


ISSN: (Print) (Online) Journal homepage: <https://www.tandfonline.com/loi/ieop20>


Strategies for the diagnosis and management of meningitis in HIV-infected adults in resource limited settings

Marise Bremer, Yakub E Kadernani, Sean Wasserman, Robert J Wilkinson & Angharad G Davis

To cite this article: Marise Bremer, Yakub E Kadernani, Sean Wasserman, Robert J Wilkinson & Angharad G Davis (2021) Strategies for the diagnosis and management of meningitis in HIV-infected adults in resource limited settings, Expert Opinion on Pharmacotherapy, 22:15, 2053-2070, DOI: [10.1080/14656566.2021.1940954](https://doi.org/10.1080/14656566.2021.1940954)


To link to this article: <https://doi.org/10.1080/14656566.2021.1940954>

 View supplementary material [↗](#)

 Published online: 21 Jun 2021.

 Submit your article to this journal [↗](#)

 Article views: 70

 View related articles [↗](#)

 View Crossmark data [↗](#)

REVIEW



Strategies for the diagnosis and management of meningitis in HIV-infected adults in resource limited settings

Marise Bremer^a, Yakub E Kadernani^a, Sean Wasserman^{a,b}, Robert J Wilkinson^{a,b,c,d,e} and Angharad G Davis^{a,d,e}

^aWellcome Centre for Infectious Disease Research in Africa, Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Observatory; ^bDepartment of Medicine, University of Cape Town, Groote Schuur Hospital, Observatory, Republic of South Africa; ^cDepartment of Infectious Diseases, Imperial College London, London, UK; ^dFrancis Crick Institute, London, UK; ^eFaculty of Life Sciences, University College London, London, UK

ABSTRACT

Introduction: The incidence of human immunodeficiency virus-1 (HIV-1) associated meningitis has been declining in the post-combination antiretroviral treatment (ART) era, although survival rates remain low for the common causes like tuberculosis and cryptococcal disease. Diagnosis and treatment of meningitis in HIV-1 is complicated by atypical clinical presentations, limited accuracy of diagnostic tests, access to diagnostic tests, and therapeutic agents in low- and middle-income countries (LMIC) and immune reconstitution inflammatory syndrome (IRIS).

Areas covered: We provide an overview of the common etiologies of meningitis in HIV-1-infected adults, suggest a diagnostic approach based on readily available tests, and review specific chemotherapeutic agents, host-directed therapies, supportive care, timing of ART initiation, and considerations in the management of IRIS with a focus on resource-limited settings. They identify key knowledge gaps and suggest areas for future research.

Expert opinion: Evidence-based management of HIV-1-associated meningitis is sparse for common etiologies. More readily available and sensitive diagnostic tests as well as standardized investigation strategies are required in LMIC. There is a lack of availability of recommended drugs in areas of high HIV-1 prevalence and a limited pipeline of novel chemotherapeutic agents. Host-directed therapies have been inadequately studied.

ARTICLE HISTORY

Received 22 May 2020

Accepted 07 June 2021

KEYWORDS

Meningitis; opportunistic infection; HIV; tuberculosis; cryptococcal; IRIS

1. Introduction

As a result of combination antiretroviral therapy (ART), introduced in 1996, the incidence of new human immunodeficiency virus (HIV) infections had decreased by 40% in 2019 [1]. Despite effective ART and a reduction in the incidence of people living with HIV (PLWH), in 2019, 38.0 million people globally were living with HIV and at risk for opportunistic infections (OI) like meningitis [1]. OI in the context of HIV-1 are frequent and often life threatening, but a major reduction in risk has been observed with the use of ART, particularly within the first year of treatment [2]. The all-cause incidence of HIV-1-associated meningitis, one of the most serious OI in PLWH, is not known. However, a large United Kingdom cohort demonstrated that the incidence of central nervous system (CNS) OI in HIV-1 has decreased from 13.1 cases per 1000 patient years at the start of the ART era to 1.0 in later years [3]. This decline is more pronounced in high-income countries (HIC), where a 43–97% reduction was observed, compared to low- and middle-income countries (LMIC), where this was 30–79% [4]. With the high distribution of HIV seroprevalence and OI [1] in LMIC, the burden of meningitis is still substantial and

certain infections such as pneumococcal meningitis persists even with immune reconstitution.

Cryptococcal meningitis (CM) is the most serious form of HIV-1-associated meningitis with 1-year mortality around 70% in low-income countries (LIC) and 20% in HIC [5], accounting for approximately 15% of all acquired immunodeficiency syndrome (AIDS) related deaths [6]. This is followed closely by tuberculous meningitis (TBM), with an associated mortality of 50–70% and the majority of deaths occurring within the first 2 months of diagnosis [7,8]. Although these etiologies predominate, other causes of meningitis, including bacteria such as *S. pneumoniae*, *L. monocytogenes* and *T. pallidum*, as well as viral and parasitic infections result in substantial morbidity in PLWH. Determining the underlying cause in these cases can be challenging due to atypical clinical presentations in HIV-1 co-infection, lack of accurate and point of care diagnostic tests, complexity of accessing samples from the site of disease and limited resources in countries where HIV-1 prevalence is high. Treatment is further complicated by HIV-specific issues such as immune reconstitution inflammatory syndrome (IRIS), drug–drug interactions, poor adherence to treatment, and shared toxicity with ART.

ARTICLE HIGHLIGHTS

- The incidence of meningitis varies significantly in the context of HIV-1, especially for bacterial pathogens, and should be considered by the treating physician when prescribing empirical therapy.
- There is overlap in the clinical presentations of HIV-1-associated meningitis and therefore a pragmatic approach to diagnostic testing as described in [Figure 1](#) should be applied.
- Timing of initiation of antiretroviral therapy must consider the risk of IRIS. Factors such as low CD4 in TBM and persistent cryptococcal growth at time of ART initiation will affect this risk and should be accounted for.
- In CM, LAmB has been shown to be more beneficial than conventional amphotericin B in the treatment of CCM. At present access to conventional amphotericin B and flucytosine is severely limited in resource limited settings where CM is prevalent. Novel treatments such as VT-1129 which is currently undergoing phase I trials are needed.
- At present, the recommended antitubercular drug regimen in TBM is identical to pulmonary TB. Repurposed drugs such as linezolid, and higher doses of rifampicin may be better suited to treat TB within the CNS are currently being assessed in clinical trials.
- Host-directed therapy in HIV-1-associated meningitis is under-researched yet critical to manage associated CNS inflammation. Drugs such as corticosteroids and aspirin for TBM, daptomycin for bacterial meningitis and dexamethasone for HSV-1 encephalitis are currently under investigation in clinical trials.
- Supportive management is critical, in particular the management of raised intracranial pressure which is lethal when not treated. The utility of pharmacological versus surgical interventions and the scenario in which either would be most beneficial is poorly understood. This is an important area for future research.

This box summarizes key points contained in the article.

The purpose of this narrative review is to provide a detailed overview of etiology, assessment, and management of meningitis in PLWH, with a focus on adults in resource limited settings. We suggest a clinician focused pragmatic approach to diagnostic evaluation with a view to overcoming the diagnostic and treatment challenges described above. We provide an up to date commentary on established and emerging treatments including; management of underlying HIV-1 disease, specific chemotherapeutic management, host-directed therapies and supportive care. We conclude with commentary on key knowledge gaps and suggest areas for future research.

2. Etiology and Epidemiology

The etiology of meningitis in HIV-1 varies by geographical location. Global epidemiology is poorly characterized, but CM appears to be the most common cause in LIC [5], followed by TBM [9]. Systemic misdiagnosis of CM may lead to an underestimation of global incidence, with epidemiological publications frequently presenting data from major centers of care in LMIC not reflecting what could be the majority of cases being treated in more rural settings [10]. While the global epidemiology of CM is well described in terms of the variation between the different molecular types of *C. neoformans* and *C. gatti*, data is largely lacking for many countries in Africa, Asia, and Eastern Europe [11]. The occurrence of CM and TBM co-infection has been reported in LMIC such as China, but due to a lack of specific symptoms in these patients there may be an

underestimation of the incidence of co-infection [12]. Neurosyphilis (NS) is the cause in approximately 3% of cases in Africa, but is poorly studied in this setting compared to HIC and further research is needed to establish the true prevalence in patients with HIV-1 infection [13]. Estimating the incidence of various viral etiologies of HIV-1-associated meningitis is complex due to the fact that some viruses more commonly present as an encephalitis and the distinction isn't made between the two conditions in published data, despite varying treatment approaches and prognosis. This is true for cytomegalovirus (CMV) and herpes simplex virus-1 (HSV-1), commonly presenting as encephalitis and grouped together with other common causes of meningitis like HSV-2. Epstein-Barr virus (EBV) is the most prevalent CNS viral pathogen reported in LIC, frequently associated with CM and TBM co-infection in a Zambian study [14]. The clinical importance of this is unclear as viral reactivation may occur in uncontrolled HIV-1 infection where EBV DNA is observed more frequently in the cerebrospinal fluid (CSF) of individuals with higher levels of HIV-1 RNA in their CSF or plasma [15]. Varicella-zoster virus (VZV) and CMV were also detected together with CM and TBM in studies from Zambia and Botswana [14,16]. The incidence of bacterial meningitis were comparable between HIC and LMIC; with strong predomination of pneumococcal meningitis and followed by meningococcal meningitis. PLWH have a 20–150 times higher relative risk of developing pneumococcal meningitis compared to the general population as demonstrated in several studies conducted in HIC and LMIC [17]. *L. monocytogenes* meningitis occurs more frequently in HIV-1 infected populations, with a relative risk of 19.4 (13.6–27.5) compared to HIV-1 uninfected age-matched controls [18], in **Table 1** reflected as the least common pathogen in BM. While the introduction of the *Haemophilus influenzae* Type B (Hib) vaccine as well as the pneumococcal conjugate vaccine (PCV) has influenced the prevalence of bacterial meningitis (BM) in children, the same effect has not been demonstrated in adults [19,20].

We pooled data in **Table 1** to show the distribution of different etiologies of meningitis in HIV-1 infected individuals or populations with a high HIV-1 seroprevalence, alongside clinical, radiological and laboratory features typical for each causative organism. Further information about the literature sources used to demonstrate the proportion of different meningitis etiologies per geographical location is shown in **Supplementary Table 1**. No dual infection was reported in the HIC listed in **Table 1**. The treating clinician must consider the differing incidence of common etiologies and rates of dual infection in their given setting to ensure that the diagnostic approach suggested later in this review can be tailored to their patient population. Rare causes like drug-induced, JC and BK polyomavirus, strongyloidiasis, as well as meningitis due to HIV-1 seroconversion are not covered in this review, but should be considered as a potential differential in atypical presentations.

Table 1. Common fungal, viral, bacterial and mycobacterial etiologies of HIV-1-associated meningitis with description of CD4 count, mortality and clinical, laboratory and radiological clues to diagnosis.

Clinical, radiological and laboratory clues to diagnosis

Etiology and pathogens	Proportion of meningitis cases per geographical location	Typical CD4 count at onset (cells/ μ L)	Mortality in routine care setting in sub-Saharan Africa [21]	Clinical	Radiological	Cerebrospinal fluid
Fungal <i>Cryptococcus neoformans</i>	China [22]: 63% US [23]: 8% Uganda [24]: 60% South Africa [25]: 62.3% Botswana [16]: 89%	<100	Short term (<2 weeks): 44% Medium term (<10 weeks): 51% Long term (9–12 months): 63%	Signs of raised intracranial pressure (e.g. nausea/vomiting, blurred vision, cranial nerve palsy)	Diffuse pattern of leptomeningeal enhancement \pm communicating hydrocephalus \pm ring enhancing lesions \pm basal ganglia pseudocysts	High opening pressure, lymphocyte predominance, often low glucose
Tuberculous <i>Mycobacterium tuberculosis</i>	US [23]: 1.2% China [22]: 13% Zambia [14]: 14.5% South Africa [25]: 24.6%	<100 [26], but frequently observed at higher counts	Short term (<2 weeks or in-hospital): 46% Medium term (<10 weeks): 46% Long term (6–12 months): 56–78%	Subacute onset. May have symptoms suggesting TB elsewhere (cough, weight loss, fatigue). May present with seizures \pm stroke. Consider radiculomyelopathy/arachnoiditis in those with leg weakness \pm bladder/bowel dysfunction	Basal pattern of leptomeningeal enhancement \pm hydrocephalus \pm ring enhancing lesions. Infarcts (often multiple) typically in tubercular zone (caudate, anterior thalamus, anterior limb and genu of the internal capsule)	Lymphocyte predominance with low glucose (<2.2 mmol/L) and high protein
Bacterial <i>Streptococcus pneumoniae</i> <i>Neisseria meningitidis</i> <i>Haemophilus influenzae</i> <i>Escherichia coli</i> <i>Treponema pallidum</i> <i>Listeria monocytogenes</i>	US [18]: 10.9% (<i>S. pneumoniae</i> 2.1%, <i>E.coli</i> 0.7%, <i>N. meningitidis</i> 0.3%, <i>H. influenzae</i> 0.3%, <i>L. monocytogenes</i> 0.3%) Uganda [24]: 1.6% (<i>S. pneumoniae</i> 1.3%, <i>N. meningitidis</i> 0.3%) Zambia [14]: 3% (<i>S. pneumoniae</i> 80%, <i>N. meningitidis</i> 20%) Botswana [16]: 11% (<i>S. pneumoniae</i> 7.6%, <i>E. coli</i> 0.2%, <i>H. influenzae</i> 0.2%) South Africa [25]: 12% (<i>S. pneumoniae</i> 10.1%, <i>N. meningitidis</i> 0.8%, <i>E. coli</i> 0.6%, <i>H. influenzae</i> 0.2%, <i>L. monocytogenes</i> 0.1%)	Occurs at any CD4	Short term (14–30 days and in hospital): 54% Medium term (<10 weeks): 47–69% Long term (6 months): 49–69%	Acute (<1 week) May have symptoms of otitis/sinusitis (<i>S. pneumoniae</i>), <i>L. monocytogenes</i> and <i>E.coli</i> may GI symptoms <i>T. pallidum</i> commonly cranial neuropathy and neuropsychosis	Diffuse leptomeningeal enhancement \pm ring enhancing lesions \pm ventriculitis <i>T. pallidum</i> : infarct of middle cerebral or basilar artery branches territory, cerebral gummas	Polymorph predominance

Viral

(Continued)

(Continued).

			Clinical, radiological and laboratory clues to diagnosis			
Etiology and pathogens	Proportion of meningitis cases per geographical location	Typical CD4 count at onset (cells/ μ L)	Mortality in routine care setting in sub-Saharan Africa [21]	Clinical	Radiological	Cerebrospinal fluid
<i>Non-Polio Enteroviruses (NPE)</i> <i>(coxsackievirus, echovirus, enterovirus)</i> <i>VZV, HSV, Mumps, CMV, EBV</i> <i>Selected arthropod-borne viruses e.g. West Nile virus (WNV), Dengue virus (DENV), Zika virus (ZV)</i>	US [18]: 14.2% (HSV 4.9%, Enterovirus 2.7%, VZV 1.6%, EBV 0.9%) China [17]: 31.5% (CMV 22.2%, VZV 3.7%, EBV 1.9%) Uganda [19]: 8.2% (EBV 7%, CMV 0.3%, VZV 0.3%, Enterovirus 0%) Zambia [11]: 45% (EBV 27.4%, CMV 6%, VZV 3.9%, HSV-1 1.5%)	CMV < 50 [66]	Not known, generally low mortality rates	History of preceding systemic symptoms (e.g. myalgias, fatigue, or anorexia) NPE may follow episode of GI symptoms (5–17% cases) [27] Prior genital herpes infection (HSV-2) or shingles/chicken pox (VZV) HSV-2 commonly benign presentation of meningitis with recurrence Mumps meningitis occurs 2–4 days following onset of parotitis DENV acute meningism, retro-orbital pain, arthralgia, myalgia, and petechial rash [28] WNV maculopapular rash \pm encephalitis and acute polio-like flaccid paralysis \pm parkinsonism and myoclonus [29], more prominent presentation of meningitis as compared to DENV ZV sudden onset meningism + petechial/maculopapular rash and conjunctivitis	HSV-1 asymmetrical involvement of the limbic system, medial temporal lobes, insular cortices and inferolateral frontal lobes – can be more diffuse (involving brainstem) with immunocompromise VZV vasculitis presenting with infarcts	Lymphocytic predominant, often with normal glucose and raised protein. Note that CSF can have predominant polymorph appearance in early stages

CMV, cytomegalovirus; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; GI, gastrointestinal; HSV, herpes simplex virus; TB, tuberculosis; US, United States; VZV, varicella zoster virus.

3. Diagnostic approach

A number of similarities in the clinical presentation exist between cryptococcal, tuberculous, viral and bacterial meningitis. In many cases, patients present with a lymphocytic CSF, which, in the absence of a positive cryptococcal antigen (CrAg) test, can present a diagnostic challenge to the attending physician. Treating physicians should also keep in mind the possibility of multiple pathogens in the CSF; while uncommon, co-infection with TBM and CM can occur and CM is easily diagnosed, a challenge arises in excluding TBM. Figure 1 provides a pragmatic diagnostic algorithm designed to guide the physician in the work up of patients with HIV-1-associated meningitis, including in the above scenario. Rationale for the use of the listed tests and other potential new diagnostics are expanded in the text below. While diagnostic methods are always being improved, highly sensitive tests are often not available in resource-limited settings or the turnaround time for gold standard testing is too slow to assist with rapid diagnosis; for example, the long turnaround time of tuberculosis culture, the current limited use of Xpert Ultra, unavailability of CT scans or local laboratories to obtain results CrAg results urgently. Clinicians in these settings should rely on their knowledge of regional incidence patterns and the clinical context to assist with diagnosis. There are a number of scoring systems that can aid the diagnosis of meningitis where microbiological confirmation of causative organism is delayed or unavailable, as

is often the case in LMIC. The Thwaites diagnostic score has recently been shown to have high sensitivity (93%) in differentiating between TBM and bacterial meningitis, while the Lancet Consensus Score has high specificity (up to 100%) in distinguishing between TBM and other forms of meningitis [30].

3.1. Cryptococcal meningitis

Rapid assays for detecting CrAg in blood and CSF are now first line diagnostic tests for CM recommended by the World Health Organization (WHO) [6]. Preemptive screening for serum CrAg, which can be positive an average of 22 days preceding symptoms [31], has also been recommended since 2011. The lateral flow assay (LFA) is a point-of-care, inexpensive test that halves sample processing time [32]. In multiple validation studies it has proved superior when compared to culture, microscopy, latex agglutination (LA) or enzyme immunoassay (EIA) [33], with a sensitivity of 93% in serum [34] and in CSF a sensitivity and specificity of 99% [35]. In settings where rapid assay testing isn't available, direct microscopy of CSF using the India ink stain is recommended [6], despite its relatively poor sensitivity (86%) which is lower (42%) in samples with a fungal burden <1000 CFU/mL [35]. A recent study using acrinine orange fluorescent staining showed a higher sensitivity than India ink (96% vs. 79%) [36], which could be a valid alternative in LIC. While culture is considered a diagnostic gold standard, the slower turn-around time of up to 2 weeks prove less efficient than the current point of care tests in high disease burden settings. Culture remains valuable in monitoring treatment response by measuring fungal burden.

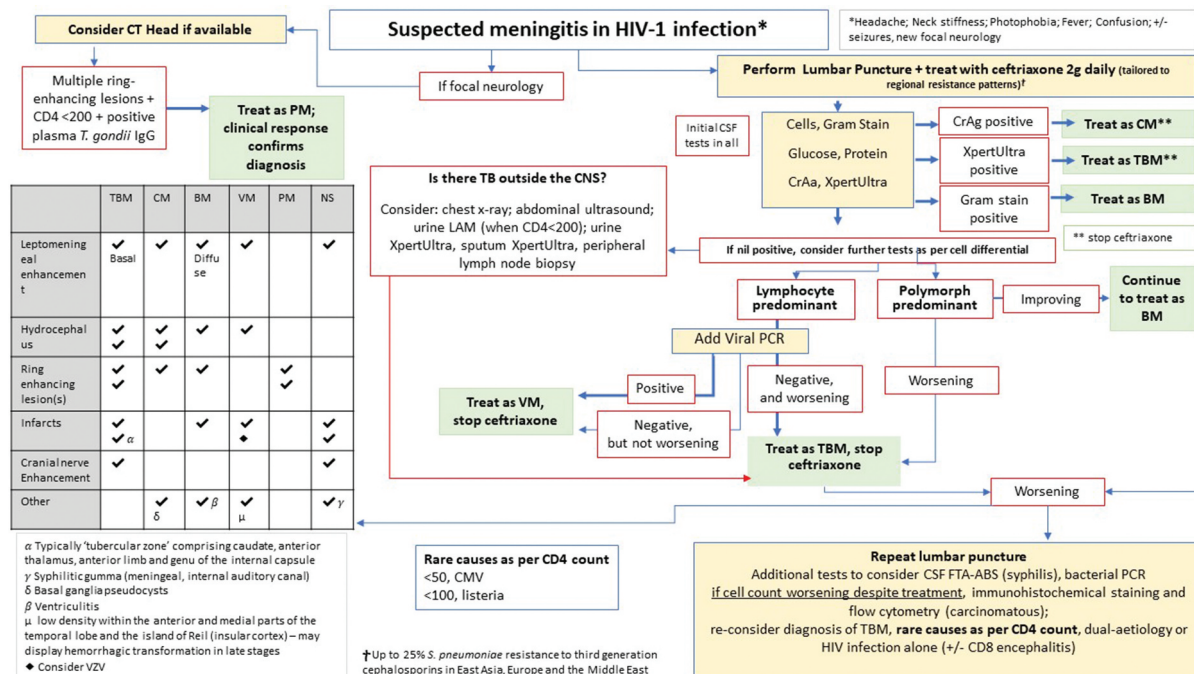


Figure 1. A diagnostic algorithm for HIV-1-infected patients presenting with meningitis.

3.2. Tuberculous meningitis

The diagnosis of TBM is challenging due to a paucibacillary CSF and lack of rapid diagnostic tests with high sensitivity and specificity. Ziehl-Neelsen stain microscopy is the most commonly implemented method for rapid diagnosis of TBM through detection of acid-fast bacilli, despite a sensitivity of 10–20% [37]. The gold standard for diagnosis and drug susceptibility testing (DST) is CSF culture, with sensitivity just over 70% (higher when using liquid vs solid media) when compared to case definition of probable or definite TBM [38]; however, the long culture duration (6–8 weeks) means this test is seldom useful for initial treatment decisions.

The introduction of nucleic acid amplification testing on CSF has shortened the turnaround time to hours; however, these tests are not without limitations. The Xpert MTB/RIF assay had sensitivity of 72% in CSF that underwent centrifugation when compared to a definite TBM diagnosis [38]. Xpert Ultra was introduced in 2017 and a small ($n = 23$) cohort demonstrated a sensitivity of 70% for possible and definite TBM cases [39]. When recently compared to mycobacterial culture ($n = 205$, 31 participants with HIV co-infection), the sensitivities of Xpert MTB/RIF was 81% and Xpert Ultra was 90% with specificity at 93% and 96%, respectively [40]. Although having a low diagnostic yield of 41% HIV-1-infected patients ($n = 348$) with definite TBM, a prospective study demonstrated that mortality was 6-fold higher in those with positive urine Xpert Ultra testing ($p = 0.04$) [41]. South Africa is the only country with a high burden of TB currently using Xpert Ultra as a first line diagnostic test for TB [9]. As per the June 2020 WHO TB detection guidelines, this test is now recommended as first line diagnostics for suspected TBM, rather than microscopy and culture [42]. This will lead to increased utilization of this highly sensitive test in low-income countries. Both tests require electricity, servicing and cartridges; and thus may be challenging to implement in rural settings, and has not shown to improve survival when used for diagnostics [43]. These diagnostics rely on the rapid isolation of the bacilli, however given the low cerebrospinal bacillary load in TBM effective diagnostics may also need to make use of discovery technologies including mass spectroscopy and RNA sequencing analysis or microarray to identify a characteristic immune response.

Rapid, point-of care testing in the form of Lipoarabinomannan (LAM) LFA can be done on CSF, but as with other tests sensitivity is sub-optimal and variable (sensitivity 21–68%, specificity 94%) [43,44]. FujiLAM has superior sensitivity to AlereLAM on CSF (50% vs. 14%) with a specificity of 98% for patients without probable or definite TBM; and with a sensitivity that approaches that of Xpert Ultra this could improve the time-to-treatment in lower resource settings [45].

3.3. Bacterial meningitis

In CSF analysis, polymorph leucocytosis of >1000 cells/mm³ is the best discriminator between bacterial and other causes of meningitis [46,47]. CSF culture remains the gold standard with a sensitivity of 81% when compared by to Gram stain and

polymerase chain reaction (PCR) [48]. A study on repeated CSF cultures after normal initial CSF showed an increased diagnostic yield in clinically deteriorating patients, either by new bacteriological growth or the emergence of cell abnormalities [49]. This can assist with confirming the diagnosis of BM in this subset of patients. Gram stain is a widely used, rapid test that is valuable in early diagnosis with a sensitivity of 97.5% when referenced to culture, but less affected than culture by antibiotic activity in the CSF [48]. Antigen detection by latex agglutination (LA) is rapid, but when compared to culture sensitivity is 66% [50]. In culture negative BM pre-treated with antibiotics LA was also negative in all samples [51], showing no added value compared to other rapid testing modalities. The ongoing development of PCR assays has shown sensitivities up to 100% [52] and detection in culture negative samples [53]. These tests are also becoming less expensive and time consuming [54].

3.4. Neurosyphilis

Symptomatic meningitis due to infection of the CNS with *Treponema pallidum* is one of many early and late clinical manifestations of NS, including cranial neuropathies, ocular disease, vasculitis, neuropsychiatric presentations, spinal cord disease, and tabes dorsalis [55]. While syphilitic meningitis commonly presents with meningeal symptoms and cranial nerve involvement, asymptomatic meningitis commonly occurs following initial infection [56]. Diagnosis is made by serological and CSF non-treponemal tests (NTT) together with treponemal tests (TT). NTT has high specificity; $>99\%$ for CSF venereal disease research laboratory (VDRL) and rapid plasma regain (RPR) [57], and TT has moderate sensitivity; 66% for fluorescent treponemal antibody absorption (FTA-ABS) and 77% for *Treponema pallidum* particle agglutination (TPPA) in CSF [58]. Sensitivity increases to $>95\%$ when combined with a reactive CSF VDRL [58]. While the Centers for Disease Control and Prevention (CDC) define verified neurological syphilis as both a reactive CSF VDRL and consistent clinical signs without any other known cause [59], the low sensitivity of the VDRL test is an obstacle to diagnosis. A symptomatic NS diagnosis is unlikely unless a positive serum FTA-ABS (confirming previous syphilis) and positive CSF VDRL is demonstrated, while a non-reactive CSF VDRL is highly specific in ruling out asymptomatic NS [60]. In the case of a non-reactive CSF VDRL, a CSF TPPA titer of $>1:640$ in untreated patients may aid the diagnosis of asymptomatic NS, but is not routinely performed [58]. While European guidelines also suggest CSF analysis in HIV patients with $CD4 \leq 350$ cells/ μ L and/or VDRL/RPR titers $\geq 1:32$ [61], there is no evidence that this reduces the incidence of symptomatic NS or improves outcomes and is not routinely recommended in LMIC. Following adequate treatment for syphilis a number of cases will not achieve a serological cure, defined as a ≥ 4 -fold decrease in NTT titers. In HIV this number is high, with 54% of cases at 6 months and 36% of cases at 12 months [62]. When tested, 41% of serofast cases had asymptomatic NS. Larger studies are needed to assess the use of titer monitoring and CSF testing in serofast HIV-1 patients.

Table 2. Overview of commonly recommended regimens for the treatment of meningitis, based on causative organisms and emerging therapies.

Type of meningitis	Causative organism	Chemotherapeutic management	Source	Host-directed therapies	Current/future research
Cryptococcal	<i>Cryptococcus neoformans</i> , <i>Cryptococcus gattii</i>	HIV-infected patients: Initiate with amphotericin B (1 mg/kg/day) and flucytosine (25 mg/kg/dose four times a day) for 1 week, THEN fluconazole (1200 mg/day for adults and 12 mg/kg/day for children and adolescents) for 1 week. This is followed by fluconazole 800 mg/day for 8 weeks, during the consolidation phase. The maintenance phase consists of fluconazole 200 mg/day until there is evidence of sustained ART-related immune reconstitution [6]	WHO	Use of corticosteroids in the induction phase is strongly discouraged in adults. [6]	Initiation of treatment with high dose LAmB (10 mg/kg as a single dose), fluconazole (1200 mg per day) and flucytosine [6,86] VT-1129 is currently in Phase I clinical trials in the US [92,93]
Tuberculous	<i>Mycobacterium tuberculosis</i>	Rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months, followed by rifampicin and isoniazid for 6–9 months [73–75].	WHO	Initiate adjuvant corticosteroid therapy using either prednisone or dexamethasone, tapered over 6–8 weeks [74,75]	LASER-TBM (NCT03927313) ALTER (NCT04021121) SIMPLE (NCT03537495) ACT-HIV (NCT03092817)

(Continued)

Table 2. (Continued).

Type of meningitis	Causative organism	Chemotherapeutic management	Source	Host-directed therapies	Current/future research
Bacterial	<i>Streptococcus pneumoniae</i>	Initiate ceftriaxone 2 g IV 12-hourly until confirmation (culture or PCR). If confirmed, continue with ceftriaxone or switch to penicillin G 2.4 MU IV four hourly (if MIC < 0.1 µg/mL). If penicillin and cephalosporin resistant, add vancomycin 15–20 mg/kg IV 12 hourly and rifampicin 600 mg IV/orally 12 hourly for 10 days (if ceftriaxone MIC > 2 µg/mL). Use ceftriaxone plus vancomycin if ceftriaxone MIC > 0.5 µg/mL. If patient unrecovered, continue treatment for 14 days [103,104]	FIDSSA Royal College of Physicians	Dexamethasone 10 mg IV 6 hourly for four days may be beneficial in developed countries [103]. In resource limited settings with a high HIV-1 prevalence, the use of steroids is not recommended [113]	AddaMAP (NCT03480191)
	<i>Neisseria meningitidis</i>	Initiate ceftriaxone 2 g IV 12 hourly until confirmation (culture or PCR). If confirmed, continue with ceftriaxone or switch to penicillin G 4 MU IV 4 hourly for 7 days if patient recovers [103,104]	FIDSSA Royal College of Physicians	Initiate dexamethasone 10 mg IV 6 hourly until confirmed NOT pneumococcal meningitis, then STOP [76,103]. In resource-limited settings with a high HIV-1 prevalence, the use of steroids is not recommended [113]	Study to Assess Immunogenicity & Safety of Pentavalent Meningococcal Vaccine (NmCV-5, NCT03964012)
	<i>Haemophilus influenzae</i>	Initiate ceftriaxone 2 g IV 12 hourly, switch to penicillin G 2.4 MU IV 4 hourly if susceptibility confirmed for 10 days [103,142]	FIDSSA Royal College of Physicians	Initiate dexamethasone 10 mg IV 6 hourly until confirmed NOT pneumococcal meningitis, then STOP [103]. In resource limited settings with a high HIV-1 prevalence, the use of steroids is not recommended [113]	No data
	<i>Treponema pallidum</i>	Penicillin G 3 to 4 MU IV four hourly for 10 to 14 days followed by penicillin G 2.4 MU intramuscular once a week for 3–2 weeks [114]. Ceftriaxone recently shown to be similarly effective [115],	CDC NHI HIVMA IDSA	No recommendations in resource limited settings	No data
	<i>Listeria</i>	<i>monocytogenes</i>	Ampicillin 2 gm IV 4–6 hourly (or penicillin G 4 MU IV 4 hourly) for ≥ 3 weeks (some add gentamicin 1.7 mg/kg IV 8 hourly). Monitor renal function and, if possible, trough levels with gentamicin. May stop after 1–2 weeks if patient is significantly improved and/or renal function declines.	CDC NIH HIVMA IDSA	AVOID dexamethasone: associated with worse outcomes [77]. If started as empiric therapy and patient found to have listeria- stop dexamethasone.

No data

(Continued)

Table 2. (Continued).

Type of meningitis	Causative organism	Chemotherapeutic management	Source	Host-directed therapies	Current/future research
Viral	Enteroviruses	No specific treatment. Symptomatic management (analgesia and anti-emetics) and supportive care. Most infections are self-limiting		No data	No data
	VZV	Acyclovir 10–15 mg/kg IV 8 hourly for 14 days. [120]	IDSA	Corticosteroids may be considered, however no reliable data to support their use [120]	There is promise regarding the use of oral valacyclovir for the treatment of VZV meningitis [121]
	CMV	Ganciclovir 5 mg/kg IV 12 hourly 3 to 6 weeks [74,78,114]	CDC NIH HIVMA IDSA	No data indicating benefit of adding corticosteroids [78]	Numerous trials investigating the safety of valganciclovir in organ transplant patients
	HSV-1	Acyclovir 10 mg/kg IV 8 hourly for 21 days in immunocompromised individuals such as PLWH [78,79,104]	FIDSSA French Infectious Diseases Society	No data indicating benefit of adding corticosteroids [78,79]	DexEnceph (NCT03084783)
	HSV-2	No specific antiviral treatment recommended. Acyclovir and valacyclovir have been used for recurrent presentations [118,119]		No data	No data
Parasitic	<i>Toxoplasma gondii</i>	Cotrimoxazole 25 mg/5 mg per kg 12 hourly OR Pyrimethamine 200 mg oral stat, followed by: >60 kg: 75 mg daily <60 kg: 50 mg daily PLUS Clindamycin 600–900 mg 6 hourly or Sulfadiazine: >60 kg: 3000 mg 12 hourly <60 kg: 2000 mg 12 hourly PLUS Folinic acid 10–15 mg/day Induction treatment for at least 6 weeks [80]	Konstantinovic et al. 2019	Adjunctive corticosteroids to be administered only when clinically indicated to treat a mass effect associated with focal lesions or associated edema. Discontinued when clinically feasible [125].	Adjunctive Dexamethasone for Cerebral Toxoplasmosis (NCT04341155)

3.5. Viral meningitis

Highly specific molecular tests in the form of pathogen specific or multiplex CSF PCR assays enables the diagnosis of viral meningitis [63]. Confirming viral etiology may reduce unnecessary antibiotic use for suspected bacterial meningitis and reassure the clinician that common presentations like tuberculous meningitis is less likely. Potential viral pathogens in HIV-1 include enterovirus, herpesviruses (most notably HSV-2 and VZV), EBV and less commonly CMV. Specific consideration should be given to clinical syndrome, as the same virus can present as a self-limiting meningitis or a more severe encephalitis. Enterovirus was the most common pathogen encountered in a cohort of 26,429 adults with meningitis and encephalitis in the USA [64], and while usually presenting as a mild meningitis it can be prolonged and more severe in those with impaired B-cell responses commonly observed in HIV. PCR testing on stool samples might be more sensitive than CSF (96% vs. 74%) if enterovirus meningitis symptoms have been present for more than two days [65]. CMV rarely presents as a pure meningitis syndrome and should be considered in PLWH with CD4 counts <50 cells/ μ L [66] with features of encephalitis.

3.6. Parasitic meningitis (PM)

The most common opportunistic parasite in HIV-1 infection is *T. gondii*. Cerebral toxoplasmosis predominantly presents as an encephalitis and in rare cases as a meningitis, but still may be underdiagnosed in areas where advanced diagnostic techniques are lacking [16]. Seropositivity for anti-Toxoplasma-IgG in HIV-associated toxoplasma encephalitis is as high as 91%, with higher titers (1:4000 in ELISA, $p < 0.001$) a strong indicator of active disease when correlated with confirmed cerebral toxoplasmosis by CDC criteria. This figure varies between geographical locations. PCR detection of *T.gondii* DNA in serum has variable sensitivity of 25–97% and specificity of 100% [67,68]. When performed on peripheral blood mononuclear cells sensitivity is increased, but further studies are needed to validate this result [69]. When lumbar puncture is deemed safe in suspected toxoplasma encephalitis, CSF PCR has a high specificity (95–100%) and positive predictive value (86%) and is useful in confirming the diagnosis [70,71]. Histopathological diagnosis by brain biopsy remains the definitive diagnostic method, but is not widely used.

3.7. Other

Carcinomatous meningitis can mimic cryptococcal and tuberculous meningitis with CSF findings like increased opening pressures, elevated protein and lymphocyte predominance [72]. Confirmed or suspected systemic malignancy, as well as failure to respond to treatment for alternative diagnoses should prompt further investigation by CSF cytology, immunohistochemical staining, and flow cytometry.

4. Management

4.1. Specific chemotherapeutic management

Specific chemotherapeutic management of meningitis should be driven by local guidelines, particularly in the context of geographical resistance patterns to antimicrobials and variable availability of drugs. Meningitis frequently warrants empirical treatment as microbiological confirmation is often delayed or unavailable, especially in LMIC, and should be guided by clinical findings. Table 2 provides an overview of commonly recommended regimens for each causative organism with further information on new and emerging agents in respective sections below.

4.1.1. Cryptococcal Meningitis

The international standard induction treatment is 1 week of amphotericin B deoxycholate with flucytosine [6]. Fluconazole mono-therapy, even at 1200 mg daily, is not a suitable treatment during induction, associated with a mortality rate of 55% during the first 10 weeks of treatment [81]. In light of the problems associated with administering and obtaining intravenous (IV) amphotericin B and the shortage of flucytosine, especially in resource limited countries, the Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa (ACTA) trial of 2018 set out to assess the efficacy of two regimens that would be more sustainable in LMIC [82]. This was the largest trial on HIV-1 CM up to date ($n = 721$) and proved that 1 week of treatment with amphotericin B plus flucytosine is the most effective option for induction therapy for HIV-1-associated CM in settings with limited resources. In situations where amphotericin B is unavailable or cannot be administered safely, an oral regimen of fluconazole plus flucytosine proved effective. Both regimens were noninferior to the international standard induction treatment mentioned. A recent systematic review and meta-analysis comparing data from 13 trials supported these results [83] and these two regimens have since been endorsed by the WHO [6]. Different molecular types and subtypes of cryptococcus may have differing susceptibilities to azole antifungal drugs, which may influence treatment outcomes as well as resistance patterns in regions where *C. gatti* is prevalent [84].

Liposomal Amphotericin B (LAmB) is known to cause fewer adverse events with lower rates of drug-induced toxicity than the standard formulation of amphotericin B [85]. The Ambisone Therapy Induction Optimization (AMBITION) phase II trial concluded that a single dose of LAmB at 10 mg/kg has noninferior early fungicidal activity compared to the standard recommended regimen and is tolerated well [86]. Phase III recruitment started in 2018 and will be using 10-week mortality as a clinical primary endpoint. In a recent Cochrane review published in 2018 comparing the outcomes of early (less than 4 weeks after starting antifungal treatment) versus delayed (more than 4 weeks after starting antifungal treatment) initiation of ART in CM, the authors found that although there is some evidence to demonstrate a higher risk of developing IRIS following early initiation of ART following CM diagnosis, the certainty of this evidence was low and there is an increased risk of mortality when ART is initiated within 4 weeks of

diagnosis than when compared to initiation after 4 weeks [87]. These findings are consistent with those from the Cryptococcal Optimal ART Timing (COAT) trial, which was stopped early due to excess deaths in the group where ART was initiated within 2 weeks of antifungal treatment [88].

The CryptoDex trial published in 2016 investigated the adjunctive use of glucocorticoids in HIV-1-associated CM from time of diagnosis. The rationale for this study was that in TBM (where some pathophysiological features are similar to CM) dexamethasone decreases mortality in HIV-1 uninfected people [89] and retrospective data, which suggested a reduction in risk of blindness when used in HIV-1-associated CM [90]. The trial was stopped for safety reasons, with participants in the dexamethasone group showing higher mortality, disability and adverse event rates together with slower CSF fungal clearance compared to the placebo group. As such, co-administration of intravenous corticosteroids in CM is not recommended [91].

A potential new treatment for CM is VT-1129 (Quilseconazole, Viamet Pharmaceuticals); a tetrazole-pyridine hybrid compound which has shown promising results *in vitro* against *cryptococcus* and preclinical studies *via* oral administration. It has received fast-track orphan designation by the Food and Drug Administration (FDA) and is currently undergoing Phase I clinical trials in the USA [92,93].

4.1.2. Tuberculous Meningitis

The current WHO recommended regimen is 2 months of treatment with RIF, INH, pyrazinamide (PZA), and ethambutol (ETH), followed by 6–9 months of RIF and INH. The combination of drugs and their doses used are based on studies of pulmonary (rather than CNS) TB and do not account for the differing ability of the drugs to penetrate the blood brain barrier or the brain parenchyma. RIF, the key sterilizing drug in TB, has CSF penetration of around 10–20% [94] at the recommended dose of 10–15 mg/kg. Two key RTCs designed to assess the efficacy of higher doses of RIF in TBM have demonstrated inconsistent results; the first, smaller RCT

($n = 60$) showed a reduction in mortality of 50% using 13 mg/kg IV compared to standard dose [95], while the second much larger RCT ($n = 817$) showed no effect on mortality at 9 months with 15 mg/kg orally compared to standard dose [96]. In a pharmacokinetics (PK) study oral doses of 20–30 mg/kg didn't increase grade three and four adverse events and improved early bactericidal activity [97]. Biodistribution of drugs beyond CSF into the brain parenchyma has recently been investigated using noninvasive C-11-rifampin positron emission tomography; within rabbit models of TBM, rifampicin penetration to brain lesions was limited, spatially heterogenous and did not correlate with CSF or plasma concentrations [98]. Another recent PK study demonstrated that oral RIF doses of 15 mg/kg almost doubled CSF exposure when compared to 10 mg/kg on day 14, although this did not correlate with survival based on *in silico* simulations [99].

Although a number of RCT [100] have investigated the efficacy of adjunctive corticosteroids in TBM, only one included HIV-1 infection (98/545 participants) [89]. In this subgroup (although not powered to show an effect), there was no benefit on morbidity or mortality. The Adjunctive Corticosteroids for Tuberculous Meningitis in HIV-infected Adults (ACT-HIV) trial is currently underway to further correlate these findings.

The Linezolid, Aspirin, and enhanced dose Rifampicin in HIV-TBM (LASER-TBM), Pharmacokinetic Study of Linezolid for TB Meningitis (SIMPLE) and Adjunctive Linezolid for the Treatment of Tuberculous Meningitis (ALTER) trials examine the use of linezolid and aspirin in TBM. The first trial exclusively studies HIV-1-infected participants, while the other two also consider HIV-1-uninfected participants. All three trials also include linezolid PK sub-studies.

For drug-resistant TBM, the WHO recommends drug susceptibility testing of the infecting strain, and knowledge of the pharmacokinetics of TB medicines, specifically, their ability to cross the BBB. Treatment of MDR/rifampicin-resistant (RR) TBM may require prolonged regimens. A number of agents have shown good permeability across the BBB; levofloxacin, moxifloxacin, ethionamide/prothionamide, cycloserine/terizidone, linezolid, imipenem-cilastatin, high dose isoniazid and pyrazinamide, while amikacin and streptomycin are only able to penetrate the CNS in the presence of meningeal inflammation [101]. In a small case series, delamanid as one of the newer agents for treatment of pulmonary MDR-TB, was shown to achieve adequate concentration in brain tissue and despite low total CSF drug levels there may be sufficient free drug available to make this a promising candidate for the treatment of RR-TBM in the future [102]. Insufficient data is available for newer agents such as bedaquiline and pretomanid, which may have potential in the treatment of DR-TBM. A reasonable regimen for RR-TBM, if full DST is not available, includes linezolid, fluoroquinolones, delamanid, high dose isoniazid, terizidone, and clofazimine based on pharmacokinetic and efficacy considerations.

4.1.3. Bacterial meningitis

Suspected BM is treated empirically or according to Gram stain until confirmation of the causative organism *via* culture or

Table 3. Incidence, onset and prognostic factors for TBM- and CM-IRIS with guidelines on the timing of ART initiation.

Condition	Incidence	Onset	Prognostic factors	ART initiation
CM-IRIS	17% [132]	± 29 days [132]	Persistent CSF cryptococcal growth on ART [133] Elevated CD4 response [134] Low CSF protein and lymphocytes [135]	WHO: 4–6 weeks [6] COAT trial: significantly improved mortality rate with initiation at 5 weeks as opposed to early [88]
TBM-IRIS	47% [129]	±14 days [129]	<i>M. tuberculosis</i> culture positive at presentation [137] High CSF neutrophil count (median 50 cells $\times 10^6/L$) and percentage (median 36%) [137]	No global recommendation Török et al: 8 weeks, no significant effect on mortality but significant reduction in grade 4 adverse events [136]

PCR. Empiric treatment is tailored to suspected pathogens and their susceptibility to available antimicrobials as well as local incidence patterns. Empirical treatment is with the use of ceftriaxone, given that penicillin non-susceptibility is common for *S. pneumoniae* meningitis and meningococcal meningitis [103]. Ampicillin should be added if there is a risk of listeria meningitis [104]. Ceftriaxone resistance is in general uncommon, however resistance to third generation cephalosporins have in some settings been reported in up to 25% of blood isolates for *S.pneumoniae* (highest in East Asia, Europe and the Middle East; also reported in South Asia and North Africa) as per the 2018 Global Antimicrobial Resistance Surveillance System (69 countries included, of which 16 LMICs) [105]. By contrast a study from South Africa found that cephalosporin non-susceptibility was as low as 7% [106]. Clinicians should know local susceptibility patterns to inform selection of appropriate empiric therapy.

In HIC (such as in the US and parts of Europe), where strains of *S. pneumoniae* resistant to cephalosporins are prevalent, vancomycin is added to ceftriaxone as empiric treatment [107–109]. In low income settings where alternative agents such as vancomycin are too expensive or not easily available, empiric treatment for pneumococcal meningitis is often still limited to cheaper and available agents such as ceftriaxone [110] until definitive treatment can be tailored to culture and sensitivity results.

Once the causative organism has been confirmed, therapy should be directed. For infections caused by *S. pneumoniae* and *H. influenzae*, ceftriaxone can be continued, or treatment can be switched to penicillin G for 10 days. For infections caused by *N. meningitidis*, therapy is continued for five days.

A meta-analysis on the use of corticosteroids in 4121 patients with acute BM demonstrated no significant reduction in mortality, but reduced the rate of hearing loss and short-term neurological sequelae. This shows that the addition of corticosteroids may be of value in HIC [111], and adjunctive dexamethasone can be administered simultaneously with the first dose of antibiotic, or 15 to 20 minutes prior [112]. However, in resource-limited settings with a high prevalence of HIV-1, it was found that adjuvant therapy with dexamethasone provided no additional benefit to morbidity and mortality. Therefore, their inclusion is not recommended in these settings, with antibiotics the mainstay of therapy [113].

The Adjunction of Daptomycin for the Treatment of Pneumococcal Meningitis (AddaMAP) trial is an open-label phase II trial being conducted across hospitals in France, evaluating the effect of daptomycin on bacterial proliferation and subsequently, inflammation, where daptomycin will be added to existing treatments, at the same dosage used for other conditions (10 mg/kg/day for 8 days). Results from this study will provide further information on whether the addition of daptomycin, due to its synergism with beta-lactam antibiotics and *in vivo* effect on the inflammatory response, is beneficial.

NS is treated with penicillin G for 10–14 days followed by penicillin G once a week for 3 weeks [114]. Recently, ceftriaxone has proven to be a similarly effective alternative that could potentially shorten hospitalization, but randomized controlled trials are needed to confirm these findings [115].

4.1.4. Viral meningitis

VM commonly occurs as a mild disease, but importantly, the clinical features of encephalitis and meningitis can overlap and emphasis needs to be placed on determining the clinical syndrome, as both these conditions have very different outcomes and treatments [116]. For example, while a herpes meningitis (commonly caused by HSV-2) is mild and self-limiting and will only be treated with acyclovir or valacyclovir if recurrent, encephalitis due to HSV-1 will lead to severe disability in 20% [117] of patients and treatment with acyclovir should be initiated promptly [117–119]. While enterovirus meningitis has been demonstrated as the most common pathogen causing VM in immunocompetent patients [64], the disease is mild and no antivirals are indicated. Other viral pathogens of meningitis such as VZV and CMV are more common in HIV-1 infection and in the context of encephalitis are also treated with acyclovir and ganciclovir respectively [120]. A recent case study showed oral valacyclovir (2 g every 6 hours for 10–14 days, and up to 21 days in severe cases) to be effective following a short course of IV acyclovir [121], which may be promising for the future.

There is currently no data supporting the use of corticosteroids as adjunctive therapy in VM, despite promising results in animal models [122]. The German trial on Acyclovir and Corticosteroids in Herpes-simplex-virus-Encephalitis (GACHE) which sought to study the effect of adjuvant dexamethasone versus placebo to existing acyclovir therapy, was stopped prematurely due to poor recruitment, and as a result, was inconclusive [123]. However, the Dexamethasone in Herpes Simplex Virus Encephalitis (DexEnceph) trial, an open-label phase III trial, will evaluate whether treatment with dexamethasone (in addition to acyclovir) improves long-term health outcomes in patients with HSV-1 encephalitis.

4.1.5. Parasitic meningitis

Treatment options for cerebral toxoplasmosis include cotrimoxazole, pyrimethamine plus sulfadiazine, pyrimethamine plus clindamycin or atovaquone. Folinic acid is given as an adjunct to pyrimethadine. In sub-Saharan Africa cotrimoxazole is recommended as first line treatment due to its wide availability and if pyrimethamine is the agent of choice it's paired with clindamycin for the same reason. Secondary prophylaxis should be given if CD4 count <200 cells/mm³ [124] and again cotrimoxazole is preferred due to protection against pneumocystis pneumonia and isosporiasis. Therapy is discontinued when CD4 count >200 cells/mm³, for more than 6 months, in response to ART. There is limited data regarding the use of corticosteroids (such as dexamethasone) for the treatment of HIV-associated cerebral toxoplasmosis. These agents, which may predispose infected patients to other infections due to their immunosuppressive potential, are only clinically indicated to treat life-threatening mass effect associated with focal lesions or associated edema, and should be discontinued as soon as it is clinically feasible [125].

The Adjunctive Dexamethasone for Cerebral Toxoplasmosis trial (NCT04341155), a phase 2 double-blinded RCT will compare the effect of dexamethasone to placebo in 160 participants in Indonesia, to look at the efficacy of dexamethasone

(as adjunctive therapy) in reducing mortality in cerebral toxoplasmosis patients.

Table 2: Empirical treatment prior to detection of a causative organism is covered in [Figure 1](#). All data on clinical trials was obtained from www.clinicaltrials.gov website (last accessed on 31 August 2020). Where specific guidelines are available, these have been listed under the 'source' column. Local guidelines in a particular geographical area should take preference. *Abbreviations:* CDC, Centers for Disease Control and Prevention; CMV, cytomegalovirus; FIDSSA, Federation of Infectious Diseases Societies of Southern Africa; HIVMA, HIV Medicine Association; HSV, herpes simplex virus; IDSA, Infectious Diseases Society of America; IV, intravenous; LAmB, liposomal amphotericin B; MU, million units; NIH, National Institutes of Health; PCR, polymerase chain reaction; VZV, varicella zoster virus; WHO, World Health Organization

4.2. Managing the underlying HIV: ART and IRIS

Current recommendations state that all patients newly diagnosed with HIV-1 should be initiated on ART regardless of CD4 count [126] based reduction in mortality and severe HIV-1-related illnesses [127]. However, the delayed initiation of ART in the treatment of CNS OI is important given the risk of IRIS. Paradoxical IRIS defined as worsening of symptoms following initiation of ART despite initial clinical improvement [128], is well described for TBM and CM where it carries high mortality (30% [129] and 20%, respectively [130]). [Table 3](#) reviews the current recommendations surrounding the timing of initiation of ART in TBM and CM. There is no data on IRIS following bacterial or viral meningitis. Low CD4 count at the time of ART initiation, especially below 50 cells/ μ L, as a global predictor for IRIS in AIDS-defining illnesses [130]. A recent review by Bowen *et al* proposed a case definition for CNS-IRIS based on T-cell dysfunction/counts, leukopenia, HIV viral loads, worsening neurological function, and brain imaging [131]. This is an update on the International Network for Studies Against HIV-Associated IRIS (INSHI) definitions and might be more encompassing of the spectrum of CNS-IRIS conditions, although this definition is limited in LMIC in terms of available diagnostic modalities.

Corticosteroids are widely used in the treatment of CNS-IRIS, however no dedicated studies have investigated its role in TBM-IRIS. Immunopathogenesis studies showed high levels of CSF cytokines such as tumor necrosis factor- α (TNF- α) in both CM- and TBM-IRIS [128,137], suggesting anti-TNF agents such as thalidomide and adalimumab may have a role in treating IRIS in the context of chronic relapses following tapering or stopping of corticosteroids [138,139]. One case report noted the development of TBM-IRIS after chronic adalimumab treatment for rheumatoid arthritis was stopped [140]. Further studies as required to investigate potential host directed therapies in IRIS following HIV-1-associated meningitis.

ART, antiretroviral therapy; CM, cryptococcal meningitis; CSF, cerebrospinal fluid; IRIS, immune reconstitution inflammatory response; WHO, World Health Organization.

4.3. Supportive care

4.3.1. Managing raised intracranial pressure (ICP)

Therapeutic lumbar puncture in CM decreases mortality risk by 69%, regardless of initial opening pressure [141]. The WHO recommendation is to drain CSF to below 20 cmH₂O, where clinical signs of raised ICP should suggest the frequency of taps [6]. In resource poor setting where manometers are scarce, the flow of CSF through a standard 22 G needle can accurately determine high pressures in 84% of cases where the rate is above 40 drops/min [142]. Patients with sustained symptoms of intracranial hypertension following multiple LPs and initiated on antifungal treatment showed sustained relief, especially from headaches, following ventriculo-peritoneal shunts [143], although its impact on morbidity and mortality is not established. In BM, however, aggressive treatment of raised ICP with extra-ventricular drainage within 8 hours in patients with severely impaired mental status decreased the relative risk of mortality by 68% and relative risk for unfavorable outcome by 40% [144]. Hydrocephalus is one of the most common features on brain imaging in TBM [145] and ventriculo-peritoneal shunting is one of the most prevalent surgeries performed to address this problem. The outcome of a recent systematic review showed poorer outcomes when this procedure was used to treat those with HIV-1 co-infection [146]. Medical management for cerebral edema in the form of diuretics is described and in traumatic brain injury hypertonic saline was slightly more effective than mannitol, particularly in refractory intracranial hypertension [147], but remains mostly subject to institutional protocols for the use in TBM. Raised ICP secondary to viral etiologies are rarely described, but a case series of seven patients in 2017 shows that it might be less rare and sometimes wrongfully classified as idiopathic intracranial hypertension [148].

4.3.2. Metabolic abnormalities

Monitoring for hypokalaemia, hypomagnesaemia and bone marrow/renal toxicity is imperative with Amphotericin B treatment and standardized preemptive IV hydration and electrolyte replacement should be in place, as this can improve survival by 30% [149]. In resource limited settings, while IV hydration was becoming more prevalent, toxicities, and electrolyte abnormalities can be as high as 43% [150].

Hyponatremia presents in 44% of TM cases, with cerebral salt wasting syndrome more frequently the underlying cause and relating to severity of the condition, than the syndrome of inappropriate secretion of antidiuretic hormone [151]. Distinction between these two causes is critical and clinical estimation of intravascular fluid volume can guide the diagnosis [152]. Fever in TBM increases 1 year mortality, but aggressive temperature control still requires further investigation [153].

5. Expert opinion

While the impact of OI causing meningitis in HIV has been increasingly studied in the post-ART era, global data that can aid the index of suspicion of clinicians is lacking. Especially in LMIC, limitations are frequently reported regarding the availability of inexpensive, sensitive and specific diagnostic tests and the absence of standardized investigation strategies

despite the high mortality associated with these conditions. As long as the limitation of delayed microbiological confirmation exists in the diagnosis of meningitis, clinicians have to rely on clinical presentation as well as knowledge of regional incidence patterns. Standardized clinical scoring systems can be of aid. HIV-1-associated CNS infections tends to be more prevalent in resource poor settings, which has a significant impact on its management; the limited availability of medications such as amphotericin B, LAmB and flucytosine, with only three manufacturers in 2017 and no availability in any Africa country as per the WHO, has led to the validation of shorter treatment courses. If LAmB becomes widely available, it would significantly improve the treatment of CM in LMIC. Data are lacking on the impact of different molecular types and subtypes of cryptococcus, which influences their susceptibility toazole antifungals. The commonly available CrAg and lateral flow assays cannot distinguish between molecular types. More robust epidemiological data and more targeted diagnostic tests are needed in LMIC. Treatment in the case of TBM may be suboptimal due to the use of an aging four-antitubercular-drug regimen that was never designed for use in TBM; drugs that account for the unique requirements of treating CNS infection such as passage across the blood brain barrier are needed. There are as yet no host directed therapy with proven benefit in HIV-associated TBM. While there exist differences in causative pathogens and resistance patterns in LMIC and HIC, there remains an imbalance in the availability of these drugs. It has been shown that clinical presentation is a poor predictor for the aetiology of meningitis; however, in resource-constrained settings, the clinician has to rely on clinical findings to aid in a differential diagnosis and often empirical treatment needs to be initiated before microbiological confirmation is achieved. The empirical administration of antibiotics and antiviral medication is a costly treatment strategy in the setting of HIV-1 where CM and TBM is more prevalent. IRIS complicates the management of meningitis in HIV-1-infected patients and further research regarding the use of corticosteroids and suitable alternative medications like anti-TNF agents is required. Management of raised ICP is an important aspect of supportive care and is tailored to the specific disease. Data are lacking on the benefit to mortality and morbidity in many of these methods, and the use of diuretics or other drugs to reduce ICP is not standardized. By acknowledging difficulties in existing systems and the inequities that exist between LMIC and HIC, the goal is for future research to focus on timeous diagnosis through novel, point of care diagnostic tests. There are a number of randomized clinical trials currently underway, focusing on CM and TBM, that can potentially offer more effective and readily available drugs, such as aspirin and dexamethasone.

Funding

This manuscript was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (***) to readers.

- UNAIDS. Global HIV & AIDS Statistics - 2020 fact sheet. Available from: <https://www.unaids.org/en/resources/fact-sheet> Last accessed 2020 Sept 28].
- Low A, Gavriilidis G, Larke N, et al. Incidence of Opportunistic Infections and the Impact of Antiretroviral Therapy among HIV-Infected Adults in Low- and Middle-Income Countries: a Systematic Review and Meta-analysis. *Clin Infect Dis.* 2016;62(12):1595–1603.
- Garvey L, Winston A, Walsh J, et al. HIV-associated central nervous system diseases in the recent combination antiretroviral therapy era. *Eur J Neurol.* 2011;18:527–534.
- Iroezindu M. Disparities in the magnitude of human immunodeficiency virus-related opportunistic infections between high and low/middle-income countries: is highly active antiretroviral therapy changing the trend? *Ann Med Health Sci Res.* 2016;6(1):4–18.
- Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect Dis.* 2017;17(8):873–881.
- WHO. Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2018. Available from: <https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/> [Last accessed 2020 Feb 4].
- Tenforde MW, Mokomane M, Leeme TB, et al. Mortality in adult patients with culture-positive and culture-negative meningitis in the Botswana national meningitis survey: a prevalent cohort study. *Lancet Infect Dis.* 2019;19(7):740–749.
- Marais S, Pepper DJ, Schutz C, et al. Presentation and outcome of tuberculous meningitis in a high HIV prevalence setting. *PLoS One.* 2011;6(5):740–749.
- WHO Global Tuberculosis Report. 2019. Available from: <https://www.who.int/tb/publications/globalreport/en/> [Last accessed 2020 Feb 4].
- Chen M, Xu N, Xu J. Cryptococcus Neoformans Meningitis Cases Among China's HIV-Infected Population may have been Severely Under-Reported. *Mycopathologia.* 2020;185(6):971–974.
- Global Molecular CM. Epidemiology of Cryptococcus neoformans and Cryptococcus gattii : an Atlas of the Molecular Types. Scientifica (Cairo). 2013;2013:1–23.
- Chen M, Al-Hatmi AM, Chen Y, et al. Cryptococcosis and tuberculosis co-infection in mainland China. *Emerg Microbes Infect.* 2016;5(1):2–4.
- Marks M, Jarvis JN, Howlett W, et al. Neurosyphilis in Africa: a systematic review. *PLoS Negl Trop Dis.* 2017;11(8):1–14.
- Siddiqi OK, Ghebremichael M, Dang X, et al. Molecular diagnosis of central nervous system opportunistic infections in HIV-infected Zambian adults. *Clin Infect Dis.* 2014;58(12):1771–1777.
- Lupia T, Milia MG, Atzori C, et al. Presence of EBV DNA in Cerebrospinal Fluid is Associated with Greater HIV RNA and Inflammation. *AIDS.* 2020;34(3):373–380.
- Tenforde MW, Mokomane M, Leeme T, et al. Epidemiology of adult meningitis during antiretroviral therapy scale-up in southern Africa: results from the Botswana national meningitis survey. *J Infect.* 2019;79(3):212–219.
- Veltman JA, Bristow CC, Klausner JD. Meningitis in HIV-positive patients in sub-Saharan Africa: a review. *J Int AIDS Soc.* 2014;17(1):19184.
- Domingo P, Suarez-Lozano I, Torres F, et al. Bacterial meningitis in HIV-1-infected patients in the era of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2009;51(5):582–587.
- Wall EC, Everett D B, Mukaka M, et al. Bacterial Meningitis in Malawian Adults, Adolescents, and Children During the Era of Antiretroviral Scale-up and *Haemophilus influenzae* Type b Vaccination, 2000–2012. *Clin Infect Dis.* 2014;58(10):137–145.
- June J, Regev-yochay G, Reisenberg K, et al. Pneumococcal Meningitis in Adults after Introduction of PCV7 and PCV13, Israel, July 2009–June 2015. *Emerg Infect Dis.* 2018;24(7):1275–1284.
- Tenforde MW, Gertz AM, Lawrence DS, et al., Mortality from HIV-associated meningitis in sub-Saharan Africa: a systematic review and meta-analysis. *J Int AIDS Soc.* 23(1): e2541. 2020.
- ** A recent meta-analysis describing common aetiology and mortality of meningitis in the HIV infected host.**
- Yang R, Zhang H, Xiong Y, et al. Molecular diagnosis of central nervous system opportunistic infections and mortality in HIV-infected adults in Central China. *AIDS Res Ther.* 2017;14(1):1–7.

23. Vigil KJ, Salazar L, Hasbun R. Community-acquired meningitis in HIV-infected patients in the United States. *AIDS Patient Care STDS*. 2018;32(2):42–47.
24. Rajasingham R, Rhein J, Klammer K, et al. Epidemiology of meningitis in an HIV-infected Ugandan cohort. *Am J Trop Med Hyg*. 2015;92(2):274–279.
25. Britz E, Perovic O, Von Mollendorf C, et al. The epidemiology of meningitis among adults in a south African province with a high HIV prevalence, 2009–2012. *PLoS One*. 2016;11(9):2009–2012.
26. Nelson CA, Zunt JR. Tuberculosis of the central nervous system in immunocompromised patients: HIV infection and solid organ transplant recipients. *Clin Infect Dis*. 2011;53(9):915–926.
27. Soares CN, Cabral-Castro MJ, Peralta JM, et al. Review of the etiologies of viral meningitis and encephalitis in a dengue endemic region. *J Neurol Sci*. 2011;303(1–2):75–79.
28. Waterman SH, Margolis HS, Sejvar JJ. Surveillance for dengue and dengue-associated neurologic syndromes in the United States. *Am J Trop Med Hyg*. 2015;92(5):996–998.
29. Sánchez-Seco MP, Navarro JM. Infections due to Toscana virus, West Nile virus, and other arboviruses of interest in Europe. *Enferm Infecc Microbiol Clin*. 2005;23(9):560–568.
30. Imam YZ, Ahmedullah H, Chandra P, et al. Accuracy of clinical scoring systems for the diagnosis of tuberculosis meningitis in a case mix of meningitides a retrospective cohort study. *J Neurol Sci*. 2020;416:116979.
31. French N, Gray K, Watera C, et al. Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. *AIDS*. 2002;16(7):1031–1038.
32. Binnicker MJ, Jespersen DJ, Bestrom JE, et al. Comparison of four assays for the detection of cryptococcal antigen. *Clin Vaccine Immunol*. 2012;19(12):1988–1990.
33. Tang MW, Clemons KV, Katzenstein DA, et al. The cryptococcal antigen lateral flow assay: a point-of-care diagnostic at an opportune time. *Crit Rev Microbiol*. 2016;42(4):634–642.
34. Drain PK, Hong T, Kr M, et al. Validation of clinic-based cryptococcal antigen lateral flow assay screening in HIV-infected adults in South Africa. *Sci Rep*. 2019;9:2687.
35. Boulware DR, Rolles MA, Rajasingham R, et al. Multisite validation of cryptococcal antigen lateral flow assay and quantification by laser thermal contrast. *Emerg Infect Dis*. 2014;20(1):45–53.
36. Kwizera R, Akampurira A, Williams D, et al. Acridine orange fluorescent microscopy is more sensitive than India ink light microscopy in the rapid detection of cryptococcosis among CrAg positive HIV patients. *PLoS One*. 2017;12(7):1–9.
37. Chaidir L, Annisa J, Dian S, et al. Microbiological diagnosis of adult tuberculous meningitis in a ten-year cohort in Indonesia. *Diagn Microbiol Infect Dis*. 2018;91(1):42–46.
38. Bahr N, Tugume L, Rajasingham R, et al. Improved diagnostic sensitivity for tuberculous meningitis with Xpert® MTB/RIF of centrifuged CSF. *Int J Tuberc Lung Dis*. 2015;19(10):1209–1215.
39. Bahr NC, Nuwagira E, Evans EE, et al. Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. *Lancet Infect Dis*. 2018;18(1):68–75.
40. Donovan J, Thu DDA, Phu NH, et al., Xpert MTB/RIF Ultra versus Xpert MTB/RIF for the diagnosis of tuberculous meningitis: a prospective, randomised, diagnostic accuracy study. *Lancet Infect Dis*. 20(3): 299–307. 2020.
- One of two recent studies exploring sensitivity of GXP Ultra in the diagnosis of TB.
41. Cresswell FV, Ellis J, Kagimu E, et al., Standardized urine-based tuberculosis screening with TB-LAM and Xpert MTB/Rif Ultra in Ugandan adults with advanced HIV disease and suspected meningitis. *Open Forum Infect Dis*. 7(4): 1–8. 2020.
- One of two recent studies exploring sensitivity of GXP Ultra in the diagnosis of TBM.
42. WHO. Operational Handbook on Tuberculosis. Module 3: diagnosis. 2020. Available at: <https://www.who.int/publications/i/item/who-operational-handbook-on-tuberculosis-module-3-diagnosis—rapid-diagnostics-for-tuberculosis-detection> [Last accessed 2020 Sept 14].
- **Updated diagnostic guidelines for TB meningitis.**
43. Siddiqi OK, Birbeck GL, Ghebremichael M, et al. Prospective Cohort Study on Performance of Cerebrospinal Fluid (CSF) Xpert MTB/RIF, CSF Lipoarabinomannan (LAM) Lateral Flow Assay (LFA), and Urine LAM LFA for Diagnosis of Tuberculous Meningitis in Zambia. *J Clin Microbiol*. 2019;57(8):1–9.
44. Cox JA, Lukande RL, Kalungi S, et al. Accuracy of lipoarabinomannan and Xpert MTB/RIF testing in cerebrospinal fluid to diagnose tuberculous meningitis in an autopsy cohort of HIV-infected adults. *J Clin Microbiol*. 2015;53(8):2667–2673.
45. Quinn CM, Kagimu E, Okirworth M, et al. Fujifilm SILVAMP TB LAM Assay on Cerebrospinal Fluid for the Detection of Tuberculous Meningitis in Adults With Human Immunodeficiency Virus. *Clin Infect Dis* 2021;ciaa1910.
46. Alkholi UM, Abd Al-Monem N, Abd El-Azim AA, et al. Serum procalcitonin in viral and bacterial meningitis. *J Glob Infect Dis*. 2011;3(1):14–18.
47. Khatib U, van de Beek D, Lees JA, et al. Adults with suspected central nervous system infection: a prospective study of diagnostic accuracy. *J Infect*. 2017;74(1):1–9.
48. Wu HM, Cordeiro SM, Harcourt BH, et al. Accuracy of real-time PCR, Gram stain and culture for *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* meningitis diagnosis. *BMC Infect Dis*. 2013;13(1):26.
49. Costerus JM, Brouwer MC, van der Ende A, et al. Repeat lumbar puncture in adults with bacterial meningitis. *Clin Microbiol Infect*. 2016;22(5):428–433.
50. Mohammadi SF, Patil AB, Nadagir SD, et al. Diagnostic value of latex agglutination test in diagnosis of acute bacterial meningitis. *Ann Indian Acad Neurol*. 2013;16(4):645–649.
51. Nigrovic LE, Kuppermann N, McAdam AJ, et al. Cerebrospinal Latex Agglutination Fails to Contribute to the Microbiologic Diagnosis of Pretreated Children with Meningitis. *Pediatr Infect Dis J*. 2004;23(8):786–788.
52. Bhagchandani SP, Kubade S, Nikhare PP, et al. Nested PCR Assay for Eight Pathogens: a Rapid Tool for Diagnosis of Bacterial Meningitis. *Mol Diagnosis Ther*. 2016;20(1):45–54.
53. Wagner K, Springer B, Pires VP, et al. Pathogen Identification by Multiplex LightMix Real-Time PCR Assay in Patients with Meningitis and Culture-Negative Cerebrospinal Fluid Specimens. *J Clin Microbiol*. 2018;56(2):1–8.
54. Vuong J, Collard J-M, Whaley MJ, et al. Development of real-time PCR methods for the detection of bacterial meningitis pathogens without DNA extraction. *PLoS One*. 2016;11(2):1–7.
55. Hobbs E, Vera JH, Marks M, et al. Neurosyphilis in patients with HIV. *Pract Neurol*. 2018;18(3):211–218.
56. Khamaysi Z, Bergman R, Telman G, et al. Clinical and imaging findings in patients with neurosyphilis: a study of a cohort and review of the literature. *Int J Dermatol*. 2014;53(7):812–819.
57. Castro R, Prieto ES, Pereira FDL. Nontreponemal tests in the diagnosis of neurosyphilis: an evaluation of the Venereal Disease Research Laboratory (VDRL) and the Rapid Plasma Reagin (RPR) tests. *J Clin Lab Anal*. 2008;22(4):257–261.
58. Marra CM, Maxwell CL, Dunaway SB, et al. Cerebrospinal fluid Treponema pallidum particle agglutination assay for neurosyphilis diagnosis. *J Clin Microbiol*. 2017;55(6):1865–1870.
59. CDC. Syphilis (*Treponema pallidum*) 2018 Case Definition. Available from: <https://wwwn.cdc.gov/nndss/conditions/syphilis/case-definition/2018/> [Last accessed 8 March 2020].
60. Ropper AH, Longo DL. Neurosyphilis. *N Engl J Med*. 2019;381(14):1358–1363.
61. Janier M, Hegyi V, Dupin N, et al. European guideline on the management of syphilis. *Przegl Dermatol*. 2014;2015(102):459–475.
62. Pastuszczak M, Sitko M, Bociaga-Jasik M, et al. Lack of antiretroviral therapy is associated with higher risk of neurosyphilis among HIV-infected patients who remain serofast after therapy for early syphilis. *Medicine (Baltimore)*. 2018;97(45):e13171.
63. Bahr NC, Boulware DR. Methods of rapid diagnosis for the etiology of meningitis in adults. *Biomark Med*. 2014;8(9):1085–1103.

64. Anastasina M, Domanska A, Palm K, et al. Human picornaviruses associated with neurological diseases and their neutralization by antibodies. *J Gen Virol*. 2017;98(6):1145–1158.
65. Kupila L, Vuorinen T, Vainionpää R, et al. Diagnosis of Enteroviral Meningitis by Use of Polymerase Chain Reaction of Cerebrospinal Fluid, Stool, and Serum Specimens. *Clin Infect Dis*. 2005;40(7):982–987.
66. Silva CA, Augusto C, Penalva de O, 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*. 2010;52(6):305–310.
67. Mesquita RT, Âp Z, Hiramoto RM, et al. Real-time quantitative PCR in cerebral toxoplasmosis diagnosis of Brazilian human immunodeficiency virus-infected patients. *J Med Microbiol*. 2010;59(6):641–647.
68. Aizenberg D, Lamaury I, Demar M, et al. Performance Testing of PCR Assay in Blood Samples for the Diagnosis of Toxoplasmic Encephalitis in AIDS Patients from the French Departments of America and Genetic Diversity of *Toxoplasma gondii*: a Prospective and Multicentric Study. *PLoS Negl Trop Dis*. 2016;10(6):1–17.
69. Bokharai-Salim F, Esteghamati A, Khanaliha K, et al. Evaluation of a PCR assay for diagnosis of toxoplasmosis in serum and peripheral blood mononuclear cell among HIV/AIDS patients. *J Parasit Dis*. 2020;44(1):159–165.
70. Alfonso Y, Fraga J, Fonseca C, et al. Molecular diagnosis of *Toxoplasma gondii* infection in cerebrospinal fluid from AIDS patients. *Cerebrospinal Fluid Res*. 2009;6(1):1–6.
71. Mikita K, Maeda T, Ono T, et al. The utility of cerebrospinal fluid for the molecular diagnosis of toxoplasmic encephalitis. *Diagn Microbiol Infect Dis*. 2013;75(2):155–159.
72. Anwar A, Gudlavalleti A, Ramadas P. *Carcinomatous Meningitis*. Treasure Island (FL): StatPearls Publishing; 2020.
73. Wasserman S, Davis A, Wilkinson RJ, et al. Key considerations in the pharmacotherapy of tuberculous meningitis. *Expert Opin Pharmacother*. 2019;20(15):1791–1795.
74. Bowen LN, Smith B, Reich D, et al. HIV-associated opportunistic CNS infections: pathophysiology, diagnosis and treatment. *Nat Rev Neurol*. 2016;12(11):662–674.
75. WHO. Guidelines for treatment of drug-susceptible tuberculosis and patient care. 2017. Available from: <https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1> [Last accessed 2020 Mar 8].
76. Sigfrid L, Perfect C, Rojek A, et al. A systematic review of clinical guidelines on the management of acute, community-acquired CNS infections. *BMC Med*. 2019;17(1):170.
77. Charlier C, É P, Leclercq A, et al. Clinical features and prognostic factors of listeriosis: the MONALISA national prospective cohort study. *Lancet Infect Dis*. 2017;17:510–519.
78. Steiner I, Budka H, Chaudhuri A, et al. Viral meningoencephalitis: a review of diagnostic methods and guidelines for management. *Eur J Neurol*. 2010;17(8):999–e57.
79. Stahl JP, Azouvi P, Bruneel F, et al. Guidelines on the management of infectious encephalitis in adults. *Med Mal Infect*. 2017;47(3):179–194.
80. Konstantinovic N, Guegan H, Stäjner T, et al. Treatment of toxoplasmosis: current options and future perspectives. *Food Waterborne Parasitol*. 2019;15:e00036.
81. Gaskell KM, Rothe C, Gnanadurai R, et al. A prospective study of mortality from cryptococcal meningitis following treatment induction with 1200mg oral fluconazole in Blantyre, Malawi. *PLoS One*. 2014;9(11):9–12.
82. Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal combinations for treatment of cryptococcal meningitis in Africa. *N Engl J Med*. 2018;378(11):1004–1017.
83. Tenforde MW, Shapiro AE, Rouse B, et al. Treatment for HIV-associated cryptococcal meningitis. *Cochrane Database Syst Rev*. 2018;7(7):CD00564.
84. Lockhart SR, Iqbal N, Bolden CB, et al. Epidemiologic cutoff values for triazole drugs in *Cryptococcus gattii*: correlation of molecular type and in vitro susceptibility. *Diagn Microbiol Infect Dis*. 2012;73(2):144–148.
85. Hamill RJ, Sobel JD, El-Sadr W, et al. Comparison of 2 Doses of Liposomal Amphotericin B and Conventional Amphotericin B Deoxycholate for Treatment of AIDS-Associated Acute Cryptococcal Meningitis: a Randomized, Double-Blind Clinical Trial of Efficacy and Safety. *Clin Infect Dis*. 2010;51(2):225–232.
86. Jarvis JN, Leeme TB, Molefi M, et al. Short-course High-dose Liposomal Amphotericin B for Human Immunodeficiency Virus-associated Cryptococcal Meningitis: a Phase II Randomized Controlled Trial. *Clin Infect Dis*. 2019;68(3):393–401.
87. Eshun-Wilson I, Okwen MP, Richardson M, et al. Early versus delayed antiretroviral treatment in HIV-positive people with cryptococcal meningitis. *Cochrane Database Syst Rev*. 2018;7:CD009012.
- **Article reviewing evidence (trial data) for the early versus delayed initiation of ART in HIV-positive people with CM, and the development of IRIS**
88. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med*. 370(26): 2487–2498. 2014.
- **Key study informing guidance on the timing of ART after diagnosis of CM.**
89. Thwaites GE, Bang ND, Dung NH, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med*. 351(17): 1741–1751. 2004.
- **Key study informing guidance on the use of dexamethasone in TBM.**
90. Seaton RA, Verma N, Naraqi S, et al. The effect of corticosteroids on visual loss in *Cryptococcus neoformans* var. *gattii* meningitis. *Trans R Soc Trop Med Hyg*. 1997;91(1):50–52.
91. Beardsley J, Wolbers M, Kibengo FM, et al. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. *N Engl J Med*. 2016;374(6):543–554.
92. Wiederhold NP. The antifungal arsenal: alternative drugs and future targets. *Int J Antimicrob Agents*. 2018;51(3):333–339.
93. Wang SQ, Wang YF, Xu Z. Tetrazole hybrids and their antifungal activities. *Eur J Med Chem*. 2019;170:225–234.
94. Donald PR. Cerebrospinal fluid concentrations of antituberculosis agents in adults and children. *Tuberculosis*. 2010;90(5):279–292.
95. Ruslami R, Ganiem AR, Dian S, et al. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase II trial. *Lancet Infect Dis*. 2013;13(1):27–35.
96. Heemskerck AD, Bang ND, Mai NTH, et al. Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis. *N Engl J Med*. 2016;374(2):124–134.
97. Dian S, Yunivita V, Ganiem AR, et al. Double-blind, randomized, placebo-controlled phase II dose-finding study to evaluate high-dose rifampin for tuberculous meningitis. *Antimicrob Agents Chemother*. 2018;62(12):e01014–18.
98. Tucker EW, Guglieri-lopez B, Ordonez AA, et al. Noninvasive ¹¹C-rifampin positron emission tomography reveals drug biodistribution in tuberculous meningitis. *Sci Transl Med*. 2019;10(470): e00965.
99. Ding J, Thuy Thuong Thuong N, Van PT, et al. Pharmacokinetics and Pharmacodynamics of Intensive Antituberculosis Treatment of Tuberculous Meningitis. *Clin Pharmacol Ther*. 2020;107(4):1023–1033.
100. Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev*. 2016;4(4):CD002244.
101. Consolidated WHO Guidelines on Drug-Resistant Tuberculosis Treatment. 2019. Available from: <https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/> [Last accessed 2020 Aug 31].
102. Tucker EW, Pieterse L, Zimmerman MD, et al. Delamanid Central Nervous System Pharmacokinetics in Tuberculous Meningitis in Rabbits and Humans. *Antimicrob Agents Chemother*. 2019;63(10): e00913–19.

103. Griffiths MJ, McGill F, Solomon T. Management of acute meningitis. *Clin Med J R Coll. Physicians London*. 2018. . 18. 164–169.
104. Boyles TH, Bamford C, Bateman K, et al. Guidelines for the management of acute meningitis in children and adults in South Africa. *South African J Epidemiol Infect*. 2013;28(1):5–15.
105. WHO. Global Antimicrobial Resistance Surveillance System (GLASS) Report 2017–2018. Available from: <https://www.who.int/glass/resources/publications/early-implementation-report-2017-2018/en/> [Last accessed 14 September 2020].
106. von Mollendorf C, Cohen C, de Gouveia L, et al. Factors Associated with Ceftriaxone Nonsusceptibility of *Streptococcus pneumoniae*: analysis of South African National Surveillance Data, 2003 to 2010. *Antimicrob Agents Chemother*. 2014;58(6):3293–3305.
107. van de Beek D, Brouwer M, Hasbun R, et al. Community-acquired bacterial meningitis. *Nat Rev Dis Prim*. 2016;2(1):16074.
108. van de Beek D, Cabellos C, Dzapova O, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. *Clin Microbiol Infect*. 2016;22:S37–S62.
109. McGill F, Heyderman RS, Michael BD, et al. The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. *J Infect*. 2016;72:405–438.
110. Scarborough M, Thwaites GE. The diagnosis and management of acute bacterial meningitis in resource-poor settings. *Lancet Neurol*. 2008;7(7):637–648.
111. Brouwer MC, McIntyre P, Prasad K, et al. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2015;9:CD004405.
- **Evidence supporting the use of corticosteroids in HIC, with a reduction in hearing loss and neurological sequelae**
112. de Gans J, van de Beek D. van de Beek D. Dexamethasone in Adults with Bacterial Meningitis. *N Engl J Med*. 2002;347(20):1549–1556.
113. Scarborough M, Gordon SB, Whitty CJM, et al., Corticosteroids for Bacterial Meningitis in Adults in Sub-Saharan Africa. *N Engl J Med*. 357(24): 2441–2450. 2007.
- **Examines the use of corticosteroids as adjunct to antibiotic therapy in developing countries in sub-saharan Africa, with a high HIV burden through a randomised, double-blind placebo controlled trial.**
114. CDC. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV Recommendations from the Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 2019;40:424.
115. Bettuzzi T, Jourdes A, Robineau O, et al. Ceftriaxone compared with benzylpenicillin in the treatment of neurosyphilis in France: a retrospective multicentre study. *Lancet Infect Dis*. 2021;S1473-3099(20):30857.
116. Lyons JL. Viral Meningitis and Encephalitis. *Continuum*. 2018;24(5):1284–1297.
117. Raschilas F, Wolff M, Delatour F, et al. Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. *Clin Infect Dis*. 2002;35(3):254–260.
118. Landry ML, Greenwold J, Vikram HR. Herpes Simplex Type-2 Meningitis: presentation and Lack of Standardized Therapy. *Am J Med*. 2009;122(7):688–691.
119. Miller S, Mateen FJ, Aksamit AJ. Herpes simplex virus 2 meningitis: a retrospective cohort study. *J Neurovirol*. 2013;19(2):166–171.
120. Tunkel AR, Glaser CA, Bloch KC, et al. The Management of Encephalitis: clinical Practice Guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;47(3):303–327.
121. Gnoni M, Zaheer K, Vasser MM, et al. Varicella Zoster aseptic meningitis: report of an atypical case in an immunocompetent patient treated with oral valacyclovir. *IDCases*. 2018;13:e00446.
122. Ramos-Estebanez C, Lizarraga KJ, Merenda A. A systematic review on the role of adjunctive corticosteroids in herpes simplex virus encephalitis: is timing critical for safety and efficacy? *Antivir Ther*. 2013;19(2):133–139.
123. Meyding-Lamadé U, Jacobi C, Martinez-Torres F, et al. The German trial on Aciclovir and Corticosteroids in Herpes-simplex-virus-Encephalitis (GACHE): a multicenter, randomized, double-blind, placebo-controlled trial. *Neurol Res Pract*. 2019;1(1):26.
124. Nel J, Dlamini S, Meintjes G, et al. Southern African HIV Clinicians Society guidelines for antiretroviral therapy in adults: 2020 update. *South Afr J HIV Med*. 2020;21(1):a1115.
125. US Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2019. Available from: <http://aidsinfo.nih.gov/contentfiles/vguidelines/AdultandAdolescentGL.pdf> [Last accessed 2020 Aug 31].
126. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: chapter 4.1: clinical guidelines : antiretroviral therapy. 2016;480. Available from: <http://www.who.int/hiv/pub/arv/chapter4.pdf?ua=1> [Last accessed 2020 Feb 4].
127. Danel C, Moh R, Gabillard D, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med*. 2015;373:808–822.
128. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*. 2008;8(8):516–523.
129. Marais S, Meintjes G, Pepper DJ, et al. Frequency, severity, and prediction of tuberculous meningitis immune reconstitution inflammatory syndrome. *Clin Infect Dis*. 2013;56(3):450–460.
130. Müller M, Wandel S, Colebunders R, et al. Incidence and Lethality of Immune Reconstitution Disease in HIV-Infected Patients Starting Antiretroviral Therapy: systematic Review and Meta-Analysis. *Lancet Infect Dis*. 2010;10(4):251–261.
131. Bowen L, Nath A, Smith B. CNS immune reconstitution inflammatory syndrome. *Handb Clin Neurol*. 2018;152:167–176.
132. Bicanic T, Meintjes G, Rebe K, et al. Immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis: a prospective study. *J Acquir Immune Defic Syndr*. 2009;51(2):130–134.
133. Chang CC, Dorasamy AA, Gosnell BI, et al. Clinical and mycological predictors of cryptococcosis-associated immune reconstitution inflammatory syndrome. *AIDS*. 2013;27(13):2089–2099.
134. Mahnke YD, Greenwald JH, DerSimonian R, et al. Selective expansion of polyfunctional pathogen-specific CD4+ T cells in HIV-1 - Infected patients with immune reconstitution inflammatory syndrome. *Blood*. 2012;119(13):3105–3112.
135. Jarvis JN, Meintjes G, Bicanic T, et al. Cerebrospinal Fluid Cytokine Profiles Predict Risk of Early Mortality and Immune Reconstitution Inflammatory Syndrome in HIV-Associated Cryptococcal Meningitis. *PLoS Pathog*. 2015;11(4):1–18.
136. Török ME, Yen NTB, Chau TTH, et al., Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated tuberculous meningitis. *Clin Infect Dis*. 52(11): 1374–1383. 2011.
- **Key study informing guidance on the timing of ART in HIV associated TBM.**
137. Marais S, Wilkinson KA, Lesosky M, et al. Neutrophil-associated central nervous system inflammation in tuberculous meningitis immune reconstitution inflammatory syndrome. *Clin Infect Dis*. 2014;59(11):1638–1647.
138. Brunel A-S, Reynes J, Tuaille E, et al. Thalidomide for steroid-dependent immune reconstitution inflammatory syndromes during AIDS. *AIDS*. 2012;26(16):2110–2112.
139. Gaube G, De Castro N, Gueguen A, et al. Treatment with adalimumab for severe immune reconstitution inflammatory syndrome in an HIV-infected patient presenting with cryptococcal meningitis. *Med Mal Infect*. 2016;46(3):154–156.
140. Tanaka T, Sekine A, Tsunoda Y, et al. Central nervous system manifestations of tuberculosis-associated immune reconstitution inflammatory syndrome during adalimumab therapy: a case report and review of the literature. *Intern Med*. 2015;54:847–851.
141. Rolfes MA, Hullsiek KH, Rhein J, et al. The effect of therapeutic lumbar punctures on acute mortality from cryptococcal meningitis. *Clin Infect Dis*. 2014;59(11):1607–1614.

142. Boyles TH, Gatley E, Wasserman S, et al. Brief Report: flow Rate of Cerebrospinal Fluid Through a Spinal Needle Can Accurately Predict Intracranial Pressure in Cryptococcal Meningitis. *J Acquir Immune Defic Syndr.* **2017**;74(3):e64–e66.
143. Cherian J, Atmar RL, Gopinath SP. Shunting in cryptococcal meningitis. *J Neurosurg.* **2016**;125(1):177–186.
144. Glimåker M, Johansson B, Halldorsdottir H, et al. Neuro-intensive treatment targeting intracranial hypertension improves outcome in severe bacterial meningitis: an intervention-control study. *PLoS One.* **2014**;9:22–24.
145. Azeemuddin M, Alvi A, Sayani R, et al. Neuroimaging Findings in Tuberculosis: a Single-Center Experience in 559 Cases. *J Neuroimaging.* **2019**;29(5):657–668.
146. Rizvi I, Garg RK, Malhotra HS, et al. Ventriculo-peritoneal shunt surgery for tuberculous meningitis: a systematic review. *J Neurol Sci.* **2017**;375:255–263.
147. Gu J, Huang H, Huang Y, et al. Hypertonic saline or mannitol for treating elevated intracranial pressure in traumatic brain injury: a meta-analysis of randomized controlled trials. *Neurosurg Rev.* **2019**;42(2):499–509.
148. Beal JC. Increased Intracranial Pressure in the Setting of Enterovirus and Other Viral Meningitides. *Neurol Res Int.* **2017**;2017:2854043.
149. Bahr NC, Rolfes MA, Musubire A, et al. Standardized Electrolyte Supplementation and Fluid Management Improves Survival During Amphotericin Therapy for Cryptococcal Meningitis in Resource-Limited Settings. *OFID.* **2014**;1(2):ofu070.
150. Meiring S, Fortuin-de Smidt M, Kularatne R, et al. Prevalence and Hospital Management of Amphotericin B Deoxycholate-Related Toxicities during Treatment of HIV-Associated Cryptococcal Meningitis in South Africa. *PLoS Negl Trop Dis.* **2016**;10(7):1–14.
151. Uk M, Kalita J, Sk B, et al. A study of hyponatremia in tuberculous meningitis. *J Neurol Sci.* **2016**;367:152–157.
152. Donovan J, Figaji A, Imran D, et al. The neurocritical care of tuberculous meningitis. *Lancet Neurol.* **2019**;18(8):771–783.
153. Van Laarhoven A, Dian S, Ruesen C, et al. Clinical parameters, routine inflammatory markers, and LTA4H genotype as predictors of mortality among 608 patients with tuberculous meningitis in Indonesia. *J Infect Dis.* **2017**;215(7):1029–1039.