Invited Review

CROI 2023: Neuropsychiatric Complications in People With HIV

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Abstract. *The 2023 Conference on Retroviruses and Opportunistic Infections (CROI) featured new and impactful findings about neuropsychiatric complications in people with HIV and other infections. Reports included new evidence of (a) the importance of myeloid cells in the pathogenesis of HIV disease in the central nervous system, including as an HIV reservoir; (b) eukaryotic and prokaryotic viruses in cerebrospinal fluid during suppressive antiretroviral therapy; (c) the influence of sex on pathogenesis, including in novel neuropsychiatric biotypes identified by machine learning and other methods; (d) premature aging in people with HIV, including the brain-age gap observed on magnetic resonance imaging; (e) cellular and soluble biomarkers of neuropsychiatric complications in people with HIV; and (f) the neurotoxicity of certain antiretroviral drugs. This review summarizes these and other new findings and highlights new research directions for the neuro-HIV field.*

Keywords: HIV, CROI 2023, cognition, brain, CSF, depression, neurologic complications, neuroimaging, comorbidities

Introduction

The effects of HIV-1 in the central nervous system (CNS) were an important theme of several presentations at the 2023 Conference on Retroviruses and Opportunistic Infections (CROI). This summary is organized into 8 categories that highlight the substantial breadth of the data that were presented: pathogenesis of HIV disease in the CNS, persistence of HIV in the CNS, cognitive trajectories of people with HIV, aging and aging-related complications, neuropsychiatric biotypes, sex differences in neuropsychiatric complications of HIV disease, antiretroviral therapy (ART) and the CNS, and coinfections and the CNS. The exciting data this year inform new research opportunities as well as new implementation strategies to improve the health and welfare of people with HIV and other infections that affect the CNS.

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Pathogenesis of HIV Disease in the CNS

Substantial research supports the importance of myeloid cells, such as brain macrophages and microglia, in the pathogenesis of HIV disease in people with HIV. This research includes several reports that link CD14+CD16+ monocytes, a subset of circulating myeloid cells, to neurocognitive impairment in people with HIV,[1-5] possibly because they are more highly activated,[6] have higher HIV DNA content,[7] and migrate more readily across the blood-brain barrier[8] than other monocyte subsets. Veksler and colleagues built on these findings using specimens collected from participants in the Manhattan HIV Brain Bank, a member of the National NeuroAIDS Tissue Consortium (Abstract 486). They confirmed prior ex vivo findings by using a blood-brain barrier model to demonstrate greater transmigration of CD14+CD16+ monocytes in people with HIV who had neurocognitive impairment (particularly in working memory and speed of information processing) than in unimpaired people with HIV. This increased transmigration was associated with greater expression of CC chemokine receptor 2 on CD14+CD16+ monocytes. The authors also identified associations between higher levels of this cellular subset of myeloid cells and a higher glutamate/glutamine-to-creatine ratio, which can indicate imbalance in excitatory neurotransmission, in the left caudate nucleus using 1H-magnetic resonance spectroscopy.

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Another study evaluated the consequences of ex vivo infection of primary human microglia cells isolated from human postmortem brain tissue (Abstract 477). Dual-tropic envelope protein Morpheus–enhanced green fluorescent protein, an HIV construct encoding reporters for which expression was either HIV long-terminal repeat (LTR) dependent (heat-stable antigen and Cherry) or independent (enhanced green fluorescent protein) was used. The investigators found that more than 70% of the infected microglial cells harbored LTR-silent proviruses and that nonproductive HIV infection was 5 times more common than productive infection. Proteins that were secreted after infection were quantified by proximity extension assay. Infection with the construct resulted in significant microgliosis compared with controls, predominantly with LTR-silent infection that persisted 30 days after infection. Several markers were significantly secreted by infected microglia compared with controls, including vascular endothelial growth factor A, latency-associated peptide (LAP) transforming growth factor (TGF)-β1, urokinase plasminogen activator, colony-stimulating factor-1, and cluster of differentiation (CD)40, which provides evidence for the biologic mechanisms underpinning microgliosis in people with HIV and provides preliminary evidence for biomarkers of HIV infection of microglia in vivo.

The investigators found that more than 70% of the infected microglial cells harbored LTR-silent proviruses and that nonproductive HIV infection was 5 times more common than productive infection

Cross talk between microglia, astrocytes, and neurons was the focus of another presentation (Abstract 482). HIV latently infected microglia from the HC69 cell line that were cocultured with pluripotent stem cell–derived astrocytes had a significant reduction in HIV expression. A similar decrease in HIV expression was demonstrated when pluripotent stem cell–derived microglia cells were also cocultured with astrocytes. This occurred in an adenosine triphosphate–dependent manner that was abrogated by blocking adenosine production, but was reactivated with the addition of tumor necrosis factor (TNF)-β. The addition of astrocytes and pluripotent stem cell–derived neurons resulted in an even greater decrease in HIV expression.

Although CD4+ T cells are the primary reservoir for latent HIV, myeloid cells have been implicated as a secondary reservoir. An evaluation of monocytes and monocyte-derived macrophages from the blood of people with HIV taking long-term suppressive ART was performed with modified versions of the intact proviral DNA assay and the quantitative viral outgrowth assay (Abstract 419). Gag DNA was quantifiable from monocyte-derived macrophages from all participants, although levels were substantially lower than from CD4+ T cells. Within a subset of participants, quantifiable Gag DNA was repeatedly identified from monocyte-derived macrophages over several months. On the intact proviral DNA assay, latent HIV was frequently quantifiable from monocytes, although again levels were lower than for CD4+ T cells. Similarly, several participants had quantifiable latent HIV from monocyte-derived macrophages using the modified quantitative viral outgrowth assay, including a couple of participants who had repeatedly quantifiable levels over several months. Participants who had quantifiable latent HIV from monocyte-derived macrophages also had higher levels of HIV Gag DNA than those with undetectable HIV. This study provides strong evidence that myeloid cells can be a source of latent HIV that could reactivate.

In a rhesus macaque model of HIV, the effect of interleukin (IL)-15 antagonism was studied given its relationship to natural killer and CD8+ T cells (Abstract 479). To deplete these cell populations, 2 doses of rhesusized monoclonal antibody against IL-15 (or phosphate-buffered saline as a control) were given at days –21 and –7 prior to challenge with simian immunodeficiency virus (SIV) SIVmac239X, followed by necropsy at 7 or 14 days after infection. IL-15 neutralization of natural killer and CD8+ T cells resulted in higher SIV RNA levels in the blood but not in the brain, with a modest impact on barcoded virus variants in other tissues. However, IL-15 neutralization did appear to alter the brain immune response: IL-6+ perivascular and parenchymal microglia counts were substantially lower than in the control animals at 7 days as well as at 14 days in parenchyma only. In contrast, TGF-β+ perivascular and parenchymal microglia counts were substantially higher than in control animals at 7 days, with the difference persisting at 14 days only in the perivascular space. Although the reduction in IL-6 and increase in TGF-β in the absence of an increase in SIV RNA in the brain is reassuring, the observed immune changes could more easily allow establishment of a viral reservoir in the brain over a longer period of observation.

Several studies assessed plasma biomarkers as indicators of pathogenesis. Blackwell and colleagues examined associations between plasma biomarkers of neuronal injury, systemic inflammation, and innate immune activation and their relationship with changes in cognitive performance (Abstract 463). This study was performed among people with HIV and demographically similar people without HIV who were followed in the POPPY (Pharmacokinetic and Clinical Observations in People Over Fifty) study conducted in the United Kingdom and Ireland. Ten plasma protein biomarkers were measured: (1) neuronal injury biomarkers (neurofilament light chain, S100β); (2) systemic inflammation biomarkers (IL-2, IL-6, TNF-α); and (3) innate immune activation biomarkers (soluble CD14 [sCD14], IL-10, monocyte chemotactic protein-1 [MCP-1], soluble CD163 [sCD163], macrophage inflammatory protein-1 alpha [MIP-1α]). Within this cohort of predominantly virologically well-controlled White men, only biomarkers of innate immune activation (sCD14, sCD163, MCP-1), and not measures of neuronal injury or systemic inflammation, significantly differed between people with and people without HIV. For both groups, cognitive performance improved over time. Among people with HIV, changes in cognitive performance were associated with only MIP-1α and sCD14, with higher concentrations of each being associated with a worsening of cognition (global T-score) over a 2-year interval. These results suggest that innate immune activation and not neuronal injury or systemic inflammation differs between people with HIV and risk-similar people without HIV, and accounts for the continued cognitive dysfunction seen in people with HIV. Cooley and colleagues assessed neuronal injury (as measured by neurofilament light chain) in older, primarily Black people with HIV who had good virologic control. In this group, neurofilament light chain was associated with cardiorespiratory and physical health but not virologic or cognitive measures (Abstract 468). These results suggest that neurofilament light chain may not be a specific biomarker of cognitive performance, but instead may reflect cerebrovascular disease or metabolic changes seen in people with HIV. In a separate presentation, Cooley and colleagues also assessed the relationship between Alzheimer's disease (AD) plasma biomarkers (Aβ42/Aβ40 ratio, a clinically available blood-based biomarker for brain amyloidosis) and cognition in 4 groups of individuals: (1) cognitively impaired people with HIV; (2) cognitively unimpaired people with HIV; (3) cognitively unimpaired people without HIV; and (4) people without HIV who had symptomatic AD. Aβ42/Aβ40 ratios were low in people without HIV who had AD but not in the other groups (Abstract 487). A lower plasma Aβ42/Aβ40 ratio was also associated with smaller hippocampal volume but, again, only in individuals without HIV who had AD. Thus, the plasma Aβ42/Aβ40 ratio appears to differentiate cognitive impairment due to AD from other cognitive disorders in people with HIV.

After 32 months of antiretroviral therapy, HIV-infected cells decreased significantly within the lymph nodes but remained stable in cerebrospinal fluid

Persistence of HIV in the CNS

Single-cell profiling technologies continue to advance. In a pilot study of a single individual with chronic HIV infection before and after ART from the RV304/SEARCH (South East Asia Research Collaboration with Hawaii) study, Corley and colleagues evaluated blood, cerebrospinal fluid (CSF), sigmoid colon cells, inguinal lymph nodes, and T-follicular helper cells (Abstract 480). Before ART, lymph nodes harbored the highest frequency of HIV RNA-positive cells (3.75%). Less than 1% of all other cell types were HIV infected, with T-follicular helper cells being the least frequently infected (0.55%). After 32 months of ART, HIV-infected cells decreased significantly within the lymph nodes (to 0.03%) but remained stable in CSF (0.09%). HIV-infected cells appeared to express different genes than HIV-uninfected cells, and the genes expressed were different in blood than in lymph nodes (eg, *CD4*, *CD74*, interferon-stimulated gene of 20 kDa protein [*ISG20*], and others from blood and eukaryotic translation initiation factor [EIF], stathmin 1 [STMN1], and others from lymph nodes). To determine whether cryopreserved cells from CSF could be accurately used for these assessments, the cellular yield of fresh CSF was compared with that of cryopreserved CSF. Although the number of cells appeared to be similar, only fresh CSF had detectable HIV-infected cells. Based on receptor data, T-cell clones were shared across the compartments before and after ART, even though overall cell diversity was different across compartments.

In an ART interruption study, the authors evaluated CSF collected from 11 people with HIV, the majority of whom had viremia at the time of interruption (Abstract 478).

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Participants who had pleocytosis (CSF leukocyte count >5 cells/μL) during follow-up had a higher CSF-to-plasma HIV RNA ratio (P = .002). In the setting of pleocytosis, the CSF viral population was dominated by clonally expanded lineages, which were determined by single genome amplification or Illumina MiSeq. In contrast, the viral populations in blood and CSF were similar in the absence of pleocytosis. Using the assay for viral entry based on low surface density of CD4, the authors found that compartmentalized, clonal rebound of HIV in CSF was mostly T-cell tropic, but that CSF clonal rebound with pretherapy virus was rare. Pleocytosis was associated with higher CSF CXCL10 and matrix metalloproteinase-9 (MMP-9) concentrations but not with neurocognitive performance. Although corresponding results from blood during treatment interruption were not reported, the study results support the presence of a T-cell HIV reservoir in the CNS.

The development of single-copy assays has allowed for the identification of low-level HIV RNA in the central nervous system

The development of single-copy assays has allowed for the identification of low-level HIV RNA in the CNS. Single-copy assay results from the CSF and blood were evaluated in relation to soluble biomarkers, cognition, and depressive symptoms among people with HIV receiving ART with HIV suppression by standard assay (Abstract 485). Among 69 participants, 39% had less than or equal to 1 copy/mL of HIV RNA in plasma using a single-copy assay, and in a subset of 50 participants, 48% had less than or equal to 1 copy/mL of HIV RNA in CSF. Compared with participants who had more than 1 copy/mL, those who had less than or equal to 1 copy/mL of HIV RNA in either CSF or plasma had lower Aβ42 (in CSF and plasma), higher 8-hydroxydeoxyguanosine (in CSF and plasma), higher IL-6 (in CSF only), and higher total Tau (in CSF only). In addition, having less than or equal to 1 copy/mL of HIV RNA in plasma was also associated with higher plasma protein carbonyls, and having less than or equal to 1 copy/mL of HIV RNA in CSF was associated with higher CSF soluble TNF-α receptor II (sTNFR-II), lower CSF chemokine ligand 2 (CCL2), and lower plasma D-dimer levels. Having less than or equal to 1 copy/mL of HIV RNA in CSF, but not in plasma, was also associated with more depressive symptoms (P = .005). The use of either tenofovir alafenamide (TAF) (P = .003) or abacavir (P = .014) was associated with having less than or equal to 1 copy/mL of HIV RNA in CSF. Combined, the findings suggest that the combined pharmacologic and immunologic pressure needed to achieve very low HIV RNA concentrations during ART may have detrimental CNS effects.

The gut-brain axis was explored in an analysis of romidepsin for HIV latency reversal (Abstract 481). Neurocognitive performance was characterized with a panel of 6 tests, with impaired performance defined by a composite z score of -0.5 or lower. Three of 15 participants who had lower z scores before administration of romidepsin had stool that was enriched for certain taxa (including *Methanosphaera stadtmanae* and *Ruminococcus obeum*) but depleted of others (*Clostridium* species, *Paraprevotella*, and others). The lower z score group was also functionally enriched in 1,2-propanediol degradation (a pathway of propionic acid synthesis) before administration of romidepsin. An index of the significant taxa was created that decreased longitudinally from before romidepsin to the end of the study (P = .039) in participants with a lower z score. When the analysis was stratified by 2 study groups based on viremic control and the romidepsin intervention, *Desulfovibrio desulfuricans* was consistently associated with worse cognition, and *Parabacteroides johnsonii* was associated with more neuropsychiatric symptoms. The P-values for these findings were less than .05 after false discovery rate correction. This study expands on existing data on the gut microbiome and the CNS in people with HIV.

Cognitive Trajectories of People With HIV

Several studies longitudinally assessed the cognitive trajectories of people with HIV. Paul and colleagues studied the cognitive profile of people with HIV before and after starting ART (on average 6 days after diagnosis of HIV) in the Sabes study ("¿Sabes?" in Spanish means "Do you know?") in Lima, Peru (Abstract 460). Hierarchical longitudinal clustering identified 5 cognitive trajectory subgroups: Group 1 (16% of participants) exhibited above-average performance; Groups 2 (19%) and 3 (35%) performed within the average range; Group 4 (18%) exhibited mild difficulty in memory at baseline, with unimpaired performance on all tests by week 12; and Group 5 (12%) was the lowest-performing group (except for fluency), with scores that became unimpaired only by week 24. Each subgroup achieved unimpaired cognitive performance independent of the timing of ART initiation. These results confirm the findings of previous studies that starting ART soon after seroconversion leads to improvement that is sustained with continued viral control. Damas and colleagues examined cognitive

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performance over 4 years in people with HIV who were enrolled in the NAMACO (Neurocognitive Assessment in the Metabolic and Aging Cohort) study in Switzerland (Abstract 461). The authors focused on the changes in cognitive performance over time as defined by the mean yearly changes in global mean *z* scores from baseline. In this virologically well-controlled group of well-educated, predominantly White men with HIV, neurocognitive performance remained stable or improved over the course of 4 years. Executive function and sensory and perceptual skills particularly improved over time. The observed changes were not due to practice effects, as the tests were administered 2 years apart and different variations of tests were used.

Those with very-low-level viremia or low-level viremia performed worse on tests of memory and attention/working memory than those with effective viral control

The importance of good viral control was further confirmed by Trunfio and colleagues, who studied people with HIV receiving ART in Italy (Abstract 462). These authors assessed the impact of cognitive impairment on adherence as assessed by viral suppression. Participants were classified according to viral control as follows: (1) persistent very-low-level viremia (VLLV): HIV RNA values between not detected and 50 copies/mL at various, consecutive time points; (2) persistent low-level viremia (LLV): HIV RNA values between 50 and 200 copies/mL at various, consecutive time points; (3) viral failure: HIV RNA values greater than 200 copies/mL at various, consecutive time points; or (4) optimal viral control: either all HIV RNA values were not detected or only 1 HIV RNA value was greater than 50 copies/mL. Participants were predominantly White men, and those with VLLV or LLV performed worse on tests of memory and attention/working memory than those with effective viral control. Participants with viral failure performed worse in several cognitive domains than those with viral control. Asymptomatic neurocognitive impairment was associated with higher odds of VLLV or LLV (odds ratio [OR], 2.4; $P = .004$), and the odds were even higher in people with symptomatic neurocognitive impairment (OR, 5.2; $P = .001$). Although this was a longitudinal analysis, the authors did not address the sequence of the effects: Did neurocognitive impairment precede loss of viral suppression, perhaps by impairing memory and reducing ART adherence, or did loss of viral suppression precede neurocognitive impairment, perhaps by increasing immune activation and neuronal injury (or both)? The authors indicated that they are performing these and other analyses to address this issue.

Aging and Aging-Related Complications: Vascular Disease and Frailty

Petersen and colleagues studied the effects of comorbidities and social determinants of health on brain aging as assessed by neuroimaging (Abstract 186). This study was performed within a predominantly Black male group of people with HIV and people without HIV who underwent neuroimaging. A brain-age gap (BAG), defined as the difference between brain-predicted age and chronological age, was modeled as a function of clinical, comorbid, and social factors for these 2 groups. BAG was significantly elevated in people with HIV compared with people without HIV. Among people with HIV, worse BAG was associated with higher Framingham cardiovascular risk score, detectable HIV RNA level, and hepatitis C virus (HCV) coinfection. In subsequent models, BAG was affected by early-life stress and area deprivation index, a socioeconomic measure that combines geospatial data on housing, employment, education, and income. Educational attainment was linked with better BAG for people without HIV but not for those with HIV, consistent with a loss of resilience in people with HIV. Overall, these results suggest that additional comorbid conditions and socioeconomic factors are associated with brain aging along with HIV clinical metrics such as HIV RNA level.

Vascular disease occurs more frequently in people with HIV than in people without HIV and is associated with greater risk of cognitive and mental health disorders. For these reasons, Holroyd and colleagues evaluated relationships between Framingham risk score–based 10-year cardiovascular risk, estimated vascular age, and neurocognitive performance approximately 6 years after ART initiation during acute HIV infection in 356 virally suppressed participants in the RV254 project in Thailand (Abstract 464). Nearly two-thirds of participants had a higher estimated vascular age than their chronologic age, and greater vascular age deviation, defined as the difference between estimated vascular age and chronological age, was associated with higher CD4+ T-cell counts (mean, 0.5 years per 100 CD4+ cells/μL) but

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not with neurocognitive performance as assessed with a brief 4-test battery. One limitation of this project was that the incidence of cardiovascular events was low, likely because participants were generally young (mean age, 32 years at 288 weeks).

Investigators from the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) analyzed the relationships between vascular disease and mental health disorders (Abstract 145). This analysis included a 20-year period from 1997 to 2017 and focused on 2 types of myocardial infarction: type 1 (plaque rupture) and type 2 (demand ischemia). Among 33,071 participants, 49% had a diagnosis of anxiety or depression at baseline. A total of 869 participants subsequently developed myocardial infarction, with 57% of cases being type 1. In multivariable analysis, the diagnosis of depression, but not anxiety, at baseline was associated with incident type 1 myocardial infarction (OR, 1.23). Other covariates included male sex at birth, older age, tobacco use, diabetes mellitus, chronic kidney disease, and protease inhibitor use, as well as 2 covariates with ORs greater than 2 (hypertension and high cholesterol level or statin use). In contrast, the diagnosis of anxiety (OR, 1.42), but not depression, was associated with the occurrence of type 2 myocardial infarction. Older age, tobacco use, cocaine use, hypertension, diabetes mellitus, and detectable HIV RNA level were also associated with type 2 myocardial infarction, with chronic kidney disease (estimated glomerular filtration rate, <60 mL/min/1.73 m^2) having the strongest association (OR, 3.05).

Cerebrovascular disease has been linked to the presence of endothelial cell–derived microvesicles,[9] which can also be present in higher concentrations in people with HIV than in people without HIV.[10] Fandl and colleagues performed ex vivo experiments of human cerebral microvascular endothelial cells and endothelial cell–derived microvesicles that were isolated from the blood of people with and without HIV (Abstract 467). Compared with microvesicles derived from people without HIV, microvesicles from those with HIV were associated with greater inflammation (ie, greater release of IL-6 and IL-8), active endothelial nitric oxide synthase, and endothelin-1 production as well as impaired fibrinolytic capacity. If these events occur in vivo, they could increase the risk of cerebrovascular disease and stroke; thus, this may be another target for intervention.

In addition to the effects mentioned earlier, activation of myeloid cells, including CD14+CD16+ monocytes, influences vascular pathology and increases the risk of cardiovascular disease,[11,12] including carotid intima media thickness.[13] Based on findings on intermediate and nonclassical monocytes and work of their group on platelets,[14-16] Singh and colleagues compared platelet-monocyte complexes with an indicator of cerebral small-vessel disease (white matter hyperintensities on structural brain magnetic resonance imaging) in 110 people with HIV (Abstract 465). They found that people with HIV who had evidence of cerebral small-vessel disease had the highest levels of nonclassical monocytes and the strongest correlation between the circulating percentage of these cells and worse neurocognitive performance, compared with people with HIV without cerebral small-vessel disease and people without HIV. They also found that platelet-monocyte complexes had higher levels of numerous indicators of monocyte and endothelial activation (CCR2, CD40, P-selectin glycoprotein ligand-1 [PSGL-1], TNF receptor 2 [TNFR 2], and tissue factor) than noncomplexed monocytes. These findings are potentially impactful, because measurement of these cells may identify a subgroup of people with HIV whose brain injury is driven more by HIV and cerebrovascular disease than by other conditions. These cells could be targeted by therapeutic interventions.[17]

In multivariable analysis, the diagnosis of depression, but not anxiety, at baseline was associated with incident type 1 myocardial infarction

Frailty continues to be a common comorbidity in older people with HIV and has been associated with cognitive impairment in them.[18] Two presentations on frailty were presented from the multicenter Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort in the US. In the first, the authors compared the full Fried frailty phenotype assessment, which includes objective (strength and slowness) and subjective assessments, with a modified version in which the objective assessments were removed and a subjective mobility assessment was added to ease administration (Abstract 698). Among 522 participants, performance using the modified version significantly correlated ($\rho = 0.81$; $P < .001$) with that using the full version. The area under the receiver operating characteristic curve with the modified version was high for frailty (0.93) and prefrailty (0.86), and higher score on the modified version was also associated with falls in participants aged 55 years

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and older. The modified Fried frailty phenotype could be helpful if an in-person assessment is not possible. In the second CNICS report, the group evaluated comorbidities and symptoms associated with falls (Abstract 699). From a cohort of 2386 people with HIV, 435 (18.2%) reported having a fall in the previous 12 months. After adjustment for demographic factors, frailty was most strongly associated with an increased risk of falls, along with diabetes and self-reported symptoms of memory loss, fatigue, depression, neuropathy, and dizziness. People with HIV could be screened for these common neuropsychiatric symptoms (in addition to common comorbidities) to improve clinical assessments of fall risk.

Focà and colleagues from Italy also focused on falls, evaluating 1331 people with HIV aged 65 years and older (Abstract 700). Overall, they recorded 437 falls over a median of 3.4 years of follow-up, for an incidence of 0.67 falls per person-year. After adjustment for age, HIV infection duration, CD4+ T-cell count, HIV RNA level, and body mass index, multimorbidity (defined as at least 3 comorbidities) was associated with a substantially higher risk of falls (hazard ratio, 2.23; 95% CI, 1.19-4.21). The group also evaluated a subset of 311 people with HIV and compared them with 109 people without HIV who were also aged 65 years and older. After adjustment for age, sex, and multimorbidity, people with HIV had a higher fall risk than people without HIV (hazard ratio, 1.62; 95% CI, 1.07-2.46).

A key component of frailty is sarcopenia, or loss of muscle mass. A study from Thailand evaluated risk factors for sarcopenia in 277 people with HIV taking suppressive ART compared with 130 controls matched for age and sex (Abstract 696). Sarcopenia was defined by objective criteria (grip strength, walking speed, and muscle mass). Additionally, osteoporosis (by dual-energy X-ray absorptiometry scan), frailty (by Fried frailty phenotype), and nutritional status were assessed in the cohort, which had a median age of 55 years. People with HIV had higher rates of sarcopenia (8.3% vs 3.1%; $P = .05$), frailty (9.0% vs 3.1%; $P = .001$), malnutrition risk (18.0% vs 7.0%; $P = .002$), and HCV (9.0% vs 2.3%; $P = .011$) than controls. In multivariable models, several factors were associated with sarcopenia: male sex, body mass index less than 18.5 kg/m^2, HCV coinfection, prefrail or frail status, and malnutrition risk (all $P < .05$). Several of these factors are modifiable.

Brañas and colleagues also addressed frailty, reporting on longitudinally assessed sedentary people with HIV and people without HIV older than 50 years in Spain who were exposed to a 12-week multicomponent exercise program or a control program (Abstract 701). Those who completed the exercise program had improvements in anxiety and depression scores along with increases in muscle mass, strength, and aerobic endurance regardless of HIV serostatus. Overall, a multicomponent exercise program could lead to numerous benefits, including in neuropsychiatric symptoms.

After adjustment for age, sex, and multimorbidity, people with HIV had a higher fall risk than people without HIV

Neuropsychiatric Biotypes: Cognition, Depression, and Sleep Disturbances

Substantial research has focused on neurocognitive impairment in people with HIV, but other neuropsychiatric conditions such as depression and insomnia also commonly occur in this population. For instance, people with HIV are at greater risk than those without HIV for depression, including treatment-resistant depression. Such conditions can coexist in the same individual and can influence each other. To better understand this complexity, efforts have been made to combine these diseases into phenotypes (or biotypes) that might be more consistently linked to biologic mechanisms and therefore be associated with better response to therapeutic interventions.

Several presentations at CROI this year focused on depression. Meeder and colleagues analyzed multidimensional data from 1615 participants in the Dutch cohort study 2000HIV (Abstract 472). Participants completed assessments of substance use, depression, anxiety, impulsivity, sexual risk behavior, and quality of life, as well as ART adherence. In this cross-sectional analysis, the cohort had a low prevalence of symptoms of depression (6.1%) and anxiety (9.3%) compared with historical reports, but a unique aspect of this analysis was the inclusion of Ising network modeling, which indicated that symptoms of depression and anxiety were most strongly associated with impulsivity. More depressive symptoms were also associated with worse quality of life, and substance use was associated with more sexual partners and more sexually transmitted infections (STIs). Although these findings may not be surprising, they do support the use of assessments that extend beyond cognition alone and reinforce the need to implement additional measures in the clinic to better manage depression and substance use.

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An important and mostly unanswered question is what drives the greater risk of depression in people with HIV. Petersen and colleagues attempted to answer this question by comparing 6 soluble biomarkers in plasma from 150 people with HIV and 138 people without HIV who participated in research at the University of California San Diego (Abstract 475). Using factor analysis, they found that the 6 biomarkers loaded onto 2 factors, the first of which included IL-6, C-reactive protein, and D-dimer. This factor was associated with more depressive symptoms, and this relationship was modified by sex: men had a statistically significantly stronger association than women, particularly for IL-6. Rakshasa-Loots and colleagues also analyzed the relationship between soluble biomarkers and depressive symptoms in the COBRA (Comorbidity in Relation to AIDS) cohort and included several soluble biomarkers from both CSF and plasma (Abstract 476). These analyses included 125 people with HIV and 79 people without HIV. Like Petersen and colleagues, they found that IL-6 (in CSF) was associated with more depressive symptoms, along with TNF-α and monocyte induced by gamma interferon (or CXCL9) in plasma and MIP-1α (or CCL3) in CSF. Additional analyses provided evidence that these 4 soluble biomarkers mediated the relationship between HIV status and depressive symptoms, further supporting a role for inflammation in the depressive symptoms seen in people with HIV.

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Two presentations focused on the relationship between ART regimens and depressive symptoms. One was hypothesis driven, focusing on the use of dolutegravir in 280 participants from the CHARTER (CNS HIV Antiretroviral Therapy Effects Research) cohort (Abstract 471). The use of this integrase strand transfer inhibitor (InSTI) was associated with more depressive symptoms, and this association was modified by age, race, and use of antidepressants. People with HIV who used dolutegravir without an antidepressant had a level of depressive symptoms similar to that of people who used an antidepressant. Some of these associations are consistent with published reports (eg, older age[19]), but this is the first report to focus specifically on depressive symptoms and on use of antidepressants. Parra-Rodriguez and colleagues adopted a more discovery-driven approach in their analyses of data from 1538 participants in the WIHS (Women's Interagency HIV Study) (Abstract 469). A categorical transformation of data collected with the Center for Epidemiologic Studies-Depression scale indicated that 29.8% of participants were in a "high depression" group, that is, they had a value of at least 16 on at least 50% of assessments over time. Within this group, novel Bayesian machine learning methods showed that the combination of TAF with either a cobicistat-boosted InSTI or a protease inhibitor was associated with more somatic symptoms, such as poor concentration, sleep, and motivation. As cobicistat is not used to boost InSTIs other than elvitegravir, these findings differ from those that have implicated dolutegravir in neuropsychiatric adverse events. The observed association with TAF may be consistent with the previously mentioned report from Anderson and colleagues that identified associations between the use of TAF, single-copy HIV RNA suppression in CSF, and depressive symptoms (Abstract 485).

In addition to depression, neurocognitive impairment in people with HIV is associated with sleep disturbances, the focus of another set of analyses of data from the WIHS cohort (Abstract 473). A total of 337 women with HIV underwent neurocognitive testing and completed the Pittsburgh Sleep Quality Index questionnaire. About one-third met criteria for neurocognitive impairment, and in this subgroup, worse sleep quality was associated with worse neurocognitive performance. Additional analyses of components of sleep quality and cognitive domains indicated that mid-sleep waking was associated with poorer processing speed and executive function, bad dreams were associated with poorer processing speed, pain was associated with poorer working memory, and shorter sleep duration was associated with poorer attention and executive function. Another presentation summarized analyses of multidimensional data (objectively measured cognitive domains, depressive symptom subscales, subjective cognitive symptoms, and instrumental activities of daily living [ADLs]) from 1580 people with HIV in the CHARTER cohort using a 2-stage, unsupervised, machine learning clustering approach of self-organizing maps for dimension reduction followed by k-means clustering by Mahalanobis distance (Abstract 474). The goal was to identify novel phenotypes that are distinct from those

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typically identified based on neurocognitive testing alone. Analyses identified 4 phenotypes: a healthy group with good performance on the 17 analyzed features (38.5% of the cohort), a second group with a combination of mild neurocognitive impairment, moderate-to-severe depression, and mild impairment in ADLs (17.1%), a third group with mild neurocognitive impairment and very poor measurements on all other dimensions (12.9%), and a fourth group with mild-to-moderate neurocognitive impairment but largely without depressive or cognitive symptoms or impaired ADLs (31.5%). No data were presented to support that these phenotypes were more strongly associated with biologic indicators than, for example, neurocognitive impairment alone or that they may be associated with better response to therapeutic interventions, but the findings do support the potential importance of broadening our understanding of the various ways in which HIV and syndemic conditions may affect brain function.

An area of active investigation is the degree to which HIV-syndemic conditions, such as substance use and STIs, account for the brain-related complications seen in people with HIV, compared with HIV itself. For example, a published study showed similar prevalence of neurocognitive impairment in men who have sex with men (MSM) whether they had HIV or not.[20] Robertson and colleagues extended these prior findings by measuring 4 soluble biomarkers in CSF and blood in 135 participants (50 MSM with HIV who were taking suppressive ART, 50 MSM without HIV who were taking preexposure prophylaxis [PrEP], and 35 people who did not have HIV-related behavioral risk factors and who did not take PrEP ["controls"]) (Abstract 184). They found that both groups of MSM had higher levels of 3 of the 4 biomarkers than the control group (β_2-microglobulin, neopterin, neurofilament light), but they did not differ from each other. This important finding highlights the need to better understand the biologic effects of HIV-related behavioral risk factors such as substance use and STIs. Contributing effects of drugs used for PrEP must also be considered.

Sex Differences in Neuropsychiatric Complications of HIV Disease

Several studies addressed the influence of sex on neuropsychiatric complications in people with HIV. Chow and colleagues studied whether sex modifies the effects of traditional and HIV-related risk factors on stroke in people with HIV (Abstract 183). This group evaluated data from 5 CNICS sites that follow people with HIV who receive medical care. Strokes were adjudicated by neurologists. Among 13,584 people with HIV, there were 147 incident strokes during follow-up. Within this group, age but not sex was a risk factor for stroke, and a substantial age-by-sex interaction was observed. At younger ages, the risk of stroke was higher for women than for men. However, at older ages, women and men had similar risks of stroke. The risk of stroke in women was greater when they had a detectable HIV RNA level or used methamphetamine. These results suggest that additional risk factors for stroke, including viremia and drug use, should be considered for women, especially those who are younger.

Giron and colleagues studied the effects of long-term HIV infection on host glycomic alterations, including the loss of galactose (agalactosylation; measured as high levels of G-terminal ratio and G0 glycan groups), among men and women from the MACS (Multicenter AIDS Cohort Study)/WIHS Combined Cohort Study (Abstract 260). This study compared people with HIV on ART to people without HIV. HIV was associated with sex-dependent glycomic alterations: men and women had an induction of the proinflammatory agalactosylated glycans, but men had a reduction of anti-inflammatory sialylated glycans and women had a greater reduction of fucosylated glycans. HIV also accelerated the pace of age-associated agalactosylation. An increase in agalactosylation also correlated with inflammatory biomarkers of biologic aging and subclinical atherosclerosis. Overall, these results indicate new adverse, glycomic effects in HIV that appear to be sex dependent.

An area of active investigation is the degree to which HIV-syndemic conditions, such as substance use and sexually transmitted infections, account for the brain-related complications seen in people with HIV, compared with HIV itself

In addition to the effects of HIV, long-term ART may also play a role in these findings. Wells and colleagues studied whether sex-based differences affect the natural and treated history of HIV infection and immune responses within the ALLRT (AIDS Clinical Trials Group Longitudinal Linked Randomized Trials) cohort (Abstract 261). For a panel of 27 cytokines, the team did not observe significant differences in concentrations between men and women, with the sole exception of IL-18. For men and women, myeloid activation biomarkers were the ones that principally

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declined after initiation of ART. Leskov and colleagues studied whether shifts in innate immunity transcriptome signatures occur during the menopause transition and affect HIV pathogenesis (Abstract 262). The presenters noted that the latent HIV reservoir expands in women with HIV during reproductive aging. This reservoir expansion is accompanied by a shift of CD4+ T cells toward a more cytotoxic pro-inflammatory state that occurs during the premenopausal to perimenopausal transition.

Based in part on published data linking higher anti-cytomegalovirus (CMV) immunoglobulin G (IgG) levels to neurocognitive impairment[21] and higher Epstein-Barr virus (EBV) DNA levels in CSF to higher CSF neopterin levels,[22] Riggs and colleagues measured CMV and EBV DNA levels in peripheral blood mononuclear cells as well as anti-CMV IgG and anti-EBV viral capsid antigen IgG levels in plasma collected from 486 people with HIV who participated in cohort studies at the University of California San Diego (Abstract 491). Lower CMV DNA level correlated with worse neurocognitive performance, but only among women with HIV. The direction of this correlation was opposite to what was expected, which might be explained by the observation that lower CMV DNA level correlated with higher anti-CMV IgG level only in women. These analyses were limited to people with HIV who were taking suppressive ART and who did not have an acute coinfection. Henderson and colleagues described the correlates of CSF viral escape in 114 people with HIV who had a clinical indication for lumbar puncture (Abstract 185). One in 6 participants met criteria for CSF viral escape (ie, HIV RNA level in CSF greater than HIV RNA level in plasma), which was associated with the presence of ART drug resistance mutations and the use of ART drugs other than InSTIs. As in a prior publication,[22] the presence of EBV DNA in CSF was associated with CSF pleocytosis (median, 26 cells/μL) along with fewer CD4+ T cells, but EBV was not considered clinically related to any of the clinical conditions being evaluated (eg, neurosyphilis).

In addition to these more virus-focused analyses, Eden and colleagues from the University of Gothenburg presented new findings on an under investigated aspect of the host immune response, complement (Abstract 483). They measured components of the complement cascade (complement factor B, C1q, C3a, C4b2a, C5, C5a, and C3b) in CSF collected from 45 people with HIV and 28 people without HIV and found differences between the groups for components of all complement activation pathways, with generally lower levels in people with HIV. Lower levels would be consistent with complement consumption, perhaps by complexing with viral antigens or immune complexes. In people with HIV who were not taking ART, levels of complement components also correlated with neopterin levels in CSF, which in turn correlated with neurofilament light, 2 biomarkers that have been well linked to neurocognitive impairment in people with HIV. While small and cross-sectional, this project suggests that the complement system may influence the myeloid activation and neuronal injury that can occur in people with HIV.

ART and the CNS: Neurotoxicity and Novel Formulations

The potential neurotoxicity of ART continues to warrant investigation. Using a zebrafish model, Zizioli and colleagues evaluated dolutegravir exposure with and without folate rescue in relation to locomotor activity (Abstract 470). The group found that without folate rescue, dolutegravir-exposed embryos had substantially reduced locomotor activity, an effect that was abrogated by folate rescue. Raltegravir administration with or without folate did not impact locomotion. The group also evaluated neurogenin 1, a transcription factor that plays an important role in the development of dopaminergic neurons. In animals exposed to dolutegravir, neurogenin 1 expression was decreased in brain areas enriched with dopaminergic neurons, and spinal cord neurons that were peripheral projections of central dopaminergic neurons were consistently missing. This effect appeared to be strongest in the absence of folate.

Lower cytomegalovirus DNA level correlated with worse neurocognitive performance, but only among women with HIV

Structural modification of ART may reduce toxicity potential. A long-acting nanoformulation of dolutegravir was tested in the C3H/HeJ mouse model of pregnancy (Abstract 784). Intramuscular administration of nanoformulated dolutegravir resulted in maternal plasma dolutegravir concentrations in the blood similar to those of standard dolutegravir administration but was associated with a significantly lower dolutegravir concentration in embryonic brain tissue. Standard dolutegravir also led to less T1 relaxivity (indicative of more oxidative stress) on magnetic resonance imaging than that seen with nanoformulated dolutegravir, which was similar to that in control animals. Standard dolutegravir was also associated with significantly more changes in brain proteins than nanoformulated dolutegravir. While current guidelines endorse

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dolutegravir use in pregnancy, the results of this study support further research on dolutegravir nanoformulation.

In a study evaluating the effect of long-acting ART on myeloid cells (Abstract 427), rilpivirine and cabotegravir were loaded into lipid-wrapped polymeric nanoparticles expressing GM3, the CD169 ligand. The nanoparticle-ART regimen was retained in CD169+ monocyte-derived macrophages after almost 1 month in vitro and was associated with antiviral potency at this time point that was not present with the standard formulation of the drugs. In BALB/c mice, GM3 poly-lactic acid nanoparticles persistently colocalized with CD169+ macrophages in secondary lymphoid tissues, which did not occur with GM3-deficient nanoparticles. Lastly, treatment with GM3+ nanoparticle ART was associated with sustained virologic suppression for 3 weeks in bone marrow–liver–thymus humanized mice; this suppression did not occur with free drugs and was not as robust with GM3-deficient nanoparticles. Although the study did not evaluate brain tissue concentrations, it did demonstrate that nanoparticle ART could be tailored to reach specific cell types.

In another study evaluating the effect of long-acting ART on myeloid cells, bictegravir prodrugs were synthesized and then encased in nanocrystals in different formulations (dimeric: NMXBIC; monomeric: NMBIC, NM2BIC, and NM3BIC) (Abstract 540). These modifications allowed for enhanced hydrophobicity and lipophilicity without decrease in stability at 90 days. When tested in vitro with monocyte-derived macrophages, the drugs appeared to have minimal toxicity and preserved antiviral potency compared with standard bictegravir. Uptake and retention of all 4 nanoformulated drugs was high, with no loss of p24 inhibition after HIV-1ADA challenge. After a single intramuscular injection, the drugs were evaluated in BALB/cJ mice, Sprague Dawley rats, and rhesus macaques. Therapeutic bictegravir concentrations persisted long enough with the NMXBIC and NM2BIC formulations that the investigators concluded that they could be dosed every 6 months, which would substantially improve on the currently approved once daily dosing of bictegravir.

Coinfections and the CNS

Cryptococcal meningitis continues to be a devastating opportunistic infection worldwide in people with HIV. A trio of studies involving individuals with HIV and cryptococcal meningitis in Uganda were presented. In Abstract 489, CSF immune biomarkers reflecting different T-helper cell responses were evaluated in relation to survival in 480 individuals. Women were significantly less likely to survive than men over 18 weeks of follow-up (47% vs 59%; $P = .02$). Several CSF immune markers were lower in women who died than in women who survived, including TNF-α, CXCL10, and IL-10. IL-10 was also lower in men who died than in those who survived, whereas the only other biomarker that differed between the 2 groups of men was IL-15, which was higher in those who died. These data suggest that immune responses may differ in women and men with cryptococcal meningitis and may influence survival. In a second presentation (Abstract 748), neuropsychologic testing was performed in 210 participants 12 weeks after their first episode of cryptococcal meningitis in the ASTRO-cm (Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis) trial. A total of 72% of participants were neurocognitively impaired on an 8-test battery at 12 weeks. Compared with participants who were unimpaired at 12 weeks, these participants had lower Glasgow Coma Scale values, lower serum sodium levels, and more seizures at baseline. Individuals with impairment at 12 weeks also were less likely to have had sterile CSF at baseline (5.3% vs 13.8%; $P = .04$) and had fewer CSF leukocytes at day 7 (median, <5 cells/μL vs 25 cells/μL; $P = .03$). Clearly, more effective treatments for cryptococcal meningitis are needed to optimize neurocognitive outcomes as well as survival. One limitation to this study was that flucytosine, an important adjunct to amphotericin, was not used.

The third and largest of the analyses from Uganda involved 874 people with HIV with cryptococcal meningitis combined from the ASTRO-cm study and the AMBITION-cm (AMBIsome Therapy Induction Optimisation) study (Abstract 749). Total CSF protein was evaluated in relation to clinical characteristics, CSF immune markers, and survival. Participants who had a CSF protein level above 100 mg/dL at baseline had better survival at 18 weeks (log-rank $P = .02$) as well as a higher baseline CD4+ T-cell count ($P < .001$), a lower CSF cryptococcal fungal burden ($P < .001$), and a higher percentage of sterile CSF cultures at day 14 ($P = .02$). In addition, participants with elevated CSF protein level were more likely to have a Glasgow Coma Scale value below 15 ($P < .01$) and self-reported seizures ($P = .03$). Combined, these associations may be due to a stronger immune response to *Cryptococcus*, which might cause more symptoms during the acute illness, but then more rapid resolution of symptoms and survival. This conclusion was supported by higher CSF protein level being associated with higher CSF concentrations of multiple cellular and soluble biomarkers, including CSF leukocytes ($P < .001$), IL-1β, IL-1Ra, IL-6, CXCL8/IL-8, IL-17, granzyme B, CXCL1/GROA, and programmed cell death ligand 1 (all $P < .05$).

The impact of COVID-19 on people with HIV continues

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to be substantial. Data were presented from a study in Thailand in which 112 MSM were followed longitudinally (Abstract 188) after acute HIV infection. After baseline evaluation, which included brain magnetic resonance imaging as well as testing for cognition and mood, 54 of the 112 participants later developed COVID-19 (median follow-up, 79 weeks). Although the 2 groups generally did not differ in terms of demographics, those who developed COVID-19 had significantly smaller pallidum volume at baseline (false discovery rate–adjusted P= .025). In machine learning models, several brain region volumes (particularly the right brain) were associated with the development of COVID-19, including smaller right pallidum. More depression symptoms, higher IL-6 level, and amyl nitrite (poppers) use were also associated with the development of COVID-19. These imaging differences may translate into differences in risk-taking behavior between the 2 groups. A separate article in *Topics in Antiviral Medicine* reviews other presentations on COVID-19, including its neuropsychiatric effects.[23]

Detection of viral sequences in CSF did not relate to neurocognitive performance, depressive symptoms, or soluble myeloid and neuronal biomarkers in CSF

Another common coinfection in people with HIV is HCV. In another analysis from the Bangkok acute HIV cohort, 79 people with HIV acquired HCV after starting ART; 50 were subsequently treated with direct-acting antiviral agents and achieved sustained virologic response (Abstract 490). In addition to improvements in liver enzyme levels and CD4+ T-cell counts, sustained virologic response was associated with improvement on a 4-test cognitive battery (P = .004) as well as 1 measure of stress. This study adds more evidence of HCV treatment benefits in people with HIV that extend beyond the liver.

Based on the potential contribution of the human virome to HIV comorbidities and other diseases, Trunfio and colleagues evaluated CSF from 81 people with HIV receiving suppressive ART for viral RNA and DNA levels (Abstract 488). Fifty-eight of these samples had retrievable results for prokaryotic and eukaryotic viruses, and 25.9% had a CSF HIV RNA level greater than 20 copies/mL. The most common eukaryotic viruses identified in CSF were EBV, HCV, human herpesvirus-6, human papillomavirus-96 and -201, and Torque Teno virus. Meanwhile, 13 classes of prokaryotic viruses were identified, with Siphoviridae being the most abundant. Detection of viral sequences in CSF did not relate to neurocognitive performance, depressive symptoms, or soluble myeloid and neuronal biomarkers in CSF. However, CSF virome within-sample diversity (alpha diversity) was greater in participants with polymerase chain reaction-detectable CSF HIV-1 RNA level, lower CSF glucose level, and a CD4+ count of less than 500 cells/μL. These results were significant in correlational analysis as well.

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Financial relationships with ineligible companies within the past 24 months: Dr Anderson reported grant funding paid to his institution by Eli Lilly in 2023. (Updated June 27, 2023) Dr Ances reported no relevant financial relationships with ineligible companies. (Updated June 27, 2023) Dr Letendre reported grant funding paid to his institution from Merck & Co., Inc. (Updated June 27, 2023)

Reviewer 1 reported consultant or received advisor fees from Antiva, Assembly Biosciences, Generate Biomedicines, and IGM Biosciences, and fees for participation in review activities, eg, data monitoring boards, statistical analysis, or endpoint adjudication committees with Gilead Sciences, Inc. (Updated June 30, 2023) Reviewers 2 and 3 reported no relevant financial relationships with ineligible companies. (Updated April 23, 2023)

All relevant financial relationships with ineligible companies have been mitigated.

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