

Review

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Review

HIV-Associated Cryptococcal Meningitis: A Call for Action for New Treatment Options

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Abstract

Cryptococcal meningitis diagnosis at 62% is the leading cause of meningitis among adults with advanced HIV disease in areas with a high burden of infection. Despite attempts to improve treatment, in-hospital mortality remains unprecedentedly high. Disease complications associated with unmasking symptoms and relapse of fungal infections delay treatment and increase the risk of individuals succumbing to cryptococcal meningitis. In this narrative review, we highlight published clinical trials evaluating the treatment of HIV-associated cryptococcal meningitis with survival as the primary endpoint. Aggregated clinical trial data show a significant decrease in survival from diagnosis to 2 weeks of treatment, from 88.5% to 74% (p=0.001). The WHO standard of care was used as the control arm. Survival rates were similar between the control and trial arms. High in-hospital mortality remains a challenge for new survival-modifying treatments for cryptococcal meningitis. We provide evidence-based updates on cryptococcal meningitis treatment to inform new antifungal formulations or research approaches for improved outcomes. The consistency and generalizability of fungal clearance in the cerebrospinal fluid and the efficacy of antifungal drugs to clear fungi in the brain parenchyma remain unclear.

Keywords: cryptococcal meningitis; clinical trials; antifungal therapy; human immunodeficiency virus; mortality improved regimen

Introduction

Cryptococcal meningitis (CM) is the leading cause of meningitis in people with advanced HIV disease, accounting for decreased hospital survival from admission to 85% (Interquartile range, (IQR); 76%-87% survival) followed by tuberculous meningitis at 21% [1]. Though the highest burden of disease is reported in low- and middle-income countries [2], the cases in the developed world show high in-hospital mortality (~30%) compared to 19% global mortality estimates [3,4]. The global cryptococcal meningitis mortality rate of 19% is lower compared to 28%-33% mortality in the predominantly Caucasian (67%-73% of patient), young (age; 40 -70 years old), and male (79%-82%) patients with cryptococcal meningitis in the developed countries [3,4]. Unlike in low-income settings where HIV infection is the predominant risk factor for cryptococcosis (96%) [5], several studies in developed countries show multiple comorbidities contributing to cryptococcosis including: HIV infection (44.4%), exposure to corticosteroid therapy (28.3%), malignancy (25.5%), smoking (20.0%), transplant-related conditions (18.9%), and presence of lung disease (18.2%) [3,4].

Though multiple comorbidities are associated with cryptococcosis, the pathogenesis, the adverse outcome, and the degree of disease impairment among patients are similar across the globe. Frequently observed abnormalities include: hearing impairment (16%), muscle weakness (40%), cognitive deficits (33%), hydrocephalus (with need for a ventriculoperitoneal shunt) (7.4%), stroke

(33%), and relapse occurring in 23% of patients [3]. The finding that 23% of patients with cryptococcal meningitis in the United States cohorts will experience relapse of infection/disease and the high mortality rates with treatment compared to the rest of the world [2,3,5,6], aligns with the hypothesis of possible limited antifungal drug bioavailability and persistence of disseminated fungal infection in deep tissue niches. Unfortunately, no human study has attempted to investigate whether fungal clearance in CSF correlates with clearance of disseminated fungal infection in tissues [7].

Despite attempts to improve treatment, high mortality rates remain a concern with mortality of up to 45% reported by 10 weeks of treatment [8,9]. Early diagnosis and treatment are complicated by disease presentation and high burden of concomitant comorbidities in the developed world and high burden of infections with similar symptoms in areas with high burden of advanced HIV disease [2,8,10]. Despite evidence of effective antifungal therapy, mortality remains high and unpredictable due to complications impacting survival [7]. The individuals at risk of death are those with significantly low systemic evoked immune response in peripheral and central nervous system (CNS) compartments [11].

Modern Therapeutic Advances for Cryptococcal Meningitis

Therapeutic advances to improve survival have relied on the rapid killing of the fungus associated with higher early fungicidal activity based on fungal clearance from the CSF compartment. This infection and fungal clearance in the CSF compartment are used as an accessible means to monitor the kinetics of antifungal efficacy in the CNS [7]. The fungal killing and clearance from the CSF using antifungal drugs is reported as the early fungicidal activity (EFA) reported as $\times \log_{10}$ colony forming units/ml of CSF/day [12]. Even better, is the early fungicidal activity reported with the use of a combination of antifungal drugs which surmount rapid and synergistic effects to fungal killing and fungal clearance compared to antifungal monotherapies [13]. Though the rate of fungal clearance in the CNS is determined by negative CSF fungal culture conversion, [14] the holistic view of the host can inform unmet host-directed needs for personalized therapy. Consistently, individuals with low evoked and poorer immune response experience the highest risk of succumbing to cryptococcal meningitis compared to their counterparts with elevated immune responses [15,16,17]. This group of patients with paucity of immune response present an opportunity for trials of adjunctive immune therapy to improve survival.

We searched PubMed for primary peer-reviewed articles on cryptococcal meningitis clinical trials conducted between January 2000 and January 2024 using the search term "Cryptococcal meningitis Clinical Trials" (Figure 1). Our goal was to consolidate knowledge of survival using improved regimens and emerging therapies, and to determine how different regimens have impacted survival in clinical trials over the past 24 years.

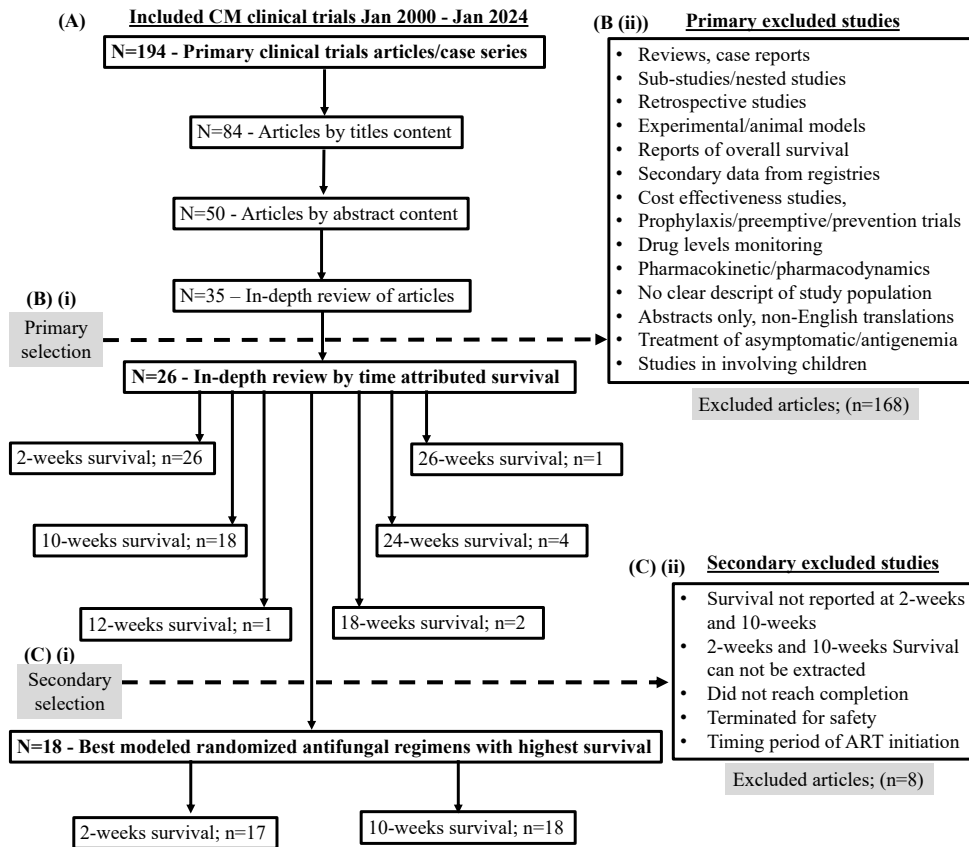


Figure 1. Inclusion and exclusion approach for studies which contributed metadata. A- all articles published or indexed in PubMed by “Cryptococcal meningitis Clinical Trials free word search customized to a period between January 2000 to January 2024”. B - (i-ii) - articles that underwent primary selection for follow-up reported survival. C - (i-ii) – articles that underwent secondary selection for the best modeled antifungal regimen. N- total article collection. n- number of articles by subcategories. Included were CM clinical trials reporting findings in adults (sex - male and female) >18 years of age and follow-up survival after diagnosis or enrolment into the randomized antifungal clinical trials.

Evolution of Antifungal Clinical Trials to Improve Survival with Cryptococcal Meningitis

In attempts to improve the quality of life and survival following HIV associated cryptococcal meningitis, new antifungal regimens and patient-centered interventions emerged in the era of peak HIV-related deaths prior to increased availability of antiretroviral therapy (ART). Today, the persistently low survival rates among hospitalised patients even with WHO-recommend antifungal therapy still drive the need to do more trials [18]. HIV infection is prevalent in Africa, and the hotspots of the disease also have the highest burden of HIV-associated cryptococcal meningitis. Most global cryptococcal meningitis clinical trials are conducted in Africa, particularly in Uganda, Malawi, South Africa, Tanzania, and Botswana, with some in other parts of the world (Map: Figure 2). In Asia, most trials are in Thailand, Vietnam, and China. In North America, trials are in the US, Canada, Indonesia, and Laos (Map: Figure 2).

Cryptococcal meningitis remains a significant problem for treatment and survival improvement in Africa, despite a 40-year HIV epidemic. Since clinical trials emerged, global public health participation has increased substantially, leading to improvements in survival (Figure 3). Trials compared trial regimens with the WHO-recommended standard of care for antifungal treatment of cryptococcal meningitis (Figure 3). The WHO recommended regimen includes Amphotericin B Liposomal (Ambisome) or deoxycholate formulations for induction therapy, Fluconazole consolidation combination therapy, and Fluconazole maintenance monotherapy. Despite variations

in survival on trial regimens, 96% of randomized trial regimens used old antifungal molecules tested against the standard WHO regimen (Figure 4). Amphotericin B and Fluconazole were the standard regimen in 92% of trials (25/27), while Amphotericin B and Fluconazole were the standard regimen in 4% of trials (1/27) (Figure 4 and Table 1).

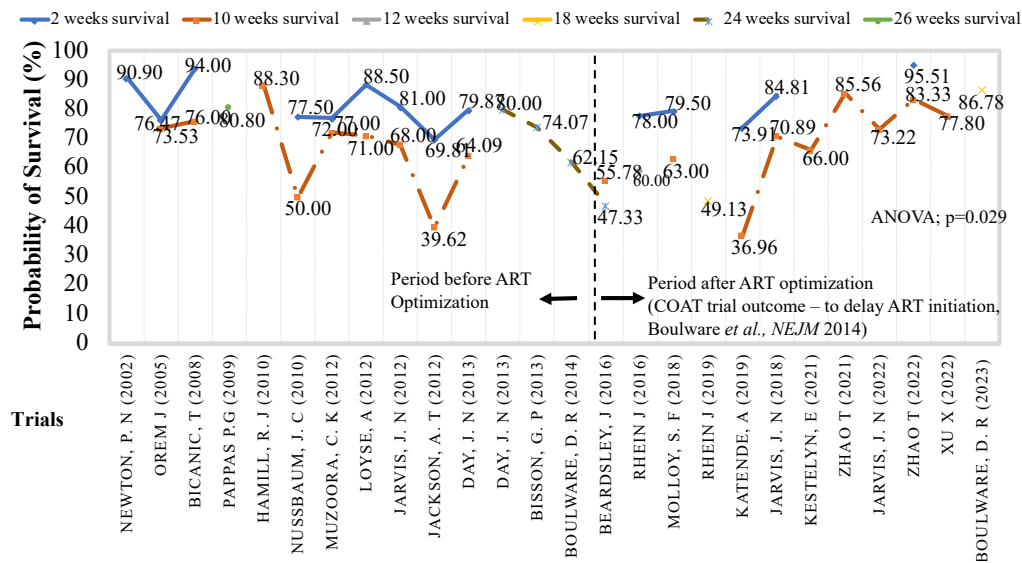


Figure 3. Survival among participants enrolled in cryptococcal meningitis treatment and survival improvement clinical trials conducted between January 2000 to January 2024.

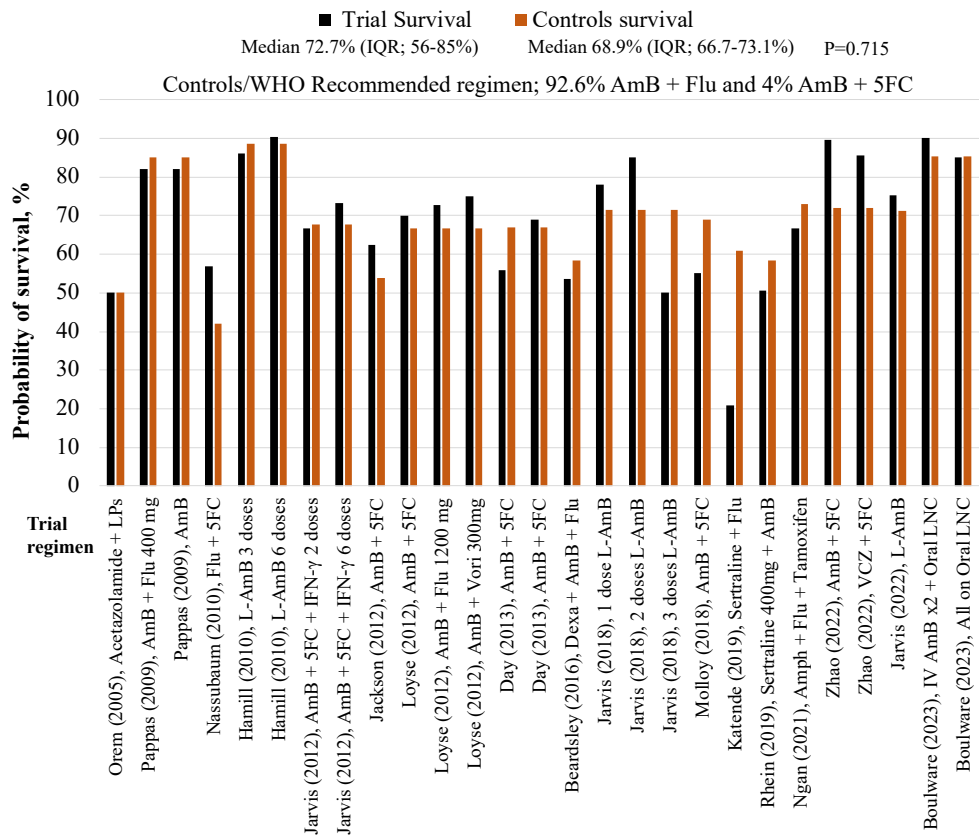


Figure 4. Survival by randomization on inductive trial drugs arm or WHO recommended regimens that formed the standard therapy.

Table 1. Summary of Trials by 10-Week Survival Included in Secondary Analyses/models.

Author	Trial regimen	Trial arm, N	10-week, survival, n (%)	Control arm, N, AmB + Flu,	10-week survival, n (%)
Boulware (2023)	IV AmB x2 + Oral AmB Nanocrystals	40	35 (90%)	41**	35 (85.4%)
Boulware (2023)	All - Oral AmB Nanocrystals	40	34 (85%)	41**	35 (85.4%)
Zhao (2022)	10-week AmB + 5FC	78	70 (89.7%)	50	36 (72%)
Zhao (2022)	10-week VCZ + 5FC	28	24 (85.7%)	50	36 (72%)
Jarvis (2022)	L-AmB 10 mg/kg x1	101	76 (75.2%)	117**	117 (71.3%)
Ngan NTT, (2021)	AmB + Flu + Tamoxifen	24	16 (66.7%)	26	19 (73.1%)
Rhein, (2019)	AmB + Fluconazole + Sertraline 400mg	229	113 (50.7%)	231	135 (58.4%)
Katende, (2019)	Sertraline + Fluconazole	28	6 (21%)	18	11 (61%)
Jarvis, (2018)	Single dose L-AmB + fluconazole	18	14 (78%)	21	15 (71.4%)
Jarvis, (2018)	2 doses L-AmB + fluconazole	20	17 (85%)	21	15 (71.4%)
Jarvis, (2018)	3 doses L-AmB + fluconazole	20	10 (50%)	21	15 (71.4%)
Molloy (2018)	AmB + 5FC	225	124 (55%)	228	157 (68.9%)
Beardsley (2016)	Dexa + AmB + Flu	224	120 (53.6%)	226	132 (58.4%)
Day J (2013)	AmB	99	55 (56%)	99	66 (67%)
Day J (2013)	AmB + 5FC	100	70 (69%)	99	66 (67%)
Jarvis (2012)	AmB + 5FC + IFN-γ	57	40 (70.2%)	62	42 (67.7%)
Jackson T (2012)	AmB + 5FC	40	25 (62.5%)	39	21 (53.8%)
Loyse (2012)	AmB + 5FC	20	14 (70%)	21	14 (66.7%)
Loyse (2012)	AmB + Flu 1200 mg	22	16 (72.7%)	21	14 (66.7%)
Loyse (2012)	AmB + Vori 300mg	12	9 (75%)	21	14 (66.7%)
Nussbaum, 2010	Flu + 5FC	21	12 (57%)	19	8 (42%)
Hamill J.R, (2010)	L-AmB 3 mg/kg	74	64 (86%)	77	68 (88.5%)
Hamill J.R, (2010)	L-AmB 6 mg/kg	85	77 (90.4%)	77	68 (88.5%)
Pappas (2009)	AmB + Flu 400 mg	48	41 (85%)	45	44 (97%)
Pappas (2009)	AmB	47	40 (85%)	45	44 (97%)
Orem J (2005)	Acetazolamide + LPs	10	5 (50%)	8*	4 (50%)

AmB – Amphotericin B deoxycholate. Flu - Fluconazole. 5FC – Flucytosine. L-Amp - Liposomal amphotericin B deoxycholate. VCZ – voriconazole. Vori – Voriconazole. Dexa -Dexamethasone. IV – intravenous. 2x – twice. LPs -lumbar punctures. N – number of enrolled participants per trial randomization arm. * Acetazolamide. ** Flucytosine.

The published clinical trial literature in the last 24 years show the field has maintained the old antifungal formulations of Amphotericin B, (discovered in 1953) [19], Flucytosine (discovered in 1957) [20], and Fluconazole (discovered in 1978) [21], as the primary antifungal candidate models in cryptococcal meningitis clinical trials (Figure 4 and Supplementary Table 1). The new antifungals in cryptococcal meningitis clinical trials are reconfigured antifungal formulations of amphotericin B (e.g., intravenous liposomal amphotericin B, amphotericin B deoxycholate or the oral lipid nanocrystal formulation of amphotericin B at 0.7-1 mg/kg body weight). Fluconazole 800mg - 1200mg daily, or Flucytosine 100mg/kg four times daily administered in inductive phases (first 7 -14 days, depending on fungal clearance colony-forming units in CSF cultures. The consolidation phase with 800mg daily of 6-12mg per kg body weight of Fluconazole for 8 weeks after induction therapy. The maintenance phase is implemented with 200mg daily dose of Fluconazole for secondary prophylaxis [22,23].

Survival significantly decreased from admission to 2 weeks and 10 weeks of therapy, regardless of the trial regimen (Figure 3). Aggregated data from 14 studies before and 12 studies following ART optimization showed similar survival rates, with or without ART initiation after cryptococcal meningitis diagnosis [24]. Other factors, besides antifungals, could contribute to the significant difference in survival among patients with cryptococcal meningitis on antifungal therapy. Reasons

for persistent mortality after initial hospital discharge include immune reconstitution inflammatory syndrome (IRIS) [25], fungal infection relapse [26,27], delayed return to hospital [28], or other opportunistic infections [1], and low CD4 T cell counts [28,29]. These factors negatively impact survival after CM diagnosis or initial hospital admission. The extra social support needed to improve outcomes after hospital discharge explains why clinical care engagement rates were better in a cohort of people living with HIV who received community follow-up care after hospital discharge compared to those who did not [30].

Trials of Antifungal Dosage Formulations to Improve Cryptococcal Meningitis Survival

Evidence from clinical trials has improved clinical practice and infrastructure, but funding gaps can limit the transfer of knowledge from clinical trials to lower public healthcare settings, hindering patient benefits [8,10]. Differences in the funding scope and standard of care contribute to the differences in survival between patients receiving treatment in the tertiary hospital setting at 85 - 90% 2-week survival [2] compared to 51- 61% 2-week survival observed in the lower public healthcare facilities [8]. The factors influencing poor survival in public healthcare settings include limited capabilities to perform and provide extensive diagnostic packages of care critical to inform clinical decisions for patient-centered care in areas of high burden of co-infections [10]. The varied diagnostic algorithms are important given the diversity of alternative co-infections among patients with cryptococcal meningitis [1]. Improving survival following HIV associated cryptococcal meningitis remains a daunting challenge.

In response to the research and development needs for discovering new antifungal molecules and drug formulations to improve treatment, a few new antifungal formulations have joined the market for the treatment of invasive fungal infections. Adjunctive therapies including dexamethasone [31,32], sertraline [33,34], interferon gamma [35], tamoxifen [36], acetazolamide [37,38] have been tested as adjuncts to current antifungal regimens for the treatment of CM. However, these adjunctive therapies have yielded either none or limited additive efficacy. Unfortunately, with all efforts to model antifungal drug formulations in clinical trials, 2- and 10-week survival remains staggeringly low (Figure 5). The 2-week survival in 17 studies was 88.5% (IQR; 82.1-93.15%) compared to the 10-week median 74.0% survival (IQR; 62.13-85.0% survival) in 18 studies ($p=0.001$) (Figure 5). The collective clinical trial observations show a significant drop in survival from 100% to 2-week survival rates ranging between (60 - 99% survival) and 10 week survival dropping down to between (49% - 90% survival) (Figure 5). The majority of trials did not exceed 10-weeks of follow-up, which limits the interpretation of cryptococcal meningitis-related survival to no more than 10 weeks.

Evolution of Promising Cryptococcal Meningitis Optimal Antifungal Therapy

Four seminal studies demonstrated superior efficacy of antifungal regimens used for the treatment of cryptococcal meningitis (Figure 5). The antifungal regimen with the lowest frequency of cryptococcal-related mortality had 1% mortality at 2 weeks and 10% mortality at 10 weeks of observation [23]. The regimen included 2-loading doses of intravenous Liposomal Amphotericin B Deoxycholate, an oral lipid nanocrystal formulation of Amphotericin B Deoxycholate and Flucytosine (Boulware *et al.*, 2023) [23] (Figure 5) tested against WHO-recommended standard antifungal regimen (0.7-1mg per kg Amphotericin B deoxycholate and 800mg Fluconazole). This antifungal drug formulation was modeled in the phase II cryptococcal meningitis clinical trial in three tertiary hospitals in Uganda [23]. Phase III trials are needed to demonstrate the survival benefit of the oral formulation. This could improve the management of cryptococcal meningitis patients by reducing the need for intravenous drug administration and intensive nursing care for monitoring antifungal drug toxicity.

Among the seminal antifungal regimens for treatment of cryptococcal meningitis and the two WHO-recommended antifungal regimens for treatment of cryptococcal meningitis (Figure 4). 1)

Liposomal Amphotericin B deoxycholate and Flucytosine inductive therapy [39], with 3% attrition after 2-weeks and 10% at 10-weeks using the WHO standard of care antifungal regimen (0.5 -0.7mg per kg Amphotericin B deoxycholate and 100mg per kg per day Flucytosine). 2) Liposomal Amphotericin B and Fluconazole inductive regimen [40], resulted in 3% mortality at 2-weeks and 15% mortality at 10-weeks of observations. Both outcomes were reported on the WHO standard antifungal regimen (0-7 1mg per kg Amphotericin B deoxycholate and 800mg Fluconazole).

The inclusion of at least two therapeutic lumbar punctures to monitor and manage persistently elevated intracranial pressure or for the alternative diagnosis of co-infections or demonstration of fungal clearance improve survival. These clinical and treatment-modifying attempts yielded the significant increase in 2-week survival by 18% from (76 -87%) compared to 94 -99% at 2-weeks and 80-90% at 10-weeks during cryptococcal meningitis clinical trials (Figure 5).

Conclusion

In summary, persistent high mortality among hospitalized individuals with CM at 19% overall, means more efficacious antifungal regimens are needed for host-directed therapies to improve survival. Continued collaborative engagement is required with the public health enterprises, pharmaceuticals, governments, and donor agencies to support cryptococcal meningitis treatment and the package of care with essential medicines, diagnostics, technical expertise, and continued research to move the field forward to scale up care to improve survival.

Limitations

The primary literature was from peer-reviewed articles published in PubMed-indexed Journal where most funding agencies for clinical trials require data to be deposited for public access and immediate use. We might have left out important articles published elsewhere on funding agencies' websites or authors' preferred archives. Based on the search criteria and interest in follow-up survival outcomes, we did not include articles with no traceable survival outcomes during clinical trials' implementation.

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Conflicts of Interest: No competing interests

Cryptococcal meningitis clinical trials implementing collaborations

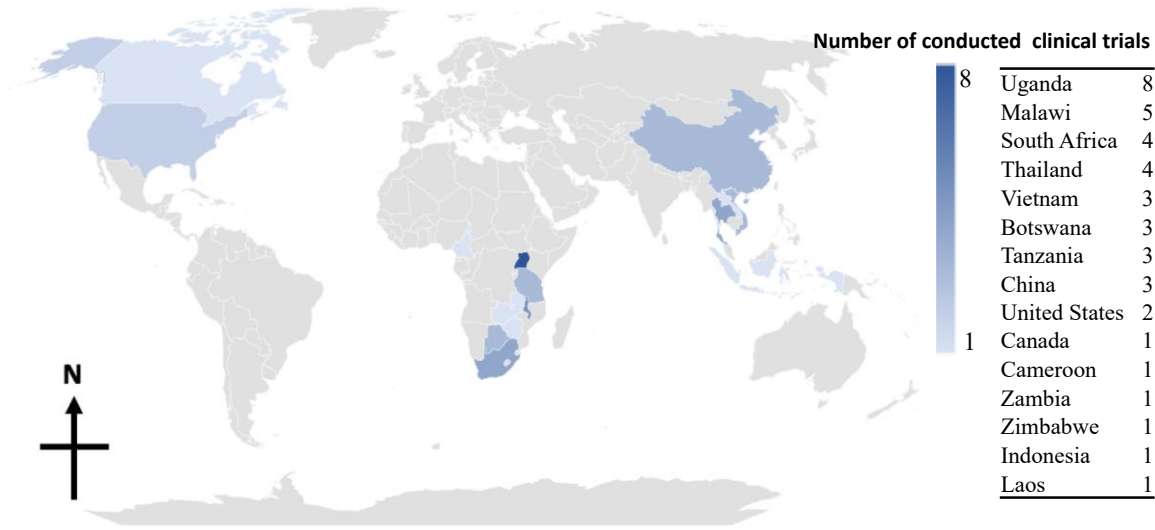


Figure 2. Global distribution of cryptococcal meningitis clinical trials sites among peer-reviewed published case series reporting follow-up survival outcomes between January 2000 to January 2024. Included were 17 studies that reported survival with a specified follow-up period that was of interest for data comparison [24,33,35,36,38,39,41–52]. Excluded were studies that reported overall survival with no specific timeframe of follow-up and follow-up sub-studies exploiting parent clinical trials generated data. The rationale for exclusion was to avoid repetition, duplication, and compounding of location data by follow-up sub-studies’ reports.

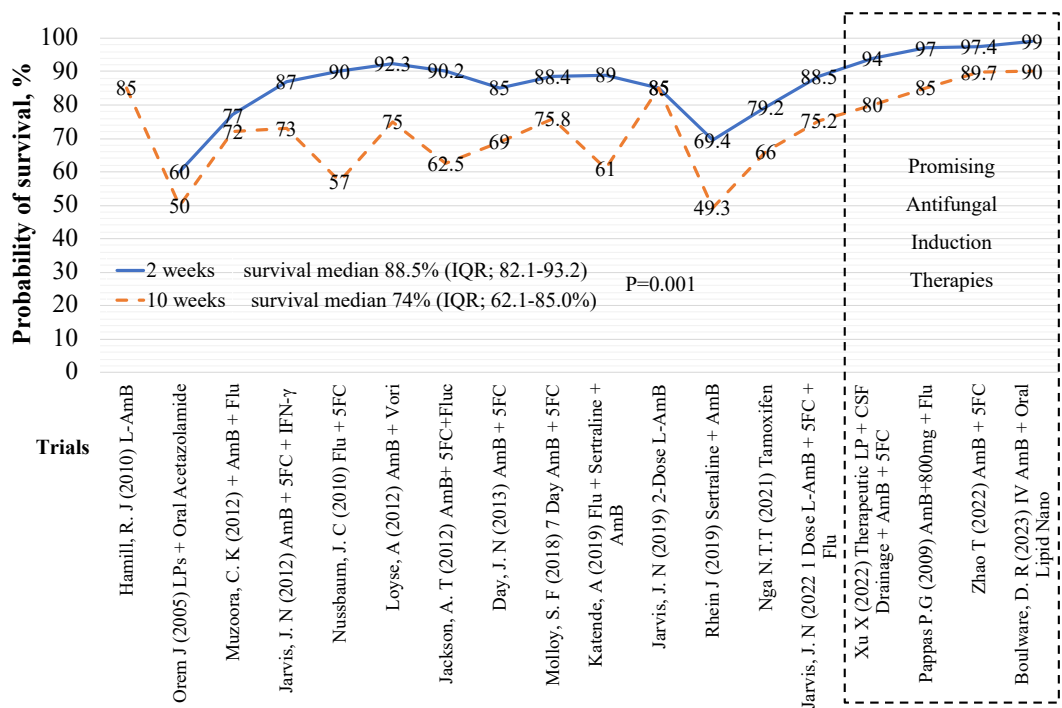


Figure 5. Cryptococcal meningitis induction therapies to improved survival. **Aggregated survival in cryptococcal meningitis clinical trials among peer-reviewed published Clinical trials reporting primary outcomes published between January 2000- to- January 2024.** A- survival by clinical trials and year of publications before or after the period of timing of antiretroviral therapy among participants diagnosed with CM. B – 10-week survival by clinical trials randomizations among cases, those on randomized to the trial drug and controls, those randomized to the WHO standard therapy. Amp – amphotericin B deoxycholate. Flu - Fluconazole. 5FC – Flucytosine. L-Amp - Liposomal Amphotericin B deoxycholate. VCZ – voriconazole. Vori – Voriconazole. Crypto-Dexa – Cryptococcal – Dexamethasone. Adjunctive therapies include – dexamethasone,

sertraline, tamoxifen, and acetazolamide. A - Included were (N=4605 participants) enrolled in the parent clinical trials that reported survival with a specified follow-up which was of interest for comparison of outcomes [23,24,31,33–36,38,39,41–46,48,50,51,53–56]. Excluded were studies that reported overall survival with no follow-up period or whose survival data could not be traced and sub-studies among parent clinical trials. The rationale for excluding sub-studies was to avoid repetition and compounding of clinical trials data by sub-studies reports. B - Included were (N=3,434 participants), (n=1710 trial arms randomized cases and n=1724 control randomized arm, randomized in a 1:1 ratio) among 18 studies with completed trial data . Excluded were studies that reported overall survival and all sub-studies among parent clinical trials. The rationale was to avoid repetition and compounding of clinical trial data by sub-studies reports. Further excluded were trials that were prematurely terminated or those that were in phase I efficacy trials or were setting the stage for subsequent trials e.g., studies that timed ART among participants with HIV-associated cryptococcal meningitis.

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