Invited Review

CROI 2026: Neuro-HIV at the Crossroads of Coinfections, Reservoirs, Antiretroviral Therapy, and Comorbidities

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Abstract: *The 2026 Conference on Retroviruses and Opportunistic Infections (CROI) featured important new and impactful findings relevant to the neurologic HIV (neuro-HIV) field. Reports included new evidence linking herpesvirus coinfections to cognitive heterogeneity; studies on neuroinflammation, neuronal injury, and amyloid-related processes in treated HIV; and studies using advanced technologies to address the HIV-infected cells that persist in the central nervous system during antiretroviral therapy and the mechanisms that may maintain those populations. New therapeutic findings were presented on low-dose hydrocortisone and pregnenolone as potential strategies to improve cognition and reduce inflammatory signaling. Additional studies linked brain health in people with HIV to antiretroviral-associated neuropsychiatric effects and to aging-related comorbidities, including cerebrovascular disease, diabetes, metabolic syndrome, insulin resistance, and metabolic dysfunction-associated steatohepatitis. This review summarizes these findings and highlights new mechanistic and therapeutic directions for the neuro-HIV field.*

Keywords: antiretroviral therapy, ART, brain aging, central nervous system, CNS reservoirs, cognitive heterogeneity, herpesvirus coinfections, microglia, neuro-HIV, neuroinflammation, neuropsychiatric

Introduction

The effects of HIV on the central nervous system (CNS) were the focus of several important presentations at the 2026 Conference on Retroviruses and Opportunistic Infections (CROI). As people with HIV (PWH) are living longer on effective antiretroviral therapy (ART), the neurologic HIV (neuro-HIV) field has increasingly shifted beyond the question of whether viral suppression can be achieved in the CNS to the broader challenge of preserving brain health across the lifespan. This includes understanding the biologic basis of cognitive heterogeneity, defining the mechanisms that sustain HIV persistence in the CNS, and identifying modifiable contributors to neuroinflammation, neuronal injury, and neuropsychiatric symptoms. There is growing interest in how contemporary ART regimens may influence brain structure, neuropsychiatric symptoms, and cognitive trajectories, supported by recent studies underscoring that brain health in PWH reflects a complex interplay between ART-specific effects, treatment timing, and cumulative vascular and metabolic risk, reinforcing the need for integrated approaches to optimize neurologic and mental health across the lifespan. This review is organized around 5 themes from CROI 2026: coinfections and cognitive heterogeneity in treated HIV; neuroendocrine interventions for cognition and neuroinflammation; HIV CNS reservoirs; ART and brain health; and neurologic effects of medical comorbidities. Together, these studies advance the understanding of the multifactorial basis of neuropsychiatric complications in PWH and highlight emerging mechanistic and therapeutic targets.

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Coinfections, Brain Aging, and Cognitive Heterogeneity in Treated HIV

In aging PWH, chronic coinfections may represent an underrecognized contributor to accelerated brain aging and cognitive heterogeneity by sustaining neuroinflammation, neuronal injury, and altered antiviral immune responses beyond the effects of HIV alone. Riggs and colleagues (Abstract 481) examined relationships between herpesvirus measures and cerebrospinal fluid (CSF) biomarkers of neuronal injury, neuroinflammation, and amyloid pathology in 107 virally suppressed PWH from the CHARTER (CNS HIV Anti-Retroviral Therapy Effects Research) and HNRC (HIV Neurobehavioral Research Center) cohorts (mean patient age, 55 years; 83% male; 41% Black and 51% White). The

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median CD4+ count was 577 cells/μL and median duration of HIV infection was 22 years; 94% were cytomegalovirus (CMV) immunoglobulin G (IgG) seropositive and 100% were Epstein-Barr virus (EBV) IgG seropositive. Cell-associated CMV, EBV, and HIV DNA levels were quantified in peripheral blood mononuclear cells (PBMCs) by digital droplet polymerase chain reaction (ddPCR) and plasma IgG titers were measured by immunoassay.

Eleven CSF biomarkers were assessed, including neurofilament light (NFL), soluble tumor necrosis factor receptor-II (sTNFR-II), total tau, amyloid-β 1-42 (Aβ42), and monocyte chemotactic protein-1 (MCP-1).

In multivariable models, 6 CSF biomarkers remained associated with viral measures after adjustment for age, sex, race, ethnicity, CD4+ cell count, CD4+ cell nadir, and CSF/serum protein ratio. EBV (IgG and DNA) was associated with neuronal injury markers (NFL and tau), whereas CMV (IgG and DNA) was associated with neuroinflammation (sTNFR-II) and complex effects on amyloid processing and clearance (Aβ42 and soluble amyloid precursor protein α [sAPPα]). HIV DNA level was not significantly associated with any CSF biomarker. A clustering analysis confirmed a significant association between viral cluster measures (EBV IgG, EBV DNA, CMV IgG, CMV DNA) and CSF biomarker clusters (NFL, sTNFR-II; β=0.230; R^2=0.394; P<.0001). These exploratory, cross-sectional findings suggest that CMV- and EBV-related mechanisms, rather than residual HIV, may drive ongoing neurologic injury in virally suppressed PWH, and raise the possibility that antiviral interventions targeting herpesviruses could benefit brain health in aging PWH.

Herpesvirus coinfection may modify the profile of neurologic injury in virally suppressed individuals with HIV

Riggs and colleagues presented complementary data using a high-resolution virome-wide antibody profiling approach (Abstract 470). Using the VirSIGHT molecular indexing of proteins by self-assembly (MIPSA) platform, which characterizes antibody reactivity against 286,793 DNA-barcoded viral peptides from more than 500 human viruses, the investigators profiled antiviral antibody responses in paired CSF and plasma samples from 88 PWH on suppressive ART (81% male; mean age, 52 years; median CD4+ count, 680 cells/μL) from the CHARTER and HNRC cohorts. Total antibody reactivity burden did not differ by cognitive impairment status, arguing against global immune senescence and in favor of virus-specific immune phenotypes as determinants of cognitive heterogeneity. After correction for false discovery rate (FDR), working memory and executive function showed the strongest association compared with other cognitive domains. In CSF and plasma, herpes simplex virus (HSV-1) antibody responses were associated with intact working memory (P=.009) and executive function (P=.034). HSV-2 and EBV antibody responses were associated with better working memory. In contrast, HIV-1 envelope antibody responses consistently tracked with worse cognitive performance across numerous domains. These associations remained after adjustment for age, sex, and CD4+ cell count, supporting the conclusion that the antiviral immune repertoire may shape cognitive outcomes in PWH.

These observations underscore the need for methods capable of detecting low-level, compartment-specific herpesvirus activity at single-cell resolution, particularly for EBV, CMV, and HSV, which may contribute to neuroinflammation, neuronal injury, and cognitive heterogeneity in treated HIV. Addressing this gap, Duchen and colleagues (Abstract 465) developed the primary and opportunistic pathogen recovery via quasi-mapping and single-cell transcriptomics (POP-ROQS), a computational workflow designed to jointly capture human and viral transcripts from single-cell RNA (scRNA) sequencing data, including CSF cells. Standard scRNA pipelines are largely host-centric and routinely exclude low-abundance viral transcripts during barcode filtering and quality-control steps, causing pathogen-associated droplets to be missed. POP-ROQS overcomes this limitation by aligning reads to a joint human-viral reference genome that includes representative HIV-1, HIV-2, simian immunodeficiency virus, CMV, EBV, HSV-1, and HSV-2 genomes, and by applying postalignment FASTQ parsing to classify droplets as containing intracellular (infected host cell) or extracellular/ambient viral RNA. In paired CSF and peripheral blood sample analyses, 7 participants who were virally suppressed and 1 participant who was ART naive were sampled longitudinally after ART initiation. POP-ROQS substantially outperformed the standard Cell Ranger pipeline for viral detection. Although the most striking gains were observed for HIV, the platform concurrently detected EBV, CMV, and HSV transcripts, providing an important proof of concept for studying various neurotropic and immunomodulatory viruses in parallel within scarce CSF samples. Performance improved further when reference indexes incorporated diverse representative viral genomes rather than single or redundant genomes, an important consideration

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for sensitively capturing herpesvirus diversity. By enabling simultaneous detection of EBV, CMV, HSV, and HIV transcripts at single-cell resolution across compartments, POP-ROQS provides a valuable new tool for defining the cellular sources and tissue context of chronic viral activity that may shape brain aging and cognitive outcomes in PWH.

Targeting Neuroendocrine Pathways to Improve Cognition and Neuroinflammation

Women with HIV experience high rates of trauma, chronic stress, and depression, all of which are linked to cognitive impairment. Candidate mechanisms include dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, glucocorticoid (GC) receptor function, neuroinflammation, and HIV persistence, yet no existing interventions directly target these pathways. Rubin and colleagues (Abstract 112) conducted a phase II clinical trial at Johns Hopkins University (2018–2024) to determine whether low-dose hydrocortisone (LDH), a pharmacologic modulator of HPA axis function, could improve cognition in virally suppressed women with HIV and to examine neuroendocrine, immune, and HIV-related mechanisms underlying treatment effects. Eligible participants (aged 18–65 years) had self-reported stress or a mood or anxiety disorder and objective impairment in at least 1 cognitive domain. The primary outcome was the Hopkins Verbal Learning Test–Revised (HVLT-R). The initial study was a double-blind, placebo-controlled, crossover trial testing the immediate (30-minute) and delayed (4-hour) cognitive effects of a single 10 mg LDH dose; 81 participants were randomly assigned (mean age, 55.2 years [standard deviation, 8.0 years]; 81% Black). LDH produced a robust cortisol increase (5.14-fold) peaking 75 minutes post dose ($P < .001$). At 4 hours, LDH significantly improved HVLT-R total learning compared with placebo ($P = .03$; Cohen $d = 0.27$) and showed a trend toward improved delayed recall ($P = .08$; Cohen $d = 0.21$). Attention improved at the 30-minute and 4-hour timepoints ($P < .05$ for each).

A follow-up study was a randomized, double-blind, placebo-controlled trial of daily LDH for 4 weeks. LDH significantly improved delayed recall ($P = .005$; Cohen $d = 0.34$) and prevented decline on an attentional measure compared with placebo ($P = .016$), although the effect on treatment-time interaction did not reach significance ($P = .14$). LDH was well tolerated, with no serious adverse events (AEs). Notably, there were no significant associations between changes in peripheral biomarkers including cortisol, inflammatory markers, GC receptor expression, and HIV reservoir measures, and LDH-related cognitive improvements, suggesting that other biologic mechanisms, potentially including direct CNS effects, may underlie the observed benefits.

Complementing this clinical evidence, Daly and colleagues (Abstract 476) investigated the immunomodulatory properties of pregnenolone, an endogenous neuroactive steroid (NAS) synthesized in the mitochondria of adrenal, gonadal, and brain cells, in 33 PWH (all on ART; plasma HIV-1 RNA level <200 copies/mL) and 20 people without HIV (PWoH). Endogenous plasma NAS levels were measured by mass spectrometry. Although pregnenolone levels did not differ significantly between groups, higher endogenous pregnenolone levels were inversely correlated with levels of interleukin-6 (IL-6; $r = -0.52$; $P < .01$) and monocyte chemotactic protein-1 (MCP-1; $r = -0.39$; $P = .03$) in the full cohort. Among PWH, the correlation with IL-6 remained significant ($r = -0.52$; $P = .03$). Soluble CD163, a marker of monocyte/macrophage activation, was significantly higher in PWH than in PWoH ($P < .01$). In vitro experiments using PBMCs from PWH and PWoH stimulated with the toll-like receptor 4 (TLR4) agonist lipopolysaccharide (LPS) or the TLR1/2 agonist PAM3CSK4 demonstrated that pregnenolone dose-dependently reduced IL-6 production ($P < .001$) in CD14+CD16– classical monocytes and increased regulatory cytokines interleukin-10 (IL-10; $P < .001$) and transforming growth factor-β (TGF-β; $P < .001$). This immunomodulatory effect, mediated primarily through innate immune pathways, suggests that pregnenolone shifts monocytes toward a regulatory phenotype. These preclinical data support the ongoing phase II SOOTHE (Neuroactive Steroid to Treat Depressed Mood: A Trial for People With HIV) trial, which is evaluating pregnenolone in PWH who have major depressive disorders.

HIV CNS Reservoirs

Despite intense investigation in recent years, fundamental questions about the nature and significance of HIV reservoirs in the CNS remain unresolved. At CROI 2026, several presentations addressed key issues, including determining which HIV-infected cells persist in the CNS during ART, how CNS reservoirs are maintained, and whether CNS reservoirs contribute to viral rebound during treatment interruption.

One study presented by Kincer (Abstract 458) analyzed HIV RNA sequences in CSF and plasma collected from untreated individuals to infer which CNS cell types are infected during untreated infection—and thus, which cells may seed long-lived CNS reservoirs. Genetically distinct (ie, compartmentalized) viral lineages in the CSF were found

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in 32% of participants, indicating that they had virus populations independently replicating in the CNS. Importantly, CNS replication was associated with neurologic symptoms, elevated CSF-to-plasma viral load ratios, and evidence of inflammation. To further investigate the cellular origins of these CNS-derived viral populations, they examined the cellular tropism of *env* genes cloned from the CSF in a subset of these individuals and determined that 58% had HIV

The nature and significance of HIV reservoirs in the CNS, along with the mechanisms underlying viral persistence, remain to be fully elucidated

populations in their CSF that were adapted to replication in myeloid cells (macrophage/microglia). This phenotype (M tropism) is rarely observed in the periphery, suggesting that these lineages were likely produced by HIV-infected myeloid cells. The remaining 42% of individuals had HIV in their CSF that was adapted to replication in CD4+ cells (ie, T tropic) and was likely produced by sustained replication in CD4+ cells in the CNS. These results suggest that HIV-1 replication in the CNS can occur in CD4+ cells or myeloid cells (macrophage/microglia), emphasizing the possibility that each cell type may contribute to CNS reservoirs. In addition, they observed that replication in each cell type is associated with neurologic symptoms, raising questions about whether replication in CD4+ cells and myeloid cells generates brain injury through different mechanisms.

Studies of CD4+ cells in the periphery have clearly shown that clonal expansion is fundamental to the persistence of HIV-infected cells during ART. To better understand the contribution that clonal expansion makes to the maintenance of HIV reservoirs in the CNS, Thomas and colleagues (Abstract 110) performed HIV integration site analyses on brain and spleen cells isolated from 3 PWH who were virologically suppressed at death and donated their bodies to the Last Gift Project. Surprisingly, for 1 participant, the same integration site was observed in CD4+ cells in the brain and spleen as well as in microglia in the brain. Observing the same integration site in CD4+ cells isolated from different compartments is easily explained by the migration of HIV-infected, clonally expanding CD4+ cells, but it is difficult to understand how the same integration site can be observed in different cell types (eg, microglia and CD4+ cells). To better understand this result, the investigators performed T-cell receptor (TCR) sequencing and inferred that more than 1.8% of cellular DNA in the microglia population was derived from T cells. These results are consistent with phagocytosis of HIV-infected CD4+ cells by microglia or contamination of microglia populations with HIV-infected CD4+ cells. Although this work clearly illustrates that HIV-infected cells can be detected in the CNS during ART and suggests that proliferation is a mechanism that maintains CNS reservoirs, additional studies are needed to understand whether the microglia population contains phagocytosed HIV-infected CD4+ cells.

Although many studies have identified HIV-infected cells in the CNS during ART, it remains unclear whether these cells contribute to viremia when ART is stopped. Henrich and colleagues (Abstract 113) utilized advanced imaging approaches to assess HIV expression and CD4+ cell activation during analytic treatment interruption (ATI) in humans. Addressing these issues in the CNS involves many challenges, including the need for markers that can penetrate the CNS and the challenges of timing 2 complex protocols (ATI and imaging) to detect the early stages of viral rebound. In their first study, ^{89}Zr-labeled VRC01 antibody with positron emission tomography/magnetic resonance imaging was used to visualize cells expressing HIV Env during ATI (before viral RNA was detectable n the blood). They observed increased uptake of ^{89}Zr-labeled VRC01 in inguinal lymph nodes (mean tissue-blood ratio of the maximum standardized uptake value, 0.33 vs 0.15), colorectal tissue (0.5 vs 0.21 in PWH on ART) and femoral bone marrow (1.09 vs 0.4 in PWH on ART). Surprisingly, elevated uptake signals of ^{89}Zr-labeled VRC01 were also detected in the perivascular brain parenchyma during ATI. However, it is unclear how to interpret this result, given the poor penetration of ^{89}Zr-labeled VRC01 into the CNS and the lack of signal in the brain parenchyma.

Henrich and colleagues (Abstract 113) also performed a longitudinal imaging study to assess whether ATI increased cellular activation, using a tracer (^{18}F-AraG) that penetrates the CNS efficiently and accumulates in activated cells (particularly in CD4+ cells, but it may also accumulate in myeloid cells). They did not observe a substantial change in tracer uptake during ATI, suggesting that ATI did not have a major impact on cell activation in the brain. Overall, these studies illustrated the power of longitudinal imaging analyses and the challenges of observing HIV and HIV-associated inflammation in the brain.

Suzuki and colleagues (Abstract 459) explored whether HIV expression in the periphery during ART is associated with CNS injury. Expression of long translation-competent

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HIV-1 transcripts in peripheral CD4+ cells was associated with lower N-acetyl aspartate (NAA; a marker of neuronal integrity) levels in frontal white matter as measured by magnetic resonance spectroscopy ($P = .003$). In contrast, transcripts edited by apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC)-3, ie, translationally incompetent transcripts, were not associated with worse neuronal integrity. Although the study was unable to show causation, it raises questions about whether the specific HIV transcripts expressed in CD4+ cells in the periphery are a marker of expression in cells trafficking through the CNS, ie, the cells directly contributing to brain injury, or whether there is a systemic phenomenon that could increase APOBEC-mediated hypermutation and reduce brain injury (eg, by blocking CCL2 signaling).

These studies are consistent with the idea that HIV can persist in the CNS before and during ART, but many questions remain about the mechanisms that facilitate HIV persistence in that compartment and the impact that HIV may have on brain health during ART. Although the technologies highlighted in these studies provide new opportunities for understanding CNS reservoirs, they illustrate that there is no single approach that can comprehensively profile CNS reservoirs.

Antiretroviral Agents and Brain Health

As ART continues to extend life expectancy for PWH, attention has increasingly shifted beyond viral suppression to the long-term health of organ systems that are vulnerable to aging and chronic disease, particularly the brain. Notably, Makinson and colleagues (Abstract 454) conducted a 5-year study comparing cognitive changes between PWH aged 55 to 70 years receiving ART and matched PWoH. This multisite French study of 117 PWH and 585 PWoH assessed cognitive changes using a 5-test cognitive battery screening tool. PWH demonstrated worse global neuropsychologic (NP) Z-scores at baseline and experienced greater declines in NP Z-scores during the 5-year study period, with a pronounced decrease in verbal semantic fluency. These findings highlight the need to identify and address risk factors that may negatively affect brain health in PWH.

During the past decade, integrase strand transfer inhibitors (InSTIs), particularly dolutegravir (DTG), have become widely used as components of the initial ART regimens. However, DTG use has been increasingly reported to be associated with the onset or worsening of neuropsychiatric AEs, including insomnia, sleep disturbances, anxiety, and depression. Rodriguez-Evaristo and colleagues (Abstract 464) conducted a randomized, open-label trial at the Hospital de Infectología, Centro Médico Nacional "La Raza" between June 2023 and December 2024 to evaluate changes in depressive and anxiety symptoms, insomnia, and sleep quality among PWH initiating DTG or boosted darunavir (DRV/c) in combination with TDF/FTC. In this study, DTG was associated with higher rates of ART discontinuation due to worsening neuropsychiatric symptoms, including new-onset suicidality and an increased need for psychiatric interventions such as antidepressant therapy. These findings highlight the importance of screening for neuropsychiatric changes after initiating or switching ART regimens.

Dolutegravir was associated with higher rates of ART discontinuation due to worsening neuropsychiatric symptoms, including new-onset suicidality and an increased need for psychiatric interventions

Foster and colleagues (Abstract 463) examined whether DTG inhibits acetylcholinesterase (AChE), a mechanism that could potentially contribute to neuropsychiatric AEs following DTG usage. Using 3-dimensional docking analyses, they demonstrated that DTG interacts with the active site of AChE with high binding affinity, suggesting inhibitory potential. Furthermore, postmortem human brain analyses revealed significantly less AChE activity in the frontal cortex of PWH on DTG-based regimens than in those not on DTG-based regimens. In addition, among PWH who switched from a DTG-based to a non-DTG-based regimen, AChE activity in plasma was significantly reduced. These observations underscore the need for further investigation into DTG-associated modulation of AChE activity and its potential role in neuropsychiatric AEs.

Cooley and colleagues (Abstract 462) examined whether regional brain volume changes differed with lamivudine (3TC) use in middle-aged PWH. Individuals receiving 3TC demonstrated larger brain volumes in the basal ganglia and regions throughout the frontal lobe (eg, orbitofrontal and superior frontal cortices), but significantly smaller parahippocampal volumes, than those on non-3TC-based regimens. The 3TC users exhibited a steeper age-related decline in parahippocampal volume, alongside a lesser decline in regions of the basal ganglia, than those on

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non-3TC-based regimens. However, there were no group differences in cognitive performance cross-sectionally or longitudinally. Given that parahippocampal atrophy is associated with mild cognitive impairment and Alzheimer's disease in the general population, these findings underscore the need for longer-term follow-up studies incorporating neuroimaging and Alzheimer's disease biomarker outcomes.

In addition to neuropsychiatric AEs, previous research suggested an increased risk of stroke among PWH during ART initiation or reinitiation following treatment interruption. Smuts and colleagues (Abstract 442) estimated the annual incidence of stroke and examined the association between stroke occurrence and the timing of ART initiation in a large prospective cohort of PWH in South Africa. They identified 688 PWH with acute or subacute stroke confirmed by neuroimaging, corresponding to an annual incidence rate of 171 per 100,000 adult PWH. More than 85% of strokes were ischemic, most commonly involving the middle cerebral artery territory. Notably, nearly one-quarter of affected individuals had initiated or reinitiated ART within 6 months preceding the stroke event. These findings are consistent with previous studies suggesting an increased risk of stroke during the early months following ART initiation, potentially reflecting an immune reconstitution–like phenomenon. Collectively, these studies reinforce the concept that brain health in PWH is shaped by sustained virologic suppression and by potential ART-related mechanisms.

Several abstracts reported associations between antiretroviral drugs and CNS outcomes, including neuropsychiatric adverse events, brain volume changes, and stroke incidence

Potential Neurologic Impacts of Concurrent Medical Conditions

Beyond the elevated risk of stroke observed in the early months following ART initiation, stroke is more prevalent among PWH than among PWoH, even during the maintenance phase of virologically suppressive ART. Farrell and colleagues (Abstract 448) examined the burden of subclinical cerebrovascular injury among PWH receiving ART in the MACS (Multicenter AIDS Cohort Study)/WIHS (Women's Interagency HIV Study)-CCS (Combined Cohort Study), stratifying findings by cerebral vessel size (small vessel disease [SVD] vs large artery disease [LAD]) and by sex-specific effects of modifiable risk factors. Neuroimaging assessments included brain magnetic resonance imaging, magnetic resonance angiography with vessel wall imaging, and phase-contrast 4-dimensional flow imaging of the intracranial arteries. In the study, female participants exhibited a higher prevalence of hypertension, elevated body mass index, greater depressive symptom burden, lower levels of physical activity, and higher rates of current smoking than male participants. These differences were accompanied by a significantly greater burden of SVD, but not LAD, among women, independent of age, race, cardiovascular disease, and other traditional risk factors. Interventions targeting these modifiable factors may help reduce the observed sex-based disparities in cerebrovascular risk among women with HIV.

Many studies at CROI 2026 explored the association between cognitive changes and metabolic conditions, including diabetes, metabolic dysfunction-associated steatohepatitis (MASH), and metabolic syndrome. Vance and colleagues (Abstract 445) examined cognitive intraindividual variability (IIV), the dispersion in cognitive performance across numerous test results within the same individual, among women with and without HIV in the WIHS and evaluated associated risk factors. A comprehensive cognitive battery of tests spanning 7 cognitive domains demonstrated that women with HIV exhibited greater cognitive IIV across the lifespan than women without HIV. In addition to older age and depressive symptoms, diabetes was identified as a factor associated with increased cognitive IIV, suggesting a potential link between diabetes and neuropathology in women with HIV.

Hockney and colleagues (Abstract 451) investigated whether metabolic syndrome was associated with cognitive impairment in the MACS. The study included 1588 men with or at risk of HIV. A cognitive global deficit score was derived from 6 cognitive domain scores generated by a comprehensive cognitive battery of tests. The findings revealed that older age (≥65 years) was the dominant predictor of cognitive impairment, particularly among PWH. Moreover, the presence of metabolic syndrome among older PWH further increased the risk of cognitive impairment.

In a Thailand-based study, Porkaew and colleagues (Abstract 453) examined longitudinal changes in performance on the Montreal Cognitive Assessment (MoCA) test among 291 PWH aged 50 years or older, stratified by

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the presence of MASH as assessed by transient elastography (FibroScan). Over a median follow-up period of 5.9 years, PWH with MASH experienced a greater decline in MoCA performance than those without MASH. In adjusted models, the association between MASH and MoCA performance decline remained independent of age, sex, body mass index, education level, employment status, smoking, alcohol use, diabetes, hypertension, duration of HIV infection, and ART regimen. These findings underscore the need for prospective studies to determine whether early identification and management of MASH in PWH would reduce the risk of cognitive decline.

Tavasoli and colleagues (Abstract 473) examined the association between cognitive performance and markers of metabolic dysfunction, including glycosylated acetyl groups, the diabetes risk index (DRI), the lipoprotein insulin resistance index (LP-IR), branched-chain amino acids, and gut metabolites. The study included 200 participants equally stratified by HIV status and diabetes mellitus status. Higher DRI and LP-IR levels were associated with worse cognitive performance among PWH, but not among PWoH. These findings suggest that insulin resistance, a key pathophysiologic feature of diabetes, metabolic syndrome, and MASH, may contribute to cognitive vulnerability in PWH, and that HIV infection may confer a unique metabolic susceptibility affecting brain function.

Clinical studies have linked metabolic disorders, including diabetes, metabolic syndrome, and MASH, to adverse neurovascular and cognitive outcomes

Conclusion

The studies presented at CROI 2026 suggest that metabolic comorbidities that accompany aging and some ART regimens used in PWH may play a role in brain health. Given the expanding literature on weight change and metabolic effects of ART drugs, future studies may benefit from investigating whether ART-associated metabolic alterations mediate or modify neurologic outcomes in PWH. These findings underscore the importance of individualized ART selection, vigilant monitoring for neuropsychiatric and cognitive changes, and appropriate screening and management of modifiable metabolic conditions in clinical settings.

All abstracts cited in the text appear in the CROI 2026 Abstract eBook, available online at www.CROIconference.org

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