Health care costs and life years gained from treatments within the ACTA trial on cryptococcal meningitis: a comparison of antifungal induction strategies in sub Saharan Africa

Tao Chen, PhD[1*], Lawrence Mwenge, PhD [2*], Shabir Lakhi MD [3], Duncan Chanda MD [4], Peter Mwaba MD [5], Síle F Molloy PhD [6], Adrian Gheorghe PhD [7], Ulla K Griffiths PhD [7], Prof Robert S Heyderman MD [8, 9, 10], Cecilia Kanyama MD [11], Charles Kouanfack PhD[12, 13], Prof Sayoki Mfinanga MD [14,1], Adrienne K Chan MD [15,16], Elvis Temfack MD [17,18], Sokoine Kivuyo MD [14], Mina C Hosseinipour MD [11,19], Prof Olivier Lortholary MD [18, 20], Angela Loyse MD [6], Prof Shabbar Jaffar PhD [1§], Prof Thomas S Harrison MD [6§], Prof Louis W Niessen PhD [1, 21§] on behalf of the ACTA Trial Team *

1Liverpool School of Tropical Medicine, Liverpool, United Kingdom,
2 Zambart, Health Economics Unit, Lusaka, Zambia
3 University Teaching Hospital, Lusaka, Zambia,
4 Institute for Medical Research and Training, University Teaching Hospital, Lusaka, Zambia,
5 Department of Internal Medicine and Directorate of Research and Post graduate studies, Lusaka Apex Medical University, Lusaka, Zambia,
6 Centre for Global Health, Institute for Infection and Immunity, St George's University of London, United Kingdom,
7 London School of Hygiene and Tropical Medicine, London, United Kingdom,
8 Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, Malawi,
9 College of Medicine, University of Malawi, Blantyre, Malawi,
10 University College London, London, United Kingdom
11 University of North Carolina Project-Malawi, Kamuzu Central Hospital, Lilongwe, Malawi,
12 Hôpital Central Yaoundé/Site Agence Nationale de Recherche sur le Sida (ANRS) Cameroun, Yaoundé
13. University of Dschang, Dschang, Cameroon
14 National Institute Medical Research, Muhimbili Medical Research Centre, Dar Es Salaam, United Republic of Tanzania,
15 Dignitas International, Zomba Central Hospital, Zomba, Malawi,
16 Division of Infectious Diseases, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada
17 Douala General Hospital, Douala, Cameroon,
18 Institut Pasteur, Molecular Mycology Unit, CNRS URA3012, Paris, France,
19 University of North Carolina, Chapel Hill, United States,
20 Paris Descartes University, Necker Pasteur Center for Infectious Diseases and Tropical Medicine, IHU Imagine, APHP, Paris, France.
21 Department of International Health, Johns Hopkins School of Public Health, USA.

* equal contributions
§ equal contributions

* ACTA trial team listed in the Supplementary material annex

Corresponding author: shabbar.jaffar@lstmed.ac.uk

Alternative corresponding author: tharriso@sgul.ac.uk

40-word summary

In comparison of 2-weeks amphotericin B (AmB) + flucystosine (5FC), both 1-week AmB+5FC and 2-weeks oral fluconazole (FLU)+5FC are cost-saving; 1-week AmB+5FC is more effective in reducing mortality and somewhat more costly than 2-weeks oral FLU+5FC

Abstract

Background
Mortality from cryptoccocal meningitis remains high. The ACTA trial demonstrated that, compared with 2 weeks of amphotericin B (AmB) plus flucystosine (5FC), 1 week of AmB+5FC was associated with lower mortality, and 2 weeks of oral flucanozole (FLU) plus 5FC was non-inferior. Here, we assess the cost-effectiveness.

Methods
Participants were randomised in a ratio of 2:1:1:1:1 to 2 weeks oral 5FC+FLU, 1 week AmB+FLU, 1 week AmB+5FC, 2 weeks AmB+FLU or 2 weeks AmB+5FC in sites in Malawi, Zambia, Cameroon and Tanzania. Data on individual resource use and health outcomes were collected from all participants. A costing study from the health care perspective was done in Zambia.

Treatment costs were estimated using the ingredient-based approach. Cost-effectiveness was measured as incremental costs per life year saved . We used non-parametric bootstrapping of all patients by arm. Cost-effectiveness planes and acceptability curves were done to assess uncertainties, and a tornado sensitivity graph to examine the impact of individual trial parameters.

Results
Total costs per patient were US$1442 for 2 weeks oral FLU+5FC, $1763 for 1 week AmB+FLU, $1861 for 1 week AmB+5FC, $2125 for 2 weeks AmB+FLU, and $2285 for 2 weeks AmB+5FC.

One-week AmB+5FC was less costly and more effective than 2 weeks AmB+5FC. Two-weeks oral FLU+5FC was less costly and as effective as 2 weeks AmB+5FC. The incremental cost-effectiveness ratio for one week AmB+5FC versus oral FLU+5FC was US $208 (95% CI: 91, 1210) per life year saved.

Conclusions
Both 1-week AmB+5FC and 2-weeks oral FLU+5FC are cost-effective treatments.

Background

Mortality from cryptoccocal meningitis (CM) remains high in resource-limited settings [1]. The international standard induction treatment of 2 weeks amphotericin B deoxycholate (AmB) plus flucytosine (5FC) [2] is not available, while the alternative of fluconazole (FLU) monotherapy is associated with mortality of 50-60% at 10 weeks and >70% at 1 year [3-5]**.**

The ACTA trial [6] tested new induction strategies, based on promising phase 2 data. Two weeks oral combination therapy with FLU plus flucytosine, and short, 1-week, AmB with either FLU or 5FC, were compared against the internationally recommended 2 weeks AmB with either FLU or 5FC, in a 2:1:1:1:1 ratio. The aim was to improve upon the efficacy of FLU monotherapy with regimens that, unlike 2 weeks AmB, could be more readily sustained in resource-limited settings. The trial showed that 1 week AmB+5FC was associated with lower mortality and the oral combination was non-inferior compared with the recommended 2 weeks AmB+5FC.

Given the scarcity of resources, detailed evidence on the health care costs of treatment and on associated health impact are essential to inform policy decisions. AmB is intravenous and requires hospitalization and stringent laboratory monitoring, FLU is oral and available through donation programmes or as low-cost, generic manufacture. The current availability of 5FC is very limited.

There are very few detailed studies of the costs of alternative CM treatments available to date. Therefore, within the ACTA trial, we conducted a comparative cost-effectiveness study of the 5 regimens tested, in order to support and guide policy decisions.

Methods

The ACTA trial [6] was an open label, phase 3, randomised non-inferiority, multi-centre trial, in which patients with HIV-associated cryptococcal meningitis from 9 African centres in four countries (Malawi, Zambia, Tanzania and Cameroon) were enrolled between January 2013 and November 2016. Participants were first randomised to three strategies: oral combination regimen, 1 week AmB, and standard 2 weeks AmB and those in the AmB arms were further randomised to 5FC or FLU in a 1:1 ratio, as the partner drug treatment. This resulted in 5 arms i) oral 5FC+FLU 2 weeks, ii) one week AmB+FLU, iii) one week AmB+5FC, iv) 2 weeks AmB+FLU and v) 2 weeks AmB+5FC in a ratio of 2:1:1:1:1.

A full economic costing and cost-effectiveness analysis of the cryptococcal meningitis treatments was done, by the CHEERS appraisal guidelines [7], from the health care perspective. Resource use data were collected using an ingredients-based approach [8, 9]. The data on individual resource use and health outcomes, including trial-related complications and treatment of complications, were collected from all participants onto case-report forms (CRFs). A detailed costing study was done in the Zambian hospital (See Table 1 and Supplementary Material). CM -specific and overhead costs, including costs of admissions and laboratory tests, were collated from the hospital's financial and utilisation documents. The treatment-related utilisation data were collated from the CRFs. These were collected on length of stay in hospital, types of diagnostic tests, medical supplies and drugs used. Discussions were held with relevant hospital staff for data triangulation. The ACTA study team were consulted on the trial-related expenditure and resource utilization data in relation to complications. Where unit costs were not available in the expenditure records,

local market prices were used.

A time-and-motion study was conducted to inform the monetary valuation for care received provided by health staff at the bed-side. It collected information on the type and intensity of care received by a purposive sample of 59 trial participants. Each participant was observed for two consecutive days. Findings on time spent on patient care were combined with salaries (including all financial benefits) to estimate total staff costs spent on caring for CM patients. (See Table 1). We collected data on health care resource and unit prices, adjusted to 2015 US$ price level and included the effects of bulk purchasing, and delivery / shipping charges. An average annual exchange rate for the trial baseline year and subsequent inflation corrections were used in the currency conversion and inflation correction.

Aggregated hospital expenditures were allocated proportionally to relevant institutional units and departments. This was complemented with observations to establish costs allocation factors (e.g. floor surface, number of beds, number of medical staff), in particular in the allocation of overhead costs. These additional costs were disaggregated and summarized in costs per bed-day, CM treatment-specific costs and laboratory test costs according to recurrent and capital costs,and non-specific costs of additional use of antibiotics in relation to complications. Recurrent cost items were considered to be goods/services with a life span of less than one year whereas capital costs were defined as costs which were incurred to purchase good/services which last for more than one year. Capital costs were few and limited to those related to diagnostics and were annualised over their economic life (informed by the Zambian hospital's accounting documents) using a discount rate of 3% [9, 10]. The analysis included institutional and department overheads including for hospital administration, drug and other supply chain management. A detailed listing is given in Table 1 while a more detailed description of the cost component is presented in the Supplementary Material.

The health outcome included in the cost-effectiveness analysis is life year saved, based on the age of the patients saved from dying. Here we multiplied the additional deaths prevented with the observed CD4-specific weighted life expectancy [11]. The average life expectancy of the additional survivors was estimated conservatively at 18 years [11]. We did not make a long-term quality-of-life adjustment as the mortality reduction is substantial and defined as the main outcome of the trial. Quality-of-life outcomes after CM meningitis in these patient groups are lacking. We used a differential discount rate for health care costs (3% per international standard) and life years gained (0% as given in the literature) [12, 13].

Statistical analysis

Total cost – that is observed use of resources multiplied by a specific unit price, increased for specific overhead costs - was adjusted using a Kaplan-Meier average estimator to account for censoring from death or lost to follow-up [14]. Individual patient costs were calculated and non-parametric bootstrapping was used to draw a stable sample (defined as the percentage change in standard deviation between two subsequent samples [15]) from patient records by treatment arm to allow for the skewed distribution of costs and the correlation between costs and effectiveness [16].

The 95% confidence intervals for the total cost per patient and probability of death were calculated using bias-corrected percentile acceleration method [15]. The five ACTA treatments were ranked by their increasing cost and we ruled out strategies that were less effective and more costly than the comparator (less economically attractive or dominated in economic terms) and strategies that were less effective and had a higher incremental cost-effectiveness ratio (extended dominance). Of the remaining strategies, incremental cost-effectiveness ratios were calculated for each strategy relative to standard treatment and the next best alternative.

Costs per life year saved were estimated by dividing mean incremental costs by mean number of life years saved. Cost-effectiveness planes and an acceptability curve were used to show the uncertainties around incremental cost-effectiveness ratios. A series of (one-way) sensitivity analyses were done varying one parameter at a time to address uncertainty in the data inputs (including, especially, the observed uncertainty range around patient-level resources use shown in Table 2 and the uncertainties in the observed mortality rate and observed range of life expectancy(12.8 to 40.81) [17] to compute the uncertainties in incremental cost-effectiveness ratios [18]. Here, the parameters in the standard treatment arm were kept constant. The effects of the top-ranking individual parameters are presented by a tornado sensitivity graph.

Ethics

The trial protocol and data collection was approved by London School of Hygiene and Tropical Medicine Research Ethics Committee and by the national ethics and regulatory bodies in each country. Written informed consent was obtained from all participants or, in the case of those with altered mental status, from the next of kin (the participants were re-consented on recovery).

Results

The ACTA trial analysis comprised 678 eligible participants.[6] Only 4 patients were lost to follow-up. Mortality at 10 weeks (Table 3) was 251 (37%) overall, and was lowest for one week AmB + 5FC (24%, 95% CI 16, 31) [6].

Resource use, costs and health outcomes

The unit prices are shown in Table 1. The cost per bed day was 2015 US$ 48. This excludes CM treatment-specific costs and laboratory test costs. Detailed resource use by trial arm is presented in Table 2. The differences between the trial arms in resource use were largely driven by the component drugs and complication-related resource use. Thus, blood transfusions and potassium and magnesium supplementation were highest for participants in the 2 week AmB arms and lowest for the oral 5FC+FLU combination. The duration of hospitalisation was largely similar between the trial arms as this was protocol-driven. Participants were asked to remain in hospital as inpatients for at least 14 days for trial safety monitoring.

Mean per patient total costs were lowest for the oral 5FC+FLU combination (US $1442) and highest for 2 AmB + 5FC (US$ 2285) (Table 3). The total cost of bed-days per patient (both hospitalisation and re-hospitalisation) was the major cost component, from 36% for 2 weeks AmB+FLU to 56% of costs for the oral arm. More than 75% of the costs were incurred during the first two weeks.

Cost effectiveness and uncertainty

1 week AmB+5FC was less costly and more effective than (i.e. dominated) 2 weeks AmB+5FC (Table 3, Figure 1). The 2 weeks oral 5FC+FLU combination was also less costly than 2 weeks AmB+5FC but the reduction in mortality was marginal (Table 3 and Figure 1). Both 2 weeks AmB+FLU and 1 week AmB+FLU were cost-saving compared with 2 weeks AmB+5FC, but these treatments were associated with increased mortality (Table 3 and Figure 1).

Therefore, 1-week AmB+5FC and the 2 weeks oral combination were the two most attractive induction treatments. Figure 2 shows the uncertainty around the health service cost savings in relation to the number of lives saved, in scatter plots of the cost-effectiveness plane. In comparison to 2 weeks AmB+5FC, 2 weeks oral 5FC+FLU combination is robustly cost saving but the health gain is much less certain. The 1 week AmB+ 5FC arm shows a robust reduction in both cost and deaths. Finally, in a head-to-head comparision (Table 3, right side) 1-week AmB+ 5FC shows a robust health gain at some additional cost compared with the oral 5FC+FLU regimen (US$ 208 (95% CI: 91-1210, per life year gained).

Figure 2 shows the probability (y-axis) that 1 week AmB+5FC is cost-effective when compared with 2 weeks oral 5FC+FLU at the complete full range of willingness to pay thresholds (x-axis). The probability of being cost-effective exceeds 90% at a threshold of US$490 and is around 80% at a threshold of US$330 per life year saved.

Multi-variate sensitivity analysis

We varied all the resource parameters (Table 2) and the health outcomes (Table 3) in an empirical multi-variate sensitivity analysis (Figure 3). The top five drivers of the incremental cost-effectiveness ratio were mortality rate, life expectancy, number of bed days hospitalised, re-hospitalization days and total AmB dosage. The latter and all other parameters did not substantially influence the incremental cost-effectiveness results. The tornado graph in Figure 3 shows the effect of varying the value for each important parameter on the incremental cost-effectiveness ratio of 1 week AmB+5FC compared with the oral regimen, given the uncertainty ranges in the individual parameters in probabilistic analyses.. If the mortality for 1 week AmB+5FC was varied from 16% to 31% (i.e. the lower and upper 95% CI of the mortality estimate), then the incremental cost-effectiveness ratio would vary between $121 and $638, assuming other parameters were constant.

Discussion

This study shows that 1-week AmB+5FC and oral FLU+5FC were the most cost-effective regimens and both are suitable to replace 2-weeks AmB+5FC as the preferred regimens in many settings. In comparison with 2 weeks AmB+5FC, both regimens were less costly and one week AmB+5FC led to substantial health gains while the oral combination was at least as effective.

The findings for one 1-week AmB+5FC were very robust. Even when the mortality of 1-week AmB+5FC was varied to the upper 95%CI limit of 31%, 1-week AmB+5FC still dominated 2 weeks AmB+5FC. In an arm-to-arm comparison, the estimated incremental cost effectiveness ratio for 1-week AmB+5FC versus oral 5FC+FLU combination was $208 per life year saved. The 1-week AmB+5FC combination represents a cost-effective option in clinical settings in Africa where AmB can be given and monitored. Importantly however, oral fluconazole and flucytosine provides a cost-effective option for more severely resource-limited settings where AmB therapy is not possible, that is as effective as the current international standard of care and reduces service costs. The findings re-emphasise the absolute necessity of current international efforts to secure immediate and wide access to flucytosine.

This is the first large study based on the collection of protocol-driven patient-level resource use data across different African countries. These data were supplemented with medical and nursing staff time information and an empirical costing study in the Zambian public hospital site. Here, as in many other sub-Saharan African countries, costs data are not included in routine health service data collection. Therefore, as part of ACTA, we undertook substantial efforts to obtain reliable, consistent and accurate data on components of the service cost per

bed day, the main driver of total costs per patient. The resulting cost per bed day was relatively high (US$ 48) – it reflected the real-life local cost of intensive treatment and local procurement, and excluded CM treatment-specific costs and specific laboratory test costs.

In a prior study to compare the cost-effectiveness of alternative regimens, Rajasingham et al concluded that 1-week AMB plus fluconazole would likely be much more cost effective than 2-week AmB courses [11]. A limitation acknowledged by the authors was that the efficacy component was based on pooled mortality data available at that time across small, often non-comparative studies, and from different settings. Our service costs and resource use data are linked to the largest trial to date. The results confirm the economic attractiveness of 1-week AmB in relation to 2-weeks AmB, in terms of cost savings and higher effectiveness, but only in combination with 5FC as the partner drug, and also demonstrate the attractiveness of the combination of the two oral drugs, fluconazole and 5FC. The 1-week course with AmB comes at an additional price compared wth oral FLU+5FC, that may be affordable in many SSA country settings, and compares well with a range of other clinical interventions, including prevention of mother to child HIV transmission, MDR TB treatment, and intrapartum care [19] [20] [21].

The cost-effectiveness advantage of 1-week AmB+5FC and oral FLU+5FC over 2-week AmB regimens is underestimated in our analysis. We measured actual durations of hospitalisation of the ACTA trial participants, which for trial safety monitoring reasons, required participants to be hospitalised under close observation for the first 2 weeks. In real-life implementation, the duration of hospitalisation for patients on the oral or 1-week AmB regimens would, in all likelihood, be lower and the cost of these regimens would decrease in relation to 2-week AmB regimens which require a minimum duration of hospitalisation of 14 days. If we included all societal cost consequences, including those at household level, the total societal cost savings of the oral or 1-week AmB regimens over 2-week AmB regimens would increase further, as travel and loss of household productivity in relation to hospitalisation would be reduced, as well as the out-of pocket patient-related cost born by carers.

In an explorative scenario, we subtracted the cost of the second week's admission from the total for any patient discharged on day 14 or earlier who was on oral treatment or on 1-week AmB+5FC (using the original trial data). This short hospital stay scenario results in a total per patient cost of US$ 767(95% CI: 722, 841) for the oral arm and US$ 1161 (95% CI: 1114, 1225) for 1 week AmB. These costs are about half those of per protocol hospital stays for patients on these arms and substantially lower than the costs of 2 weeks AmB+ 5FC ($2285), making the oral and 1 week AmB+5FC even more attractive. Importantly, the incremental cost effectiveness of 1-week AmB+5FC versus the oral combination would not be altered by this consideration since all CM patients require some period of hospitalisation for optimal care, including measurement and management of raised cerebrospinal fluid pressure.

The study provides further strong support for the recently updated WHO guidelines for the treatment of HIV-associated cryptococcal meningitis that recommend 1-week AmB+5FC and oral FLU+5FC as the first and second preferred regimens. Flucytosine needs to be made available widely to reduce cryptococcal-associated mortality

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Author contributions

TC analysed the data. TC and LM wrote the first draft. LWN supervised the analysis. TSH, SJ and LWN led the writing and interpretation with input from AG and UKG. TSH led the design of the study with input from SL, DC, PM, MCH, OL, SJ. LM led the costing study in Zambia with input from SL, DC, and PM. SFM provided oversight and monitored the data collection. CKa, CKo, ET, SK, RSH, AL were responsible for data collection, study supervision. All authors contributed to drafts of the paper and approved the final version.

Acknowledgements: Supported by grants from the Medical Research Council, United Kingdom (100504) and the French Agency for Research on AIDS and Viral Hepatitis (ANRS) (ANRS12275), a strategic award from the Wellcome Trust UK (to the Malawi–Liverpool–Wellcome Clinical Research Programme), We thank all the patients and their families, as well as the staff at all the sites not directly involved in the trial; Andrew Nunn, Halima Dawood, Andrew Kitua, and William Powderly for serving on the data and safety monitoring committee; Graeme Meintjes, Calice Talom, Newton Kumwenda, and Maryline Bonnet for serving on the trial steering committee; and the ANRS Staff in Paris (Brigitte Bazin, Claire Rekacewicz, and Paula Garcia) for constant support.

The authors declare no conflicts of interest.

Table 1. Unit prices (US $ in 2015) by resource item and source of unit price.

Resource Item	Supplies**	Staff	Capital	Total	Source
Costs per bed-day	9.45	37.06	1.14	47.64	Costing study
Lumber puncture, per time	0.94	7.49	1.14	9.57	Costing study
Bio-chemistry, per test					
Total Bilirubin	1.9	2.63	0.27	4.8	Costing study
C-reactive protein	5.77	2.63	0.27	8.67	Costing study
Alanine transaminase	4.04	2.63	0.27	6.94	Costing study
Magnesium	2.05	2.63	0.27	4.95	Costing study
Urea	1.94	2.63	0.27	4.84	Costing study
Creatinine	1.83	2.63	0.27	4.73	Costing study
Proteinuria	1.96	2.63	0.27	4.86	Costing study
Microbiology, per test					
Urine culture - negative	1.5	5.92	0.43	7.84	Costing study
Urine culture - positive	2.08	8.65	0.43	11.16	Costing study
Blood culture - negative	1.03	6.17	0.55	7.74	Costing study
Blood culture - positive	3.39	9.79	0.55	13.73	Costing study
Sputum culture - negative	2.13	4.4	0.45	6.98	Costing study
Sputum culture - positive	4.04	8.02	0.45	12.5	Costing study
CSF - negative	9.06	13.15	0.46	22.66	Costing study
CSF - positive	9.98	15.88	0.46	26.31	Costing study
Full Blood Count, per test	32.28	4.04	0.28	36.59	Costing study
CD4 Count, per test	7.38	9.04	1.37	17.79	Costing study
CM-specific treatment					

Trial drug			
Fluconazole per 1200mg	0.55	0.55	Provider
flucytosine per 500mg	1.53	1.53	Provider
Amphotericin B per 1 mg	1.18	1.18	Provider
Antibiotics			
Flucloxacillin per day	0.2	0.2	Pharmacy
Gentamicin per day	0.26	0.26	Pharmacy
Ceftriaxone per ampoule	0.52	0.52	Pharmacy
Amoxicillin/Ampicillin per ampoule	0.066	0.066	Pharmacy
Doxycycline per day	0.038	0.038	Pharmacy
Erythromycin per day	0.144	0.144	Pharmacy
Ciprofloxacin per day	0.10	0.10	Pharmacy
Other intervention			
Potassium	0.105	0.105	Pharmacy
Magnesium	1.45	1.45	Pharmacy
Blood transfusion per unit	35	35	Hospital department
Potassium	2.90	2.90	Costing study
Sodium	2.90	2.90	Costing study

Table 2. Mean (standard deviation) resource use per patient by trial arm, over 10 weeks trial period.

Service use item	Service use item	2 weeks oral FLU and 5FC	1 week AmB+FLU	1 week AmB+5FC	2 weeks AmB+FLU	2 weeks AmB+5FC
Hospitalization	Days	17.33(15.29)	17.14(18.04)	17.99(15.06)	16.09(12.27)	19.31(18.31)
Re-hospitalization	Days	2.02(5.23)	2.14(6.31)	0.88(2.72)	1.77(5.48)	1.38(4.10)
CM-specific treatment						
Trial drug						
Fluconazole	Tablet (200 mg)	187.96(123.83)	147.18(130.65)	161.50(148.25)	170.68(125.26)	120.37(159.31)
flucytosine	Tablet (500mg)	131(56)	0.00(0.00)	74(23)	0.00(0.00)	131(59)
Amphotericin B (AmB)	Vial (50mg)	0.00(0.00)	6.50(2.60)	7.35(2.12)	12.71(5.53)	13.07(5.94)
Antibiotics						
Flucloxacillin	times	0.03(0.17)	0.06(0.24)	0.05(0.23)	0.13(0.34)	0.09(0.28)
Gentamicin	times	0.02(0.13)	0.00(0.00)	0.01(0.09)	0.02(0.13)	0.03(0.18)
Ceftriaxone	Ampoule	0.62(0.49)	0.65(0.48)	0.58(0.50)	0.60(0.49)	0.66(0.48)
Amoxicillin/Ampicillin	Ampoule	0.06(0.24)	0.06(0.24)	0.11(0.31)	0.07(0.26)	0.04(0.20)
Doxycycline	times	0.01(0.09)	0.05(0.21)	0.00(0.00)	0.04(0.18)	0.01(0.09)
Erythromycin	times	0.00(0.00)	0.01(0.09)	0.01(0.09)	0.01(0.09)	0.00(0.00)
Ciprofloxacin	times	0.05(0.22)	0.03(0.16)	0.04(0.21)	0.04(0.21)	0.01(0.09)
Other intervention						
Potassium	days	0.00(0.00)	6.05(2.20)	6.72(1.43)	11.71(4.41)	11.83(4.62)
Magnesium	days	0.00(0.00)	6.05(2.20)	6.72(1.43)	11.71(4.41)	11.83(4.62)
Blood transfusion	Units	0.12(0.52)	0.23(0.66)	0.15(0.57)	0.31(0.73)	0.37(0.86)
Lumbar puncture	times	3.13(1.84)	2.62(1.07)	3.26(1.39)	2.93(1.59)	2.98(1.44)
Bio-chemistry						
Total Bilirubin	times	1.69(2.95)	1.57(2.77)	1.74(2.99)	1.44(2.79)	1.63(2.94)
CRP	times	0.06(0.31)	0.09(0.39)	0.04(0.21)	0.11(0.42)	0.10(0.41)
ALT	times	3.48(2.09)	3.04(1.73)	3.69(2.00)	3.66(2.32)	3.40(1.99)
Magnesium (Mg)	times	0.19(0.73)	0.20(0.75)	0.20(0.67)	0.16(0.66)	0.22(0.81)
Potassium (K)	times	7.00(3.15)	6.23(3.21)	7.22(2.35)	7.07(3.12)	6.83(3.21)
Sodium (Na)	times	7.02(3.09)	6.25(3.21)	7.27(2.41)	7.12(3.14)	6.90(3.23)
Urea	times	6.99(3.12)	6.22(3.14)	7.19(2.44)	7.04(3.07)	6.79(3.12)

Creatinine	times	7.15(3.17)	6.32(3.32)	7.39(2.45)	7.18(3.12)	6.98(3.29)
Proteinuria	times	7.64(3.48)	6.82(3.80)	7.82(2.71)	7.87(3.63)	7.47(3.65)
Full Blood Count	times	4.62(2.39)	4.26(2.62)	4.68(1.96)	4.69(2.41)	4.63(2.60)
CD4 Count	times	0.97(0.37)	1.01(0.37)	0.93(0.29)	0.97(0.45)	0.98(0.30)
Microbiology *						
Urine culture - negative	times	0.08(0.34)	0.07(0.32)	0.04(0.19)	0.11(0.36)	0.09(0.45)
Urine culture - positive	times	0.05(0.26)	0.04(0.23)	0.02(0.13)	0.04(0.18)	0.02(0.13)
Blood culture - negative	times	0.12(0.36)	0.08(0.27)	0.10(0.33)	0.12(0.44)	0.10(0.40)
Blood culture - positive	times	0.07(0.27)	0.09(0.35)	0.04(0.19)	0.13(0.45)	0.04(0.24)
Sputum culture - negative	times	0.00(0.00)	0.00(0.00)	0.01(0.09)	0.00(0.00)	0.00(0.00)
Sputum culture - positive	times	0.07(0.27)	0.09(0.35)	0.07(0.29)	0.06(0.28)	0.08(0.27)
CSF - negative	times	0.64(0.88)	0.77(0.99)	1.27(1.04)	0.75(0.84)	1.34(1.21)
CSF - positive	times	2.44(1.88)	1.83(1.14)	1.95(1.39)	2.17(1.63)	1.56(1.02)

* Negative cultures are less costly than positive cultures.

Table 3. Probabilistic cost-effectiveness analyses comparing the trial arms in terms of mean total health care costs and death rate (%).

	Total cost per patient and death rate (%) per arm		Incremental comparison of 1 week of AmB+5FC versus 2 weeks of FLU+5FC		
ACTA treatment arms	**Mean total costs**	**Deaths (%)**	**Incremental costs per patient**	**Incremental death rate (%)**	**Incremental costs per life year saved**
2 week Oral FLU+5FC	1442 (1336 -1565)	35(28-41)	Reference	Reference	Reference
1 week AmB+FLU	1763 (1567 -1979)	49(39-58)	-	-	-
1 week AmB+5FC	1861 (1724 -2033)	24(16-31)	419 (236, 619)	11 (0.6, 21)	208 (91, 1210)
2 weeks AmB+FLU	2125 (1946 -2313)	41(32-49)	-	-	-
2 week AmB+5FC (Comparator)	2285 (2070 -2525)	38(29-46)	-	-	-

Note: Two weeks of oral treatment and 1 week AmB+5FC show lower costs and better health outcomes than the other treatment combinations (i.e. cost less and averted more deaths). In economics terms: these two treatments 'dominate' the other options. Incremental cost-effectiveness is calculated for these remaining favourable options on the right half of the table. Average estimated life expectancy is 18 years as reported in Rajasingham' study[11]. The numbers in parenthesis are estimates of the 95% confidence intervals as estimated by boot-strapping. Abbreviation: AmB - amphotericin B; FLU- Fluconazole; 5FC- flucytosine

LEGENDS TO FIGURES

Figure 1. Cost-effectiveness planes after bootstrap iterations (1000 selected at random are shown) to present incremental costs and death prevented (%) after the 10 week trial period, for Oral 5FC+FLU versus 2 weeks AmB+5FC (A), 1 week AmB+5FC versus 2 weeks AmB+5FC (B) and 1 week AmB+5FC versus Oral FLU+5FC (C). Ellipses show 95% confidence intervals. Red dots indicate the means for both axes. Abbreviation: AmB - amphotericin B; FLU-Fluconazole; 5FC- flucytosine.

Figure 2. Cumulative probability of the incremental cost-effectiveness ratio being below different thresholds for the comparison of 1-week AmB+5FC versus oral FLU+5FC combination.

Figure 3. Tornado diagram of incremental cost-eff effectiveness ratio (ICER) for 1-week AmB+5FC vs. oral combination for major components. All other resource parameters were not influential. NB. The analyses use the 95% of the input distribution for resource use and health outcomes parameters to eliminate extreme outliers. The input ranges are based on the overall results from bootstrap methods described in the methods section, using individual participant data. Life expectancy input data are from a comparable cohort[11, 17] Abbreviations: AmB - amphotericin B; 5FC- flucytosine; ICER- incremental cost-eff effectiveness ratio.

Reference:

1. Rajasingham, R., et al., *Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis.* Lancet Infect Dis, 2017. **17**(8): p. 873-881.
2. Perfect, J.R., et al., *Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america.* Clin Infect Dis, 2010. **50**(3): p. 291-322.
3. Gaskell, K.M., et al., *A prospective study of mortality from cryptococcal meningitis following treatment induction with 1200 mg oral fluconazole in Blantyre, Malawi.* PLoS One, 2014. **9**(11): p. e110285.
4. Longley, N., et al., *Dose response effect of high-dose fluconazole for HIV-associated cryptococcal meningitis in southwestern Uganda.* Clin Infect Dis, 2008. **47**(12): p. 1556-61.
5. Rothe, C., et al., *A prospective longitudinal study of the clinical outcomes from cryptococcal meningitis following treatment induction with 800 mg oral fluconazole in Blantyre, Malawi.* PLoS One, 2013. **8**(6): p. e67311.
6. Molloy, S.F., et al., *Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa.* N Engl J Med, 2018. **378**(11): p. 1004-1017.
7. Husereau, D., et al., *Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.* Value Health, 2013. **16**(2): p. e1-5.
8. Drummond, M. and M. Sculpher, *Common methodological flaws in economic evaluations.* Med Care, 2005. **43**(7 Suppl): p. 5-14.
9. Mueller, D.H., et al., *Costs and cost-effectiveness of tuberculosis cultures using solid and liquid media in a developing country.* Int J Tuberc Lung Dis, 2008. **12**(10): p. 1196-202.
10. Griffiths, U.K., et al., *Cost-effectiveness of eye care services in Zambia.* Cost Eff Resour Alloc, 2014. **12**(1): p. 6.
11. Rajasingham, R., et al., *Cryptococcal meningitis treatment strategies in resource-limited settings: a cost-effectiveness analysis.* PLoS Med, 2012. **9**(9): p. e1001316.
12. Brouwer, W.B., et al., *Need for differential discounting of costs and health effects in cost effectiveness analyses.* Bmj, 2005. **331**(7514): p. 446-8.
13. Gravelle, H., et al., *Discounting in economic evaluations: stepping forward towards optimal decision rules.* Health Econ, 2007. **16**(3): p. 307-17.
14. Lin, D.Y., et al., *Estimating medical costs from incomplete follow-up data.* Biometrics, 1997. **53**(2): p. 419-34.
15. Barber, J.A. and S.G. Thompson, *Analysis of cost data in randomized trials: an application of the non-parametric bootstrap.* Stat Med, 2000. **19**(23): p. 3219-36.
16. Khan, I., , C.a. Hall, Editor. 2015, CRC Biostatistics Series.
17. Mills, E.J., et al., *Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: a cohort analysis from Uganda.* Ann Intern Med, 2011. **155**(4): p. 209-16.
18. Iftekhar, K., *Design & Analysis of clinical trial for economic evaluation & Reimbursement applied approach using SAS & STATA*. 2015: Chapman and Hall/CRC.
19. Horton, S. *Cost-Effectiveness Analysis in Disease Control Priorities, Cost-Effectiveness Analysis in Disease Control Priorities, Third Edition DCP3 Disease Control Priorities project Economic Evaluation for Health. http://dcp-3.org/chapter/2561/cost-effectiveness-analysis (accessed March 2018)*.
20. Bilinski, A., et al., *When cost-effective interventions are unaffordable: Integrating cost-effectiveness and budget impact in priority setting for global health programs.* PLoS Med, 2017. **14**(10): p. e1002397.

21. Sculpher, M.J., et al., *Generalisability in economic evaluation studies in healthcare: a review and case studies.* Health Technol Assess, 2004. **8**(49): p. iii-iv, 1-192.