Section 6. 3

Application to move Flucytosine (5FC)to Core List

Application for WHO Model List of Essential Medicines: *Flucytosine (5FC)*

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1. Summary statement of the proposal for inclusion, change or deletion

This is a proposal for inclusion of flucytosine (5FC) as a WHO Essential Medication, essentially moving 5-FC from the *complimentary list* to the *essential list.*

Cryptococcal meningitis is the most common cause of meningitis in adults in sub-Saharan Africa, accounting for 20-25% of AIDS-related mortality [1].

The principal reasons for requesting the inclusion of 5-FC in the WHO essential list are as follows:

1. 2011 WHO rapid advice for cryptococcal treatment recommend 5-FC in conjunction with Amphotericin B as first line induction therapy for cryptococcal meningitis. These recommendations are based on randomized controlled trial evidence which demonstrate that the combination of amphotericin B plus 5-FC provide the greatest survival benefit. (Table 2) Amphotericin alone does not provide as great of a survival benefit as amphotericin plus 5-FC.Where amphotericin B is unavailable, flucytosine plus fluconazole is the preferred induction antifungal regimen [2].
2. Flucytosine is currently unavailable in Africa and Asia where cryptococcal disease burden is greatest [1]. Current cryptococcal meningitis mortality rates with widely available fluconazole monotherapy are unacceptably high (≥60% 10-week mortality). Flucytosine is a simple, off patent molecule that should be used in conjunction with amphotericin or fluconazole, in accordance with

the latest cryptococcal meningitis guidelines, to significantly improve patient outcomes [3].

2. Name of the focal point in WHO submitting or supporting the application

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3. Name of the organizations consulted and/or supporting the application

Centers for Disease Control and Prevention, USA
St. George's University of London, UK
Médecins Sans Frontières
Clinton Health Access Initiative (CHAI)
University of Minnesota, USA
Management Sciences for Health, USA
National Institute for Communicable Diseases, South Africa

4. International Nonproprietary Name (INN, generic name) of the medicine

Flucytosine

5. Formulation proposed for inclusion

Oral

6. International availability

Flucytosine (5-FC) was originally manufactured by Valeant, under the trade name of Ancotil ® (IV) and Ancobon ® (oral). This molecule is no longer under patent however remains unavailable in all low and middle income countries where the need is greatest due to the high burden of cryptococcal meningitis. We believe that the inclusion of 5-FC in the EML will facilitate negotiation with drug manufacturers to increase drug production and access to this life saving medication.

Flucytosine (5-FC)

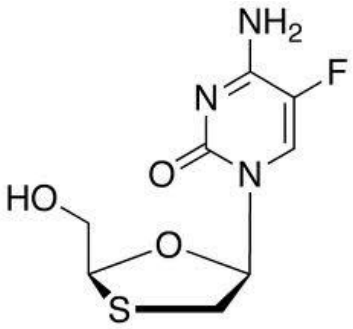
Ancotil®2.5g/250ml solution for infusion
Ancobon®500mg capsules (Valeant, now Medicis Pharmaceutical Corporation)

Flucytosine generic availability is very limited, although the chemical compound is relatively simple.

CAS No: 2022-85-7

Bulk chemical manufacturing occurs worldwide, non-

pharmaceutical
http://www.lookchem.com/cas-202/2022-85-7.html

5-Flucytosine is half of the chemical structure of emtricitabine (Emtriva®), an HIV antiretroviral medicine. 5FC is used in the last chemical synthesis step an input component in emtricitabine manufacturing. Emtricitabine is a one of three medicines in Atripla® the most commonly prescribed HIV therapy in Europe and North America. Thus, 5FC is available as a chemical compound.	Emtricitabine 

7. Whether listing is requested as an individual medicine or a therapeutic group

Individual medicine under EML section **6.3 Antifungal medicines**

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population):

Cryptococcal meningitis is the most common cause of adult meningitis in sub-Saharan Africa [4-6], accounting for 20-25% of AIDS-related mortality in Africa [1]. In meningitis surveillance studies from South Africa, Malawi, and Uganda, cryptococcal meningitis is more common than all causes of bacterial meningitis combined [4-6]. Cryptococcosis primarily occurs among HIV-infected persons living with AIDS, predominantly when CD4 T cell counts are < 100 cells/mcL.

Despite the fact that the combination of amphotericin B plus flucytosine is the most effective therapy for cryptococcal meningitis (with demonstrated survival benefit in randomized clinical trials) flucytosine is currently unavailable in all middle and low income countries. (Table 2, Table 5)

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills):

Flucytosine 100mg/kg/day orally coupled with intravenous amphotericin B deoxycholate dosed at 0.7-1.0 mg/kg/day for 2 weeks is the first-line choice of induction therapy as recommended by the WHO [2], Infectious Disease Society of America [3], and U.S. Department of Health and Human Services [7]. (Table 1) (Figures 1 & 2) Where amphotericin is unavailable, or cannot be monitored safely, treatment guidelines recommend 5-FC 100mg/kg/day in conjunction with high dose fluconazole [2].

Table 1. WHO, IDSA & SA HIV Clinician Society Guidelines for the induction treatment of CM depending on the clinical setting

Clinical setting for treatment of cryptococcal meningitis		**WHO 2011 Rapid Guidelines[2]**	**IDSA 2010 Guidelines [3]**	**South African HIV Clinician Society 2007 guidelines [8]**
AmB	**5FC**			
Accessible Facilities for toxicity management* available	Accessible	AmBd (0.7-1 mg/kg/day) **+** 5-FC (100 mg/kg/day)	AmBd (0.7–1.0 mg/kg/day) + 5-FC (100 mg/kg per day) *or* Liposomal AmB (3–4 mg/kg/day) *or* ABLC (5 mg/kg per day) + 5-FC (100 mg/kg/day)	Not applicable- 5-FC currently unavailable in SA
Accessible	Not accessible	AmBd (0.7-1 mg/kg/day) **+** Fluconazole (800 mg/day)	AmBd (0.7–1.0 mg/kg/day) *or* liposomal AmB (3–4 mg/kg/day) *or* ABLC (5 mg/kg/day) *or* AmBd plus fluconazole	AmBd (1 mg/kg/day) IV For 2 weeks (minimum 1 week)
Accessible Facilities for toxicity management* limited	Not accessible	AmBd (0.7-1 mg/kg/day) For 5-7 day**s** **+**Fluconazole (800 mg/day) For 2 weeks		AmBd (1mg/kg/day) Minimum 1 week
Not accessible	Accessible	Fluconazole (1200 mg/day) **+** 5-FC (100 mg/kg/day) f For $\geq$ 2 weeks	Fluconazole (800 – 1200(favoured) mg/day)**+** 5-FC (100 mg/kg/day orally) For 6 weeks	Not applicable- 5-FC currently unavailable in SA
Not accessible Facilities for toxicity management* not available	Not accessible	Fluconazole (1200 mg/day) For $\geq$2 weeks	Fluconazole (800–2000 mg/day) For 10–12 weeks (Fluconazole 1200 mg/day favoured)	Transfer patient to centre where AmBd available. If not possible, Fluconazole

				(800mg/day) For 4 weeks

All induction CM courses are for 2 weeks' duration, unless stated
*Minimum package of pre-hydration, electrolyte replacement and toxicity monitoring/management available[9]

Figure 1. WHO Rapid Advice: Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children (Dec 2011): Text description
[2] http://www.who.int/hiv/pub/cryptococcal_disease2011/en/

Summary of induction, consolidation and maintenance treatment recommendations and dosage for HIV-infected adults, adolescents and children (See Table 1)

1. Induction phase treatment

For the induction phase of treatment in HIV-infected adults, adolescents and children with cryptococcal disease (meningeal and disseminated non-meningeal), the following two-week anti-fungal regimens are recommended in order of preference.

a. Amphotericin B + flucytosine
[Strong recommendation, high quality of evidence]

b. Amphotericin B + fluconazole
[Strong recommendation, moderate quality of evidence]

c. Amphotericin B short course (5-7 days) + high-dose fluconazole (to complete two weeks of induction) when a minimum package of pre-emptive hydration and electrolyte replacement and toxicity monitoring and management cannot be provided for the full two week induction period.
[Conditional recommendation, low quality of evidence]

d. Fluconazole high dose + flucytosine, when amphotericin B is not available
[Conditional recommendation, low quality of evidence]

e. Fluconazole high dose alone, when amphotericin B is not available
[Conditional recommendation, low quality of evidence]

Figure 2. WHO Rapid Advice: Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents & children (Dec 2011): Table summary

Drugs available	Pre-hydration + electrolyte replacement + toxicity monitoring/ management	Induction phase options[14] (2 weeks)	Consolidation phase options (8 weeks)	Maintenance/ secondary prophylaxis options
Amphotericin B[15] ± flucytosine	Available	**a.** Amphotericin 0.7-1 mg/kg/day + flucytosine 100 mg/kg/day **b.** Amphotericin 0.7-1 mg/kg/day + fluconazole 800 mg/day	Fluconazole 400-800 mg/day	Fluconazole 200 mg daily
Amphotericin B[15]	Not available for full 2 week induction period	Amphotericin 0.7-1 mg/kg/day short course (5-7 days) + fluconazole 800 mg/day (2 weeks)	Fluconazole 800 mg/day	
Amphotericin B not available	Not available	**a.** Fluconazole 1200 mg/day ± flucytosine 100 mg/kg/day **b.** Fluconazole 1200 mg/day alone	Fluconazole 800 mg/day	

10. Summary of comparative effectiveness in a variety of clinical settings

• ***Identification of clinical evidence*** (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

(a) During the WHO cryptococcal guidelines development process a systematic review was performed to identify all relevant clinical trials involving flucytosine for the treatment of cryptococcal meningitis.

(b) In 2012, a systematic review assessed the cost-effectiveness of cryptococcal treatment outcomes in resource-limited settings [10]. In brief, Rajasingham et al performed a MESH search of “Cryptococcal Meningitis” AND “Therapy”, and limited their findings to Humans, Adults, and English language results, to identify 10-week mortality data from trials and cohort studies evaluating treatment outcomes of cryptococcal meningitis induction regimens from 1996 onwards in the antiretroviral therapy (ART) era [10]. This search yielded 33 publications. After manually reviewing abstracts and references, 18 studies were included that presented mortality data for HIV-infected adults from resource-limited settings. Rajasingham et al excluded studies that did not report 10-week mortality, and U.S.-based, and European-based CM studies. The systematic review was limited to resource-constrained settings, as a cost-effectiveness analysis would be most pertinent and generalizable to these settings. From these studies, pooled 10-week mortality estimates were calculated for each of the treatment regimens.

(c) Differences in 10-week survival correspond with the known anti-fungal activities of the various induction treatment regimens as quantified by the clearance of *Cryptococcus neoformans* yeast colony forming units (CFU) per mL of

cerebrospinal fluid (CSF) per day (Δlog_{10} CFU/mL CSF/day) – termed the early fungicidal activity (EFA) [11]. Rhein et al, summarized recent clinical trials that have compared the EFA of various induction treatment regimens. [12]

• ***Summary of available data***

a) Several phase II and phase III randomized controlled trials (RCT) as well as a large prospective cohort study support the use of 5-FC as a second drug in conjunction with either Amphotericin B or high dose fluconazole for the treatment of cryptococcal meningitis [13-18]. Resistance precludes the use of flucytosine monotherapy.

In an important phase III Vietnamese randomized clinical trial (recently presented in Sept 2011, now *In Press*) a survival benefit of amphotericin B deoxycholate with flucytosine (100mg/kg/day) over amphotericin B deoxycholate alone was demonstrated for the first time [19]. In this head-to-head clinical trial, amphotericin B + flucytosine had the best survival (Hazard Ratio = 0.56, P=.01) when compared to amphotericin x4 weeks alone (Hazard Ratio = 1.0 as reference) and a non-statistical benefit over amphotericin +fluconazole 800mg/day x 2 weeks (Hazard Ratio = 0.78, P=.23) or [19]. Two weeks of amphotericin B plus 5-FC thus remains the current gold standard for induction treatment of CM.

b) See Table 2 for summary of 10-week mortality outcome measures for various treatment regimens including those containing flucytosine. The systematic review performed by Rajasingham et al demonstrates that flucytosine added to fluconazole, a purely oral regimen, has superior survival compared to fluconazole alone [10].

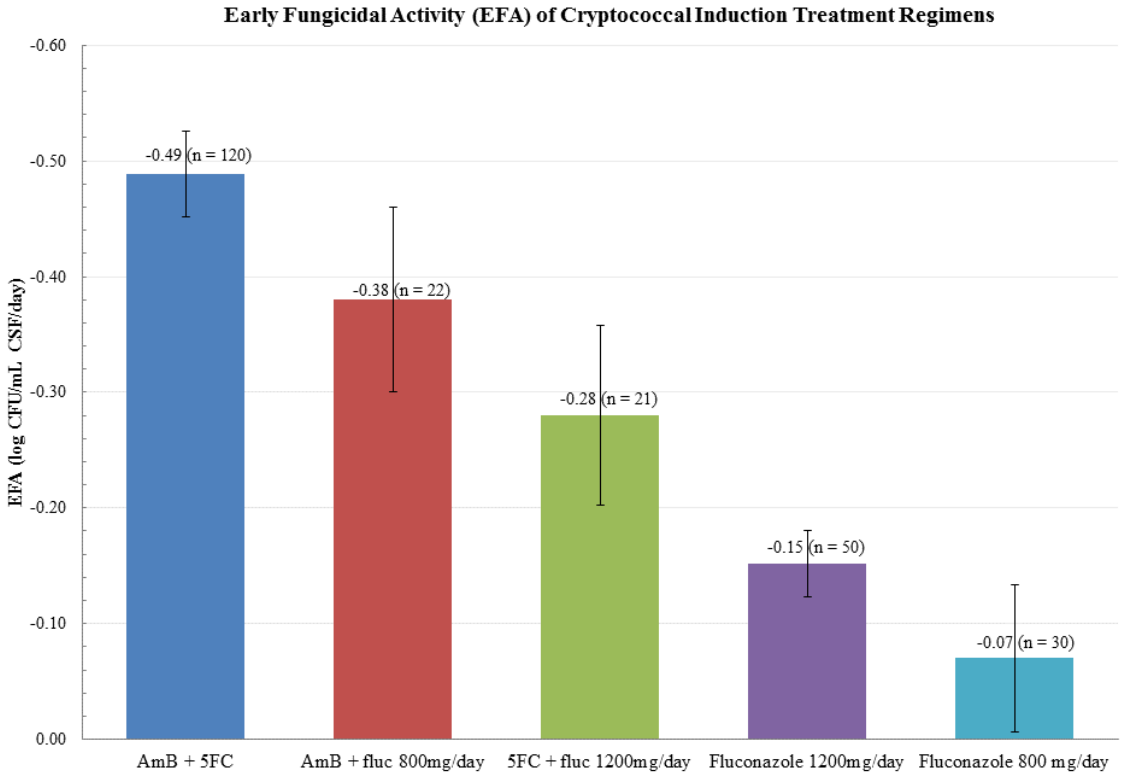
c) See Figure 3 for summary of EFA outcome measures. Data from the review performed by Rhein et al demonstrate that amphotericin coupled with 5FC has the best microbiologic activity. Fluconazole+5FC has nearly twice the rate of fungal clearance as fluconazole alone [12]. For reference, based on a pooled series of Phase II clinical trials, the mean rate of clearance of infection for those who survived at 2 weeks was -0.40 log CFU/ml CSF/day compared to -0.17 log CFU/ml CSF/day in those who died at 2 weeks [11]. At 10 weeks, mean EFA was -0.41 log CFU/ml CSF/day in those who survived compared to -0.27 log CFU/ml CSF/day in those who died.

Table 2. Treatment outcomes in Resource-Limited Settings [10]

Induction Regimen	Induction Duration	10-week Mortality	95% CI	Ref
Fluconazole 800-1200mg	14 days	54.9% (73/133)	46.0-63.5%	[20-23]
Flucytosine + fluconazole 1200mg	14 days	43.5% (20/46)	28.9-58.9%	[23, 24]
Amphotericin + fluconazole 1200mg	5-7 days	26.0% (33/127)	18.6-34.5%	[25-28]
Amphotericin	14 days	34.4% (128/372)	29.6-39.5%	[28-34]
Amphotericin + fluconazole 800mg	14 days	30.0% (61/203)	23.8-36.9%	[19, 33-35
Amphotericin + flucytosine (5FC)	14 days	26.8% (62/231)	21.2-33.0%	[19, 34-37

95% CI = 95% confidence interval for the 10-week mortality

Figure 3. Comparative Early Fungicidal Activity (EFA) of Cryptococcal Induction Treatment Regimens [12]



• ***Summary of available estimates of comparative effectiveness***

Amphotericin and flucytosine (5FC) is the most microbiologically active regimen. In resource-limited settings, where intravenous amphotericin therapy is not available or not-feasible to administer, 5-FC can be safely and effectively paired with high-dose fluconazole(1200 mg/day), as recommended by both IDSA and WHO guidelines [2, 3] Neither amphotericin nor flucytosine are currently considered WHO Essential Medications [38]. Fluconazole, an essential cornerstone of pre-emptive, maintenance and consolidation phases of cryptococcal meningitis treatment is listed as an essential medication. However, induction therapy with fluconazole monotherapy is associated with unacceptably high mortality rates (≥60% 10-week mortality) [10, 20, 22, 23, 27]. Therefore, current treatment guidelines advocate the use of 5-FC as a second drug in conjunction with either amphotericin (where available and where adequate monitoring facilities exist) or high dose fluconazole [2, 3, 7].

11. Summary of comparative evidence on safety

• ***Estimate of total patient exposure to date***

5FC has been used since the late 1960s for systemic candidiasis and cryptococcosis. In clinical settings where it is available, 5-FC is widely used as a second drug in conjunction with amphotericin, in accordance with the latest clinical treatment guidelines [2, 3, 7].

• ***Description of adverse effects/reactions***

The adverse reactions which have occurred during treatment with Ancobon are grouped according to organ system affected.

Cardiovascular: Cardiac arrest, myocardial toxicity, ventricular dysfunction.

Respiratory: Respiratory arrest, chest pain, dyspnea.

Dermatologic: Rash, pruritus, urticaria, photosensitivity.

Gastrointestinal: Nausea, emesis, abdominal pain, diarrhea, anorexia, dry mouth, duodenal ulcer, gastrointestinal hemorrhage, acute hepatic injury with possible fatal outcome in debilitated patients, hepatic dysfunction, jaundice, ulcerative colitis, bilirubin elevation, increased hepatic enzymes.

Genitourinary: Azotemia, creatinine and BUN elevation, crystalluria, renal failure.

Hematologic: Anemia, agranulocytosis, aplastic anemia, eosinophilia, leukopenia, pancytopenia, thrombocytopenia.

Neurologic: Ataxia, hearing loss, headache, paresthesia, parkinsonism, peripheral neuropathy, pyrexia, vertigo, sedation, convulsions.

Psychiatric: Confusion, hallucinations, psychosis.

Miscellaneous: Fatigue, hypoglycemia, hypokalemia, weakness, allergic reactions, Lyell's syndrome.

Frequency of adverse events
Reported 5-FC toxicity is significantly less in recent trials using shorter courses of lower dose 5-FC. In the van der Horst study, there was a 3% rate of drug discontinuation in the first two weeks with two weeks 5-FC, equally split between 202 patients receiving and 179 not receiving 5-FC [15]. Almost all drug discontinuation was clearly amphotericin-related, with no discontinuations due to neutropenia [15]. Similarly in Thailand, two weeks amphotericin plus 5-FC (100 mg/kg/day) was well tolerated with no incidences of grade 4 neutropenia and no drug discontinuations within the two weeks of combination therapy [34].

• Identification of variation in safety due to health systems and patient factors

Pregnancy (Teratogenic Effects. Pregnancy Category C)

Flucytosine was shown to be teratogenic (vertebral fusions) in the rat at doses of 40 mg/kg/day (298 mg/M2/day or 0.051 times the human dose) administered on days 7 to 13 of gestation. At higher doses (700 mg/kg/day; 5208 mg/M2/day or 0.89 times the human dose administered on days 9 to 12 of gestation), cleft lip and palate and micrognathia were reported. Flucytosine was not teratogenic in rabbits up to a dose of 100 mg/kg/day (1423 mg/M2/day or 0.243 times the human dose) administered on days 6 to 18 of gestation. In mice, 400 mg/kg/day of flucytosine (1380 mg/M2/day or 0.236 times the human dose) administered on days 7 to 13 of gestation was associated with a low incidence of cleft palate that was not statistically significant. There are no adequate and well-controlled studies in pregnant women. Flucytosine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Renal impairment

The dose of flucytosine must be carefully adjusted in the context of renal impairment:

Table 3. Flucytosine renal dose adjustment [39]

Creatinine Clearance	**>40mL/min**	**20-40mL/min**	**10-20mL/min**	**<10mL/min**
5-FC dosage	25mg/kg P0 6 hourly	25mg/kg PO 12 hourly	25mg/kg PO 24 hourly	12.5mg/kg PO >24 hourly

• Summary of comparative safety against comparators

Flucytosine (5FC) use was originally limited by toxicity at higher doses (150mg/kg/d); however, clinical trials in cryptococcosis since the 1980s using progressively shorter courses of 5-FC at lower doses (100mg/kg/day) have shown that 5FC can be used safely and effectively in combination with either amphotericin or fluconazole [23, 27].The most important side effect of 5-FC is bone marrow depression, particularly neutropenia. Other side effects include hepatotoxicity, diarrhea, and vomiting. Bone marrow depression and hepatotoxicity are associated with prolonged high serum 5-FC concentrations, generally >100mg/L, and are thought to be 5-FU-mediated.In the era of HIV, and with the use of lower doses of 5-FC (100mg/kg/day) in combination antifungal therapy, phase II and III clinical trials in Africa and Asia have demonstrated that 5-FC can be used safely, without the need for 5-FC level monitoring in the context of cryptococcal meningitis [23, 27, 34]. Renal function must however be monitored carefully, and the dose of 5-FC adjusted according to the renal adjustment table above.

12. Summary of available data on comparative cost and cost-effectiveness

• *Range of costs of the proposed medicine*

Very limited published data exists on flucytosine costs [40]. The international wholesale cost of generic 5FC 500 mg tablet has been previously reported as US$0.44.The NHS tender price at a major UK hospital was GB£0.85 (US$1.33) per 500mg tablet for Ancobon® while oral generic 5FC, manufactured by Sigmapharm currently retails in the US at US$34 per 500mg tablet. There is only one registered U.S. formulation.

• *Comparative cost-effectiveness presented as range of costs per routine outcome*

The cost of cryptococcal care as per WHO guidelines is summarized in Table 4[10], and is based on the range of 2010 international reference medication costs for amphotericin (50 mg vial) (median of US$5.27 (range: US$4.23–US$6.97 in Africa), and fluconazole (200-mg tablet), median of US$0.16 (range: US$0.14–US$0.19 in Africa) [41]. The cost of 5FC was derived from an international wholesale cost of US$0.44 for a generic 500 mg tablet, as cited in [40] .For a 50 kg adult, the total cost of 5FC would be approximately US$4.40/day and US$61.60 for two weeks of induction treatment.

The cost-effectiveness of cryptococcal treatment, comparing the cost of various induction cryptococcal meningitis treatments with expected mean quality adjusted life years (QALY) saved, is summarized in Figure 4.[10]

Table 4. Cost of cryptococcal care (utilizing WHO guidelines) [10]

Induction Regimen	Duration of Induction	Costs					Total Cost of Care
		Medication	3 LPs with Manometers	Hospital Supplies	Lab Costs	Personnel (Uganda)	
Fluconazole 800–1,200 mg	14 d	$8.23 – $12.34	$53.85	$32.63	$36.95	$18.40[a]	$150.06– $154.17
5FC + fluconazole 1,200 mg	14 d	$85.98	$53.85	$32.63	$49.35	$20.74[a]	$242.55
Amphotericin + fluconazole 1,200 mg	7 d	$53.85	$53.85	$54.53	$36.95	$18.40[a]	$217.58
Amphotericin	14 d	$83.02	$53.85	$108.21	$107.35	$41.41	$393.84
Amphotericin + fluconazole 800 mg	14 d	$91.25	$53.85	$108.21	$107.35	$41.41	$402.07
Amphotericin + 5FC	14 d	$156.66	$53.85	$108.21	$107.35	$41.41	$467.48

Figure 4. Cost-effectiveness of comparative cryptococcal meningitis treatment regimens [10]

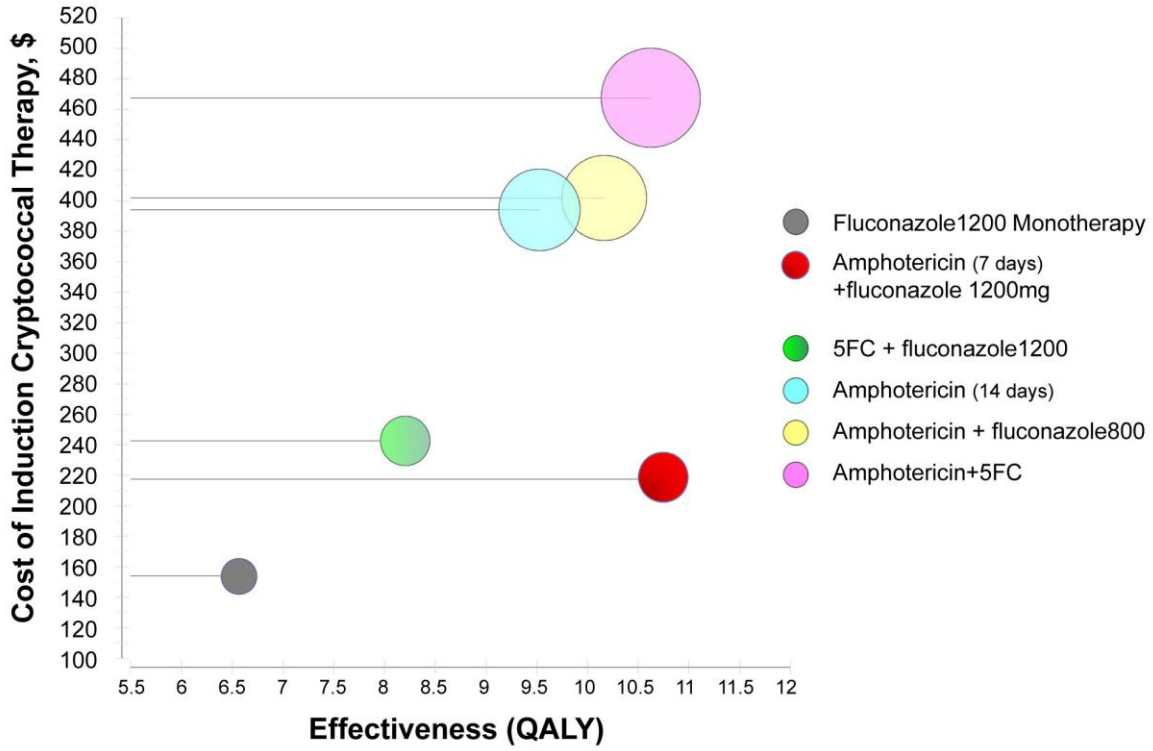


Figure 4 displays the cost of induction therapy for cryptococcal meningitis in resource-limited regions (in US$) versus the effectiveness as measured by QALYs saved per regimen [10]. The radius of the circles represents the standard deviation of the cost estimate. Short-course of 1-week of amphotericin + fluconazole (1200mg/day) regimen has marginally higher cost but significantly greater effectiveness than oral fluconazole-based therapies. However, where amphotericin is not available, the addition of 5FC (100mg/kg/day) to fluconazole has a significant survival benefit over fluconazole alone.

One limitation of the systematic review was that the cost data for flucytosine (5FC) was not very robust. As opposed to fluconazole and amphotericin, 5FC is not available in resource limited settings nor from international wholesalers.

Detailed references on model assumptions can be found in Rajasingham et al. [10]

13. Summary of regulatory status of the medicine

Flucytosine (5FC) was developed in 1957 and has been a generic medication for decades. The originator manufacturer is Meda Pharmaceuticals (France). 5FC is registered in Europe and North America; however, there is only one FDA- approved manufacturer (Sigmapharm (US)). 5-FC is currently unavailable in most countries. 5FC availability in Africa is zero.

Table 5. Summary of 5FC drug registration and availability in Africa

Country	Currently Registered	Available
Cameroon	No	No
Dem. Rep. of Congo	No	No
Ethiopia	No	No

Guinea	No	No
Kenya	No	No
South Africa	Previously	No (Previously)
Sudan	No	No
Swaziland	N/A	No
Tanzania	No	No
Uganda	No	No

Modified from table at: http://tinyurl.com/857zxdf

14. Availability of pharmacopoeial standards

Current WHO: http://apps.who.int/phint/en/p/docf/
U.S. monograph available at: http://www.drugs.com/monograph/flucytosine.html
Brief monograph at: https://online.epocrates.com/u/10a1725/flucytosine

15. Proposed text for the WHO Model Formulary:

Flucytosine	**Capsule:** 250 mg **Infusion:** 2.5 g in 250 ml.

References

1. 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.
2. WHO. Rapid advice: Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Geneva: World Health Organization, **2011**.
3. Perfect JR, Dismukes WE, Dromer F, 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: 291-322.
4. Jarvis JN, Meintjes G, Williams A, Brown Y, Crede T, Harrison TS. Adult meningitis in a setting of high HIV and TB prevalence: findings from 4961 suspected cases. *BMC Infect Dis* **2010**; 10: 67.
5. Cohen DB, Zijlstra EE, Mukaka M, et al. Diagnosis of cryptococcal and tuberculous meningitis in a resource-limited African setting. *Trop Med Int Health* **2010**; 15: 910-7.
6. National Institute for Communicable Diseases. Group for Enteric, Respiratory and Meningeal disease Surveillance in South Africa. GERMS-SA Annual Report 2010. In: Govender N, Quan V, **2010**.
7. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* **2009**; 58: 1-207.
8. McCarthy KM, Meintjes G, Arthington-Skaggs B, et al. Southern African HIV Clinicians Society: Guidelines for the prevention, diagnosis and management of cryptococcal meningitis and disseminated cryptococcosis in HIV-infected patients. *South Afr J HIV Med* **2007**; 28: 25-35.
9. Shelburne SA, 3rd, Darcourt J, White AC, Jr., et al. The role of immune reconstitution inflammatory syndrome in AIDS-related Cryptococcus neoformans disease in the era of highly active antiretroviral therapy. *Clin Infect Dis* **2005**; 40: 1049-52.
10. Rajasingham R, Rolfes MA, Birkenkamp KE, Meya DB, Boulware DR. Cryptococcal meningitis treatment strategies in resource-limited settings: a cost-effectiveness analysis. *PLoS Med* **2012**; 9: e1001316.
11. Bicanic T, Muzoora C, Brouwer AE, et al. Independent association between rate of clearance of infection and clinical outcome of HIV associated cryptococcal meningitis: analysis of a combined cohort of 262 patients. *Clin Infect Dis* **2009**; 49: 702-9.
12. Rhein J, Boulware DR. The prognosis and management of cryptococcal meningitis in HIV infected patients. *Neurobehavioral HIV Med* **2012**; 4: 45-61.
13. Bennett JE, Dismukes WE, Duma RJ, et al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptoccal meningitis. *N Engl J Med* **1979**; 301: 126-31.
14. Dismukes WE, Cloud G, Gallis HA, et al. Treatment of cryptococcal meningitis with combination amphotericin B and flucytosine for four as compared with six weeks. *N Engl J Med* **1987**; 317: 334-41.
15. van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. *N Engl J Med* **1997**; 337: 15-21.

16. Saag MS, Cloud GA, Graybill JR, et al. A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *Clin Infect Dis* **1999**; 28: 291-6.
17. Dromer F, Bernede-Bauduin C, Guillemot D, Lortholary O. Major role for amphotericin B-flucytosine combination in severe cryptococcosis. *PLoS One* **2008**; 3: e2870.
18. Dromer F, Mathoulin-Pelissier S, Launay O, Lortholary O. Determinants of disease presentation and outcome during cryptococcosis: the CryptoA/D study. *PLoS Med* **2007**; 4: e21.
19. Day JN, Chau TTH, Dung NT, et al. Combination antifungal therapy for HIV associated cryptococcal meningitis. Abstract M-1141a. In: Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). Chicago, IL, 2011.
20. Longley N, Muzoora C, Taseera K, et al. Dose response effect of high-dose fluconazole for HIV-associated cryptococcal meningitis in southwestern Uganda. *Clin Infect Dis* **2008**; 47: 1556-61.
21. Kisenge PR, Hawkins AT, Maro VP, et al. Low CD4 count plus coma predicts cryptococcal meningitis in Tanzania. *BMC Infect Dis* **2007**; 7: 39.
22. Wajanga BM, Kalluvya S, Downs JA, Johnson WD, Fitzgerald DW, Peck RN. Universal screening of Tanzanian HIV-infected adult inpatients with the serum cryptococcal antigen to improve diagnosis and reduce mortality: an operational study. *J Int AIDS Soc* **2011**; 14: 48.
23. 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.
24. Mayanja-Kizza H, Oishi K, Mitarai S, et al. Combination therapy with fluconazole and flucytosine for cryptococcal meningitis in Ugandan patients with AIDS. *Clin Infect Dis* **1998**; 26: 1362-6.
25. 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.
26. Muzoora CK, Kabanda T, Ortu G, et al. Short course amphotericin B with high dose fluconazole for HIV-associated cryptococcal meningitis. *J Infect* **2012**; 64: 76-81.
27. Jackson AT, Nussbaum JC, Phulusa J, et al. A phase II randomized controlled trial adding oral flucytosine to high-dose fluconazole, with short-course amphotericin B, for cryptococcal meningitis. *AIDS* **2012**; 26: 1363-70.
28. Tansuphaswadikul S, Maek-a-Nantawat W, Phonrat B, Boonpokbn L, Mctm AG, Pitisuttithum P. Comparison of one week with two week regimens of amphotericin B both followed by fluconazole in the treatment of cryptococcal meningitis among AIDS patients. *J Med Assoc Thai* **2006**; 89: 1677-85.
29. 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.
30. Chang CC, Dorasamy AA, Elliott JH, et al. HIV-infected patients with cryptococcal meningitis who attain CSF sterility pre-cART commencement experience improved outcomes in the first 24 weeks. Abstract 955. Conference on Retroviruses and Opportunistic Infections (CROI). Seattle, WA, **2012**.
31. 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.

32. Boulware DR, Bonham SC, Meya DB, et al. Paucity of initial cerebrospinal fluid inflammation in cryptococcal meningitis is associated with subsequent immune reconstitution inflammatory syndrome. *J Infect Dis* **2010**; 202: 962-70.
33. Pappas PG, Chetchotisakd P, Larsen RA, et al. A phase II randomized trial of amphotericin B alone or combined with fluconazole in the treatment of HIV-associated cryptococcal meningitis. *Clin Infect Dis* **2009**; 48: 1775-83.
34. Brouwer AE, Rajanuwong A, Chierakul W, et al. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. *Lancet* **2004**; 363: 1764-7.
35. Loyse A, Wilson D, Meintjes G, et al. Comparison of the early fungicidal activity of high-dose fluconazole, voriconazole, and flucytosine as second-line drugs given in combination with amphotericin B for the treatment of HIV-associated cryptococcal meningitis. *Clin Infect Dis* **2012**; 54: 121-8.
36. 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: 123-30.
37. Jarvis JN, Meintjes G, Rebe K, et al. Adjunctive interferon-gamma immunotherapy for the treatment of HIV-associated cryptococcal meningitis: a randomized controlled trial. *AIDS* **2012**; 26: 1105-13.
38. WHO. WHO Model List of Essential Medicines, 17th Edition. Available at: http://www.who.int/medicines/publications/essentialmedicines. Accessed May 31, 2012.
39. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of systemic antifungal drugs. *Clin Pharmacokinet* **1983**; 8: 17-42.
40. Bartlett JG, Auwaerter PG, Pham PA. Johns Hopkins ABX Guide: Diagnosis and Treatment of Infectious Disease, Third Edition. **2012**.
41. Management Sciences for Health. International Drug Price Indicator Guide. Available at: http://erc.msh.org/dmpguide. Accessed May 31, 2012.