A randomized controlled trial for the treatment of HIV-associated cryptococcal meningitis in Africa: oral fluconazole plus flucytosine or one week amphotericin-based therapy versus two weeks amphotericin-based therapy. The ACTA Trial

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Background: Cryptococcal meningitis (CM) accounts for 10–20% of HIV-related deaths and >100,000 deaths/year. Amphotericin (AmB) plus flucytosine for 2 weeks is considered the gold standard but is unavailable in resource-limited settings where fluconazole treatment predominates.

Methods: Based on Phase II studies, we tested, against 2 weeks AmB-based treatment, 2 new strategies, which could be sustainable in Africa, and more effective than fluconazole: optimized oral therapy of high dose fluconazole plus flucytosine, and short (1 week) induction with AmB-based treatment. In the AmB arms, we compared fluconazole and flucytosine as adjunctive treatments. Between 2013 and 2016, 721 participants from 9 centres in Malawi, Zambia, Cameroon and Tanzania with first-episode CM were randomized to:

- **Oral (238):** fluconazole (1200mg/day) plus flucytosine (100mg/kg/day) for 2 weeks.
- **1-week (240):** AmB (1mg/kg/d), plus fluconazole (1200mg/day), or flucytosine (100mg/kg/day) (ratio 1:1), for 7 days. Days 8–14, fluconazole 1200mg/day.
- **2-weeks (243):** AmB (1mg/kg/d) plus fluconazole (1200mg/day), or flucytosine (100mg/kg/day) (ratio 1:1), for 14 days.

After 2 weeks, all received standard fluconazole consolidation. ART was started, or restarted, at 4 weeks, and patients followed-up to 10 weeks.

Results: Only 4 participants were lost-to-follow-up. Mortality at 2 and 10 weeks for oral, 1-week and 2-weeks was 18%, 22%, 21%, and 35%, 36%, 40%, respectively. The upper 1-sided 95% CI limits for the difference in mortality comparing oral and 1-week against 2 weeks AmB-based treatment (primary endpoint) were 3.0% and 6.8%, below the pre-specified 10% non-inferiority margin. Hazard ratios (95% CI) were 0.82 (0.54–1.25) and 1.01 (0.68–1.51) at 2, and 0.83 (0.61–1.13) and 0.89 (0.66–1.21) at 10 weeks, for oral and 1-week versus 2-weeks, respectively. As adjunctive treatment with AmB, flucytosine was superior to fluconazole (HR(95% CI): 1.62 (1.19–2.02) p = 0.002). One week AmB plus flucytosine had the lowest 10-week mortality (24%), significantly lower than all other AmB arms (HR(95%CI): 0.56(0.35–0.91) comparing 1-week with 2-weeks AmB plus flucytosine). Side effects were more frequent with 2 weeks AmB than with 1 week AmB, or oral therapy.

Conclusions: One week AmB plus flucytosine and the oral combination provide safe, effective and sustainable induction therapy in resource-limited settings. Flucytosine should be made widely available for treatment of cryptococcosis.
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