RESEARCH NOTE

REVISED Induction-phase treatment costs for cryptococcal meningitis in high HIV-burden African countries: New opportunities with lower costs [version 3; peer review: 3 approved]

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Abstract

Introduction: Access to and the cost of induction treatment for cryptococcal meningitis (CM) is rapidly changing. The newly-announced price for flucytosine ($0.75 per 500 mg pill) and possibly lower prices for liposomal amphotericin B (AmB-L) create opportunities to reduce CM treatment costs compared to the current standard treatment in low- and middle-income countries.
Methods: We developed an Excel-based cost model to estimate health system treatment costs for CM over a two-week induction phase for multiple treatment combinations, newly feasible with improved access to flucytosine and AmB-L. CM treatment costs include medications, laboratory tests and other hospital-based costs (bed-day costs and healthcare worker time). We report results from applying the model using country-specific information for South Africa, Uganda, Nigeria, and Botswana.

Open Peer Review

Approval Status ✓ ✓ ✓

	1	2	3
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version 2 (revision) 29 Mar 2022	✓ view		✓ view
version 1 04 Jun 2021	? view	? view	

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Results: A 14-day induction-phase of seven days of inpatient AmB-D with flucytosine, followed by seven days of high-dose fluconazole as an outpatient, will cost health systems less than a 14-day hospital stay with AmB-D and fluconazole. If daily AmB-L replaces AmB-D for those with baseline renal dysfunction, with a cost of $50 or less per 50 mg vial, incremental costs would still be less than the AmB-D with fluconazole regimen. Simple oral combinations (e.g., seven days of flucytosine with fluconazole as an inpatient) are practical when AmB-D is not available, and treatment costs would remain less than the current standard treatment.
Conclusions: Improved access to and lower prices for flucytosine and AmB-L create opportunities for improving CM treatment regimens. An induction regimen of flucytosine and AmB-D for seven days is less costly than standard care in the settings studied here. As this regimen has also been shown to be more effective than current standard care, countries should prioritize scaling up flucytosine access. The cost of AmB-L based regimens is highly dependent on the price of AmB-L, which currently remains unclear.

Keywords
HIV/AIDS, cryptococcal meningitis, induction phase, amphotericin B deoxycholate, flucytosine, liposomal amphotericin B, fluconazole, South Africa, Uganda, Botswana, Nigeria

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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED **Amendments from Version 2**

In this revision, we made a few minor edits for grammar. As suggested by Reviewer 3, we also edited one sentence in the last paragraph of the method section. We also agree with Reviewer 3 that fewer inpatient days with some regimens would free up limited hospital resources for other patients.

Any further responses from the reviewers can be found at the end of the article

Introduction

Cryptococcal meningitis (CM) among people living with advanced HIV disease remains a leading cause of AIDS-related deaths globally. Meningitis deaths continue, in part, because of health system failures to diagnose, initiate, retain and achieve viral suppression in patients on antiretroviral therapy quickly after HIV infection, and for patients who develop CM, failures to treat patients with efficacious induction-phase regimens including off-patent medications[1–9]. In short, the continued high incidence of CM cases and deaths are programmatic indicators of these failures[2].

Prior to 2018, the WHO recommended two-weeks of hospital-based care with daily amphotericin B deoxycholate (AmB-D) infusions plus oral fluconazole as one of the preferred treatment options. This regimen became a standard treatment in many settings due to the lack of flucytosine regulatory approvals and limited access in most low- and middle-income countries (LMICs)[1,10–13]. The updated 2018 WHO guideline recommends AmB-D with flucytosine in place of fluconazole for week one and high-dose fluconazole for week two[1]. This regimen is more efficacious and, due to the shorter duration of AmB-D infusion, less toxic and allows for a shorter hospital stay. To date, flucytosine has been largely unavailable in LMICs despite being included in the WHO essential medicines list[9,10,14].

After years of advocacy[8,9,15], the lack of access to old and off-patent medications is beginning to change. Flucytosine is now available for $75 per 100 pack (500 mg pills) *ex works* although use in country remains very limited (mainly LMICs with a high HIV burden), while Gilead announced the company will seek to make liposomal amphotericin B (AmB-L) available for a substantially lower price as well[16].

This research note reports on costs of treatment for CM patients during the initial two-week induction phase as access to key medications improves (and prices fall) and to complement new research evaluating effectiveness of alternative regimens containing combinations of AmB-D, fluconazole, flucytosine, and AmB-L (see, e.g. 10,17). In this analysis, treatment costs are based on World Health Organization guidelines[1], and include medications as well as laboratory tests and other hospital-based costs, which vary based on drug regimen. Using country-specific cost information, example results are presented for Botswana, Nigeria, South Africa, Uganda.

Methods

Background

Model overview

We used a basic micro-costing approach following standard costing recommendations[18,19], organized into an Excel-based model, to estimate per-protocol treatment costs from the health-system perspective (reported in 2019 $US) per CM patient and per 1,000 CM patients over a 14-day induction phase, where treatment costs include medications, laboratory tests and other hospital-based costs (bed-day/hotel cost and staff if not included in bed-day costs). Using the basic model, we completed four-country specific applications, which are available along with a User's Guide at the OpenBU data repository[20]. Any country-specific case study can also be used as a template for replication in other locations or with new assumptions (or for readers to conduct additional sensitivity analyses).

The model first estimates cost for what has been a standard treatment across many LMICs: daily infusion of AmB-D for 14 days in hospital, if available, with high-dose oral fluconazole daily. Costs for a main alternative regimen, AmB-D with flucytosine for seven days (followed by fluconazole monotherapy in the second week), are then estimated along with additional regimens with AmB-L or simple oral combinations such as flucytosine plus fluconazole (in the absence of AmB-D or AmB-L). Fluconazole monotherapy is not included in this analysis because effectiveness is very low[21]. However, the oral regimen (fluconazole plus flucytosine) can be easily edited to be fluconazole monotherapy only.

Model structure and assumptions

The Excel model for each country contains the same five worksheets: table of contents; assumptions for all regimens; cost per patient for each regimen (seven total regimens are included); cost per 1,000 patients (which includes nine total regimens that consider alternative ways of addressing baseline renal dysfunction (RD) for patients as well as incident RD for a standard two-week regimen with AmB-D). All assumptions on resource quantities and unit costs for such resources are provided in the assumptions for all regimens sheet and the cost by regimen per patient sheet. The model is adapted as needed for each country, for example based on medication price information (price per pill or per pack of pills, laboratory monitoring guidelines or practices, or information requiring inflation adjusting).

Unit costs for all medications except flucytosine and AmB-L, laboratory tests, therapeutic lumbar punctures, health worker time and hospital in-patient bed days are based on country-specific sources (referenced within the Excel model application for each country-specific analysis). For flucytosine, we use the reported price ($75 per 100 pack of 500 mg pills) plus 25% to include additional shipping and handling costs[15,22,23]. The cost of AmB-L remains uncertain at this time. In South Africa, for example, while the 2019 single exit price of AmB-L was $194 per 50 mg vial, a price of $16.25 per

50 mg vial has been reported[24] but currently remains unconfirmed by Gilead. For this analysis, we have used a price of $50 per vial (e.g., $40 *ex works* plus an additional 25% for shipping, handling, etc.). As procurement of these medication grows, better estimates will likely be available in the near future. Using the Excel-based models provided in the OpenBU repository, interested readers can easily conduct additional sensitivity analyses by adjusting specific parameters list in the worksheet labelled "Assumptions for all regimens".

Results and discussion

Main results from these analyses are provided in Figure 1. For each country, five main treatment regimens are presented.

AmB-D plus fluconazole (14 hospital days)

For each country, the first regimen reported in Figure 1 is a 14-day hospitalization with daily infusion of AmB-D with high-dose oral fluconazole daily. We use this regimen as a basic reference point for comparing costs for the other regimens. Given recommended daily dosages for this combination (50 kilogram adult; 1 mg/kg/day AmB-D; 1200 mg/day fluconazole)[1], medication costs per day are estimated at $7.11, $8.93, $6.22, and $14.40 for South Africa, Botswana, Uganda, and Nigeria, respectively. As summarized in Figure 1 (after dividing by 1,000), total costs per patient for this regimen are $2,043 (South Africa), $1,548 (Botswana), $822 (Nigeria) and $487 (Uganda). The basic hospital in-patient costs per day (excluding medications, and laboratory tests) in South Africa ($97) and Botswana ($88) are substantially higher than in Nigeria ($24) and Uganda ($11), which explains most of the differences between the higher- and lower-cost countries for this regimen. Treatment costs for this AmB-D/fluconazole regimen provide the reference point for discussing other regimens.

AmB-D plus flucytosine (seven hospital days)

As included in the WHO 2018 guidelines, the preferred but previously unavailable combination is AmB-D/flucytosine for seven days followed by seven days of fluconazole. This regimen allows for seven hospital days among patients who do not need a more prolonged admission for other clinical reasons. With the newly-reduced daily cost for flucytosine at $9.38, this lower cost compares more favorable to the daily cost of fluconazole (e.g., the daily cost of 1200 mg fluconazole is estimated at $6.79, $0.43, $3.11, and $4.40 in South Africa, Uganda, Botswana, and Nigeria, respectively).

In all four country examples analyzed (see Figure 1), total costs with AmB-D/flucytosine (seven days) and then fluconazole monotherapy (seven days), with seven inpatient and

Figure 1. Cryptococcal meningitis treatment costs with alternative regimens*. *Total cost for the induction phase is provided at the top of each colored bar. The vertical axis (for costs) is not comparable (visually) across countries because the scale varies. For Botswana, hospital-based staff costs are included within the basic hospital costs.

seven outpatient days, are substantially less than with the AmB-D/fluconazole regimen. In each case, the additional daily medication costs for the first week (AmB-D with flucytosine instead of fluconazole) are offset by lower hospital costs and somewhat lower medication costs during week two (only fluconazole monotherapy). In the future, as more experience grows with the use of this regimen in routine or study settings, it is clearly possible that the number of actual in-patient days could extend beyond seven days. Such adjustments can be easily estimated using the models provided (e.g., cost of this regimen in South Africa for 7 in patient days is $1,101 but $1,484 with 10 in-patient days).

Replacing AmB-D with AmB-L

AmB-L is therapeutically equivalent and less toxic than AmB-D. Given the considerable morbidity associated with AmB-D infusion, benefits from improved access to AmB-L are clear. Assuming flucytosine is available, one option is to replace AmB-D with AmB-L and combine this with flucytosine during the seven hospital days. With dosing of 3 mg/kg/day and a patient weighing ≤50 kg, the daily cost for AmB-L is $150 per day (assuming a cost of $40 per vial (50 mgs) plus an additional 25% for insurance, transport, and customs). While significantly less than in the past, this daily cost would remain substantially higher than the daily cost of AmB-D during the induction phase ($0.31, $5.83, $5.78, and $10 for South Africa, Botswana, Uganda, and Nigeria, respectively).

From Figure 1, treatment costs with AmB-L/flucytosine compared to AmB-D/flucytosine during the first week of treatment (followed by fluconazole monotherapy in the second week for both regimens) increases significantly for all countries analyzed, while other costs largely remain the same. Additional research remains needed to consider how the possible benefits (ease of administration, side effects of medications, and treatment outcomes) of switching to standard doses of AmB-L for all patients might compare to the additional costs as well as the budgetary impact.

While a substantially lower price ($16.25 per vial) has been reported by advocacy organizations (e.g., https://www.gaffi.org/gilead-reduces-price-of-ambisome-liposomal-amphotericin-b-for-cryptococcal-meningitis-in-hiv-aids/), this price has not yet been confirmed by Gilead. Obviously, costs would fall substantially for this regimen with the lower price. For example, costs per day for AmB-L would fall from $150 to $60 per patient with this cost (a low-end estimate), but overall costs would remain substantially higher than with AmB-D.

Target AmB-L to patients with baseline renal dysfunction

One option to manage the costs of AmB-L, as included in the Southern African HIV Clinicians Society's 2019 cryptococcal disease management guideline, is to target AmB-L/flucytosine to patients with known renal dysfunction at baseline, with AmB-D/flucytosine for the remainder, given that new AmB-D toxicities are uncommon in the first week of induction therapy[25]. AmB-L is also a logical backup to manage AmB-D shortages or stock outs. Results for this option is provided as the fourth option in Figure 1 for each country.

When the proportion of patients with renal dysfunction is 'modest' (8% of CM patients with renal dysfunction from 26), prioritizing these patients for AmB-L/flucytosine may be medically preferred and probably affordable within the overall HIV care and treatment budget. For example, costs per 1,000 patients for this approach (fourth regimen in Figure 1) compared to AmB-D plus flucytosine for all (second regimen in Figure 1) increase by about $83,000 in South Africa, $79,000 Botswana, $80,500 Uganda, $77,800 Nigeria. However, when compared to the 14-day regimen of AmB-D plus fluconazole (first regimen in Figure 1), costs for this fourth regimen are lower per 1,000 patients.

Regarding national budget implications in, for example, South Africa, with an additional cost per 1,000 patients of $83,000 (comparing the second and fourth regimen in Figure 1) and an estimated 21,000 new CM cases annually in South Africa[2], the annual additional cost of this approach would be $1.74 million annually, which is less than 0.12% of the $1.4 billion included in the national budget for 2019/2020 for the HIV and AIDS program budget[27]. Given that new CM cases are, at least to some important degree, a consequence of health system failures, it seems logical for the program to internalize this cost of failures.

Oral regimens (flucytosine/fluconazole)

The WHO recommends an oral regimen of flucytosine/fluconazole (for 14 days) when AmB-D is not available. In Figure 1, costs for this regimen are included for seven inpatient days and seven outpatient days. Treatment costs with this oral regimen are similar to costs for AmB-D/flucytosine (lower costs from no daily infusions are offset by higher costs of the additional seven days of flucytosine). The cost of this flucytosine/fluconazole regimen would fall or increase depending on the number of days of inpatient care (e.g., only three or four days post-CM diagnosis to monitor intracranial pressure and other possible complications; or more if patients require ongoing management of raised intracranial pressure). The effectiveness of the alternative regimens, not just the costs, need to be addressed for a full comparison of the two regimens. In highly resource limited settings, however, the oral regimens make home-based care feasible at least for some subset of patients (i.e., those without severe CM at the time of treatment initiation, for example as measured by reduced level of consciousness).

Conclusions

With flucytosine accessible at a price of $0.75 per 500 mg pill, an opportunity exists to reduce CM treatment costs over the initial two-week induction phase compared to standard care in LMICs (14 inpatient days with daily infusions of amphotericin B deoxycholate plus fluconazole). Although medication costs with flucytosine are higher than those of current standard treatment, cost reductions from fewer inpatient days (14 down to seven) more than offset the additional

medication costs. Cost savings with flucytosine are substantial even in the examples presented in Figure 1 with lower hospital costs (Uganda and Nigeria).

If flucytosine is available, substituting AmB-L for AmB-D would substantially increase costs per patient if provided to all patients with CM. Nevertheless, the benefits of AmB-L (less toxicity and adverse reactions, easier administration, easier procurement and training to use one medication, etc.) warrant further analysis. One cost reducing strategy is to reserve use for patients presenting with renal dysfunction, who stand to gain the most from its use. In this case, AmB-L only to patients presenting with renal dysfunction, the incremental costs per 1,000 patients are modest in aggregate based on a cost of $50 per 50 mg vial. Clarity from Gilead on actual price(s) for AmB-L will allow for better cost estimates.

As new studies investigate new treatment strategies for CM cases, the costs for these new strategies can be easily estimated and compared using the costing model developed and used for this analysis. Such information on costs can then support discussions of budgetary impact and future economic evaluations of alternative treatment strategies.

Data availability

Underlying data

OpenBU: An Excel-based template for estimating induction-phase treatment costs for cryptococcal meningitis in high HIV-burden African countries. https://hdl.handle.net/2144/41876[20].

This project contains the following underlying data:

- CM Induction Phase Treatment Costs -- Botswana May 17 2021.xlsx
- CM Induction Phase Treatment Costs -- Nigeria May 17 2021.xlsx
- CM Induction Phase Treatment Costs -- South Africa May 17 2021.xlsx
- CM Induction Phase Treatment Costs -- Uganda Dec May 17 2021.xlsx

Extended data

OpenBU: An Excel-based template for estimating induction-phase treatment costs for cryptococcal meningitis in high HIV-burden African countries. https://hdl.handle.net/2144/41876[20].

This project contains the following extended data:

- User_Guide_CM_treatment_costs May 17 2021.pdf

Disclaimer

The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the CDC, NIH, NIHR, the Department of Health and Social Care, or other funding entities.

References

1. World Health Organization: **Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.** Geneva, Switzerland; 2018.
PubMed Abstract

2. Rajasingham R, Smith RM, Park BJ, *et al.*: **Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis.** *Lancet Infect Dis.* 2017; **17**(8): 873–81.
PubMed Abstract | Publisher Full Text | Free Full Text

3. Tang Z, Pan SW, Ruan Y, *et al.*: **Effects of high CD4 cell counts on death and attrition among HIV patients receiving antiretroviral treatment: An observational cohort study.** *Sci Rep.* 2017; **7**(1): 3129.
PubMed Abstract | Publisher Full Text | Free Full Text

4. Kwarisiima D, Kamya MR, Owaraganise A, *et al.*: **High rates of viral suppression in adults and children with high CD4+ counts using a streamlined ART delivery model in the SEARCH trial in rural Uganda and Kenya.** *J Int AIDS Soc.* 2017; **20**(Suppl 4): 21673.
PubMed Abstract | Publisher Full Text | Free Full Text

5. Bor J, Fox MP, Rosen S, *et al.*: **Treatment eligibility and retention in clinical HIV care: A regression discontinuity study in South Africa.** *PLoS Med.* 2017; **14**(11): e1002463.
PubMed Abstract | Publisher Full Text | Free Full Text

6. Kneale M, Bartholomew JS, Davies E, *et al.*: **Global access to antifungal therapy and its variable cost.** *J Antimicrob Chemother.* 2016; **71**(12): 3599–606.
PubMed Abstract | Publisher Full Text

7. Loyse A, Burry J, Cohn J, *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): e143–7.
PubMed Abstract | Publisher Full Text

8. Loyse A, Dromer F, Day J, *et al.*: **Flucytosine and cryptococcosis: Time to urgently address the worldwide accessibility of a 50-year-old antifungal.** *J Antimicrob Chemother.* 2013; **68**(11): 2435–44.
PubMed Abstract | Publisher Full Text | Free Full Text

9. Loyse A, Thangaraj H, Easterbrook P, *et al.*: **Cryptococcal meningitis: improving access to essential antifungal medicines in resource-poor countries.** *Lancet Infect Dis.* 2013; **13**(7): 629–37.
PubMed Abstract | Publisher Full Text

10. Molloy SF, Kanyama C, Heyderman RS, *et al.*: **Antifungal combinations for treatment of cryptococcal meningitis in Africa.** *N Engl J Med.* 2018; **378**(11): 1004–17.
PubMed Abstract | Publisher Full Text

11. World Health Organization: **Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy.** Geneva; 2017.
PubMed Abstract

12. World Health Organization: **Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children.** Geneva, Switzerland; 2011.
PubMed Abstract

13. 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**(1): 76–81.
PubMed Abstract | Publisher Full Text

14. Merry M, 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): 1564–8.
PubMed Abstract | Publisher Full Text | Free Full Text

15. Shroufi A, Govender NP, Meintjes G, *et al.*: **Time to embrace access programmes for medicines: lessons from the South African flucytosine access programme.** *Int J Infect Dis.* 2020; **95**: 459–61.
PubMed Abstract | Publisher Full Text

16. **Gilead Sciences Announces Steep Discounts for Ambisome to Treat Cryptococcal Meningitis in Low- and Middle-Income Countries**. 2020; [cited 2020 Sep 10].
Reference Source

17. Lawrence DS, Youssouf N, Molloy SF, *et al.*: **AMBIsome Therapy Induction OptimisatioN (AMBITION): High Dose AmBisome for Cryptococcal Meningitis Induction Therapy in sub-Saharan Africa: Study Protocol for a Phase 3 Randomised Controlled Non-Inferiority Trial.** *Trials.* 2018; **19**(1): 649.
PubMed Abstract | Publisher Full Text | Free Full Text

18. Cunnama L, Baena IG, Gomez G, *et al.*: **Costing guidelines for tuberculosis interventions**. Geneva; 2019.
Reference Source

19. Drummond MF, O'Brien B, Stoddart GL, *et al.*: **Methods for the Economic Evaluation of Health Care Programmes.** *American Journal of Preventive Medicine.* Second Edition. Oxford University Press; 1998; **14**: 243.

20. Larson B, Shroufi A, Muthoga C, *et al.*: **An Excel-based template for estimating induction-phase treatment costs for cryptococcal meningitis in high HIV-burden African countries**. 2021.
http://hdl.handle.net/2144/41876

21. Hope W, Stone NRH, Johnson A, *et al.*: **Fluconazole monotherapy is a suboptimal option for initial treatment of cryptococcal meningitis because of emergence of resistance.** *mBio.* 2019; **10**(6): e02575–19.
PubMed Abstract | Publisher Full Text | Free Full Text

22. Milan: **Milan 5FC Product Sheet**. 2020; 1.

23. The Clinton Health Access Initiative: **The Unitaid / CHAI Advanced HIV Disease Newsletter.** The Unitaid/CHAI Advanced HIV Disease Newsletter. 2020; 1–5.

24. Global Action Fund for Fungal Infections: **Gilead reduces price of AmBisome (liposomal amphotericin B) for cryptococcal meningitis in HIV/AIDS**. 2020.
Reference Source

25. Govender NP, Meintjes G, Mangena P, *et al.*: **Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update.** *South Afr J HIV Med.* 2019; **20**(1): 1030.
PubMed Abstract | Publisher Full Text | Free Full Text

26. Govender NP, Mering S, Fortuin-de Smidt M, *et al.*: **Liposomal amphotericin B as a 2nd-line agent for induction treatment of cryptococcal meningitis in South African hospitals.** In: *2nd EMBO Workshop on AIDS related mycoses.* Cape Town; 2016.

27. National Treasury: **Estimates of National Expenditure 2019.** Pretoria, South Africa; 2019.
Reference Source

Open Peer Review

Current Peer Review Status: ✔ ✔ ✔

Version 3

Reviewer Report 25 July 2022

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✔ **Katharine Elizabeth Stott**
Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool, UK

No further comments - all comments/queries addressed by authors.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Antimicrobial pharmacology, PKPD, mycology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 09 June 2022

https://doi.org/10.21956/wellcomeopenres.19667.r50590

✔ **Clinton J Pecenka**
Center for Vaccine Innovation and Access, PATH, Seattle, WA, USA

Summary
This is a well written paper on the costs of cryptococcal meningitis treatment in African countries.

New drug prices have been announced with may lower the costs of treatment compared to current front-line drugs. The analysis is methodologically sound and straightforward for the reader. Additional data could be included in the manuscript itself, but it also easily accessible in the Excel files. Given some uncertainty in drug prices, the primary value of this work may be subsequent analyses undertaken with the tools presented here.

Introduction
No comments

Methods
The following sentence could be simplified. As procurement of these medication grows in the near future, better estimates will likely be available in the near future.

Results and discussion
The authors could further note the value of reducing the need for inpatient services in some regimens. In many LMICs, hospital space is limited and reducing in facility resource requirements may allow additional patients, potentially with other illnesses, to be treated.

Conclusion
No comments

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Global health economics, vaccine economics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 13 April 2022

https://doi.org/10.21956/wellcomeopenres.19667.r49536

Angela Kairu
Health Economics Research Unit, KEMRI-Wellcome Trust Research Programme Nairobi, Nairobi, Kenya

I have reviewed the revised article and Approve the revised version.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 24 January 2022

https://doi.org/10.21956/wellcomeopenres.18501.r47861

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Katharine Elizabeth Stott
Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool, UK

This paper addresses an important question for the long overdue implementation of flucytosine and amphotericin-B based induction treatment regimens for HIV-associated cryptococcal meningitis in LMICs – namely, the costs associated with those regimens. By comparing historically-recommended induction regimens to those currently recommended, the authors conclude that flucytosine and amphotericin-B-based regimens are affordable. This has positive implications for ongoing advocacy efforts to increase access to these essential medications.

My comments mainly concern the clarity with which the analysis is presented and the rationale behind some of the analytical decisions. In addition, a number of assumptions are [necessarily] made and these should be highlighted more clearly.

Clarity
The first two paragraphs of the methods section would be more appropriately included in the introduction section, since they provide background information.

The authors state that they estimated costs for fluconazole monotherapy (second paragraph, 'Model overview'). However, these estimates are not presented or stated in the paper, nor could I see them in the Excel downloads. I would recommend either including the data if they are available, or not stating that costs were estimated for fluconazole monotherapy, if these estimates are not available (in which case the authors might state why they decided against modelling those estimates - presumably because this regimen is not recommended).

Assumptions
A major assumption made is that patients who are administered AmB-D plus 5FC for 7 days, followed by fluconazole for 7 days, are able to complete days 8 to 14 of their induction therapy as outpatients. Can the authors discuss what proportion of patients are able to be discharged from hospital after 7 days? Many patients may require ongoing inpatient care?

As discussed by the authors, there is uncertainty surrounding the cost of AmB-L. In the absence of accurate cost information and because potential costs of AmB-L vary so widely, have the authors considered a highest and lowest potential cost calculation for the treatment strategies that contain AmB-L? i.e. offer a range of potential costs?

I'm not sure I understand the third paragraph under 'Target AmB-L to patients with baseline renal dysfunction' in the results section ('Note that the...'). I don't see that the statements made are reflected in figure 1? It appears to me that in all country case studies, the AmB-L/5FC option incurs the highest cost, with the option of AmB-L targeted to those with renal dysfunction incurring a lower cost than the reference regimen in all cases?

Additional comments
Second sentence in Introduction section: deaths are also due to ART failure; data show that improved access to ART does not necessarily correlate with reduction in deaths from HIV-associated CM.

Under Model structure and assumptions subheading: should '...incident RD for a standard two regimen...' read, '...incident RD for a standard two ***week*** regimen...'?

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pharmacology, cryptococcal meningitis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 10 Mar 2022

Bruce Larson, Boston University School of Public Health, Boston, USA

Authors' responses and revisions based on Reviewer Reports (on Version1)

In the following, we provide a point-by-point response to each comment and suggestion provided by Reviewer 2. We have numbered each comment to ensure a complete response and to note information across comments and reviewers.

Reviewer 2

24 Jan 2022 | for Version 1
Katharine Elizabeth Stott, Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool, UK

Approved With Reservations

This paper addresses an important question for the long overdue implementation of flucytosine and amphotericin-B based induction treatment regimens for HIV-associated cryptococcal meningitis in LMICs – namely, the costs associated with those regimens. By comparing historically-recommended induction regimens to those currently recommended, the authors conclude that flucytosine and amphotericin-B-based regimens are affordable. This has positive implications for ongoing advocacy efforts to increase access to these essential medications.

My comments mainly concern the clarity with which the analysis is presented and the rationale behind some of the analytical decisions. In addition, a number of assumptions are [necessarily] made and these should be highlighted more clearly.

Clarity

1. The first two paragraphs of the methods section would be more appropriately included in the introduction section, since they provide background information.

Authors: Thank you for the recommendation. We have revised and moved the paragraphs as recommended. Based on comments from the other Reviewer (Reviewer 1, comment 2), we deleted the original last paragraph of the introduction given that such information is also included in the conclusions section.

2. The authors state that they estimated costs for fluconazole monotherapy (second paragraph, 'Model overview'). However, these estimates are not presented or stated in the paper, nor could I see them in the Excel downloads. I would recommend either including the data if they are available, or not stating that costs were estimated for fluconazole monotherapy, if these estimates are not available (in which case the authors might state why they decided against modelling those estimates - presumably because this regimen is not recommended).

Authors. Thank you for catching this omission. We originally included fluconazole monotherapy in our analysis, but then excluded given its poor effectiveness. We have revised the Model Overview section to explain this point.

Assumptions

3. A major assumption made is that patients who are administered AmB-D plus 5FC for 7 days, followed by fluconazole for 7 days, are able to complete days 8 to 14 of their induction therapy as outpatients. Can the authors discuss what proportion of patients are able to be

discharged from hospital after 7 days? Many patients may require ongoing inpatient care?

Authors: This is a very relevant point for real-world patient care. Patients may need to remain in hospital even after their intravenous treatment is completed for continued management of raised intracranial pressure, for example. As noted in the introduction, the main focus of this Research Note is on treatment costs based on WHO guidelines. The 4 country-specific case studies (in the Excel files), however, can be used to address other questions and sensitivity analyses. For example, as noted above for Reviewer 1, comment 3, future data from a clinical trial or monitoring patient care in routine settings might suggest that actual in-patient care typically extends to 10 inpatient days on average for the flucytosine plus fluconazole regimen. Such adjustments can be easily estimated using the models provided (e.g., cost of this regimen in South Africa for 7 in patient days is $1,101 and $1,484 for 10 days. We have added this point into the main text of the paper (Section AmB-D plus flucytosine (seven hospital days)).

4. As discussed by the authors, there is uncertainty surrounding the cost of AmB-L. In the absence of accurate cost information and because potential costs of AmB-L vary so widely, have the authors considered a highest and lowest potential cost calculation for the treatment strategies that contain AmB-L? i.e. offer a range of potential costs?

Authors: We have added a last paragraph into the AmB-L section to include the recommendation of the reviewer. "While a substantially lower price ($16.25 per vial) has been reported by advocacy organizations (e.g., https://www.gaffi.org/gilead-reduces-price-of-ambisome-liposomal-amphotericin-b-for-cryptococcal-meningitis-in-hiv-aids/), this price has not yet been confirmed by Gilead. Obviously, costs would fall substantially for this regimen with the lower price. For example, costs per day for AmB-L would fall from $150 to $60 per patient with this cost (a low-end estimate), but overall costs would remain substantially higher than with AmB-D."

5. I'm not sure I understand the third paragraph under 'Target AmB-L to patients with baseline renal dysfunction' in the results section ('Note that the…'). I don't see that the statements made are reflected in figure 1? It appears to me that in all country case studies, the AmB-L/5FC option incurs the highest cost, with the option of AmB-L targeted to those with renal dysfunction incurring a lower cost than the reference regimen in all cases?
Authors: Thank you very much for highlighting the confusing paragraph. We have revised the section to clarify the comparisons being made. The AmB-L to patients with baseline renal dysfunction approach is the fourth option provided in Figure 1, which is mainly compared to the second option in Figure 1 AmB-D plus flucytosine for all patients. We then note that when compared to the 14-day regimen of AmB-D plus fluconazole (first regimen in Figure 1), costs for this fourth regimen are lower per 1,000 patients.

Additional comments

6. Second sentence in Introduction section: deaths are also due to ART failure; data show that improved access to ART does not necessarily correlate with reduction in deaths from

HIV-associated CM.

Authors: We agree with the reviewer's comment. We have revised this sentence to include diagnose, initiate, retain, and achieve viral suppression.... We think the addition of "retain and achieve viral suppression" includes a broader set of reasons for ART failure.

7. Under Model structure and assumptions subheading: should '...incident RD for a standard two regimen...' read, '...incident RD for a standard two week regimen...'?

Authors: Yes. Thank you. We have revised.

Competing Interests: No competing interests were disclosed.

Reviewer Report 11 October 2021

https://doi.org/10.21956/wellcomeopenres.18501.r46070

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Angela Kairu
Health Economics Research Unit, KEMRI-Wellcome Trust Research Programme Nairobi, Nairobi, Kenya

This paper succinctly describes different treatment regimens for cryptococcal meningitis in HIV patients and their associated costs. This paper highlights the use and costs of the different drug regimens against the context of resource constraints and patient contraindications of some of the medications.

My main comments are in the structuring of the various sections in the paper, and description of study methods.

The introduction gives a brief summary of the disease and outcomes. However, the 2nd and 3rd paragraph capture information that would better fit in the methods and conclusion sections respectively. Additionally, the introduction does not include any literature (past/current) on the drug regimens being costed. Perhaps the background provided in the methods sections would better fit in the introduction.

The methods provide a good overview of the costing model and assumptions used (additional files). However, some details on costing methods are not reported as these ensure replicability of the work. A useful guide for this may be (Cunnama L, Garcia Baena I, Laurence Y, Sweeney S, Vassall A, Sinanovic E et al. Costing guidelines for tuberculosis interventions. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO[1])

For the hospital based costs, which level of health facilities were sampled and costed? Or was this based on secondary data? This is not clear.

In addition it may be beneficial to conduct a sensitivity analysis on the uncertain cost parameters given the cost variations across the countries. This will strengthen the analysis and the results of the work.

The results and discussion sections are merged together which generally interpret the costs across the study countries. However, there are no comparisons to similar settings on the same drug regimens which would give a comprehensive understanding of the cost estimates and the variances. This ties to the limited literature of the drug regimens that is provided in this paper. Also, important to include is the limitations and strengths of this analysis.

References

1. Cunnama L, Garcia Baena I, Laurence Y, Sweeney S, et al.: Costing guidelines for tuberculosis interventions. *WHO*. 2019.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: economic evaluations of healthcare programmes

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 10 Mar 2022

Bruce Larson, Boston University School of Public Health, Boston, USA

Authors' responses and revisions based on Reviewer Reports (on Version1)

In the following, we provide a point-by-point response to each comment and suggestion provided by Reviewer 1. We have numbered each Reviewer comment to ensure a complete response and to note information across comments and reviewers.

Reviewer 1:

11 Oct 2021 | for Version 1
Angela Kairu, Health Economics Research Unit, KEMRI-Wellcome Trust Research Programme Nairobi, Nairobi, Kenya

Approved With Reservations

1. This paper succinctly describes different treatment regimens for cryptococcal meningitis in HIV patients and their associated costs. This paper highlights the use and costs of the different drug regimens against the context of resource constraints and patient contraindications of some of the medications.

Authors: Thank you for your efforts and guidance on this manuscript. In the following, we will respond to questions and explain how and where we have revised the manuscript based on the Reviewers comments (Dr. Kairu and Dr. Stott).

My main comments are in the structuring of the various sections in the paper, and description of study methods.

2. The introduction gives a brief summary of the disease and outcomes. However, the 2nd and 3rd paragraph capture information that would better fit in the methods and conclusion sections respectively. Additionally, the introduction does not include any literature (past/current) on the drug regimens being costed. Perhaps the background provided in the methods sections would better fit in the introduction.

Authors: Thank you for these comments. As recommended, we moved the "Methods Background" section to the introduction, which also provides additional literature on drug regimens. Also as suggested, we removed the last paragraph of the introduction from the introduction section. In hindsight, the information in that paragraph is essentially already in the conclusions section, so we just deleted it to avoid duplication. We hope it is acceptable to leave the original paragraph two in the introduction (now the final paragraph). We think it helps the reader to understand the main objective of the paper and what's to come.

3. The methods provide a good overview of the costing model and assumptions used (additional files). However, some details on costing methods are not reported as these ensure replicability of the work. A useful guide for this may be (Cunnama L, Garcia Baena I, Laurence Y, Sweeney S, Vassall A, Sinanovic E et al. Costing guidelines for tuberculosis interventions. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO1)

Authors: As recommended, we added the reference to Cunnama et al. along with the Drummond book (also a standard reference for costing methods). Regarding replication, all cost-related information, assumptions, and results for this manuscript come directly from the country-specific analyses (one Excel file per country) provided in the OpenBU repository referenced in this manuscript.

As importantly, any of these country-specific analyses can be used as a template for replication and adaptation in other contexts. For example, in the future, data from a clinical trial or observational study might suggest that actual in-patient care in that study extended from 7 to 10 inpatient days on average for the flucytosine plus fluconazole regimen. Such adjustments can be easily incorporated into the analysis for a study-specific analysis.

4. For the hospital based costs, which level of health facilities were sampled and costed? Or was this based on secondary data? This is not clear.

Authors: Because this article is intended as a Research Note, we did not review all of the specific assumptions used in each of the country-specific analyses. As noted in the section "Model structure and assumptions", such details can be found in the Excel file for each country. For example, for South Africa, the hospital cost assumptions (see sheet "Assumptions for all regimens") are in cells D63-D67 (and reference is in cell G63). In this base analysis presented in the paper, the hospital bed-day cost was 50% of the national average bed-day cost, which is considered a conservative assumption when comparing costs for different regimens.

5. In addition it may be beneficial to conduct a sensitivity analysis on the uncertain cost parameters given the cost variations across the countries. This will strengthen the analysis and the results of the work.

Authors: Because this article is intended as a Research Note, we did not include additional discussion based on sensitivity analyses. However, as noted in the section "Model overview", the Excel files for any country can be used as a template for additional analyses and for readers to explore the sensitivity of results to assumptions. For example, in the South Africa file, the base case hospital cost assumption is chosen as "50% of the national average" (cell c659 is 4). The file contains four other hospital cost possibilities that could be used for sensitivity analyses (the same structure exists in all the Excel files). We added additional information on conducting sensitivity analyses at the end of the methods section.

6. The results and discussion sections are merged together which generally interpret the costs across the study countries. However, there are no comparisons to similar settings on the same drug regimens which would give a comprehensive understanding of the cost estimates and the variances. This ties to the limited literature of the drug regimens that is provided in this paper. Also, important to include is the limitations and strengths of this analysis.

Authors: For each country, we consider AmB-D plus fluconazole with 14 in-patient days as reference point for discussing the results for the other regimens. This regimen is the comparison for the same setting for the other regimens evaluated (and presented in Figure 1). We have retitled the Results section to Results and Discussion to note the combination, which we think in this case makes sense. The focus here is on medications and combinations that are already recommended by the WHO (see reference 1 that provides substantial review of medications, etc.).

Competing Interests: No competing interests were disclosed.