Cost-effectiveness of single, high-dose, liposomal amphotericin regimen for HIV-associated cryptococcal meningitis in five countries in sub-Saharan Africa: an economic analysis of the AMBITION-cm trial

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Summary

Background HIV-associated cryptococcal meningitis is a leading cause of AIDS-related mortality. The AMBITION-cm trial showed that a regimen based on a single high dose of liposomal amphotericin B deoxycholate (AmBisome group) was non-inferior to the WHO-recommended treatment of seven daily doses of amphotericin B deoxycholate (control group) and was associated with fewer adverse events. We present a five-country cost-effectiveness analysis.

Methods The AMBITION-cm trial enrolled patients with HIV-associated cryptococcal meningitis from eight hospitals in Botswana, Malawi, South Africa, Uganda, and Zimbabwe. Taking a health service perspective, we collected country-specific unit costs and individual resource-use data per participant over the 10-week trial period, calculating mean cost per participant by group, mean cost-difference between groups, and incremental cost-effectiveness ratio per life-year saved. Non-parametric bootstrapping and scenarios analyses were performed including hypothetical real-world resource use. The trial registration number is ISRCTN72509687, and the trial has been completed.

Findings The AMBITION-cm trial enrolled 844 participants, and 814 were included in the intention-to-treat analysis (327 from Uganda, 225 from Malawi, 107 from South Africa, 84 from Botswana, and 71 from Zimbabwe) with 407 in each group, between Jan 31, 2018, and Feb 17, 2021. Using Malawi as a representative example, mean total costs per participant were US$1369 (95% CI 1314–1424) in the AmBisome group and $1237 (1181–1293) in the control group. The incremental cost-effectiveness ratio was $128 (59–257) per life-year saved. Excluding study protocol-driven cost, using a real-world toxicity monitoring schedule, the cost per life-year saved reduced to $80 (15–275). Changes in the duration of the hospital stay and antifungal medication cost showed the greatest effect in sensitivity analyses. Results were similar across countries, with the cost per life-year saved in the real-world scenario ranging from $71 in Botswana to $121 in Uganda.

Interpretation The AmBisome regimen was cost-effective at a low incremental cost-effectiveness ratio. The regimen might be even less costly and potentially cost-saving in real-world implementation given the lower drug-related toxicity and the potential for shorter hospital stays.

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See **Comment** page e1705

For the Chichewa translation of the abstract see **Online** for appendix 1

For the Isixhosa translation of the abstract see **Online** for appendix 2

For the Luganda translation of the abstract see **Online** for appendix 3

For the Setswana translation of the abstract see **Online** for appendix 4

For the Shona translation of the abstract see **Online** for appendix 5

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Introduction

HIV-associated cryptococcal meningitis is the second leading cause of AIDS-related mortality worldwide and causes approximately 15% of AIDS-related deaths.[1] The previous WHO-recommended first-line treatment regimen for cryptococcal meningitis was 1 week of amphotericin B deoxycholate (AmB) plus flucytosine followed by 1 week of high-dose fluconazole.[2] A detailed economic analysis showed this regimen to be less costly and more effective than the previous international standard of 2 weeks of AmB plus flucytosine.[3]

However, treatment with AmB, even for only 1 week, is associated with substantial drug-related toxic effects[4] that lead to long-term hospital stays and high health-care

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Research in context

Evidence before this study

HIV-associated cryptococcal meningitis is a leading cause of AIDS-related mortality and is an often-overlooked poverty-related disease associated with high mortality. The AMBIsome Therapy Induction OptimisatioN (AMBITION-cm) trial showed that a single, high-dose, liposomal amphotericin regimen was non-inferior to the previous WHO-recommended regimen of seven once-per-day doses of amphotericin B deoxycholate and was associated with significantly fewer adverse events. These results led to rapid changes in global guidance for cryptococcal meningitis treatment, with the WHO releasing updated guidelines recommending this simpler, safer treatment for cryptococcal disease in people living with HIV. However, the widespread use of liposomal amphotericin in areas with a high prevalence of advanced HIV disease has thus far been limited by both cost and access. A key part of the evidence needed to advocate for access to this novel treatment regimen is detailed costing and cost-effectiveness data. Having shown the clinical efficacy and safety of this treatment, it is therefore essential to present full economic analyses at country levels. To provide this, we conducted a five country, in-trial empirical economic analysis. We did not perform a systematic review as this was the first time the AmBisome regimen had been used in clinical practice and this is the first economic analysis of such an approach.

Added value of this study

This is the first cost-effectiveness analysis of the AMBITION-cm regimen compared with the previous WHO-recommended standard of care. We found incremental cost-effectiveness ratios ranging from US$91 to $152 per life-year gained in five diverse individual country settings. When we excluded protocol-driven costs, such as blood tests, the cost-effectiveness ratio ranged from $71 to $121 per life-year gained. We also present sensitivity data factoring in the potential effect if the AMBITION-cm regimen leads to a reduction in the length of hospital stays, and how the cost-effectiveness would be affected by fluctuations in antifungal drug prices.

Implications of all the available evidence

These findings show that the novel WHO-recommended AMBITION-cm regimen is highly cost-effective for the treatment of HIV-associated cryptococcal meningitis. These findings provide the essential evidence that key stakeholders require to initiate the wide-scale implementation of the AMBITION-cm regimen. The study findings also support ongoing advocacy efforts to ensure that the essential medicines required for this treatment, liposomal amphotericin B and flucytosine, are made available by the manufacturers at the agreed access prices.

costs. Liposomal AmB (L-AmB, AmBisome) is an alternative to AmB that is less toxic and can be safely given in high doses.[5–7] The AMBIsome Therapy Induction Optimisation (AMBITION-cm) trial was a phase-3 non-inferiority trial comparing a single high dose (10 mg/kg) of L-AmB given alongside 14 days of flucytosine and fluconazole (AmBisome group) with the previous WHO-recommended standard of care (control group).[8] A non-inferiority approach was adopted for the primary analysis because of the potential for the regimen to be simpler to administer and to be associated with fewer drug-related toxic effects.

The AMBITION-cm trial enrolled 844 participants and 814 were included in the intention-to-treat analysis, with 407 in each group. The proportion who died at 10 weeks was 24·8% (101 of 407; 95% CI 20·7–29·3%) in the AmBisome group compared with 28·7% (117 of 407; 24·4–33·4%) in the control group. The absolute difference in 10-week mortality risk between the AmBisome group and control group was –3·9% and the upper limit of the one-sided 95% CI for this mortality risk difference was 1·2%, within the prespecified 10% non-inferiority margin. In the prespecified adjusted analysis, the AmBisome group was superior to the control group at 10 weeks. In addition, fewer participants had grade 3 or 4 adverse events in the AmBisome group than in the control group (50·0% *vs* 62·3%).[8]

On the basis of the AMBITION-cm trial results, WHO updated its guidelines to include the single high-dose L-AmB regimen as recommended first-line therapy.[9] However, additional analyses of costs and potential cost-effectiveness are essential for informing policy and practice and enabling the uptake of the intervention. L-AmB is more expensive per vial than AmB and the L-AmB regimen requires an additional 7 days of flucytosine and fluconazole. Given the established superiority in the adjusted analysis of adverse events,[8] we performed a cost-effectiveness analysis to identify the economic implications of widespread implementation within low-resource settings. Our hypothesis was that the L-AmB regimen would be more expensive than the control regimen, but that the potential for increased or equivalent effectiveness combined with lower toxic effects and increased ease of use would result in the regimen being cost-effective.

Methods

Study design and participants

The AMBITION-cm trial enrolled patients with HIV-associated cryptococcal meningitis from eight hospitals in five countries (Botswana, Malawi, South Africa, Uganda, and Zimbabwe). The protocol[10] was approved by the research ethics committees at the London School of Hygiene & Tropical Medicine (UK), Botswana Ministry of Health and Wellness (Botswana), Malawi National Health Sciences (Malawi), University of Cape Town (South Africa), Uganda National Council for Science and Technology (Uganda), and Zimbabwe Medical Research

Council (Zimbabwe). Written informed consent was obtained from participants or from the next-of-kin if participants were incapable of consenting because of their clinical condition. If a participant recovered the capacity to provide consent, written informed consent was obtained from that participant. The primary outcome of the original study was all-cause mortality at 10 weeks.

Randomisation and masking

Participants were randomly assigned to either: (1) a single dose of L-AmB (10 mg/kg) plus 14 days of flucytosine (100 mg/kg per day) and fluconazole (1200 mg per day), which was the AmBisome group; or (2) AmB (1 mg/kg per day) plus flucytosine (100 mg/kg per day) for 7 days, followed by fluconazole (1200 mg per day) on days 8–14, which was the control group.

Data collection on service resource use and outcomes

The economic analysis methods have been described in detail previously.[11] We completed a full costing and cost-effectiveness analysis of the two treatment regimens over the 10-week trial period from the health-care provider perspective. The trial paid for all costs related to medical care during the trial, including travel, so out-of-pocket expenses were not included in this analysis. The study was designed in alignment with and conformed to the Consolidated Health Economic Evaluation Reporting Standards guidelines.[12] Resource use data were collected by use of an ingredients-based approach, in which each resource required for the intervention was identified and valued. The data on individual resource use and health outcomes were collected from all trial participants, based on data entered into and stored on a bespoke, securely encrypted, and fully validated Electronic Data Capture tool.

Health service costs

A detailed costing tool was developed that aimed to describe individual resource items grouped into six categories: hospitalisation costs, including the duration of hospital stay and both diagnostic and therapeutic lumbar punctures; blood tests; microbiology tests; radiology; cryptococcal treatment; and other treatment costs (intravenous fluids, electrolyte supplementation, blood transfusions, and antibiotics). We collated the costs for the resource use in each of the five country sites in the country-specific analyses (table 1). The first analysis was done on data from Malawi because the overall costs were closest to the average across all sites. The sites in Botswana and South Africa, which are upper-middle-income countries, were associated with higher-than-average hospital costs, and Uganda with lower-than-average costs. During the trial the economic situation in Zimbabwe was volatile and subject to substantial currency and price fluctuations, mainly because of high levels of inflation. The methods used to develop the Botswana, South Africa, Uganda, and Zimbabwe costing tools are described in detail elsewhere; however, the process involved modifying or updating, or both, existing costing tools.[11] Overhead costs, including the costs of admission and laboratory tests, were typically collated from a combination of hospital financial and utilisation documents and invoices provided to the trial administration.

Malawi costing

All costs in Malawi were collected in either Malawian Kwacha or US$ and were adjusted to 2020 US$ prices using the Campbell and Cochrane Economics Methods Group Evidence for Policy and Practice Information and Coordination Centre cost converter tool.[13] The

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	Malawi	Botswana	South Africa	Uganda	Zimbabwe
Hospitalisation					
Hospital admission, per bed-day	18·36	88·80	80·66	13·85	15·90
Lumbar puncture	18·36	27·20	33·89	10·31	5·99
Blood tests					
Chemistry	21·60	9·49	12·93	9·77	11·44
Chemistry plus alanine aminotransferase	35·64	16·30	16·38	11·16	22·88
Full blood count	11·34	8·99	6·83	4·19	25·20
CD4 count	19·66	32·29	5·05	11·16	17·68
HIV viral load	64·80	25·66	25·81	55·82	31·10
Microbiology					
Cerebrospinal fluid analysis	24·89	14·40	3·75	13·96	21·20
Urine culture	11·66	7·20	4·17	2·79	15·60
Bacterial blood culture, aerobic	18·36	22·08	9·19	18·14	15·60
Sputum culture, mycobacteria	30·18	18·20	4·17	13·96	7·80
Sputum acid fast bacilli	30·18	18·20	4·17	8·37	7·80
Sputum GeneXpert	26·88	18·58	14·60	22·68	36·40
Cerebrospinal fluid GeneXpert	26·88	18·58	14·60	22·68	36·40
Radiology					
Chest x-ray	24·00	23·18	14·76	2·77	7·93
CT head	169·11	291·55	174·06	41·92	43·59
Cryptococcal specific treatment					
Fluconazole, per 200 mg	0·13	0·13	0·13	0·13	0·13
Flucytosine, per 500 mg	0·93	0·93	0·93	0·93	0·93
Amphotericin B deoxycholate, per 50 mg	8·10	8·10	8·10	8·10	8·10
Liposomal amphotericin B deoxycholate, per 50 mg	16·25	16·25	16·25	16·25	16·25
Other treatment					
5% dextrose, per L	1·40	1·11	1·32	0·80	1·61
0·9% normal saline, per L	1·54	1·11	1·08	1·30	1·92
Intravenous potassium, per ampoule	0·55	0·84	0·55	2·33	1·00
Oral potassium, per tablet	0·03	0·03	0·03	0·03	0·03
Oral magnesium, per tablet	0·23	0·23	0·23	0·23	0·23
Blood transfusion, per unit	44·28	262·85	146·57	44·21	34·91
Thrombophlebitis treatment (oral)*	0·31	0·22	0·38	0·19	0·35
Thrombophlebitis treatment (intravenous)*	3·18	5·16	2·08	3·93	18·22
Bacteraemia*	81·13	805·90	634·90	122·11	84·00

*A standard, complete course of antimicrobial treatment for the indication listed.

Table 1: **Unit prices (US$ in 2020) by resource item in each of the five countries**

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hospital admission costs (hotel costs) per day were adapted from a detailed micro-costing study conducted in Blantyre, Malawi—an AMBITION-cm site.[14] These estimates included the time spent by health staff (doctors, nurses, and health-care auxiliaries) and non-medical staff (eg, maintenance and management), basic consumables, and institutional overheads. The costs of blood tests and microbiological investigations were derived from the same study.[14] Costs for radiological investigations were based on the average costs incurred in Lilongwe—another AMBITION-cm site in Malawi.[15]

Antifungal drugs were procured centrally and were distributed by the trial management group. The L-AmB for the trial was donated by the manufacturer (Gilead Sciences, Foster City, CA, USA). The L-AmB unit cost was based on the advertised cost per vial within their expanded access programme for cryptococcosis, which was $16·25.[16] Flucytosine ($0·93), fluconazole ($0·13), and AmB ($8·10) were costed per tablet or per vial on the basis of the most recent procurement during the trial, as were oral potassium and magnesium supplementation, which were given to avert amphotericin-related toxicity. Ancillary drugs used to administer antifungals (potassium chloride, intravenous saline, and antiemetics), as well as supplementary drugs to treat and prevent other HIV coinfections, such as antibiotics, were costed on the basis of tender price lists at Malawi Central Medical Stores, which has the mandate of procuring, stocking, and distributing health-care commodities to Malawi Government health-care facilities.

Health effects and cost-effectiveness measures

Our economic analyses used life-years saved as a generic health outcome. The primary outcome of the cost-effectiveness analyses was the health service cost per life-year saved. The life-years gained was based on the age-specific life expectancies in the relevant country life table in the WHO Global Observatory database.[17] We did not adjust the increase in survival for health-related quality of life. There were no significant differences between quality-of-life and disability outcomes by treatment regimen observed at the end of the 10-week trial: 11·9% of AmBisome group participants and 12·2% of control group participants reported ongoing symptoms, needing assistance from another person for everyday activities.[8] We assumed that surviving patients had normal life expectancies given the efficacy of current antiretroviral therapy.[18] As a result there was no discounting in our analysis.

See Online for appendix 6

Statistical and sensitivity analyses

In the original study, for the power calculation, assuming 35% mortality at 10 weeks in both groups, we calculated that a sample size of 390 per group would provide 90% power to show non-inferiority of the AmBisome regimen with a specified non-inferiority margin of 10%. Our primary empirical analysis was based on actual resource use observed per participant during the trial. For each country-specific analysis we applied the individual country-specific costs to the clinical data from the entire pooled trial population rather than those recruited in each individual country. Of note, there were no significant differences between groups at baseline when considering the effect of factors associated with outcome, such as age, sex, and antiretroviral therapy status. The total service cost per individual participant was calculated for each of the two treatment groups, as well as the difference in treatment costs. Next, we calculated the number of life-years saved to estimate the incremental cost-effectiveness ratio (ICER). The ICER was defined as the increment cost per life-year saved because the life-year saved was the primary health outcome, accounting for the distributions among individual participant input data. Data were analysed using Stata/SE version 15.1 combined with Excel version 16.1.

We conducted a probabilistic sensitivity analysis using Monte Carlo simulations with bootstrapping. Individual participants and their outcomes were sampled at random. Sampled participants were replaced and made available for repeat sampling with 10 000 samples drawn. Treatment effect, mean cost, and uncertainties were depicted on cost-effectiveness planes with 95% CIs and cost-effectiveness acceptability curves.

Additional scenario analyses included first establishing the real-world costs when implementing both treatment regimens outside of a controlled trial setting. A practical and feasible clinical blood monitoring schedule for both regimens, considering the differing toxicity profiles, was adopted on the basis of updated WHO guidance.[9] These schedules were less intensive than the monitoring schedule driven by the research protocol (appendix 6 p 4). Here, blood tests scheduled per trial protocol and not in the new monitoring schedule or required for toxicity reasons were omitted in these additional analyses. The second additional scenario analysis explored the effect of the length of hospital stay. Representative data on hospital admission duration were not provided by the main trial because all trial participants, including those in the AmBisome group, were in hospital for a minimum of 7 days for trial-mandated blood tests and lumbar punctures, including a lumbar puncture on day 7. Hospitalisation data from the clinical trial found that, among all participants who survived the initial hospital admission, 97 (28%) of 342 in the AmBisome group were discharged on day 7 or 8 compared with 67 (20%) of 336 in the control group, which might indicate that a proportion of participants were well enough to go home but were waiting to complete the protocol-mandated procedures (appendix 6 p 7). In the implementation of this regimen in a real-world scenario, it might therefore be possible to discharge some of the less-sick

	Mean total costs of services per participant	Deaths	Incremental cost per participant	Incremental death rate (%)	Incremental cost per life-year saved
Malawi: in-trial resource use					
Control group	1237 (1181 to 1293)	28·7% (24·4 to 33·4%)	Reference	Reference	Reference
AmBisome group	1369 (1314 to 1424)	24·8% (20·7 to 29·3%)	132 (53 to 211)	−3·9% (−10·0 to 2·2%)	128 (59 to 257)
Malawi: potential real-life resource use					
Control group	1125 (1071 to 1179)	28·7% (24·4 to 33·4%)	Reference	Reference	Reference
AmBisome group	1208 (1155 to 1261)	24·8% (20·7 to 29·3%)	84 (8 to 158)	−3·9% (−10·0 to 2·2%)	80 (15 to 275)
Botswana: in-trial resource use					
Control group	2049 (1939 to 2158)	28·7% (24·4 to 33·4%)	Reference	Reference	Reference
AmBisome group	2164 (2049 to 2280)	24·8% (20·7 to 29·3%)	116 (−43 to 274)	−3·9% (−10·0 to 2·2%)	91 (53 to 221)
Botswana: potential real-life resource use					
Control group	1993 (1885 to 2102)	28·7% (24·4 to 33·4%)	Reference	Reference	Reference
AmBisome group	2084 (1970 to 2198)	24·8% (20·7 to 29·3%)	91 (−67 to 248)	−3·9% (−10·0 to 2·2%)	71 (40 to 182)
South Africa: in-trial resource use					
Control group	1858 (1761 to 1956)	28·7% (24·4 to 33·4%)	Reference	Reference	Reference
AmBisome group	1994 (1890 to 2097)	24·8% (20·7 to 29·3%)	135 (−7 to 277)	−3·9% (−10·0 to 2·2%)	131 (65 to 251)
South Africa: potential real-life resource use					
Control group	1800 (1703 to 1896)	28·7% (24·4 to 33·4%)	Reference	Reference	Reference
AmBisome group	1906 (1804 to 2008)	24·8% (20·7 to 29·3%)	106 (−34 to 246)	−3·9% (−10·0 to 2·2%)	101 (80 to 140)
Uganda: in-trial resource use					
Control group	669 (644 to 694)	28·7% (24·4 to 33·4%)	Reference	Reference	Reference
AmBisome group	810 (784 to 836)	24·8% (20·7 to 29·3%)	141 (104 to 177)	−3·9% (−10·0 to 2·2%)	143 (85 to 217)
Uganda: potential real-life resource use					
Control group	628 (604 to 652)	28·7% (24·4 to 33·4%)	Reference	Reference	Reference
AmBisome group	748 (723 to 772)	24·8% (20·7 to 29·3%)	120 (85 to 154)	−3·9% (−10·0 to 2·2%)	121 (55 to 231)
Zimbabwe: in-trial resource use					
Control group	850 (819 to 881)	28·7% (24·4 to 33·4%)	Reference	Reference	Reference
AmBisome group	990 (956 to 1022)	24·8% (20·7 to 29·3%)	140 (94 to 184)	−3·9% (−10·0 to 2·2%)	152 (36 to 381)
Zimbabwe: potential real-life resource use					
Control group	760 (731 to 788)	28·7% (24·4 to 33·4%)	Reference	Reference	Reference
AmBisome group	857 (828 to 887)	24·8% (20·7 to 29·3%)	98 (57 to 139)	−3·9% (−10·0 to 2·2%)	107 (17 to 328)

Data shown as US$ or % (95% CI). Mean service costs per participant, case-fatality differences, incremental costs per participant, and incremental costs and effects for each of the five countries using actual in-trial resource use and the potential real-life resource use scenarios.

Table 2: **In-trial and potential real-life costs and deaths associated with resource use in each of the five countries**

individuals administered the AmBisome regimen earlier than day 7. We calculated by how many days, on average, the AmBisome regimen would need to reduce hospital stay to become cost-saving in a tipping point analysis. Finally, we conducted a bivariate sensitivity analysis showing the effect of fluctuations in the price of antifungal medications on the ICER.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The AMBITION-cm trial enrolled 844 participants, and 814 were included in the intention-to-treat analysis (327 from Uganda, 225 from Malawi, 107 from South Africa, 84 from Botswana, and 71 from Zimbabwe) with 407 in each group, between Jan 31, 2018, and Feb 17, 2021. On the basis of the efficacy findings, we conducted a cost-effectiveness analysis comparing the two trial groups.[11] In this economic analysis, we excluded one participant in the AmBisome group who withdrew consent immediately after enrolment and did not receive any study medication.

Detailed observed resource use by trial group is presented in the appendix 6 (pp 5–6). Differences in resource use were driven by the difference in the two antifungal regimens and the resources required to prevent or manage drug-related toxicity, or both. The mean duration of hospital stay was 13 days in both groups, which was a function of the research protocol that required that all participants stay in hospital for a minimum of 7 days, regardless of trial group, for safety reasons.

In Malawi, the mean actual per participant total costs were US$1369 (95% CI $1314–1424) in the AmBisome group and $1237 ($1181–1293) in the control group

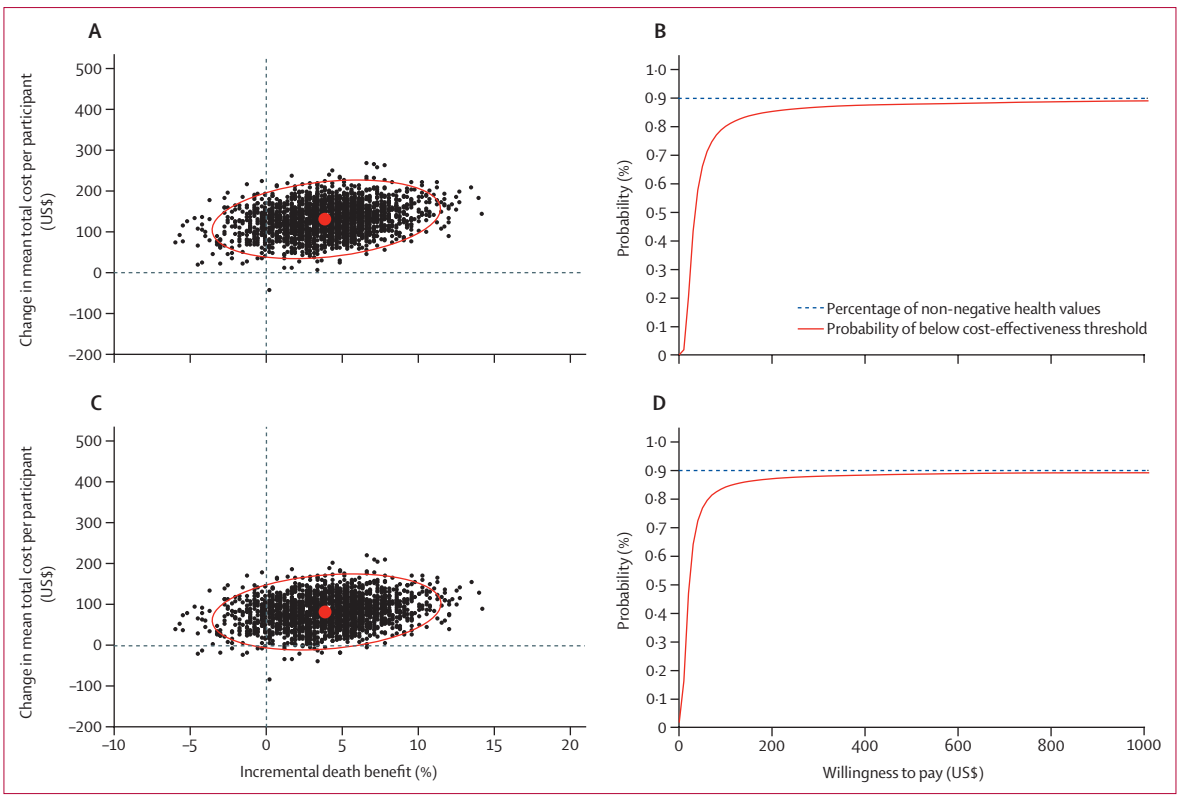

Figure 1: **Monte Carlo simulation for Malawi**

(A) Cost-effectiveness plane of deaths prevented (%) and incremental health service cost (US$ in 2020) in the in-trial scenario. (B) Cost-effectiveness acceptability curve of AmBisome treatment against the control in the in-trial scenario. (C) Cost-effectiveness plane of deaths prevented (%) and incremental health service cost (US$ in 2020) based on the potential real-life resource use scenario. (D) Cost-effectiveness acceptability curve of AmBisome treatment against the control based on the potential real-life resource use scenario. Panels (A) and (C) had 10 000 bootstrap iterations with 2000 shown with a 95% CI ellipse. The red dot denotes the mean. For panels (B) and (D), the red line denotes the cumulative probability of the AmBisome group being more cost-effective than the control treatment at a particular willingness to pay threshold (ie, cost per life-year gained). The dashed line denotes the cumulative probability of positive health benefits.

(table 2). The mean difference in cost between the groups was $132 ($53–211). The largest proportion of the total cost was due to hospital stay, at 42% ($576) in the AmBisome group and 48% ($591) in the control group, followed by blood tests (25% [$346] in the AmBisome group and 28% [$351] in the control group) and antifungal drugs (25% [$342] in the AmBisome group and 13% [$155] in the control group; appendix 6 p 8).

The median age of participants in both groups was 37 years (range 18–71 years). We calculated an estimated 27·2 years of life remaining per participant in Malawi and a total of 409 additional life-years saved among the 406 participants in the AmBisome group. On the basis of the actual resource use in the trial, we established an ICER of $128 (95% CI $59–257) per life-year saved in the AmBisome group (table 2). The average service costs per participant, case-fatality differences, incremental costs per participant, and incremental costs and effects in the other four countries are also presented in table 2 and show an ICER per life-year saved of $91 in Botswana ($53–221), $131 in South Africa ($65–251), $143 in Uganda ($85–217), and $152 in Zimbabwe ($36–381).

Figure 1 shows the Monte Carlo simulation for the Malawi setting. Figure 1A shows a cost-effectiveness plane in a scatter plot presenting the incremental costs and death prevented (%) in the AmBisome group, and figure 1B shows a cost-effectiveness acceptability curve denoting the probability of the AmBisome group being more cost-effective at a particular willingness to pay threshold. From the simulations, the mean increase in the AmBisome treatment costs per patient was calculated to be $132 (95% CI $53 to $210) with a 3·9% reduction in mortality (95% CI −2·3 to 10·0%). The cost-effectiveness acceptability curve shows that at a willingness to pay threshold of $300 per life-year saved, the probability that the AmBisome treatment is cost-effective compared with the control treatment would be 87·0%, and with a willingness to pay threshold of $500 per life-year saved, it would be 88·0%. Similar findings for the other four countries are available in the appendix 6 (pp 9–12).

Using realistic schedules for laboratory monitoring in Malawi, we calculated a mean cost of $1208 (95% CI $1155–1261) per participant in the AmBisome group and of $1125 ($1071–1179) in the control group, with a

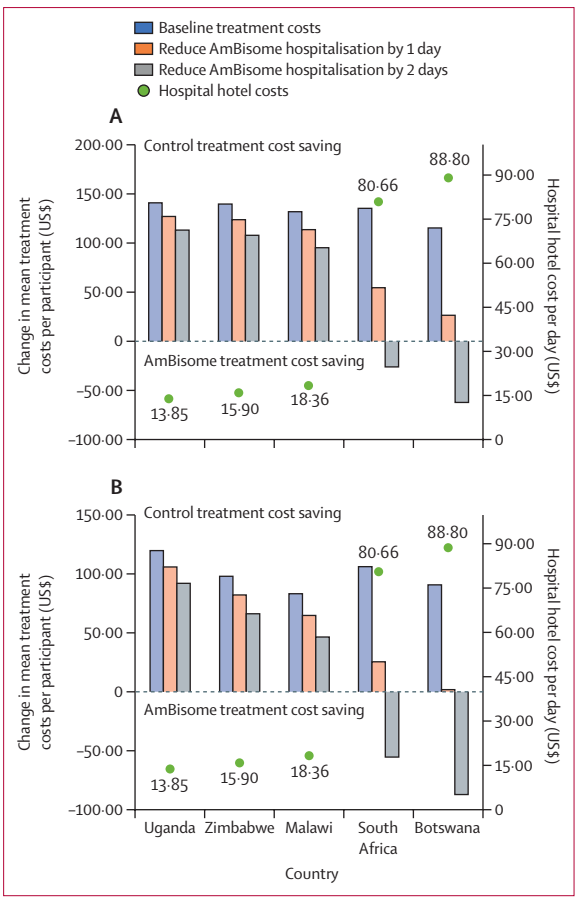

Figure 2: **Tipping point scenario analysis**
Figure shows the change in mean treatment costs per participant if the admission duration in the AmBisome group was reduced by 1 or 2 days in each of the five country settings, in either (A) in-trial resource use or (B) potential real-life resource use.

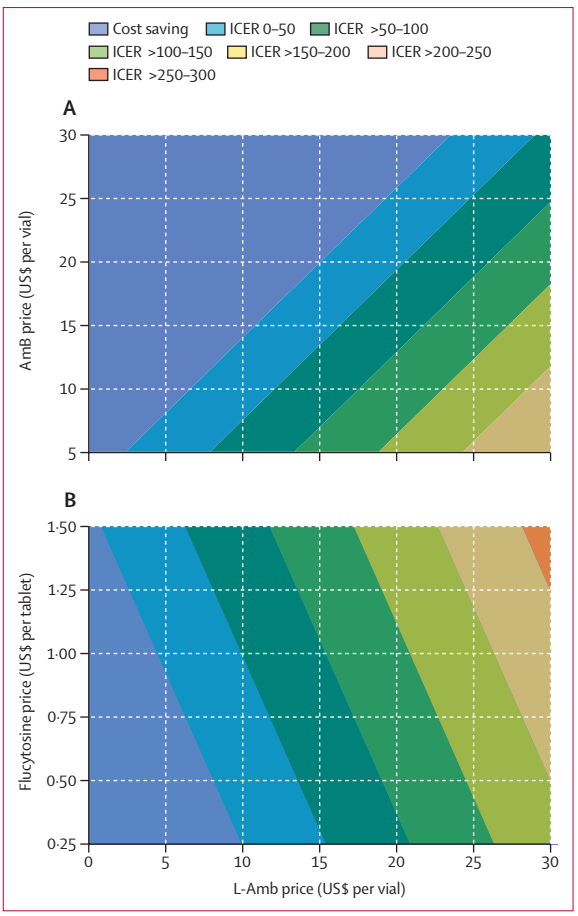

Figure 3: **Bivariate sensitivity analysis on the effect of fluctuations in antifungal medication prices on the ICER using the potential real-life resource use in Malawi**
All other variables held constant. (A) Fluctuations in the price of L-AmB, with costs ranging from US$5 to $30 per 50 mg vial, and AmB, with costs ranging from $2 to $20 per 50 mg. (B) Fluctuations in the price of L-AmB, with values ranging from $5 to $30 per 50 mg vial, and flucytosine, with values ranging from $0·30 to $1·50 per 500 mg pill. In this analysis the price of AmB was constant at $8·10. 5FC=flucytosine. AmB=amphotericin B deoxycholate. ICER=incremental cost-effectiveness ratio. L-AmB=liposomal amphotericin B deoxycholate.

difference between the groups of $84 ($8–158) and an ICER of $80 ($15–275) per life-year saved (table 2). Figure 1C shows a cost-effectiveness plane and figure 1D shows a cost-effectiveness acceptability curve for this scenario. From the simulations, the mean increase in the AmBisome treatment costs per patient was calculated to be $83 (95% CI $7 to 158) with a 3·9% reduction in mortality (–2·3 to 10·0%). The cost-effectiveness acceptability curve shows that at a willingness to pay threshold of $300 per life-year saved, the probability that the AmBisome treatment is cost-effective compared with the control treatment would be 88·0%, and with a willingness to pay threshold of $500 per life-year saved, it would be 88·7%.

Using this scenario, we calculated an ICER of $71 in Botswana ($40–182), $101 in South Africa ($80–140), $121 in Uganda ($55–231), and $107 in Zimbabwe ($17–328). The appendix 6 (pp 13–16) shows these findings for the other four countries on cost-effectiveness planes and in cost-effectiveness acceptability curves.

The mean duration of hospital stay in the trial within both groups was 13 days, which, as described above, is unlikely to reflect the required hospital stay in non-trial settings. The hospital hotel cost of 1 day in hospital was $13·85 in Uganda, $15·90 in Zimbabwe, $18·36 in Malawi, $80·66 in South Africa, and $88·80 in Botswana. A tipping point scenario analysis calculated that if patients in the AmBisome group were clinically stable to be discharged on average 5 days earlier than those in the control group in Malawi, this would result in overall cost savings. A similar analysis for the other sites projected cost savings with the AmBisome group if patients were able to be discharged earlier by 2 days in Botswana and South Africa, 8 days in Zimbabwe, and 9 days in Uganda (figure 2).

Bivariate sensitivity analyses showing how fluctuations in the cost of AmB, L-AmB, and flucytosine would affect the total service costs in the ICER calculation in the implementation scenario are shown in figure 3 and show that increases in the cost of L-AmB and flucytosine would result in a larger ICER, whereas increases in the cost of AmB would result in a lower ICER. Given the increased quantity of flucytosine used in the AmBisome group, reductions in both flucytosine cost and L-AmB cost reduce the ICER in favour of the AmBisome group.

Discussion

A single, high-dose, L-AmB-based regimen for HIV-associated cryptococcal meningitis is cost-effective in comparison with the previous WHO-recommended standard of care, with an additional cost of $128 per life-year saved in Malawi and similar results in the other four countries. The cost per life-year saved was low and in some countries we identified a high chance of cost reduction, indicating excellent cost-effectiveness. These costs per life-year gained and incremental cost-effectiveness ratios are low, because they are driven both by the increase in life-years as patients are saved from dying young and also the potential major reduction in the number of admission days, which are a notable driver of cost. The results are consistent across the five countries and indicate cost-effectiveness compared with other cryptococcal meningitis regimens,[3] with other similar interventions in similar country settings,[19] and with international approaches such as the use of gross domestic product per person for the individual countries and other comparative approaches.[20]

The actual net benefits of the L-AmB regimen, both clinically and economically, over standard care in a real-life setting might not have been fully realised in the trial because the protocol mandated that participants should stay in hospital for a minimum of 7 days. Some individuals with milder disease might be able to leave hospital sooner and this would reduce hospitalisation costs, which make up the largest proportion of the overall costs. The trial also adopted an intensive monitoring schedule. Given the reduced toxicity profile of the L-AmB regimen, the monitoring schedule adopted in routine care could include fewer blood tests than required for the control regimen, without compromising care and further reducing costs, as shown in our sensitivity analyses. Furthermore, within the trial we administered pre-emptive fluids and electrolytes to reduce the risk of AmB toxicity and actively managed adverse events when they occurred. However, the reality of routine care in settings with few resources is that the necessary resources are often not available to implement such an intensive approach. The better-tolerated L-AmB regimen might therefore confer larger survival benefits over the 1-week AmB regimens than we have been able to present in our analyses.

There is an urgent need for increased access to antifungal medication, particularly L-AmB and flucytosine, at an affordable price. Our sensitivity analysis found fluctuations in price to strongly affect economic outcomes. L-AmB is difficult and expensive to manufacture and most of the global supply is produced by a single manufacturer, Gilead Sciences. To date, there has been a low roll-out of the expanded access programme for cryptococcosis, which provides L-AmB at $16·25 per vial. However, after the presentation of the AMBITION-cm results, Gilead reaffirmed their commitment to this programme.[21]

Since the Advancing Cryptococcal Meningitis Treatment for Africa trial,[22] the availability of flucytosine has increased in sub-Saharan Africa, after advocacy efforts and a joint Unitaid and Clinton Health Access Initiative programme that has distributed antifungals to high-incidence countries.[23] Additional pharmaceutical companies are now manufacturing flucytosine and new formulations are under development, which might continue to drive down the price. The April, 2021 Global Fund reference price for flucytosine is $0·75 per tablet[24] and the Unitaid and Clinton Health Access Initiative programme has reported accessing flucytosine at $0·65 per tablet.[25] These costs would result in an ICER of $68 per life-year saved in the in-trial scenario and $61 per life-year saved in the potential real-life scenario if L-AmB is sold at $16·25 per 50 mg vial.[26] Although the most recent purchase of standard AmB for the trial in December, 2020 was at a rate of $8·10 per 50 mg vial, and this was the price used in this analysis, the cost in each of the included countries fluctuated during the trial and was sometimes both higher and lower. AmB has become more expensive in sub-Saharan Africa since 2018 because of interruptions to availability resulting from changes in manufacturer. In addition, AmB requires a cold chain with storage in a 2–8°C refrigerator, which can be logistically complex, whereas L-AmB can be stored at an ambient temperature.

This economic analysis was conducted within a single trial, so the reproducibility of the results might be limited; however, we aimed to partly overcome this by adopting a multicountry approach. We applied each of the five country costing tools to all trial participants across all sites, rather than just to those recruited in each specific country. This approach was to ensure a large sample size from which we could draw conclusions, but some of the heterogeneity in resource use between country settings might have been lost. Compared with our empirical, in-trial scenario, the hypothetical real-life scenario was based on expert consensus among clinicians and might not be an accurate prediction when it comes to real-world implementation. Finally, these results were heavily affected by the cost of the antifungal medications, which fluctuated in price throughout the trial; however, we attempted to address this by performing bivariate sensitivity analyses.

In conclusion, the single, high-dose L-AmB regimen is cost-effective in various resource-limited settings. This study provides complementary evidence to the clinical data from the AMBITION-cm trial in support of the change of guidelines and practice for the management of HIV-associated cryptococcal meningitis. There is an urgent need to increase access to L-AmB and flucytosine to ensure that the improvements in survival from cryptococcal meningitis made possible by novel treatment regimens are realised globally.

Contributors

All authors conceptualised the work, developed the methods, and contributed to project administration, data collection, and curation. DSL, TB-C, SFM, NY, SJa, TSH, and JNJ developed the software. DSL, CMut, TB-C, and NY verified the data. DSL and NY had access to the raw data. DSL, CMut, and TC analysed the data, validated the results, and created the visualisations, and SJa, TSH, JNJ, and LWN supervised. DSL, CMut, TSH, JNJ, and LWN wrote the original manuscript and all authors reviewed and edited the manuscript. DSL, CMut, TSH, JNJ, and LWN had final responsibility for the decision to publish. SJa, TSH, JNJ, and LWN acquired the funding.

Declaration of interests

TSH was the recipient of an investigator award to his institution from Gilead Sciences; speaker fees from Pfizer and Gilead Sciences; and serves as an adviser for F2G. JNJ and GM both declare speaker fees from Gilead Sciences. All other authors declare no competing interests.

Data sharing

Anonymised, individualised participant data are available upon request from the London School of Hygiene & Tropical Medicine Data Compass (https://datacompass.lshtm.ac.uk). The study protocol, informed consent forms, and standard operating procedures are available at https://blogs.lshtm.ac.uk/ambition.

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