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Parkinsonism in people with virally suppressed HIV

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Abstract

Parkinsonism is increasingly recognised in people who are ageing with virally suppressed HIV, with bradykinesia emerging earlier and more frequently than in idiopathic Parkinson's disease. Despite effective antiretroviral therapy (ART), studies report persistent motor symptoms—such as motor slowing, postural instability, and symmetric postural tremor—and non-motor features, including sleep disturbance, cognitive decline, and autonomic dysfunction. Neuroimaging reveals basal ganglia atrophy, white matter hyperintensities, and reduced dopamine transporter activity, underscoring a pathophysiology distinct from idiopathic Parkinson's disease. Proposed mechanisms include chronic neuroinflammation, cerebrovascular dysfunction, mitochondrial injury, disturbed iron metabolism, and possible ART-induced neurotoxicity, all contributing to basal ganglia dysfunction. Diagnosis is made complex by under-recognition, non-specific assessment tools, and comorbidities. Standardised rating scales, such as the Unified Parkinson's

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Contributors

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Declaration of interests

We declare no competing interests.

Disease Rating Scale and the HIV Dementia Motor Scale, can support clinical evaluation, but evidence-based management strategies are scarce. Although dopamine replacement therapy and deep brain stimulation show promise in case reports, no established guidelines exist for parkinsonism in people with virally suppressed HIV. As the global population of older adults with HIV grows, parkinsonism is expected to become an increasingly prevalent and underdiagnosed cause of frailty, highlighting the urgent need for targeted epidemiological, mechanistic, and interventional research, particularly in low-income and middle-income settings.

Introduction

Parkinsonism, defined clinically by bradykinesia accompanied by at least one core motor feature of tremor, rigidity, or postural instability, encompasses a wide spectrum of motor and non-motor manifestations. Although most commonly presenting as idiopathic Parkinson's disease, parkinsonism also arises from secondary causes, including parkinsonism-plus syndromes (eg, multiple system atrophy and progressive supranuclear palsy), typical pressure hydrocephalus, vascular injury, and drug-induced or toxin-induced conditions. Infectious contributors, such as hepatitis C, herpes simplex virus, influenza, and SARS-CoV-2, have been epidemiologically linked to increased parkinsonism risk, potentially via immune-mediated neuronal injury or by unmasking latent susceptibilities to dopaminergic neuron loss.^{1,2} Beyond the core motor criteria, parkinsonism might feature additional motor symptoms, including hypomimia, hypophonia, micrographia, reduced arm swing, festinating or freezing gait, and stooped posture, as well as non-motor symptoms, such as autonomic dysfunction, sensory alterations, neuropsychiatric features, and sleep disturbances (figure 1).

HIV represents a unique infectious context, in which parkinsonism has been reported to occur both after acute infection and following uncontrolled viraemia.²⁻⁴ Early studies on HIV-associated dementia highlighted parkinsonian motor impairments alongside cognitive deterioration, leading to descriptions such as mild cognitive motor disorder in 1991, which evolved into HIV-associated neurocognitive disorder in 2007. The advent of combination ART has substantially reduced the prevalence of HIV-associated neurocognitive disorder and opportunistic infections, which were common contributors to parkinsonism in people with HIV.⁴ Despite ART, HIV persists in the CNS in reservoirs in perivascular macrophages and microglia, which sustain low-level viral transcription and release proteins such as trans-activator of transcription (Tat) and envelope glycoprotein GP120 (gp120).⁵

Although ART is effective against many HIV-related neurological manifestations, it does not fully prevent parkinsonism. Studies of people with virally suppressed HIV across continents consistently note high prevalence of bradykinesia (ranging between 15% and 45%).^{6,7} As most people living with HIV nowadays are virologically suppressed and ageing, the persistence of parkinsonian features in this population demands focused investigation. Examining this subgroup of people with HIV that are on ART allows clear attribution of neurological changes to chronic HIV-associated mechanisms, rather than opportunistic infections or untreated viraemia. Importantly, although much of the current literature originates from high-income countries, more than 80% of the global ageing HIV population resides in low-income and middle-income countries (LMICs), where delayed access to ART

and a greater burden of comorbidities can further elevate neurological risk.^{8,9} Beyond motor symptoms, non-motor features of parkinsonism—such as cognitive, sleep, and autonomic dysfunction—might also occur in this population, further compounding disability.

The impact of parkinsonism on quality of life in people with HIV is significant, increasing the risk of falls and frailty, driving impairments, and correlating with cognitive decline and dementia.^{10,11} Furthermore, as the population of people with virally suppressed HIV is ageing, the prevalence of parkinsonism is expected to increase. Efforts to improve health outcomes in the ageing population of ART-treated people with HIV will ultimately demand a focus on parkinsonism. The occurrence of parkinsonism, despite viral suppression, raises crucial questions about how HIV continues to influence the nervous system and about the limitations of ART in preventing neurological sequelae.

Epidemiology

Neurodegenerative conditions such as parkinsonism that arise predominantly in ageing populations are emerging as a substantial clinical concern in people with virally suppressed HIV. Due to the success of ART, by 2040, an estimated 9.1 million people living with HIV in sub-Saharan Africa will be older than 50 years, representing 25% of the regional HIV population.⁹ In the USA, more than 50% of people with HIV are older than 50 years.¹² Although the proportion of people living with HIV older than 50 years is increased in high-income countries, more than 80% of this ageing cohort live in LMICs, where delayed ART access can amplify neurological susceptibility.⁸ Understanding the epidemiology of parkinsonism in this context is essential to guide clinical screening, resource allocation, and targeted intervention.

An early indication of elevated risk came from a case series in Australia, in which Tisch and Brew observed 4–8-fold increased risk of parkinsonism in people with HIV on ART aged 40–59 years, relative to age-matched individuals without HIV, over a 2-year period.¹³ Additional case series suggest an earlier age of onset compared with the general population (younger than 60 years) and a male predominance, although these observations are limited by small sample sizes.^{13–16} These findings, which encompassed the full clinical syndrome of parkinsonism, highlight a neurodegenerative susceptibility in the ART-treated HIV population that warrants further investigation.

Cross-sectional and longitudinal studies provide converging evidence of high burden of bradykinesia, the core feature of parkinsonism, ranging from 15% to 45% in people with virally suppressed HIV in diverse global settings (table 1).^{7,10,17–30} In Cameroon, Kanmogne and colleagues reported 23% prevalence of bradykinesia in ART-treated people with HIV—significantly higher than that in people without HIV—despite 54% of participants being on ART.²² Similarly, in Thailand, Do and colleagues found bradykinesia in 43% of people with virally suppressed HIV, highlighting a persistent motor burden despite viral suppression.²⁵ Multiple cross-sectional studies have been done in the USA, reaching similar conclusions.^{19,24,27}

Longitudinal studies further illuminate the progressive nature of motor impairments in people with virally suppressed HIV. The Multicenter AIDS Cohort Study, following 506 newly diagnosed men with HIV over 19 years, showed significantly faster decline in motor speed in people with virally suppressed HIV than in people without HIV.¹⁷ Similarly, Rubin and colleagues tracked 239 women with HIV (aged 47.5 years, 100% on ART) for 4 years, finding greater decline in motor speed compared with 301 women without HIV, irrespective of viral suppression.¹⁸ These findings are supported by additional longitudinal analyses in diverse populations, although some studies did not have control groups.^{30–33} Together, these data suggest that ART, although essential for controlling viral replication, might not fully protect against progressive motor slowing.

Although bradykinesia is well documented, other cardinal features such as tremor, rigidity, and postural instability, are less frequently reported, potentially due to underdiagnosis or reliance on neuropsychological rather than neurological assessments.^{4,7,28,34} Postural instability, although its true prevalence remains unclear, is frequently noted in clinical settings and can reflect both central and peripheral nervous system involvement.^{7,20,34–36} Sullivan and colleagues found disproportionate stability deficits in people with virally suppressed HIV compared with people without HIV when assessed with eyes closed, suggesting subtle balance impairments detectable via posturography.²⁰ In a meta-analysis of objective impairments in gait and balance by Berner and colleagues, people with HIV aged 18–65 years were found to have impairments similar to those seen in older seronegative populations.³⁴ Tremor and rigidity, although less common, have been documented in ART-treated cohorts, often presenting as action or postural tremors rather than the classic asymmetric resting tremor of idiopathic Parkinson's disease.^{6,7,10,35}

Pathophysiology

Neuroinflammation

Neuroinflammation is increasingly recognised as a key contributor to motor dysfunction in people with virally suppressed HIV, particularly affecting motor speed and coordination.^{5,37} In HIV, chronic neuroinflammation arises from persistent immune activation, even in the absence of detectable plasma viraemia, and has been implicated in the pathogenesis of parkinsonism (figure 2).

HIV enters the CNS primarily via infected monocytes that migrate across the blood–brain barrier. Once inside the CNS, HIV preferentially infects perivascular macrophages and microglia, triggering a protracted immune response. These HIV-positive and activated cells release pro-inflammatory cytokines, reactive oxygen species, and viral proteins, which together disrupt typical neuronal function and promote neurodegeneration.³⁸ This sustained activation, reflected by elevated concentrations of soluble CD163 and other inflammatory cytokines, persists despite ART and correlates with slow motor speed.^{5,24,38}

The basal ganglia, a crucial hub for motor control, appears to be particularly susceptible to HIV-associated neuroinflammation. Postmortem studies of people with virally suppressed HIV have revealed increased accumulation of macrophages, microglia, and viral proteins in this region.³⁹ Additionally, PET imaging with markers of microglial activation has shown

increased binding of the marker in the basal ganglia and a correlation between increased binding and worse fine motor performance in this population.⁴⁰

HIV proteins, particularly Tat, also exert direct neurotoxic effects. Tat is actively released from infected microglia, triggering apoptotic pathways that can lead to widespread neuronal damage.⁴¹ Experimental evidence has also revealed that Tat is capable of reducing the activity of tyrosine hydroxylase (the rate-limiting enzyme for dopamine synthesis).⁴² Using whole-cell patch clamping, a 2018 study also showed reduced firing rate of dopaminergic neurons exposed to Tat.⁴² Clinically, the presence of Tat in the cerebrospinal fluid correlates with worse motor function.⁴³ Together, these findings suggest a direct mechanistic link between HIV neurotoxicity and dopaminergic dysfunction, mirroring the neurochemical alterations observed in idiopathic Parkinson's disease.⁴⁴

Vascular injury

Vascular dysfunction, driven by chronic inflammation and endothelial activation, might contribute to parkinsonism in people with virally suppressed HIV. Common vascular risk factors in this population, such as hypertension, dyslipidaemia, diabetes, and smoking, accelerate vascular ageing and arterial stiffening, leading to impaired cerebral blood flow, microvascular damage, and white matter disease linked to slow motor and cognitive performance.⁴⁵ Progression of the carotid intima-media thickness, particularly at the carotid bifurcation, occurs preferentially in people with HIV and is predicted by inflammatory markers, underscoring the interplay between vascular pathology and immune activation.⁴⁶ A 2020 study further connects immune activation, as reflected by elevated plasma tissue factor, with carotid intima-media thickness progression in treated HIV, suggesting that chronic HIV-related inflammation can directly drive subclinical atherosclerosis and contribute to motor impairment.⁴⁷

HIV infection significantly increases the risk of both ischaemic and haemorrhagic stroke, with HIV accounting for up to one-third of ischaemic strokes in people with virally suppressed HIV.^{48,49} Ageing further compounds the risk of vascular disease, and the intersection between age-related and HIV-associated vascular pathologies might represent a key mechanism underlying parkinsonism in this population. In particular, treated HIV was associated with reduced perfusion and altered metabolism of the caudate nucleus,^{50,51} and vascular pathology likely causing lacunar infarcts in subcortical regions, was linked to motor slowing.⁵²

Mitochondrial dysfunction and oxidative injury

The basal ganglia generate high metabolic demand, making them particularly susceptible to mitochondrial dysfunction. In people with virally suppressed HIV, mitochondrial dysfunction manifests as reduced mitochondrial capacity, elevated superoxide concentrations, and disrupted antioxidant defences, compared with individuals without HIV.³⁷ This dysfunction is evidenced by decreased basal and maximal oxygen consumption rates, leading to reduced spare respiratory capacity and increased reactive oxygen species production.^{37,53} Disruption of mitochondrial function leads to an imbalance in the redox environment, characterised by increased production of superoxide and hydrogen peroxide. In

people with HIV, hydrogen peroxide-sensitive mechanisms were shown to directly modulate sensorimotor neural dynamics, highlighting their potential role in motor dysfunction.⁵³

One potential contributor to these disruptions is the HIV membrane protein gp120, which impairs mitochondrial function by altering mitochondrial movement and morphology.⁵⁴ In dopaminergic neurons, gp120 exposure preferentially leads to mitochondrial disruption, increased oxidative stress, decreased dopamine reuptake, and reduced cell viability.⁵⁵ Another factor might involve alterations in mitochondrial DNA, which were shown to be related to motor performance and gait speed in people with HIV, although the mechanisms underlying these effects are complex and not fully understood.⁵⁶

Disturbed iron metabolism

Iron metabolism is substantially disrupted in people with HIV, contributing to parkinsonism via global deficiencies and local excesses in the brain, which can exert distinct yet interconnected effects on motor function. Chronic HIV-associated inflammation increases the production of hepcidin, a hormone that reduces iron availability by sequestering it within macrophages and microglia.⁵⁷ This sequestration can reduce iron delivery to iron-dependent cells, such as oligodendrocytes and neurons, crucial for motor function. Oligodendrocytes, which require substantial amounts of iron for myelin synthesis, are particularly susceptible to this deficiency.⁵⁸ Impaired myelination disrupts nerve conduction, potentially manifesting as psychomotor slowing. In neurons, reduced iron availability impairs enzymatic processes, including those involved in neurotransmitter synthesis, and increases susceptibility to oxidative stress, further compromising motor function.⁵⁷

Concurrently, focal iron accumulation occurs in the basal ganglia of people with HIV, promoting ferroptosis—a form of programmed cell death driven by iron-dependent lipid peroxidation and oxidative stress.⁵⁹ Excess iron in the basal ganglia, particularly in the substantia nigra, mirrors the early iron overload observed in idiopathic Parkinson's disease, in which ferroptosis of dopaminergic neurons leads to motor deficits.⁶⁰ In people with HIV, this iron excess might amplify local oxidative stress, sustain low-level viral replication in reservoir cells, and exacerbate dopaminergic neuronal loss, contributing to parkinsonism. The dual nature of iron dysregulation—ie, global iron deficiency impairing myelination and neuronal function, and accumulation of iron in the basal ganglia, driving ferroptosis—likely creates a synergistic insult to motor circuits. These mechanisms are not mutually exclusive but rather reflect regional and cellular differences in iron handling within the brains of people living with HIV.

ART neurotoxicity

In people with non-virally suppressed HIV, ART initiation can substantially reduce parkinsonism symptoms by suppressing HIV replication and mitigating neuroinflammation, with case reports documenting resolution of parkinsonian features within 1 year when combined with levodopa therapy.^{4,16} The advent of ART has also led to an overall decline in HIV-associated movement disorders, predominantly due to reduced opportunistic infections and severe HIV-related neurological sequelae.⁴

Despite the overall benefit of ART, long-term ART exposure, particularly in people who are ageing with virally suppressed HIV, might contribute to parkinsonism via neurotoxic mechanisms. Nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors, such as efavirenz, have been implicated in mitochondrial dysfunction and increased oxidative stress, which can exacerbate dopaminergic neuronal loss in the basal ganglia.⁶¹ Additionally, contemporary integrase inhibitors have been shown to dysregulate iron transport and contribute to mitochondrial dysfunction in microglia, potentially promoting ferroptosis and subsequent motor deficits.⁶² Ageing further amplifies these risks, as altered enzyme kinetics and cumulative ART exposure increase susceptibility to neurotoxicity.⁶³ Therefore, although ART is crucial for viral control and can acutely improve motor symptoms, its long-term use in people who are ageing with virally suppressed HIV might paradoxically contribute to parkinsonism. The nuance regarding the beneficial versus potentially detrimental effects of ART highlights the need for further research and personalised evidence-based therapeutic strategies.

Non-motor symptoms of parkinsonism in people with HIV

Although parkinsonism is defined by motor features, associated non-motor features, including neuropsychiatric, sleep, autonomic, and sensory disturbances, have also been observed in people with HIV. Cognitive dysfunction, predominantly encompassing executive dysfunction and inattention, is thought to occur in between 20% and 50% of people living with HIV.^{64,65} Co-occurring mental health conditions can exacerbate cognitive dysfunction. Depression and anxiety, commonly observed in idiopathic Parkinson's disease, remain highly prevalent in people with HIV, despite ART, and can reflect a hypodopaminergic state.^{44,66,67}

Sleep disturbances represent another prominent, yet underappreciated, category of non-motor symptoms in individuals with virally suppressed HIV. Some studies report that up to 58% of people with HIV on ART had sleep disturbances, which have been associated with chronic immune activation.^{68,69} Although data on rapid eye movement sleep behaviour disorder in HIV are sparse, this condition is a well established prodromal marker of idiopathic Parkinson's disease and other synucleinopathies. Immune activation is a core driver of α -synuclein aggregation and, given evidence that α -synuclein expression is elevated in the substantia nigra of people with virally suppressed HIV, rapid eye movement sleep behaviour disorder or subclinical rapid eye movement dysfunction might plausibly be present or under-recognised in this population, warranting further investigation.^{70,71}

Autonomic dysfunction is highly prevalent yet under-recognised in people with HIV, and is most commonly attributed to a peripheral nervous system aetiology; however, co-occurring central contributions are also possible.^{72,73} Despite ART, autonomic symptoms, such as light-headedness, dry mouth, dry eyes, and constipation, are common complaints in people with HIV.⁷⁴ Additionally, seborrheic dermatitis, a common dermatological condition in both idiopathic Parkinson's disease and HIV, potentially reflects underlying autonomic dysregulation or altered immune responses in these overlapping disease processes.⁷⁵ Non-motor aspects of parkinsonism have an enormous impact on quality of life and warrant further investigation in the context of people with virally suppressed HIV.

Clinical assessment

Clinical bedside measures

Parkinsonism in people with HIV appears to differ from idiopathic Parkinson's disease, often presenting with atypical tremor patterns.³ Tremor, when present, can be either unilateral or bilateral, and is often postural or action-based, rather than the classic asymmetric resting tremor of idiopathic Parkinson's disease. When symmetric, the pattern closely resembles vascular parkinsonism. Rigidity can also be observed and typically affects all limbs symmetrically: it can be assessed with passive range-of-motion testing for cogwheel resistance. Postural instability is another common feature and can manifest as a shuffling gait, with festination and retropulsion, often evaluated with the so-called pull test, in which the clinician applies a sudden backward force to the shoulders of the patient and assesses the corrective response. Despite these emerging observations, phenotypic characterisation remains incompletely understood because of the scarcity of targeted studies and the variability in clinical and research assessment tools. Nonetheless, several bedside measures and structured instruments are available to aid in clinical evaluation, the advantages and disadvantages of which are summarised in table 2.

The Unified Parkinson's Disease Rating Scale (UPDRS), extensively used to monitor idiopathic Parkinson's disease, has proven valuable in people with HIV. Notably, 80% of the variability in UPDRS motor scores in this population was explained by slowness of hand movement, body bradykinesia, action or postural tremor, or hypomimia.⁷ The HIV Dementia Motor Scale, developed by Robinson-Papp and colleagues in 2008, provides a motor assessment across five motor domains: tone, strength, reflex, coordination, and gait.^{6,35} The HIV Dementia Motor Scale aligns well with both the UPDRS and neuropsychological tests assessing motor function, and is predictive of future cognitive decline. The scale has since been modified to be shorter and more specific than previously to HIV motor symptoms.⁶

Not all motor dysfunction in people with virally suppressed HIV is parkinsonian. Ponto-cerebellar degeneration, evidenced by infratentorial volume loss in neuroimaging studies, can contribute to postural instability and ataxia in this population.^{20,29,76} Moreover, slowed information processing is a well documented feature of HIV-related neurocognitive disorders and can present clinically as global motor slowing, rather than true bradykinesia.⁷⁷ Thus, distinguishing between parkinsonian bradykinesia and motor impairment due to cerebellar or cognitive dysfunction is crucial for accurately characterising movement disorders in this group.

Research tools

Movement speed and fine motor skill are commonly assessed in neuropsychological testing with the grooved pegboard task. This task requires hand-eye coordination, sensorimotor integration, and fine motor control, as participants manipulate metal pegs (first with the dominant hand) into a board with uniquely configured holes. The grooved pegboard is primarily sensitive to detecting motor impairment when the dominant hand is used in people with virally suppressed HIV.^{19,22,32} However, multiple motor and sensory pathways are involved, making lesion localisation complex. The task cannot be used in MRI scanners,

and access to grooved pegboard instruments reduces its use in resource-limited settings.²⁵ As an alternative, the finger-tapping task can be done during MRI, offering simplicity and practicality.

Digital assessment of handwriting can measure motor speed and provide some insight into tremor, potentially serving as a useful tool to study parkinsonism in people with virally suppressed HIV.²⁷ However, these tools have not been widely used or validated in this population. Balance posturography has proven useful in identifying HIV-specific mechanisms that can contribute to postural instability.³⁶

Structural neuroimaging

Brain MRI indicates notable atrophy of the basal ganglia in some people with HIV, a subcortical pattern that overlaps with the basal ganglia involvement seen in other atypical parkinsonism syndromes, although evidence is mixed regarding whether ART can halt this process or whether progression continues despite treatment.^{19,78,79} Crucially, bilateral basal ganglia atrophy has been associated with a decline in UPDRS scores in people with virally suppressed HIV.⁸⁰

White matter hyperintensities (WMHs) on T2-weighted MRI are another common structural irregularity observed in people with HIV, although weak associations were made between WMH burden and UPDRS scores.⁸¹ A 2024 study correlated WMH burden with postural instability, suggesting a functional relevance to motor circuits in people with HIV.³⁶ By contrast, in vascular parkinsonism, WMHs are typically attributed to chronic cerebral small vessel disease and are consistently associated with parkinsonian features, particularly gait impairment.⁸² Notably, WMHs in vascular parkinsonism are frequently located in strategic motor pathways, including the periventricular and deep subcortical regions, and show stronger correlations with motor deficits.^{83,84} Although HIV-associated WMHs might also reflect small-vessel pathology, they appear to be diffusely distributed, and can arise from complex interplay between immune activation, inflammation, and neurotoxic viral proteins.^{36,85} Thus, although superficially similar, the anatomical distribution and pathophysiological drivers of WMHs differ in HIV and vascular parkinsonism, and might underlie distinct contributions to parkinsonian symptoms.

Functional and metabolic imaging

Functional MRI uses the change in blood oxygen concentrations in particular brain regions as a marker of local metabolic activity. In people with HIV, functional MRI studies have shown reduced blood flow in the basal ganglia and altered functional connectivity within multiple neural circuits, including sensory–motor networks, that are consistent with parkinsonism.^{51,76} Furthermore, diminished resting-state functional connectivity of the frontostriatal network has been observed in predominantly virally suppressed HIV cohorts.⁸⁶

PET imaging uses radiolabelled tracers to track various aspects of neurophysiology, including neurotransmitter dynamics. In people with HIV who have dementia, PET imaging has revealed reduced activity of dopamine transporters (DATs) in the basal ganglia. Moreover, decreased DAT activity has been associated with decreased fine motor control and

bradykinesia in people with HIV.^{87,88} Future longitudinal studies are necessary to compare the rate of change in DAT activity in people with HIV on ART to that in people without HIV.

Treatment and management

No standard guidelines currently exist for the management of parkinsonism in people with virally suppressed HIV. In individuals who are not virally suppressed, initiation of ART can lead to improvement of parkinsonism symptoms.⁴ However, management is unclear given the likely multifactorial aetiologies of parkinsonism in this population. Most instances of parkinsonism are currently subclinical and do not require specific treatment. However, as the population of people with virally suppressed HIV becomes older, more severe cases will likely arise that need additional management.

Some studies have shown the benefit of treating parkinsonism in people with virally suppressed HIV with dopamine replacement therapy (DRT).^{4,16} In some case reports, improvement in motor symptoms was noted with levodopa (a DRT) at a dose of at least 200 mg/day.^{13,15} However, treatment can be limited by medication side-effects secondary to DRT. Such side-effects include dyskinesias, which can be exacerbated by interactions between ART (specifically protease inhibitors) and DRT.⁸⁹ In addition, increased occurrence of psychiatric symptoms appears to be secondary to DRT in people with virally suppressed HIV compared with the general population.⁹⁰ Although some research evaluates the impact of ART on the dopaminergic system in relation to depression,⁹¹ prospective studies directly addressing ART and DRT interactions are recommended.

In patients with medically refractory parkinsonism or intolerable side-effects, reports have shown successful treatment of the subthalamic nucleus with deep brain stimulation. Concerns have been raised regarding implantation of hardware into patients who are immunocompromised, although this procedure appears to be safe in people with virally suppressed HIV.⁹² Interestingly, one study reported that one individual was unable to continue DRT due to the side-effects. This patient underwent deep brain stimulation without complications, despite not being virally suppressed preoperatively, and was able to restart ART and discontinue DRT following deep brain stimulation.⁹³

Aside from medical and surgical management of parkinsonism, the focus should be on non-medical management, such as the management of patients with parkinsonism from alternative aetiologies. This focus includes access to occupational, speech, and physical therapies, in addition to options for psychological support. These approaches complement medical and surgical strategies and should be used together for comprehensive patient care. A flowchart showing the strategy for diagnostic testing and management of parkinsonism in people with HIV is provided in figure 3; however, further evidence and global consensus are required to establish definitive guidelines. Assessment includes documentation of motor and non-motor symptoms, CD4 count, plasma HIV viral load, and ART regimen. Secondary causes, including opportunistic infections, CNS lymphoma, medications, toxins, vascular disease, and metabolic disorders, should be excluded. Diagnostic testing involves brain MRI, lumbar puncture if CNS infection is suspected, a comprehensive medication review, UPDRS staging, and consideration of dopamine transporter imaging (DaTscan). HIV-associated

parkinsonism is diagnosed when parkinsonian features show a temporal relationship with HIV or ART exposure and secondary causes are excluded, although overlap with idiopathic Parkinson's disease or vascular parkinsonism might occur. Management includes optimising ART, cautious carbidopa or levodopa titration, monitoring for drug interactions, and deep brain stimulation in refractory cases, along with physiotherapy, occupational therapy for optimisation of activities of daily living and fall prevention, education, exercise, and nutritional support.

Research challenges and future directions

Global disparities in ART access, particularly in LMICs, contribute to prolonged viraemia and can alter neurodegenerative risk.⁹⁴ These disparities also exist across urban or rural lines and gender identities, and should be considered when identifying subpopulations at risk.^{95,96} Furthermore, the current instability of global funding mechanisms and humanitarian aid for ART in LMICs could exacerbate susceptibility, underscoring the need for continued global surveillance.

Despite evidence of parkinsonism in the increasingly ageing population of people with HIV, precise incidence and prevalence estimates remain elusive, due in large part to a historical focus on younger cohorts aged 30–50 years and the scarcity of longitudinal studies.^{29,76,77} As a result, the burden, natural history, and heterogeneity of parkinsonism in older individuals with virally suppressed HIV are poorly characterised. Additionally, disentangling HIV-associated parkinsonism from cases that pre-date HIV infection remains a challenge because data on the timing of symptom onset are scarce; an omission common to many case series. Why some people with HIV are more prone to developing parkinsonism than others is also largely unknown.

A symptom-level approach might offer key insights into the spectrum and variability of parkinsonism in people with HIV. Although bradykinesia is the most frequently documented motor feature, other cardinal symptoms, including rigidity, tremor, and postural instability, are under-reported. This reporting likely reflects both the young age of many long-term ART-treated individuals and a research emphasis on neuropsychological rather than neurological assessment. As a result, classic motor features might be systematically underdetected. Moreover, disentangling direct HIV-related pathology from indirect contributors is challenging. Chronic neuroinflammation, concurrent vascular risk factors (eg, obesity and diabetes), and polypharmacy might either modulate parkinsonism risk or mimic symptoms.⁹⁷

Such clinical doubts are further compounded by methodological challenges. The heterogeneity in assessment tools and protocols present in various studies restricts the comparability of findings. For instance, the grooved pegboard and similar tests can capture motor slowing but do not directly evaluate rigidity, tremor, or postural control. Moreover, performance on these tasks can be confounded by a host of comorbidities common in people with HIV, such as peripheral neuropathy, arthritis, vision problems, frailty, and depression, making attribution of deficits solely to extrapyramidal dysfunction difficult.

To date, no autopsy studies have examined people with virally suppressed HIV with parkinsonism, leaving a large gap in our understanding of the underlying neuropathology. Ongoing research, such as the Last Gift Study, uses deep phenotyping to better understand how host and virus factors contribute to parkinsonism in this population.³⁹ Autopsy findings suggest a potential overlap between HIV-associated neuropathology and traditional neurodegenerative mechanisms: α -synuclein accumulation in the substantia nigra was observed in 16% of people with HIV compared with 0% in people without HIV.⁷⁰ However, whether this difference represents an acceleration of idiopathic Parkinson's disease, a distinct HIV-related process, or a combination thereof, remains unclear. Importantly, these findings are derived from an older, predominantly male cohort with historical untreated HIV, raising the possibility that the observed pathology reflects a legacy effect. Contemporary autopsy studies focused on individuals who are virally suppressed are urgently needed to establish whether similar neuropathological features persist in the ART era.

Future research should leverage large, ageing HIV cohorts and health registries in diverse geographical settings, including LMICs, to do prospective, age-matched and comorbidity-matched comparisons with control populations. Such studies should (1) include follow-up extending well beyond age 50 years to capture incidence; (2) incorporate standardised neurological screening at regular intervals (eg, structured motor examinations with the UPDRS or the Movement Disorder Society revision of the UPDRS, finger-tapping tests, tremor and rigidity assessments, and, when feasible, instrumental measures) within existing cognitive or general HIV study protocols; (3) collect detailed histories to establish precise timelines of motor symptom onset relative to HIV diagnosis and treatment initiation; (4) adjust analyses for potential confounders, such as chronic neuroinflammation (eg, via inflammatory biomarkers), vascular risk factors (eg, diabetes and obesity), medication exposures (to identify drug-induced parkinsonism), and lifestyle factors; (5) ensure rigorous exclusion of secondary causes (eg, opportunistic infections and vascular events) when adjudicating parkinsonism; and (6) integrate biomarker-driven investigations (longitudinal cerebrospinal fluid α -synuclein and neuroinflammatory panels and dopaminergic imaging such as DaTscan or PET) in people who are virally suppressed that show signs and symptoms of parkinsonism, to clarify the mechanistic links between chronic HIV, ART exposure, and dopaminergic neurodegeneration.

Conclusion

Several lines of evidence support the notion that HIV-associated parkinsonism represents a clinical phenotype in the ART era that warrants more consideration. Firstly, multiple longitudinal and cross-sectional studies done in diverse populations suggest that motor slowing persists in people with HIV despite effective viral suppression. Secondly, chronic HIV infection is hypothesised to promote a hypodopaminergic state akin to idiopathic Parkinson's disease.⁴⁴ Thirdly, clinical observations in people with HIV describe an earlier age of onset than expected in the general population, bilateral symptomatology, and pronounced bradykinesia and action tremor—features that differ from the typical asymmetric resting tremor characteristic of idiopathic Parkinson's disease. Fourthly, neuroimaging and neuropathological findings show that damage to basal ganglia circuits remains detectable in people with virally suppressed HIV, correlating with parkinsonian

features.³⁹ Finally, case reports describe improvement with dopaminergic therapies, suggesting an overlap with idiopathic Parkinson's disease pathophysiology.

Although parkinsonism in people with virally suppressed HIV is expected to become more prevalent, substantial research gaps still exist. Future epidemiological studies are recommended to focus on older people with virally suppressed HIV, using comprehensive parkinsonian screening tools and adjustments for confounders such as biological sex, depression, vascular comorbidities, ART regimens, and polypharmacy. Prospective investigations that document symptomatic evolution and response to dopaminergic treatment will also help with establishing whether bradykinesia is merely an early prodromal feature or represents the core manifestation of a unique parkinsonian syndrome. Finally, mechanistic studies are needed to disentangle how neuroinflammation, vascular dysfunction, oxidative stress, and HIV-related neurotoxicity converge to produce a parkinsonism phenotype in this population. Such insights are key for designing novel therapeutics that could include anti-inflammatory, neuroprotective, or even HIV eradication strategies aimed at preserving dopaminergic function and mitigating the long-term neurological sequelae of HIV infection.

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Search strategy and selection criteria

PubMed (MEDLINE) and Embase were searched from Jan 1, 1996, to June 30, 2025, for studies of parkinsonism in people with virally suppressed HIV focusing on the ART era. Search terms included HIV-related keywords (“HIV”, “people living with HIV”, “PWH”, “cART”, and “ART”) combined with parkinsonism-related keywords (“parkinson”, “bradykinesia”, “psychomotor speed”, “tremor”, “postural instability”, “rigidity”, and “UPDRS”). Results were limited to peer-reviewed original research, reviews, meta-analyses, and case series, regardless of language. Titles and abstracts were double-screened for relevance, followed by a full-text review. Data on motor symptoms, ART regimens, and epidemiological outcomes were then extracted to produce a comprehensive synthesis of HIV-associated parkinsonism in the ART era. Some studies included participants who had parkinsonian signs pre-dating their HIV diagnosis—these cases were evaluated individually and either excluded or analysed separately to avoid confounding HIV-related motor symptom attribution.

Primary symptom (required for dx)	• Bradykinesia	
Core features (≥ 1 required for dx)	<ul style="list-style-type: none"> • Resting tremor • Rigidity • Postural instability 	
Associated motor features (not required for dx)	<ul style="list-style-type: none"> • Hypomimia (masked facies) • Hypophonia • Micrographia • Reduced arm swing 	<ul style="list-style-type: none"> • Festinating gait • Freezing gait • Stooped posture • Dystonic posturing
Associated non-motor features (not required for dx)	Autonomic and sensory <ul style="list-style-type: none"> • Orthostatic hypotension • Constipation • Urinary dysfunction • Sexual dysfunction • Anosmia or hyposmia 	Neuropsychiatric and sleep <ul style="list-style-type: none"> • Depression and anxiety • Cognitive impairment • REM sleep behaviour disorder • Excessive daytime sleepiness • Restless leg syndrome

Figure 1: Diagnostic classification of parkinsonism

Parkinsonism is diagnosed based on the presence of bradykinesia as the primary symptom, accompanied by at least one core feature—resting tremor, rigidity, or postural instability. Although not required for diagnosis, various additional motor features (eg, hypomimia, hypophonia, micrographia, and festinating or freezing gait) and non-motor features (eg, autonomic, sensory, neuropsychiatric, and sleep disturbances) might accompany the core criteria and contribute to clinical heterogeneity. dx=diagnosis. REM=rapid eye movement.

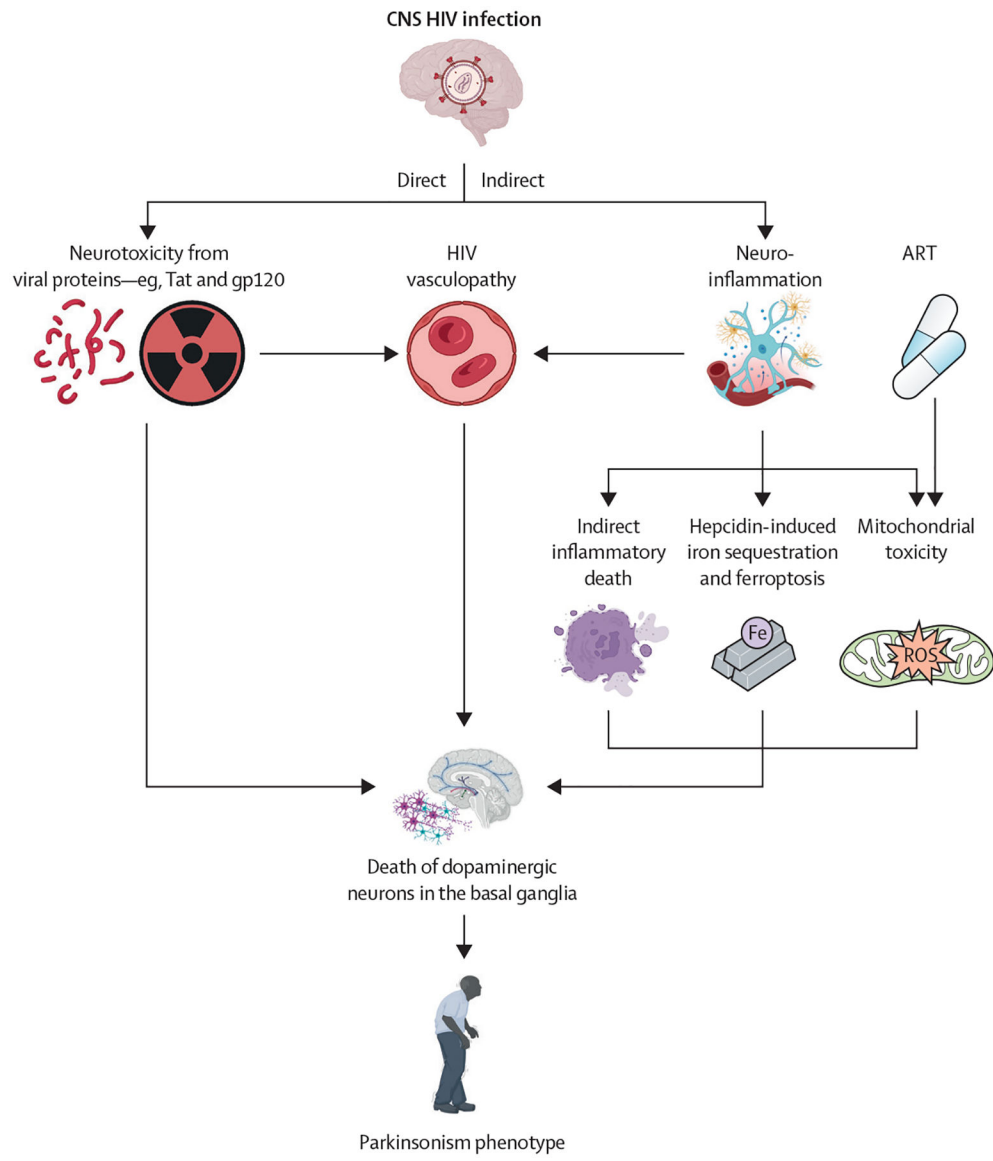


Figure 2: Interacting pathophysiological mechanisms leading to parkinsonism in HIV
ART=antiretroviral therapy. ROS=reactive oxygen species. Created in BioRender.

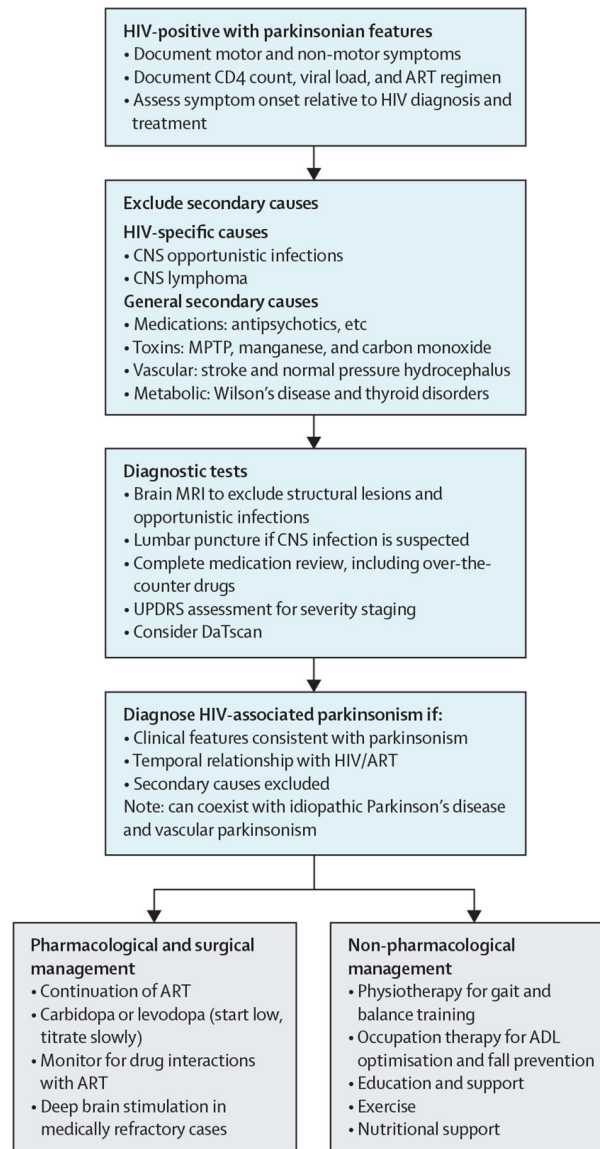


Figure 3: Diagnostic and management approach for HIV-associated parkinsonism

Algorithm outlining the evaluation and treatment of parkinsonian features in people living with HIV. ADL=activities of daily living. ART=antiretroviral therapy. MPTP=1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. UPDRS=Unified Parkinson's Disease Rating Scale.

Table 1:

Studies documenting parkinsonism motor features

	Year	Population	Measurement tool	Conclusion
Longitudinal studies				
Qu et al ¹⁷	2022	Study duration=19 years; MACS cohort People with HIV: n=506 (100% male); age=43.9 years (SD 7.8); CD4=unknown; ART=100% ART-naive initiating ART People without HIV: n=506 (100% male); age=44.7 years (SD 8.2)	GPT	Bradykinesia: people with HIV had a significantly faster decline in function over 19 years, particularly those whose baseline function was similar to people without HIV at ART initiation
Tierney et al ¹⁰	2019	Study duration=14 months; HNRP cohort; only considered older population People with HIV: n=109 (84% male, 16% female); age=56.2 years (SD 5.4); CD4=585.1 cells per μ L (SD 309.1); on ART=90% People without HIV: n=74 (76% male, 24% female); age=56.8 years (SD 5.9)	UPDRS	Bradykinesia: older people with HIV significantly more likely to have bradykinesia than older people without HIV; no difference in gait speed, tremor, or rigidity; overall UPDRS score: older people with HIV more likely to show a decline in motor function over 14 months than older people without HIV
Rubin et al ¹⁸	2017	Study duration=4 years; WIHS cohort People with HIV: n=239 (100% female); age=47.5 years (SD 8.5); CD4=657 cells per μ L (SD 359); on ART=100% People without HIV: n=301 (100% female); age=43.2 years (SD 9.9)	GPT	Bradykinesia: people with HIV showed a greater decline and were more likely to be impaired (motor T-score <40) than people without HIV
Cross-sectional studies				
McMahan et al ¹⁹	2023	People with HIV: n=155 (79% male, 21% female); age=53.2 years (SD 5.8); CD4=619 cells per μ L (range 450–833); on ART=100% People without HIV: n=100 (79% male, 21% female); age=53.2 years (SD 6.1)	GPT	Bradykinesia: significantly worse in people with HIV than in people without HIV
Sullivan et al ²⁰	2023	People with HIV: n=125 (69% male, 31% female); age=52.8 years (SD 8.0); CD4=594.5 cells per μ L (SD 295.5); on ART=100% People without HIV: n=88 (61% male, 39% female); age=48.9 years (SD 14.4)	Balance platform posturography	Postural instability: stability deficit disproportionately greater with eyes closed than with eyes open in people with HIV relative to people without HIV
Liang et al ²¹	2021	People with HIV: n=39 (68% male, 32% female); age=46.8 years (SD 11.9); CD4=475 cells per μ L (SD 326); on ART=89% People without HIV: n=45 (44% male, 54% female); age=47.2 years (SD 12.2)	GPT	Bradykinesia: significantly worse in people with HIV than in people without HIV (in women only)
Kannogne et al ²²	2020	People with HIV: n=320 (22% male, 78% female); age=37.8 years (SD 9.4); CD4=405 cells per μ L (range 246–574); on ART=54% People without HIV: n=363 (34% male, 66% female); age=34.3 years (SD 10.6)	GPT	Bradykinesia: significantly worse in people with HIV than in people without HIV
Prabhakar et al ²³	2020	People with HIV: n=28 (64% male, 36% female); age=59.8 years (SD 6.9); CD4=769.5 cells per μ L; on ART=100% People without HIV with Parkinson's disease: n=36 (58% male, 42% female); age=65.5 years (SD 7.7) People without HIV without Parkinson's disease: n=28 (46% male, 54% female); age=61.1 years (SD 8.6)	UPDRS and finger tapping	UPDRS: no difference between people with HIV and people without HIV and Parkinson's disease, except for bradykinesia, which was worse in people with HIV; Bradykinesia (finger tapping) significantly worse in people with HIV than in people without HIV without Parkinson's disease. Similarity between people with HIV and people without HIV with Parkinson's disease
Montoya et al ²⁴	2019	People with HIV: n=90 (87% male, 13% female); aged between 35 and 65 years; CD4=629 cells per μ L; on ART=100% People without HIV: n=94 (70% male, 30% female); aged between 35 and 65 years	GPT	Bradykinesia: significantly worse in people with HIV than in people without HIV

Year	Population	Measurement tool	Conclusion
Do et al ²⁵	2018 People with HIV: n=329 (57% male, 43% female); age=45.7 years (SD 7.7); CD4=175 cells per μ L (range 69–241); on ART=100% People without HIV: n=510 (44% male, 56% female); age=45.3 years (SD 15.8)	GPT	Bradykinesia: significantly worse in people with HIV than in people without HIV
Toro et al ²⁶	2018 People with HIV without ANI or MND: n=28 (100% male); age=37.5 years (SD 8.9); CD4=436 cells per μ L (SD 209); on ART=93% People with HIV-ANI: n=18 (100% male); age=45.0 years (SD 13.4); CD4=509 cells per μ L (SD 240); on ART=89% People with HIV-MND: n=21 (100% male); age=39.4 years (SD 8.5); CD4=377 cells per μ L (SD 176); on ART=95% People without HIV: n=39 (100% male); age=42.7 years (SD 11.8)	Heidelberg neurological soft signs	Motor coordination: significantly worse in people with HIV-ANI and people with HIV-MND than people without HIV and people with HIV without ANI or MND; complex motor tasks: significantly worse in people with HIV-ANI and HIV-MND than in people without HIV; sensorimotor integration and gait: significantly worse in all groups of people with HIV than in people without HIV
Kronemer et al ²⁷	2017 People with HIV: n=25 (76% male, 24% female); age=58.0 years (SD 7.5); CD4=unknown; on ART=100% People without HIV: n=22 (27% male, 73% female); age=60.3 years (SD 8.0)	Figure of eight and finger-tapping	Bradykinesia: significantly worse in people with HIV than in people without HIV on the figure-of-eight task; difference compounded when multitasking
Maki et al ²⁸	2015 WIHS cohort People with HIV: n=1019 (100% female); age=47.5 years (SD 8.8); CD4=51% >500 cells per μ L; on ART=76% People without HIV: n=502 (100% female); age=43.5 years (SD 10.0)	GPT	Bradykinesia: people with HIV did significantly worse on GPT; no analyses were done comparing people with virally suppressed HIV with people without HIV
Sullivan et al ²⁹	2011 People with HIV: n=40 (70% male, 30% female); age=42.0 years (SD 9.7); CD4=550 cells per μ L (SD 221); on ART=78% People without HIV: n=83 (48% male, 52% female); age=44.0 years (SD 9.8)	Standing heel-to-toe; walking heel-to-toe; standing on one foot	Postural stability: significantly worse in people with HIV at single-leg stands and walking heel-to-toe than in people without HIV
Gonzalez et al ³⁰	2008 People with HIV: n=48 (67% male, 33% female); age="in their fourth decade of life"; CD4=359 cells per μ L (range 249–555); on ART=50% People without HIV: n=48 (81% male, 19% female); age="in their fourth decade of life"	Rotary pursuit and star mirror tracing	Bradykinesia: people with HIV significantly slower than people without HIV
Valcour et al ⁷	2008 Hawaii Ageing with HIV cohort: only older cohort aged >50 years, included Younger people with HIV: n=108 (28% male, 78% female); age=35.0 years (SD 4.8); CD4=433 cells per μ L (SD 220) Younger people without HIV: n=98 (75% male, 25% female); age=34.9 years (SD 5.1) Older people with HIV: n=121 (92% male, 8% female); age=55.5 years (SD 5.4); CD4=483 cells per μ L (SD 263) Older people without HIV: n=106 (90% male, 10% female); age=55.4 years (SD 5.2)	UPDRS	Rigidity: more prevalent in younger people with HIV compared with younger people without HIV; prevalence was similar between older people with and without HIV Hypomimia: significantly more prevalent in both younger and older people with HIV compared with all people without HIV Resting tremor: more prevalent in older people without HIV compared with older people with HIV, with no difference by serostatus in the younger group Action tremor: more prevalent in both younger and older people with HIV compared with people without HIV Bradykinesia: more prevalent in both younger and older people with HIV compared with people without HIV Gait speed: slower gait (ie, impaired gait speed) more prevalent in older people with HIV compared with older people without HIV. Postural instability: more prevalent in the younger group compared with older people with HIV compared with people without HIV

Studies selected for this table included those with a population of ART-treated people with HIV and a control population of people without HIV. ART=antiretroviral therapy. MACS=Multicenter AIDS Cohort Study. HNRP=HIV Neurobehavioural Research Programme. GPT=grooved pegboard test. UPDRS=Unified Parkinson's Disease Rating Scale. ANI=asymptomatic neurocognitive impairment. MND=mild neurocognitive disorder. WIHS=Women's Interagency HIV Study

Table 2:

Tests assessing parkinsonism motor symptoms

	Aspect of parkinsonism tested	Advantages	Disadvantages
Comprehensive assessments			
Unified Parkinson's Disease Rating Scale	Bradykinesia, rigidity, resting tremor, gait, postural instability, hypomimia, speech changes, and cognitive or affective symptoms	Most comprehensive motor assessment; also includes non-motor symptoms	Time-intensive; requires training
Modified HIV Motor Scale	Bradykinesia, rigidity, tremor, gait, and postural instability	Rapid assessment tailored for HIV	Requires trained personnel; lacks speech or hypomimia evaluation
Bradykinesia			
Finger tapping test	Bradykinesia	Simple; MRI-compatible	Lacks sensitivity
Speeded finger tapping with alternation	Bradykinesia	Assesses fine motor control and coordination	Can be confounded by cognitive impairment
Most rapid alternate finger movements and most rapid index finger extensions	Bradykinesia	Sensitive to subclinical deficits; allows spectral analysis	Requires specialised instrumentation and expertise
Grooved pegboard test	Bradykinesia, fine motor control	Continuous measure of motor speed; sensitive to subtle deficits	Involves multiple motor pathways; low availability in resource-poor settings
Handwriting analysis	Bradykinesia, fine motor control	Digital handwriting tasks allow objective movement quantification	Not widely validated in HIV
Gait and postural instability			
Retropulsion (pull) test	Postural instability	Quick and easy to administer	Risk of fall if not properly done
Timed gait	Gait speed	Quick and easy to administer	Might not be suitable for patients who are severely impaired
Sit-to-stand (five times) test	Postural instability	Quick and easy to administer	Might not be suitable for patients who are severely impaired
Timed up and go	Gait speed, balance, bradykinesia	Quick and easy to administer	Reduced specificity
Balance platform posturography	Postural instability	Provides quantitative balance assessment	Requires specialised equipment
Tremor and rigidity			
Tone evaluation	Rigidity	No equipment required; rapid bedside assessment	Subjective; lacks quantification
Spiral drawing task (digitised or paper-based)	Tremor	Quantifies tremor amplitude and frequency	Not universally validated in HIV
Hand-held tremor analysis (accelerometry-based devices)	Tremor	Objective quantification of tremor patterns	Requires specialised equipment