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

**EFFECT: Efficacy of Fluconazole and Fluconazole as Early Cryptococcal Treatment**

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**Introduction**

Cryptococcal meningitis (CM) is the commonest form of meningitis in sub-Saharan Africa (SSA), accounting for approximately 20% of all AIDS-related deaths.1 Screen 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.2-4 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.5 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.6 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

**Secondary outcomes include:**

1. Time to all-cause mortality within first 6 months
2. All-cause mortality at 12 weeks
3. Time to all-cause mortality within first 12 months
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 45% reduction in mortality with fluconazole plus flucytosine versus fluconazole alone (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
2. HIV-seropositive
3. CD4 count of <100 cells/µl
4. Serum/plasma CrAg test positive withing the last 14 days
5. Cerebrospinal fluid (CSF) CrAg test positive 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

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**References**