Le Infezioni in Medicina, n. 1, 12-27, 2026
doi: 10.53854/liim-3401-2

Neurological Infections in HIV: A Case-Based Review for Clinicians

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Article received 16 December 2025 and accepted 22 January 2026

SUMMARY

Central Nervous System (CNS) disease remains a significant cause of morbidity and mortality in people with advanced HIV infection. This case-based review presents eight illustrative scenarios to demonstrate a structured clinical approach to common CNS manifestations in HIV in low-resource settings. The cases cover meningeal syndromes (cryptococcal and tuberculous meningitis), focal mass-like lesions (toxoplasmosis, tuberculoma, and primary CNS lymphoma), and diffuse or multifocal white matter disorders (HIV encephalopathy, progressive multifocal leukoencephalopathy, and cytomegalovirus encephalitis). Each case highlights key clinical reasoning steps, including interpretation of neuroimaging and cerebrospinal fluid analysis, and integration of serologic and molecular diagnostics. A syndromic framework is used to classify presentations and refine the differential diagnosis based on CD4 count, rate of progression, and radiological patterns. The review also discusses principles of management, including targeted antimicrobial or oncologic therapy, timing of antiretroviral therapy initiation, and the prevention and treatment of immune reconstitution inflammatory syndrome. Through these illustrative examples, the article provides a practical, context-appropriate guide to evaluating and managing HIV-associated CNS disease, particularly in settings where diagnostic resources and access to surgical interventions may be limited.

Keywords: tuberculosis, toxoplasmosis, progressive multifocal leukoencephalopathy, Cryptococcus, HIV.

INTRODUCTION

Central Nervous System (CNS) involvement represents one of the most severe and life-threatening complications of HIV infection, particularly among individuals with advanced immunosuppression [1]. Despite a significant decrease in opportunistic infections following the

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introduction of antiretroviral therapy (ART), CNS disorders continue to account for substantial morbidity and mortality worldwide, disproportionately affecting people in low- and middle-income countries (LMICs), where delayed HIV diagnosis, limited access to ART, and high prevalence of tuberculosis and other endemic infections remain significant challenges. Recent estimates suggest that CNS opportunistic infections contribute to 10–25% of AIDS-related deaths globally, with even higher burdens reported in sub-Saharan Africa and Southeast Asia [2]. CNS presentations can be protean, ranging from meningitis and encephalitis to focal mass lesions and diffuse white-matter disease, often complicating timely diagnosis.

The pathogenesis of CNS disease in HIV is multifactorial. Direct neuronal injury from HIV itself contributes to cognitive and motor dysfunction. At the same time, progressive immune deterioration predisposes patients to a broad spectrum of opportunistic infections and malignancies, including cryptococcosis, tuberculosis, toxoplasmosis, cytomegalovirus (CMV), progressive multifocal leukoencephalopathy (PML), and primary CNS lymphoma [3-8]. These disorders frequently share overlapping clinical and radiological features, making accurate differentiation challenging, especially in settings with restricted access to advanced neuroimaging and molecular diagnostics [9]. Moreover, the altered immune milieu of advanced HIV may produce atypical presentations, further complicating diagnostic algorithms.

Although ART has markedly improved survival, it has not eliminated CNS complications [10]. Many patients continue to present late in the course of infection, with CD4 counts well below 100 cells/μL, even in ART-accessible regions, resulting in persistent opportunities for opportunistic infections [11]. In addition, immune reconstitution inflammatory syndrome (IRIS) remains a significant clinical challenge, particularly in cryptococcal and tuberculous meningitis, requiring careful timing of ART initiation and corticosteroid administration [12-14].

This review adopts a syndromic, case-based framework to simplify the diagnosis and management of HIV-associated CNS disease, integrating clinical patterns, neuroimaging, and targeted laboratory testing. Through eight illustrative cases, it highlights practical diagnostic reasoning, context-specific therapy, and key management principles, while emphasizing the need to maintain a broad differential that includes common community-acquired CNS infections.

CASE 1: CRYPTOCOCCAL MENINGITIS

A woman living with HIV, with poor adherence to ART (CD4 count: 28 cells/μL, HIV Viral Load unavailable), presented with a 2-week history of progressive headache, vomiting, and visual blurring, accompanied by horizontal diplopia. Neurological examination revealed bilateral lateral rectus palsy, and oral candidiasis was noted, suggesting advanced immunosuppression. Contrast-enhanced MRI of the brain was normal, but lumbar puncture demonstrated raised opening pressure, cell count of 10 cells/mL, low sugar, and raised protein. CSF India ink staining and cryptococcal antigen lateral flow assay were positive (*Figure 1A*). She received standard antifungal induction therapy with deoxycholate amphotericin B plus flucytosine for 1 week, followed by fluconazole 1200 mg for 1 week, consolidation therapy with fluconazole 800 mg for 8 weeks, and maintenance therapy with fluconazole 200 mg daily, along with serial therapeutic lumbar punctures. ART initiation was intentionally delayed for 6 weeks, reducing the risk of severe cryptococcal IRIS. She showed gradual clinical improvement over 6 months.

CASE 2: TUBERCULOUS MENINGITIS

A young woman with newly diagnosed HIV infection, ART-naïve (CD4 count: 67 cells/μL, HIV Viral Load unavailable), presented with three weeks of fever, progressive confusion, and neck stiffness, consistent with a chronic meningeal syndrome. MRI brain demonstrated basal meningeal enhancement and inflammatory exudates (*Figure 1B*). CSF analysis showed 80 cells/mL, high protein, and normal glucose, which was microbiologically confirmed by CSF GeneXpert MTB/RIF, indicating rifampicin-sensitive disease. She was started on first-line antitubercular therapy (isoniazid, rifampicin, pyrazinamide, ethambutol). ART initiation was deferred for 6 weeks to minimise the risk of paradoxical CNS IRIS. Her mental status improved gradually during the intensive phase of treatment and was doing well at one-year follow-up.

CASE 3: CEREBRAL TOXOPLASMOSIS

A man with long-standing untreated HIV infection (CD4 count: 5 cells/µL, HIV Viral Load unavailable) presented with fever, confusion, and reduced responsiveness. Contrast-enhanced MRI revealed multiple ring-enhancing lesions, including classic concentric and eccentric target signs (*Figure 1C&D*), with associated mass effect precluding lumbar puncture. Toxoplasma IgG positivity supported prior exposure, consistent with reactivation disease. He was treated empirically with trimethoprim–sulfamethoxazole (TMP–SMX), resulting in rapid neurological improvement in two weeks, with marked radiological resolution on interval imaging. ART was initiated early and was well tolerated. He made a near-complete neurological recovery at 6 weeks.

CASE 4: CNS TUBERCULOMAS

A newly diagnosed HIV-positive man (CD4 count: 500 cells/µL, HIV Viral Load unavailable), not yet on antiretroviral therapy, and with a history of incomplete tuberculosis treatment, presented with chronic intermittent headache, fever, and a brief episode of altered consciousness. Examination revealed cervical lymphadenopathy without focal neurological deficits. MRI brain demonstrated multiple conglomerate ring-enhancing lesions consistent with tuberculomas (*Figure 1E*). Extrapulmonary sampling from cervical lymph nodes, with GeneXpert MTB/RIF testing, confirmed tuberculosis. He was treated with antitubercular therapy and adjunctive corticosteroids, and ART was deferred for 6 weeks due to the high risk of CNS IRIS. Follow-up imaging at two months showed a reduction in lesion burden, accompanied by clinical improvement.

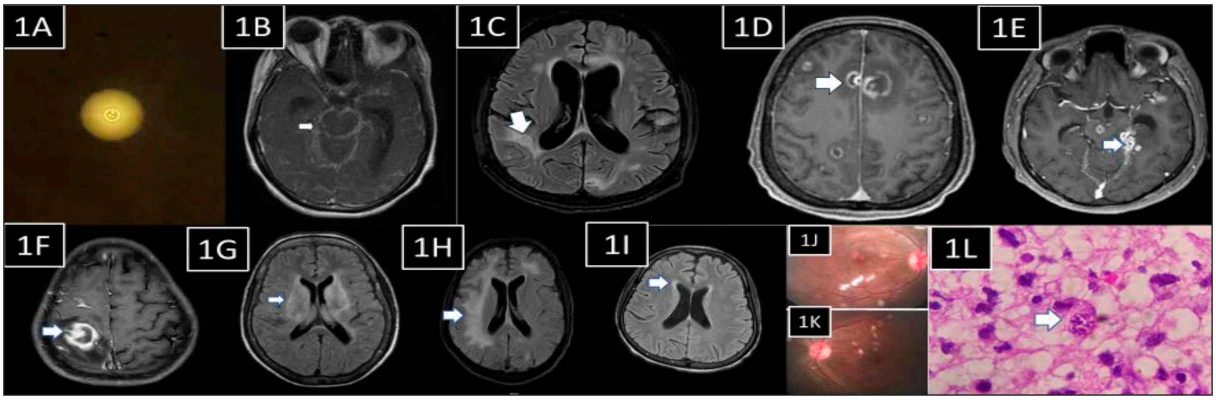

Figure 1 - Representative microbiological, neuroimaging, ophthalmic, and histopathological features of HIV-associated central nervous system infections.
(A) India ink staining of cerebrospinal fluid showing encapsulated yeast forms consistent with *Cryptococcus neoformans* in an HIV-positive patient with cryptococcal meningitis.
(B) Axial post-contrast T1-weighted MRI demonstrating basal exudates and diffuse leptomeningeal enhancement in an 18-year-old woman with tuberculous meningitis.
(C, D) Axial brain MRI in cerebral toxoplasmosis: **(C)** FLAIR image showing a concentric target sign in the right parieto-occipital region; **(D)** post-contrast T1-weighted image demonstrating an eccentric target sign with ring enhancement and mural nodule.
(E) Contrast-enhanced MRI showing multiple conglomerate ring-enhancing lesions with surrounding edema involving the midbrain and pons, consistent with CNS tuberculomas.
(F) Axial post-contrast T1-weighted MRI with FLAIR fat suppression demonstrating a solitary peripherally enhancing right parietal lesion with vasogenic edema, consistent with primary CNS lymphoma.
(G) Axial FLAIR MRI showing symmetrical diffuse white matter hyperintensities consistent with HIV-associated encephalopathy.
(H) Axial FLAIR MRI demonstrating asymmetrical right-sided subcortical white matter hyperintensities without enhancement, consistent with progressive multifocal leukoencephalopathy.
(I–K) Findings in CMV encephalitis: **(I)** periventricular white matter hyperintensities on FLAIR MRI; **(J, K)** fundus photographs showing CMV retinitis.
(L) Brain biopsy showing bradyzoites within a tissue cyst on hematoxylin and eosin staining (400×), confirming cerebral toxoplasmosis.

CASE 5: PRIMARY CNS LYMPHOMA

A man with a newly diagnosed HIV infection, ART-naïve (CD4 count: 90 cells/µL, HIV Viral Load unavailable), presented with subacute progressive fatigue and left-sided weakness. MRI brain revealed a solitary enhancing mass lesion with significant vasogenic oedema (*Figure 1F*). CSF Epstein–Barr virus PCR was positive, and the diagnosis of primary CNS lymphoma was confirmed on stereotactic brain biopsy. He received high-dose methotrexate–based chemotherapy alongside ART initiation. His focal neurological deficits showed improvement with tumour response and structured neurorehabilitation at eight months.

CASE 6: HIV-ASSOCIATED ENCEPHALOPATHY

A woman with untreated HIV infection (CD4 count: 77 cells/µL, HIV Viral Load unavailable) presented with several months of cognitive decline, psychomotor slowing, impaired attention, and gait unsteadiness. The neurological examination revealed mild ataxia and slowed mentation. MRI brain demonstrated symmetrical diffuse white-matter hyperintensities, and CSF analysis excluded opportunistic CNS infections (*Figure 1G*). A diagnosis of HIV-associated encephalopathy was made. ART was initiated, resulting in partial improvement in cognitive and motor function on the 3-month follow-up.

CASE 7: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

A man with long-standing HIV infection, poor ART adherence (CD4 count: 22 cells/µL, HIV Viral Load unavailable), presented after a generalized tonic–clonic seizure, with persistent depressed consciousness and several weeks of preceding cognitive decline. The MRI brain scan showed multiple asymmetric, non-enhancing white-matter lesions without a mass effect, typical of PML (*Figure 1H*). CSF JC virus PCR confirmed the diagnosis. He required initial ventilatory support and was managed with ART optimisation and supportive neurorehabilitation. He demonstrated slow but sustained neurological improvement over a 3-month follow-up period.

CASE 8: CMV ENCEPHALITIS

A young man with poorly controlled HIV infection, poor ART adherence (CD4 count: 9 cells/µL, HIV Viral Load unavailable), presented with seizures, visual disturbances, and fluctuating consciousness. MRI brain revealed periventricular inflammatory changes, and CSF CMV PCR was positive, confirming CMV encephalitis (*Figure 1I-K*). He was treated with intravenous ganciclovir along with ART optimisation. His neurological and visual symptoms improved significantly during a four-week hospital stay.

DISCUSSION

Presentation

Clinical evaluation of CNS manifestations in HIV begins with a syndromic/ anatomical classification into meningeal, focal, or diffuse white matter disease based on presenting features. This framework helps clinicians rapidly narrow the differential diagnosis and prioritise investigations.

Meningitis

Fever, headache, and neck stiffness point toward infectious meningitis, such as cryptococcal or tubercular meningitis. TB meningitis is common in HIV-infected individuals compared to those without HIV and is amongst the most typical causes of HIV-associated meningitis in TB-endemic regions [2, 15]. Cryptococcal meningitis is also common, with the highest burden in sub-Saharan Africa and South Asia [2].

Focal Brain Lesions

Focal neurological symptoms such as altered sensorium, seizures, and hemiparesis suggest space-occupying lesions, such as cerebral toxoplasmosis, CNS tuberculoma, and primary CNS lymphoma. Toxoplasmosis is the most common cause of focal brain lesions in people living with HIV, particularly in those with CD4 counts below 100 cells/µL [5]. CNS tuberculomas represent a parenchymal form of neurotuberculosis and are common in areas with a high prevalence of TB [4]. While TB meningitis is the more typical CNS manifestation, tuberculomas are not uncommon and often present with seizures or focal deficits [4]. Primary CNS lymphoma, typically associated with EBV infection, is seen predominantly in patients with profound immunosuppression (CD4 <50 cells/µL) and accounts for a considerable proportion of focal brain lesions in advanced HIV [7].

Diffuse white matter involvement
The presence of subacute to chronic neurological symptoms, such as cognitive decline, gait disturbances, and, in some cases, focal neurological deficits, suggests diffuse or multifocal central nervous system involvement in advanced HIV (HIV-associated encephalopathy, PML, and CMV encephalitis). HIV encephalopathy presents with a spectrum of cognitive dysfunction related to direct viral effects on the brain. It occurs commonly in people with long-standing, untreated HIV, especially those with CD4 counts below 200 cells/µL [16]. PML, caused by the reactivation of the JC virus, is a demyelinating disorder typically seen in individuals with CD4+ T cell counts below 100 cells/µL, presenting with focal deficits and progressive cognitive impairment [17]. CMV encephalitis, seen in severely immunosuppressed patients (CD4 <50 cells/µL), can cause a combination of cognitive decline, visual disturbances, and motor deficits [18].

Clinical Assessment and Epidemiological Context
A detailed history and physical examination help narrow the aetiological differentials of CNS disease in HIV. Epidemiological context is equally important and should be actively incorporated into clinical reasoning.

Geographical distribution of disease
The relative likelihood of specific CNS infections varies substantially by geography and exposure history: tuberculosis predominates in South and Southeast Asia and sub-Saharan Africa; toxoplasmosis is more common in regions with high background seroprevalence; Chagas disease–related CNS involvement should be considered in Latin America; and other regionally endemic pathogens may influence the differential diagnosis. Importantly, HIV-positive individuals in endemic settings may also present with common community-acquired CNS infections, such as bacterial meningitis or viral encephalitides (e.g., Japanese encephalitis, HSV encephalitis), at frequencies and with disease severity comparable to HIV-negative populations, and these should not be overlooked solely because of HIV status.

History and Examination
Constitutional symptoms such as fever and weight loss are common in TB and neoplasms compared to other causes, such as toxoplasmosis [19]. Seizures commonly occur in space-occupying lesions, but may also be seen in conditions such as PML or CMV encephalitis; however, they are rare in HIV encephalopathy [20]. Skin, mucosal surfaces, eyes, and peripheral lymph nodes should always be examined, as they can provide essential clues and serve as easily accessible sampling sites. Cryptococcal meningitis can present with soft, umbilicated papules, whereas TB can exhibit a variety of dermatological manifestations [12, 13]. Lymphadenopathy is common with disseminated tuberculosis [23]. Characteristic retinal lesions can be noted on fundoscopy in CMV, TB, and toxoplasmosis [24-26]. Oral candidiasis suggests advanced immunosuppression and serves as a key indicator of opportunistic infections. It is essential to assess for clinical signs of raised intracranial pressure, such as bilateral lateral rectus palsy, as their presence warrants urgent evaluation for potential impending herniation. Caution is advised before performing a lumbar puncture in such cases.

CD4 count
CD4 count remains central to formulating a differential diagnosis. Most CNS opportunistic infections occur when the CD4 count is below 200 cells/µL. Case 4, with a CD4 count of 500 cells/µL, had CNS tuberculomas, indicating that tuberculous CNS disease can still occur in individuals who are less immunocompromised. HIV Encephalopathy can manifest over a broader range of immunosuppression, particularly in patients with long-standing, untreated HIV. CD4 count trends also help guide prophylactic strategies and indicate risk for IRIS following ART initiation.

NEUROIMAGING

Neuroimaging is fundamental to diagnosis and should be obtained whenever possible in HIV positive individuals with signs and symptoms suggestive of central neurological processes. Whilst access to state-of-the-art neuroimaging is limited in many settings, it is understood that access to neurocranial imaging can make a significant difference in distinguishing the aforementioned entities from one another, with often dramatic impacts on individual patient care by enabling the establishment of a definitive, often well-treatable diagnosis.

Meningitis

Contrast-enhanced MRI is preferred over CT due to better resolution of white matter and posterior fossa lesions [27]. In patients presenting with meningitis, leptomeningeal enhancement is best seen on contrast studies. Tubercular meningitis can additionally have basal exudates and features of hydrocephalus [28]. In patients presenting with encephalitis, MRI patterns can also suggest viral aetiologies: HSV encephalitis classically involves asymmetric signal abnormalities in the medial temporal and inferior frontal lobes, with diffusion restriction, whereas Japanese encephalitis preferentially affects the bilateral thalami, basal ganglia, brainstem, and cerebellum, often with T2/FLAIR hyperintensities and occasional hemorrhagic changes [29].

Focal Brain Lesions

Mass lesions share overlapping but distinct radiological features (*Table 1*). Toxoplasmosis and tuberculoma typically present with multiple lesions, whereas CNS lymphoma may present as either solitary or multiple lesions. Common locations for toxoplasmosis include the parietal and frontal lobes, the thalamus, the basal ganglia, and the corticomedullary junction. Lymphoma, on the other hand, favors the corpus callosum, periventricular, and periependymal regions [30]. Toxoplasmosis and tuberculoma typically exhibit ring enhancement. In contrast, lymphoma shows irregular or patchy enhancement. The concentric target sign (alternating hypo- and hyperintense rings) and the eccentric target sign (a ring-enhancing lesion with an off-centre mural nodule) are highly suggestive of toxoplasmosis [31]. These patterns correspond to histopathological changes, such as necrosis or hemorrhage [32]. The concentric sign, typically observed in deeper brain lesions, is considered more specific than the eccentric sign [32]. Tuberculosis often produces multiple granulomas that coalesce into conglomerated ring-enhancing lesions [33]. All three may exhibit surrounding edema and a mass effect, although lymphoma lesions tend to be larger (>4 cm) [30]. On MR spectroscopy, all display increased lipid/lactate peaks, but only lymphoma shows a prominent choline peak, distinguishing it from the other two [34].

Table 1 - MRI features differentiating intracranial ring-enhancing lesions in immunocompromised or HIV-infected patients

Feature	*Tuberculoma*	*Toxoplasmosis*	*Primary CNS Lymphoma*	*Bacterial Abscess*	*Fungal Abscess*
DWI/ADC (Diffusion Restriction)	Restricted if liquefied (tuberculous abscess); absent in solid caseating granuloma	No central restriction; may show peripheral/rim hyperintensity	Restricted diffusion, especially in solid lesions (high cellularity)	Marked central restriction (pus)	Variable: wall or intracavitary projections may restrict; center less consistent
T2 Signal	Solid: T2 iso-/hypointense; liquefied center hyperintense	Hyperintense center ± hypointense rim (“concentric target”)	Iso- to hypointense (sometimes mildly hyperintense)	Hyperintense necrotic center with hypointense rim	T2 iso-/hypointense center, irregular hypointense projections/rim
Contrast Enhancement	Rim or nodular; may be irregular	Thin, smooth ring ± eccentric nodule	Homogeneous in immunocompetent; ring-enhancing in HIV	Smooth thin ring (classic)	Thick, irregular, crenated ring; multiloculated
Other Radiologic Clues	May calcify with treatment	Basal ganglia/thalamic predilection; high lesion count	Periventricular / corpus callosum involvement; steroid responsive; high choline	Dual rim sign, prominent	

Abbreviations: DWI — Diffusion-weighted imaging; ADC — Apparent diffusion coefficient; WM — White matter; MRS — Magnetic resonance spectroscopy; NAA — N-acetylaspartate; HIV — Human immunodeficiency virus; CNS — Central nervous system.

Diffuse White Matter disease

HIV Encephalopathy, PML, and CMV encephalitis all typically exhibit non-enhancing or minimally enhancing lesions with hyperintense signals on T2-weighted MRI (*Table 2*). HIV Encephalopathy shows symmetrical involvement of the subcortical white matter and periventricular regions, while PML tends to be asymmetric with well-demarcated lesions. [30]. A characteristic "milky way" appearance on T2-weighted imaging, representing active demyelination at the lesion margins, has been described in PML [35]. The most common imaging finding in CMV encephalitis is nonspecific white matter hyperintensity on T2/FLAIR, resembling HIV leukoencephalopathy [6]. It is tough to differentiate between HIV encephalopathy and CMV encephalitis [36]. CMV's ventricular tropism may lead to periventricular diffusion restriction and contrast enhancement, sometimes accompanied by hydrocephalus, which may sometimes help in differentiating from HIV encephalopathy [36].

Laboratory diagnostics

Microscopy and Culture

CSF findings can help differentiate between types of meningitis. Tubercular and cryptococcal meningitis typically exhibit a lymphocytic predominance, whereas pyogenic meningitis is characterized by a neutrophilic response (*Table 3*) [37]. Between tubercular and cryptococcal disease, cell counts are usually lower in the latter [38]. Moderate protein elevation and high intracranial pressure are observed in both conditions. Glucose levels may be lower in patients with cryptococcal meningitis [37, 38]. Imaging to precede lumbar puncture when space-occupying lesions are suspected is generally recommended, especially when the lesions are in the posterior fossa. However, in a study by Milburn *et al*., routine cranial CT before lumbar puncture in HIV-positive patients often delayed diagnosis, despite a few true contraindications [39]. Although 70% had CT abnormalities, no adverse events occurred post-LP [39].

Traditionally, microscopy and culture have served as the cornerstone for diagnosing CNS infections in patients with HIV, particularly in resource-limited settings (*Table 4*). These conventional techniques, although sometimes limited by sensitivity, remain valuable due to their accessibility and ability to provide rapid preliminary results [40]. Still, India Ink staining of CSF showing a "halo-like" appearance remains a widely used diagnostic tool.

Table 2 - Radiological manifestations in patients with HIV-associated neurocognitive disorders, Progressive multifocal leukoencephalopathy, and CMV Encephalitis.

Feature	*HIV Encephalopathy / HAND*	*PML*	*CMV Encephalitis*
Etiology	Direct HIV neurotoxicity	JC virus reactivation	CMV ventriculoencephalitis
Typical CD4 count	<200	<100	<50
Clinical pattern	Gradual cognitive and motor slowing	Rapid focal neurological deficits	Altered sensorium ± cranial nerve palsies
T2/FLAIR	Diffuse deep WM hyperintensities (symmetric)	Asymmetric multifocal subcortical WM lesions (parieto-occipital; U-fibers)	Periventricular/subependymal hyperintensities; brainstem possible
T1-weighted	Iso-/hypointense	Hypointense	Iso-/hypointense
Contrast enhancement	None/minimal	Usually none (enhancing if IRIS)	Mild periventricular/ependymal enhancement
DWI	No significant restriction	Rim restriction at advancing lesion edges	Typically, no restriction
Mass effect	Minimal	None or minimal	Minimal; ↑ if active ventriculitis
Additional distinguishing findings	Confluent deep WM disease	Sharp advancing borders; minimal mass effect	Ventriculitis; microhemorrhages on SWI

Abbreviations: HIV — Human immunodeficiency virus; HAND — HIV-associated neurocognitive disorder; PML — Progressive multifocal leukoencephalopathy; CMV — Cytomegalovirus; WM — White matter; IRIS — Immune reconstitution inflammatory syndrome; DWI — Diffusion-weighted imaging; SWI — Susceptibility-weighted imaging.

Table 3 - CSF analysis of patients with pyogenic, tubercular, cryptococcal, and viral meningitis.

Parameter	*Normal CSF values*	*Pyogenic meningitis*	*Tuberculous meningitis*	*Cryptococcal meningitis*
Cell count (/μL)	*0–5* (lymphocytic)	Usually *>500* (often 1,000–5,000)	Usually *100–500*	*5–100* (commonly 5–20)
Predominant cells	*Lymphocytes*	*Neutrophils*	*Lymphocytes* (may be mixed early)	*Lymphocytes*
Protein (mg/dL)	*15–45*	Markedly *elevated*	*Elevated*	*Elevated*
Glucose (mg/dL)	*45–80* OR *>50% of serum glucose*	*Low* (<40 mg/dL or <40% of serum)	*Low* (usually 30–45 mg/dL)	*Low to normal* (often 30–60 mg/dL; may be >40 mg/dL)
Opening pressure (cm H_2O)	*6–20*	Variable (normal to high)	Usually *high*	*Very high* (often >25 cm H_2O)

Abbreviations: CSF – cerebrospinal fluid; mg/dL – milligrams per decilitre; cm H_2O – centimetres of water; μL – microlitre.

Table 4 - Microbiological diagnosis of common CNS infections in people living with HIV.

Condition	*Microscopy*	*Antigen / Antibody Tests*	*Molecular Tests*	*Culture*
Cryptococcal meningitis	India ink staining of CSF *(sensitivity ~55%)*	CSF/serum cryptococcal antigen (CrAg) *(sensitivity and specificity >95%)*	—	CSF fungal culture *(sensitivity ~70–90%; slower turnaround)*
Tuberculous meningitis	Ziehl–Neelsen stain of CSF *(very low sensitivity)*/ auramine *(higher sensitivity)*	Urine lipoarabinomannan test (Poor sensitivity but good specificity) supports TB diagnosis but does not localize to CNS	CSF GeneXpert MTB/RIF *(~43% sensitivity; specificity >95%)* / GeneXpert Ultra *(up to ~70% sensitivity; specificity >95%)*	CSF mycobacterial culture *(gold standard; time-consuming; often negative)*
Cerebral toxoplasmosis	Tachyzoites/ bardyzoites can be seen on brain biopsy *(low yield)*	IgG Serology (Poor specificity)	CSF Toxoplasma PCR *(sensitivity ~70–95%; specificity >95%)*	—
Primary CNS lymphoma	CSF cytology/flow cytometry *(diagnostic yield up to ~30%)*	—	CSF EBV PCR *(high sensitivity/specificity)*	—
PML	—	—	CSF JC virus PCR *(high specificity; sensitivity ~70–90%)*	—
CMV encephalitis	—	—	CSF CMV PCR *(sensitivity >80%; specificity >90%)*	—

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; CrAg, cryptococcal antigen; CSF, cerebrospinal fluid; EBV, Epstein–Barr virus; HIV, human immunodeficiency virus; IgG, immunoglobulin G; MTB/RIF, *Mycobacterium tuberculosis*/rifampicin resistance; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy.

Initial CSF culture, despite its low sensitivity, may serve an essential role in follow-up by demonstrating culture sterility at the end of the induction phase of treatment [41, 42].

Diagnosing tuberculous meningitis remains challenging due to the low bacillary burden in CSF, lack of a definitive gold standard test, and poor sensitivity of conventional methods [43]. In the diagnosis of tuberculous meningitis, CSF microscopy is a widely available, rapid test, but its utility is limited by low sensitivity, especially in paucibacillary specimens [44]. In tuberculoma cases, CSF is even less likely to yield a diagnosis based solely on microscopy and culture. In such cases, brain biopsy has a higher yield, but performing brain biopsy in resource-limited settings is exceptionally challenging. Stereotactic brain biopsy remains the gold standard in the diagnosis of primary central nervous system lymphoma in HIV-infected patients [7]. Brain biopsy can help demonstrate bradyzoites in patients with toxoplasmosis as well (*Figure 1L*) [45].

Antigen-Antibody-based tests

Cryptococcal antigen (CrAg) testing forms the basis of diagnosis for cryptococcal meningitis and can be performed on CSF or serum [42]. This was traditionally done using latex agglutination or enzyme-linked immunosorbent assays (ELISA). Still, the lateral flow assay (LFA) has emerged as the preferred diagnostic tool because it is rapid, inexpensive, and simple to perform, with excellent diagnostic accuracy [42]. The CRAg LFA demonstrates sensitivity and specificity exceeding 95% and often approaching 100% in HIV-associated cryptococcal disease [42]. The portability and minimal infrastructure requirements of the LFA have made it particularly valuable in resource-limited settings, where it significantly shortens time to diagnosis. In symptomatic patients, detection of CrAg in CSF is sufficient to confirm cryptococcal meningoencephalitis and initiate antifungal therapy, often before culture results become available. Serum or plasma CrAg testing is also diagnostically useful, particularly when lumbar puncture is delayed or contraindicated. In people with advanced HIV, serum CrAg testing has a sensitivity comparable to CSF testing [42]. Although baseline CrAg titers broadly reflect fungal burden and prognosis, serial titers are not recommended for assessing treatment response or predicting relapse, as titers do not reliably correlate with clinical outcomes.

Urinary detection of lipoarabinomannan (LAM) has emerged as a valuable adjunct for tuberculosis diagnosis in people living with HIV, particularly in those with advanced immunosuppression and severe illness [46]. Evidence from systematic reviews and meta-analyses demonstrates that while overall sensitivity of urinary LAM assays is variable and often suboptimal, diagnostic sensitivity is consistently higher in HIV-positive individuals, especially at low CD4 counts. At the same time, specificity remains high, supporting its role as a rule-in test in high-risk populations [46, 47]. Although urine LAM does not localise disease to the central nervous system and cannot exclude tuberculous meningitis when negative, its rapid turnaround time, high specificity, and independence from sputum production make it a valuable component of integrated diagnostic algorithms for tuberculosis in people living with HIV. It is, however, commercially unavailable in many regions at present.

Serological tests detecting *T. gondii*-specific IgG antibodies help identify prior exposure, which is critical since TE typically occurs in seropositive individuals. It must, however, be noted that in countries with high seroprevalence, IgG ELISA testing for toxoplasmosis is not particularly helpful for diagnosis [48]. Serologic IgM is usually absent in reactivation, limiting its utility [49].

Molecular tests

Molecular diagnostics, particularly GeneXpert MTB/RIF and its enhanced version GeneXpert Ultra, have emerged as valuable tools widely distributed in areas of high prevalence, even across many limited-to-low-resource settings. GeneXpert Ultra offers significantly improved sensitivity, especially in paucibacillary disease [43]. These gains are attributed to GeneXpert Ultra's larger reaction chamber and incorporation of additional multicopy amplification targets. However, even with these improvements, a negative GeneXpert Ultra result cannot reliably exclude TBM, necessitating continued reliance on clinical judgment and ancillary investigations [43]. It is good practice to look for other sites of involvement in TB meningitis patients, as they may be easier to sample, and these tissues, aspirates, or fluids may be more sensitive than CSF. Conventional PCR is instrumental in making the diagnosis of other neuroinfections in HIV as well. CSF PCR for toxoplasmosis, although less sensitive, can help diagnose toxoplasmosis [49]. For primary CNS lymphoma, the detection of EBV DNA in CSF using PCR offers high sensitivity and specificity, especially at high viral loads, though false positives can occur [7]. Similarly, the detection of JC virus DNA in CSF by PCR is a cornerstone for diagnosing PML, particularly when a brain biopsy is not feasible [17]. Although CSF JCV PCR is highly specific, its sensitivity can be limited, especially in early or asymptomatic disease, necessitating integration with clinical and radiological findings for timely diagnosis and treatment [17]. CMV PCR testing of CSF plays a pivotal role in diagnosing CMV encephalitis [18].

Treatment and Outcomes

Management of CNS infections in HIV is challenging and must be individualised, taking into account the causative agent, immune status, and IRIS risk (*Table 5*).

IRIS and Timing of ART Initiation

The timing of ART initiation in patients with opportunistic infections is critical, as it must balance the benefits of immune recovery with the risk of IRIS. Early ART initiation reduces HIV-related morbidity and mortality but increases the risk of IRIS, particularly in patients with advanced immunosuppression, low CD4 counts, and high pathogen burden [12]. For most opportunistic infections, ART should be initiated within two weeks of starting appropriate antimicrobial therapy, as the overall survival benefit outweighs the risk of inflammatory complications [12]. However, robust randomized trial data demonstrate that this approach is harmful in central nervous system infections such as cryptococcal meningitis and tuberculous meningitis. In the COAT trial, Boulware *et al*. showed that early ART initiation at 1–2 weeks after cryptococcal meningitis diagnosis was associated with significantly higher 26-week mortality compared with deferred ART at five weeks (45% vs. 30%; hazard ratio 1.73), with excess deaths occurring predominantly in the early post-diagnosis

Table 5 - Treatment principles, ART timing, and supporting evidence for major CNS infections in people living with HIV.

Condition	*First-line Treatment*	*Adjunctive / Supportive Therapy*	*ART Timing*	*Key Evidence / Rationale*
Cryptococcal meningitis	Induction: liposomal amphotericin B + flucytosine + fluconazole; consolidation and maintenance with fluconazole	Serial therapeutic lumbar punctures for raised ICP	Delay ART by up to 4-6 weeks	Randomised trials show increased mortality with early ART; delayed ART reduces severe cryptococcal IRIS and improves outcomes
Tuberculous meningitis	Standard ATT (isoniazid, rifampicin, pyrazinamide, ethambutol)	Corticosteroids; management of ICP, seizures, hydrocephalus; neurosurgical CSF diversion if needed	Delay ART by up to 4-6 weeks	Trials of intensified rifampicin/ fluoroquinolone regimens showed no mortality benefit; delayed ART reduces IRIS risk
Cerebral toxoplasmosis	TMP–SMX or pyrimethamine–sulfadiazine for ≥6 weeks, followed by maintenance	Steroids for mass effect; anticonvulsants	Early ART (within 2 weeks)	Clinical and radiologic improvement within 10–14 days is diagnostic; early ART improves HIV outcomes with low IRIS risk
Primary CNS lymphoma	High-dose methotrexate–based chemotherapy	Supportive care; rehabilitation; radiotherapy if chemotherapy not feasible	Initiate ART with chemotherapy	Combined ART and chemotherapy significantly improve survival compared with ART or radiotherapy alone
HIV-associated encephalopathy	Optimised ART	Supportive neurocognitive care	Immediate ART	Suppression of HIV replication leads to stabilisation or improvement in neurocognitive function
PML	ART optimisation	Corticosteroids only for severe IRIS; supportive care	Immediate ART	Immune reconstitution is the only proven effective therapy; JCV-specific T-cell recovery correlates with outcome
CMV encephalitis	IV ganciclovir ± foscarnet (severe); oral valganciclovir (mild)	Screen and treat CMV retinitis; supportive care	ART can be delayed by 14 days	Delayed ART reduces IRIS risk; CSF viral load response correlates with disease severity and prognosis

Abbreviations: ART, antiretroviral therapy; ATT, antitubercular therapy; CMV, cytomegalovirus; CNS, central nervous system; ICP, intracranial pressure; IRIS, immune reconstitution inflammatory syndrome; JCV, John Cunningham virus; PML, progressive multifocal leukoencephalopathy; TMP–SMX, trimethoprim–sulfamethoxazole.

period, particularly among patients with minimal cerebrospinal fluid inflammation [13]. Similarly, in a randomized trial of HIV-associated tuberculous meningitis, Török *et al.* demonstrated that immediate ART initiation did not improve survival and was associated with a higher frequency of severe adverse events compared with deferred ART, supporting delayed initiation in this setting [14].
Accordingly, ART timing should be individualized based on the causative infection, disease severity, central nervous system involvement, and baseline immune status. Management of IRIS generally involves continuation of ART alongside optimal treatment of the underlying opportunistic infection, with escalation of supportive care as required [50]. Corticosteroids are recommended for moderate to severe IRIS, particularly in tuberculosis- or cryptococcal-associated disease, where excessive inflammatory responses can result in significant neurological injury [50]. Close clinical monitoring is essential to distinguish IRIS from treatment failure or alternative diagnoses, and early HIV diagnosis with ART initiation before CD4 counts decline below 50 cells/µL remains a key strategy to reduce the overall burden of severe IRIS and opportunistic infections [50].

Cryptococcal Meningitis

The treatment of cryptococcal meningitis consists of induction, consolidation, and maintenance. In a landmark trial by Day *et al*., combination therapy with amphotericin B deoxycholate plus flucytosine for induction was associated with improved survival and significantly faster cerebrospinal fluid (CSF) fungal clearance compared with amphotericin B monotherapy, establishing flucytosine as the preferred partner drug during induction [51]. The ACTA trial subsequently demonstrated that shortened induction regimens, particularly one week of amphotericin B plus flucytosine or a fully oral fluconazole–flucytosine regimen, were non-inferior to two weeks of amphotericin B, with lower rates of severe anaemia and comparable mortality, supporting more pragmatic approaches in resource-limited settings [52]. Most recently, the AMBITION trial showed that a single high dose of liposomal amphotericin B combined with flucytosine and fluconazole was non-inferior to the WHO-recommended amphotericin B deoxycholate–based regimen, with similar fungal clearance and significantly fewer grade 3-4 adverse events, providing the strongest evidence base for the current WHO-preferred induction strategy [42, 53].
Consolidation involves fluconazole 800 mg/day for eight weeks, followed by maintenance therapy with 200 mg/day until immune recovery [42]. Adequate consolidation and maintenance therapy are essential to prevent relapse, particularly in patients with high baseline fungal burden or delayed clinical response. In parallel with antifungal therapy, management of elevated intracranial pressure with serial lumbar punctures is essential, as raised opening pressure is a major contributor to morbidity and mortality in cryptococcal meningitis. Therapeutic lumbar punctures should be performed whenever symptomatic intracranial hypertension is present, irrespective of antifungal regimen, and repeated as required to relieve pressure and prevent neurological deterioration [42]. Empiric corticosteroids should not be used during induction therapy, as randomized trials have shown no mortality benefit and worse neurological and microbiological outcomes, reinforcing that effective antifungal therapy and meticulous control of intracranial pressure remain the cornerstones of management [54].

Tuberculosis

The management of tuberculous meningitis aims to achieve rapid mycobacterial clearance within the central nervous system while mitigating inflammation-related neurological injury and treatment-associated complications, particularly in the context of advanced HIV and the risk of IRIS. CNS tuberculosis requires prolonged anti-tuberculosis therapy, typically using a standard four-drug regimen (isoniazid, rifampicin, pyrazinamide, ethambutol) [43]. However, because rifampicin has poor CNS penetration, it has been argued that the regimen could benefit from intensification with additional antitubercular agents, such as fluoroquinolones. However, in a trial by Heemskerk *et al*., adults with tuberculous meningitis received either standard therapy or an intensified regimen with high-dose rifampin and levofloxacin [55]. The intensified treatment did not reduce 9-month mortality (HR 0.94; P = 0.66) or improve outcomes, although a possible benefit was observed in cases of isoniazid resistance [55]. Corticosteroids are commonly used as adjunctive therapy in patients with TB meningitis. However, recent evidence suggests this practice offers no benefit. In a study by Donovan *et al*., 520 HIV-positive adults with tuberculous meningitis were randomized to dexamethasone or placebo [43]. No significant difference in 12-month mortality was observed (44.1% vs. 49.0%; HR 0.85; P=0.22) [43]. Secondary outcomes, including neurological disability and IRIS, were similar [43].

Morbidity of tubercular meningitis is driven by vascular complications such as infarcts. Aspirin is a potential adjunct to reduce infarcts in observational studies [56]. However, in a randomized trial (ACT-TBM), adding aspirin or clopidogrel to standard therapy in tubercular meningitis showed no benefit in reducing stroke, cerebral infarction, or mortality at one or three months [57]. Bleeding rates were low across groups [57]. Management of complications such as raised intracranial pressure, seizures, and hydrocephalus is vital but poorly evidence-based. Neurosurgical options, such as ventriculoperitoneal shunting or endoscopic third ventriculostomy, are used for treating hydrocephalus [43]. Research into supportive care, pediatric-specific outcomes, and novel therapies continues to evolve, but TBM still carries high mortality and morbidity despite treatment advances.

Toxoplasmosis

Toxoplasmosis requires prompt induction therapy with pyrimethamine, sulfadiazine, or trimethoprim–sulfamethoxazole (TMP-SMX) for at least six weeks, followed by maintenance until immune recovery (CD4 >200/µL for ≥6 months) [58]. In HIV patients, the clinical and radiologic response to anti-toxoplasma therapy is prompt and occurs as soon as 10–14 days of initiation of treatment. It also serves as a key diagnostic tool, often confirming toxoplasmic encephalitis in the absence of definitive laboratory confirmation [59]. Corticosteroids may be used for cerebral edema, and anticonvulsants may be used if seizures occur [58]. Maintenance regimens mirror induction but use lower doses, and adherence to both ART and antiparasitic therapy is essential to prevent relapse [58].

Primary CNS Lymphoma

Treatment of primary CNS lymphoma in HIV-infected patients involves ART along with high-dose methotrexate based chemotherapy when feasible [60, 61]. This approach significantly improves survival compared to radiotherapy or ART alone [60, 62]. Whole-brain radiotherapy is used when chemotherapy is not possible, but it offers only a limited benefit [60]. Antiviral agents, such as ganciclovir or zidovudine, may have adjunctive value due to their association with EBV [60, 63]. Rituximab is less commonly used due to uncertain efficacy and higher toxicity in immunocompromised patients [64].

HIV-associated neurocognitive disorder

Treatment of HIV-associated neurocognitive disorders centers on suppressing HIV replication in the brain using ART [16]. Initiating or optimizing ART can significantly improve cognitive function, especially in severely affected or treatment-naïve patients [16]. Adjusting to regimens with better CNS penetration may help [16]. While adjunct therapies (e.g., minocycline, memantine) have been explored, none show a clear benefit [16]. Early ART and effective management of comorbidities are key to prevention.

PML

The cornerstone of PML treatment is the prompt initiation or optimization of ART to restore JCV-specific cellular immunity, particularly CD4+ and CD8+ T-cell responses [65]. Successful immune reconstitution can stabilize or improve neurological symptoms, and the presence of JCV-specific CD4+ T cells is strongly associated with better outcomes [65]. However, immune restoration may trigger IRIS, characterized by paradoxical worsening of symptoms due to excessive CNS inflammation [65]. Corticosteroids may be used to manage severe PML-IRIS, though their role is controversial [65]. Other experimental therapies, such as immune checkpoint inhibitors and interleukin-7, have limited data in HIV-related PML and are not routinely recommended [65].

CMV Encephalitis

The treatment of CMV neurological disease is guided by disease severity. For severe cases, a combination of intravenous ganciclovir and foscarnet is used, whereas mild cases may be managed with oral valganciclovir [66]. In ART-naïve individuals, antiretroviral therapy can be delayed by 14 days to reduce the risk of IRIS [66]. It is essential to rule out CMV retinitis beforehand, as IRIS in the eye can lead to vision loss [66]. Maintenance therapy with oral valganciclovir is advised until CD4+ T-cell counts rise above 100 cells/µL and are sustained for at least six months [66].

CONCLUSIONS

CNS disease remains a significant cause of morbidity and mortality in advanced HIV, reflecting profound immunosuppression, delayed presentation, and a broad range of opportunistic infections and malignancies. This case-based review demonstrates how a structured syndromic approach, categorising presentations into meningeal, focal mass-like, and diffuse white-matter syndromes, can streamline early diagnosis through targeted neuroimaging, cerebrospinal fluid analysis, and focused molecular testing. The stepwise diagnostic algorithms outlined in *Figures 2* and *3* emphasise early bedside stratification and rational investigation, even in resource-limited settings. Across conditions, careful interpretation of MRI patterns, judicious use of empiric therapy, avoidance of premature corticosteroid exposure, and appropriate

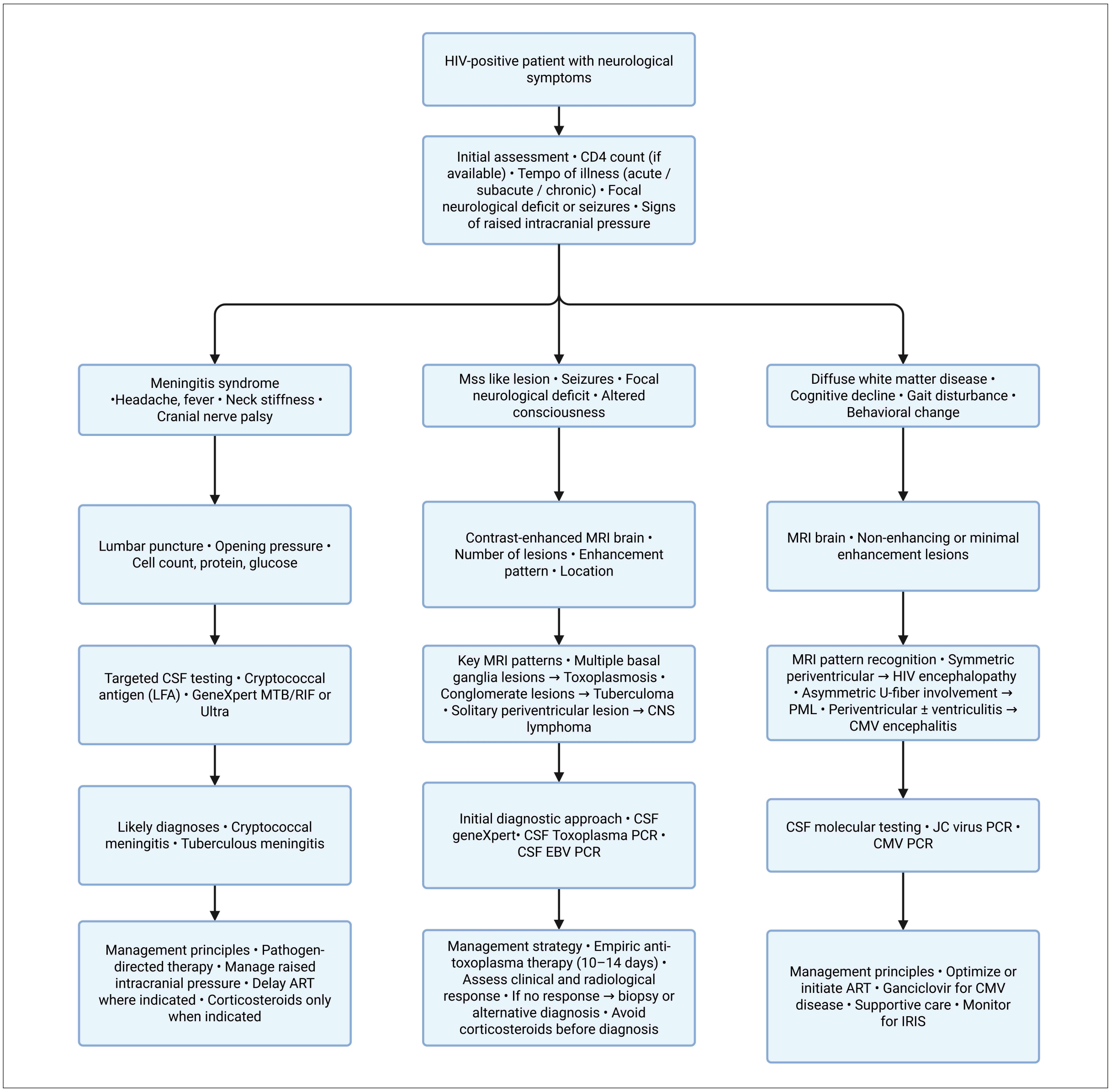

Figure 2 - Syndromic diagnostic algorithm for central nervous system disease in people with advanced HIV.

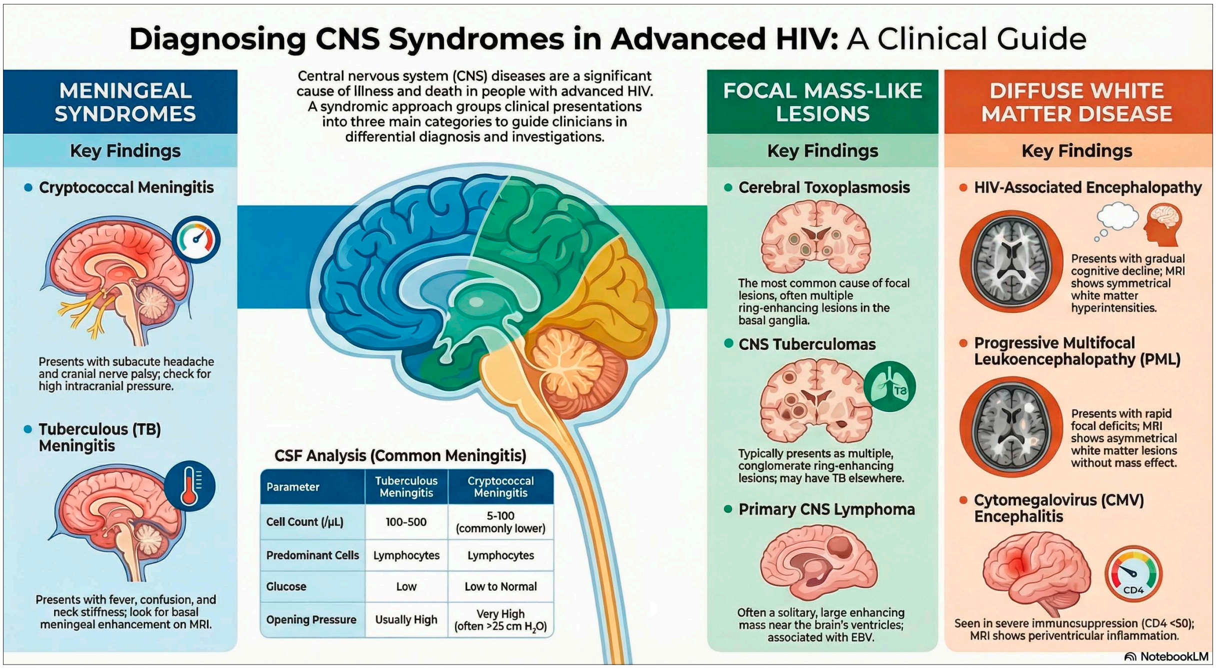

Figure 3 - Syndromic framework for differentiating major CNS pathologies in advanced HIV.
Note: Image was generated using notebook LLM for this publication

timing of antiretroviral treatment to mitigate IRIS risk emerged as central determinants of neurological outcome.

Funding
This work did not receive any specific funding from public, commercial, or not-for-profit funding agencies.

Conflict of interest
The authors declare no conflicts of interest relevant to this article.

Use of artificial intelligence tools
Language support tools were used during manuscript preparation to improve clarity and readability. All content, clinical interpretation, and conclusions were developed and verified by the authors, who take full responsibility for the work.

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