National Essential Medicines List Pharmacoeconomics and Budget impact analysis
Adult Hospital Level
Component: HIV and AIDS

Date: 30 June 2016
Medication: Flucytosine
Indication: Induction therapy in the treatment of cryptococcal meningitis in HIV patients

1. Introduction

Current treatment of cryptococcal meningitis (CM) in HIV infected patients in South Africa comprises either a combination of amphotericin B+fluconazole or amphotericin B as monotherapy. South African guidelines (1) currently recommend an induction-phase treatment of Amphotericin B (1mg/kg/day IV) + fluconazole (800mg/day PO), however, this is in the absence of availability of flucytosine in South Africa. The WHO guidelines (2011)(2) recommend eitherAmphotericin B (0.7-1 mg/kg/day) + flucytosine (100mg/kg/day) or Amphotericin B (0.7-1 mg/kg/day) + fluconazole (800 mg/day) for the 2 week induction period.

Lack of availability of flucytosine is a common problem, especially in low-middle income countries, however recently an opportunity has arisen whereby flucytosine may be distributed in South Africa by Meda, a local pharmaceutical company. A major concern is around the cost of this medicine as it is likely to be unaffordable at current international prices. To this end a pharmacoeconomics model and budget impact analysis needed to be developed to assess the cost-effectiveness and affordability of including flucytosine on the Essential Medicines List.

2. Model

A decision analysis model was developed with distinct time cycles based on the clinical efficacy outcomes from the trial data; 0-2 weeks, 2-10 weeks, 10-26 weeks, 26 weeks to 12 months, per year thereafter. Three treatment arms were considered based on the 2 week's initiation phase treatment regimens; Amphotericin B plus Flucytosine (Am+5FC), Amphotericin B plus Fluconazole (Am+Flu) and Amphotericin B as monotherapy (Am mono). Following the initiation-phase, all arms followed the same treatment regimens.

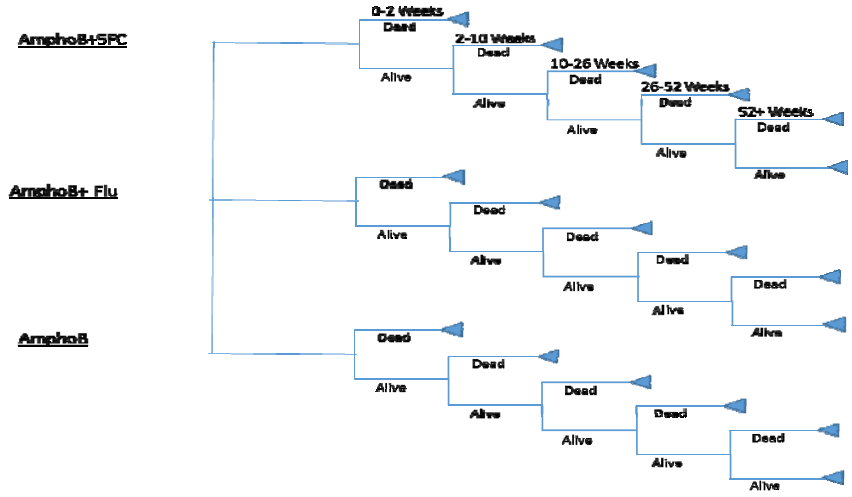

Figure 1. Decision Analysis diagram of model

The budget impact analysis model reflected total drug costs per patient but did not include cost-offsets in the form of reduced hospitalisation or reduction in additional resources as the primary endpoint use was a mortality measure and all three treatment arms assumed similar resource utilisation and a 14 day hospital length-of-stay.

3. Clinical Inputs

The pharmacoeconomic model uses mortality rates as a primary efficacy endpoint to arrive at an incremental cost-effectiveness ratio (ICER) of cost/LYG (Life Years Gained) or cost/QALY (Quality Adjusted Life Years).

The base case analysis used clinical efficacy outcomes of mortality based on network meta-analysis published in 2015 by Campbell et al (3) and a 2013 Vietnamese study by Day et al (4). Data was available for 2 and 10 weeks from Campbell. Survival data at 26 weeks was obtained from the Day studyand additional per annum mortality was used from the Rajasingham cost-effectiveness study and based on a pooled analysis of a South African (n=262), Ugandan (n=1010 and Thai (n=277) cohort (5).

Mortality Rate	2 weeks	10 weeks	26 weeks	1 year
Ampho+5FC	0.094	0.213	0.343	0.35
Ampho+Flu	0.149	0.27	0.450	0.34
Ampho	0.099	0.197	0.535	0.42

Table 1. Survival data based on mortality rates for model. Green blocks = data from Campbel et al, Blue blocks = data from Day et al, Yellow blocks = data from Rajasingham et al

Rajasingham and other publications assumed that all patients with CM who were alive would accrue life years adjusted by a post-treatment utility decrement of 5%. However, the average utility for a well HIV patient is unlikely to be 0.95. A review of quality of life measures in well HIV patients on ARVs showed a range of 0.11 to 0.17 adjusted reduction in utility values depending on the HQoL measures used (6)(7) . In South Africa, a review of studies on the HRQoL values for patients with HIV suggested that the wide range of values from 0.5-0.8 revealed a limitation in research however the EQ5D was considered to be an adequate tool for measurement (8). In this model a disutility of 0.1 was selected with a range from 0.05 to 0.2. A utility of 0.5 was selected for the initial 2 weeks period

of illness and treatment, thereafter patients were assumed to revert to the utility of well patients with HIV.

Life expectancy of 25 years for an HIV-infected patient at 35 years of age who is receiving ART was based on estimates from a recent South African collaborative study (9) with a weighted average of CD4 counts and ratio of male:female demographics.

4. Costs

The study perspective was that of a third party payer, in this instance the South African Government, and therefore only direct costs were considered.

Costs of medicines were based on the Master Price Catalogue March 2016 (fluconazole), Single Exit Price database 3 May 2016 (amphotericin B) and a proposed price of R3 092.36 (500mg x 100) from the manufacturer.

The base-case treatment regimen chosen was for a 2 week induction-phase, 8 weeks consolidation phase and up to 1 year maintenance phase.

The total medicine cost, including infusion fees and monitoring are presented inTable 2.

Ampho + 5FC

Medicine costs **Treatment duration / phase**		**Dose**	**Number of days**	**Cost per phase**	**Total cost**
Initial phase	Amphotericin	1mg/kg daily	14	81.20	
	Infusion Fee	daily	14	832.76	
	Flucytosine	100mg/kg daily	14	6061.03	
Consolidation phase	Fluconazole	400mg daily	56	106.88	
Maintenance phase	Fluconazole	200mg daily	300	286.29	
Monitoring costs	Full Blood Count	twice weekly	2	100.32	**7468.47**

Ampho + Flu

Medicine costs **Treatment duration / phase**		**Dose**	**Number of days**	**Cost per phase**	**Total cost**
Initial phase	Amphotericin	1mg/kg daily	14	81.20	
	Infusion Fee	daily	14	832.76	
	Fluconazole	400mg bd	14	53.44	
Consolidation phase	Fluconazole	400mg daily	56	106.88	
Maintenance phase	Fluconazole	200mg daily	300	286.29	**1360.56**

Ampho

Medicine costs **Treatment duration / phase**		**Dose**	**Number of days**	**Cost per phase**	**Total cost**
Initial phase	Amphotericin	1mg/kg daily	14	81.20	
	Infusion Fee	daily	14	832.76	
Consolidation phase	Fluconazole	400mg daily	56	106.88	
Maintenance phase	Fluconazole	200mg daily	300	286.29	**1307.12**

Table 2. Total medicine costs for each treatment arm

Costs from the Meda study (submitted to NDoH, unpublished) for Infusion Fees (R800 per day) and Hospital Days (R2 000 per day) were very high. Based on local costing data from the public sector, infusion fees were calculated to be R59.48 per day and a hospital stay in a level 2 facility general ward was R478 per day (inclusive of medical practitioner visit) (10). The infusion fee amount in this study was similar to that published in Rajasingham et al (5) where the hospital supply costs were $108 for 2 weeks in 2012. Exchange rate and CPI inflation adjustment to 2015 brings this to R73.41 per day for 2015.

Discounting was carried out at 5% as per the current South African Pharmacoeconomic Guidelines. Since the costs were incurred in the first 10 weeks, these were not discounted and in currently published cost-effectiveness studies no discounting was used at all based on the rationale that the benefits and costs were accrued immediately within the first 2-10 weeks of therapy. A sensitivity analysis was carried out to determine the impact of including discounting the benefits (ie QALY's gained as they continued to accrue over the lifespan of the patient.

5. Base-case Results

The discounted and undiscounted Cost/LYG and Cost/QALY for the base-case variables in the model are presented in Table 3

Undiscounted

	LYG	QALY	Cost
Am+5FC	7.9252	6.947	7 754.75
Am+Flu	5.8498	5.084	1 646.85
Am Mono	5.2386	4.497	1 593.41

vs Am+5FC	**LYG**	**QALY**	**Cost**	**ICER (R/LYG)**	**ICER (R/QALY)**
Am+Flu	2.0753	1.8626	6 107.9056	2 943.10	3 279.22
Am Mono	2.6866	2.4505	6 161.3456	2 293.38	2 514.32
vs Am+Flu				**ICER (R/LYG)**	**ICER (R/QALY)**
Am+5FC	2.0753	1.8626	6 107.91	2 943.10	3 279.22
Am Mono	0.6112	0.5879	53.44	87.43	90.90

Discounted

	LYG	QALY	Cost
Am+5FC	5.2151	4.508	7 754.75
Am+Flu	3.8719	3.304	1 646.85
Am Mono	3.5021	2.934	1 593.41

vs Am+5FC	**LYG**	**QALY**	**Cost**	**ICER (R/LYG)**	**ICER (R/QALY)**
Am+Flu	1.3432	1.2037	6 107.9056	4 547.24	5 074.27
Am Mono	1.7130	1.5743	6 161.3456	3 596.78	3 913.71
vs Am+Flu				**ICER (R/LYG)**	**ICER (R/QALY)**
Am+5FC	1.3432	1.2037	6 107.91	4 547.24	5 074.27
Am Mono	0.3698	0.3706	53.44	144.51	144.20

Table 3. Incremental cost-effectiveness ratios for undiscounted and discounted base-case analysis

6. Assumptions and Uncertainty

A number of assumptions were made and therefore sensitivity analysis was used to test the uncertainty of these assumptionTable 4.

Life expectancy in patients surviving to 1 year was assumed to be an additional 24 years with a range of 18-33 years. Patients who died in the 2 weeks of initiation treatment were credited with 1 week of life. The mid-points of 6 weeks and 18 weeks were chosen for those who died between 2 and 10

weeks and those who died between 10 and 26 weeks. Patients who were still alive at 26 weeks were assumed to survive to the end of 1 year and accrue full life expectancy thereafter. Changing the life expectancy in the first year did not impact the model outcomes substantially. Reducing life expectancy to 18 years increased the ICER of Am+5FC to R4 542.14/QALY vs Am+Flu

It is reasonable to assume that patients who recover fully from CM are no worse off than HIV patients who have never contracted CM. The utility measures in the Meda model were based on the Rajasingham study. A range of utilities was tested to assess the impact on the outcomes.

The average weight of patient in the Meda model was 50kg. Generally average weight of a standard patient is set at 70kg. Given that in the Day et al trial over 80% of the trial population was male (weight was not reported), it would be reasonable to assume a weight of 70kg. In the Brouwer trial, the mean weight of the patients was 47kg, however 40% of the population was female.

All patients would be treated in-hospital for 14 days regardless of which treatment option they undertake, therefore there is no incremental difference in hospital cost between treatment arms. Likewise, patients will receive similar laboratory monitoring and supportive i/v fluids in each arm (e.g. 3 lumbar punctures, blood counts, creatinine, sodium and potassium). The only incremental cost was in the flucytosine arm whereby an additional 2 full blood counts were considered. Increasing this to 2 FBCs per week (ie 4 in the initiation phase) increased the ICER to R3333.08/QALY vs Am+Flu

The treatment regimen of the Vietnamese study for the Ampho B arm was for 28 days monotherapy followed by fluconazole for 6 weeks. This would have an impact on the hospitalisation costs, increasing the Ampho medicine total cost to R2 480.64 and thereby reducing the ICER vs Am+5FC to R2152.26/QALY

There is considerable heterogeneity in dosing in the clinical trials, especially with the amphotericin B and fluconazole. The doses range from 0.7-1mg/kg for amphotericin B and from 400mg-1200mg daily for the initiation phase of fluconazole and 400mg-800mg daily for the follow-on phase.

If an assumption is made that there is no statistically significant difference in mortality between the amphotericin B+flucytosine and amphotericin B+fluconazole arms and the mortality rate is fixed for both arms at the amphotericin B+flucytosine mortality outcomes, then amphotericin B+fluconazole becomes dominant (ie same benefit, less cost).

Variable	Am+Flu vs Am+5FC	Am mono vs Am+5FC	Base case Reference value
Base Case ICER (R/QALY)	3 279.22	2 514.32	
Mortality rates			
Day et al for 14 and 70 days	4 440.53	1 938.54	Campbell et al
1 year mortality at 45% for all	3 856.62	3 755.50	Rajasingham et al
Assuming NS in mortality			
Day et al for 5FC at 14, 70 and 128 days	**Dominant**	1 938.54	Campbell et al
Utility for well_CM (0.85)	3 472.00	2 662.21	Utility for well_CM (0.9)
Utility for well_CM (0.95)	3 106.72	2 381.99	Utility for well_CM (0.9)
Life Expectancy			
2-10 weeks (2)	3 290.44	2 513.57	2-10 weeks (6 weeks)
2-10 weeks (10)	3 268.07	2 515.06	
10-26 weeks (10)	3 310.34	2 533.21	10-26 weeks (18 weeks)
10-26 weeks (26)	3 248.68	2 495.71	
26-52 weeks (26)	3 279.22	2 514.32	26-52 weeks (26)
26-52 weeks (52)	3 215.36	2 464.84	
LE 18 years	4 542.14	3 497.14	LE 25 years
LE 33 years	2 488.47	1 903.08	
Discount rate 5%	5 074.27	3 913.71	Discount rate 0%
Discount rate 3%	4 214.47	3 241.36	
Dose and Duration of Treatment			
Ampho Induction monotherapy for 28 days based on Day et al	2 152.26		Ampho B for 14 days
Fluconazole consolidation phase 600mg daily	3 264.87	136.35	Fluconazole 400mg
Costs			
Amphotericin B SEP-25%	3 279.22	2 514.32	
Amphotericin B SEP-50%	3 279.22	2 514.32	
Fluconazole +50%	3 250.53	3 293.56	
Fluconazole -50%	2 514.32	2 514.32	
Flucytosine -25% SEP	2 465.71	1 895.97	
Flucytosine -50% SEP	1 652.19	1 277.63	
Flucytosine -75% SEP	838.68	659.28	
FBC Monitoring x 4 (2 x week)	3 333.08	2 555.26	FBC Monitoring x 2 (1 x week)

Table 4. One-way sensitivity analysis of variables in the model

7. Budget Impact Analysis

The budget impact analysis was based on 5 967 061 HIV infected patients in 2015 (11) with a CM prevalence of 100: 100 000 based on confirmed cases of CM from the GERMS 2014 report (12). Past trends seem to suggest that cases of CM may be decreasing year on year and therefore a constant number of cases was used for 2017 to 2020. Costs of treatment were adjusted annually using a predicted CPI of 5%. It was assumed that not every patient would access flucytosine in 2016 and therefore an update of 60% was selected for the base case, increasing to 80% uptake by 2020 (Table 5).

	2 016	2017	2018	2019	2020
Eligible patients	5 967	6000	6000	6000	6000
Current Cost					
Ampho B mono	7 799 671	8 234 863	8 646 606	9 078 936	9 532 883
Ampho B + Fluc	8 118 551	8 571 535	9 000 112	9 450 117	9 922 623
Add Flucytosine	**2 016**	**2017**	**2018**	**2019**	**2020**
% Uptake	60%	70%	80%	80%	80%
AmB+5FC	26 738 878	32 935 938	39 523 126	41 499 282	43 574 246
AmB+Flu	3 247 420	2 571 460	1 800 022	1 890 023	1 984 525
AmB mono	3 119 869	2 470 459	1 729 321	1 815 787	1 906 577
Incremental vs Am+Flu	23 491 457	30 364 478	37 723 103	39 609 259	41 589 722
Incremental vs Am m	23 619 009	30 465 479	37 793 805	39 683 495	41 667 670
Incremental Am+flu vs Am m	318 880	336 672	353 506	371 181	389 740

Table 5. Budget Impact Analysis of introducing Flucytosine to the CM treatment regimen

Since there are no additional savings accrued from use of Am+5FC, only the medicines and related administration costs were used in the incremental budget impact analysis.

8. Discussion

Most cost-effectiveness analyses have used data based on the recent Vietnamese study by Day et al (4) where a statistically significant difference in mortality was shown between amphotericin B+flucytosine vs amphotericin B alone at 70 and 128 days but not at 14 days. No statistically significant difference was seen between amphotericin B+flucytosine and amphotericin B+fluconazole at any of the time points.This lack of mortality benefit is further reflected in 2 recent meta-analyses of the use of flucytosine as induction therapy in the treatment of CM in HIV infected patients showed no statistically significant difference in mortality between groups treated with either amphotericin B+flucytosine or fluconazole+flucytosine compared to amphotericin B alone or fluconazole alone either at 2 weeks or 10 weeks (13) (3). In another meta-analysis Yao et al (2014) (14) found a statistically significant reduction in mortality between Am+5FC and Am+Flu at 2 weeks but not at 3 months. It should be noted that the dose regimens in the Day study differed and the patient population had higher rate of impairment due to CM than in other studies

Therefore the low cost-effectiveness ratio in this study and other published cost-effectiveness studies is based on the assumption that there *is a* difference between the treatment arms in terms of mortality reduction. However, if this assumption is not made, then the amphotericin B+fluconazole treatment option is dominant and becomes the most cost-effective option.

The difference in infusion fee and hospital costs in the Meda study compared to this study is only relevant in the context of the budget impact analysis as there is no incremental difference between these costs in the treatments arms for the cost-effectiveness analysis.

Even when the benefits (QALYs and LYG) accrued over time were discounted, this did not impact the ICER substantially although the model was sensitive to a discount rate.

The cost-effectiveness study by Merry et al (15), looked at 3 similar treatment strategies but based on US costings. The two most important cost differences were that of flucytosine at around $2000 per day and the use of liposomal amphotericin B ($14 120 for 2 weeks) which is considerably more expensive than amphotericin B ($713.85 for 2 weeks).

9. Conclusion

The health economics model is based on actual mortality rates from the various clinical trials and meta-analyses and the base case does not take into consideration whether the outcomes are statistically significantly different in each of the treatment arms. This returns a favourable cost-effectiveness outcome (<R5000/QALY). If a cost minimization approach is taken, ie. there is no significant difference in mortality in the outcomes comparing Am+5FC and Am+Flu, then the model outcomes change and Am+Flu becomes dominant (ie same benefit, lower cost). The Am+5FC treatment arm is still cost effective against Am mono with an ICER <R5000/QALY based on evidence of a statistically significant reduction in mortality.

Improvements in CSF clearance rates are evident but this has not been shown to reduce resource utilization or improve clinical outcomes such as survival rate or downstream complications.

The cost of flucytosine at the current proposed price is nearly 6 fold higher than current treatment options (Am+Flu or Am mono) and this has a significant impact on the incremental budget analysis. Given the lack of statistically significant outcomes in mortality, flucytosine should ideally be priced similarly to fluconazole.

Further research is required to better understand actual resource utilization differences between the treatment arms in the South African setting and measuring clinical outcomes in a clinical trial or registry setting would better inform future models.

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