Invited Review

CROI 2025: Neuropsychiatric Complications in People With HIV

Michael J. Corley, MA, PhD[1]; Phillip Chan, MBChB, PhD[2]; Sarah B. Joseph, PhD[3]

[1]University of California San Diego; [2]Yale School of Medicine, New Haven, Connecticut; [3]University of North Carolina at Chapel Hill

Abstract: *The 2025 Conference on Retroviruses and Opportunistic Infections (CROI) showcased advances in understanding neuropsychiatric complications among people with HIV (PWH). This review synthesizes key findings related to central nervous system (CNS) reservoirs, neuropathogenesis, and biomarkers of brain health. Emerging data underscore the persistence of HIV in brain tissues despite antiretroviral therapy (ART), with compartmentalization occasionally observed in the spinal cord and brain, and evidence suggesting that HIV-infected cells may contribute to chronic inflammation in the CNS. Single-cell and epigenetic profiling of cerebrospinal fluid cells revealed immune dysregulation in myeloid and B cells, suggesting ongoing CNS dysfunction during suppressive ART. Longitudinal neuroimaging and cognitive studies reinforced that incomplete or unstable HIV suppression correlates with worse brain outcomes. Notably, higher blood phosphorylated tau 217 and systemic inflammation predicted cognitive decline in aging PWH. Promising therapeutic avenues included observations that glucagon-like peptide-1 receptor agonists, such as semaglutide, improve visuospatial performance in PWH and cannabinoid receptor 2 agonists reduced neuroinflammatory pathways in preclinical models. Additionally, early initiation of ART was associated with normalization of brain volumes and attenuation of neuronal injury markers. Together, these findings highlight the complexity of neuro-HIV interactions and underscore the need for targeted interventions to protect brain health in PWH.*

Keywords: biomarkers, central nervous system, cognitive decline, CROI, early antiretroviral therapy, epigenetics, HIV, long COVID, neuroinflammation, neuropsychiatric complications, reservoirs, semaglutide

Introduction

At the 2025 Conference on Retroviruses and Opportunistic Infections (CROI), a number of presentations highlighted the evolving understanding of the complex effects of HIV on the central nervous system (CNS). This review synthesizes findings on viral and immunologic mechanisms of neuropathogenesis, novel neuroimaging and biomarker approaches, and implications for early and long-term antiretroviral therapy (ART). Highlighted work includes the potential role of emerging treatments such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and cannabinoid modulators for neuropsychiatric complications in people with HIV (PWH). Cure-related research examining HIV persistence in the CNS and the potential for continued dysregulation of cells in the CNS during ART is also discussed. Finally, emerging findings concerning the impact of SARS-CoV-2 infections on the CNS are presented.

HIV Central Nervous System Reservoirs

HIV persistence in the CNS during ART was discussed in 2 oral sessions and in poster presentations. A great deal of interest remains in characterizing HIV in brain tissues, particularly in tissue from individuals who are virally suppressed. To address this issue, Trunfio and colleagues (Abstract 168) utilized postmortem tissue collected from 20 people (18 who had been virally suppressed; 2 who had been viremic) enrolled in the University of California San Francisco Last Gift Cohort to examine HIV-infected cells in primary peripheral blood mononuclear cells (PBMCs) and 8 CNS tissues, with an emphasis on viral persistence in the spinal cord. Proviral DNA and cell-associated (CA)-RNA levels were quantified in autopsy samples from 20 participants. Examination of proviral diversity in samples from 8 participants

Author Correspondence
Write to Sarah B. Joseph, PhD, University of North Carolina at Chapel Hill, 450 West Drive, Chapel Hill, NC, 27599-7295, or email sbjoseph@email.unc.edu.

Published May 21, 2025 © IAS–USA

revealed that diversity was low in the brain. In contrast, viral diversity in the spinal cord was high and reached levels similar to those in PBMCs. Furthermore, they identified evidence of compartmentalized HIV in the CNS (brain or spinal cord) of some donors as well as examples of frequent viral migration between compartments. This illustrates that HIV-infected cells in the CNS may either represent persistent reservoirs or HIV-infected cells trafficking through that compartment.

Several abstracts raise questions about how to distinguish persistent CNS reservoirs from HIV-infected CD4+ T cells trafficking through the CNS

Eddine and colleagues (Abstract 587) used phylogenetic analyses to examine potential CNS reservoirs in postmortem tissue from 5 people who had been on ART for longer than 2 years. They examined proviral promoter sequences in brain tissue (frontal lobe) and in the periphery (gut, spleen, and lymph nodes) to examine whether there was evidence that proviral promoters in the brain were genetically or functionally distinct from those in the periphery. They did not observe compartmentalized promoter sequences in the brain. In 2 people, they observed identical sequences in the brain and periphery, possibly due to migration between compartments. They were also able to show that promoters from the brain and peripheral tissues were functional and responded similarly to latency-reversing agents.

To explore whether CNS reservoirs have pathogenic effects during ART, Byrnes and colleagues (Abstract 630) examined inflammation and HIV DNA in frontal cortex tissue from PWH who were viremic (n = 17) and who were virally suppressed (n = 18). Consistent with previous studies, there was no difference in the frequency of HIV-infected cells in brain tissue from people who were viremic and those who were suppressed. Antiviral type I interferon signaling (Mx1) was positively correlated with the frequency of HIV-infected cells in brain tissue from suppressed people. Although the mechanistic relationship between HIV persistence in the brain during ART and interferon signaling is unknown, this finding raises the possibility that HIV-infected cells could contribute to inflammation in the brain during ART.

Given the challenges to studying HIV reservoirs in brain tissue, several groups presented studies examining HIV persistence in the cerebrospinal fluid (CSF) or using ex vivo models of CNS reservoirs. CSF is relatively easy to sample and may be a site of HIV persistence during ART. Many studies examined HIV in the CSF before or during ART and the relationship between viral persistence in the CSF and neuropathogenesis. Kincer and colleagues (Abstract 588) examined the cellular source of HIV RNA in the CSF of 109 PWH who were untreated and enrolled in Italy, India, Sweden, and the US. Higher HIV RNA levels in the CSF were associated with adverse outcomes, including increased CNS inflammation, monocyte/macrophage activation, neurologic symptoms, and neuronal damage. They also used genetic and phenotypic analyses to show that HIV RNA in the CSF can be derived from HIV-infected CD4+ T cells trafficking through the CNS and releasing virus, or from replication in either CD4+ T cells or macrophage/microglia in the CNS. This and other studies (see Abstracts 168 and 587) illustrate challenges to distinguishing persistent CNS reservoirs from HIV-infected CD4+ T cells trafficking through the CNS.

Higher HIV RNA levels in the CSF were associated with adverse outcomes including increased CNS inflammation, monocyte/macrophage activation, neurologic symptoms, and neuronal damage

In recent years, there has been great interest in examining CSF cells as a potential reservoir and as a measure of inflammation/cellular dysregulation in the CNS during ART. Using sophisticated single-cell multiomics approaches, 2 studies led by Farhadian and colleagues examined diverse features of CSF cells, including expression, chromatin accessibility, and immune function. In the first, Filippidis and colleagues (Abstract 607) examined B cells in CSF and blood to identify differences in B-cell receptor (BCR) repertoire and transcriptomes between PWH on ART (n = 13) and people without HIV (PWoH) (n = 11). Memory B cells (MBCs) in the CSF of PWH display expression patterns consistent with reduced antigen presentation and interferon signaling. The implications of impaired MBC responses in the

CNS of PWH remain unknown. In the second study, Corley and colleagues (Abstract 170) explored whether epigenetic changes to myeloid cells in the CSF leads to immune dysfunction in the CNS of PWH. They compared CSF cells from neurologically asymptomatic PWH on suppressive ART (n = 14) and demographically matched PWoH (n = 12). CSF cells from a subset of these people (PWH, n = 6; PWoH, n = 5) were examined using a single nucleus multiomic platform (assay for transposase-accessible chromatin using sequencing [ATAC-Seq] + RNA sequencing [RNA-Seq]) (10x Genomics), which revealed that CSF cells from PWH and PWoH had cell–type-specific open chromatic regions. However, they also observed cell–type-specific differences between cells from PWH and PWoH, including that CSF dentritic cells from PWH had more accessible chromatin and had impaired antigen presentation and antiviral responses relative to cells from PWoH. These studies suggest changes to specific subsets of immune cells may contribute to ongoing dysfunction in the CNS during ART.

Many presentations at CROI 2025 explored how early initiation of ART may improve brain health

In a unique longitudinal study of 16 men on long-term ART and enrolled in ACTG (AIDS Clinical Trials Group) A5341s, Cyktor and colleagues (Abstract 169) examined changes in HIV cell-free RNA (cfRNA) and cell-associated DNA (CA-DNA) levels, neuronal injury, and inflammatory markers in CSF. Although CA-DNA was detectable in approximately half of the samples, HIV cfRNA was only detected in 4% of the samples. In this cohort of durably suppressed people, there was no evidence of longitudinal changes in CA-DNA, inflammation, or neuronal injury in the CSF. In addition, markers of inflammation, and neuronal injury were not related to the number of timepoints at which a person had detectable CA-DNA.

An ongoing consideration for HIV cure strategies is whether they will impact the brain. Using PBMCs longitudinally collected from 64 PWH on ART, Suzuki and colleagues (Abstract 627) used magnetic resonance spectroscopy (MRS) to show that residual HIV RNA expression in PBMCs was negatively associated with N-acetyl aspartate (NAA) level, a marker of neuronal health, and positively associated with viral blips in the blood. Together, these findings suggest that people with lower levels of HIV expression during ART may be at reduced risk of brain injury and may be better candidates for cure interventions.

Early Antiretroviral Therapy and Brain Health

Early initiation of ART has many well-established benefits, including reducing the risk of developing AIDS-related illnesses and transmitting HIV. Many presentations at CROI 2025 explored how early initiation of ART may improve brain health. At a population level, Lam and colleagues (Abstract 636) examined a cohort of older PWH to examine whether delays in HIV diagnosis or ART initiation are associated with greater risk of developing dementia later in life. They conducted a retrospective cohort study including 23,201 PWH aged older than 50 years who received care at Kaiser Permanente Healthcare Systems in California, Maryland, Virginia, and Washington, DC, between 2000 and 2023. During a mean follow-up period of 6.8 years, the team observed 748 cases of incident dementia. Additionally, low CD4+count (<200 cells/μL) at the first ART prescription was associated with a greater risk of developing dementia (adjusted hazard ratio [aHR], 1.24; 95% CI, 1.03-1.49), highlighting the importance of continuing assertive HIV screening and ART initiation in the community.

Three abstracts examined PWH who initiated ART early to assess neurologic outcomes in the first year of HIV infection. In a CSF study, Chan and colleagues (Abstract 615) compared the levels of CSF neurofilament light (NFL) between PWoH and participants from the RV254 Thai acute HIV infection (AHI) study during pre-ART AHI and at follow-up visits after immediate ART initiation during AHI. After adjusting for the effect of age on NFL levels, RV254 participants exhibited higher CSF NFL levels than PWoH during pre-ART and follow-up visits, up to 240 weeks post ART, despite concomitant plasma HIV suppression. Although only 2% of PWoH had elevated CSF NFL, NFL was elevated in 15% of RV254 CSF samples collected during pre-ART AHI, and in 5% to 9% of RV254 CSF samples collected from 24 to 240 weeks post ART. Kelentse and colleagues (Abstract 598) examined longitudinal changes in plasma (n = 336) and CSF NFL (n = 166) levels in PWH who initiated ART within the first year of HIV infection. The team demonstrated a strong correlation between plasma and CSF NFL levels, and they observed a trend (not statistically

Published May 21, 2025 © IAS–USA

significant) of increasing CSF NFL levels during the pre-ART period. Surprisingly, they did not see changes in plasma or CSF NFL levels after ART initiation, despite 98% of participants achieving plasma HIV suppression during CSF sampling post ART.

Paul and colleagues (Abstract 167) compared the volumetric brain changes between 119 RV254 AHI study participants who initiated ART during AHI and 45 PWoH over 96 weeks of follow-up. They observed larger volumes in the hippocampus and thalamus and lower volumes in the amygdala and nucleus accumbens among PWH than among PWoH during the first scan (ie, pre-ART AHI). Additionally, larger hippocampal and caudate volumes were correlated with worse depressive symptoms and lower cognitive performance in a 4-test battery at week 0. However, volumetric differences between groups were not observed in the week-96 follow-up scans. The team did not observe any increased loss of brain volume in the PWH group compared with the PWoH group. The findings suggest normalization in brain volumes following ART initiation during AHI with subsequent HIV control.

Importance of Maintaining HIV Suppression

Three abstracts explored the importance for brain health of maintaining plasma HIV suppression using neuroimaging, cognitive assessments, and biomarker measurement. Kennedy and colleagues (Abstract 591) examined the longitudinal relationships between brain volumes in magnetic resonance imaging (MRI), cognition, and aging in 259 PWoH and PWH with or without viral suppression (n = 260 and n = 84, respectively). The application of a 4-test cognitive battery (Category Fluency, Hopkins Verbal Learning Test-Learning Scale, Trails A, and Trails B) and generalized additive mixed models in statistical analysis showed similar slopes of change in age vs brain volumes and age vs cognitive function in PWoH and PWH with HIV suppression. However, viremic PWH demonstrated a greater decline in cognitive test performance than the other 2 groups.

Strain and colleagues (Abstract 590) applied diffusion tensor imaging (DTI), a type of diffusion-weighted MRI sequence based on water molecule movement, to examine white matter (WM) changes in 111 PWoH and 193 PWH stratified by plasma HIV suppression and cognitive impairment status. Compared with virally suppressed PWH, viremic PWH exhibited reduced WM integrity in the brain, indicated by a decrease in fractional anisotropy (FA) and an increase in mean diffusivity (MD) and radial diffusivity (RD). These DTI metrics did not differ between PWH with and without cognitive impairment. Chun and colleagues (Abstract 594) examined the anatomic heterogeneity of the brain using MRI in PWH, with a machine learning approach termed heterogeneity through discriminative analysis (HYDRA). Comparing structural brain MRI data between 366 PWH and 244 PWoH, 3 clusters of PWH with distinctive structural brain features were identified. The first cluster (28%) displayed cerebral atrophy in the lateral occipital and paracentral regions, with increased corpus callosum volume. The second cluster (25%) had widespread cortical volumetric increases, and the third cluster (47%) exhibited widespread cortical and subcortical atrophy and enlarged ventricles. The third cluster, which exhibited the worst structural brain changes, also demonstrated the worst performance in psychomotor speed and global deficit score (GDS), along with the worst virologic control among the 3 cluster groups. Together, these neuroimaging reports highlight the importance of sustained HIV suppression.

Incomplete or unstable HIV suppression is associated with worse neuroimaging results and cognitive test performance

Calcagno and colleagues (Abstract 600) examined the neurologic impact of a complicated ART history (heavily treatment experienced [HTE]), defined by the presence of at least 4-class drug resistance. They compared the levels of blood-based biomarkers of the CNS, including NFL for neuroaxonal injury, total tau protein for neurodegeneration, and glial fibrillary acidic protein (GFAP) for astrocyte activation, between HTE-PWH with or without plasma HIV suppression (n = 106 and n = 32, respectively) and controls (PWH without HTE, n = 84). The analysis revealed lower levels of NFL, tau, and GFAP in HTE-PWH than in the control group. Surprisingly, despite HIV viremia and a substantially reduced CD4+ T-cell count, HTE-PWH without HIV suppression had the lowest level of NFL, technically implying the lowest level of ongoing neuroaxonal injury among the 3 groups. These findings may highlight the potential challenges of utilizing blood-based NFL measurements in CNS research, as its levels are

Published May 21, 2025 © IAS–USA

substantially influenced by age and comorbidities, such as renal impairment and peripheral neuropathy.

In a longitudinal cohort of 43 PWH on ART with HIV RNA levels in plasma and CSF under 50 copies/mL, Cysique and colleagues (Abstract 628) examined whether very low levels of HIV RNA in plasma and CSF (measured by single-copy assay with a detection limit <0.3 copies/mL) are associated with neurocognition,

Older PWH who have higher levels of blood p-tau217 showed a greater decline in MoCA performance

CSF neopterin, and levels of brain metabolites on MRS. Participants were examined at baseline and every 6 months for 24 months. Greater CSF RNA level was associated with higher CSF neopterin level, and higher CSF neopterin level was associated with worse measures on MRS, including lower N-acetyl aspartate and higher myo-inositol levels. Although the mechanistic relationship between low levels of HIV RNA in the plasma/CSF during ART and inflammation are unknown, these results raise the possibility that even small amounts of HIV RNA may contribute to ongoing inflammation in the CNS during ART.

The availability of ART with improved barriers against HIV drug resistance has fueled the use of 2-drug ART regimens (2DRs) rather than traditional 3-drug regimens (3DRs) in ART-naive and virally suppressed PWH. To date, data regarding the neurologic impacts of 2DRs use remains limited. In a study involving 238 ART-naive PWH, Henderson and colleagues (Abstract 605) compared plasma biomarkers and cognitive outcomes between PWH who commenced darunavir/ritonavir with either tenofovir disoproxil fumarate/emtricitabine (ie, 3DR) or raltegravir (ie, 2DR) in a 1:1 ratio. Over 96 weeks, the 2 groups demonstrated similar changes in composite cognitive test performance, determined by a battery covering 7 cognitive domains. Furthermore, both groups demonstrated statistically similar changes in plasma biomarkers, including NFL, GFAP, cluster of differentiation 14 (sCD14), C-X-C motif chemokine ligand 10, and interleukin-6, except for a greater decline in neopterin in the 2DR group. Similarly, Renborg and colleagues (Abstract 620) evaluated the changes in CSF biomarkers in 20 virally suppressed PWH who switched from 3DR to dolutegravir/lamivudine (2DR). During a mean follow-up duration of 384 days, all participants' virus remained suppressed in blood. One participant developed asymptomatic CSF HIV escape with CSF HIV RNA level of 70 copies/mL, without elevation of CSF white blood cell (WBC) count or CSF NFL level. At the group level, there were no significant changes in CSF NFL, albumin ratio, IgG index, ß2-microglobulin, or CSF WBC measurements during the study period. These studies support the neurologic safety of modern 2DRs.

Biomarkers of Brain Health in People With HIV

Two abstracts reported outcomes related to the application of novel neuroimaging techniques in PWH. Diffusion-based spectral imaging (DBSI) is a form of diffusion-weighted MRI sequencing. In a previous experimental autoimmune encephalomyelitis mouse study, DBSI-derived global cellularity (GC) was associated with activated microglia. In a study with 277 PWH and 45 PWoH, Srinivas and colleagues (Abstract 592) investigated correlations between DBSI-derived GC

A substantial and widespread decline in SV2A radioligand binding across regions of interest, even though the participants were cognitively asymptomatic during the study period, suggests possible ongoing cerebral changes in PWH despite suppressive ART

and levels of immune activation markers in their blood samples. They observed higher DBSI-derived GC in PWH than in PWoH. Additionally, GC increased with age and the level of classical monocyte marker (CD14+CD16–) and decreased with sCD163 among PWH. However, these trends were not observed in PWoH.

In a pilot study involving 8 middle-aged, virally suppressed PWH over a period of 2.6 years, Chan and colleagues (Abstract 595) used synaptic vesicle protein 2A (SV2A) positron emission tomography (PET) to evaluate the longitudinal changes in radioligand binding to the presynaptic SV2A transmembrane protein in

Published May 21, 2025 © IAS–USA

the brain, a proxy for synaptic density. They reported a substantial and widespread decline (7%-11%) in SV2A radioligand binding across regions of interest (ROIs), including the frontal, parietal, temporal, and occipital grey matter, even though the participants were cognitively asymptomatic during the study period. These findings suggest that there may be ongoing synaptic changes in the brains of PWH despite suppressive ART.

Several abstracts explored the predictive values of blood-based markers on neurologic outcomes. The systemic immune-inflammation index (SII), derived from neutrophil, platelet, and lymphocyte counts in the clinical complete blood picture (CBP) test, has shown prognostic value for immune activation and systemic inflammation in non-HIV conditions. In a study that included 1867 participants from the HNRP (HIV Neurobehavioral Research Program), Wang and colleagues (Abstract 638) examined the relationship between the SII and neurocognitive outcomes and whether this relationship would differ in PWH between those older than 50 years (n = 850) and younger than 50 years (n = 1017). The team observed an association between SII and worse performance in numerous cognitive domains, as well as worse global cognitive scores in younger and older PWH. Furthermore, the effects of the SII were moderated by age for psychomotor speed, suggesting the potential usefulness of SII in identifying psychomotor decline in older PWH.

Gonzalez and colleagues (Abstract 602) examined the predictive value of soluble urokinase plasminogen activator (suPAR), another blood-based biomarker for chronic inflammation, on cognitive test performance in 188 women with HIV (WWH) on suppressive ART from the MWCCS (MACS-WIHS Combined Cohort Study). The team observed a negative relationship between log suPAR levels and psychomotor speed, verbal learning, verbal fluency, and motor function. The study also identified substantial differences in log suPAR levels between participants with impairment in the psychomotor speed and motor domains compared with those without impairment in those specific domains.

Blood neopterin level, a marker of immune activation and inflammation, has been extensively used in HIV research for years. In a study of 100 PWH and 50 PWoH matched for age and sex, Prats and colleagues (Abstract 633) compared blood neopterin levels and performance with 3 cognitive screening tests (Mini-Mental State Examination [MMSE], FACEmemory, and NEU Screen). Among the 3 screening tests, PWH had a higher rate of positive screens in the NEU Screen than PWoH but not in the other 2 tests. Additionally, PWH also had a higher level of blood neopterin than PWoH controls, along with a correlation between neopterin level and NEU Screen results. PWH in this study had higher rates of polypharmacy, active substance use, and history of substance use disorder than PWoH.

Hiransuthikul and colleagues (Abstract 622) compared the longitudinal MoCA performance in a Thai Aging PWH cohort with 287 individuals aged older than 50 years (62% male). In the follow-up MoCA assessment conducted 5.9 years later, participants with an initial score greater than 25 (out of 30) demonstrated a greater decline (−2.4 points) than those who scored 25 or less (+0.3 points). In Abstract 171, the same team also measured the levels of blood phosphorylated tau 217 (p-tau217), a blood-based biomarker for Alzheimer's disease (AD), in the same cohort of participants (n = 255). They found a greater drop in MoCA performance among the quartile of participants with the highest p-tau217 levels than in the lower 75% group. Their findings raise the question of whether such decline is related to AD pathologies in the brain, and the usefulness of blood-based AD biomarkers in identifying PWH at risk of cognitive decline. A detailed study involving comprehensive CNS evaluation, including neuroimaging, cognitive assessments, and preferably amyloid and tau PET scans, will provide a deeper understanding of this observation.

Johnston and colleagues (Abstract 612) studied 87 virally suppressed PWH aged 50 years or older, measuring epigenetic aging calculated from DNA methylation profiles at baseline and following cognitive performance over a median of 58 months. Using first- (Horvath1, Horvath2), second- (PhenoAge, GrimAge), and third-generation (DunedinPACE) epigenetic clocks, they found distinct patterns linking advanced epigenetic age to future cognitive trajectories. Higher Horvath1/Horvath2 residuals correlated with better processing speed, and higher PhenoAge and GrimAge residuals were associated with poorer learning and memory performance. DunedinPACE similarly predicted poorer

Epigenetic modifications are increasingly recognized as a biologic link between HIV, biologic aging, and cognitive decline

learning and memory, highlighting the nuanced and domain-specific relationships between epigenetic aging and cognition in older PWH.

Further DNA methylation data were presented by Baum and Colleagues (Abstract 613), who examined how HIV and cocaine use may jointly influence epigenetic dysregulation in 31 older adult PWH. All participants were virally suppressed and predominantly non-Hispanic Black men with an average age of 63 years. Investigators identified a significant CpG site (cg08287344) where methylation levels differed markedly between those with HIV who used cocaine and showed cognitive frailty, relative to HIV-negative, non–cocaine-using individuals without cognitive frailty. Lower DNA methylation at this site suggested potential links to inflammation, neurocognitive decline, or drug-related stress. These results point to cocaine use as an added epigenetic stressor that may exacerbate the impact of HIV on brain health.

The impact of persistent CNS immune activation stood out prominently across numerous studies. Anesten and colleagues (Abstract 601) retrospectively analyzed more than 600 PWH and 59 HIV-negative controls. They measured levels of β2-microglobulin (β2M), neopterin, NFL chain, and HIV RNA, as well as albumin ratio, immunoglobulin G (IgG) index, and leukocyte counts in the CSF and blood. They divided PWH into 7 clinically defined groups (eg, neuroasymptomatic HIV, HIV-associated dementia [HAD], CSF escape variants) and observed markedly elevated CSF β2M in those with HAD and symptomatic CSF escape. Importantly, β2M remained abnormally high even after 6 months of ART, suggesting that β2M is a robust marker of intrathecal inflammation in HIV. Additionally, work presented by Riggs and colleagues (Abstract 610) utilized a CSF proteomic profiling approach (Olink) to compare traditional classification methods of neurobehavioral dysfunction (eg, global deficit scores, total Beck Depression Inventory-II) against more granular, data-driven phenotypes and subscale metrics. Their analyses showed stronger immune-protein associations with specific subscales for depression and cognitive deficits, including T-cell and monocyte activation pathways, highlighting how subphenotyping may better capture the underlying biologic heterogeneity of neurobehavioral disorders in PWH.

Subphenotyping may better capture the underlying biologic heterogeneity of neurobehavioral disorders in PWH

Aging-Related Comorbidities and Brain Health in People With HIV

Cardiovascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, and metabolic syndrome, increase with age and occur more frequently in PWH than in PWoH. Several CROI abstracts this year examined the association between these factors and adverse brain health outcomes in PWH. In a 2-center study conducted in Senegal, Couturier and colleagues (Abstract 623) examined the potential association between hypertension and cognitive outcomes in 290 PWH aged older than 50 years who had been on ART for at least 6 months. Hypertension, diabetes, and hyperlipidemia were seen in 50%, 14%, and 63% of the study participants, respectively. Multivariate analysis further revealed independent associations between worse verbal fluency and hypertension, female sex, and lower education. Their findings highlight the crucial need to implement management of blood pressure and other vascular risk factors in HIV clinics.

In a neuroimaging study, Decloedt and colleagues (Abstract 626) investigated the impact of obesity and metabolic syndrome on cerebral perfusion alterations. Utilizing the arterial spin labeling (ASL) technique with MRI, they reported an association between worsening arterial transit time (ATT) (the time it takes for blood to travel from the arteries to the capillaries in the brain) and adverse measures of metabolic syndrome and body fat composition in a group of 27 WWH, who had a mean body mass index (BMI) of 41.9 ±7.8 kg/m². The inclusion of appropriate controls, such as PWoH with metabolic syndrome or PWH without metabolic syndrome, would help clarify whether the findings are linked to HIV infection.

Several reports examined the complex relationships among comorbidities, medications and polypharmacy, and adverse brain health in PWH. In a multicenter study involving 1158 PWH and 272 PWoH from the CHARTER (CNS HIV ART Effects Research) and HNRC (HIV Neurobehavioral Research Center) cohort studies, Tavasoli and colleagues (Abstract 625) found an inverse and independent relationship between the number of antihypertensive medications taken by PWH and their

global cognitive performance over time, as measured by summary regression-based change scores. This association was not observed in PWoH, who also had a lower mean arterial pressure (MAP) than PWH. The findings suggest that health care practitioners may have increased the number of antihypertensive drugs over time due to either treatment-resistant hypertension or poor adherence, especially among those with cognitive decline over time. Kosana and colleagues (Abstract 599) evaluated the association between polypharmacy (use of 5 or more non-ART prescription medications), neuroaxonal injury, and immune activation, determined by blood NFL and sCD14 levels, respectively. The study included 600 participants (median age, 54 years; 81% men) from the ACTG 5322 HAILO (Long-Term Follow-up of Older HIV-infected Adults in the ACTG: Addressing Issues of Aging, HIV Infection and Inflammation) study. An independent association between elevated levels of blood NFL and polypharmacy and recurrent falls was observed after accounting for comorbidities that could influence the outcomes. These studies highlight the importance of medication management to improve brain health and geriatric syndromes in PWH.

Two studies investigated sleep disorders in PWH. In a multicenter Canadian study, Brouillette and colleagues (Abstract 635) investigated the prevalence of obstructive sleep apnea (OSA) and its potential cognitive impacts in 707 PWH (85% men; mean age, 55 years). Participants were screened for OSA using the Berlin (low/high risk) and STOP-Bang (low/intermediate/high risk) questionnaires, along with self-reported cognitive difficulties and the Brief Confusion Assessment Method (B-CAM), a computerized battery that covers several cognitive domains. More than a third of participants screened positive for OSA, which was associated with higher self-reported cognitive difficulties and worse B-CAM performance. However, the impact of OSA on B-CAM performance was below 0.5 SD, which is the threshold for clinical significance.

Mazzitelli and colleagues (Abstract 617) examined the complex relationship between sleep metrics (Pittsburgh Sleep Quality Index [PSQI], ≥5 for poor sleep quality; Insomnia Severity Index [ISI], score ≥15 for moderate/severe insomnia; Epworth Sleepiness Scale [ESS], ≥13 for daily sleepiness) and the burden of anticholinergic drugs via the Anticholinergic Burden Scale (ACBS). In this cross-sectional study with 1200 PWH on ART, positive screens for ISI, PSQI, and ESS were 12%, 51%, and 6%, respectively, suggesting clinically relevant insomnia, poor sleep quality, and significant daily sleepiness among the participants. After adjusting for polypharmacy, multimorbidity, depressive mood and anxiety symptoms, and other confounding variables (eg, age, sex, HIV acquisition route, use of benzodiazepines and antidepressants), higher ACBS was independently associated with worse scores on ISI and PSQI. The findings suggest that ACB could disrupt sleep quality and increase the risk of insomnia independently in PWH.

Two abstracts focused specifically on mood disorders and highlighted the need for attention to depression and the use of antidepressants in PWH. Gasana and colleagues (Abstract 618) conducted a cross-sectional study to estimate the prevalence of mood disorders among PWH in Rwanda. Participants included 428 PWH from 12 HIV clinics across the area, selected using random sampling. The prevalence of major depressive episodes, posttraumatic stress disorder, and generalized anxiety disorder was evaluated using the Mini International Neuropsychiatric Interview conducted by trained nurses. At least 1 mental health condition was present in 16.4% of the study participants, with major depressive episodes being the most common form of mental health conditions (14.0% among the participants). Only a small subset of participants who screened positive was aware of their condition (5.7%) or under active care (7.2%). Sims and colleagues (Abstract 593) examined the neurologic impact of depressive mood and the use of antidepressants in PWH. The team compared the relationship between cognition, brain volume, and severity of depression in 353 PWH on stable ART and 302 PWoH, plus the potential effects of antidepressants. They observed a significantly higher rate of depressive symptoms, measured by the Beck Depression Inventory (BDI), in PWH than in PWoH. A greater proportion of PWH with depression was on antidepressant medications than PWoH with depression. Among PWH, a higher BDI score (ie, worse depressive symptoms) was associated with worse performance in learning, executive function, psychomotor function, and language function,

Among PWH, a higher BDI score (ie, worse depressive symptoms) was associated with worse performance in learning, executive function, psychomotor function, and language function

and PWoH only demonstrated negative associations between BDI and executive and psychomotor functions. Importantly, PWH who were depressed and on antidepressants had significantly smaller brain volumes, although without a significant correlation with cognitive performance.

Three reports focused on the stability of cognitive function in PWH and other clinical associates of cognitive dysfunction. Brouillette and colleagues (Abstract 634) examined the significance of fluctuations in cognitive test performance over time in 268 older PWH (mean age, 53.7 years) who took part in the multisite Canadian + Brain Health Now study. The participants underwent B-CAM, a computerized battery assessing several cognitive domains, every 9 to 12 months over a period of at least 5 years. Using a group-based trajectory analysis (GBTA) approach, they identified 2 trajectory groups: stable (68.7%) and declining (31.3%) performance in the B-CAM. More than half of the participants experienced at least 1 meaningful worsening in B-CAM performance; however, these episodes did not reliably predict long-term decline. In contrast, older individuals and those with worse overall B-CAM performance were at higher risk of exhibiting true decline in performance over time.

Vance and colleagues (Abstract 603) examined intraindividual variability (IIV) in cognitive performance and its correlation with the capacity for activities of daily living between women without HIV (WWoH) and WWH with or without HIV suppression. Cognitive IIV refers to the variation observed in cognitive performance when various cognitive tests are administered to the same person (ie, dispersion). Greater cognitive IIV has been associated with poorer cognitive performance and decline over time, as well as cortical brain atrophy in PWH. Using a cognitive battery that covered 7 cognitive domains and the self-rated modified Lawton and Brody scale of Instrumental Activities of Daily Living (IADL), the team observed slightly greater cognitive IIV among WWH than WWoH. Furthermore, cognitive IIV was predictive of everyday functioning, such as managing money and bills, performing various household tasks, taking/keeping track of medications, and caring for others.

Rubin and colleagues (Abstract 619) compared a range of brain health complications between 338 PWH on stable ART and 249 PWoH from Rakai, Uganda, an area where residents have fewer confounding conditions affecting cognitive changes, such as substance use and the occurrence of posttraumatic stress disorder (PTSD). PWH in the study were more likely to have impaired performance on Color Trails, Symbol Digit, grooved pegboard, Figure-8, and auditory verbal learning test (AVLT) recognition than PWoH, but this difference in performance was not observed in AVLT learning and memory. Additionally, PWH reported more sensory symptoms (29% vs 21%) and a greater frequency of childhood sexual abuse (27% vs 15%) than PWoH.

Emerging Therapeutics for Brain Health

A preclinical study by Akay-Espinoza and colleagues (Abstract 614) investigated the endocannabinoid system in primary human monocyte-derived macrophages and induced microglia. By exposing these cells to the cannabinoid receptor 2 (CB2)-specific agonist JWH-133, they demonstrated reduced viral replication, suppression of proinflammatory signaling, and modulation of pathways linked to synapse maintenance. These preclinical findings highlight CB2 as a promising target to mitigate HIV-related neuroinflammation within the CNS. Cooley and colleagues (Abstract 596) studied the impact of cannabis use on measures of structural brain integrity. A 2×2 design compared cannabis users and nonusers among PWH and PWoH, using MRI to assess regional brain volumes and cortical thickness. Heavy cannabis use correlated with decreased structural integrity in frontal and temporal lobes, plus cortical thinning; these effects were most pronounced in PWH. Greater lifetime cannabis exposure also predicted poorer delayed recall, underscoring a heightened vulnerability of the brain of PWH to cannabis-related damage.

Heavy cannabis use correlated with decreased structural integrity in frontal and temporal lobes, plus cortical thinning; these effects were most pronounced in PWH

Atieh and colleagues (Abstract 172) presented a randomized clinical trial of semaglutide in PWH with lipohypertrophy, revealing notable cognitive benefits, especially in visuospatial functioning over 32 weeks of therapy. These improvements were linked to reductions in systemic inflammation rather than changes

Published May 21, 2025 © IAS–USA

in adiposity, indicating that targeting inflammatory pathways through GLP-1 RA use may be a viable strategy for neurocognitive protection in PWH. Following the positive outcomes in the REPRIEVE (Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in HIV-Infected Adults) trial, prompted interest in the potential neuroprotective effects of pitavastatin, or statins in general, on PWH on stable ART of mild to moderate risk of cardiovascular disease. Utilizing a 4-test battery that assessed learning, psychomotor function, and processing speed, Erlandson and colleagues (Abstract 624) compared the cognitive changes of 88 pitavastatin users and 93 placebo users within REPRIEVE. During a median duration of 2.9 years of follow-up, cognitive test performance did not differ between the 2 groups, suggesting no positive or negative impacts of pitavastatin on cognitive performance. The initial data presented on semaglutide and pitavastatin emphasize an important opportunity for further study to clarify their potential neurocognitive benefits and to drive the development of novel therapeutic strategies for the neuro-HIV field.

A randomized clinical trial of semaglutide in PWH with lipohypertrophy revealed notable cognitive benefits, especially in visuospatial functioning over 32 weeks of therapy

Neuropathogenesis of SARS-CoV-2 Infection

Several abstracts examined the neuropathology of COVID-19, including long COVID and the effects of COVID-19 in PWH. People with long COVID often experience cognitive dysfunction and other neurologic issues. As part of the COVID Mind study, McAlpine and colleagues (Abstract 173) performed MRIs on people with long COVID and cognitive dysfunction (n = 32) to assess whether there were structural brain differences that distinguished them from controls who recovered fully after COVID-19 (n = 22). T1 imaging and fluid attenuated inversion recovery were used to examine brain volume, DTI was used to assess white-matter tract integrity and ASL was used to assess cerebral blood flow. People with long COVID had significantly lower gray matter volume in various brain regions, including regions associated with symptoms of long COVID. They also observed patterns of reduced blood flow in people with long COVID that may be functionally related to lower gray matter volume and cognitive dysfunction in this cohort. These findings suggest brain structural changes could be used as biomarkers of cognitive dysfunction and long COVID.

In another study examining samples from people enrolled in the COVID Mind Study, Chakravarty and colleagues (Abstract 946) examined whether autoimmune antibodies in the CNS were associated with neurologic long COVID. In this study, CSF was collected from people with long COVID and cognitive symptoms or headache (n = 39) and from healthy controls (22 healthy prepandemic and 3 with no long COVID symptoms after recovering from COVID-19). CSF was used to stain mouse brain slices for evidence of antineural autoantibodies, but no consistent differences were detected between CSF from people with long COVID and controls. For CSF samples from people with long COVID and evidence of autoantibodies, phage immunoprecipitation sequencing was used to explore whether autoantibodies in these people consistently recognized the same antigens. Based on these analyses, SOX5 was selected for further investigation but additional analyses did not yield evidence that SOX5 was a shared autoantigen in people with long COVID.

Ocampo and colleagues (Abstract 926) performed a longitudinal study examining changes in cognitive performance in PWH after having COVID-19. This study examined cognitive performance in RV254/SEARCH010 (South East Asia Research Collaboration in HIV 010) participants who initiated ART during acute infection, were on stable ART before enrolling and had a high rate of vaccination against SARS-CoV-2 (85% received ≥2 doses of COVID-19 vaccine prior to testing positive for SARS-CoV-2). Cognition was assessed approximately 1 year before testing positive for SARS-CoV-2, at the time of testing positive and again, every 3 months for a year. Significant, but transient declines were observed in a measure of psychomotor speed (Trail Making A) and in overall cognitive performance (Composite Neuropsychological Test Z Score-4). These results illustrate the need for continued monitoring to assess the long-term impact of COVID-19 infections in PWH.

All abstracts cited in the text appear in the CROI 2025 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 financial relationships with ineligible companies (May 8, 2025) *Dr Chan reported no financial relationships with ineligible companies* (Updated May 8, 2025) *Dr Joseph reported no financial elationships with ineligible companies* (Updated May 8, 2025)

Reviewer 1 reported consulting or advisor fees from Generate Biomedicines and Gilead Sciences, Inc. (Updated March 10, 2025) *Reviewers 2 and 3 reported no relevant financial relationships with ineligible companies.* (Updated April 19, 2025)

All relevant financial relationships with ineligible companies have been mitigated.

Top Antivir Med. 2025;33(2):483-493