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Global HIV Neurology: A Comprehensive Review

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Abstract

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 CNS may serve as a reservoir for viral replication, which has major implications for HIV eradication strategies. Though 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, ARVs considered second or third line in the U.S., which carry substantial neurotoxicity, remain mainstays of treatment, and patients continue to present with severe immunosuppression and central nervous system (CNS) opportunistic infections. Despite this, increased global access to cART has coincided with an aging HIV+ population with cognitive sequelae, cerebrovascular disease, and peripheral neuropathy. Further neurological research in low- and middle-income countries (LMICs) is needed to address the burden of neurological complications in HIV+ 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 (ARV) 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 due to primary HIV infection, secondary to opportunistic infection (OI) or immune reconstitution, or associated with ARV 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+ population with longstanding HIV including cognitive sequelae, cerebrovascular disease, and peripheral neuropathy. There is also an ongoing impact of neurotoxicity due to continued use of older generation ARVs 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, etiology, 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 below.

Neurological Disorders Associated with Primary HIV Infection

HIV does not productively infect neurons, instead damaging neurons and neuronal support cells through inflammatory mediators and excitotoxicity.[7 8] HIV invades the central nervous system early in infection, crossing the blood brain 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 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 one week after initial infection and changes in brain structure visualized within three 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 blood brain barrier (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 and 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 six months of cART treatment. [21] However, these neurological signs and symptoms are only captured clinically with thorough neurological and cognitive evaluations, which remains a challenge since identifying the more subtle neurologic signs and symptoms of HIV is often challenging in resource-limited settings.[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 due to 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, most resource-poor settings do not have access to p24-sensitive tests and there lacks structured practices of follow-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- Ugandans found high rates of symptomatic neuropathy in both HIV+ and HIV- participants, and 20% of total participants had objective signs but no symptoms 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 body mass index 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 conditions 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, pseudobulbar syndrome, and classic amyotrophic lateral sclerosis (ALS).[28] Table 1 highlights the most common peripheral manifestations of HIV.

HIV-Associated Cerebrovascular Disorders

There is evidence of an increased stroke risk in adults and children in HIV infected patients when controlling for traditional cerebrovascular risk factors.[29–33] 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 to HIV- individuals, suggesting a more pronounced risk in females. [34] HIV also increases the incidence ratio of intracerebral hemorrhage (ICH) by 1.85. [35] 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. [29 36]

Several mechanisms have been proposed for HIV-associated stroke, including premature atherosclerosis, OIs, cardioembolism, coagulopathy, and HIV vasculopathy (Table 2).[29 31 37–39] Immunosuppression due to HIV resulting in low CD4 counts (≤ 200) and high viral loads has been identified as another significant risk factor for strokes.[34] A recent study in the U.S. of 60 HIV-infected and 60 HIV-uninfected stroke cases found that the among those

with HIV, the most recent plasma HIV viral load prior to the stroke predicted stroke subtype. Among HIV-infected patients with virologic suppression, a trend toward a greater proportion of strokes attributable to large artery atherosclerosis was observed.[40] Furthermore, with the widespread global use of cART, increasing rates of HIV+ patients face previously rare complications of treatment. [41] One 2008 study found a 26% increase in vascular disease incidence for each year of exposure to cART, and particular cART drugs, including lopinavir and ritonavir, may lower cerebral vasoreactivity by weakening endothelial function, independent of vascular risk factors, cART duration, and time since HIV diagnosis. [39] Interestingly, a 2017 study found association in illegal drug use, low CD4 count, and high viral load with ischemic cerebral events and no association with cART use or treatment compliance. [42] A thinner media layer might be a preclinical stage in HIV vasculopathy development.[43] A study in China found that cerebrovascular endothelial dysfunction associated with HIV seropositivity may be important in the pathogenesis of cerebrovascular dysfunction.[44]

$CD8^+$ 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. [45–47] 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. Since this $CD8^+$ encephalitis responds well to glucocorticoids, it 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 LMIC remains underestimated due to limited access to neuroimaging, the subtlety of clinical presentations, and misdiagnosis of HIV-associated cerebrovascular conditions as HIV encephalopathy. [48] In such regions, HIV is becoming a more significant contributor to the growing global burden of cerebrovascular disease.[49]

CNS Opportunistic Infections

Many CNS OIs are AIDS-defining conditions with high mortality risk, including Progressive Multifocal Encephalopathy (PML), CNS cytomegalovirus (CMV), CNS tuberculosis (TB), cryptococcal meningitis, and cerebral toxoplasmosis.[50 51] CNS OIs most commonly occur when the CD4 cell count is ≤200 cells/μl, and in up to 15% of HIV infected patients, multiple CNS OIs exist concurrently.[52 53] Unfortunately, clinical manifestations of CNS OIs are often non-specific (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.[54 55] 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.[56] 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 OIs simultaneously.

cART is the most important strategy to prevent CNS OIs: the restoration of cellular immunity brought about by cART decreases the risk of CNS OIs among HIV+ patients who discontinue antimicrobial therapy following adequate immune recovery.[57–59] 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. [60] Of note, timely initiation of prophylaxis can substantially reduce incidence of OIs. However, of the CNS OIs, only toxoplasmosis and varicella zoster virus (VZV) have effective prophylactic regimens available. For CNS toxoplasmosis, prophylaxis consists of one double-strength trimethoprim-sulfamethoxazole tablet daily, while prevention of VZV infection is achieved with vaccination in patients with CD4 counts ≥200 cells/μL who have no known prior exposure to VZV or are known to be VZV seronegative. [61] For a comprehensive review, refer to the 2016 review by Albarillo & O'Keefe.[62] See Table 3 for an overview of the epidemiology, clinical presentation, prophylaxis, and treatment of the most common CNS OIs.

CNS-Immune Reconstitution Syndrome

Although the use of cART markedly improves immune function and prognosis in HIV-infected patients, immune reconstitution inflammatory syndrome (IRIS) is a significant complication of ARV initiation.[63 64] 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.[65 66] Those in LMIC regions may be at particularly high risk given lower CD4 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 <100 cells/μl.[67] Comparatively, a meta-regression reported mean CD4 count at presentation in developed countries was 336 cells/μl in 2011.[68]

IRIS affects a quarter of patients starting ARV, and though CNS-IRIS is a rare phenomenon compared to other organ system involvement (including the lymphatic and pulmonary system), it has the highest associated morbidity and mortality.[69 70] 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.[71] Two forms of IRIS have been described: *paradoxical* IRIS manifests with recurrence of symptoms of a previously recognized and treated OI, and *unmasking* IRIS manifests with the inflammatory presentation of a newly diagnosed OI.[72 73] IRIS can be challenging to distinguish from progression of an underlying opportunistic infection.

Tuberculosis, Cryptococcus, and PML are the most frequent pathogens associated with CNS-IRIS, though a number of other causes of CNS-IRIS have been identified.[70 74] Prospective studies have reported an incidence of paradoxical cryptococcal meningitis-IRIS (CM-IRIS) in 13%–30% of persons with CM surviving to receive ARV.[75–80] High serum cryptococcal antigen titer and level of immunosuppression at ARV initiation are the main risk factors for paradoxical CM-IRIS. Among those who are diagnosed, mortality is unacceptably high (>50%).[76 81] In patients who develop unmasking Cryptococcosis, pre-ARV cryptococcal antigen screening with preemptive fluconazole therapy for those positive is recommended for patients with CD4 counts <100 cells/μl.[82] Ongoing studies in resource-limited settings are studying the utility of screening and treatment for cryptococcal infection pre-ARV initiation as a public health strategy to prevent unmasking CM-IRIS.[70] The high risk of CM-IRIS in those who are ARV-naïve makes the decision of ARV initiation timing challenging; clinicians must weigh the risks of CM-IRIS and high mortality associated with deferring ARV in advanced HIV patients.[83]

Tuberculosis-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.[84–86] 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 one year of starting ARV.[87] TB-IRIS can be challenging to differentiate from progression of TB due to 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 12-25%. Risk factors for TB-IRIS include low CD4 count and recent diagnosis of TB. However, the optimal time to start ARV 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.[88–93]. 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. [66]

PML, a demyelinating disease of the brain caused by JC-polyomavirus, occurs in 3%–5% of persons with advanced HIV.[94 95] This is likely an underestimation, since diagnosis requires ancillary data that are often not available in resource-limited settings.[96] 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. [76] Diagnosis of PML is reliant on histology, lab evidence, and neuroimaging findings, which are not often available in developing countries. [97] Fortunately, incidence of PML in HIV+ individuals has declined substantially in the post-cART era.[94] An observational study in Northeastern India reported HIV+ PML patients as having very low CD4 counts (107±87.5 cells/μl).[98] Up to 16% of HIV+ patients develop PML-IRIS upon commencing ARVs, with a median ARV start-to-IRIS time of 4 weeks for paradoxical IRIS and 7-8 weeks for unmasking IRIS.[99 100] PML-IRIS can typically be distinguished from PML without IRIS through the presence of contrast

enhancement on Magnetic Resonance Imaging (MRI), often with significant mass effect. [76] 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 may benefit from steroids, but there are no randomized controlled trials and observational studies have yielded conflicting results[76,81].

Neurotoxic Effects of HIV Treatment

ARVs may lead to a wide spectrum of adverse effects along the neuro-axis, sometimes leading to adherence problems, regimen changes, or withdrawal from therapy.[101–110] The lack of access to newer, less neurotoxic ARVs is particularly concerning in resource-limited settings. Table 4 highlights some of the major adverse neurological effects associated with ARVs; ARV side effects tend to vary by drug class.

The nucleoside analogues (NAs) didanosine (ddI), stavudine (d4T), and zalcitabine (ddC) are most frequently associated with peripheral neuropathy, and as a result have largely been phased out in high-resource settings.[103] However, in many resource-limited settings these drugs remain in use. Zidovudine (AZT) 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 in some patients. [103 104]

The NNRTI Efavirenz has the highest rate of CNS side effects, affecting more than 50% of patients in some studies.[101] 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 NAs. 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. [105] In addition, protease inhibitor induced hyperlipidemia presents theoretically could induce incidence of stroke, though this has yet to demonstrated in studies.

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 due to side effects is rare with these drugs. [111–113]

Given growing evidence that the CNS is a viral reservoir, another important aspect of ARV therapy is its ability to cross the blood brain barrier and penetrate CNS brain parenchyma. The CNS is an immune-privileged compartment and few ARVs are efficient with 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 ARVs remain the mainstay of treatment due to cost.[88 114]

Comorbid Conditions

Co-Infection with Malaria and Tuberculosis (TB)—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 illness 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.[115] A significantly higher prevalence of co-infection has also been observed among non-cART patients compared to cART patients.[116] However, cotrimoxazole prophylaxis has demonstrated a 69%–80% reduction in the risk of malaria in HIV+ adults.[116–118] 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 to control.[119] Newborns of mothers co-infected with HIV and malaria are at high risk of congenital malaria when maternal CD4 count is <200 cells/μl.[120] Among children with cerebral malaria, HIV-coinfection is associated with marked blunting of the inflammatory response but does not affect parasite density or outcome.[121]

Tuberculosis (TB) is a leading cause of death among HIV+ individuals worldwide. HIV significantly increases the risk of TB co-infection, including central nervous system (CNS) TB, which often manifests as meningitis, tuberculomas, and radiculomyelitis. Early diagnosis and treatment of CNS TB is essential to minimizing morbidity and mortality.[122] However, CNS TB recognition in HIV+ populations is especially challenging due to the increased risk of CNS OIs and malignancies that may present similar to or along with CNS TB.[123] HIV-TB coinfection management is complicated by drug-drug interactions, uncertainty of optimal ARV start time, and IRIS.[88–93 124 125]

Mental and Substance Use Disorders—Mental and substance use disorders are common among HIV+ individuals.[126] When HIV+ individuals suffer from multiple stigma-laden medical conditions, the effect is more than additive.[127] Adherence to cART is negatively associated with depressive symptoms and drug use.[128 129]

There is some evidence that depression may be associated with the same underlying HIV-mediated inflammatory process that causes HAND.[27 130] Elevated plasma pro-inflammatory cytokine levels contribute to the development of depression and depressive-like behaviors in HIV+ subjects.[131] A study of HIV+ patients in an Irish clinic reported 51.1% (N=604) screened positively for cognitive impairment; of those positive, 9.1% positively screened for depression and 24.5% positively screened for anxiety.[132] Moreover, depression prevalence among HIV+ individuals has been found to increase with age.[133]

Seizures and Chronic Seizure Disorders

Seizures are thought to occur in at least 11% of people with HIV.[134] OIs and associated CNS structural lesions are among the most common cause of HIV-associated seizures. In resource-limited settings, key questions about seizures and seizure disorders in caring for people with HIV include: (1) what is the underlying cause of the seizure(s), (2) who warrants long-term treatment with antiepileptic drugs (AEDs) (i.e. who is going to have further seizures), and (3) 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.[135 136] The only identifiable risk factor for seizure recurrence was survival with 37% of patients dying within less than 1 year of the index seizure.[137 138] High early mortality in the setting of advanced immune suppression highlights the urgent need for immune reconstitution and necessary avoidance of non-urgent initiation of any enzyme-inducing medications (including AEDs) that might decrease the ARV efficacy. Seizure etiologies most commonly include co-infection with CNS OIs (Cryptococcus, JC-virus, TB, CMV, and VZV) and very low CD4 counts (median: 112 cells/μl). Failure to identify a seizure etiology in the CHASE study population, which underwent imaging, EEG, and extensive CSF PCR evaluation for OIs, 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.[138]

More than 80% of people with epilepsy live in LMICs, and most live in tropical areas.[139] 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.[140] All of these AEDs are 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 ARVs is not recommended since single pill cART therapies do not allow for dose adjustment and subtherapeutic levels of PIs or NRTS due to AED-associated enzyme induction could result in the development of ARV-resistant HIV strains (Table 5).[141 142] Among low-cost, older generation AEDs, valproic acid is probably the safest medication to combine with ARV medication though adverse effects to the liver and/or mitochondrial dysfunction remain a concern. Adverse AED-ARV interactions can also occur due to 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 ARVs than can independently lead to osteoporosis.[143]

Aging in the HIV+ 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 due to ongoing sociocultural challenges, stigma, and minimal access to newer, less toxic ARVs; however,

global trends demonstrate an aging population of HIV+ individuals who receive adequate ARVs in resource-limited regions.[144] For example, HIV+ Ugandans in their 40s who are receiving ARVs can expect to live into their 60s.[145] Approximately 1/8 HIV+ adults and 1/10 HIV+ patients receiving ARVs in sub-Saharan Africa are >50 years old.[146] Despite global decreases in HIV-associated mortality, infection remains a leading cause of disability-adjusted life years (DALYs).[147] Neurological disease remains common among treated HIV+ patients due to 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.[148] Co-existing conditions and risk factors, including hypertension, hyperlipidemia, substance abuse, and ARV 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 due to chronic systemic inflammation, which occurs despite virological suppression, long-term ARV toxicity, lifestyle factors, or a combination thereof. [149 150] 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.[151 152] 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. [153–159] Furthermore, frailty at the time of cART initiation was predictive of lower AIDS-free survival, increased mortality rates, and was inversely related to CD4 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. [160] 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.[161 162]

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. [163] 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, while less severe HAND stages predominate today, the overall prevalence of HAND remains relatively unchanged compared to the pre-cART era, affecting up to 50% of HIV-infected persons and remaining one of the most common neurological complications of HIV. [164–166] Recognition of HAND is important as individuals with HAND have higher rates of cART non-adherence and steeper declines in adherence over time compared to individuals without HAND.[167–169]

The reported prevalence of HAND in LMIC varies widely, ranging from 6%–64% in children and adults,[148 170–176] 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-naïve versus cART-treated patients). In a study of adult HIV+ Malawians on cART, 15% reported symptomatic neurocognitive impairment (12% MND, 3% HAD) while 55% met criteria for ANI.[177] In a meta-analysis on the epidemiology of neurodegenerative disease in sub-Saharan Africa, 47/144 (33%) studies reported HAND as a major contributor to neurodegenerative disease.[178] Accurate epidemiologic data about HAND in sub-Saharan Africa is important, however, as rates may differ from Western population due to differences in risk factors including differing genetics and rates of co-morbidities 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 to Western populations, but results conflict regarding the effect of HIV subtypes on HAND (Supplemental Table 8). 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. [179] 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 mounting evidence suggests that HIV exacerbates age-associated cognitive decline[180–183] and older age is associated with increased risk of HAND.[168, 169, 184–187] Older HIV+ individuals also demonstrate greater than expected brain atrophy on neuroimaging studies which was associated with impaired performance in multiple cognitive domains compared to older HIV- individuals.[188] Longitudinal studies demonstrate synergistic effects of HIV and aging on cognitive function.[189–193] Cognitive decline is likely multifactorial due to direct damage from the virus and indirect damage through secondary risk factors, including vascular disease, chronic drug use, and toxic long-term effects of ARVs. Importantly, premature age-associated neurocognitive decline correlated with structural and functional brain changes on neuroimaging and histopathology, including signs of Alzheimer's disease pathology, is observed in some HIV+ patients at younger ages than would otherwise be expected and may be related to accelerated aging as discussed above. [194–196]

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 while trials of intranasal insulin are ongoing after *in vitro* evidence suggested insulin may have neuroprotective effects in HIV infection. [197–201] 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.

Aspects of Pediatric HIV Neurology

More than 3 million children worldwide are HIV+, with >90% residing in low-resource settings.[202] HIV may cause neurologic disorders in children through primary viral effects

or immune suppression resulting in OIs.[203] In addition, perinatally-infected HIV+ children are at risk of complications through *in utero* exposure to maternal HIV.[204] Pediatric HIV infection may affect any part of the nervous system and is more likely to cause brain disorders than affect the spinal cord or peripheral nerves in children compared with adults.[134 203] 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.[205 206] The spectrum of OIs in children is similar to that in adults, though certain OIs, such as JC-virus-associated progressive multifocal leukoencephalopathy (PML), are rare in children.[203] Cerebral toxoplasmosis is uncommon in younger children but may be seen in older children and adolescents.[207] For a summary of the most common neurologic manifestations of HIV in children, see Table 7.

HIV-Associated Neurocognitive Effects in Children—Since HIV was first described in the 1980s, neurocognitive sequelae have been a common occurrence in HIV-infected children.[140, 203] 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 (Figure 1). However, determining the extent of the contribution of HIV to cognitive impairment in children can be challenging due to confounding effects of multiple overlapping factors, including parental illness, low socioeconomic status (SES), stigma, malnutrition, and reduced educational opportunities.[208]

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 due to 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.[203] If HPE is detected early, cognitive deterioration may be arrested and partially reversed by cART initiation, yet static encephalopathy often remains in treated patients.[209]

Studies suggest that 10%–50% of cART-treated children will develop significant cognitive deficits.[143, 203, 205, 210] This may be due to poor ARV-CNS penetration, sustained immune activation leading to neuronal excitotoxicity, ARV neurotoxicity, or comorbidities such as depression impacting cognitive functioning.[211] One South African study found 45% of HIV+ youths met criteria for HIV-associated neurocognitive disorders.[212]

Effects of In Utero Exposure to Maternal HIV and ARVs—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.[213–216] The precise mechanisms are unclear but may be due to systemic maternal illness, teratogenic effects of ARVs, 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.

[207] Whether this is associated with in utero antiretroviral drug toxicity or secondary to direct effects of HIV is unclear. [217] There may be selective toxicity related to specific ARV regimens used to treat pregnant women with HIV.[218]

Compartmentalization of HIV in the CNS

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” due to the semipermeable nature of the BBB which leads to differing mechanisms of immune surveillance in the CNS compared to 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.[219]

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. [220] It is clinically relevant as it may be an important mechanism in the development of HIV-associated neurocognitive disorders (HAND) in cART-treated patients with plasma viral suppression. [221–223] 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.[224] 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, and diagnosis of viral escape is currently impossible in most low-resource settings.[224–225]

CNS compartmentalization occurs when virus that enters the CNS undergoes divergent evolution from systemic virus resulting in genetically distinct viral strains in the CNS.[226] This process usually begins during primary or uncontrolled chronic HIV infection and has also been associated with the development of neurocognitive impairment. [227] 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.[19 228] 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.[229–230]

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 severely immunosuppressed. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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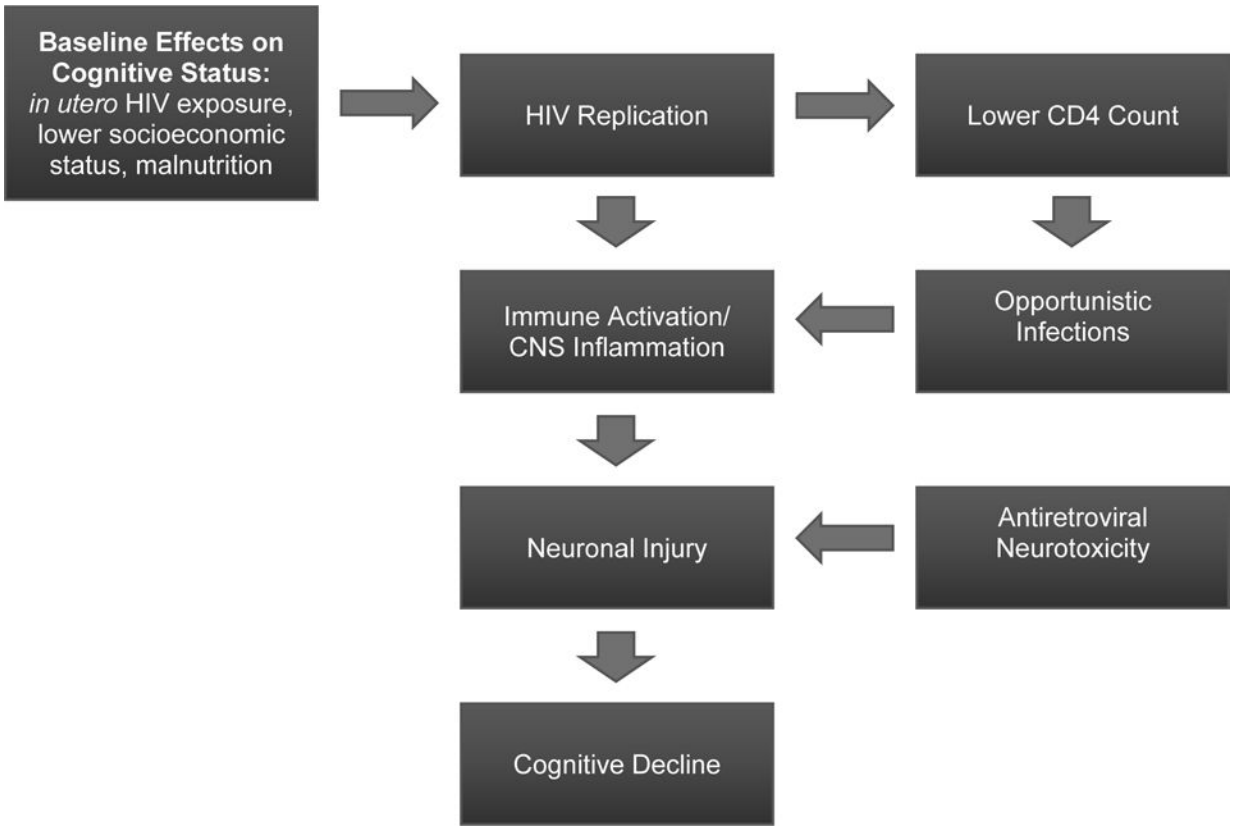

Figure 1.
Conceptual model of HIV-associated neurocognitive impairment in children.

Table 1

Peripheral Nervous System Manifestations of HIV.

Peripheral Manifestation	Clinical Presentation	Mechanism
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) [231–235]	• Slowly progressive weakness over ≥8 weeks • Impaired sensory function in arms and legs	• Autoimmune • Peripheral nerve myelin sheath damage
Acute Inflammatory Demyelinating Polyneuropathy (AIDP) [231–235]	• Acutely to subacutely progressive weakness over < 8 weeks • Impaired sensory function in arms and legs • Paralysis	• Autoimmune • Peripheral nerve myelin sheath damage
Distal Symmetric Polyneuropathy (DSP) [108 236–239]	• 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) [240 241]	• 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 [104 242–245]	• 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 [246]	• Lower motor neuron facial weakness • Usually associated with aseptic meningitis during primary HIV infection	• Inflammatory/autoimmune
Vasculitic Neuropathy/ Mononeuritis Multiplex [247]	• Multiple asymmetric motor and sensory deficits • Very painful	• Autoimmune • May be related to CMV infection late in disease course
Brachial Plexopathy (Parsonage Turner Syndrome) [96 248]	• Acute arm pain followed by weakness, sensory changes and atrophy	• Autoimmune
Motor Neuron Disease [249]	• Progressive asymmetric weakness, spasticity and bulbar symptoms	• Neurodegeneration

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.* 2016; Narayan *et al.* 2002
	Tuberculosis (TB)	• 455/2205 pts. with TB, also had HIV infection • 45/455 had *M. tuberculosis* isolated from CSF	Lammie *et al.* 2009; Berenguer *et al.* 1992
	Varicella Zoster Virus (VZV)	• VZV infection might cause cerebral vasculitis and stroke in immunosuppressed patients • Skin manifestation can be absent at the time of presentation in ~1/3 pts. with stroke, making diagnosis difficult	Gutierrez *et al.* 2011; Gilden *et al.* 2009; Nagel *et al.* 2008
	Syphilis	• Co-infection with HIV compounds the diagnosis of neurosyphilis, which is another potential cause of stroke	Zetola *et al.* 2007; Timmermans *et al.* 2004
	Neoplasia	• Lymphoma involving cerebral blood vessels	Tipping *et al.* 2007; Chetty *et al.* 2000
Cardioembolism	• Secondary to HIV-associated cardiomyopathy • Coagulopathies concomitant with HIV may contribute emboli formation resulting in ischemic stroke		Goyal *et al.* 2014
Cardioembolism	Non-atherosclerotic 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.* 2015
	Bacterial and Marantic Endocarditis	• Mycotic Aneurysm (secondary to bacterial endocarditis) • Associated with cardio-thromboembolism	Berger *et al.* 1990
	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.* 2008
	Ischemic Heart Disease and HIV-Associated Cardiac Dysfunction	• Cardiac and pulmonary complications of HIV disease are generally late manifestations and may be due to prolonged immunosuppression and interaction the virus with OIs, viral infections, autoimmune response to viral infection, drug-related cardiotoxicity, and nutritional deficiencies	Barbaro 2001

	Stroke Mechanism	Evidence	Key Studies
	HIV-Associated Hyperviscosity	• Risk factor in adults and children includes high serum IgG levels	Garderet *et al.* 2004; Hague *et al.* 1990
	Coagulopathy *E.g.:* protein S and protein C deficiency	• Unknown if this independently contributes to increased stroke risk	Zimba *et al.* 2017; Mochan *et al.* 2005
	Coagulopathy *E.g.* antiphospholipid antibodies	• The contribution of these antibodies to hypercoagulability is unclear in pediatric HIV+ pts.	Ortiz *et al.* 2007; Abuaf 1997
	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.* 2017
CNS Vasculopathy	• Often identified on pathological study • Can also be identified in based on radiological findings on magnetic resonance angiography (MRA)		Benjamin *et al.* 2016, Tipping *et al.* 2007
	Premature Atherosclerosis	• Case study of 13-year-old girl with AIDS found progressive non-atherosclerotic occlusive disease of middle/anterior cerebral arteries • Virologically-suppressed HIV+ individuals demonstrated a trend toward a greater proportion of strokes attributable to large artery atherosclerosis	Chow *et al.* 2017; Narayan *et al.* 2002
	Low CD4 Count and HIV-Associated Vasculopathy	• Association with low CD4 count and stroke • Possible mechanisms include inflammatory damage from viral-induced cytokines, damage from T-cell and leukocyte invasion, and vessel wall remodeling	Benjamin *et al.* 2012
	Pediatric Cerebrovascular Disease	• 1/68 HIV-infected pediatric stroke pts. 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 • 4/68 pts. clinically suffered stroke • 38/68 pts. 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 has 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	Blockhuis *et al.* 2017; Potchen *et al.* 2016; Park *et al.* 1990

	Stroke Mechanism	Evidence	Key Studies
		high levels of p24 protein and HIV-associated subclinical vasculopathy	

Table 3

Epidemiology, Clinical Characteristics, Prophylaxis and Treatment of the Most Common CNS OIs

CNS Opportunistic Infection	Epidemiology	Clinical Characteristics	Prophylaxis/Treatment
CNS Toxoplasmosis [250–253]	The most commonly reported CNS OI 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 more economical 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 two weeks of therapy initiation to evaluate for primary CNS lymphoma, which has a similar clinical and radiographic presentation.
Primary CNS Lymphoma [254–256]	Pre-HAART 5.33 per 1,000 person years Post-HAART 0.32 per 1,000 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) [96 257–261]	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 (CM) [262–274]	In sub-Saharan Africa, cryptococcal infection is a leading cause of meningitis in adult HIV+ pts. Accounted for 63% of cases of adult meningitis in study in South Africa. CM is responsible for 1/5 of global AIDS-related mortality.	Initially presents with non-specific headache followed by focal neurological deficits. Definitive diagnosis is made with a positive CSF cryptococcal antigen (CrAg) or CSF fungal culture. If LP is unavailable, serum CrAg titers ≥ 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 ×2 weeks followed by oral fluconazole ×8 weeks is the recommended antifungal treatment. Monotherapy with high dose fluconazole is often used in low resource settings.

CNS Opportunistic Infection	Epidemiology	Clinical Characteristics	Prophylaxis/Treatment
Cytomegalovirus (CMV) [275]	With increased cART availability, CMV incidence has decreased as this is a late stage manifestation of HIV infection usually occurring at CD4 count < 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) [102 122 276–285]	Occurs in ~1% of TB cases. Exact incidence of HIV-associated TBM is unknown due to 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+ pts. Rapid detection is crucial in HIV+ pts. 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 pts (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 4 anti-TB drugs for at least the first 2 months of therapy, followed by treatment with 2 drugs (rifampin and isoniazid) for an additional 7-10 months. Current standard dosing regimens may put pts. 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 [286]		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.

Table 4

Major adverse neurological effects associated with ARVs.

Family/Drug	Mechanism of Injury	Neurological Adverse Effects
Nucleoside Analogs ("D Drugs") ddI, d4T, ddC [102 103 109 287]	• Neurotoxicity results in 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 Abacav [104]	• Mitochondrial myopathy seen primarily with older NRTI (AZT) and much less common with newer agents	• Mitochondrial myopathy • Neuropathies
Non-nucleoside reverse transcriptase inhibitors (NNRTIs) Efavirenz Nevirapine Rilpivirine [44 106 114]	• 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 [107 110]	• 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

Table 5

Specific Reported AED-ARV Interactions.

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

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 2008 Boulware et al 2011 Kapetanovic et al 2014 De Luca et al 2013
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 2008 Boulware et al 2011 Tenorio et al 2014 Ancuta et al 2008 Kapetanovic 2014
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 2014
Soluble 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 2014
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 2013
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 2008
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 2007Davidson 2012
Heme-oxygenase 1 (HO-1)	Marker of oxidative stress	Associated with dementia in adults; associated with cognitive decline in children.	Gill et al 2014Bearden et al 2017

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.* 2015; Patel *et al.* 2009
Other cognitive impairment	Untreated children: >90% With early cART: 10–50%	Abubakar 2008; Nachman *et al.* 2009
Stroke	Uncommon (exact prevalence unknown)	Izbudak 2013; Shah *et al.* 1996
Seizures/Epilepsy	3–14%	Samia *et al.* 2013; Bearden *et al.* 2015
Myelopathy	Rare (exact prevalence unknown)	Sharer *et al.* 1990
Peripheral neuropathy	5–50%	Floeter *et al.* 1997; Peters *et al.* 2014