MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

Management of cryptococcosis and penicilliosis

Professor Jeremy Day

Wellcome Trust Intermediate Fellow;
Head, CNS & HIV Infections Research Group
Oxford University Clinical Research Unit
Ho Chi Minh City, Vietnam

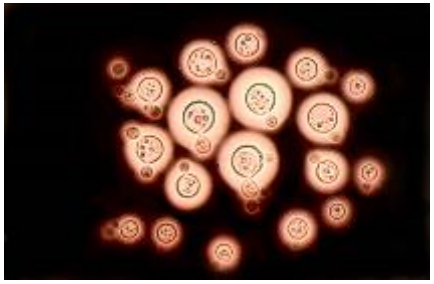
ASIA FUNGAL WORKING GROUP an ISHAM working group

ISHAM INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Presented at MMTN Vietnam Conference
1–3 December 2017, Ho Chi Minh City, Vietnam

Treatment of Cryptococcosis and Talaromycosis

Jeremy Day
Head, CNS and HIV Infections Research Group,
Oxford University Clinical Research Unit Viet Nam



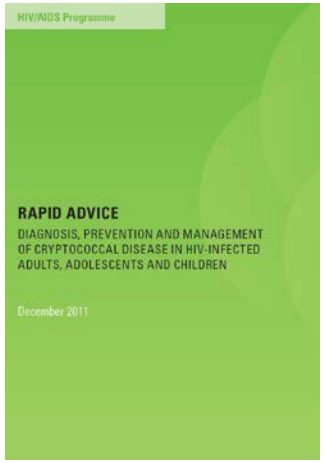
Overview

Cryptococcal Meningitis

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

Talaromycosis

- Local Evidence



1. IDSA and CDC guidelines 2009; **2**. British HIV guidelines 2013; **3**. Vietnam MoH 2013;
4. Sirisanthana T, et al. Clinical Infectious Diseases 1998

Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America

John R. Perfect,[1] William E. Dismukes,[2] Francoise Dromer,[11] David L. Goldman,[3] John R. Graybill,[4] Richard J. Hamill,[5] Thomas S. Harrison,[6] Robert A. Larsen,[67] Olivier Lortholary,[11,12] Minh-Hong Nguyen,[8] Peter G. Pappas,[9] William G. Powderly,[10] Nina Singh,[68] Jack D. Sobel,[68] and Tania C. Sorrell[15]

Clinical Infectious Diseases 2010; 50:291–322

1058-4838/2010/5003-0001$15.00

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

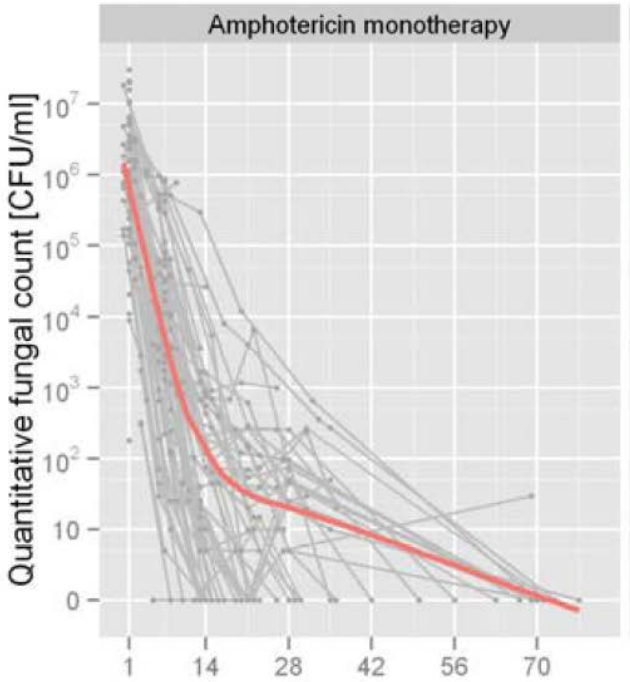
Good diagnostics for cryptococcosis:

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



*Lancet Infect Dis. 2017 Aug;17(8):873-881

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?

Treatment Arm	Week										
	1	2	3	4	5	6	7	8	9	10	26
I	**Amphotericin B 1 mg/kg/day**				Fluconazole 400mg daily						Fluconazole 200 mg/day
II	**Amphotericin 1mg/kg/day + Flucytosine 100mg/kg/day**				Fluconazole 400mg daily						Fluconazole 200 mg/day
III	**Amphotericin 1mg/kg/day + Fluconazole 400mg bid**				Fluconazole 400mg daily						Fluconazole 200 mg/day

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

Study Design - 2

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.

Study Recruitment April 2004 – March 2011

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

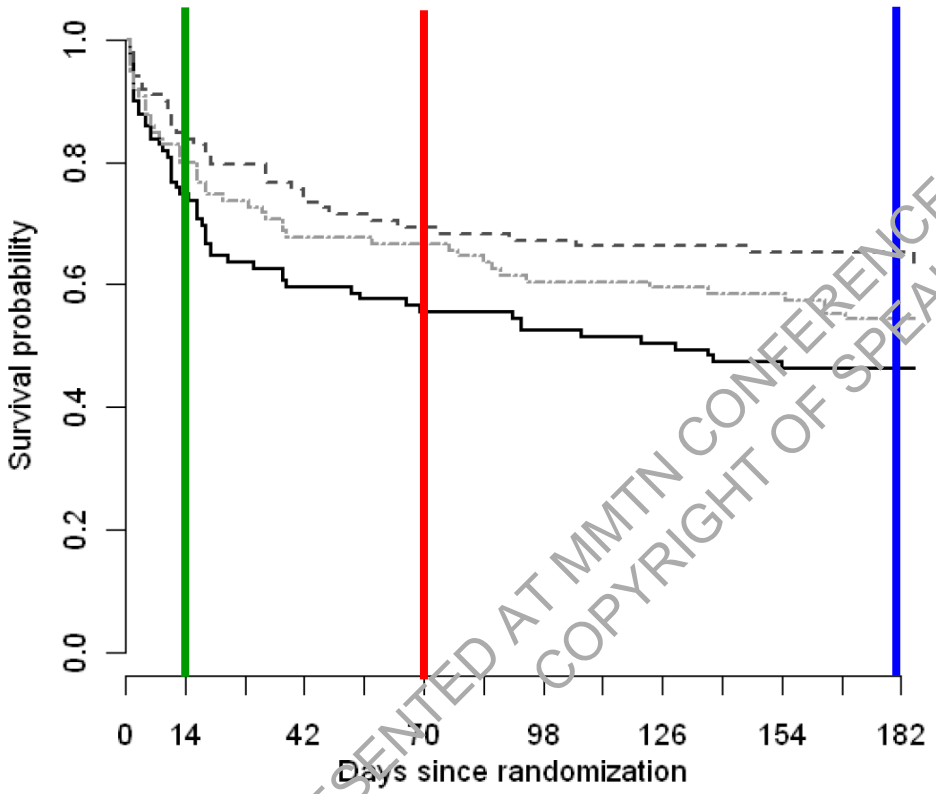
Baseline Characteristics 1

Characteristics	n	Amphotericin monotherapy (N=99, Arm I)	Amphotericin plus flucytosine (N=100, Arm II)	Amphotericin plus fluconazole (N=99, Arm III)
Age in years	297	28 (25, 31)	28 (25, 33)	27 (24, 31)
Male sex	298	81 (82%)	80 (80%)	84 (85%)
Intravenous drug use	281	51 (57%)	49 (52%)	53 (55%)
Duration of symptoms days	276	15 (7, 22)	14 (8, 18)	12 (7, 20)
Glasgow Coma Score	294			
15		66 (68%)	67 (68%)	78 (80%)
11-14		21 (22%)	24 (24%)	15 (15%)
≤10		10 (10%)	8 (8%)	5 (5%)

Baseline Characteristics 2

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

Results



No. at risk								
Ampho monotherapy	99	74	59	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

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

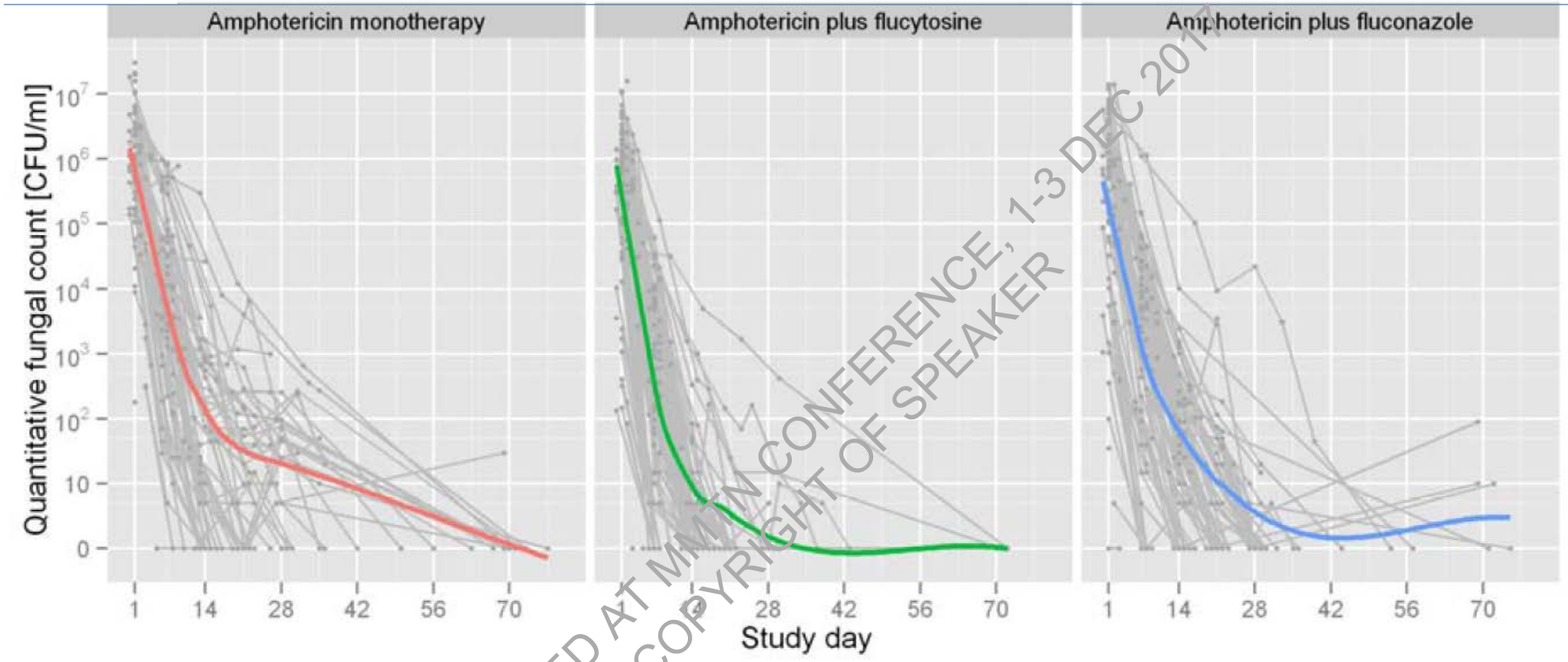
III vs. I: 0.71 (0.45,1.11); p=0.13

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

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%

Event		Arm I	Arm II	Arm III
Anaemia	all	62 (63%)	63 (63%)	57 (58%)
	Grade 3 or 4	46 (46%)	35 (35%)	29 (29%)
Neutropenia	all	19 (19%)	34 (34%)	32 (32%)
	Grade 3 or 4	2 (2%)	9 (9%)	9 (9%)
Renal impairment	all	34 (34%)	41 (41%)	46 (46%)
	Grade 3 or 4	2 (2%)	2 (2%)	2 (2%)

Summary

- Combination therapy with amphotericin B 1mg/kg/day and flucytosine100mg/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.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combination Antifungal Therapy for Cryptococcal Meningitis

Jeremy N. Day, M.D., Ph.D., Tran T.H. Chau, M.D., Ph.D., Marcel Wolbers, Ph.D., Pham P. Mai, M.D., Nguyen T. Dung, M.D., Nguyen H. Mai, M.D., Ph.D., Nguyen H. Phu, M.D., Ph.D., Ho D. Nghia, M.D., Ph.D., Nguyen D. Phong, M.D., Ph.D., Cao Q. Thai, M.D., Le H. Thai, M.D., Ly V. Chuong, M.D., Dinh X. Sinh, M.D., Van A. Duong, B.Sc., Thu N. Hoang, M.Sc., Pham T. Diep, R.Sc., James I. Campbell, M.I.R.M.S., Tran P.M. Sieu, M.D., Stephen C. Baker, Ph.D., Nguyen V.V. Chau, M.D., Ph.D., Tran T. Hien, M.D., Ph.D., David G. Lalloo, M.D., and Jeremy J. Farrar, M.D., D.Phil.

ABSTRACT

BACKGROUND

Combination antifungal therapy (amphotericin B deoxycholate and flucytosine) is the recommended treatment for cryptococcal meningitis but has not been shown to reduce mortality, as compared with amphotericin B alone. We performed a randomized, controlled trial to determine whether combining fluconazole or high-dose fluconazole with high-dose amphotericin B improved survival at 14 and 70 days.

METHODS

We conducted a randomized, three-group, open-label trial of induction therapy for cryptococcal meningitis in patients with human immunodeficiency virus infection. All patients received amphotericin B at a dose of 1 mg per kilogram of body weight per day; patients in group 1 were treated for 4 weeks, and those in groups 2 and 3 for 2 weeks. Patients in group 2 concurrently received flucytosine at a dose of 100 mg per kilogram per day for 2 weeks, and those in group 3 concurrently received fluconazole at a dose of 400 mg twice daily for 2 weeks.

RESULTS

A total of 299 patients were enrolled. Fewer deaths occurred by days 14 and 70 among patients receiving amphotericin B and flucytosine than among those receiving amphotericin B alone (15 vs. 25 deaths by day 14; hazard ratio, 0.57; 95% confidence interval [CI], 0.30 to 1.08; unadjusted P=0.08; and 30 vs. 44 deaths by day 70; hazard ratio, 0.63; 95% CI, 0.39 to 0.97; unadjusted P=0.04). Combination therapy with fluconazole had no significant effect on survival, as compared with monotherapy (hazard ratio for death by 14 days, 0.71; 95% CI, 0.44 to 1.41; P=0.42; hazard ratio for death by 70 days, 0.71; 95% CI, 0.45 to 1.11; P=0.13). Amphotericin B plus flucytosine was associated with significantly increased rates of yeast clearance from cerebrospinal fluid (–0.42 $\log_{10}$ colony-forming units [CFU] per milliliter per day vs. –0.31 and –0.32 $\log_{10}$ CFU per milliliter per day in groups 1 and 3, respectively; P<0.001 for both comparisons). Rates of adverse events were similar in all groups, although neutropenia was more frequent in patients receiving a combination therapy.

CONCLUSIONS

Amphotericin B plus flucytosine, as compared with amphotericin B alone, is associated with improved survival among patients with cryptococcal meningitis. A survival benefit of amphotericin B plus fluconazole was not found. (Funded by the Wellcome Trust and the British Infection Society; Controlled-Trials.com number, ISRCTN95125028.)

From the Oxford University Clinical Research Unit, Wellcome Trust Major Overseas Programme Vietnam (J.N.D., T.T.H.C., M.W., N.H.M., N.H.P., H.D.N., C.Q.T., L.H.T., V.A.D., T.N.H., P.T.D., S.G.B., T.T.H., J.J.F.), and the Hospital for Tropical Diseases (T.T.H.C., P.P.M., N.T.D., N.H.M., N.H.P., H.D.N., N.D.P., L.V.C., D.X.S., T.P.M.S., N.V.V.C.) — both in Ho Chi Minh City, Vietnam; and the Centre for Tropical Medicine, Oxford University, Oxford (J.N.D., M.W., J.J.C., S.G.B., T.T.H., J.J.F.), and the Liverpool School of Tropical Medicine, Liverpool (D.G.L.) — both in the United Kingdom. Address reprint requests to Dr. Day at the Oxford University Clinical Research Unit, 764 Vo Van Kiet, Ho Chi Minh City QI, Vietnam, or at jday@oucru.org.

Drs. Lalloo and Farrar contributed equally to this article.

N Engl J Med 2013;368:1291-301.
DOI: 10.1056/NEJMoa1204905
Copyright © 2013 Massachusetts Medical Society.

1291

The New England Journal of Medicine
Downloaded from nejm.org at the Bodleian Libraries of the University of Oxford on October 31, 2013. For personal use only. No other uses without permission.
Copyright © 2013 Massachusetts Medical Society. All rights reserved.

N Engl J Med 2013; 368:1291-1302

Why a trial of adjunctive treatment?

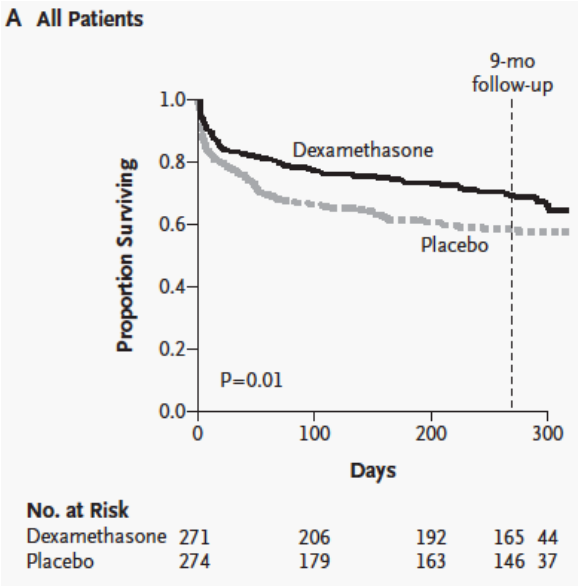
Mortality 30-40% at 10 weeks

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

Infect Immun 1999, **67**(12):6314-6320.
Antimicrob Agents Chemother 1996, **40**(5):1194-1197.
J Antimicrob Chemother 1999, **43**(6):817-824

Corticosteroids – clinical practice & evidence

Current IDSA indications

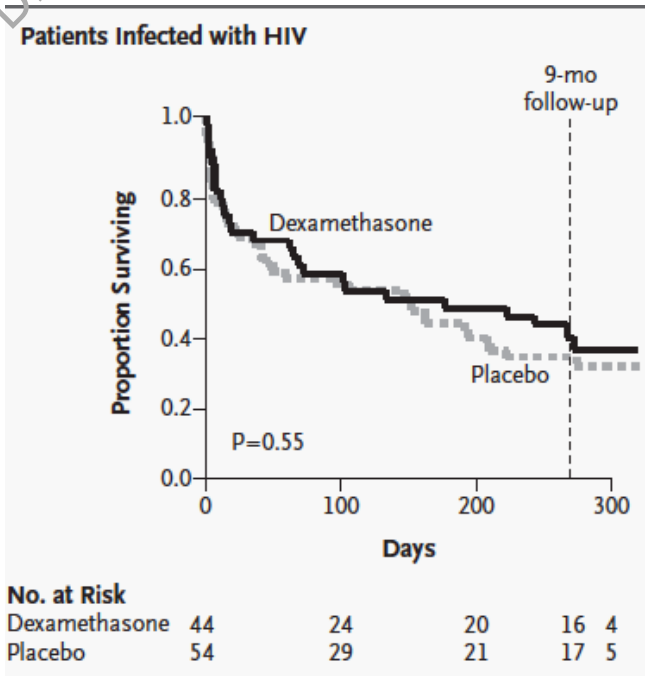
- Mass effect, IRIS, ARDS - expert opinion

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



N Engl J Med 2004, **351**(17):1741-1751.
Trans R Soc Trop Med Hyg 1997, **91**(1):50-52.
Clin Infect Dis 2010, **50**(3):291-322.

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

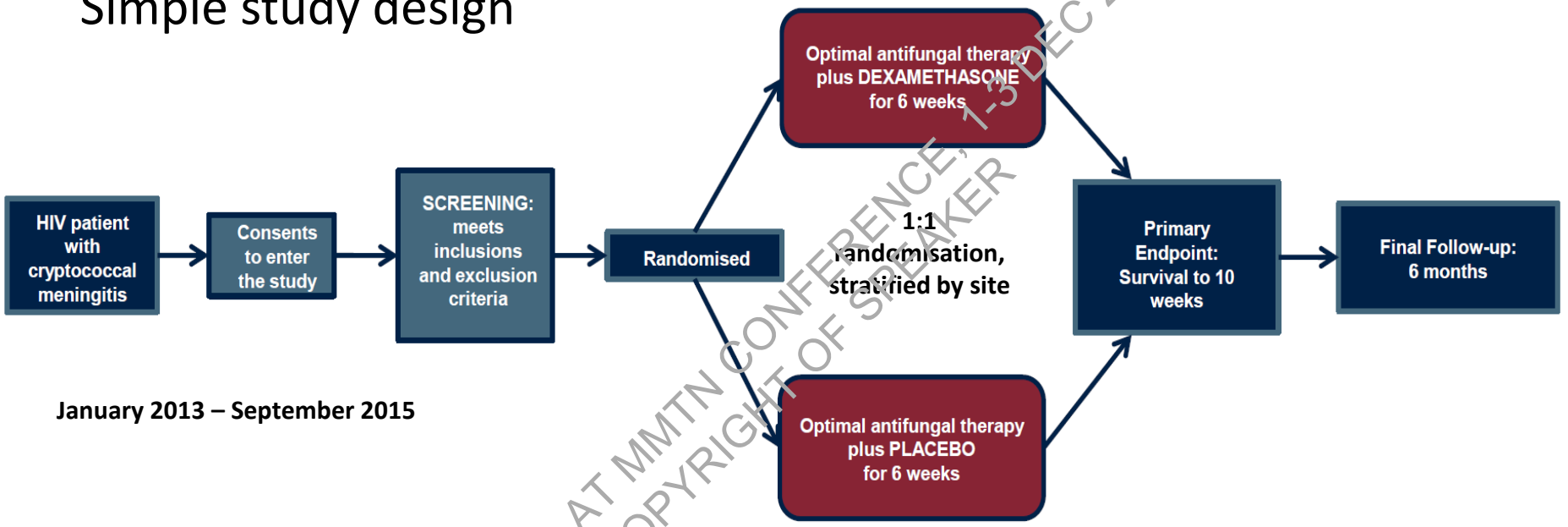
Sample size and power

- 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

Simple study design



January 2013 – September 2015

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

CryptoDex 2015 Study drug and antifungal dosing schedule

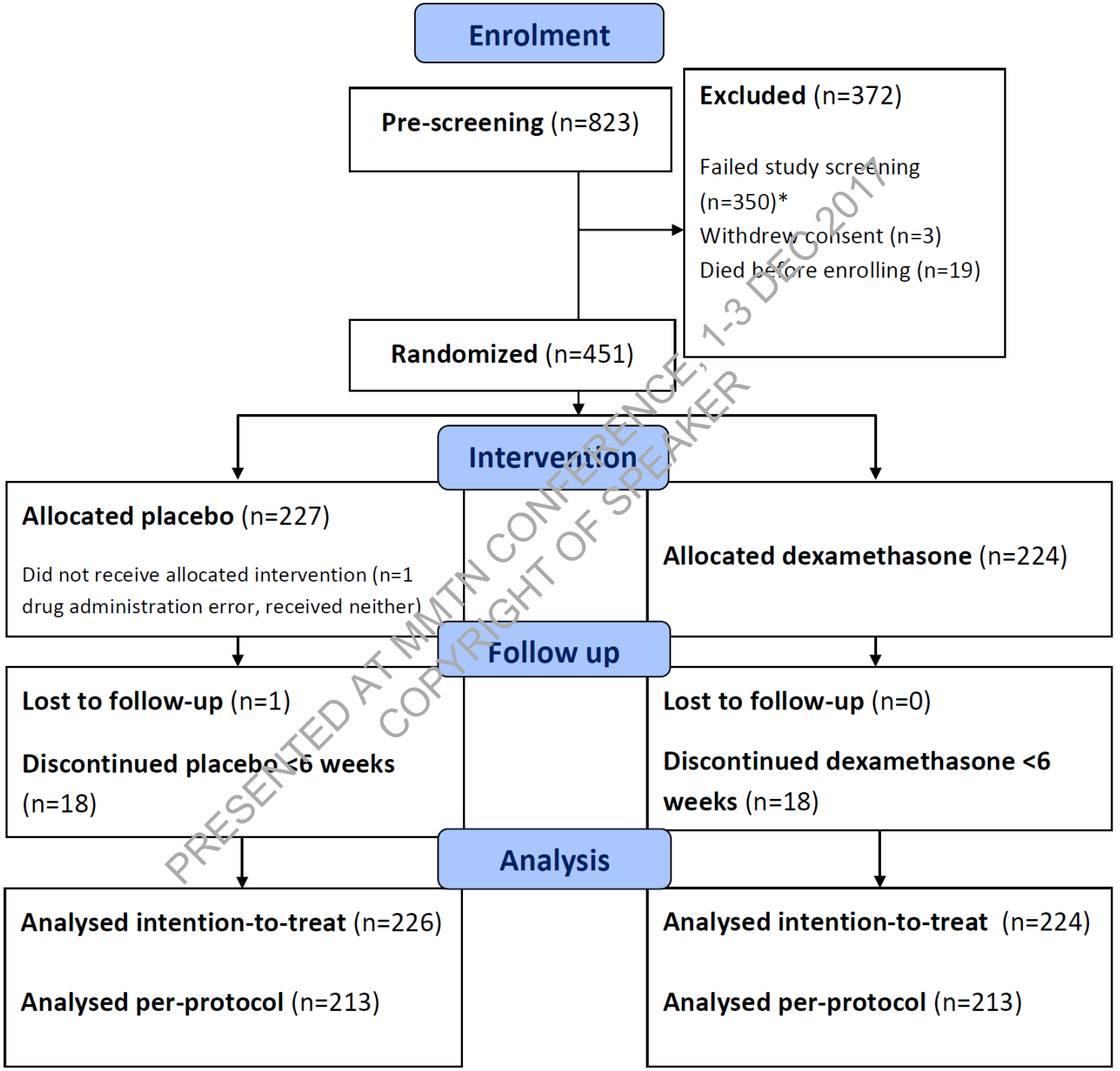
Week 1	• 0.3mg/kg/day IV	→ 21mg
Week 2	• 0.2mg/kg/day IV	→ 14mg
Week 3	• 0.1mg/kg/day Oral	→ 7mg
Week 4	• 3mg/day Oral	
Week 5	• 2mg/day Oral	
Week 6	• 1mg/day Oral	

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+

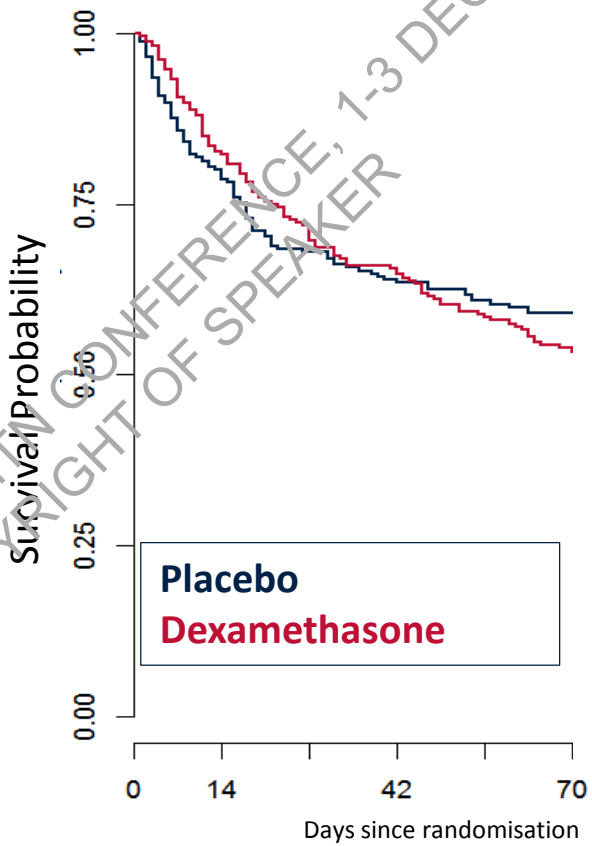
Results

Study stopped early after 3rd interim safety analysis



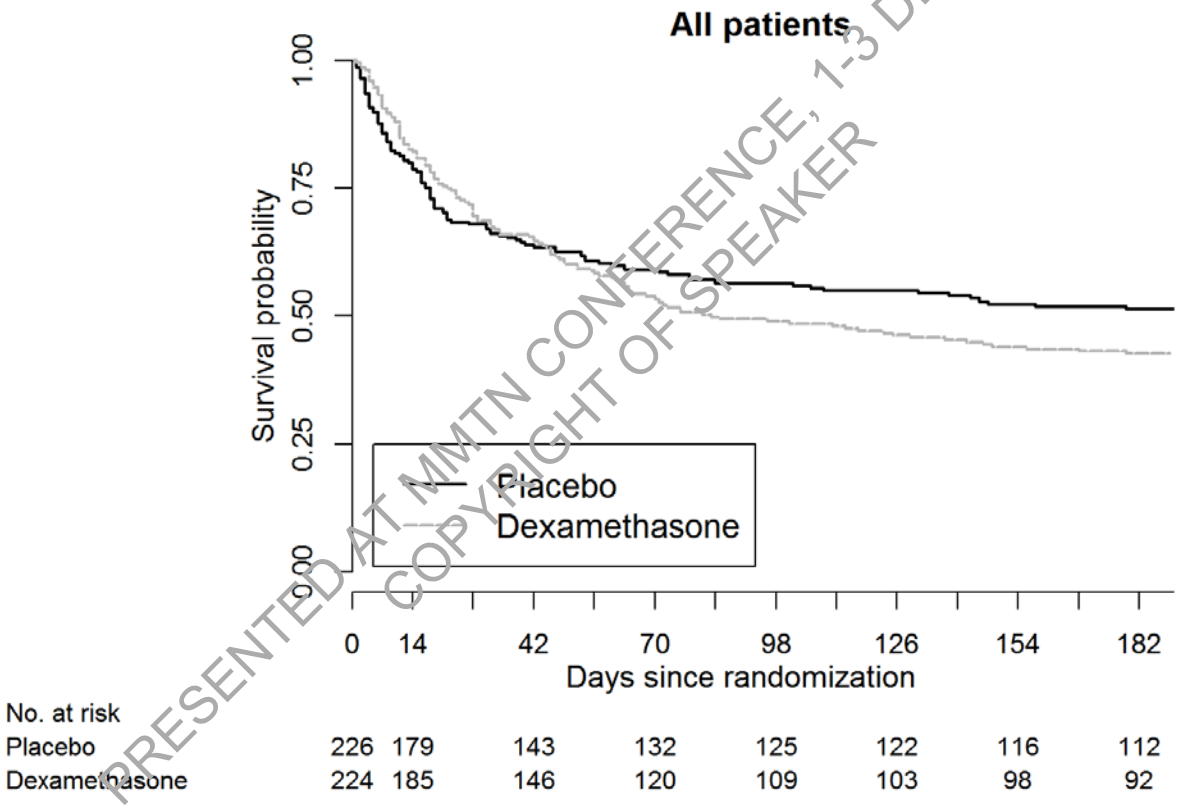
10 week survival

Dexamethasone **does not reduce mortality**



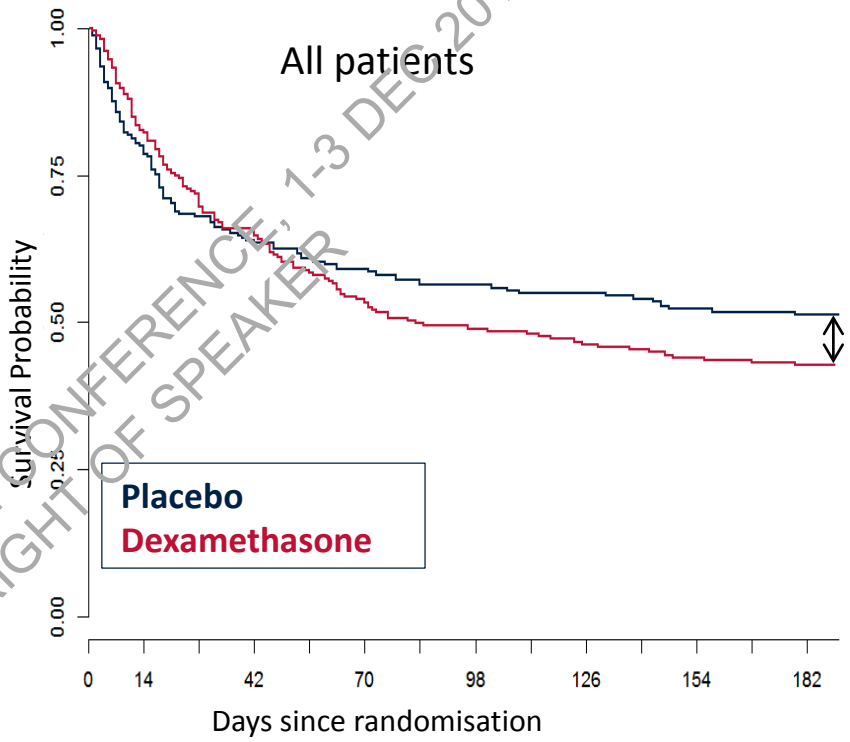
Deaths by week 10 events (risk)	**Placebo**	**Dexamethasone**	**Hazard ratio:**
- Intention-to-treat population (ITT)	93/226 (41%)	106/224 (47%)	1.11 (0.84-1.47); p=0.45
- Per protocol population	87/213 (41%)	103/213 (49%)	1.16 (0.87-1.54); p=0.31

Dexamethasone **does not reduce mortality** by 6 months



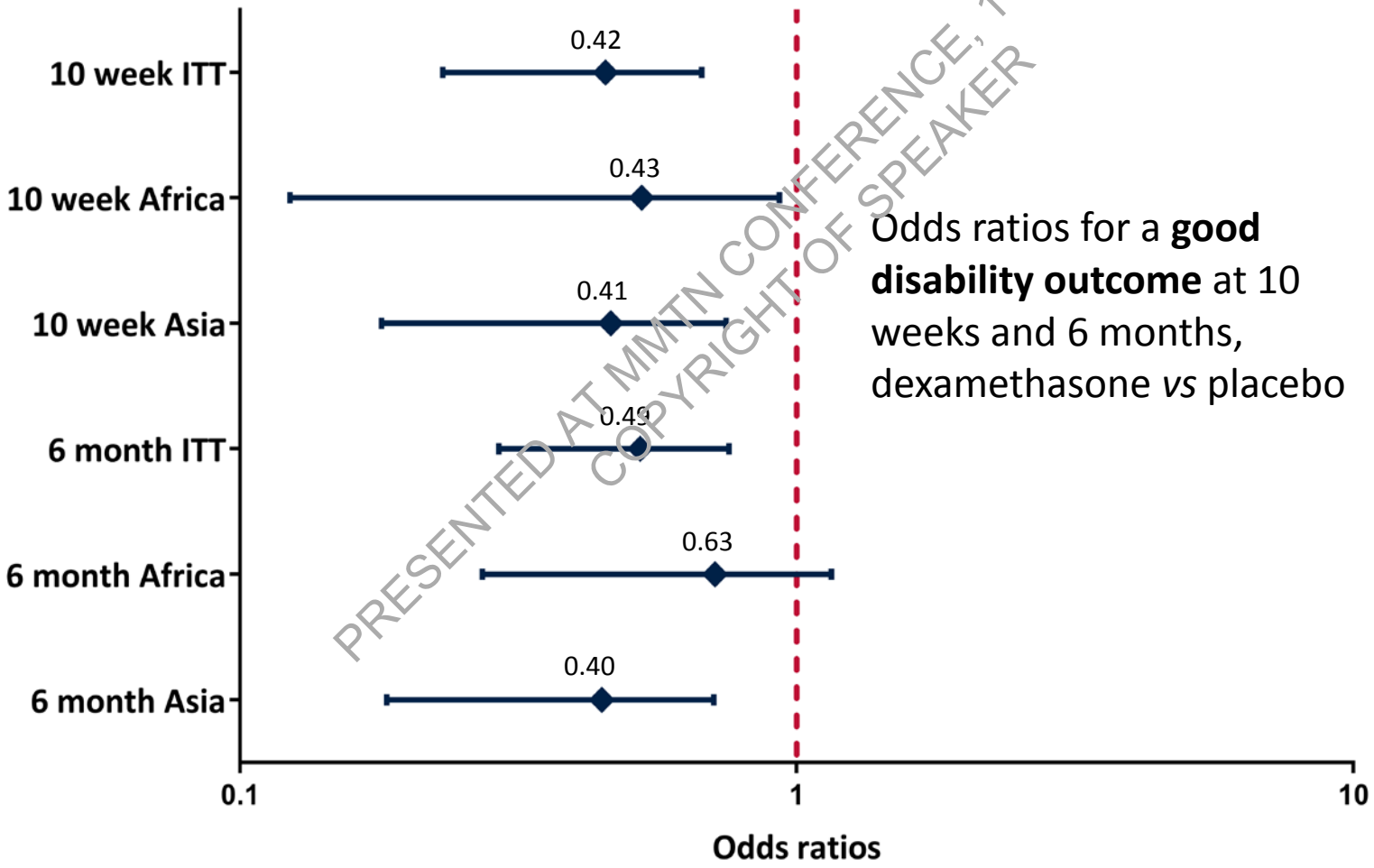
Deaths by month 6 – events (risk)	**Placebo**	**Dexamethasone**	**Hazard ratio:**
- ITT	109/226 (49%)	128/224 (57%)	1.18(0.91-1.53); p=0.20
- Per protocol population	103/213 (48%)	125/213 (59%)	1.23(0.95-1.60); p=0.12

Formal comparison of risks at 6 months: Dexamethasone **may increase mortality** at 6 months



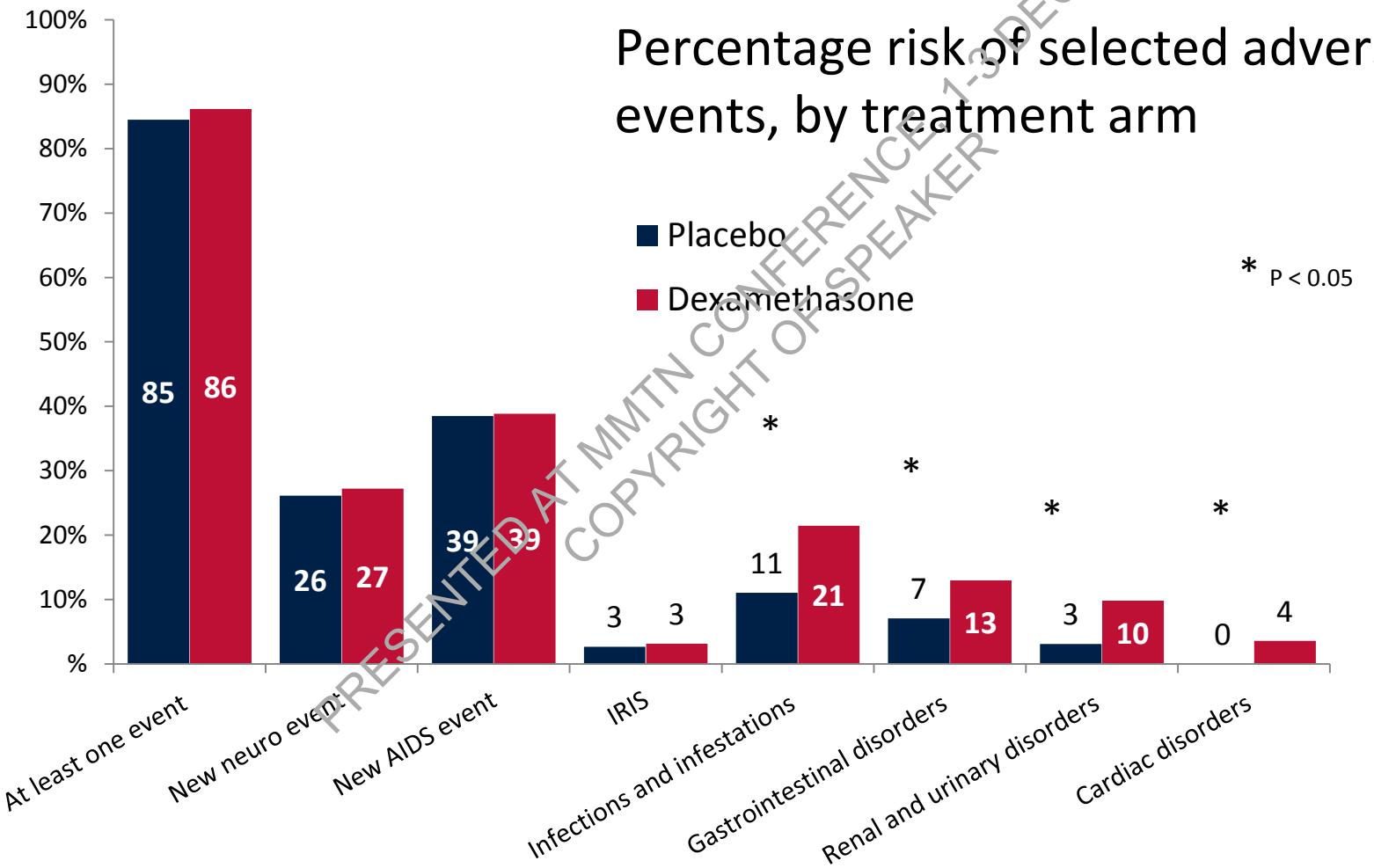
) 53/102 (52.0)

Dexamethasone was associated with **worse disability outcomes**

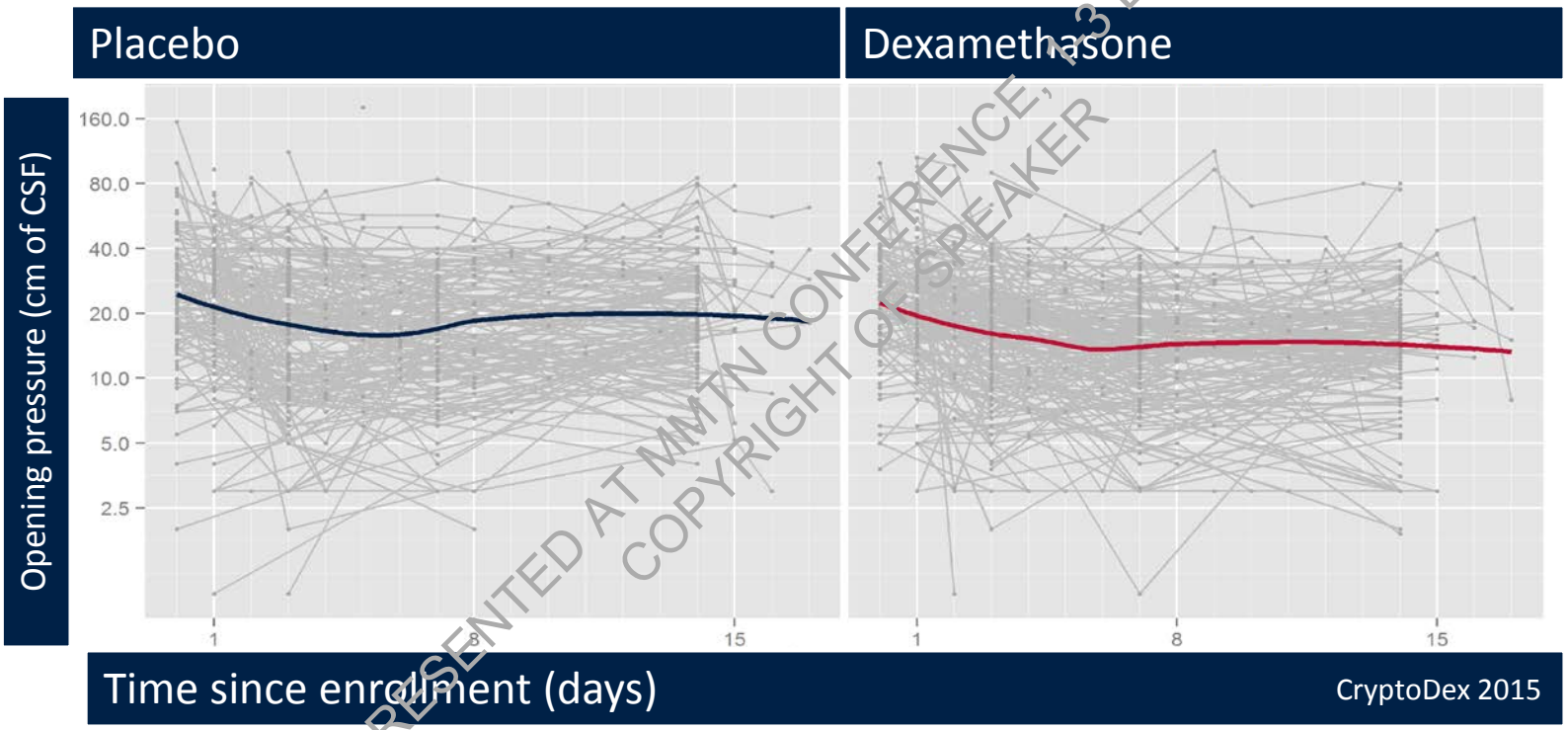


Odds ratios for a **good disability outcome** at 10 weeks and 6 months, dexamethasone *vs* placebo

P
<0.001
0.04
0.005
0.002
0.15
0.003

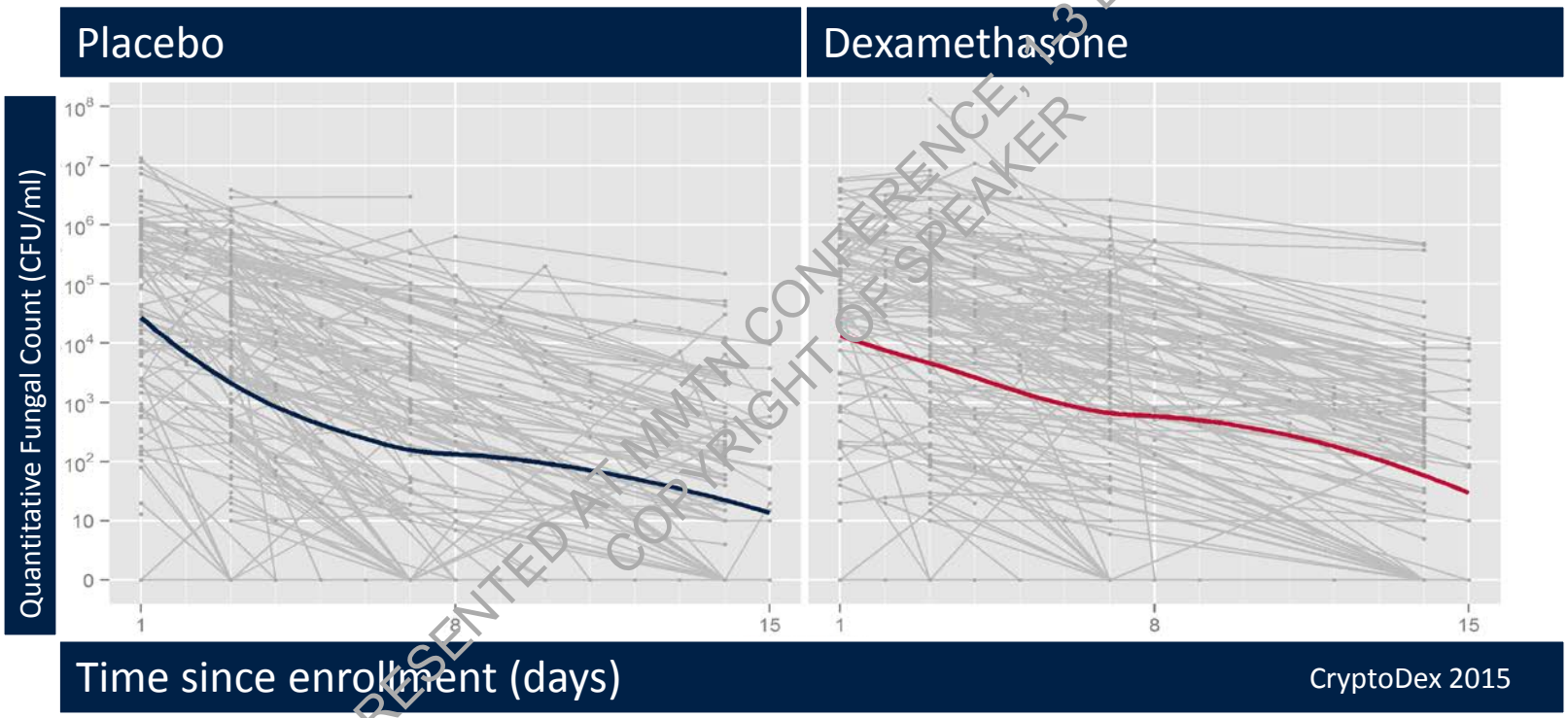


Intracranial pressure reduced more in the dexamethasone arm



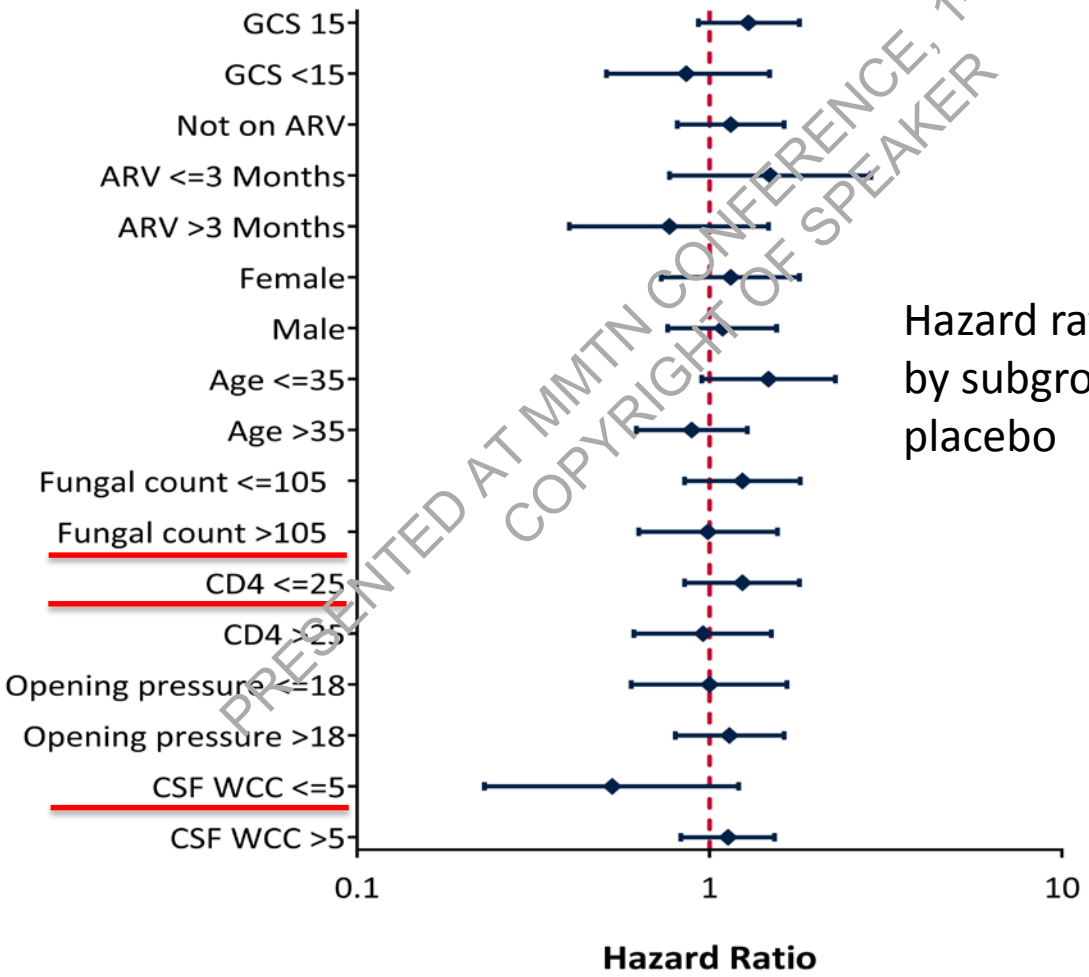
Longitudinal CSF opening pressures during the first 2 weeks	**Placebo**	**Dexamethasone**	**Estimated relative difference:**
-Estimated percentage change over 14 days	-10%	-36%	-28% (-39 to -16%); p<0.001
-(95% CI)	(-20% to +2%)	(-43% to -27%)	

Yeast **clearance was slower** in the dexamethasone arm



Estimated change (95% CI) [log10 CFU/mL of CSF per day]	**Placebo**	**Dexamethasone**	**Difference in estimated change**
- ITT	-0.30 (-0.33,-0.27)	-0.21 (-0.23,-0.18)	0.09 (0.06,0.13); p <0.001
- African patients	-0.26 (-0.30,-0.22)	-0.19 (-0.23,-0.16)	0.07 (0.02,0.12); p=0.005
- Asian patients	-0.35 (-0.40,-0.30)	-0.22 (-0.26,-0.19)	0.12 (0.07,0.18); p <0.001

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

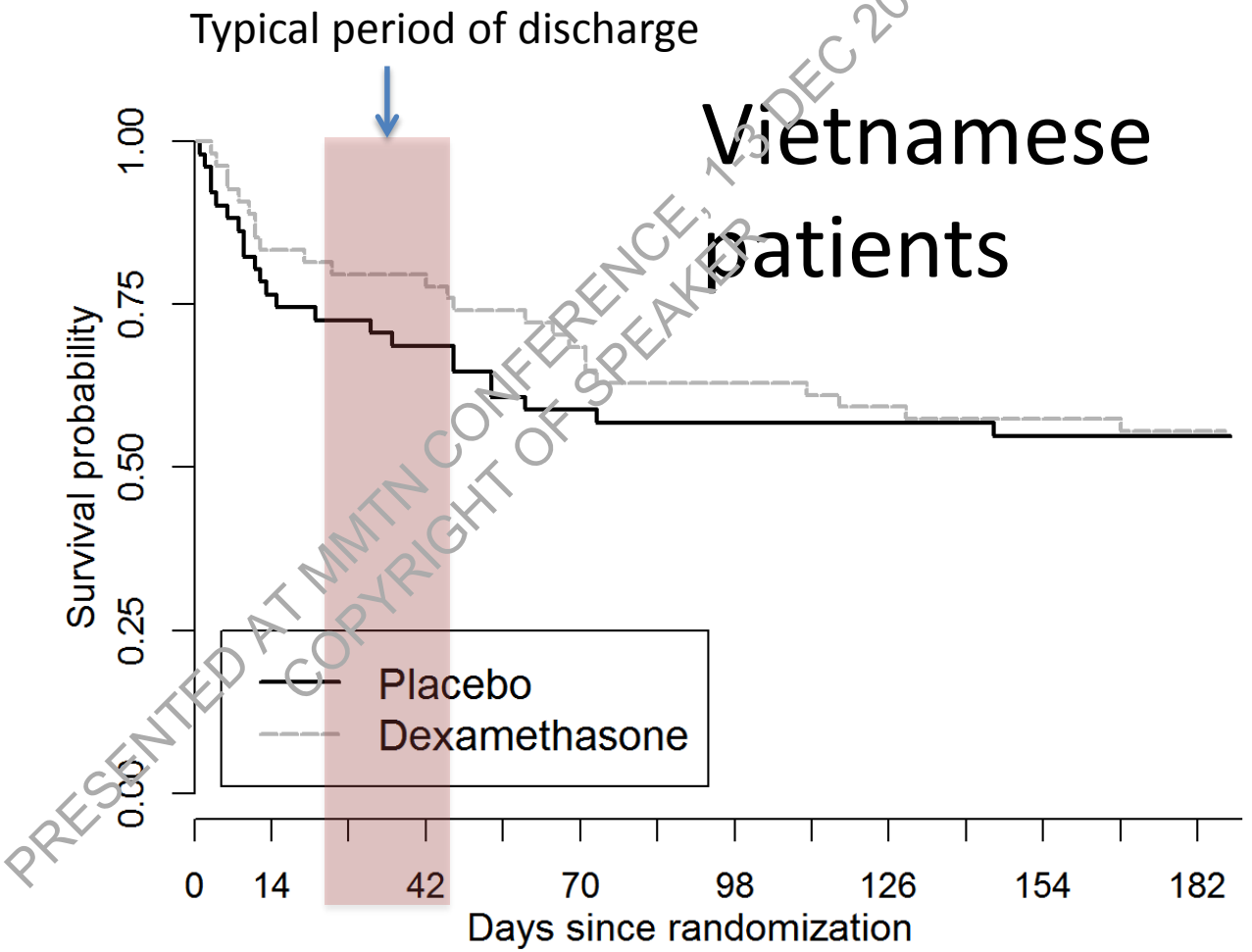
Summary…

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

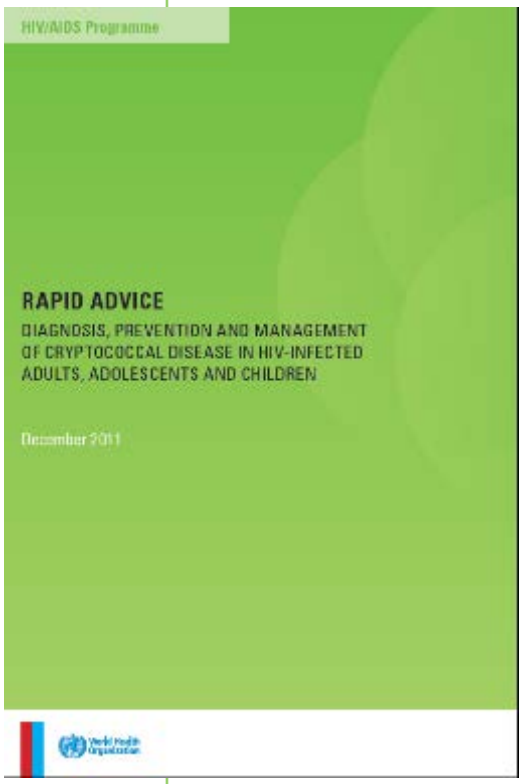
Why do we do clinical trials?



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

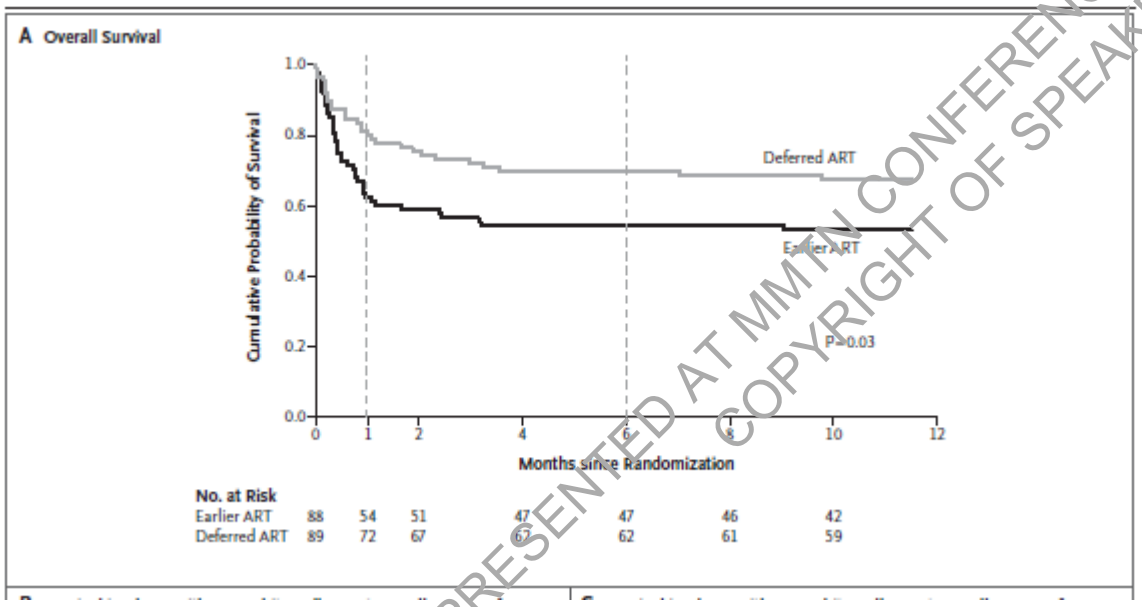
Table 1: Summary of treatment recommendations and dosage for HIV-infected adults, adolescents and children with cryptococcal disease (meningeal and disseminated non-meningeal)

Target Population	Drugs available	Pre-hydration + electrolyte replacement + toxicity monitoring/ management	Induction phase options[14] (2 weeks)	Consolidation phase options (8 weeks)	Maintenance/ secondary prophylaxis options
Adults	Amphotericin B[15] ± flucytosine	Available	**a.** Amphotericin 0.7-1 mg/kg/day + flucytosine 100 mg/kg/day **b.** Amphotericin 0.7-1 mg/kg/day + fluconazole 800 mg/day	Fluconazole 400-800 mg/day	Fluconazole 200 mg daily
	Amphotericin B[15]	Not available for full 2 week induction period	Amphotericin 0.7-1 mg/kg/day short course (5-7 days) + fluconazole 800 mg/day (2 weeks)	Fluconazole 800 mg/day	
	Amphotericin B not available	Not available	**a.** Fluconazole 1200 mg/day ± flucytosine 100 mg/kg/day **b.** Fluconazole 1200 mg/day alone	Fluconazole 800 mg/day	



Timing of antiretroviral therapy

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



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Timing of Antiretroviral Therapy after Diagnosis of Cryptococcal Meningitis

David R. Boulware, M.D., M.P.H., David B. Meya, M.Med., Conrad Muzoora, M.Med., Melissa A. Rolfes, Ph.D., Katherine Huppler Hullsiek, Ph.D., Abdu Musubire, M.Med., Kabanda Taseera, M.Med., Henry W. Nabeta, M.B., Ch.B., Charlotte Schutz, M.B., Ch.B., M.P.H., Darlisha A. Williams, M.P.H., Radha Rajasingham, M.D., Joshua Rhein, M.D., Friedrich Thienemann, M.D., Ph.D., Melanie W. Lo, M.D., Kirsten Nielsen, Ph.D., Tracy L. Bergemann, Ph.D., Andrew Kambugu, M.Med., Yukari C. Manabe, M.D., Edward N. Janoff, M.D., Paul R. Bohjanen, M.D., Ph.D., Graeme Meintjes, M.B., Ch.B., Ph.D., for the CGAT Trial Team*

ABSTRACT

BACKGROUND

Cryptococcal meningitis accounts for 20 to 25% of acquired immunodeficiency syndrome–related deaths in Africa. Antiretroviral therapy (ART) is essential for survival; however, the question of when ART should be initiated after diagnosis of cryptococcal meningitis remains unanswered.

METHODS

We assessed survival at 26 weeks among 177 human immunodeficiency virus–infected adults in Uganda and South Africa who had cryptococcal meningitis and had not previously received ART. We randomly assigned study participants to undergo either earlier ART initiation (1 to 2 weeks after diagnosis) or deferred ART initiation (5 weeks after diagnosis). Participants received amphotericin B (0.7 to 1.0 mg per kilogram of body weight per day) and fluconazole (800 mg per day) for 14 days, followed by consolidation therapy with fluconazole.

RESULTS

The 26-week mortality with earlier ART initiation was significantly higher than with deferred ART initiation (45% [40 of 88 patients] vs. 30% [27 of 89 patients]; hazard ratio for death, 1.73; 95% confidence interval [CI], 1.06 to 2.82; P=0.03). The excess deaths associated with earlier ART initiation occurred 2 to 5 weeks after diagnosis (P=0.007 for the comparison between groups); mortality was similar in the two groups thereafter. Among patients with few white cells in their cerebrospinal fluid (<5 per cubic millimeter) at randomization, mortality was particularly elevated with earlier ART as compared with deferred ART (hazard ratio, 3.17; 95% CI, 1.41 to 10.58; P=0.008). The incidence of recognized cryptococcal immune reconstitution inflammatory syndrome did not differ significantly between the earlier-ART group and the deferred-ART group (20% and 13%, respectively; P=0.32). All other clinical, immunologic, virologic, and microbiologic outcomes, as well as adverse events, were similar between the groups.

CONCLUSIONS

Deferring ART for 5 weeks after the diagnosis of cryptococcal meningitis was associated with significantly improved survival, as compared with initiating ART at 1 to 2 weeks, especially among patients with a paucity of white cells in cerebrospinal fluid. (Funded by the National Institute of Allergy and Infectious Diseases and others; COAT ClinicalTrials.gov number, NCT01075152.)

From the University of Minnesota, Minneapolis (D.R.B., D.B.M., M.A.R., K.H.H., D.A.W., K.N., J.R., M.W.L., K.N., T.L.B., P.R.B.); the Infectious Disease Institute (D.B.M., A.M., H.W.N., D.A.W., R.R., J.R., M.W.L., A.K., Y.C.M.) and School of Medicine, College of Health Sciences (D.B.M.), Makerere University, Kampala, and Mbarara University of Science and Technology, Mbarara (C.M., K.T.) — both in Uganda; the University of Cape Town, Cape Town, South Africa (C.S., F.T., G.M.); Johns Hopkins School of Medicine, Baltimore (T.C.M.); the Vaccine and Infectious Disease Research Program, Colorado Springs (C.M.), University of Colorado Denver, Aurora, and Denver Health Medical Center, Denver (E.N.J.); and Imperial College London, London (G.M.) — Address reprint requests to Dr. Boulware at MTRF 2-222, 2001 6th St. SE, Minneapolis, MN 55455, or at boulw003@umn.edu.

*A list of members of the Cryptococcal Optimal ART Timing (COAT) Trial Team is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2014;370:2487-98
DOI: 10.1056/NEJMoa1312884

N Engl J Med. 2014 Jun 26;370(26):2487-98

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

AMBITION-*cm*

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)

EDCTP
European & Developing Countries Clinical Trials Partnership

UKaid from the British people

MRC Medical Research Council

wellcome

CROI 2017 abstract #82 AMBITION-CM

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

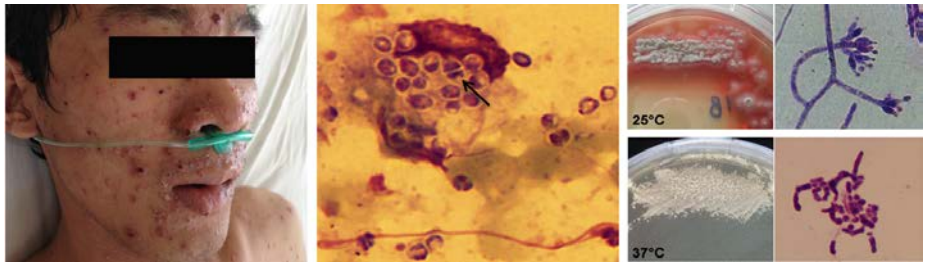
Secondary Endpoints:
1. Mortality at 10 weeks
2. Relapse and IRIS
3. Disability
4. Grades III/IV adv

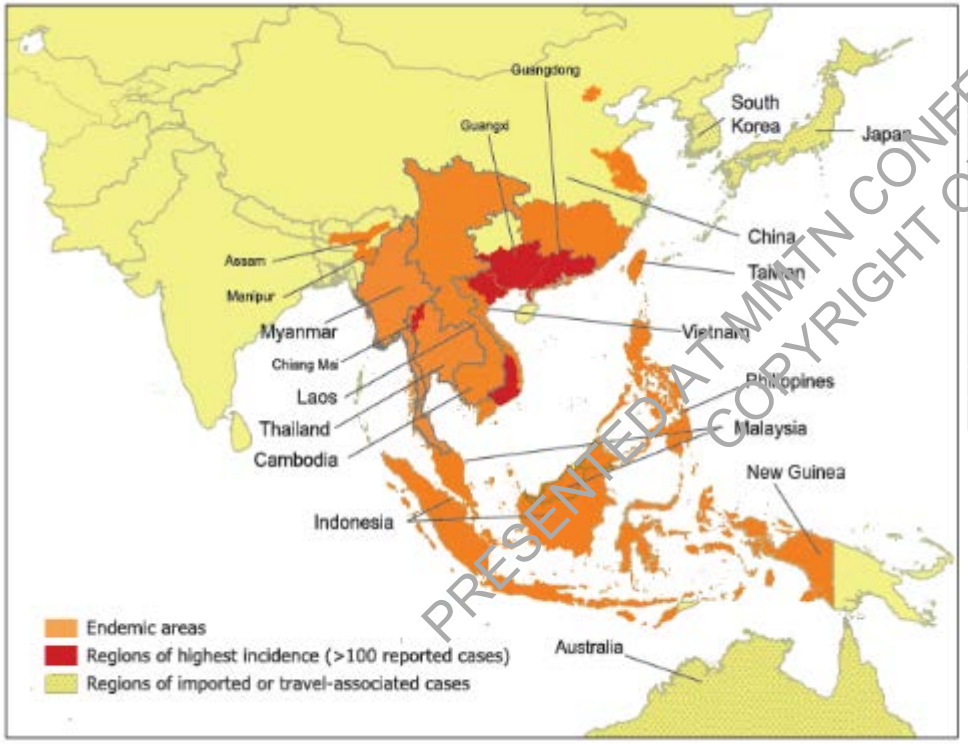
PI: Jeremy Day, clinicaltrials.org NCT03112031, enrolment begin July 20

Conclusions

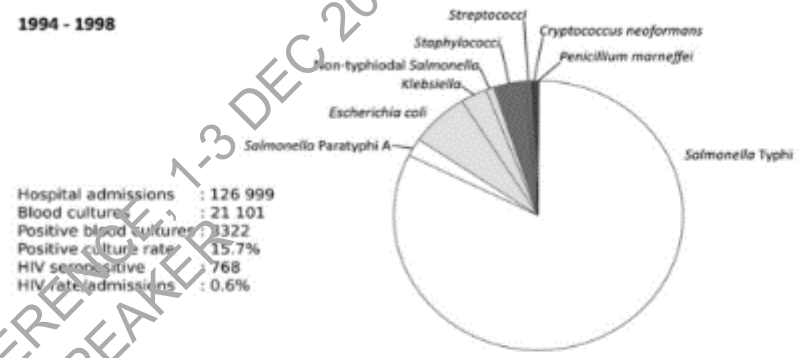
- Amphotericin and and flucytosine remain the best treatment combination
  - We need better access to current drugs
  - We need better antifungal drugs…
- Trials need adequate follow-up – 6 months
- Don't give ARVs early – wait at least 5 weeks after diagnosis
- Dexamethasone is harmful in HIV associated cryptococcal meningitis

Talaromycosis (penicilliosis) in Asia



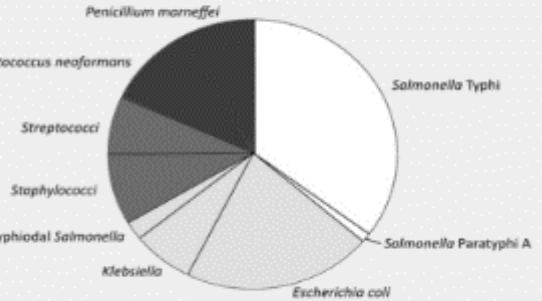


1994 - 1998



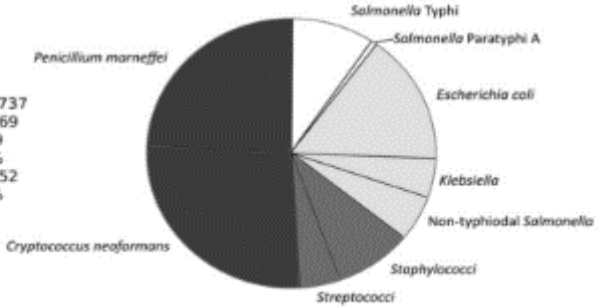
Hospital admissions : 126 999
Blood cultures : 21 101
Positive blood cultures : 3322
Positive culture rate : 15.7%
HIV seropositive : 768
HIV rate/admissions : 0.6%

1999 - 2003



Hospital admissions : 138 798
Blood cultures : 18 341
Positive blood cultures : 1755
Positive culture rate : 9.6%
HIV seropositive : 4758
HIV rate/admissions : 3.4%

2004 - 2008



Hospital admissions : 152 737
Blood cultures : 26 669
Positive blood cultures : 2559
Positive culture rate : 9.6%
HIV seropositive : 12 552
HIV rate/admissions : 8.2%

Le, T et al. Lancet ID, in press.

Nga, TVT et al. TRSTMH 2012 .

International treatment guidelines

- Amphotericin B x 2 wks, itraconazole 400 mg/d x 10 wks, then 200 mg/d until CD4 counts >100 cells/mm^3 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]

1. IDSA and CDC guidelines 2009; 2. British HIV guidelines 2013; 3. Vietnam MoH 2013;
4. Sirisanthana T, et al. Clinical Infectious Diseases 1998

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 peniciliosis

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

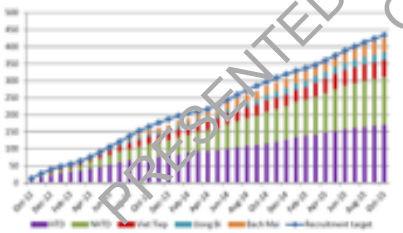
Survival during first 2 wks

Monthly follow up for 6 months

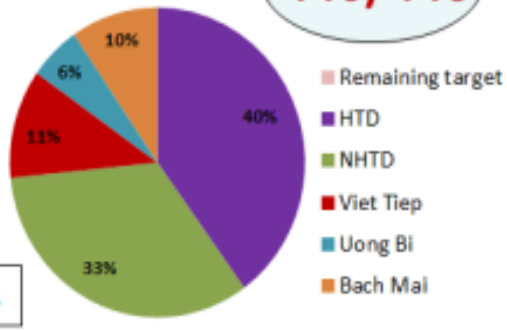
MRC Medical Research Council

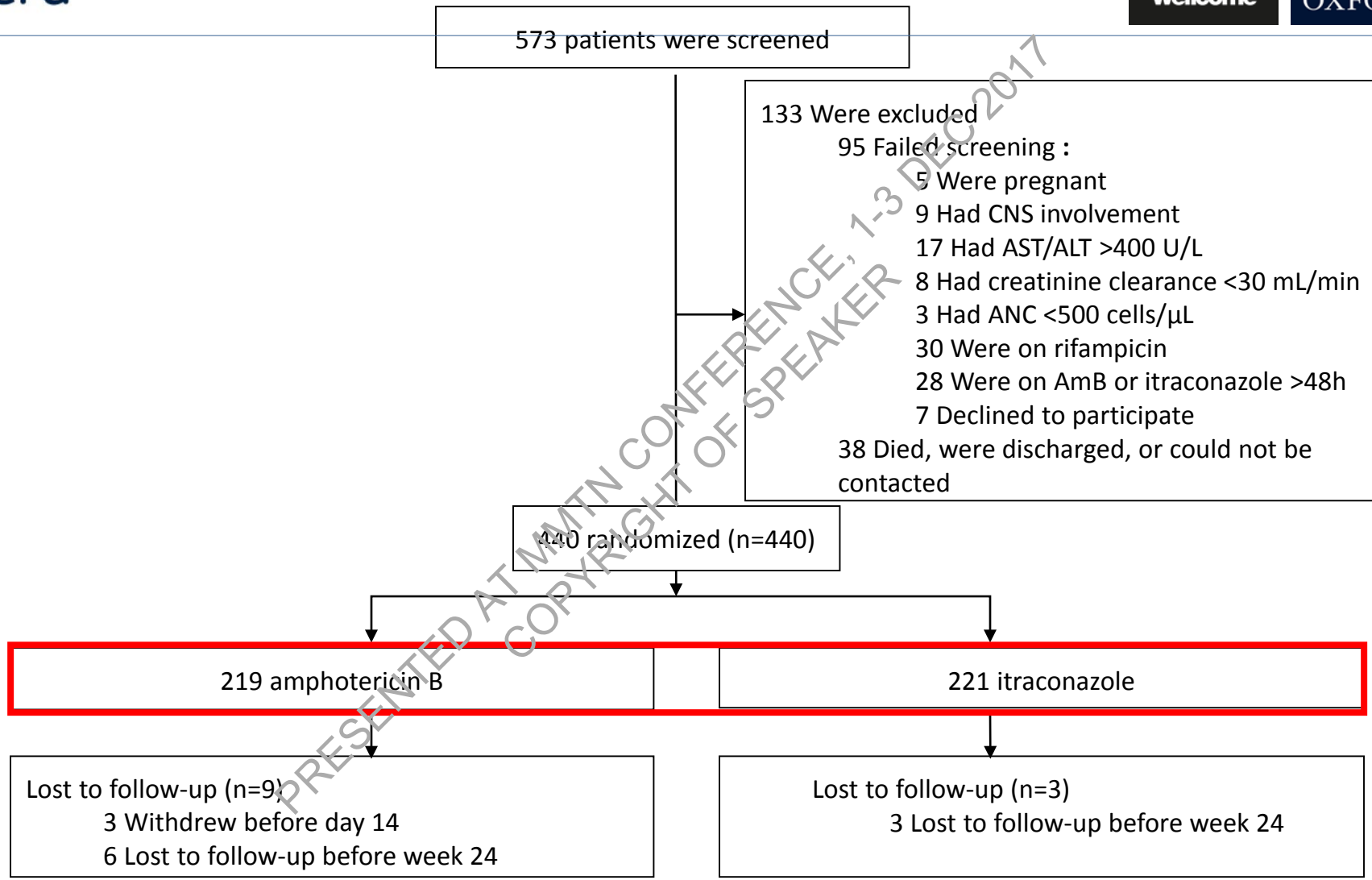
DFID Department for International Development

wellcome trust



440/440





Le T, et al. NEJM, in press

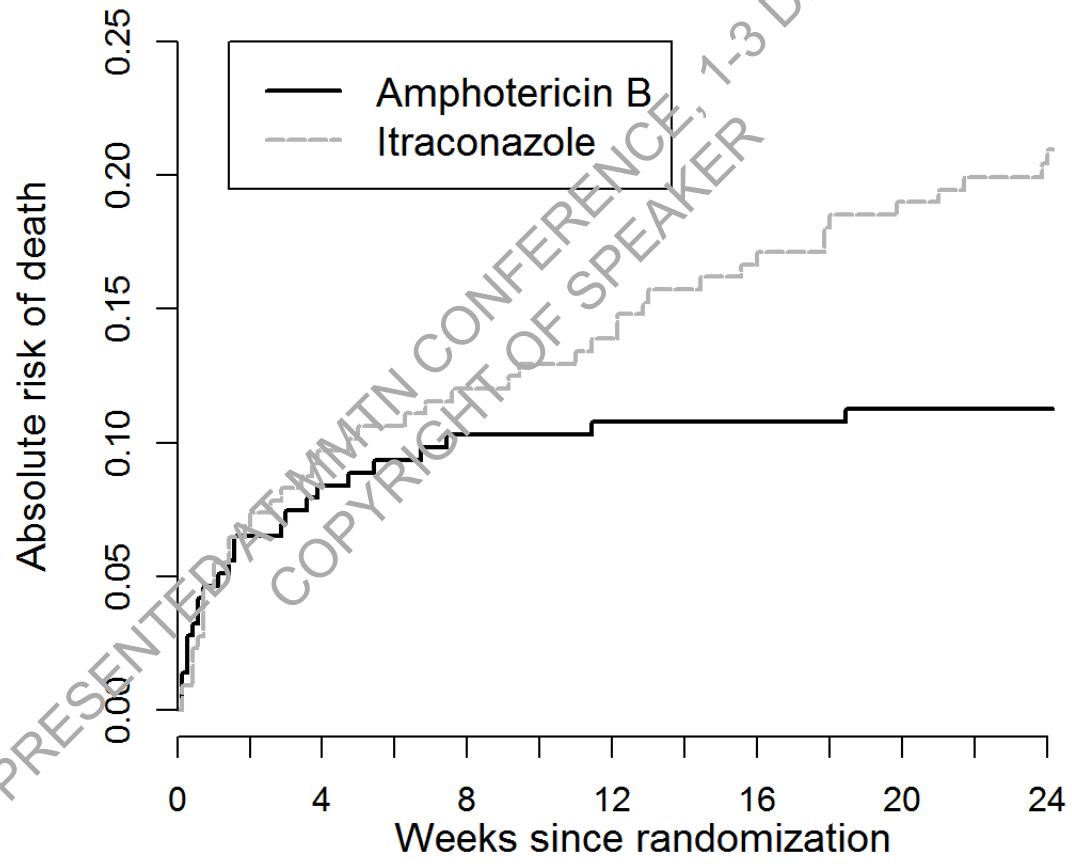
Baseline clinical characteristics

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

Baseline laboratory characteristics

Laboratory measures:	Amphotericin B (N=217)	Itraconazole (N=218)
WBC count [x10^9/L]	3.7 (2.3,5.3) [n=210]	3.7 (2.4,5.9) [n=213]
Haemoglobin [g/dL]	8.9 (7.7,10.0) [n=210]	8.8 (7.7,10.3) [n=213]
Platelet [x10^9/L]	121 (52,228) [n=210]	118 (51,215) [n=213]
CD4 cell count [cells/µL]	10 (6,19) [n=205]	11 (6,27) [n=212]
Creatinine [µmol/L]	67 (57,82) [n=210]	69 (57,86) [n=213]
AST [U/L]	121 (72,208) [n=210]	121 (68,193) [n=214]
ALT [U/L]	48 (31,82) [n=210]	48 (30,73) [n=214]
LDH [U/L]	421 (262,730) [n=141]	483 (303,813) [n=136]
HBsAg: Positive	38/194 (20%)	40/195 (21%)
AntiHCV: Positive	78/195 (40%)	62/194 (32%)
Skin culture for *T. marneffei*: Positive	117/135 (87%)	131/148 (89%)
Blood culture for *T. marneffei*: Positive	156/214 (73%)	145/216 (67%)
Blood fungal count - Detectable: Yes - Count in detactables [$\log_{10}$ CFU/ml]	 143/201 (71%) 2.16 (1.54,3.11) [n=143]	 148/200 (74%) 2.49 (1.54,3.17) [n=148]

Absolute risk of death over 24 weeks



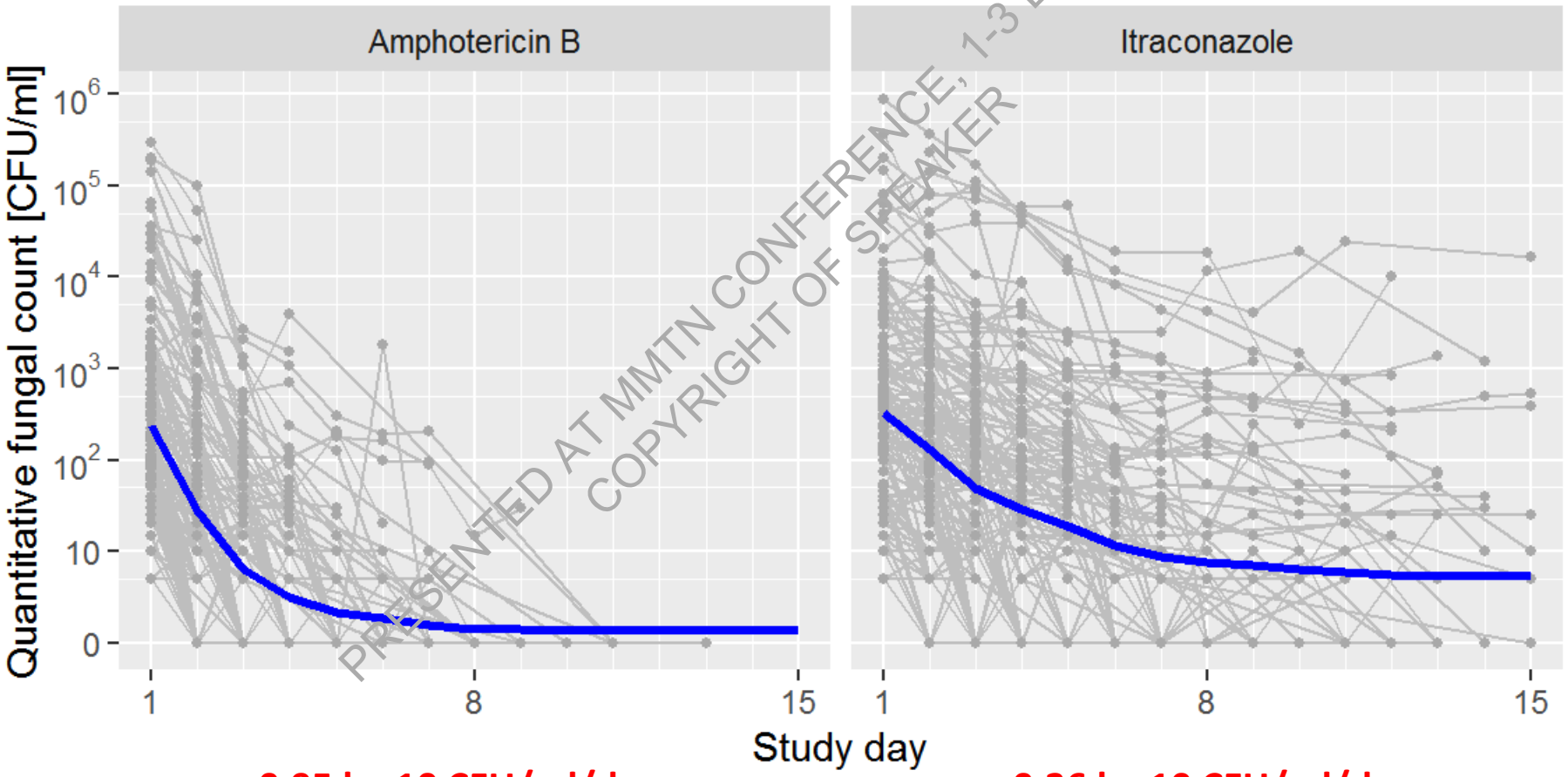
No. at risk							
Amphotericin B	217	194	189	187	187	185	165
Itraconazole	218	194	189	185	179	174	147

Summary of secondary endpoints

Outcome	Amphotericin B (N=217)	Itraconazole (N=218)	Comparison Estimate (95% CI); p-value
Time to treatment success - ITT			Ratio of subdistribution hazards:
- Patients with treatment success - events (%)	199/217 (93.4)	196/218 (90.7)	
- Median time [days]	8 (6 to 11)	9.00 (6 to 12)	0.83(0.69 to 1.00); P=0.049
Relapse, IRIS, or death until 24 weeks – events (%)			Absolute risk difference [%]:
- Relapse	3/217 (1.5)	15/218 (7.0)	5.45(1.63 to 9.27); P=0.005
- IRIS	0/217 (0.0)	14/218 (6.6)	6.56(3.24 to 9.88); P=0.0001
Blood EFA during first 14 d	-0.95	-0.36	Difference in change:
- Median [log10 CFU/mL per day]	(-1.29 to -0.53)	(-0.70 to -0.19)	0.52 (0.41 to 0.63);P<0.0001

Le T, et al. NEJM, in press

Longitudinal quantitative fungal counts in blood



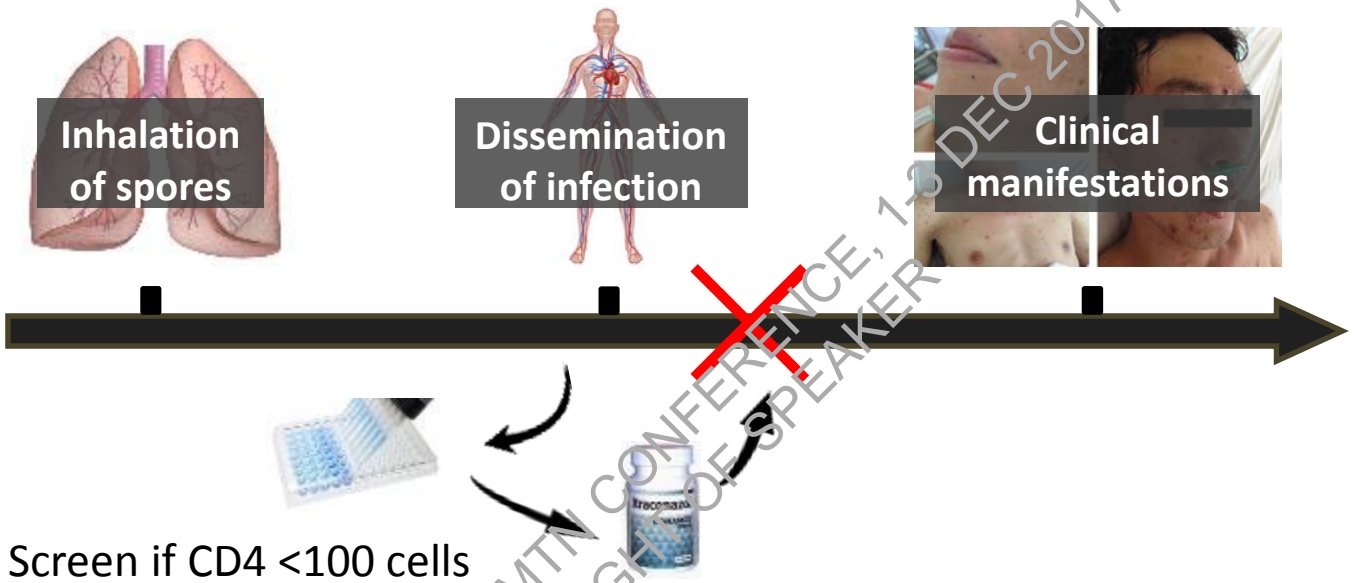
- 0.95 log10 CFU/ml/d

- 0.36 log10 CFU/ml/d

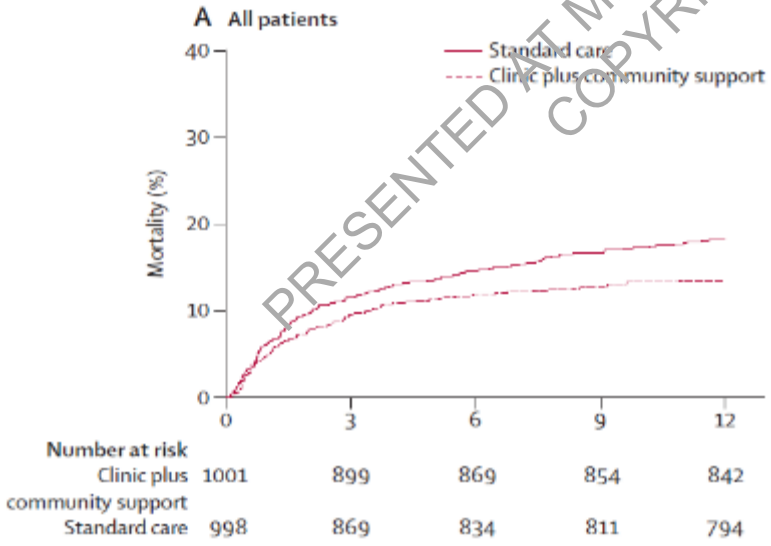
Grade ≥3 adverse events in IVAP

Adverse event name	Amphotericin B (n=217)	Itraconazole (n=218)	Comparison (p-value)
Patients with at least one AE – n(%)	116 (53.46%)	109 (50%)	0.50
T. m COMPLICATIONS	21 (9.68%)	57 (26.15%)	<0.0001
- respiratory failure	12 (5.53%)	12 (5.5%)	1.00
- relapse	3 (1.38%)	15 (6.88%)	0.006
- poor treatment response	1 (0.46%)	13 (5.96%)	0.002
- paradoxical IRIS	0 (0%)	14 (6.42%)	<0.0001
HIV-ASSOCIATED STAGE III DISEASES	14 (6.45%)	21 (9.63%)	0.29
HIV-ASSOCIATED STAGE IV DISEASES	18 (8.29%)	22 (10.09%)	0.62
Infusion reaction	49 (22.58%)	1 (0.46%)	<0.0001
Haemoglobin (<7.9 gm/dl)	89 (41.01%)	64 (29.36%)	0.012
Potassium (<2.4 mEq/L)	25 (11.52%)	7 (3.21%)	0.0009
Magnesium (<0.6 mEq/L)	10 (4.61%)	2 (0.92%)	0.021
Creatinine (>3 x ULN)	6 (2.76%)	2 (0.92%)	0.18

Screening and pre-emptive therapy



Screen if CD4 <100 cells



Jarvis J, et al. CID 2009
Mfinanga S, et al. REMSTART. Lancet 2015
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 ampho B therapy
- Corticosteroids do not improve survival and increases 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 distrubances:
  - Monitor potassium, magnesium and calcium

Thank You

UNIVERSITY OF OXFORD

UNIVERSITY OF HAWAI'I

HERC
NUFFIELD DEPARTMENT OF

THE UNIVERSITY OF HONG KONG

UNIVERSITY OF LIVERPOOL

MRC Medical Research Council

UKaid
from the British people

wellcome

CFAR
CENTER FOR AIDS RESEARCH
UNIVERSITY OF WASHINGTON

FICRS-F
Fogarty International Clinical Research Scholars & Fellows
Support Center @ Vanderbilt

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, MasakaGeneral 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