Global HIV neurology: a comprehensive review

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Neurological conditions associated with HIV remain major contributors to morbidity and mortality and are increasingly recognized in the aging population on long-standing combination antiretroviral therapy (cART). Importantly, growing evidence shows that the central nervous system (CNS) may serve as a reservoir for viral replication, which has major implications for HIV eradication strategies. Although there has been major progress in the last decade in our understanding of the pathogenesis, burden, and impact of neurological conditions associated with HIV infection, significant scientific gaps remain. In many resource-limited settings, antiretrovirals considered second or third line in the United States, which carry substantial neurotoxicity, remain mainstays of treatment, and patients continue to present with severe immunosuppression and CNS opportunistic infections. Despite this, increased global access to cART has coincided with an aging HIV-positive population with cognitive sequelae, cerebrovascular disease, and peripheral neuropathy. Further neurological research in low-income and middle-income countries (LMICs) is needed to address the burden of neurological complications in HIV-positive patients, particularly regarding CNS viral reservoirs and their effects on eradication.

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Introduction

The landscape of global HIV is changing with increased access to combination antiretroviral therapy (cART). In 2015, the number of people living with HIV on antiretroviral therapy reached 17 million individuals, increasing by approximately one-third from the previous year [1]. In sub-Saharan Africa, the world's most affected region, the number of people on treatment has more than doubled in the last 5 years. Since 2003, annual AIDS-related deaths have decreased by approximately 43% globally [1]. Despite these achievements, significant challenges remain as there were 1.8 million new infections in 2016 (a 16% decrease since 2010) and approximately 36.7 million people worldwide continue to live with HIV [1,2].

HIV-associated neurological syndromes cause significant morbidity and mortality globally and may be because of primary HIV infection, secondary to opportunistic

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infection or immune reconstitution, or associated with antiretroviral treatment. HIV can primarily or secondarily affect all parts of the nervous system, including the brain, meninges, spinal cord, nerve roots, peripheral nerves, and muscles. Neurological disease is the first manifestation of symptomatic HIV infection in approximately 10–20% of individuals, and about 60% of patients with advanced HIV have clinical evidence of neurologic dysfunction during the course of their illness [3–5]. Given increased global access to cART, neurological conditions are becoming more frequent in an aging HIV-infected (HIV+) population with longstanding HIV including cognitive sequelae, cerebrovascular disease, and peripheral neuropathy. There is also an ongoing impact of neurotoxicity because of continued use of older generation antiretroviral drugs in resource-limited regions. Here we review the most common neurological complications of HIV with an emphasis on their impact in low and middle-income countries (LMICs), as well as the current knowledge gaps in the field including the impact of the central nervous system (CNS) as a reservoir for HIV and its effects on eradication efforts [6].

Methods

A review of available literature was performed to identify data on the prevalence, cause, outcomes, and treatment of neurologic disorders in patients living with HIV in resource-limited settings. Online databases (Ovid Medline and PubMed) were searched to identify relevant articles published in English using combinations of the terms 'neurology,' 'nervous system diseases,' 'developmental disabilities,' 'neurological impairment,' and 'HIV' with the specifiers 'developing countries,' 'global health,' and 'low- and middle-income countries.' Abstracts from any potentially relevant study were reviewed for inclusion, and the most relevant publications were included in the final review. Web sites from the World Health Organization were scanned for further references. The abstracts of any articles identified in this search strategy were screened for relevance and electronic or paper copies of the full text were obtained for all relevant articles. References from each relevant article were scanned for further relevant articles and a snowball search was performed. Commercial search engines, including Google, were then used to check for any missing publications. Identified publications were then prioritized for relevance to the topic and coded for themes and key emerging themes were summarized in each section as follows.

Neurological disorders associated with primary HIV infection

HIV does not productively infect neurons, instead HIV damages neurons and neuronal support cells through inflammatory mediators and excitotoxicity [7,8]. HIV invades the CNS early in infection, crossing the blood–brain (BBB) barrier through infected monocytes and lymphocytes in what is often described as a 'Trojan Horse' mechanism [8]. Infected monocytes then differentiate into resident macrophages and establish low-level viral replication, typically infecting neighboring microglia. Astrocytes may also be susceptible to infection, but do not develop productive infection. Viral proteins (e.g. Tat) released from infected monocyte-derived cells may directly damage neurons [9,10]. Simultaneously an increase in translocation of bacteria across a leaky gut membrane may increase lipopolysaccharide (LPS)-derived factors, further increasing systemic inflammation and monocyte activation [11,12]. Activated monocytes and macrophages produce a series of cytokines and chemokines, which increase transmigration of inflammatory cells as well producing increased concentrations of excitatory neurotransmitters [7,8]. The increase in excitatory amino acids and excessive activation of N-methyl-D-aspartate (NMDA) receptors may increase intraneuronal calcium concentrations to toxic levels, with this process compounded by increased oxidative stress and dysregulation of normal autophagic processes [13–15].

HIV has been cultured from brain, nerve, and muscle tissue in individuals at all stages of infection. HIV enters the nervous system in the beginning stages of infection, with evidence of the virus in cerebrospinal fluid (CSF) as early as 1 week after initial infection and changes in brain structure visualized within 3 months of primary infection [16–18]. The most favored theory on viral entry and migration into the CNS suggests trafficking of HIV-infected $CD4^+$ cells into the CNS as part of routine immune inspection. HIV-1 virions may also cross the BBB or blood-CSF barrier in the setting of high blood viral load [19]. This is supported by a recent study which found evidence of BBB disruption early in the course of primary HIV infection that was associated with CSF markers of neuronal injury that persisted essentially unchanged over the first year of cART treatment [20]. HIV's initial seeding of the nervous system is thought to be asymptomatic, though mounting evidence suggests this may not be true. A study performed in Thailand showed a significant number of patients have mild neurological manifestations at the time of acute infection, including mild cognitive impairment (MCI), motor findings, and neuropathy [6]. Another Thai study identified neurocognitive impairments in one-quarter of participants with acute HIV infection, which did not improve in the first 6 months of cART treatment [21]. These neurological signs and symptoms are only captured clinically with thorough neurological and cognitive evaluations, which remains a challenge as identifying more subtle neurologic signs and symptoms of HIV is often challenging in resource-limited settings where few neurological experts exist [16]. The first study identified

higher plasma HIV RNA levels at diagnosis in those with one or more neurologic findings, and the latter study found higher CSF HIV RNA levels correlated with the presence of neurocognitive impairment. This suggests that both systemic disease severity and early CNS invasion play a role in the development of neurologic symptoms. More severe neurological manifestations may occur during seroconversion, including acute meningoencephalitis and acute inflammatory demyelinating polyneuropathy (AIDP). In patients presenting with aseptic meningitis, a strong correlation with CSF viral load has been identified [22]. The true prevalence of acute CNS manifestations of HIV in resource-poor settings at the time of seroconversion is not known, as individuals may not present reliably for care, and if they do, many resource-poor settings do not have access to p24-sensitive tests, limiting their ability to diagnose acute HIV infections, and lack routine protocols for following up antibody testing post discharge [23,24].

Peripheral manifestations of HIV

HIV infection can also cause deleterious effects on the peripheral nervous system (PNS). Distal symmetric polyneuropathy (DSP) is the most common HIV-associated peripheral nerve disorder, affecting up to half of HIV+ patients [25]. A recent cohort study of 400 HIV+and 400 HIV-uninfected (HIV−) Ugandans found high rates of symptomatic neuropathy in both HIV+and HIV− participants, and 20% of total participants had objective signs of neuropathy [26]. Older age was also associated with increased neuropathy risk in HIV+ individuals. HIV− individuals were notably healthy with low rates of diabetes. This suggests that additive effects, which may be environmental or diet-related, may increase neuropathy risk in both HIV+ and HIV− individuals in this region. A rural Zambian study of HIV+ adults prior to the initiation of cART found that food insecurity and lower BMI but not HIV stage were risk factors for peripheral neuropathy symptoms further supporting the potential importance of diet in HIV-associated neuropathies in sub-Saharan Africa [27].

Other PNS complications of HIV include polyradiculopathy, mononeuropathies, mononeuropathy multiplex, and autonomic neuropathy. Moreover, there are multiple reports of motor neuron diseases in HIV+ patients, including primary lateral sclerosis, brachial amyotrophic diplegia, and classic amyotrophic lateral sclerosis (ALS) [28]. Table 1 highlights the most common peripheral manifestations of HIV [29–50].

HIV-associated cerebrovascular disorders

In HIV+ children and adults there is evidence of an increased risk of cerebrovascular disease when controlling for other traditional cerebrovascular risk factors [51–55]. Data adjusted for demographics and ischemic stroke risk factors show incidence ratios of 1.05 and 1.76 for HIV-infected men and women, respectively, compared with

Table 1. Peripheral nervous system manifestations of HIV.

Peripheral manifestation	Clinical presentation	Mechanism
Chronic inflammatory demyelinating polyneuropathy (CIDP) [29–33]	Slowly progressive weakness over ≥4 weeks	Autoimmune Peripheral nerve myelin sheath damage
Acute inflammatory demyelinating polyneuropathy (AIDP) [29–33]	Acute to sunacute progressive weakness over less than 4 weeks Impaired sensory function in arms and legs	Autoimmune Peripheral nerve myelin sheath damage
Distal symmetric polyneuropathy (DSP) [34–38]	Small-fiber sensory neuropathy Low levels of virological replication may lead to ongoing nerve damage	Autoimmune Systemic and CNS immune activation
Diffuse infiltrative lymphocytosis syndrome (DILS) [39,40]	Causes peripheral neuropathy and inflammatory myopathy Sjögren-like disease	$CD8^+$ T-cell lymphocytosis associated with a $CD8^+$ T-cell infiltration of multiple organs
HIV-associated myopathy [41–45]	Clinically and pathologically similar to autoimmune polymyositis and/or inclusion body myositis Slowly progressive proximal and symmetric weakness	Inflammatory infiltrates of $CD8^+$ T cells and macrophages surrounding major histocompatibility complex-I-expressing muscle fibers in endomysial parenchyma
Bell's palsy [46]	Lower motor neuron facial weakness Usually associated with aseptic meningitis during primary HIV infection	Inflammatory/autoimmune
Vasculitic neuropathy/mononeuritis multiplex [47]	Multiple asymmetric motor and sensory deficits Very painful	Autoimmune May be related to CMV infection late in disease course
Brachial plexopathy (Parsonage Turner syndrome) [48,49]	Acute arm pain followed by weakness, sensory changes and atrophy	Autoimmune
Motor neuron disease [50]	Progressive asymmetric weakness, spasticity and bulbar symptoms	Neurodegeneration

CNS, central nervous system.

Table 2. Summary of key HIV-associated cerebrovascular disorders in adults and children with HIV.

	Stroke mechanism	Evidence	Key studies
Opportunistic infection or neoplasia	Immunosuppression caused by HIV increases susceptibility to acquisition or reactivation of these infections		Benjamin *et al.* [51] Narayan *et al.* [62]
	Tuberculosis (TB)	Four hundred and fifty-five of 2205 patients with TB, also had HIV infection	Lammie *et al.* [63]
		Forty-five of 455 had *Mycobacterium tuberculosis* isolated from CSF	Berenguer *et al.* [64]
	Varicella Zoster Virus (VZV)	VZV infection might cause cerebral vasculitis and stroke in immunosuppressed patients	Gutierrez *et al.* [65] Gilden *et al.* [66]
		Skin manifestation can be absent at the time of presentation in ~1/3 patients with stroke, making diagnosis difficult	Nagel *et al.* [67]
	Syphilis	Co-infection with HIV compounds the diagnosis of neurosyphilis, which is another potential cause of stroke	Zetola *et al.* [68] Timmermans *et al.* [69]
	Neoplasia	Lymphoma involving cerebral blood vessels	Tipping *et al.* [70] Chetty *et al.* [71]
Cardioembolism	Secondary to HIV-associated cardiomyopathy		Goyal *et al.* [72]
	Coagulopathies concomitant with HIV may contribute emboli formation resulting in ischemic stroke		
Cardioembolism	Nonatherosclerotic vasculopathy	After repeated damage to the vascular endothelium by HIV and/or its viral particles, it is conceivable that vessel wall remodeling arises	Gutierrez *et al.* [73]
	Bacterial and marantic endocarditis	Mycotic aneurysm (secondary to bacterial endocarditis) Associated with cardiothromboembolism	Berger *et al.* [74]
	Thrombotic thrombocytopenic purpura (TPP)	HIV may be a direct precipitant of TTP through damage of vascular endothelial cells resulting in dysfunction, localized thrombin generation, and consumption of ADAMTS13 (metalloprotease enzyme that cleaves von Willebrand factor)	Brecher *et al.* [75]
	Ischemic heart disease and HIV-associated cardiac dysfunction	Cardiac and pulmonary complications of HIV disease are generally late manifestations and may be because of prolonged immunosuppression and interaction the virus with opportunistic infections, viral infections, autoimmune response to viral infection, drug-related cardiotoxicity, and nutritional deficiencies	Barbaro [76]
	HIV-associated hyperviscosity	Risk factor in adults and children includes high serum IgG levels	Garderet *et al.* [77] Hague *et al.* [78]
	Coagulopathy, for example, protein S and protein C deficiency	Unknown if this independently contributes to increased stroke risk	Zimba *et al.* [79] Mochan *et al.* [80]
	Coagulopathy, for example, antiphospholipid antibodies	The contribution of these antibodies to hypercoagulability is unclear in pediatric HIV+ patients.	Ortiz *et al.* [53] Abuaf [81]
	Cerebral venous thrombosis (CVT)	When CVT was associated with HIV+ status, patients reported headache, vomiting, and seizures 11.5% of patients expired during the acute state	Netravathi *et al.* [82]
CNS vasculopathy	Often identified on pathological study		Benjamin *et al.* [51]
	Can also be identified based on radiological findings on magnetic resonance angiography (MRA)		Tipping *et al.* [70]
	Premature atherosclerosis	Case study of 13-year-old girl with AIDS found progressive nonatherosclerotic occlusive disease of middle/anterior cerebral arteries	Chow *et al.* [83] Narayan *et al*. [62]
		Virologically-suppressed HIV+ individuals demonstrated a trend toward a greater proportion of strokes attributable to large artery atherosclerosis	
	Low $CD4^+$ count and HIV-associated vasculopathy	Association with low $CD4^+$ cell count and stroke Possible mechanisms include inflammatory damage from viral-induced cytokines, damage from T-cell and leukocyte invasion, and vessel wall remodelling	Benjamin *et al.* [84]
	Pediatric cerebrovascular disease	One of 68 HIV-infected pediatric stroke patients. had aneurysmal dilation of the circle of Willis arteries demonstrating intimal fibroplasia, medial thinning and elastic destruction and stained positive for monoclonal antibody to HIV glycoprotein gp41	Blockhuis *et al.* [85] Potchen *et al.* [86] Park *et al.* [87]
		Four of 68 patients. clinically suffered stroke	
		Thirty-eight of 68 patients. died during 4.5-year longitudinal study; 6/18 autopsies revealed cerebrovascular disease	
		Cerebral blood flow (CBF) was higher in white matter (WM), basal ganglia, and thalamus in cART-treated perinatally-infected children	
		HIV-infected children with lower grey matter CBF have a higher volume of WM lesions, which could reflect vascular disease as a risk for WM injury	
		Children co-infected with HIV and cerebral malaria are at higher risk for strokes in the same subcortical regions where prior autopsy studies showed high levels of p24 protein and HIV-associated subclinical vasculopathy	

CNS, central nervous system.

HIV− individuals, suggesting a more pronounced risk in women [56]. One study also showed that HIV also increases the incidence ratio of intracerebral hemorrhage (ICH) by 1.85 [57]. In high HIV-prevalence pediatric studies, HIV may be one of the main contributors to stroke. In fact, the effect of HIV on ICH poses a lesser risk with increasing age [51,58].

Several mechanisms have been proposed for HIV-associated stroke, including premature atherosclerosis, opportunistic infections, cardioembolism, coagulopathy, and HIV vasculopathy (Table 2) [51,53,59–87]. Immunosuppression because of HIV resulting in low $CD4^+$ cell counts ($\leq$ 200) and high viral loads has been identified as another significant risk factor for strokes [56]. Among

HIV-infected patients with virologic suppression, a trend toward a greater proportion of strokes, attributable to large artery atherosclerosis was observed [83]. Furthermore, with the widespread global use of cART, increasing rates of HIV+ patients face previously rare complications of treatment [88]. One 2008 study found a 26% increase in vascular disease incidence for each year of exposure to cart. Mechanisms include antiretroviral drugs which lower cerebral vasoreactivity (i.e. lopinavir and ritonavir), cART duration, and duration of HIV infection [61]. Interestingly, a 2017 study found association in illegal drug use, low $CD4^+$ cell count, and high viral load with ischemic cerebral events and no association with cART use or treatment compliance [89]. A thinner carotid–intima layer might be a preclinical stage in HIV vasculopathy development [90]. A study in China found that cerebrovascular endothelial dysfunction associated with HIV seropositivity may be important in the pathogenesis of cerebrovascular dysfunction [91].

$CD8^+$ encephalitis, an emerging clinical entity pathologically associated with marked perivascular infiltrates with polyclonal $CD8^+$ lymphocytes, may be a newly recognized HIV vasculopathy though further studies are needed to fully delineate the pathophysiological processes underlying this condition. A 2013 case-series of 14 cases of $CD8^+$ encephalitis all exhibited radiographic features of diffuse hyperintensity of the white matter and multiple punctate or linear lesions in patients with, on average, a decade of treated HIV infection [92–94]. Most reported cases of $CD8^+$ encephalitis have occurred in patients with systemic viral suppression. Multinucleated giant cells, typically seen in HIV encephalitis, are not present in $CD8^+$ encephalitis. $CD8^+$ encephalitis responds well to glucocorticoids, is an important condition to include in the differential diagnosis of individuals with well controlled, long-standing HIV who present with acute or subacute CNS dysfunction.

The incidence rate of HIV-associated cerebrovascular diseases in LMICs remains underestimated because of limited access to neuroimaging, the subtlety of clinical presentations, and misdiagnosis of HIV-associated cerebrovascular conditions as HIV encephalopathy and CNS OIs [95]. In such regions, HIV is becoming a more significant contributor to the growing global burden of cerebrovascular disease [96].

Central nervous system opportunistic infections

Many CNS opportunistic infections are AIDS-defining conditions with high mortality risk, including progressive multifocal leukoencephalopathy (PML), CNS cytomegalovirus (CMV), CNS tuberculosis (TB), cryptococcal meningitis, and cerebral toxoplasmosis [97,98]. CNS opportunistic infections most commonly occur when the $CD4^+$ cell count is 200 cells/μl or less, and in up to 15% of HIV-infected patients, multiple CNS opportunistic infections exist concurrently [99,100]. Unfortunately, clinical manifestations of CNS opportunistic infections are often nonspecific (headaches, fevers, delirium, seizures, focal neurologic deficits) and the rather broad differential may be only marginally narrowed with imaging and CSF analyses. Therefore, diagnosis is especially challenging in resource-limited settings with limited laboratory testing and neuroimaging and can be further complicated by underutilization of lumbar puncture in these regions [101,102]. The differential diagnosis can be further guided by the degree of immunosuppression in the host, as CNS mass lesions are most common in acutely immunosuppressed patients with $CD4^+$ cell counts 200 cells/μl or less [103]. But in reality, a patient with advanced AIDS who presents with fever and headache could suffer from toxoplasmosis, TB, lymphoma, syphilis, or PML, or a combination of more than one of these opportunistic infections simultaneously.

cART is the most important strategy to prevent CNS opportunistic infections: the restoration of cellular immunity brought about by cART decreases the risk of CNS opportunistic infections among HIV+ patients who discontinue antimicrobial therapy following adequate immune recovery [104–106]. Strategies for patients who do not receive cART or are not adherent remain exposure avoidance and antimicrobial therapy. Many infections, such as *Streptococcus pneumoniae* and hepatitis B virus, can be prevented by vaccination; however, vaccine efficacy may be compromised in advanced HIV [107]. Of note, timely initiation of prophylaxis can substantially reduce incidence of opportunistic infections. However, of the CNS opportunistic infections, toxoplasmosis and varicella zoster virus (VZV) have effective prophylactic regimens available. For CNS toxoplasmosis, prophylaxis consists of one double-strength trimethoprim-sulfamethoxazole tablet daily, whereas prevention of VZV infection is achieved with vaccination in patients with $CD4^+$ counts at least 200 cells/μl who have no known prior exposure to VZV or are known to be VZV seronegative [108]. For a comprehensive review, refer to the 2016 review by Albarillo and O'Keefe [109]. Table 3 presents an overview of the epidemiology, clinical presentation, prophylaxis, and treatment of the most common CNS opportunistic infections [48,110–148].

Central nervous system-immune reconstitution syndrome

Although the use of cART markedly improves immune function and prognosis in HIV-infected patients, immune

Table 3. Epidemiology, clinical characteristics, prophylaxis and treatment of the most common central nervous system opportunistic infections.

CNS opportunistic infection	Epidemiology	Clinical characteristics	Prophylaxis/treatment
CNS toxoplasmosis [110–113]	The most commonly reported CNS opportunistic infection since cART was introduced. Rates vary according to the seroprevalence of *Toxoplasma gondii* in the population.	Presents with headache, fever, and subacute neurologic deficits. Seizures are common. Diagnosis is often established by clinical and radiographic improvements after empirical treatment and by a positive test for IgG antibodies to *T. gondii* in serum. Radiographically defined by multiple ring enhancing lesions frequently involving basal ganglia structures.	Combined pyrimethamine, folinic acid, and sulfadiazine has traditionally been used. Trimethoprim-sulfamethoxazole was equally effective in a small randomized trial, and is the most economical one in resource-poor regions. Corticosteroids are indicated when substantial mass effect is seen. Induction treatment should be continued for at least 6 weeks (until significant clinical improvement). Maintenance therapy should be continued in all patients until immune reconstitution is achieved. Brain biopsy is indicated if no significant improvement within 2 weeks of therapy initiation to evaluate for primary CNS lymphoma, which has a similar clinical and radiographic presentation.
Primary CNS Lymphoma [114–116]	Pre-cART 5.33 per 1000 person-years Post-cART 0.32 per 1000 person-years	Usually presents with headaches, mental status changes, seizures, and focal neurological deficits in the absence of fever. Imaging usually reveals a solitary ring-enhancing lesion but can be multiple. CSF Epstein Barr Virus (EBV) PCR is suggestive but not specific for the diagnosis. The primary differential diagnosis is toxoplasmosis. Brain biopsy is often needed for definitive diagnosis but is usually not obtained until empiric therapy for toxoplasmosis is unsuccessful.	Immediate ART initiation is essential to any treatment regimen. High-dose methotrexate and ART are associated with good long-term survival and low-relapse rates. Whole brain radiation and chemotherapy can also be considered.
Progressive multifocal leukoencephalopathy (PML) [48,117–121]	PML incidence has declined in the cART era and prognosis has improved with initiation of cART upon PML diagnosis.	Characterized by demyelinating infection of oligodendrocytes by the JC polyomavirus (JCV), PML presents with slowly progressive multifocal neurological deficits. Visual symptoms are most common, and seizures often occur. Definitive diagnosis requires clinical (compatible history and examination), radiographic (multifocal lesions in the subcortical and periventricular white matter), and virological evidence (positive CSF JCV PCR or typical histopathological findings on brain biopsy).	Primary treatment is immune reconstitution with immediate cART initiation as no JCV-specific treatment exists. Anecdotal reports of improved outcomes with mirtazapine and interleukin-7 have not been confirmed in clinical trials. Topotecan showed promise in a phase 2 trial, but no phase 3 trial has been performed.
Cryptococcal meningitis [122–134]	In sub-Saharan Africa, cryptococcal infection is a leading cause of meningitis in adult HIV+ patients. Accounted for 63% of cases of adult meningitis in study in South Africa. Cryptococcal meningitis is responsible for one-fifth of global AIDS-related mortality.	Initially presents with nonspecific headache followed by focal neurological deficits. Definitive diagnosis is made with a positive CSF cryptococcal antigen (CrAg) or CSF India Ink staining. If LP is unavailable, serum CrAg titers $\geq$1:160 are highly suggestive of CM and virtually all individuals with serum CrAg titer >1:640 have CM. Cryptococcal antigen lateral flow assay (CrAg LFA), a dipstick immunochromatographic assay, was recently developed; it requires little to no lab infrastructure and has applicability in resource-limited settings.	Aggressive management of raised ICP is crucial to lower the risk of early death. Repeated high-volume lumbar puncture leads to immediate symptomatic relief and can reverse neurological morbidity; therapeutic LPs were associated with a 69% relative improvement in survival. Intravenous amphotericin B and oral flucytosine $\times$2 weeks followed by oral fluconazole $\times$8 weeks is the recommended antifungal treatment. Monotherapy with high-dose fluconazole is often used in low-resource settings.
Cytomegalovirus (CMV) [135]	With increased cART availability, CMV incidence has decreased as this is a late stage manifestation of HIV infection usually occurring at $CD4^+$ count less than 50 cells/μl.	Clinical syndromes include ventriculoencephalitis, micronodular encephalitis, retinitis, and polyradiculitis. CSF CMV PCR is sensitive and specific for the diagnosis.	No specific treatment.
Latent tuberculous meningitis (TBM) [136–147]	Occurs in ~1% of TB cases. Exact incidence of HIV-associated TBM is unknown because of limited epidemiological data.	Characterized by progressive granulomatous inflammation in the basal meninges (may result in hydrocephalus, vasculitis-associated strokes, and death if left untreated). Diffuse brain involvement often exists in HIV+ patients. Rapid detection is crucial in HIV+ patients. Cohort studies have evaluated the use of GeneXpert, a PCR-based diagnostic tool, on CSF in possible TBM cases. According to the WHO, Xpert should be used as the initial CSF diagnostic test for potential TBM patients (strong recommendation given the urgency of rapid diagnosis, very low-quality evidence).	Early treatment with anti-TB chemotherapy and adjunctive treatment with glucocorticoids reduce the rate of death and disability from TBM. Current WHO guidelines recommend treatment with four anti-TB drugs for at least the first 2 months of therapy, followed by treatment with two drugs (rifampin and isoniazid) for an additional 7–10 months. Current standard dosing regimens may put patients at risk of treatment failure from suboptimal rifampicin exposure and may potentially increase the risk of adverse CNS events independently correlated with pyrazinamide CSF exposure. Optimum timing of cART initiation with anti-TB therapy remains controversial.
Varicella Zoster Virus (VZV) Vasculitis [148]		Can present with encephalitis, cranial neuropathies, strokes, seizures and myelitis. Often occurs in the weeks or months after a typical shingles rash. Diagnosis is confirmed with positive CSF VZV PCR or IgM.	Intravenous acyclovir for at least 14 days.

CNS, central nervous system.

reconstitution inflammatory syndrome (IRIS) is a significant complication of antiretroviral initiation [149,150]. IRIS describes a constellation of symptoms and clinical features that may occur in previously immunosuppressed patients during rapid restoration of immune function in the presence of a pathogen or foreign antigen. Low $CD4^+$ cell count and high viral load at treatment initiation, as well as recent diagnosis of an opportunistic infection, are the most significant risk factors [151,152]. Those in LMIC regions may be at particularly high risk given lower $CD4^+$ cell counts and higher prevalence of opportunistic infections at treatment initiation. Prevalence of CNS-IRIS in resource-limited settings is unknown, but at least 25% of individuals in these settings present to medical attention with $CD4^+$ cell counts less than 100 cells/μl [153]. Comparatively, a meta-regression reported mean $CD4^+$ cell count at presentation in developed countries was 336 cells/μl in 2011 [154].

IRIS affects a quarter of patients starting antiretrovirals, and though CNS-IRIS is a rare phenomenon compared with other organ system involvement (including the lymphatic and pulmonary systems), it has the highest associated morbidity and mortality [155,156]. A recent epidemiological study in Southern India found one-third of patients experienced at least one IRIS event at a median of 27 days post cART initiation [157]. Two forms of IRIS have been described: paradoxical IRIS manifests with recurrence of symptoms of a previously recognized and treated opportunistic infection, and unmasking IRIS manifests with the inflammatory presentation of a newly diagnosed opportunistic infection [158,159]. IRIS can be challenging to distinguish from progression of an underlying opportunistic infection.

TB, cryptococcus, and PML are the most frequent pathogens associated with CNS-IRIS, though a number of other causes of CNS-IRIS have been identified [156,160]. Prospective studies have reported an incidence of paradoxical cryptococcal meningitis-IRIS (CM-IRIS) in 13–30% of persons with cryptococcal meningitis surviving to receive antiretroviral drugs [161–166]. High-serum cryptococcal antigen titer and level of immunosuppression at antiretroviral initiation are the main risk factors for paradoxical CM-IRIS. Among those who are diagnosed, mortality is unacceptably high (>50%) [162,167]. In patients who develop unmasking cryptococcosis, pre-antiretroviral cryptococcal antigen screening with preemptive fluconazole therapy for those positive is recommended for patients with $CD4^+$ cell counts less than 100 cells/μl [168]. Ongoing studies in resource-limited settings are studying the utility of screening and treatment for cryptococcal infection pre-antiretroviral initiation as a public health strategy to prevent unmasking CM-IRIS [156]. The high risk of CM-IRIS in those who are antiretroviral-naive makes the decision of antiretroviral initiation timing challenging; clinicians must weigh the risks of CM-IRIS and high mortality associated with deferring antiretroviral in advanced HIV patients [169].

TB-associated IRIS (TB-IRIS) is the most common form of IRIS in high HIV/TB co-infection settings, with neurological involvement in up to 30% of cases [170–172]. A study in South Africa found paradoxical neurological TB-IRIS to be the most common cause (21% of cases) for CNS deterioration in patients within 1 year of starting antiretrovirals [173]. TB-IRIS can be challenging to differentiate from progression of TB because of drug resistance, but should be suspected in patients who appear to initially respond to anti-TB therapy followed by deterioration after initiation of cART. Neurologic TB-IRIS tends to present later than other forms of IRIS, often occurring 5–10 months after cART initiation. Paradoxical neurologic TB-IRIS is a potentially life-threatening condition, often presenting with signs and symptoms of meningitis and increased intracranial pressure. Mortality is high, ranging from 12 to 25%. Risk factors for TB-IRIS include low $CD4^+$ cell count and recent diagnosis of TB. The optimal time to start antiretrovirals in patients with HIV-associated neuro-TB remains uncertain. Patients with HIV and comorbid TB treated earlier with cART have higher rates of IRIS, but lower overall mortality [174–179]. Oral and intravenous steroids are typically utilized in cases of neuro-TB-IRIS, and a single randomized controlled trial demonstrated improved outcomes in patients with TB-IRIS treated with a 4-week course of oral prednisone [152].

PML, a demyelinating disease of the brain caused by JC polyomavirus (JCV), occurs in 3–5% of persons with advanced HIV [180,181]. This is likely an underestimation, as diagnosis requires ancillary data that are often not available in resource-limited settings [48]. Additionally, in a recent study, PCR for JCV in CSF was positive in only 84% of cases of clinical PML, yet brain biopsy confirmed PML diagnosis in 90% of cases and demonstrated histological signs of IRIS in 95% of cases [162]. Diagnosis of PML is reliant on histology, lab evidence, and neuroimaging findings, which are not often available in developing countries [182]. Fortunately, incidence of PML in HIV+ individuals has declined substantially in the post cART era [180]. An observational study in Northeastern India reported HIV+ PML patients as having very low $CD4^+$ cell counts [183]. Up to 16% of HIV+ patients develop PML-IRIS upon commencing antiretroviral drugs, with a median antiretroviral start-to-IRIS time of 4 weeks for paradoxical IRIS and 7–8 weeks for unmasking IRIS [184,185]. PML-IRIS can typically be distinguished from PML without IRIS through the presence of contrast enhancement on MRI, often with significant mass effect [162]. In the absence of typical MRI findings, brain biopsy may be necessary. There are no specific strategies known to prevent or treat PML-IRIS. The role of steroids in PML-IRIS is controversial. Patients with increased intracranial pressure in the setting of PML-IRIS

Table 4. Major adverse neurological effects associated with antiretrovirals.

Family/drug	Mechanism of injury	Neurological adverse effects
Nucleoside analogs ('D Drugs') ddI, d4T, ddC [136,187,191,193]	Neurotoxicity results from mitochondrial DNA (mtDNA) depletion Inflammatory damage to sensory axons and dorsal root ganglia	Neuromuscular syndrome of acute progressive ascending weakness Neuropathies
Nucleoside reverse transcriptase inhibitor (NRTI) Zidovudine Abacavir [41]	Mitochondrial myopathy seen primarily with older NRTI (zidovudine) and much less common with newer agents	Mitochondrial myopathy Neuropathies
Nonnucleoside reverse transcriptase inhibitors (NNRTIs) Efavirenz Nevirapine Rilpivirine [91,189,194]	mtDNA depletion and disruption of BBB integrity Altered calcium hemostasis Decrease in brain creatinine kinase Increase in brain pro-inflammatory cytokines and involvement of the cannabinoid system	Efavirenz Significant side effects reported in ~50% Neuropsychiatric symptoms Increased stroke severity (in mice) Increased vasoreactivity (compared with use of lopinavir or ritonavir) Seizures Nevirapine-few neurologic side effects Rilpivirine-side effects similar to Efavirenz but lower incidence of these
Protease inhibitors Ritonavir Saquinavir Darunavir Lopina [190,192]	Oxidative stress Lipid metabolism alterations Induction of endoplasmic reticulum stress response in macrophages	Circumoral and peripheral paresthesias Taste alterations Increased risk of cerebrovascular disease, given the atherogenic side-effect profile Darunavir does not show neuronal toxicity in cell culture
Integrase inhibitors Raltegravir Dolutegravir Elutegravir	Activates integrated stress response Elutegravir demonstrates toxicity in cell culture	Insomnia, sleep disturbance, mood change but lower incidence than EFV

may benefit from steroids, but there are no randomized controlled trials and observational studies have yielded conflicting results [162,167].

Neurotoxic effects of HIV treatment

Antiretroviral drugs may lead to a wide spectrum of adverse effects along the neuroaxis, sometimes leading to adherence problems, regimen changes, or withdrawal from therapy [34,41,136,186–192]. The lack of access to newer, less neurotoxic antiretrovirals is particularly concerning in resource-limited settings. Table 4 highlights some of the major adverse neurological effects associated with antiretroviral drugs; antiretroviral side effects tend to vary by drug class [41,91,136,187,189–194].

The nucleoside analogs, didanosine (ddI), stavudine (d4T), and zalcitabine (ddC) are most frequently associated with peripheral neuropathy, and as a result have largely been phased out in resource-rich settings [187]. However, in many resource-limited settings, these drugs remain in use. Zidovudine and abacavir both remain cornerstones of therapy in many resource-limited settings, and have minimal association with peripheral neuropathy, though both have been reported to cause myopathy and psychiatric symptoms [41,187].

The nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz has the highest rate of CNS side effects, affecting more than 50% of patients in some studies [186]. Side effects include insomnia, confusion, nightmares, and psychiatric symptoms including anxiety and depression. In contrast, nevirapine appears to have few CNS side effects. The newer NNRTI, etravirine, has also been associated with peripheral neuropathy, though at lower rates than the older nucleoside analogs. Rilpivirine appears to have relatively few CNS side effects, though depression, headache, and insomnia have been reported.

Protease inhibitors have largely been thought to have minimal CNS side effects, although in-vitro data suggests that there is at least a theoretical risk of neurotoxicity [187]. In addition, protease inhibitor-induced hyperlipidemia increases risk for cerebrovascular disease.

The integrase inhibitors (raltegravir, dolutegravir, elutegravir) have only recently become available in many resource-limited settings, and are primarily used in those settings as third-line or salvage therapy. Although the profile of CNS side effects is similar to those reported for efavirenz (sleep disturbance, confusion, and psychiatric changes), the incidence is much lower and in practice discontinuation because of side effects is rare with these drugs [195–197].

Given growing evidence that the CNS is a viral reservoir, another important aspect of antiretroviral therapy is its ability to cross the BBB and penetrate brain parenchyma. The CNS is an immune-privileged compartment and few

antiretrovirals demonstrate effective penetration. Newer therapeutic agents with good CNS penetration and minimal neurotoxicity are appealing but are often unavailable in resource-limited settings where older-generation antiretrovirals remain the mainstay of treatment because of cost [174,194].

Comorbid conditions

Co-infection with malaria and tuberculosis

Globally, a significant number of HIV-infected individuals reside in sub-tropical climates where infections or exposures present comorbid health risks. Malaria remains among the most common devastating illnesses in Africa. HIV+ people living in malaria-endemic regions experience frequent malaria infections; some have suggested that malaria co-infections can speed the progress of HIV, but studies in both adults and children have found acute mortality rates comparable in HIV-infected and uninfected individuals [198]. A significantly higher prevalence of co-infection has also been observed among non-cART patients compared with cART patients [199]. Cotrimoxazole prophylaxis has demonstrated a 69–80% reduction in the risk of malaria in HIV+adults [199–201]. HIV-infected pregnant women did not demonstrate reduced risk of placental or maternal malaria nor improved birth conditions with daily treatment of trimethoprim-sulfamethoxazole (TMP-SMX) compared with controls [202]. Newborns of mothers co-infected with HIV and malaria are at high risk of congenital malaria whenever maternal $CD4^+$ count is less than 200 cells/μl [203]. Among children with cerebral malaria, HIV-coinfection is associated with marked blunting of the inflammatory response but does not affect parasite density or outcome [204].

TB is a leading cause of death among HIV+ individuals worldwide. HIV significantly increases the risk of TB co-infection, including CNS TB, which often manifests as meningitis, tuberculomas, and radiculomyelitis. Early diagnosis and treatment of CNS TB is essential to minimizing morbidity and mortality [137]. However, CNS TB recognition in the HIV+ populations is especially challenging because of the increased risk of CNS opportunistic infections and malignancies that may mimic CNS TB [205]. HIV-TB coinfection management is complicated by drug–drug interactions, uncertainty of optimal antiretroviral start time, and IRIS [174–179,206,207].

Mental and substance use disorders

Mental and substance use disorders are common among HIV+ individuals [208]. When HIV+ individuals suffer from multiple stigma-laden medical conditions, the effect is more than additive [209]. Adherence to cART is negatively associated with depressive symptoms and drug use [210,211].

There is some evidence that depression may be associated with the same underlying HIV-mediated inflammatory process that causes HIV-associated neurocognitive disorders (HAND) [27,212]. Elevated plasma pro-inflammatory cytokine levels contribute to the development of depression and depressive-like behaviors in HIV+ patients [213]. A study of HIV+ patients in an Irish clinic reported 51.1% ($N = 604$) screened positive for cognitive impairment; of those positive, 9.1% screened for depression and 24.5% screened positive for anxiety [214]. Moreover, depression prevalence among HIV+ individuals screened positive for depression has been found to increase with age [215].

Seizures and chronic seizure disorders

Seizures are thought to occur in at least 11% of people with HIV [216]. Opportunistic infections and associated CNS structural lesions are among the most common causes of HIV-associated seizures. In resource-limited settings, key questions about seizures and seizure disorders in caring for people with HIV include: what is the underlying cause of the seizure(s), who warrants long-term treatment with antiepileptic drugs (AEDs; i.e. who is going to have further seizures), and given the limited AED options available, when and what AEDs should be utilized?

A cohort study of HIV-Associated Seizures and Epilepsy (CHASE) Study in HIV+ Zambian adults with new onset seizure has identified significant functional impairment in 44% of patients, with 25% of patients experiencing recurrent seizures [217,218]. The only identifiable risk factor for seizure recurrence was survival with 37% of patients dying within less than 1 year of the index seizure [219,220]. High early mortality in the setting of advanced immune suppression highlights the urgent need for immune reconstitution and necessary avoidance of nonurgent initiation of any enzyme-inducing medications (including AEDs) that might decrease the antiretroviral efficacy. Causes of seizure most commonly included co-infection with CNS opportunistic infections (cryptococcus, JCV, TB, CMV, and VZV) and very low $CD4^+$ counts (median: 112 cells/μl). Failure to identify a seizure cause in the CHASE study population, which underwent imaging, EEG, and extensive CSF PCR evaluation for opportunistic infections, was associated with a higher mortality, suggesting that primary HIV effects on the CNS might be responsible for the seizure and be a marker for more fatal disease [220].

More than 80% of people with epilepsy live in LMICs, and most live in tropical areas [221]. Evidence-based guidelines for the co-treatment of epilepsy and HIV are largely informed by small pharmacokinetic studies and case reports that conclude levetiracetam, lacosamide, gabapentin, and pregabalin are the most ideal agents for HIV/epilepsy co-treatment [222]. All of these AEDs are

Table 5. Specific reported antiepileptic drugs–antiretroviral interactions.

Interaction	Effect
Ritonavir with valproic acid	Decreased VPA levels
Efavirenz with valproic acid	Decreased VPA levels
Phenytoin with lopinavir/ritonavir	Decreased lopinavir by 33% and ritonavir by 28%
Valproic acid with lopinavir	Increased lopinavir by 38%
Atazanavir/ritonavir with lamotrigine	Decreased lamotrigine by 32%
Lopinavir/ritonavir with lamotrigine	Decreased lamotrigine by 50%
Lopinavir/ritonavir with phenytoin	Decreased phenytoin by 31%
Carbamazepine with efavirenz	Decrease efavirenz by 36%
Carbamazepine with nevirapine	Decrease nevirapine half-life by ~20%
Phenytoin with nevirapine	Decrease nevirapine half-life
Valproic acid with zidovudine	Doubled zidovudine level
Efavirenz with carbamazepine	Decreased carbamazepine by 27%

costly, and none are routinely available in most LMIC settings. Enzyme-inducing AEDs (phenobarbital, phenytoin, and carbamazepine) are the most widely available treatment options in LMIC, but their co-use with antiretrovirals is not recommended as single-pill cART therapies do not allow for dose adjustment and subtherapeutic levels of protease inhibitors or NNRTIs because of AED-associated enzyme induction could result in the development of antiretroviral-resistant HIV strains (Table 5) [223,224]. Among low-cost, older generation AEDs, valproic acid is probably the safest medication to combine with antiretroviral medication though adverse effects to the liver and/or mitochondrial dysfunction remain a concern. Adverse AED−antiretroviral interactions can also occur because of HIV-associated hypoalbuminemia, which can lead to elevated free levels of highly protein-bound AEDs, increased AED hypersensitivity responses in people with HIV, and increased risk of bone loss from combining AEDs and antiretroviral that can independently lead to frailty [225].

Aging in the HIV-positive population

The widespread availability of cART in resource-rich settings has led to the transition of HIV from an acute, deadly illness to a chronic disease. In LMIC regions, HIV remains a cause of significant morbidity and mortality in younger populations because of ongoing sociocultural challenges, stigma, and minimal access to newer, less toxic antiretrovirals; however, global trends demonstrate an aging population of HIV+ individuals who receive adequate antiretrovirals in resource-limited regions [226]. For example, HIV+ Ugandans in their forties who are receiving antiretrovirals can expect to live into their sixties [227]. Approximately one in eight HIV+ adults and one in ten HIV+ patients receiving antiretrovirals in sub-Saharan Africa are more than 50 years old [228]. Despite global decreases in HIV-associated mortality, infection remains a leading cause of disability-adjusted life years (DALYs) [229]. Neurological disease remains common among treated HIV+ patients because of early viral entry into the CNS and ongoing inflammation and immune activation that persist in chronic infection. Progressive brain atrophy despite persistent viral suppression in HIV+ adults over age 60 is also of concern [230]. Co-existing conditions and risk factors, including hypertension, hyperlipidemia, substance abuse, and antiretroviral treatment effects, contribute to the effects of primary HIV infection on the nervous system. In addition, neurological conditions often associated with older age, including stroke and dementia, are occurring at younger ages in people with chronic HIV infection, a phenomenon referred to as 'accelerated aging.' This may be because of chronic systemic inflammation, which occurs despite virological suppression, long-term antiretroviral toxicity, lifestyle factors, or a combination thereof [231,232]. Therefore, it is important for providers to be aware of this and screen for neurologic diseases of older age in younger adults with chronic HIV infection.

Systemically, HIV is associated with frailty, a geriatric syndrome characterized by unintentional weight loss, diminished gait speed and grip strength, exhaustion, and low-energy expenditure [233,234]. In Western HIV+ cohorts, frailty has been associated with increased mortality and morbidity, including hospitalizations, and occurs at younger ages than in HIV-uninfected populations [235–241]. Furthermore, frailty at the time of cART initiation was predictive of lower AIDS-free survival, increased mortality rates, and was inversely related to $CD4^+$ cell counts. Frailty is likely a major contributor to neurological deterioration in aging HIV+ patients. Studies have shown an increased risk of cognitive impairment among HIV− older adults with frailty, and HIV+ adults with cognitive impairment have significantly increased odds of frailty [242]. However, little is known about the burden of frailty in LMIC, particularly in sub-Saharan Africa, and gaps in knowledge regarding the health of older people in this region is increasingly being recognized as a public health concern [243,244].

HAND refers to a spectrum of neurocognitive impairment that includes asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-

associated dementia (HAD). HAND is diagnosed using neuropsychological testing and functional status assessments, and HAND stages are differentiated based on the severity of deficits on these tests [245]. Although HAND stabilizes and sometimes improves with initiation of cART, it rarely resolves completely, even in the setting of optimal systemic virological suppression, and incident HAND can occur in patients on cART. Thus, although less severe HAND stages predominate today, the overall prevalence of HAND remains relatively unchanged compared with the pre-cART era, affecting up to 50% of HIV-infected persons and remaining one of the most common neurological complications of HIV [246–248]. Recognition of HAND is important as individuals with HAND have higher rates of cART nonadherence and steeper declines in adherence over time compared with individuals without HAND [249–251].

The reported prevalence of HAND in LMICs varies widely, ranging from 6 to 64% in children and adults [230,252–258], likely reflecting vast differences in methodology (e.g. use of screening tests versus full neuropsychological test batteries for diagnosis) and patient populations (e.g. cART-naive versus cART-treated patients). In a study of adult HIV+ Malawians on cART, 15% reported symptomatic neurocognitive impairment (12% MND, 3% HAD) whereas 55% met criteria for ANI [259]. In a meta-analysis on the epidemiology of neurodegenerative disease in sub-Saharan Africa, 47 of 144 (33%) studies reported HAND as a major contributor to neurodegenerative disease [260]. Accurate epidemiologic data about HAND in sub-Saharan Africa is important, however, as rates may differ from Western population because of differences in risk factors including differing genetics and rates of comorbidities known to increase HAND risk such as hypertension and diabetes. The biology of HIV itself also differs in this region with different circulating HIV subtypes compared with Western populations, though there are conflicting results regarding the effect of HIV subtypes on HAND (Supplemental Table 8, http://links.lww.com/QAD/B246). Some studies suggest subtype D is most neurovirulent, followed by subtypes B, C, and A, respectively, but other studies suggest HAND prevalence is not affected by subtype [261]. Methodological limitations may account for at least some of these differences, but further investigation is needed to definitively answer these questions.

The impact of HAND will likely continue to grow as the global HIV+ population ages as there is mounting evidence that HIV exacerbates age-associated cognitive decline [262–265] and older age is associated with increased risk of HAND [250,251,266–269]. Older HIV+ individuals also demonstrate greater than expected brain atrophy on neuroimaging studies, which is associated with impaired performance in multiple cognitive domains compared with older HIV− individuals [270]. Longitudinal studies demonstrate synergistic effects of HIV and aging on cognitive function [271–275]. Cognitive decline is likely multifactorial because of direct damage from the virus and indirect damage through secondary risk factors, including vascular disease, chronic drug use, and toxic long-term effects of antiretrovirals. Importantly, premature age-associated neurocognitive decline correlated with structural and functional brain changes on neuroimaging and histopathology, including signs of Alzheimer's disease pathology. This is observed in some HIV+ patients at younger ages than would otherwise be expected and may be related to accelerated aging as discussed above [276–278].

Currently, no HAND-specific therapies exist, but small trials of paroxetine and maraviroc showed some benefit in improving neurocognitive function in HIV+ cART-treated adults. Trials of intranasal insulin are ongoing after in-vitro evidence suggested insulin may have neuroprotective effects in HIV infection [279–283]. Development of validated biomarkers and improved clinical neurocognitive tests that can holistically and accurately assess the risk of developing HAND are also needed to facilitate future trials of novel HAND therapies. Table 6 includes a review of key biomarkers associated with HIV-associated cognitive impairment [284–294].

Aspects of pediatric HIV neurology

More than three million children worldwide are HIV+, with more than 90% residing in low-resource settings [295]. HIV may cause neurologic disorders in children through primary viral effects or immune suppression resulting in opportunistic infections [296]. In addition, perinatally infected HIV+ children are at risk of complications through in-utero exposure to maternal HIV [297]. Pediatric HIV infection may affect any part of the nervous system but is more likely to cause brain disorders than to affect the spinal cord or peripheral nerves in children compared with adults [216,296]. The primary effects of HIV in the pediatric nervous system may manifest differently than in adults, particularly with HIV-associated cognitive impairment and HIV-associated cerebrovascular disease [298,299]. The spectrum of opportunistic infections in children is similar to that in adults, though certain opportunistic infections, such as JCV-associated progressive multifocal leukoencephalopathy (PML), are rare in children [296]. Cerebral toxoplasmosis is uncommon in younger children but may be seen in older children and adolescents [300]. For a summary of the most common neurologic manifestations of HIV in children (Table 7) [52,298–306].

HIV-associated neurocognitive effects in children

As HIV was first described in the 1980s, neurocognitive sequelae have been a common occurrence in HIV-

Table 6. Review of key biomarkers associated with HIV-associated cognitive impairment.

Biomarker	Pathway	Outcome	Key studies
C-reactive protein (CRP)	General marker of systemic inflammation; acute phase reactant. Associated with complement system activation.	Associated with cognitive impairment and mortality in adults; associated with cognitive impairment in children when associated with other biomarkers.	Kuller *et al.* [284]; Boulware *et al.* [285]; Kapetanovic *et al.* [286]; De Luca *et al.* [287]
Interleukin-6 (IL-6)	Marker of T-cell and macrophage activation; Stimulates immune response in response to infection.	Associated with cognitive impairment and mortality in adults; associated with cognitive impairment in children when associated with other biomarkers.	Kuller *et al.* [284]; Boulware *et al.* [285]; Tenorio *et al.* [288]; Ancuta *et al.* [289]
Fibrinogen	Involved in blood clotting; Marker of systemic inflammation and vascular injury.	Associated with cognitive impairment and mortality in adults; associated with cognitive impairment in children when associated with other biomarkers.	Kapetanovic *et al.* [286]
Soluble tumor necrosis factor (TNF) receptors 1 and 2 (sTNFR1 and sTNFR2)	Produced in response to increased levels of TNF; may modulate effects of TNF.	Associated with cognitive impairment and non-AIDS events in adults. Stronger association noted for sTNFR2 than for sTNFR1.	Tenorio *et al.* [288];
Soluble $CD163^+$ (sCD163)	Marker of monocyte/macrophage activation; induced by endotoxin and toll-like receptor activation	Associated with coronary events and cognitive impairment in adults	Burdo *et al.* [290]
Soluble $CD14^+$ (sCD14)	Produced by monocytes in response to lipopolysaccharide (LPS); marker of monocyte response to LPS.	Associated with cognitive impairment and mortality in adults.	Ancuta *et al.* [289];
Soluble $CD40^+$ ligand (sCD40L)	Produced by activated platelets; pro-inflammatory; promotes monocyte adhesion to endothelium and increases blood–brain barrier permeability	Associated with atherosclerosis and dementia in adults.	Sui *et al.* [291]; Davidson [292]
Heme-oxygenase 1 (HO-1)	Marker of oxidative stress	Associated with dementia in adults; associated with cognitive decline in children.	Gill *et al.* [293]; Bearden *et al.* [294]

infected children [222,296]. The spectrum of HIV-associated neurocognitive impairment is broad, ranging from a severe and often fatal encephalopathy in untreated children to milder forms of cognitive impairment largely characterized by deficits in attention and executive function (Fig. 1). However, determining the extent of the contribution of HIV to cognitive impairment in children can be challenging because of confounding effects of multiple overlapping factors, including parental illness, low socioeconomic status (SES), stigma, malnutrition, and reduced educational opportunities [307].

HIV-associated progressive encephalopathy (HPE) is the most severe form of HIV-associated neurocognitive impairment, and is characterized by impaired brain growth associated with developmental regression. In the pre-cART era HPE was thought to affect up to 50% of children with perinatally acquired HIV; in the current era, it is almost exclusively seen in children who do not receive early treatment with cART. HPE is rarely encountered in resource-rich settings because of ubiquitous early treatment with cART but remains a major cause of morbidity and mortality in resource-poor settings; thus, early initiation of cART is an important preventive measure [296]. If HPE is detected early, cognitive deterioration may be arrested and partially reversed by cART initiation, yet static encephalopathy often remains in treated patients [308].

Studies suggest that 10–50% of cART-treated children will develop significant cognitive deficits [225,296,298,302].

Table 7. Summary of key primary neurologic complications in children with HIV.

Complication	Prevalence	Key studies
Progressive encephalopathy	Untreated children: 30–50% With early cART: <1%	Donald *et al.* [296]; Patel *et al.,* [301]
Other cognitive impairment	Untreated children: >90% With early cART: 10–50%	Abubakar *et al.* [302]; Nachman *et al.* [298]
Stroke	Uncommon (exact prevalence unknown)	Izbudak *et al.* [52]; Shah *et al.* [299]
Seizures/epilepsy	3–14%	Samia *et al.* [302]; Bearden *et al.* [300]
Myelopathy	Rare (exact prevalence unknown)	Sharer *et al.* [303]
Peripheral neuropathy	5–50%	Floeter *et al.* [304]; Peters *et al.,* [305]

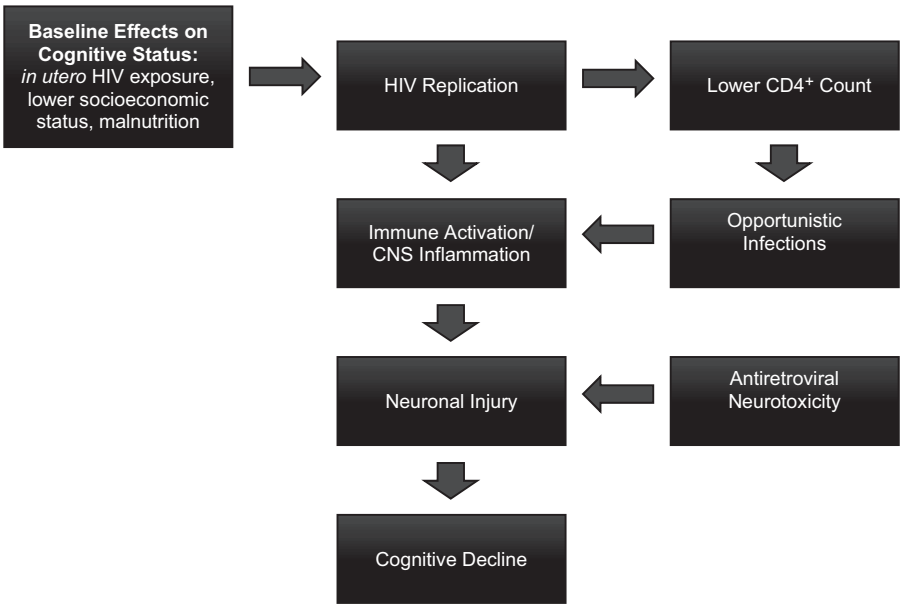

Fig. 1. Conceptual model of HIV-associated neurocognitive impairment in children.

This may be because of poor antiretroviral-CNS penetration, sustained immune activation leading to neuronal excitotoxicity, antiretroviral neurotoxicity, or comorbidities such as depression impacting cognitive functioning [309]. One South African study found 45% of HIV+ youths met criteria for HIV-associated neurocognitive disorders [310].

Effects of in-utero exposure to maternal HIV and antiretrovirals

Multiple studies have found an increased risk of certain neurologic disorders and an effect on development in children who are born to HIV-infected mothers even in the absence of active HIV infection in the child [311–314]. The precise mechanisms are unclear but may be because of systemic maternal illness, teratogenic effects of antiretrovirals, or in-utero exposure to high levels of inflammatory cytokines. HIV-uninfected children born to infected mothers have higher rates of premature birth, and maternal HIV infection is a risk factor for pediatric cerebral palsy [300]. Whether this is associated with in-utero antiretroviral drug toxicity or secondary to direct effects of HIV is unclear [315]. There may be selective toxicity related to specific antiretroviral regimens used to treat pregnant women with HIV [316].

Compartmentalization of HIV in the central nervous system

The CNS is rich in macrophages and microglia, which house the virus similarly to $CD4^+$ T cells [19]. It is also a unique anatomic compartment that is 'immune privileged' because of the semipermeable nature of the BBB, which leads to differing mechanisms of immune surveillance in the CNS compared with the periphery. As a result, the CNS may serve as a reservoir for viral replication outside the reach of systemic immune surveillance, giving rise to two important phenomena – CSF viral escape and CNS compartmentalization – that have major implications for HIV eradication strategies [317].

CNS infection is generally well controlled by systemic suppressive cART; yet there are some instances when HIV RNA can be detected in the CSF despite plasma virus suppression below measureable clinical limits. This is known as CSF viral escape. It occurs in approximately 10% of cART-treated patients with plasma viral suppression and most likely originates from local viral reservoirs [318]. It is clinically relevant as it may be an important mechanism in the development of HAND in this popuation [319–321]. In some cases, disproportionate viral replication in the CSF or CSF viral escape may occur in addition to attack on HIV-infected $CD4^+$ lymphocytes and autoreactive $CD8^+$ cells. A better understanding of CSF viral escape could lead to important insights about CNS HIV infection including the CNS cell types producing HIV during infection and whether CNS infection could re-seed systemic infection over time [322]. However, studies of CSF viral escape are limited in all settings by its relatively low prevalence and the need for a lumbar puncture for identification [322,323].

CNS compartmentalization occurs when virus that enters the CNS undergoes divergent evolution from systemic virus resulting in genetically distinct viral strains in the CNS [324]. This process usually begins during primary or uncontrolled chronic HIV infection and has also been associated with the development of neurocognitive

impairment [325]. Even in virologically suppressed cART-treated patients without CSF viral escape, HIV may persist in CNS reservoirs in a dormant state of infection that is capable of reactivation and replication of new viral particles [19,326]. This viral population will likely pose a major barrier to HIV cure strategies. Further research is necessary to understand the reservoir role of the CNS and to develop CNS-active latency-reversing agents (LRAs) and biomarkers to enable monitoring and treatment evaluation [327,328].

Conclusion

Neurological conditions associated with HIV infection continue to cause major disability and mortality, particularly in resource-limited settings, where a large portion of patients present with severe immunosuppression. Barriers continue to limit quality of life in HIV+ patients suffering from major neurological manifestations. There is mounting evidence that the CNS plays an essential role in HIV persistence and is likely a major barrier to disease eradication. Lastly, acute and chronic effects of HIV infection on the nervous system are increasing in aging populations around the world with synergistic effects on the risk of cognitive dysfunction and cerebrovascular disease.

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Conflicts of interest

There are no conflicts of interest.

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