Sertraline and High-dose Fluconazole Treatment of Cryptococcal Meningitis in Tanzania

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BACKGROUND

- *Cryptococcus* is the leading cause of adult meningitis in sub-Saharan Africa.
- First-line anti-fungals are largely unavailable, and fluconazole monotherapy remains the standard of care in most sub-Saharan African settings.
- Sertraline has shown to have in-vitro and in-vivo activity against *Cryptococcus*, is synergistic activity with fluconazole and shows promise as an adjunctive antifungal therapy[1,2].
- Short course amphotericin B deoxycholate has previously shown to be as effective and better tolerated than standard 2 week therapy[4].
- We assessed the safety and efficacy of adjunctive sertraline and short course amphotericin B added to standard fluconazole monotherapy for the treatment of cryptococcal meningitis in Ifakara[5], rural southern Tanzania.

METHODS

- Design: Open label non-randomized clinical trial
- We prospectively enrolled 46 HIV-infected adults with cryptococcal meningitis at the Saint Francis Referral Hospital, Ifakara, Tanzania, from October 2014 to December 2016.
- Participants received induction treatment with either:
  i) Fluconazole 1200 mg/d for 2 weeks (n=28) + sertraline 400mg/d + ; or
  ii) Fluconazole 1200 mg/d for 2 weeks + sertraline 400mg/d plus amphotericin B deoxycholate 1mg/kg/day for 5 days (n=14).
- Lumbar punctures were performed on days 1, 3,7,10 and 14.
- Consolidation phase consisted of sertraline 200mg/day and fluconazole 800mg/day for 12 weeks.
- The primary outcome was early fungicidal activity (EFA) in CSF over the first 2 weeks calculated by linear regression.

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Table 1. Baseline Demographic Characteristics

Baseline Variable	Sertraline and Fluconazole (N=28)	Amphotericin, Sertraline and Fluconazole (N=18)
Women, n(%)	15 (54)	7 (39)
Age in years	37 (33 – 45)	36 (31 – 43)
Body Mass Index, kg/m^2	20.4 (17.1 – 22.1)	20.7 (19.9 – 21.3)
CD4, cells/μL	40 (11 – 60)	25 (13 – 47)
Hemoglobin, g/dL,	10.0 (9.0 – 11.5)	10.6 (9.5 – 11.2)
Serum potassium, mmol/L	-	3.7 (3.4 – 4.0)
eGFR, ml/min/1.73m^2	118 (97 – 136)	130 (91 – 145)
AST, IU/L	31 (22 – 40)	22 (17 – 64)
ALT, IU/L	19 (13 – 27)	15 (10 – 40)
CSF Opening pressure, mmH_2O	-	230 (190 – 400)
CSF WBC cell count, cells/μL	220 (5 – 525)	5 (5 – 350)
CSF quantitative culture, CFU/mL	8,000 (1500 – 70,000)	5,350 (800 – 250,000)

Values are median (IQR) or n (%); CFU: Colony Forming Units; eGFR: estimated Glomerular Filtration Rate calculated using the CKD- EPI formula

Figure 1. *Cryptococcus* Early Fungicidal Activity in CSF

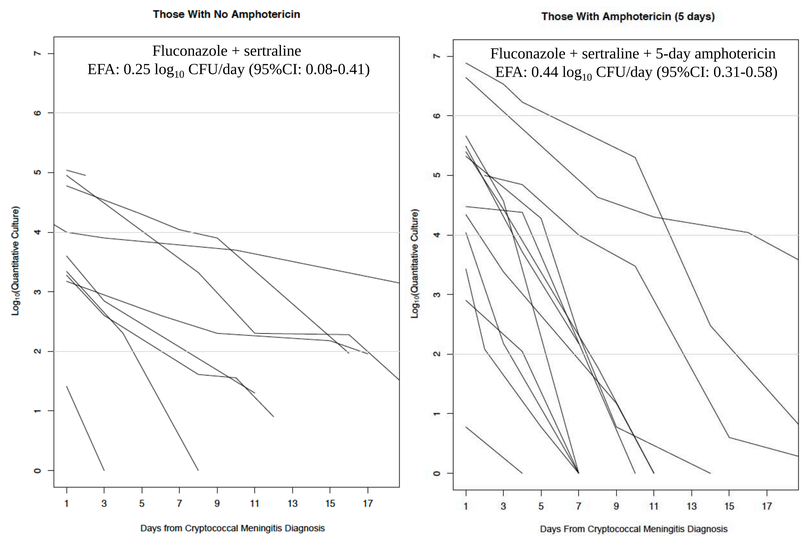


Table 2. Follow-up characteristics

	Baseline	Day 7	Day 14
Fluconazole + Sertraline			
Haemoglobin, g/dL,	10 (9 – 11.5)	10.2 (6.9 – 12.3)	10 (9.7 – 10.8)
GFR, ml/min/1.73m^2	118 (97 – 136)	116 (113 –143)	124 (90 - 132)
ALT, IU/L	19 (13 – 27)	27 (15 – 35)	58 (17 - 93)
AST, IU/L	31 (22 - 40)	26 (12 – 30)	49 (26 – 81)
Fluconazole + Sertraline + 5-day Amphotericin			
Haemoglobin, g/dL,	10.6 (9.5 – 11.2)	9.4 (8.0 – 10.8)	9.7 (8.2 – 10.6)
Serum potassium, mmol/L	3.7 (3.4 – 4.0)	3.4 (2.9 – 4.04)	3.6 (3.3 – 4.1)
GFR, ml/min/1.73m^2	130 (91 – 145)	101 (77 – 133)	129 (91 – 144)
ALT, IU/L	15 (10 – 40)	18 (14 – 25)	39 (19 – 50)
AST, IU/L	22 (17 – 64)	33 (16 – 50)	58 (41 – 94.1)

Values are median (IQR)

RESULTS

- The CSF *Cryptococcus* clearance rate was with:
  - Fluconazole + sertraline: 0.25 $\log_{10}$ CFU/day (95%CI: 0.08-0.41)
  - Fluconazole + sertraline + 5-day amphotericin: 0.44 $\log_{10}$ CFU/day (95%CI: 0.31-0.58) (p=0.05).
- The 2 and 10-week survival were respectively with:
  - Fluconazole + sertraline: 64% (18/28) and 21% (6/28)
  - Fluconazole + sertraline + 5-day amphotericin: 89% (16/18) and 61% (11/18).
- Overall sertraline was well tolerated:
  - In two patients, sertraline was prematurely tapered to 200mg/d.
  - In two patients, sertraline was stopped due to worsening confusion, restlessness, and hallucinations.
- Severe hypokalemia (<2.5 mEq/L) occurred in 21% (3/14) of persons treated with amphotericin, and responded to KCl supplementation.

CONCLUSIONS

- Sertraline added to fluconazole improved the 2-week CSF fungal clearance by 40% when compared with previously published clearance of fluconazole monotherapy (0.25 vs 0.18 $\log_{10}$ CFU/mL CSF/day).[3]
- Similarly, when sertraline was added to short course amphotericin and fluconazole, fungal clearance improved by 46% (0.44 vs 0.30 vs $\log_{10}$ CFU/mL CSF/day).[4]
- The addition of short course amphotericin increased CSF clearance, reduced early in-hospital mortality, and was safely implementable.
- Further efforts are needed to improve outpatient survival of persons with cryptococcal meningitis in rural sub-Saharan Africa.

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