Current Neurology and Neuroscience Reports (2019) 19:81
https://doi.org/10.1007/s11910-019-0993-0

INFECTION (JOHN HALPERIN, SECTION EDITOR)

New Insights Into *Cryptococcus* Spp. Biology and Cryptococcal Meningitis

Elvis Temfack[1] · Timothée Boyer-Chammard[2,3] · David Lawrence[4,5] · Sarah Delliere[3] · Angela Loyse[2,6] · Fanny Lanternier[2,3] · Alexandre Alanio[2,7] · Olivier Lortholary[2,3]

Abstract

Purpose of Review Defective cell–mediated immunity is a major risk factor for cryptococcosis, a fatal disease if untreated. Cryptococcal meningitis (CM), the main presentation of disseminated disease, occurs through hematogenous spread to the brain from primary pulmonary foci, facilitated by yeast virulence factors. We revisit remarkable recent improvements in the prevention, diagnosis and management of CM.

Recent Findings Cryptococcal antigen (CrAg), main capsular polysaccharide of *Cryptococcus* spp. is detectable in blood and cerebrospinal fluid of infected patients with point of care lateral flow assays. Recent World Health Organization guidelines recommend 7-day amphotericin B plus flucytosine, then 7-day high dose (1200 mg/day) fluconazole for induction treatment of HIV-associated CM. Management of raised intracranial pressure, a consequence of CM, should rely mainly on daily therapeutic lumbar punctures until normalisation. In HIV-associated CM, following introduction of antifungal therapy, (re)initiation of antiretroviral therapy should be delayed by 4–6 weeks to prevent immune reconstitution inflammatory syndrome, common in CM.

Summary CM is a fatal disease whose diagnosis has recently been simplified. Treatment should always include antifungal combination therapy and management of raised intracranial pressure. Screening for immune deficiency should be mandatory in all patients with cryptococcosis.

Keywords *Cryptococcus* · Cryptococcal antigen · Lateral flow assay · Intracranial pressure · Induction therapy

Introduction

Cryptococcal meningitis (CM) is a leading cause of mortality in patients with impaired cell–mediated immunity. Prior to the 1980s, CM was mostly iatrogenic, common among patients with solid organ transplantation who received extensive immunosuppressive therapy [1]. The recent HIV pandemic, a major cause of acquired depletion of T lymphocyte-mediated immunity, has led to a dramatic increase in the incidence of CM, which still causes roughly 15% of HIV-related deaths, most of which occur in sub-Saharan Africa [2•]. Acquisition of this ubiquitous environmental yeast is through inhalation to the lungs where yeast-host cell-mediated immune interaction, modulated by yeast virulence factors,

Elvis Temfack and Timothée Boyer-Chammard contributed equally to this work.

This article is part of the Topical Collection on *Infection*

✉ Olivier Lortholary
olivier.lortholary@pasteur.fr

[1] Internal Medicine unit, Douala General Hospital, Douala, Cameroon

[2] Molecular Mycology Unit, UMR2000, CNRS, Institut Pasteur, 25 – 28 Rue du Dr Roux, 75015 Paris, France

[3] Necker Pasteur Center for Infectious Diseases and Tropical Medicine, Hôpital Necker Enfants malades, AP-HP, IHU Imagine, Paris Descartes University, Université de Paris, Paris, France

[4] Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK

[5] Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana

[6] Centre for Global Health, Institute for Infection and Immunity, St Georges University of London, London, UK

[7] Laboratory of Parasitology-Mycology, Saint-Louis Hospital, University Paris Diderot, Sorbonne Paris Cité, Université de Paris, Paris, France

Published online: 31 October 2019

determines the outcome of the primary infection. In this review, we revisit different aspects of cryptococcosis that have had some remarkable progress within the past few years. Table 1 summarises key messages for neurologists from infectious diseases physicians' perspective.

Yeast Biology

Cryptococcus spp., a basidiomycetous organism capable of both sexual and asexual (clonal expansion) reproduction [3], is responsible for CM. Initially, *Cryptococcus* spp. was considered to exist in two varieties: *Cryptococcus neoformans* (*C. neoformans*) and *Cryptococcus gattii* (*C. gattii*), but recent taxonomy considers each as a distinct species [4]. As such, *C. neoformans* exists in two varieties: *grubii* (serotype A) which is globally ubiquitous, and *neoformans* (serotype D), mainly European. Clinically, species identification is important in determining the therapeutic approach because *C. gattii* infections require more intensive management [5]. However, recent sophisticated methods of identification suggest the recognition of seven species within the *Cryptococcus* spp. species complex [6]; the acceptance and validation of which is still pending due to lack of clinical relevance [7].

Cryptococcus which was discovered through two independent isolation sources: environmental in peach juice and clinical from a tibial lesion of a patient is now known to be a facultative intracellular organism [8]. Environmental presence includes soil contaminated with pigeon guano (*C. neoformans*) or eucalyptus trees and decaying wood (*C. gattii*). However, in this environmental niche, it can interact with various organisms as simple as protozoans (amoeba, paramecium) and more complex organisms like nematodes, birds and even mammals such as koalas, felines and humans [9]. Indeed, pigeons (*Columbia livia*) are thought to be responsible for the worldwide dissemination of *C. neoformans* serotype A [10]. Of note, *C. neoformans* has been extensively studied and different fates have been observed including phagocytosis by host cell, non-lytic exocytosis, host cell lysis, cell to cell transfer, and yeast killing [11].

Major features of *Cryptococcus* spp. are its ability to grow at 37 °C (capable of infection in mammals) and the presence of a polysaccharide capsule around the cell wall [12]. This capsule composed mainly of glucuronoxylomannan (GXM) and glucuronoxylomannogalactan, produced both environmentally and, in infected hosts, represents a major virulence factor of the yeast. Capsular contents, specifically GXM, strongly inhibit phagocytosis [13] and are immunomodulatory through downregulation of inflammatory cytokines, depletion of complement components and inhibition of monocyte antigen-presentation [14]. In-host production and shedding of soluble GXM, also known as cryptococcal antigen (CrAg), usually occur in considerable quantities which are detectable by different tools and are used as a surrogate diagnosis of Cryptococcal infection [15].

Other virulence factors of *Cryptococcus* include externalization of enzyme-containing vesicles also known as virulence factors delivery bags [16]. These enzymes include laccase, phospholipase and urease. Laccase is a key enzyme in the production of melanin from catecholamine, and melanin protects the yeast against host immune defence and environmental stress [17]. Phospholipase C has been shown to be an important factor in the resistance of an intracellular oxidative burst and dissemination to the central nervous system [18]. Urease is important for brain invasion by increasing the number of transmigration sites into the brain [19].

Clinically, meningoencephalitis is the main presentation of cryptococcosis [20] whereby brain invasion occurs during or after dissemination from a primary focus through reactivation of dormant infecting strains of the yeast acquired long before

Table 1 The ID physician speaks to the neurologist: the optimal management of cryptococcal meningitis

Diagnosis of CM	CM should always be considered in adults with underlying cellular immune deficiency and presenting with sub-acute meningoencephalitis.
	Be aware that CM may reveal HIV infection.
	Lack of serum cryptococcal antigen detection does not rule out CM in HIV-negative patients.
	Normal CSF analysis does not exclude CM and is a poor prognostic indicator.
Management of CM	Initial treatment of HIV-associated CM systematically relies on antifungal combination consisting of 7 days of amphotericin B + flucytosine or 14 days of oral combination with flucytosine + high-dose fluconazole.
	CSF opening pressure should be systematically measured during CM, and therapeutic LPs are an essential component of management.
Other considerations	Because CM does not exist in true immunocompetent patients, careful screening of any cell-mediated primary immune deficiency is recommended.
	For HIV-infected patients, initiation or re-initiation of antiretroviral therapy should be delayed by 4 to 6 weeks after the start of antifungal therapy.
	In non-HIV infected patients, any measure aiming to reduce immunosuppression should not be considered until 4 to 6 weeks after the start of antifungal therapy.

onset of CM [21, 22]. Therefore, crossing the blood-brain barrier (BBB) leads to brain invasion and yeast seeding in the leptomeninges, a process associated with capsular composition changes [23]. In the brain, the yeasts can be observed in endothelial cells as well as in leptomeningeal capillaries circulating monocytes [24], thus evidence of some brain invasion facilitation by monocytes through a Trojan horse mechanism [25]. Findings of high levels of monocytes chemoattractant protein 1 (MCP-1) in the brain of patients with cryptococcosis seem to support its role in *Cryptococcus* crossing the BBB in in vitro models through monocyte recruitment [26].

Emerging Risk Factors for Cryptococcosis

Host-Associated Factors

Worldwide, HIV infection remains the main risk factor to develop cryptococcosis [2•]. However, other well-known risk factors are of increasing importance in countries with a low HIV prevalence. Cryptococcosis classically is reported in solid organ transplant patients, representing 7% of invasive fungal diseases in this group [27]. Graft-transmitted cryptococcal infections have also been reported [28, 29]. Sarcoidosis has also been associated with cryptococcosis sometimes before any corticosteroids or immunosuppressive therapy [30]. Corticosteroids and cirrhosis are also predisposing factors. Patients with primary immunodeficiency with T cell deficiency can develop cryptococcosis, as well as severe combined immune deficiency and CD4 idiopathic lymphopenia. Cryptococcosis has been reported in patients with hyper IgE syndrome, hyper IgM syndrome, GATA2, IL12RB1 deficiency and STAT1 gain of function mutations [31–33]. Anti-IFN-gamma and anti-GM-CSF also predispose to cryptococcal infection [34, 35].

Immunosuppressive Therapies

Additionally, some CM cases have been reported in patients with relapsing-remitting multiple sclerosis treated with specific therapies, such as fingolimod, a sphingosine analogue that modulates the sphingosine-1-phosphate receptor, which results in lymphocyte migration and in sequestration of lymphocytes in lymph nodes or natalizumab, a recombinant monoclonal antibody [36, 37].

Environmental Factors

Interestingly, a highly virulent lineage of *Cryptococcus gattii* has been reported in recent outbreaks among healthy individuals in Vancouver Island, the Canadian mainland, and the Pacific Northwest.

Therefore, patients developing cryptococcosis without known risk factors should systematically be investigated with immunological and genetic work up to look for primary immunodeficiencies.

Innovative Diagnostic Approaches

Confirmatory diagnosis of CM is by microscopy following Indian ink staining of fresh cerebrospinal fluid (CSF) or after culture in Sabouraud dextrose agar [38]. Microscopically, *Cryptococcus* spp. appears as a rounded cell with a thick halo on Indian ink background which represents the polysaccharidic capsule. However, following dissemination from its initial pulmonary focus, cryptococcosis becomes a systemic infection capable of affecting any organ. As such, histopathological assessment of tissue specimens with stains can identify the *Cryptococcus* capsule (mucicarmine and alcian blue) or presence of melanin (Fontana-Masson stain) [39].

The polysaccharide capsule of *Cryptococcus*, which is phenotypically identified in stained CSF or tissues, is soluble and detectable in biological milieus as a marker of infection, and thus, is a potential surrogate for timely diagnosis. The earliest of such detection techniques used latex agglutination (LA) particles coated with specific antibodies that agglutinated CrAg in serum of infected patients [40]. Other techniques such as enzyme-linked immunosorbent assays (ELISA) were also developed with good sensitivity and specificity.

Within the last 10 years, diagnosis of cryptococcal disease has been revolutionised by the development of highly sensitive and specific CrAg lateral flow assays (LFA) [41–43]. LFA CrAg detection in blood plays an important role within CrAg-screening programs [44, 45] because up to a third of positive antigenemia patients have underlying asymptomatic CM [46••], many of whom become symptomatic within weeks to months following CrAg positivity [47] at an estimated risk of up to 21.4% [46••]. Therefore, CrAg LFAs can be effectively used at the bedside as a POC test or within traditional laboratory structures on both blood and CSF samples.

One CrAg LFA is the IMMY LFA (Immuno-mycologics, Norman, OK, USA), a qualitative immunochromatographic test which renders results within 10 min [48]. With growing evidence on the association between high serum CrAg titres and underlying CM [44, 49•] as well as difficulties in obtaining and analysing CSF, there was an urgent need for semi-quantitative POC CrAg tests capable of predicting underlying CM [50]. As such, the Biosynex CryptoPS (Biosynex, Strasbourg, France) semi-quantitative immunochromatographic CrAg LFA which also provides results within 10 min, was developed between Institut Pasteur of Paris and industry [49•]. The assay has two bands: a qualitative T1-band and a semi-quantitative T2-band which only appears in case of high serum titres [49•]. Data from

a single site in Cameroon shows that the T2-band strongly correlates with CSF Indian ink and culture evidence of underlying CM [49•], thereby promising for tailoring more aggressive combination antifungal therapy not only for confirmed cases of CM but also subclinical cases of meningitis in asymptomatic CrAg positive patients [51•]. Nevertheless, additional validation studies are ongoing.

Currently, there are other manufacturers of CrAg LFAs, including the StrongStep (Liming Bio, Nanjing, Jiangsu, China) whose initial evaluation in a Ugandan site shows lack of specificity in plasma [52].

Regardless of the technique used, it is important to highlight that serum CrAg testing in HIV-negative patients does not allow one to rule out CM, as the sensitivity is lower than in HIV-infected patients [20].

Assessment and Management of Elevated CSF Opening Pressure

Raised intracranial pressure (ICP) defined as a CSF opening pressure of ≥ 20 cm H_2O, is a common complication of CM which may occur in up to 60% of cases. Raised ICP, is a consequence of the cryptococcal polysaccharide capsule and yeasts obstructing resorption of circulating CSF. Measurement of CSF opening pressure (OP) occurs during lumbar puncture (LP) with a graduated glass manometer whereby the length of ascension of CSF by capillary action against gravity estimates the pressure in the meningeal space.

Clinically, raised ICP may present as headache, 6th cranial nerve palsy, diplopia, hypoacusis and in severe cases, visual and/or hearing loss, altered consciousness and/or seizures [53], all of which are generally associated with worse outcomes [54]. To date, there exists no proven pharmacological approach for the treatment of raised ICP in the context of CM. Though steroids and acetazolamide have been tested in clinical trials, they are not recommended because they show poor impact on patient outcome [55••, 56]. Consequently, management of raised ICP relies mainly on therapeutic lumbar punctures (LP), shown to be associated with up to 69% improved survival, irrespective of baseline opening pressure [57]. Draining up to 30 ml of CSF each day is safe. However, in case of persistently raised ICP, LPs may be required twice per day. Nevertheless, in settings with access to neurosurgical services, percutaneous lumbar drain is a therapeutic option for patients with persistently high OP albeit daily therapeutic LP [58], though risk of infection is a major concern.

Proactive daily monitoring of signs and symptoms (headache most especially) of raised ICP during induction treatment of CM is strongly advised. Nevertheless, in the case of ICP > 30 cm H_2O, it is advisable that the patient undergoes another LP the following day, regardless of symptoms, likewise symptomatic patients with pressure between 20 and 30 cm H_2O. It is worth noting that patients could present at baseline with normal ICP but subsequently develop raised ICP due to induction antifungal treatment causing rapid killing of many *Cryptococcus* resulting in obstruction of CSF resorption.

In most high CM burden settings, manometers for OP measurement are not always readily available. An alternative widely used approach is to attach an infusion tube to the spinal needle during LP, hold it vertically and measure the height of CSF ascent. Recently, a South African study which compared manometer readings to the rate of CSF flow through a standard 22-G spinal needle showed that a cutoff rate above 40 drops/min was indicative of raised ICP [59]. Comprehensive raised ICP management therefore requires physicians to be well versed with the technique of OP measurement during LP as well patients being informed of the importance of diagnostic and therapeutic LP. Patient information and sensitisation are crucial especially in communities where LPs are frequently refused [60].

Overview on the 2018 World Health Organization Guidelines

Within the last 10 years, there have been some major evidence-driven changes in the management approach of CM, especially in HIV patients, and these advances aim at improving patient outcome as well as mitigating treatment-related adverse events. However, management of CM still relies on the three-phase antifungal approach encompassing induction, consolidation and maintenance as suggested by the Infectious Disease Society of America (IDSA) 2010 guidelines [61]. Patients with severe presentation of disseminated infection without meningitis, such as fungemia, severe pneumonia or high antigen titres, should be treated as patients with CNS infection.

The induction phase, determinant for patient survival, aims at reducing as much as possible, the CSF fungal burden within the first 2 weeks. Available evidence clearly shows survival benefits of using combination antifungal therapy during this phase of treatment. As such, combination of amphotericin B (AmB) and flucytosine (5FC) [62, 63] has been shown to be the best option for better survival at 14 and 70 days with hazard ratio (HR) of 0.57 and 0.61 respectively, compared with amphotericin B monotherapy [64]. Though AmB plus fluconazole (FLU) was considered an option for induction [65], it has similar survival outcomes to AmB monotherapy at day 14 and 70 [64]. Nevertheless, oral combination of high dose FLU (1200 mg daily) and 5FC (100 mg/kg daily) showed better early fungicidal activity and survival than FLU monotherapy on a small sample of 41 patients [66]

rendering FLU monotherapy absolutely not an option for CM induction therapy even at high doses [67, 68, 69•].

Though AmB combination regimen, as well as oral combination of FLU and 5FC, have been shown to be respectively better than AmB or FLU monotherapy, administration of AmB containing regimens requires 2 weeks of in-hospital infusion, which is very challenging in low-income, high-burden settings where it can be difficult to monitor AmB-induced toxicity. Moreover, it was not clear which is better: AmB plus 5FC or an oral combination of high dose FLU plus 5FC. These questions were at the core of the Advancing Cryptococcal Meningitis Treatment for Africa (ACTA) trial [70••], an open-label phase 3 randomised non-inferiority multicentre trial, including 721 HIV-infected patients, comparing 14 and 70-day survival rates of a short course of 1-week AmB (combined with either FLU or 5FC), or 2-weeks oral combination (5FC plus FLU) with the standard 2-weeks AmB (combined with either FLU or 5FC).

In the ACTA trial, it was demonstrated that 7-day AmB was non-inferior to 14 days in terms of survival benefits and was associated with fewer drug-induced severe adverse events. More so, the trial also showed that 5FC compared with FLU is a superior partner drug, associated with significant mortality reduction, 38% at day 70. The oral combination regimen of FLU with 5FC was the second-best performing arm with a 10-week mortality of 35%.

Considering these results and those of a recent Cochrane review [71••], World Health Organization (WHO) recommends as preferred first line within the 2-weeks induction phase of treatment, 7 days AmB plus 5FC, then 7 days oral FLU 1200 mg/day. In case AmB is not readily available or administration is not possible, an alternative induction regimen is 2-week oral combination of 5FC and high-dose FLU (1200 mg/day). However, AmB plus high dose FLU is also considered when 5FC is not available [72].

Though the ACTA trial showed fewer severe adverse events with 1-week AmB, it is worth noting that the occurrence of adverse events also depends on the formulation of AmB used, with lipid formulations presenting with even fewer adverse events [73, 74]. Therefore, in perspective of ensuring even better patient outcome during induction therapy for CM, an ongoing phase III AMBITION randomised trial [75] aimed at determining 14- and 70-day survival of 850 patients with HIV-related CM, treated with either the currently preferred WHO regimen of 1-week AmB plus 5FC regimen or with single high dose (10 mg/kg) liposomal AmB at day 1 combined with 2 weeks of 5FC and FLU.

Considering timing for ART initiation during CM, WHO guidelines recommend a delay of 4 to 6 weeks after initiating combination antifungal therapy [76, 77••].

Updates on Immune Reconstitution Inflammatory Syndrome

Advances in antiretroviral therapy (ART) have paved the way to a new clinical entity termed immune reconstitution inflammatory syndrome (IRIS), a consequence of exaggerated inflammatory response from recovering immune cells.

Currently, there exist two clinical pictures: paradoxical IRIS which occurs during antifungal therapy and immunodeficiency reversal and unmasking IRIS whereby symptoms appear for the first time after immune recovery. As concerns paradoxical IRIS, HIV-associated is commonly described with an incidence of 8–49% [78] as well as solid organ transplants-related [79–81], and paradoxical IRIS has also been described following treatment with immunomodulatory agents such as alemtuzumab [82].

Till date, the pathophysiology of IRIS remains unclear. A recent review highlights the current understanding of the syndrome associated with fungal infections [83•]. In brief, IRIS is the consequence of an inadequate balance between pro-inflammatory response Th1/T17 and anti-inflammatory response Th2/regulatory T cell (Treg) leading to an increase production of interferon-γ (IFNγ) [79, 83•]. IFNγ induces differentiation of macrophages toward M1 macrophages known to be predominant in granuloma formation commonly found on histopathological reports on IRIS, when available [84, 85].

In HIV, in the presence of circulating CrAg, the introduction of ART leads to a rapid redistribution and later, proliferation of naïve CD4+ T cells and consequently to a shift to Th1 response [86, 87]. In solid organ transplant recipients, graft survival is dependent on the inhibition of the Th1/Th17 response with immunosuppressive agents such as mycophenolate mofetil, calcineurin inhibitors and corticosteroids [79]. Drug–drug interactions or intentional drug dosage modification in the context of an ongoing infection can alter the balance required for graft tolerance, thereby increasing Th1/Th17 response. However, so far, only calcineurin inhibitor discontinuation have been found to be associated with up to 5-fold increase in risk of IRIS development [88], and an excessive inflammatory response could have consequences as severe as graft loss due to chronic rejection, as described in a prospective study of renal allografted patients with cryptococcosis [89].

The diagnosis of IRIS in the context of CM is challenging especially as symptoms are non-specific (headaches, seizures, neurological deficit) and may occur in other organs that were not initially infected but in which excessive inflammatory response occurs (skin and soft tissue, pneumonitis) [61]. Nevertheless, diagnosis remains clinical and relies on exclusions of other diagnoses, among which is worsening or relapse of CM, but in the case of IRIS, CSF is typically sterile [61]. Monitoring (1–3)-ß-D-glucan in CSF could be helpful [90].

Risk factors for IRIS can be grouped into three main categories [83•]:

- Host-related factors: blood and CSF findings suggestive of paucity of immune response toward *Cryptococcus* among which low pre-ART blood CD4 count [91–93], total and specific IgM [94] and low level of TNFα, IFNα confirmed by modified IFNα release assay of whole blood stimulated with cryptococcal mannoprotein [95], granulocyte- and granulocyte macrophage-colony stimulating factor (G-CSF and GM-CSF) are considered risk factors [96]. Similarly, in CSF, decreased leucocytes count and low levels of IFN, IL-6, IL-8, TNF and, global protein < 50 mg/dL [93, 97].
- Pathogen-related factors: high fungal burden assessed by serum cryptococcal antigen (CrAg) titre, high colony forming unit/mL in CSF and confirmed fungemia [85, 93, 96].
- Treatment-related factors: early initiation of ART following introduction of induction antifungal treatment and/or rapid decrease of HIV viral load (> 2.5 log at the time of IRIS compared with RNA levels before ART) [92] as well as the type of ART regimen (boosted protease inhibitor, dolutegravir) may increase the risk of subsequent IRIS [98, 99].

However, no cutoffs have been established for these parameters, and more studies are needed to include them in patient care guidelines. Therefore, based on the risk factors, IRIS can partly be prevented by delaying and/or tapering immune restoration through adequate timing of ART introduction in CM [72, 77••].

Optimal management of IRIS remains unclear. IDSA guidelines do not recommend treatment of minor IRIS manifestations but consider the administration of corticosteroids (0.5–1 mg/kg/day) in the context of raised ICP. Currently dexamethasone is the only drug that can be used for more severe central nervous system cases [61]. However, in case of severe cryptococcal IRIS in solid organ transplant recipients, or in case of corticosteroid resistant cryptococcal IRIS, the use of a recombinant human monoclonal TNFα antagonist, adalimumab can improve prognosis, and the use of thalidomide has also been shown to be beneficial [100–102].

Conclusion

Cryptococcus spp. is a ubiquitous basidiomycetous yeast environmentally acquired through inhalation. Major risk factors for severe disease are cell mediated immune deficiencies including advanced HIV infection, solid organ transplantation, underlying lymphoid haematological malignancies and prolonged steroid therapy. Cryptococcal antigen can be detected in serum and CSF using LFA and can be considered as one of the most attractive diagnostic tests ever developed in clinical microbiology, and high antigen titre impacts the prognosis. Early detection of cryptococcal antigenemia in severely immunosuppressed antiretroviral-naive HIV-infected patients in sub-Saharan Africa is now mandatory and should lead to pre-emptive fluconazole therapy in absence of CM. Since 2018, WHO recommends induction treatment for HIV-associated CM with either a 7-day combination therapy of amphotericin B plus flucytosine, followed by high dose oral fluconazole for 7 extra days, or a 14-day oral combination therapy of flucytosine and high dose fluconazole, according to local drugs availability. Reducing CSF-opening pressure with sequential lumbar punctures is an essential component of the therapeutic strategy. In addition, initiation of antiretroviral therapy should occur 4–6 weeks following initiation of antifungal therapy. Finally, either immune reconstitution inflammatory syndrome or microbiologically confirmed CM relapse should be considered in case of recurrent symptoms.

Acknowledgements The authors wish to thank Dr. John C.M. Brust for providing the full review of this article.

Compliance with Ethical Standards

Conflict of Interest Elvis Temfack, David Lawrence, Sarah Delliere, Angela Loyse each declare no potential conflicts of interest. Alexandre Alanio reports personal fees (Educational symposium) from Gilead sciences, outside the submitted work. Fanny Lanternier reports personal fees from Gilead, and from Basilea, outside the submitted work. Olivier Lortholary reports personal fees (Speaker during congresses) from Gilead, Merck, Pfizer, Astellas, outside the submitted work. Timothée Boyer-Chammard reports personal fees (Educational symposium) from Gilead Science, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Kwon-Chung KJ, Fraser JA, Doering TL, Wang Z, Janbon G, Idnurm A, et al. Cryptococcus neoformans and Cryptococcus gattii, the etiologic agents of cryptococcosis. Cold Spring Harbor Perspect Med. 2014;4(7):a019760. https://doi.org/10.1101/cshperspect.a019760.
2.• Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis. 2017;17(8):873–81. https://doi.org/10.1016/S1473-3099(17)30243-8 **This paper gives an update on the epidemiology of**

cryptococcal meningitis cases worldwide, with an estimated number of cases of 223,000 and 180,000 deaths, mainly in sub-Saharan Africa.

3. Ni M, Feretzaki M, Sun S, Wang X, Heitman J. Sex in fungi. Annu Rev Genet. 2011;45:405–30.
4. Kwon-Chung KJ, Boekhout T, Fell JW, Diaz M. (1557) Proposal to conserve the name Cryptococcus gattii against C. hondurianus and C. bacillisporus (Basidiomycota, Hymenomycetes, Tremellomycetidae). Taxon. 2002;51(4):804–6.
5. Chen SC-A, Korman TM, Slavin MA, Marriott D, Byth K, Bak N, et al. Antifungal therapy and management of complications of cryptococcosis due to Cryptococcus gattii. Clin Infect Dis. 2013;57(4):543–51.
6. Hagen F, Khayhan K, Theelen B, Kolecka A, Polacheck I, Sionov E, et al. Recognition of seven species in the Cryptococcus gattii/Cryptococcus neoformans species complex. Fungal Genet Biol. 2015;78:16–48.
7. Kwon-Chung KJ, Bennett JE, Wickes BL, Meyer W, Cuomo CA, Wollenburg KR, et al. The case for adopting the "species complex" nomenclature for the etiologic agents of cryptococcosis. mSphere. 2017;2(1):e00357–16.
8. Lin X, Heitman J. The biology of the Cryptococcus neoformans species complex. Annu Rev Microbiol. 2006;60:69–105.
9. Casadevall A, Steenbergen JN, Nosanchuk JD. 'Ready made'virulence and 'dual use' virulence factors in pathogenic environmental fungi—the Cryptococcus neoformans paradigm. Curr Opin Microbiol. 2003;6(4):332–7.
10. Litvintseva AP, Carbone I, Rossouw J, Thakur R, Govender NP, Mitchell TG. Evidence that the human pathogenic fungus *Cryptococcus neoformans* var. grubii may have evolved in Africa. PloS One. 2011;6(5):e19688.
11. Bliska JB, Casadevall A. Intracellular pathogenic bacteria and fungi—a case of convergent evolution? Nat Rev Microbiol. 2009;7(2):165–71.
12. Kronstad JW, Attarian R, Cadieux B, Choi J, D'souza CA, Griffiths EJ, et al. Expanding fungal pathogenesis: Cryptococcus breaks out of the opportunistic box. Nat Rev Microbiol. 2011;9(3):193–203.
13. Kozel T, Gotschlich E. The capsule of Cryptococcus neoformans passively inhibits phagocytosis of the yeast by macrophages. J Immunol. 1982;129(4):1675–80.
14. O'Meara TR, Alspaugh JA. The Cryptococcus neoformans capsule: a sword and a shield. Clin Microbiol Rev. 2012;25(3):387–408.
15. Chammard TB, Temfack E, Lortholary O, Alanio A. Diagnostic and therapeutic strategies in cryptococcosis: impact on outcome. Mem Inst Oswaldo Cruz. 2018;113(7).
16. Rodrigues ML, Nakayasu ES, Oliveira DL, Nimrichter L, Nosanchuk JD, Almeida IC, et al. Extracellular vesicles produced by Cryptococcus neoformans contain protein components associated with virulence. Eukaryot Cell. 2008;7(1):58–67.
17. Nosanchuk JD, Casadevall A. The contribution of melanin to microbial pathogenesis. Cell Microbiol. 2003;5(4):203–23.
18. Shea JM, Kechichian TB, Luberto C, Del Poeta M. The cryptococcal enzyme inositol phosphosphingolipid-phospholipase C confers resistance to the antifungal effects of macrophages and promotes fungal dissemination to the central nervous system. Infect Immun. 2006;74(10):5977–88.
19. Shi M, Li SS, Zheng C, Jones GJ, Kim KS, Zhou H, et al. Real-time imaging of trapping and urease-dependent transmigration of Cryptococcus neoformans in mouse brain. J Clin Invest. 2010;120(5):1683–93.
20. Dromer F, Mathoulin-Pélissier S, Launay O, Lortholary O, Group FCS. Determinants of disease presentation and outcome during cryptococcosis: the CryptoA/D study. PLoS Med. 2007;4(2):e21.
21. Garcia-Hermoso D, Janbon G, Dromer F. Epidemiological evidence for dormant Cryptococcus neoformans infection. J Clin Microbiol. 1999;37(10):3204–9.
22. Alanio A, Vernel-Pauillac F, Sturny-Leclère A, Dromer F. *Cryptococcus neoformans* host adaptation: toward biological evidence of dormancy. mBio. 2015;6(2):e02580–14.
23. Charlier C, Chrétien F, Baudrimont M, Mordelet E, Lortholary O, Dromer F. Capsule structure changes associated with Cryptococcus neoformans crossing of the blood-brain barrier. Am J Pathol. 2005;166(2):421–32.
24. Chrétien F, Lortholary O, Kansau I, Neuville S, Gray F, Dromer F. Pathogenesis of cerebral Cryptococcus neoformans infection after fungemia. J Infect Dis. 2002;186(4):522–30.
25. Charlier C, Nielsen K, Daou S, Brigitte M, Chretien F, Dromer F. Evidence of a role for monocytes in dissemination and brain invasion by Cryptococcus neoformans. Infect Immun. 2009;77(1):120–7.
26. Santiago-Tirado FH, Onken MD, Cooper JA, Klein RS, Doering TL. Trojan horse transit contributes to blood-brain barrier crossing of a eukaryotic pathogen. mBio. 2017;8(1):e02183–16.
27. Neofytos D, Fishman J, Horn D, Anaissie E, Chang CH, Olyaei A, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. Transpl Infect Dis. 2010;12(3):220–9.
28. Camargo JF. Donor-derived infections in solid organ transplant recipients: challenging the 30-day paradigm. Transpl Infect Dis. 2017;19(2):e12665.
29. Kusne S, Taranto S, Covington S, Kaul D, Blumberg E, Wolfe C, et al. Coccidioidomycosis transmission through organ transplantation: a report of the OPTN ad hoc disease transmission advisory committee. Am J Transplant. 2016;16(12):3562–7.
30. Bernard C, Maucort-Boulch D, Varron L, Charlier C, Sitbon K, Freymond N, et al. Cryptococcosis in sarcoidosis: cryptOsarc, a comparative study of 18 cases. QJM Int J Med. 2013;106(6):523–39.
31. Hutto JO, Bryan CS, Greene FL, White CJ, Gallin JI. Cryptococcosis of the colon resembling Crohn's disease in a patient with the hyperimmunoglobulinemia E-recurrent infection (Job's) syndrome. Gastroenterology. 1988;94(3):808–12.
32. Jacobs DH, Macher AM, Handler R, Bennett JE, Collen MJ, Gallin JI. Esophageal cryptococcosis in a patient with the hyperimmunoglobulin E-recurrent infection (Job's) syndrome. Gastroenterology. 1984;87(1):201–3.
33. Garty BZ, Wolacfr B, Ashkenazi S, Weisman Y, Rachmel A, Nitzan M. Cryptococcal meningitis in a child with hyperimmunoglobulin E syndrome. Pediatr Allergy Immunol. 1995;6(3):175–7.
34. Lanternier F, Cypowyj S, Picard C, Bustamante J, Lortholary O, Casanova J-L, et al. Primary immunodeficiencies underlying fungal infections. Curr Opin Pediatr. 2013;25(6):736.
35. Pilmis B, Puel A, Lortholary O, Lanternier F. New clinical phenotypes of fungal infections in special hosts. Clin Microbiol Infect. 2016;22(8):681–7.
36. Chong I, Wang KY, Lincoln CM. Cryptococcal meningitis in a multiple sclerosis patient treated with Fingolimod: a case report and review of imaging findings. Clin Imaging. 2019;54:53–6.
37. Gundacker ND, Jordan SJ, Jones BA, Drwiega JC, Pappas PG, editors. Acute cryptococcal immune reconstitution inflammatory syndrome in a patient on natalizumab. Open forum infectious diseases; 2016: Oxford University Press.
38. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European organization for research and treatment of cancer/invasive fungal infections cooperative group and the national institute of allergy and infectious diseases mycoses study

group (EORTC/MSG) consensus group. Clin Infect Dis. 2008;46(12):1813–21.
39. Lazcano O, Speights JV, Strickler J, Bilbao J, Becker J, Diaz J. Combined histochemical stains in the differential diagnosis of Cryptococcus neoformans. Mod Pathol. 1993;6(1):80–4.
40. Bloomfield N, Gordon MA, Elmendorf DF Jr. Detection of Cryptococcus neoformans antigen in body fluids by latex particle agglutination. Proc Soc Exp Biol Med. 1963;114(1):64–7.
41. Jarvis JN, Percival A, Bauman S, Pelfrey J, Meintjes G, Williams GN, et al. Evaluation of a novel point-of-care cryptococcal antigen test on serum, plasma, and urine from patients with HIV-associated cryptococcal meningitis. Clin Infect Dis. 2011;53(10):1019–23.
42. Lindsley MD, Mekha N, Baggett HC, Surinthong Y, Autthateinchai R, Sawatwong P, et al. Evaluation of a newly developed lateral flow immunoassay for the diagnosis of cryptococcosis. Clin Infect Dis. 2011;53(4):321–5.
43. Vidal JE, Boulware DR. Lateral flow assay for cryptococcal antigen: an important advance to improve the continuum of HIV care and reduce cryptococcal meningitis-related mortality. Rev Inst Med Trop Sao Paulo. 2015;57:38–45.
44. Longley N, Jarvis JN, Meintjes G, Boulle A, Cross A, Kelly N, et al. Cryptococcal antigen screening in patients initiating ART in South Africa: a prospective cohort study. Clin Infect Dis. 2015;62(5):581–7.
45. Mfinanga S, Chanda D, Kivuyo SL, Guinness L, Bottomley C, Simms V, et al. Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial. Lancet. 2015;385(9983):2173–82. https://doi.org/10.1016/S0140-6736(15)60164-7.
46.•• Temfack E, Bigna JJ, Luma HN, Spijker R, Meintjes G, Jarvis JN, et al. Impact of routine Cryptococcal antigen screening and targeted preemptive fluconazole therapy in antiretroviral-naive human immunodeficiency virus–infected adults with CD4 cell counts< 100/μL: a systematic review and meta-analysis. Clin Infect Dis. 2018;68(4):688–98 **This systematic review and meta-analysis emphasise the high rate of cryptococcal meningitis (more than a third) in asymptomatic patients with cryptococcal antigenemia, and the major role for pre-emptive fluconazole.**
47. French N, Gray K, Watera C, Nakiyingi J, Lugada E, Moore M, et al. Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. Aids. 2002;16(7):1031–8.
48. Kozel TR, Bauman SK. CrAg lateral flow assay for cryptococcosis. Exp Opin Med Diagn. 2012;6(3):245–51.
49.• Temfack E, Kouanfack C, Mossiang L, Loyse A, Fonkoua MC, Molloy SF, et al. Cryptococcal antigen screening in asymptomatic HIV-infected antiretroviral naive patients in Cameroon and evaluation of the new semi-quantitative Biosynex CryptoPS test. Front Microbiol. 2018;9:409 **In this study, the authors show the very important role of cryptococcal antigen screening for patients with advanced HIV disease, to guide pre-emptive treatment and identify asymptomatic cases of cryptococcal meningitis.**
50. Jackson AT, van der Horst CM. Cryptococcosis in AIDS: new data but questions remain. OXFORD UNIV PRESS INC JOURNALS DEPT, 2001 EVANS RD, CARY, NC 27513 USA; 2016.
51.• Wake RM, Britz E, Sriruttan C, Rukasha I, Omar T, Spencer DC, et al. High cryptococcal antigen titers in blood are predictive of subclinical cryptococcal meningitis among human immunodeficiency virus-infected patients. Clin Infect Dis. 2017;66(5):686–92 **In this study the authors found that about a third of asymptomatic HIV-infected patients with cryptococcal antigenemia had cryptococcal meningitis, and that the antigen titres in blood were a good tool to predict meningitis diagnosis.**
52. Mpoza E, Mukaremera L, Kundura DA, Akampurira A, Luggya T, Tadeo KK, et al. Evaluation of a point-of-care immunoassay test kit 'StrongStep'for cryptococcal antigen detection. PLoS One. 2018;13(1):e0190652.
53. Graybill JR, Sobel J, Saag M, van der Horst C, Powderly W, Cloud G, et al. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. Clin Infect Dis. 2000;30(1):47–54.
54. Bicanic T, Brouwer AE, Meintjes G, Rebe K, Limmathurotsakul D, Chierakul W, et al. Relationship of cerebrospinal fluid pressure, fungal burden and outcome in patients with cryptococcal meningitis undergoing serial lumbar punctures. Aids. 2009;23(6):701–6.
55.•• Beardsley J, Wolbers M, Kibengo FM, Ggayi A-BM, Kamali A, Cuc NTK, et al. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. N Engl J Med. 2016;374(6):542–54 **This major clinical trial definitely ruled out the use of concomitant steroids with induction phase antifungals for cryptococcal meningitis, as it led to higher mortality and higher impairment than placebo.**
56. Newton PN, Thai LH, Tip NQ, Short JM, Chierakul W, Rajanuwong A, et al. A randomized, double-blind, placebo-controlled trial of acetazolamide for the treatment of elevated intracranial pressure in cryptococcal meningitis. Clin Infect Dis. 2002;35(6):769–72.
57. Rolfes MA, Hullsiek KH, Rhein J, Nabeta HW, Taseera K, Schutz C, et al. The effect of therapeutic lumbar punctures on acute mortality from cryptococcal meningitis. Clin Infect Dis. 2014;59(11):1607–14.
58. Fessler RD, Sobel J, Guyot L, Crane L, Vazquez J, Szuba MJ, et al. Management of elevated intracranial pressure in patients with Cryptococcal meningitis. J Acquir Immune Defic Syndr Hum Retrovirol. 1998;17(2):137–42.
59. Boyles TH, Gatley E, Wasserman S, Meintjes G. 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–e6.
60. Thakur KT, Mateyo K, Hachaambwa L, Kayamba V, Mallewa M, Mallewa J, et al. Lumbar puncture refusal in sub-Saharan Africa: a call for further understanding and intervention. Neurology. 2015;84(19):1988–90.
61. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010;50(3):291–322.
62. Van der Horst CM, Saag MS, Cloud GA, Hamill RJ, Graybill JR, Sobel JD, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. N Engl J Med. 1997;337(1):15–21.
63. Brouwer AE, Rajanuwong A, Chierakul W, Griffin GE, Larsen RA, White NJ, et al. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. Lancet. 2004;363(9423):1764–7.
64. Day JN, Chau TT, Wolbers M, Mai PP, Dung NT, Mai NH, et al. Combination antifungal therapy for cryptococcal meningitis. N Engl J Med. 2013;368(14):1291–302.
65. Pappas PG, Chetchotisakd P, Larsen RA, Manosuthi W, Morris MI, Anekthananon T, et al. A phase II randomized trial of amphotericin B alone or combined with fluconazole in the treatment of HIV-associated cryptococcal meningitis. Clin Infect Dis. 2009;48(12):1775–83.
66. Nussbaum JC, Jackson A, Namarika D, Phulusa J, Kenala J, Kanyemba C, et al. Combination flucytosine and high-dose fluconazole compared with fluconazole monotherapy for the treatment of cryptococcal meningitis: a randomized trial in Malawi. Clin Infect Dis. 2010;50(3):338–44.

67. Gaskell KM, Rothe C, Gnanadurai R, Goodson P, Jassi C, Heyderman RS, 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): e110285.
68. Rothe C, Sloan DJ, Goodson P, Chikafa J, Mukaka M, Denis B, et al. A prospective longitudinal study of the clinical outcomes from cryptococcal meningitis following treatment induction with 800 mg oral fluconazole in Blantyre, Malawi. PloS One. 2013;8(6):e67311.
69.• Beyene T, Zewde AG, Balcha A, Hirpo B, Yitbarik T, Gebissa T, et al. Inadequacy of high-dose fluconazole monotherapy among cerebrospinal fluid Cryptococcal antigen (CrAg)–positive human immunodeficiency virus-infected persons in an Ethiopian CrAg screening program. Clin Infect Dis. 2017;65(12):2126–9 **This study confirmed that the use of fluconazole monotherapy should not be an option for cryptococcal meningitis treatment.**
70.•• Molloy SF, Kanyama C, Heyderman RS, Loyse A, Kouanfack C, Chanda D, et al. Antifungal combinations for treatment of cryptococcal meningitis in Africa. N Engl J Med. 2018;378(11):1004–17 **This major phase III randomised clinical trial found 1 week of amphotericin B given with flucytosine to be noninferior to two weeks, flucytosine to be a better partner for amphotericin than fluconazole and for oral combination antifungal treatment with flucytosine and fluconazole to be an acceptable alternative to intravenous treatment. It has led to change the latest WHO guidelines for management of cryptococcal meningitis**.
71.•• Tenforde MW, Shapiro AE, Rouse B, Jarvis JN, Li T, Eshun-Wilson I et al. Treatment for HIV-associated cryptococcal meningitis. Cochrane Database Syst Rev. 2018(7). **This Cochrane review has confirmed the recent WHO guidelines using results from recent clinical trials for cryptococcal meningitis therapy.**
72. World Health Organisation. 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. https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/. 2018.
73. Aguirre JPB, Hamid AMR. Amphotericin B deoxycholate versus liposomal amphotericin B: effects on kidney function. Cochrane Database Syst Rev. 2015;11.
74. Hamill RJ, Sobel JD, El-Sadr W, Johnson PC, Graybill JR, Javaly K, 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):225–32.
75. Lawrence DS, Youssouf N, Molloy SF, Alanio A, Alufandika M, Boulware DR, et al. Correction to: AMBIsome Therapy Induction OptimisatioN (AMBITION): high dose AmBisome for cryptococcal meningitis induction therapy in sub-Saharan Africa: study protocol for a phase 3 randomised controlled non-inferiority trial. Trials. 2019;20(1):48. https://doi.org/10.1186/s13063-018-3155-9.
76. Boulware DR, Meya DB, Muzoora C, Rolfes MA, Huppler Hullsiek K, Musubire A, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. N Engl J Med. 2014;370(26):2487–98.
77.•• Eshun-Wilson I, Okwen MP, Richardson M, Bicanic T. Early versus delayed antiretroviral treatment in HIV-positive people with cryptococcal meningitis. Cochrane Database Syst Rev. 2018(7). **This Cochrane review has reconfirmed the need to delay antiretroviral therapy initiation for at least 4 weeks from initiation of antifungal treatment for cryptococcal meningitis**.
78. Haddow LJ, Colebunders R, Meintjes G, Lawn SD, Elliott JH, Manabe YC, et al. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. Lancet Infect Dis. 2010;10(11):791–802.
79. Sun H-Y, Singh N. Immune reconstitution inflammatory syndrome in non-HIV immunocompromised patients. Curr Opin Infect Dis. 2009;22(4):394–402.
80. Legris T, Massad M, Purgus R, Vacher-Coponat H, Ranque S, Girard N, et al. Immune reconstitution inflammatory syndrome mimicking relapsing cryptococcal meningitis in a renal transplant recipient. Transpl Infect Dis. 2011;13(3):303–8.
81. Singh N, Sifri CD, Silveira FP, Miller R, Gregg KS, Huprikar S, et al. Cryptococcosis in patients with cirrhosis of the liver and posttransplant outcomes. Transplantation. 2015;99(10):2132–41.
82. Ingram PR, Howman R, Leahy MF, Dyer JR. Cryptococcal immune reconstitution inflammatory syndrome following alemtuzumab therapy. Clin Infect Dis. 2007;44(12):e115–e7.
83.• Dellière S, Guery R, Candon S, Rammaert B, Aguilar C, Lanternier F, et al. Understanding pathogenesis and care challenges of immune reconstitution inflammatory syndrome in fungal infections. J Fungi. 2018;4(4):139 **This review aims to understand the recent challenges of immune reconstitution inflammatory syndrome in all fungal infections, including cryptococcal meningitis.**
84. Legrand F, Lecuit M, Dupont B, Bellaton E, Huerre M, Rohrlich P-S, et al. Adjuvant corticosteroid therapy for chronic disseminated candidiasis. Clin Infect Dis. 2008;46(5):696–702.
85. Lortholary O, Fontanet A, Mémain N, Martin A, Sitbon K, Dromer F, et al. Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococcosis in France. Aids. 2005;19(10):1043–9.
86. Shearer GM. HIV-induced immunopathogenesis. Immunity. 1998;9(5):587–93.
87. Becker Y. The changes in the T helper 1 (Th1) and T helper 2 (Th2) cytokine balance during HIV-1 infection are indicative of an allergic response to viral proteins that may be reversed by Th2 cytokine inhibitors and immune response modifiers–a review and hypothesis. Virus Genes. 2004;28(1):5–18.
88. Sun H-Y, Alexander BD, Huprikar S, Forrest GN, Bruno D, Lyon GM, et al. Predictors of immune reconstitution syndrome in organ transplant recipients with cryptococcosis: implications for the management of immunosuppression. Clin Infect Dis. 2014;60(1):36–44.
89. Singh N, Lortholary O, Alexander BD, Gupta KL, John GT, Pursell K, et al. Allograft loss in renal transplant recipients with Cryptococcus neoformans associated immune reconstitution syndrome. Transplantation. 2005;80(8):1131–3.
90. Rhein J, Bahr NC, Morawski BM, Schutz C, Zhang Y, Finkelman M et al, editors. Detection of high cerebrospinal fluid levels of (1→ 3)-β-d-glucan in cryptococcal meningitis. Open forum infectious diseases; 2014: Oxford University Press.
91. Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. Lancet Infect Dis. 2010;10(4):251–61.
92. Manabe YC, Campbell JD, Sydnor E, Moore RD. Immune reconstitution inflammatory syndrome: risk factors and treatment implications. J Acquir Immune Defic Syndr. 2007;46(4):456–62.
93. Chang CC, Dorasamy AA, Gosnell BI, Elliott JH, Spelman T, Omarjee S, et al. Clinical and mycological predictors of cryptococcosis-associated immune reconstitution inflammatory syndrome. Aids. 2013;27(13):2089–99.
94. Yoon HA, Nakouzi A, Chang CC, Kuniholm MH, Carreño LJ, Wang T, et al. Association between plasma antibody responses and risk for Cryptococcus-associated immune reconstitution inflammatory syndrome. J Infect Dis. 2018;219(3):420–8.
95. Chang CC, Lim A, Omarjee S, Levitz SM, Gosnell BI, Spelman T, et al. Cryptococcosis-IRIS is associated with lower cryptococcus-

specific IFN-γ responses before antiretroviral therapy but not higher T-cell responses during therapy. J Infect Dis. 2013;208(6):898–906.
96. Boulware DR, Meya DB, Bergemann TL, Wiesner DL, Rhein J, Musubire A, et al. Clinical features and serum biomarkers in HIV immune reconstitution inflammatory syndrome after cryptococcal meningitis: a prospective cohort study. PLoS Med. 2010;7(12): e1000384.
97. Boulware DR, Bonham SC, Meya DB, Wiesner DL, Park GS, Kambugu A, et al. Paucity of initial cerebrospinal fluid inflammation in cryptococcal meningitis is associated with subsequent immune reconstitution inflammatory syndrome. J Infect Dis. 2010;202(6):962–70.
98. Psichogiou M, Basoulis D, Tsikala-Vafea M, Vlachos S, Kapelios CJ, Daikos GL. Integrase strand transfer inhibitors and the emergence of immune reconstitution inflammatory syndrome (IRIS). Curr HIV Res. 2017;15(6):405–10.
99. Vitoria M, Ford N, Clayden P, Pozniak AL, Hill AM. When could new antiretrovirals be recommended for national treatment programmes in low-income and middle-income countries: results of a WHO think tank. Curr Opin HIV AIDS. 2017;12(4):414–22.
100. Gaube G, De Castro N, Gueguen A, Lascoux C, Zagdanski A, Alanio 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):154–6.
101. Brunel A-S, Reynes J, Tuaillon E, Rubbo P-A, Lortholary O, Montes B, et al. Thalidomide for steroid-dependent immune reconstitution inflammatory syndromes during AIDS. Aids. 2012;26(16):2110–2.
102. Scemla A, Gerber S, Duquesne A, Parize P, Martinez F, Anglicheau D, et al. Dramatic improvement of severe cryptococcosis-induced immune reconstitution syndrome with adalimumab in a renal transplant recipient. Am J Transplant. 2015;15(2):560–4.