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ABSTRACT – The field of HIV medicine has changed rapidly in the last two decades since effective and tolerable antiretroviral treatment became available. As a result, although classical opportunistic infections of the brain have become less common, clinicians need to be aware of a wider range of acute and chronic complications of HIV and its treatment. In this article, we summarise major opportunistic infections, immune reconstitution inflammatory syndrome, HIV-associated neurocognitive disorders, and cerebrovascular disease in HIV positive patients. We also emphasise the preventability and reversibility of most of the central nervous system complications of HIV, and hence the importance of early diagnosis of HIV and involvement of clinicians with special expertise in HIV medicine.

KEY WORDS: HIV, AIDS, HAART, IRIS, neurocognitive disorders, cerebrovascular disease

Epidemiology

Highly active antiretroviral therapy (HAART) has radically altered the prognosis for human immunodeficiency virus (HIV) positive (HIV+) people since the mid-1990s. There is, however, little evidence for reduced incidence of HIV infection in most countries (including the UK),[1] and increased survival has led to a higher prevalence. There are now around 100,000 patients living with HIV in the UK[2] and 34 million worldwide.[3] Healthcare workers in the UK are increasingly likely to encounter HIV+ patients who are receiving HAART, who do not have severe immunodeficiency, or who are older (around 22% of those in care are aged over 50 years)[2] and therefore are more likely to have age-related comorbidities and polypharmacy. Furthermore, changing practice towards HAART initiation at higher CD4 counts can prevent most complications of immunodeficiency in HIV+ patients who are diagnosed and under care. As a result, patients who do present with opportunistic infections (OIs) of the brain are more likely to have previously undiagnosed HIV, and clinicians need to be vigilant and carry out HIV testing without unnecessary delay. This article summarises the latest changes in the investigation and management of people with neurological conditions in the HIV+ population.

Major opportunistic infections of the central nervous system

Fig 1 shows the declining incidence rates of cryptococcal meningitis (CM), progressive multifocal leukoencephalopathy (PML), toxoplasmosis of the brain and HIV encephalopathy (HIVE) in the UK from 1996 to 2007.[4] Despite this overall decline in incidence, it is essential that clinicians are vigilant to the possibility of undiagnosed HIV in patients who have acute neurological symptoms; failure to diagnose HIV early may confound diagnosis and lead to an increased risk of disability or death. The UK National Guidelines for HIV Testing 2008 recommend HIV testing for all medical admissions where the local prevalence exceeds 2 in 1,000, all patients in certain higher-risk groups and all patients with 'indicator diseases', many of which are neurological in nature (Table 1).[5]

Physicians should also be aware of the presenting features and initial management of central nervous system (CNS) OI;[6] these are summarised in Table 2. Importantly, there is survival benefit from prompt diagnosis and treatment. The British HIV Association (BHIVA) recommends that patients with suspected acquired immunodeficiency syndrome (AIDS)-related conditions are transferred to an HIV specialist centre within 24 hours.

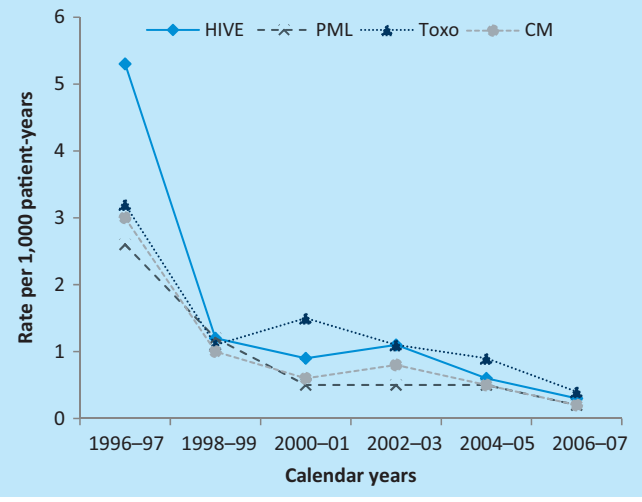

Fig 1. Rates of four AIDS-defining central nervous system conditions in UK HIV+ adults during the first 10 years of highly active antiretroviral therapy (estimates from UK Collaborative HIV Cohorts data).[4]
CM = cryptococcal meningoencephalitis; HIV = human immunodeficiency virus; HIVE = HIV encephalopathy; PML = progressive multifocal leukoencephalopathy; Toxo = toxoplasmosis of the brain.

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Table 1. Indications for HIV testing that are potentially applicable to patients with neurological conditions. Adapted with permission from UK National Guidelines for HIV Testing (2008).[5]

Category of testing	Situation where HIV testing is indicated
Universal HIV testing is recommended in the following healthcare services	Services for those diagnosed with tuberculosis, chronic viral hepatitis or lymphoma
All patients registering in general practice	Where diagnosed HIV prevalence in the local population exceeds 2 in 1,000
All general medical admissions	Where diagnosed HIV prevalence in the local population exceeds 2 in 1,000
Patients presenting for care where HIV enters the differential diagnosis, including (but not limited to) the following indicator diseases	Cerebral toxoplasmosis
	Aseptic meningitis or encephalitis
	Primary cerebral lymphoma
	Cerebral abscess
	Cryptococcal meningitis
	Space-occupying lesion of unknown cause
	Progressive multifocal leucoencephalopathy
	Guillain–Barré syndrome
	Transverse myelitis
	Peripheral neuropathy
	Dementia
	Leucoencephalopathy
	Mononucleosis-like syndrome
	Pyrexia of unknown origin
	Lymphadenopathy of unknown cause
High-risk groups*	Men who have disclosed sexual contact with other men
	Men and women known to be from a country of high HIV prevalence (>1%)
	Patients reporting a history of injecting drug use

HIV = human immunodeficiency virus.
*This is not an exhaustive list of high-risk groups.

Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) is common in patients starting HAART who have advanced immunodeficiency and a pre-existing OI. The syndrome is believed to be the result of rapid restoration of pathogen-specific immune responses in the absence of sufficient regulatory immune activity. This leads to worsening signs and symptoms of a known infection ('paradoxical' IRIS) or to the clinical presentation of a previously occult infection ('unmasking' IRIS), often with rapidly progressing or atypical clinical features.[7] A meta-analysis of rates of paradoxical IRIS found that around 20% of patients with known cryptococcosis and 17% of those with known PML upon starting HAART develop paradoxical IRIS related to the original OI.[8] Delaying the start of HAART by weeks or months after starting treatment for an OI appears to reduce the incidence of IRIS, but studies of patients with tuberculosis (TB) and other infections[9,10] found survival benefit in initiating HAART after just a 2-week wait. Those studies were mainly of patients who had opportunistic lung disease, and CNS disease may be an exception to the rule that more rapid initiation of HAART improves outcome. Two randomised studies (one unpublished) of the timing of anti-retroviral therapy (ART) in cryptococcal meningitis have suggested that starting HAART earlier leads to higher mortality.[11]

Rates of unmasking CNS IRIS are highly dependent on the underlying prevalence of the OI and the intensity of pre-HAART investigation. It is estimated that 0.5–1% of patients without known cryptococcosis starting HAART in high-prevalence African countries develop unmasking IRIS related to this infection, a condition of very high mortality,[12] although rates are likely to be lower in the UK. The ideal balance between detailed pre-HAART investigation to prevent unmasking IRIS of untreated OI and the need to start therapy in severely immunodeficient patients has yet to be determined (other than the proven mortality benefit of screening for serum cryptococcal antigen in those with low CD4 counts in regions of high cryptococcosis prevalence).[13]

The optimal treatment of IRIS is not clear. Although systemic corticosteroids are often used to reduce inflammation and oedema in the enclosed intracranial compartment, the only clinical trial on their use (which showed a benefit in mild-to-moderate TB IRIS) specifically excluded those with CNS involvement.[14] It is possible that immunosuppressive therapy might have a negative impact on outcome, especially in CM where there is a high fungal burden and steroids could delay clearance of the pathogen. In cryptococcal IRIS, rising intra-cranial pressure (ICP) may be recalcitrant,[15] and controlling pressure with repeated therapeutic lumbar puncture or shunting is necessary. Cessation of HAART is not recommended except to reduce the immune response as a temporary life-saving measure or when the diagnosis is unclear and drug toxicity is suspected.

An unusual complication of immune reconstitution in HIV is the emergence of lymphocytic cerebritis without an underlying opportunistic infection.[16,17] Clinically, this may present with confusion, focal neurology, reduced conscious level and seizures, occurring weeks to months after HAART initiation, and death often ensues. Neuroimaging may show large flitting T2 hyperintense white matter lesions, and histology shows a CD8+ lymphocytic infiltrate in the brain. It is believed that an immunological response to HIV underlies the pathogenesis. Several of the reported cases were fatal and treatment with systemic corticosteroids may be beneficial.[16,17]

HIV-associated neurocognitive disorders

The direct neurovirulence of HIV has been known for over 25 years. In 1988, Price and Brew[18] described and graded the clinical syndrome of AIDS Dementia Complex (ADC, also known as HIV-associated dementia [HAD]). This is a progressive dementia in which cognitive symptoms, mainly concentration impairment, memory loss and mental slowing, are frequently accompanied by motor signs and behavioural symptoms such as apathy, mood disorders and psychosis. HAART is effective in reducing

Table 2. Summary of important clinical features of major HIV-related central nervous system opportunistic infections. Adapted with permission from British HIV Association guidelines for the treatment of opportunistic infections.[6]

Condition	Typical presenting symptoms	Neuroimaging findings	Diagnostic test	First-line treatment
Progressive multifocal leucoencephalopathy	Focal neurology, often indicating multiple lesions, altered mental status, seizures. Progressive over weeks or months. No constitutional symptoms	Bilateral, asymmetric, well-demarcated, non-enhancing T2 hyperintense white matter lesions, which may be large in size. Usually no oedema or mass effect except in IRIS	Detection of JC virus nucleic acid in CSF, supported by clinical and neuroimaging appearances	No specific treatment. Initiate HAART
Cerebral toxoplasmosis	Focal neurological signs and symptoms progressing over days to weeks, reduced consciousness level, seizures, confusion or odd behaviour, symptoms of raised ICP	Multiple ring-enhancing masses (abscesses), often at the grey-white interface or deep grey matter. Frequently significant oedema and mass effect	Diagnosis usually based on contrast-enhanced neuroimaging appearances, supported by clinical response to anti-parasitic therapy Occasionally supported by nuclear medicine brain imaging or detection of *Toxoplasma* nucleic acid in CSF (lumbar puncture is often contraindicated)	Induction: oral sulphadiazine (15 mg/kg four times daily) and pyrimethamine (loading dose 200 mg then 50–75 mg daily) with folinic acid (10–15 mg daily) for 6 weeks Maintenance: sulphadiazine (500 mg four times daily) and pyrimethamine (25 mg daily) with folinic acid (10 mg daily)
Cryptococcal meningitis	Headache, fever, features of raised ICP including drowsiness and reduced level of consciousness, meningism, pulmonary or cutaneous manifestations of cryptococcosis. Onset may initially be insidious	Occasional small or large space-occupying lesions, which may be multiple. Variable degree of associated inflammation and oedema. Features of raised ICP	Detection of typical capsulated yeasts in CSF with appropriate staining (eg India ink); detection of cryptococcal antigen testing in CSF; fungal culture of CSF. CSF white cell count may be low in severely immuno-deficient patients; CSF protein usually high	Induction: liposomal amphotericin B (4 mg/kg/day) and 5-flucytosine (100 mg/kg/day) for 2 weeks. Maintenance: fluconazole (400 mg daily) for 8 weeks Reduction of ICP by serial CSF tap or shunting is an essential adjunct to antifungal therapy[38]
Cytomegalovirus encephalitis	Highly variable. Subacute apathy, disorientation, cranial nerve palsies, often accompanied by retinitis or polyradiculitis	Bilateral, symmetrical, diffuse, T2 hyperintense white matter lesions. Periventricular enhancement. Neuroimaging may be normal	Detection of cytomegalovirus nucleic acid in CSF, supported by neuroimaging findings and frequent coexistence of retinal lesions. Serology and plasma detection of viral nucleic acid are usually unhelpful	Induction: IV ganciclovir (5 mg/kg twice daily) for 3 weeks Maintenance: IV ganciclovir (5 mg/kg daily) or oral valganciclovir (900 mg daily)
HIV encephalopathy	Progressive global cognitive impairment, apathy, psychomotor slowing, depression, psychosis. Often accompanied by motor signs caused by vacuolar myelopathy	Bilateral, symmetrical, diffuse, T2 hyperintense white matter lesions. Neuroimaging may be normal. May be difficult to distinguish from other viral encephalitis, eg cytomegalovirus or PML	Exclusion of other causes of viral encephalitis. Detection of high levels of HIV nucleic acid in CSF relative to plasma levels, supported by neuroimaging and clinical findings	Initiate HAART

CSF = cerebrospinal fluid; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; ICP = intracranial pressure; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; JC virus = John Cunningham virus; PML = progressive multifocal leucoencephalopathy.

the rate of onset of encephalopathy and there has been a rapid decline in the incidence of HAD since 1997.[4] Furthermore, several observational studies have shown rates of resolution of dementia on HAART of 30–70%.[19] Thus HAD is one of the few types of dementia that is both preventable and reversible.

Several areas of uncertainty make HIV-associated neurocognitive disorders (HAND) a field of ongoing research and discovery. First, not all HAD significantly improves on HAART. There is likely to be irreversible neuronal loss, despite suppression of the virus, together with reduction of the inflammatory response, as evidenced by chronic cerebral atrophy in affected patients. A low nadir CD4+ lymphocyte count in the past is associated with persistent atrophy, even in those without significant cognitive impairment. An important question for HIV clinicians is which patients with HAD will experience the greatest improvement in neurocognitive function on HAART and there are no specific biomarkers to predict prognosis.

Second, there is evidence that mild-to-moderate HAND is common in patients receiving HAART; it remains unclear why this should be the case and whether it is of clinical importance to

those living with HIV. In two large studies, one of virologically suppressed HIV+ patients from Switzerland[20] and one of a more diverse HIV+ sample in the USA with only 41% with an undetectable viral load,[21] around 50% had neurocognitive impairment, even though most were asymptomatic and without any impact on activities of daily living. Studies of HAND prevalence are dogged by methodological concerns around patient selection, generalisation between populations, confounding factors and the lack of gold-standard methods for assessment or classification. Neuropsychological evaluation tools might be over-sensitive because 15–20% of the HIV-negative background population would be 'impaired' under some published definitions. Also, neuropsychological tests are complex and likely to be culturally and educationally biased: in Europe, a large number of HIV+ patients are migrants and in the US many are low-income African-Americans with relatively poor education. Both of these demographic groups show lower levels of performance on standard neuropsychological testing.[22,23] Confounding factors that have increased prevalence in HIV+ patients and are associated with poorer neuropsychological scores include hepatitis C infection, drug and alcohol use, and depression. In our practice, milder cognitive impairment in HIV is often attributable to a number of possible aetiologies and the diagnosis is rarely clearcut.

Third, there are concerns that there may be ongoing replication of HIV within microglia and other virally infected cells in the CNS, even when peripheral virological suppression and immunological recovery have been achieved. The CNS is a relatively separate physiological compartment from both an immunological and a pharmacological perspective. It is reported that 8–10% of neurologically stable patients with an undetectable plasma viral load have quantifiable levels of HIV RNA in their cerebrospinal fluid (CSF),[24] known as 'CSF viral escape'. The clinical consequences and natural history of this phenomenon are unknown, but the tendency to detect such patients after repeated investigation of unexplained neurology has led to several case reports.[25,26] Current European and British HIV treatment guidelines recommend altering HAART in patients who have a detectable CSF viral load when the plasma viral load is undetectable.[27,28] Checking for genotypic resistance in CSF viral isolates is important, as viral resistance in the CSF may differ from that detected in the plasma.

The failure of some severely impaired patients to improve on HAART, the high prevalence of mild cognitive impairment in patients receiving treatment and the frequency of patients with detectable HIV RNA in CSF have all led to an interest in the ability of different antiretroviral agents to penetrate the CNS. Two US-based groups have developed and evaluated scores[29,30] to estimate the likelihood of achieving virological control in the CNS. Unfortunately, both scores are based on a combination of observational data and pharmacokinetic principles, and although they can guide drug choice in treated and untreated patients with neurocognitive impairment, or in those with CNS viral escape, this approach has not been successfully evaluated in a randomised trial. (A recent attempt to conduct such a trial failed to recruit sufficient numbers of participants.) Genetic differences in genes coding for host endothelial transporter molecules at the blood-brain barrier and differences in target cell tropism in the virus itself have also been considered as possible explanations for the phenomena described above. Finally, there is evidence that antiretroviral drugs themselves may be neurotoxic.[31] Concerns that antiretroviral toxicity might negatively affect cognition were supported in a trial in which stopping treatment was associated with improvements in assessments of cognitive function,[32] though increased mortality is associated with even short, structured ART interruptions.[33]

Cerebrovascular disease

There is considerable epidemiological evidence for an increased risk of acute coronary events in HIV+ patients.[34] While the role of confounders in this association cannot be ignored, there is mounting support for a role for a low-grade chronic inflammatory state and endothelial dysfunction in HIV+ patients, even when treated with virally suppressive HAART. A recent review[35] and a Danish study[36] support the hypothesis that HIV infection can cause ischaemic stroke. This is distinct from the embolic complications of intravenous drug use, from OIs that present with stroke-like syndromes and from the phenomenon of an immunologically driven or infectious cerebral arteritis (caused by TB or varicella zoster virus), all of which are now seen relatively rarely in HIV+ patients in the UK. The epidemiological evidence for a higher stroke risk in HIV+ people is problematic, particularly because of high rates of cigarette, cocaine and amphetamine use in young HIV+ adults. Furthermore, protease inhibitors form part of the treatment of a large proportion of HIV+ patients, and prolonged use of drugs of this class is associated with a rising incidence of stroke.[37] Small-vessel cerebrovascular disease has not been studied in HIV, but indirect evidence of its occurrence comes from the presence, on brain magnetic resonance imaging, of white matter lesions of similar character and distribution to those seen in normal ageing and in HIV-negative adults with high cerebrovascular risk profiles.

What does the future hold for HIV and the brain?

There has been dramatic progress in increasing the life expectancy and quality of life of HIV+ patients in the past 15 years, largely due to HAART and the resulting decrease in the complications of immunodeficiency. The incidence of OIs of the CNS is likely to continue to decline in regions where HAART is available, but doctors must remain vigilant to the possibility of undiagnosed HIV in any patient with a neurological presentation. The prognosis is good, even in the most severely ill patients with CNS disease. It is vital, therefore, to investigate and treat this disease aggressively and to enlist the help of colleagues with HIV expertise early on. In patients who are diagnosed with HIV early and treated prior to developing severe immunodeficiency, healthy ageing is now a real possibility. Cohort studies in the UK and elsewhere are currently measuring the incidence of neurodegenerative and cerebrovascular diseases in HIV+ people aged 50 and above. At present, it is not clear whether they will experience a higher rate of dementia, stroke or small vessel cerebrovascular disease than the general population.

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