HIV and Neuropsychiatry

CHAPTER 22

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Definition and Aetiology

The human immunodeficiency virus (HIV) is a retrovirus that primarily infects CD4+ T lymphocytes, resulting in progressive immune suppression and a wide range of associated clinical manifestations[1,2]. In the absence of treatment, HIV advances to acquired immunodeficiency syndrome (AIDS), a condition characterised by severe immunodeficiency in which the immune system is no longer capable of effectively preventing disease, often leading to death from opportunistic infection[2,3].

Both the central and peripheral nervous systems may be affected early in the course of HIV infection[4,5], resulting in neurological injury that can manifest as a variety of neuropsychiatric complications[5]. These include cognitive impairment and a broad spectrum of psychiatric disorders[6]. Neurologic damage / injury results from a one or more of the following mechanisms: direct viral neuro-invasion (with glial activation and encephalitis), immune-mediated mechanisms (through inflammatory chemokine and cytokines), opportunistic infections (such as JC virus), neoplastic processes (such as lymphoma), or adverse effects associated with antiretroviral therapy (ART)[7].

These in turn may result in a spectrum of neuropsychiatric manifestations. These differ in presentation and course depending mainly on whether the Person with HIV is suppressed. In this way cognitive and neurologic symptoms present in the face of immunocompromise[8]. While in suppressed individuals, the effects of antiretrovirals, other treatments and life stressors more associated with the development of psychiatric symptoms[7].

The presence of severe and ongoing neurocognitive impairment is usually associated with unsuppressed HIV: in the modern era, this arises through ART non-adherence leading to progressive immune suppression with declining CD4 counts, and a higher susceptibility to opportunistic infections[7,9]. Milder and stable cognitive impairment may arise from pre-treatment neurologic injury known as “legacy effects”[7].

Epidemiology

By the end of 2024, an estimated 41 million individuals globally were living with HIV[10,11]. During the same year, 1.3 million people acquired HIV, reflecting a considerable decrease from the 2.2 million new cases reported in 2010[10,11]. In 2024, HIV-related illnesses resulted in 630,000 deaths, which represents a 54% reduction compared to figures from 2010, attributable to the widespread implementation of ART[10,11]. Worldwide, 31.6 million people, accounting for 89% of those living with HIV, had access to ART[10,11]. Among those receiving ART, 94% achieved viral suppression. These represented significant advances in the global efforts to control HIV infection, but prevention and treatment gaps remain[10].

Prior to the advent of antiretroviral therapy (ART), the prevalence of what is now classified as HIV-associated dementia (HAD) was notably higher, affecting approximately 16% of persons living with HIV (PLWH)[9]. In the era following the introduction of ART, the prevalence of HAD has declined significantly to below 5%[9]. In the face of effective viral suppression, progressive and severe neurocognitive impairment due to HIV is very uncommon[9]. There is considerable debate regarding milder forms of neurocognitive impairment in People with HIV. Residual cognitive deficits may result in

mild neurocognitive impairment due to legacy effects, estimated by some to occur in nearly 50% of individuals[12,13]. A more nuanced understanding of this problem suggest that poor performance on neuropsychological testing in People with HIV is due to a range of factors. These include background education and psycho-social variables, vascular comorbidity and aging, psychiatric comorbidity, and statistical over-estimation[7].

Demographic trends:

- **Age:** With improved survival associated with ART, the population of older adults living with HIV continues to increase. Advancing age is an established risk factor for the development of neuropsychiatric complications including Major Neurocognitive Disorder[14].
- **Sex:** Some studies suggest that women may be at greater risk for certain neuropsychiatric complications associated with HIV (such as depression), although findings remain inconsistent across the literature[15].
- **Socioeconomic Status and Geography:** Lower socioeconomic status, limited access to healthcare services, and coexisting substance use disorders are associated with an increased prevalence of neuropsychiatric manifestations in individuals living with HIV[6,7].

Pathophysiology

Central nervous system (CNS) invasion occurs within days to weeks following acute HIV infection[4]. This process is hypothesised to occur through the infection of CD4+ T lymphocytes and monocytes, which subsequently migrate across the blood-brain barrier (BBB)[4,5,16]. This mechanism is widely described as the “Trojan horse” hypothesis[5]. Following CNS entry, HIV disrupts the structural and functional integrity of the BBB and alters the expression of CNS-associated proteins. Infected immune cells release pro-inflammatory cytokines and viral proteins, including Tat and gp120, which promote BBB dysfunction and perpetuate a neuroinflammatory milieu[4,5]. Figure 1[17] illustrates the neuropathogenesis of HIV.

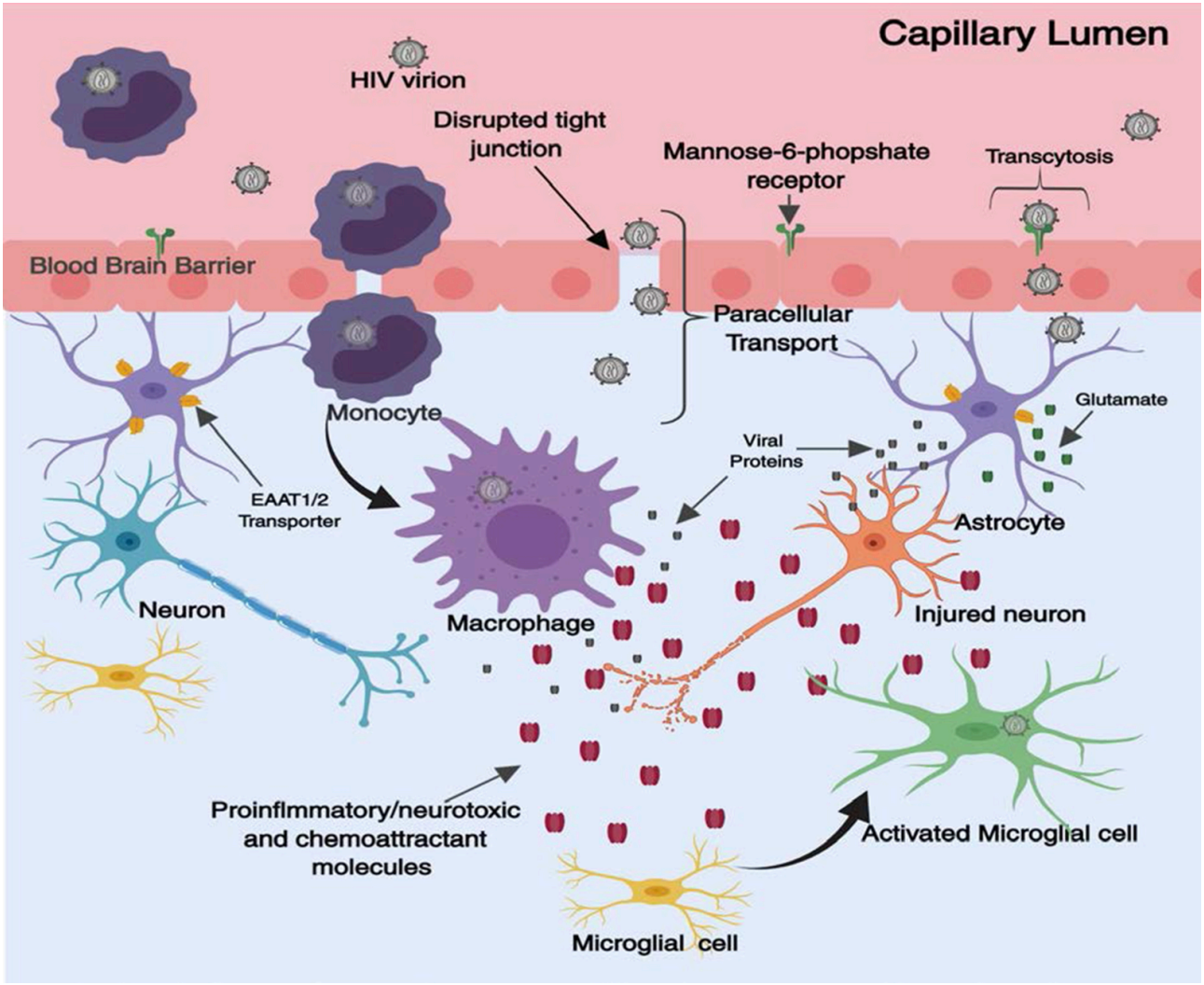


Figure 1: A depiction of the neuropathogenesis associated with HIV infection. This figure has been taken from Omeragic et al 2020[17] and reused under the Creative Commons Attribution 4.0 International License.

Subsequently, CNS-resident cells, including perivascular macrophages, microglia, and astrocytes, become activated and damaged, facilitating local viral replication and the establishment of a persistent inflammatory state[4,5,18]. The extent to which this process takes hold and causes HIV-associated brain injury is directly related to the time from infection to effective HIV suppression: known as the “duration of untreated exposure” or DUE[7]. Astrocyte activation, particularly in response to Tat protein exposure, impairs glutamate regulation, while viral proteins interfere with dopamine transporter function and reuptake mechanisms[4,7]. These alterations contribute to neuronal excitotoxicity through sustained synaptic stimulation, particularly in the subcortical regions and frontstriatal circuits. In addition, the accumulation of neurotoxic mediators, increased oxidative stress, and ongoing BBB injury further exacerbate neuronal dysfunction and neurodegeneration[4].

The choroid plexus, situated within the lateral ventricles and principally responsible for cerebrospinal fluid (CSF) production, also represents an important site of CNS involvement[5,19]. HIV may access the CNS through the blood-CSF barrier, resulting in disruption of choroid plexus integrity and subsequent injury to surrounding CNS[19]. Damage to the choroid plexus impairs glymphatic clearance mechanisms and contributes to the maintenance of chronic neuroinflammation, thereby promoting the development of cognitive impairment[19].

In a small number of PLWH, perhaps 1-2%, despite peripheral HIV suppression, the virus may separately avoid ART through genetic resistance, in a process known as “escape”[20,21]. Localised HIV replication within the CNS occurs, with detectable HIV RNA in the CSF and brain parenchyma, resulting in “CNS compartmentalisation.”[19]

Table 1: HIV CNS Pathophysiology Overview

Stage	Key Processes	Effects
Early CNS Invasion	HIV infects CD4+ T lymphocytes and monocytes, crossing the blood-brain barrier (“Trojan horse” hypothesis)	Disruption of blood-brain barrier, entry of infected cells into CNS
Neuroinflammation	Release of pro-inflammatory cytokines and viral proteins (Tat, gp120)	BBB dysfunction, ongoing neuroinflammatory environment
CNS Cell Activation	Activation and damage of perivascular macrophages, microglia, and astrocytes	Local viral replication, persistent inflammation
Neuronal Dysfunction	Astrocyte activation impairs glutamate regulation, viral proteins disrupt dopamine transporters	Excitotoxicity, oxidative stress, neurodegeneration
Choroid Plexus Involvement	HIV disrupts blood-CSF barrier and choroid plexus integrity	Impaired glymphatic clearance, chronic neuroinflammation, cognitive impairment
CNS Compartmentalisation	Localised HIV replication in CNS despite peripheral suppression (“escape” phenomenon)	Detectable HIV RNA in CSF, compartmentalised brain infection

Assessment and Diagnosis

Clinical Evaluation:

- Comprehensive history, including HIV disease course (including an estimation of DUE if possible, and nadir CD4 count), ART regimen and adherence, psychiatric and medical comorbidities, substance use, and psychosocial factors.
- Physical examination for medical comorbidities and exclusion of focal neurological deficits
- Assessment of cognitive, behavioural, and motor symptoms.

- Psychiatric Assessment: Screening for depression, anxiety, substance use, and psychosis should be routine, given the high prevalence of these disorders in PLWH
- Collateral history from family or caregivers may be invaluable, especially in cases of cognitive impairment.

Diagnostic Criteria:

- Neuropsychiatric syndromes in People with HIV are diagnosed appropriate diagnostic criteria (DSM-5 criteria or ICD11) with consideration of HIV as an aetiological factor.

- Where HIV associated syndromes are present, consideration must be given to HIV-associated factors, ART and other treatments, and psycho-social stress and stigma.
- The diagnosis of Neurocognitive Disorders in People with HIV are now aligned with these diagnostic approaches, and less with disease-specific criteria such as the Frascati Criteria of 2007, due to changes in the nature of the epidemic as outlined above[22].

Differential Diagnosis:

- Opportunistic CNS infections (e.g., cryptococcal meningitis, toxoplasmosis, PML)
- Primary CNS lymphoma and other neoplasms
- Metabolic and nutritional disorders (e.g., vitamin B12 deficiency, hypothyroidism)
- Medication side effects or intoxication
- Other neurodegenerative diseases (e.g., Alzheimer's disease, vascular dementia)

Investigations

Laboratory Tests:

- CD4 count: is relevant and useful in the face of immunocompromise and less when the person is suppressed.
- HIV viral load: plasma and CSF (when there is clinical concern of CNS viral escape in someone who has a suppressed viral load)
- Routine bloods: Full blood count, urea and electrolytes, liver function tests, thyroid function, vitamin B12 and folate levels, syphilis serology- to exclude reversible causes of cognitive impairment and/or delirium
- Screening for co-infections (e.g., hepatitis B/C, tuberculosis)

Neuroimaging:

Access to neuro-imaging varies widely across settings. The indications for imaging are based on the clinical diagnostic assessment where intra-cranial pathology is suspect. This is more likely the case where the Person with HIV is unsuppressed, or the clinical symptoms are unusual[23].

- MRI Brain: Preferred modality. May reveal cerebral atrophy, white matter hyperintensities, basal ganglia involvement, or focal lesions suggestive of opportunistic infection or neoplasm.
- CT Brain: Useful if MRI unavailable or contraindicated; less sensitive for early or subtle changes.

CSF Analysis:

- Indicated in suspected CNS infection, neoplasm, or when diagnosis is unclear.
- May show mild lymphocytic pleocytosis, elevated protein, or detectable HIV RNA (in cases of CNS viral escape) [7].
- Specific PCR and antigen testing for pathogens (e.g., JC virus, cryptococcus, toxoplasmosis) as clinically indicated.

Other Investigations:

- Electroencephalogram (EEG): May be useful in suspected seizure activity or encephalopathy.

- Cognitive screening for neurocognitive disorders in People with HIV: tools such as the IHDS (sensitive for HAD in immunocompromised patients) and MOCA (can assess for milder cognitive impairment) can be used.

- Neuropsychological Battery: Formal testing for neurocognitive disorders in People with HIV is useful when available and especially in milder forms of impairment. Domains commonly affected include attention, processing speed, memory, executive function, and psychomotor speed.
- Brain biopsy: Rarely required, reserved for diagnostic uncertainty after other modalities exhausted.

Biomarkers of HIV neuropathogenesis:

These are mainly research tools. Biomarkers give important insights into neuronal dysfunction and inflammation, impairment of the BBB integrity and immune-mediated response to viral entry into the brain[7]. These include inflammatory cytokines such as IL-6 and TNF- α, and neopterin, which is released by activated monocytes, macrophages and microglia and can be found in the blood and CSF[7]. Neurofilament light chains, also found in the blood and CSF, is an indicator of neuronal white matter damage and can remain elevated despite ART[7].

Neuropsychiatric Disorders related to HIV

HIV-associated neuropsychiatric manifestations are prevalent complications observed in People with HIV. These arise not only from direct central nervous system exposure to the virus but also as a consequence of the sustained psychological stress associated with managing a chronic illness[6].

Table 2: Neuropsychiatric Disorders Associated with HIV

No.	Disorder	Key Features	Management
1	Neurocognitive Disorders	Impairments in memory, attention, executive function; may range from mild cognitive dysfunction to HIV-associated dementia.	ART to reduce viral load, cognitive rehabilitation, supportive interventions, management of comorbidities.
2	Depression	Frequently observed in PLWH; can be primary or secondary to HIV or ART; may present with low mood, anhedonia, fatigue, cognitive impairment.	SSRIs and other antidepressants as first-line; psychotherapy (CBT, supportive therapy); address psychosocial stressors; monitor drug interactions.
3	Mania	Often linked to ART adherence; mood disturbances; risk of drug interactions.	ART mainstay; antipsychotics and mood stabilisers (with caution); avoid carbamazepine and valproate in specific populations.
4	Substance Use Disorders	Bidirectional relationship with HIV; high prevalence; alcohol most common.	Dual diagnosis approach; harm reduction; psychotherapeutic and pharmacological interventions (e.g., naltrexone, methadone).

No.	Disorder	Key Features	Management
5	Psychotic Disorders	Disturbances in thought, perception, paranoia; may be worsened by immunosuppression.	ART, antipsychotics (prefer atypical), monitor for metabolic/EPSEs; investigate reversible causes.
6	Anxiety Disorders	Common in PLWH; includes GAD, panic disorder, PTSD; often comorbid.	SSRIs first-line; benzodiazepines for acute use; psychotherapy (CBT); breathing exercises.
7	Delirium	Acute cognitive alteration, inattention, disorientation; may indicate advanced HIV.	Treat underlying cause; non-pharmacological interventions; haloperidol for severe disturbance.
8	Other	Sleep disturbances, including insomnia and hypersomnia. Personality and behavioural changes.	Standard treatments for insomnia (CBTi, sleep hygiene, medications second-line). Little data to support treatments for personality change in HIV.

1. *Neurocognitive Disorders in People with HIV*

Neurocognitive disorders in People with HIV were frequent in the pre-ART era but are less prevalent now. Its most severe form, HIV encephalopathy, is a delirium characterised by confusion, slowing, and memory impairment, with significant fluctuation[6]. Individuals with HIV who are not receiving antiretroviral therapy (ART), or who exhibit suboptimal adherence, are at heightened risk[6,7]. Additional contributing factors for the development of neurocognitive disorders include[7]:

- Low nadir and current CD4+ count
- High serum and CSF viral load
- Co-infections (e.g., hepatitis C, tuberculosis)
- Substance misuse (notably stimulants and alcohol)
- Psychiatric comorbidities and genetic predisposition

In People with HIV prior to the widespread use of ART, neurocognitive disorders were common. In these cases, HIV infection was the major driver of brain injury and its clinical manifestations[6,22,24]. Therefore diagnostic terminology reflected this dominant contribution of HIV. The Frascati criteria, introduced in 2007, proposed the following categories of HIV-associated neurocognitive disorder[18,25,26]: (1) Asymptomatic Neurocognitive Impairment (ANI), with mild to moderate impairment of neuropsychological performance but no functional impairment[18,25]; (2) Mild Neurocognitive Disorder (MND), with mild to moderate impairment of neuropsychological performance plus only mild impairment in daily functioning (mostly independent activities of daily living- IADLs[18,25]); and (3) HIV-associated Dementia (HAD), with moderate to severe impairment of neuropsychological performance plus functional impairment significantly affecting ADLs[18,25].

The decline in prevalence of HIV-associated dementia is associated with the growing availability of effective ART, including regimen robustness to lower-than-perfect adherence, as well as less neurotoxicity. The reported increase in prevalence of milder neurocognitive disorders in People with HIV, could be accounted for by several factors:

1. A Type-1 measurement (false positive error), where epidemiologic studies have not fully accounted for a normal prevalence of lowered test performance of 10-20% of non-affected individuals.
2. The impact of early childhood and psycho-social factors on neurocognitive test performance, which is thought to differ among HIV+ and HIV- sub-populations[27].
3. Co-morbidities such as depression, substance use and vascular brain disease.
4. The aging of the HIV population



Figure 2. HIV-Associated Neurocognitive Disorder prevalence: 2020-2025

Neurocognitive Disorders in People with HIV, who are not virally suppressed in the CNS, develop a typical subcortical disease due to microglial activation and related encephalitis. The pattern of impairment reflects deficits in attention and concentration, processing speed, and memory recall[6]. Apathy is also often observed in this group of patients[7]. The presence of a neurocognitive disorder elevates the risk of medication non-adherence and increases susceptibility to additional neuropsychiatric manifestations associated with HIV[7,28].

In the era of ART, with effective CNS suppression, the role of HIV is vastly reduced. It no longer is central to neuropathology or brain injury, other than through residual legacy effects[7,29]. Early brain injury due to HIV (in the DUE period), together with possible low grade inflammation is considered a possible risk factors for the development of Major Neurocognitive Disorders normally associated with aging- specially Alzheimer's Disease and Vascular Dementia[7,9,12,29]. The clinical assessment of a neurocognitive disorder in a Person with HIV must now consider not only the HIV disease history and treatment but also[7]:

- Vascular risk factors including hypertension, diabetes, and high cholesterol
- Psychiatric comorbidity
- Sensory impairments
- Psycho-social risk factors such as isolation

Management of neurocognitive disorder in a Person with HIV will depend on the presence or not of active CNS HIV disease. In these instance, careful attention to ART regimen and adherence must be given[24]. The notion of using ART regimens with increased CNS penetration is of less importance than confirming general drug sensitivity[30]. Additionally, it is essential to address coexisting psychiatric (especially depression and alcohol use) and medical conditions, including neurosyphilis, hepatitis C, and vascular risk factors such as hypertension and diabetes[7,24].

2. *Depressive disorders in HIV*

Depressive disorders are the most prevalent psychiatric manifestations in People with HIV, occurring in an estimated 20-40% of people[6,7,24]. Recent studies have indicated a higher risk of depression in women compared to men with HIV[15]. Additional risk factors for depression include a personal or family history of mood disorders, substance misuse, limited psychosocial support, and coexisting medical conditions[7,24]. The diagnosis of depression in People with HIV is frequently complicated by symptom overlap with the broader clinical course of untreated HIV, leading to underrecognition. In addition, in settings where HIV is highly prevalent, depression symptoms may present with cognitive symptoms, such as “thinking too much”, or somatic symptoms, such as “my heart is heavy”. In addition, psycho-social stressors, poverty and HIV-related stigma continue play a critical role in driving distress and depression among People with HIV. Screening tools such as the PHQ9 or shorter versions, and CES-D are sometimes used. Culturally and linguistically tailored tools (e.g. the South African Depression Scale (SADS)[7]) may more accurately reflect depressive symptoms, particularly in non-Western populations.

A thorough assessment should encompass a detailed history, physical examination, and appropriate medical investigations to exclude alternative medical causes or ART-induced effects. These are more frequent with certain antiretrovirals such as efavirenz.

Management strategies for depression are guided by severity: mild depressive episodes may be addressed through counselling and psychotherapy, including supportive, cognitive behavioural, and interpersonal approaches[7,24]. A Cochrane review reported that antidepressants are effective in improving depressive symptoms in people living with HIV, with no clear evidence that any one antidepressant is consistently more effective than another[31]. For moderate to severe depression, selective serotonin reuptake inhibitors (SSRIs), such as citalopram and escitalopram, are recommended as first-line pharmacological agents due to their favourable pharmacokinetic profiles and reduced potential for drug interactions[32]. Mirtazapine is considered an effective second-line treatment and offers additional benefits in cases of HIV-associated wasting, methamphetamine use, and depressive symptoms[32]. Serotonin–noradrenaline reuptake inhibitors (SNRIs) demonstrate comparable efficacy to SSRIs, while tricyclic antidepressants (TCAs) may be useful for individuals experiencing insomnia or peripheral neuropathy, although their use is limited by increased adverse effects and risk in overdose[32]. Untreated depression in PLWH is associated with reduced quality of life, diminished adherence to treatment, impaired cognitive functioning, and a heightened risk of mortality[33].

Several considerations are important when selecting an antidepressant, such as:[7]

- Accessibility of the medication
- Experiences with prior treatments and effectiveness

- Specific characteristics of depressive symptoms
- Compatibility and safety with ART
- The patient's preferences and ability to tolerate the drug

3. *Mania in HIV*

Mania is marginally more prevalent in People with HIV compared to the general population, typically presenting during the later stages of untreated HIV in cases of secondary mania, or what is known as “AIDS Mania”[7,24,32]. This manifestation is frequently associated with deteriorating cognitive function and a less favourable prognosis. Mania may also occur in individuals with pre-existing primary mood disorders. Additional causes of secondary mania in PLWH include substance misuse and medication-induced effects (efavirenz or zidovudine)[7,24]. The presence of manic symptoms heightens the risk of disinhibition and impulsivity, which can lead to engagement in high-risk behaviours.

The management of mania in HIV primarily focuses on achieving and maintaining viral suppression, making ART the cornerstone of treatment[7]. Psychotropic medications, such as antipsychotics and mood stabilisers, may be utilised in the treatment of mania, though these agents carry risks of adverse effects and potential drug interactions[32]. Lithium may be effective when administered with caution; however, its use is problematic in patients with renal impairment or those receiving tenofovir-based regimens[32]. Valproate should be avoided in women of child-bearing potential due to its teratogenic risks and must be used cautiously in individuals taking hepatotoxic drugs or those with severe alcohol use disorders[24,32]. Carbamazepine is generally not recommended because of its substantial risk of drug interactions[32]. Patients may respond positively to mood-stabilising antipsychotics, including risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone[32].

4. *Substance use disorders*

Substance use and HIV exhibit a bidirectional relationship: substance use elevates the risk of HIV transmission through disinhibited and impulsive behaviours, while HIV increases susceptibility to substance use, particularly in the presence of cognitive impairment and depressive symptoms[7,34]. Consequently, a dual diagnosis approach is essential for the assessment and management of substance use disorders in People with HIV. Prevalence rates range from 40-60%, with alcohol being the most frequently abused substance[7,14]. Other commonly used substances include stimulants (methamphetamine and cocaine), benzodiazepines, cannabinoids, and opioids, all of which pose risks for drug interactions with ART[32]. Tools such as the CAGE questionnaire, WHO-Assist and AUDIT are sometimes used[7]. Management requires evaluation of the stage of behavioural change and implementation of harm reduction strategies[24]. Psychotherapeutic interventions such as motivational interviewing, cognitive behavioural therapy (CBT), and supportive therapy are effective options[24]. Pharmacological treatments may include naltrexone for alcohol use disorder,
which is considered safe for People with HIV, as well as opioid substitution therapies such as methadone or buprenorphine in those with an opioid use disorder[32].

5. *Psychotic disorders*

Psychosis and HIV possess a multifaceted relationship, each significantly influencing the clinical course of the other[24]. Psychosis can manifest as disturbances in thought processes, reasoning, perception, paranoia, and may impair complex decision-making and capacity[24]. In People with HIV

who are not on ART or non-adherent, elevated viral load, and immunosuppression may result in a range of additional features, such as neurocognitive impairment, and fluctuations in psychotic symptoms[7]. Investigation may reveal abnormalities in cerebrospinal fluid or brain imaging[7].

Treatment principles largely mirror those for mania, emphasising viral suppression through ART, evaluation of reversible causes and comorbidities, including substance use, medical illnesses, and ART-induced effects[7,32]. Open-label studies suggest that standard psychiatric medications, particularly antipsychotic agents, can be effective in the management of psychosis in people living with HIV[35]. Pharmacological management typically includes antipsychotic medications; however, caution is warranted as People with HIV are at increased risk for extrapyramidal side effects (EPSEs), and both HIV and ART elevate metabolic complication risks[7,32]. Atypical antipsychotics are generally preferred with vigilant monitoring of metabolic parameters[32]. Risperidone is associated with a favourable tolerability profile and a lower incidence of adverse effects compared to other antipsychotics[36]. Emerging evidence also supports the efficacy of aripiprazole, which appears to have minimal metabolic and extrapyramidal side effects[36]. Long-acting injectables should be used conservatively, and clozapine may be considered for treatment-resistant individuals with normal white cell counts who are not immunocompromised[32].

6. *Anxiety disorders*

Anxiety disorders are common among People with HIV and may stem from the ongoing stress of managing a chronic illness or from inadequate psychosocial support[24]. Frequently encountered conditions include generalised anxiety disorder, panic disorder, and post-traumatic stress disorder, which often occur alongside mood disorders, substance use issues, and personality disorders[24,32]. SSRIs are generally recommended as first-line treatments[32]; while benzodiazepines can be used in acute situations, their long-term use should be avoided due to risks such as misuse, cognitive decline, and excessive sedation[32]. Lorazepam and clonazepam are preferred because they present fewer drug interaction concerns[32]. Mild anxiety symptoms respond well to psychotherapy, especially CBT[24]. Additional interventions, like breathing exercises and other behavioural techniques, may also be beneficial[24].

7. *Delirium*

People with HIV are susceptible not only to neurocognitive disorders but also delirium, especially when not on ART or non-adherent[24]. This is characterised by an acute alteration in cognition accompanied by fluctuating levels of consciousness, inattention, and disorientation- features that distinguish it from HIV-associated brain injury[24]. They may also present with behavioural and psychotic symptoms, potentially complicating management. Delirium frequently arises from organic and reversible causes but can also indicate advanced HIV disease. Comprehensive assessment is essential to determine the underlying cause. Management primarily focuses on treating the identified aetiology and implementing non-pharmacological interventions. For severe behavioural disturbances, haloperidol may be prescribed at the lowest effective dose, with careful monitoring for extrapyramidal side effects (EPSEs)[32].

8. *ART neurotoxicity*

The introduction of ART has greatly reduced the overall impact of HIV and decreased the likelihood of developing a neurocognitive disorder associated with HIV. However, lifelong ART treatment does come with certain complications, one of which is neurotoxicity, a set of behavioural, physical, and neuropsychiatric symptoms attributed to the effects of ART[7,37]. These symptoms may range from mild issues like insomnia and depression to severe conditions such as psychosis and suicidal thoughts, as well as cognitive problems and peripheral neuropathies[7]. Efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is particularly known for its high CNS penetration and an elevated risk of causing these complications[7]. Once the underlying cause is identified and addressed, these symptoms generally resolve without further intervention. Newer agents such as dolutegravir are thought to be associated with fewer sleep issues and anxiety, although worsened weight gain[38]. Figure 3[37] illustrates mechanisms of ART-induced neurotoxicity.

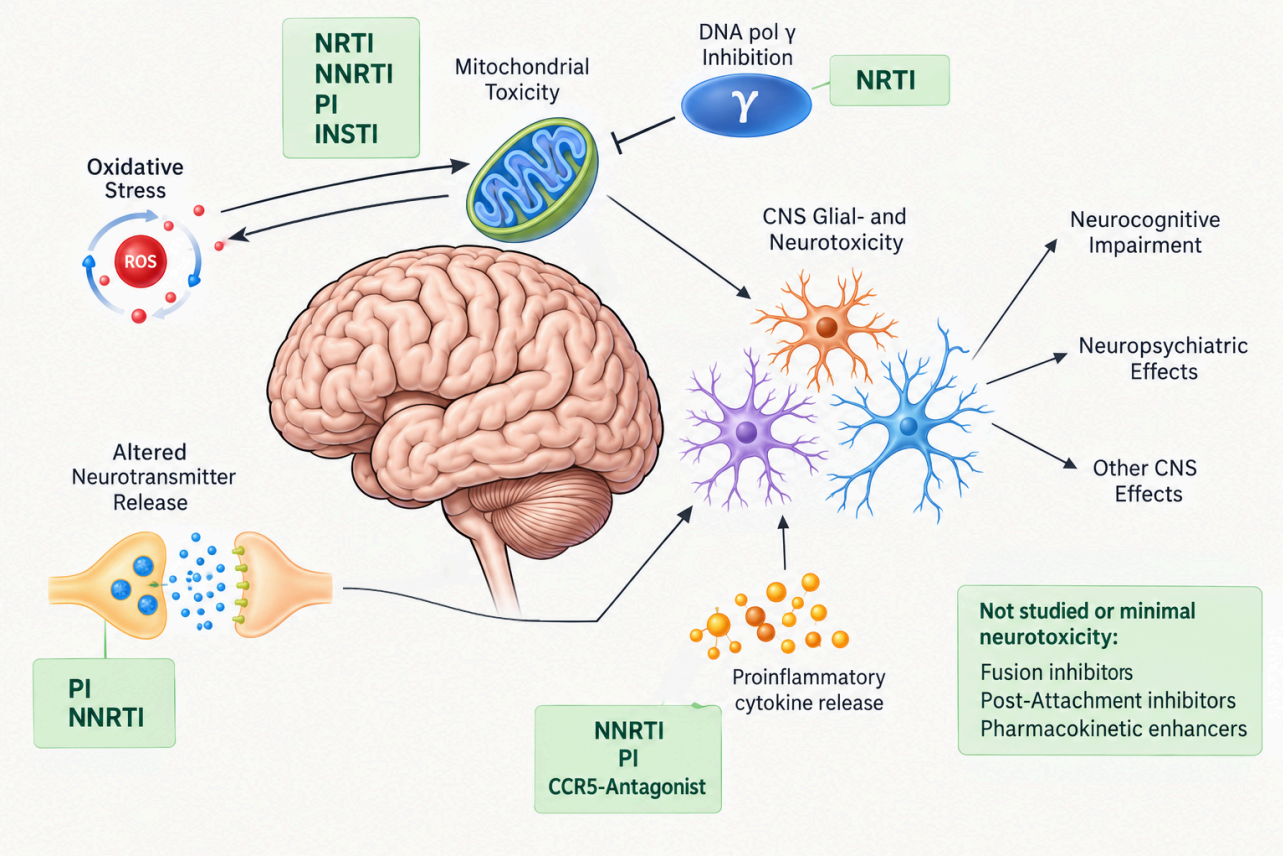


Figure 3: Illustration of ART-induced neurotoxicity[37] . Figure data taken from Lanman, T., Letendre, S., Ma, Q., Bang, A. & Ellis, R. CNS Neurotoxicity of Antiretrovirals. *J Neuroimmune Pharmacol* **16**, 130–143 (2021). https://doi.org/10.1007/s11481-019-09886-7. NRTI - Nucleoside Reverse Transcriptase Inhibitor; NNRTI – Non- Nucleoside Reverse Transcriptase Inhibitor; PI - Protease Inhibitor; INSTI - Integrase Strand Transfer Inhibitor.

Chapter summary

Definition and Aetiology: HIV neuropsychiatric disorders refer to cognitive, behavioural, and psychiatric complications associated with HIV infection. These disorders arise from direct viral effects on the central nervous system and secondary factors such as immune activation, opportunistic infections, and ART neurotoxicity.

Epidemiology: the introduction of ART has reduced the prevalence and severity of neurocognitive disorders related to HIV. However, neuropsychiatric manifestations remain clinically relevant due to lifelong ART use and the persistence of mild to moderate cognitive and behavioural symptoms.

Pathophysiology: HIV enters the CNS early in infection, causing neuroinflammation and neuronal injury. ART can contribute to neurotoxicity, resulting in a spectrum of neuropsychiatric symptoms, ranging from mild insomnia and depression to severe psychosis and neuropathies. The pathogenesis involves direct viral effects, immune responses, and medication-related complications.

Assessment and Diagnosis: assessment involves clinical evaluation for cognitive changes, behavioural disturbances, and psychiatric symptoms. Identifying delirium, inattention, and disorientation is essential, particularly in advanced HIV. Diagnosis relies on excluding other causes and recognising ART-related neuropsychiatric effects.

Investigations: investigations typically include neuropsychological testing, laboratory studies, and imaging where indicated. Determining the underlying cause of symptoms is crucial for guiding management and differentiating ART toxicity from primary HIV-related CNS complications.

Neuropsychiatric disorders associated with HIV: People with HIV frequently experience depression, anxiety disorders, and a range of neurocognitive impairments. Psychosis, mania, and delirium may manifest as a result of direct neurological involvement by HIV, secondary infections, or adverse effects of pharmacological interventions. Substance use is prevalent among PLWH and is recognised as a significant factor that can adversely impact treatment outcomes.

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