Chapter 3: HIV and Neuropsychiatry

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Introduction

- HIV is a neurotropic and neuro-virulent virus- this means that it has a propensity to invade the nervous system, as well as cause pathological damage. The result is a range of neuropsychiatric and neurological complications.
- HIV and mental disorders have a bidirectional relationship: HIV can cause mental disorders and mental disorders increase the risk of HIV infection due to risk-taking behaviors
- Mental or Neuropsychiatric disorders in Persons with HIV can therefore arise from direct effects of HIV on the brain, the effects of secondary infections or tumours, the stress of living with HIV, and medications used to treat HIV and related disorders.
- Some antiretroviral drugs used in the treatment of HIV have neuro-psychotropic effects and can precipitate or aggravate mental symptoms and disorders.
- Co-infection with hepatitis C virus (HCV) infection is common in people with HIV (who abuse injectable drugs). There is some global variability in the prevalence of HCV co-infection. HCV also causes neurocognitive impairment.

Pathophysiology of HIV neuro-infection

- Neuro-invasion: is thought to occur early during HIV infection and lymphocytic involvement. HIV copies may enter the CNS in activated monocytes ("trojan horse"), or through damaged or inflamed tight junctions, or through a damaged or inflamed blood-brain-barrier.
- As neurons do not bear CD4 receptors they are not directly infected. It is more the case that astrocytes and CNS macrophages (glia) are infected.
- Neuroinflammation: activated astrocytes and CNS resident macrophages increase the production of cytokines and proinflammatory markers
- Neuro excitotoxicity: HIV viral proteins affects the reuptake of dopamine and glutamate from the synapses (leading to prolonged neuronal stimulation, increased intracellular calcium, and synaptic degeneration)
- Increase oxidative stress and Impaired mitochondrial respiration

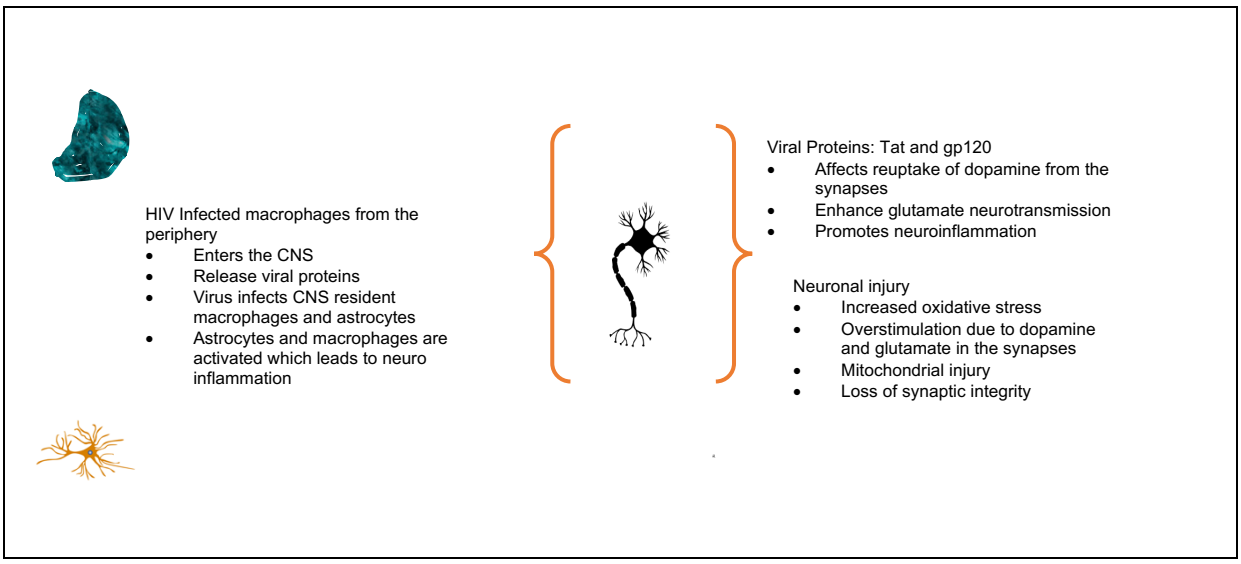
The result is an interplay of host and viral factors during uncontrolled CNS infection leading to the syndrome of HIV encephalitis.

Primary pathology from HIV related injury

The following structures are more prone to injury caused by HIV

- Basal ganglia: regions expressing a high density of dopamine receptors
- Myelinated white matter tracts: loss of white matter integrity due to injury to oligodendrocytes (may manifest as periventricular white matter disease)

Figure 1: Pathophysiology of NeuroHIV



(see(González-Scarano & Martín-García, 2005))

The course of neuroHIV and its impact on clinical disorders

- Before ART became widespread, CNS infection with HIV was often uncontrolled, and a persistent inflammatory state would lead to HIV encephalitis, with typical white matter disease, damage to deep grey nuclei, and ultimately neuronal loss. This sub-cortical picture was responsible for what was clinically observed as psychomotor slowing, impaired memory and executive function and apathy. Even nowadays, with ART being widely available, this state can occur under 2 conditions: (1) when the person has stopped ART (interruption) and HIV has again become generally uncontrolled, and (2) when HIV in the CNS manages to evade ART, and "escape" in a compartmental fashion.
- For persons who endured a long period of untreated HIV, but who have now managed to control their HIV, residual damage may have remained. This is termed a "legacy effect". The resulting neuropsychiatric disorder is stable.
- For a very small proportion of people with HIV, who control both their serum and CNS HIV, a low grade smoldering inflammatory state may persist, and result in gradually progressive disease. This is the subject of intensive research.

The burden of mental illness related to HIV

- The global burden of HIV infection falls to sub-Saharan Africa, and southern Africa in particular. There are about 7.7 million people are living with HIV in South Africa in 2021.
- People with HIV have a higher prevalence of mental disorders compared to people without.
- There are different reports on the prevalence of mental / neuropsychiatric disorders in PWH compared to the general population, with the burden being 20-100% greater, depending on the disorder under study, the population under study, the method used, and the presence (or absence) of a control group.
- In one large US-based study, the estimated prevalence of any screened mental disorder was 38%, while substance abuse was present in around 10% (Burnam et al., 2001).
- In terms of the impact of (untreated) mental and neuropsychiatric disorders in PWH, we often consider:
  - Impact on function and quality of life (see (Heaton et al., 2004) and (Gonzalez, Batchelder, Psaros, & Safren, 2011))
  - Impact on disease progression and mortality (see (Ickovics et al., 2001))
  - Impact on care engagement, testing, ART adherence and viral suppression

Biomarkers of HIV neuro- infection

Several investigations and biomarkers can be used to assess the extent and or ongoing CNS dysfunction related to HIV. Some of the plasma, CSF, and imaging studies/biomarkers are listed in table 2 and 3.

Of the commonly available fluid markers, viral load in serum and CSF is most commonly used. The CSF viral load is used mainly when the serum VL is suppressed, but there is clinical reason to believe that CNS disease is present due to viral escape / compartmentalization. The other listed markers are used mainly in research settings.

The indications for brain imaging in HIV are firstly to rule out confounding co-morbidities such as focal or diffuse pathologies other than HIV; and then to confirm the diagnosis of an inflammatory or structural lesion. In routine primary care settings, imaging should be requested when clinical features are atypical, and/or when focal neurological signs are present. In hospital settings, CT or MRI is used most often in first episodes of more severe forms of HIV associated neuropsychiatric disorders. Special techniques such as diffusion tensor imaging (which delineates white matter tracts), volumetrics, spectroscopy (for inflammatory and neuronal integrity markers) and other sequences are usually reserved for high-resource or research settings. These scans require high Tesla magnets, special MRI sequences, and data processing skills.

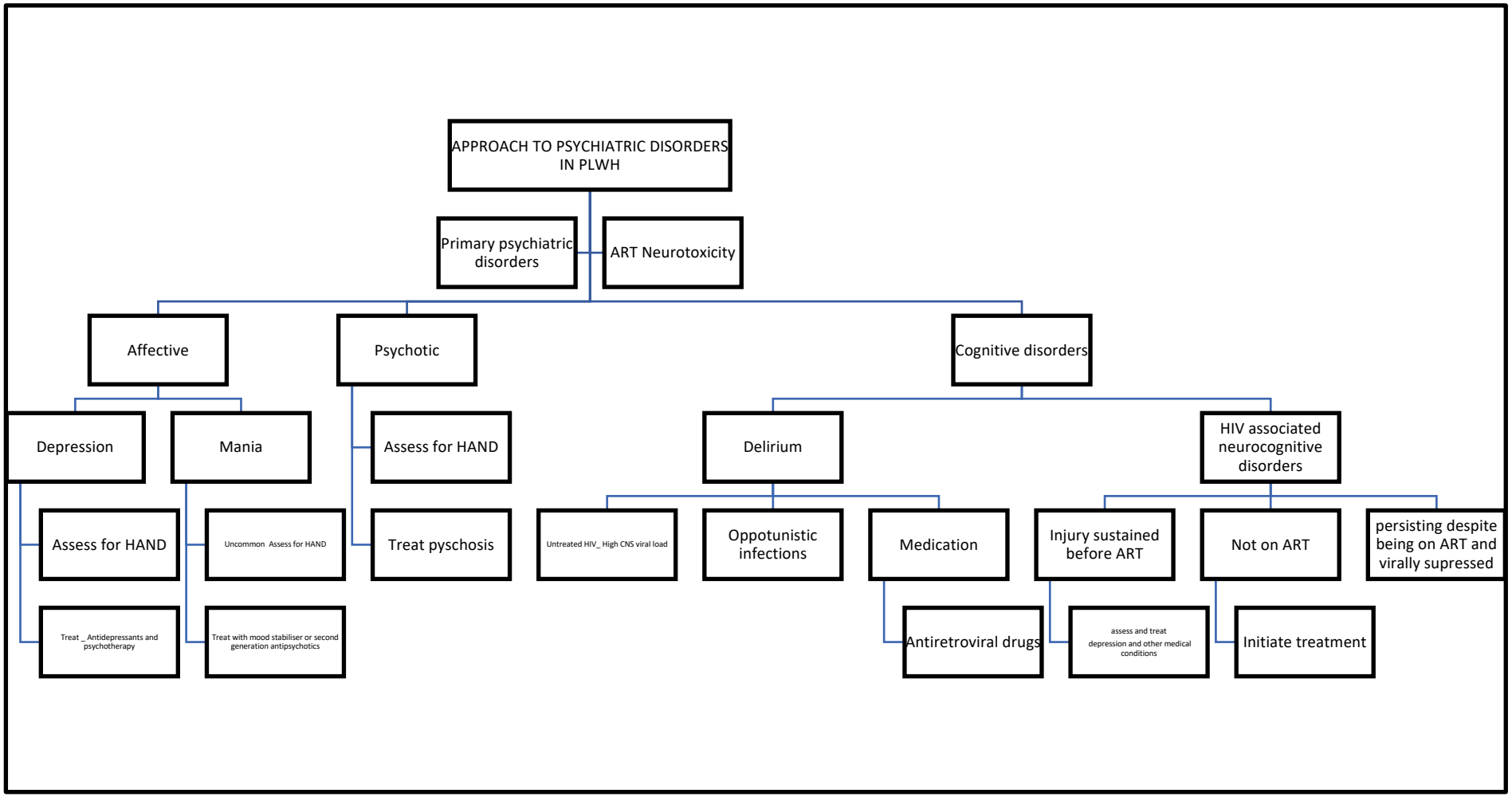
Table 2. Fluid surrogate biomarkers of current injury to the brain parenchyma in HIV neuro infection

Fluid Biomarkers	**Source**	**Current utility**	**Surrogate marker**
CSF Viral load	CSF	Clinical and research	CSF viral escape
Neopterin	Blood and CSF	Research	Activated monocytes, macrophages, and dendritic cells
Neurofilament light chains	Blood and CSF	Research	Damage of white matter
S100b	Blood and CSF	Research	Astrocytic injury

Table 3. Some of the imaging biomarkers related to injury of the brain parenchyma in HIV neuro infection

Imaging modality	**Current utility**	**Surrogate marker**
CT scan	Clinical and research	Loss of brain volume and white matter disease
MRI structural	Clinical and research	Brain volume and injury to the brain tissue
Proton MR spectroscopy	Primarily research	Brain metabolites e.g., choline, glutamate, N- acetyl aspartate
MRI Diffusion tensor imaging	Primarily research	White matter integrity _ assesses the diffusion of water molecules along the axis of the axons

Figure 2: Psychiatric disorders related to HIV



1. Depressive disorder due to HIV

1.1. General

Depressive disorders are the most common neuropsychiatric disorders diagnosed in people with HIV. The prevalence of depressive disorders varies according to study, setting, method and disease stage. Severe forms (MDD) are reported in 10-15% of PWH; while the mild forms are present in 20-30% of PWH. Depressive disorders / states may fluctuate over time, depending on changing psycho-social circumstances, and treatment factors.

Depression (untreated) is associated with poor outcome in HIV. It has been associated with poor adherence, poor viral suppression and early mortality in people with HIV

Assessment of depression is clinical. Rating scales are commonly used where clinical training is limited (such is in task-sharing) or in research settings. Scales used include the PH9, K10, CESD, SAMISS and the brief MINI screen. Assessment of suicidality is important as this is a common phenomenon, and is amenable to intervention.

1.2. Treatment of depressive disorder due to HIV

Treatment of depressive disorders in people with HIV depends on severity, chronicity and impact on function. Mild depression may be amenable to counselling, support and a conservative approach. Commonly used therapies include supportive counselling, cognitive behavioural therapy (and aspects of CBT including problem-solving therapy and behavioural activation). For a review of therapeutic interventions in PWH, see (Sikkema et al., 2015)
Counseling and psychotherapies can augment biological therapies if required.

The choice of anti-depressant medication when indicated is based on several patient and health-system considerations:

- Availability of the medication
- History of previous use and/or treatment response
- Profile of depressive symptoms (eg apathetic, agitated, insomniac, pain-related)
- Safety of the drug in relation to ART (some drugs may interact with protease inhibitors)
- Patient choice and tolerability

There have been very few trials of anti-depressants in HIV and no single drug has proven more effective than any other. See (Eshun-Wilson et al., 2018) for a review. The selection of an agent is based on the above criteria.

2. Substance use disorders in HIV

2.1. General

Substance use in people living with HIV is common, with figures between 7-12% alcohol dependence reported. In sub-Saharan Africa, binge-drinking or heavy episodic drinking is frequent, with rates as high as 25% reported.

Substance use is linked with multiple barriers to HIV care, and outcomes. These include delays in HIV testing, entry into care, ART adherence and retention in care (Hahn, Woolf-King, & Muyindike, 2011). Substance abuse is also associated with secondary neuropsychiatric effects, such as depression and neurocognitive disorders. Sharing of needles is linked with an increased risk of HCV infection as well as HIV. In addition to the behavioural risks associated with methamphetamine use, methamphetamine use is linked with increased peripheral dopamine concentrations. Peripheral dopamine is linked with enhancing viral replication and facilitation of HIV viral migration into the CNS.

Screening and diagnosis of substance and alcohol use is key to addressing the challenges. In primary health care settings, tools such as the CAGE questions, SAMISS, AUDIT (and C version), and the WHO ASSIST have been used in both clinical and research settings.

2.2. Treatment of Substance Use Disorders in PWH

Treatment of substance abuse follows the same principles of care, as for persons without HIV. In addition to assessing the person's stage of change, and applying the principles of motivational interviewing, clinicians needs to be aware of the burden of dual or intersecting stigmas: the shame and stigma of living with HIV, as well as substance abuse may lead to challenges in care engagement in both areas.

3. Bipolar disorders in PWH

3.1. General

The presence of a manic syndrome in a person living with HIV may arise due to several factors:

- Underlying vulnerability to BPAD itself
- Medications used to treat HIV
- Uncontrolled neuroHIV infection (so-called "AIDS mania")

- Substance abuse

  The presence of a manic syndrome or bipolar disorder can significantly interfere with HIV treatment goals, and should be addressed by a skilled mental health provider.

3.2. Treatment of manic syndromes and bipolar disorder in PWH

Achieving and sustaining HIV suppression is a cornerstone. If the person remains manic, then acute anti-manic treatment should consist of selecting one or more agents from either the anti-psychotic or anti-convulsant classes of drugs. The same principles of use apply to PWH as they do for persons without HIV infection. The following are additional considerations:

- Risk of extra-pyramidal side effects with typical anti-psychotics
- Risks of metabolic syndrome with atypical agents
- Risks of haematological (platelet) effects and liver enzyme effects with valproate
- Carbamazepine is generally avoided
- Lithium may be used with usual cautions around renal function. Note the effects of tenofovir on renal function.

4. Psychotic Disorders in HIV

4.1. General

In the same way as bipolar disorders, psychotic disorders may arise in PWH due to multiple factors. In well-treated persons, the prevalence is similar to the general population, while in untreated samples, this increases due the effects of neuroHIV. In high-income countries, the presence of a Severe Mental Illness (SMI) such as schizophrenia, is thought to confer a 10x increased risk of HIV acquisition. These risks have been harder to quantify in low and middle income countries due to the high background HIV prevalence.

The clinical features of psychosis due to HIV itself, versus primary psychosis are described as:

- The presence of neurocognitive (motor and sub-cortical) features
- The presence of relative immune-compromise and high viral load
- Fluctuating mental state / instability of psychotic symptoms over days
- Abnormal CSF and brain imaging findings (usually non-specific)

4.1. Treatment of psychotic disorders

The same principles as for Bipolar Disorder treatment apply: control HIV disease, ensure adherence and support, consider drug side effects and interactions.

Due to the risk of extrapyramidal side effects, atypical agents are most used. Long acting injectables may be used with caution. Clozapine may be used in treatment resistant cases, under the guidance of a specialist. This is possible where white cell count is normal (ie the person is not immune-compromised), and the fact that the mechanisms of white cell count suppression are different for HIV and clozapine.

5. Neurocognitive Disorders in HIV

5.1. General

The Neurocognitive Disorders as a category include delirium. This occurs primarily in persons with immunocompromise, older age, and / or secondary infection or illness. In untreated HIV, it may be as common as 40%.

The HIV- Associated Neurocognitive Disorders (HAND) or otherwise termed “Neurocognitive Disorder in a Person with HIV” are a group of disorders that result from chronic neurological infection. The prevalence of severe HAND has declined since the widespread use of ART from around 20% to <3%.

The diagnosis of NCD in PWH rests on 3 pillars:

- The presence of neuropsychological / neurocognitive impairment
- The presence of some degree of functional impairment as a result of cognitive disorder
- The consideration of confounders and contributors to poor neuropsychological / neurocognitive test performance. These include a range of early life and demographic factors (such as education, age, gender), and clinical factors (psychiatric conditions, neurological conditions, stress). Some of these are included in Table 5 below.

The methods used to assess these have been widely written about and debated in the literature. The diagnosis of neuropsychological / neurocognitive impairment usually relies on the administration of tests within a larger battery intended to tap domains affected by HIV. In practice, the availability of these is extremely limited, so clinicians rely on screening tools to guide the assessment. These include the International HIV Dementia Scale (IHDS), Cognitive Assessment Tool- Rapid Version, and the Montreal Cognitive Assessment (see (Joska et al., 2016)). In both instances, language, cultural and normative test issues are a challenge. The concept of “domain” is applicable as in both American Academy of Neurology (AAN), and DSM5 approaches, at least 2 domains must be impaired.

As HIV is a sub-cortical disease when untreated, affected domains include: psychomotor speed, impaired memory recall, attention and concentration, and social cognition (Apathy). As HIV is eradicated from the CNS during effective therapy, the neuropsychological picture may be less restricted to the sub-cortex, and include some cortical features (such as aphasia, agnosia, and executive function impairment).

The AAN approach describes 3 diagnostic categories of HAND. These are simplified in Table 4.

Table 4. AAN Diagnostic Categories

	ANI	**MND**	**HAD**
Number of domains	A minimum of 2		
Deviations	At least 2 std deviations		More than 2
Interference with day-to-day functioning	No	Mild to moderate	Marked
Prevalence out of the total 44.5%	30% of the 44.5%	20% out of 44.5%	2% out of 44.5%

ANI = asymptomatic neurocognitive impairment
MND = mild neurocognitive disorder
HAD = HIV associated dementia

The presence of a neurocognitive disorder in PWH is associated with poor medication adherence and poor quality of life. HAD is associated with a high mortality rate.

Table 5. Non-HIV factors contributing to poor neurocognitive test performance

Factors	**Impact or pathophysiology**
Demographic	
Age Education / cognitive reserve	Aging-related brain tissue loss. Age-related inflammation
Viral factors	
Uncontrolled viral replication Longstanding high viral load	Persisting injury to the brain parenchyma Early irreversible injury of the neurons “legacy effect”

Host immune factors		
	Nadir CD4 count Persisting neuroinflammation	<200 cells linked with HAND Linked with persisting neuronal injury
Mental illnesses		
	Anxiety and depression Substance use disorder	Poor mental health is linked with low CD4 count and high viral load Substance uses has been linked with increased viral replication and migration of viruses into the CNS
Comorbid illnesses		
	Hepatitis C infection Cardiovascular disorders	A known cause of neurocognitive disorders Small vessel disease and strokes

5.2. Treatment of Neurocognitive Disorder in PWH

HAND is typically not a progressive disorder if HIV if treated optimally. Therefore, prevention may be better than cure. The following are key considerations:

- Viral factors

  The gold standard treatment of HAND is viral suppression using ART. Thus, people diagnosed with HIV should be started immediately on ART to prevent early irreversible injury "legacy effect" to the brain. Patients who demonstrate evidence of progressive neurocognitive decline despite optimal ART adherence and peripheral viral suppression should be investigated for other causes of dementia (and CSF viral escape).
- Psychiatric comorbidities

  Identification and treating comorbid psychiatric disorders is essential in patients with HAND. Psychiatric disorders associated with worsening of HAND.
- Medical illness comorbidities

  Neurosyphilis and HCV are not uncommon in people living with HIV, and both may cause or aggravate cognitive impairment. Uncontrolled hypertension, diabetes (and other vascular risk factors), as well as all other chronic conditions are key to reducing the burden of disease of neuroHIV.
- ART neurotoxicity

ART neurotoxicity can occur in some people living with HIV. The biggest culprit being Efavirenz a Non-nucleoside reverse transcriptase inhibitor (NNRTI). Patients who present with worsening of neuropsychological function on EFV should have EFV plasma levels checked. In some patients neurotoxicity may occur within normal plasma levels. Ideally these patients should be switched to an alternative ART regimen e.g., Dolutegravir

ART can cause neurotoxicity which can manifest with behavioral symptoms. Symptoms can range from mild to severe symptoms that interfere with functioning. In the majority of cases, the symptoms are transient and appear within the first days of treatment initiation. EFV is less used now that integrase inhibitors are first-line in most settings. EFV has been known to cause: Both mild symptoms (Insomnia, Anxiety, Depression) and more severe ones (psychosis, suicidality and neurocognitive impairment). These symptoms are USUALLY short-lived.

Risk factors associated with EFV neurotoxicity include: Genetic predisposition _ EFV is cleared by CYP2B. Polymorphism of this enzyme is associated with poor metabolism of EFV and thus elevated levels (common in black African females); and Concomitant use of isoniazid_ INH inhibits the CYP2A6 which is also involved in the metabolism of EFV. Low body mass index may also be a factor.

Data on the neuropsychiatric profile of dolutegravir are being accumulated. They are considered to be much milder than EFV. Mild anxiety, depression and insomnia are described.

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