MOAX0201LB

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 (1.19–2.20) 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.

Journal Information

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The *Journal of the International AIDS Society*, an official journal of the Society, provides a peer-reviewed, open access forum for essential and innovative HIV research, across all disciplines.

All articles published by the *Journal of the International AIDS Society* are freely accessible online. The editorial decisions are made independently by the journal's editors-in-chief.

Email: editorial@jiasociety.org
Website: http://www.jiasociety.org
eISSN: 1758-2652

Publisher

International AIDS Society
Avenue de France 23
1202 Geneva, Switzerland
Tel: +41 (0) 22 710 0800
Email: info@iasociety.org
Website: http://www.iasociety.org

Indexing/abstracting

The *Journal of the International AIDS Society* is indexed in a variety of databases including PubMed, PubMed Central, MEDLINE, Science Citation Index Expanded and Google Scholar. The journal's impact factor is 6.296 (*2016 Journal Citation Report® Science Edition - a Clarivate Analytics product).

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