High Rates of Meningitis or Mortality Among CrAg+ PLHIV with CD4 100-200 cells/mm^3

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BACKGROUND

- Cryptococcal antigen (CrAg) screening with fluconazole prophylaxis prevents cryptococcal meningitis and mortality for people living with HIV (PLWH) with CD4 <100 cells/mm^3.
- Cryptococcal meningitis does occur in individuals with CD4 100-200 cells/mm^3
- There is limited evidence that CrAg screening predicts cryptococcal meningitis or mortality among this group
- WHO clinical guidelines mention it may be reasonable to raise the CrAg screening threshold to 200 cells/mm^3, but do not specify when this would be appropriate.

METHODS

- Prospective cohort study of PLWH 18+ years who had not initiated ART in South Africa.
- We followed participants for 14 months to determine onset of cryptococcal meningitis or all-cause mortality
- Our primary outcomes of interest were all-cause mortality, cryptococcal meningitis, and a combined outcome of mortality or cryptococcal meningitis
- For participants lost to follow-up, we searched the national South African death registry to obtain mortality outcomes
- At study completion, we retrospectively tested stored serum samples for CrAg using an enzyme immunoassay (EIA).
- Analyses were stratified by CD4 count at enrollment (<100 or 100-200 cells/mm^3).

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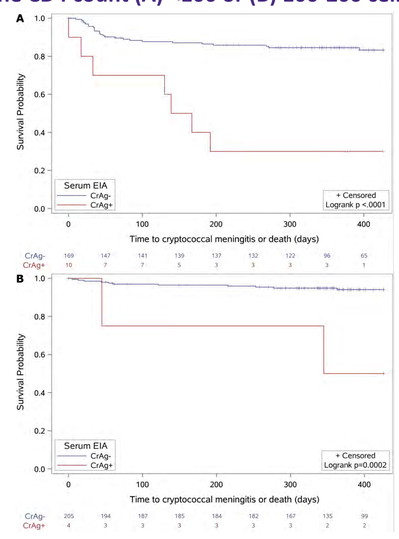
In a cohort of PLWH in South Africa, cryptococcal antigenemia was associated with increased risk of crypotococcal meningitis or death in participants with CD4 100-200 cells/mm^3 (HR 10.0, 95% CI 2.2-45.3)

Table. Study participants at enrollment (N=2,383)

	N (%)
Sociodemographics	
Age (years): mean (SD)	33·1 (9·3)
Female gender	1,372 (57·6)
Education	
None, primary or some high school	1,300 (54·6)
Completed high school or higher degree	1,079 (45·4)
Employed	1,026 (43·0)
Income level (South African rand/month) (N=2,360)	
<2,000 rand (< USD $150)	1,785 (75·6)
>2,000 rand (> USD $150)	575 (24·4)
Clinical and Laboratory Testing	
CD4 count (cells/mm^3): median (IQR)	317 (173, 491)
<100 cells/mm^3	325 (13·6)
100 – 199 cells/mm^3	354 (14·9)
200+ cells/mm^3	1,656 (69·5)
Not available	48 (2·0)
Laboratory-based serum Cryptococcal Antigen EIA (N=1,308)	
Positive	15 (1·1)
Negative	1,294 (98·8)

Time to cryptococcal meningitis or death with baseline CD4 count (A) <100 or (B) 100-200 cells/mm^3



FINDINGS

- We enrolled 2,383 PLWH, and 1,309 participants had serum samples tested by CrAg EIA.
- Of 209 individuals with a CD4 count of 100-200 cells/mm^3 and four (1.9%) tested Crag positive.
- Two of four (IR: 58.8 per 100 person-years) CrAg+ participants and 11 of 205 (IR: 5.6 per 100 person-years) CrAg- participants developed cryptococcal meningitis or died
- In this group the overall rate of death or cryptococcal meningitis that was 10.0-times higher for those who were CrAg+ (95% confidence interval: 2.2-45.3).
- As expected, CrAg positivity was associated with an increased risk of death or cryptococcal meningitis among those with CD4 <100 cell/mm^3

Table. Incidence of cryptococcal meningitis or death within 14 months of enrollment

CD4 count at enrollment	N	Events (n)	py	Incidence Rate[1]	HR (CI)	p=
100-200 cells/mm^3						
CrAg positive	4	2	3.4	58.8	10.0 (2.2, 45.3)	0.003
CrAg negative or indeterminate	205	11	196.2	5.6	Ref	
<100 cells/mm^3						
CrAg positive	10	7	5.1	137.6	6.3 (2.7, 14.6)	<0.001
CrAg negative or indeterminate	169	26	145.8	17.8	Ref	

DISCUSSION

- Few PLWH with moderate immunosuppression screened CrAg positive
- However, a positive CrAg test was predictive of increased risk of cryptococcal meningitis or death
- Systematic CrAg screening may reduce morbidity and mortality in PLWH with CD4 100-200 cells/mm^3.