Management of cryptococcosis and penicilliosis

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Treatment of Cryptococcosis and Talaromycosis

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Overview

Cryptococcal Meningitis

Treatment challenges
Antifungal therapy
Local evidence
Future trends
Antiretroviral therapy
Complications
Guideline review


Talaromycosis

Local Evidence
Overview

Early diagnosis and instigation of effective treatment are KEY in obtaining good outcomes from infections.

Delay in diagnosis is a major cause of morbidity and mortality.

Good diagnostics for cryptococcosis:
IMMY LFA point of care antigen detection test
2USD/test...
Cryptococcal Meningitis - Challenges

1. Burden of disease
   - Global incidence 223 100* (95% CI 150 600 - 282 400)
   - 181 000 deaths (95% CI 119 400 - 234 300)

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

3. Poor access to key drugs

Cryptococcal Meningitis – weaknesses of current therapy

• Mortality remains high
  15+% USA,
  30 – 40% Vietnam,
  50-70% Sub-Saharan Africa

• What has the promise of significantly reducing mortality?
<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 8</th>
<th>Week 9</th>
<th>Week 10</th>
<th>Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Amphotericin B</td>
<td>Fluconazole 400mg daily</td>
<td>Fluconazole 400mg daily</td>
<td>Fluconazole 200 mg/day</td>
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<tr>
<td>III</td>
<td>Amphotericin</td>
<td>Fluconazole 400mg daily</td>
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<td>Fluconazole 200 mg/day</td>
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<td>400 mg bid</td>
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</tr>
</tbody>
</table>
Study Design -1

Study Location
Hospital for Tropical Diseases,
Ho Chi Minh City,
Vietnam

Inclusion Criteria
Syndrome consistent with CM
>15 years
HIV positive
1 or more of:
  positive CSF India ink or Ag
  positive CSF/blood culture
  positive blood Ag
Informed consent

Exclusion Criteria
>3 days antifungal therapy
Previous Cryptococcosis
Pregnancy
Renal/Hepatic Failure
Concurrent Rifampicin
Co-Primary Endpoint:
- Mortality at 2 and 10 weeks

Secondary endpoints
- Survival to 6 months
- Disability at 70 days and 6 months
- Change in CSF yeast cell counts over 2 weeks
- Time to clearance of yeast from CSF

Power:
- 80% to detect a mortality difference of 45% vs. 25% at 10 weeks
- N = 297 patients.
375 patients screened
76 did not meet inclusion criteria

299 patients randomised
1 excluded (misdiagnosis)

298 patients in ITT analysis
7 patients lost to follow-up

267 patients in per protocol analysis
26 did not complete randomised treatment
4 on rifampicin at study entry
1 received > 3 days antifungal therapy
## Baseline Characteristics 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>Amphotericin monotherapy (N=99, Arm I)</th>
<th>Amphotericin plus flucytosine (N=100, Arm II)</th>
<th>Amphotericin plus fluconazole (N=99, Arm III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>297</td>
<td>28 (25, 31)</td>
<td>28 (25, 33)</td>
<td>27 (24, 31)</td>
</tr>
<tr>
<td>Male sex</td>
<td>298</td>
<td>81 (82%)</td>
<td>80 (80%)</td>
<td>84 (85%)</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>281</td>
<td>51 (57%)</td>
<td>49 (52%)</td>
<td>53 (55%)</td>
</tr>
<tr>
<td>Duration of symptoms days</td>
<td>270</td>
<td>15 (7, 22)</td>
<td>14 (8, 18)</td>
<td>12 (7, 20)</td>
</tr>
<tr>
<td>Glasgow Coma Score</td>
<td>294</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>66</td>
<td>67</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>11-14</td>
<td>21</td>
<td>24</td>
<td>15</td>
<td></td>
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<tr>
<td>≤10</td>
<td>10</td>
<td>8</td>
<td>5</td>
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</tbody>
</table>
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>Amphotericin monotherapy (N=99, Arm I)</th>
<th>Amphotericin plus flucytosine (N=100, Arm II)</th>
<th>Amphotericin plus fluconazole (N=99, Arm III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF Opening Pressure &gt;</td>
<td>244</td>
<td>56 (67%)</td>
<td>61 (76%)</td>
<td>55 (68%)</td>
</tr>
<tr>
<td>18cmCSF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log10 CSF Yeast Count</td>
<td>236</td>
<td>5.91 (5.49, 6.48)</td>
<td>5.81 (4.74, 6.15)</td>
<td>5.74 (4.80, 6.34)</td>
</tr>
<tr>
<td>CFUs/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF Cryptococcal Antigen</td>
<td>223</td>
<td>2048 (512, 8192)</td>
<td>2048 (256, 4096)</td>
<td>1024 (256, 2048)</td>
</tr>
<tr>
<td>Titre</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 count/μl</td>
<td>218</td>
<td>18 (8.00, 37)</td>
<td>17 (9, 28)</td>
<td>14 (8, 41)</td>
</tr>
</tbody>
</table>
Results

HR (95% CI)

14 days
II vs. I: 0.57 (0.30, 1.08); p=0.08
III vs. I: 0.78 (0.44, 1.41); p=0.42

70 days
II vs. I: 0.61 (0.39, 0.97); p=0.04
III vs. I: 0.71 (0.45, 1.11); p=0.13

182 days
II vs. I: 0.56 (0.36, 0.86); p=0.01
III vs. I: 0.78 (0.53, 1.16); p=0.23

No. at risk
Ampho monotherapy 99 74 69 54 51 49 46 30
Ampho plus flucytosine 100 84 73 67 64 63 62 46
Ampho plus fluconazole 99 79 67 65 59 58 57 39

PRESENTED AT MMTN CONFERENCE, 1-3 DEC 2017
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CSF Fungal Clearance

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
II 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
II v I P = 0.10
Adverse events

- Similar rates of serious and grade 3 & 4 adverse events between groups
- Incidence of other OIs 30%

<table>
<thead>
<tr>
<th>Event</th>
<th>Arm I</th>
<th>Arm II</th>
<th>Arm III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>all</td>
<td>62 (63%)</td>
<td>63 (63%)</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>46 (46%)</td>
<td>35 (35%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>all</td>
<td>19 (19%)</td>
<td>34 (34%)</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>2 (2%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>all</td>
<td>34 (34%)</td>
<td>41 (41%)</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>
Summary

- Combination therapy with amphotericin B 1mg/kg/day and flucytosine 100mg/kg/day for 2 weeks improves mortality in HIV associated cryptococcal meningitis.
- Treatment is well tolerated.
- Combination therapy with fluconazole 400 mg b.i.d. for 2 weeks offers no survival benefit compared to 4 weeks therapy with amphotericin monotherapy.
- Improving access to both amphotericin and flucytosine in poorly resourced countries has the potential to significantly impact the global death rate from this disease.

Why a trial of adjunctive treatment?

Mortality 30-40% at 10 weeks

No imminent novel anti-cryptococcal drugs

Evidence of significant effects in other CNS infections

• Bacterial meningitis

• TB meningitis

Relatively untested in CM

Thwaites et al, TB Meningitis, NEJM 2004
Dexamethasone – mechanisms of action

- Anti-inflammatory
  Mouse model... mimics HIV infected patients
  Dexamethasone prolongs mouse survival

- Reduce cerebral oedema/brain swelling
  Key feature of CM
  Perhaps mediated through VEDGF
  Dexamethasone modifies vascular permeability in rat model

- Moderate raised ICP

- Moderate Cerebral Vasculitis
  Part of the pathogenesis of CM
  Resultant ischaemia and infarction

J Antimicrob Chemother 1999, 43(6):817-824
Corticosteroids – clinical practice & evidence

Current IDSA indications
  Mass effect, IRIS, ARDS - expert opinion

Evidence of benefit
  C. gattii (HIV uninfected)

Effective in disease with similar pathophysiology - TBM
  Subacute/chronic course
  Raised ICP
  Cerebral vasculitis and infarction
  High mortality and morbidity
  CD4 counts in HIV patients similar to those with CM

Study aims and design

**Aim** - reduce mortality from cryptococcal meningitis

**Credible**
- Africa and Asia
- Powered to mortality

**Deliver results rapidly**
- 13 sites in 6 countries: Vietnam, Laos, Thailand, Indonesia, Uganda, Malawi
Sample size and power

- Powered to survival during the first 10 weeks (the primary end point)
- Effect size... HR 0.7 (treat between 7-10 patients to save a life)
- 10 week mortality estimated at 30% in Asia, 50% in Malawi and Uganda
- 80% power requires observation of 247 deaths
- Assigned same number of deaths to each continent
- Need to recruit 300 patients from Africa and 500 from Asia
- Allowing for 10% loss to follow-up = **880 patients**
Secondary endpoints

- Survival to 6 months
- Disability at 10 weeks and 6 months
- Rates of CSF sterilisation
- Rates of IRIS
- Time to new AIDS defining events
- Visual deficit at 10 weeks
- Rates of raised intracranial pressure
- Cost effectiveness
**Inclusion**
- HIV associated CM confirmed
- >18 years old
- Consents

**Exclusion**
- Pregnancy, renal failure, active GI bleeding,
- already received steroids, needs to receive
- steroids, already received >1wk anti-fungal drugs
Antifungal therapy

**Induction**
- Amphotericin B 1mg/kg, Fluconazole 800mg/day
  - Day 1-14

**Consolidation**
- Fluconazole 800mg/day
  - Day 15-70

**Maintenance**
- Fluconazole 200mg/day
  - Day 71+
Results

Study stopped early after 3rd interim safety analysis
10 week survival

Dexamethasone does not reduce mortality

Deaths by week 10 events (risk)
- Intention-to-treat population (ITT)
  - Placebo: 93/226 (41%)
  - Dexamethasone: 106/224 (47%)
  - Hazard ratio: 1.11 (0.84-1.47); p=0.45
- Per protocol population
  - Placebo: 87/213 (41%)
  - Dexamethasone: 103/213 (49%)
  - Hazard ratio: 1.16 (0.87-1.54); p=0.31
Dexamethasone does not reduce mortality by 6 months.

Deaths by month 6 – events (risk)

- ITT
  - Placebo: 109/226 (49%)
  - Dexamethasone: 128/224 (57%)
  - Hazard ratio: 1.18 (0.91-1.53); p=0.20

- Per protocol population
  - Placebo: 103/213 (48%)
  - Dexamethasone: 125/213 (59%)
  - Hazard ratio: 1.23 (0.95-1.60); p=0.12
Formal comparison of risks at 6 months: Dexamethasone may increase mortality at 6 months.
Dexamethasone was associated with worse disability outcomes.

Odds ratios for a good disability outcome at 10 weeks and 6 months, dexamethasone vs placebo:

- 10 week ITT: 0.42 (p < 0.001)
- 10 week Africa: 0.43
- 10 week Asia: 0.41
- 6 month ITT: 0.49 (p = 0.002)
- 6 month Africa: 0.63 (p = 0.15)
- 6 month Asia: 0.40 (p = 0.003)

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Percentage risk of selected adverse events, by treatment arm

- Placebo
- Dexamethasone

* P < 0.05
Intracranial pressure reduced more in the dexamethasone arm

Longitudinal CSF opening pressures during the first 2 weeks

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Dexamethasone</th>
<th>Estimated relative difference:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-10%</td>
<td>-36%</td>
<td>-28% (-39 to -16%); p&lt;0.001</td>
</tr>
<tr>
<td>-Estimated percentage change over 14 days</td>
<td>(-20% to +2%)</td>
<td>(-43% to -27%)</td>
<td></td>
</tr>
</tbody>
</table>
Yeast clearance was slower in the dexamethasone arm.

Estimated change (95% CI) [log10 CFU/mL of CSF per day]

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Dexamethasone</th>
<th>Difference in estimated change</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>-0.30 (-0.33,-0.27)</td>
<td>-0.21 (-0.23,-0.18)</td>
<td>0.09 (0.06,0.13); p &lt;0.001</td>
</tr>
<tr>
<td>African patients</td>
<td>-0.26 (-0.30,-0.22)</td>
<td>-0.19 (-0.23,-0.16)</td>
<td>0.07 (0.02,0.12); p=0.005</td>
</tr>
<tr>
<td>Asian patients</td>
<td>-0.35 (-0.40,-0.30)</td>
<td>-0.22 (-0.26,-0.19)</td>
<td>0.12 (0.07,0.18); p &lt;0.001</td>
</tr>
</tbody>
</table>
Pre-specified sub-group analyses: No reduction in 10 week mortality in any subgroup

Hazard ratios for 10 week mortality by subgroup for dexamethasone vs placebo
Summary...

Dexamethasone did not reduce mortality, caused more disability and more adverse events.

Poorer early fungicidal activity and excess of other infections possible biological explanation for clinical findings.

It should not be given as a universal adjunct
Why do we do clinical trials?

Typical period of discharge

Vietnamese patients

Survival probability

No. at risk
Placebo          51  39  35  30  28  28  27  27
Dexamethasone    54  45  43  37  34  32  31  30

Days since randomization
### Table 1: Summary of treatment recommendations and dosage for HIV-infected adults, adolescents and children with cryptococcal disease (meningeal and disseminated non-meningeal)

<table>
<thead>
<tr>
<th>Target Population</th>
<th>Drugs available</th>
<th>Pre-hydration + electrolyte replacement + toxicity monitoring/management</th>
<th>Induction phase options(^{14})</th>
<th>Consolidation phase options</th>
<th>Maintenance/secondary prophylaxis options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td></td>
<td>Available</td>
<td>(2 weeks)</td>
<td>(8 weeks)</td>
<td>Fluconazole 200 mg daily</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B(^{15}) ± flucytosine</td>
<td>Available</td>
<td>a. Amphotericin 0.7-1 mg/kg/day + flucytosine 100 mg/kg/day</td>
<td>Fluconazole 400-800 mg/day</td>
<td>Fluconazole 200 mg daily</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B(^{15})</td>
<td>Not available for full 2 week induction period</td>
<td>a. Amphotericin 0.7-1 mg/kg/day/short course (5-7 days) + fluconazole 800 mg/day (2 weeks)</td>
<td>Fluconazole 800 mg/day</td>
<td>Fluconazole 200 mg daily</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B not available</td>
<td>Not available</td>
<td>a. Fluconazole 1200 mg/day ± flucytosine 100 mg/kg/day</td>
<td>Fluconazole 800 mg/day</td>
<td>Fluconazole 200 mg daily</td>
</tr>
</tbody>
</table>
Timing of antiretroviral therapy

Increased risk of death with early (within 1 week) versus deferred (5 weeks after diagnosis)

Other issues

Raised intracranial Pressure
  Common and associated with poor outcomes
  Rx therapeutic drainage of CSF by lumbar puncture

Co-diagnoses
  TB often diagnosed...
  Abnormal chest X-ray but no microbiological proof

PROBABLY NOT TB!!!

TB TREATMENT WILL RENDER FLUCONAZOLE INEFFECTIVE!!
AMBITION Phase-III study – clinical endpoint non-inferiority trial

L-AmB 10 mg/kg day 1 (single dose) vs Amphotericin B deoxycholate 1.0 mg/kg/d 14 days

All patients will receive fluconazole 1200 mg/d for first 2 weeks, then 800 mg/d until 10 weeks and 200 mg/d thereafter. ART will be initiated 4-6 weeks post initiation of antifungal therapy.

Endpoints:
Primary: All-cause mortality within the first 10 weeks

Secondary: Early Fungicidal Activity (EFA); 2-week mortality; tolerability and adverse events; cost-effectiveness

850 patients total (425 per arm) (10% NI margin)
Phase II clinical trial of tamoxifen boosted antifungal therapy

Tamoxifen 300mg/d + dAmB 1mg/kg/d + fluconazole 800mg/d x 14 days vs.

dAmB 1mg/kg/d + fluconazole 800mg/d x 14 days

Primary Endpoint:
Early antifungal activity

Secondary Endpoints:
1. Mortality at 10 weeks
2. Relapse and IRIS
3. Disability
4. Grades III/IV adv

PI: Jeremy Day, clinicaltrials.org NCT03112031, enrolment begin July 20
Conclusions

• Amphotericin and flucytosine remain the best treatment combination
  – We need better access to current drugs
  – We need better antifungal drugs...

• Trials need adequate follow-up – 6 months

• Don’t give ARVs early – wait at least 5 weeks after diagnosis

• Dexamethasone is harmful in HIV associated cryptococcal meningitis
Talaromycosis (penicilliosis) in Asia

International treatment guidelines

- Amphotericin B x 2 wks, itraconazole 400 mg/d x 10 wks, then 200 mg/d until CD4 counts >100 cells/mm³ for 6 months\(^1,3\)

- Based on a Chiang Mai study: 74 patients with HIV-associated talaromycosis treated with amphotericin B x 2 wks, followed by oral itraconazole for 10 wks. There was only one death, and treatment response was 97\%\(^4\)

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IVAP research question

Is itraconazole non-inferior to amphotericin, with the advantages of reduced toxicity and costs, allowing outpatient administration and wider access to treatment?
Primary endpoint

Mortality at week 2

Secondary endpoints

• Mortality over 24 weeks
• Time to treatment success (fever clearance, resolution of skin lesions, and/or absence of fungal growth)
• EFA
• Incidence of relapse and IRIS
• Adverse events grade ≥3
**IVAPeni Trial**

Microbiologically confirmed *penicillosis*

- Consent
- Inclusion/Exclusion criteria
- Randomisation

- Amphotericin B 0.7 mg/kg/d x 2 wks
- Itraconazole 400 mg/d x 2 wks (600 mg/ngày x 3d loading)

- Itraconazole 10 wks
- Survival during first 2 wks
- Monthly follow up for 6 months

- 440/440

**Legend:**
- Remaining target
- HTD
- NHTD
- Viet Tiep
- Uong Bi
- Bach Mai
573 patients were screened

133 Were excluded
  95 Failed screening:
  5 Were pregnant
  9 Had CNS involvement
  17 Had AST/ALT >400 U/L
  8 Had creatinine clearance <30 mL/min
  3 Had ANC <500 cells/µL
  30 Were on rifampicin
  28 Were on AmB or itraconazole >48h
  7 Declined to participate
  38 Died, were discharged, or could not be contacted

440 randomized (n=440)

219 amphotericin B

Lost to follow-up (n=9)
  3 Withdrew before day 14
  6 Lost to follow-up before week 24

221 itraconazole

Lost to follow-up (n=3)
  3 Lost to follow-up before week 24

Le T, et al. NEJM, in press
## Baseline clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amphotericin B (N=217)</th>
<th>Itraconazole (N=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Male</td>
<td>152/215 (71%)</td>
<td>144/217 (66%)</td>
</tr>
<tr>
<td>Age [years]</td>
<td>34 (30,38) [n=215]</td>
<td>34 (29,38) [n=217]</td>
</tr>
<tr>
<td>Intravenous Drug User: Yes</td>
<td>70/215 (33%)</td>
<td>66/217 (30%)</td>
</tr>
<tr>
<td>Prior ART: Yes</td>
<td>93/215 (43%)</td>
<td>95/217 (44%)</td>
</tr>
<tr>
<td>Duration of prior ART [days]</td>
<td>141 (60,1014) [n=81]</td>
<td>106 (46,386) [n=87]</td>
</tr>
<tr>
<td>Prior <em>T. marneffei</em> infection: Yes</td>
<td>6/215 (3%)</td>
<td>8/217 (4%)</td>
</tr>
<tr>
<td>Duration of illness [days]</td>
<td>28 (14,30) [n=215]</td>
<td>30 (14,33) [n=214]</td>
</tr>
<tr>
<td>Fever: Yes</td>
<td>196/215 (91%)</td>
<td>190/216 (88%)</td>
</tr>
<tr>
<td>Fatigue/anorexia/weight loss: Yes</td>
<td>207/215 (96%)</td>
<td>205/216 (95%)</td>
</tr>
<tr>
<td>Respiratory: Yes</td>
<td>114/215 (53%)</td>
<td>116/216 (54%)</td>
</tr>
<tr>
<td>Gastrointestine: Yes</td>
<td>85/215 (40%)</td>
<td>76/216 (35%)</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>47 (41,51) [n=213]</td>
<td>47 (42,53) [n=214]</td>
</tr>
<tr>
<td>Temperature [°C]</td>
<td>38.0 (37.4,39.0) [n=211]</td>
<td>38.0 (37.3,39.0) [n=216]</td>
</tr>
<tr>
<td>oropharyngeal ulcers: Yes</td>
<td>81/215 (38%)</td>
<td>88/215 (41%)</td>
</tr>
<tr>
<td>Skin lesions: Yes</td>
<td>168/215 (78%)</td>
<td>177/216 (82%)</td>
</tr>
<tr>
<td>Dyspnoea/requirement for oxygen: Yes</td>
<td>22/215 (10%)</td>
<td>20/217 (9%)</td>
</tr>
</tbody>
</table>
## Baseline laboratory characteristics

<table>
<thead>
<tr>
<th>Laboratory measures</th>
<th>Amphotericin B (N=217)</th>
<th>Itraconazole (N=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count (x10^9/L)</td>
<td>3.7 (2.3,5.3) [n=210]</td>
<td>3.7 (2.4,5.9) [n=213]</td>
</tr>
<tr>
<td>Haemoglobin [g/dL]</td>
<td>8.9 (7.7,10.0) [n=210]</td>
<td>8.8 (7.7,10.3) [n=213]</td>
</tr>
<tr>
<td>Platelet [x10^9/L]</td>
<td>121 (52,228) [n=210]</td>
<td>118 (51,215) [n=213]</td>
</tr>
<tr>
<td>CD4 cell count [cells/µL]</td>
<td>10 (6,19) [n=205]</td>
<td>11 (6,27) [n=212]</td>
</tr>
<tr>
<td>Creatinine [µmol/L]</td>
<td>67 (57,82) [n=210]</td>
<td>69 (57,86) [n=213]</td>
</tr>
<tr>
<td>AST [U/L]</td>
<td>121 (72,208) [n=210]</td>
<td>121 (68,193) [n=214]</td>
</tr>
<tr>
<td>ALT [U/L]</td>
<td>48 (31,82) [n=210]</td>
<td>48 (30,73) [n=214]</td>
</tr>
<tr>
<td>LDH [U/L]</td>
<td>411 (262,730) [n=141]</td>
<td>483 (303,813) [n=136]</td>
</tr>
<tr>
<td>HBsAg: Positive</td>
<td>38/194 (20%)</td>
<td>40/195 (21%)</td>
</tr>
<tr>
<td>AntiHCV: Positive</td>
<td>78/195 (40%)</td>
<td>62/194 (32%)</td>
</tr>
<tr>
<td>Skin culture for (T. marneffei): Positive</td>
<td>117/135 (87%)</td>
<td>131/148 (89%)</td>
</tr>
<tr>
<td>Blood culture for (T. marneffei): Positive</td>
<td>156/214 (73%)</td>
<td>145/216 (67%)</td>
</tr>
<tr>
<td>Blood fungal count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Detectable: Yes</td>
<td>143/201 (71%)</td>
<td>148/200 (74%)</td>
</tr>
<tr>
<td>- Count in detectables [log_{10} CFU/ml]</td>
<td>2.16 (1.54,3.11) [n=143]</td>
<td>2.49 (1.54,3.17) [n=148]</td>
</tr>
</tbody>
</table>
Absolute risk of death over 24 weeks

- Amphotericin B: 11%
- Itraconazole: 21%

No. at risk:
- Amphotericin B: 217, 194, 189, 187, 187, 185, 165
- Itraconazole: 218, 194, 189, 185, 179, 174, 147

Presented at MMTN Conference, 1-3 Dec 2017
Copyright of speaker.
**Summary of secondary endpoints**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Amphotericin B (N=217)</th>
<th>Itraconazole (N=218)</th>
<th>Comparison Estimate (95% CI); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to treatment success - ITT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Patients with treatment success - events (%)</td>
<td>199/217 (93.4)</td>
<td>196/218 (90.7)</td>
<td>Ratio of subdistribution hazards:</td>
</tr>
<tr>
<td>- Median time [days]</td>
<td>8 (6 to 11)</td>
<td>9.00 (6 to 12)</td>
<td>0.83 (0.69 to 1.00); P=0.049</td>
</tr>
<tr>
<td><strong>Relapse, IRIS, or death until 24 weeks – events (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Relapse</td>
<td>3/217 (1.5)</td>
<td>15/218 (7.0)</td>
<td>Absolute risk difference [%]:</td>
</tr>
<tr>
<td>- IRIS</td>
<td>0/217 (0.0)</td>
<td>14/218 (6.6)</td>
<td>5.45 (1.63 to 9.27); P=0.005</td>
</tr>
<tr>
<td><strong>Blood EFA during first 14 d</strong></td>
<td></td>
<td></td>
<td>6.56 (3.24 to 9.88); P=0.0001</td>
</tr>
<tr>
<td>- Median [log10 CFU/mL per day]</td>
<td>-0.95 (-1.29 to -0.53)</td>
<td>-0.36 (-0.70 to -0.19)</td>
<td>Difference in change:</td>
</tr>
</tbody>
</table>

*Le T, et al. NEJM, in press*
Longitudinal quantitative fungal counts in blood

- 0.95 log10 CFU/ml/d

- 0.36 log10 CFU/ml/d
## Grade ≥3 adverse events in IVAP

<table>
<thead>
<tr>
<th>Adverse event name</th>
<th>Amphotericin B (n=217)</th>
<th>Itraconazole (n=218)</th>
<th>Comparison (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one AE – n(%)</td>
<td>116 (53.46%)</td>
<td>109 (50%)</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>T. m COMPLICATIONS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- respiratory failure</td>
<td>12 (5.53%)</td>
<td>12 (5.5%)</td>
<td>1.00</td>
</tr>
<tr>
<td>- relapse</td>
<td>3 (1.38%)</td>
<td>15 (6.88%)</td>
<td>0.006</td>
</tr>
<tr>
<td>- poor treatment response</td>
<td>1 (0.46%)</td>
<td>13 (5.96%)</td>
<td>0.002</td>
</tr>
<tr>
<td>- paradoxical IRIS</td>
<td>0 (0%)</td>
<td>14 (6.42%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>HIV-ASSOCIATED STAGE III DISEASES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 (6.45%)</td>
<td>21 (9.63%)</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>HIV-ASSOCIATED STAGE IV DISEASES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18 (8.29%)</td>
<td>22 (10.09%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>49 (22.58%)</td>
<td>1 (0.46%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Haemoglobin (&lt;7.9 gm/dL)</td>
<td>89 (41.01%)</td>
<td>64 (29.36%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Potassium (&lt;2.4 mEq/L)</td>
<td>25 (11.52%)</td>
<td>7 (3.21%)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Magnesium (&lt;0.6 mEq/L)</td>
<td>10 (4.61%)</td>
<td>2 (0.92%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Creatinine (&gt;3 x ULN)</td>
<td>6 (2.76%)</td>
<td>2 (0.92%)</td>
<td>0.18</td>
</tr>
</tbody>
</table>
Screening and pre-emptive therapy

Inhalation of spores → Dissemination of infection → Clinical manifestations

Screen if CD4 <100 cells

Jarvis J, et al. CID 2009
Longley N, et al. CID 2016
Summary

Cryptococcosis

- Gold standard induction treatment is amphotericin B and flucytosine (2 weeks)
- Amphotericin B combined with fluconazole (2 weeks) is second line induction treatment
- Carefully monitor electrolytes (K, Mg, Ca) when administering amphotericin
- Clinical trials are currently evaluating safety and efficacy of short-course amphotericin B therapy
- Corticosteroids do not improve survival and increase AEs + disability
- Clinical trials of adjunctive therapy (tamoxifen) to improve antifungal clearance and mortality
- Raised intracranial pressure is a frequent life-threatening complication - therapeutic LPs
Summary

Talaromycosis

• Amphotericin induction therapy is superior to itraconazole induction therapy

• Amphotericin is associated with anaemia and electrolyte disturbances:
  – Monitor potassium, magnesium and calcium
Thank You
Thanks!
Thanks!

Participating centres:
Vietnam: Hospital for Tropical Diseases, Cho Ray Hospital, National Hospital for Tropical Diseases, Bach Mai Hospital
Indonesia: Cipto Mangunkusum Hospital, Hasan Sadikin Hospital, RSKO Drug Dependence Hospital
Laos: MORU and Mahosot Hospital
Thailand: MORU and Udon Thani and Ubon Ratchatani Hospitals
Malawi: Zomba Hospital and MLW
Uganda: MRC Uganda, Masaka General Hospital, Entebbe District Hospital

Members of the OUCRU CNS-HIV Research Group

Funders: Wellcome Trust, DfID, MRC UK

Trial steering Committee – David Cooper, Robin Grant, Robin Bailey, Jimmy Whitworth
DSMBs – Diederik van de Beek, Ronald Geskus, Janet Darbyshire, David Mabey, Andrew Kambugu
Patients and relatives