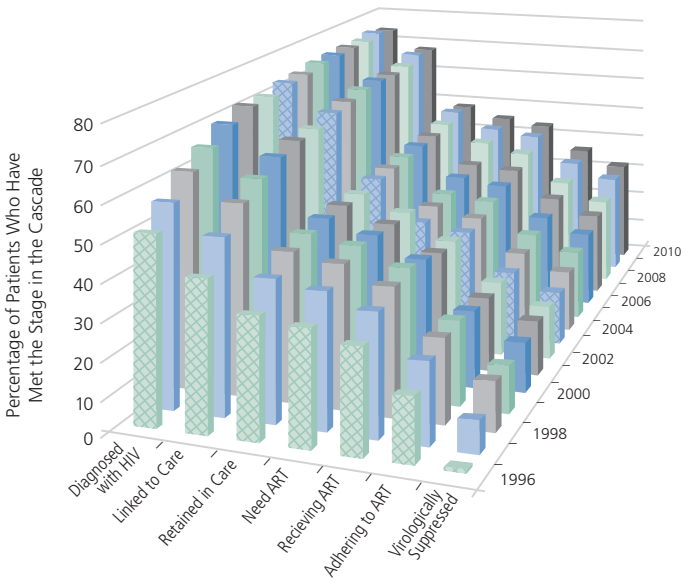


Figure 4. Changes over time in stages in the cascade of care in British Columbia, Canada: diagnosis of HIV infection, linkage to care, retention in care, and proportions of individuals needing and receiving antiretroviral therapy (ART), adhering to ART, and having sustained viral suppression on ART. Adapted with permission from Nosyk et al.[7,13]

linkage, and retention through maximizing receipt of and adherence to antiretroviral therapy among patients eligible for treatment. Strengthening of the cascade of care requires the establishment and maintenance of supportive environments in which HIV-infected individuals can access treatment and achieve optimal health outcomes.

Gardner and colleagues recently estimated that of approximately 1.1 million HIV-infected individuals in the United States, 874,000 were diagnosed, 656,000 were linked to care, 437,000 were retained in care, 350,000 needed antiretroviral therapy, 262,000 were on antiretroviral therapy, and 210,000 were adherent to antiretroviral therapy and had undetectable viral loads (approximately 19% of the entire HIV-infected population).[12] The CDC recently revised the estimated proportion of HIV-infected individuals with undetectable viral load to 28%. Whether the proportion is 20% or 30%, it is still too low to achieve optimal population health outcomes. Changes in components of the cascade of care in British Columbia over time are shown in Figure 4.[13] Current levels of viral suppression among all diagnosed and undiagnosed persons with HIV infection are estimated at approximately 40% to 50% depending on the definition of sustained viral suppression. Although the improvement in the cascade of care that has already been achieved is heartening, there is clearly more work to be done.

Programmatic Focus

A programmatic focus is needed to improve HIV care and optimize prevention. If HIV care is going to be made available throughout health care systems without a clear and aggressive focus, the effort will be diluted and the opportunity to achieve optimal prevention of HIV disease will be missed. The gains achieved in British Columbia thus far are the result of an intense programmatic focus. Of note, British Columbia remains the only province in Canada with truly free health care services, including no copayments or deductibles for HIV/AIDS-specific services (ie, antiretroviral therapy), and the only one with an interdisciplinary program dedicated exclusively to HIV. In other Canadian provinces, HIV care tends to be diluted within the health care system, and as a likely result, some provinces have seen an increase in new diagnoses of HIV.[14] Thus, the success of treatment-as-prevention programs is not only dependent on having the tools available but also on working hard to bring those tools to people in need, who often cannot effectively access the services themselves.

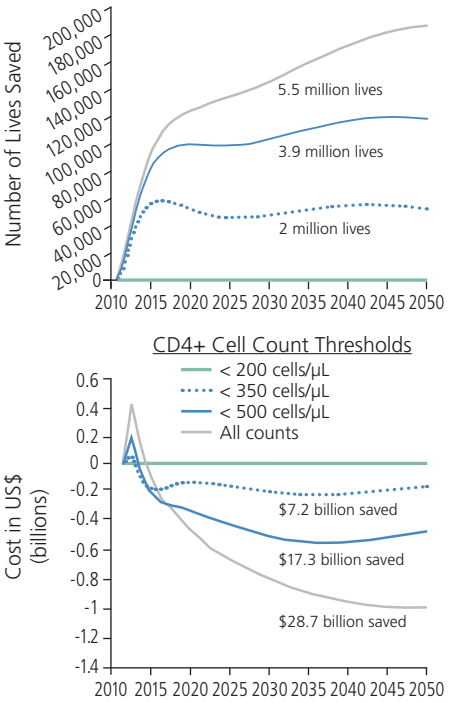


Figure 5. Estimate of lives saved by starting antiretroviral therapy at varying CD4+ cell count thresholds in South Africa (top). Costs associated with starting antiretroviral therapy at these thresholds, along with the cumulative cost savings over time (bottom). Adapted from Granich et al.[15]

Cost?

Granich and colleagues recently analyzed the cost and cost-effectiveness of starting antiretroviral treatment at various CD4+ cell count thresholds or at HIV diagnosis in South Africa.[15] As shown in Figure 5, raising the CD4+ cell count threshold for starting antiretroviral treatment is associated with millions of additional lives saved. Although expansion of treatment comes at an initial cost, over time it becomes a cost-saving endeavor. The conclusion that beckons is that there is no good reason for us not to bring more HIV-infected individuals into treatment and care—treatment as prevention saves lives and saves money.

Summary

Efforts toward the treatment and prevention of HIV infection are associated with the greatest preventive benefit from a societal perspective when the investment in improving care is focused on treating those who need it, who are relatively easy to define, and who are highly motivated to achieve their individual health goals.

There is an opportunity to optimize the health outcomes of antiretroviral therapy through focused HIV treatment-as-prevention programs. The question is whether there is the will, focus, and commitment to do it. A unique opportunity will be missed if it is not done.

Presented by Dr Montaner in March 2013. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Montaner in June 2013.

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Thank You ZATA Donors and Art Buyers

The Zimbabwe AIDS Treatment Project (ZATA) was established in 2004 to raise funds to support the University of Zimbabwe AIDS Research Centre (*photograph*) through the sale of original paintings, sculptures, and other artwork from talented Zimbabwe artists. ZATA was fortunate in being able to draw on the expertise of its Board and Advisory Board comprised of HIV/AIDS experts in both the United States and Zimbabwe—Drs Robert Schooley, Constance Benson, Thomas Campbell, James Hakim, and Margaret Borok-Williams—to name but a few.

ZATA was especially fortunate to have the support of the IAS–USA, which allowed us to sell thousands of dollars of beautiful artwork at IAS–USA presentations and workshops held in 2004 and 2005 in New York, Washington, DC, and San Francisco. Because of these and other auctions and sales throughout the United States, ZATA funds began to grow steadily. We are pleased to inform our IAS–USA friends that after 9 years of fundraising, ZATA has sent almost *a quarter of a million US dollars* to Zimbabwe, including support for talented artists who would otherwise never find an audience for their work, funds for HIV/AIDS medications and medications to treat opportunistic diseases, pharmacy and nursing salary support, funds for a clean-water well to prevent cholera, and educational support for AIDS orphans through Nancy Padian, PhD, and the University of California San Francisco.

Original oil painting by artist Peter Kwangware

The ZATA Board thanks the IAS–USA for being there with us at the beginning and for supporting our mission by allowing the sale of ZATA artwork at their course sites. ZATA also welcomes IAS–USA audiences, supporters, and contributors to visit www.zataproject.org to view and select original artwork for purchase or to make a donation to allow ZATA to continue to support the AIDS Research Centre for many years to come. The ZATA website also has information about a Zimbabwe Art and Sculpture Auction on October 19, 2013, at the Dairy Arts Center in Boulder, Colorado, for our local friends.

Sincerely,
Jane Oppenheim
President
ZATA Project Board

Perspective

Challenges in the Management of Osteoporosis and Vitamin D Deficiency in HIV Infection

Until 2013, the National Osteoporosis Foundation guidelines did not include HIV infection and highly active antiretroviral therapy as osteoporosis risk factors that should trigger dual-energy x-ray absorptiometry (DEXA) screening for low bone mineral density (BMD) in older adults, but numerous data indicate that individuals with HIV infection are at early and increased risk for osteoporosis and fracture. For this reason, experts support the use of DEXA screening for HIV-infected postmenopausal women and men older than 50 years. Factors contributing to increased risk of low BMD in individuals with HIV infection include inflammation, effects of antiretroviral therapy, and numerous patient risk factors, including vitamin D deficiency. Workup for low BMD should include assessment for fracture risk and secondary causes of low BMD, including vitamin D deficiency, hyperparathyroidism, subclinical hyperthyroidism, hypogonadism, and phosphate wasting. Bisphosphonates are the preferred treatment to prevent fracture in low BMD but are not appropriate for treating osteomalacia, which is characterized by vitamin D deficiency and phosphate wasting. This article summarizes a presentation by Todd T. Brown, MD, PhD, at the IAS–USA continuing education program held in Atlanta, Georgia, in April 2013.

Keywords: *HIV, bone mineral density, osteoporosis, fracture, vitamin D, deficiency, tenofovir, bisphosphonates, osteomalacia*

The risk of vertebral, hip, or wrist fracture in the general population dramatically increases after approximately age 65 years in women and age 70 years in men. These fractures are associated with increased mortality and morbidity. The 2008 US National Osteoporosis Foundation (NOF) guidelines recommended dual-energy x-ray absorptiometry (DEXA) screening of bone mineral density (BMD) to detect osteoporosis for people with a history of fragility fracture, women aged 65 years or older and men aged 70 years or older, and postmenopausal women and men aged 50 years to 70 years if there is concern based on risk factor profiles. HIV infection and antiretroviral therapy were not listed among the risk factors.

Numerous studies, however, have shown that HIV-infected persons are at increased risk for osteoporosis, with a meta-analysis showing an overall prevalence of osteoporosis of 15% in an HIV-infected population with an average age of 41 years and a 3.68-fold increased risk of osteoporosis compared with their HIV-uninfected counterparts.[1] Further, a study in the Massachusetts General Hospital/Partners Healthcare System involving 8528 HIV-infected persons and more than 2 million HIV-uninfected persons showed a substantially increased prevalence of fracture in HIV-infected persons (Figure 1).[2] The increase in risk was observed after approximately age 30 years in men and age 40 years in women; the difference in prevalence rates between HIV-infected and HIV-uninfected persons continued to increase with age, suggesting an HIV-age interaction with regard to fracture risk. Given these findings, Dr Brown and colleagues recommended in 2010 that DEXA screening be used for all HIV-infected postmenopausal women and men older than 50 years.[3] The 2013 NOF guidelines finally list HIV infection and antiretroviral therapy among the risk factors that should prompt DEXA screening in older individuals.

Assessing BMD and Fracture Risk

Consider the case of patient A, a 62-year-old white man who was referred to the Johns Hopkins Lipodystrophy Clinic because of body fat changes. His HIV infection was diagnosed in 1987 and he had a CD4+ cell count nadir of 22/µL. He is receiving tenofovir, emtricitabine, and efavirenz. He has a history of hypogonadism and transdermal testosterone, a history of chronic obstructive pulmonary disease, and a 60 pack-year smoking habit. He has received numerous steroid courses but has no history of fracture and no height loss. On DEXA, his T scores were -2.2 for lumbar spine

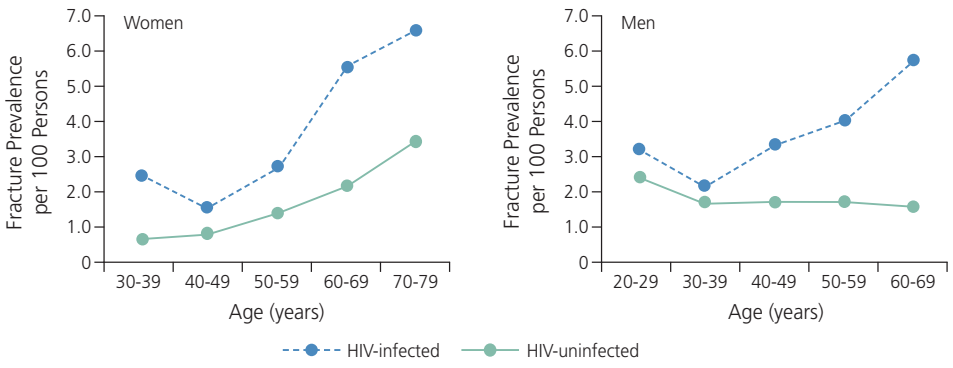

Figure 1. Fracture prevalence in HIV-infected and HIV-uninfected men and women in the Massachusetts General Hospital/Partners Healthcare System, 1996-2008. Adapted from Triant et al.[2]

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L1-L4, -2.1 for the femoral neck, and -2.3 for total hip.

According to the World Health Organization (WHO) guidelines, osteoporosis is defined by a T score below -2.5, osteopenia by a score between -1.0 and -2.5, and normal by a score above -1.0. The risk of fracture is estimated to increase 1.5- to 3.0-fold for each standard deviation decrease in T score. It is important to note that T scores are valid only in older individuals. Z scores (ie, the number of standard deviations from age-matched controls) are used in premenopausal women and men younger than 50 years of age, with a Z score below -2.0 indicating low BMD. Patient A is thus considered to have osteopenia, not osteoporosis. However, it is important to keep in mind that low BMD explains only approximately half of fracture risk.

As with many of the other metabolic complications in HIV infection, the pathophysiology of bone changes in HIV-infected patients is multifactorial but appears to include inflammation and the presence of HIV viral proteins, such as TAT and Vpr, that result in increased bone resorption and decreased bone formation. With regard to factors associated with medication use, tenofovir and certain HIV protease inhibitors (eg, ritonavir-boosted atazanavir and ritonavir-boosted lopinavir) have deleterious effects, and a 2% to 6% decrease in BMD has been observed 96 weeks after initiation of antiretroviral therapy, even in the context of viral suppression and reduced levels of inflammatory markers. Patient risk factors include low body weight, smoking, alcohol use, opiate use, coinfection with hepatitis C virus, physical inactivity, hypogonadism, and low vitamin D levels.

Given these considerations, what should be the next step in managing and treating patient A? The 2013 NOF guidelines recommend treatment for postmenopausal women and men aged 50 years and older who have hip or vertebral fractures; individuals with BMD T scores at or below -2.5 at the femoral neck, total hip, or spine on DEXA; and those with T scores between -1 and -2.5 (osteopenia) at these sites *and* a 10-year hip fracture probability of 3% or higher or a 10-year all major osteoporosis–related fracture probability of 20% or higher based on the WHO Fracture Risk Assessment Tool (FRAX®) model. FRAX assessment includes age, sex, weight, height, history of fracture, parental history of hip fracture, current smoking habits, glucocorticoid use, rheumatoid arthritis status, secondary osteoporosis status, alcohol ingestion per day, and femoral neck BMD. In the case of patient A, his 10-year risk of major osteoporotic fracture was 18% (under the treatment threshold) and his risk of hip fracture was 4.10%, making him a candidate for bisphosphonate or other treatment to reduce fracture risk.

However, before starting a patient on bisphosphonate treatment, potential secondary causes of low BMD must be evaluated. Those that should be evaluated in all patients include vitamin D deficiency, hyperparathyroidism, subclinical hyperparathyroidism, hypogonadism, and phosphate wasting, the latter of which can occur in patients receiving tenofovir. Other potential causes include idiopathic hypercalciuria, celiac sprue, multiple myeloma, mastocytosis, and Cushing syndrome.

Among these conditions, severe vitamin D deficiency and phosphate wasting are of particular note because low BMD occurring in either of these settings may be related to osteomalacia, the most important differential diagnosis in low BMD. Osteomalacia is characterized by impaired bone mineralization. The collagen matrix is normal but is not mineralized with calcium phosphate crystals. It can be accompanied by weakness, fracture, pain, anorexia, and weight loss. Osteomalacia needs to be treated not with bisphosphonates but with vitamin D and calcium and possibly phosphate replacement (if the cause is phosphate wasting). Consideration should be given to switching patients off tenofovir if they have phosphate wasting. Bisphosphonate treatment in this syndrome could actually inhibit bone mineralization.

Low Vitamin D

Consider the case of patient B, a 51-year-old white man diagnosed with HIV infection in 2001 who had a CD4+ cell count nadir of 30/µL. His plasma HIV RNA level is less than 50 copies/mL on tenofovir, emtricitabine, and efavirenz, but his CD4 + cell count remains low at 150/µL to 250/µL. He drinks 3 to 4 glasses of wine per day and is a former smoker. His sister has osteoporosis but no history of fracture. Patient B has had 2 traumatic fractures during recreational activities (boating and glade skiing). On DEXA, his T scores are -2.9 for L1-L4 (Z score, -2.5), -1.4 for the femoral neck (Z score, -0.6), and -0.8 for total hip (Z score, -0.4). On FRAX assessment, his 10-year risks are 4.7% for all osteoporotic fracture and 0.5% for hip fracture, low risks not indicative of a need for bisphosphonate treatment.

Secondary workup shows a low 25-hydroxyvitamin D level of 15 ng/mL. The rest of the secondary workup is normal: parathyroid hormone (PTH) of 44 pg/mL, calcium (Ca^{2+}) of 9.5 mg/dL, thyroid-stimulating hormone of 1.8 mU/L, free testosterone of 61 pg/mL, serum phosphate of 3.0 mg/dL, and fractional excretion of phosphate of 10%. Although vitamin D is low, it is not in the single digits, a level commonly seen in osteomalacia. Osteomalacia would also be accompanied by elevated PTH and elevated alkaline phosphatase. Patient B has vitamin D deficiency but not osteomalacia.

Vitamin D deficiency is defined as a level less than 20 ng/mL, with vitamin D inadequacy defined as a level from 20 ng/mL to 30 ng/mL. Vitamin D deficiency is very common in the general population, occurring in association with inadequate physical activity, inadequate exposure to sunlight, high body mass index, and other factors. In HIV-infected individuals, medications also play a role. For example, patients initiating antiretroviral therapy that includes efavirenz have been found to have a 5 ng/mL reduction in vitamin D levels compared with patients starting antiretroviral therapy without efavirenz.[4] This reduction is approximately

half the difference observed in the general population between summer and winter in some parts of the world, and approximately one-third that observed between white persons and black persons.

The optimal regimen for replacing vitamin D is unclear. Popular approaches are to provide replacement with ergocalciferol (D_2) at 50,000 IU once or twice per week for 8 weeks to 12 weeks or cholecalciferol (D_3) at 2000 IU/day and maintenance with ergocalciferol at 50,000 IU once or twice per month or cholecalciferol at 1000 IU/day to 2000 IU/day. It is of interest that a study examining very high replacement doses found that they did not provide protection from falls or fractures. In this study, 2256 women aged 70 years or older were randomized to receive 500,000 IU of vitamin D_3 once yearly each fall or to receive placebo and were followed up for 3 years to 5 years.[5] After the initial spike in vitamin D levels in those receiving replacement, levels declined but remained in the target range of 30 ng/mL to 50 ng/mL for all or most of the year. However, women receiving the annual high replacement dose had a statistically significant 16% increase in risk for falls (hazard ratio [HR], 1.16; $P = .003$) and a borderline statistically significant 26% increase in risk for fracture (HR, 1.26; $P = .06$). The explanation for this unexpected result is unclear, although it may be that the body's response to such a large replacement dose is to catabolize the vitamin D and eliminate it without sufficient conversion to the biologically active 1,25-dihydroxyvitamin D form.

Dr Brown's approach to vitamin D replacement is to check a patient's 25-hydroxyvitamin D levels if BMD is low or the patient has a history of falls. If levels are greater than 30 ng/mL, the patient is given vitamin D_3 at 1000 IU/day. For levels of 20 ng/mL to 30 ng/mL, a patient is given vitamin D_3 at 2000 IU/day. For levels of 15 ng/mL to 20 ng/mL, replacement is given with ergocalciferol at 50,000 IU a week for 8 weeks followed by vitamin D_3 at 2000 IU/day. For levels less than 15 ng/mL, patients receive replacement with ergocalciferol at 50,000 IU once or twice a week for 8 weeks to 12 weeks followed by vitamin D_3 at 2000 IU/day. More aggressive replacement should be used if PTH or alkaline phosphatase levels are elevated or if a patient has signs or symptoms suggestive of osteomalacia.

For management of patient B, plain films were taken of the thoracic and lumbar spine. The vitamin D deficiency was addressed by ergocalciferol replacement with 50,000 IU once a week for 12 weeks, followed by vitamin D_3 at 2000 IU/day along with 1000 mg/day of calcium. He was advised to continue exercising but perhaps avoid glade skiing.

Treatment for Low BMD

If patient B were 71 years old instead of 51 years old, there would be greater incentive to treat low BMD with a bisphosphonate, because the additional 20 years of age confers a much higher risk of fracture at the same BMD value. Management in the 71-year-old patient B would include calcium and vitamin D supplementation, smoking cessation (if he were still smoking), reduction in alcohol intake, weight-bearing exercise, and assessment of fall risk. Fall risk assessment may be as simple as asking "Are you worried about falling?" People can recognize if they are at risk for falls and change the way in which they move in their environment. Patients who acknowledge being afraid of falling and those who are otherwise at increased risk should be given a referral for physical therapy for strength and balance training.

As in the general population, the initial, preferred treatment for low BMD in individuals with HIV infection is a bisphosphonate. Women may also be treated with selective estrogen receptor modulators, and those with hot flashes can be treated with estrogen. PTH analogues are an additional option. Comparative characteristics of available bisphosphonates are shown in the Table. Alendronate and zoledronate have the best efficacy, reducing fracture risk by approximately 30% to 40%. BMD changes with risedronate are less than those with alendronate, and ibandronate has not yet been shown to reduce the risk of nonvertebral fracture. Alendronate is the only bisphosphonate currently available in generic form and is less expensive. Oral bisphosphonates are associated with gastrointestinal side effects. Adherence can be an issue, in which case the once-yearly zoledronate is an attractive option.

There is concern about how long and how often patients should take

Table. Comparison of Efficacy, Cost, Adherence, and Associated Adverse Effects of Selected Bisphosphonates

Consideration	Alendronate	Risedronate	Ibandronate	Zoledronate
Efficacy	High	Medium	Low	High
Cost (for 1 year)	$350	$1200	$1200	$1100
Level of adherence	Low	Low	Oral: low Intravenous: high	High
Gastrointestinal side effects	Yes (20%)	Yes (20%)	Oral: yes Intravenous: no	No
Osteonecrosis of the jaw	Yes	Yes	Yes	Yes
Acute phase reaction	No	No	Oral: no Intravenous: yes	Yes (approximately 10%)
Esophageal cancer	Unclear	Unclear	Unclear	No
Oversuppression of bone turnover	Yes	Yes	Yes	Yes

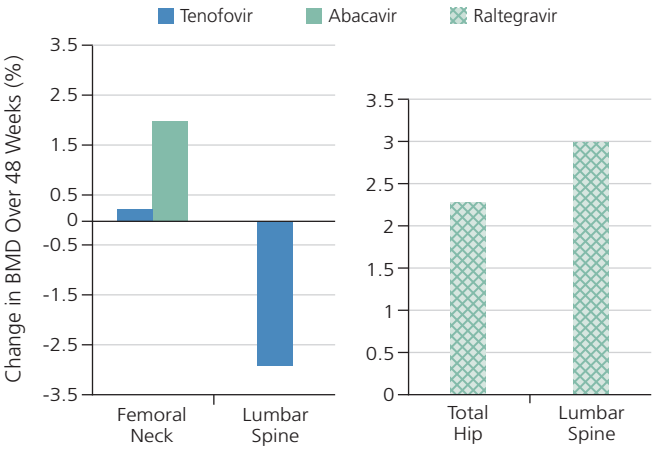

Figure 2. Effects on bone mineral density (BMD) of switching from tenofovir to abacavir (left) or to raltegravir (right) in patients with low BMD. Adapted with permission from Negredo et al and Bloch et al.[6,7]

bisphosphonates, and when they should take a drug holiday from treatment. Bisphosphonates suppress bone turnover, which is necessary for repair of microfractures that can occur with simple everyday wear and tear. As a result, prolonged use of bisphosphonates can in rare instances result in increased risk of fracture, particularly in subtrochanteric areas at the top of the femur, below the hip. Similarly, all bisphosphonates have been associated with osteonecrosis of the jaw, although this is a rare occurrence. Given the potential long-term risks, there is some belief that patients should be given a drug holiday after approximately 5 years or after 10 years in those with very low BMD. There are also concerns regarding atrial fibrillation, acute phase reactions with intravenous bisphosphonates, and esophageal cancer, although the risks of such effects are not yet well defined.

The 71-year-old patient B is receiving tenofovir. Although he has no evidence of phosphate wasting, consideration might be given to drug substitution. Recent studies have shown improvements in BMD with substitution for tenofovir in patients with low BMD (Figure 2). A study conducted over a 48-week period that randomized patients to switch from tenofovir to abacavir or remain on tenofovir showed that switching to abacavir use resulted in a marked increase in femoral neck BMD compared with continued tenofovir use; no change in lumbar spine BMD was seen in those patients switching to abacavir and it decreased in those who continued tenofovir.[6] In a single-arm study of a nucleoside analogue reverse transcriptase–sparing regimen, tenofovir was replaced with raltegravir, which resulted in marked increases in total hip and lumbar spine BMD over the 48-week study period.[7]

Conclusions

DEXA screening is recommended in HIV-infected men older than 50 years and HIV-infected postmenopausal women. In general, guidelines for treatment of low BMD in HIV-infected patients are the same as those established for the general population. It is important to consider secondary causes of low BMD, particularly vitamin D deficiency and phosphate wasting. The absolute risk of fracture should be used to help guide decisions in management and treatment.

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Perspective

HIV, Aging, and Cognition: Emerging Issues

The prevalence of HIV-associated neurocognitive disorder has not changed from the pre– to the potent antiretroviral therapy era, remaining at approximately 50%. In research settings, mild neurocognitive disorder (MND) and so-called asymptomatic neurocognitive impairment (ANI) are now more common than HIV-associated dementia. The diagnosis of ANI is misleading because functional deficits, when tested in a laboratory, and degree of neuropsychologic testing abnormalities are often comparable in patients with ANI and those with symptomatic MND. Age-related comorbidities increase the risk of cognitive impairment in HIV infection. In a cohort of patients aged 60 years or older with excellent antiretroviral therapy adherence, correlates to cognitive impairment were apolipoprotein (Apo) E4 genotype and a novel measure of the effectiveness of antiretroviral drugs in monocytes, the monocyte efficacy (ME) score, with trend associations for diabetes and nadir CD4+ cell count. Management of impairment includes ensuring that patients are on and adhere to antiretroviral therapy and addressing comorbidities. Switching from effective and well-tolerated antiretroviral therapy for patients with mild cognitive impairment is not routinely recommended, but this must still be addressed on a case-by-case basis. This article summarizes a presentation by Victor G. Valcour, MD, at the IAS–USA continuing education program held in Atlanta, Georgia, in April 2013.

Keywords: *HIV, HIV-associated cognitive disorder, asymptomatic neurocognitive impairment, fluctuating cognitive impairment, progression, age-related factors, Alzheimer's disease*

HIV-associated neurocognitive disorder (HAND) reflects a spectrum of neurocognitive impairment. Mild neurocognitive disorder (MND) is defined by mild to moderate impairment in at least 2 cognitive domains on neuropsychologic testing and is typically associated with mild to moderate impairment of function. HIV-associated dementia (HAD) is defined by more severe impairment in at least 2 cognitive domains and is associated with more severe functional impairment. A third entity identified in the research setting is asymptomatic neurocognitive impairment (ANI), which is defined as any degree of neuropsychologic testing impairment in at least 2 cognitive domains but with no identified functional impairment. As discussed below, however, closer examination reveals that functional deficits can be identified in most ANI cases when tested in the laboratory.

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Characteristics of HAND

A comparison of data on cognitive diagnoses from the pre–antiretroviral therapy era with data acquired from the CHARTER (Central Nervous System [CNS] HIV Antiretroviral Therapy Effects Research) cohort in the current era indicates that there has been no change in the prevalence of cognitive impairment, with neuropsychologic testing impairment identified in approximately 50% of patients in both eras. It is estimated that the prevalence of HAD has decreased (from 18% to <5%), whereas there is an increased prevalence of mild symptomatic impairment (from 12% to 17%) and of ANI (from 20% to 28%).[1,2]

Some of the presentations of HAND may be missed by clinicians if they focus on pure memory impairment. Common cognitive symptoms observed include deficits in concentration, attention, and working memory, for example, the inability to juggle numerous tasks at the same time. Other cognitive symptoms include mental slowing and decreased comprehension. Motor components of the disorder may also be overlooked; these may include changes in gait, poor coordination, and tremor, with patients sometimes developing Parkinsonian features. Behavioral features commonly include apathy and depression but can also include agitation or mania. Although some of these behavioral features have been attributed to stress associated with having a chronic disease, imaging studies suggest anatomic correlates in a manner that supports a more direct contribution of HIV infection.[3]

Other data from the CHARTER cohort reinforce the fact that the probability of having a cognitive diagnosis is clearly associated with the presence of comorbidities in the form of confounding factors (Figure 1).[2,4] Confounding factors may include more overt factors such as drug use and less overt factors such as cerebrovascular disease. A high burden of white matter lesions on brain magnetic resonance imaging is often used as evidence for substantial small vessel ischemic disease, although HIV encephalitis can also cause white matter changes. In patients without confounding or contributing factors, the association of low CD4+ cell count and high plasma HIV RNA level with risk of cognitive diagnosis is more evident.

Determining an accurate incidence rate for cognitive impairment and particularly documenting progression in individual patients are hindered by fluctuation of impairment, which is common. A study comparing cognitive trajectories in HIV-infected and HIV-uninfected individuals showed that approximately 30% of HIV-infected patients changed cognitive status (improving, declining, or fluctuating) over time, a rate approximately twice

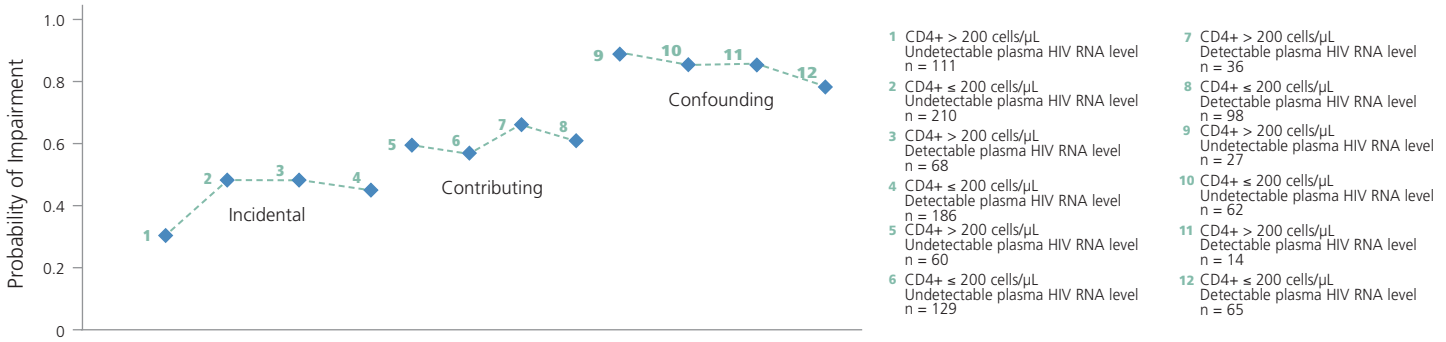

Figure 1. Probability of cognitive impairment by CD4+ cell count (below, at, or above 200 cells/μL) and plasma HIV RNA level (detectable or not) according to the presence of incidental, contributing, or confounding comorbidities. Adapted from Heaton et al.[4]

that seen for normal variation among HIV-uninfected controls.[5] Fluctuation of impairment is also suggested by findings in an ACTG (AIDS Clinical Trials Group) study reported by Robertson and colleagues. In this study, 21% of patients without cognitive impairment at baseline who either switched from failing antiretroviral therapy or started antiretroviral therapy exhibited testing performance in the impaired range after 48 weeks of treatment.[6]

It is important that clinicians convey to their patients that the course of cognitive impairment in HIV infection is typically not one of the relentless decline typical of neurodegenerative disorders such as Alzheimer's disease, which is supported by the fact that HAD remains relatively uncommon today. Thus, although many patients are afflicted by an irritating inefficiency in cognitive abilities, often affecting their quality of life and ability to perform typical work functions, progression to frank dementia is uncommon.

Asymptomatic Impairment

A recent study of more than 1500 community-dwelling HIV-infected persons with access to combination antiretroviral therapy, not all of whom had suppression of HIV RNA in plasma, showed that approximately 70% of those with nonconfounded HAND had ANI.[4] Although ANI might sound relatively innocuous, it may not be. It is commonly recognized that patients with cognitive disorders may not retain sufficient insight into their disease to self-report cognitive impairment. Yet, they are often the primary source of information about their cognitive symptoms as they come to clinical and research visits alone. Moreover, many are retired, on disability, or underemployed and may not have a complete understanding of whether they are functioning at their full cognitive potential. Further, cognitive changes may be insidious in onset, allowing for compensation without full awareness of these adjustments.

Neuropsychologic testing impairments have long been associated with functional impairment on tests of everyday functioning regardless of whether they are symptomatic or not.[7] A recent study involving neuropsychologic testing in persons aged 60 years or older in the University of California San Francisco (UCSF) HIV Over 60 Cohort showed no difference in degree of neuropsychologic testing impairment between HIV-infected individuals with ANI and those with symptomatic impairment (MND or HAD) (Figure 2, top).[8] In these same subjects and using a functional battery consisting of components for memory, judgment, driving (attention and executive function), bill paying (language and calculation), and map tasks (spatial ability), there was no difference in degree of impairment between the 2 groups (Figure 2, bottom).[8] Other studies similarly demonstrate problems with function related to employment capacity in subjects with ANI and those with MND.[9] Imaging studies from the UCSF HIV Over 60 Cohort also demonstrate broad areas of abnormal diffusion tensor imaging (DTI) suggestive of damage to white matter tracts.[10] In unpublished data from these same study participants, the DTI abnormalities correlate well with functional deficits regardless of whether subjects are symptomatic. Moreover, functional testing scores correlate to anatomic abnormalities, including the size of the corpus callosum, a major white matter structure in the brain.[11]

Individuals with ANI have a substantial risk of becoming symptomatic over time (Figure 3).[12] A major challenge in assessing and following cognitive function in asymptomatic and symptomatic impairment in HIV-infected individuals is the adequacy of proxy informants. In studies of patients aged 60 years or older at UCSF, patients are required to attend visits with a proxy informant or have one available via telephone. Although contacting informants for virtually all control and Alzheimer's disease subjects has been possible in this cohort, it has not been possible to reach 13% of informants for HIV subjects. Further, although approximately three-fourths of informants for control and Alzheimer's disease subjects live with the subjects, only 35% of HIV subject informants do so. Barriers to self-reporting are inherent among all subjects with cognitive disorders, but HIV patients may also have barriers stemming from stigma and other factors that may exacerbate the problem of acquiring accurate real-time assessments of functional capabilities.

Aging

By simply extrapolating data published by the Centers for Disease Control and

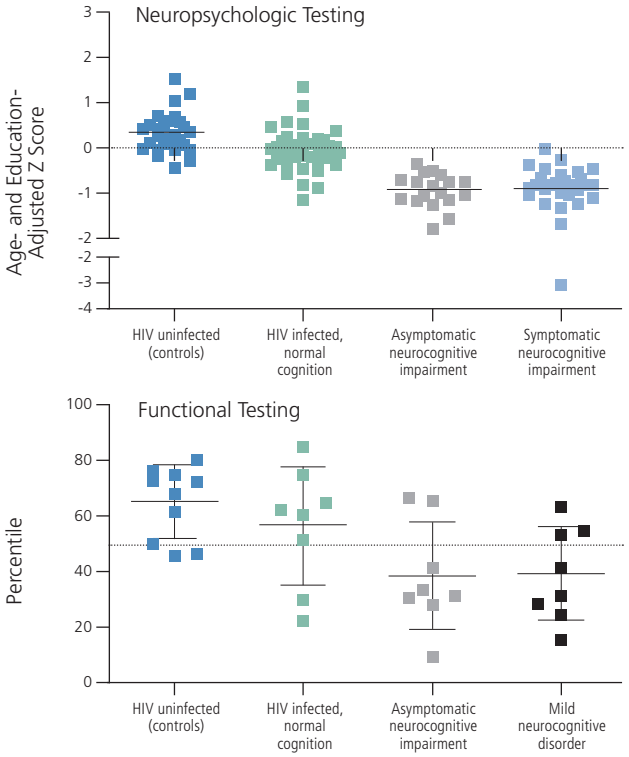

Figure 2. Similar deficits in patients with asymptomatic neurocognitive impairment (ANI) and symptomatic impairment on neuropsychologic testing performance (mild neurocognitive disorder [MND] and HIV-associated dementia combined) in the University of California San Francisco (UCSF) HIV Over 60 Cohort (top). Similar deficits on functional performance among patients with ANI and MND (bottom). Adapted from Chiao et al.[8]

Prevention (CDC), one can estimate that by 2017, 50% of HIV-infected individuals in the United States will be aged 50 years or older. The aging of the HIV-infected population, in association with effective antiretroviral therapy, might seem to be a phenomenon limited to developed countries, but this is not the case. In some areas of Africa, 5% to greater than 15% of individuals with HIV infection are older than 50 years.[13]

In the United States, most of the HIV-infected patients older than 50 years have been living with infection for a long time, with only approximately 11% acquiring infection after the age of 50 years. In the United States, many of these patients have polypharmacy and multimorbidity characterized by the interaction of comorbidities. By virtue of long-standing survival with HIV infection, often despite the death of their peers during a time when less optimal treatment options existed, these patients have characteristics of a survival cohort. This confounds the ability to understand risk factors for complications as this feature introduces heterogeneity. Although advancing age is consistently associated with declining cognitive performance in HIV infection, early data from the UCSF HIV Over 60 Cohort—ANI in 42%, MND in 53%, and HAD in 5%—do not appear to identify higher rates of impairment than rates published from younger populations.[11] Aside from survival influences, these rates may also be influenced by very high adherence to antiretroviral therapy and may thus differ from the younger CHARTER cohort.

In the UCSF HIV Over 60 Cohort, predictors of cognitive impairment consist of apolipoprotein (Apo) E4 genotype and the monocyte efficacy (ME) score, a novel measure of the effectiveness of antiretroviral drugs in monocytes,[14] with trend associations noted for diabetes and nadir CD4+ cell count. The ME score was recently defined to address the likely neuropathogenic mechanisms of infected monocytes trafficking virus to the brain as a substrate for cognitive impairment and appears to be independent of the CNS Penetration Effectiveness Score (CPE).[14,15] Factors not correlated with impairment include age (all patients were older than 60 years) and duration of HIV infection, current CD4+ cell count, plasma HIV RNA level (although most patients were fully suppressed), cardiovascular risk factors other than diabetes, and CPE score.

There is reason to be cautious about the utility of the CPE score in predicting outcomes or modifying approaches to antiretroviral therapy. Although limited by enrollment challenges, 2 randomized studies evaluated intensification of antiretroviral therapy based on CPE and neither supported the efficacy of this strategy.[16,17] One of these studies found worse outcomes with intensification for higher CPE. Findings such as these should lead to some skepticism with regard to changing regimens in patients with chronic, although possibly fluctuating, impairment. Currently, there are no data to support such a strategy as a means of preventing cognitive impairment. One must also consider that such strategies may, in fact, cause harm in patients who are otherwise tolerating or doing well on their existing regimen as it could expose them to new toxicities or impact adherence.

However, it is important to recognize that there have been clear cases of CNS escape, a phenomenon whereby HIV RNA is detectable in cerebrospinal fluid (CSF) when it is below the level of detection in plasma.[18] Such escape with concurrent clinical consequences seems to be relatively rare. Nevertheless, it complicates the approach to the evaluation of patients with cognitive disorders in HIV infection and necessitates a case-by-case evaluation.

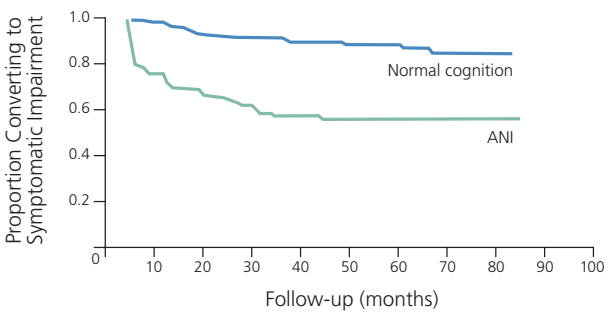

Figure 3. Conversion to symptomatic impairment over time in 347 patients with asymptomatic neurocognitive impairment (ANI) or normal findings on neuropsychologic testing in the CHARTER (Central Nervous System HIV Antiretroviral Therapy Effects Research) cohort. Adapted with permission from Grant et al.[12]

Are HIV-Infected Patients at Risk for Early Alzheimer's Disease?

It is not yet known whether HIV-infected persons are at risk for early Alzheimer's disease or a course of disease that is more aggressive. Many factors are at play in older patients that can contribute to cumulative brain damage and the clinical presentation of cognitive, behavioral, and motor disorders, including such potential age-related factors as neurodegenerative disorders, chronic immune activation, cumulative cerebrovascular comorbidities, and chronic exposure to antiretroviral agents. Studies have shown that amyloid burden in the brain increases with duration of HIV infection and appears greater among patients receiving antiretroviral therapy than in patients treated prior to the potent antiretroviral therapy era.[19,20] Although these findings are worrisome, the characteristics of these amyloid changes are not typical of the neuritic plaques seen in Alzheimer's disease.

More recently, novel brain imaging techniques have been used to investigate amyloid burden. One study using the Pittsburgh Compound B (PiB) amyloid biomarker noted no increase in amyloid among predominantly younger and cognitively normal HIV-infected subjects, whereas another study noted changes in CSF biomarkers that mimicked some characteristics of Alzheimer's disease patients.[21,22] Data from another, very small study have suggested that HIV-infected subjects with cognitive impairment have somewhat elevated brain amyloid compared with HIV-infected subjects without impairment, but this work requires confirmation in larger studies.[23]

Reports on the role of Apo E4, an Alzheimer's disease risk factor, in HIV have been mixed, and Apo E4 appears to be more relevant in older age.[24] After adjustment for CD4+ cell count, nadir CD4+ count, duration of HIV infection, and plasma HIV RNA level, patients positive for Apo E4 in the UCSF Over 60 Cohort had substantially greater deficits in global, psychomotor, and executive functions on neuropsychologic testing (Figure 4).[25] Although such findings suggest that cognitive impairment in HIV infection may share some pathways with Alzheimer's disease, it should be noted that the presence of Apo E4 has also been associated with poorer outcomes in a variety of cases, including cognitive problems associated with head injury.

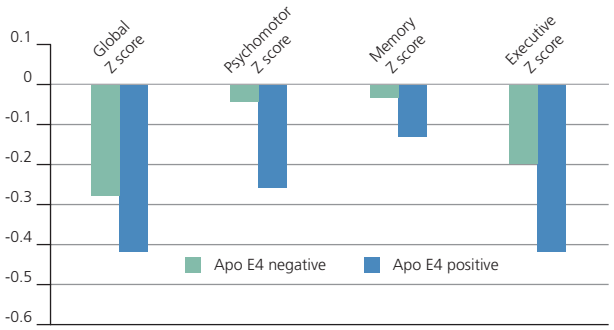

Figure 4. Association of apolipoprotein (Apo) E4 with poorer neuropsychologic testing performance shown by Z scores in patients in the University of California San Francisco (UCSF) HIV Over 60 Cohort (adjusted for CD4+ cell count, nadir CD4+ cell count, years HIV seropositive, and plasma HIV RNA level). Adapted with permission from Atputhasingam et al.[25]

Conclusions

HAND remains frequent despite the use of antiretroviral therapy. Asymptomatic cognitive impairment may not in fact be silent. Comorbid illnesses are important contributors to impairment, particularly in older age. To date, there are insufficient data to determine whether older HIV-infected patients are at increased risk of Alzheimer's disease.

The single most important intervention in managing cognitive impairment remains to ensure that patients are on antiretroviral therapy and are adherent to treatment, with suppression of HIV RNA in plasma. In patients not on treatment, the presence of cognitive impairment indicates that antiretroviral therapy is necessary. In most cases of cognitive impairment, there are insufficient data to support a standard empiric change in antiretroviral therapy if the current regimen is tolerated and plasma HIV RNA is maximally suppressed. However, cases of CNS escape have been described, necessitating an elevated index of suspicion and case-by-case management. In particular cases, lumbar puncture may be used to determine whether HIV RNA is detectable in cerebrospinal fluid, and in these cases, changing the antiretroviral therapy regimen to target this discordance is required. In addition, it is crucial to address comorbidities in patients with impairment, including drug or alcohol use, depression, and cerebrovascular risk factors.

At present, there are insufficient data to support the use of medications indicated for Alzheimer's disease, such as acetylcholinesterase inhibitors. One study failed to identify benefit for memantine, another drug approved for use in Alzheimer's disease.[26]

Exercise is a reasonable recommendation for all HIV-infected patients based on knowledge evidencing benefit for cognitive disorders in HIV-uninfected patients.[27] It can be beneficial for the psyche, helps with depression, gets people out of the house, and may reduce cerebrovascular risk factors. Cognitive stimulation may also have a role. Activities that patients find enjoyable, such as taking a course, learning something new, and being involved in an active social environment, are an easy way to introduce this and may provide a great deal of cognitive stimulation. Information on the potential benefits of formal cognitive stimulation exercises is emerging. Head-to-head comparisons of engaging in computer-based formal activities versus stimulating daily life activities are needed.

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