

*Invited Review***CROI 2024: Neuropsychiatric Complications in People With HIV****Michael J. Corley, PhD¹; Scott L. Letendre, MD²; Sam Nightingale, MBBS, PhD³**¹Weill Cornell Medicine, New York, New York; ²University of California San Diego; ³University of Cape Town, South Africa

Abstract: *The 2024 Conference on Retroviruses and Opportunistic Infections featured new and impactful findings about neuropsychiatric complications in people with HIV and other infections. Reports included new evidence from low- and middle-income countries, HIV persistence in the central nervous system, aging-related complications (including cerebrovascular disease), additional data relevant to pathogenesis, and therapeutics. Also included were new evidence of active HIV RNA transcription in cells from cerebrospinal fluid and the brain during virally suppressive antiretroviral therapy as well as links between neuropsychiatric complications or brain imaging findings in people with HIV and a) carotid artery inflammation and cerebrovascular disease, b) Alzheimer's disease genetic risk, c) social determinants of health, including exposure to pollution, and d) epigenetic aging. New therapeutic findings were presented on the cerebrospinal fluid inhibitory quotient, the effects of polypharmacy, and clinical trials of tesamorelin and telmisartan. This review summarizes these and other new findings and highlights new research directions for the neuro-HIV field.*

Keywords: HIV, CROI, neuropsychiatric complications, cognition, brain, depression, cerebrospinal fluid, neuroimaging, comorbidities

Introduction

The effects of HIV on the central nervous system (CNS) were the focus of several presentations at the Conference on Retroviruses and Opportunistic Infections (CROI) again in 2024. This summary is

Author Correspondence:

Write to Scott L. Letendre, MD, University of California San Diego, 220 Dickinson St, Suite A, San Diego, CA, 92103, or email sletendre@ucsd.edu.

organized into 5 categories that reflect the breadth of the data that were presented: reports from low- and middle-income countries, HIV persistence in the CNS, aging-related complications (including cerebrovascular disease), additional data relevant to pathogenesis, and therapeutics. These data provided novel insights into how HIV affects the brain and will continue to inform new research and treatment strategies to improve the health and welfare of people with HIV (PWH) and other infections that affect the CNS. This year's review is dedicated to Albert (Bert) Anderson, MD, who made many valuable contributions to the neuro-HIV field and coauthored this article in past years. Bert passed away in the past year and will live on in the memory of his family and all the friends, patients, and colleagues whose lives he touched.

Reports From Low- and Middle-Income Countries

Most people with HIV live in low- and middle-income countries, but most reports about the neuropsychiatric complications of HIV have historically been published by researchers in high-income countries. Several reports at CROI 2024 helped narrow that gap. Nakasujja and colleagues (Abstract 569) compared the verbal learning (a list-learning task) and memory (recall after 20 minutes) performance of 350 virally suppressed PWH with few comorbidities from the Rakai Community Cohort Study in Uganda with the performance of 250 sociodemographically similar people without HIV from the same region. No statistically significant differences were identified in performance on these brief assessments between the groups. The South African CONNECT (Cognition, Neuropsychiatric Symptoms, and Neuroinflammation Switching to Dolutegravir in Cape Town) study, presented by Nightingale and

colleagues (Abstract 553), administered a more comprehensive assessment that included tests in 7 cognitive domains to 145 PWH who switched from efavirenz- to dolutegravir-containing antiretroviral therapy (ART) and compared their performance with 95 sociodemographically similar people without HIV. PWH were more likely to have impaired cognitive performance at baseline when they were taking efavirenz (30.1% vs 11.7%; $P < .001$), but not a year later when they were taking dolutegravir (8.3% vs 7.5%; $P > .99$). Combined, these findings provide reassurance that cognitive impairment may not be as common as in past reports when the HIV-associated neurocognitive disorder (HAND) approach was used.

In contrast, Wilson and colleagues (Abstract 571) presented a study that administered a brief assessment of 5 tests to 2737 people living in Nigeria, Kenya, Uganda, and Tanzania (the AFRICOS [African Cohort Study] cohort) and found that neuropsychologic test z-scores were lower in PWH than in people without HIV whether they had achieved viral suppression ($n=1393$) or not ($n=871$). A panel of 4 inflammation-associated protein biomarkers (CXCL10, CCL2, soluble CD163, and soluble CD25) in blood indicated that greater inflammation was associated with worse cognitive performance in PWH even in those with viral suppression. None of the biomarkers were associated with worse cognitive performance in people without HIV. Consistent with prior reports, a test of motor performance, grooved pegboard, had the strongest associations, implicating subcortical processes in HIV-driven brain injury. Reports from Uganda and Lebanon also found that mental health issues appeared to be common among PWH. In a Lebanese study presented by Rizk and colleagues (Abstract 570), 61.5% of 39 participants had depression and 46.2% had anxiety, and each of these was associated with experiencing HIV stigma. In a second study from Uganda, Rubin and colleagues (Abstract 573) presented results on 277 PWH who underwent a mental health assessment. The data were analyzed using a pipeline of dimension reduction, hierarchical density-based spatial clustering, and gradient-boosted multivariate regression, and

this identified 4 clusters, 1 with minimal symptoms ($n=39$), 1 with prominent posttraumatic stress disorder symptoms ($n=76$), 1 with prominent anxiety symptoms ($n=32$), and 1 with mixed anxiety and depression symptoms ($n=130$). Early life adversity, particularly sexual abuse, emerged as a risk determinant for unfavorable mental health, highlighting the importance of addressing the psychosocial challenges faced by PWH globally.

HIV Persistence in the CNS

Several impactful presentations on HIV persistence in the CNS during ART were presented in an oral session. Kincer and colleagues (Abstract 112) presented cross-sectional findings from 78 PWH who

Low levels of HIV RNA during ART appear to stimulate an immune response that can injure the brain

had taken ART for at least 1 year and did not have neurologic symptoms. They compared HIV RNA level in cerebrospinal fluid (CSF) measured by standard (40 copies/mL) and single-copy (limit of detection of 0.25 copies/mL) assays with a panel of 12 inflammation-associated protein biomarkers as well as performance on 11 neuropsychologic tests. Higher HIV RNA level in the CSF was significantly associated with higher CSF matrix metalloproteinase-9, higher plasma tissue inhibitor of matrix metalloproteinase-1, higher CSF total protein, higher CD4+ T-cell count, and worse global and processing speed performance. These findings confirm prior findings that low levels of HIV RNA during ART appear to stimulate an immune response that can injure the brain.

Farhadian and colleagues (Abstract 114) applied single-cell immune profiling and T-cell receptor repertoire analyses to CSF and blood cells from 8 virally suppressed PWH. The group examined 129,544 CSF cells and 262,818 blood cells: transcriptionally active HIV RNA-producing cells were present in 72.7%

of CSF and 54.5% of blood samples. Most (83.6%) HIV RNA-producing cells were CD4+ central memory cells and a higher frequency of infected cells was observed in CSF than in blood. Thirty-six T-cell clones contained infected cells with 22% of clones containing infected cells shared between CSF and

Findings support that the brain is a transcriptionally active HIV reservoir even during viral suppression with ART

blood and 28% with evidence of clonal expansion, which suggests that maintenance and expansion of infected T-cell clones contribute to the CNS reservoir even during ART.

Churchill and colleagues (Abstract 113) extended findings of a transcriptionally active reservoir in the CNS by using digital droplet polymerase chain reaction HIV transcriptional profiling in postmortem brain tissue specimens from the frontal cortex of 12 virally suppressed donors. Transcription initiation (HIV TAR), early elongation (long LTR), multiple splicing (Tat/Rev), completion of HIV transcription (PolyA), and HIV p24 protein were detected in some or all specimens. Total and intact HIV proviruses were quantified by the intact proviral DNA assay and correlated with HIV transcripts. Together, the findings support that the brain is a transcriptionally active HIV reservoir even during viral suppression with ART. Tang and colleagues (Abstract 494) presented data highlighting the extended survival of infected human brain myeloid cells during ART. The group used RNAscope to show that levels ranged from 0.67 to 16.67 RNA dots/1000 nuclei in the brains of 4 virally suppressed PWH following a rapid autopsy. Brain myeloid cells were resistant to cytopathic effects after viral infection, and cell viability remained comparable between infected cells and mock-infected cells. Together, these findings indicate that infected resident cells in the brain can have extended survival and produce HIV transcripts, which present challenges for HIV cure efforts.

Aging-Related Complications

The effects of premature aging on the brain are increasingly important and were the subject of several abstracts. This area of investigation encompasses a broad range of research, including cognitive decline as PWH age into their 60s and beyond; aging-related complications including cerebrovascular disease and frailty; and indicators of biologic aging including epigenetics and brain imaging.

Cerebrovascular disease was the focus of many abstracts at this year's conference. Berry and colleagues (Abstract 567) measured circulating endothelial cell-derived microvesicles, which have been linked to cerebrovascular disease risk, in 8 untreated PWH and 8 people without HIV. Levels of circulating endothelial cell-derived microvesicles were higher in PWH, and cells treated with endothelial cell-derived microvesicles from PWH had lower nitric oxide production than those from people without HIV. Although sparse, the data supported the conclusion that HIV is associated with a phenotype of pathologic circulating endothelial cell-derived microvesicles, which could increase the risk of ischemic stroke. One important consideration in this study is that the participants were not taking ART.

Shifting to large, clinical cohorts, Chow and colleagues (Abstract 565) presented data from the WIHS (Women's Interagency HIV Study) and the MACS (Multicenter AIDS Cohort Study) on atherosclerotic cardiovascular disease in 1773 PWH and 1264 people without HIV. They found that traditional cerebrovascular disease risk factors predicted subsequent cognitive performance in all participants irrespective of HIV infection, but this was not true in subgroup analyses of women. Greater cerebrovascular risk only predicted worse subsequent cognitive performance in women with HIV but not women without HIV. A separate report from the same cohort (Abstract 566) extended this finding; cumulative exposure to several cerebrovascular disease risk factors (eg, body mass index, lipid profile, methamphetamine use) had stronger associations with cognition in women, including women with HIV, than men. This effect was modest, and they

concluded that the clinical significance is unclear but the combined findings reinforce the importance of screening for and treating cerebrovascular disease risk factors in women with HIV. Consistent with the links between vascular risk factors and cognition, Brouillette and colleagues (Abstract 597) presented another cohort of 865 adults with a mean age of 53 years who underwent longitudinal cognitive assessments for a mean duration of 7.3 years. Cognition declined in a quarter of participants, and this was associated with higher number of cardiovascular disease risk factors but not HIV disease factors.

Moving beyond clinical risk factors to brain imaging, a magnetic resonance imaging (MRI) study by Bolden and colleagues (Abstract 587) quantified white matter hyperintensity volume using high-resolution T1-weighted images in 97 PWH and 37 sociodemographically similar people without HIV. White matter hyperintensity volume is a structural indicator that is historically associated with vascular disease and cognitive performance. This volume was greater in those with cerebrovascular disease risk factors, older age, and Black race. In contrast, investigators found only a trend association with HIV status ($P=.07$), but in the subgroup of PWH, longer HIV disease duration and lower CD4:CD8 ratio were associated with larger white matter hyperintensity volume. A study by Cassidy and colleagues (Abstract 564) measured white matter hyperintensities using T2 MRI in 71 participants with acute HIV in Thailand. White matter hyperintensities increased in 75% of participants over a 2-year period following diagnosis and initiation of ART. White matter hyperintensity volume was associated with higher blood pressure, tobacco smoking, and larger body mass index, but not HIV disease indicators such as CD4+ T-cell count. In contrast with reports in people with chronic HIV infection, white matter hyperintensity volume was not associated with cognitive performance. In this same cohort, Bolzenius and colleagues (Abstract 590) found evidence of larger brain volumes in the later stages of acute HIV infection. Prior studies of large brain volumes in PWH have suggested that this may be due to the migration of immune cells to the brain and inflammation.

Vascular inflammation has been demonstrated in the heart and aorta of PWH on virally suppressive ART. Few studies have examined carotid arterial inflammation in people with HIV. During the oral session, Wilson and colleagues (Abstract 111)

Greater carotid, but not aortic, inflammation was associated with worse cognitive performance

presented data on 47 virally suppressed PWH (98% men; mean age, 60 years) with moderate to high risk for cerebrovascular disease who underwent 18F-fluorodeoxyglucose positron emission tomography to examine arterial inflammation. Greater carotid, but not aortic, inflammation was associated with worse cognitive performance. Adjusting for current tobacco smoking (which was associated with poorer cognition) attenuated the correlation. Since no people without HIV had imaging performed, investigators were unable to conclude whether the findings differed in PWH. Like the previously mentioned study from Uganda, Rubin and colleagues (Abstract 573) also collected data on social determinants of health (posttraumatic stress, early childhood stress). Not only were these associated with global cognitive performance, but the correlation between carotid inflammation and cognition became nonsignificant after adjusting for early childhood stress. This highlights the complex interplay between social determinants of health, cerebrovascular disease risk, and cognitive performance.

As noted by El Helou and colleagues in Abstract 570, depression is common among PWH. It has also been linked to stroke risk. An oral presentation by Ma and colleagues (Abstract 110) adjudicated 173 incident strokes in 13,817 people with HIV (mean age, 45 years) with at least 1 assessment for self-reported depressive symptoms. Depressive symptom severity was associated with higher stroke risk (adjusted hazard ratio, 1.16), with greater impact in those younger than 50 years. New-onset depressive

symptoms were associated with the highest stroke risk. A causative link is plausible, perhaps via common mechanisms of inflammation, depression, and cerebrovascular disease. Medications used to treat

Depressive symptom severity was associated with higher stroke risk

depression can also have metabolic adverse reactions. Alternatively, lifestyle (eg, physical inactivity) and comorbid factors (eg, stimulant use) in PWH who are depressed could increase risk. Of note, adjustment for sociodemographic factors reduced the strength of the association but did not eliminate it.

Transitioning to studies that reported on the effects of aging separate from cerebrovascular disease, Kennedy and colleagues (Abstract 599) compared the cognitive aging trajectories of 391 PWH with those of 269 people without HIV for up to 15 years. Although PWH performed worse than those without HIV at baseline, global cognitive change over time did not differ between virally suppressed PWH (76% of the cohort) and people without HIV. In contrast, those with detectable HIV RNA (>50 copies/mL) performed more poorly and had faster rates of decline, underlining the importance of maintaining virologic control as PWH age.

Discussion of the effects of aging on cognition must also consider Alzheimer's disease-type pathology. Curtis and colleagues (Abstract 589) found that an Alzheimer's disease polygenic risk score was associated with worse cognitive performance in 115 PWH with a mean age of 58 years. Polygenic risk scores were associated with smaller total gray matter volume and lower caudate cerebral blood flow. HIV disease factors were not associated with polygenic risk scores. The investigators concluded that worse cognitive performance in older PWH may be related to age-related factors that are prevalent in people without HIV. Wilson and colleagues (Abstract 591) performed a retrospective analysis of 74 cognitively impaired PWH (mean age,

67 years) who underwent amyloid positron emission tomography. Unexpectedly, they found lower rates of amyloid positivity in PWH than in 65 cognitively unimpaired people without HIV of a similar age (8.5% vs 21.5%; $P=.024$). Although this finding remains unexplained, the investigators commented that it may be due to selection bias. The eligibility

Alzheimer's disease polygenic risk score was associated with worse cognitive performance in PWH

criteria required the pattern of cognitive impairment to be typical for HIV but not for Alzheimer's disease. Indeed, 2 PWH who were excluded went on to develop Alzheimer's disease. Investigators also found no differences in cognitive decline between PWH with amyloid positron emission tomography positivity and those without it.

Data on an Alzheimer's disease mouse model were also presented by Bhattarej and colleagues (Abstract 575), with humanized T cells and microglia allowing for HIV infection in the CNS, as well as the Swedish mutation associated with familial Alzheimer's disease. Mice infected with HIV had higher levels of soluble and insoluble amyloid- β (1-42) in the brain than in those not exposed to HIV. In several areas where HIV colocalized with amyloid- β (1-42) plaques, transcriptional changes in neurons, microglia, and astrocytes were increased compared with brain areas with amyloid- β (1-42) plaques alone. Investigators interpreted this to indicate that HIV could enhance amyloid pathology, at least when untreated.

A study presented by Thomas and colleagues (Abstract 586) assessed the impact of the *apolipoprotein E* (*APOE*) $\epsilon 4$ allele (the major genetic risk for sporadic Alzheimer's disease) on white matter microstructure on MRI in 76 people (mean age, 56 years), 58 of whom were PWH. *APOE* $\epsilon 4$ carriers with and without HIV had significantly reduced fractional anisotropy in various regions of the left arcuate fasciculus compared with people without

an *APOE* $\epsilon 4$ allele. Interactions between *APOE* $\epsilon 4$ status and HIV disease were present, and after controlling for age there was a steeper disease duration-related decline in fractional anisotropy in *APOE* $\epsilon 4$ carriers in PWH than in people without HIV. Although published data in this area are inconsistent, these investigators concluded based on their findings that PWH who have *APOE* $\epsilon 4$ allele could be at greater risk of HIV brain disease as they age.

Some assessments mentioned in this section are unavailable or not routinely ordered in the clinic. The VACS (Veterans Aging Cohort Study) 1.0 index is a score that was developed in part to be easily implemented in outpatient settings. It combines

Higher cytomegalovirus immunoglobulin G titers correlated with higher VACS 1.0 index, HIV DNA level, and Epstein-Barr viral DNA

age, CD4+ cell count, HIV RNA level, hemoglobin, FIB-4 index, hepatitis C status, and estimated glomerular filtration rate. It more accurately discriminates mortality risk in virally suppressed PWH than traditional HIV disease markers alone. Yan and colleagues (Abstract 601) compared an updated index, VACS 2.0, which additionally includes body mass index and white blood cell count, with brain imaging findings and cognitive performance in 162 PWH who were age 50 years or older. The VACS 1.0 and 2.0 indexes correlated with smaller brain volumes, but only VACS 2.0 was associated with performance in some cognitive domains and was higher in PWH who were frail. They concluded that clinicians could consider incorporating this index into routine assessments. Riggs and colleagues (Abstract 602) investigated the relationship between the VACS 1.0 index and coinfection with cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Almost all the 485 virally suppressed PWH (mean age, 53 years) were seropositive for CMV (96.5%) and EBV (100%), with DNA detected in peripheral

blood mononuclear cells for EBV (95.6%) and HIV (99.2%). In contrast, CMV DNA was detected in peripheral blood mononuclear cells in 47.8%. Higher CMV immunoglobulin G (IgG) titers correlated with higher VACS 1.0 index, HIV DNA level, and EBV DNA level. The authors concluded that an immune response to CMV is an important predictor of adverse clinical outcomes in older PWH. VACS was not associated with CMV DNA suggesting that the immune dysregulation triggered by CMV (indicated by CMV IgG titers) may not be directly related to the burden of CMV DNA in peripheral blood mononuclear cells.

Strano and colleagues (Abstract 598) investigated plasma biomarkers of brain injury in older PWH. Four brain-derived protein biomarkers were measured in plasma from 102 PWH older than 50 years, and 44 people without HIV. None of the brain-derived biomarkers were significantly higher in PWH than people without HIV. In both groups, neurofilament light chain and glial fibrillary acidic protein increased with age. Higher glial fibrillary acidic protein was associated with low nadir CD4+ T-cell count, but not current CD4+ T-cell count, and a longer duration of ART, which the authors interpret as an indication of legacy brain injury with reactive gliosis from previously untreated HIV infection. Higher glial fibrillary acidic protein also had clinical correlates, being associated with reduced handgrip, balance, and digit span.

Additional Data Relevant to Pathogenesis

Several groups assessed epigenetic biomarkers as indicators of CNS complications in HIV. Johnston and colleagues (Abstract 595) used genome-wide DNA methylation profiling and derived epigenetic age estimates of 158 older PWH. Epigenetic age analysis indicated an average epigenetic age advancement of 5.4 years in older PWH. This epigenetic age advancement was associated with a lower Montreal Cognitive Assessment score adjusted for age, sex, and race. Epigenetic age estimates trended toward association with frailty state as well as with survival, with greater estimated age advancement associated with shorter survival over 7 years.

In a separate presentation, Peterson and colleagues (Abstract 594) presented DNA methylation data from 440 participants (261 women with HIV and 179 women without HIV) in the WIHS. A cell-type-specific epigenetic age estimate, the monocyte epigenetic age, was assessed and significantly associated with nonsomatic depression symptoms reflecting anhedonia. Stanley and colleagues (Abstract 592) described preliminary efforts to establish cell-type-specific single-cell transcriptomic and epigenetic signatures across various brain regions in postmortem tissues from PWH, people with opioid use disorder, and people with both conditions from the SCORCH (Single Cell Opioid Responses in the Context of HIV) consortium. The team generated single-nuclei gene expression and chromatin accessibility data on the 10x Genomics multiome platform (Single Cell Discoveries) from 4 groups, 3 regions per individual, 136 samples, and more than 1 million nuclei. They found that gene expression differed between cell types and brain regions, supporting the complexity of HIV pathogenesis in the brain. Although substantial neuro-HIV research has focused on myeloid cells and more recently lymphoid cells, the investigators conclude based on these preliminary findings that HIV disease and opioid use disorder directly or indirectly affect many other cell types that differ between brain regions and warrant further investigation.

Advances in proteomics assay methods have enhanced disease-associated biomarker detection in biologic fluids. Mukerji and colleagues (Abstract 546) investigated the relationships between baseline plasma neurofilament light, plasma glial fibrillary acidic protein, and longitudinal neuropsychologic performance on a 4-test battery over 6.2 years in 503 participants (median age, 52 years) of the ACTG (AIDS Clinical Trials Group) HIV Infection Aging and Immune Function Long-term Observation Study A5322. Higher baseline plasma neurofilament light and plasma glial fibrillary acidic protein were associated with worse baseline cognitive performance. Higher baseline plasma neurofilament light was associated with subsequent cognitive decline, but baseline glial fibrillary acidic protein was not. This confirms and extends prior published

findings on plasma neurofilament light. Coughlin and colleagues (Abstract 109) assessed the contribution of glial activation assessed by positron emission tomography imaging with the translocator protein-ligand, N,N-diethyl-2-(4-[2-fluoroethoxy]phenyl)-5,7-dimethylpyrazolo(1,5-a)pyrimidine-3-acetamide, to cognitive control and declarative memory in 25 virally suppressed PWH. The team found localized microglial activation in the prefrontal cortex, dorsal anterior cingulate cortex, and inferior parietal lobule associated with lower cognitive control. No statistically significant associations were present between microglial activation and declarative memory.

Riggs and colleagues (Abstract 596) investigated proteomic signatures of 206 virally suppressed PWH. They compared proteomic relationships with traditional neurocognitive classifications and 4 biopsychosocial phenotypes identified by unsupervised machine learning. The 4 previously defined biopsychosocial phenotypes were described as

Several novel associations with proteomics were identified, highlighting the potential value of proteomics and more discovery-driven approaches

healthy, mild cognitive impairment with moderate depressive symptoms, mild to moderate cognitive impairment with severe depressive symptoms and instrumental activities of daily living dependence, and mild to moderate cognitive impairment without depressive symptoms or instrumental activities of daily living dependence. Using the Olink Target-96 inflammation panel Genewiz, CD8 antigen, IL-17C, FGF-21, and FGF-23 were the most frequently associated proteins with neuropsychiatric classifications. Discriminant analysis correctly classified more than 75% of participants in only the phenotypes with mild to moderate cognitive impairment. Several novel associations with proteomics were identified, highlighting the

potential value of proteomics and more discovery-driven approaches.

Lozano and colleagues (Abstract 551) performed an immune checkpoint profiling study using multiparametric flow cytometry in a cohort of 50 virally suppressed PWH on stable ART (for ≥ 12 months) and 50 people without HIV. They found that higher PD-1+ CD4+ T-cell frequencies correlated with better verbal memory ($P=.0003$) and worse fine motor performance ($P=.005$). Higher TIGIT+ CD4+ T cells were found to only correlate with worse verbal memory in PWH ($P=.01$). The group cocultured CD4+ T cells expressing immune checkpoint markers with neuroblastoma cells and found PD-1+ CD4+ T cells increased PD-L1 ligand expression and increased tumor necrosis factor (TNF)- α protein production. PD-L1 blockade reduced the expression of ligand PD-L1, but TNF- α did not decline, highlighting the complex interaction of immune checkpoints on T cells with neuronal cells.

Using data and biospecimens from ACTG A5322, Giron and colleagues (Abstract 549) conducted glycomic biomarker profiling in 40 PWH with longitudinal plasma samples over 8 years (10 in each of 4 subgroups defined by sex and cognitive impairment). Cognitive impairment was associated with higher levels of several proinflammatory bisected and agalactosylated IgG glycans. Many of the associations were present in both sexes but some were present only in women. Consistent with their proinflammatory roles, these glycans, specifically G0FB, correlated with higher levels of the inflammatory marker TNF- α . Cognitive impairment was also associated with lower levels of glycans that contain the antiinflammatory sialic acid and fucose. Among inflammation markers, interleukin-10 (IL-10) and sCD14 exhibited positive correlations with cognitive impairment. Although the sample size is small, these exploratory findings suggest aging- and inflammation-associated glycomic dysregulations are linked to the presence of cognitive impairment in PWH on ART in a sex-dependent manner.

Additional findings relevant to the social determinants of health were also presented. Cooley

and colleagues (Abstract 581) examined the effects of recent air pollution exposure in the St. Louis, Missouri, region on cognition, immunophenotyping, and plasma biomarkers of inflammation and neurodegeneration in 227 PWH and 107 people

Higher recent exposures to PM2.5, PM10, and low-volume lead were associated with worse learning, delayed recall, worse executive functioning, and worse global cognition in people with HIV and people without HIV

without HIV. Pollution monitoring data from the US Environmental Protection Agency were used to calculate the average exposure to pollutants in the week before assessment. The average inhalable particulate matter (PM) exposure over the past calendar year was estimated using satellite data from the US National Aeronautics and Space Administration. Higher recent exposures to PM2.5, PM10, and low-volume lead were associated with worse learning, delayed recall, worse executive functioning, and worse global cognition in PWH and people without HIV. Higher recent ozone and PM2.5 exposure was associated with higher levels of myeloid activation (soluble CD14, soluble CD163) in PWH. Higher recent ozone and PM10 exposures were associated with higher markers of neurodegeneration (neurofilament light, glial fibrillary acidic protein) in PWH and people without HIV. The impact of sociodemographic factors as classifiers of cognitive profiles compared with neuroimaging was also explored in an analysis of 225 PWH (Abstract 583). Sociodemographic features, but not clinical or neurologic features, were the strongest distinguishers of cognitive profiles in PWH. Specifically, lower education and worse premorbid intelligence quotient (estimated by the Wide Range Achievement Test 3) were identified as risk factors for worse cognitive performance.

Therapeutics

Past published reports have identified that anti-retroviral drugs, such as efavirenz and dolutegravir, may have adverse neurologic effects, including effects on sleep, mood, and cognition. Most of these have focused on individual drugs rather than combinations of drugs, as they currently are prescribed. Parra-Rodriguez and colleagues (Abstract 554) addressed this by analyzing data from 1928 assessments in 1072 PWH (mean, 1.8 assessments) residing in the US. The most common regimens in this cohort were: (1) dolutegravir, abacavir, lamivudine (22%); (2) elvitegravir, cobicistat, tenofovir alafenamide, emtricitabine (14%); and (3) efavirenz, tenofovir disoproxil fumarate, emtricitabine (10%). Tenofovir (either formulation) and emtricitabine combined with darunavir (and cobicistat), rilpivirine, or efavirenz were associated with worse cognitive performance over time than other regimens, particularly in memory and executive functioning. One reason this may occur is interindividual differences in pharmacogenetics, which can lead to substantial differences in metabolism and elimination of antiretroviral drugs.

Zhao and colleagues (Abstract 556) investigated the pharmacogenetics of neuropsychiatric adverse events in 128 PWH in South Africa within 14 days of switching from efavirenz, tenofovir, emtricitabine to dolutegravir, tenofovir, lamivudine. Participants were randomly assigned to receive supplemental dolutegravir (50 mg daily; $n=65$) or placebo ($n=63$). Seventeen (13.3%) reported insomnia after 2 weeks, but this did not differ between arms. A trend toward higher dolutegravir exposure did occur in those with UGT1A1 rs887829 homozygous TT genotype ($P=.058$) and the CYP2B6 slow efavirenz metabolizer genotype was associated with lower dolutegravir exposure, but this was only statistically significant in those who received supplemental dolutegravir ($P=.006$). Although this pharmacogenetic analysis identified associations with dolutegravir concentrations, the clinical relevance is uncertain since neither the genotypes nor the drug concentrations were associated with insomnia.

Another issue related to HIV therapeutics is the distribution of drugs into protected compartments, like the CNS. A limitation of some past published studies, however, is that they again considered only 1 antiretroviral drug at a time. Avedissian and colleagues (Abstract 558) addressed this by modeling antiretroviral drug concentrations for an entire regimen in CSF. The 44 participants took regimens that included tenofovir disoproxil fumarate and emtricitabine and 1 of 6 other drugs (efavirenz, atazanavir [with ritonavir], raltegravir, elvitegravir [with cobicistat], darunavir [with ritonavir], or dolutegravir). They calculated a CSF inhibitory quotient for each drug as a ratio of modeled CSF trough to published 50% or 90% inhibitory concentration values and then calculated the geometric mean of CSF inhibitory quotients of all drugs in each participant's regimen. They found that higher CSF inhibitory quotient for the entire regimen was associated with lower HIV DNA level in CSF ($P=.027$) and better global cognitive performance ($P=.05$), but not with a panel of 6 inflammation-associated biomarkers. Although the findings of this small study should be confirmed, they reinforce the potential value of optimizing ART to protect the CNS.


Beyond ART, the search continues for interventions that may prevent or treat the neuropsychiatric disorders that occur in PWH. Ellis and colleagues (Abstract 552) reported the early results of a clinical trial of tesamorelin, a synthetic growth-hormone-releasing hormone, for the treatment of cognitive impairment in PWH who also had abdominal obesity (men, waist circumference ≥ 95 cm; women, waist circumference ≥ 94 cm or waist-to-hip ratio ≥ 0.88). Participants were randomly assigned to start a 24-week course of tesamorelin (1.4 mg by subcutaneous injection daily) immediately ($n=43$) or after a 24-week delay ($n=30$). This initial report compared the arms after 24 weeks and, although waist circumference improved more in those who received tesamorelin, cognitive performance did not. Although these preliminary findings do not support the use of tesamorelin for cognitive impairment, additional analyses are underway, including analyses of brain imaging.

Corley and colleagues from the SEARCH018/RV408 study group (Abstract 593) applied a new ultra-low-input genome-wide DNA methylation profiling assay to CSF cells obtained from 21 men

A cell-type-specific epigenetic age estimate, the monocyte epigenetic age, was assessed and significantly associated with nonsomatic depression symptoms

with acute HIV infection who were randomly assigned 2:1 to initiate treatment with ART and with or without the antiinflammatory drug, telmisartan, for 48 weeks. At 48 weeks, those who received telmisartan had 11,433 differentially methylated loci (mean difference in DNA methylation, $\geq 10\%$), including the marker of proliferation Ki-67 (*MKI67*), inflammatory gene *IL1B*, immune checkpoint receptor gene *LAG3*, central regulator of stress response gene *CRH*, and interferon-stimulated gene *IFI27*. Twenty-four weeks later, only 5.46% of the differentially methylated loci in CSF cells were still present. Although telmisartan did not appear to alter a small panel of inflammation and neuronal injury biomarkers in CSF, its long-term epigenetic effects may warrant further investigation.

In addition to ART, PWH are often prescribed numerous other medications. As a result, polypharmacy (use of at least 5 prescribed drugs other than antiretroviral drugs) is more common among PWH than people without HIV and is associated with worse neuropsychiatric and other health outcomes. Using data from 870 participants in ACTG A5322, Paul and colleagues (Abstract 555) applied an unsupervised machine learning method, hierarchical density-based spatial clustering, to identify subgroups based on performance on a four-test neuropsychological battery and then compared the results with polypharmacy and hyperpolypharmacy (use of at least 10 prescribed drugs other than ART). Analyses identified 8 cognitive clusters, one of which performed well on all tests (the healthy cluster). Polypharmacy or hyperpolypharmacy was

more common in 3 clusters (polypharmacy, 6 and 8; hyperpolypharmacy, 7 and 8) than in the other clusters. Compared with the healthy cluster, the clusters that had more frequent polypharmacy or hyperpolypharmacy (6, 7, 8) included more women and Black or Hispanic people. Consistent with the presence of polypharmacy, people in these clusters were also more likely than the other clusters to have multiple medical diagnoses, including cardiovascular disease, diabetes mellitus, hepatitis C, peripheral neuropathy, and substance use. If validated, these findings could help identify PWH suffering adverse effects from polypharmacy based on just 4 neuropsychological tests. 

All cited abstracts appear in the CROI 2024 Abstract eBook, available online at www.CROIconference.org

The IAS–USA will identify and resolve ahead of time any possible conflicts of interest that may influence CME activities with regard to exposition or conclusion. All financial relationships with ineligible companies for the authors and planners/reviewers are below.

Financial relationships with ineligible companies within the past 24 months: Dr Corley reported no relevant financial relationships with ineligible companies. (Updated June 6, 2024) Dr Letendre reported grant funding paid to his institution from Merck & Co, Inc. (Updated June 5, 2024) Dr Nightingale reported no relevant financial relationships with ineligible companies. (Updated June 6, 2024)

Reviewer 1 reported consulting or advisor fees from Antiva, Assembly Biosciences, Generate Biomedicines, and Gilead Sciences, Inc. (Updated March 6, 2024) Reviewers 2 and 3 reported no relevant financial relationships with ineligible companies. (Updated March 6, 2024)

All relevant financial relationships with ineligible companies have been mitigated.

Top Antivir Med. 2024;32(4):513-522.
©2024, IAS–USA. All rights reserved.