Fluconazole plus flucytosine vs. fluconazole alone for cryptococcal antigen-positive patients identified through screening: A phase III randomised controlled trial

EFFECT: Efficacy of Flucytosine and Fluconazole as Early Cryptococcal Treatment (ISRCTN30579828)

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Introduction

Cryptococcal meningitis (CM) is the commonest form of meningitis in sub-Saharan Africa (SSA), accounting for 15%-20% of all AIDS-related deaths[1,2]. Screening patients with advanced HIV disease using a simple point-of-care test to detect cryptococcal antigen (CrAg) and treatment of CrAg-positive patients in advance of severe cryptococcal disease represents a practical and cost-effective approach to reducing mortality, with such screening programmes now recommended in many SSA countries[3-5].

However, recent data has shown that current pre-emptive treatment with fluconazole alone may be suboptimal with a substantial number of patients going on to develop cryptococcal meningitis and die[6,7]. Testing of more effective antifungal regimens is thus urgently required. A combined treatment of fluconazole and flucytosine was shown to be safe and effective in the recent phase III ACTA trial of those with symptomatic meningitis, with mortality halved compared to historic cohorts treated with fluconazole alone[8].

Although the ACTA trial results cannot be directly generalised to CrAg-positive patients without symptomatic meningitis, flucytosine plus fluconazole could also be effective in reducing mortality associated with asymptomatic CrAg-positive patients. And importantly, this oral combination could be given to outpatients without any need for hospitalisation.

Study Design, Objectives and Outcomes

Study design

The EFFECT trial is a **phase III**, multi-centre, pragmatic open-label, 1:1 randomised treatment trial **embedded into existing CrAg screening programmes** at 11 sites in South Africa and Tanzania (see Fig 1).

Primary objective

To determine whether combination treatment of *fluconazole plus flucytosine* for 2 weeks will be superior to *standard treatment of fluconazole alone* in reducing 6-month all-cause mortality for CrAg-positive individuals with advanced HIV disease.

Primary outcome measure

All-cause mortality at 6 months after randomisation

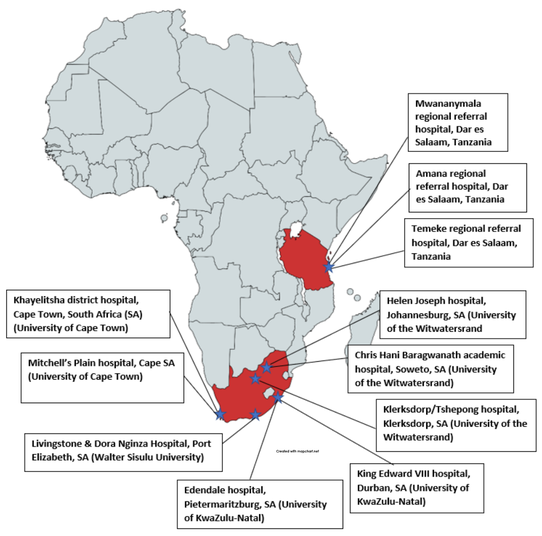

Fig 1: Map of trial sites -Tanzania (3) and South Africa (8)

Secondary outcomes include:

1. Time to all-cause mortality within first 6 months
2. All-cause mortality at 10 weeks
3. Time to all-cause mortality within first 10 weeks
4. CM-free survival to 6-months
5. Incidence rate of symptomatic CM over 6 months
6. Tolerability and safety: Proportions of patients developing clinical and laboratory-defined grade III/IV adverse events
7. Efficacy outcomes by baseline CrAg titre/ CrAg semi-quantitative (SQ) assay score
8. Health service costs per life year saved

Sample size and statistical analysis

Using a two-sided α=0.05, 540 participants (270 per arm) will provide 91% power to detect a 40% relative reduction in mortality with fluconazole alone versus flucytosine plus fluconazole (an observed mortality of 30% vs. 18%, respectively). We aim to enrol ***600 participants***, to conservatively account for up 10% loss to follow-up.

The primary analysis will use a log binomial model (generalised linear model), including treatment arm as the sole predictor, to derive the relative risk (RR) of 6-month all-cause mortality between the two arms. Covariate adjusted and sensitivity analyses will also be performed.

Inclusion and Exclusion criteria

INCLUSION CRITERIA

1. Consecutive patients aged ≥18 years old
2. HIV-seropositive
3. CD4 count of <100 cells/µl
4. Serum/plasma CrAg test positive within the last 14 days
5. Cerebrospinal fluid (CSF) CrAg test negative or lumbar puncture not done (declined)
6. Willing to participate in the study

EXCLUSION CRITERIA

1. Prior episode of cryptococcal meningitis
2. Pregnancy (confirmed by urine or serum pregnancy test) or breastfeeding
3. Previous serious reaction to flucytosine or fluconazole
4. Already taking high-dose fluconazole for ≥1 week
5. Contraindicated concomitant medications
6. HIV-seronegative
7. Clinical symptoms/signs of symptomatic meningitis i.e. a progressively severe headache OR a headache and marked nuchal rigidity OR a headache and vomiting OR seizures OR a Glasgow Coma Scale (GCS) score of <15
8. Jaundice
9. CSF positive for CM

Acknowledgements

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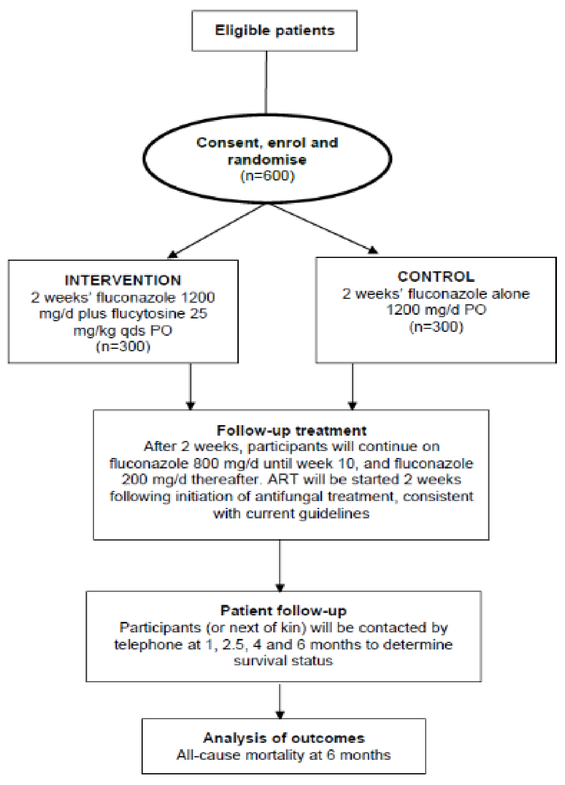
Allocation, Intervention and Follow-up

Following informed consent, participants will be enrolled and randomised individually 1:1 via permuted-block randomisation method and stratified by site. Block sizes will vary at 4 and 6.

Participants will be randomised to one of 2 treatment arms:

1. Fluconazole 1200 mg/d plus flucytosine 25 mg/kg qds PO (intervention arm) for 2 weeks
2. Fluconazole alone 1200 mg/d PO (standard dose "control arm") for 2 weeks

All participants will then receive fluconazole 800 mg/d to 10 weeks, and fluconazole 200 mg/d thereafter for a minimum of 12 months as per national guidelines. ART will be commenced on day 14 as per current international World Health Organization and national guidelines.



Clinical (e.g. age, sex, medical history, time on ART and adherence assessment**,** physical examination) and laboratory (full blood count (FBC) and differential count, serum creatinine, serum alanine transaminase and urine lipoarabinomannan) data will be collected at baseline. Bloods will be drawn on day 14 to check FBC and differential count. ART will be started or re-started on day 14, consistent with current guidelines. Participants will be contacted on days 3 and 9 by telephone for adherence counselling and at 1, 2.5 (10 weeks), 4 and 6 months to determine survival status.

Trial Management and Ancillary Studies

Trial management

We expect to begin recruitment at all sites by the end of 2021 / beginning 2022. Prior to opening, the trial will be approved by St George's University of London (SGUL) Research Ethics Committee (REC) and national and other relevant ethics committees in each country. Regulatory approvals will be sought from SAPHRA in South Africa and TMDA in Tanzania.

Electronic case report form (eCRF) data will be collected using an appropriately-validated and secured electronic data capture (EDC) system. Trial oversight will be provided by the Trial Management Group (TMG), Trial Steering Committee (TSC) and Independent Data Monitoring Committee (DMC). The study sponsor is SGUL. Trial sites will be monitored at regular intervals with visits by the Trial Manager/Monitor and an external audit will be conducted in the first year of recruitment.

Ancillary studies

Sub-studies include a **health economics** study to estimate the average health care cost per patient and to compare the differences in health care costs and health outcomes in both arms. We will also model the incremental cost per life year gained.

The association between baseline **CrAg titre and/or semi-quantitative (SQ) score** and outcome (expected to be strongly correlated) will be determined and treatment effects will be assessed according to the initial levels of CrAg. If such a differential response was observed, this sub-study could provide the rationale for and demonstrate the means for individualized treatment, based on a rapid assessment of antigen concentration.

Discussion and Potential Impact

The impact of a combined oral antifungal treatment regimen for CrAg-positive patients identified through screening has not yet been tested and robust clinical trial data are urgently needed to inform policy and practice. Demonstrating the effectiveness of the addition of flucytosine to the fluconazole treatment currently in use could have an important global impact on the reduction of advanced HIV mortality as has been seen for CM inpatients.

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