

# **Addition of flucytosine to fluconazole for the treatment of cryptococcal meningitis in Africa: a multi-country cost-effectiveness analysis**

Tinevimbo Shiri<sup>1\*</sup>, Angela Loyse<sup>2\*</sup>, Lawrence Mwenge<sup>3</sup>, Tao Chen,<sup>1</sup> Shabir Lakhi,<sup>4</sup> Duncan Chanda,<sup>4,5</sup> Peter Mwaba,<sup>6</sup> Síle F Molloy,<sup>2</sup>, Robert Heyderman,<sup>7,8,9</sup> Cecilia Kanyama,<sup>10</sup> Mina C. Hosseinipour,<sup>10,11</sup> Charles Kouanfack,<sup>12,13</sup> Elvis Temfack,<sup>14,15</sup> Sayoki Mfinanga,<sup>1,16</sup> Sokoine Kivuyo,<sup>16</sup> Adrienne K. Chan,<sup>17,18</sup> Joseph N. Jarvis,<sup>19,20</sup> Olivier Lortholary,<sup>15,21</sup> Shabbar Jaffar,<sup>1</sup> Louis W Niessen,<sup>1,22</sup> Thomas S Harrison,<sup>2§</sup>.

1 Liverpool School of Tropical Medicine, Liverpool, United Kingdom,

2 Centre for Global Health, Institute for Infection and Immunity, St George's University of London, United Kingdom,

3 Zambart, Health Economics Unit, Lusaka, Zambia

4 University Teaching Hospital, Lusaka, Zambia,

5 Institute for Medical Research and Training, University Teaching Hospital, Lusaka, Zambia,

6 Department of Internal Medicine and Directorate of Research and Post graduate studies, Lusaka Apex Medical University, Lusaka, Zambia

7 Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, Malawi,

8 College of Medicine, University of Malawi, Blantyre, Malawi

9 University College London, London, United Kingdom

10. University of North Carolina Project-Malawi, Kamuzu Central Hospital, Lilongwe, Malawi

11. Division of Infectious Diseases, University of North Carolina at Chapel Hill School of Medicine

12 Hôpital Central Yaoundé/Site Agence Nationale de Recherche sur le Sida (ANRS) Cameroun, Yaoundé

13. University of Dschang, Dschang, Cameroon

14 Douala General Hospital, Douala, Cameroon

15 Institut Pasteur, Molecular Mycology Unit, CNRS CMR 2000, Paris, France,

16 National Institute Medical Research, Muhimbili Medical Research Centre, Dar Es Salaam, United Republic of Tanzania,

17 Dignitas International, Zomba Central Hospital, Zomba, Malawi,

18 Division of Infectious Diseases, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada

19 Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom

20 Botswana Harvard AIDS Institute Partnership, Gabarone, Botswana

21 Paris Descartes University, Necker Pasteur Center for Infectious Diseases and Tropical Medicine, IHU Imagine, APHP, Paris, France.

22 Department of International Health, Johns Hopkins School of Public Health, USA.

\* contributed equally

§ corresponding author

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Corresponding author: Dr Thomas S Harrison, Centre for Global Health, Institute for Infection and Immunity, St George's University of London, London SW17 0RE , UK. Tel 0044 208 7250447, email tharriso@sgul.ac.uk

Alternate corresponding author: Dr Angela Loyse, Centre for Global Health, Institute for Infection and Immunity, St George's University of London, London SW17 0RE , UK Tel 0044 208 7250443, email aloyse@sgul.ac.uk

Key points: Combination flucytosine (5FC) plus fluconazole (FLU) is highly cost effective, compared with the commonly used regimen of FLU monotherapy, for cryptococcal meningitis treatment in Africa; with an incremental cost-effectiveness ratio of US\$65 per life year saved at current 5FC price.

## **Abstract**

### **Background**

Mortality from cryptococcal meningitis remains very high in Africa. In the ACTA trial, 2 weeks of fluconazole (FLU) plus flucytosine (5FC) was as effective and less costly than 2-week amphotericin B-based regimens. However, many African settings treat with FLU monotherapy and the cost effectiveness of adding 5FC to FLU is uncertain.

### **Methods**

The effectiveness and costs of FLU+5FC were taken from ACTA, which included a costing analysis at the Zambian site. The effectiveness of FLU was derived from cohorts of consecutively enrolled patients, managed in respects other than drug therapy, as were participants in ACTA. FLU costs were derived from the costs of FLU+5FC in ACTA, by subtraction of 5FC drug costs and 5FC monitoring tests. Cost-effectiveness of FLU+5FC vs FLU alone was measured as the incremental cost-effectiveness ratio (ICER). Probabilistic sensitivity analysis assessed uncertainties, and a bivariate deterministic sensitivity analysis examined the impact of varying mortality estimates and 5FC drug costs on the ICER.

### **Results**

Mean costs per patient were US\$847 (95%CI:776-927) for FLU+5FC, and US\$628 (95%CI:557-709) for FLU. 10 week mortality was 35.1% (95%CI 28.9-41.7) with FLU+5FC and 53.8% (95%CI: 43.1–64.1) with FLU. At the current 5FC price of \$US1.30 per 500mg tablet, the ICER of 5FC+FLU versus FLU alone was US\$65 (95%CI: 28-208) per life year saved. Reducing 5FC cost to between US\$0.80 and US\$0.40 per 500mg resulted in an ICER between US\$44 and US\$28 per life year saved.

### **Conclusions**

Addition of 5FC to FLU is cost effective for cryptococcal meningitis treatment in Africa and if made available widely could substantially reduce mortality rates among HIV-infected persons in Africa.

## **Background**

Mortality from cryptococcal meningitis (CM) remains unacceptably high in Sub-Saharan Africa [1]. The most widely used treatment, fluconazole (FLU) monotherapy is associated with mortality of 50-60% at 10 weeks and >70% at 1 year, even in study cohorts [2-5]. Access to amphotericin B and, in particular, flucytosine is currently limited, despite the fact that the latter is off patent and a relative simple molecule to manufacture.

The ACTA trial [6] recently tested new induction treatment strategies. Two weeks oral combination therapy with FLU+flucytosine (5FC), and short, 1-week, amphotericin B (AmB) regimens, were compared against the internationally recommended 2 week AmB-based induction regimen. The aim was to improve upon the efficacy of FLU monotherapy with regimens that could be sustained in resource-limited settings.

While 1 week AmB+5FC was the regimen associated with the lowest mortality in the trial, the oral combination of FLU+5FC was non-inferior compared with the then recommended regimen of 2 weeks of AmB+5FC. Furthermore, in a detailed cost effectiveness analysis, oral FLU+5FC was the least expensive regimen [7]. Thus, for resource limited centres currently using FLU monotherapy, where even one week of AmB would be difficult to sustain, oral FLU+5FC is an attractive option, and new WHO guidelines following the trial recommend this option if AmB is not available [8].

The ACTA trial did not include an arm treated with fluconazole monotherapy, due to lack of equipoise. In addition, changing clinical practice in centres currently treating

with FLU will be a challenge because of resource constraints. Therefore, to inform local policy and practice, and guide efforts to improve flucytosine access, we have conducted an analysis of the cost-effectiveness of oral FLU+5FC versus FLU monotherapy.

## **Methods**

The costs and effectiveness of FLU+5FC were derived from the ACTA trial [6]. ACTA was a large open label, phase 3, randomised non-inferiority, multi-centre trial, in which 721 patients with HIV-associated cryptococcal meningitis from centres in Malawi, Zambia, Tanzania and Cameroon were randomised to three strategies: 2 weeks oral FLU+5FC, 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 given with AmB.

A full economic costing and cost-effectiveness analysis of the ACTA treatments was done from the health care perspective [7]. Resource use data were collected using an ingredients-based approach [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, including CM-specific and overhead costs, including costs of admissions and laboratory tests. Prices were adjusted to 2015 US\$ price level for consistency with our prior analysis [7]. Of note however, the inflation change for 2015 to 2018 was modest at 5.9%.

The costs of FLU+5FC in this study were derived from the ACTA analysis of

FLU+5FC cost, adapted to a short stay scenario, reflective of the duration of hospitalisation in implementation, as opposed to that within the trial (Supplementary Table S1). In the trial, participants were asked for safety monitoring reasons to stay for 14 days in hospital. Thus, in this scenario, we presumed one week of hospitalisation for patients treated with FLU+5FC and for those treated with FLU alone, plus an average of 2 days of re-hospitalisation, as observed in the ACTA trial. Hospitalisation costs were US\$47.65 per day, giving a total cost of US\$428.85 per patient. Of note, all CM patients, including those treated with oral drugs, require some days of hospitalisation for optimal care, including measurement and management of raised cerebrospinal fluid pressure.

CM-treatment-specific costs, diagnostics, drug costs, laboratory monitoring, complication-related resource use, hospital care, equipment and personnel costs were considered (Supplementary Table S1). The cost of FLU was US\$0.55 per 200mg tablet, with a 14 day course costing US\$7.70. The 5FC cost was \$US1.30 per 500 mg tablet, taken from the current cost of procurement for the AMBITION trial (ISRCTN10248064). Thus for a 50 kg patient, the cost for 2 weeks was US\$182.

Laboratory costs included biochemistry tests as used in the ACTA trial for individual patient care, as well as routine baseline and one follow-up test for electrolytes, urea and creatinine, and ALT. A routine follow-up full blood count was costed for the oral combination to monitor for neutropenia with 5FC. Blood, cerebrospinal fluid (CSF) and sputum cultures as used for patient care, and the cost of antibiotics used to treat other infections was included. A single CD4 count and an average of 3 lumbar punctures during hospitalisation for each patient were included.

The total costs of FLU monotherapy are derived from the costs of FLU+5FC, from the ACTA trial data, as above, by subtraction of the day 7 5FC monitoring full blood count and 5FC drug costs (Supplementary Table S1).

Mortality at 10 weeks in the 5FC+FLU combination arm of the ACTA trial was 79/225 (35.1%,95% CI: 28.9 – 41.7). For the effectiveness of FLU treatment, we analysed data from research participants in 3 cohorts of patients treated with FLU at 1200 mg/day in Malawi [2, 5], and Uganda [3]. These research cohorts consisted of consecutively enrolled patients with near complete follow-up to 10 weeks. The 2 Malawi sites were later involved in ACTA, and patient management in all 3 cohorts involved members of our group and was similar in all respects other than antifungal therapy to the management of participants in the ACTA trial. In the Malawi cohorts, 10-week mortality was 26/47 [2] and 11/19 [5] while in Uganda it was 13/27 [3], giving a weighted mortality of 53.8% (95% CI: 43.1–64.1). The health outcomes included in the cost-effectiveness analysis were deaths averted and life years saved. The average life expectancy of the additional survivors was estimated conservatively at 18 years [10-12].

We conducted a decision analysis to estimate the incremental cost-effectiveness ratio of adding 5FC to FLU versus FLU monotherapy. We did a probabilistic sensitivity analysis, varying hospital care costs, driven in large part by length of stay, and the mortality estimates in the two arms. In the ACTA cost-effectiveness analysis, mortality rate was the major driver of the incremental cost-effectiveness ratios [7]. Given this, and the current international drive to make 5FC widely available for the

treatment of cryptococcal meningitis [13], a bivariate deterministic sensitivity analyses was performed by varying mortality rate in the FLU monotherapy arm and the cost of 5FC from the currently available price, to explore the changes in the incremental cost-effectiveness ratio. A previous cost-effectiveness analysis [10] used a theoretical price for a generic 5FC tablet of US\$0.44 [14].

## **Ethics**

The ACTA 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 [6]. 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**

### **Costs and health outcomes**

The mean total costs per patient were US\$847 (95% CI: 776-927) for FLU+5FC treatment, and US\$628 (95% CI: 557-709) for FLU monotherapy, thus giving US\$219 (95% CI: 110-329) extra cost for the addition of 5FC to FLU.

The only differences in costs between the two treatments were due to 5FC drug costs and full blood count costs (Supplementary Table S2). The total cost (per patient) for flucytosine was US\$182, making up 21% of the total cost in the oral combination arm. Per patient drug costs for FLU alone was US\$8, making up 1% of the total costs in the FLU monotherapy arm. Hospital costs contributed at least 50% of the total cost in both arms.

The 10 week mortality with FLU+5FC was 35.1% (95%CI 28.9-41.7) and 53.8% (95% CI: 43.1–64.1) with FLU alone. Thus, the risk ratio of FLU+5FC (79/225) versus FLU alone (50/93) was 0.65 (95% CI: 0.50 - 0.85).

### **Cost effectiveness, uncertainty, and sensitivity analyses**

The addition of 5FC to FLU was more costly but more effective than FLU monotherapy (Table 1). At the current 5FC price of \$US1.30 per 500mg tablet, the incremental cost-effectiveness ratio of FLU+5FC versus FLU alone was estimated to be US\$65 (95% CI:28-208) per life year saved.

Figure 1 shows the effect of varying the mortality rate in the FLU arm and the price of 5FC, on the incremental cost-effectiveness ratio. Increasing the fluconazole mortality to 60%, given the ongoing high mortality after 10 weeks seen in fluconazole-treated cohorts [4], reduces the ICER to US\$49 per life year saved. Reducing the price of 5FC to US\$0.60 per 500 mg tablet, the ICER is reduced by nearly half to US\$36 per life year saved. If the cost of 5FC was varied from US\$0.80 to US\$0.40 per 500mg tablet, then the incremental cost-effectiveness ratio would be between US\$44 and US\$28, assuming other parameters were constant.

### **Discussion**

Our analysis demonstrates that adding 5FC to FLU for the treatment of cryptococcal meningitis in Africa is cost effective compared with the current practice of fluconazole

monotherapy. The estimated ICER for FLU+5FC versus FLU alone was only US\$65 per life year saved, even at the current 5FC price. Reducing the current price of 5FC by half, as is expected will be possible [10, 15], makes FLU+5FC even more attractive, with the ICER falling below US\$40 per life year saved. Thus, the oral combination of FLU+5FC will be affordable in many Sub-Saharan African countries. The costs compare favourably with those of other interventions that cost around US\$100 per disability adjusted life year, including treating tuberculosis with first-line drugs and treating malaria with artemisinin-based combination therapy [16].

We have used prospectively collected data on patient level resource use from a large study to estimate CM treatment-specific costs. Outcome data is from the same large trial and from three studies of high dose FLU monotherapy with consecutive enrolment, near complete follow-up, and management practice in line with the ACTA trial. The mortality rates observed with high dose FLU monotherapy were very similar to a prior pooled estimate with use of 800–1200mg FLU (54.9% (95% CI: 46.0 – 63.5))[17]. Further, our results are comparable to those of a previous study by Rajasingham et al that estimated the ICER of FLU+5FC versus FLU alone at US\$53 per quality adjusted life year (QALY), based on a theoretical price of 5FC of US\$0.44 per 500mg tablet [10]. Nevertheless, it is a limitation of the analysis that the mortality rates for fluconazole were derived from separate cohorts, rather than from within the trial. In addition, unit costs were derived from the Zambian study site, meaning that generalization of total costs to other settings must be made with caution.

In this analysis, we assumed equal bed days for patients in the two treatment arms. However, given the poorer efficacy of FLU treatment, admission duration,

readmission and complications could be greater, thus increasing the hospital care cost of patients receiving FLU monotherapy, and reducing the incremental cost between the two treatment options. For example, increasing the number of readmission days to 3 with FLU monotherapy versus 2 with the oral combination, results in a reduction in ICER from US\$65 to US\$51 per life year saved. Also, while our analysis is based on 10 week outcomes, long term follow-up data shows that the survival curve for FLU patients does not plateau after 10 weeks, despite introduction of ART. In a prior cohort, patients kept on dying after 10 weeks such that at 1 year, survival was less than one quarter [4]. Conversely, long term follow-up data from ACTA (Kanyama, Molloy, Harrison, unpublished), confirms our prior experience [17] that with appropriate introduction of ART and more fungicidal induction treatment, survival curves are almost flat after 10 weeks up to 12 months.

This study provides further strong health economic evidence supporting the urgent need to make 5FC widely available to reduce cryptococcal meningitis mortality in resource-limited settings, including those currently using FLU monotherapy, and where even one week of AmB treatment would be difficult to sustain.

### **Author contributions**

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

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Table. Probabilistic cost-effectiveness analyses comparing the trial arms in terms of total health care costs cost per patient and death rate per arm<sup>a</sup>

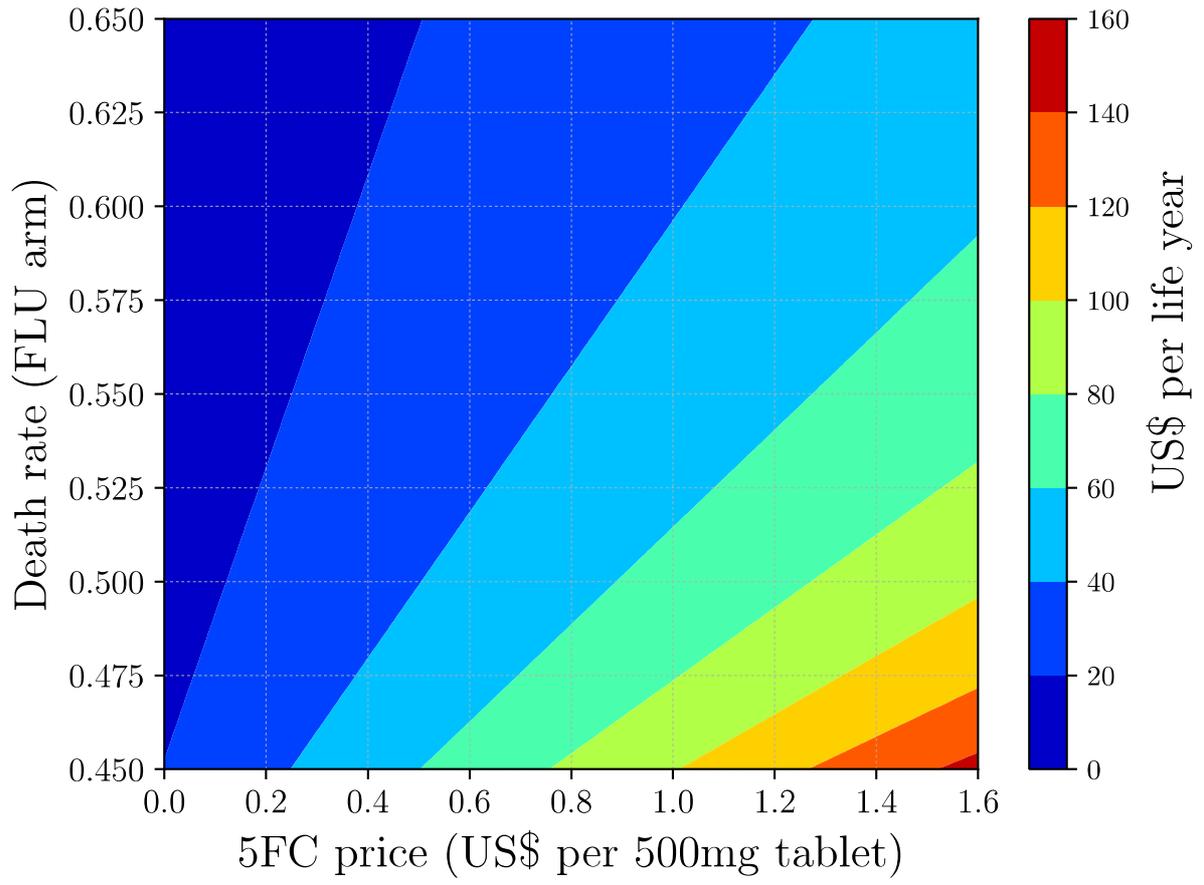
Total costs per patient and death rate (%)			Incremental comparison of 2 weeks of oral FLU + 5FC versus oral FLU monotherapy		
Treatment	Total costs (\$)	Deaths (%)	Incremental costs/patient (\$)	Incremental death (%)	ICER/life year saved
FLU alone	628(557-709)	54(43-64)	reference	reference	
FLU + 5FC	847(776-929)	35(29-42)	219(110-329)	19(6-30)	65(28-208)

<sup>a</sup>Parameters varied in the probabilistic sensitivity analysis are hospital care costs

(both hospitalisation and re-hospitalisation as these constituted at least 50% of the total costs in both arms), and mortality rates in the two arms. To account for variations in hospital care costs we used the standard deviation of the number of bed days during admission, and for mortality we incorporated the 95% confidence intervals.

## Figure Legend

Bivariate deterministic sensitivity analysis showing the impact of 5FC price (values ranging from US\$0 to US\$1.60) and FLU death rate (values ranging from 0.45 to 0.65) on the incremental cost-effectiveness ratio (ICER). All the other parameters were held constant at the base case scenario (Supplementary Table S2).



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