Best Options in Cryptococcosis

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Ho Chi Minh City
Viet Nam
1. Challenges with cryptococcal meningitis
2. Current antifungal recommendations and evidence underlying them
3. New data - drug repurposing
4. Novel treatments and the future
Cryptococcal Meningitis - Challenges

1. Burden of disease (HIV)
   - Global incidence: 223,100 (95%CI 150,600 - 282,400)
   - Global deaths: 181,000 (95%CI 119,400 - 234,300)
   - Cryptococcal antigenaemia: 6.5% (CD4 count <100 cells/μL)

2. Current treatments
   - Very few drugs...
   - Poor *in vivo* efficacy
   - Toxicities

3. Poor access to key drugs

4. Trial data relate to HIV infected patients

*Lancet Infect Dis. 2017 Aug;17(8):873-881*
Treatment guidelines
# Current WHO recommendations (adults)

<table>
<thead>
<tr>
<th>Induction therapy</th>
<th>Consolidation therapy</th>
<th>Maintenance/secondary prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Option</strong></td>
<td><strong>Week 1</strong></td>
<td><strong>Week 2</strong></td>
</tr>
<tr>
<td>1</td>
<td>Amphotericin + 5FC</td>
<td>Fluconazole 1200mg/day</td>
</tr>
<tr>
<td>2</td>
<td>Fluconazole 1200mg/day + 5 FC</td>
<td>Fluconazole 800mg/day</td>
</tr>
<tr>
<td>3</td>
<td>Amphotericin + fluconazole 1200mg/day</td>
<td>Fluconazole 800mg/day</td>
</tr>
</tbody>
</table>

**Amphotericin dose:** 1mg/kg/day  
**5FC = Flucytosine = 100mg/kg/day in 4 divided doses**  
A minimum package of pre-emptive hydration and electrolyte replacement and toxicity monitoring and management should be provided to minimize treatment toxicity related to amphotericin B and flucytosine.
Step 1: Amphotericin monotherapy versus amphotericin + flucytosine

CSF cultures negative in 60% by 2 weeks vs 51% (p = 0.06)

Step 2: Itraconazole versus fluconazole

72% of flucon versus 60% of itra patients had sterile CSF by 10 weeks

No difference in mortality
14 Days

Π vs. I: 0.57 (0.30, 1.08); p=0.08

Π vs. ΙΙΙ: 0.78 (0.44, 1.41); p=0.42

70 Days

Π vs. I: 0.61 (0.39, 0.97); p=0.04

Π vs. ΙΙΙ: 0.71 (0.45, 1.11); p=0.13

6 Months

Π vs. I: 0.56 (0.36, 0.86); p=0.01

Π vs. ΙΙΙ: 0.78 (0.53, 1.16); p=0.23
Fungal decline
log10 CFU/ml/day

-0.31 (0.34, -0.29)

-0.42 (-0.44, -0.40)

-0.32 (-0.34, -0.29)

II v I P < 0.0001

III v I P = 0.83

Fungal clearance rate person weeks of follow-up

0.17 (0.13, 0.23)

0.39 (0.31, 0.50)

0.26 (0.20, 0.34)

II v I P < 0.0001

III v I P = 0.10
More rapid yeast clearance $\rightarrow$ better survival
ACTA - Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa

N Engl J Med
Volume 378(11):1004-1017
March 15, 2018
ACTA trial Overview

Randomized controlled open label trial

2 Treatment strategies tested
1. Oral versus standard (intravenous amphotericin based) therapy
2. Shortened (1 week) versus standard (2 week) amphotericin based therapy

Amphotericin was combined, through randomization, with either:
- fluconazole 1200mg/day or
- flucytosine 100mg/kg/day

9 sites across Africa
# ACTA treatment arms

<table>
<thead>
<tr>
<th>Week</th>
<th>Strategy</th>
<th>1</th>
<th>2</th>
<th>N</th>
<th>3-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1</td>
<td>Oral</td>
<td>Fluconazole 1200mg/day + flucytosine 100mg/kg/day</td>
<td></td>
<td>225</td>
<td>Fluconazole 800mg/day then 400mg/day</td>
</tr>
<tr>
<td>Arm 2</td>
<td>1 week amphotericin</td>
<td>Amphotericin + fluconazole</td>
<td>Fluconazole 1200mg/day</td>
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</tr>
<tr>
<td>Arm 3</td>
<td>2 week amphotericin</td>
<td>Amphotericin + flucytosine</td>
<td>Fluconazole 1200mg/day</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>Arm 4</td>
<td>2 week amphotericin</td>
<td>Amphotericin + fluconazole</td>
<td></td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>Arm 5</td>
<td></td>
<td>Amphotericin + flucytosine</td>
<td></td>
<td>115</td>
<td></td>
</tr>
</tbody>
</table>

Non-inferiority design, inferiority margin 10%

Primary endpoint: 2 week mortality

Amphotericin dose 1mg/kg/day

Flucytosine dose 100mg/kg/day
Primary outcome: non-inferiority by 2 weeks
Again, this study underlines the importance of flucytosine as the partner drug:

Deaths by Week 10
45% versus 31%

HR 0.62 (95CI 0.45 – 0.84)
p=0.002

EFA Fluconazole
-0.36 log_{10} CFU/ml/day

EFA flucytosine
-0.46 log_{10} log_{10} CFU/ml/day
Hazard Ratios by partner treatment

Rate of fungal clearance correlates with survival benefits

Table 3. Unadjusted Time-to-Event Analysis of Mortality and Rate of Fungal Clearance in CSF According to Partner Treatment with Amphotericin B in the Intention-to-Treat Population.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Amphotericin B + Fluconazole (N=225)</th>
<th>Amphotericin B + Flucytosine (N=228)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at 10 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths</td>
<td>101</td>
<td>71</td>
<td>45.0 (38.5 to 51.5)</td>
<td>0.62</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td></td>
<td></td>
<td>31.1 (25.3 to 37.3)</td>
<td>0.56</td>
</tr>
<tr>
<td>Mortality at 2 wk</td>
<td></td>
<td></td>
<td>27.1 (21.3 to 32.9)</td>
<td>0.56</td>
</tr>
<tr>
<td>No. of deaths</td>
<td>61</td>
<td>37</td>
<td>16.3 (11.5 to 21.1)</td>
<td>0.56</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td></td>
<td></td>
<td>25.1 (19.4 to 30.7)</td>
<td>0.59</td>
</tr>
<tr>
<td>Mortality at 4 wk</td>
<td></td>
<td></td>
<td>38.2 (31.9 to 44.6)</td>
<td>0.59</td>
</tr>
<tr>
<td>No. of deaths</td>
<td>86</td>
<td>57</td>
<td>25.1 (19.4 to 30.7)</td>
<td></td>
</tr>
<tr>
<td>% (95% CI)</td>
<td></td>
<td></td>
<td>25.1 (19.4 to 30.7)</td>
<td></td>
</tr>
<tr>
<td>Fungal clearance‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>175</td>
<td>186</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearance rate — log_{10} CFU/ml/day</td>
<td>-0.36±0.23</td>
<td>-0.46±0.25</td>
<td>-0.06 (-0.03 to -0.08)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD. Missing values were not imputed.
†P value for the between-group differences in all-cause mortality were calculated with the use of a log-rank test.
‡Data are from a mixed-effects model with treatment, day, and interaction between treatment and day as fixed effects, the log baseline measurement of fungal count as a covariate, and patient as a random effect.
Table 2. Unadjusted Analysis of Mortality and Rate of Fungal Clearance in CSF According to Treatment Strategy in the Intention-to-Treat Population.

| Outcome                  | Oral Regimen (N = 225) | 1-Wk Amphotericin B (N = 224) | 2-Wk Amphotericin B (N = 229) | Difference (95% CI)†
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>Oral Regimen vs. 2-Wk Amphotericin B</td>
</tr>
<tr>
<td><strong>Mortality at 2 wk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths</td>
<td>41</td>
<td>49</td>
<td>49</td>
<td>−3.18 (−10.50 to 4.15)</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>18.2 (13.2 to 23.3)</td>
<td>21.9 (16.5 to 27.4)</td>
<td>21.4 (16.1 to 26.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality at 4 wk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths</td>
<td>56</td>
<td>66</td>
<td>77</td>
<td>−8.74 (−17.06 to −0.41)</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>24.9 (19.2 to 30.5)</td>
<td>29.5 (23.6 to 35.5)</td>
<td>33.6 (27.5 to 39.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality at 10 wk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths</td>
<td>79</td>
<td>81</td>
<td>91</td>
<td>−4.63 (−13.52 to 4.27)</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>35.1 (28.9 to 41.3)</td>
<td>36.2 (30.0 to 42.7)</td>
<td>39.7 (33.5 to 46.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Fungal clearance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>182</td>
<td>179</td>
<td>182</td>
<td></td>
</tr>
<tr>
<td>Clearance rate — log10 CFU/ml/day</td>
<td>−0.26±0.18</td>
<td>−0.40±0.24</td>
<td>−0.42±0.25</td>
<td>0.10 (0.07 to 0.13)</td>
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</tbody>
</table>
Unadjusted Analysis of Mortality and Rate of Fungal Clearance in CSF According to Treatment Strategy in the Intention-to-Treat Population.

**Table 2. Unadjusted Analysis of Mortality and Rate of Fungal Clearance in CSF According to Treatment Strategy in the Intention-to-Treat Population.**

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<tr>
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<tr>
<td>% (95% CI)</td>
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</table>

**Fungal clearance‡**

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>182</th>
<th>179</th>
<th>182</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance rate</td>
<td>−0.26±0.18</td>
<td>−0.40±0.24</td>
<td>−0.42±0.25</td>
</tr>
</tbody>
</table>

0.10 (0.07 to 0.13)§

0.01 (−0.01 to 0.04)¶
All cause mortality by treatment arm

10 week AmB/5FC mortality: 24.2%; 95% CI, 16.2 to 32.1

HR 1 week AmB-5FC versus any other AmB regimen: 0.56 [95% CI, 0.35 to 0.91]

1 week AmB-fluconazole: HR 2.54 (95% CI, 1.60 to 4.05)

Oral combination: HR 1.56 [95%CI, 1.01 to 2.42]
Conclusions

• All treatment combinations were non-inferior to two weeks amphotericin combinations

• The most effective treatment appeared to be 1 week of amphotericin combined with 1 week of flucytosine

• Amphotericin combined with flucytosine delivered better survival outcomes by 10 weeks than amphotericin combined with fluconazole

• 1 week amphotericin and oral, amphotericin sparing, regimens were associated with lower rates of adverse events.

• The fluconazole-flucytosine combination had unexpectedly ‘good’ outcomes given its EFA
Ambition Studies

<table>
<thead>
<tr>
<th>Arm</th>
<th>Amphotericin</th>
<th>Additional treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>L-AmB Day 1: 10mg/kg</td>
<td>Fluconazole 1200mg/day 14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flucytosine 100mg/kg/day 14 days</td>
</tr>
<tr>
<td>Control</td>
<td>Amphotericin deoxycholate</td>
<td>Flucytosine 100mg day 7 days then</td>
</tr>
<tr>
<td></td>
<td>1mg/kg/day for 7 days</td>
<td>Fluconazole 1200mg/day 7 days</td>
</tr>
</tbody>
</table>

Powered to survival (N = 850). Botswana, Zimbabwe, Uganda, Malawi, South Africa

http://www.isrctn.com/ISRCTN72509687
Flucytosine – key drug

But…

Essentially unavailable where disease burden is highest
Very few manufacturers
Few indications outside cryptococcal disease
USA now 30 000USD/course

Could a specific anti-cryptococcal drug ever be commercially viable?
Repurposing

Off-patent

Frequent indications for other, common, diseases – availability.

Commercial viability driven by high numbers of prescriptions rather than high per tablet profit margins,

Affordability - multiple manufacturers, competition
Sertraline

Sertraline has previously demonstrated *in vitro* and *in vivo* activity against *Cryptococcus*\(^1\)

Inhibits intracellular vesicle transport

The ASTRO-CM trial

- Double-blind, randomized, placebo controlled trial of sertraline
- Participants received standard therapy for cryptococcal meningitis in addition to **adjunctive sertraline vs placebo** for cryptococcal meningitis

ASTRO-CM Pilot Study

N=173, Adults with CM

Standard therapy plus adjunctive sertraline at doses of 100-400mg daily

Improved rate of CSF fungal clearance compared to historical controls (p=0.05)

85% of isolates had MIC ≤ 4 µg/mL

At doses of 400mg daily, sertraline levels predicted to exceed MIC in CNS\(^1,2\)

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Astro-CM

Study design: multicenter, double-blind, placebo-controlled RCT

Population: HIV-infected Ugandan adults

Participants randomly assigned to:
- Standard therapy: 7-14 days of amphotericin B + fluconazole starting at 800 mg/day
- Standard therapy plus Sertraline 400 mg/day for 2 weeks, then 200 mg/day

Primary outcome: 18-week survival
Results

Trial stopped for futility after enrolling 460 of planned 550 patients

18-week mortality

- 52% in sertraline group vs.
- 46% in the placebo group

- HR 1.21 (95% CI, 0.93-1.57; p=0.15)

Mortality was similar among ART naïve and ART experienced patients
Rate of Fungal Clearance from CSF

Early fungicidal activity was similar to pilot study
Conclusions

Sertraline did not reduce mortality

The reasons for sertraline inactivity are likely multifactorial:

- Therapeutic sertraline concentrations only achieved between 7-14 days?
- Inadequate drug concentrations with 200mg dose used after 14 day?
- Induction of metabolism by ART?
- Possible immunomodulatory effects of sertraline?

Is there a role for sertraline at higher doses, longer durations, in the absence of amphotericin?
Tamoxifen

Triphenylethylene
Selective Estrogen Receptor Modulator
Breast cancer
Anti-yeast activity:
1989: *S. cerevisae*
1993: *Candida* spp
2009: *Cryptococcus neoformans*

Tamoxifen

Mechanism – inhibits binding of calmodulin to calcineurin
Calcineurin moderates stress response in *C. neoformans*
Concentrated in macrophage phagosomes
Excellent levels in brain (10-100 fold concentration c.f. serum)
Synergy described with amphotericin *in vitro*
Boosts effect of fluconazole monotherapy in mouse model
MIC (H99): 8-16ug/mL (CLSI)

Tamoxifen

Orally bioavailable
Cheap and off-patent
Widely available
Safe and well tolerated (1000s of years of patient experience)
10, 20 and 40mg tablet formulations
20mg tablet 10 US cents
## Susceptibility of Vietnamese clinical isolates to tamoxifen, amphotericin and fluconazole

<table>
<thead>
<tr>
<th>Antifungal (N)</th>
<th>Minimum Inhibitory Concentration (MIC, µg/mL)</th>
<th>Range</th>
<th>MIC50</th>
<th>MIC90</th>
<th>Geometric Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C. neoformans †</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen (30)</td>
<td></td>
<td>2 - 16</td>
<td>4</td>
<td>16</td>
<td>7.1</td>
</tr>
<tr>
<td>Amphotericin B (30)</td>
<td></td>
<td>0.25 - 2</td>
<td>1</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Fluconazole (20)</td>
<td></td>
<td>0.5 - 64</td>
<td>8</td>
<td>64</td>
<td>9.2</td>
</tr>
<tr>
<td>Flucytosine (20)</td>
<td></td>
<td>4 - 32</td>
<td>8</td>
<td>16</td>
<td>8.9</td>
</tr>
<tr>
<td><strong>C. gattii</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen (8)</td>
<td></td>
<td>2 - 8</td>
<td>4</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Amphotericin B (8)</td>
<td></td>
<td>0.25 - 2</td>
<td>0.5</td>
<td>1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

†Excludes results for H99. Numbers in brackets are number of isolates tested.
Synergy between tamoxifen and amphotericin or fluconazole in Vietnamese clinical isolates

<table>
<thead>
<tr>
<th>Antifungal combination</th>
<th>Proportion (%) of isolates where particular drug interactions was observed †</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Synergy FICI ≤0.5</td>
<td>No interaction 0.5 &lt; FICI ≤ 4</td>
</tr>
<tr>
<td>C. neoformans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen + amphotericin</td>
<td>67 (20/30)</td>
<td>33 (10/30)</td>
</tr>
<tr>
<td>Tamoxifen + fluconazole</td>
<td>5 (1/20)</td>
<td>95 (19/20)</td>
</tr>
<tr>
<td>Tamoxifen + flucytosine</td>
<td>0 (0/20)</td>
<td>100 (20/20)</td>
</tr>
<tr>
<td>C. gattii</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen + amphotericin</td>
<td>75% (6/8)</td>
<td>25% (2/8)</td>
</tr>
</tbody>
</table>

†Numbers in brackets: Numerators are the numbers of strains where interaction was observed; denominators are the numbers of isolates tested
**Synergy between amphotericin, tamoxifen and fluconazole in Vietnamese clinical isolates**

<table>
<thead>
<tr>
<th>Isolate</th>
<th>MIC ug/mL</th>
<th>FICI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amphotericin B</td>
<td>Fluconazole</td>
</tr>
<tr>
<td></td>
<td>Alone</td>
<td>Combined</td>
</tr>
<tr>
<td>BK03</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>BK59</td>
<td>1</td>
<td>0.25</td>
</tr>
<tr>
<td>BK287</td>
<td>2</td>
<td>0.125</td>
</tr>
<tr>
<td>BK301</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>H99</td>
<td>0.5</td>
<td>0.0625</td>
</tr>
</tbody>
</table>

FIC <1: synergy  
FIC = 1: no interaction  
FIC > 1: antagonism
Promising candidate?

No human data...
Needs exploratory study

What dose...?
Dose in Breast Ca – 20-80mg/day
Serum levels in order of 2µg/mL with doses of 20-40mg/day
MIC$_{90}$ 16µg/mL
Around 300mg/day...
10-100 fold concentration in tissues cf serum
Phase II open label randomized controlled trial

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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<tbody>
<tr>
<td><strong>Intervention arm</strong></td>
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<td>Tamoxifen 300mg/day</td>
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<td>Amphotericin 1mg/kg/day</td>
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<td>Fluconazole 800mg/day</td>
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<th>4</th>
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<tbody>
<tr>
<td><strong>Control arm</strong></td>
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</tbody>
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Study sites: Hospital for Tropical Diseases and Cho Ray Hospital, Ho Chi Minh City
N = 50
Primary endpoint

Early Fungicidal Activity over the first 2 weeks following randomisation

Secondary endpoints

• Survival to 10 weeks following randomisation
• Rates of disability and visual deficit
• Rates of adverse events
• Rates of IRIS
• Rates of CM relapse
• Rates of QT prolongation
RESULTS

69 patients were assessed for eligibility

50 cases underwent randomization
Stratified by hospital and HIV serostatus

Control arm: 26 patients
Intervention arm: 24 patients
RESULTS

Primary outcome

- Intention-to-treat population (ITT)

<table>
<thead>
<tr>
<th>Group</th>
<th>Quantitative fungal count [CFU/ml]</th>
<th>Study day</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
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<td>15</td>
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<tr>
<td>Tamoxifen</td>
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<td>8</td>
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</tbody>
</table>

Control: \(-0.563 (-0.705, -0.421)\)
Tamoxifen: \(-0.565 (-0.716, -0.413)\)

Difference in change (95% CI) - P value
-0.002 (-0.200, 0.196); 0.9838
RESULTS

Survival rate

No. at risk

Control 26 22 21 19 18 18
Tamox 24 19 18 17 15 15

HR 1.58
(95CI 0.51-4.88)
P = 0.43
# RESULTS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Control</th>
<th>Tamoxifen</th>
<th>HR</th>
<th>p</th>
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<tbody>
<tr>
<td>Death by 10 weeks</td>
<td>6</td>
<td>8</td>
<td>1.58 (0.51-4.88)</td>
<td>0.43</td>
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<tr>
<td>QTc prolonged events</td>
<td>11</td>
<td>33</td>
<td>0.002</td>
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<td>Clinical adverse events</td>
<td>239</td>
<td>254</td>
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<td>Laboratory adverse events</td>
<td>242</td>
<td>203</td>
<td>0.48</td>
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</tbody>
</table>
RESULTS

P-value for difference in change over 2 weeks: < 0.001
CONCLUSION

• Tamoxifen has significant *in vitro* activity against *C. neoformans*

• **BUT** there was no significant difference in the Early Fungicidal Activities of tamoxifen boosted treatment compared with standard antifungal therapy.

• Tamoxifen treatment resulted in prolonged QTc compared with standard therapy; no excess cardiac deaths were noted.

• Death rate and other adverse events were not significantly different between the two treatment groups.
Cryptococcal meningitis – what’s coming?

Novel Drugs

**VT1598** – highly specific fungal CYP51 inhibitor

**APX001A** - targets Gwt1, a highly conserved inositol acylase.

Prevents the appropriate localization of cell wall mannoproteins, which compromises cell wall integrity, biofilm formation, germ tube formation, and fungal growth.
Cryptococcal meningitis – what’s coming?

Neurapheresis

CSF filtration developed for treatment of haemorrhagic stroke
Summary

Combination therapy with amphotericin B and flucytosine remains key in delivering the best outcomes from cryptococcal meningitis.

We may have hit peak efficacy with current doses of AmB deoxycholate – on-going trials in optimizing dosing of Liposomal-AmB may deliver survival benefits.

Novel treatments on the horizon – how will we keep them affordable?

Effective oral treatment would be a major breakthrough where the burden of disease is highest.
Thanks

Patients and relatives
Funders
Wellcome Trust, UK MRC, UKAID