Cost-effectiveness of CrAg screening for PLHIV with advanced HIV disease in Malawi

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BACKGROUND

- Cryptococcal meningitis (CM) is a leading cause of death among people living with HIV (PLHIV), accounting for 90,000 deaths worldwide in 2020.
- In southern Africa, 7% of PLHIV with CD4 <100/μL and 2% with CD4 100-200/μL are serum cryptococcal antigen (CrAg)-positive and at risk of CM.
- Diagnosis and treatment of asymptomatic cryptococcal antigenemia before the development of symptomatic CM can reduce mortality.

OBJECTIVE

- To project the clinical impact and cost-effectiveness of WHO-recommended serum CrAg screening with pre-emptive fluconazole (FLU) therapy in asymptomatic PLHIV with CD4 <200/μL initiating ART in Malawi.

METHODS

- We used the validated Cost-Effectiveness of Preventing AIDS Complications (CEPAC) microsimulation model to examine two strategies among PLHIV with CD4 <200/μL at ART initiation: 1) no CrAg screening, and 2) a serum CrAg screening test.[1]
- PLHIV who test serum CrAg-positive initiate 12-month FLU therapy, which has 76% efficacy in preventing progression from asymptomatic cryptococcal antigenemia to symptomatic CM.[2]
- PLHIV who do not receive a serum CrAg screening test or who test CrAg-negative but later develop CM could link to CM care upon presentation with meningitis symptoms.
- Modeled outcomes included one year survival, CM deaths, life expectancy, costs, and incremental cost-effectiveness ratios (ICER, $/year of life saved (YLS)).
- We considered ICERs <$640 (Malawi 2021 *per capita* GDP) cost-effective.

Table 1. Selected model input parameters

Parameter	Value	Source
Initial CD4, mean (SD), cells/μL	97 (49)	Assumption
Age, mean (SD), years	37 (10)	3
Sex, female/male, %	51 / 49	3
Prevalence of asymptomatic cryptococcal antigenemia, %		
Asymptomatic CM	1.3	
Cryptococcemia	2.7	2, 4
No cryptococcal disease	96.0	
Serum CrAg screening test characteristics		
Testing uptake, %	95	Assumption
Sensitivity/specificity, %	97.6 / 98.1	5
Linkage to pre-emptive FLU therapy, %	80	Assumption
Cost per test, $	3.44	6,7
Cost of FLU pre-emptive therapy, per month, $	4.39	8
One-month CM mortality / cost, by induction treatment regimen, % / $		
FLU monotherapy	47 / 270	6,9,10,11, 12,13,14
AmB-D and FLU	35 / 160	
Single high-dose LAmB, 5FC, and FLU	17 / 490	

CM, cryptococcal meningitis; CrAg, cryptococcal antigen; FLU, fluconazole; AmB-D, amphotericin B deoxycholate; LAmB, liposomal amphotericin B; 5FC, flucytosine.

1. WHO *Guidelines for diagnosing, preventing and managing cryptococcal disease* 2022
2. Temfack *CID* 2019
3. Wake *CID* 2018
4. Ford *CID* 2018
5. Huang *PLoS One* 2015
6. Global Fund *Reference Pricing* 2022
7. Larson 2021 OpenBU
8. MSF *Intl. Med Products Price Guide* 2015
9. Nussbaum *CID 2010*
10. Shiri *CID* 2020
11. Molloy *NEJM* 2018
12. Jarvis *NEJM* 2022
13. WHO *WHO-CHOICE Estimates of Cost* 2021
14. Tagar *PLoS One* 2014

RESULTS

Table 2. Clinical benefits, costs, and cost effectiveness of serum CrAg screening among people with advanced HIV disease (AHD) in Malawi

	Strategy	Survival at 1y (%)	Reduction in CM deaths (%)	Total LYs [undisc.][a]	Total LYs [disc.] [b]	Cost, $ [disc.]	ICER, $/YLS
Base case							
AmB/FLU to treat CM*	No CrAg screening	87.4	--	17.61	11.44	1290	--
	CrAg screening	87.6	22.9	17.67	11.48	1300	**200**
Scenario analyses							
LAmB/5FC/FLU to treat CM	No CrAg screening	87.5	--	17.64	11.46	1300	--
	CrAg screening	87.7	21.8	17.69	11.49	1300	**200**
FLU monotherapy to treat CM	No CrAg screening	87.3	--	17.57	11.41	1290	--
	CrAg screening	87.5	23.5	17.64	11.46	1300	**180**

[a] Lifetime horizon. [b] Annual discount rate of 3%. * In people with symptomatic CM.

CrAg, cryptococcal antigen; CM, cryptococcal meningitis; LY, life year; undisc, undiscounted; disc, 3% discounted; ICER, incremental cost-effectiveness ratio; YLS, years of life saved; AmB, amphotericin B; FLU, fluconazole; LAmB, liposomal amphotericin B; 5FC, flucytosine.

Serum CrAg screening would be cost-effective in low-resource settings even in populations with low cryptococcal antigenemia prevalence and when more effective CM treatments are available.

- Compared with no screening, serum CrAg screening reduced overall CM deaths by 22.9%, resulting in 0.04 years of life gained (YLG), and was cost-effective (ICER, $200/YLS).
- Among people with asymptomatic cryptococcal antigenemia, serum CrAg screening reduced CM deaths by 39.0%, resulting in 1.14 per person YLG.
- Serum CrAg screening remained cost-effective even with LAmB-based treatment for CM and was more cost-effective in settings that offer FLU monotherapy for CM, due to reduced treatment efficacy of FLU for CM.

Figure 1. CM deaths at 1y per 10,000 PLHIV with CD4 <200/μL entering HIV care with and without serum CrAg screening, by treatment for CM

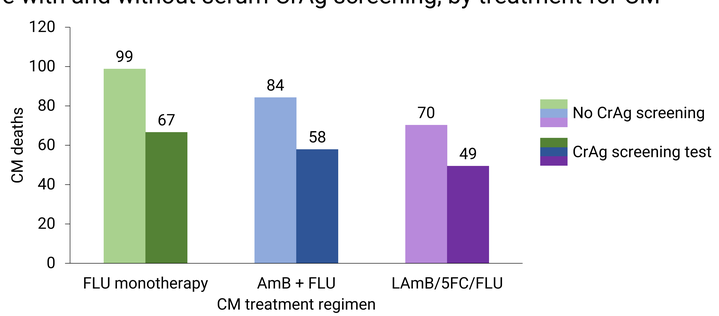
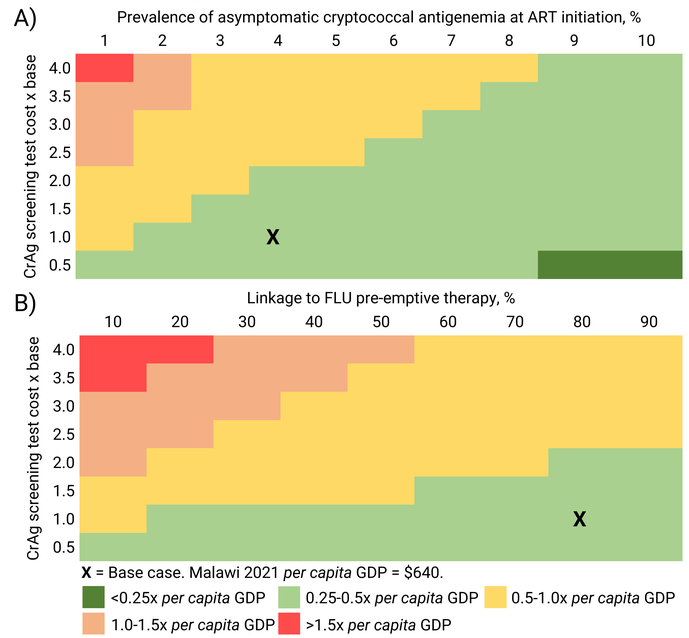


Figure 2. Two-way sensitivity analysis: cost-effectiveness as a function of CrAg screening test cost and (A) asymptomatic cryptococcal antigenemia prevalence, and (B) linkage to FLU pre-emptive therapy



- Sex at birth, serum CrAg sensitivity and specificity, and LAmB cost did not substantially affect cost-effectiveness.

LIMITATIONS

- To model cryptococcal disease within the structure of the microsimulation model, we simplified complex disease processes.
- We include labor and transport costs in the serum CrAg test cost but do not account for initial investments needed to expand access to CrAg.

CONCLUSIONS

- Serum CrAg screening at ART initiation in PLHIV with CD4 <200/μL would offer substantial clinical benefits and would be cost-effective in Malawi.
- Screening would likely remain cost-effective at lower prevalence/linkage, higher test cost, and as better CM treatment becomes available.

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