

Reducing AIDS deaths by preventing Cryptococcal Meningitis

April 12, 2024

ACACIA trial team



Infectious Diseases Institute
College of Health Sciences, Makerere University
Investing In the Future: Impacting Real Lives



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Outline

- Cryptococcal meningitis
- Cryptococcal screening
- Gaps in cryptococcal screening programs
- ACACIA trial



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BACKGROUND



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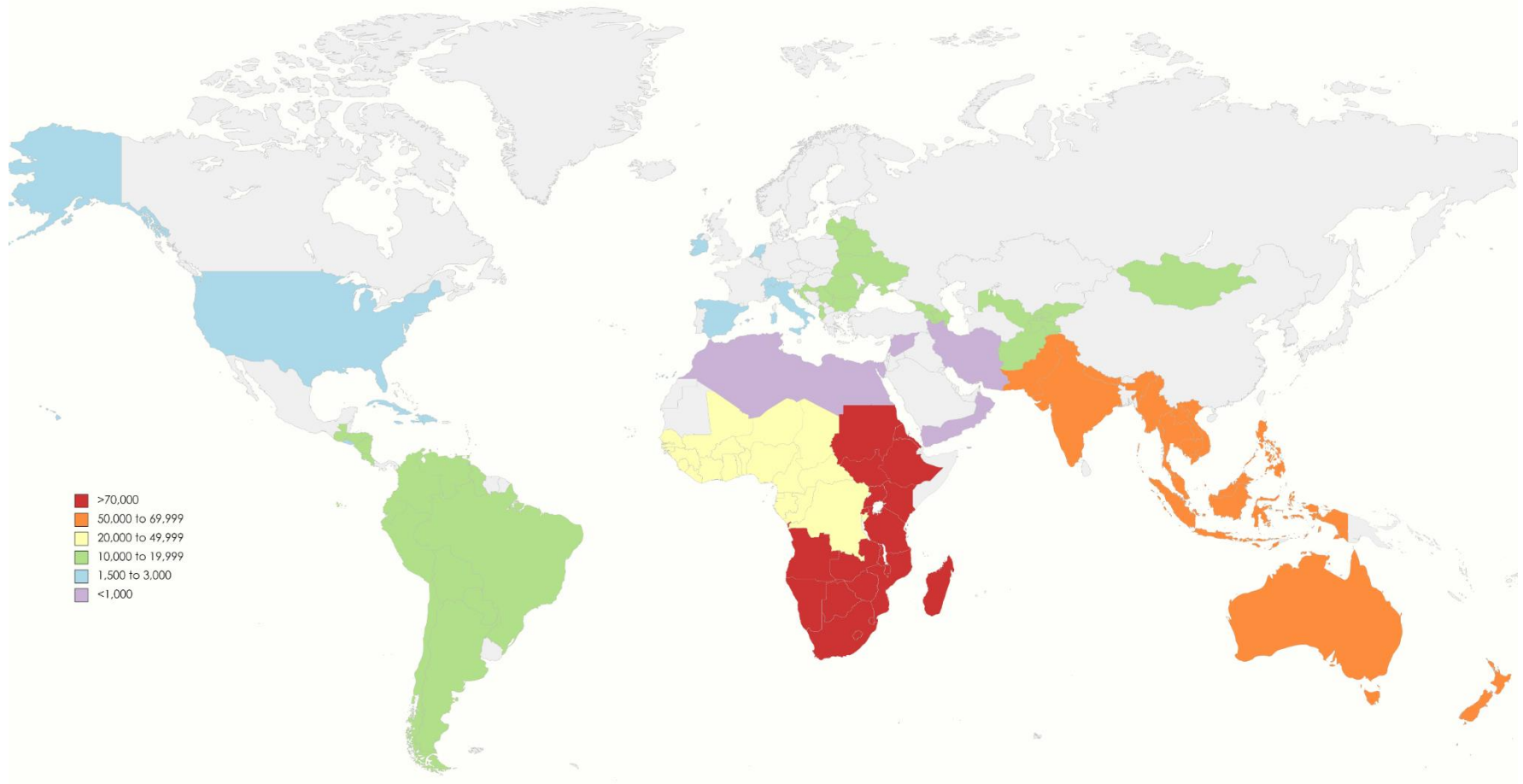
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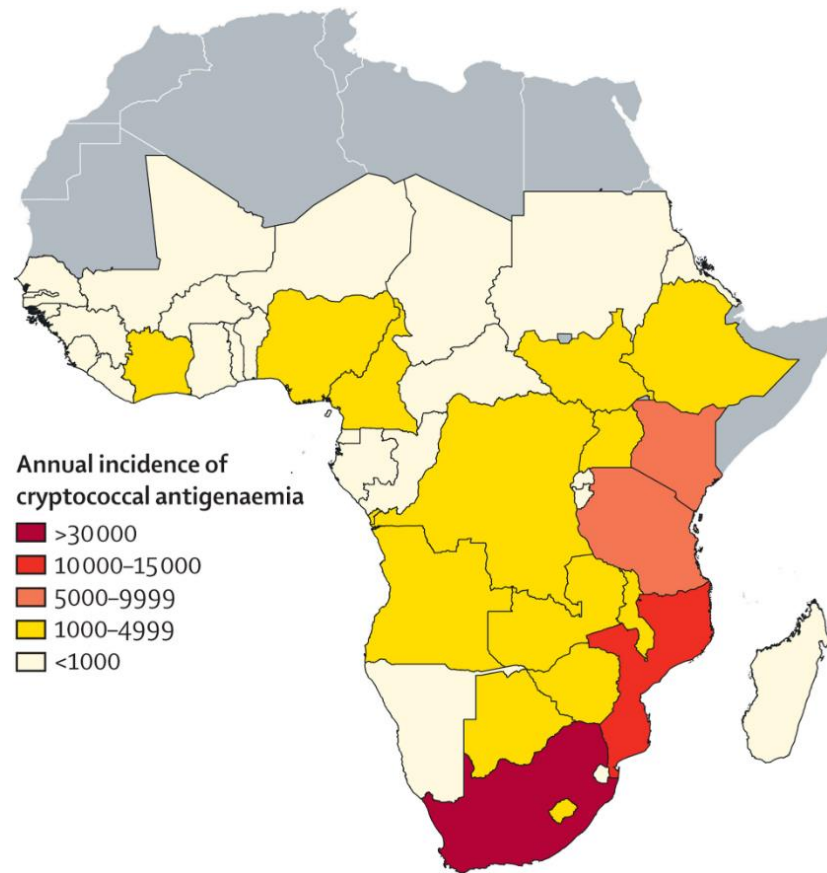
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Annual incidence of cryptococcal infection by region

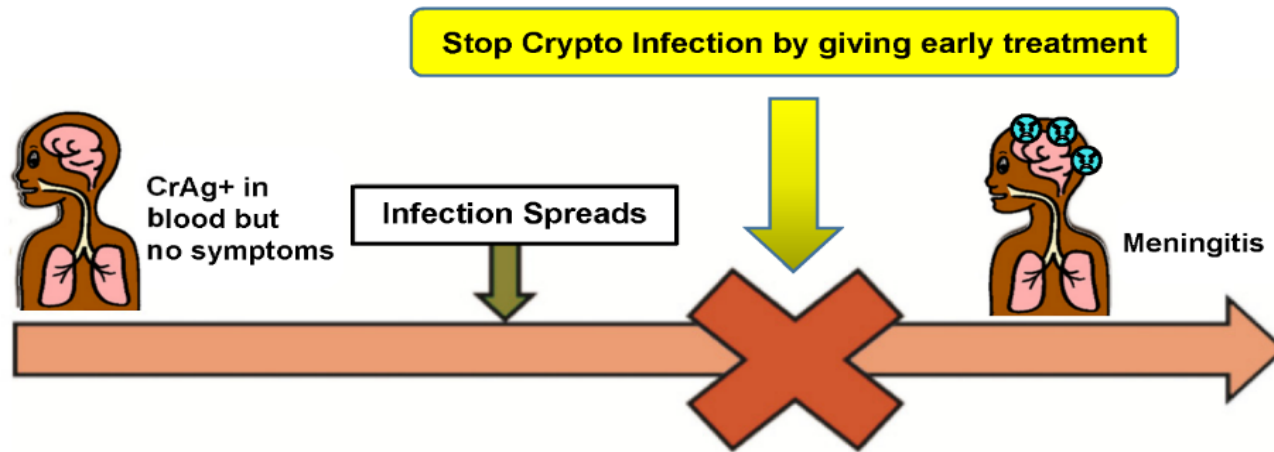
Globally: 179,000 CrAg+, 152,000 meningitis cases, 112,000 deaths



Cryptococcal infection causes 19% of AIDS-related deaths

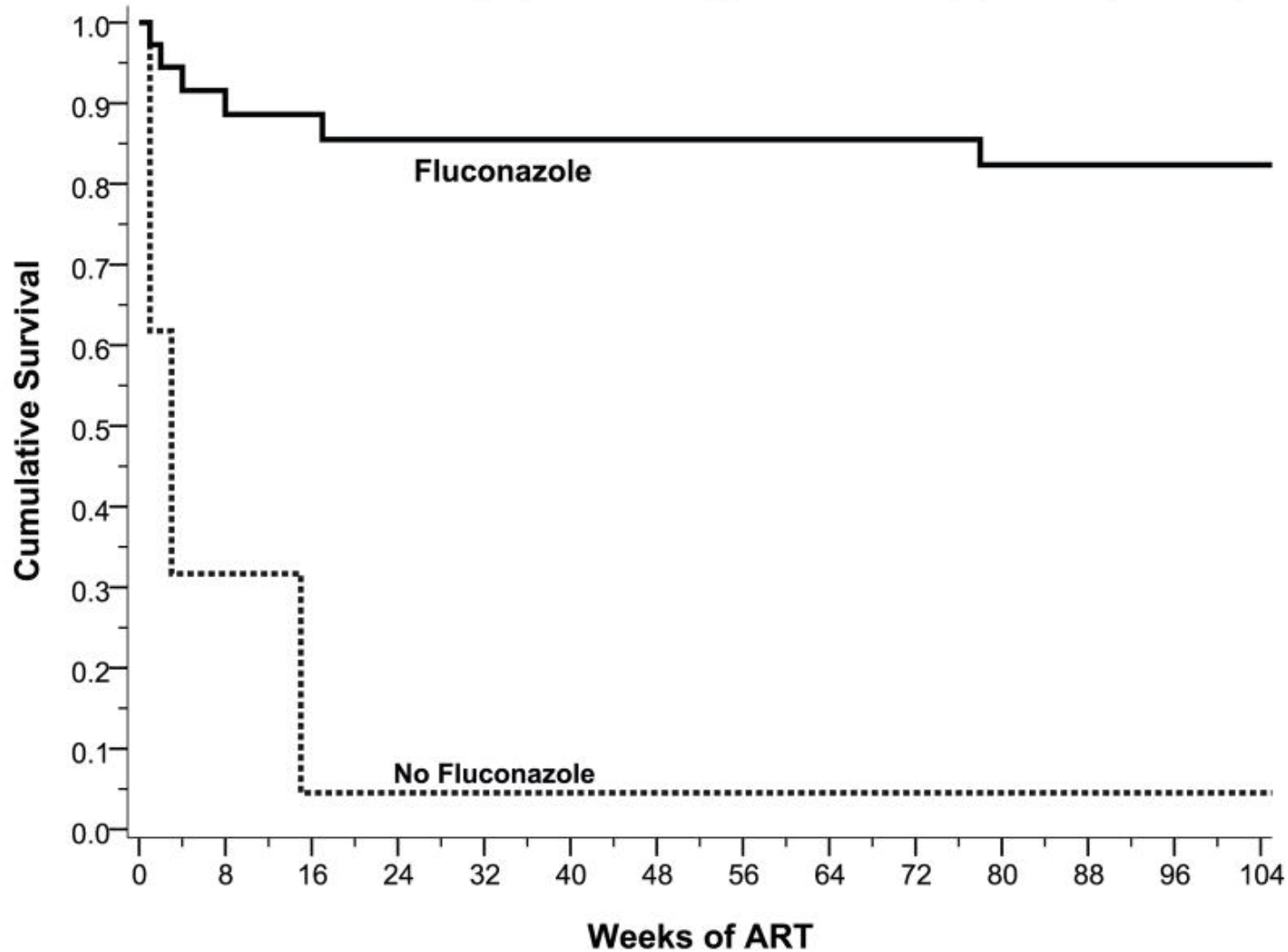


Cryptococcal meningitis can be prevented

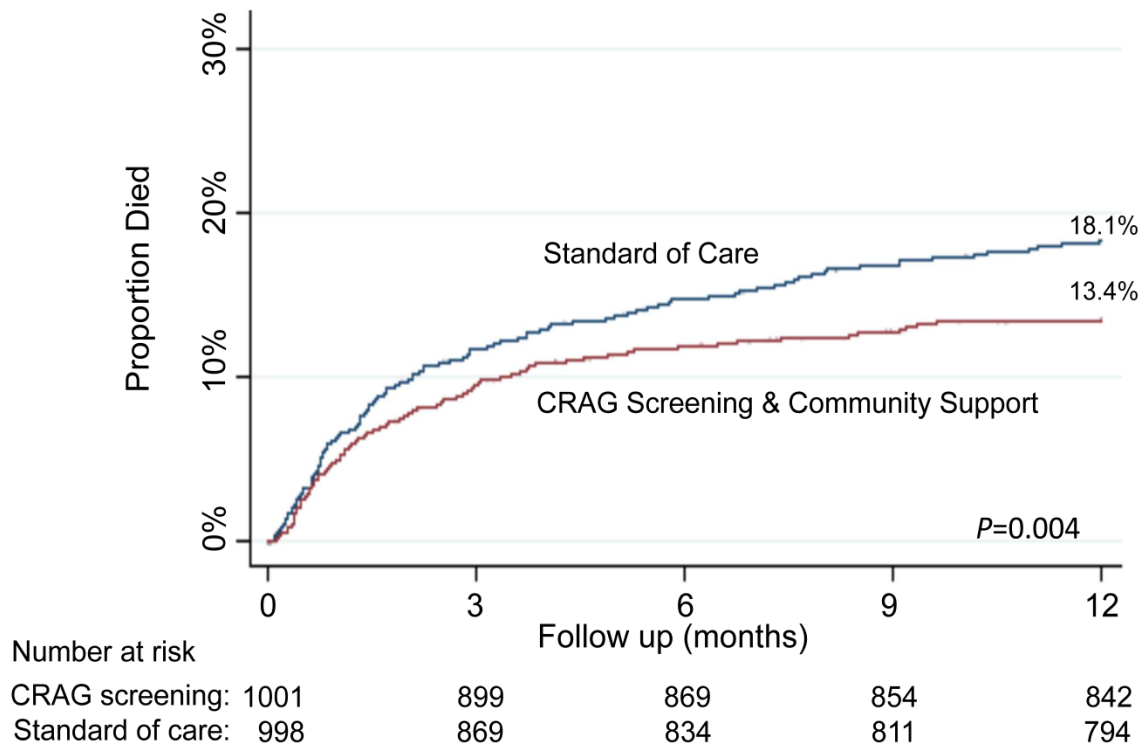


- Cryptococcal antigen (CrAg) can be detected in blood weeks before onset of meningitis
- CrAg is a strong predictor of development of cryptococcal meningitis

Survival in Persons with Asymptomatic Cryptococcal Antigenemia (CRAG+)

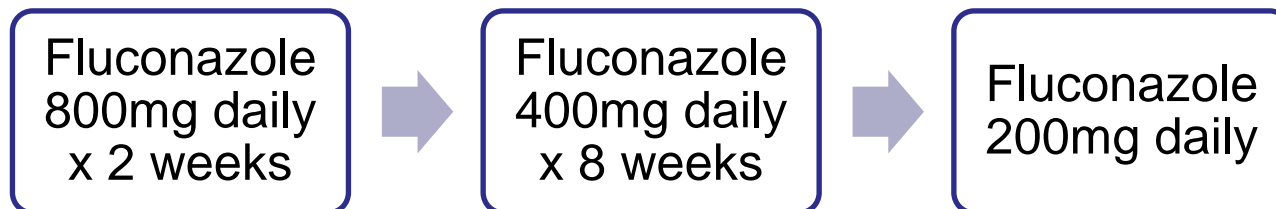


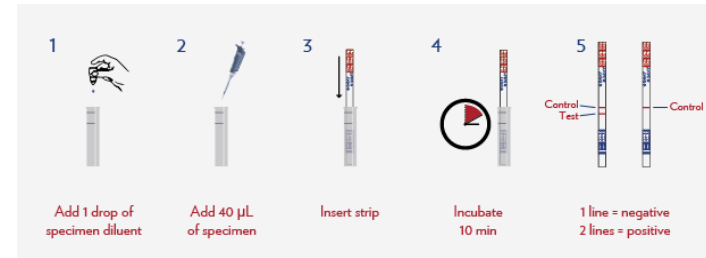
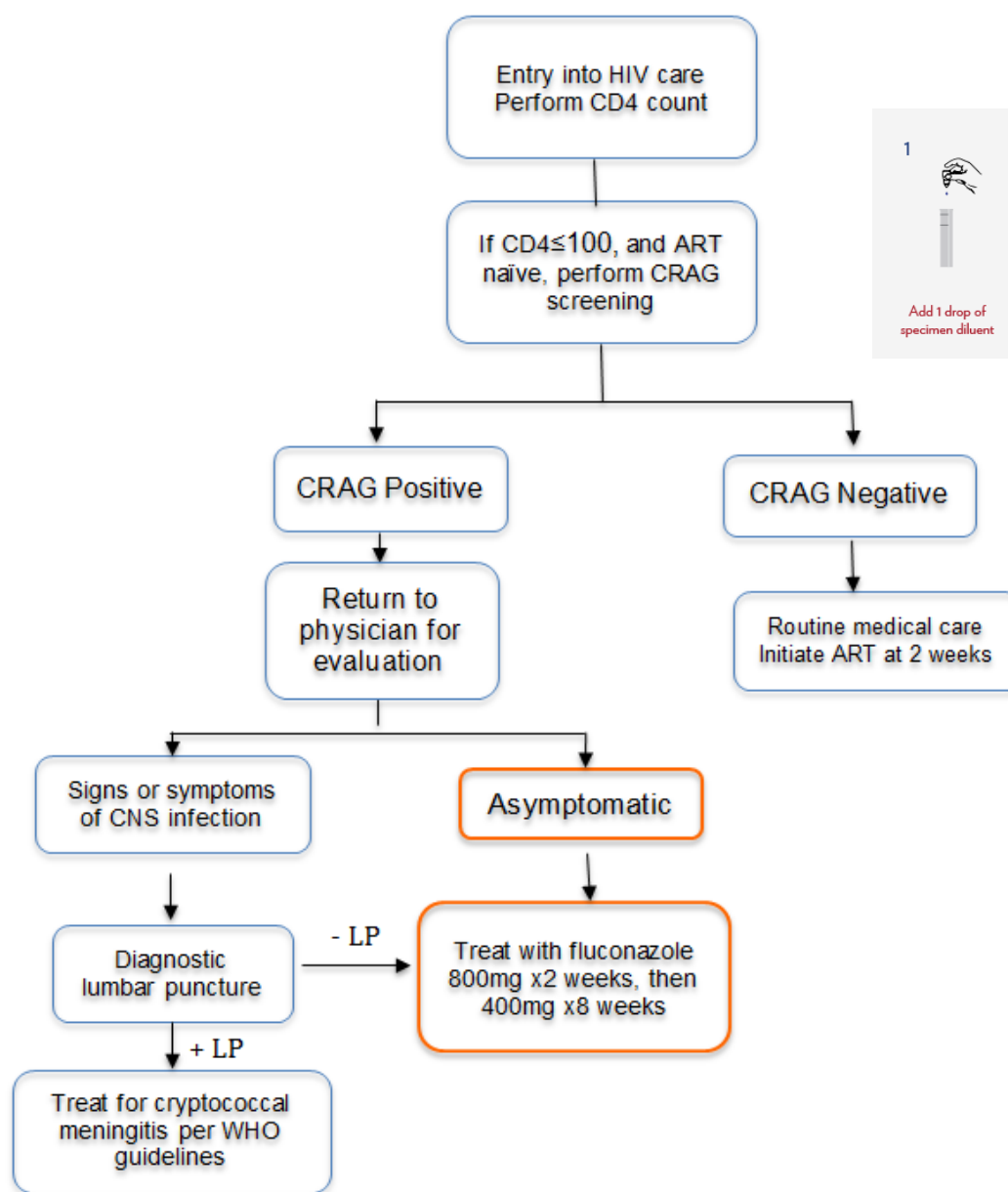
CrAg screening and preemptive treatment is life saving



WHO Recommendations

- CrAg screening recommended for adults with $CD4 < 100$ cells/ μ L
 - May be considered at $CD4 < 200$ cells/ μ L
- If CrAg+ and asymptomatic, preemptive treatment with:





GAPS IN CURRENT CRAG SCREENING PROGRAMS



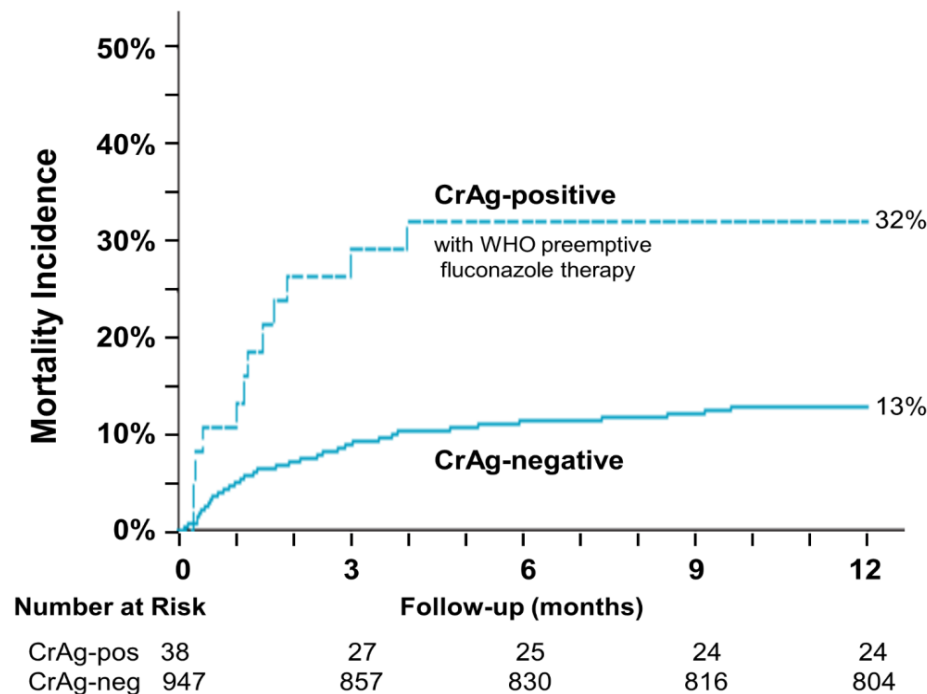
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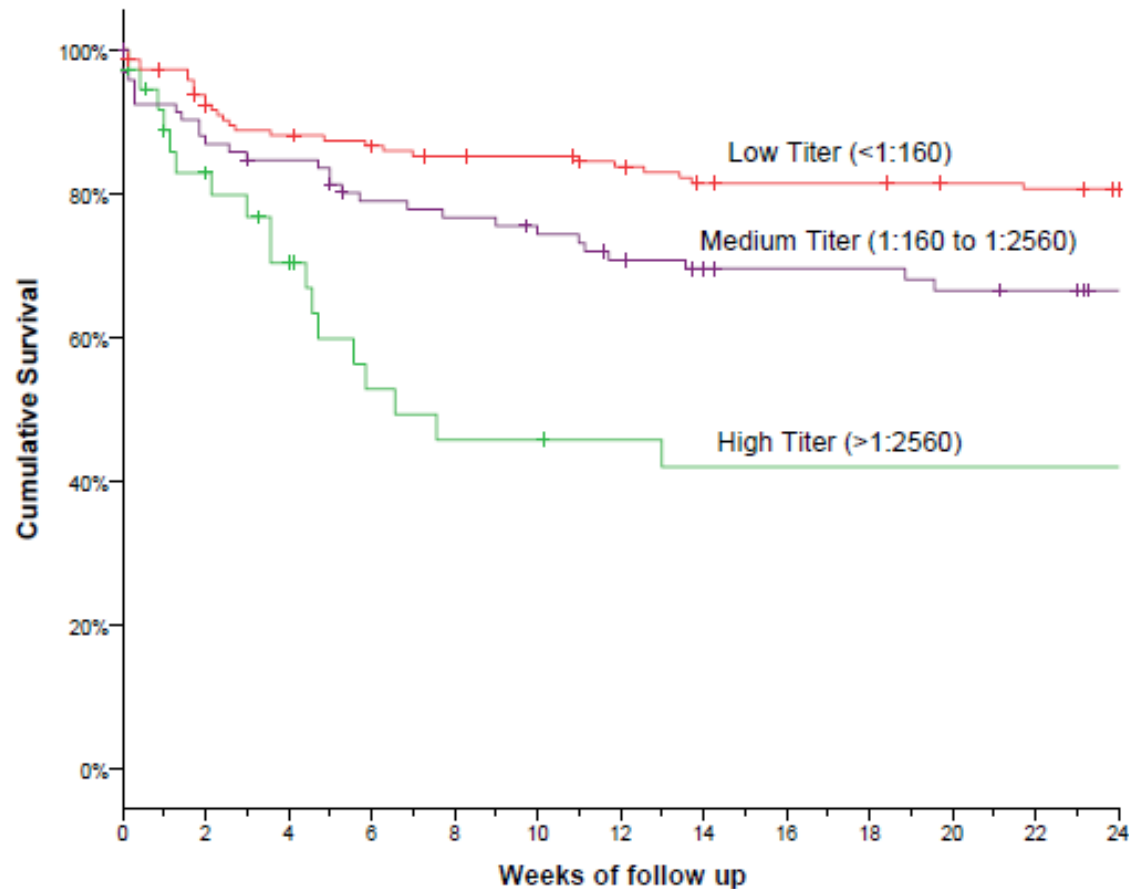


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Despite standard of care fluconazole, CrAg+ people have higher mortality



Survival stratified by CrAg titer



Alternative considerations for preemptive antifungal therapy

- Liposomal amphotericin –one time doses have been used for leishmaniasis



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ACACIA TRIAL

**SINGLE DOSE LIPOSOMAL AMPHOTERICIN FOR
ASYMPTOMATIC CRYPTOCOCCAL ANTIGENEMIA**



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ACACIA Trial: Design

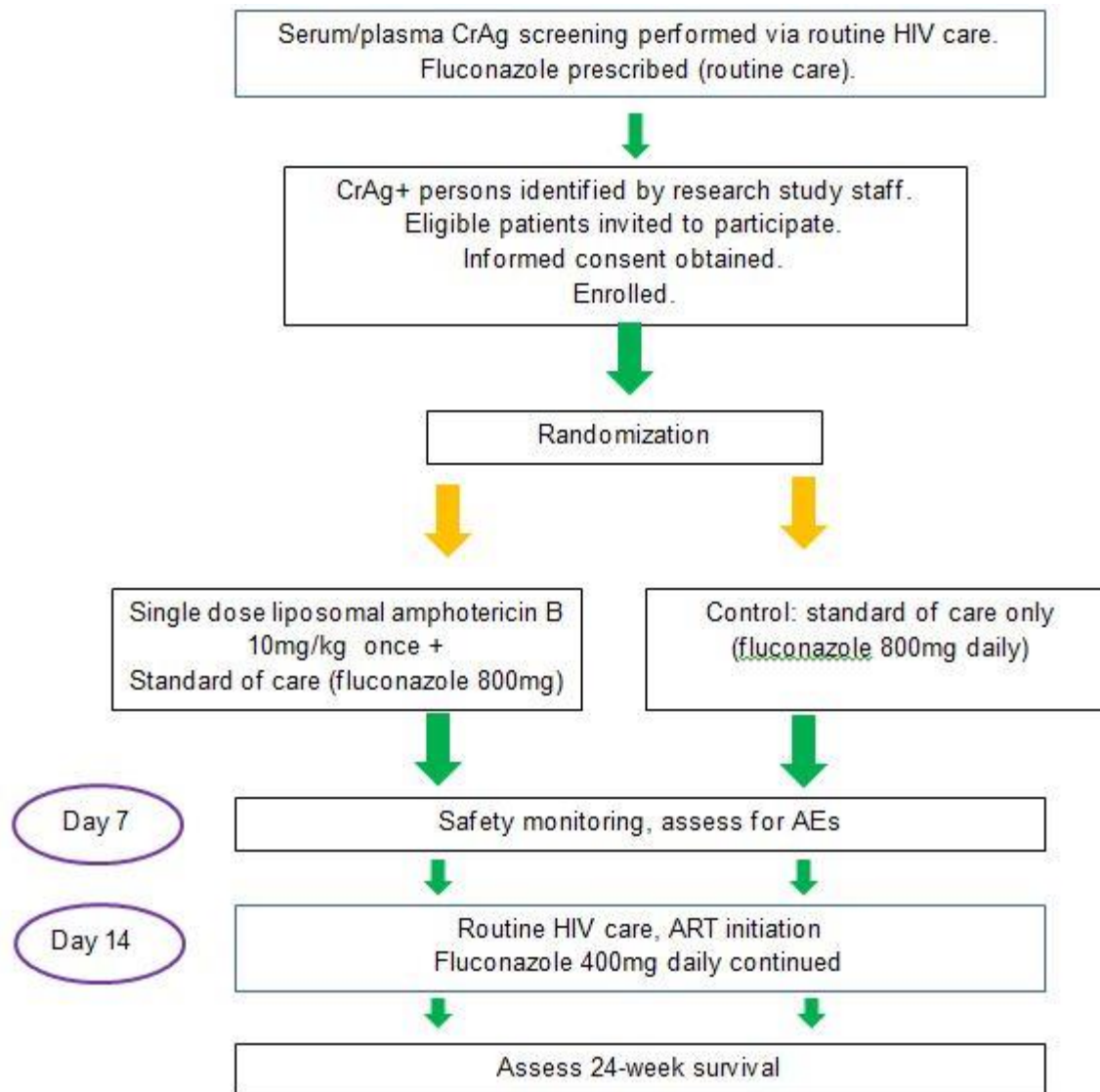
- Randomized controlled trial
- Phase II/III
- Intervention: Single dose AmBisome at 10mg/kg IV + fluconazole
- Control: Fluconazole



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ACACIA Trial: Objectives

1. Determine 24-week meningitis-free survival in asymptomatic CrAg+
 - liposomal amphotericin + fluconazole vs.
 - standard of care fluconazole
2. Safety, tolerability
3. Cost-effectiveness



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Study inclusion and exclusion criteria

Inclusion:

- ❖ HIV +, Age ≥ 15 , CrAg+, consent

Exclusion:

- ❖ History of CM
- ❖ Symptomatic CM disease
- ❖ >14 day od fluconazole
- ❖ Pregnancy or currently breastfeeding



Our request of the Jinja sites

- Perform CrAg screening on all CD4<200 + those from lower facilities.
- If you identify a CrAg+ person, call the ACACIA team immediately.
- If a CrAg+ person is identified at a lower facility, A sample or patient to be brought to JRRH for screening.



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HARVEST STUDY

INCLUSION

- First episode TBM suspected by clinician (>3 days of meningitis symptoms and CSF abnormalities) and anti-TB planned)
- Age >18
- Provision of written informed consent

EXCLUSION

- Jaundice, liver cirrhosis, ALT >5XULN.
- More than 5 doses of anti-TBs
- Known allergy to RHZE
- Current/previously diagnosed Rifampicin resistant M.b TB
- Additional active and confirmed CNS infection
- Corticosteroids contradicted
- Pregnant/ breastfeeding
- Can't attend regular visits
- Renal failure eGFR <30
- HIV protease inhibitor ongoing use.



Questions?



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