

18.1 Approach to neurological symptoms

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In HIV-related neurological disease, the differential diagnosis of the pathology is largely determined by the stage of disease. The best measure of the stage of HIV disease is the CD4 cell count, particularly the nadir CD4 cell count. In HIV-related central nervous system (CNS) disease, it is useful to consider whether the clinical presentation is predominantly focal or non-focal (Table 18.1), as well as the likelihood of several co-existent neuropathologies in the same or different parts of the nervous system.

Case study 18.1 illustrates several diagnostic and management issues in approaching neurological symptoms in the patient with HIV infection and Table 18.2 outlines an approach to a patient with neurological symptoms in the context of immunodeficiency.

Table 18.1 Differential diagnosis of causes of central nervous system symptoms

Focal deficits	Absence of focal neurological signs
Cerebral toxoplasmosis	HIV-1-associated dementia (HAD)
Primary cerebral lymphoma	Cryptococcal meningitis
Progressive multifocal leukoencephalopathy	Aseptic (HIV) meningitis
Meningovascular syphilis	Cytomegalovirus encephalitis
Cryptococcoma	HIV headache
Varicella-zoster virus	Diffuse meningeal lymphoma
Tuberculoma	Tuberculous meningitis
Aspergilloma	Varicella-zoster virus encephalitis
Stroke	

Case Study 18.1 Neurological symptoms in an immunodeficient patient

Joe is a 48-year-old married man with HIV infection. He has partially adhered to antiretroviral therapy and has had multiple antiretroviral regimens, including nucleoside analogues, non-nucleoside reverse transcriptase inhibitors and protease inhibitors. He has not tolerated some agents and experienced virological failure with others. Joe is currently taking an antiretroviral regimen of tenofovir, emtricitabine, ritonavir and fosamprenavir. His most recent CD4 cell count is 80 cells/ μ L and HIV viral load is 79 432 (4.9 \log_{10}) HIV RNA copies/mL. It is unclear whether Joe has adhered to cotrimoxazole prophylaxis, as he has not required repeat prescriptions as regularly as predicted.

He is referred to a specialist HIV physician after his wife reported that he has had difficulty walking and 'isn't quite himself' lately. On review, he reports slowness and difficulty walking at times. He and his wife confirm incomplete adherence to antiretroviral therapy, as he has experienced significant nausea with the prescribed regimen. On specific questioning, he agrees that he has experienced intermittent headaches and possibly fevers, although no rigors. He does not drink alcohol and does not take illicit drugs or non-prescribed medications. Examination reveals peripheral neuropathy, with reduced pinprick and light touch sensation to the ankles bilaterally, with preservation of the ankle jerks. Heel-toe gait is impaired, with the patient predominantly falling to the left. He is afebrile.

The serum *Toxoplasma gondii* immunoglobulin G assay was positive and syphilis serology was non-reactive when last performed two years ago. Biochemical tests reveal an absence of hyponatraemia or renal failure. Serum B12, folate and thyroid-stimulating-hormone levels are normal. Repeat syphilis serology is non-reactive.

A computed tomography (CT) scan of the brain with intravenous contrast is undertaken, looking for space-occupying lesions, ring-enhancing lesions, evidence of raised intracranial pressure, and cerebral atrophy. The CT scan is shown (Image 18.1). A magnetic resonance imaging scan does not reveal any focal pathology. As there are no stigmata of raised intracranial pressure or focal neurological signs, a lumbar puncture is performed.

The opening pressure is 16 cm H₂O and the cerebrospinal fluid (CSF) appears clear and colourless. CSF biochemistry reveals a normal glucose concentration and a raised protein concentration of 0.56 g/L (normal range 0.15–0.45 g/L). Microscopy of CSF reveals a mononuclear cell pleocytosis of 10 cells/mm³, and no organisms are seen on Gram stain or India ink stain. Tests for CSF and serum cryptococcal antigen reveal titres of less than one in four. CSF mycobacterial culture is pending.

Further investigation of the CSF is undertaken including measurement of CSF HIV viral load, beta 2-microglobulin and neopterin. The CSF HIV viral load is 11 000 (4.04 \log_{10}) HIV RNA copies/mL and the CSF beta 2-microglobulin concentration is 4 mg/L. Neuropsychometric testing reveals some deficits in attention and motor functions.

Given the absence of an alternative cause for the neurological manifestations and the consistent clinical and laboratory findings, the physician makes a diagnosis of HIV-1-associated dementia (HAD) stage 1. Genotypic HIV viral resistance assays are pending. The physician reviews the antiretroviral history, identifies an appropriate regimen for the management of advanced HIV infection and selects agents with activity in HAD.

Table 18.2 Approach to diagnosis of persistent headache, seizures, altered level of consciousness or focal neurological systems or signs and fever in the immunodeficient patient

Initial assessment:

History:

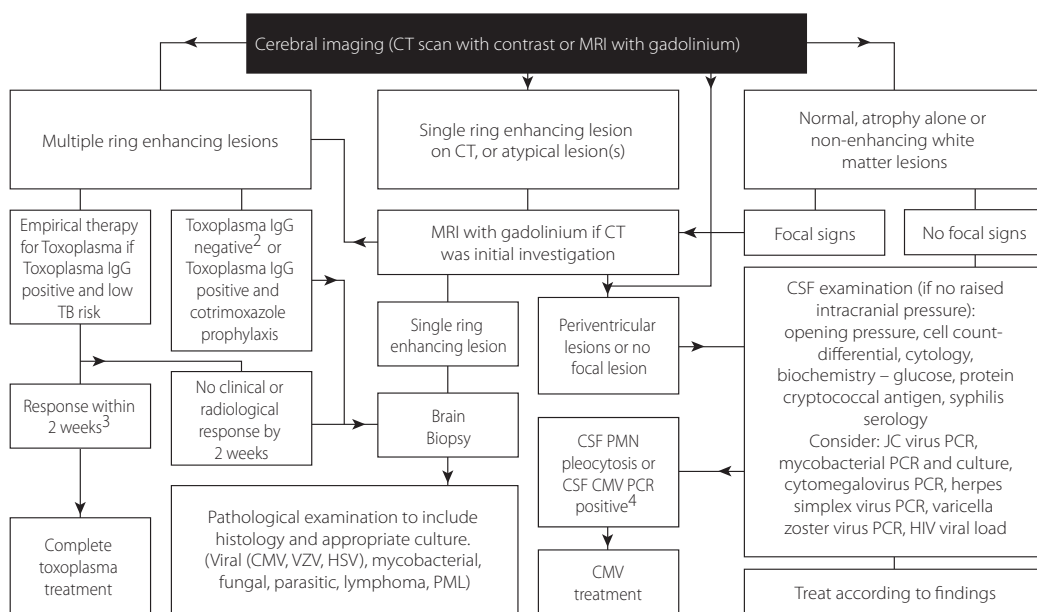
- Level of immunodeficiency – alters differential diagnosis
- Headache – persistent headache should be investigated, as even mild headache may be indicative of significant neurological pathology
- Recent commencement of cART – immune reconstitution disease
- Adherence to cotrimoxazole prophylaxis – reduces likelihood of cerebral toxoplasmosis
- Focal neurological symptoms
- Systemic symptoms – sinusitis and other infections (e.g. pneumococcal pneumonia with bacteraemia) may cause headache and fever, with or without altered neurological status)
- Seizures
- Prior neurological disease
- A history of exposure to tuberculosis

Examination:

- Focal neurological signs
- Seizures
- Signs of raised intracranial pressure
- Clinical evidence of immunodeficiency when CD4 cell count unknown (e.g. oral candidiasis)
- Evidence of disseminated disease processes (e.g. pulmonary tuberculosis, cytomegalovirus retinitis)

Blood testing:

- Serum *Toxoplasma gondii* IgG status – most cases of cerebral toxoplasmosis are IgG positive
- Serum syphilis serology – interpreted in conjunction with treatment history and consideration of possible reinfection
- Serum cryptococcal antigen titre
- CD4 cell count if unavailable historically



CSF = cerebrospinal fluid; CT = computed tomography; HSV = herpes simplex virus; IgG = immunoglobulin; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; PML = progressive multifocal leukoencephalopathy; PMN = polymorphonuclear; VZV = Varicella-zoster virus; JC = John Cunningham; CMV = cytomegalovirus.

- Potential pointers to incomplete treatment adherence may be readily identified. For example, the patient who does not request or require a repeat prescription when the medication should have run out may not be taking medication as prescribed
- Although the signs are not completely consistent with a focal neurological deficit, the suggestion of possible focal pathology

warrants cerebral imaging. Magnetic resonance image (MRI) scanning is more sensitive than a computed tomography scan for focal neurological lesions.¹ The differential diagnosis is broad (Table 18.1)

- An examination of cerebrospinal fluid (CSF) is warranted in immunodeficient people with headache and possible fever as cryptococcal meningitis may not present with meningism.

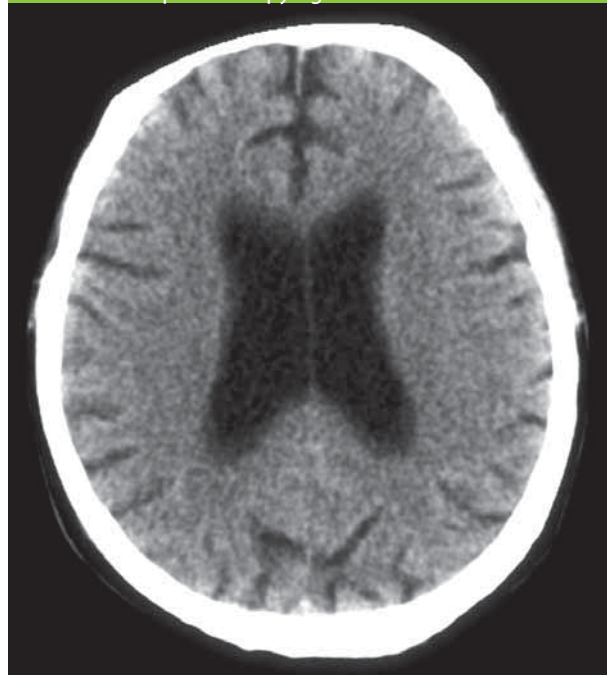
The symptoms attributable to the CNS may be mild and apparently non-specific. If the opening pressure of the CSF is raised and the diagnosis is consistent with cryptococcal meningitis, repeat lumbar punctures and possibly shunting are important aspects of management

- CSF findings of a mild mononuclear pleocytosis and slightly raised protein are consistent with HIV infection, although, in the context of positive CSF syphilis serology or the possibility of past untreated syphilis, these findings are also consistent with neurosyphilis
- Non-infective causes must be excluded as the origin of neurological symptoms;
- HIV-1-associated dementia (HAD) is a diagnosis of exclusion, as other pathology may present similarly and other opportunistic processes may unmask HAD. There is no single diagnostic test for HAD. Elevation of CSF beta 2-microglobulin and HIV viral load are correlated with the degree of severity of HAD in patients not taking cART, but are not diagnostic;
- Multiple co-existing pathological processes can occur in the neuraxis (termed parallel tracking). In the case study, HAD and peripheral neuropathy are present concurrently
- The serum cryptococcal antigen titre is elevated in 94 - 100% of cases of cryptococcal meningitis. A titre of less than one in four is within the normal range for the assay

References

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Image 18.1 Cerebral computerised axial tomograph scan reveals cerebral atrophy with no evidence of space-occupying lesions



Source: Jeffrey J Post, University of NSW, Sydney, NSW. Used with permission.

- 3 Luft BJ, Hafner R, Korzun AH, et al. Toxoplasmic encephalitis in patients with the acquired immunodeficiency syndrome. Members of the ACTG 077p/ANRS 009 Study Team. *N Engl J Med* 1993;329:995-1000.
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18.2 Neurological disorders in HIV

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Despite the availability of combination antiretroviral therapy (cART), HIV sensory neuropathy and HIV-1-associated dementia (HAD, formally AIDS dementia complex) remain common problems in people with HIV infection. The diagnosis and management of these conditions are discussed in this section. Other less common neurological diseases, including vacuolar myelopathy and mononeuritis multiplex, are also addressed.

18.2.1 HIV-associated spinal cord diseases

White matter vacuolisation of the spinal cord, known as vacuolar myelopathy (VM), was clinically evident in 25% of patients with HIV and found in 40% of patients at post-mortem in the pre-cART era.¹ A productive HIV myelitis occasionally accompanies VM, or occurs alone.² In VM, pathological changes in the spinal cord are strikingly similar to those found in vitamin B12 deficiency and, indeed, patients with HIV infection with

VM have been shown to have abnormalities in their vitamin B12-dependent transmethylation pathway which leads to reduced levels of s-adenosyl-methionine.³ The prevalence of HIV myelopathy in the cART era is not well defined.

Patients with VM and HIV myelitis typically present with features of a spastic paraparesis (Table 18.3). The antemortem diagnosis of either condition is presumptive and relies on the exclusion of other causes of spinal cord pathology. In particular, patients require: investigations to exclude syphilis, vitamin B12 or folate deficiency; imaging of the spinal cord to exclude a mass lesion; and lumbar puncture to exclude CNS infection with cytomegalovirus (CMV), varicella-zoster virus, herpes simplex virus or human T-lymphotropic virus I or II. A placebo controlled trial comparing methionine to placebo in patients with HIV infection with VM did not show any improvement in cord conduction times, or clinical disease state.⁴

Table 18.3 The clinical, diagnostic and management approach to patients with vacuolar myelopathy and HIV myelitis

	HIV myelitis	Vacuolar myelopathy
Clinical features	Spastic paraparesis Sensory level Variable proprioceptive loss	Spastic paraparesis No clear sensory level Prominent sensory ataxia
Onset	Late (CD4 cell count usually <50 cells/ μ L)	Late (CD4 cell count usually <50 cells/ μ L)
	Spastic paraparesis occurring earlier in the course of HIV disease is probably due to another cause.	
Diagnosis	Presumptive CSF viral load may be high Exclude other causes	Presumptive CSF viral load may be low ⁵ Exclude other causes
MRI findings	The main role of imaging is to exclude a mass lesion.	Normal, cord atrophy or increased white matter signal (T2) ⁶
Pathology	Inflammation present	Vacuolation of posterolateral white matter Little inflammation seen
Management	May respond to cART ⁷	Trial of cART recommended ⁸
	HIV is thought to be important in the pathogenesis of both conditions, and there is no reliable test to differentiate between them. Consequently, although controlled data are lacking, the use of cART (including agents known to penetrate the central nervous system) is recommended in both cases. ⁶¹ Both conditions require ongoing supportive therapy, including physiotherapy, occupational therapy, management of incontinence and walking aids.	

CSF = cerebrospinal fluid; cART = combination antiretroviral therapy.

18.2.2 Diseases of the peripheral nervous system in HIV

Sensory neuropathy

Clinical manifestations

A symmetrical, predominantly sensory, peripheral neuropathy is the most common neurological complication of HIV infection. Sensory neuropathy (SN) due to HIV itself (HIV-SN) is typically a complication of advanced HIV infection, and was clinically apparent in more than 30% of people with AIDS in the pre-cART era.¹⁰ HIV-SN is characterised by distal, symmetrical numbness, hyperaesthesia and often burning pain.^{11,12} Neurological examination may be normal, but ankle reflexes are often reduced or absent. The pathology of HIV-SN includes axonal degeneration and macrophage infiltration of the nerve. Cytokine dysregulation is thought to play a role in the pathogenesis of this condition, as it does in VM and HAD.^{10,11,13}

A SN may also occur as a complication of the use of nucleoside reverse transcriptase inhibitors (NRTIs) – stavudine, didanosine or zalcitabine.^{10,12} This condition is variably called nucleoside or antiretroviral-toxic SN. The condition is clinically and pathologically similar to HIV-SN, but is temporally related to therapy with one or more of the NRTIs mentioned above.¹⁰ SN related to the use of NRTIs may occur at any stage of HIV disease, but people with more advanced HIV disease, a previous diagnosis of HIV-SN or risk factors for peripheral neuropathy of any kind (such as diabetes or nutritional deficiencies) may be at increased risk.¹⁴ Increasing height and host genetics have also been implicated.¹⁵ The pathogenesis of SN related to the use of NRTIs is thought to relate to NRTI-induced mitochondrial dysfunction.^{10,12}

Australian data have demonstrated a significant increase in the prevalence of SN since the introduction of cART (from

13% in 1993 to 44% in 2001).¹⁶ This increase has occurred despite an overall improvement in the morbidity of people with HIV infection. A major risk factor for SN in 2001 was the prior prescription of didanosine or stavudine, suggesting that nucleoside and antiretroviral-toxic SN had become an important cause of the HIV-SN seen in clinical practice. However, despite a significant reduction in the use of stavudine and didanosine in Australia since 2001¹⁷ and the removal of zalcitabine from clinical use, the prevalence of HIV-SN has remained unchanged.¹⁶ There are some recent data suggesting an epidemiological link between exposure to protease inhibitors and HIV-SN.^{16,18,19} Protease inhibitors are not known to be neurotoxic. It is unclear at this time whether this association is causal and, if so, whether this represents a direct drug toxicity or a secondary complication of the metabolic effects of protease inhibitors (such as glucose intolerance).

Diagnosis

Sensory neuropathy is a clinical diagnosis.¹² Nerve conduction studies may confirm the diagnosis, but are often normal in the setting of SN and are not routinely recommended.

Management

For most patients with established SN, the management is symptomatic^{10,12} (Table 18.4). The therapeutic agents recommended in Table 18.4 have been used with variable success to treat neuropathic pain, but controlled data to support their use in the treatment of SN are lacking.¹¹ As in other forms of neuropathy, symptom control is difficult and often incomplete.

Acute demyelinating and chronic inflammatory demyelinating polyneuropathy

Acute demyelinating polyneuropathy, which closely resembles Guillain-Barré syndrome, may occur at HIV seroconversion, early

Table 18.4 The diagnostic and therapeutic approach to patients with HIV sensory neuropathy

Aim	Suggested options
Exclude other causes	Exclude diabetes and heavy alcohol consumption Exclude deficiencies of thiamine, B12 and folate Remove any other neurotoxins (including isoniazid, dapsone, thalidomide, high-dose pyridoxine or metronidazole)
Remove the underlying cause	HIV-SN - may improve when viral replication is controlled ATSN - cease or reduce the dose of the causative NRTI where practical (symptoms may worsen initially)
Provide analgesia (relief rarely complete)	Simple or compound analgesics (mild pain): Paracetamol or NSAIDs plus or minus codeine Narcotic analgesics (severe pain): Trial of oral morphine for efficacy, then switch to long-acting alternative
Pain modification (in combination with analgesia for more severe pain or when relief is incomplete)	Antidepressant agents: Tricyclic antidepressants (start with low dose, e.g. amitriptyline 10 mg at night, and increase gradually according to side-effects and efficacy) New antidepressants may be useful when tricyclics are not tolerated Anticonvulsant agents: Sodium valproate (start 200 mg three times daily, increase gradually) Carbamazepine (leukopenia may limit use) Phenytoin (drug interactions may limit use) Gabapentin (not funded under the Pharmaceutical Benefits Scheme for this indication, but available at some tertiary referral centres); lack of interactions with antiretroviral agents useful; start 300 mg at night and titrate according to relief and sedation
Other treatments	Anecdotal reports support the use of various complementary therapies to relieve the symptoms of SN, including acupuncture and massage
Treat any co-existing depression	Depression is common with chronic pain, and requires adequate assessment and treatment

ATSN = antiretroviral-toxic sensory neuropathy; NRTI = nucleoside reverse transcriptase inhibitor; NSAID = Non-steroidal anti-inflammatory drugs; SN = sensory neuropathy.

in the course of HIV disease or as an immune reconstitution phenomenon.^{20,21} Chronic inflammatory demyelinating polyneuropathy may occur during the early or later stages of HIV disease.

Acute demyelinating polyneuropathy and chronic inflammatory demyelinating polyneuropathy are both characterised by progressive, ascending weakness with early loss of reflexes. The pathogenesis of both entities is undetermined, but may have an autoimmune basis.

Patients should be investigated with nerve conduction studies (confirming a demyelinating process) and lumbar puncture. CSF examination typically shows a mild, mononuclear pleocytosis and raised protein, rather than the CSF findings of classical non-HIV-associated Guillain-Barré syndrome in which the CSF is acellular, but the protein concentration is elevated.^{20,22} The response to immune-based therapies (including plasmapheresis or intravenous immunoglobulin) is similar to that seen in non-HIV-associated acute demyelinating polyneuropathy and chronic inflammatory demyelinating polyneuropathy.²²

Mononeuritis multiplex

Mononeuritis multiplex is characterised by the acute onset of one or more nerve palsies. The likely underlying cause of mononeuritis multiplex varies at different stages of HIV disease.^{11,12} A relatively benign form of mononeuritis multiplex may occur early in the course of HIV infection, and commonly

resolves without specific treatment.^{12,22} In patients with moderate immunosuppression (CD4 cell count 200-500 cells/ μ L), mononeuritis multiplex may be related to immune complex disease secondary to hepatitis B or hepatitis C,^{22,23} to vasculitis²⁴ or to an underlying infiltrating malignancy. In advanced HIV disease, mononeuritis multiplex is more likely to be due to nervous system involvement with an opportunistic infection, notably CMV.²⁵

A presumptive diagnosis of mononeuritis multiplex can be made on clinical findings,²² but investigations should include serology for hepatitis B and hepatitis C, CSF cytology and polymerase chain reaction (PCR) assays for HIV viral load, CMV, herpes simplex virus and varicella-zoster virus in CSF.

Around 80% of patients with CMV-associated mononeuritis multiplex will respond to treatment, and a trial of therapy with ganciclovir or foscarnet is warranted.²⁶

18.2.3 HIV-associated neurocognitive disorders

Neurocognitive disorders represent a significant problem for people living with HIV infection. The spectrum of severity of neurocognitive impairment ranges from having none to having a dementing illness, HAD. However the progression of disease may vary wherein up to 20% of patients may fluctuate between being impaired and normal.²⁷ Recently the nomenclature used to describe HIV-associated neurocognitive disorders (HAND) was changed²⁷ and the new terminology will be used here.

HIV-associated asymptomatic neurocognitive impairment

HIV-associated asymptomatic neurocognitive impairment refers to those patients who are fully functional without obvious neurocognitive impairment, but who are found to have neurocognitive abnormalities upon formal neuropsychological testing.²⁷

HIV-1-associated mild neurocognitive disorder

HIV-1-associated mild neurocognitive disorder refers to those patients with clinical and neuropsychological evidence of neurocognitive impairment and impairment in their daily functioning.²⁷

HIV-1-associated dementia

The availability of cART has been associated with a significant decrease in the incidence of HAD^{28,29} from 7%³⁰ to approximately 3% per year in immunocompromised patients.²² Furthermore, Dore et al have shown that since 1996 there has been a significant increase in the median survival of patients with HAD in Australia from 11.9 to 48.2 months.³¹ However, cART has also been associated with a shift in the natural history of HAD. Since 1996 there has been an increase in the proportion of patients presenting with HAD as their AIDS-defining illness in Australia³¹ and, overall, patients appear to be developing HAD with higher CD4 cell counts, notably within the 200-350 cells/ μ L range.^{28,32}

A further shift in the natural history of HAD is anticipated. As the Australian population with HIV infection ages, different cART regimens may be imperfect in the neuroprotection they afford, and the effect of persistent low-grade viraemia on the CNS of patients who are taking cART remains unknown. These concerns, and the possibility of neurotoxicity from long-term cART, need to be addressed by future clinicopathological studies of patients with HIV infection. Risk factors for HAD include older age,³³ insulin resistance,³⁴ diabetes³⁵ and host genotype.³⁶ Increased cerebrovascular small-vessel disease was recently noted to be more prevalent in older patients and in those with hypertension.³⁷ HIV-1 subtype C is associated with less severe HAND.^{38,39}

HAD is a subacute and subcortical dementia that principally involves the deep white matter and the basal ganglia.⁴⁰ The chief neuropathological findings associated with HAD are cerebral

atrophy, myelin pallor and the presence of multinucleated giant cells, predominately within the deep white matter and the basal ganglia.

Productive HIV infection in the brain occurs within microglial cells, macrophages and multinucleated giant cells. Restricted, non-productive infection occurs within astrocytes, and latent infection may occur within neurons. Overall, there is reasonable, albeit incomplete, correlation between the presence of HIV in the brain and the clinical and neuropathological severity of HAD.⁴¹⁻⁴³

Clinical manifestations

HAD occurs in the setting of moderate-to-severe immune suppression. In the pre-cART era, the median CD4 cell count in Australian patients presenting with HAD as their AIDS-defining illness was 70 cells/ μ L, whereas the median CD4 cell count in the cART era in the same population is 120 cells/ μ L ($p = 0.012$).³¹ Some of the noted clinical risk factors for the development of HAD include the presence of minor cognitive and motor disorders, extant cognitive deficits and depression,⁴⁴ mania,⁴⁵ older age at presentation²⁵ and low educational level.⁴⁶

Staging of HAD may be performed by using the Modified Staging Scheme for AIDS dementia complex,²² otherwise known as the Memorial Sloan-Kettering dementia scale. This scheme rates people from stage zero (normal) to stage four (end-stage dementia), and incorporates the assessments of an individual's cognition, ability to perform activities of daily living, fine motor movements and ability to walk unaided. Table 18.5 outlines the symptoms and signs associated with HAD.

Diagnosis

No single clinical, laboratory or neuroradiological finding is pathognomonic of HAD; instead, the diagnosis of HAD rests on a composite of findings wherein other major differential diagnoses have been excluded. An example of the diagnostic process and differential diagnoses for HAD is found in Table 18.6.

Management

Combination antiretroviral therapy has been shown to improve the neurocognitive performance of patients with HIV-associated neurocognitive impairment.⁴⁷ Some data suggest that the optimum treatment for HAD should include at least three antiretroviral agents that have good central nervous system

Table 18.5 Symptoms and signs of HIV-1-associated dementia (HAD)

Symptoms	Comments
Poor concentration Forgetfulness Slow thought processes Difficulty in performing fine motor tasks Clumsiness Change in personality Progression of HAD leads to profound dementia, mutism, incontinence and paraparesis	Patient's family or partner may notice these changes first These changes generally take place over several months Patients may notice difficulty with their handwriting or using their computer, and may report difficulty with driving
Signs	Comments
Decreased facial expression Poor performance of fine finger movements Impaired tandem gait Hyperreflexia Action tremor	Patients may demonstrate one or more of these signs Focal sensory or motor signs, or cranial nerve palsies are not a feature of HIV-associated dementia

penetration.^{48,49} Enting et al⁵⁰ give a detailed discussion of the pharmacodynamics of antiretroviral drugs and the CNS.

The issue of how to determine the efficacy of individual antiretroviral agents within the CNS is complex. Letendre et al determined the CNS penetration-effectiveness (CPE) score of different antiretroviral regimens being used by 467 HIV-positive patients.⁵¹ Regimens were classified as having a low or a high CPE score. Patients taking regimens with low CPE scores were significantly more likely to have a detectable CSF HIV viral load. In turn, the same group had previously demonstrated that patients with detectable CSF HIV viral load were less likely to experience neurocognitive improvement than those with undetectable CSF viral loads.⁵²

Table 18.7 provides the CPE score for individual antiretroviral agents. The score for each agent in a patient's antiretroviral regimen is summed to provide the CPE score.⁵³

The following antiretroviral regimens are recommended assuming that there is no evidence that the patient is resistant to any of these agents:

- Zidovudine, lamivudine and abacavir (in fixed dose combination tablet Trizivir™) twice a day, plus abacavir 300 mg twice a day or 600 mg daily, plus nevirapine
- Zidovudine, lamivudine and abacavir (in fixed dose combination tablet Trizivir™) twice a day, plus abacavir 300 mg twice a day or 600 mg daily, plus lopinavir/ritonavir OR fosamprenavir/ritonavir OR atazanavir/ritonavir OR indinavir/ritonavir (800 mg/100 mg twice a day) at the usual ritonavir-boosted doses.

Monitoring response to treatment of HIV-1-associated dementia

A reasonable approach for monitoring would be to recommend that the patient undergo a repeat lumbar puncture with analysis of CSF viral load, repeat neuropsychological testing, and repeat MRI or magnetic resonance spectroscopy (MRS) after 12 weeks of the new antiretroviral regimen. Although this

Differential diagnoses to be excluded	Comments
Depression	In patients with a CD4 cell nadir < 200 cells/μL who have been diagnosed with depression, repeat neuropsychological testing should be performed once the depression has been treated, to exclude residual, underlying HAD
Cerebral toxoplasmosis, cerebral lymphoma and progressive multifocal leukoencephalopathy (PML)	The lesions of cerebral toxoplasmosis, PML and lymphoma should be evident upon neuroimaging of the brain
Cryptococcal meningitis	If the serum cryptococcal antigen is positive, then CSF cryptococcal antigen, CSF India ink stain and fungal culture are recommended to exclude cryptococcal meningitis
Neurosyphilis	In patients with positive serum anti-treponemal antibodies, a diagnosis of neurosyphilis should be considered and the CSF should be tested for anti-treponemal antibodies and the Venereal Disease Research Laboratory tests should be performed. In a patient with documented loss of treponemal antibodies as a result of advancing HIV disease, an empiric course of 15 days of intravenous penicillin should be considered
Other uncommon causes of dementia	In individual patients, consideration may be given to the possibility of other causes of dementia, including Alzheimer's disease, multi-infarct dementia, Pick's disease, Creutzfeldt-Jacob disease, hypothyroidism and heavy metal poisoning
Recommended investigations	Comments
MRI and MRS brain	Cerebral atrophy usually seen. T2-weighted hyperintensities seen in deep white matter and periventricular areas. MRS shows increased choline and myo-inositol, and decreased n-acetyl aspartate. Note: none of these findings is specific to HAD
Neuropsychological testing	Findings include decreased concentration, reduced psychomotor speed, reduced verbal and visual memory, and reduced executive function
General CSF analysis	Protein, glucose, microscopy, culture and sensitivity should be performed. A mononuclear pleocytosis is compatible with, but not specific for, a diagnosis of HAD ²²
Plasma HIV viral load	Plasma HIV viral load has been found to predict the risk of developing HAD in one study, ⁵⁷ but not in another ⁵⁸
CSF HIV viral load	There is no cut-off above which the CSF viral load is pathognomonic for HAD; rather, the CSF HIV viral load correlates best with the severity of HAD in patients with CD4 cell counts <200 cells/μL. ⁵⁹ A recent study suggested that a baseline CSF HIV viral load >400 copies/mL in neurologically intact patients significantly predicts progression to neurocognitive impairment, ⁵⁸ but larger studies are needed to confirm this
Plasma and CSF HIV genotype if patient is currently using antiretroviral agents	Resistance to NRTIs, NNRTIs and PIs has been reported in HIV isolated from the CSF, ⁶⁰ and discordance between resistance patterns in CSF and plasma has also been reported ⁶¹

HAD = HIV-1-associated dementia; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; NRTIs = nucleoside analogue reverse transcriptase inhibitors; NNRTIs = non-nucleoside reverse transcriptase inhibitors; PIs = protease inhibitors.

Table 18.7 The central nervous system penetration-effectiveness (CPE) score for different antiretroviral agents.

	Central nervous system penetration scale (Increasing penetration with increasing score)		
Antiretroviral agent	0	0.5	1.0
Nucleoside reverse transcriptase inhibitors	didanosine tenofovir	emtricitabine lamivudine stavudine	abacavir zidovudine
Non- nucleoside reverse transcriptase inhibitors		efavirenz	delavirdine nevirapine
Protease inhibitors	nelfinavir ritonavir saquinavir tipranavir-ritonavir	atazanavir fosamprenavir indinavir	atazanavir- ritonavir fosamprenavir- ritonavir indinavir-ritonavir lopinavir-ritonavir
Fusion inhibitors	enfuvirtide		

Note: darunavir, etravirine, maraviroc and raltegravir have not been assigned CPE scores⁵¹
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approach remains unproven in clinical trials, it allows for the autonomous nature of CNS HIV infection, which has different and slower decay kinetics than that of plasma HIV infection.⁵⁴ MRS may show some reversal of abnormality in patients with HAD who have been treated with cART.⁵⁵

One of the key endpoints of antiretroviral therapy for HAD is an undetectable HIV CSF viral load. In practice, patients with HAD do not routinely have a lumbar puncture performed once the CSF viral load becomes undetectable. However, it is reasonable to continue to perform neurological and neuropsychological follow-up every six months, and to repeat a lumbar puncture if there is evidence of a relapse of the symptoms of HAD and a significant rise in the plasma HIV viral load. Patients continue to experience improvement in their symptoms and signs of HAD for more than six months.⁴⁷ A study has shown that improved neurocognitive performance ascribed to cART was most marked after 18 months of treatment.⁵⁶

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