

# Cryptococcal meningitis: epidemiology and therapeutic options

Derek J Sloan  
Victoria Parris

Tropical and Infectious Disease Unit,  
Royal Liverpool University Hospital,  
Liverpool, UK

**Abstract:** Cryptococcal meningitis causes morbidity and mortality worldwide. The burden of disease is greatest in middle- and low-income countries with a high incidence of human immunodeficiency virus (HIV) infection. Patients taking immunosuppressive drugs and some immunocompetent hosts are also at risk. Treatment of cryptococcal meningitis consists of three phases: induction, consolidation, and maintenance. Effective induction therapy requires potent fungicidal drugs (amphotericin B and flucytosine), which are often unavailable in low-resource, high-endemicity settings. As a consequence, mortality is unacceptably high. Wider access to effective treatment is urgently required to improve outcomes. For human immunodeficiency virus-infected patients, judicious management of asymptomatic cryptococcal antigenemia and appropriately timed introduction of antiretroviral therapy are important.

**Keywords:** cryptococcosis, HIV, immunosuppression, antifungal therapy, immune reconstitution inflammatory syndrome, antiretroviral therapy

## Introduction

Cryptococcosis is an important infectious disease globally. The majority of illness is among patients with defective cell-mediated immunity. Human immunodeficiency virus (HIV) infection is the main risk factor, accounting for 95% of cases in middle- and low-income countries (MLICs)<sup>1</sup> and 80% of cases in high-income countries (HICs).<sup>2</sup> Individuals taking immunosuppressive drugs (eg, transplant recipients) constitute most of the remaining caseload, although immunocompetent hosts are susceptible in some settings.

The most common clinical presentation is cryptococcal meningitis (CM), with over 1 million cases and 600,000 deaths per year.<sup>3</sup> Nonmeningeal (eg, pulmonary and cutaneous) presentations also occur,<sup>4</sup> and bloodstream infection (cryptococemia) may disseminate to multiple sites.<sup>5</sup>

This review describes the epidemiology and management of cryptococcal disease. Worldwide distribution of the pathogen is outlined, incidence trends in patients with varying risk factors are assessed, and the prognostic implications of differing treatment protocols are highlighted.

## Epidemiology of the infectious pathogen

Cryptococci are encapsulated saprophytic yeasts. Two species, transmitted by inhalation, are the principal human pathogens: *Cryptococcus neoformans* and *Cryptococcus gattii*.<sup>6</sup> *C. neoformans* was identified by Sanfelice in 1894,<sup>7,8</sup> and may be divided into two subtypes on the basis of capsular agglutination assays.<sup>9</sup> *C. neoformans* var.

Correspondence: Derek J Sloan  
Tropical and Infectious Disease Unit,  
Royal Liverpool University Hospital,  
Prescot Street, Liverpool,  
Merseyside L7 8XP, UK  
Tel +44 151 706 3835  
Fax +44 151 706 5944  
Email djsloan@liverpool.ac.uk

*grubii* (capsular serotype D) is the most common, and causes 82% of cryptococcal disease worldwide. *Var. neoformans* (capsular serotype A) is responsible for 20%–30% of HIV-associated CM in northern Europe (notably France, Italy, and Denmark),<sup>9–11</sup> but is less common in other global regions.<sup>12,13</sup> Although both subtypes predominantly cause disease in immunocompromised individuals, several reports from the US<sup>14</sup> and Asia<sup>15</sup> suggest that *var. grubii* cryptococcosis in patients with normal immune systems is more common than previously assumed. The environmental reservoir of both subtypes is avian guano, decaying organic matter, and soil.<sup>8,16</sup>

*C. gattii* is traditionally associated with illness in immunocompetent individuals<sup>17–19</sup> from tropical and subtropical regions, including Thailand,<sup>20</sup> northern Australia,<sup>21,22</sup> New Zealand, and Papua New Guinea.<sup>23–26</sup> More recently, four molecular subtypes of *C. gattii* have been identified with distinct epidemiological characteristics that challenge this perspective.<sup>6</sup> Whilst VGI (*var. gattii* I) is the main subtype in Australasia, an outbreak of disease attributable to VGII has been described in immunocompetent patients from British Columbia, Canada.<sup>27–29</sup> Between 1999 and 2010, 218 cases were identified on Vancouver Island.<sup>30,31</sup> In 2006, a further case was reported on Orcas Island, Washington, USA,<sup>32</sup> and *C. gattii* is now endemic throughout the Pacific Northwest of the US.<sup>29</sup> Sporadic disease has also been notified in other parts of North America, including Florida, North Carolina, Rhode Island, New Mexico, Michigan, Georgia, and Montana.<sup>33</sup> Additionally, *C. gattii* subtypes VGIII and -IV are more likely to be found in HIV-infected than immunocompetent patients. These strains may account for 2.4%–30% of HIV-associated cryptococcosis in some parts of Central and South America<sup>6</sup> and southern Africa.<sup>34–37</sup> The burden of human disease due to *C. gattii* is probably underrecognized, as many laboratories do not undertake detailed speciation of cryptococci.<sup>6</sup>

The environmental reservoirs of *C. gattii* are incompletely understood. In Australia, India, and other Asian countries, it has been isolated in eucalyptus trees.<sup>38</sup> In British Columbia, it has been isolated from noneucalyptus tree species, soil, air, freshwater, and seawater.<sup>29</sup> Discovery of this organism in heterogeneous biogeoclimatic zones suggests that its ecological niche was previously underestimated or that its distribution is expanding.<sup>39,40</sup> Possible explanations for a changing distribution include climate change or altered land-use practices, such as logging.

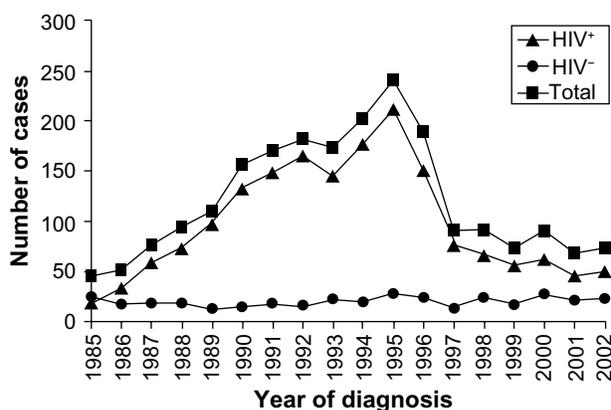
## HIV as a risk factor

The largest influence on the epidemiology of cryptococcal disease over the last 30 years has been the evolution of

the HIV pandemic. Figure 1 shows that a fivefold increase in the incidence of cryptococcosis in France from 1985 to 1993 was almost entirely due to burgeoning disease in HIV-infected patients, while the number of cases in HIV-uninfected patients remained stable.<sup>41</sup> Similar trends were observed in other HICs. In the UK, the number of annual cryptococcal case notifications rose from 13 (8% HIV-associated) in 1982 to 66 (83% HIV-associated) in 1991.<sup>42</sup> Of 517 cryptococcal infections in New York City in 1991, 96% were HIV-related.<sup>43</sup>

HIV-infected patients are mainly at risk of cryptococcosis when they become very immunosuppressed and their CD4 count drops below 100 cells/ $\mu$ L.<sup>44,45</sup> Consequentially, Figure 1 indicates that after the development of effective combination antiretroviral therapy (ART) in 1997, the upsurge in new cases of cryptococcal disease from HICs was reversed and incidence began to decline.<sup>46–48</sup> From 1997–2001, France saw a 46% decrease in cases,<sup>41</sup> from 1996 to 2007, incidence per 1,000 persons in the UK fell from three to 0.2,<sup>49</sup> and from 1992 to 2000, incidence per 1,000 persons in Atlanta, Georgia, USA fell from 66 to seven.<sup>50</sup>

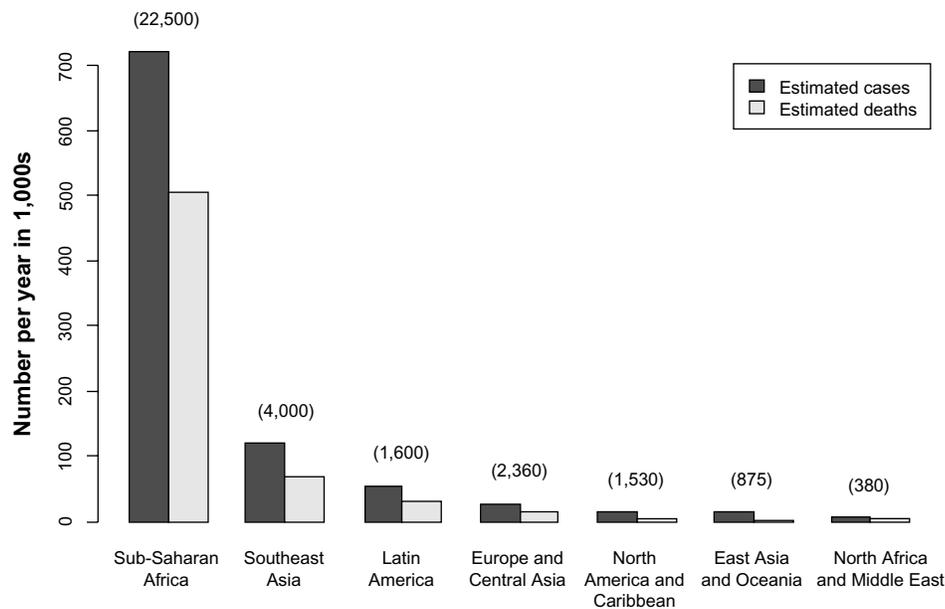
Figure 2 shows that disease trends in MLICs have been much worse. It is well recognized that sub-Saharan Africa has been the global region most heavily affected by HIV, with an estimated 2.6 million new infections per year at the peak of the epidemic in 1997.<sup>51</sup> Contemporaneously, in the 1990s, CM became the leading cause of adult meningitis in many African countries, including Malawi



**Figure 1** Evolution of the incidence of cryptococcosis, by year of diagnosis in France (1985–2001), as reported to the National Reference Centre for Mycosis.

**Note:** Reproduced with permission from Dromer F, Mathoulin-Pelissier S, Fontanet A, Ronin O, Dupont B, Lortholary O, Epidemiology of HIV-associated cryptococcosis in France (1985–2001): comparison of the pre- and post-HAART eras, *AIDS*, 18:555–562.<sup>41</sup> Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact [journalpermissions@lww.com](mailto:journalpermissions@lww.com) for further information.

**Abbreviation:** HIV, human immunodeficiency virus.



**Figure 2** Global incidence and mortality from cryptococcal meningitis among United Nations global regions from 1997 to 2007.

**Notes:** Figures in brackets and italics indicate human immunodeficiency virus prevalence in 1,000s from each region during the period studied. Data from Park et al.<sup>3</sup>

(27% of cases),<sup>52</sup> Zimbabwe (45% of cases),<sup>53,54</sup> and South Africa (31% of cases).<sup>55</sup> Delayed and incomplete access to ART meant that unlike Europe and North America, the incidence of CM did not recede after the turn of the millennium; a tertiary referral hospital in Botswana described *C. neoformans* growth from 15% of all cerebrospinal fluid (CSF) samples submitted for analysis in 2003,<sup>56</sup> and a report from Cape Town, South Africa noted that CM still accounted for 31% of all inpatient days in new ART patients in 2007.<sup>57</sup> A similar persistent elevation of the cryptococcal disease burden since the 1990s has been described from MLICs in Southeast Asia<sup>56,58</sup> and Latin America.<sup>59</sup>

In addition to disparities in incidence between HICs and MLICs, there are well-documented differences in outcomes (Figure 2).<sup>3</sup> A combination of earlier access to ART and availability of fungicidal drugs has contributed to falling mortality in HICs,<sup>2,60,61</sup> while the death rate in MLICs has been relentlessly high.<sup>62</sup> Analysis of pooled data from case series, surveillance reports, and clinical trials has estimated that the 90-day case-fatality rate from HIV-associated CM in East Asia, Oceania, Western Europe and the US is 9%, compared with 55% in other parts of Asia and South America and 70% in sub-Saharan Africa.<sup>3</sup> Even acknowledging that some North American studies exclude the sickest patients,<sup>63</sup> and some studies in MLICs show better case-fatality rates than others,<sup>64–67</sup> these results are unacceptable.

## Other risk factors

Although HIV is the largest driver of cryptococcal disease, it is important to acknowledge other factors. Prior to the HIV era in the UK, the incidence of cryptococcosis per 1,000 persons increased from 1.4 in 1963–1968 to 7.4 in 1973–1978.<sup>68</sup> This was predominantly attributable to disease in patients on immunosuppressive medications. Use of potent immunosuppressants (eg, corticosteroids, calcineurin inhibitors,<sup>69</sup> cytotoxic agents,<sup>70</sup> and monoclonal antibodies<sup>71,72</sup>) for transplant conditioning or treatment of cancer and inflammatory conditions has continued to expand in HICs over the last 30 years, sustaining a small but important minority of cryptococcal illness in settings where HIV-related cases are in decline.<sup>73</sup>

Cryptococcosis disease occurs after 2.8%–8% of solid-organ transplants, and is the third-commonest invasive fungal infection in this setting, after *Candida* and *Aspergillus*.<sup>69,74</sup> In a retrospective review of US data from 1996 to 2010, kidney-transplant recipients were most often affected, followed by liver, heart, lung, and pancreas recipients.<sup>5</sup> The median time to diagnosis after solid-organ transplantation is 20 months, and the etiology is normally reactivation of latent disease.<sup>5,74,75</sup> Symptoms may emerge sooner after lung or liver transplants, perhaps because the required level of postoperative immunosuppression is higher.<sup>69</sup> The overall likelihood of cryptococcal disease does not vary between patients using tacrolimus, cyclosporine, or azathioprine as the primary immunosuppressive agent, but patients who

are coadministered high-dose corticosteroids may be at higher risk.<sup>5</sup>

Infrequently, cryptococcal infection is acquired from donor tissue. This is particularly suspected if disease occurs within 30 days of transplantation, at surgical graft sites, or in multiple organ recipients of a single donor.<sup>75–77</sup> Screening of donors is not routinely performed, but should be undertaken if the donor has unexplained pulmonary lesions, undiagnosed neurological illness, or unexplained fever with relevant comorbid risk factors.<sup>76,77</sup>

Cryptococcal disease is rare following hematopoietic stem cell transplant or corneal tissue transplant.<sup>78</sup> Data from a consortium of US transplant centers (Transplant-Associated Infection Surveillance Network) revealed an incidence of only 0.6% in hematopoietic stem cell-transplant recipients between 2001 and 2006.<sup>79,80</sup> For unknown reasons, the risk is higher in autologous than allogenic transplants.<sup>78</sup>

Non-HIV-infected, nontransplant recipients with cryptococcosis are a heterogeneous group. Except for *C. gattii* outbreaks in immunocompetent hosts, most patients have immune dysfunction related to the pathophysiology or treatment of an underlying autoimmune disease, malignancy, or innate immunological disorder. It is difficult to generalize about these cases, but in HICs they tend to experience higher mortality than their HIV-infected counterparts. The reasons for this include the effects of underlying illness and late diagnosis, because the pathogen was not initially suspected.<sup>5,73,81</sup>

## Clinical presentation

Epidemiological variables, including the nature of immunosuppressive risk factors and pathogen species, influence the presentation of cryptococcal disease. CM is the leading presentation overall,<sup>19,41,42,78</sup> but nonmeningeal manifestations are proportionally more frequent in non-HIV-infected individuals.<sup>5,42,73,82</sup> Transplant-associated cryptococcosis is often limited to the lungs,<sup>83,84</sup> with disseminated or neurological disease in 52%–61% of cases.<sup>69,84</sup>

Presentation of *C. gattii* infection in immunocompetent hosts varies according to molecular subtype. In Australia, where the majority of disease is due to VGI, CM is most common,<sup>6,85</sup> but in North America, VGII disease presents with respiratory symptoms in 76%, neurological symptoms in 7.8%, and both respiratory and neurological symptoms in 10.1% of cases.<sup>19,24,31</sup>

The commonest features of CM are subacute headache and confusion. Intracranial pressure (ICP) is often elevated, and may cause cranial nerve palsies or seizures. Classical features of “meningism” (eg, neck stiffness) occur in less

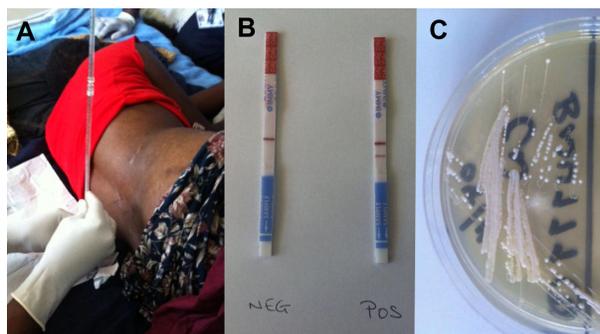
than 20% of patients.<sup>86</sup> Altered mental state is associated with higher mortality.<sup>5,50,87</sup>

Neurological infection may be complicated by mass lesions (cryptococcomas). This is more common with *C. gattii* than *C. neoformans*. Clinical sequelae of cryptococcomas include hydrocephalus and blindness.<sup>88,89</sup> Some patients require neurosurgical intervention.<sup>17,18</sup>

Forty percent of patients with CM have ocular involvement, including papilledema and uveitis with multifocal chorioretinitis.<sup>90,91</sup> Immune-mediated optic nerve dysfunction and blindness have been particularly reported amongst *C. gattii* patients from Papua New Guinea.<sup>54,89,92</sup> The spectrum of pulmonary illness ranges from asymptomatic colonization to severe, progressive pneumonia and cryptococcomas in the lungs. Skin lesions often contain the infecting organism. In severely immunocompromised individuals, disseminated disease (involvement of two or more sites) may present as fever and rash before other symptoms and signs appear.

## Investigations

Confirmation of CM requires lumbar puncture (LP) and examination of CSF, as shown in Figure 3A. Lack of LP equipment may result in underestimation of the disease burden in MLICs.<sup>93</sup> Typical CSF features include a raised opening pressure (reflecting elevated ICP), lymphocytic pleocytosis, and evidence of inflammation. However, CSF may be normal in 10%–17% of patients,<sup>54,94</sup> especially in HIV-endemic populations.<sup>5</sup> Identification of the infecting organism is traditionally done by light microscopy after India ink staining, but this method is user-dependent with variable sensitivity. Detection of cryptococcal antigen (CrAg)



**Figure 3 (A–C)** Diagnosis of cryptococcal meningitis. **(A)** Lumbar puncture being performed on a human immunodeficiency virus-infected patient with suspected meningitis in Malawi. **(B)** Lateral flow immunoassay test strips for cryptococcal antigen detection (the strip on the left shows a negative result, indicated by a single horizontal “control” band in the center; the strip on the right shows a positive result, indicated by adjacent horizontal “control” and “test” bands). **(C)** *Cryptococcus neoformans* growing on Sabouraud media. Images kindly supplied by Kate Gaskell, College of Medicine, University of Malawi, and Brigitte Denis, Malawi Liverpool Wellcome Trust Clinical Research Programme.

by a latex-agglutination test<sup>63</sup> or lateral flow immunoassay (LFA) is better (Figure 3B). The lateral flow immunoassay is cheaper than latex agglutination,<sup>95,96</sup> and may be applied to urine samples when CSF is unobtainable.<sup>97,98</sup> Fungal culture of CSF on Sabouraud media is required to isolate the organism for antimicrobial susceptibility testing. Characteristic colonies grow after 36 hours (Figure 3C).

Radiology has little role in the diagnosis of CM, but computed tomography and magnetic resonance imaging scans are necessary to detect complications (eg, cryptococcomas and noncommunicating hydrocephalus). These modalities are generally unavailable in MLICs.

Nonmeningeal cryptococcosis may be confirmed by tissue sampling for microbiological analysis. Cryptococemia is identified from fungal blood cultures or CrAg detection in serum samples. Asymptomatic antigenemia (a positive serum CrAg in the absence of clinical disease) has been described in HIV-infected patients, and may predict impending CM. Screening and treatment for asymptomatic antigenemia will be discussed later.

## Treatment and prognosis

The Infectious Diseases Society of America (IDSA)<sup>4</sup> and World Health Organization (WHO)<sup>99</sup> have recently issued updated treatment guidelines to reflect advances over the last decade, but routine practice in MLICs continues to be impeded by poor drug availability. Figure 4 summarizes current recommendations.

### Induction and consolidation antifungal therapy for HIV-associated CM

CM treatment consists of three phases: induction, consolidation, and maintenance. IDSA and WHO guidelines emphasize the importance of potent fungicidal drugs during induction therapy, because the rate of fungal clearance from the CSF during the first 2 weeks, known as early fungicidal activity (EFA),<sup>100</sup> predicts 10-week survival,<sup>101</sup> and CSF sterilization by 14 days predicts long-term prognosis.<sup>63</sup>

Amphotericin B (AmB), the drug with the greatest EFA, is administered intravenously for 14 days during induction therapy whenever possible. Its activity is concentration-dependent,<sup>102</sup> but the required dose (0.7–1.0 mg/kg) of the commonest preparation (AmB deoxycholate [AmBd])<sup>33,63–65</sup> can be nephrotoxic.<sup>103,104</sup> A solution in HICs is the use of lipid drug formulations with fewer renal side effects, including liposomal AmB (LAmB; 3–6 mg/kg/day) and AmB lipid complex (ABLC, 5 mg/kg/day).<sup>105–107</sup> The cost of these (over US\$1,000 per day<sup>108</sup>) is prohibitive for MLICs, so alternative

strategies, including preemptive hydration and electrolyte supplementation, have been developed to minimize the toxicity of AmBd.<sup>99</sup> Studies in Kampala,<sup>62</sup> Cape Town,<sup>65</sup> and Bangkok<sup>109</sup> support this approach.

Even a 2-week course of AmBd (US\$12–\$15 per day) is too expensive for some LICs.<sup>110</sup> In this scenario, data from South Africa and Malawi have demonstrated that 5–7 days of AmBd is better than treatment that is restricted to less fungicidal drugs.<sup>64,111</sup> AmBd-treated patients who survive the first 6 months have a subsequent 5-year survival rate of 88%.<sup>112</sup> This advocates for investment in early AmBd to achieve satisfactory long-term outcomes.

Flucytosine should accompany AmB during induction therapy at an intravenous or oral dose of 100 mg/kg/day.<sup>100,113–115</sup> Omission of this agent has been associated with higher rates of mortality,<sup>113</sup> treatment failure,<sup>116</sup> and late relapse.<sup>117</sup> Toxic cytopenias can occur during flucytosine therapy, and so regular full blood counts and therapeutic drug monitoring (TDM) are advised by IDSA guidelines.<sup>4,57,118</sup> TDM is arduous, and the absolute need for it in MLICs was questioned by a recent study in Vietnam that did not use TDM but demonstrated safe and effective use of AmBd-flucytosine.<sup>113</sup>

Despite its value, flucytosine remains unlicensed in most African and Asian countries,<sup>114,119,120</sup> so alternative agents have been considered for combination with AmB. The obvious contender is fluconazole, which is freely distributed in MLICs ([http://www.pfizer.com/responsibility/global\\_health/diflucan\\_partnership\\_program](http://www.pfizer.com/responsibility/global_health/diflucan_partnership_program)), but is fungistatic rather than fungicidal in the normal human dose range. Definitive evidence to support AmB-fluconazole induction therapy is lacking, but reports from several countries describe rapid EFA when intravenous AmBd (0.7–1 mg/kg/day) is prescribed alongside oral fluconazole (800–1,200 mg/day).<sup>109,113,121,122</sup> A meta-analysis of various induction strategies in resource-poor settings has described AmBd-fluconazole as cost-effective.<sup>123</sup> The WHO recommends this approach when flucytosine cannot be obtained.<sup>99</sup>

After a 14-day induction phase, treatment proceeds with a consolidation phase of 400 mg once daily (od) for a further 8 weeks. This dose may be increased to 800 mg when gold-standard induction therapy with AmB-flucytosine is unavailable.

Gaps in drug provision leave fluconazole as the only agent for induction and consolidation therapy in many high-burden countries, contributing to significant variation in prognosis. The response to this requires discussion. Until recently, the routine dose of fluconazole for CM monotherapy was 200–400 mg od, and 8-week mortality was 78%–90%.<sup>86,124</sup> In

	HIV-associated CM			Non-HIV-associated CM	
	All drugs available	No flucytosine	No AmB	Transplant recipients	Non-HIV, non-transplant recipient
<b>Induction</b>	2 weeks AmB <sup>a</sup> (0.7-1.0 mg/kg/day) + flucytosine (100 mg/kg/day)	2 weeks AmB <sup>a</sup> (0.7-1.0 mg/kg/day) + fluconazole (800 mg od)	2 weeks Fluconazole (1200 mg PO od) +/- flucytosine (100 mg/kg/day)	2 weeks LAmB or ABLC + flucytosine (100 mg/kg/day)	4-6 weeks <sup>c</sup> AmBd (0.7-1.0 mg/kg/day) + flucytosine (100 mg/kg/day)
<b>Consolidation</b>	8 weeks Fluconazole (400 mg od)	8 weeks Fluconazole (400-800 mg od)	8 weeks Fluconazole (400-800 mg od)	8 weeks Fluconazole (800 mg PO od)	8 weeks Fluconazole (800 mg PO od)
<b>Maintenance</b>	Until HIV controlled By ART <sup>d</sup> Fluconazole (200 mg od)	6-12 months Fluconazole (200 mg od)	6-12 months Fluconazole (200 mg od)	Until HIV controlled ART <sup>d</sup> Fluconazole (200 mg PO od)	Until HIV controlled by ART <sup>d</sup> Fluconazole (200 mg PO od)

**Figure 4** Treatment options for cryptococcal meningitis (CM), summarized from Infectious Diseases Society of America and World Health Organization guidelines.

**Notes:** <sup>a</sup>In HIV-infected patients with renal impairment or concern about nephrotoxicity, LAmB or ABLC should be used. <sup>b</sup>In settings of limited AmB availability or difficulty with toxicity monitoring, an abbreviated 5- to 7-day induction course of AmB may be used. <sup>c</sup>Non-HIV, nontransplant patients are a heterogeneous group, including individuals with hematological malignancies and immunocompetent hosts with *Cryptococcus gattii* infection. There is no consensus on optimal treatment; some authors suggest identical induction and consolidation therapy as for HIV-associated CM. <sup>d</sup>Undetectable HIV viral load and CD4 > 100/μL should be demonstrated on two occasions 6 months apart before stopping fluconazole.

**Abbreviations:** HIV, human immunodeficiency virus; AmB, amphotericin B; LAmB, liposomal amphotericin B (3–6 mg/kg/day); ABLC, amphotericin B lipid complex (5 mg/kg/day); od, once daily; PO, per os (by mouth); ART, antiretroviral therapy.

one South African study from 2006, median patient survival on induction- and consolidation-phase fluconazole (400 mg od) was only 76 days.<sup>125</sup>

Such poor outcomes prompted dose escalation. Clinical studies in Uganda and Malawi based on 800 mg od induction and 400 mg od consolidation therapy reported improved 10-week mortality rates of 58%–60%.<sup>87,126</sup> A further induction-phase dose increase to 1,200 mg was associated with faster EFA<sup>126</sup> but did not improve survival,<sup>126,127</sup> and a pharmacokinetic–pharmacodynamic bridging study from a mouse model indicated that 1,200 mg od will fail to achieve fungal stasis in the CSF of 33% of patients.<sup>128</sup> An exploratory clinical trial has suggested that induction with 1,600–2,000 mg of fluconazole would be more efficacious,<sup>126,129</sup> but additional evaluation of these doses is required. WHO guidelines currently advocate that where fluconazole monotherapy is the only option, 1,200 mg od should be used for 2-week induction therapy followed by a consolidation phase of 800 mg od for 8 weeks.<sup>99</sup>

A final option when intravenous drug administration is not feasible is a fully oral induction phase of fluconazole and flucytosine. Trials in Malawi have confirmed that fluconazole (1,200 mg od) and flucytosine (100 mg/kg/day) achieve faster EFA and lower 10-week mortality than fluconazole alone,<sup>70,111,127</sup> suggesting that fluconazole monotherapy should

be augmented by induction-phase flucytosine wherever possible.

Overall, reduced availability of fungicidal drugs continues to compromise outcomes in high-burden countries. An ongoing multicenter clinical trial (Advancing Cryptococcal meningitis Treatment in Africa [ACTA]<sup>130</sup>) in sub-Saharan Africa hopes to confirm the shortest, simplest effective regimens, but will require backup by universal provision of medicines for routine care.

## Maintenance antifungal therapy for HIV-associated CM

After consolidation therapy, secondary prophylaxis with fluconazole (200 mg od) minimizes the risk of CM relapse.<sup>131</sup> Alternative, less effective maintenance regimens include oral itraconazole (200 mg od)<sup>117</sup> and intravenous AmBd (1 mg/kg/once weekly).<sup>132</sup>

The required duration of maintenance therapy has recently been examined, particularly as the 1-year default rate from secondary prophylaxis in some African settings exceeds 90%.<sup>133,134</sup> In the pre-ART era, lifelong fluconazole was recommended after a presentation with CM, but it now appears that late relapse is unlikely during successful ART.<sup>135–138</sup> International guidelines state that immune restoration by ART permits discontinuation of maintenance therapy (Figure 4). However, evidence to support cessation of

secondary prophylaxis is weaker when induction/consolidation therapy is not fungicidal (eg, fluconazole monotherapy), and isolated CM relapses have been described in patients on ART with CD4 counts up to 495 cells/ $\mu$ L.<sup>139</sup>

## Differences in antifungal therapy for non-HIV-associated CM

Treatment of non-HIV-associated CM varies from that described above, dependent on characteristics of the host and pathogen (Figure 4). Patients developing CM after solid-organ transplant often take nephrotoxic immunosuppressants (tacrolimus, cyclosporine or sirolimus) to prevent graft rejection, and 25% of transplant recipients have renal dysfunction at CM diagnosis. Therefore, kidney-friendly liposomal preparations of AmB (eg, LAmB or ABLC) are recommended during induction therapy.<sup>4</sup> It is uncertain whether immunosuppressive therapy should be stopped during CM treatment; this may accelerate eradication of the pathogen, but poses a risk of proinflammatory immune reconstitution syndrome or transplant rejection.<sup>140</sup> Although clear evidence is lacking, some authors report good outcomes with a staged reduction in immunosuppressive therapy alongside antifungal drugs.<sup>141</sup>

Secondary fluconazole prophylaxis in transplant recipients may stop after 6–12 months, as the late cryptococcal relapse rate is only 1%–3%.<sup>142</sup> There is no standard regimen for non-HIV, nontransplant patients with CM. Some authors advocate a longer (4–6 weeks) induction phase of AmB/flucytosine (Figure 4), while others favor a standard 2-week induction phase. Consolidation and maintenance therapy are identical to transplant recipients. *C. gattii* infection should be treated with the same drugs as *C. neoformans*, but the response to therapy may be slower, due to higher azole minimum inhibitory concentrations<sup>143,144</sup> and poor drug penetration of cryptococcomas.<sup>17,18,85</sup>

## Asymptomatic antigenemia and primary prophylaxis

Between 4% and 20% of patients with newly identified HIV infection and a CD4 count  $<150$  cells/ $\mu$ L have a positive serum CrAg test in the absence of clinical cryptococcosis.<sup>145–147</sup> Asymptomatic antigenemia predicts impending CM,<sup>148</sup> and is associated with increased mortality.<sup>149</sup> Serum CrAg screening of new HIV patients is being implemented in South Africa,<sup>150</sup> prompting debate on the use of preemptive therapy for those at highest risk.

Treatment of asymptomatic antigenemia is not recommended in HICs,<sup>4</sup> but some studies support fluconazole

therapy for serum CrAg-positive patients in MLICs.<sup>151–153</sup> A management algorithm is shown in Figure 5.<sup>154</sup> However, deployment of preventive screening and therapy strategies is operationally difficult, and an implementation study in Kenya achieved effective fluconazole administration for only 52% of eligible patients.<sup>155</sup> The benefit of presumptive therapy for asymptomatic antigenemia will depend on the logistics of integrating this strategy into routine practice at ART clinics.

An alternative means of CM prevention is primary prophylaxis with fluconazole for all patients with CD4 counts  $<100$  cells/ $\mu$ L, irrespective of serum CrAg testing. Studies of this approach in Thailand<sup>156</sup> and Uganda<sup>157</sup> demonstrated that fluconazole 200 mg once daily reduced the incidence of CM, but there was no reduction in overall mortality and rates of fluconazole-resistant *Candida albicans* infection increased.<sup>158</sup> The cost-effectiveness of no preventive treatment, therapy for asymptomatic antigenemia, or primary prophylaxis is likely to vary between regions, based on the underlying epidemiology of cryptococcal infection and availability of ART.

## Additional therapeutic considerations

Outcomes from CM may be improved by reduction of raised ICP during early therapy, careful management of immune reconstitution inflammatory syndrome (IRIS) and appropriately timed ART initiation for HIV-infected patients.

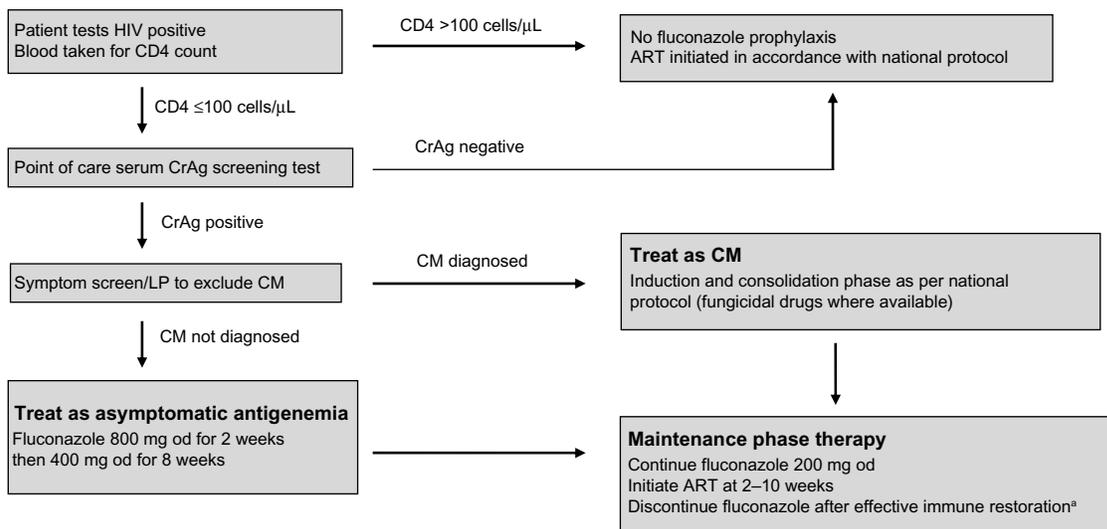
### Reducing raised intracranial pressure

Increased ICP ( $>25$  cm/ $H_2O$ ) is associated with greater CSF fungal burden<sup>159</sup> and higher mortality.<sup>160</sup> Regular CSF drainage by serial LPs is recommended.<sup>115,161–164</sup> Insertion of a temporary CSF-drainage catheter<sup>165</sup> or ventriculoperitoneal shunt may also be used.<sup>166</sup> Drug therapy (eg, acetazolamide or corticosteroids) to reduce CSF pressure or prevent blindness in CM patients is not beneficial, and acetazolamide may cause harm.<sup>88,160,167</sup>

### Managing immune reconstitution inflammatory syndromes

IRIS in CM patients occurs when host immune recovery triggers inflammatory reactions to persistent fungal antigens. There are two main forms: unmasking and paradoxical (Figure 6).<sup>168</sup>

Unmasking IRIS occurs in HIV-infected patients when subclinical cryptococcal disease emerges after ART is commenced. This might be prevented by careful pre-ART screening. However, late ART is generally associated with



**Figure 5** A screening and management strategy for asymptomatic antigenemia.

**Notes:** <sup>a</sup>Undetectable HIV viral load and CD4 >100/μL should be demonstrated on two occasions 6 months apart before stopping fluconazole. Jarvis JN, Govender N, Chiller T, et al. *J Int Assoc Physicians AIDS Care (Chic)* (11), pp 374–379, copyright © 2012 by SAGE Publications. Adapted by permission of SAGE Publications.<sup>154</sup>

**Abbreviations:** HIV, human immunodeficiency virus; CrAg, cryptococcal antigen; LP, lumbar puncture; CM, cryptococcal meningitis; od, once daily; ART, antiretroviral therapy.

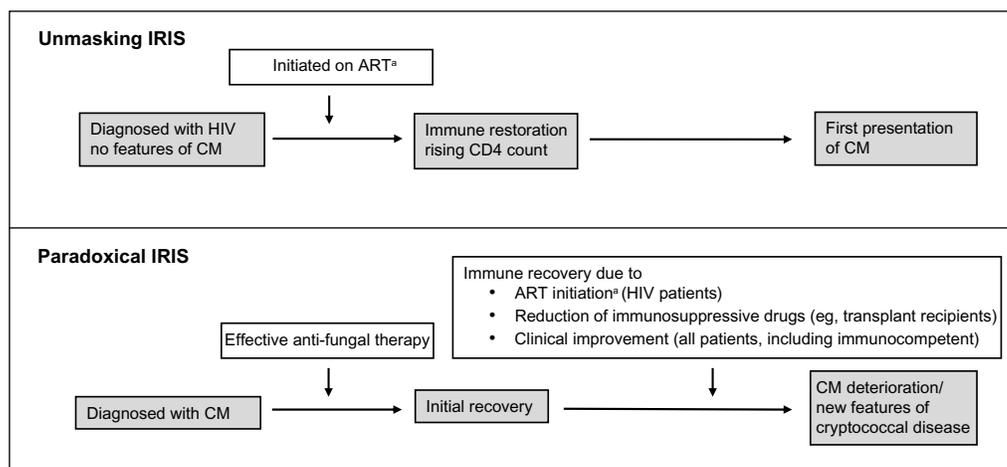
lower survival,<sup>169</sup> and patients who are already on HIV therapy when they present with CM tend to have better outcomes,<sup>64,170</sup> so excessive delays should be avoided.

Paradoxical IRIS is best described in HIV-associated CM patients who initially respond to antifungal drugs and then deteriorate within 12 months of starting ART. Studies from South Africa and Ethiopia estimate an incidence of 7%–33%.<sup>171–173</sup> Paradoxical IRIS also affects solid organ-transplant patients when antirejection medications are interrupted during CM therapy,<sup>141</sup> and apparently healthy hosts may suffer from reactivation of immune defenses that were previously overwhelmed by high fungal burden.

Paradoxical IRIS in the central nervous system has a mortality of up to 36%.<sup>174,175</sup> Risk factors include severe disease at presentation and slow fungal elimination.<sup>176,177</sup> The benefit of anti-inflammatory drugs (eg, corticosteroids<sup>100</sup>) is unproven.<sup>178</sup> Highly fungicidal induction-phase therapy and rapid CSF sterilization is the best way to minimize unwanted reactions.<sup>179,180</sup>

### Combining anticryptococcal and anti-HIV medications

In HIV-associated CM, IRIS is more likely during immune reconstitution from lower baseline CD4 counts, and is



**Figure 6** Types of immune restoration inflammatory syndrome (IRIS) in cryptococcal disease.

**Note:** <sup>a</sup>HIV-associated CM IRIS should occur within 12 months of ART initiation.

**Abbreviations:** ART, antiretroviral therapy; HIV, human immunodeficiency virus; CM, cryptococcal meningitis.

**Table 1** Prospective open-label randomized trials to assess optimal timing of antiretroviral therapy (ART) initiation in human immunodeficiency virus (HIV)-infected patients with cryptococcal meningitis (CM)

Study and site	Study design	Baseline CD4 count, cells/ $\mu$ L, median (IQR)	CM induction-phase drugs	Initiation of ART during CM therapy	Study outcomes
Zolopa et al, <sup>182</sup> USA <sup>a</sup> and South Africa	282 patients with OIs (35 with CM) 48-week follow-up	29 (10–55)	Not stated	<2 weeks versus 4–32 weeks	All patients: fewer AIDS events/ deaths in early (20 of 141 [14%]) versus late (34 of 141 [24%]) ART (OR 0.5, 95% CI 0.3–0.9)  CM patients: no difference in AIDS events/deaths in early (one of 13 [8%]) versus late (three of 22 [14%]) ART (OR 0.5, 96% CI 0.1–5.7)
Makadzange et al, <sup>184</sup> Zimbabwe	54 patients with CM 3-year follow-up	37 (17–69)	Fluconazole only	<72 hours versus >10 weeks	Higher mortality in early (23 of 28 [82%]) versus late (12 of 26 [46%]) ART (HR 2.3, 95% CI 1.1–4.9)
Bisson et al, <sup>183</sup> Botswana	27 patients with CM 24-week follow-up	29 (11–50)	AmB + fluconazole	<7 days versus >28 days	No difference in mortality in early (two of 13 [15%]) versus late (five of 14 [36%]) ART (OR 0.3, 95% CI 0.1–2.1)
Boulware et al, <sup>185</sup> Uganda and South Africa	177 patients with CM 6-month follow-up	19 (9–69)	AmB + flucytosine	<14 days versus >28 days	Higher mortality in early (40/88 [45%]) versus late (27 of 89 [30%]) ART (HR 1.7, 95% CI 1.1–2.8; P=0.03)

**Note:** <sup>a</sup>Includes patients from Puerto Rico.

**Abbreviations:** IQR, interquartile range; AIDS, acquired immunodeficiency syndrome; OR, odds ratio; HR, hazard ratio; CI, confidence interval AmB, amphotericin B; OIs, opportunistic infections.

influenced by the timing of ART introduction. Balancing the danger of early mortality from advanced immunosuppression against that of accelerated immune recovery is difficult, and best practice remains to be established. A retrospective study of mortality after ART initiation in Thailand at time points 1–12 months into CM therapy did not show any association between timing of ART and outcome.<sup>181</sup> Table 1 summarizes subsequent prospective trials.<sup>135,136,182–185</sup> The most convincing data come from a recent study in Uganda and South Africa, which was terminated early because ART initiation within the first 28 days of CM treatment led to a higher risk of IRIS and death.<sup>185</sup> Introduction of ART 4–10 weeks after starting antifungal treatment is currently considered the safest approach.

## Conclusion

Advanced HIV infection continues to drive cryptococcal disease worldwide. Patients on immunosuppressive drugs and some immunocompetent hosts are also at risk. Although treatment with potent drug combinations provides effective cure, poor availability of fungicidal drugs in MLICs results in high case-fatality rates. Expanded provision of fungicidal treatment is urgently required. Ongoing research on management of asymptomatic antigenemia and optimal timing

of ART initiation is important to improve the prognosis of HIV-associated CM.

## Disclosure

The authors report no conflicts of interest in this work.

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