Cost-effectiveness and budget impact of flucytosine as induction therapy in the treatment of cryptococcal meningitis in HIV-infected adults in South Africa

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Abstract
Background Cryptococcal meningitis in HIV-infected patients in sub-Saharan Africa accounts for three-quarters of the global cases and 135 000 deaths per annum. Current treatment includes the use of fluconazole and amphotericin B. Recent evidence has shown that the synergistic use of flucytosine improves efficacy and reduces toxicity, however affordability and availability has hampered access to flucytosine in many countries. This study investigated the evidence and cost implications of introducing flucytosine as induction therapy for cryptococcal meningitis in HIV-infected adults in South Africa.

Methods A decision analytic cost-effectiveness and budget impact model was developed based on survival estimates from the ACTA trial and local costs for flucytosine as induction therapy in HIV-infected adults with cryptococcal meningitis in a public sector setting in South Africa. The model considered four treatment arms: (a) standard of care; 2-week course of amphotericin B/fluconazole (2wk AmBd/Flu), (b) 2-week course of amphotericin B/flucytosine (2wk AmBd/5FC), (c) short course; 1-week course amphotericin B/flucytosine (1wk AmBd/5FC) and (d) oral course; 2-week oral fluconazole/flucytosine (oral). A sensitivity analysis was conducted on key variables.

Results The highest total treatment costs were in the 2-week AmBd/5FC arm followed by the 2-week oral regimen, then the 1-week AmBd/5FC with the lowest cost in the standard of care arm. Compared to standard of care the 1-week flucytosine course is most cost-effective at USD31/QALY, followed by the oral 2-week course at USD155/QALY and the 2-week flucytosine course at USD568/QALY. The budget impact analysis shows that the 1-week course has the lowest incremental cost, followed by the oral course and then the 2-week flucytosine course compared to what is currently spent on standard of care. Sensitivity analyses suggest that the model is most sensitive to the price of flucytosine and hospital costs, particularly length of stay.

Conclusions The addition of flucytosine as induction therapy for the treatment of cryptococcal meningitis in patients infected with HIV is cost-effective regardless of whether it is used as a 1-week, 2-week or oral regimen. Savings could be achieved with early discharge of patients as well as a reduction in the price of flucytosine.
Background
Cryptococcal infection is the most common cause of meningitis in adults living with HIV in sub-Saharan Africa. Cryptococcal meningitis (CM) is a serious opportunistic infection, which mainly affects persons with severe immunodeficiency. Most cases are observed in patients with CD4 T lymphocyte (CD4) cell counts < 100 cells/µL. In 2014, an estimated 280,000 people were reported to be positive for serum cryptococcal antigen globally and 220,000 new cases of cryptococcal meningitis occurred, of which sub-Saharan Africa contributed three-quarters of the cases and 135,000 deaths (1). In South Africa, the number of cases of laboratory-diagnosed CM fell from 7,140 in 2016 to 6,636 in 2017 but the in-hospital case fatality ratio remained unchanged (2).
Generally, cryptococcal meningitis in HIV-infected patients in South Africa is treated initially with intravenous amphotericin B either alone or in combination with oral fluconazole (3). Fluconazole and amphotericin B have been the mainstay of treatment for many years, however recent evidence has shown that the synergistic use of flucytosine improves efficacy and reduces toxicity (4). The World Health Organization (WHO) has updated its guideline to recommend a combination induction phase of one week of intravenous amphotericin B and oral 5-flucytosine or, as an alternative, two weeks of oral flucytosine and fluconazole (5).
Lack of availability and access to 5-flucytosine is a common problem, especially in low-middle income countries. Also, the current international price renders it unaffordable in such countries (4)(6). In South Africa, flucytosine is not currently registered by the South African Health Products Regulatory Authority (SAPHRA) and therefore is only available on a named-patient basis under Sect. 21 of the South African Medicines and Related Substances Act of 1965, as amended (7). In anticipation of the registration of flucytosine, the Southern African HIV Clinicians Society recently released an updated guideline for the management of cryptococcal disease in PLHIV, which includes a recommendation for 1-week amphotericin B and flucytosine as induction therapy (8).
Findings from the Advancing Cryptococcal Meningitis Treatment for Africa (ACTA) trial (9) and a recent updated Cochrane Review (10) prompted an appraisal by the National Essential Medicines List Committee of the current treatment regimens used in South Africa including an updated cost-
effectiveness and budget impact analysis (11). The aim was to review the evidence and cost implications of introducing flucytosine as induction therapy for cryptococcal meningitis in HIV-infected adults in a public sector setting in South Africa. We present the key findings.

Methods

A decision analytic model was developed based on survival estimates from the ACTA trial, a randomised controlled trial of flucytosine as induction therapy in HIV-infected adults with cryptococcal meningitis. The details of this study are available elsewhere (9). Briefly, the study randomised HIV-infected adults with cryptococcal meningitis to one of five arms. The first was an entirely oral regimen of fluconazole 1,200 mg daily with flucytosine 100 mg per kilogram daily for 2 weeks. This was compared to two regimens of one week of amphotericin B with two weeks of either flucytosine or fluconazole and two further regimens of 2 weeks of amphotericin B with two weeks of either flucytosine or fluconazole. After completing induction treatment, all the patients received fluconazole consolidation therapy (800 mg daily until initiation of antiretroviral therapy, then 400 mg daily until 10 weeks and 200 mg daily thereafter). Mortality rates were compared at 2, 4, and 10 weeks. The model was built in Microsoft Excel (2016). The costs and outcomes from the model were used to arrive at an incremental cost-effectiveness ratio (ICER) of cost/LYG (Life Years Gained) or cost/QALY (Quality Adjusted Life Years). In order to assess the impact of uncertainty in the parameters used in the model, a deterministic univariate sensitivity analysis was conducted on key input parameters.

Population and setting

The population of interest in this analysis were HIV-infected adults presenting with cryptococcal meningitis to a public health facility in South Africa. In general, these patients are treated at either a secondary (district or regional hospital) or tertiary and quaternary (specialist or teaching hospital) facility. Patients are usually treated in a general ward rather than an ICU or high-care setting.

Study perspective

The study perspective was that of a provider, in this instance the South African Government, and therefore costs and outcomes were considered from the viewpoint of the public healthcare system.

Interventions
The decision analytic model considered four treatment arms: (a) standard of care; 2-week course of amphotericin B/fluconazole (2wk AmBd/Flu), (b) 2 week course of amphotericin B/flucytosine (2wk AmBd/5FC), (c) short course; 1-week course amphotericin B/flucytosine (1wk AmBd/5FC) and (d) oral course; 2-week oral fluconazole/flucytosine (oral). An analysis was not conducted for the 1-week course compared to the 2-week course of amphotericin B/fluconazole because the mortality outcomes were poorer for the 1-week course than standard of care (SC).

**Time horizon**

The time horizon of 25 years for this model was based on the average life expectancy of an HIV-infected patient at 35 years of age who is receiving ART from estimates from a recent South African collaborative study with a weighted average of CD4 counts and ratio of male: female demographics (12). A sensitivity analysis was conducted to determine the impact of varying the time horizon.

**Discount rate**

A discount rate of 5%, based on the South African Pharmacoeconomic Guidelines (13) was used for the outcomes but not for the costs as they only incurred in the first year of the analysis.

**Clinical and health outcomes**

The model uses mortality rates from the full ACTA trial at at 2 and 10 weeks (8) and 6 and 12 month mortality rates from the Malawian long-term outcome ACTA study (14). An average annual mortality rate for both men and women aged 35-39 years living with HIV in South Africa was determined from the Institute for Health Metrics and Evaluation (IHME) data tool based on the Global, regional, and national age-sex specific mortality tables for HIV/AIDS (1980-2017) of the Global Burden of Disease study (http://ghdx.healthdata.org/gbd-results-tool) (15)

Utilities were obtained from the Merry et al cost-effectiveness study and a sensitivity analysis on these was conducted (16).

**Resource use and costs**

All costs were determined for 2018. If necessary, prices or tariffs from previous years were adjusted by average annual Consumer Price Index to bring them up to 2018 prices. All costs are presented in US dollars (USD) based on an average South African Rand to US dollar exchange rate for 2018
(Average R13.25) (Table 1) (17).

Table 1. Model input parameters
| Parameter                          | Value  | Reference |
|-----------------------------------|--------|-----------|
| **Mortality rates**               |        |           |
| Mortality rates at 2 weeks        |        | (9)       |
| 1-week AmBd/5FC                  | 0.115  |           |
| 2-week AmBd/5FC                  | 0.209  |           |
| 2-week AmBd/Flu (SC)             | 0.219  |           |
| Oral 5FC/Flu                     | 0.182  |           |
| Mortality rates at 10 weeks       |        | (9)       |
| 1-week AmBd/5FC                  | 0.239  |           |
| 2-week AmBd/5FC                  | 0.383  |           |
| 2-week AmBd/Flu (SC)             | 0.412  |           |
| Oral 5FC/Flu                     | 0.351  |           |
| Mortality rates at 6 months       |        | (13)      |
| 1-week AmBd/5FC 2-week AmBd/5FC  | 0.275  |           |
| 2-week AmBd/Flu (SC)             | 0.459  |           |
| Oral 5FC/Flu                     | 0.472  |           |
|                                |        |           |
| Mortality rates at 12 months      |        | (13)      |
| 1 week AmBd/5FC                  | 0.275  |           |
| 2 week AmBd/5FC                  | 0.459  |           |
| 2 week AmBd/Flu (SC)             | 0.500  |           |
| Oral 5FC/Flu                     | 0.440  |           |
| Mortality rate per annum (year 2 onwards) | 0.65% | (15)      |
| **Utilities**                     |        |           |
| Well with HIV                     | 0.95   | (25)      |
| Ill with CM (induction)           | 0.5    | (25)      |
| Well with CM (maintenance)        | 0.8    | (25)      |
| **Medicine costs (per dose)**     | USD    |           |
| Amphotericin B Deoxycholate (50mg) | 0.63  | (18)      |
| Fluconazole (200mg)               | 0.13   | (18)      |
| Flucytosine (500mg)               | 34.02  | (pc)*     |
| Saline 0.9% 1 l                   | 0.62   | (18)      |
| Potassium chloride inj (15% in 10ml) | 0.13  | (18)      |
| Potassium tablets 600mg           | 0.08   | (18)      |
| Magnesium tablets 250mg           | 0.02   | (18)      |
| Flucloxacillin (50mg)             | 0.04   | (18)      |
| Ceftriaxone 1g vial               | 0.44   | (18)      |
| Ampicillin 500mg vial             | 12.14  | (18)      |
| Ciprofloxacin 400mg vial          | 2.76   | (18)      |
| **Infusion fee per day**          | 15.25  | (20)      |
| **Hospital cost per day**         | 85.06  | (20)      |
| **Laboratory monitoring**         |        |           |
| Serum potassium                   | 2.17   | (19)      |
| Serum creatinine                  | 2.17   | (19)      |
| Serum magnesium                   | 2.17   | (19)      |
| Haemoglobin                       | 4.38   | (19)      |
| Full blood count                  | 4.14   | (19)      |
| Blood draw                        | 2.79   | (19)      |
| **Lumbar puncture**               |        |           |
| Diagnostic                        | 60.75  | (19)(20)  |
| Therapeutic                       | 46.02  | (19)(20)  |
| Blood transfusion                 | 170    | (21)      |

*pc: personal communication on buy-out price in Western Cape
Medicine prices were sourced from the public sector Master Procurement Catalogue for September 2018 (17). The price of flucytosine was obtained from a quote for named-patient use in Western Cape, South Africa (National Department of Health communication on file, T Leong 2019). Pre-emptive hydration and electrolyte supplementation were included as recommended in the WHO guidelines (5) and as per the ACTA trial (9). Laboratory costs were obtained from the NHLS State Price List 2017 (19) and lumbar puncture costs were determined either as a diagnostic cost (including rapid antigen assay and culture) or a therapeutic cost (to relieve raised intracranial pressure). The utilisation of laboratory tests was based on the WHO guidelines of twice weekly monitoring of potassium, magnesium and creatinine, weekly haemoglobin monitoring and full blood count for flucytosine monitoring (twice weekly for duration of treatment).

Base-line hospital costs were determined for a Level 2 facility with an in-patient stay of 17 days as per the ACTA trial. This took into consideration additional length of stay in a proportion of patients due to adverse drug reactions (ADRs) or failure to respond to treatment. ADR costs incorporated the costs of managing anaemia and neutropenia. Treatment of anaemia included the cost of whole blood, administration sets and a delivery fee. The utilisation rate of antibiotics to treat neutropenia was taken from the Chen et al study although only antibiotics that are available in South Africa on the EML were included (22).

**Budget Impact Analysis**

The budget impact analysis was based on 7,497,774 HIV-infected patients in 2018 (23) with a CM prevalence of 93/100,000 population based on confirmed cases of CM from the GERMS 2017 report (2). Past trends seem to suggest that cases of CM may be decreasing year on year. It was assumed that not every patient would access flucytosine in 2018 and therefore an uptake of 60% was selected for the base case. The results of the BIA were based on absolute total costs per patient in the first year (i.e. assuming all patients lived the full year) as well as proportional total costs per patient in the first year (i.e. taking into consideration the probability of patients dying, thus not requiring further treatment).

The cost inputs were the same as those used in the cost-effectiveness analysis.
Assumptions

For managing relapses or recurrences, the WHO Guidelines recommend restarting the induction phase as per the initial recommendations. This model did not specifically include relapses or recurrences; however, these were included in the total count of cases of CM per year and assumed to have similar costs to first infections. Although paradoxical cryptococcal immune reconstitution inflammatory syndrome does occur with an estimated frequency of 10-50% (24) in patients initiating ART in all the treatment regimens and this condition is associated with a high mortality, it is assumed that this is already included in the overall mortality rate attributed to CM as per the outcomes based on the clinical trial data.

It was assumed that patients had one diagnostic LP and one therapeutic LP regardless of which regimen they were treated with. In the ACTA trial patients received on average 3 LPs, at baseline and on days 7 and 14, however this was conducted under clinical trial conditions and the WHO guidelines do not recommend routine follow up LPs in resource limited countries (4) A sensitivity analysis was conducted to assess the impact of increasing the number of LPs.

Generally, there is no vial sharing for Amphotericin B for patients, so it was assumed that 2 vials per dose were used. This was based on expert opinion of an estimated patient weight of 60kg at a dose of 1mg/kg/day (personal communication, Adult Hospital Level Essential Medicines List Committee meeting May 2019). Although the average weight of a patient is usually assumed to be 70kg, in the ACTA trial the average weight range was 50-53kg across treatment cohorts. Differences in weight and the opportunity for vial sharing were tested in the sensitivity analysis.

For the base-case it was assumed that all patients stayed in hospital for an average length of stay of 17 days (range 12.27-19.31 across all arms) based on the utilisation data from the ACTA trial (22). There is little published information on the use of antibiotics as treatment of neutropenia in patients with CM so assumptions were based on availability of these medicines on the Essential Medicines List. It was assumed that all patients who experienced neutropenia requiring IV antibiotics were still in hospital for CM treatment and therefore did not incur additional hospital costs, only those of the antibiotic treatment.
Results

Base-case analysis

When the proportion of patients alive at each time point in each arm is taken into consideration, the highest treatment costs were in the 2-week AmBd/5FC arm (USD 2,458) followed by the 2-week oral regimen (USD 2,140), then the 1-week AmBd/5FC (USD 2,039), with the lowest medicines cost in the standard of care arm (USD 1,959). Monitoring costs are highest in the 2-week Am/5FC arm followed by the standard of care. Supportive medicine costs are lowest in 1-week course with no additional costs for the oral regimen (Figure 1).

Figure 1. Total cost per patient per treatment arm

The total LYGs and QALYs for each treatment arm are shown in Table 2. As expected, the 1-week flucytosine arm has the highest numbers of LYGs and QALYs, followed by the oral regimen, then the 2-week flucytosine arm with the lowest in the standard of care arm.

Table 2. Total LYG, QALYs and Costs per treatment arm

| Treatment arm                        | LYG   | QALY  | Cost (USD) |
|--------------------------------------|-------|-------|------------|
| 1-week AmBd/5FC                      | 16.02 | 15.08 | 1,985      |
| 2-week AmBd/5FC                      | 11.99 | 11.29 | 2,320      |
| 2-week AmBd/Flu (standard of care)   | 11.10 | 10.44 | 1,840      |
| Oral 5FC/Flu                         | 12.42 | 11.69 | 2,033      |

The ICERs for the different treatment arms compared to standard of care show that the 1-week flucytosine course is most cost-effective at USD31/QALY, followed by the oral 2-week course at USD155/QALY. None of the ICERs are more than USD1 000/QALY, which is considered to be very cost-effective (Table 3). For the comparator to the oral regimen, the 1-week flucytosine course dominates with better clinical benefits (QALYs) and lower costs, whereas the 2-week flucytosine course is dominated by the oral regimen as it has poorer clinical outcomes and higher costs than the oral course. Compared to the oral regimen, the 2-week standard of care has poorer clinical outcomes but lower costs.

Table 3. Incremental LYG, QALYs and Costs and ICERs per treatment arm
| Treatment arm          | Incremental LYG | Incremental QALY | Incremental Cost (USD) | ICER (USD/LYG) | ICER (USD/QALY) |
|-----------------------|-----------------|-----------------|------------------------|----------------|-----------------|
| vs 2-week AmBd/Flu (standard of care) |                 |                 |                        |                |                 |
| 1-week AmBd/5FC       | 4.92            | 4.64            | 144                    | 29             | 3               |
| 2-week AmBd/5FC       | 0.89            | 0.84            | 479                    | 536            | 56              |
| Oral 5FC/Flu          | 1.32            | 1.24            | 193                    | 146            | 15              |

**Sensitivity Analysis**

When a sensitivity analysis was conducted to assess the uncertainty in the model it was found that varying most parameters did not have a substantial impact on the outcomes. The model is most sensitive to probability of survival at 12 months, hospital length of stay, infusion fees and the cost of flucytosine (Figure 2). Even when the survival rate is fixed to be the same as the standard of care for each arm, (i.e. survival probability at 2 weeks for all arms is 0.781), there is no significant change in the ICERs and the flucytosine regimens are still cost-effective compared to the standard of care. If the 12-month mortality rate for the 1-week regimen or oral regimen is set at the same as that for the standard of care (p=0.50) then the ICER increases to USD1 967/QALY and USD7 529/QALY respectively. The inclusion of costs for treatment of anaemia (blood transfusions) or neutropenia (antibiotics) does not impact substantially on the ICER outcomes, nor for the inclusion or exclusion of use of potassium or magnesium supplementation. Increasing the number of LPs had very little impact on the ICERs. Increasing weight resulted in higher costs but only slightly increased ICERs likewise modelling for vial sharing which reduced the costs for the AmBd arms.

The model is sensitive to the price of flucytosine with the oral arm becoming cost saving at a 50% price discount and when the price is discounted to 50% the 1-week flucytosine course also becomes cost saving although the 2-week flucytosine course still has an ICER of USD300/QALY. The price at which the 1-week regimen is cost-neutral is around USD 109 per pack of 100 tablets and USD 90 per week of treatment.

When the cost of infusion fees is increased, the 1-week flucytosine and oral course become dominant although not at the cost of tertiary level facility infusion fees (USD17 per infusion) where there is still a low ICER for all three arms compared to SC. Although other published cost-effectiveness analyses included an infusion fee as a separate cost item, in South Africa it most likely included in the hospital
daily rate. The impact of excluding the infusion fee cost was assessed and found to increase the ICERs slightly but not to more than USD1 000/QALY for any arm.

Due to the trial protocol in ACTA the average length of stay (LOS) in the trial was 17 days regardless of which treatment arm they were in. It is possible that patients who are well enough to be discharged may leave sooner if they are on the 1-week AmBd/5FC or oral regimen. This has a substantial impact on the model so that if the length of stay in hospital is reduced to 10 or 7 days for either the 1-week or oral flucytosine course, the ICERs become increasingly dominant in those arms.

**Figure 2. Tornado diagram of ICER sensitivity for 1wk AmBd/5FC compared to standard of care**

**Budget Impact Analysis**

The incremental costs were presented as well as the budget impact if only medicine costs are considered or if all the related costs (including hospital stay, monitoring, ADRs) are considered. Assuming the base case inputs, modelling the same LOS (17 days) for all treatment arms, the greatest total budget impact for 2018 is with the 2-week AmBd/5FC course of treatment (USD9 692 934), followed by the oral regimen (USD8 495 346), then the 1-week course (USD8 293 411) and the current standard of care having the lowest budget impact at USD7 689 918.

**Table 4. Incremental budget impact (total and per patient) compared to standard of care**

| Total Incremental impact vs 2wk AmBd/Flu (SC) | Total Incremental cost (USD) | Ave. Incremental cost per patient (USD) |
|---------------------------------------------|-----------------------------|-----------------------------------------|
| 1wk AmBd/5FC                               | 603 494                     | 144                                     |
| 2wk AmBd/5FC                               | 2 003 016                   | 477                                     |
| Oral                                       | 805 428                     | 192                                     |

If all patients were switched to the flucytosine regimens, the average additional cost per patient (total costs) over what is currently spent on standard of care would be USD144 and USD192 per patient per year for the 1-week and oral course, respectively (Table 4). As the price of flucytosine is reduced so the incremental budget impact decreases until at a 50% price reduction the oral regimen becomes cost saving and at a 75% price reduction both the 1-week flucytosine arm and oral regimen are cost saving. The 1-week course becomes cost saving at a pack price of around USD109 (USD90 per week of treatment).
In addition, the model is sensitive to whether an infusion fee is included or not with the incremental budget increasing for the 1-week course and the oral regimen, whilst the cost of treatment in the 2-week courses is reduced. As the infusion fee increases so the cost of the 2-week course increases and the oral and 1-week courses become cost-saving. The greatest impact is seen when the LOS is reduced for the 1-week and oral regimens assuming that patients may be discharged sooner. If the LOS is reduced to 10 days or 7 days, the 1-week and oral courses become increasingly cost-saving.

**Discussion**

The introduction of flucytosine as the mainstay of induction therapy for the treatment of cryptococcal meningitis has been hampered by issues of affordability and sustainable access, particularly in LMICs in Africa (24). This study, using outcomes data from the ACTA trial, has shown that it is cost-effective to treat patients with a 1-week short course of flucytosine and amphotericin B or a 2-week oral regimen of flucytosine and fluconazole compared to the standard of care. In addition to improved mortality outcomes, both of these treatment options provide an opportunity for patients to be discharged earlier than 2 weeks, resulting in a substantial reduction in costs, as well a reduction in toxicity related to shorter duration of amphotericin B treatment. Data on length of stay in patients on flucytosine from a study in the Eastern Cape, South Africa, indicates that the average LOS post introduction of flucytosine was reduced to a median of 14 days (IQR 14–27) from 20 days (IQR 9–21) in the pre-flucytosine cohort, however this was not significant (25). The fluconazole dosing in the ACTA trial differs from that of the WHO Guidelines (5). The initial oral regimen used in the trial is 1200 mg fluconazole for 14 days (or 7 days in the case of the short course). The WHO Guidelines recommend 800 mg per day. However, using the WHO regimen in the sensitivity analysis did not impact the outcomes of the model.

Amphotericin has widely been implicated in the development of nephrotoxicity and anaemia (26) (27). The development of nephrotoxicity or anaemia is associated with increased 10-week mortality and therefore these are important ADRs to monitor and manage (28). The probability of patients developing Grade IV anaemia was based on the ACTA trial and it was assumed that these patients all received a transfusion. The utilisation of blood units was obtained from the Chen et al study (22).
However, in a study conducted in South Africa, it was noted that of all the patients with Grade IV anaemia, only around 20% of those actually received a transfusion (26). Nephrotoxicity is largely managed by pre-emptive saline, hydration and electrolyte replacement. However, if patients do develop nephrotoxicity Grade III or IV, management begins with omitting the next AmBd dose and giving additional fluids. If creatinine levels are still rising, then the patient is either moved to alternate day dosing or treatment is stopped altogether (27) (28). In neither the Bicanic nor ACTA trials were any mention made of patients who required dialysis as management of nephrotoxicity. Similarly, renal dialysis was considered to be very rare in the local setting (personal communication, Adult Essential Medicines List Committee meeting May 2019). It is possible an extended length of stay may be required to complete the course of treatment.

A limitation of our model was the assumption that all the costs would be incurred in the first year and there would be no additional incremental cost impacts in the following years. However, relapses do occur, particularly in patients who default on their fluconazole maintenance therapy or who stop their ARVs (30)(31). Therefore it is possible that some patients will incur additional expenses in subsequent years. However we assumed this would be similar in incidence across all arms of the model and presumably with similar costs.

Cost-effectiveness thresholds vary by country and in many cases are not explicit. The commonly used WHO threshold of one to three times per capita GDP has been increasingly refuted (32) and more recent estimates have suggested a threshold of between USD 1,175/QALY and USD 4,714/QALY for South Africa (33). As such, the ICERs determined in this study would be considered cost-effective as they are below the lower limit of this threshold. Economic evaluations in both the USA (16) and Africa (22)(34)(35) have shown that flucytosine is cost-effective compared to current standard of care, although affordability through budget impact analysis had not been considered. In this study we estimated the budget impact and determined a price at which the introduction of flucytosine would become affordable and cost-neutral to introduce to the essential medicines list in South Africa.

However, the outcomes and resource utilisation in a general clinical practice setting such as that in the public sector in South Africa may differ from utilisation in other countries. It is recommended that
if flucytosine is included on the Essential Medicines List in South Africa, a monitoring and evaluation study is conducted to verify these outcomes and costs.

Conclusions
This updated cost-effectiveness analysis in a public health setting in South Africa confirms that the addition of flucytosine as induction therapy in the treatment of cryptococcal meningitis in patients infected with HIV is cost-effective regardless of whether it is used as a 1-week, 2-week or oral regimen. As to be expected the 1-week flucytosine course is most cost-effective with an ICER of USD36/QALY, followed by the oral regimen compared to the standard of care. The model is most sensitive to changes in costs rather than outcomes with the greatest impact seen where cost savings can be achieved by reducing the price of flucytosine, reducing the infusion fee costs and reducing the hospital length of stay.

Although the incremental budget impact of flucytosine compared to current standard of care is in the region of USD600 000 per annum, savings could be achieved with early discharge of patients as well as a reduction in the price of flucytosine.

Improved access to flucytosine at a reasonable cost in South Africa, and particularly with the introduction of the 1-week course, has the potential to reduce the length of stay from 14 days to 7 days of treatment with an associated reduction in mortality. With the availability of robust evidence and cost-effectiveness data, access to flucytosine in LMICs and UMICs as an essential medicine is imperative and affordability can be achieved with appropriate price reduction negotiations.

Declarations

Author's contributions
JM, TL, AP designed the model. JM developed and conducted the economic evaluation and drafted the manuscript. HD and ST contributed the clinical inputs to the manuscript and for the input variables. JM, TL, ST, AP, HD reviewed the data and manuscript.

Availability of data and materials
The datasets analysed during the current study are available in the following repositories: Master
Procurement Catalogue (http://www.health.gov.za/index.php/component/phocadownload/category/196) and the Institute for Health Metrics and Evaluation (IHME) data tool (http://ghdx.healthdata.org/gbd-results-tool)

Any additional datasets generated for use and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

HD has participated as a member of the DSBM in the ACTG (Cryptococcal meningitis) and as an investigator in the ACTG- A 5225 trial

**Consent for publication**

Not applicable.

**Ethics approval and consent to participate**

Not applicable. Research ethics was not required as the study did not involve human subjects or materials.

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**References**

1. Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis. 2017; 17(8): 873-881. DOI: https://doi.org/10.1016/S1473-3099(17)30243-8

2. GERMS-SA Annual Report 2017. Available from: http://www.nicd.ac.za/index.php/publications/germs-annual-reports/

3. Southern African HIV Clinicians Society. Govender N, Meintjes G, Bicanic T, Dawood
H, Harrison T, Jarvis, Karstaedt A et al. Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-infected persons. S Afr J HIV Med. 2013;14(2):76-86

4. Loyse A, Burry J, Cohn J, Ford N, Chiller T, Ribeiro et al. Leave no one behind: response to new evidence and guidelines for the management of cryptococcal meningitis in low-income and middle-income countries. Lancet Infect Dis. 2019;19(4):e143-e147. doi: 10.1016/S1473-3099(18)30493-6.

5. WHO. Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. 2018. http://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/ (accessed May 2019)

6. Kneale M, Bartholomew J, Davies E, Denning D. Global access to antifungal therapy and its variable cost. J Antimicrob Chemother. 2016; 71(12):3599-3606.

7. South African National Department of Health. 1965. Medicines and Related Substances Act (Act 101 of 1965)

8. Govender N, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D et al. South African HIV Clinicians Society guidelines for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med. 2019;20(1), a1030. Doi.org/10/sajhivmed.v20i1.1030

9. Molloy S, Kanyama C, Heyderman R, Loyse A, Kouanfack C, Chanda D et al, ACTA Trial Study Team. Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa. N Engl J Med. 2018;378(11):1004-1017. doi: 10.1056/NEJMoa1710922.

10. Tenforde MW, Shapiro AE, Rouse B, Jarvis JN, Li T, Eshun-Wilson I, Ford N. Treatment for HIV-associated cryptococcal meningitis. Cochrane Database Syst Rev. 2018;7:CD005647. doi: 10.1002/14651858.CD005647.pub3.

11. South African National Essential Medicine List Adult Hospital Level Medication Review
12. Johnson LF, Keiser O, Fox MP, Tanser F, Cornell M, Hoffmann CJ, et al. International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration. Life expectancy trends in adults on antiretroviral treatment in South Africa. AIDS. 2016;30(16):2545-2550.

13. South African National Department of Health. Publication of the guidelines for pharmacoeconomic submissions. 2013. Government Notice No. R.68, Government Gazette No. 36118, 1 February 2013. South Africa

14. Kanyama C, Molloy SF, Chan AK, Luniya D, Chawinga C, Adams J, Bright P, Laloo DG, Heyderman RS, Lortholary O, Jaffar S, Loyse A, van Oosterhout JJ, Hosseinipour MC, Harrison TS. One year mortality outcomes from the ACTA trial of cryptococcal meningitis treatment in Malawi. Clin Infect Dis. 2019 Jun 1. pii: ciz454. doi: 10.1093/cid/ciz454.

15. GBD 2017 Mortality Collaborators. Global, regional, and national age-sex-specific mortality and life expectancy, 1950-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1684-1735. doi: 10.1016/S0140-6736(18)31891-9. Global, regional, and national age-sex specific mortality tables for HIV/AIDS (1980-2017) of the Global Burden of Disease study (http://ghdx.healthdata.org/gbd-results-tool)

16. Merry M and Boulware DR. Cryptococcal meningitis treatment strategies affected by the explosive cost of flucytosine in the United States: a cost-effectiveness analysis. Clin Infect Dis. 2016;62(12): 1564-1568.

17. South African Reserve Bank. Historical Exchange Rates (Daily) 01 January 2018 to 31 December 2018.
18. South African National Department of Health. Master Procurement Catalogue, September 2018. http://www.health.gov.za/index.php/component/phocadownload/category/196

19. National Health Laboratory Services. NHLS State Price List 2017. South African Department of Health.

20. South African National Department of Health, Uniform Patient Fee Schedule (UPFS) 2018. Approved UFS 2018 Fee Schedule for full paying patients, Annexure 1A

21. South African National Department of Health, National Blood Service (SANBS) State Patients Pricelist (1 April 2018 to 31 March 2019)

22. Chen T, Mwenge L, Lakhi S, Chanda D, Mwaba P, Molloy SF et al, ACTA Trial Team. Healthcare Costs and Life-years Gained From Treatments Within the Advancing Cryptococcal Meningitis Treatment for Africa (ACTA) Trial on Cryptococcal Meningitis: A Comparison of Antifungal Induction Strategies in Sub-Saharan Africa. Clin Infect Dis. 2019; 69(4): 588–595.

23. Johnson L and Dorrington R. Thembisa Model version 4.1: A model for evaluating the impact of HIV/AIDS in South Africa August 2018. www.thembisa.org.

24. Loyse A, Burry J, Cohn J, Ford N, Chiller T, Ribeiro I et al. Leave no one behind: response to new evidence and guidelines for the management of cryptococcal meningitis in low-income and middle-income countries. Lancet Infect Dis. 2019 Apr;19(4):e143-e147. doi: 10.1016/S1473-3099(18)30493-6. Epub 2018 Oct 18.

25. Boretti N, Meiring S, Quan V, Black JM, Govender N. Amphotericin B and flucytosine combination treatment among patients with HIV-associated cryptococcal meningitis at a tertiary-level hospital in the Eastern Cape. ePoster 10656, FIDSSA Conference
26. Bicanic T, Meintjes G, Rebe K, Williams A, Loyse A, Wood R, et al. Immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis: a prospective study. J Acquir Immune Defic Syndr. 2009;51(2):130-134.

27. Bicanic T, Bottomley C, Loyse A, Brouwer AE, Muzoora C, Taseera K, et al. Toxicity of Amphotericin B Deoxycholate-Based Induction Therapy in Patients with HIV-Associated Cryptococcal Meningitis. Antimicrob Agents Chemother. 2015;59(12):7224-31. doi: 10.1128/AAC.01698-15.

28. Meiring S, Fortuin-de Smidt M, Kularatne R, Dawood H, Govender N; GERMS-SA. Prevalence and Hospital Management of Amphotericin B Deoxycholate-Related Toxicities during Treatment of HIV-Associated Cryptococcal Meningitis in South Africa. PLoS Negl Trop Dis. 2016;10(7):e0004865. doi: 10.1371/journal.pntd.0004865.

29. Patel R, Leeme T, Azzo C, Tlhako N, Tsholo K, Tawanana E, et al. High Mortality in HIV-Associated Cryptococcal Meningitis Patients Treated With Amphotericin B-Based Therapy Under Routine Care Conditions in Africa. Open Forum Infect Dis. 2018;5(11):ofy267. doi: 10.1093/ofid/ofy267. eCollection 2018 Nov.

30. Jarvis JN, Meintjes G, Williams Z, Rebe K, Harrison TS. Symptomatic relapse of HIV-associated cryptococcal meningitis in South Africa: the role of inadequate secondary prophylaxis. S Afr Med J. 2010 Jun; 100(6):378-82.

31. Govender N, Dlamini S. Management of HIV-associated cryptococcal disease in South Africa. S Afr Med J 2014;104(12):896. DOI:10.7196/SAMJ.9070

32. Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost-effectiveness of interventions: alternative approaches. Bull World Health Organ 2015;93:118-24. doi:2471/BLT.14.138206.

33. Woods B, Revill P, Sculpher M, Claxton K. Country-Level Cost-Effectiveness
Thresholds: Initial Estimates and the Need for Further Research. 2015.

34. 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(9):e1001316. doi: 10.1371/journal.pmed.1001316.

35. Shiri T, Loyse A, Mwenge L, Chen T, Lakhi S, Chanda D et al. Addition of flucytosine to fluconazole for the treatment of cryptococcal meningitis in Africa: a multi-country cost-effectiveness analysis. Clin Infect Dis. 2019;pii: ciz163. doi: 10.1093/cid/ciz163.

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Abbreviations

5FC  5-Flucytosine
ACTA  Advancing Cryptococcal Meningitis Treatment for Africa
ADRs  Adverse drug reactions
AmBd  Amphotericin B
ART   Antiretroviral therapy
BIA   Budget impact analysis
CD4   CD4 T lymphocyte
CM    Cryptococcal meningitis
Flu   Fluconazole
ICER  Incremental cost effectiveness ratio
IHME  Institute for Health Metrics and Evaluation
LOS   Length of stay
LP    Lumbar puncture
LYG   Life years gained
QALY  Quality adjusted life year
SAHPRA South African Health Products Regulatory Authority
SANBS  South African National Blood Service
SC    Standard of care
UPFS  Uniform Patient Fee Schedule
WHO   World Health Organisation

Figures
Figure 1

Total cost per patient per treatment arm
Figure 2

Tornado diagram of ICER sensitivity for 1wk AmBd/5FC compared to standard of care