Muhimbili Medical Research Centre

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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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Collaborating Institutions

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University
Teaching
Hospital

State of Art and Problem Statement

- Mortality from AIDS remains high in sub-Saharan Africa
- 25% to 30% of HIV-infected persons in low and middle income countries present to care with a CD4<100 cells/□L .

- This group has high mortality before and just after starting ART

- Cryptococcal meningitis (CM) is estimated to account for 15-20% of HIV-related mortality in people presenting at health facilities in Africa

Health Solutions for the Problem

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- A search for an effective intervention to reduce mortality in this group will transform treatment outcomes for HIV/AIDs patients

- A new approach to care for patients with advanced HIV in Tanzania and Zambia, reduces mortality by 28%.

- The research, published in The Lancet, suggests that this simple low-cost intervention could be an effective approach in reducing HIV-related deaths in Africa

Objective of this trial

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We assessed the effect of combining a short period of community support and screening for meningitis using a new test, the cryptococcal antigen (CrAg) test, plus pre-emptive treatment with fluconazole for antigen positives individuals with HIV infection who presented at health centres with advanced HIV disease compared with standard care

The REMSTART PACKAGE

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- Community weekly visits for 4 weeks by a trained lay worker
- screening for meningitis using a new test, the cryptococcal antigen (CrAg) test,
  - pre-emptive treatment with fluconazole for antigen positives/2 then 8weeks for those declined lumbar puncture,
  - Lumber Puncture +Ve - Amphoteresin B/14 days plus Fluconazole/8 weeks
- Rapid ART initiation within two short-spaced visits; within 4–7 days

Methodology

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Study design and participants

- An open-label, randomized controlled trial in 6 urban public health facilities: 3 in Dar es Salaam, Tanzania, and 3 in Lusaka, Zambia: started in February, 2012

Inclusion criteria

- **HIV infected individuals**
  - Older than 18 years with a CD4 count < 200 cells per µL,
  - Lived in the clinic catchment area and had not been on ART.

Exclusion criteria

- Those who needed immediate hospital admission.

Randomization

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- Participants were randomly assigned individually to either standard clinic-based care or to the REMSTART package

- Randomization 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.
- NOTE: All participants were screening for TB using the GeneXpert MTB/RIF assay and a repeated test at 6 weeks for Tanzania only

Statistical analysis

- 2030 participants in both groups need 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

Trial Outcomes

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- 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 and adherence on ART, hospital admissions, and active tuberculosis at re-screening.

Ethical approval

- 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 Committee in Tanzania

Results

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- Feb 9, 2012, and Sept 30, 1001 patients were randomly assigned to clinic plus community support and 998 to standard care: Total 1,999
- Each participant was followed up for up to 12 months; and the last follow-up ended on Sept 30, 2014.

Results

- The characteristics of the two groups were well balanced.
- TB screening was done at baseline

89/1001 (8.9%) of patients in the clinic plus community care group and 100/998 (10.0%) in standard of care group either presented or were diagnosed with tuberculosis at baseline,

- Only 147/291 (51%) patients were re-screened, which was done at a median of 58 days (IQR 44–72) from first presentation to clinic.

TB

- Eight (5.4%, 95% CI 2.4–10.4) of 147 tested positive on X pert, 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.

Cryptococcal mortality

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- 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, could not be traced
- 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.
- 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

Conclusion

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

Acknowledgement

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- REMSTART team

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Thank you