HIV-associated opportunistic CNS infections: pathophysiology, diagnosis and treatment

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Abstract | Nearly 30 years after the advent of antiretroviral therapy (ART), CNS opportunistic infections remain a major cause of morbidity and mortality in HIV-positive individuals. Unknown HIV-positive disease status, antiretroviral drug resistance, poor drug compliance, and recreational drug abuse are factors that continue to influence the morbidity and mortality of infections. The clinical and radiographic pattern of CNS opportunistic infections is unique in the setting of HIV infection: opportunistic infections in HIV-positive patients often have characteristic clinical and radiological presentations that can differ from the presentation of opportunistic infections in immunocompetent patients and are often sufficient to establish the diagnosis. ART in the setting of these opportunistic infections can lead to a paradoxical worsening caused by an immune reconstitution inflammatory syndrome (IRIS). In this Review, we discuss several of the most common CNS opportunistic infections: cerebral toxoplasmosis, progressive multifocal leukoencephalopathy (PML), tuberculous meningitis, cryptococcal meningitis and cytomegalovirus infection, with an emphasis on clinical pearls, pathological findings, MRI findings and treatment. Moreover, we discuss the risk factors, pathophysiology and management of IRIS. We also summarize the challenges that remain in management of CNS opportunistic infections, which includes the lack of phase II and III clinical trials, absence of antimicrobials for infections such as PML, and controversy regarding the use of corticosteroids for treatment of IRIS.

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doi:10.1038/nrneurol.2016.149
Published online 27 Oct 2016

Since the introduction of the first antiretroviral therapy (ART) drug zidovudine in 1987, followed by combination ART (CART) in 1996, there has been an expected decrease in the incidence of HIV-related opportunistic infections of the CNS. However, nearly 30 years after the advent of ART, patients continue to be affected by opportunistic CNS infections. Several factors influence the landscape of HIV-associated CNS infections: for example, many HIV-positive individuals are unaware of their disease status, and resistance to ART is common and can be further exacerbated by lack of ART compliance. Moreover, recreational drug use not only increases the risk of initial HIV infection and can interfere with ART compliance, but also affects drug clearance and protein binding, and predisposes individuals to hepatitis C virus infection.

Several infections of the nervous system, such as toxoplasmosis, are much more common in patients with HIV than in other immunosuppressed states (such as in haematopoietic stem cell transplant recipients), although the mechanisms underlying this observation are not fully understood. Moreover, the clinical and radiographic presentation of opportunistic CNS infections in the setting of HIV infection is often different from that seen in immunocompetent patients.

In 2015, an estimated 36.9 million people globally were living with HIV[1]. Increased availability and compliance with ART has resulted in an overall decrease in the incidence of overall CNS opportunistic infections, as shown by a study from the UK, where patients with HIV routinely receive modern CART therapy: the overall incidence of opportunistic infections of the CNS declined from 13.1 per 1,000 person-years in 1996–1997 to 1.0 per 1,000 person-years in 2006–2007 (REF. 2). However, the number of patients with new CNS infections who were not aware of their HIV status more than doubled[2].

In patients with HIV infection, vulnerability to various opportunistic infections is largely dictated by the degree of T cell-mediated immunosuppression (FIG. 1). According to a study drawing from a French database of almost 10,000 HIV-positive patients with a neurological

Key points

- Opportunistic infections of the CNS, such as cryptococcal meningitis, cerebral toxoplasmosis, and tuberculous meningitis, are a major cause of morbidity and mortality in HIV-positive individuals
- Cerebral toxoplasmosis should be suspected in patients with AIDS who present with movement disorders; progressive multifocal leukoencephalopathy (PML) should be suspected in those patients with AIDS who present with cortical blindness
- Cerebrospinal fluid sample analyses can facilitate diagnosis of PML, cryptococcal or tuberculous meningitis and cytomegalovirus encephalitis
- A definitive diagnosis of cerebral toxoplasmosis requires a combination of serological testing, MRI findings, and in certain cases, brain biopsy
- On MRI, toxoplasmosis often manifests with several brain abscesses with predilection for the basal ganglia, whereas PML typically manifests as diffuse white matter lesions with predilection for the subcortical U fibres
- In patients with HIV or AIDS, treatment with antiretroviral drugs in the setting of opportunistic infections can lead to a paradoxical worsening of symptoms, caused by immune reconstitution inflammatory syndrome

event, increased CNS penetrance of ART was associated with increased survival after opportunistic infection before the year 2000, when CART therapies were not available or were in their infancy[3]. In the CART era, high CNS penetrance has been associated with improved survival after toxoplasmosis or cryptococcal meningitis; however, the association was not maintained after adjustment for plasma viral loads[3]. Increased age, baseline CD4$^+$ T helper (T_H) cell count, and baseline HIV RNA levels of >100,000 copies/ml are associated with increased odds of both HIV-associated dementia and combined opportunistic infections[4]. The risk of progressive multifocal leukoencephalopathy (PML), cryptococcal meningitis and, to a lesser degree, HIV encephalopathy, increases with age in HIV-infected individuals[2]. As cohort demographics change over time, it will be essential to continue to re-evaluate the risks and patterns of HIV-associated CNS infections. Of note, treatment of these infections can pose several challenges, including the development of an immune reconstitution inflammatory syndrome (IRIS).

In this Review, we discuss several of the most common CNS opportunistic infections, with an emphasis on clinical pearls, pathology, MRI findings and management. Moreover, we review common clinical presentations of IRIS in opportunistic infections, discuss paradoxical and unmasking IRIS, summarize the use of MRI as a diagnostic tool in HIV-IRIS, and suggest treatment strategies.

Cerebral toxoplasmosis

Humans are susceptible to *Toxoplasma gondii* infection throughout their lives. Seroprevalence rates for *T. gondii* increase with age, and are higher in populations in which uncooked meat is commonly ingested. When a previously uninfected individual consumes (most often via uncooked meat) a toxoplasmosis tissue cyst, the bradyzoites released from the cyst infect intestinal epithelial cells and proliferate intracellularly. Conversion of the bradyzoites to active tachyzoites in the gut can result in infection of other host tissues including, but not limited to, skeletal muscle, eye tissue, and brain grey and white mater. Bradyzoites, through modification of host intracellular signalling, are able to evade the host immune system and can survive intracellularly for indefinite periods of time[5,6] (FIG. 2a). Dormant tissue cysts composed of bradyzoites can reactivate during periods of immune suppression and can convert to active, proliferative tachyzoites.

In immunocompetent patients, the infection is typically asymptomatic, although some individuals develop lymphadenopathy, splenomegaly, low-grade fever, malaise, myalgia, or ocular manifestations[7]. Immunocompromised patients can develop a more-severe disease, which usually represents reactivation of previously dormant disease. Tachyzoites are capable of infecting any CNS cells, initiating a cascade of immune-mediated responses against the disseminated tachyzoites that eventually results in a necrotic lesion[8].

Cerebral toxoplasmosis was rare until the 1980s, when the incidence markedly increased in concert with the AIDS pandemic. The first cases of toxoplasmosis complicating an HIV infection were described in 1983 (REF. 9). Today, *T. gondii* remains the most prevalent HIV-associated opportunistic CNS infection, with an estimated seroprevalence of 13.2% in the general populace of the USA, and 75% in endemic areas[10]. The risk of cerebral toxoplasmosis is markedly increased in patients with HIV who are seropositive for *T. gondii*, indicating prior infection. In one cohort from Edinburgh, UK, cerebral toxoplasmosis was 35-fold more likely to occur in seropositive patients than in seronegative patients, and occurred in only 1.3% of seronegative patients with CD4$^+$ cell counts <50 cells/mm^3 (REF. 11).

Conversion from latent bradyzoites to active tachyzoites is dependent on the degree of immunosuppression, irrespective of ART (FIG. 1), and occurrence increases in HIV-infected individuals with CD4$^+$ cell counts of <100 cells/mm^3 (REFS 12,13). The use of antiretroviral drugs has markedly reduced the risk of developing cerebral toxoplasmosis[14].

Clinical presentations

Cerebral abscess. Cerebral abscesses, also known as toxoplasmosis encephalitis, are the most common manifestation of toxoplasmosis in patients with HIV infection. The onset is subacute, and the symptoms gradually evolve over several weeks. Focal neurological signs are referable to the site of the abscess.

Multiple cerebral abscesses are common, resulting in multifocal symptoms, including visual field reductions, focal seizures, aphasia, apraxia, hemiparesis or hemisensory deficits, or cerebellar dysfunction. Nonfocal symptoms, such as confusion, cognitive abnormalities or personality disorder, can be an early manifestation, but as the disease progresses, focal symptoms begin to predominate. In rare cases, cerebral abscesses can present as a solitary mass that mimics a neoplasm[15].

Interestingly, in patients with HIV, toxoplasma tends to localize in the basal ganglia to a greater extent than in any other area besides the cortex; thus, toxoplasmosis results in movement disorders more often than does

Immune reconstitution inflammatory syndrome (IRIS)
In the context of HIV infection, effective antiretroviral therapy can normalise CD4$^+$ T cell counts and thereby lead to immune reconstitution, which can result in a dysregulated inflammatory immune response against the infecting pathogen and the host and the subsequent paradoxical worsening of symptoms (paradoxical IRIS). Immune reconstitution can also result in a sudden presentation of the previously asymptomatic and therefore unrecognized opportunistic infection (unmasking IRIS).

Bradyzoites
The slowly dividing cellular stage of the *Toxoplasma gondii* parasite that makes up tissue cysts, and is able to evade the host immune system.

Tachyzoites
The infectious, motile cellular stage of the *Toxoplasma gondii* parasite that is efficient at disseminating the parasitic infection in the host.

Posterior uveitis
Inflammation of the choroid of the eye.

any other HIV-associated opportunistic infection. In one Brazilian cohort, 35% of HIV-associated movement disorders, such as parkinsonism, hemichorea or hemiballismus, hemidystonia or a rubral tremor, were caused by *T. gondii*[16,17]. However, it is notable that in this population that is known to be highly seropositive to *T. gondii*, movement disorders comprised only 2.7% of neurological complications[17].

Diffuse encephalitis. Diffuse encephalitis caused by toxoplasmosis is a very rare condition and is only seen in patients with AIDS or, rarely, in other immunosuppressed states. The onset is typically subacute (lasting for several weeks). In diffuse encephalitis, toxoplasmosis is usually limited to the brain, with generalized nonfocal symptoms, such as altered state of consciousness, cognitive deficits, or seizures. The cerebrospinal fluid (CSF) shows a mild mononuclear pleocytosis, an elevated total protein level, and normal or reduced glucose level[18]. Pathological evaluation shows widespread microglial nodules containing bradyzoites and tachyzoites, but no necrosis that is typical of cerebral abscesses[19].

Chorioretinitis. Toxoplasmosis chorioretinitis is rare even in immunocompromised patients. *T. gondii* has a predilection for the eye, as demonstrated by the fact that this infection is the most common cause of infectious posterior uveitis[20,21]. In patients with AIDS, toxoplasmosis chorioretinitis can manifest as retinal lesions that are predominantly unilateral and necrotic. Nearly 30% of individuals with this toxoplasmosis chorioretinitis will have concomitant cerebral toxoplasmosis[22,23]. In immunocompetent patients, lesion borders are ill-defined and often adjacent to a prior scar, whereas in patients with AIDS, acute lesions are well-circumscribed and grayish yellow on funduscopic evaluation[22]. The retina can be oedematous and have small haemorrhages (Roth spots) and exudates[24]. Once the acute inflammation subsides, cells within the pigmented layer at the margins of the lesion proliferate; therefore, healed lesions are densely pigmented with irregular borders and central atrophy. Multiple lesions at various stages of inflammation and healing are common[22,25].

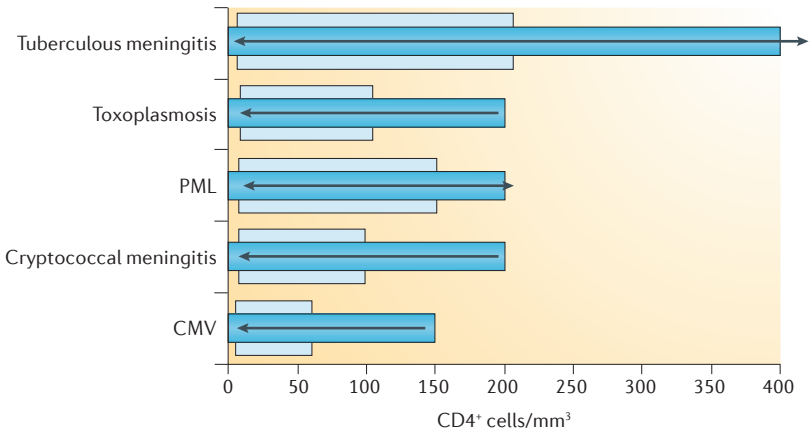


Figure 1 | **Level of immunosuppression and risk of opportunistic infections.** This figure depicts the concentration of $CD4^+$ cells in which a given HIV-associated CNS opportunistic infection can develop (dark blue bars). Rare cases of infections reported past these limits are indicated by arrows. The light blue overlay grossly depicts the most common $CD4^+$ cell counts for each respective opportunistic infection[14,34,106,113–115]. CMV, cytomegalovirus infection, PML, progressive multifocal leukoencephalopathy.

Diagnosis

PCR. Several assays for the detection of IgG antibodies against toxoplasma are commercially available. Laboratory testing for toxoplasmosis has improved in recent years, with newer genetic targets increasing the sensitivity of the previous PCR analyses of serum and CSF samples. Older PCR methods targeted the B1 gene sequence of *T. gondii*, and had a relatively low overall sensitivity (55%), leading to high rates of false negatives. The B1 sequence is, therefore, increasingly being replaced by PCR that targets the parasitic repeated sequence REP-529 (REF. 26); nevertheless, false negative results are common.

MRI. In patients with focal neurological signs who have negative CSF tests, MRI is required for diagnosis of toxoplasmosis. Multiple ring-enhancing brain lesions — often located in the basal ganglia, thalamus, and/or dentate nucleus — are a common MRI finding at presentation (FIG. 3a).

Serology. In one cohort from Brazil, *T. gondii* IgG antibodies were detected in 91% of patients with cerebral toxoplasmosis, but in only 56% of AIDS patients without cerebral toxoplasmosis[27]; in this cohort, a positive PCR finding had a sensitivity of 94%. However, it should be noted that seropositivity for toxoplasmosis varies depending on the population, meaning that the IgG antibody figures reported in this study are not generalizable.

Elevated titres of IgG1 and IgG4 against *T. gondii* excretory or secretory antigens have been detected in patients with cerebral toxoplasmosis, whereas patients with latent infection do not have these antibodies[28]. Serology should be used in combination with PCR testing for diagnosis, but caution should be taken if patients are seronegative and the pre-test probability of cerebral toxoplasmosis is high. In the Brazilian cohort, 9% of patients with known cerebral toxoplasmosis were seronegative[27].

Brain biopsy. Owing to the variable sensitivity of laboratory testing, brain biopsy should be considered in atypical patients with negative serology. CNS IRIS, although rare, can present as atypical progression of classic toxoplasmosis lesions, with leptomeningeal enhancement, perilesional oedema and lesion enhancement (FIG. 4).

Treatment

The first-line treatment for cerebral toxoplasmosis is a combination of pyrimethamine and sulfadiazine, or co-trimoxazole if sulfadiazine is not available. Clindamycin is used a second-line therapy (BOX 1). Empirical therapy is often employed in seropositive patients presenting with classic CNS mass lesions. Seronegative patients, especially those on prophylaxis with trimethoprim–sulfamethoxale[29], do not benefit from

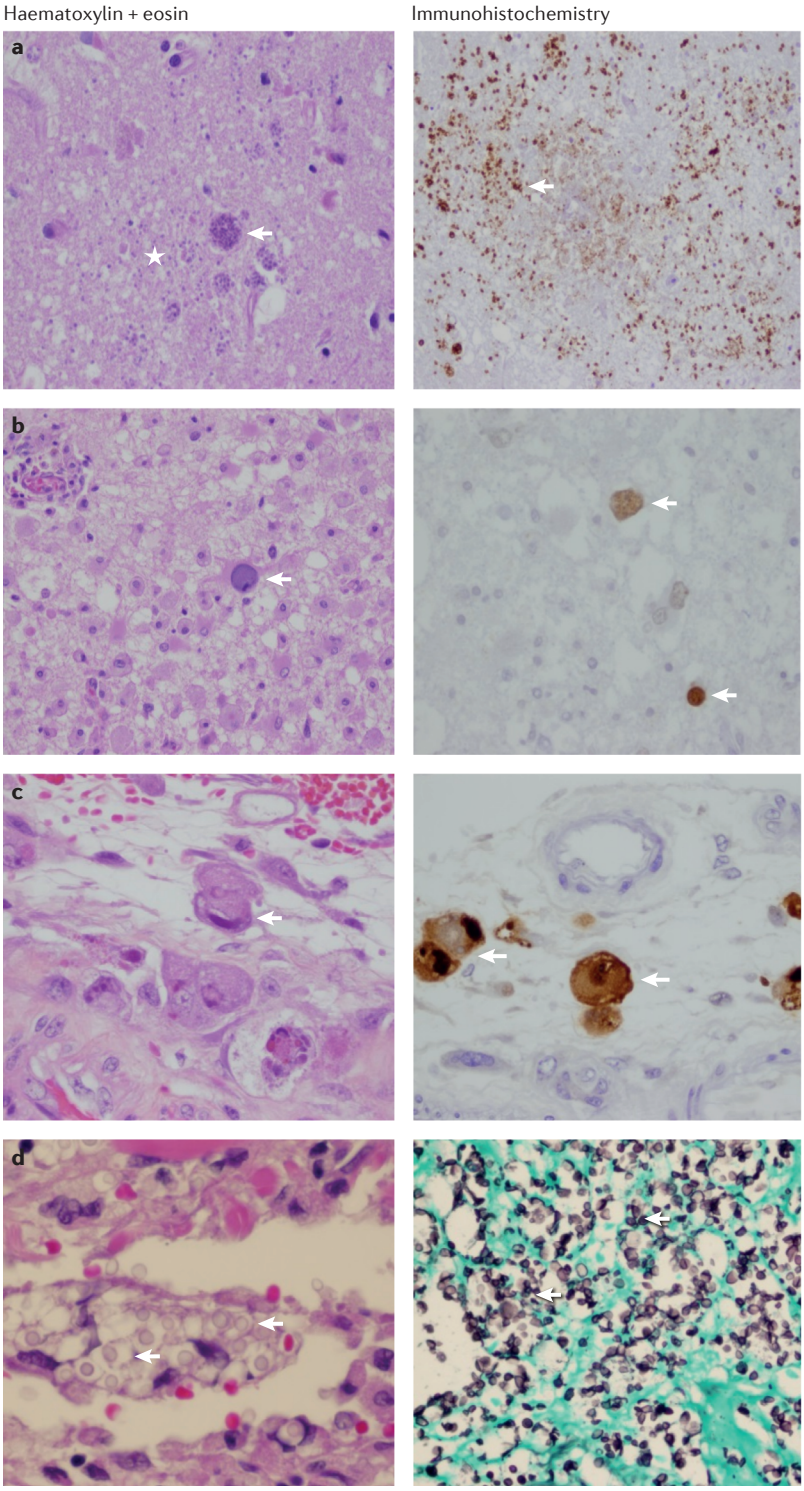


Figure 2 | **Pathological features of opportunistic infections of the CNS.** For each slide set, the left panel shows haematoxylin and eosin (H+E) staining, and the right panel shows immunohistochemistry. **a** | Toxoplasma encephalitis. H+E shows an infected cell with abundant bradyzoites (arrow) and extracellular tachyzoites (star) in neuropil, and abnormal microglial morphology indicating microglial activation. Antibody staining for *Toxoplasma gondii* is positive, as indicated by brown chromogen (arrow). **b** | Progressive multifocal leukoencephalopathy. H+E staining shows infected oligodendrocytes with enlarged nuclei and bizarre astrocytes (arrow) in a background of 'foamy' histiocytes (a marker of inflammation-associated intracellular lipid accumulation). Immunostaining was carried out with an antibody to Simian vacuolating virus 40 that cross-reacts with JC virus (brown). Infected oligodendrocyte (upper arrow) and an abnormal astrocyte (lower arrow) are seen. **c** | Cytomegalovirus encephalitis. H+E staining shows cells in the leptomeningeal spaces with cytomegalovirus inclusions (arrow). Immunostaining detects the cells with cytomegalovirus inclusions (arrows). **d** | Cryptococcal meningitis. H+E staining shows collections of fungal organisms in the meningeal spaces (arrows), as highlighted by the Grocott-Gomori methenamine silver stain (arrow).

a trial of empirical therapy, as the risk:benefit ratio of misdiagnosis is high. Use of empirical therapy for seronegative patients has been estimated to carry >10% risk of death, because these patients are more likely to have an alternative diagnosis[30].

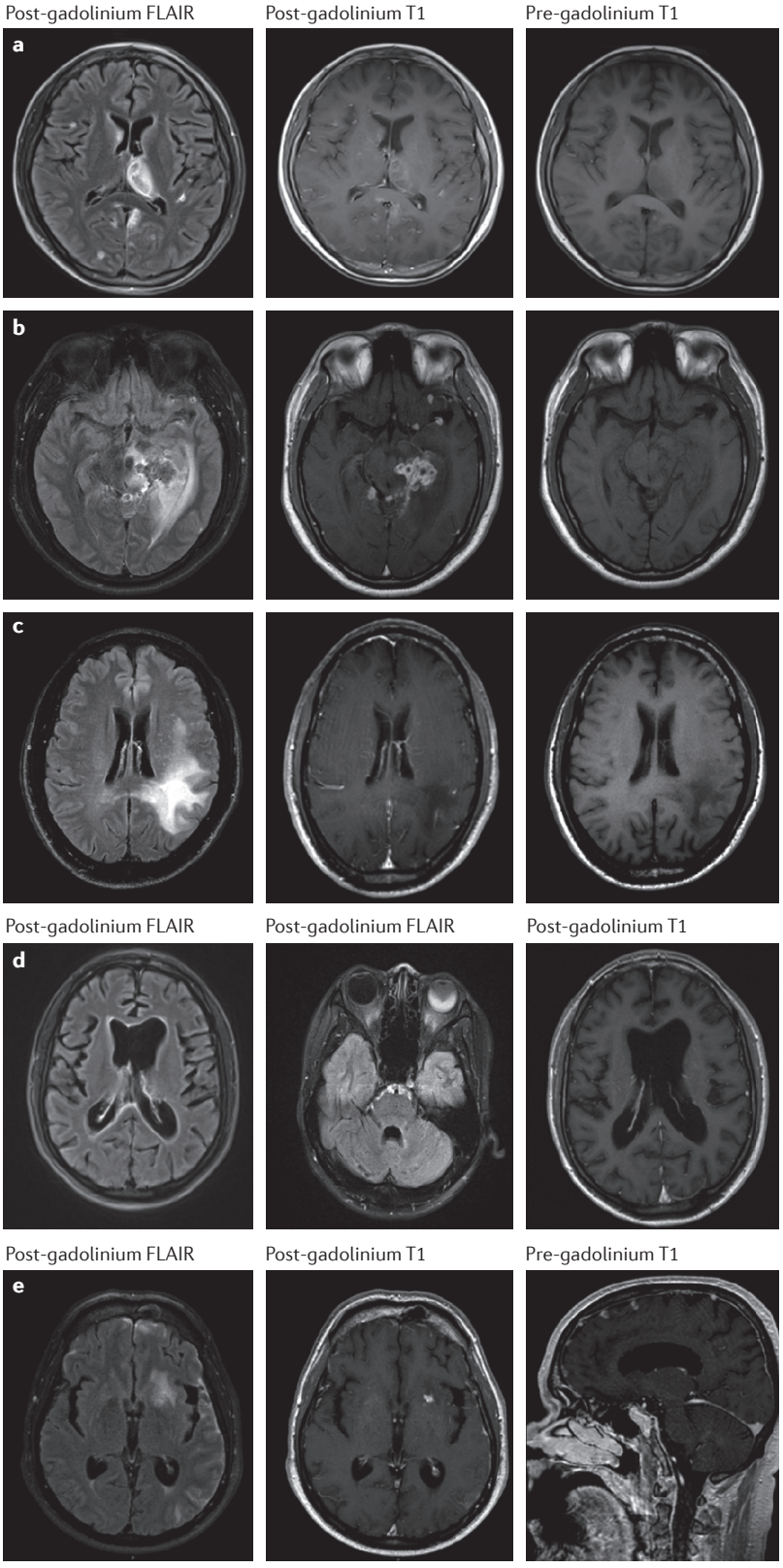
Although the current first-line agents are effective in treating acute *T. gondii* infection, they are potentially teratogenic. Moreover, none of the currently available therapies are able to eliminate the bradyzoites and latent infection. Animal model studies suggest that a variety of drugs have efficacy against toxoplasma: novel therapy targeting calcium-dependent cellular processes that control motility, such as *T. gondii* calcium-dependent protein kinase 1, have shown promise against the reservoir of latent bradyzoites in mouse models[31,32].

Progressive multifocal leukoencephalopathy

PML is a demyelinating disease of the brain caused by lytic JC virus (JCV) infection of oligodendrocytes and astrocytes. The JCV is a ubiquitous human polyomavirus that is carried by 50–90% of the population[33] (FIG. 5). PML was exceptionally rare until the AIDS era in the 1980s, but by the mid-1990s the PML incidence rate in the HIV-positive population was estimated to be >3 per 1,000 patient-years[34]. Although incidence rates have decreased considerably with the widespread availability of ART, PML remains a common CNS manifestation of HIV[34].

Initial JCV infection is asymptomatic, but in immunosuppressed patients, the infection can reactivate, leading to PML. Reactivation typically takes place at a $CD4^+$ cell count of <100 cells/mm^3; however, JCV infection is one of the few opportunistic infections that can occur with much higher $CD4^+$ cell counts[34,35] (FIG. 1).

PML presents almost invariably as a focal white matter syndrome. The range of clinical presentations is wide, and manifestations can be dramatic: it can include symptoms such as ataxia from cerebellar lesions, hemiparesis from subcortical white matter involvement, movement disorders from disruption of basal ganglia circuits, and behavioural and cognitive abnormalities from frontal lesions[36–39]. Cortical visual impairment, including homonymous hemianopia, inability to recognize objects, and even cortical blindness, can occur in



◀ Figure 3 | **MRI findings in opportunistic infections of the CNS.** Each MRI series includes a representative image from the following sequences, from left to right: post-gadolinium fluid-attenuated inversion recovery (FLAIR), post-gadolinium T1, and pre-gadolinium T1 sequences. **a** | Toxoplasma encephalitis. MRI sequences show numerous foci of FLAIR hyperintensity and gadolinium enhancement. Lesions are present in the basal ganglia as well as on the pial surfaces and in the CSF along the subarachnoid space. Oedema and mass effect are minimal. **b** | Tuberculous meningitis. The post-gadolinium FLAIR image shows extensive oedema throughout much of the left temporal lobe. The post-gadolinium T1 image shows a dense, multinodular exudate with extensive enhancement throughout the brainstem that extends into the cerebral hemispheres. **c** | Progressive multifocal leukoencephalopathy. A large left parietal lesion seen on the FLAIR sequence extends into the centrum semiovale and corpus callosum. Minimal enhancement limited to the leading edge of the lesion is visible on post-gadolinium sequences. No oedema or mass effect is present. **d** | Cytomegalovirus encephalitis and retinitis. A linear area of high-intensity signal is visible throughout the periventricular margins, and is best seen on the FLAIR sequence. T1 post-gadolinium sequences demonstrate subtle hyperintensity of these areas. Post-gadolinium FLAIR sequence at the level of the orbits shows cytomegalovirus retinitis. **e** | Cryptococcal meningitis and cerebritis. Post-gadolinium FLAIR images reveal extensive leptomeningeal enhancement, most prominently throughout the left hemisphere. A large left frontal hyperintensity with associated enhancement on T1 post-gadolinium sequences indicates a focus of cerebritis, which can co-occur with the more typical signs of cryptococcal meningitis.

isolation and are unique symptoms of PML; such presentations are only very rarely seen in other HIV-associated opportunistic infections[40,41]. Seizures can occur at initial presentation, but more commonly develop later in the disease course. Headaches are uncommon. Cerebellar granule-cell neuronopathy and a diffuse, fulminant encephalitis have both been reported, but are very rare[42].

IRIS in PML

Higher $CD4^+$ cell counts at the time of PML diagnosis have been associated with lower rates of mortality[43]; however, this improved survival could in part be confounded by undiagnosed PML-IRIS. PML-IRIS is more likely to occur at relatively high $CD4^+$ cell counts (>100 cells/mm^3). Patients with HIV who develop PML-IRIS have a higher likehood of surviving the PML than do HIV-positive patients who do not develop IRIS[44]. Moreover, patients who were diagnosed with PML-IRIS at the onset of ART, referred to as having an unmasking IRIS, had longer survival, lower mortality, and lower lesion loads seen on brain MRI than did patients with paradoxical IRIS[45,46].

Low viral titres can result in difficulty with accurately diagnosing PML-IRIS, as HIV-associated PML-IRIS often does not produce the dramatic brain parenchyma inflammation and enhancement seen with PML-IRIS attributed to other immunosuppressive conditions. Moreover, in a case series of PML-IRIS secondary to natalizumab treatment, 57.1% of patients had initial CSF JC viral loads <500 copies/ml (REF. 46) — a negative low-sensitivity JC virus assay cannot, therefore, rule out a diagnosis. In suspected HIV-associated PML-IRIS,

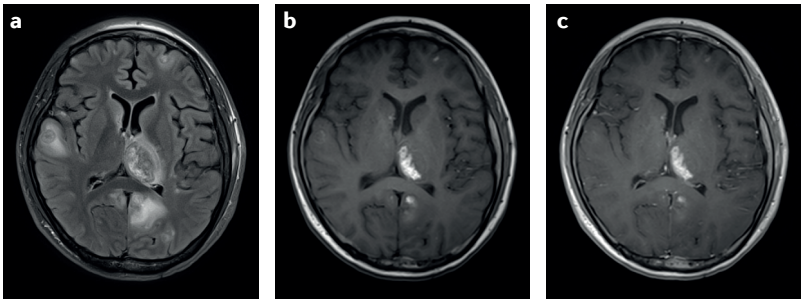


Figure 4 | **Paradoxical immune reconstitution inflammatory syndrome.** This representative series of MRI scans depicts a case of paradoxical immune reconstitution inflammatory syndrome (IRIS) attributed to toxoplasmosis-associated encephalitis in an HIV-negative immunocompromised patient with lymphopenia who underwent allogeneic stem cell transplantation. **a** | Post-gadolinium fluid-attenuated inversion recovery (FLAIR) MRI sequence. **b** | Pre-gadolinium T1-weighted MRI sequence. **c** | Post-gadolinium T1-weighted sequence. The MRI sequences depicted here show numerous foci of FLAIR hyperintensity and gadolinium enhancement in the cortex, left thalamus and parietal–occipital regions, indicating toxoplasmosis-associated lesions (white). Perilesional enhancement and oedema are particularly prominent on T2-FLAIR MRI (part **a**) and surround the left thalamic, right temporal, left frontal and left parietal–occipital lesions. Haemorrhage into the large left basal ganglia lesion can be seen on the pre-contrast T1 image (part **b**).

CSF samples should therefore be sent to laboratories that use high-sensitivity assays, such as the NIH in the USA or the University Hospital Basel or the University of Bern in Switzerland[46].

In the presence of significant mass effect or impending herniation, corticosteroids can be life-saving. However, the use of corticosteroids in mild forms of IRIS in the setting of opportunistic infections is controversial because clinical trials are lacking. The rationale for corticosteroid use in IRIS is to prevent bystander neuronal injury from the inflammatory response; however, inhibiting the immune response against the organism causing the underlying opportunistic infection can be detrimental, particularly in PML, because no effective antiviral drug is available against JC virus.

Diagnosis

Since the initial description and early cases of HIV-PML, which were diagnosed solely on the basis of histopathology, the diagnostic approach has greatly improved. A definite diagnosis of PML can be made on the basis of imaging and clinical characteristics combined with PCR detection of JCV DNA in the CSF[47]. PCR has a high specificity for JCV (98%), although its sensitivity is limited, and can be as low as 76% if copy numbers of the virus are low. Pleocytosis and elevated protein levels in the CSF are rare in PML, and cannot therefore serve as sole diagnostic tools, although they can support a diagnosis.

Imaging. In HIV-PML, poorly demarcated white matter hyperintensities are visible on T2-weighted and T1-weighted fluid-attenuated inversion recovery (FLAIR) MRI (FIG. 3c). Restricted diffusion on MRI, with high diffusion-weighted imaging (DWI) signal intensity and low apparent diffusion coefficient (ADC) value, can reveal tissue death and are frequently seen in early lesions[48]. One or more lesions can be present, and be located in different hemispheres. Mass effect is often absent in HIV-associated PML-IRIS, whereas in toxoplasmosis encephalitis and cryptococcal meningitis, focal mass lesions with mass effect can be present.

Histopathology. Histopathological staining of biopsy samples from the infected tissue reveals characteristic findings in PML, including multifocal demyelination, hyperchromatic and enlarged oligodendroglia nuclei, and bizarre astrocytes with hyperchromatic nuclei[49] (FIG. 2b). The SV40 polyomavirus stain can be used for supportive evidence; however, screening the brain biopsy sample with JCV PCR provides a more definitive diagnosis.

Treatment

No effective antiviral therapy exists for PML. Despite promising *in vitro* data, treatment trials of cidofovir, cytosine arabinoside and mefloquine showed no clear clinical benefit in trials[50–52]. Mirtazapine has been suggested as an adjunctive agent to ART on the basis of a small case series, but no clinical trial has been done to establish a comparative benefit of ART and mirtazapine over ART alone[53].

Tuberculosis

Tuberculosis is caused by *Mycobacterium tuberculosis* infection, and is one of the most prevalent infections in the world, with an estimated 2–3 billion people infected worldwide[54]. Patients co-infected with tuberculosis and HIV are at increased risk of developing disseminated forms of tuberculosis, which can also result in tuberculous meningitis[55].

In highly endemic areas, tuberculous meningitis can account for 27% of meningitis cases in HIV-positive patients, making tuberculosis the second-most common cause of meningitis behind cryptococcal meningitis in certain populations, most notably in South-East Asia and sub-Saharan Africa[56].

M. tuberculosis is transmitted by inhalation of airborne bacilli. Cell-mediated immunity is critical to control haematogenous spread through macrophages; hence, the disease disseminates readily in HIV-infected individuals with reduced $CD4^+$ cells (FIG. 5).

When *M. tuberculosis* infects the meninges, it can cause a caseating focus in the meninges or the brain cortex, known as the Rich focus. Rupture of this focus can result in dissemination of the bacilli throughout the adjacent subarachnoid space, causing a tuberculous meningitis.

Meningitis is the most common result of subarachnoid rupture of cortical Rich foci; however, in individuals with preserved cell-mediated immune responses, deeper parenchymal Rich foci can form tuberculomas, or, more rarely, tuberculous abscess layers[57] (FIG. 3b). Tuberculomas should be considered in the differential diagnosis of CNS intracranial mass lesions in areas where tuberculous meningitis is endemic, particularly if the patient has $CD4^+$ cell counts of >200 cells/mm^3, is negative for IgG antibodies against *T. gondii* and/or if findings suggest tuberculosis infection elsewhere in the body.

Mass effect
A focal lesion or inflammation of a structure or tissue of the brain causes increased pressure within the skull space, displacing an adjacent area of the brain, which often results in injury.

Heminested PCR
A series of PCR reactions that uses the products from the first PCR reaction as a template for the second, and uses one different primer in the second reaction to 'nest' within the first set of primer amplicons, thereby increasing specificity.

The most common findings of tuberculous meningitis at presentation are fever, headache, impaired consciousness, meningismus, and palsies of the lower cranial nerves[58]. Focal neurological findings such as hemiplegia, bulbar signs, or sensory deficits are common. Patients often have disseminated tuberculosis or extrameningeal involvement, including spinal, lung, or abdominal disease[58].

Diagnosis

CSF findings in HIV-associated tuberculous meningitis are typically abnormal, although some individuals, particularly those with $CD4^+$ cell counts <50 cells/mm^3, can have a completely normal CSF profile[58] (FIG. 1). In patients with HIV infection and tuberculous meningitis, CSF white cell counts are, on average, very low (<100 cells/mm^3), with neutrophils as the predominant white cell type, protein levels are often elevated, and hypoglycorrhachia is common[58]. By contrast, in immunocompetent individuals with tuberculous meningitis, CSF cell counts are much higher, and lymphocytes predominate[58].

Rapid diagnosis by detecting the infectious organism is crucial in patients with HIV-associated tuberculous meningitis, but detection of acid-fast bacilli by staining, culturing, or even by PCR is difficult[59]. The sensitivities of these tests have traditionally been poor — about 50% — although their sensitivities in patients with HIV infection are higher (up to 80%), possibly owing to impaired immune response that lead to elevated bacterial loads[60].

Improvements in PCR platforms have led to the development of the Xpert MTB/RIF assay (GeneXpert, Cepheid), a heminested PCR that amplifies the rifampin-resistance determining region of the *rpoB* gene, a sequence specific to *M. tuberculosis*[61]. The assay can yield results within 2 h, with a 'hands-on' time of about 15 min, enabling easy, rapid diagnosis and detection of rifampin resistance in sputum cultures[62]. The Xpert MTB/RIF assay has high sensitivity: the overall sensitivity is 97.6%, with sensitivity in smear-negative, culture-positive cases of tuberculosis being 72.5–90.2%; in these cases, serial testing increases the sensitivity[62]. In HIV-positive patients with tuberculosis, overall sensitivity was lower (93.9%), but specificity remained high (>98%), and the assay showed a 99.1% sensitivity and 100% specificity in detecting rifampin resistance and susceptibility[62]. The WHO endorsed the Xpert MTB/RIF assay in 2010, and in 2013, issued a strong recommendation for the use of Xpert MTB/RIF as the initial diagnostic test in suspected cases of HIV-associated tuberculosis[63]. The pooled sensitivity of the assay in detecting *M. tuberculosis* in the CSF is 79.5% — lower than with peripheral samples — but the specificity of CSF Xpert MTB/RIF is high (95.8-99.6%)[64].

Neither a negative tuberculin skin test nor a negative IFNγ release assay can exclude tuberculosis in individuals with HIV infection, especially if $CD4^+$ cell counts are <200 cells/mm^3 (REF. 65). Repeated, large-volume lumbar punctures are necessary to increase the possibility of detecting the organism, and the sensitivity of the Xpert MTB/RIF assay has been shown to increase if the lumbar puncture sample is concentrated[58,64].

In some cases, the diagnosis is made by clinical and radiographic findings rather than by laboratory confirmation. CSF analysis routinely shows a low CSF glucose level (<70% of corresponding serum glucose), elevated protein level, and a lymphocytic pleocytosis (>20 cells/mm^3)[66]. Basilar exudates, arachnoiditis, tuberculomas, and meningeal enhancement can be seen on MRI. Typical clinical signs of meningitis, such as fever, headache, nausea and/or vomiting, altered mental status, meningismus, papilloedema, and/or cranial nerve involvement are seen in more than 50% of patients[67]. In a cohort study of 141 patients with tuberculous meningitis, prominent signs — such as basal exudates (seen in 27% of the cohort), tuberculomas (18%), hydrocephalus (19%), optochiasmatic arachnoiditis (9%) and spinal arachnoiditis (3%) — were relatively common[67].

Interestingly, in the same cohort, 31% of all patients (that is, patients with or without HIV infection) with tuberculous meningitis developed IRIS; however, patients with HIV were at a starkly increased risk of developing IRIS (85%). It should be noted that all of these patients started ART between 2 weeks and 2 months after diagnosis of tuberculous meningitis, which could have contributed to the high rate of IRIS seen in the study[67].

Treatment

Treatment of tuberculous meningitis is similar regardless of HIV status. According to AIDSinfo (see AIDSinfo), an NIH-funded centre for disseminating information about HIV and AIDS, four-drug therapy with isoniazid, pyrazinamide, ethambutol, and rifampin should be maintained for an induction phase of 2 months[68]. When treating HIV-positive patients, it is important to note that rifampin can alter levels and bioavailability of several antiretroviral drugs through activation of the cytochrome P450 pathway, UDP-glucuronosyltransferase 1–1 enzymes, and

Box 1 | **Treatment of cerebral toxoplasmosis**

Induction therapy

This phase should consist of triple therapy with the combination of the drugs below; treatment should last 1–2 weeks beyond resolution of clinical manifestations.

- Pyrimethamine 200 mg on the first day, then 75–100 mg daily
- Sulfadiazine 1–1.5 g four times daily
- Folinic acid 10–50 mg daily

Maintenance therapy

Maintenance therapy is mandatory if $CD4^+$ cell count remains <100 cells/mm^3. The use of combination therapy is suggested below:

- Pyrimethamine 25–50 mg daily
- Sulfadiazine 0.5–1.0 g four times daily
- In addition, supplementary folinic acid 10–50 mg daily

In case of sulfadiazine allergy, substitute sulfadiazine with clindamycin 600–1200 mg intravenously four times daily for initial therapy, and 450–600 mg orally four times daily for maintenance.

These recommendations are based on guidelines by AIDS*info*[68].

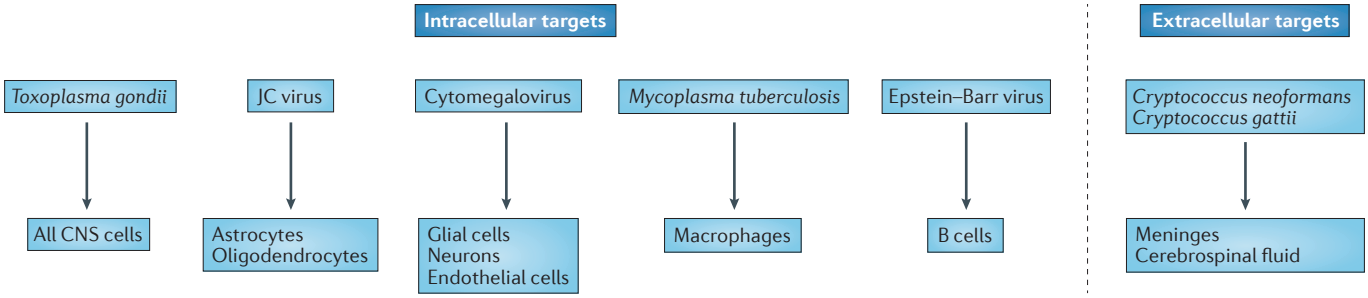


Figure 5 | **Cellular tropism of organisms causing opportunistic infections in the CNS.** The major HIV-associated opportunistic infections preferentially infect specific cell types in the CNS, a phenomenon referred to as cellular tropism.

ATP-binding cassette transporter P-glycoprotein; the use of rifampin in combination with protease inhibitors should not, therefore, be recommended.[69] In patients on an HIV treatment regimen based on a protease inhibitor, rifabutin (another member of the rifamycin family) is the preferred antitubercular drug, and combination of efavirenz and rifampin should be used as a second-line treatment[69,70]. After the induction phase, isoniazid and rifampin or rifambutin should be continued for at least 9–12 months, and longer if $CD4^+$ cells do not rise above 200 cells/mm^3 (REF. 54).

Adjunctive treatment. Adjunctive corticosteroids can reduce the risk of death in tuberculous meningitis by 30%[71]: in a randomized, controlled trial that involved 545 patients with tuberculous meningitis, including both HIV-infected and uninfected individuals, the benefit of corticosteroids was limited to reduced mortality, and there was no significant decrease in the proportion of severely disabled individuals[71].

A smaller study of 253 patients assessed the effect of timing of ART in relation to antituberculous therapy, including corticosteroids. During the 1-year follow-up, immediate initiation of ART did not improve outcomes compared with ART deferred for 2 months[72]. Thus, delaying of ART initiation by up to 8 weeks is recommended for patients with HIV-associated tuberculous, because it can prevent IRIS.

Challenges. Mortality from HIV-associated tuberculous meningitis exceeds 50%, which is roughly double that among patients without HIV infection. Even with the addition of ART, mortality has not improved[55]. Worldwide, about 3.6% of tuberculosis infections are resistant to isoniazid and rifampin (termed multidrug-resistant tuberculosis)[63]. Moreover, some extensively drug-resistant strains of *M. tuberculosis* that are also resistant to fluoroquinolones and second-line injectable drugs have been found in at least 84 countries since 2013 (REF. 64). Not surprisingly, multidrug-resistant HIV-associated tuberculous meningitis has an extremely high mortality rate. The multi-drug resistant infections are of particular concern in resource-poor settings, because the cost of treatment in multi-drug resistant tuberculous meningitis is 100-fold higher than the standard or second-line treatments[73,74].

Cryptococcal meningitis

Cryptococcal meningitis is a fungal infection most commonly caused by *Cryptococcus neoformans* or, more rarely, *Cryptococcus gattii*. Cryptococcus is a ubiquitous environmental yeast found in soil and bird droppings, typically acquired through inhalation of spores. Initial infection with *C. neoformans* can lead to a primary pulmonary infection, latent infection (asymptomatic cryptococcal antigenaemia), or disseminated infection with a predilection for the CNS (FIG. 2d).

HIV-associated cryptococcal meningitis has a high global burden. For example, in Sub-Saharan Africa, where mortality from AIDS is in excess of 790,000 deaths per year and accounts for nearly 66% of the global HIV mortality estimate[75], HIV-associated cryptococcal meningitis is the leading type of CNS opportunistic infection, and accounts for 15–20% of deaths attributed to HIV-associated opportunistic infections[76].

Patients with cryptococcal meningitis typically present with subacute symptoms over a 2-4-week period, often complaining of headache, lethargy, fever and/or malaise[77]. Classic meningeal signs, such as a stiff neck, occurs in only a quarter of patients. 25% of patients will present with altered mental status, which confers poor prognosis[78,77]. In specific populations, mortality in HIV-associated cryptococcal meningitis can reach 70%[76].

In HIV-infected individuals, cryptococcal meningitis occurs in the setting of severe immune suppression, often with $CD4^+$ cell counts of <50 cells/mm^3, although rare cases of $CD4^+$ cell counts >200 cells/mm^3 have been reported (FIG. 1). In one study conducted in Cape Town, South Africa, a positive cryptococcal antigen titre ≥1 in patients with no history of cryptococcal meningitis and $CD4^+$ cell counts ≤100 cells/μl was 100% sensitive and 96% specific for predicting the development of cryptococcal meningitis during the first year of ART[79].

A temporal association has been seen between asymptomatic cryptococcal antigen titres and death[80]. In one Ugandan cohort, positive cryptococcal antigen titres were present for a mean of 22 days before the onset of CNS or non-neurological symptoms of cryptococcal disease[80]. Cryptococcal antigenaemia was shown to increase the risk of mortality in asymptomatic patients by more than fourfold in one Ugandan cohort[81] and by more than threefold in a Cape Town cohort[79]. A subsequent follow-up trial conducted in Tanzania and Zambia

showed that early screening for and treatment of cryptococcal antigenaemia reduces mortality by 30%, and that in patients with HIV, cryptococcal antigens in the serum are associated with an almost threefold increase in risk of mortality, regardless of $CD4^+$ cell count, even after receiving gold-standard therapy[82].

A mouse model study of cryptococcal infections demonstrated that clearance of cryptococcus relies on robust $CD4^+$ cell responses and the production of cytokines, such as IFNγ, that are secreted by type 1 T_H cells[83]. In HIV-positive patients, cryptococcal infections often result in proinflammatory cytokine and type 2 T_H cell response, which is associated with higher mortality[84]. Acute mortality from cryptococcal meningitis has been directly correlated with CSF fungal burden, altered mental status at presentation, and the rate of infection clearance[78].

Diagnosis

At diagnosis, HIV-associated cryptococcal meningitis differs notably from its non-HIV counterpart in that the inflammatory response in the CSF is weaker, fungal burdens are larger, and the number of mass lesions is lower[76].

Antigen detection in the CSF. Diagnosis of cryptococcal meningitis is made primarily on the basis of detecting cryptococcal antigen in the CSF, a method that has a high sensitivity (92–100%) and specificity (83–98%). Change in antigen titre does not have a clear correlation with prognosis[77,85]. Although rarely used in resource-rich settings, India ink staining of the CSF yields approximately 75–86% sensitivity, and is used as an adjunct assay in clinical practice in countries where health-care resources are limited[85–87]. In Africa, the antigen is commonly detected by the latex agglutination assay, which has a sensitivity and specificity of >99%, but the price of reagents and extensive laboratory infrastructure required for this assay can make costs of this method prohibitive. Lateral flow immunochromatographic assay has a sensitivity and specificity >99%, and has therefore been used as an alternative fast and low-cost test: the result is ready in less than 10 min, with a price of US$2 per test[87]. Diagnostic lumbar puncture in suspected cryptococcal meningitis can reveal pleocytosis, high CSF protein, increased CSF pressure and communicating and even obstructive hydrocephalus in medically refractory cases.

Neuroimaging. Although space-occupying mass lesions in HIV-associated cryptococcal meningitis are uncommon, they have been reported in patients with $CD4^+$ cell counts of <50 cells/mm^3, and are found in up to a quarter of all patients[88–90]. Initial brain MRI findings are normal in 2–8% of patients, and CT findings are normal in 47% of patients[89,90]. MRI is more sensitive than CT at revealing the key radiological features associated with cryptococcal meningitis: intracerebral masses, dilated Virchow–Robin spaces, cortical and lacunar infarcts, pseudocysts[91,92], hydrocephalus, cerebritis and/or meningitis[89,90] (FIG. 3e). Less commonly, focal lesions in the midbrain, corpus callosum or cerebellum are seen on MRI[91]. Lacunar strokes are present in up to 20% of patients, and cortical strokes are equally common. These ischaemic lesions are often located in the small penetrating branches of the major cerebral arteries[90,91].

Elevated CSF pressure

Elevated CSF pressure is present in 50–75% of patients with cryptococcal meningitis, and elevated opening pressures >47 cmH20 have been associated with the development of papilloedema in these patients[78,93]. Elevated CSF opening pressure confers poor prognosis; nearly 30% of patients who have normal opening pressure at diagnosis will eventually develop intracranial hypertension[93,94]. In a study published in 2016, 58% of these patients required serial lumbar punctures for the relief of intracranial hypertension, and 45% of them ended up needing ventriculoperitoneal shunt procedures[93]. In this study, survival of the patients who required shunting was 54% at 1 year[93]. Management of increased intracranial hypertension with repeat lumbar punctures is associated with decreased mortality, and even a single therapeutic lumbar puncture has been associated with a 69% improvement in survival[78,93,95].

Immune reconstitution inflammatory syndrome

Paradoxical cryptococcal IRIS has been reported in 10–45% of ART-naive HIV-positive patients with cryptococcal meningitis, and approximately 60% of IRIS cases occur within the first month of ART[91,96]. Manifestations of cryptococcal IRIS vary, and many patients get clinically worse after an initial period of stabilization or improvement on therapy. MRI findings typically show leptomeningeal enhancement and, if present, peri-lesional enhancement and oedema[91]. IRIS is more common in patients who fail to mount an initial pleocytosis (<25 cells/μl), protein, and IFNγ responses at the diagnosis of cryptococcal meningitis[97].

Interestingly, in the Cryptococcal Optimal ART Timing (COAT) trial, patients who had received early ART and did not show CSF pleocytosis at diagnosis had 18% higher CSF pleocytosis at day 14 of amphotericin therapy than did patients with delayed ART; moreover, the early ART group had increased mortality[98]. This finding suggests that an unknown immune-mediated mechanism contributes to the excess mortality in early ART patients. Further analysis of the COAT cohort showed that excess mortality in the early ART group was associated with an increased immune response involving macrophages and type 2 T_H cells and increased levels of chemokine MIP-1-α and cytokines IL-13, IL-4 and IL-17 (REF. 98). These results are in line with previous findings that demonstrated the development of IRIS to be associated with the expression of chemokines MCP-1 and MIP-1-α in the CSF, leading to the hypothesis that trafficking of $CD8^+$ T cells and myeloid cells in response to these chemokines results in the aberrant immune response[84].

Treatment

The treatment of cryptococcal meningitis consists of three phases: induction, consolidation, and maintenance therapy. For HIV-positive patients, AIDSinfo

recommends induction therapy for cryptococcal meningitis that consists of combination antifungal therapy with amphotericin B (0.7–1 mg/kg daily) plus flucytosine (100 mg/kg daily), administered in four doses divided over ≥2 weeks[99,100]. This therapy has been shown to be more effective than combination therapy with amphotericin B and fluconazole, or amphotericin B alone[99]. Consolidation therapy, typically with fluconazole, is recommended for at least 8 weeks. Maintenance therapy typically consists of a lower dose (200 mg) of fluconazole for at least 1 year[100], after which maintenance can be terminated if viral load is suppressed and $CD4^+$ cell counts are >100 cells/mm^3 (REF. 100). A fall in $CD4^+$ cell counts or occurrence of HIV viraemia should prompt reinitiation of maintenance therapy.

In the COAT trial, a delay of ≥5 weeks in ART initiation after the start of cryptococcal treatment in ART-naive HIV-positive patients decreased the risk of all-cause mortality at 26 days by one-third compared with early (within 1–2 weeks) ART initiation (30% versus 45%)[98]. This decrease was shown across all subgroup analyses, including patients at high risk of death, such as those with altered mental status and lower $CD4^+$ cell count (<50 cells/mm^3), as well as those at lower risk of death, such as patients with lower CSF fungal burden[98].

Itraconazole can be used as an alternative to fluconazole for maintenance therapy (at the same dosage as fluconazole), but has been found to be inferior (class C, level I evidence)[101]. Newer azoles, such as voriconazole or posaconazole, have been used for induction and maintenance therapy, but data on their effectiveness are limited[94,102]. New anticryptococcal agents to prevent the activation of the CYP51 pathway, which can increase fluconazole resistance, are on the horizon, with phase I studies underway[103].

The use of off-label dexamethasone has become increasingly common in clinical practice, but a recent double-blind placebo-controlled trial reported an increased mortality in the dexamethasone group (47%) compared with the placebo group (41%)[104]. Moreover, disability and adverse events were more common in the dexamethasone group[104]. It should be noted that the use of steroids in the primary treatment of cryptococcal meningitis is a topic that is independent of and should not be confused with the use of steroids in the setting of cryptococcal-IRIS.

Cytomegalovirus infection

Neurological diseases caused by cytomegalovirus are rare, but are often debilitating and potentially fatal. The virus can cause an encephalitis, polyradiculitis or retinitis. Myelitis has also been described, and can be concurrent with encephalitis or polyradiculitis. All of these manifestations occur almost exclusively in patients with a severely suppressed immune system, most commonly with $CD4^+$ cell counts of <50 cells/mm^3 (REF. 105) (FIG. 1). Serum can be positive for cytomegalovirus on PCR testing in patients with low $CD4^+$ cell counts who do not have cytomegalovirus-associated neurological disease. Owing to the poor predictive value, screening for cytomegalovirus-mediated end-organ disease is not recommended[100].

Diagnosis

PCR testing of CSF for cytomegalovirus is recommended in patients who exhibit a clinical syndrome consistent with neurologically-involved cytomegalovirus infection. Sensitivity of PCR testing is 95% and specificity 85%[75].

Clinical presentations

Encephalitis. Cytomegalovirus encephalitis presents subacutely with symptoms that are often less focal than in other opportunistic infections. Lethargy, confusion, gait impairment and headaches are common presenting symptoms, and can be accompanied by seizures, cranial nerve palsies, or ataxia[105,106]. Prior or concurrent cytamegalovirus infection at extra-neural sites (such as colitis and pneumonitis) has been described. Imaging with MRI reveals a linear periventricular hyperintensity, often symmetrical and with gadolinium enhancement (FIG. 3d). A normal MRI does not rule out cytomegalovirus encephalitis. CSF testing commonly reveals neutrophilic pleocytosis (with a negative gram stain) and elevated protein levels, although abnormalities are not always seen[106].

Polyradiculitis. Cytomegalovirus polyradiculitis presents with lower extremity sensory loss and motor weakness combined with areflexia and urinary retention. If polyradiculitis is accompanied by a myelopathy, reflexes may be brisk. The presentation is often acute or subacute and the symptoms are often severe, with paraplegia being common. Similar to cytomegalovirus-associated encephalitis, brain MRI scans can be normal; however, post-gadolinium images can show enhancement in several nerve roots, which is associated with leptomeningeal involvement on histopathological samples (FIG. 2c). CSF examination often reveals both neutrophilic predominant pleocytosis and elevated protein levels.

Retinitis. Cytomegalovirus-associated retinitis often presents with floaters or decreased peripheral or central vision[107]. Cytomegalovirus retinitis is much more common than the other neurologic manifestations of cytomegalovirus infection, and is estimated to account for approximately 25% of AIDS-related cytomegalovirus disease[108,109]. Cytomegalovirus-related vision loss commonly results from retinal necrosis, although various combinations of retinal detachment, macular oedema and papillitis can also occur (FIG. 3d). Retinitis is typically diagnosed by funduscopic findings of haemorrhagic infarction, perivascular sheathing, and retinal opacification, combined with a detection of the virus in serum by PCR[107].

Treatment

The first-line treatment for cytomegalovirus encephalitis or polyradiculitis is intravenous ganciclovir, 5 mg/kg twice daily, in combination with foscarnet, 90 mg/kg twice daily, typically for 3–6 weeks[109]. If the virus is resistant to ganciclovir, prolonged foscarnet therapy is needed. The clinical response to therapy and the CSF PCR titre (at least one negative test result) can guide the decision to transition therapy of post-primary induction with oral

valganciclovir, 900 mg twice daily. However, the role of valganciclovir in cytomegalovirus encephalitis has not been fully established, and optimization of ART continues to be a mainstay of gold-standard care. Owing to the high morbidity and mortality associated with cytomegalovirus encephalitis, arguments have been presented for the initiation of intravenous foscarnet plus ganciclovir, despite the potential toxicity[100].

Treatment of cytomegalovirus retinitis depends on the location of retinitis and whether systemic disease is concurrent. Oral valganciclovir, 900 mg twice daily for 3 weeks is the preferred induction treatment, followed by 900 mg once daily[110]. Lesions that are centrally located pose a greater risk to vision loss, and are often treated with a local therapy such as an ocular implant or intravitreal therapy, although intravitreal therapy has been associated with both retinitis progression and severe loss of visual field[111]. When the local interventional therapy is given, oral valganciclovir is used concurrently to prevent cytomegalovirus infection and protect the other eye. Intravitreal triamcinolone acetonide intravitreous injections can be used for immune recovery uveitis[112].

Conclusions

Opportunistic infections that are common in HIV-infected patients have typical clinical and radiological presentations that are often sufficient to establish the diagnosis. Establishing the correct diagnosis is critical, as the treatment is specific for each condition. In PML, cryptococcal meningitis and tuberculous meningitis, the microbial organism underlying the disease can be detected in the CSF. However, *T. gondii* is cell-associated, and the sensitivity of CSF testing is variable. Patients who are seropositive for toxoplasma but for whom the diagnosis of a mass lesion is not clear, empirical toxoplasmosis treatment is warranted before brain biopsy is considered.

Early initiation of ART after the diagnosis of an opportunistic infection has the advantage of improving immune defense against the infection, however, early ART initiation also carries the risk of developing IRIS. Regardless of the ART timing, IRIS is always a concern, and steroids should be used if IRIS is severe.

Challenges in the management of opportunistic infections include the fact that most recommendations for treatment are made in the absence of controlled studies and/or phase II or III trials. Other challenges include lack of treatment for the elimination of bradyzoites in toxoplasmosis, lack of effective antiviral drugs to treat PML, and the requirement of long-term therapy for tuberculosis, which must be strictly adhered to. Moreover, corticosteroid treatment of IRIS is a double-edged sword; hence, better drugs are necessary. It remains unknown whether patients with opportunistic infections, despite effective treatment, are at greater risk of developing HIV-associated neurocognitive deficits associated with the infiltration of HIV-infected inflammatory infiltrates. Effective and continued ART therapy to maintain stable CD4+ cell counts >200 cells/mm^3 and maintain viral suppression is the best strategy to prevent the majority of CNS opportunistic infections in HIV-infected individuals.

1. Wong, A. A., Pabbaraju, K., Wong, S. & Tellier, R. Development of a multiplex real-time PCR for the simultaneous detection of herpes simplex and varicella zoster viruses in cerebrospinal fluid and lesion swab specimens. *J. Virol. Methods* **229**, 16–23 (2016).
2. Garvey, L. *et al.* HIV-associated central nervous system diseases in the recent combination antiretroviral therapy era. *Eur. J. Neurol.* **18**, 527–534 (2011).
3. Lanoy, E. *et al.* Survival after neuroAIDS: association with antiretroviral CNS Penetration-Effectiveness score. *Neurology* **76**, 644–651 (2011).
4. Caniglia, E. C. *et al.* Antiretroviral penetration into the CNS and incidence of AIDS-defining neurologic conditions. *Neurology* **83**, 134–141 (2014).
5. Ferguson, D. J. & Hutchison, W. M. The host-parasite relationship of *Toxoplasma gondii* in the brains of chronically infected mice. *Virchows Arch. A Pathol. Anat. Histopathol.* **411**, 39–43 (1987).
6. Chew, W. K., Wah, M. J., Ambu, S. & Segarra, I. *Toxoplasma gondii*: determination of the onset of chronic infection in mice and the *in vitro* reactivation of brain cysts. *Exp. Parasitol.* **130**, 22–25 (2012).
7. McCabe, R. E., Brooks, R. G., Dorfman, R. F. & Remington, J. S. Clinical spectrum in 107 cases of toxoplasmic lymphadenopathy. *Rev. Infect. Dis.* **9**, 754–774 (1987).
8. Zhang, Y. H. *et al.* Activated microglia contribute to neuronal apoptosis in toxoplasmic encephalitis. *Parasit. Vectors* **7**, 372 (2014).
9. Luft, B. J. *et al.* Outbreak of central-nervous-system toxoplasmosis in western Europe and North America. *Lancet* **1**, 781–784 (1983).
10. Coelho, L. *et al.* Trends in AIDS-defining opportunistic illnesses incidence over 25 years in Rio de Janeiro, Brazil. *PLoS ONE* **9**, e98666 (2014).
11. Laing, R. B., Flegg, P. J., Brettle, R. P., Leen, C. L. & Burns, S. M. Clinical features, outcome and survival from cerebral toxoplasmosis in Edinburgh AIDS patients. *Int. J. STD AIDS* **7**, 258–264 (1996).
12. Jones, J. L., Kruszon-Moran, D., Rivera, H. N., Price, C. & Wilkins, P. P. *Toxoplasma gondii* seroprevalence in the United States 2009–2010 and comparison with the past two decades. *Am. J. Trop. Med. Hyg.* **90**, 1135–1139 (2014).
13. Montoya, J. G. & Liesenfeld, O. Toxoplasmosis. *Lancet* **363**, 1965–1976 (2004).
14. Antinori, A. *et al.* Prevalence, associated factors, and prognostic determinants of AIDS-related toxoplasmic encephalitis in the era of advanced highly active antiretroviral therapy. *Clin. Infect. Dis.* **39**, 1681–1691 (2004).
15. Leon Ruiz, M. A. Novel case of solitary cerebral toxoplasmosis mimicking glioblastoma as the first presentation of HIV. *J. Clin. Neurol.* **12**, 248–250 (2016).
16. Nath, A., Hobson, D. E. & Russell, A. Movement disorders with cerebral toxoplasmosis and AIDS. *Mov. Disord.* **8**, 107–112 (1993).
17. Mattos, J. P., Rosso, A. L., Correa, R. B. & Novis, S. A. Movement disorders in 28 HIV-infected patients. *Arq. Neuropsiquiatr.* **60**, 525–530 (2002).
18. Herrera Rubio, J., Farinas, M. C., Tejido, R., Garcia Palomo, J. D. & Tejido, R. [Aspecific chorioretinitis as initial manifestation of HIV infection and diffuse Toxoplasma encephalitis]. *Med. Clin. (Barc.)* **106**, 198–199 (in Spanish) (1996).
19. Gray, F. *et al.* Diffuse "encephalitic" cerebral toxoplasmosis in AIDS. Report of four cases. *J. Neurol.* **236**, 273–277 (1989).
20. de-la-Torre, A. *et al.* Clinical patterns of uveitis in two ophthalmology centres in Bogota, Colombia. *Clin. Exp. Ophthalmol.* **37**, 458–466 (2009).
21. Rodriguez, A. *et al.* Referral patterns of uveitis in a tertiary eye care center. *Arch. Ophthalmol.* **114**, 593–599 (1996).
22. Crosson, J. N., Laird, P. W., Grossniklaus, H. E. & Hendrick, A. M. Toxoplasma chorioretinitis diagnosed by histopathology in a patient with AIDS. *Retin. Cases Brief Rep.* **9**, 162–163 (2015).
23. Cochereau-Massin, I. *et al.* Ocular toxoplasmosis in human immunodeficiency virus-infected patients. *Am. J. Ophthalmol.* **114**, 130–135 (1992).
24. Furtado, J. M., Toscano, M., Castro, V. & Rodrigues, M. W. Roth spots in ocular toxoplasmosis. *Ocul. Immunol. Inflamm.* http://dx.doi.org/10.3109/09273948.2015.1047035 (2015).
25. Gagliuso, D. J., Teich, S. A., Friedman, A. H. & Orellana, J. Ocular toxoplasmosis in AIDS patients. *Trans. Am. Ophthalmol. Soc.* **88**, 63–86 (1990).
26. Belaz, S., Gangneux, J. P., Dupretz, P., Guiguen, C. & Robert-Gangneux, F. A. 10-year retrospective comparison of two target sequences, REP-529 and B1, for *Toxoplasma gondii* detection by quantitative PCR. *J. Clin. Microbiol.* **53**, 1294–1300 (2015).
27. Colombo, F. A. *et al.* Diagnosis of cerebral toxoplasmosis in AIDS patients in Brazil: importance of molecular and immunological methods using peripheral blood samples. *J. Clin. Microbiol.* **43**, 5044–5047 (2005).
28. Meira, C. S. *et al.* IgG4 specific to *Toxoplasma gondii* excretory/secretory antigens in serum and/or cerebrospinal fluid support the cerebral toxoplasmosis diagnosis in HIV-infected patients. *J. Immunol. Methods* **395**, 21–28 (2013).
29. Marra, C. M., Krone, M. R., Koutsky, L. A. & Holmes, K. K. Diagnostic accuracy of HIV-associated central nervous system toxoplasmosis. *Int. J. STD AIDS* **9**, 761–764 (1998).
30. Mathews, C., Barba, D. & Fullerton, S. C. Early biopsy versus empiric treatment with delayed biopsy of non-responders in suspected HIV-associated cerebral toxoplasmosis: a decision analysis. *AIDS* **9**, 1243–1250 (1995).
31. Neville, A. J. *et al.* Clinically available medicines demonstrating anti-toxoplasma activity. *Antimicrob. Agents Chemother.* **59**, 7161–7169 (2015).
32. Vidadala, R. S. *et al.* Development of an orally available and central nervous system (CNS) penetrant *Toxoplasma gondii* calcium-dependent protein kinase 1 (TgCDPK1) inhibitor with minimal human ether-a-go-go-related gene (hERG) activity for the treatment of toxoplasmosis. *J. Med. Chem.* **59**, 6531–6546 (2016).

33. Gorelik, L. *et al.* Anti-JC virus antibodies: implications for PML risk stratification. *Ann. Neurol.* **68**, 295–303 (2010).
34. Engsig, F. N. *et al.* Incidence, clinical presentation, and outcome of progressive multifocal leukoencephalopathy in HIV-infected patients during the highly active antiretroviral therapy era: a nationwide cohort study. *J. Infect. Dis.* **199**, 77–83 (2009).
35. Fong, I. W. & Toma, E. The natural history of progressive multifocal leukoencephalopathy in patients with AIDS. Canadian PML Study Group. *Clin. Infect. Dis.* **20**, 1305–1310 (1995).
36. Worthley, D. L., Sandhu, A. & Norton, G. Progressive multifocal leukoencephalopathy: a confused woman, an ambitious virus and an unusual MRI. *Intern. Med. J.* **32**, 266–267 (2002).
37. Saito, H., Sakai, H., Fujihara, K., Fujihara, K. & Itoyama, Y. Progressive multifocal leukoencephalopathy in a patient with acquired immunodeficiency syndrome (AIDS) manifesting Gerstmann's syndrome. *Tohoku J. Exp. Med.* **186**, 169–179 (1998).
38. Willott, R. H., Sunman, W. & Munshi, S. K. Progressive multifocal leukoencephalopathy masquerading as cerebellar infarction. *Age Ageing* **45**, 564–565 (2016).
39. Stockhammer, G. *et al.* Progressive multifocal leukoencephalopathy presenting with an isolated focal movement disorder. *Mov. Disord.* **15**, 1006–1009 (2000).
40. Jeyaraman, V. A. *et al.* Isolated cortical blindness without simultaneous neurological involvement in progressive multifocal leukoencephalopathy in a patient with human immune deficiency virus infection. *J. Ophthalmic Inflamm. Infect.* **3**, 3 (2013).
41. Boster, A. L. *et al.* Lessons learned from fatal progressive multifocal leukoencephalopathy in a patient with multiple sclerosis treated with natalizumab. *JAMA Neurol.* **70**, 398–402 (2013).
42. Koralnik, I. J. *et al.* JC virus granule cell neuronopathy: a novel clinical syndrome distinct from progressive multifocal leukoencephalopathy. *Ann. Neurol.* **57**, 576–580 (2005).
43. Casado, J. L. *et al.* Continued declining incidence and improved survival of progressive multifocal leukoencephalopathy in HIV/AIDS patients in the current era. *Eur. J. Clin. Microbiol. Infect. Dis.* **33**, 179–187 (2014).
44. Khanna, N. *et al.* Incidence and outcome of progressive multifocal leukoencephalopathy over 20 years of the Swiss HIV Cohort Study. *Clin. Infect. Dis.* **48**, 1459–1466 (2009).
45. Tan, K., Roda, R., Ostrow, L., McArthur, J. & Nath, A. PML-IRIS in patients with HIV infection: clinical manifestations and treatment with steroids. *Neurology* **72**, 1458–1464 (2009).
46. Clifford, D. B. *et al.* Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol.* **9**, 438–446 (2010).
47. Berger, J. R. *et al.* PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. *Neurology* **80**, 1430–1438 (2013).
48. Kuker, W. *et al.* Progressive multifocal leukoencephalopathy: value of diffusion-weighted and contrast-enhanced magnetic resonance imaging for diagnosis and treatment control. *Eur. J. Neurol.* **13**, 819–826 (2006).
49. Astrom, K. E., Mancall, E. L. & Richardson, E. P. Jr. Progressive multifocal leuko-encephalopathy; a hitherto unrecognized complication of chronic lymphatic leukaemia and Hodgkin's disease. *Brain* **81**, 93–111 (1958).
50. Marra, C. M. *et al.* A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. *AIDS* **16**, 1791–1797 (2002).
51. Aksamit, A. J. Treatment of non-AIDS progressive multifocal leukoencephalopathy with cytosine arabinoside. *J. Neurovirol.* **7**, 386–390 (2001).
52. Clifford, D. B. *et al.* A study of mefloquine treatment for progressive multifocal leukoencephalopathy: results and exploration of predictors of PML outcomes. *J. Neurovirol.* **19**, 351–358 (2013).
53. Cettomai, D. & McArthur, J. C. Mirtazapine use in human immunodeficiency virus-infected patients with progressive multifocal leukoencephalopathy. *Arch. Neurol.* **66**, 255–258 (2009).
54. Blumberg, H. M. *et al.* American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. *Am. J. Respir. Crit. Care Med.* **167**, 603–662 (2003).
55. Kwan, C. K. & Ernst, J. D. HIV and tuberculosis: a deadly human syndemic. *Clin. Microbiol. Rev.* **24**, 351–376 (2011).
56. Jarvis, J. N. *et al.* Adult meningitis in a setting of high HIV and TB prevalence: findings from 4961 suspected cases. *BMC Infect. Dis.* **10**, 67 (2010).
57. Simmons, C. P. *et al.* Pretreatment intracerebral and peripheral blood immune responses in Vietnamese adults with tuberculous meningitis: diagnostic value and relationship to disease severity and outcome. *J. Immunol.* **176**, 2007–2014 (2006).
58. Marais, S., Pepper, D. J., Marais, B. J. & Torok, M. E. HIV-associated tuberculous meningitis—diagnostic and therapeutic challenges. *Tuberculosis (Edinb.)* **90**, 367–374 (2010).
59. Marais, S. *et al.* Tuberculous meningitis: a uniform case definition for use in clinical research. *Lancet Infect. Dis.* **10**, 803–812 (2010).
60. Thwaites, G. E. *et al.* Comparison of conventional bacteriology with nucleic acid amplification (amplified mycobacterium direct test) for diagnosis of tuberculous meningitis before and after inception of antituberculosis chemotherapy. *J. Clin. Microbiol.* **42**, 996–1002 (2004).
61. Raja, S. *et al.* Technology for automated, rapid, and quantitative PCR or reverse transcription-PCR clinical testing. *Clin. Chem.* **51**, 882–890 (2005).
62. Boehme, C. C. *et al.* Rapid molecular detection of tuberculosis and rifampin resistance. *N. Engl. J. Med.* **363**, 1005–1015 (2010).
63. Zignol, M. *et al.* Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007–2010. *Bull. World Health Organ.* **90**, 111–119D (2012).
64. World Health Organization. Multidrug-resistant tuberculosis *(MDR-TB): 2013 Update*. http://www.who.int/tb/challenges/mdr/MDR_TB_FactSheet.pdf (2013).
65. Syed Ahamed Kabeer, B. *et al.* Role of interferon γ release assay in active TB diagnosis among HIV infected individuals. *PLoS ONE* **4**, e5718 (2009).
66. Kaur, H. *et al.* Prospective analysis of 55 cases of tuberculosis meningitis (TBM) in North India. *J. Clin. Diagn. Res.* **19,** DC15–DC19 (2015).
67. Singh, A. K. *et al.* Paradoxical reaction in tuberculous meningitis: presentation, predictors and impact on prognosis. *BMC Infect. Dis.* **16**, 306 (2016).
68. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *AIDSinfo*. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf (accessed July 31 2016).
69. Regazzi, M., Carvalho, A. C., Villani, P. & Matteelli, A. Treatment optimization in patients co-infected with HIV and *Mycobacterium tuberculosis* infections: focus on drug-drug interactions with rifamycins. *Clin. Pharmacokinet.* **53**, 489–507 (2014).
70. Luetkemeyer, A. F. Current issues in the diagnosis and management of tuberculosis and HIV coinfection in the United States. *Top. HIV Med.* **18**, 143–148 (2010).
71. Thwaites, G. E. *et al.* Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N. Engl. J. Med.* **351**, 1741–1751 (2004).
72. Torok, M. E. *et al.* Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)—associated tuberculous meningitis. *Clin. Infect. Dis.* **52**, 1374–1383 (2011).
73. Daikos, G. L., Cleary, T., Rodriguez, A. & Fischl, M. A. Multidrug-resistant tuberculous meningitis in patients with AIDS. *Int. J. Tuber. Lung Dis.* **7**, 394–398 (2003).
74. Patel, V. B. *et al.* Multidrug-resistant tuberculous meningitis in KwaZulu-Natal, South Africa. *Clin. Infect. Dis.* **38**, 851–856 (2004).
75. Dodt, K. K. *et al.* Development of cytomegalovirus (CMV) disease may be predicted in HIV-infected patients by CMV polymerase chain reaction and the antigenemia test. *AIDS* **11**, F21–F28 (1997).
76. Rhein, J. *et al.* Efficacy of adjunctive sertraline for the treatment of HIV-associated cryptococcal meningitis: an open-label dose-ranging study. *Lancet Infect. Dis.* **16**, 809–818 (2016).
77. Albarillo, F. & O'Keefe, P. Opportunistic neurologic infections in patients with acquired immunodeficiency syndrome (AIDS). *Curr. Neurol. Neurosci. Rep.* **16**, 10 (2016).
78. Jarvis, J. N. *et al.* Determinants of mortality in a combined cohort of 501 patients with HIV-associated cryptococcal meningitis: implications for improving outcomes. *Clin. Infect. Dis.* **58**, 736–745 (2014).
79. Jarvis, J. N. *et al.* Screening for cryptococcal antigenemia in patients accessing an antiretroviral treatment program in South Africa. *Clin. Infect. Dis.* **48**, 856–862 (2009).
80. French, N. *et al.* Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. *AIDS* **16**, 1031–1038 (2002).
81. Liechty, C. A. *et al.* Asymptomatic serum cryptococcal antigenemia and early mortality during antiretroviral therapy in rural Uganda. *Trop. Med. Int. Health* **12**, 929–935 (2007).
82. Mfinanga, S. *et al.* Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial. *Lancet* **385**, 2173–2182 (2015).
83. Hardison, S. E. *et al.* Pulmonary infection with an interferon-γ-producing *Cryptococcus neoformans* strain results in classical macrophage activation and protection. *Am. J. Pathol.* **176**, 774–785 (2010).
84. Boulware, D. R. *et al.* Human immune response varies by the degree of relative cryptococcal antigen shedding. *Open Forum Infect. Dis.* **3**, ofv194 (2016).
85. Tan, I. L., Smith, B. R., von Geldern, G., Mateen, F. J. & McArthur, J. C. HIV-associated opportunistic infections of the CNS. *Lancet Neurol.* **11**, 605–617 (2012).
86. Kammalac Ngouana, T. *et al.* Cryptococcal meningitis in Yaounde (Cameroon) HIV infected patients: diagnosis, frequency and *Cryptococcus neoformans* isolates susceptibility study to fluconazole. *J. Mycol. Med.* **25**, 11–16 (2015).
87. Boulware, D. R. *et al.* Multisite validation of cryptococcal antigen lateral flow assay and quantification by laser thermal contrast. *Emerg. Infect. Dis.* **20**, 45–53 (2014).
88. Troncoso, A. *et al.* CNS cryptococcoma in an HIV-positive patient. *J. Int. Assoc. Physicians AIDS Care (Chic.)* **1**, 131–133 (2002).
89. Charlier, C. *et al.* Cryptococcal neuroradiological lesions correlate with severity during cryptococcal meningoencephalitis in HIV-positive patients in the HAART era. *PLoS ONE* **3**, e1950 (2008).
90. Loyse, A. *et al.* Neurological, visual, and MRI brain scan findings in 87 South African patients with HIV-associated cryptococcal meningoencephalitis. *J. Infect.* **70**, 668–675 (2015).
91. Katchanov, J. *et al.* Cryptococcal meningoencephalitis relapse after an eight-year delay: an interplay of infection and immune reconstitution. *Int. J. STD AIDS* **26**, 912–914 (2015).
92. Offiah, C. E. & Naseer, A. Spectrum of imaging appearances of intracranial cryptococcal infection in HIV/AIDS patients in the anti-retroviral therapy era. *Clin. Radiol.* **71**, 9–17 (2016).
93. Cherian, J., Atmar, R. L. & Gopinath, S. P. Shunting in cryptococcal meningitis. *J. Neurosurgery* **125**, 177–186 (2016).
94. Chen, C. H. *et al.* Epidemiological characterization and prognostic factors in patients with confirmed cerebral cryptococcosis in central Taiwan. *J. Venom. Anim. Toxins Incl. Trop. Dis.* **21**, 12 (2015).
95. Rolfes, M. A. *et al.* The effect of therapeutic lumbar punctures on acute mortality from cryptococcal meningitis. *Clin. Infect. Dis.* **59**, 1607–1614 (2014).
96. Boulware, D. R. *et al.* Clinical features and serum biomarkers in HIV immune reconstitution inflammatory syndrome after cryptococcal meningitis: a prospective cohort study. *PLoS Med.* **7**, e1000384 (2010).
97. Boulware, D. R. *et al.* Paucity of initial cerebrospinal fluid inflammation in cryptococcal meningitis is associated with subsequent immune reconstitution inflammatory syndrome. *J. Infect. Dis.* **202**, 962–970 (2010).
98. Boulware, D. R. *et al.* Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N. Engl. J. Med.* **370**, 2487–2498 (2014).
99. Day, J. N. *et al.* Combination antifungal therapy for cryptococcal meningitis. *N. Engl. J. Med.* **368**, 1291–1302 (2013).
100. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.Cytomegalovirus disease (N-1). *AIDSinfo*. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf, (accessed August 4 2016).

101. Saag, M. S. *et al.* A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. *Clin. Infect. Dis.* **28**, 291–296 (1999).
102. Yao, Y. *et al.* Voriconazole: a novel treatment option for cryptococcal meningitis. *Infect. Dis. (Lond.)* **47**, 694–700 (2015).
103. Warrilow, A. G. *et al.* The investigational drug VT-1129 is a highly potent inhibitor of cryptococcus species CYP51 but only weakly inhibits the human enzyme. *Antimicrob. Agents Chemother.* **60**, 4530–4538 (2016).
104. Beardsley, J. *et al.* Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. *N. Engl. J. Med.* **374**, 542–554 (2016).
105. Anduze-Faris, B. M. *et al.* Induction and maintenance therapy of cytomegalovirus central nervous system infection in HIV-infected patients. *AIDS* **14**, 517–524 (2000).
106. Silva, C. A. *et al.* Neurologic cytomegalovirus complications in patients with AIDS: retrospective review of 13 cases and review of the literature. *Rev. Inst. Med. Trop. Sao Paulo* **52**, 305–310 (2010).
107. Kuo, I. C., Kempen, J. H., Dunn, J. P., Vogelsang, G. & Jabs, D. A. Clinical characteristics and outcomes of cytomegalovirus retinitis in persons without human immunodeficiency virus infection. *Am. J. Ophthalmol.* **138**, 338–346 (2004).
108. Jabs, D. A. *et al.* Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: 1. Retinitis progression. *Ophthalmology* **111**, 2224–2231 (2004).
109. Mofenson, L. M. *et al.* Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. MMWR. Recommendations and reports: morbidity and mortality weekly report. *MMWR Recomm. Rep.* **58**, 1–166 (2009).
110. Martin, D. F. *et al.* A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. *N. Engl. J. Med.* **346**, 1119–1126 (2002).
111. Jabs, D. A., Ahuja, A., Van Natta, M., Dunn, J. P. & Yeh, S. Comparison of treatment regimens for cytomegalovirus retinitis in patients with AIDS in the era of highly active antiretroviral therapy. *Ophthalmology* **120**, 1262–1270 (2013).
112. Morrison, V. L. *et al.* Intravitreal triamcinolone acetonide for the treatment of immune recovery uveitis macular edema. *Ophthalmology* **114**, 334–339 (2007).
113. Alvarez-Uria, G., Naik, P. K., Pakam, R., Bachu, L. & Midde, M. Natural history and factors associated with early and delayed mortality in HIV-infected patients treated of tuberculosis under directly observed treatment short-course strategy: a prospective cohort study in India. *Interdiscip. Perspect. Infect. Dis.* **2012**, 502012 (2012).
114. Luma, H. N. *et al.* Tuberculous meningitis: presentation, diagnosis and outcome in hiv-infected patients at the douala general hospital, cameroon: a cross sectional study. *AIDS Res. Ther.* **10**, 16 (2013).
115. Xiao, J. *et al.* Spectrums of opportunistic infections and malignancies in HIV-infected patients in tertiary care hospital, China. *PLoS ONE* **8**, e75915 (2013).

Author contributions

A.N., L.N.B. and B.S. wrote the article and participated in reviewing and editing of the manuscript. All authors researched data for the article and provided substantial contribution to discussion of content.

Competing interests statement

The authors declare no competing interests.

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