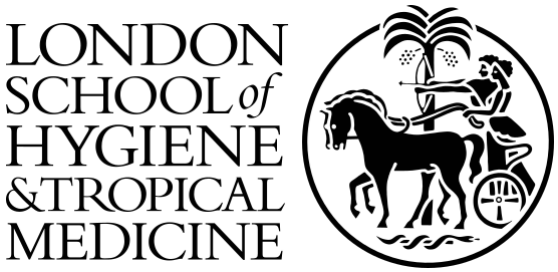

Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: a cost-effectiveness analysis.

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Summary: In a large phase III randomised-controlled trial among HIV-infected persons presenting with late stage HIV-infection , we showed that cryptococcal meningitis screening and community-based early adherence support was a highly cost-effective strategy in reducing all-cause mortality.

ABSTRACT

Background

A randomised trial demonstrated that among late-stage HIV-infected patients initiating ART, screening serum for cryptococcal antigen (CrAg) combined with community -based adherence support reduced all-cause mortality by 28%, compared with standard clinic-based care. Here, we present the cost-effectiveness estimates.

Methods

HIV-infected adults with CD4 count<200 cells/μl were randomised individually to either CrAg screening plus 4-weekly home visits conducted by lay-workers to provide adherence support or to standard clinic-based care in Dar es Salaam and in Lusaka. Data on individual resource use and health outcomes were collected from all participants.

Unit costs were obtained in Dar es Salaam. The primary economic outcome was health service care cost per life year saved as the incremental cost-effectiveness ratio (ICER), based on 2017 US$. Regression models were used to estimate adjusted mean incremental costs and death rates. Life years saved were estimated based on reported comparable survival data. We used non-parametric bootstrapping to assess uncertainties, and univariate deterministic sensitivity analysis to examine the impact of individual parameters on the ICER.

Results

1,001 and 998 participants from the intervention and standard arms were enrolled respectively. The annual mean costs per participant in the intervention arm was US$ 339 (95% confidence interval (CI): 331 – 347), resulting in an incremental cost of the intervention of US$ 77 (95% CI: 66 - 88). The incremental cost was similar when analysis was restricted to persons with CD4 count <100 cells /μl.

The ICER for the intervention versus standard care, per life year saved, was US$ 70 (95%CI: 43 -211) for all participants with CD4 count up to 200 cells/μl and US$91 (49–443) among those with CD4 counts <100 cells /μl. The cost-effectiveness results were most sensitive to mortality estimates.

Conclusions

Screening for cryptococcal antigen in patients with CD4 count up to 200 cells/μl, combined with a short period of home-based adherence support, is cost-effective in resource-limited settings.

KEYWORDS: cost-effectiveness, HIV late-stage disease, cryptococcal meningitis, adherence support, Africa

BACKGROUND

Antiretroviral therapy (ART) is available widely in Africa, but HIV-associated mortality remains high, particularly during the first few months that patients come into care [1-4]. Most of the early mortality is attributed to tuberculosis and cryptococcal meningitis [5-8]. We recently conducted a large randomised-controlled trial among HIV-infected patients starting ART with with CD4 count <200 cells /μl in Dar es Salaam, Tanzania and in Lusaka, Zambia, known as the REMSTART trial [9]. The intervention comprised i) screening for cryptococcal infection using serum cryptococcal antigen (CrAg) combined with pre-emptive fluconazole therapy for patients testing CrAg positive; and ii) weekly home visits for the first 4 weeks for patients on ART by trained lay workers to provide adherence support. This package was compared with standard care. Participants in both arms were screened for tuberculosis with sputum Xpert irrespective of symptoms and all were initiated rapidly on ART within a median of 14 days (interquatile range of 9-20 days) following presentation. At 12 months of follow-up, all cause mortality was 28% (95% confidence interval (CI): 11% - 43%) lower in the intervention arm compared to that in the standard care arm.

Findings from the trial informed the WHO guidelines on the management of late-stage HIV-infection in Africa [9]. However, coverage of CrAg screening remains low [10] despite the WHO recommendation and low cost of a CrAg test, and very few settings offer repeated initial adherence support to patients with advance disease starting antiretroviral therapy. To inform policy and practice considerations, we conducted a cost-effectiveness analysis of CrAg screening and early adherence support compared with standard care using data from the REMSTART trial.

METHODS

Study design and participants

The REMSTART trial results have been published [9, 11]. In brief, the participants were HIV-infected adults presenting for care at routine health services between February 2012 and September 2013. 1001 were randomised to the intervention arm and 998 to standard care. In the intervention arm, the participants were screened for serum CrAg using lateral flow tests (IMMY, Norman, OK, USA) and promptly started on fluconazole (800 mg per day for 2 weeks followed by 400 mg per day for 8 weeks) if they were CrAg positive. In addition, they received up to 4 weekly home visits by trained lay-workers during the first 4 weeks of starting ART. The primary endpoint was all-cause mortality at 12 months of follow-up.

The economic evaluation was nested within the trial and done from a health care provider's perspective [11, 12]. The resource use and related costs were collected from all participants. Unit costs were obtained from Dar es Salaam [10]. We assessed the incremental cost-effectiveness ratio (ICER) of the intervention versus standard treatment for the duration of the follow up period. It was assumed that the illness pathways of the control and treatment

group would be equivalent thereafter and that the incremental impact of the intervention on morbidity would thus be negligible.

Measurement of costs and outcomes

Health cost data were collected in 2012 and capital costs were discounted using a discount rate of 7.8% equal to the 2-year Tanzanian government bond at the time of calculation, June 2014 [13]. All costs were converted to 2017 US$ using a gross domestic product deflator and an exchange rate [14].

Life years gained was used as the primary outcome measure. As the morbidity effects of the intervention relative to the mortality effect, are likely to be minimal in this context, these can be used to approximate DALYs saved. In order to estimate life years gained, we computed the difference in the annual probability of death between the intervention and control arms (rather than the incidence rates of death per person-years of observation used in the main paper [9]), and multiplied this by the related life expectancy. We assumed that average life expectancy was 24.0 years (95% CI: 22.2 – 25.8) for all patients with CD4 count up to 200 cells/μl, 18.7 years (95% CI: 17.2 – 20.3) for patients with CD4 cell count <100 cells /μl, and for patients with CD4 cell count <50 cells /μl based on data for similar patients on ART [15].

Statistical analyses

Differences between the intervention and standard care in costs and mortality were estimated using seemingly unrelated regression equations to account for the correlation between costs and mortality [16]. The models included baseline body weight, baseline CD4 count and baseline hemoglobin levels which were shown to predict mortality at 12 months. ICERs were estimated by dividing mean incremental costs by the mean number of life years saved, and cost-effectiveness planes and acceptability curves were plotted. Confidence intervals were obtained using non-parametric bootstrapping.

Univariate deterministic sensitivity analyses were done to assess the impact of parameter uncertainty on the ICER and were presented as a standard tornado sensitivity graph. The parameter ranges used for sensitivity analysis were based on 95% confidence intervals calculated from the REMSTART data and the observed life expectancy confidence intervals [15]. We conducted a secondary analysis, restricting to participants with CD4 count level <100 cells /μl, as CrAg screening is recommended for this HIV-infected population [17].

Ethics statement

The study was approved by the ethics committee of the London School of Hygiene & Tropical Medicine, the Ethics and Research Science committee in Zambia, and the National Health Research Ethics Sub-Committee in Tanzania.

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. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

RESULTS

Table 1 presents the unit costs for the different components of antiretroviral treatment (ART) services and the quantity of resources utilised by participants. The mean cost of a home visit was almost 3 times higher than the cost of the participant visiting the health facility. The unit price for the home visit comprised monthly salary for the lay worker, training, communication and transport allowance. CrAg testing was about a quarter of the cost of either a CD4 count or Xpert test.

The total mean costs per patient did not differ by CD4 count category for either arm (Table 2). The intervention resulted in approximately 30% (95% CI: 25 – 35) increase in the cost per patient, and resulted in an incremental cost effectiveness ratio of US$ 70 (95% CI: 43, 211) for participants with CD4 <200 cells /μl.

The absolute reductions in death rates between the intervention and standard care did not differ significantly by CD4 count category (Table 2). The mortality risk ratio of the intervention (134/1001 deaths) versus standard care (180/998 deaths) was 0.74 (95% CI: 0.60 - 0.91) among all participants with CD4 <200 cells /μl. For participants with CD4 count <100 cells /μl, this risk ratio was 0.77 (95% CI: 0.62 – 0.96) (114/724 versus 144/707 deaths).

Cost-effectiveness, uncertainty and sensitivity analyses

The intervention was more costly but more effective than the standard care (Figure 1). Average incremental cost-effectiveness ratios increased somewhat with decreasing CD4 cell count category (Table 2).

The probability that the intervention is cost effective when compared with the standard care if the decision-makers are willing to pay between US$ 100 and US$ 150 for an additional life year saved varies between 84% and 95% in persons with CD4 count <200 cells /μl and between 62% and 82% in persons with CD4 count <100 cells /μ (Figure 2).

In sensitivity analyses, the most influential parameter of the incremental cost-effectiveness ratio was the mortality rate (Figure 3). If the annual mortality in the intervention arm is as low as 12%, then the incremental cost-effectiveness ratio is reduced to US$54 per life year saved.

DISCUSSION

Our analysis demonstrates that screening of patients presenting with advanced HIV disease for cryptococcal meningitis combined with a short intensive period of adherence support is

likely to be cost-effective for most settings in Africa [18-20]. The average cost per patient of the intervention compares favourably with those of other interventions in Africa such as providing outpatient HIV counselling, testing and ART treatment in Nigeria [21], and other ART services in Zambia, Kenya, Burkina Faso and South Africa [22-27]. A strength of the trial is that it was done in close to normal health service conditions, with for example, government employed health care workers managing the patients using national guidelines.

The home-based adherence support component involved the use of trained lay-workers visiting the homes of patients by public transport. The cost of home visits – up to about $80 for most participants - was the major driver of total costs. Trial participants were scattered and lay-workers travelled between patient houses. In a small sub-sample, we estimated that the lay-workers took about 50-60 minutes to travel from one patient's house to the next, and that this was about twice the amount of time that they actually spent at a patient's home. Further, on some days, particularly near the start of the trial, some lay-workers made only one or two home visits a day because we had not recruited sufficient numbers of patients. In real life, if this approach was rolled out universally, many patients would be on therapy and the increased patient density would reduce travel distances. Health services would also identify long-term lower cost ways of travelling between houses, such as field-workers travelling on bicycles or motorbikes, which were not practical during the normal course of trial. The costs could be reduced further by use of alternative methods of providing support, such as through mobile phones. If the cost per home visit decreased from $19.51 to $5, this will result in an average incremental cost of $33 for the intervention, subsequently reducing the average incremental cost effective ratio to $30 per life year saved, using a conservative life expectancy of 24 years. If we assume a life expectancy of 35 years for participants on antiretroviral therapy, the incremental cost-effective ratio becomes $20 per life year saved.

In the CrAg screening component, we have over-estimated the cost of CrAg testing. The cost of a single test was $5 and a single test was done to identify a single CrAg positive person. The CrAg test is simple and its cost will fall with expanded use. Also, the prevalence of CrAg positivity was lower in our study than the average reported in Africa [17, 28].

Finally, we calculated cost-effectiveness based on a health care perspective and did not assess societal benefits, for example the benefits of increased productivity arising from improved health status. We also used a conservative estimate of life expectancy calculated taking CD4 count into account. Had we used WHO estimates of life expectancy for Tanzania [29], the incremental cost-effectiveness ratio would have been even lower.

Thus, all-in-all, the intervention tested will be highly cost-effective, with a likely incremental cost-effectiveness ratio of somewhere between $10-$20 per life year saved.

With complex interventions, as that employed here, it is impossible to disentangle the effects of the CrAg individual component from the enhanced adherence component but it is very clear that as combined, this is an important new intervention for African HIV services to consider for HIV-infected persons with advanced HIV disease. The effects of CrAg screening beyond CD4 count of 100 cells /μl or more are unknown as there are no other data, besides ours, that have tested for CrAg at higher than this CD4 count. Our study found fewer CrAg

positive cases in the group that had CD4 counts between 100 and 200 cells /μl, and as expected, the death rate in this group was lower than in those with lower CD4 counts. This lowers the incremental cost-effectiveness ratio. In our study, the combined intervention was as cost-effective at CD4 count <200 cells /μl as at CD4 count <100 cells /μl, presumably because survival is better achieved when we initiate interventions at an earlier disease stage. More data are needed of CrAg prevalence above 100 cells /μl CD4 count.

Because of the limited evidence around cost-effectiveness, coverage of CrAg screening combined with pre-emptive fluconazole has remained low [10], despite being recommended by WHO [9]. A study from South Africa had suggested that such an intervention is cost-effective [30] but the findings from a middle-income setting are difficult to generalise to low-resource settings. In Uganda, a similar cost-effectiveness study, led to the same conclusions [31]. Both studies had modelled cost-effectiveness from the health care perspective, and have not been enough to facilitate a higher scale up of CrAg screening. Our study estimated cost-effectiveness using empirical data from a large cohort in 2 countries. We calculated costs from the health care pespective and the findings demonstrate clearly that this intervention is highly cost-effective even in low-resource settings.

For patients who are CrAg positive, mortality is 2-3 times higher even with prompt pre-emptive treatment with fluconazole and combined with enhanced adherence support than that in CrAg negatives [9]. A more potent regimen is needed. A recent large trial demonstrated that flucystosine, when added to fluconazole, is a highly effective oral combination for the management of patients with confirmed cryptococcal meningitis and even at current prices, is highly cost-effective compared with fluconazole monotherapy, with an incremental cost-effective ratio of US$65 per life year saved [32]. This oral combination needs urgent evaluation of cost-effectiveness in CrAg positive persons. Findings from Uganda [33] and South Africa [34] suggest that in asymptomatic persons, the CrAg titre predicts mortality, suggesting that the oral combination might only be needed for this group.

The number of persons presenting with advanced disease is likely to remain high for the foreseeable future, since alongside the large number of people who still delay accessing ART services, there are many dropping out of care or failing on ART. With the findings of this analysis and the recent trial of the management of cryptococcal meningitis [5], we can now begin to reduce this mortality in cost-effective and sustainable ways.

Author contributions:

SJ, SGM, TSH designed the original trial and SGM led the co-ordination of the trial with support from SK, DC and PM. CB did the original trial efficacy analysis, which was also used in the present paper.

GDK and LG designed the health economics study nested within the trial and GDK, with support from SK and DC, co-ordinated the health economics data collection.

GDK wrote the first draft of the paper and played the major role in writing therafter with regular support from LWN, LG and SJ.

TS, SK, CB, AK, NH, SGM, TSH commented on several drafts.

GDK led the initial analysis of costs and cost-effectiveness and oversaw and contributed to the final cost-effectiveness analysis, which was led by TS, TC. The analysis was supervised initially by LG and then by LWN.

All the authors contributed to the near final drafts of the paper and saw and agreed the final draft.

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Conflicts of interest: none declared by any other.

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Table 1. Unit Costs (in 2017 US$) and quantity of resources utilised (and standard deviation) per study participant in each by arm, over 12 months [a].

Cost component	Unit price($)	Unit of measurement	Intervention (n=1001)	Standard care (N=998)
Outpatients visits			**Mean (STD)**	**Mean (STD)**
Initial visits	8.93	Visit	1.05(0.36)	1.04(0.37)
ART eligibility assessment visit	7.99	Visit	1.16(0.44)	1.10(0.33)
Six-monthly clinic review visit	8.92	Visit	0.81(0.77)	0.79(0.81)
Routine follow-up visit	7.62	Visit	3.89(2.77)	3.56(2.81)
Home visit[b]	19.51	Visit	3.06(1.43)	0.01(0.18)
Laboratory				
CD4 count test	20.86	Test	1.55(0.62)	1.51(0.62)
Liver function (ALT) test	1.16	Test	1.27(0.59)	1.19(0.56)
Creatinine test	0.41	Test	0.89(0.44)	0.87(0.44)
Haemoglobin (Hb) test	1.15	Test	1.46(0.73)	1.35(0.68)
Syphilis (VDRL) test	1.13	Test	0.03(0.18)	0.03(0.17)
Pregnancy test	2.50	Test	0.14(0.47)	0.13(0.44)
Xpert test	25.23	Test	0.96(0.61)	0.82(0.46)
CrAg test	5.24	Test	0.98(0.13)	0.01(0.08)
CSF test	21.55	Test	0.01(0.09)	0.00(0.00)
Chest X-ray	2.70	X-ray	0.05(0.21)	0.04(0.19)
Medication				
Days on antiretroviral therapy	0.56	Day	260.47(137.23)	250.27(140.70)
Days on co-trimoxazole treatment	0.02	Day	263.22(136.00)	254.82(139.76)
10-week fluconazole course[c]	6.35	Course	0.07(0.37)	0.00(0.00)
Hospitalisation				
Overnight hospital stay	35.00	Day	0.18(1.17)	0.22(1.55)

CrAg, cryptococcal antigen; CSF, cerebrospinal fluid; ART, antiretroviral therapy; VDRL, veneral disease research laboratory; STD, standard deviation

[a]Unit prices for all tests apart from patients do not include overhead costs

[b]Home visit costs included monthly salary for the lay worker, communication and transport allowance and training costs

[c]800 mg per day for 2 weeks and then followed by 400 mg per day for 8 weeks, 200 mg/d thereafter (after 10 weeks)

Table 2: Incremental cost-effectiveness ratios (incremental cost per life year saved) comparing the intervention with standard care according to baseline CD4 count

	Life expectancy (years)[a], 95% CI	Standard care arm				Intervention arm				Incremental comparison of the intervention versus standard care		
		N	Mean total cost (US$) per person (95% CI)	All-cause mortality		N	Mean total cost (US$) per person (95% CI)	All-cause mortality		Incremental cost (US$) per person[b] (95% CI)	Incremental death (%)[b] (95% CI)	ICER (incremental cost per life years saved) (95% CI)
				Events (95% CI)	Death rate (95% CI)			Events (95% CI)	Death rate (95% CI)			
CD4 <200 cells /µl	24.0 (22.2 – 25.8)	998	262 (254 – 269)	180 (156-203)	18.0 (15.6-20.3)	1001	339 (331-347)	134 (113-156)	13.4 (11.3-15.6)	77 (66-88)	-4.6 (-7.8, -1.3)	70 (43, 211)
CD4<100 cells /µl	18.7 (17.2 – 20.3)	707	262 (253 – 271)	144 (123-165)	20.2 (17.4-23.3)	724	341 (331-350)	114 (94-134)	15.7 (13.0-18.5)	79 (65-92)	-4.5 (-8.6, -0.6	91 (49, 443)

ICER, incremental cost-effectiveness ratio: estimated by dividing incremental cost by the mean number of life years saved (i.e., incremental death multiplied by life expectancy).

[a]Weighted life expectancy based on a previous study[15]

[b]Differences were estimated using regression equations adjusting for body weight and heamoglobin levels measured at baseline.

Figure 1. Cost-effectiveness planes after bootstrapping showing uncertainty in the estimated incremental costs and the annual probability of death (%) for persons with CD4 cell count up to 200 cells /μl (red dots) and among persons with CD4 count <100 cells /μl (blue dots). Ellipses represent 95% confidence intervals and dots represent estimated incremental costs and death rates.

Figure 2. Cost-effectiveness acceptability curves showing the probability of cost-effectiveness at different willingness to pay thresholds according to baseline CD4 count.

Figure 3. Tornado diagram of change in the base-case incremental cost-effectiveness ratio among persons with CD4 cell count up to 200 cells /μl produced from a deterministic one-way analysis of six input parameters. The ranges used in the sensitivity analysis were based on 95% confidence intervals calculated from the REMSTART data and previous studies.