Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial

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Summary

Background Mortality in people in Africa with HIV infection starting antiretroviral therapy (ART) is high, particularly in those with advanced disease. We assessed the effect of a short period of community support to supplement clinic-based services combined with serum cryptococcal antigen screening.

Methods We did an open-label, randomised controlled trial in six urban clinics in Dar es Salaam, Tanzania, and Lusaka, Zambia. From February, 2012, we enrolled eligible individuals with HIV infection (age ≥18 years, CD4 count of <200 cells per μL, ART naive) and randomly assigned them to either the standard clinic-based care supplemented with community support or standard clinic-based care alone, stratified by country and clinic, in permuted block sizes of ten. Clinic plus community support consisted of screening for serum cryptococcal antigen combined with antifungal therapy for patients testing antigen positive, weekly home visits for the first 4 weeks on ART by lay workers to provide support, and in Tanzania alone, re-screening for tuberculosis at 6–8 weeks after ART initiation. The primary endpoint was all-cause mortality at 12 months, analysed by intention to treat. This trial is registered with the International Standard Randomised Controlled Trial Number registry, number ISCRTN 20410413.

Findings Between Feb 9, 2012, and Sept 30, 2013, 1001 patients were randomly assigned to clinic plus community support and 998 to standard care. 89 (9%) of 1001 participants in the clinic plus community support group did not receive their assigned intervention, and 11 (1%) of 998 participants in the standard care group received a home visit or a cryptococcal antigen screen rather than only standard care. At 12 months, 25 (2%) of 1001 participants in the clinic plus community support group and 24 (2%) of 998 participants in the standard care group had been lost to follow-up, and were censored at their last visit for the primary analysis. At 12 months, 134 (13%) of 1001 participants in the clinic plus community support group had died compared with 180 (18%) of 998 in the standard care group. Mortality was 28% (95% CI 10–43) lower in the clinic plus community support group than in standard care group (p=0·004).

Interpretation Screening and pre-emptive treatment for cryptococcal infection combined with a short initial period of adherence support after initiation of ART could substantially reduce mortality in HIV programmes in Africa.

Funding European and Developing Countries Clinical Trials Partnership.

Lancet 2015; 385: 2173–82

Published **Online** March 10, 2015 http://dx.doi.org/10.1016/S0140-6736(15)60164-7

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Introduction

About 10 million people in Africa are now receiving antiretroviral therapy (ART) for the treatment of HIV infection. Mortality in Africans during the first year of ART is higher than in Europeans, particularly during the first few months of treatment.[1] Additionally, in Africa, mortality[2,3] and loss to follow-up[4] are high during the pretreatment period between a patient's first presentation to clinic and ART initiation. About a third of Africans still begin ART with advanced disease,[5,6] and have a very high disease burden.

Tuberculosis and cryptococcal meningitis account for most deaths in people with HIV infection presenting at health facilities in Africa.[7–9] For tuberculosis, the median diagnostic delay is about 2 months overall[10] and diagnosis in people co-infected with HIV presenting with advanced HIV disease is particularly challenging.[11] In autopsy studies, tuberculosis has been detected in more than 50% of adults with HIV infection.[12] Cryptococcal meningitis occurs mostly in individuals with a CD4 count of less than 100 cells per μL[13] and is associated with 25–50% mortality in clinical trials and well functioning clinical settings.[9,14] The mortality associated with cryptococcal meningitis has remained high in some settings despite increased access to ART.[15,16]

The biggest challenge facing health-care delivery in Africa is the severe shortage of qualified health-care workers, particularly doctors.[17] Findings of a cluster-randomised trial[18] showed that home-based care delivered by trained lay workers was as effective as standard clinic-based care in a predominately rural setting where access to clinics was difficult.

In this trial, we assessed the effect of a short period of community-based support provided to individuals with HIV infection who presented at health centres with advanced disease combined with screening for cryptococcal meningitis, compared with standard care.

Methods

Study design and participants

This study was an open-label, randomised controlled trial that took place in six public clinics serving urban and peri-urban populations: three in Dar es Salaam, Tanzania, and three in Lusaka, Zambia.

Recruitment began in February, 2012, when consecutive individuals with HIV infection were invited to join the trial if they were older than 18 years, presented with a CD4 count of less than 100 cells per μL, lived in the trial clinic catchment population, were able to communicate with staff, and reported that they had not been on ART previously. Those who needed immediate hospital admission were excluded. The enrolment criteria were changed subsequently to include those presenting with a CD4 count of less than 200 cells per μL because of slow recruitment. This change was implemented in September, 2012, in Zambia and in December, 2012, in Tanzania.

Before the trial, patients with HIV infection were required to attend clinic on at least three occasions over a 4–6 week period before ART initiation to receive information and counselling about ART adherence; this practice is common in many well functioning African clinics. We streamlined procedures to ensure rapid ART initiation within two short-spaced visits. Patients with HIV infection presenting for the first time were asked to provide blood to measure CD4 count and to return to clinic within 4–7 days; those who did not and had a CD4 count of less than 200 cells per μL were phoned by clinic staff and encouraged to return. At the second visit, patients were started on ART unless a delay was justified on clinical grounds. They were invited to join the trial if they fulfilled the eligibility criteria.

All participants were offered screening for tuberculosis using the GeneXpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA), hereon referred to as Xpert. Sputum was requested irrespective of symptoms. In Tanzania, the test was usually done within 24 h and in Zambia within 48 h. When possible, ART initiation was delayed by 2 weeks in patients diagnosed with tuberculosis, in accordance with local guidelines. The research programme purchased Xpert cartridges and helped with access to testing machines, but the testing and management of equipment and supplies was done by health-care staff to maintain close to normal health service conditions.

The clinics at which patients were recruited were busy and run largely by clinical officers and nurses. The trial was done in conditions similar to those of actual health services, with the clinical staff working in government clinics responsible for service delivery. Interviewers employed by the research programme were based at the clinics and interviewed patients in between their usual consultations, in a separate dedicated research office. The interviewers sought written informed consent and obtained trial data. Patient information sheets, consent forms and questionnaires were translated into the local language (Swahili in Tanzania, and Bemba and Nyanja in Zambia), then back-translated into English by a second person, and cross-checked by a third person. The translators were not involved in the rest of the trial. Clinical data were transcribed onto forms from patient notes. An on-site quality control officer checked the completeness and internal consistency of the data obtained from each patient while the patient was still in clinic. No incentives or reimbursements were provided to the patients.

The trial protocol 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.

Randomisation and masking

Participants were randomly assigned individually[19] to either standard clinic-based care supplemented with community support (referred hereon as clinic plus community support), or to standard clinic-based care alone (referred hereon as standard care). Randomisation was computer generated, stratified by country and clinic and done in permuted block sizes of ten by an independent statistician using Stata version 12.1. An independent researcher placed the trial arm codes, together with a code for the patient identifier, into separate sealed envelopes that were opened sequentially by the study participants after recruitment.

Procedures

In the standard care group, patient management and schedule of clinic visits followed national guidelines. In the clinic plus community care group, these services were supplemented as follows: participants were screened at enrolment for cryptococcal meningitis using a novel serum antigen test and offered antifungal treatment if they were antigen positive; participants had weekly visits for 4 weeks by trained lay workers either to their homes or nearby locations; and in Tanzania alone, re-screening for tuberculosis with Xpert was done after about 6 weeks on ART in participants in whom tuberculosis was not diagnosed at enrolment.

Screening for cryptococcal antigenaemia was done using a point-of-care serum rapid antigen test (IMMY, Norman, OK, USA). Participants who were serum antigen negative were started on ART immediately. Those who were serum antigen positive were advised to have a lumbar puncture done and referred to hospital for the procedure if they agreed. If the lumbar puncture

showed cryptococcal antigen in the cerebrospinal fluid (CSF), the participant was started on amphotericin B at a dose of 1 mg/kg per day for 14 days followed by oral fluconazole at 400 mg per day for at least 8 weeks; if they declined lumbar puncture or if the results were negative then the patient was started on oral fluconazole at 800 mg per day for 2 weeks followed by 400 mg per day for 8 weeks. In accordance with national clinical guidelines at the time, ART was delayed by 2 weeks in participants who were serum cryptococcal antigen positive.

The lay workers delivered the ART, provided adherence support, and monitored the participants for signs and symptoms of drug toxicity or disease progression using a checklist. They referred participants to the clinic if indicated and phoned a clinician or nurse based at the clinic when they were uncertain about referral. Most lay workers had degree qualifications or college diplomas and received a small salary (lower than a nurse's salary in each country). They had 2 weeks of classroom training at the beginning followed by on-the-job training. The training package included simple definitions of major infections, adherence support, side-effects, and research ethics.

The lay workers travelled mostly on public transport and occasionally used motorbike taxis or bicycles. They often met the participant for the first time at the clinic and arranged a meeting point, either at the patient's home or a location nearby. Lay workers telephoned the participant the day before a home visit to confirm the visit. If the participant was not seen at the arranged time, the lay worker visited the following day; if the participant was absent again, then a note was left for the participant to come to clinic.

Survival status of participants was established from clinic attendance records. Those who dropped out of care were telephoned or visited at home. Towards the end of the study, we did a follow-up survey that involved visiting participants who had moved out of the area.

Outcomes

The primary endpoint was all-cause mortality at 12 months after enrolment. The secondary endpoints were costs of the two strategies to the health services, retention on ART, hospital admissions, adherence to ART, and active tuberculosis at re-screening.

Statistical analysis

We chose a sample size target of 2030 participants in both groups to provide 90% power to detect a 40% difference in mortality between the two groups assuming ten deaths per 100 person-years in the standard care group (at the 5% two-sided significance level). Analyses were done by intention to treat. We compared survival in the two trial groups with Kaplan-Meier survival curves and a log-rank test. To assess the robustness of the findings, we did three further a-priori analyses comparing mortality between the two groups: we used Poisson regression to adjust the mortality rate ratios for study site, age, sex, and baseline CD4 count; we assumed that all participants lost to follow-up had died at the time of loss to follow-up; and we assumed that all participants who were lost to follow-up in the first 28 days had died at the time that they were lost to follow-up, but that participants lost to follow-up more than 28 days after ART initiation had survived to the end of the year.

We compared the proportions of patients retained on ART, proportions reporting not having missed a pill in the previous 28 days, and proportions admitted to hospital for the first time between groups using either

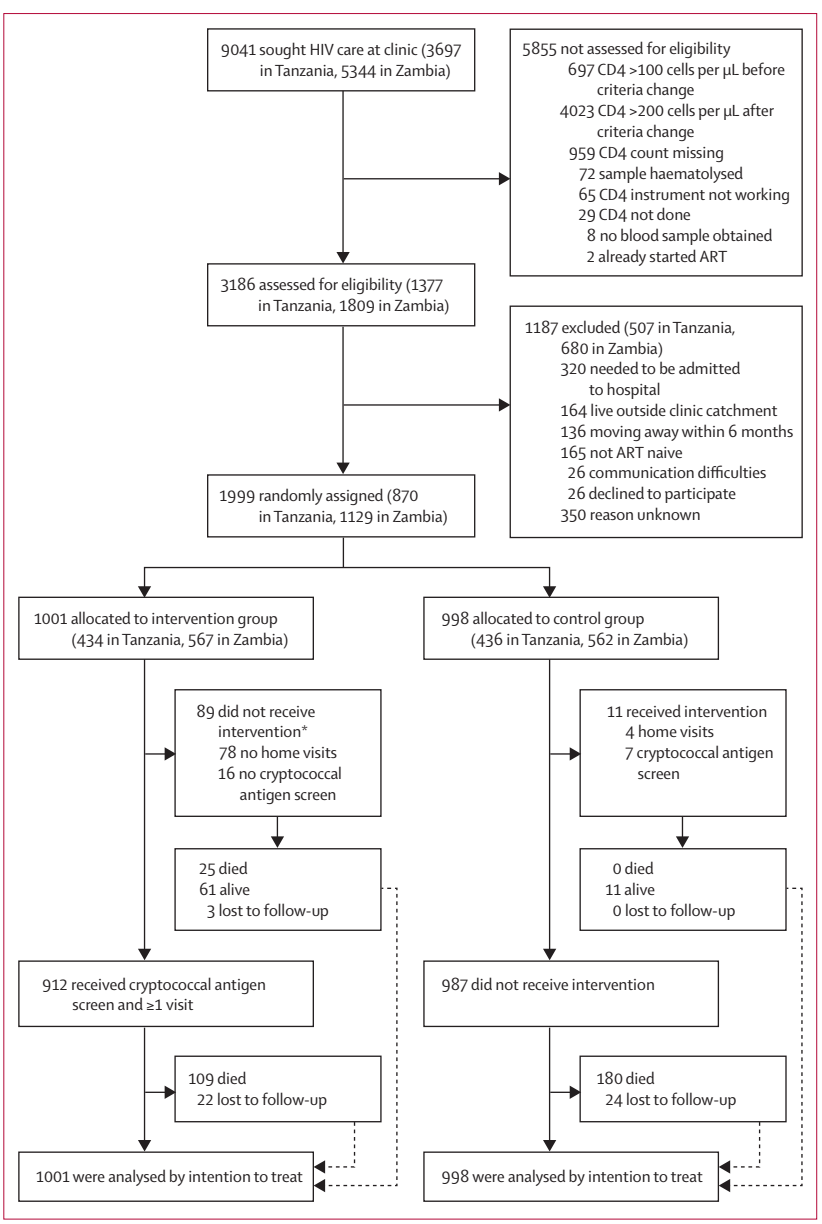

***Figure 1*: Trial profile**
ART=antiretroviral therapy. *Five participants had neither a home visit nor a cryptococcal antigen screen.

risk or rate ratios with 95% CIs. We used Poisson regression to compare mortality between participants who were cryptococcal antigen positive and those who were cryptococcal antigen negative, adjusting for baseline CD4 count, age, sex, and country.

See Online for appendix

	Clinic plus community support (n=1001)		Standard care (n=998)	
	Tanzania (n=434)	Zambia (n=567)	Tanzania (n=436)	Zambia (n=562)
Age, years	38·0 (32·0–45·0)	35·0 (30·0–41·0)	37·0 (31·0–44·0)	35·0 (30·0–42·0)
Women	273 (63%)	279 (49%)	268 (61%)	257 (46%)
WHO clinical stage				
1	33 (8%)	218 (38%)	34 (8%)	189 (34%)
2	47 (11%)	98 (17%)	45 (10%)	98 (17%)
3	251 (58%)	240 (42%)	245 (56%)	256 (46%)
4	103 (24%)	11 (2%)	112 (26%)	19 (3%)
Body-mass index, kg/m²	19·7 (17·8–22·4)	19·0 (17·1–21·4)	19·8 (17·6–22·6)	18·8 (16·8–21·2)
CD4 count, cells per μL	53·0 (22·0–89·0)	79·0 (41·0–128·0)	50·0 (18·5–90·0)	75·5 (37·0–127·0)
<50	202 (47%)	175 (31%)	217 (50%)	176 (31%)
50–99	152 (35%)	195 (34%)	131 (30%)	183 (33%)
100–200	80 (18%)	197 (35%)	88 (20%)	203 (36%)
ART regimen				
Stavudine, lamivudine, nevirapine	0	0	2 (<1%)	0
Stavudine, lamivudine, efavirenz	5 (1%)	0	3 (1%)	0
Zidovudine, lamivudine, nevirapine	38 (9%)	1 (<1%)	25 (6%)	1 (<1%)
Zidovudine, lamivudine, efavirenz	112 (26%)	1 (<1%)	139 (32%)	0
Tenofovir, lamivudine, efavirenz	181 (42%)	1 (<1%)	175 (40%)	0
Abacavir, lamivudine, nevirapine	1 (<1%)	5 (1%)	0	7 (1%)
Abacavir, lamivudine, efavirenz	6 (1%)	16 (3%)	1 (<1%)	14 (2%)
Tenofovir, emtricitabine, efavirenz	80 (18%)	511 (90%)	83 (19%)	490 (87%)
Tenofovir, emtricitabine, nevirapine	0	2 (<1%)	0	3 (1%)
Other	1 (<1%)	29 (5%)	1 (<1%)	47 (8%)
Never started ART*	10 (2%)	1 (<1%)	7 (2%)	0
Education level†				
None	80 (18%)	4 (2%)	68 (16%)	6 (2%)
Primary	292 (67%)	101 (40%)	304 (70%)	99 (39%)
Secondary	51 (12%)	139 (55%)	55 (13%)	141 (56%)
Tertiary	11 (3%)	10 (4%)	9 (2%)	5 (2%)
Marital status†				
Married	170 (39%)	143 (56%)	187 (43%)	138 (55%)
Cohabiting	18 (4%)	3 (1%)	25 (6%)	1 (<1%)
Widowed	58 (13%)	40 (16%)	29 (7%)	30 (12%)
Separated or divorced	135 (31%)	31 (12%)	122 (28%)	45 (18%)
Never married	53 (12%)	37 (15%)	73 (17%)	37 (15%)

Data are median (IQR) and number (%). In Zambia, the median time from first presentation to ART initiation was 14 days (IQR 11–19) in the clinic plus community support group compared with 14 days (12–21) in the standard care group; in Tanzania, the corresponding median times were 11 days (8–19) compared with 13 days (8–21), respectively. ART=antiretroviral therapy. *Ten participants died, five withdrew, and two were lost to follow-up after randomisation and before ART could be started, and one person refused to go onto ART (11 were in the clinic plus community support group and seven were in the standard care group); they were retained in the intention-to-treat analyses. †These data were collected at only one of the three clinics in Zambia; data for 254 patients in the clinic plus community support group were obtained, and for 251 patients in the standard care group.

***Table 1*: Demographic and clinical characteristics at trial enrolment**

We estimated incremental health service costs of the intervention according to resource use at the individual patient level. Patient resource use was tracked through records. We used an ingredients approach to cost the resources used on the basis of primary data collected in Tanzania. A combination of primary and secondary cost data were used in Zambia.[20,21] Details of the costing sources are described in the appendix. The intervention costs consisted of the direct costs of implementing the clinic plus community support intervention that were in addition to those associated with standard care. We did one-way sensitivity analyses to accommodate the uncertainty around the price of lay-worker time and the number of home visits that they could undertake. Costs are presented in US dollars, at 2012 prices. We did analyses with Stata version 13.1.

This trial is registered with the International Standard Randomised Controlled Trial Number registry, number ISCRTN 20410413.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all of the data used in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 9, 2012, and Sept 30, 2013, 26 (1%) of 3186 patients assessed for eligibility declined to join the trial and 1999 (63%) of 3186 were eligible and randomly assigned to either clinic plus community support (n=1001) or standard care (n=998; figure 1). Each participant was followed up for up to 12 months; and the last follow-up ended on Sept 30, 2014. 89 (9%) of 1001 participants in the clinic plus community support group did not receive the intervention (ie, a cryptococcal antigen screen or at least one home visit), of those, 78 did not get a home visit (16 had died, 14 withdrew, 11 were not found at home, nine had incorrect address details, one had not disclosed HIV status to family, one was in hospital, eight were incorrectly assigned to the standard care group, and for 18 the reason was not recorded). 16 participants did not get a cryptococcal serum antigen test because of a stock-out of kits (five of these individuals also did not get a home visit). In the standard care group, 11 (1%) of 998 participants received either a home visit or a cryptococcal antigen screen rather than standard care only.

The characteristics of the two groups were well balanced (table 1). Overall, median CD4 count was 52 (IQR 20–89) cells per μL in Tanzania and 77 (40–128) cells per μL in Zambia. The median time from first presentation to clinic for assessment of ART eligibility to ART initiation was 14 days (IQR 9–20) in the clinic plus community support group compared with 14 days (8–20) in the standard care group (p=0·8).

In the clinic plus community support group, lay workers visited 923 (92%) of the 1001 participants at least once, and the location that this meeting took place was recorded for 870 (94%) of these 923 participants. This meeting took place in the home for 547 (63%) of these 870 participants, at a location near the participant's home for 273 (31%), and at other locations including another family member's home and the workplace for 50 (6%). 660 (66%) of the 1001 participants in the clinic plus community support group received all four scheduled home visits, 139 (14%) had three visits, 64 (6%) had two visits, 60 (6%) had one visit, and 78 (8%) had no visits. Of the 341 participants who did not receive all four visits, 108 (32%) had died, were admitted to hospital, or had withdrawn from care. Four participants refused home visits because they had not disclosed their HIV status to their family, and contact details were incorrect in a further 14 participants.

Overall, 325 (16%) of 1999 participants presented while already on anti-tuberculosis treatment (table 2). Sputum was obtained spontaneously from 1372 (82%) of the remaining 1674 patients, of whom 189 (11%) were newly diagnosed with tuberculosis at enrolment; 69 (37%) of these 189 patients did not report a cough. In 97 (51%) of the 189 newly diagnosed patients, diagnosis was made on the basis of sputum smear and clinical examination. An additional 88 (47%) patients were diagnosed mainly on the basis of the Xpert result, and four (2%) on the basis of culture. The median time between first presentation and initiation of anti-tuberculosis treatment was 19 days (IQR 10–45) in the clinic plus community support group and 21 days (10–36) in the standard care group.

In Tanzania (where re-screening of tuberculosis by Xpert was implemented), 114 (26%) of 434 of patients in the clinic plus community care group either presented or were diagnosed with tuberculosis at baseline, 29 (7%) died or were lost to follow-up within 60 days, leaving 291 (67%) who should have had a repeat screen for tuberculosis. Only 147 (51%) of these 291 patients were re-screened, which was done a median of 58 days (IQR 44–72) from first presentation to clinic. Eight (5·4%, 95% CI 2·4–10·4) of 147 tested positive on Xpert, giving a tuberculosis incidence of 27·7 (95% CI 12·0–54·6) per 100 person-years between the start of the trial and re-screening.

Overall, 38 (4%) of the 985 patients screened for cryptococcal antigen in the clinic plus community support group tested positive for serum cryptococcal antigen; 33 (5%) of 717 tested patients with CD4 counts of less than 100 cells per µL were serum cryptococcal antigen positive compared with five (2%) of 268 tested patients with a CD4 count between 100 and 200 cells per µL. 16 participants were not tested because of a stock-out of kits. Only nine (24%) of the 38 patients who tested positive agreed to have a lumbar puncture done. Thus, only three (0·3%, 95% CI 0·06–0·8) of 985 tested patients were confirmed as having cryptococcal meningitis using the screening protocol. All three had a CD4 count of less than 100 cells per µL and were started on amphotericin B within 24 h. Of the other 35 participants who tested positive, 34 were started on fluconazole monotherapy a median of 1 day (IQR 1–3) after the test, and one refused antifungal treatment.

Survival status was recorded for 1950 (98%) of 1999 participants at 12 months; the remaining 49 (2%), who were equally distributed between the trial groups,

	Clinic plus community support (n=1001)		Standard care (n=998)	
	Tanzania (n=434)	Zambia (n=567)	Tanzania (n=436)	Zambia (n=562)
On anti-tuberculosis treatment at enrolment	72 (17%)	83 (15%)	70 (16%)	100 (18%)
Newly diagnosed with active tuberculosis at enrolment by any method	42 (10%)	47 (8%)	49 (11%)	51 (9%)
Diagnosed by sputum smear, clinical symptoms, and chest radiograph*	28 (67%)	21 (45%)	23 (47%)	25 (49%)
Diagnosed by Xpert either alone or in combination with sputum smear, clinical symptoms, or chest radiograph*	14 (33%)	23 (49%)	26 (53%)	25 (49%)
Diagnosed by culture*	0	3 (6%)	0	1 (2%)
Cryptococcal antigen positive at enrolment†	22 (5%)	16 (3%)	..	..
Agreed to have lumbar puncture‡	5 (23%)	4 (25%)	..	..
CSF positive for cryptococcus§	0	3 (75%)	..	..

CSF=cerebrospinal fluid. *Percentage presented is the proportion of patients out of the number newly diagnosed with active tuberculosis at enrolment. †354 (82%) patients in Tanzania and 370 (65%) in Zambia had a CD4 count of less than 100 cells per µL in the clinic plus community support group. ‡Percentage presented is the proportion of patients out of the number who were cryptococcal antigen-positive at enrolment. §Percentage presented is the proportion of patients out of the number who agreed to have a lumbar puncture.

Table 2: **Number of participants diagnosed with tuberculosis and cryptococcal meningitis at trial enrolment**

	Clinic plus community support			Standard care			Rate ratio (95% CI)	p value
	Events	PYO	Rate (95% CI)	Events	PYO	Rate (95% CI)		
All-cause mortality								
All	134	877	15·3 (12·9–18·1)	180	843	21·3 (18·4–24·7)	0·72 (0·57–0·90)	0·004
Tanzania	66	370	17·9 (14·0–22·7)	87	359	24·2 (19·6–29·9)	0·74 (0·54–1·01)	0·073
Zambia	68	507	13·4 (10·6–17·0)	93	484	19·2 (15·7–23·5)	0·70 (0·51–0·95)	0·027
Hospital admission*								
All	77	864	8·9 (7·1–11·1)	73	836	8·7 (6·9–11·0)	1·02 (0·74–1·41)	0·820
Tanzania	26	364	7·1 (4·9–10·5)	32	358	8·9 (6·3–12·6)	0·80 (0·48–1·34)	0·431
Zambia	51	500	10·2 (7·8–13·4)	41	478	8·6 (6·3–11·6)	1·19 (0·79–1·80)	0·366

The difference in mortality in all patients was largely unchanged after adjusting for study site, age, sex, and baseline CD4 count (rate ratio 0·74, 95% CI 0·59–0·92; p=0·008), after assuming that all participants lost from care had died (rate ratio 0·75, 0·61–0·92; p=0·008), or after assuming that only those lost in the first 28 days had died (rate ratio 0·69, 0·56–0·86; p=0·001). PYO=person-years of observation. *Only first hospital admission was included; 155 hospital admissions were recorded (four participants in the clinic and community support group and one in the standard care group were admitted to hospital twice).

Table 3: **All-cause mortality and first hospital admission in the 12 months after initiation of antiretroviral therapy**

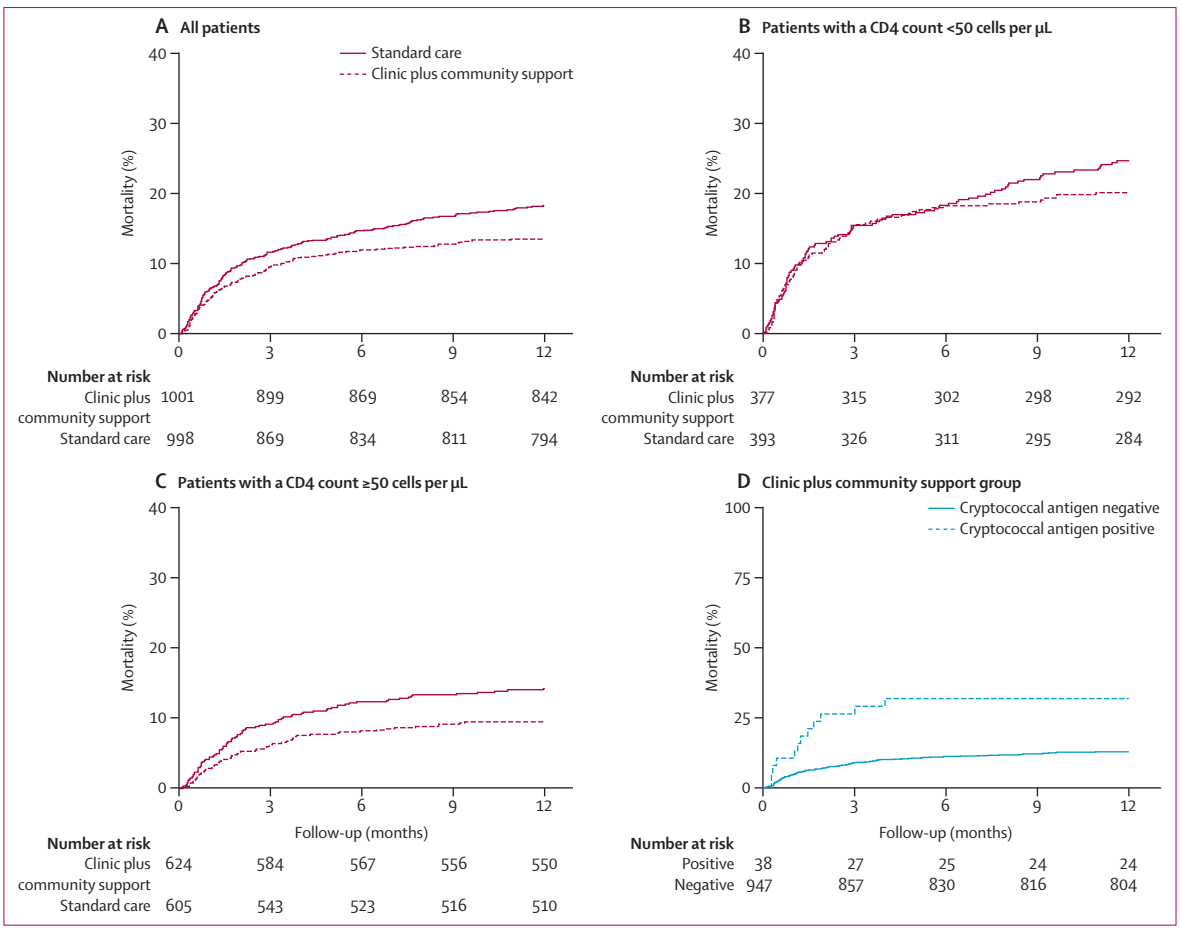

Figure 2: **All-cause mortality overall and according to CD4 cell count in both groups, and according to cryptococcal antigen status in the clinic plus community support group**

All-cause mortality in the clinic plus community support group and standard care group overall (A), in patients who presented with a CD4 count of less than 50 cells per µL (B), and in those who presented with CD4 count of 50 cells per µL or higher (C). All-cause mortality in patients who tested positive for cryptococcal serum antigen compared with those who tested negative; this test was done only in the clinic plus community support group and does not include the 16 patients in this group who were not tested due to stock-out of kit.

could not be traced (figure 1). 134 (13%) of 1001 individuals in the clinic plus community care group died compared with 180 (18%) of 998 in the standard care group, assuming that those lost to follow-up were alive at 12 months (table 3). Mortality was 28·4% (95% CI 10·5–42·8) lower in the clinic plus community care group than in the standard care group (p=0·004) and the effect was reported consistently in Tanzania and Zambia (table 3). The reduction in mortality was largely unchanged after sensitivity analyses (table 3). 107 (34%) of the 314 deaths occurred within 1 month of follow-up. In stratified analyses, mortality in individuals who had presented with a CD4 count of less than 50 cells per µL was 19·8% (95% CI –8·6–40·7) lower in the clinic plus community care group than in the standard care group; of those who presented with a CD4 count of 50 cells per µL or higher, mortality was 35·3% (95% CI 9·8–53·6) lower in the clinic plus community care group than in the standard care group (figure 2).

The proportion of patients who were alive and retained in care during the 12 month period was 842 (84%) of 1001 in the clinic plus community support group compared with 794 (80%) of 998 in the standard care group (risk ratio 1·06 [95% CI 1·01–1·10]; p=0·008).

The proportion of individuals in the clinic plus community support group who were admitted to hospital at least once did not differ significantly from that in the standard care group (table 3). The median times to the first admission were 24 days (IQR 11–43) and 26 days (14–67), respectively, in the two groups.

The proportion of patients who reported perfect adherence (ie, they did not miss a single pill) during the previous 28 days was about 90% in both the groups at 6 and 12 months after enrolment (table 4).

Mortality was higher in participants who tested positive for serum cryptococcal antigen than in those who tested negative (figure 2; table 5). Two of the three individuals in whom cryptococcal antigen was

detected in the CSF died (on days 14 and 45) and the third survived. All three had a CD4 count of less than 100 cells per µL. If these three are excluded and the analysis is restricted to participants with a CD4 count of less than 100 cells per µL at enrolment, then nine (30%) of 30 died. Mortality in this group was 43·3 (95% CI 22·5–83·3) deaths per 100 person-years and the rate ratio (in relation to serum antigen negatives) was 2·54 (95% CI 1·29–5·03) unadjusted, and 2·53 (1·27–5·01) after adjusting for CD4 count, age, sex, and country.

The mean number of home visits per participant was 2·89 (95% CI 2·76–3·08) in Tanzania and 3·51 (3·42–3·66) in Zambia at a cost of US$14·74 and $13·03 per visit, respectively. The mean per-participant costs of the lay-worker component for Tanzania and Zambia were $42·60 (95% CI 40·71–44·49) and $45·77 (44·56–46·97), respectively. The full intervention cost was $67·26 (95% CI 64·0–70·52) per person in Tanzania, including the second Xpert test, and $54·19 (52·94–55·43) per person in Zambia, where the second Xpert test was not implemented.

In the sensitivity analysis, increasing the number of home visits by lay workers to four per patients per day reduces the intervention cost to $40·99 (95% CI 38·48–43·50) in Tanzania and $27·11 (26·54–27·68) in Zambia. When a minimum wage value is used as a proxy for lay-worker salaries, the intervention costs fall to $37·59 (95% CI 35·15–40·02) and 45·78 (44·75–46·81) per person in Tanzania and Zambia, respectively.

	Clinic and community support	Standard care	Rate ratio (95% CI)	p value
All				
Month 6 review	90% (421/467)	86% (375/435)	1·05 (1·00–1·10)	0·068
Month 12 review	89% (451/509)	89% (429/481)	0·99 (0·95–1·04)	0·770
Tanzania				
Month 6 review	86% (180/209)	80% (162/202)	1·07 (0·98–1·17)	0·111
Month 12 review	89% (236/265)	90% (226/250)	0·99 (0·93–1·04)	0·616
Zambia				
Month 6 review	93% (41/258)	91% (213/233)	1·02 (0·97–1·08)	0·407
Month 12 review	88% (215/244)	88% (203/231)	1·00 (0·94–1·07)	0·937

Data are n/N (%) unless otherwise specified. The proportion of patients with perfect adherence, defined as not missing a single pill in the previous 28 days, is reported; adherence was measured by patient interview.

Table 4: **Adherence to antiretroviral therapy during the previous 28 days, as measured at 6 and 12 months**

	Serum antigen positive		Serum antigen negative		Unadjusted rate ratio (95% CI)	Adjusted* rate ratio (95% CI)
	Deaths (%)	Rate per 100 person-years (95% CI)	Deaths (%)	Rate per 100 person-years 95% CI)		
All participants	12/38 (32%)	46·3 (26·3–81·5)	120/947 (13%)	14·3 (12·0–17·1)	3·23 (1·78–5·84)	2·90 (1·60–5·26)
Participants with <100 CD4 cells per µL	11/33 (33%)	50·1 (27·8–90·5)	101/684 (15%)	17·0 (14·0–20·7)	2·95 (1·58–5·49)	2·87 (1·54–5·37)

Data are n/N (%) unless otherwise specified. *Adjusted for CD4 count, age, sex, and country.

Table 5: **Mortality according to cryptococcal serum antigen status in the clinic plus community support group**

Discussion

In this trial, just four short home visits by lay workers to provide adherence support combined with screening for cryptococcal meningitis led to a significant reduction in mortality in patients infected with HIV starting ART with advanced disease. Mortality was about 30% less than in individuals who did not receive this simple supportive package. These findings were robust to sensitivity analyses. The trial was large, done under real-life conditions, had a low loss to follow-up, and the findings were consistent in both Tanzania and Zambia.

We believe that the cryptococcal meningitis screening and the community support together resulted in the mortality reduction. We detected cryptococcal antigen in serum in 38 participants and offered pre-emptive fluconazole treatment to the 35 participants in whom cryptococcal meningitis could not be confirmed. Only a few relatively small-scale clinical studies of cryptococcal infection have been done in Africa (panel). A study from Cape Town[22] suggested that individuals who are serum cryptococcal antigen positive have a very high risk of developing cryptococcal meningitis, and an earlier study from Uganda[23] reported that antigenaemia preceded symptoms of cryptococcal meningitis by a median of 22 days. In patients entering ART programmes with a CD4 count of less than 100 cells per µL who do not have any obvious signs of cryptococcal meningitis, the presence of antigenaemia has been associated with a much increased risk of mortality. In well resourced clinical settings, mortality was more than six times higher in a study done in Uganda[24] and more than three times higher in the Cape Town study.[22] Both studies were retrospective and did not involve pre-emptive treatment as used in our study. Mortality in individuals who were serum cryptococcal antigen positive was lower in our study, which was integrated into a normal health-care setting, than in the studies done in Uganda[24] and Cape Town,[22] but the comparison involves small numbers. Finally, of 26 patients who had incident cases of cryptococcal antigenaemia in Uganda, whose CD4 counts were less than 100 cells per µL, all five patients given ART alone died compared with six (29%) of 21 deaths in those given pre-emptive fluconazole and ART,[25] although the data from Cape Town suggest that a proportion of individuals starting on ART are able to clear asymptomatic infection through immune reconstitution.[22]

Taken together, the evidence suggests most of the participants who survived despite being serum cryptococcal antigen positive would have died in the absence of pre-emptive antifungal treatment, and that

Panel: Research in context

Systematic review

Before undertaking the study, we searched PubMed and the International Standard Randomised Controlled Trial Number register for "early mortality" OR "pre-treatment mortality" AND "antiretroviral therapy" AND "Africa"; also "cryptococcal meningitis" AND "screening" AND "Africa" AND "pre-emptive treatment"; also "repeated counselling" AND "adherence" AND "Africa" AND ("lay-worker OR non-clinical workers"). The studies reported that most of the deaths occurred in patients presenting with advanced HIV disease, that mortality was very high around the period of ART initiation, and that tuberculosis and cryptococcal meningitis were the major contributors. Results of retrospective studies and modelling studies suggested that screening for cryptococcal antigen before ART and pre-emptive antifungal therapy for patients testing positive could reduce cryptococcal cases and deaths, and should be highly cost effective. In a cluster randomised trial,[18] home-based HIV care delivered by trained lay workers was cost effective compared with facility-based care, but the concept of using lay workers to support patients during just the first few crucial weeks on ART had not been assessed.

Interpretation

In patients with advanced stage HIV infection attending urban clinics in Africa, in the context of prompt ART provision and screening for tuberculosis with GeneXpert for all, screening for serum cryptococcal antigen and supplementation of clinic-based care with a short period of adherence support and monitoring in the community provided by trained lay workers reduces all-cause mortality by nearly 30%. This simple strategy could narrow the disparities in mortality in ART programmes between high-income and low-income countries. Despite pre-emptive antifungal therapy, mortality in patients who tested cryptococcal antigen positive was still higher than that in patients who tested negative, and further work is needed to address this residual increased mortality. Trained lay workers who are integrated into the health system are an effective cadre in resource-limited settings that could help to alleviate the pressures from the severe shortages of clinically qualified staff across Africa.

this component of the intervention contributed to about half of the mortality reduction reported in the intervention group. Thus, serum cryptococcal antigen screening combined with pre-emptive fluconazole treatment is an effective strategy to reduce the high HIV-associated mortality in Africa, and this strategy alone should be highly cost effective in most settings.[26,27] It might be even more effective if cryptococcal meningitis, as opposed to antigenaemia without meningitis, could be diagnosed and treated with amphotericin-based therapy rather than fluconazole[28] alone, but diagnosis of cryptococcal meningitis requires a lumbar puncture, and in our study, three-quarters of the patients refused to have one. Research is needed to identify the barriers to the acceptance of lumbar punctures, particularly in asymptomatic or minimally symptomatic infection, and to find out whether meningitis can be predicted from the titre of antigenaemia in blood and treated with more potent antifungal combinations when antigenaemia is high.

We recorded a large burden of tuberculosis at enrolment. We sought sputum samples irrespective of symptoms and most participants provided these. We noted that more than a third of patients diagnosed with tuberculosis did not report a cough, and the use of Xpert in addition to existing diagnostics doubled the number diagnosed. Implementation of re-screening for tuberculosis after a few weeks proved a challenge for the health system. Zambia could not implement this re-screening, but Tanzania did for about half of the patients in whom tuberculosis was not detected at enrolment. As a result, the number of new tuberculosis cases detected was small and unlikely to have contributed to the reduction of all-cause mortality reported in the clinic plus community support group.

We believe that about half of the reduction in mortality was the result of the lay-worker component, which involved the provision of personalised adherence support in the community to participants. Lay workers proved effective in an earlier trial done in Uganda,[18] but that trial was done in a largely poor rural setting with HIV services provided by a non-governmental organisation, and lay workers provided home care throughout the 3-year follow-up. Here we assessed a short intensive period of just 4 weeks in urban-based government clinics in which access to care was much less of a barrier. The lay workers had only about half the training as in the Ugandan study, and were less educated to keep the intervention costs low. Our findings suggest that this component of the intervention on its own is also a cost-effective strategy that could substantially enhance the effects of ART programmes in Africa. Repeated adherence support could also be important for other groups of patients, such as those presenting with suspected treatment failure. In our trial, we did not notice a difference in reported adherence to ART between the two groups, but this finding was not surprising in view of the subjective nature of adherence measurement in Africa and elsewhere.

The findings are supported by randomised trials showing improved virological suppression associated with peer support in Rakai, Uganda,[29] and with three clinic-based counselling sessions around the time of ART initiation in Nairobi, Kenya.[30] The evidence is now probably sufficient to say that trained lay workers, who are paid a salary, integrated into health systems, and who work under the supervision of clinical staff, are an effective cadre and that drug adherence support of patients in resource-limited settings, particularly in the first few weeks of ART, is crucial to the improvement of patient outcomes.

During the scale-up of ART in Africa, the emphasis has been to provide patients with information before they begin ART, but the benefits of this strategy have never been established. This pre-ART period is the time when high rates of mortality[2,3] and loss from care[4] can occur. We reduced this period by more than half and started ART at the patient's second visit in both of the trial groups. Despite the reduced preparedness of

patients, we did not notice any adverse effects on the proportion of patients lost from care—2·5% over 12 months—or on overall mortality, which was broadly in line with that reported from other African cohorts,[18,31,32] even though our patients had presented with low CD4 counts. These findings call into question the policy in most of Africa of an extended period of ART preparedness, and suggest that rapid initiation of ART combined with support given after ART initiation would be more effective.

The total cost of the entire intervention package varied between about $30 and $70 per participant depending on the scenario and the country. In a real-life scale-up of the intervention, the costs could be substantially lower because lay workers would be paid a lower salary than we paid to attract people quickly for trial purposes, they could do more home visits per day because patients would be less scattered than our participants, and the costs of the cryptococcal antigen test might fall. Some costs would be recouped because the intervention involves ART initiation with fewer clinic visits and over a shorter time window than is current standard practice. The annual costs of ART in Africa are between $270 and $450 per patient.[33] As a result, even if the actual intervention costs were to remain at the trial level, it would represent about a 10% increase to the first year's ART cost per patient and around 1% increase to the 10-year costs. For health services, costs associated with implementation of the intervention will arise, which raises questions of affordability in countries such as Tanzania and Zambia. A full cost-effectiveness analysis incorporating the long-term effects is needed to look at the intervention's total cost in relation to the benefits.

Mortality in Africans infected with HIV entering ART programmes has remained persistently high during the pre-treatment period and for a few months after ART initiation,[2,3] much higher than in high-income countries,[1] and our findings point to a simple strategy that could narrow the disparities.

In summary, findings of this large trial have shown that a simple intervention consisting of the screening of patients presenting to African health services with advanced disease for cryptococcal meningitis combined with a short period of community support from lay workers reduces mortality substantially.

Contributors

All authors contributed to the writing of the report and read and approved the final version. SM, PM, SE, TSH, and SJ conceived and designed the trial. SM, DC, SLK, BN, and CC implemented the trial and coordinated activities. CB did the statistical analysis. LG was responsible for the design of the health economics component and analysis of these data, with contributions from GK, AK, and VS. GK coordinated the health economics data collection, with contribution from AK. AM coordinated all the data collection. SLK, CC, and VS managed and cleaned the data. BN and TSH provided clinical training and support. CB, SM, DC, LG, TSH, and SJ interpreted the data. SJ coordinated the writing of the paper with contributions from SM and all the authors. SM and DC contributed equally to the work. All authors reviewed the final paper.

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Declaration of interests

TSH has been given antigen tests by IMMY for studies of cryptococcal meningitis treatment and prevention. All other authors declare no competing interests.

Acknowledgments

We thank IMMY (Norman OK, USA) for the donation of the cryptococcal serum antigen test kits; Lackson Kasonka for chairing the steering committee; the data safety monitoring committee, which consisted of Andrew Kitua (chair), Nuala McGrath, Neal Alexander, and Hedwiga Swai; Emily Webb for doing the randomisation; and the health-care staff and study participants in Dar es Salaam and Lusaka.

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