**Cryptococcal meningitis screening and community-based early adherence support reduces all-cause mortality among HIV-infected people initiating antiretroviral therapy with advanced disease: a randomised-controlled trial in Tanzania and Zambia.**

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**Background.** Mortality rates of HIV-infected Africans starting antiretroviral therapy are high, particularly among those with advanced disease. We assessed the impact of a short period of community support to supplement clinic-based services combined with serum cryptococcal antigen screening.

**Methods** We undertook a randomised trial in urban clinics in Dar es Salaam, Tanzania and in Lusaka, Zambia. 1999 HIV-infected patients were randomised individually to either the standard clinic-based care supplemented with community support (CCS) or standard clinic based care alone. CCS comprised screening for serum cryptococcal antigen combined with antifungal therapy for those 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 TB at 6-8 weeks after ART initiation. Randomisation was stratified by country and clinic and done in permuted block sizes of 10 by an independent statistician. The trial was integrated into normal service delivery. All adult patients with CD4-cell counts <200 cells/ μL who reported that they had not been on ART previously and who did not need immediate hospital admission were enrolled between February 2012 and September 2013. Follow-up ended on 30th September 2014. The primary endpoint was all-cause mortality. Analyses were by intention to treat. This trial is registered at http://isrctn.org, number (ISCRTN 20410413).

**Findings** 1001 patients were assigned randomly to CCS and 998 to standard care. Over a 12-month follow-up, 25 (2.5%) in the CCS arm and 24 (2.4%) in the standard care arm were lost to follow-up and the number of deaths was 134(13.4%) and 180 (18.1%) respectively. The mortality rate was 28% (95% CI 10%, 43%) lower in the CCS arm than in standard care (p=0.004). In the CCS arm, 38 (3.9%), were serum cryptococcal antigen positive and their mortality rate was 2.90 (95% CI 1.60, 5.26) higher than that among serum antigen negatives after adjusting for CD4 count, age, sex and country. 147 participants in Tanzania who did not have active TB at enrolment were re-screened a median of 58 (interquartile range 44, 72) days after enrolment by GeneXpert and 8 (5.4%, 95% CI 1.8, 9.0%) were newly diagnosed with TB. The full intervention cost was USD 67.26 (95% CI 64.0, 70.52) per person in Tanzania and USD 54.19 (95% CI 52.94, 55.43) per person in Zambia.

**Interpretation**. A simple low-cost intervention comprising a short period of home support combined with screening for cryptococcal meningitis reduces mortality substantially among HIV-infected with advanced disease.

**INTRODUCTION**

About 10 million people in Africa are now on antiretroviral therapy (ART) [1](#_ENREF_1). Mortality rates of Africans during the first year on ART are higher than among Europeans, particularly during the first few weeks [2](#_ENREF_2). In addition, in Africa, there is substantial mortality [3-5](#_ENREF_3) and loss-to-follow-up [6](#_ENREF_6), [7](#_ENREF_7) during the pre-treatment period between a patient’s first presentation to clinic and ART initiation. About a third of Africans still initiate ART with advanced disease [8-10](#_ENREF_8) and they have a very high disease burden.

Tuberculosis and cryptococcal meningitis account for the majority of the deaths among HIV-infected people presenting at health facilities in Africa [11-14](#_ENREF_11). For tuberculosis, the median diagnostic delay is about 2 months overall [15](#_ENREF_15) and diagnosis among HIV co-infected people presenting with advanced HIV disease is particularly challenging [16](#_ENREF_16). In autopsy studies, tuberculosis has been detected in over 50% of HIV-infected adults [17](#_ENREF_17). Cryptococcal meningitis occurs mostly among those with CD4 count<100 /μl [18](#_ENREF_18) and has an associated mortality rate of between 25% to 50% in clinical trials and well-functioning clinical settings [14](#_ENREF_14), [19](#_ENREF_19), [20](#_ENREF_20). The mortality associated with cryptococcal meningitis has remained high in some settings despite increased access to ART [21](#_ENREF_21), [22](#_ENREF_22).

The biggest challenge facing health care delivery in Africa is the severe shortage of qualified health care workers, particularly doctors [23](#_ENREF_23). In a cluster-randomised trial, it has been shown 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 [24](#_ENREF_24), [25](#_ENREF_25).

In this trial, we evaluated a short period of community-based support provided to HIV-infected individuals who presented at urban health centres with advanced disease combined with enhanced screening for tuberculosis and cryptococcal meningitis.

**METHODS**

**Study settings and patients**

We undertook the trial in 6 public clinics; 3 in Dar es Salaam, Tanzania, and 3 in Lusaka, Zambia (ISCRTN 20410413). These were busy clinics serving urban and peri-urban populations. They were run largely by clinical officers and nurses and were seeing between 100 and 300 patients daily. 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. No additional clinical staff were employed for the conduct of the trial. 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 consent and collected trial data, including on the socio-economic aspects. Participants were interviewed at every clinic visit. 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 with 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 collected from each patient while the patient was still in clinic. No incentives or re-imbursements were provided to the patients.

Recruitment to the trial began in February 2012 and ended in September 2013. Each participant was followed for up to 12 months; follow-up ended on 30th September 2014. When the trial began, consecutive HIV-infected individuals were invited to join the trial provided they were over 18 years old, presented with a CD4 count <100 cells /μl, lived in the trial clinic catchment population, were able to communicate with trial staff and reported that they had not been on ART previously. Those who needed immediate hospital admission were excluded. The trial enrolment criteria were changed subsequently to include those presenting with CD4 count <200 cells / μl in view of slow recruitment and in view of the fact such patients are still at high risk of mortality. This change was implemented in September 2012 in Zambia and in December 2012 in Tanzania.

The trial protocol was approved by the ethics committee of the London School of Hygiene and Tropical Medicine, Ethics and Research Science (ERES Converge) committee in Zambia and the National Health Research Ethics Sub-Committee (NatHREC) of Medical Research Coordinating Committee (MRCC)in Tanzania.

**Study design**

This was an open-label randomised controlled trial. The primary endpoint was all-cause mortality. Prior to the trial, HIV-infected patients were required to attend clinic on at least 3 occasions over a 4-6 week period prior to ART initiation in order to receive information and counselling on ART adherence; this practice is common in many well-functioning African clinics [26-28](#_ENREF_26). We streamlined clinic procedures in order to ensure rapid ART initiation within two short-spaced visits. HIV-infected patients presenting to one of the trial clinics for the first time were asked to provide blood for CD4 count testing and asked to return to clinic within 4-7 days; those who did not and had CD4 count <200 cells /μl were phoned by clinic staff and encouraged to return. At the second visit, patients were initiated on ART unless there were clinical grounds to delay. They were invited to join the trial if they fulfilled the eligibility criteria. All trial participants were offered screening for tuberculosis (TB) using the GeneXpert®MTB/RIF assay (Cepheid, Sunnyvale, USA) (hereon referred to as Xpert) [29](#_ENREF_29). Sputum was requested irrespective of any symptoms. In Tanzania, the test was usually done within 24 hours and in Zambia within 48 hours. Those diagnosed were initiated on anti-TB treatment, and if possible, ART initiation was delayed by 2 weeks in accordance with local guidelines. The research programme purchased Xpert cartridges and facilitated access to testing machines but the testing and management of equipment and supplies was done by health care staff in order to maintain close to normal health service conditions.

*Randomisation*

Participants were randomised individually [30](#_ENREF_30) to either the standard clinic-based care supplemented with community support (referred hereon as clinic plus community support), or to standard clinic-based care arm alone (referred hereon as standard care). Randomisation was stratified by country and clinic and done in permuted block sizes of 10 by an independent statistician using Stata 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 following recruitment.

**Models of care**

In the standard care arm, patient management and schedule of clinic visits followed national guidelines. In the clinic plus community care arm, these services were supplemented during the first weeks following ART initiation, as follows: i) participants were screened at enrolment for cryptococcal meningitis using a novel serum antigen test and offered antifungal treatment if they were antigen positive, ii) participants had weekly visits for four weeks by trained lay-workers either to their homes or nearby locations and iii) in Tanzania alone, re-screening for TB using Xpert was done after about six weeks on ART among participants in whom TB was not diagnosed at enrolment.

Screening for cryptococcal antigenaemia was done using a serum rapid antigen test (IMMY, Norman OK, USA). This was done at the point-of-care and generally provided results within 15 minutes. Participants who were serum antigen negative were initiated on ART immediately. Those who were 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), then the participant was started on amphotericin B at a dose of one mg/kg/day for 14 days followed by oral fluconazole at 400mg/day for at least 8 weeks; if they declined lumbar puncture or if this was negative, then the patient was initiated on oral fluconazole at 800mg/day for 2 weeks followed by 400mg/day for 8 weeks. In accordance with national clinical guidelines at the time, ART was delayed by two weeks among 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 this was 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 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. They were also given information on the workings of the health system.

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 not present again, then a note was left for the participant to come to clinic.

**Follow-up of study participants**

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 trial participants who had moved out of the area.

**Statistical analyses.**

A sample size target of 2030 participants in both arms was chosen. We envisaged that this would provide 90% power to detect a 40% difference in mortality rates between the two arms assuming 10 deaths per 100 person-years in the standard care arm (at the 5% two-sided significance level).

Analyses were done as intention-to-treat. Survival rates in the two trial arms were compared using a Kaplan-Meier survival curves and a log-rank test. To assess the robustness of the findings, we conducted 3 further *a priori* analyses comparing mortality rates between the two arms: i) we used Poisson regression to adjust the mortality rate ratios for study site, age, sex, and baseline CD4 count, ii) we assumed that all participants lost to follow-up had died at the time of loss to follow-up, iii) we assumed that all participants who were lost to follow-up in the first 28 days after ART initiation 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 proportion of patients retained on ART, the prevalence of adherence (not having missed a pill in the previous 28 days) and the rate of first hospital admission between arms using either risk or rate ratios with 95% confidence intervals. Poisson regression was used to compare the mortality rate between cryptococcal antigen positive and negative participants adjusting for baseline CD4 count, age sex and country.

Health service costs: Incremental health service costs of the intervention were estimated based on resource use at the individual patient level. Patient resource use was tracked through trial records. An ingredients approach was used to cost the resources used based on primary data collection in Tanzania. A combination of primary and secondary cost data were used in Zambia [31](#_ENREF_31), [32](#_ENREF_32). Details of the costing sources are described in the appendix. The intervention costs comprised the direct costs of implementing the clinic plus community support intervention over and above standard care. One-way sensitivity analyses were done to accommodate the uncertainty around the price of lay-worker time the number of home visits that they could undertake, and the possible future price falls of the serum cryptococcal antigen test. The lay-worker salary paid by the trial was below that of junior nurse. Costs are presented in US dollars, 2012 prices. All analyses were done using Stata 13.1.

**RESULTS**

***Participant characteristics***

Figure 1 shows the trial profile. Twenty-six (0.8%) patients declined to join the trial and 1999 were randomised either to the clinic plus community support (n=1001) or the standard care arm (n=998). The characteristics of the two groups were well balanced (Table 1). Overall, median (IQR) CD4 count/μl was 52 (20, 89) in Tanzania and 77 (40, 128) in Zambia. In Zambia 1001/1129 (88.7%) were treated by the single pill fixed-dose combination comprising tenofovir (TDF), emtricitabine (FTC) and efavirenz (EFV); in Tanzania, ART varied but almost 60% were receiving tenofovir (TDF), emtricitabine (FTC) or lamivudine (3TC) and efavirenz (EFV). Overall, the median time (IQR) from first presentation to clinic for assessment of ART eligibility to ART initiation was 14 (9, 20) days in the clinic plus community support arm compared with 14 (8, 20) days in the standard care arm (p=0.8).

***Frequency of lay-worker visits in the clinic plus community support arm.***

In the clinic plus community-support arm, lay-workers met 547 (62.9%) of study participants in the home, 273 (31.4%) at a location very near the participant’s home and 50 (5.8%) at other locations including another family member’s home and the workplace. 660 (65.9%) of the participants received all 4 scheduled home visits, 139 (13.9%) had 3 visits, 64 (6.4%) had two visits, 60 (6.0%) had a single visit and 78 (7.8%) had no visits. Of the 341 participants who had not received all 4 visits, 108 (31.7%) had died, were hospitalised or had withdrawn from care. Only 4 participants refused home visits because they had not disclosed their HIV status to household members and the contact details were incorrect in a further 14 participants.

***Detection of new cases of tuberculosis at baseline and follow-up***

Overall 325/1999 (16.3%) participants presented while already on anti-TB treatment (Table 2). Sputum was obtained spontaneously from 1372 /1674 (82.0%) of the remainder and 189/1674 (11.3%) were newly diagnosed with TB at enrolment; 69 (36.5%) of these did not report a cough. In 97/189 (51.3%), the TB diagnosis was made on the basis of sputum smear and the clinical picture. An additional 88 (46.6%) were diagnosed primarily on the basis of the Xpert result and 4 (2.1%) on the basis of culture. The median time between first presentation and initiation of anti-TB treatment was 19 (IQR 10-37) days.

In Tanzania (where re-screening of TB by Xpert was implemented), 114 (26.3%) of the 434 in the clinic plus community care arm either presented or were diagnosed with TB at baseline, 29 died or were lost to follow-up within 60 days, leaving 291 who should have had a repeat screen for TB. Only 147/291 (50.5%) were re-screened, which was done a median of 58 (IQR 44, 72) days from first presentation to clinic. Eight of 147 (5.4%, 95% CI 2.4 to 10.4) tested Xpert positive, giving an incidence rate 27.7 (95% CI 12.0, 54.6) per 100 person-years years between the start of the trial and re-screening.

***Prevalence of cryptococcal serum antigen positivity at baseline.***

Overall 38/ 985 (3.9%) in the clinic plus community support arm were serum cryptococcal antigen test positive; this was 33/717 (4.6%) among those with CD4 count<100 cells /μl and 5/268 (1.9%) among those with CD4 count between 100 and 200 cells /μl. Sixteen participants were not tested because of a stock-out of test kits. Only 9/38 (23.7%) cryptococcal serum antigen positive individuals agreed to have a lumbar puncture done despite medical advice. Five of the 9 were in Tanzania, and were found to be CSF negative, and 4 were in Zambia, 3 of whom tested positive for cryptococcal antigen in their CSF and one tested negative. Thus, only 3 of 985 (0.3%, 95% CI 0.06, 0.8%) were confirmed with cryptococcal meningitis using the trial screening protocol. All 3 had CD4 count<100 cells//μl and were initiated on amphotericin-B within 24 hours. Of the other 35 serum cryptococcal antigen positive participants, 34 were initiated on fluconazole monotherapy a median of 1(IQR 1, 3) days after the test and one refused antifungal treatment.

***Impact of the intervention on all-cause mortality and other outcomes.***

Survival status was determined for 1950/1999 (97.5%) participants at 12 months; the remainder 49 (2.5%), who were equally distributed between the trial arms, could not be traced (Figure 1). Table 3 shows the death rates by trial arm. Overall 134/1001 (13.4%) individuals in the clinic plus community care arm died compared with 180/998 (18.0%) in the standard care arm. The mortality rate was 28.4% (95% CI 10.5%, 42.8%) lower in the clinic plus community care arm than in the standard care arm (p=0.004) and the effect was observed consistently in Tanzania and Zambia. The reduction in mortality was unchanged after sensitivity analyses. Overall 107 (34.1%) of the deaths occurred within one month of follow-up. In stratified analyses, among those who had presented with CD4 count <50 /μl and those who presented with CD4 count ≥ 50 /μl, the mortality rates were 19.8% (95% CI: -8.6, 40.7%) and 35.3% (95% CI: 9.8, 53.6%) lower in the clinic plus community care arm than in the standard care arm respectively (Figure 2).

*Retention:* the number alive and retained in care over the 12 month period was 842 (84.1%) in the clinic plus community support arm compared with 794 in the standard care arm (79.6%) (risk ratio 1.06, 95% CI 1.01, 1.10; p=0.008).

*Admissions:* 77/1001 (7.7%) individuals in clinic plus community support arm compared with 73 /998 (7.3%) in the standard care arm were admitted at least once (rate ratio 1.02, 95 %CI 0.74, 1.41; p=0.82) (Table 3). The median (IQR) times to the first admission were 24 (11, 43) and 26 (14, 67) days respectively in the two arms.

*Adherence:* reported perfect adherence (i.e. not missing a single pill) during the last 28 days was about 90% in both the trial arms at 6 and 12 months following enrolment (Table 4).

***Mortality rates among those with cryptococcal meningitis co-infection***

The mortality was markedly higher among serum cryptococcal antigen positive participants than negatives (Figure 2, Table 5). Two of the three individuals in whom cryptocococcal antigen was detected in the CSF died (on days 14 and 45) and the third survived. All 3 had CD4 count<100/μl. If these 3 are excluded and the analysis restricted to participants with CD4 count<100/μl at enrolment, then 9/30 (30%) died. The mortality rate 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 negative) was 2.54 (95% CI 1.29, 5.03) unadjusted and 2.53 (95% CI: 1.27, 5.01) after adjusting for CD4 count, age, sex, country

***Costs associated with the delivery of the intervention***

The mean number of home visits per participant was 2.89 (95% CI: 2.76, 3.08) in Tanzania and 3.51 (95% CI: 3.42, 3.66) in Zambia at a cost of USD 14.74 and USD 13.03 per visit, respectively. The mean per participant costs of the lay-worker component for Tanzania and Zambia were USD 42.60 (95% CI: 40.71, 44.49) and USD 45.77 (95% CI: 44.56, 46.97), respectively. The full intervention cost was USD 67.26 (95% CI: 64.0, 70.52) per person in Tanzania, including the second Xpert test and USD 54.19 (95% CI:52.94, 55.43) per person in Zambia where the second Xpert test was not implemented.

In the sensitivity analysis, halving the price of the serum cryptococcal antigen test results in a cost per person of USD 65.01 (95% CI: 61.75-68.27) and USD 52.00 (95% CI: 50.76-53.24) in Tanzania and Zambia respectively. Increasing the number of home visits by lay-workers to 4 per patient per day reduces the intervention cost to USD 40.99 (CI: 38.48-43.50) in Tanzania and USD 27.11 (CI: 26.54-27.68) in Zambia. When a minimum wage value was used as a proxy for lay-worker salaries, the intervention costs fell to USD 37.59 (CI: 35.15-40.02) and 45.78 (CI: 44.75 – 46.81) per person in Tanzania and Zambia respectively.

**DISCUSSION**

In this trial, just four short home visits conducted by lay-workers to provide adherence support combined with screening for cryptococcal meningitis led to a substantial reduction in mortality among HIV-infected patients initiating antiretroviral therapy with advanced disease. The death rate was about 30% less than that among individuals who did not receive this simple supportive package. These findings were robust to sensitivity analyses. The trial was large, integrated into normal health services (i.e. done under real life conditions), had a low loss to follow-up and the findings were consistent in both Tanzania and Zambia.

The survival benefits from each component of our intervention are difficult to estimate precisely but 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. A study from Cape Town suggested that individuals who are serum cryptococcal antigen positive have a very high risk of developing cryptococcal meningitis [33](#_ENREF_33) and an earlier study from Uganda showed that antigenaemia preceded symptoms of cryptococcal meningitis by a median of 22 days [34](#_ENREF_34). Among patients entering ART programmes with CD4 count <100 cells/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 rates were over 6-fold higher in a study conducted in Uganda [35](#_ENREF_35) and over a 3-fold higher in Cape Town [33](#_ENREF_33). Both studies were retrospective and did not involve pre-emptive treatment as used in our study. The mortality rate among serum cryptococcal antigen positive individuals is lower in our study, which was integrated into a normal health care setting; but the comparison involves small numbers. Finally, among 26 incident cases of cryptococcal antigenaemia in Uganda, whose CD4 count were <100 cells/μl, 5 out of 5 patients treated with ART alone died compared with 6/21 (29%) deaths among those treated with pre-emptive fluconazole and ART [36](#_ENREF_36), although the data from Cape Town suggest that a proportion of individuals starting on ART are able to clear asymptomatic infection through immune reconstitution [33](#_ENREF_33).

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 this component of the intervention contributed to about half of the mortality reduction observed in the intervention arm. Thus, serum cryptococcal antigen screening combined with pre-emptive fluconazole treatment is an effective strategy in reducing the high HIV-associated mortality in Africa and this strategy alone should be highly cost-effective in most settings [37](#_ENREF_37), [38](#_ENREF_38). It might be more effective if cryptococcal meningitis, as opposed to antigenaemia without meningitis, could be diagnosed and treated with amphotericin-based therapy rather than fluconazole [39](#_ENREF_39) alone, but diagnosis of cryptococcal meningitis requires a lumbar puncture and in our study, three-quarters of the patients refused. Research is needed to understand the attitudes of both patients and caregivers to lumbar puncture and to determine the barriers to its acceptance, particularly in asymptomatic or minimally symptomatic infection; and to determine if meningitis can be predicted from the titre of antigenaemia in blood and treated with more potent antifungal combinations when antigenaemia is high.

We found a large burden of TB at enrolment. We sought sputum samples irrespective of symptoms and the vast majority of participants provided these; more than a third diagnosed with TB did not report a cough; and the use of Xpert in addition to existing diagnostics doubled the number diagnosed. Implementing re-screening of TB after a few weeks proved a challenge for the health system. Zambia could not implement this but Tanzania did for about half of those in whom TB was not detected at enrolment. Consequently, the number of new TB cases detected was small and unlikely to have contributed to the reduction of all-cause mortality observed in the clinic plus community support arm.

It is likely that a substantial proportion of the reduction in mortality – around a half - was the result of the lay-worker component which involved the provision of personalised adherence support in the community to study participants. Lay-workers proved effective in our earlier trial in Uganda [24](#_ENREF_24), [25](#_ENREF_25) but that trial was done in a largely poor rural setting with HIV services provided by a non-governmental organisation (NGO) and lay-workers provided home care throughout the 3-year follow-up. Here we evaluated a short intensive period of just 4-weeks in urban-based government clinics where access to care was much less of a barrier. The lay-workers had only about half the training as in Uganda and were less educated in order to keep the intervention costs low. Our findings suggest that this component of the intervention on its own is also a highly cost-effective strategy that could significantly enhance the impacts 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 observe a difference in reported adherence to ART between the two arms, but this was not surprising given the subjective nature of adherence measurement in Africa and elsewhere.

These findings are supported by randomised trials showing improved virological suppression associated with peer support in Rakai, Uganda [40](#_ENREF_40) and with 3-clinic-based counselling sessions around the time of ART initiation in Nairobi, Kenya [41](#_ENREF_41). 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 critical to improving patient outcomes.

During the scale-up of ART in Africa, the emphasis has been to provide patients information before they initiate ART but the benefits of this strategy have never been established. This pre-ART period is the time when high rates of mortality [3-5](#_ENREF_3) and loss from care [6](#_ENREF_6), [7](#_ENREF_7) can occur. We reduced this period by more than half and initiated ART at the patient’s second visit in both of the trial arms. Despite the reduced preparedness of patients, there appeared to be no adverse impacts on the rates of loss from care – this was 2.5% over 12 months – or on the overall mortality rate, which was broadly in line with that published from other African cohorts [24](#_ENREF_24), [42](#_ENREF_42), [43](#_ENREF_43) even though our patients had presented with low CD4 counts or on reported adherence [44](#_ENREF_44). These findings call into question the policy in most of Africa of a prolonged period of ART preparedness and suggest that rapid initiation of ART combined with support given following ART initiation would be more effective.

The cost of our entire intervention varied between about $40 to $70 per participant depending on the scenario and the country. This one-off cost has to be balanced against annual life-long costs of ART of between $270 and $450 per patient [45](#_ENREF_45). In a real-life scale up of the intervention, the costs could be considerably lower as lay-workers would likely be paid a lower salary than we had to pay to attract and train people quickly for trial purposes, they could visit more patients per day as patients would be less scattered than our trial participants, and the costs of the cryptococcal antigen test could fall. But even if the actual intervention cost were to remain at $70 per patient, the combined strategy is is likely to be highly cost-effective given the near 30% reduction in mortality. We also showed that ART can be initiated with fewer clinic visits and over a shorter time window, which will bring further cost savings and further reductions in mortality in ART programmes. Mortality rates among HIV-infected Africans entering ART programmes have remained stubbornly high during the pre-treatment period and for a few months following ART initiation [3-5](#_ENREF_3), much higher than in high-income countries [2](#_ENREF_2), and our findings point to a simple strategy that could narrow the disparities.

In summary, this large trial has demonstrated that a simple intervention comprising the screening 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.

**Figure 1. Trial profile**



**Note: Tz = Tanzania; Zm = Zambia**

**Figure 2:** Kaplan-Meier curves showing all-cause mortality in the clinic plus community support (CCS) and standard care arms i) overall, ii) among those who presented with CD4 count<50 /μl, iii) among those who presented with CD4 count≥50 /μl. Figure iv shows the mortality in those who were cryptococcal serum antigen positive versus those who were negative. The test was done in the clinic plus community support arm.

|  |  |
| --- | --- |
| i) overall | ii) CD4 count<50 /μl |
|  |  |
|  |  |
| iii) CD4 count≥50 /μl. | iv) clinic plus community support arm |
|  |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table 1. Participant characteristics at enrolment** | | |  |  |  |  |
|  |  | **Tanzania** |  |  | **Zambia** |  |
|  |  | **Clinic plus community support** | **Standard care** |  | **Clinic plus community support** | **Standard care** |
| Number enrolled |  | 434 | 436 |  | 567 | 562 |
|  |  |  |  |  |  |  |
| Age, Median (IQR) years |  | 38.0(32.0,45.0) | 37.0(31.0,44.0) | | 35.0(30.0,41.0) | 35.0(30.0,42.0) |
|  |  |  |  |  |  |  |
| Sex, number female (%) |  | 273(62.9) | 268(61.5) |  | 279(49.2) | 257(45.7) |
|  |  |  |  |  |  |  |
| WHO Clinical Stage, number (%) | |  |  |  |  |  |
|  | 1 | 33(7.6) | 34(7.8) |  | 218(38.4) | 189(33.6) |
|  | 2 | 47(10.8) | 45(10.3) |  | 98(17.3) | 98(17.4) |
|  | 3 | 251(57.8) | 245(56.2) |  | 240(42.3) | 256(45.6) |
|  | 4 | 103(23.7) | 112(25.7) |  | 11(1.9) | 19(3.4) |
|  |  |  |  |  |  |  |
| Body mass index (Kg/m2), median (IQR) | | 19.7(17.8,22.4) | 19.8(17.6,22.6) | | 19.0(17.1,21.4) | 18.8(16.8,21.2) |
|  |  |  |  |  |  |  |
| CD4 count /μl, |  |  |  |  |  |  |
|  | <50 | 202(46.5) | 217(49.8) |  | 175(30.9) | 176(31.3) |
|  | 50-99 | 152(35.0) | 131(30.0) |  | 195(34.4) | 183(32.6) |
|  | 100-200 | 80(18.4) | 88(20.2) |  | 197(34.7) | 203(36.1) |
|  |  |  |  |  |  |  |
|  | median (IQR) | 53.0(22.0,89.0) | 50.0(18.5,90.0) | | 79.0(41.0,128.0) | 75.5(37.0,127.0) |
|  |  |  |  |  |  |  |
| ART regimen, number (%)¶ |  |  |  |  |  |  |
|  | D4T, 3TC, NVP | 0(0.0) | 2(0.5) |  | 0(0.0) | 0(0.0) |
|  | D4T, 3TC, EFV | 5(1.2) | 3(0.7) |  | 0(0.0) | 0(0.0) |
|  | AZT, 3TC, NVP | 38(8.8) | 25(5.7) |  | 1(0.2) | 1(0.2) |
|  | AZT, 3TC, EFV | 112(25.8) | 139(31.9) |  | 1(0.2) | 0(0.0) |
|  | TDF, 3TC, EFV | 181(41.7) | 175(40.1) |  | 1(0.2) | 0(0.0) |
|  | ABC, 3TC, NVP | 1(0.2) | 0(0.0) |  | 5(0.9) | 7(1.2) |
|  | ABC, 3TC, EFV | 6(1.4) | 1(0.2) |  | 16(2.8) | 14(2.5) |
|  | TDF, FTC, EFV | 80(18.4) | 83(19.0) |  | 511(90.1) | 490(87.2) |
|  | TDF, FTC, NVP | 0(0.0) | 0(0.0) |  | 2(0.4) | 3(0.5) |
|  | Other | 1(0.2) | 1(0.2) |  | 29(5.1) | 47(8.4) |
|  | Never started ART | 10(2.3) | 7(1.6) |  | 1(0.2) | 0(0.0) |
|  |  |  |  |  |  |  |
| Education level, number (%)\* |  |  |  |  |  |  |
|  | None | 80(18.4) | 68(15.6) |  | 4(1.6) | 6(2.4) |
|  | Primary | 292(67.3) | 304(69.7) |  | 101(39.8) | 99(39.4) |
|  | Secondary | 51(11.8) | 55(12.6) |  | 139(54.7) | 141(56.2) |
|  | Tertiary | 11(2.5) | 9(2.1) |  | 10(3.9) | 5(2.0) |
|  |  |  |  |  |  |  |
| Marital Status, number (%)\* |  |  |  |  |  |  |
|  | Married | 170(39.2) | 187(42.9) |  | 143(56.3) | 138(55.0) |
|  | Cohabiting | 18(4.1) | 25(5.7) |  | 3(1.2) | 1(0.4) |
|  | Widowed | 58(13.4) | 29(6.7) |  | 40(15.7) | 30(12.0) |
|  | Separated/divorced | 135(31.1) | 122(28.0) |  | 31(12.2) | 45(17.9) |
|  | Never married | 53(12.2) | 73(16.7) |  | 37(14.6) | 37(14.7) |

Footnotes:

¶: 10 participants died, 5 withdrew and 2 were lost-to-follow-up after randomisation and before ART could be initiated and one person refused to go onto ART. These 18 participants were distributed as 11 in the clinic plus community support arm and 7 in the standard care arm. They were retained in the intention-to-treat analyses.

\* These data were collected from only 4 of the 6 clinics.

Note: In Zambia the median (IQR) time from first presentation to ART initiation was 14(11,19) days in the clinic plus community support arm compared with 14 (12,21) days in the standard care arm. In Tanzania these were 11 (8,19) days compared with 13(8,21) days respectively.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table 2. Number of participants diagnosed with tuberculosis and cryptococcal meningitis at trial enrolment** | | | | | | |
|  | | **Clinic plus community support** | | **Standard care** | |
|  | | **Tanzania** | **Zambia** | **Tanzania** | **Zambia** |
|  | |  |  |  |  |
| Number of participants | | 434 | 567 | 436 | 562 |
|  | |  |  |  |  |
| On anti-TB treatment at enrolment, n (%) | | 72 (16.6) | 83 (14.6) | 70 (16.1) | 100 (17.8) |
|  | |  |  |  |  |
| Newly diagnosed with active TB at enrolment by any method, n (%) | | 42 (9.7) | 47 (8.3) | 49 (11.2) | 51 (9.1) |
|  | |  |  |  |  |
|  | Newly diagnosed by sputum smear, clinical symptoms and chest x-ray | 28 (66.7) | 21/47 (44.7) | 23 (46.9) | 25 (49.0) |
|  | |  |  |  |  |
|  | Diagnosed on the basis of Xpert either alone or in combination with sputum smear, clinical symptoms or chest x-ray | 14 (33.3) | 23 (48.9) | 26 (53.1) | 25 (49.0) |
|  | |  |  |  |  |
|  | Diagnosed on the basis of culture | 0 | 3 (6.4) | 0 | 1 (2.0) |
|  | |  |  |  |  |
|  | |  |  |  |  |
| Cryptococcal antigen positive at enrolment, n (%)† | | 22/434 (5.1) | 16/567 (2.8) | - | - |
|  | |  |  |  |  |
| Agreed to have a lumbar puncture, n (%) | | 5/22 (22.7) | 4/16 (25.0) | - | - |
|  | |  |  |  |  |
| CSF positive for cryptococcus, n(%) | | 0 /5 (0) | 3/4 (75.0) | - | - |
|  | |  |  |  |  |

† 355 in Tanzania and 373 in Zambia had CD4 count≤100/ μl in the clinic plus community support arm.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 3: Rates of all-cause mortality and first hospitalisation over 12 months duration following initiation of antiretroviral therapy.** | | | | | | | | | |
|  | | **Clinic plus community support** | | | **Standard Care** | | |  |  |
|  | Events | | PYO | Rate (95% CI) | Events | PYO | Rate (95% CI) | RR (95% CI) | p-value |
| **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 |
|  |  | |  |  |  |  |  |  |  |
| **Hospitalisation\*** | | |  |  |  |  |  |  |  |
| *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 |

\* Only first hospitalisation included. There were 155 hospitalisations in total (4 participants in the clinic and community support arm and one on standard care were hospitalised twice).

Note: The effect sizes were unchanged after adjusting for study site, age, sex, baseline CD4 count (rate ratio 0.74, 95% CI 0.59, 0.92), assuming that all participants lost from care had died (rate ratio 0.75, 95% CI 0.61, 0.92), or assuming that only those lost in the first 28 days had died (rate ratio 0.69, 95% CI 0.56, 0.86).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table 4: Number of participants reporting perfect adherence \* to antiretroviral therapy during the previous 28 days, as measured at six and 12 monthly patient reviews.** | | | | |
|  | **Clinic and community support** | **Standard care** |  |  |
|  | **% (n)** | **% (n)** | **Rate ratio** | **p-value** |
| **All** |  |  |  |  |
| Month 6 review | 90.1(421/467) | 86.2(375/435) | 1.05(1.00,1.10) | 0.068 |
| Month 12 review | 88.6(451/509) | 89.2(429/481) | 0.99(0.95,1.04) | 0.770 |
|  |  |  |  |  |
| **Tanzania** |  |  |  |  |
| Month 6 review | 86.1(180/209) | 80.2(162/202) | 1.07(0.98,1.17) | 0.111 |
| Month 12 review | 89.1(236/265) | 90.4(226/250) | 0.99(0.93,1.04) | 0.616 |
|  |  |  |  |  |
| **Zambia** |  |  |  |  |
| Month 6 review | 93.4(241/258) | 91.4(213/233) | 1.02(0.97,1.08) | 0.407 |
| Month 12 review | 88.1(215/244) | 87.9(203/231) | 1.00(0.94,1.07) | 0.937 |

\* perfect adherence was defined as not missing a single pill in the last 28 days. Adherence was measured by patient interview.

**Table 5. Mortality rates among cryptococcal serum antigen positive and negative participants in the clinic plus community support arm.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | | |  | | |
|  | **Serum antigen positive** | | **Serum antigen negative** | |  |  |
|  | No. of deaths  (%) | Rate /100 person years (95% CI) | No. of deaths  (%) | Rate /100 person years (95% CI) | Rate ratio (95% CI)  Unadjusted | Rate ratio (95% CI)  Adjusted \* |
|  |  |  |  |  |  |  |
| All participants | 12/38  (31.6) | 46.3  (26.3, 81.5) | 120/947  (12.7) | 14.3  (12.0, 17.1) | 3.23  (1.78, 5.84) | 2.90  (1.60, 5.26) |
|  |  |  |  |  |  |  |
| Participants with <100 CD4/μl | 11/33  (33.3) | 50.1  (27.8, 90.5) | 101/684  (14.8) | 17  (14.0, 20.7) | 2.95  (1.58, 5.49) | 2.87  (1.54, 5.37) |
|  |  |  |  |  |  |  |

\* adjusted for CD4 count, age, sex, country

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