Are there opportunities to manage cryptococcal meningitis *better*?

Nelesh Govender
National Institute for Communicable Diseases

Signals

⇩

High-quality evidence

⇩

Inclusion in guidelines

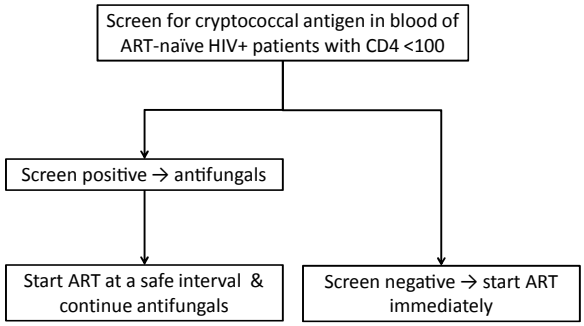
⇩

Translation into clinical practice with improved patient outcomes

Opportunities for improvement

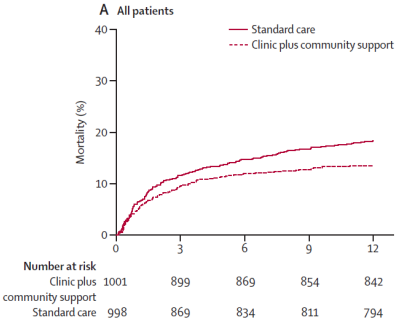
1. Earlier detection
2. First-line antifungal treatment
3. Adjunctive treatment

Cryptococcal meningitis can be prevented



Screen & treat saves lives

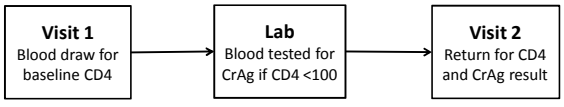
28% ↓ in all-cause mortality



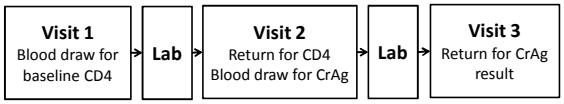
Mfinanga S, et al. Lancet 2015

CrAg screening approaches

Reflex laboratory



Provider laboratory



Govender NP, et al. S Afr J Med 2012
Vallabhaneni S, et al. J Acq Immun Defic Syndr 2016

CrAg screening approaches

Point-of-care CrAg with laboratory CD4

Visit 1
Blood draw for CD4 count → **Lab** → **Visit 2**
Return for CD4 result and test for CrAg

Point-of-care CD4 and CrAg

Visit 1
POC test for CD4 count →
POC CrAg test if CD4 <100

Wake R, et al. AIDS 2016

Rapid adoption of intervention in SA

- WHO recommended
- Teamwork
- Burden and mortality
- Seed funding
- Lab infrastructure

Provider laboratory screening

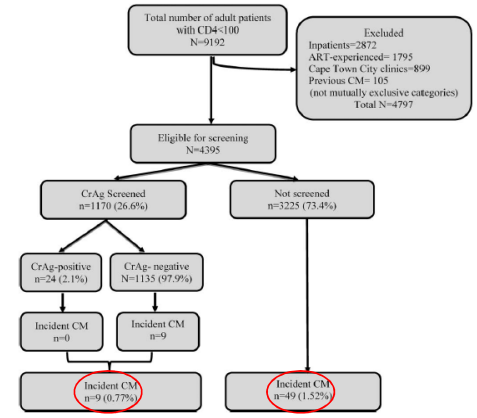
9192 patients with CD4 count <100

2872 with CD4 done at a hospital
899 with CD4 done at a Cape Town clinic
→ 105 with prior CM or prevalent CM
→ 1795 already on ART

4395 eligible patients

Only 27% screened
2.1% CLAT-positive

Vallabhaneni S, et al. J Acq Immun Defic Syndr 2016



Vallabhaneni S, et al. J Acq Immun Defic Syndr 2016

Reflex laboratory screening

53 241 patients with CD4 count <100

>95% screened
3.7% CrAg LFA-positive

NICD Surveillance Report 2016

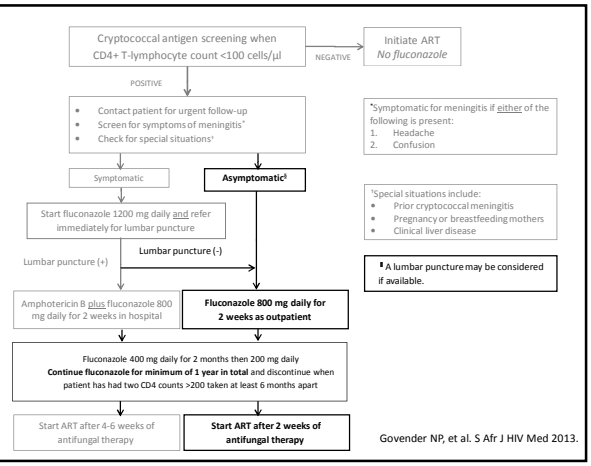
Higher screening costs
Lower treatment costs
Saves more lives

Lower screening costs
Higher treatment costs
Saves fewer lives

REFLEX **PROVIDER**

Reflex vs. provider lab screening?

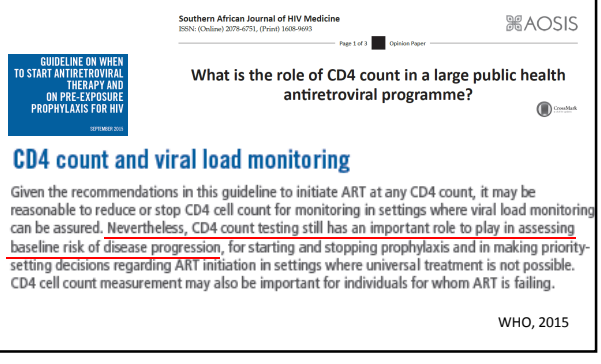
Larson B, et al. Submitted



Govender NP, et al. S Afr J HIV Med 2013.

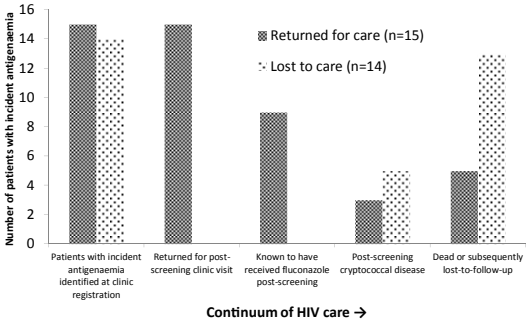
Is this evidence-based treatment?

What are the implications of "test and treat" on baseline CD4 count?



WHO, 2015

Operational barriers to screen & treat

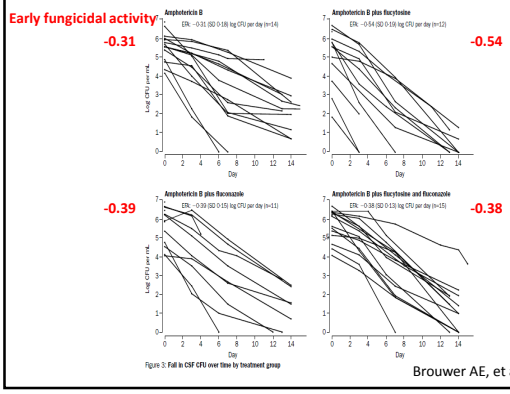


Govender NP, et al. HIV Med 2015

Opportunities for improvement

1. Earlier detection
2. First-line antifungal treatment
3. Adjunctive treatment

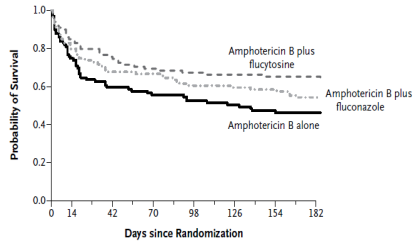
AmB plus 5FC is the *most rapidly fungicidal* regimen



Brouwer AE, et al. Lancet 2004

AmB plus 5FC: ~40% ↓ mortality

A

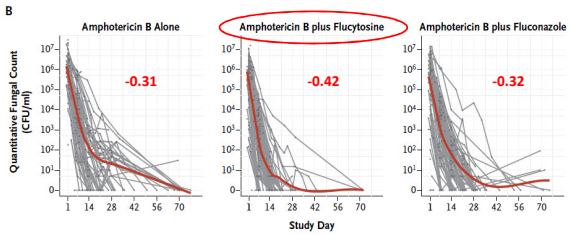


No. at Risk								
Amphotericin B alone	99	74	59	54	51	49	46	30
Amphotericin B plus flucytosine	100	84	73	67	64	63	62	46
Amphotericin B plus fluconazole	99	79	67	65	59	58	57	39

Day J, et al. N Engl J Med 2013.

Confirmed superior rate of fungal clearance

B



Day J, et al. N Engl J Med 2013.

Antifungal regimens

World Health Organization

Agents available	Toxicity prevention package	Induction (2 weeks)	Consolidation (8 weeks)
Amphotericin B <u>combination</u>	Available	– Ampho B + flucytosine [Strong/High] – Ampho B + fluconazole [Strong/Moderate]	Fluconazole 400-800 mg [Strong/Low]
Amphotericin B	Not available	– Ampho B + fluconazole *(short course)* [Conditional/Low]	Fluconazole 800 mg
No amphotericin B	Not available	– Fluconazole ± flucytosine – Fluconazole 1200 mg [Conditional/Low]	Fluconazole 800 mg

Advancing Cryptococcal meningitis Treatment for Africa (ACTA)

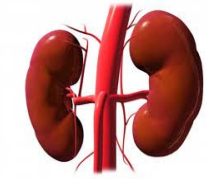
A phase III, randomised, controlled trial for the treatment of HIV-associated cryptococcal meningitis:

1. Fluconazole plus flucytosine for 2 weeks
2. Amphotericin B plus EITHER fluconazole OR flucytosine for 7 days
3. Amphotericin B plus EITHER fluconazole OR flucytosine for 14 days

Malawi, Zambia, Cameroon and Tanzania
Target: 680 patients

ISRCTN45035509; DOI 10.1186/ISRCTN45035509

Manage amphotericin B deoxycholate toxicities



30% nephrotoxicity
~40% hypokalaemia

Meiring ST, et al. Submitted

…and facilitate access to lipid formulations of amphotericin B

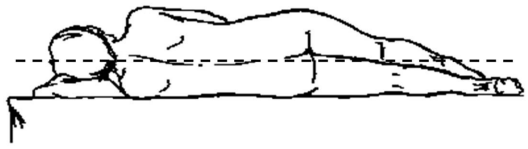
Near future: Second-line agent for those with renal dysfunction

Future: Short-course induction treatment (Jarvis JN. Ambition-CM trial)

Opportunities for improvement

1. Earlier detection
2. First-line antifungal treatment
3. Adjunctive treatment

Raised pressure must be managed

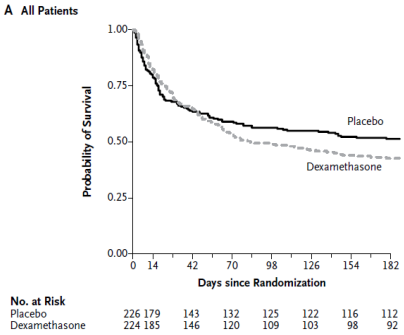


- If opening pressure is >25 cm H_20, remove 10-30 ml CSF to reduce pressure by at least 50% or to <20 cm H_20
- Repeat LP whenever there are symptoms or signs of RICP
- Daily therapeutic LPs may be required

…one drop of CSF at a time?

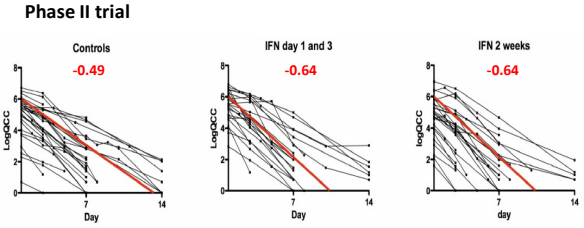
Boyles T, et al. HIV Society Conference 2016: Abstract 203

Adjunctive dexamethasone is harmful



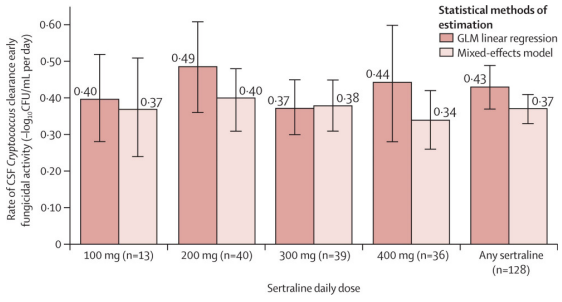
Day JN, et al. N Engl J Med 2016

Adjunctive interferon-γ is promising



Jarvis JN, et al. AIDS 2012

Adjunctive sertraline is also promising



Rhein J, et al. Lancet Infect Dis 2016

Summary

- Cryptococcal meningitis is a devastating opportunistic infection which is *still* an issue in 2016
- We have new strategies to detect cryptococcal disease earlier and manage meningitis more aggressively
- Renewed hope to improve patient outcomes if *properly* implemented

Acknowledgements

- National Department of Health
- Gauteng, Free State and WC Departments of Health
- National Institute for Communicable Diseases
- National Health Laboratory Service
- CDC-South Africa and CDC-Atlanta
- USAID-South Africa
- PEPFAR partners: HST, Aurum, FPD, SCMS, Right to Care, ANOVA, HE^{2}RO
- SA HIV Society
- Academic partners: UCT, St George's UL, Boston University, University of Minnesota

health
Department:
Health
REPUBLIC OF SOUTH AFRICA