HIV-associated opportunistic infections of the CNS
Ik Lin Tan, Bryan R Smith, Gloria von Geldern, Farrah J Mateen, Justin C McArthur

Survival in people infected with HIV has improved because of an increasingly powerful array of antiretroviral treatments, but neurological symptoms due to comorbid conditions, including infection with hepatitis C virus, malnutrition, and the effects of accelerated cardiovascular disease and ageing, are increasingly salient. A therapeutic gap seems to exist between the salutary effects of antiretroviral regimens and the normalisation of neurological function in HIV-associated neurocognitive disorders. Despite the advances in antiretroviral therapy, CNS opportunistic infections remain a serious burden worldwide. Most opportunistic infections can be recognised by a combination of characteristic clinical and radiological features and are treatable, but some important challenges remain in the diagnosis and management of HIV-associated opportunistic infections.

Introduction
HIV infection leads to substantial morbidity and mortality worldwide. In 2009, 33·3 million adults and children were living with HIV, two-thirds of whom were in sub-Saharan Africa.

Overall, the annual incidence of new infections has declined by 19% since the peak of the worldwide HIV epidemic in 1999, in line with the Millennium Development Goal. Nevertheless, about 2·6 million individuals were newly infected in 2009, and the incidence continues to increase in some regions.7 7000 new HIV infections occur daily, 95% of which are in low-income and middle-income countries, where only about a third of patients who require antiretroviral drugs have access to them.7

In high-income countries, the introduction of combination antiretroviral therapy (cART) in 1996 greatly changed the incidence of neurological opportunistic infections, from 13·1 per 1000 patient-years in 1996–97 to 1·0 per 1000 in 2006–07 (tables 1, 2).27 Many of the opportunistic infections that affect the CNS are AIDS-defining conditions, including progressive multifocal leukoencephalopathy (PML), CNS cytomegalovirus, CNS tuberculosis, cryptococcal meningitis, and cerebral toxoplasmosis, including toxoplasmic encephalitis (table 2), and all have high associated mortality.5 Treatment of CNS opportunistic infections in conjunction with cART improves survival, but such infections continue to be important, especially where access to cART is limited.

In this Review we focus on the most common CNS opportunistic infections associated with HIV infection worldwide, and provide a summary of each in terms of epidemiology, clinical presentations, diagnosis, and treatment.

Biology of HIV-1
HIV-1 infection accounts for most of the global HIV pandemic. Only 1–2 million of the 33 million HIV infections are caused by HIV-2. HIV-1 belongs to the family Retroviridae and genus Lentivirus.8 It is a single-stranded, positive-sense RNA virus that contains a reverse transcriptase, which transcribes viral RNA into DNA that is integrated into the host’s genome as a provirus. HIV-1 primarily targets CD4 receptors and infects CD4-positive T lymphocytes and cells of the monocyte or macrophage lineages. HIV-1 also infects CD4-negative cells, including astrocytes, but in a restrictive manner. HIV-1 subtypes are defined by chemokine co-receptors: T-tropic viruses use CXCR4 (receptor for SDF1, also termed CXCL12) to infect lymphocytes, and M-tropic viruses use CCR5 (receptor for RANTES, also termed CCL5, and MIP1α or CCL3/4) to infect macrophages.31^

HIV infection is characterised by three stages: acute primary infection, an asymptomatic (latent) stage, and symptomatic chronic illness. Disease progression is highly variable: from 6 months after seroconversion to more than 20–30 years, or minimal progression might be seen in elite suppressors. In the absence of cART, the mean time to the development of AIDS is 10–11 years,12 and median survival after AIDS develops is 1·3–3·7 years, depending on the CD4-cell count.13

After primary infection, acute disseminated viraemia is seen.14 The initial massive depletion of gut-associated memory T cells15 leads to physical and immunological breaches of the gut mucosa, as well as expansions of some HIV-specific CD8-positive T-cell responses,16 the crucial

<table>
<thead>
<tr>
<th>Incidence per 1000 person-years</th>
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<tbody>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>Toxoplasmic encephalitis</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
</tr>
<tr>
<td>Data are from 2006–07. *The sum of the individual opportunistic infections is more than 1·0 because some individuals have more than one infection.</td>
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<table>
<thead>
<tr>
<th>Common CNS opportunistic infections</th>
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<tbody>
<tr>
<td>Asian and Pacific regions</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
</tr>
<tr>
<td>Europe and North America</td>
</tr>
<tr>
<td>South America</td>
</tr>
</tbody>
</table>

PML=progressive multifocal leukoencephalopathy

Table 1: Incidence of HIV-associated CNS opportunistic infections

Table 2: Incidence of HIV-associated CNS opportunistic infections by geographical region
host immune response against HIV. This robust immune response leads to virus being trapped within dendritic cells in lymphoid tissue and a marked reduction of viraemia. The virus, however, is not completely eliminated from the body and chronic, persistent viral replication leads to systemic immune activation. Additionally, quiescent CD4-positive memory T cells and macrophages serve as long-term reservoirs for latent HIV infection. Persistent viral replication, chronic immune activation, and progressive deterioration of immune function result in symptomatic disease with severe immune deficiency in advanced HIV infection. Typically, CNS opportunistic infections occur during this stage of the HIV infection; waning immunity and high HIV load, both systemically and in the CNS, create a favourable milieu. Apart from immune deficiency, other features of HIV-1 might directly facilitate CNS opportunistic infections, for example in PML. Most CNS opportunistic infections result from reactivation of latent pathogens, including PML, toxoplasmic encephalitis, and primary CNS lymphoma. HIV infection produces substantial depletion of the CD4-cell count and preferentially destroys the cellular immune system, which is crucial for defence against viral, fungal, and parasitic infections.

Clinical features of CNS opportunistic infections
CNS opportunistic infections should be suspected in all people with advanced HIV infection. Individuals who are unaware of their HIV status can present first with CNS opportunistic infections. Additionally, in patients in whom cART is started, immune reconstitution inflammatory syndrome (IRIS) might unmask previously unsuspected CNS opportunistic infections. The main diagnostic features of CNS opportunistic infections are clinical presentation, temporal evolution, and CSF and radiographic features. These infections typically develop when the CD4-cell count is lower than 200 cells per μL. One important principle is that up to 15% of CNS opportunistic infections involve multiple concurrent processes (panel 1) and, therefore, unexpected worsening after treatment for an opportunistic infection is started should prompt consideration of a second process. Individuals who have had immunological recovery from cART might still be at risk of developing CNS opportunistic infections.

Some infections, such as toxoplasmic encephalitis and cryptococcal meningitis, evolve over hours, whereas others, such as PML and CNS lymphoma, typically have a more indolent course, with development often taking weeks to months. Many exceptions to these patterns may, however, be seen. Although many CNS opportunistic infections are associated with non-specific symptoms, such as fever and lethargy, the combination of symptoms such as a new pattern of headache or headache lasting longer than 3 days, new-onset seizures, or altered mental function strongly suggest an acute focal brain lesion.

The incidence, temporal pattern, and typical CD4-cell count for common CNS opportunistic infections are presented in table 3. CSF and radiographic patterns are presented in tables 4 and 5, respectively. The neuroimaging features provide a guide, but diagnosis should never be made on neuroimaging findings alone.

A diagnostic and management algorithm for the assessment and management of intracranial mass lesions in patients with AIDS was issued by the Quality Standard Subcommittee of the American Academy of Neurology in 1998. We present an algorithm for the management of patients presenting with headaches and symptoms suggestive of CNS infections (figure 1). Although many advances have been made in the diagnosis and treatment of CNS opportunistic infections, the algorithm approach remains applicable, especially in resource-poor settings—for example, in patients with multiple CNS lesions, empirical treatment with antitoxoplasmotherapy might be appropriate. Patients with severe immune suppression (CD4-cell count lower than 200 cells per μL) are at risk of toxoplasmic encephalitis, cryptococcal meningitis, cytomegalovirus infection, primary CNS lymphoma, and PML, whereas patients with moderate immune suppression (CD4-cell counts of 200–500 cells per μL) are at risk of tuberculous meningitis and PML.

In resource-rich settings, a battery of investigations is used to diagnose CNS opportunistic infections (panel 2). Assessment of CSF with antibody testing or PCR detection can be especially helpful in the definitive identification of the causative organism. However, the availability and sensitivity of these tests vary, and in some cases diagnosis remains a challenging task. Stereotactic brain biopsy might lead to a definitive diagnosis in such cases, or sometimes after failed empirical therapy. Image-guided stereotactic brain biopsy, particularly with MRI-compatible stereotactic systems that are associated with high diagnostic yields (up to 88–90%) for focal CNS lesions and low mortality (2–3%), facilitates early detection, diagnosis,
appropriate treatment, and improved prognosis. The opportunistic infections most frequently diagnosed with stereotactic biopsy are PML (29–30%), primary CNS lymphoma (23–25%), and toxoplasmosis (15–16%). MRI-guided stereotactic brain biopsy might be indicated in patients with solitary lesions on neuroimaging, those who have multiple lesions that have not responded to antitoxoplasmosis treatment, and those with multiple lesions and neurological progression.

**cART and management of CNS opportunistic infections**

In patients with CNS opportunistic infections, the timing of cART initiation is pertinent to the management of treatment-naive patients as well as those who have previously received cART. The use of cART to achieve immune restoration is especially effective in patients with opportunistic infections for which no effective antimicrobial therapy is available, including PML, but several complications are of concern, including drug interactions, toxic effects, and IRIS.

CNS opportunistic infections that develop in patients who are already taking cART might be due to IRIS, especially within the first 12 weeks after cART is started (table 6). Alternatively, infection could be due to cART treatment failure, and the patient’s adherence should be assessed and antiretroviral resistance should be tested. In both scenarios, cART should be continued and modified if virological failure (inability to achieve or maintain viral replication to an HIV RNA level lower than 200 copies per mL), immunological failure (inability to achieve or maintain an adequate CD4 response despite virological suppression), or adverse reactions develop, in addition to antimicrobial therapy.

In resource-poor countries where cART is not available, a prophylactic antimicrobial regimen might help to prevent CNS opportunistic infections. Region-specific policies on the timing and type of prophylaxis are needed. Guidelines from the Centers for Disease Control and Prevention (CDC) on the prevention and treatment of opportunistic infections in adults and adolescents infected with HIV provide useful recommendations.

### Table 3: Clinical characteristics of HIV-associated CNS opportunistic infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>CD4-cell count at presentation (cells per µL)</th>
<th>Time from symptom onset to presentation</th>
<th>Change in mental status</th>
<th>Seizures</th>
<th>Headache</th>
<th>Fever</th>
<th>Focal deficits</th>
<th>Cranial neuropathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasmic encephalitis(21,22)</td>
<td>&gt;200</td>
<td>Days</td>
<td>+ to +++</td>
<td>+ to ++</td>
<td>+++</td>
<td>++ to +++</td>
<td>+ to +++</td>
<td>+</td>
</tr>
<tr>
<td>PML(23,24)</td>
<td>&lt;100, but occasionally higher</td>
<td>Generally weeks to months, sometimes acute, mimicking stroke</td>
<td>+ to +++</td>
<td>+</td>
<td>+ to ++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Primary CNS lymphoma (25,26)</td>
<td>&lt;100</td>
<td>Weeks</td>
<td>+++</td>
<td>+ to ++</td>
<td>++ to +++</td>
<td>None</td>
<td>++ to +++</td>
<td>+</td>
</tr>
<tr>
<td>Cytomegalovirus encephalitis(27,28)</td>
<td>&lt;50</td>
<td>Days</td>
<td>+++</td>
<td>+ to +++</td>
<td>++ to +++</td>
<td>+ to +++</td>
<td>+ to +++</td>
<td>+</td>
</tr>
<tr>
<td>Cryptococcal meningitis(29,30)</td>
<td>&lt;50 (rarely, up to 200)</td>
<td>Days</td>
<td>+ to +++</td>
<td>+</td>
<td>+++</td>
<td>+ to +++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tuberculous meningitis(31,32)</td>
<td>Variable, but &lt;200</td>
<td>Days to weeks</td>
<td>+ to +++</td>
<td>+</td>
<td>+++</td>
<td>+ to +++</td>
<td>+ to +++</td>
<td>+</td>
</tr>
<tr>
<td>Herpes simplex virus(33)</td>
<td>Variable</td>
<td>Weeks</td>
<td>+ to +++</td>
<td>+</td>
<td>+++</td>
<td>+ to +++</td>
<td>+ to +++</td>
<td>+</td>
</tr>
</tbody>
</table>

+=uncommon (0–30%). ++=sometimes (30–60%). +++=often (>60%). PML=progressive multifocal leukoencephalopathy.

### Table 4: CSF characteristics of HIV-associated CNS opportunistic infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>White-blood-cell count</th>
<th>Glucose concentration</th>
<th>Protein concentration</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasmic encephalitis(21,22,23)</td>
<td>Normal or increased lymphocytes</td>
<td>Decreased or normal</td>
<td>Normal or increased</td>
<td>Toxoplasma gendt PCR nearly 100% specific and 50–80% sensitive</td>
</tr>
<tr>
<td>PML(23,24)</td>
<td>Normal, rarely increased lymphocytes</td>
<td>Normal</td>
<td>Normal or increased</td>
<td>JC-virus PCR sensitivity variable at 50–90%, but specificity 90–100%</td>
</tr>
<tr>
<td>Primary CNS lymphoma(25,26)</td>
<td>Normal or increased lymphocytes</td>
<td>Normal</td>
<td>Normal or increased</td>
<td>Epstein-Barr virus PCR nearly 100% sensitive and about 50% specific</td>
</tr>
<tr>
<td>Cytomegalovirus encephalitis(27,28)</td>
<td>Normal, rarely increased neutrophils</td>
<td>Normal</td>
<td>Normal or increased</td>
<td>PCR &gt;90% sensitive and specific and &lt;25% culture positive</td>
</tr>
<tr>
<td>Cryptococcal meningitis(29,30,31)</td>
<td>Normal, rarely increased lymphocytes</td>
<td>Decreased or normal</td>
<td>Normal or increased</td>
<td>Opening pressure frequently raised; India ink stain 75% sensitive; CSF cryptococcal antigen sensitivity 92% and specificity 83%; high CSF antigen titre associated with poor prognosis, but change of titre with treatment has little correlation with prognosis</td>
</tr>
<tr>
<td>Tuberculous meningitis(32,33)</td>
<td>Increased lymphocytes</td>
<td>Decreased</td>
<td>Normal or increased</td>
<td>Mycobacterium tuberculosis culture has variable sensitivity, but use of microscopy for acid-fast bacilli and CSF NAAT can increase sensitivity to &gt;80%</td>
</tr>
<tr>
<td>Herpes simplex virus(34)</td>
<td>Usually increased lymphocytes</td>
<td>Decreased</td>
<td>Normal or increased</td>
<td>CSF PCR sensitivity 100%, specificity 99 6%</td>
</tr>
</tbody>
</table>

PML=progressive multifocal leukoencephalopathy. NAAT=nucleic-acid amplification test.
Table 5: Radiographic characteristics of HIV-associated CNS opportunistic infections

<table>
<thead>
<tr>
<th>Mass effect</th>
<th>Proportion of solitary lesions (%)</th>
<th>Typical locations</th>
<th>Enhancement</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplastic encephalitis(^{2,11,12,36})</td>
<td>Frequent</td>
<td>&lt;20%</td>
<td>Frontal, basal ganglia, parietal</td>
<td>Frequent, mainly ring enhancing</td>
</tr>
<tr>
<td>PML(^{23,34,38})</td>
<td>Rare</td>
<td>~50%</td>
<td>Subcortical white matter, cerebellum, brainstem</td>
<td>~25% show enhancement, (especially in patients with IRIS)</td>
</tr>
<tr>
<td>Primary CNS lymphoma(^{2,3,26,36})</td>
<td>Frequent</td>
<td>30–50%</td>
<td>Periventricular, frontal, cerebellum, temporal</td>
<td>Frequent, potentially with heterogeneous enhancement</td>
</tr>
<tr>
<td>Cytomegalovirus encephalitis(^{2,12})</td>
<td>None</td>
<td>NA</td>
<td>Periventricular</td>
<td>&lt;50% show periventricular enhancement</td>
</tr>
<tr>
<td>Cryptococcal meningitis(^{13,36})</td>
<td>Communicating hydrocephalus with raised intracranial pressure</td>
<td>Typically multiple</td>
<td>Basal ganglia</td>
<td>Potentially leptomeningeal enhancement, especially in patients with IRIS</td>
</tr>
<tr>
<td>Tuberculous meningitis(^{23,34})</td>
<td>Hydrocephalus possible</td>
<td>Mainly ill-defined exudates</td>
<td>Infratentorial with basal ganglia or cortical infarcts</td>
<td>&lt;50% show basilar enhancement on CT</td>
</tr>
<tr>
<td>Herpes simplex virus(^{2})</td>
<td>Minimal</td>
<td>NA</td>
<td>Inferomedial temporal lobes</td>
<td>Frequent enhancement</td>
</tr>
</tbody>
</table>

PML=progressive multifocal leukoencephalopathy. IRIS=immune reconstitution inflammatory syndrome. FLAIR=fluid-attenuated inversion recovery. NA=not applicable.

Tuberculous meningitis and brain abscesses

WHO estimates that a third of the world’s population is infected with *Mycobacterium tuberculosis* and that individuals with HIV co-infection are at increased risk of disseminated, active forms of disease, including tuberculous meningitis.\(^1\) The exact incidence of HIV-associated tuberculous meningitis is uncertain because epidemiological data are limited, especially for areas where co-infection rates are highest, such as sub-Saharan Africa.\(^2\)

Infection with *M. tuberculosis* occurs after inhalation of airborne bacilli that traverse the alveoli into the bloodstream. Intact T-cell-mediated immunity helps to control haematogenous spread. The disease disseminates readily in patients infected with HIV who have reduced CD4-cell counts. In the brain, granulomas or Rich foci can form within the subpial and subependymal layers\(^3\) and these can expand to create tuberculomas or parenchymal brain abscesses (table 5), or, more commonly, rupture to cause meningitis.

Rapid detection is crucial in patients with HIV-associated tuberculous meningitis, but detection of acid-fast bacilli or the causative organism by positive culture or PCR is often difficult (table 4).\(^4\) Sensitivities for these tests have traditionally been poor at about 50%, although patients infected with HIV have higher yield rates of up to 80%, possibly owing to incomplete immune responses and increased bacterial loads.\(^5\) Neither tuberculin skin tests (sensitivity 31%) nor the interferon-γ-release assay Quantiferon-TB Gold (Cellexis, Valencia, CA, USA; sensitivity 60%) can precisely exclude tuberculosis in individuals with HIV, especially when CD4-cell counts are lower than 200 cells per μL.\(^6\) Repeated, large-volume lumbar punctures might improve the yield.\(^7\) CSF tests that include a nucleic-acid amplification test have substantially shortened detection times and can improve test sensitivities when used in combination with acid-fast bacillus microscopy and repeated sample testing (table 4).\(^8\)

Treatment for tuberculosis does not differ significantly between patients with and without HIV infection. The standard regimen begins with isoniazid, pyrazinamide, ethambutol, and rifampicin for 2 months. Rifampicin notably lowers levels of protease inhibitors and nevirapine in plasma, but rifabutin is an appropriate alternative.\(^9\) After this initial phase, isoniazid and rifampicin or rifabutin are continued for at least 9–12 months.\(^10\) The role of corticosteroids and the optimum timing of the initiation of cART in conjunction with antituberculosis therapy remain controversial issues. In a randomised, controlled trial of 545 patients with tuberculous meningitis in Vietnam, an adjuvant corticosteroid (dexamethasone) was associated with a 30% reduction in the relative risk of death, but not a significant reduction in the proportion of severely disabled patients.\(^11\) A smaller study assessed 253 patients who were treated with standardised anti-tuberculosis treatment, adjuvant dexamethasone, and prophylactic co-trimoxazole and who were followed-up for 12 months. Immediate start of cART did not improve outcomes compared with cART deferred for 2 months.\(^12\) Thus, delayed initiation of cART is recommended for patients with HIV-associated tuberculous meningitis.

Mortality from HIV-associated tuberculous meningitis often exceeds 50%, which is roughly double the rate in patients without HIV.\(^13\) Even with the addition of cART, mortality is not improved.\(^14\) Multidrug-resistant tuberculosis (resistant to at least isoniazid and rifampicin) is estimated to account for 3·6% of incident tuberculosis diagnoses worldwide, and extensively drug-resistant disease (also resistant to
fluoroquinolones and second-line injectable drugs) has been documented in at least 58 countries since 2010.1 Case series of multidrug-resistant HIV-associated tuberculous meningitis suggest that mortality is extremely high.45,51 This disease is of notable concern in resource-poor settings because the cost of treatment is 100 times greater than that for susceptible tuberculous meningitis.52 Further studies are needed to better characterise HIV-associated multidrug-resistant and extensively drug-resistant tuberculous meningitis.

Toxoplasmic encephalitis

Toxoplasmic encephalitis remains the most commonly reported neurological opportunistic infection since cART was introduced, although declines in incidence have been seen: in 2007, the incidence in the UK was 0.4 per 1000 person-years, which was a notable decline from 3.2 only 10 years earlier.7 Because toxoplasmic encephalitis is caused by reactivation of encysted bradyzoites rather than primary infection, rates vary according to the seroprevalence of Toxoplasma gondii in the population. Risk factors for toxoplasmic encephalitis include the degree of immunosuppression and whether or not prophylaxis for Pneumocystis jiroveci pneumonia is being used, since trimethoprim is also an effective preventive therapy for toxoplasmic encephalitis.

After human ingestion of oocysts containing oocytes, usually from feline definitive hosts, the active tachyzoites replicate and transform into latent bradyzoites that persist in the brain and muscle.53 In immunodeficient individuals, CD4-positive T cells are unable to suppress this latent infection, and the tachyzoites re-emerge and replicate.53 The tachyzoites commonly produce focal necrotising cerebritis surrounded by a thick wall of histiocytes and inflamed vessels, although a more diffuse encephalitis, known as microglial nodular encephalitis, can occur in people with severe immunosuppression.53

The diagnosis of toxoplasmic encephalitis is often established by clinical and radiographic improvements after empirical treatment and by a positive test for IgG antibodies to T gondii in serum. Only about 3% of patients have negative serology.24 When clinically feasible, PCR of CSF obtained by lumbar puncture can be helpful to detect the parasite. The specificity of PCR is excellent, although the sensitivity is only about 50% when tested at or near the time of treatment initiation (table 4).31 New PCR techniques and testing for CSF excretory-secretory antigens offer increased sensitivity, but the costs of these tests remain prohibitively high in resource-poor areas.26-28 Primary CNS lymphoma is often the principal differential diagnosis. MRI, 18F-fluorodeoxyglucose PET, and SPECT might help to distinguish specific features,29,30 but a brain biopsy could be necessary if equivocal or worsened response to empirical treatment is seen.

Combined pyrimethamine, folinic acid, and sulfadiazine has traditionally been used, although trimethoprim-sulfamethoxazole was equally effective in a
Table 6: Distinguishing features of IRIS and worsening or recurrent opportunistic infections

<table>
<thead>
<tr>
<th>Context</th>
<th>IRIS</th>
<th>Worsening or recurrent opportunistic infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset early (average 2 months) after start of cART, generally in patients with good adherence to treatment</td>
<td>Generally not closely related to start of cART, often seen in patients with a history of non-adherence to treatment</td>
<td></td>
</tr>
<tr>
<td>Plasma HIV RNA concentration</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>CD4-positive T-cell count</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>CSF profile</td>
<td>Lymphocytosis, raised protein concentrations, and, frequently, sterile culture</td>
<td>Lymphocytosis less intense than with IRIS, raised protein concentrations, possibly low glucose, and generally positive culture</td>
</tr>
<tr>
<td>Neuroradiology</td>
<td>Worsening lesion with cerebral oedema and contrast enhancement</td>
<td>May have worsening lesions, but surrounding cerebral oedema might be less intense than with IRIS, contrast enhancement</td>
</tr>
<tr>
<td>Treatment</td>
<td>Corticosteroid (anecdotal)</td>
<td>Antimicrobial</td>
</tr>
</tbody>
</table>

IRIS=immune reconstitution inflammatory syndrome. cART=combination antiretroviral therapy.

Small randomised trial, and is perhaps more economical for resource-poor regions. 64 In a large clinical study of patients treated presumptively for toxoplastic encephalitis, the median time to treatment response was 5 days; 74% improved within 7 days and 91% responded within 14 days. Failure to improve within 10–14 days of starting treatment should, therefore, prompt reassessment of the diagnosis, with either thallium SPECT or brain biopsy. 65 Corticosteroids are indicated only when a substantial mass effect is seen, and should be discontinued as soon as possible. Induction treatment should be continued for at least 6 weeks, until substantial radiographic improvement is recorded, including the loss of contrast enhancement,9 although in a few patients contrast enhancement might persist for months or even years. Maintenance therapy should be continued in all patients until immune reconstitution is achieved (persistent CD4-cell count of more than 200 cells per μL). Anticonvulsants are indicated only in patients with a history of seizures related to toxoplastic encephalitis. Despite the introduction of cART, mortality for toxoplastic encephalitis remains high at 20–60% within 1 year of diagnosis. 64, 66 Low CD4-cell counts at the time of diagnosis, a history of other AIDS-defining illnesses, age older than 45 years, and the presence of encephalopathy portend a poor prognosis. 9

Cryptococcal meningitis

Before the introduction of cART, 5–10% of patients with AIDS developed cryptococcal meningitis. Although the incidence has fallen, this disease remains a major concern in sub-Saharan Africa and south and southeast Asia.64

Cryptococcus neoformans is an encapsulated yeast commonly found in soil and in excrement from pigeons. Cryptococcus gattii is generally found in tropical and subtropical regions, and causes disease in immunocompetent individuals. 65 Exposure to Cryptococcus spp probably occurs via inhalation of spores, which leads to primary pulmonary infection, latent infection, or disseminated disease. Cryptococcal meningitis is thought to be the result of reactivation of latent infection in immunocompromised patients.65 Although described as meningitis, the yeast typically forms cystic accumulations in Virchow-Robin spaces, around the deep-penetrating blood vessels in the brain and cranial nerves, termed soap-bubble cysts.

Lumbar puncture with manometry is especially helpful for the diagnosis of cryptococcal meningitis, as the CSF opening pressure is typically raised (table 4). 66 The CSF profile at presentation is normal in about 30% of patients.66 Microscopic detection with India ink staining and fungal culture of the CSF are diagnostic. Immunoassays of cryptococcal antigens are rapid, sensitive, and specific, and confer prognostic value. 68 Urinary antigen detection has high sensitivity, and can be useful, especially in resource-poor settings, in the appropriate clinical context. 69

Clinically, cryptococcal meningitis is most notable for its propensity to cause communicating hydrocephalus with increased intracranial pressure, which develops in more than 15% of patients. 70 Aggressive management of raised intracranial pressure is crucial to lessen the risk of early death. Impaired reabsorption of CSF by the arachnoid villi is thought to be due to sticky polysaccharide capsules. Patients with increased intracranial pressure typically present with headache, vomiting, visual changes, hearing loss, palsy of the abducens nerve, and impaired consciousness; however, this complication can be silent and is potentially fatal. Dysfunction in multiple cranial nerves might occur owing to associated basal meningitis. Repeated high-volume lumbar puncture frequently leads to immediate symptomatic relief, and can reverse neurological morbidity, such as blindness or deafness. 71 Data on the management of raised intracranial pressure in cryptococcal meningitis are limited. Guidelines recommend serial daily lumbar punctures if the opening pressure is persistently greater than 25 cm H2O.72 Drainage of CSF to reduce the pressure by 50% or to a pressure in the normal range (less than 20 cm H2O) is recommended. Lumbar drains or even ventriculo-peritoneal shunts have been used if increased intracranial pressure remains difficult to control.73

The recommended treatment for cryptococcal meningitis is intravenous amphotericin B in combination with oral flucytosine for a minimum of 2 weeks, followed by oral fluconazole for at least 8 weeks.74 Liposomal amphotericin B is associated with lower risks of renal toxic effects and other side-effects than conventional amphotericin B and has similar efficacy, but it is more expensive.75 Combined flucytosine with amphotericin B leads to faster and greater sterilisation of CSF than does amphotericin B alone.76 Prophylaxis with fluconazole is required until a durable immune reconstitution with a CD4-cell count higher than 200 cells per μL is achieved.

Guidelines recommend serial daily lumbar punctures if the opening pressure is persistently greater than 25 cm H2O.72 Drainage of CSF to reduce the pressure by 50% or to a pressure in the normal range (less than 20 cm H2O) is recommended. Lumbar drains or even ventriculo-peritoneal shunts have been used if increased intracranial pressure remains difficult to control.73

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In resource-limited settings, only amphotericin B and fluconazole are generally available. A large trial in Africa supports the use of fluconazole as primary prophylaxis, irrespective of whether patients are receiving cART. IRIS affects 30–40% of patients with cryptococcal meningitis, and the risk is increased in individuals who are antiretroviral naive and who have high concentrations of HIV RNA. Mortality for IRIS associated with cryptococcal meningitis is 33–66%. Appropriate management of IRIS includes continuation of cART, antifungal therapy, and a course of corticosteroids.

Cytomegalovirus encephalitis

Neurological diseases caused by cytomegalovirus are rare but very serious. Infection can lead to encephalitis, retinitis, radiculomyelitis, or mononeuritis multiplex. Although cytomegalovirus encephalitis seems to occur at similar rates worldwide, retinitis has a distinct geographical distribution—it is the predominant HIV-associated eye disease in Asia, where up to a third of HIV-infected patients are affected.

The ubiquitous herpes virus, cytomegalovirus is endemic worldwide and usually causes asymptomatic or clinically benign infections. Most people have been infected by the time they reach adulthood. The high neurovirulence of some cytomegalovirus strains and host genetic risk factors might play a part in the development of neurological disease.

In cases of suspected cytomegalovirus encephalitis, brain imaging with contrast should be done. Meningeal enhancement or periventricular inflammation can be seen in infected patients, but these findings are not specific to cytomegalovirus encephalitis (table 5). PCR of CSF is highly sensitive and specific in the diagnosis of cytomegalovirus encephalitis (table 4) and might also be positive in patients with cytomegalovirus radiculomyelitis. Quantitative PCR results can also help in the assessment of disease severity and in monitoring response to antiviral therapy, having a sensitivity of 250 copies per mL and a diagnostic specificity of 90–99%. A neutrophil-predominant CSF pleocytosis with negative bacterial culture is highly suggestive of cytomegalovirus infection. Retinitis associated with cytomegalovirus infection is typically diagnosed by areas of haemorrhagic infarction, perivascular sheathing, and retinal opacification on fundoscopy.

Patients with cytomegalovirus encephalitis commonly present with rapidly progressive encephalopathy, often with hyponatraemia due to adrenal involvement. Brainstem symptoms and seizures can also occur. Patients with extraocular complications frequently have previous or concurrent cytomegalovirus retinitis and should undergo fundoscopy, as blindness can develop if retinal disease remains untreated. Visual symptoms can include floaters, loss of peripheral vision, or central scotoma, but not all patients are symptomatic. The visual loss in cytomegalovirus retinitis is usually the result of retinal necrosis, but macular oedema, retinal detachment, and papillitis might also reduce visual acuity. Radiculomyelitis typically affects the lumbosacral regions and can present as a rapidly progressive cauda equina syndrome. The clinical presentation resembles Guillain-Barré syndrome, except that the CSF generally has a neutrophilic predominance and MRI imaging shows contrast-enhancing and greatly thickened nerve roots.

Little evidence is available to definitively guide the treatment of cytomegalovirus encephalitis. A combination of ganciclovir and foscarnet was generally used before the introduction of cART, but this regimen is associated with substantial adverse effects. The use of cART plus one anticytomegalovirus treatment is favoured. Ganciclovir was the first available agent and remains the first-line treatment, although mutations in the viral genes UL97 or UL54 can lead to drug resistance. Ganciclovir is only available intravenously, but its prodrug, valganciclovir, can be given orally. While a sustained-release intraocular implant treats cytomegalovirus retinitis in the affected eye, oral ganciclovir is recommended to prevent cytomegalovirus retinitis or extracellular disease. Foscarnet is used when patients develop dose-limiting leucopenia while taking ganciclovir or in ganciclovir-resistant cases, although some cross-resistance has been shown. Cidofovir is a competitive inhibitor of the viral DNA polymerase after conversion to an active form. As the activation of cidofovir does not rely on viral kinases, it retains its activity for cytomegalovirus with UL97 mutations, but mutations in DNA polymerase genes, such as UL54, lead to resistance. Secondary prophylaxis with long-term oral anticytomegalovirus therapy should be continued until sustained immune recovery is achieved with cART. Drug susceptibility testing based on screening for known resistance-inducing mutations in the viral genome can help to guide antiviral therapy.

Progressive multifocal leukoencephalopathy

PML is a rare but severe CNS opportunistic infection that is caused by the reactivation of latent JC virus, a polyomavirus, in immunosuppressed individuals. Unlike most of the other HIV-associated CNS opportunistic infections, which are very rare when the CD4-cell count is higher than 100–200 cells per μL, PML occasionally occurs in patients with much higher CD4-cell counts (table 3). The seroprevalence of JC virus in the general population is 50–90%, and about 30% of people shed the virus in urine. The incidence of PML has declined from seven cases per 1000 patient-years before the introduction of cART to 0.7 per 1000 (table 1). The mechanisms underlying the pathogenesis of PML, especially the mode of acquisition, latency, and dissemination of JC virus, site of reactivation, and the escape of CNS immunosurveillance, remain unclear. Primary JC-virus infection is typically asymptomatic and the virus remains in the kidneys, bone marrow, and lymphoid tissue. JC-virus DNA is detectable in brain
tissue from individuals without PML, but with variable frequency (11–68%).127 The pathogenic sequence of events in the development of PML is uncertain. The archetypal virus is non-pathogenic, and for neurovirulence and PML to occur, mutational changes are required in the non-coding control region and in the capsid viral protein VP1, which modulates ganglioside binding.6 Whether PML develops from a primary brain ingress of neurovirulent JC virus from circulating lymphocytes after reactivation in the bone marrow96,100,101 or whether the latent virus undergoes secondary reactivation within the brain is unclear. In the brain, JC virus infects mainly oligodendrocytes102 and astrocytes,103 and, occasionally, neurons.105,106 HIV-1 may act directly as a cofactor for JC-virus replication via the HIV-1 TAT protein, through transactivation of the JC-virus late promoter in glial cells, which provides an additional pathogenic mechanism.107

PML typically causes multifocal demyelinating lesions in white matter, and patients often present with focal neurological deficit that has developed over several weeks. Rarely, the deficit will develop acutely and could be mistaken for stroke.108 Other, less common diseases associated with JC-virus infection have been reported, including JC-virus granule cell neuronopathy93 with cerebellar ataxia, JC-virus encephalopathy, and JC-virus meningitis.104,105

Unifocal or multifocal areas of hyperintensity in subcortical white matter on T2-weighted, fluid-attenuated inversion recovery MRI associated with well-demarcated hypointense lesions on T1-weighted MRI are highly suggestive of PML. The cortical ribbon is classically spared (table 5, figure 2). Minimal tissue oedema or no contrast enhancement is usual unless PML is complicated by IRIS.109,110 Rarely, the only radiological finding is severe cerebellar atrophy.111

A definitive diagnosis of PML is established by the detection of JC virus in CSF by PCR. The diagnostic sensitivity varies across laboratories, but specificity is high (table 4).112,113 Brain biopsy might occasionally be required to confirm the diagnosis.

The mainstay of treatment for PML in patients infected with HIV is immune reconstitution with cART. This approach has improved survival from 10% before the introduction of cART to 50–75% since.114–116 The presence of JC-virus-specific CD8-positive cytotoxic T lymphocytes in plasma is associated with improved survival.117 No antiviral therapy with proven efficacy is available. Various agents, including interferon alfa,118 cytarabine,119 melphalan, mirtazapine (a 5-HT1a-receptor blocker that can prevent JC-virus entry into glial cells),105 and cidofovir,120 have shown little or no efficacy. The low efficacy of cidofovir might be due to poor CNS penetration and dose-limiting side-effects, but a lipid derivative, CMX001 (Chimerix, Durham, NC, USA), has shown promising results in vitro.121 A common complication, the exaggerated inflammatory response, IRIS, that is associated with cART, might unmask or paradoxically worsen PML, with variable outcomes.122 Corticosteroids administered at various doses and for different treatment durations have had some positive effects on brain inflammation. The CDC guidelines suggest the use of corticosteroids for PML-associated IRIS, but not in individuals without any evidence of inflammation.6

Primary CNS lymphoma
HIV infection is a well-established risk factor for primary CNS lymphoma.123 Since cART was introduced, the incidence among people with HIV infection has substantially declined,124 and it is now a rare disease. Between 2001 and 2007 in the USA, around 26 new cases of primary CNS lymphoma per 100 000 person-years were reported among people with AIDS compared with 0·38 cases among people without AIDS.125

Primary CNS lymphoma must be distinguished from secondary involvement of the CNS in systemic lymphoma. The pathogenesis of primary CNS lymphoma in HIV/AIDS is variably associated with multiple genetic alterations, including proto-oncogene activation (MYC, PIM1, RH0H, also known as TTF, and PAX5),126 and monoclonal Epstein-Barr virus infection.127 Most primary CNS lymphomas are high-grade B-cell tumours that are multicentric and express markers of the germinal centre, including BCL-6 and IRF-4 (also known as MUM1) and pan-B-cell markers, including CD19, CD20, CD22, and CD79a.128

Clinical features of primary CNS lymphoma are non-specific, and may include lethargy, cognitive changes, headache, and focal neurological symptoms from an intracranial mass lesion. Presentations may also be limited to the leptomeninges and, exceptionally, to the spinal cord. Lymphoma cells are seen in the anterior chamber of the eye in 20% of patients.129 Typical B systemic symptoms are not usually present.

Contrast-enhanced CT or MRI usually reveals multifocal lesions, predominantly supratentorial, that spread along the white-matter tracts, which show heterogeneous contrast enhancement with gadolinium (table 5). Use of contrast-enhanced body imaging, such as CT of the chest, abdomen, and pelvis, or whole-body PET scanning, is imperative to exclude systemic lymphoma. The gold standard for diagnosis of primary CNS lymphoma is brain biopsy. PCR is highly sensitive (table 4) and should be used to test for Epstein-Barr virus DNA in CSF unless lumbar puncture is contraindicated. The positive predictive value of Epstein-Barr virus DNA might be as low as 29%, and specificity is also low.129 Quantification of Epstein-Barr virus DNA present in the CSF can improve the specificity for primary CNS lymphoma compared with qualitative detection (96% vs 66% when a cut-off DNA load of 10 000 copies per mL is used).129 CSF cytology is almost never informative.201 Thallium SPECT can help to distinguish primary CNS lymphoma from other infections, such as toxoplasmic
encephalitis, with sensitivity and specificity of about 90%. We recommend 201thallium SPECT imaging when empirical treatment for toxoplasmonic encephalitis seems to be failing, as tracer uptake generally indicates neoplasm rather than infection.

Corticosteroids can obscure biopsy results and, therefore, they should be avoided unless required to prevent imminent herniation. Patients with HIV infection and primary CNS lymphoma generally have poor outlook despite treatment,132 with a median survival of 2 months.134 The level of evidence for the treatment of primary CNS lymphoma is low; people with HIV infection have been excluded from two phase 3 trials and one randomised phase 2 chemotherapy trial for primary CNS lymphoma.136 cART is the definitive treatment for HIV-related primary CNS lymphoma, and radiotherapy might improve survival.136

**Herpes simplex virus encephalitis**

Herpes simplex virus is an infrequent cause of CNS opportunistic infections. In studies from before and after the widespread use of cART, PCR detection in CSF of DNA for herpes simplex virus type 1 or 2 was only 2%,135,136 whereas detection of cytomegalovirus was 74% in adults with HIV infection and neurological symptoms.135 Coinfection of herpes simplex virus 2 and Epstein-Barr virus has been reported.136

Herpes simplex virus is a neurotropic virus. Type 1 is commonly acquired in early life and may remain latent in specific CNS sensory ganglia. Type 2 is acquired through contact with infected mucosal surfaces, and seroprevalence increases with age and number of sexual partners.135 Necrotising encephalitis, which frequently affects the temporal and inferior frontal lobes, occurs in patients with HIV infection, although fatal encephalitis can occur even in the absence of a vigorous inflammatory response. Cutaneous herpetic lesions are not predictive of CNS infection by herpes simplex virus.

Clinical presentation of CNS herpes simplex virus infection in the setting of HIV/AIDS varies widely, and includes fever, headache, neck stiffness, vomiting, disorientation, memory loss, dysphasia, depression, confusion, personality change, seizures, visual hallucinations, and photophobia.136 Herpes simplex virus type 1 typically causes encephalopathy that might develop subacutely over several weeks. Herpes simplex virus type 2 typically causes a diffuse meningoencephalitis that can recur. PCR of the CSF is highly sensitive (100%) and specific (99-6%) for herpes simplex virus DNA, as confirmed by autopsy,137 and can help to identify cases of mild encephalitis, although false-negative results are possible when testing is done less than 72 h after the onset of symptoms.138 Electroencephalography most commonly shows periodic lateralised epileptiform discharges in frontotemporal regions.139 T2-weighted brain imaging shows hyperintensities in most cases and sometimes gadolinium-enhancing lesions involving the inferomedial temporal lobes,139 but lesions can also involve the brainstem, cerebellum, diencephalon, and periventricular zones.

The treatment of choice is 30 mg/kg aciclovir daily, given intravenously for 14–21 days. The drug is converted to aciclovir triphosphate, a potent inhibitor of herpes simplex virus DNA polymerase, which is required for viral replication. Progression can occur despite treatment, especially if CD4-cell counts are low.140 Ganciclovir and foscarnet have also been used with some success,141,142 and aciclovir resistance has been described.143 Relapses within 3 months of treatment have been reported, and a trial of 90 days of valaciclovir after induction treatment has been
Additional materials were found by manual searches of the reference lists of selected articles. We used the search term “human immunodeficiency virus” AND (“primary central nervous system lymphoma” OR “Epstein Barr virus” OR “JC virus” OR “progressive multifocal leukoencephalopathy” OR “tuberculosis” OR “toxoplasmosis” OR “cytomegalovirus” OR “herpes simplex virus” OR “cryptococcus.” We only reviewed papers published in English. Additional materials were found by manual searches of the reference lists of selected articles, textbooks, and relevant disease-specific guidelines.

completed, but the results are awaited (ClinicalTrials.gov, NCT00031486).

Conclusions

Although CNS opportunistic infections are decreasing in frequency, they continue to have a devastating effect on HIV-positive individuals, especially those in whom diagnosis is delayed or HIV treatment is inadequate. Mortality is often high even with appropriate treatment, and recurrences and residual neurological deficits are common. For some disorders, such as PML, primary CNS lymphoma, and multidrug-resistant tuberculosis, curative treatments are not yet available, which underscores the urgent need for prevention and early detection of HIV and associated CNS opportunistic infections. Access to cART can be lifesaving, and global programmes to roll out this treatment in resource-poor countries are clearly major factors in reducing the incidence of CNS opportunistic infections.

Concurrent infection with more than one CNS opportunistic infection is an important consideration in the care of patients infected with HIV, which adds to the challenge of managing the neurological complications of HIV infection. The relations between HIV and infectious diseases such as neurosyphilis, varicella zoster, and some that are uncommon in high-income settings (eg, cerebral malaria, Chagas disease, and neurocysticercosis) are not discussed here, but they deserve further research and attention. Vigilance is required in patients with HIV infection receiving CART because CNS-associated IRIS must always be considered when a patient clinically worsens after treatment is started (table 6). Owing to the dearth of data from clinical trials, the treatment of nearly all CNS opportunistic infections requires a therapeutic choice based on data from patients without HIV infection or indirect evidence from cohort studies or case series.

Overall, the burden of CNS opportunistic infections in people with HIV/AIDS has declined substantially, which is a measure of widespread, successful treatment with cART. Knowledge acquired as the HIV epidemic unfolds has led to improved understanding of multiple infections that were previously rare. This knowledge can now be used to treat patients in other settings, such as in the context of immunosuppression for transplanted allografts and in the testing of new immunomodulatory drugs for autoimmune diseases. Nevertheless, patients with unrecognised, and thus untreated, HIV infections will continue to present with CNS opportunistic infections. Whether due to stigma associated with a diagnosis of HIV, poor access to medical care, unavailability of cART, non-adherence, or other factors, the persistence of this vulnerable group of individuals must prompt efforts to improve the outcomes for patients with CNS opportunistic infections in the context of HIV.

Contributors

All authors contributed to the literature search, the writing, and the review of the paper.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

This work is supported by a grant from the Johns Hopkins National Institute for Mental Health Research Center (P30MH075673). ILT is supported by a Whitehurst foundation gift. BRS is supported by the Johns Hopkins University T32 Training Program in Hematology. GvG is supported by John Hopkins University Project RESTORE and Multiple Sclerosis Center. FJM is supported by an American Academy of Neurology Practice Research Fellowship grant.

References

616

