Long term mortality and disability in Cryptococcal Meningitis: a systematic literature review.

Pasquier Estelle[1], Kunda John[1], De Beaudrap Pierre[2], Loyse Angela[3], Temfack Elvis[4], Molloy Síle F[3], Harrison Thomas S[3], Lortholary Olivier[4, 5].

[1] London School of Hygiene and Tropical Medicine, Faculty of Public Health and Policy, London, United Kingdom;

[2] CEPED - UMR 196 – IMSERM U1244, Institut de Recherche pour le Développement (IRD), Paris Descartes University, Paris, France; [3] Centre for Global Health, Institute for Infection and Immunity, St. George's University of London, London, United Kingdom;

[4] Institut Pasteur, Molecular Mycology Unit, National Reference Center for Invasive Mycoses & Antifungals, CNRS URA3012, Paris, France; [5] Paris Descartes University, APHP, Necker Pasteur Center for Infectious Diseases and Tropical Medicine, IHU Imagine, Necker Enfants Malades Hospital, Paris, France.

Corresponding author:

Prof Olivier Lortholary, M.D. ; Ph.D

Necker Pasteur Center for Infectious Diseases and

Tropical Medicine,

Necker Enfants malades Hospital, Paris, France.

Email : olivier.lortholary@aphp.fr

Summary: One year after induction treatment, cryptococcal meningitis mortality reaches almost 80% in HIV-infected cohorts and more than 70% of non-HIV and HIV-infected survivors live with impairments. Early therapeutic intervention and early management of disability could significantly improve prognosis.

Running title: Long term prognosis of cryptococcal meningitis

Abstract :

Cryptococcal meningitis (CM) is the primary cause of meningitis in HIV-infected adults and an emerging disease in HIV-seronegative individuals. No literature review has studied the long-term outcome of CM. We performed a systematic review on the long-term (≥3 months) impact of CM (*C. neoformans* and *C. gattii*) on mortality and disability in HIV-infected and non-HIV-infected adults. Though the quality of current evidence is limited, the long-term impact of CM on survival and disability appears to be high. One-year mortality ranged from 13% in an Australian non-HIV *C. gattii* infected cohort to 78% in a Malawian HIV-infected cohort treated with fluconazole monotherapy. One-year impairment proportions among survivors ranged from 19% in an Australian *C. gattii* cohort to more than 70% in a Taiwanese non-HIV and HIV-infected cohorts. Ongoing early therapeutic interventions, early detection of impairments and access to rehabilitation services may significantly improve patients' survival and quality of life.

INTRODUCTION

Cryptococcal meningitis (CM) is a leading cause of meningitis in many low and middle income countries (LMICs) where it accounts for 15-20% of all HIV-related mortality[1]. Despite the expansion of antiretroviral therapy (ART) programmes, rates of CM remain high as many HIV-infected persons start ART late and face difficulties maintaining effective treatment[2]. Moreover, sustainable access to the current reference induction treatment, flucytosine (5-FC) and amphotericin B (AmB), is a major challenge in these settings. Fluconazole monotherapy is the only alternative but is associated with higher short-term mortality, even at high dosages[3]. Consequently, CM mortality remains high in LMICs ranging from 19% to 96%[4,5] at 10-12 weeks. In contrast, it has been estimated to range from 9% to 15% in Western Europe and North America[6,7].

Additionally, a growing number of CM-associated deaths occur in non-HIV patients in high-income countries (HIC)[8]. CM caused by *C. neoformans,* is increasingly observed among patients with non-HIV immunosuppression[8]. In parallel, *C. gattii* CM, endemic in Australia, appeared recently as an outbreak in North America, mainly among patients without apparent immunosuppression (up to 72% of cases). It appears that non HIV-associated CM (non-HIV-CM) mortality outcomes are no better than HIV-associated CM in similar settings [8].

Beyond mortality, CM survivors may experience different long-term (≥3 months after CM diagnosis) neurological and sensorial impairment resulting into disability and poor quality of life[6,9].

However, data on the long-term outcome of CM remain scarce [10,11]. Indeed, while short-term mortality of HIV-CM has been well reviewed [7,8,12,13], literature reviews including longer-term overall cryptococcosis mortality are limited[8,13] and none have reported long-term CM-related neuro-sensorial impairment and disability.

To address this gap, we exhaustively reviewed published data on the long-term mortality, impairment and disability following CM caused by *C. neoformans* or *C. gattii* occurring in either immunodeficient or immunocompetent adults. The following questions were addressed: what are the proportions/rates and predictive factors for mortality occurring ≥3 months after CM diagnosis or treatment induction? What are the nature, frequency and predictive factors of CM sequelae/impairment, disability and decreased quality of life occurring ≥3 months after CM treatment induction? Finally, are there differences in the ≥3 month prognosis between HIV and non-HIV infected patients?

METHODS

This systematic review was conducted in line with the PRISMA Statement[14].

Search strategy and study selection

PubMed/Medline, Web of Science, Cochrane Library, Embase, Global Health, LILACS and WHO online libraries were searched for studies published in English, French and Spanish between Jan 1st, 2005 and June 30th, 2015 (Figure 1). The search combined two groups of words including synonyms and MeSH terms of (group 1) "Cryptococcal Meningitis" and (group 2) "Outcome and risk factors" (see Supplementary Table 1).

All types of study design were considered for eligibility. Studies were included if they fulfilled the following criteria: 1) reporting the mortality rate/proportion and/or the proportion of sequelae/impairments/disability occurring ≥3 months after CM diagnosis or after induction treatment, 2) participants ≥18 years-old, 3) with documented first episode of CM diagnosed by positive India Ink and/or positive Cryptococcal Antigen and/or positive cerebrospinal fluid (CSF) culture (*C. neoformans* or *C. gattii)*. Both immunodeficient and apparently immunocompetent patients were considered.

Studies on cryptococcomas without CM and studies where CM data could not be individualized from other causes of meningitis were excluded. Additional studies were manually searched for from reference lists of all identified articles.

Quality assessment

The quality of the selected studies was assessed at outcome level[14] using the Critical Appraisal Skills Programme (CASP) tools[15]. Domains assessed were: (1) validity: appropriate design, appropriate sampling methods, risk of bias and confounding; (2) importance: effect size, power, precision of the study; and (3) comparability/generalizability. Studies that fulfilled more than 70% of criteria were considered of good quality and those that fulfilled less than 50% of CASP criteria were excluded for providing weak evidence.

Data extraction and synthesis

For each study included, the following data were extracted: (1) study characteristics (setting, design, sample size, statistical method used, potential bias and confounding), (2) participants characteristics (eligibility criteria, age, sex, immunological, mental and ART status at diagnosis, ART timing of initiation), (3) Cryptococcus species, (4) outcome (mortality proportion/rate, impairments/disability proportions and quality of life) stratified by outcome timing (6, 12, >12 months after diagnosis) and (5) predictive factors (age, immunological status, viral load, CSF characteristics, clinical presentation, mental and ART status at diagnosis, antifungal and ART treatment received, adjunctive therapy, setting, cryptococcus species, Immune Reconstitution Inflammatory Syndrome (IRIS) occurrence, opportunistic co-infections/affections).

Quality assessment of included studies showed high heterogeneity; therefore we decided to undertake a qualitative synthesis rather than a meta-analysis, which included describing the studies, their results and

limitations without pooling estimates. Further synthesis of the results was done with predefined sub-groups by the patients' immunological status (HIV, non-HIV).

RESULTS

Study characteristics

Of the 6035 records identified during the study period, 177 were selected for full-text review, and 25 articles (24 studies: four randomized clinical trials (RCT), eleven prospective cohorts and nine retrospective cohorts) were eventually retained (Figure 1). Only one of the studies[16] was included although not fulfilling the inclusion criteria, because it provided key results on disability.

Twenty-one studies provided information on mortality outcomes, six on impairments, two on disability and none on quality of life. All continents were represented with fifteen studies from LMIC and nine from HIC. Only six (25%) studies fulfilled at least 70% of quality criteria: two RCT and four cohorts (Table 1).

Long-term mortality and its predictive factors

In HIV-CM, seventeen articles provided information on CM-mortality (five from HIC and twelve from LMIC), and ten examined risk factors (Table 2). Five (28%) articles fulfilled at least 70% of quality criteria. Available data suggest that the high mortality rate of the first ten weeks of treatment continues to rise slowly to level off after six months of treatment [16–19]. However, evidence was weak with few studies and difference in CM management across studies. Two studies using survival analysis showed that when using both AmB-based

combination therapy and appropriately timed ART, the survival curve strongly flattens after 3 months[20,21]. There was important variation in the one-year mortality according to both setting and period: in HIC, mortality was around 50% in the pre-ART period[22] and 20% in the late ART period[22–24], while it ranged from 39.5% to 78% in LMIC[17–21,25–27]. The one-year mortality also varied according to the induction treatment received with fluconazole performing worse than AmB monotherapies, which, in turn, performed worse than AmB-based combined therapy (Figure 2 and Table 3). Nevertheless, even with the latter, the one-year mortality rate was around 40%[19,20] in LMIC and around 20%[22–24] in HIC. Other protective factors included the use of ART as shown in France[22] and Denmark[24], and, in ART-naïve patients, delaying the introduction of ART to 5 to 10 weeks after induction therapy compared to an introduction between 3 days to 2 weeks[20,28]. In LMIC, the one-year mortality observed in patients receiving aggressive Intracranial Pressure (ICP) management was lower compared to those who did not (40%[19,20] versus 59%[18], respectively).

In HIV-CM, the main independent risk factors for long-term mortality were altered neurological status[25,27], low CD4 level[23], high CSF fungal/CrAg burden[16,25], and older age[24] at diagnosis. Lastly, the evidence on an association between IRIS and higher long-term mortality is still unclear [20,29,30] with only one study of the three that addressed this question showing a significant association[29]. This may result from the small study sizes or from the IRIS definition adopted which may miss early IRIS leading to an ascertainment bias, as suggested by Boulware *et al*(2014)[20].

In non-HIV-CM, evidence on long-term mortality is weaker as only six articles (none from LMIC) were identified and none fulfilled at least 70% of quality criteria (Table 2).

One-year mortality ranged from 13.7% in an Australian cohort infected by C. *gattii* with only 28% of patients with underlying conditions [11,31] to 42.3% in a Taiwanese study with all patients having underlying conditions[23]. Non-HIV-CM mortality may continue to rise after three months, as suggested by data from Liao *et al*. [23].

The main independent risk factors for one-year mortality in non-HIV patients were delayed diagnosis[32], age>60 years[32], altered initial neurological status[23,32], high CSF CrAg[23] and non-AmB-based compared to AmB-based induction therapy[32] (Table 4). In patients with *C gattii* CM, only high CSF CrAg was found to be independently associated with one-year mortality[11].

Long-term neuro-sensorial impairments and disability and their predictive factors

Seven studies provided evidence on neuro-sensorial impairment and disability (three for HIV-CM and four for non-HIV-CM) and only one fulfilled at least 70% of quality criteria[33] (supplementary Table 2).

In HIV-CM, up to 69.2% of survivors from a Taiwanese cohort had neuro-sensorial sequelae[23], mainly residual headache (38%), motor deficit (15%) and vertigo (15%), one year after diagnosis. In a Ugandan study, cognitive function remained impaired in 41% of survivors, although the contribution of HIV encephalitis should also be questioned [33].

Only two studies assessed the long-term disability related to HIV-CM [16,33] and none used the WHO International Classification of Functioning definition[9]. In the clinical trial of Day et al., 40% of the survivors reported having some form of "disability" at six months [16] and in the cohort study reported by Carlson et al. 11% of the survivors declared themselves unable to work at one year [33].

Few predictive factors of long-term impairments and disability were found. Carlson *et al*. demonstrated that the risk of 12-month impaired cognition was increased in HIV-CM patients with lower CD4 level at induction. And paradoxically, persons with sterile CSF cultures after 14 days of AmB therapy had worse neurocognitive outcomes than those still culture-positive[33]. At six months, Day *et al*. demonstrated that patients treated with AmB+5-FC were half as likely to report having a "disability" than patients treated with AmB monotherapy[16].

In non-HIV-CM, findings were heterogeneous. In a cohort of patients infected with *C. gattii* without underlying conditions, the rates of neuro-sensorial sequelae among one-year survivors were between 19% and 24% [11,34]. This proportion reached 73.3% in a cohort of patients with underlying conditions (*Cryptococcus* species not known)[23]. The main impairments were vertigo (13% to 24%), visual loss (13% to 23%), hearing impairment (6% to 17%), and motor deficit (3% to 16%).

MRI sylvian fissure enhancement and CSF CrAg titres >1/256 at induction were, respectively, independently associated with hearing loss in any non-HIV-CM,[35] and neurological sequelae in *C. gattii* cohorts [11].

Comparison between HIV and non-HIV-CM

The three studies comparing long-term mortality between HIV and non-HIV-CM[23,36,37] gave contradictory results. Nevertheless, the studies' heterogeneity in terms of proportions of ART-naïve patients for HIV-CM and in terms of proportions of patients with underlying conditions for non-HIV-CM prevents any valid comparisons.

DISCUSSION

Long-term impact of CM on mortality, impairments and disability

To our knowledge, this is the first literature review focusing on long-term outcomes of CM, including mortality, neuro-sensorial impairment and disability. Our review shows that the mortality can reach rates up to 78% in HIV-CM[27] and 42% in non-HIV-CM[23] at one year. In addition, regardless of the species studied (*C. neoformans*, *C gattii*), we found supportive evidence for an important long-term burden of CM on impairments and disability with proportions reaching up to 70% in both HIV-infected and HIV-non-infected survivors[23]. These findings demonstrate that the long-term prognosis of CM in adults may be at least as poor as that associated with other aetiologies of encephalitis in France (33% with impairment at 3 years)[38]or, that associated with tuberculosis meningitis (TBM) (20% to 60% of mortality and 20% to 50% of impairments among survivors)[39,40].

Prevention of risk factors of long-term adverse CM outcomes

Evidence regarding risk factors for long-term outcomes was limited showing an important gap in knowledge. Each of the risk factors for long-term outcomes identified were found to be predictive in only 1 to 3 studies. Some studies did not adjust for confounders (ART[22] and IRIS[20,29] in HIV-CM patients, underlying conditions[11,32] and high CSF antigen titers[35] in non-HIV-CM patients). Some important potential predictive factors have not been studied (e.g. *Cryptococcus* species, phenotypes and genotypes, ICP management) and discordant results regarding the effect of IRIS in HIV-CM or of underlying conditions in non-

HIV-CM were reported. Moreover, definitions of some risk factors varied according to studies (abnormal neurology, fungal burden assessment tools and threshold, underlying pathologies) limiting the potential for comparison. Therefore, future research should systematically assess the long-term impact of all these risk factors using standardized and validated definitions and tools.

Nevertheless, some key actions can be identified to prevent long-term mortality, impairment and disability.

In HIV-CM, some of the well-known short-term mortality risk factors (baseline altered neurology, high fungal burden or immunosuppression)[21] seem to be also predictive of long-term adverse outcomes. Their identification could orient clinicians in providing closer clinical follow-up. More importantly, our review identified some evidence for a protective effect of AmB-based combined antifungal regimens for long-term mortality and AmB+5FC therapy on long-term disability. In addition, it has to be noted that only 1/7[33] of the cohorts assessing impairments and disability in this review provided an AmB-based combined therapy to all patients. Moreover, while ART does not appear to influence short-term HIV-cryptococcosis mortality[41], it plays a key role in reducing long-term mortality[20,22,24,26,28,42]. As in TBM[43], if introduced appropriately (after 4-5 weeks), ART might protect against other opportunistic infections[20]. Therefore, in order to prevent not only short-term but also longer-term adverse outcomes, there is an urgent need to scale up access and coverage of ART, AmB and especially 5-FC therapy, usually not available in LMICs [44]. Additionally, future research on antifungal therapy, as well as adjuvant therapy (especially IRIS and ICP management), should assess the effect on long-term outcomes, including disability.

In non-HIV-CM, the limited number of studies along with their heterogeneity preclude firm conclusion on long-term mortality risk factors. In *C.gattii* cohorts, our results suggest that underlying conditions and altered mental status at induction might be poor long-term prognostic factors[11,34]. But, these univariable associations might be confounded by other factors. For instance, experimental studies have shown that a

difference in virulence of the *C.gattii* genotype infecting Australian patients (mainly VGI)[45] compared to the one of Canadian patients (mainly VGII A)[46] might be another explanation for the difference in mortality. In general, the identified risk factors of non-HIV-CM long-term mortality advocate for early CM diagnosis in people >60 years old with underlying conditions. Nevertheless, management guidelines are based on results from trials involving patients with HIV-CM that may not apply to those with non-HIV-CM. Further multi-centric cohorts/trials, as already conducted for Solid Organ Transplant patients[47], should therefore be proposed, assessing further these potential predisposing factors and looking for the best therapeutic choice.

Poor attention to impairment and disability

Despite the fact that many studies were initially identified, few had quality data on long-term outcomes and only seven assessed long-term impairments and disability. Only three studies assessed impairments/disability and their predictive factors as a primary outcome and five did not describe the method of outcome measurement [11,23,31,34,36]. None used the WHO definition of disability[9], nor assessed quality of life. Similarly, reviews of long-term outcomes of other meningo-encephalitis causes identified a paucity of studies and very few data on morbidity and impairment[38,48]. This is indicative of the low value placed on the collection of long-term meningo-encephalitis outcomes, especially impairment/disability data. Very few studies conducted systematic screening for impairments with validated tools, which may lead to misclassifications and underreporting. Indeed, the two studies that systematically assessed the patients with validated tools found much higher proportions of impairments compared to the others (impaired cognition in 41% of HIV-CM survivors[33] and hearing impairment in 31% of non-HIV-CM survivors[35]). Therefore, future CM research should not only focus on short-term medical outcomes, but also on longer-term impairments,

disability and quality of life. WHO definitions of disability[9] as well as validated neurocognitive, sensorial and quality of life assessment tools should be used as in studies of other forms of encephalitis[38,48].

Implication for rehabilitation

Despite the limited amount of evidence, it is alarming to see that at one year, 20% to 70% of survivors have long-term impairments limiting cognitive, motor, visual and/or hearing function in both HIV and non-HIV-CM patients in both LMICs and HICs. And, while research and guidelines focus mainly on the management of the acute phase of CM to prevent acute mortality[49], little attention is given to long-term follow-up and the identification of, and support for, impairments and disability. Therefore, ensuring access to physical, occupational, sensorial and cognitive rehabilitation services is as important as enhancing prevention by fluconazole pre-emptive treatment and access to ART and AmB-based therapy[9]. While these services are routinely accessible in developed countries, they are limited in LMICs due to a lack of rehabilitation personnel and high costs[50]. For this reason, the development and adaptation of context specific rehabilitation models should be one of the global research priorities for CM and CNS infections, as already advocated by John et al.[50].

Limitations

In addition to the limitations related to the quality and heterogeneity of included studies, our review has some external limitations. Our inclusion and exclusion criteria might have restricted the panel of literature found. Eleven studies have been excluded because they included patients aged less than eighteen

(Supplementary Table 3). Moreover, the chosen threshold of quality is arbitrary as the CASP group has yet to propose a validated scoring system. This has led to exclusion of an additional eleven articles in order to decrease the risk of inaccurate conclusions (Supplementary Table 3). Nevertheless, each article excluded due to age or quality was carefully examined and its exclusion impact assessed. Subsequently, one article was then reintroduced in our review based on this assessment[16].

CONCLUSION

CM has an important long-term impact on mortality and disability. Nevertheless, the quality of evidence is limited, and future CM research should not only focus on short-term medical outcomes, but also on the longer-term mortality, impairments, disability and quality of life. In the meantime, fluconazole pre-emptive treatment, early diagnosis, as well as improved access to timely effective combined antifungal therapy should be implemented to prevent CM mortality and its long-term consequences. Additionally, early detection of impairments and access to rehabilitation services will improve CM-infected survivors' quality of life.

Acknowledgement:

Funding

REFERENCES:

1. Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect. Dis. **2017**; Available at: http://www.ncbi.nlm.nih.gov/pubmed/28483415. Accessed 22 May 2017.

2. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. AIDS **2008**; 22:1897–1908. Available at: http://www.aidsonline.com.

3. Nussbaum JC, Jackson A, Namarika D, 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**; 50:338–44. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2010081479.

4. Dammert P, Bustamante B, Ticona E, et al. Treatment of cryptococcal meningitis in Peruvian AIDS patients using amphotericin B and fluconazole. J. Infect. **2008**; 57:260–5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18707764. Accessed 23 October 2013.

5. Mwaba P, Mwansa J, Chintu C, et al. Clinical presentation, natural history, and cumulative death rates of 230 adults with primary cryptococcal meningitis in Zambian AIDS patients treated under local conditions. Postgr. Med J **2001**; 77:769–773. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2001426193.

6. Dromer F, Mathoulin-Pelissier S, Launay O, et al. Determinants of disease presentation and outcome during cryptococcosis: the CryptoA/D study. PLoS Med **2007**; 4:e21. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=17284154.

7.   Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. AIDS **2009**; 23:525–30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19182676. Accessed 23 October 2013.

8.   Pappas PG. Cryptococcal infections in non-HIV-infected patients. Trans. Am. Clin. Climatol. Assoc. **2013**; 124:61–79. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=23874010.

9.   World Health Organisation. Towards a Common Language for Functioning , Disability and Health ICF. 2002; :1–22. Available at: http://www.who.int/classifications/icf/training/icfbeginnersguide.pdf.

10.   Loyse A, Bicanic T, Jarvis JN, et al. Combination antifungal therapy for cryptococcal meningitis. N. Engl. J. Med. **2013**; 368:1291–302. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23802522. Accessed 22 October 2013.

11.   Chen SC, Slavin MA, Heath CH, et al. Clinical manifestations of Cryptococcus gattii infection: determinants of neurological sequelae and death. Clin. Infect. Dis. **2012**; 55:789–798.

12.   Jackson A, van der Horst C. New insights in the prevention, diagnosis, and treatment of cryptococcal meningitis. Curr. HIV/AIDS Rep. **2012**; 9:267–77. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22763808. Accessed 23 October 2013.

13.   Antinori S. New Insights into HIV/AIDS-Associated Cryptococcosis. ISRN AIDS **2013**; 2013:22. Available at: http://www.hindawi.com/journals/isrn/2013/471363/.

14.   Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement (Reprinted from Annals of Internal Medicine). PLoS Med. **2009**; 6:e1000097.

15.   Critical Appraisal Skills Programme – Making sense of evidence. 2013. Available at: http://www.casp-

uk.net/ [Last access 27/08/2015]. Accessed 1 July 2014.

16.   Day JN, Chau TT, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. N.

        Engl. J. Med. **2013**; 368:1291–1302. Available at:

        http://www.nejm.org/doi/pdf/10.1056/NEJMoa1110404.

17.   Butler EK, Boulware DR, Bohjanen PR, Meya DB. Long term 5-year survival of persons with

        cryptococcal meningitis or asymptomatic subclinical antigenemia in Uganda. PLoS One **2012**;

        7:e51291. Available at:

        http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3519582&tool=pmcentrez&rendertype=a

        bstract. Accessed 8 January 2014.

18.   Kambugu A, Meya DB, Rhein J, et al. Outcomes of cryptococcal meningitis in Uganda before and after

        the availability of highly active antiretroviral therapy. Clin. Infect. Dis. **2008**; 46:1694–1701. Available

        at:

        http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2008246358.

19.   Bicanic T, Wood R, Meintjes G, et al. High-dose amphotericin B with flucytosine for the treatment of

        cryptococcal meningitis in HIV-infected patients: A randomized trial. Clin. Infect. Dis. **2008**; 47:123–

        130. Available at:

        http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2008318207.

        Accessed 23 October 2013.

20.   Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of

        cryptococcal meningitis. N. Engl. J. Med. **2014**; 370:2487–98. Available at:

        http://www.ncbi.nlm.nih.gov/pubmed/24963568. Accessed 24 September 2014.

21.   Jarvis JN, Bicanic T, Loyse A, et al. Determinants of mortality in a combined cohort of 501 patients with

HIV-associated Cryptococcal meningitis: implications for improving outcomes. Clin Infect Dis **2014**;

58:736–745. Available at:

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=2014128716.

22. Lanoy E, Guiguet M, Bentata M, et al. Survival after neuroAIDS: Association with antiretroviral CNS

Penetration-Effectiveness score. Neurology **2011**; 76:644–51. Available at:

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2011096240.

23. Liao C-HH, Chi C-YY, Wang Y-JJ, et al. Different presentations and outcomes between HIV-infected and

HIV-uninfected patients with Cryptococcal meningitis. J. Microbiol. Immunol. Infect. **2012**; 45:296–

304. Available at:

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2012415825.

Accessed 1 November 2013.

24. Mathiesen IH, Knudsen JD, Gerstoft J, Cowan S, Benfield T. Outcome of HIV-1-associated cryptococcal

meningitis, Denmark 1988-2008. Scand. J. Infect. Dis. **2012**; 44:197–200. Available at:

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2012121539.

25. Chaiwarith R, Vongsanim S, Supparatpinyo K. Cryptococcal meningitis in HIV-infected patients at

Chiang Mai University Hospital: a retrospective study. Southeast Asian J. Trop. Med. Public Health

2014; 45:636–646. Available at:

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=24974648.

26. Bicanic T, Meintjes G, Wood R, et al. Fungal burden, early fungicidal activity, and outcome in

cryptococcal meningitis in antiretroviral-naive or antiretroviral-experienced patients treated with

amphotericin B or fluconazole. Clin. Infect. Dis. **2007**; 45:76–80. Available at:

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2007309500.

27. Rothe C, Sloan DJ, Goodson P, 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:e67311. Available at: http://www.plosone.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pone.0067311&representation=PDF.

28. Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. Clin. Infect. Dis. **2010**; 50:1532–8. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2010259754.

29. Bicanic T, Meintjes G, Rebe K, et al. Immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis: a prospective study. J. Acquir. Immune Defic. Syndr. **2009**; 51:130–4. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19365271. Accessed 23 October 2013.

30. Boulware DR, Meya DB, Bergemann TL, et al. Clinical features and serum biomarkers in HIV immune reconstitution inflammatory syndrome after cryptococcal meningitis: a prospective cohort study. PLoS Med. **2010**; 7:e1000384. Available at: http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1000384.

31. Chen SC, Korman TM, Slavin MA, et al. Antifungal therapy and management of complications of cryptococcosis due to Cryptococcus gattii. Clin. Infect. Dis. **2013**; 57:543–51.

32. Zhu LP, Wu JQ, Xu B, Ou XT, Zhang QQ, Weng XH. Cryptococcal meningitis in non-HIV-infected patients in a Chinese tertiary care hospital, 1997-2007. Med. Mycol. **2010**; 48:570–9. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2010287309.

33. Carlson RD, Rolfes MA, Birkenkamp KE, et al. Predictors of neurocognitive outcomes on antiretroviral

therapy after cryptococcal meningitis: A prospective cohort study. Metab. Brain Dis. **2014**; 29:269–79. Available at: www.wkap.nl/journalhome.htm/0885-7490.

34.   Phillips P, Galanis E, MacDougall L, et al. Longitudinal Clinical Findings and Outcome among Cryptococcus gattii Patients in British Columbia. Clin. Infect. Dis. **2015**; 60:1368–76.

35.   Wang HC, Chang WN, Lui CC, et al. The prognosis of hearing impairment complicating HIV-negative cryptococcal meningitis. Neurology **2005**; 65:320–2. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed7&NEWS=N&AN=2005330505.

36.   Lizarazo J, Chaves Ó, Peña Y, Escandón P, Agudelo CI, Castañeda E. Comparación de los hallazgos clínicos y de supervivencia entre pacientes VIH positivos y VIH negativos con criptococosis meníngea en un hospital de tercer nivel. Acta Medica Colomb. **2012**; 37:49–61.

37.   Lee YC, Wang JT, Sun HY, Chen YC. Comparisons of clinical features and mortality of cryptococcal meningitis between patients with and without human immunodeficiency virus infection. J. Microbiol. Immunol. Infect. **2011**; 44:338–345. Available at: http://www.e-jmii.com.

38.   Mailles A, De Broucker T, Costanzo P, Martinez-Almoyna L, Vaillant V, Stahl J-P. Long-term outcome of patients presenting with acute infectious encephalitis of various causes in France. Clin. Infect. Dis. **2012**; 54:1455–64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22460967. Accessed 28 October 2013.

39.   Brancusi F, Farrar J, Heemskerk D. Tuberculous meningitis in adults: a review of a decade of developments focusing on prognostic factors for outcome. Future Microbiol. **2012**; 7:1101–16.

40.   Rock RB, Olin M, Baker CA, Molitor TW, Peterson PK. Central nervous system tuberculosis: Pathogenesis and clinical aspects. Clin. Microbiol. Rev. **2008**; 21:243–261.

41.   Lortholary O, Poizat G, Zeller V, et al. Long-term outcome of AIDS-associated cryptococcosis in the era

of combination antiretroviral therapy. AIDS **2006**; 20:2183–2191. Available at:

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed7&NEWS=N&AN=2006539559.

42.   Cachay ER, Caperna J, Sitapati AM, Jafari H, Kandel S, Mathews WC. Utility of clinical assessment,

imaging, and cryptococcal antigen titer to predict AIDS-related complicated forms of cryptococcal

meningitis. AIDS Res. Ther. **2010**; 7:1–6. Available at: http://www.aidsrestherapy.com/content/7/1/29.

43.   Török ME, Thi N, Yen B, et al. Timing of Initiation of Antiretroviral Therapy in Human

Immunodeficiency Virus (HIV)– Associated Tuberculous Meningitis. Clin. Infect. Dis. **2015**; 52:1374–

83.

44.   Loyse A, Dromer F, Day J, Lortholary O, Harrison TS. Flucytosine and cryptococcosis: time to urgently

address the worldwide accessibility of a 50-year-old antifungal. J. Antimicrob. Chemother. **2013**;

68:2435–44. Available at:

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3797641&tool=pmcentrez&rendertype=a

bstract. Accessed 23 October 2013.

45.   Campbell LT, Currie BJ, Krockenberger M, et al. Clonality and recombination in genetically

differentiated subgroups of Cryptococcus gattii. Eukaryot. Cell **2005**; 4:1403–1409.

46.   Galanis E, Macdougall L, Kidd S, Morshed M. Epidemiology of Cryptococcus gattii, British Columbia,

Canada, 1999-2007. Emerg. Infect. Dis. **2010**; 16:251–7. Available at:

http://www.cdc.gov/eid/content/16/2/pdfs/251.pdf.

47.   Singh N, Alexander BD, Lortholary O, et al. Cryptococcus neoformans in organ transplant recipients:

Impact of calcineurin-inhibitor agents on mortality. J. Infect. Dis. 2007; 195:756–64. Available at:

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2007094411.

48.   Venkatesan A. Epidemiology and outcomes of acute encephalitis. Curr. Opin. Neurol. **2015**; 28:277–82.

Available at: http://www.ncbi.nlm.nih.gov/pubmed/25887770. Accessed 17 September 2016.

49.   World Health Organisation. Rapid Advice - Diagnosis, Prevention and Management of Cryptococcal

Disease in HIV Infected Adults and Children. World Heal. Organ. 2011; :44.

50.   John CC, Carabin H, Montano SM, Bangirana P, Zunt JR, Peterson PK. Global research priorities for

infections that affect the nervous system. Available at:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4697933/pdf/nihms-743819.pdf. Accessed 21 July

2017.

51.   Sun HY, Alexander BD, Lortholary O, et al. Lipid formulations of amphotericin B significantly improve

outcome in solid organ transplant recipients with central nervous system cryptococcosis. Clin. Infect.

Dis. **2009**; 49:1721–8. Available at:

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=2010000604.

TABLES:

Table 1: Overview of the 25 articles included in this review

	Article	Setting	Design	Sample size - number	Mean Age (except when mentioned) – years (IQR)	Information on		
						Mortality	Sequelae/Impairments	Disability/quality of life
HIV-CM								
1	Bicanic (2008)[19]	LMIC (South Africa)	RCT	64 (30 in AmB 0.7mg arm, 34 in AmB 1 mg arm)	33 (28-38)			
2	Day (2013)[16]	LMIC (Vietnam)	RCT	298 (99 in AmB arm, 100 in AmB+5-FC arm, 99 in AmB+Fluconazole arm)	Median: 28 (24-31) (Children 14-18 years old included)			
3	Makadzange (2010)[28]	LMIC (Zimbabwe)	RCT	54 (28 in early ART arm and 26 in late ART arm)	37 +/-7.7			
4	Boulware (2014)[20]	LMIC (South Africa)	RCT	177 (88 in early ART arm and	Median: Early ART: 35 (28-			

		LMIC (Uganda)		89 in late ART arm)	40) Late ART: 36 (30-40)		
5	Kambugu (2008)[18]	LMIC (Uganda)	PC	44	36 (31-42)		
6	Bicanic (2007)[26]	LMIC (South Africa)	PC	54 (36 ART Naïve, 18 ART experienced)	34 (29-39)		
7	Bicanic (2009)[29]	LMIC (South Africa)	PC	100 (65 survived for analysis on IRIS : 11 in IRIS arm and 54 in non-IRIS arm))	>18 years		
8	Boulware (2010)[30]	LMIC (Uganda)	PC	101 (56 in IRIS arm, 45 in non-IRIS arm)	?		
9	Butler (2012)[17]	LMIC (Uganda)	PC	189	36.2 (SD +/-8.8)		
10	Rothe (2013)[27]	LMIC (Malawi)	PC	60	Median: 32 (29-39)		
11	Chaiwarith (2014)[25]	LMIC (Thailand)	RC	79	35.1 +/-7.2		

1 2	Carlson (2014)[33]	LMIC (Uganda)	PC	78	35 +/-8			
1 3	Lizarazo (2012)[36]	LMIC (Columbia)	RC	63	34 +/-9.2			
1 4	Jarvis (2014)[21]	LMIC (South Africa)	PC	263	Median: 34 (29-39)			
1 5	Lanoy (2011)[22]	HIC (France)	PC	1020	<30y: 16% 30-40: 50% 40-50: 24% >50: 11%			
1 6	Mathiesen (2012)[24]	HIC (Denmark)	RC	45	40 (33-46)			
1 7	Cachay (2010)[42]	HIC (USA)	RC	82	38 (19-57)			

	Article	Setting	Design	Sample size (number)	Age (years)	Information on		
						Mortality	Sequelae/ Impairments	Disability/quality of life
HIV and non-HIV-CM								
18	Liao (2012)[23]	HIC (Taiwan)	RC	72 HIV: 19 non-HIV: 53	HIV: 33.3 +/-7.4 non-HIV: 55.3 +/-15.7			
19	Lee (2011)[37]	HIC (Taiwan)	RC	88 HIV: 37 non-HIV: 51	HIV: 38.19 +/-12.12 non-HIV: 59.57 +/-14.17			
Non-HIV-CM								
20	Zhu (2010)[32]	LMIC (China)	RC	154	Median: 38.5			

2 1	Wang (2005)[35]	HIC (Taiwan)	PC	26	No Hearing loss group: 47 +/-21 Hearing loss group: 57 +/-17			
2 2	Phillips (2015)[34] (*C. gattii*)	HIC (British Columbia, Canada)	RC	47	Median: 50 (range 21-89)			

	Article	Setting	Design	Sample size (number)	Age (years)	Information on		
						Mortality	Sequelae/ Impairments	Disability/quality of life
23 and 24	Chen (2012)[11] and (2013)[31] (*C. gattii*)	HIC (Australia)	RC	73	?			
25	Sun (2009)[51]	HIC/MIC (USA, France, Spain, Canada, India)	PC	75	51.5 (43-60)			

RCT: Randomized Control Trial, PC: Prospective Cohort, RC: Retrospective Cohort.

HIC: High Income Countries. LMIC: Low and Middle Income Countries

Table 2: Long-term mortality:

Study	Setting	Design	Sample size	C gattii (CG) C neoformans(CN)	Mortality % –[95% CI][a] (Numbers) (PD or SA)[b]	Quality's score
HIV-CM						
>3months-4months after diagnosis or induction treatment						
Liao (2012)[23]	HIC (Taiwan)	RC	19	No data	5.3% (1/19) (PD) d90	54%
Lee (2011)[37]	HIC (Taiwan)	RC	37	No data	29.7% (11/37) (PD) d90	58%
Chaiwarith (2014)[25]	LMIC (Thailand)	RC	79	CN (92%)	32.4% (24/74) (PD) d90	65%
Lizarazo (2012)[36]	LMIC (Columbia)	RC	63	CN	54% (SA) d120	50%
6 months after diagnosis or induction treatment						
Cachay (2010)[42]	HIC (USA)	RC	82	No data	6.1% (5/82) (PD)	64%

[a] No 95% CI mentioned if not available

[b] PD: Mortality expressed as a **P**ercentage of **D**eath at the time point (lost to follow-up excluded when known), or

SA: **S**urvival **A**nalysis (probability of mortality at a time point, lost to follow-up censored)

Bicanic (2008)[19]	LMIC (South Africa)	RCT	64	No data	32% (PD)	55%
Boulware (2014)[20]	LMIC (South Africa – Uganda)	RCT	177	No data	37.9% (67/177) (PD)	82%
Day (2013)[16]	LMIC (Vietnam)	RCT	298	CN (VNI)	45% (132/291) (PD)	82%
Butler (2012)[17]	LMIC (Uganda)	PC	189	No data	52% [45-59] (SA)	58%
Bicanic (2009)[29]	LMIC (South Africa)	PC	100	No data	53% (53/100) (PD)	54%
Kambugu (2008)[18]	LMIC (Uganda)	PC	44	No data	59.1% (26/44) (PD)	73%
1 year after diagnosis or induction treatment						
Lanoy (2011)[22]	HIC (France)	PC	1020	No data	50% [45-54] (SA) during the Pre-cART period: 92-95 24% [18-29] (SA) during the Early cART period: 96-98 17% [12-22] (SA) during the Late cART period: 99-04	64%
Liao (2012)[23]	HIC (Taiwan)	RC	19	No data	22.2% (4/18) (PD)	54%
Mathiesen (2012)[24]	HIC (Denmark)	RC	45	No data	44.2% (SA) during the full period 88-08	81%

					23% (SA) during the cART period 97-08	
Boulware (2010)[30]	LMIC (Uganda)	PC	101	No data	27.7% (28/101) but first weeks deaths excluded	77%
Boulware (2014)[20]	LMIC (South Africa – Uganda)	RCT	177	No data	39.5% (70/177) (PD)	82%
Bicanic (2008)[19]	LMIC (South Africa)	RCT	64	No data	40% (PD)	55%
Jarvis (2014)[21]	LMIC (South Africa)	PC	263	No data	41% (PD)	57%
Chaiwarith (2014)[25]	LMIC (Thailand)	RC	79	No data	52.2% (36/69) (PD)	65%
Butler (2012)[17]	LMIC (Uganda)	PC	189	No data	55% [38-52] (SA)	58%
Kambugu (2008)[18]	LMIC (Uganda)	PC	44	No data	59.1% (26/44) (PD)	73%
Bicanic (2007)[26]	LMIC (South Africa)	PC	54	No data	64.7% (33/51) (PD)	69%
Rothe (2013)[27]	LMIC (Malawi)	PC	60	No data	78% [64-86] (SA)	69%

Study	Setting	Design	Sample size	*C gattii* / *C neoform*	Immune Status	Mortality %age –[95% CI][c] (Numbers) (PD or SA)[d]	Quality' score
Non- HIV-CM							
>3months-4months after diagnosis or induction treatment							
Sun (2009)[51]	HIC (USA, Canada, France, Spain) + India	PC	75	No data	100% Solid Organ Transplant	18.7% (14/75) (PD) d90	69%
Liao (2012)[23]	HIC (Taiwan)	RC	53	No data	100% with underlying conditions	30.8% (16/52) (PD) d90	54%
Lee (2011)[37]	HIC (Taiwan)	RC	51	No data	92% with underlying conditions	33.3% (17/51) (PD) d90	58%
1 year after diagnosis or induction treatment							
Chen (2012)[11]	HIC (Australia)	RC	73	CG	28% with underlying conditions	13% (10/73) (PD)	68%

[c] No 95% CI presented if not available

[d] PD: Mortality expressed as a **P**ercentage of **D**eath at the time point (lost to follow-up excluded when known), or
SA: **S**urvival **A**nalysis (probability of mortality at a time point, lost to follow-up censored)

Phillips (2015)[34]	HIC (Canada)	RC	47	CG	45% with underlying conditions	27.7% (13/47) (PD)	64%
Zhu (2010)[32]	LMIC (China)	RC	154	No data	33% with underlying conditions	28.7% (41/143) (PD)	62%
Liao (2012)[23]	HIC (Taiwan)	RC	53	No data	100% with underlying conditions	42.3% (22/52) (PD)	54%

RCT: Randomized Control Trial, PC: Prospective Cohort, RC: Retrospective Cohort.

HIC: High Income Countries LMIC: Low and Middle Income Countries

D90: at day 90 after diagnosis or induction treatment; D120: at day 120 after diagnosis or induction treatment

Table 3: HIV-CM predictive factors of long-term mortality identified by the review

Predictive factors	Number of studies	Studies	Design Quality score	Outcome measure of association (95%CI) and/or p-value if informed by the authors
Protective factors				
ART vs no ART at induction	2	Mathiesen (2012)[24]	RC 81%	Rate Ratio a[g] (Cox) for 1 year mortality=0.22 (0.06-0.77) p=0.018
		Lanoy (2011)[22]	*PC 69%*	*1-year mortality (Kaplan-Meier) in pre-ART = 50% (45-54) vs 17% (12-22) in late-ART*
Early ART initiation vs late ART initiation after induction (for ART naïve patients)	2	Boulware (2014)[20]	RCT 82%	ART initiation at 2 wks vs 5 wks: HR[e] (Cox) for 11 months mortality = 1.66 (1.03-2.68) p=0.04
		Makadzange (2010)[28]	RCT 50%	ART initiation at <72h vs 10 wks: HRa[f] (Cox) for 3 years mortality = 2.85 (1.1-7.23) p=0.031

[e] Not adjusted because RCT with similar characteristic in both arms (p>0.1 for all characteristics)

[f] Adjusted on age, sex, CSF CrAG titer, CD4 level

AmB based bitherapy vs monotherapy	1	Day (2013)[16]	RCT 82%	AmB+5FC vs AmB: HRa[i] (Cox) for 6 months mortality = 0.56 (0.36-0.87) p=0.01 AmB+5FC vs AmB+Fluconazole: HRa[i] (Cox) for 6 months mortality = 0.55(0.35-0.88) p=0.01
		Bicanic (2008)[19]	*RCT 55%*	*AmB 0.7mg/kg vs AmB 1 mg/Kg (+ 5FC) for 6 months and 12 months mortality: no difference (Fisher exact test – no data neither p-value given)*
Risk factors				
Older Age	1	Mathiesen (2012)[24]	RC 81%	Rate Ratio a[g] (Cox) for 1 year mortality for each year increase (in age) = 1.05 (0.99-1.11) p=0.054
Altered neurology at induction vs no altered	2	Chaiwarith (2014)[25]	RC 65%	Ora[h] (Logistic) for 1 year mortality = 5.27 (1.26-24.05)

---

[g] Variables included in the model: age, sex, mental status, CD4, time-updated initiation of ART, antifungal regimen, flucytosine induction, nationality, time-period (88-96/97-08), hospital centre (variables with p<0.1 were included in the model)

[h] Variables included in the model (with p<0.10 in univariate) are altered mental status, seizures, CSF CrAg titer, year of diagnosis (2005-2010)

neurology (with different items according to studies)		Day (2013)[16]	RCT 82%	HRa[i] (Cox) for 6 months mortality =2.30(1.57-3.36) p<0.001
Baseline elevated fungal burden (CSF CrAg titres or fungal load)	2	Chaiwarith (2014)[25]	RC 65%	ORal[h] (Logistic) elevated CrAg for 1 year mortality = 7.08 (1.62-31)
		Day (2013)[16]	RCT 82%	HRa[i] (Cox) elevated fungal load for 6 months mortality=1.33 (1.08-1.65) p=0.01 for each increase of 1 log10 CFU/mm3

---

[i] Adjusted on Age, Sex, Headache, Fever, Neck stiffness, Seizure, Glasgow coma score, Cranial-nerve palsy, papilledema, CSF opening pressure>18 cm H2O, CSF WCC, CSF glucose, plasma glucose

Low CD4 at induction (<20 vs >20)	1	Liao (2012)[23]	RC 54%	ORa[j] (Logistic) for > 1 year death or relapse=18(1.19-71.46) p=0.037
Contradictory results				
IRIS vs no IRIS during the CM episode	3	Boulware (2010)[30]	PC 77%	HRa[k] (Cox) for 1 year mortality = 2.3(1.1-1.51) p=0.04
		Bicanic (2009)[29]	*PC 54%*	*No association (Fisher exact test) as 36% of 6-months mortality in IRIS vs 26% in non-IRIS, p=0.49*
		Boulware (2014)[20]	*RCT 82%*	*IRIS in early ART vs late ART: 20% [17/87] and 13% [9/69], respectively, p=0.32 (while mortality significantly higher in early ART)*

Evidence based on multivariate analysis

Evidence based on univariate analysis

---

[j] Variables included in the model: clinical, laboratory variables at presentation + antifungal treatment given.

[k] Adjusted on baseline CD4, all other characteristic similar in both groups (BMI, time from CM to ART, Opportunistic infection, Baseline CD8, Baseline and subsequent VL, subsequent CD4, Eosinophils, initial serum CrAG titer median)

PC: Prospective Cohort, RC: Retrospective Cohort, RCT: Randomized Control Trial

Table 4: Non-HIV-CM predictive factors of long-term mortality identified by the review

Predictive factors	Number of studies	Studies	Design Quality score	Outcome measure of association (95%CI) and/or p-value if informed by the authors
Protective factors				
AmB based therapy	2	Zhu (2010)[32]	RC 62%	Non AmB-based vs AmB based: HRa^l (Cox) for 1-year mortality = 8.87(3.53-22.25) p<0.001
		Sun (2009)[51]	PC 69%	AmB lipid vs AmB deoxylate: Ora^n (Logistic) for 3 months mortality=0.11(0.02-0.57) p=0.008
Risk factors				
Delayed diagnosis vs no delayed	1	Zhu (2010)[32]	RC 62%	HRa^l (Cox) = 6.3(2.41-16.53) p<0.001
Older Age	1	Zhu (2010)[32]	RC 62%	No data shown

[l] Variables included in the model: age, sex, time to diagnosis>4months, pulmonary crypto, AID, hematological malignancy, solid malignancy, corticotherapy, transplantation, healthy, altered mental status, coma, seizure, cerebral herniation, non AmB based initial therapy, inclusion of 5FC, intrathecal AmB treatment, ommaya implantation

Altered neurology at induction vs no altered neurology (with different definitions according to studies: focal neurologic signs, hydrocephalus, Low Glasgow score, herniation)	3	Zhu (2010)[32] Liao (2012)[23] *Chen (2012) C. gattii*[11]	RC 62% RC 54% *RC 68%*	HRa[l] (Cox) = 8.08(2.96-16.95) p<0.001 ORa[m] (Logistic) for > 1 year death or relapse=8.7(2.23-28.98) p=0.003 *1 year mortality 19% in abnormal neuro vs 3% in normal neuro, (Fisher exact test) p=0.05*
Baseline elevated fungal burden (CSF CrAg titres)	1	Liao (2012)[23] Chen (2012) C.Gattii	RC 54% RC 68%	>1/512 vs <1/512: ORa[m] (Logistic) for > 1 year death or relapse=16.2(1.37-192.02) p=0.027 >1/256 vs <1/256: Ora for 1 year mortality=1.8(1–26) p=0,05
Fungemia vs no fungemia in SOT	1	Sun (2009)[51]	PC 69%	ORa[n] (Logistic) for 3 months mortality= 10.6 (2.08-54.55) p=0.004
Renal failure vs no renal failure in SOT	1	Sun (2009) [51]	PC 69%	ORa[n] (Logistic) for 3 months mortality= 4.61(1.02-20.8) p=0.047
Contradictory results				

---

[m] Variables included in the model: clinical, laboratory variables at presentation + antifungal treatment given.

[n] Variables included in the model (with p<0.20 in univariate) are CNIs, renal failure at baseline, abnormal mental status, fungemia, receipt of lipid AmB (backward strategy)

| Underlying conditions vs healthy | 2 | Chen (2012) C Gattii [11] | RC 68% | 1 year mortality 26% in predisposed vs 7.4% in healthy (Log-rank test) p=0.03 |
| | | Zhu (2010)[32] | RC 62% | 1-year mortality 26.5% in predisposed vs 29.8% in healthy (Fisher exact test) p=0.69 |

Evidence based on multivariate analysis

Evidence based on univariate analysis

PC: Prospective Cohort, RC: Retrospective Cohort, RCT: Randomized Control Trial, SOT: Solid Organ Transplant

FIGURES:

Figure 1: Flow diagram of the article inclusion/exclusion process (inspired from PRISMA 2009 Flow Diagram**[14])**.

Figure 2: Forest plot of proportion of one-year mortality in HIV-CM according to induction therapy received.

Legends of figure 2:

4 studies are excluded from this forest plot:

- Boulware et al (2010) study because the mortality is probably under-estimated[30]. The patients were included after ART initiation at a median time from CM diagnosis of 34 days (IQR: 24-41), missing all death happening during the first weeks.

- Lanoy et al (2011)[22], Liao et al (2012)[23] and Mathiesen et al (2012)[24] because no information was available or extractable for the treatment received by the patients infected by HIV or for the dichotomised periods.

In the Bicanic 2007 study[26], 92% of patients were treated by AmB monotherapy and 8% of patients were treated by fluconazole monotherapy.
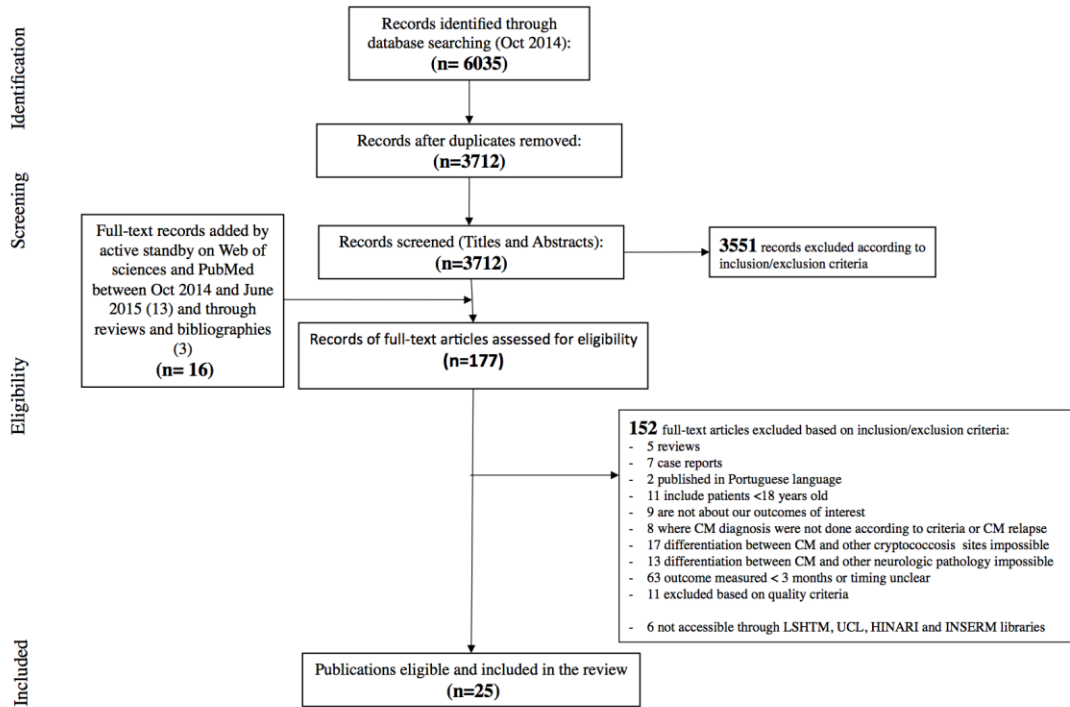
Figure 1

Figure 2

Study	Induction tx
Bicanic 2008	AmB+Fluco
Boulware 2014	AmB+5FC
Chairwarit 2014	AmB
Butler 2012	AmB
Kambugu 2008	AmB
Bicanic 2007	AmB (92%) or Fluco (8%)
Rothe 2013	Fluco 800

One-year mortality proportion (%)