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COGNITIVE AND EMOTIONAL CONSEQUENCES OF HIV: A PSYCHONEUROIMMUNOLOGY REVIEW

Emmanuel Ifeanyi Obeagu

Department of Biomedical and Laboratory Science, Africa University, Zimbabwe.

Email : emmanuelobeagu@yahoo.com,

ABSTRACT

HIV infection, historically known for its devastating impact on the immune system, is now increasingly recognized for its effects on cognitive function and emotional well-being. The intersection of HIV, brain health, and mental disorders forms a critical area of study within the field of psychoneuroimmunology, which explores how the immune and nervous systems interact. Even in the era of effective antiretroviral therapy (ART), many individuals living with HIV continue to experience neurocognitive impairments and psychiatric symptoms, indicating that viral suppression alone is insufficient to prevent central nervous system (CNS) complications. Cognitive impairments such as memory loss, decreased attention span, and executive dysfunction fall under the umbrella of HIV-associated neurocognitive disorders (HAND), which persist in a significant portion of patients despite virologic control. Contributing mechanisms include chronic immune activation, neuroinflammation, blood-brain barrier disruption, and the presence of viral reservoirs within the CNS. At the same time, emotional disorders like depression, anxiety, and post-traumatic stress disorder (PTSD) are prevalent among people living with HIV, often linked to both biological and psychosocial factors. These conditions not only reduce quality of life but also affect treatment adherence and immune recovery.

Keywords: *Cognitive Impairment, Emotional Disorders, HIV, Neuroinflammation , Psychoneuroimmunology*

Introduction

The global HIV epidemic, once synonymous with rapid immune decline and high mortality, has been transformed by advances in antiretroviral therapy (ART) into a manageable chronic illness. However, despite virologic suppression and prolonged survival, individuals living with HIV (PLWH) continue to face substantial neurocognitive and psychological challenges. These cognitive and emotional disturbances—ranging from mild attention deficits to major depressive episodes—are increasingly recognized as persistent and clinically significant components of HIV pathology [1-4]. Historically, HIV research prioritized immune system compromise and opportunistic infections, with less attention to the neuropsychiatric dimensions of the disease. Yet, the brain is a known target of HIV, and neurological involvement often begins early in infection. The virus gains access to the central nervous system (CNS) via infected monocytes and lymphocytes, establishing reservoirs and triggering chronic neuroinflammation. This process contributes to neuronal injury and dysfunction, even in individuals who are adherent to ART [5-7]. Psychoneuroimmunology—the interdisciplinary field that examines interactions between the nervous system, immune system, and psychological processes—offers a valuable lens for understanding the complex interplay between HIV infection and mental health. Within this framework, immune activation and inflammatory signaling are not merely peripheral phenomena but central mediators of behavior, cognition, and mood. HIV-induced immune dysregulation affects not only peripheral tissues but also neural circuits involved in memory, emotion regulation, and executive functioning [8-12].

Cognitive impairments in HIV, collectively referred to as HIV-associated neurocognitive disorders (HAND), remain prevalent in the ART era. These conditions vary in severity, from asymptomatic neurocognitive impairment to disabling HIV-associated dementia. HAND affects multiple domains, including learning, attention, psychomotor speed, and planning ability. The persistence of HAND despite successful ART suggests that chronic inflammation, rather than viral replication alone, plays a dominant role in its pathogenesis [13-6]. In parallel, emotional and psychological disturbances such as depression, anxiety, and post-traumatic stress disorder (PTSD) are disproportionately observed among PLWH. These disorders are influenced by a combination of psychosocial stressors, stigma, and biological changes, including altered cytokine expression and hypothalamic-pituitary-adrenal (HPA) axis dysregulation. Depression in particular has been linked to increased immune activation and poorer health outcomes, including reduced ART adherence and faster disease progression [17-20]. The gut-brain axis also emerges as a critical pathway in the neuroimmune

interface. HIV-related gut dysbiosis and microbial translocation contribute to systemic inflammation, which may further affect cognitive and emotional function. Additionally, co-morbidities such as substance use, hepatitis co-infection, and aging compound the neurocognitive burden. As HIV increasingly resembles a chronic condition, the cumulative impact of these neuroimmune interactions becomes more apparent [21-22].

Aim

This review aims to explore the cognitive and emotional consequences of HIV infection through the lens of psychoneuroimmunology, elucidating the underlying mechanisms that connect immune dysfunction, neurological impairment, and psychological disorders.

The Psychoneuroimmunological Framework

Psychoneuroimmunology (PNI) is an interdisciplinary field that explores the dynamic interactions between the central nervous system (CNS), the immune system, and psychological processes. At its core, PNI posits that the brain and immune system are engaged in bidirectional communication, mediated through neuroendocrine, cytokine, and neurotransmitter signaling. In the context of HIV, this framework provides critical insights into how immune dysregulation and chronic inflammation influence brain function and behavior, contributing to both cognitive decline and emotional disturbances [23-26]. HIV infection disrupts the delicate neuroimmune balance early in its course. Once the virus crosses the blood-brain barrier (BBB)—often through infected monocytes or T-cells—it establishes reservoirs in the CNS, particularly within microglial cells and perivascular macrophages. These reservoirs are resistant to ART and contribute to chronic neuroinflammation. Activated microglia and astrocytes release pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), which in turn interfere with synaptic transmission, neurogenesis, and neuronal viability [27-31]. Chronic inflammation in HIV is not limited to the CNS but extends systemically due to persistent immune activation, microbial translocation from a damaged gut barrier, and residual low-level viral replication. These processes maintain a state of immune exhaustion and lead to sustained elevation of inflammatory biomarkers. Such systemic immune activation feeds back into the brain via circulating cytokines and vagal nerve pathways, influencing mood regulation, stress response, and cognition [32-34].

Another key aspect of the PNI framework in HIV is the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. HIV-related stress and inflammation can lead to hyperactivation of the HPA axis, resulting in elevated cortisol levels and altered diurnal rhythms. Chronic cortisol elevation is neurotoxic, particularly to hippocampal neurons involved in memory and emotional processing, thereby exacerbating both cognitive dysfunction

and depressive symptoms in people living with HIV [35-38]. Furthermore, neurotransmitter imbalances, particularly involving serotonin, dopamine, and glutamate, are common in HIV-associated neurocognitive disorders (HAND) and depression. These imbalances are partially driven by immune-modulated enzymatic pathways, such as the indoleamine 2,3-dioxygenase (IDO) pathway, which shifts tryptophan metabolism away from serotonin synthesis toward the production of neurotoxic metabolites like quinolinic acid [39-42]

Cognitive Impairments in HIV

Cognitive impairments are a well-documented and persistent complication in individuals living with HIV, even in the presence of effective antiretroviral therapy (ART). These impairments, collectively referred to as HIV-associated neurocognitive disorders (HAND), encompass a spectrum of cognitive deficits ranging from mild to severe, and significantly impact quality of life, daily functioning, and treatment adherence. Despite reductions in the incidence of HIV-associated dementia in the ART era, milder forms of neurocognitive dysfunction remain prevalent, affecting up to 30–50% of people living with HIV (PLWH) [43-45]. The domains most commonly affected include attention and concentration, executive function, memory, information processing speed, and psychomotor coordination. Early signs may be subtle, such as increased forgetfulness, difficulty multitasking, or reduced efficiency at work. Over time, without adequate detection and management, these impairments can evolve into more pronounced limitations that interfere with independent living. These deficits are particularly concerning given the chronic nature of HIV infection and the growing population of aging PLWH, in whom cognitive decline may be compounded by other neurodegenerative risks [46-48]. The pathogenesis of HAND is multifactorial, with chronic immune activation and persistent neuroinflammation playing central roles. Infected monocytes and macrophages in the CNS release neurotoxic cytokines and viral proteins, such as gp120 and Tat, which disrupt synaptic function and lead to neuronal injury. Oxidative stress, excitotoxicity via glutamate dysregulation, and blood-brain barrier dysfunction further contribute to the cognitive decline observed in these patients. Notably, neuroimaging and neuropathological studies have revealed structural brain changes—including cortical and subcortical atrophy, white matter lesions, and reduced hippocampal volume—in individuals with HAND [49-51].

Beyond direct viral effects, other risk factors amplify cognitive vulnerability. These include co-infections (e.g., hepatitis C), substance use disorders, cardiovascular comorbidities, and socioeconomic stressors. Additionally, cognitive decline may be worsened by polypharmacy, drug-drug interactions, or ART neurotoxicity in some individuals. Aging itself adds complexity, as it is associated with both immune senescence and neurodegeneration, potentially

accelerating cognitive impairment in older PLWH [52-55]. Early diagnosis of HAND is critical but remains challenging due to its insidious onset and overlap with other neuropsychiatric conditions. Standard neuropsychological batteries, although comprehensive, are time-consuming and often inaccessible in resource-limited settings. As a result, there is growing interest in developing rapid screening tools and digital assessments that can be integrated into routine HIV care. Biomarkers—such as neurofilament light chain, monocyte activation markers, and neuroimaging correlates—are also being explored as potential diagnostic and prognostic aids [56-59].

Emotional and Psychological Disorders in HIV

In addition to cognitive deficits, emotional and psychological disorders are highly prevalent among people living with HIV (PLWH) and represent a significant, yet often underappreciated, burden. Depression, anxiety, post-traumatic stress disorder (PTSD), and substance use disorders are the most commonly reported conditions in this population, frequently coexisting and contributing to reduced quality of life, impaired immune function, and poor adherence to antiretroviral therapy (ART). These mental health challenges are not merely reactive to diagnosis or stigma but are also deeply embedded in the neuroimmunological alterations driven by HIV infection itself [60-61]. Depression affects up to 30–60% of PLWH, a rate significantly higher than that of the general population. While psychosocial stressors such as HIV-related stigma, socioeconomic adversity, and social isolation play important roles, biological mechanisms are increasingly recognized in the pathogenesis of HIV-associated depression. Chronic immune activation and elevated levels of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α) are known to influence brain regions involved in mood regulation, including the prefrontal cortex, amygdala, and hippocampus. These cytokines can also alter neurotransmitter metabolism, particularly by shifting tryptophan metabolism toward the kynurenine pathway, resulting in neurotoxic metabolites that promote depressive symptoms [62-63]. Anxiety disorders, particularly generalized anxiety and panic disorder, are also frequently observed in PLWH. These conditions may stem from anticipatory fears about disease progression, disclosure, or mortality, but are also amplified by HIV-induced dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Dysregulation of cortisol secretion and feedback inhibition in this axis not only contributes to chronic stress responses but also exacerbates vulnerability to anxiety, insomnia, and irritability. Furthermore, the neurological effects of HIV, including disruption of GABAergic and serotonergic systems, may directly influence anxiety-related behaviors [64-65]. Post-traumatic stress disorder (PTSD) is another major concern, particularly among individuals with histories of abuse, incarceration, or migration, as well as those who

experienced trauma at the time of HIV diagnosis or from witnessing others succumbs to the disease. HIV-related PTSD is associated with heightened inflammatory responses and exaggerated stress reactivity, both of which may accelerate disease progression and interfere with cognitive processing. The cyclical relationship between trauma, immune function, and neurocognition highlights the need for trauma-informed care models in HIV settings [67].

Substance use disorders—ranging from alcohol and nicotine dependence to illicit drug abuse—frequently coexist with emotional disturbances in PLWH and often serve as maladaptive coping mechanisms. Substance use not only impairs adherence to treatment and medical appointments but also synergizes with HIV to intensify neurocognitive decline. Moreover, some substances, such as methamphetamine or opioids, have direct neurotoxic effects and may exacerbate neuroinflammation when used chronically in the context of HIV [68]. The bidirectional interplay between emotional disorders and HIV progression further complicates management. Depression and anxiety are associated with poorer ART adherence, reduced engagement in care, and faster immunological decline, creating a feedback loop that worsens both physical and mental health outcomes. Conversely, successful treatment of mood disorders has been shown to improve ART adherence, reduce viral load, and enhance quality of life, underscoring the critical role of integrated mental health care in HIV treatment paradigms [69].

Mechanistic Pathways Linking HIV, Cognition, and Emotion

The relationship between HIV, cognition, and emotion is complex, with overlapping mechanistic pathways that bridge immunological, neurological, and psychological domains. Understanding these interconnected processes is critical for grasping the full scope of HIV's impact on the brain and behavior. Psychoneuroimmunological insights have revealed that HIV exerts its cognitive and emotional effects not merely through opportunistic infections or psychosocial stressors, but through specific biological mechanisms that disrupt neuronal homeostasis and psychological regulation [70]. A central pathway involves chronic immune activation and neuroinflammation. HIV's entry into the central nervous system (CNS) triggers the activation of resident immune cells—particularly microglia and astrocytes—which produce pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-a), and interleukin-6 (IL-6). These inflammatory mediators interfere with synaptic function, disrupt the blood-brain barrier (BBB), and induce oxidative stress and mitochondrial dysfunction. Such neuroinflammatory responses are directly implicated in both cognitive decline and depressive symptoms, particularly through damage to brain regions like the hippocampus and prefrontal cortex [60]. Another important mechanism is the dysregulation of the

hypothalamic-pituitary-adrenal (HPA) axis. HIV-related chronic stress and immune activation lead to sustained secretion of cortisol, a glucocorticoid hormone that, in excess, becomes neurotoxic. High cortisol levels are associated with hippocampal atrophy, impaired memory consolidation, and increased vulnerability to depression and anxiety. Additionally, altered cortisol rhythms in people living with HIV (PLWH) reflect the ongoing stress burden and contribute to emotional dysregulation and cognitive fatigue [61].

Neurotransmitter imbalance also serves as a mechanistic link. HIV infection and the resulting inflammation activate the indoleamine 2,3-dioxygenase (IDO) enzyme, diverting tryptophan metabolism from serotonin synthesis toward the kynurenine pathway. This metabolic shift not only reduces the availability of serotonin—a neurotransmitter crucial for mood regulation—but also increases the production of neurotoxic metabolites likes quinolinic acid, which contribute to excitotoxicity and neuronal injury. These changes collectively manifest as depression, anhedonia, and cognitive slowing [62]. Additionally, HIV can directly interfere with neural plasticity and neurogenesis. Viral proteins such as gp120 and Tat are known to be neurotoxic, inducing synaptic dysfunction and promoting apoptosis of neurons. These viral proteins can also amplify glutamate excitotoxicity by impairing glutamate transporters and enhancing calcium influx, leading to synaptic degeneration. The cumulative result is a structural and functional compromise of neuronal networks vital for both higher-order thinking and emotional processing [63]. Another emerging mechanism involves the gut-brain axis. HIV-induced gut dysbiosis and microbial translocation result in systemic immune activation that further influences brain function through circulating endotoxins and cytokines. The vagus nerve and circulating immune factors transmit gut-derived signals to the brain, affecting mood, cognition, and behavior. This mechanism may explain, in part, why PLWH with gastrointestinal complications frequently experience heightened emotional distress and cognitive symptoms [64]. Genetic and epigenetic factors also contribute to individual variability in neurocognitive and emotional outcomes. Polymorphisms in genes related to inflammation, neurotransmitter transporters, and neurotrophic factors may modulate susceptibility to HAND or psychiatric disorders. Additionally, HIV-related epigenetic modifications—such as DNA methylation changes in neural genes—may persist even under ART, suggesting long-term reprogramming of neuroimmune pathways[65].

Clinical Implications

The clinical implications of the cognitive and emotional disturbances associated with HIV are profound and multifaceted, affecting diagnosis, treatment adherence, quality of life, and long-term health outcomes. Recognizing these impairments as intrinsic to HIV pathology—not just secondary consequences—is essential for delivering comprehensive care to people

living with HIV (PLWH). Neurocognitive and psychiatric assessments should be an integral part of routine HIV management, particularly since subtle cognitive impairments and mood disorders often go undetected until they interfere significantly with daily functioning or treatment outcomes [66]. Cognitive impairments, especially those classified under HIV-associated neurocognitive disorders (HAND), can manifest as deficits in attention, executive function, processing speed, and memory. These impairments can severely compromise a patient's ability to adhere to antiretroviral therapy (ART), manage comorbidities, and engage meaningfully in occupational and social activities. Misinterpretation of these deficits as non-compliance or behavioral problems can lead to stigmatization and fractured patient-provider relationships. Early identification through brief neuropsychological screening tools (e.g., IHDS, MoCA) in clinical settings can facilitate timely interventions, including cognitive rehabilitation, behavioral therapy, or adjustments to medication regimens [67]. Emotional and psychological disorders—particularly depression and anxiety—are linked to reduced ART adherence, increased risk of viral rebound, and accelerated disease progression. Depression has also been associated with immune suppression, independently of ART status, through mechanisms involving chronic inflammation and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Therefore, integration of mental health services into HIV care is not optional but essential. This includes routine screening for mood and anxiety disorders, access to psychiatric evaluation, and provision of evidence-based interventions such as cognitive behavioral therapy (CBT), pharmacotherapy, and peer support systems [68].

In addition, the overlapping mechanisms that drive both cognitive decline and emotional dysregulation in HIV—such as neuroinflammation and neurotransmitter imbalance—highlight the potential utility of adjunctive treatments that target neuroimmune pathways. Anti-inflammatory agents, serotonergic drugs, and neuroprotective compounds are being investigated as possible complements to ART in addressing the neuropsychiatric sequelae of HIV. Personalized approaches based on biomarkers of inflammation, neuroimaging data, and genetic predispositions may further optimize treatment and improve long-term neurological outcomes [69]. Furthermore, the clinical trajectory of HIV in vulnerable populations such as children, adolescents, and the elderly may differ significantly due to developmental, hormonal, or age-related factors. Pediatric HIV is often accompanied by neurodevelopmental delays, while aging PLWH are at greater risk for neurodegenerative overlap with disorders like Alzheimer's and Parkinson's disease. This necessitates age-specific guidelines for neuropsychological monitoring and mental health care [70]. From a public health perspective, addressing the cognitive and emotional dimensions of HIV is also crucial for

reducing stigma, improving retention in care, and enhancing community engagement. Mental health literacy among healthcare providers, coupled with culturally sensitive communication strategies, can help mitigate the dual burden of neurological and emotional suffering often borne silently by PLWH.

Therapeutic Approaches

Therapeutic strategies aimed at addressing the cognitive and emotional consequences of HIV infection must extend beyond traditional antiretroviral therapy (ART) to encompass a multidimensional model of care that integrates neurocognitive, psychiatric, and psychosocial interventions. While ART remains the cornerstone of HIV management and has significantly reduced the incidence of severe HIV-associated neurocognitive disorders (HAND), it does not fully reverse or prevent the subtle cognitive and emotional dysfunctions that persist in many individuals. Therefore, a more comprehensive approach is required to preserve brain health and improve quality of life [65-70].

Antiretroviral Optimization and Neuroprotective ART Regimens

Certain ART drugs demonstrate better penetration into the central nervous system (CNS), as measured by the CNS Penetration Effectiveness (CPE) score. Selecting ART regimens with higher CPE scores may offer improved control over viral replication within the brain, potentially reducing neuroinflammation and slowing cognitive decline. However, it is essential to balance this with considerations of neurotoxicity, as some ART agents, like efavirenz, have been linked to neuropsychiatric side effects. Personalizing ART based on neurocognitive profiles and CNS safety profiles may enhance both viral suppression and neurological outcomes .

Anti-inflammatory and Neuroprotective Therapies

Given the role of chronic immune activation in HIV-related cognitive and emotional symptoms, adjunctive anti-inflammatory therapies have emerged as promising avenues. Agents such as minocycline, statins, and omega-3 fatty acids have been explored for their neuroprotective properties. Additionally, research into compounds that target the kynurenine pathway or restore glutamate homeostasis, such as memantine or NMDA receptor modulators, holds potential in mitigating neurotoxicity. These interventions aim to directly address the neuroinflammatory cascades and excitotoxic damage associated with HIV infection.

Psychiatric Interventions and Psychotherapy

Psychological therapies, particularly cognitive-behavioral therapy (CBT), mindfulness-based stress reduction (MBSR), and supportive counseling, have demonstrated efficacy in reducing depression, anxiety, and HIV-related distress. These interventions not only improve emotional regulation but can enhance ART adherence and reduce risky behaviors. Pharmacological treatments for

depression and anxiety, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), are also widely used and generally well-tolerated in HIV populations. Importantly, clinicians must remain vigilant about potential drug-drug interactions between psychotropic medications and ART.

Cognitive Rehabilitation and Neuropsychological Support

Cognitive rehabilitation programs designed to improve memory, attention, and executive functioning have shown promise in individuals with HAND. Techniques include computerized cognitive training, compensatory strategy education, and task-specific retraining. These programs are most effective when tailored to the individual's specific cognitive deficits and integrated into routine HIV care. In some settings, occupational therapy and social work support may further reinforce functional improvements and psychosocial adaptation.

Lifestyle and Behavioral Interventions

Physical exercise, adequate sleep, social engagement, and nutrition play important roles in maintaining cognitive and emotional health in PLWH. Exercise, in particular, has neurogenic and anti-inflammatory effects that may counteract some of the cognitive decline seen in HIV. Smoking cessation and reduced alcohol or substance use also contribute significantly to preserving neurological integrity. Lifestyle interventions are especially effective when combined with health education and motivational interviewing strategies.

Integrated, Multidisciplinary Care Models

Finally, the optimal therapeutic approach to neuropsychiatric complications in HIV involves collaboration across medical, neurological, psychiatric, and social domains. Integrated care models that co-locate mental health services within HIV clinics improve access, reduce stigma, and ensure coordinated treatment. Such models may also incorporate peer support, case management, and community outreach to provide holistic care tailored to the individual's socio-cultural context.

List of Abbreviations

ART - Antiretroviral Therapy
CNS - Central Nervous System
CBT - Cognitive Behavioral Therapy
HAND - HIV-Associated Neurocognitive Disorders
HPA - Hypothalamic-Pituitary-Adrenal
MBSR - Mindfulness-Based Stress Reduction
PLWH - People Living with HIV
SSRIs - Selective Serotonin Reuptake Inhibitors
SNRIs - Serotonin-Norepinephrine Reuptake Inhibitors

Conclusion

The cognitive and emotional consequences of HIV infection represent a significant and often underappreciated dimension of the disease, profoundly impacting the lives of those affected. Emerging evidence from the field of psychoneuroimmunology underscores the intricate interplay between the virus, the immune system, and the central nervous system, revealing how chronic

inflammation, immune dysregulation, and neurochemical imbalances contribute to a spectrum of neuropsychiatric manifestations. These include mild to severe cognitive impairments, depressive and anxiety disorders, and disruptions in emotional regulation—all of which can compromise treatment adherence, social functioning, and overall quality of life. Therapeutic strategies must go beyond viral suppression to address neuroinflammation, support mental health, and enhance cognitive resilience. Multidisciplinary and integrated care models, which bring together neurological, psychiatric, behavioral, and social services, are crucial for delivering holistic and patient-centered HIV care.

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