Maximizing Detection and Improving Outcomes of Cryptococcosis in Rural Tanzania

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BACKGROUND

The World Health Organization recommends pre-antiretroviral treatment (ART) CD4-targeted cryptococcal antigen (CRAG) screening in high burden settings [1]. The use of fluconazole in CRAG+ patients has shown a survival benefit among patients with asymptomatic cryptococcal antigenemia in sub-Saharan Africa [2]. However, implementing CRAG screening only in outpatient settings may both underestimate the true CRAG prevalence and decrease the impact of this strategy.

METHODS

Since October 2013, HIV provider initiated testing and counseling (PITC) is offered to all patients admitted at the medical wards of St Francis Referral Hospital, Ifakara, Tanzania. Lab-reflex CRAG lateral flow assay (LFA) screening is performed in all HIV+ - hospitalized patients and outpatients with CD4 ≤150/µL. All CRAG results are reported electronically and CRAG+ results by phone to the clinician in charge. All CRAG+ patients undergo a lumbar puncture (LP) and CSF CRAG LFA is performed at the bedside of the patient to rule out cryptococcal meningitis (CM). CRAG+ patients are treated with fluconazole tailored for the presence of meningitis, and CM patients also undergo serial lumbar punctures.

We assessed the impact of this strategy on CRAG detection and on mortality / loss to follow-up (LFU) 6 months after CRAG testing. Cox regression was used to identify predictors of death/ LFU after 6-month of CRAG testing.

Table 1: Baseline characteristics of study population

Variable	Total	CRAG –	CRAG +
N	500	468	32
Age, years - median (IQR)	38.7 (33.3-45.6)	38.3 (32.3-45.2)	36.7 (33.6-44.8)
Female gender – n (%)	275 (55)	256 (60)	19 (59)
BMI, kg/m² - median (IQR)	19.8 (17.8-22.1)	19.6 (17.8-22.1)	20.8 (18.9-22.2)
CD4, cells/µl – median (IQR)	58 (23-100)	60 (23-103)	52 (28-67)
0-50 cells/µl – n (%)	220 (44)	205 (44)	15 (47)
51-100 cells/µl – n (%)	156 (31)	142 (30)	14 (44)
101-150 cells/µl – n (%)	124 (25)	121 (26)	3 (9)
Hemoglobin, g/dL – median (IQR)	9.8 (8.4-11.1)	9.8 (8.4 – 11.1)	9.6 (8.2 – 11.2)
eGFR, mL/min/1.73 m²– median (IQR)	126 (107-135.5)	125 (106-136)	127 (118-132)
Tuberculosis diagnosis – n (%)	65 (13)	58 (12)	7 (22)
Xpert MTB/RIF + - n (%)	10 (15)	10 (17)	0 (0)
Xpert MTB/RIF negative – n (%)	18 (28)	14 (24)	4 (57)
Xpert MTB/RIF not done - n (%)	37 (57)	34 (58)	3 (43)
Place of CRAG screening			
Outpatient – n (%)	418 (83.6)	396 (84.6)	22 (69)
Inpatient – n (%)	82 (16.4)	72 (15.4)	10 (31)
CRAG Titer [a]			
≤1:160	-	-	9 (30)
>1:160	-	-	21 (70)
Neurological symptoms – n(%) [b]	73 (14.6)	56 (12)	17 (53)
Fluconazole treatment	-	-	26 (81)
ART initiation – n (%)	382 (76)	359 (78)	23 (72)
Time HIV - CRAG test, days – median (IQR)	1 (0-6)	1 (0-6)	1 (0-3)
Time CRAG+ to LP, days – median (IQR)	-	-	0 (0-0)
Time CRAG+ - fluconazole, days – median (IQR)	-	-	1 (1-16)
Time CRAG test – ART initiation, days – median (IQR)	11.5 (4-24)	10 (4-23)	22 (8-45)

[a] available for 30/32 patients of CRAG+; [b] available for 428 patients

RESULTS

- Of 1976 persons registered from 10/2013 to 07/2015, 500 (25%) ART-naive had CD4 ≤150/ µL, were CRAG screened, and consented to be included in the study, contributing 2965 persons-month follow-up. Median age was 39 years (IQR 33-46), 55% (275/500) were female, median CD4 count was 58 cells/µL (IQR 23-100), and median body mass index was 19.8 kg/m² (IQR 17.8-22.1). Tuberculosis was diagnosed in 13% (65/500) during follow-up, 15.4% (10/65) of them confirmed by Xpert MTB/RIF (Table 1).

- CRAG prevalence was 6.4% (32/500) and 7.7% (30/376) with CD4 counts ≤150 and ≤100 cells/µL respectively. This prevalence was 1.7-fold higher than the 2008-2012 outpatient prevalence in the same cohort (3.7% ≤150 cells/µL, p=0.021) [3]. Inpatients (n=82, 31% of all CRAG+) vs oupatients had a CRAG prevalence of 12% vs. 5.3% (p=0.02) ≤150 CD4 cells/µL and 14.5% vs. 6.2% (p=0.02) ≤100 cells/µL (Table 1).

- Median time from HIV to CRAG testing was 1 day (IQR 0-6). A lumbar puncture was done on the same day of CRAG testing in 97% (31/32) CRAG+, and 39% (12/31) had cryptococcal meningitis, of whom 17% (2/12) without neurologic symptoms.

- CRAG titers were available for 30/32 (94%) CRAG+ patients. Nine (30%) had a CRAG titer >1:160, including 50% (5/10) and 20% (4/20) of patients with and without meningitis respectively (p=0.091).

- Fluconazole tailored for CM presence was started in 81% (26/32) of CRAG+ at a median of 1 day after CRAG diagnosis (IQR 1-16), and in 90% (18/20) of CRAG+ patients without meningitis. ART was started in 72% CRAG+ (23/32) and 76% (382/500) overall.

- Known 6-month mortality did not differ between CRAG-negative and CRAG+ without CM (9.8% vs. 5%, p=0.5) (Figure 1). However, mortality was 67% (8/12) among CM patients (p<0.001), who had been treated with fluconazole mono-therapy in the absence of first-line antifungals in rural Tanzania. LFU was 23% (108/468) for CRAG-negative, 25% (5/20) for CRAG+ without meningitis, and 8.3% for patients with CM (1/12). The overall rate of death/ LFU was 5.5 cases per 100 persons-year (95% CI 4.7- 6.4), with no differences between CRAG-negative and CRAG+ patients without meningitis (5.5 vs 5.8 cases per 100 persons-year respectively). In contrast, patients with meningitis had a rate of death/LFU of 25.06 cases per 100 persons-year (95% CI 13.04 – 48.2).

- Independent predictors of death/LFU at 6 months adjusted for gender and CD4 counts were CRAG+ regardless of CM presence (adjusted hazard ratio (aHR) 2.6), CM (aHR 3.3), no ART initiation (aHR 2.5), tuberculosis diagnosis (aHR 1.8), and hemoglobin (aHR 1.1 per 1 g/dL decrease) (Table 2).

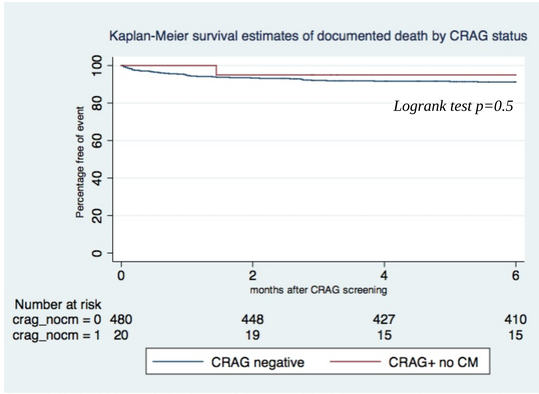

Figure 1. Kaplan-Meier survival estimates of documented death by asymptomatic cryptococcosis

Table 2. Multivariate Cox Regression Analysis of Predictors of Death / LFU (n=500)

	Hazard Ratio	P value	95% CI
CRAG			
Negative	1		
Positive[a]	2.6	0.026	1.1 – 6.1
Cryptococcal meningitis			
No	1		
Yes	3.3	0.025	1.2 – 9.5
ART initiation			
Yes	1		
No	2.5	<0.001	1.6 – 3.7
Tuberculosis diagnosis			
No	1		
Yes	1.8	0.019	1.1 – 3.1
Haemoglobin (per 1g/dL decrease)	1.1	0.003	1.04 – 1.2
CD4 cell counts			
>50 cells/ µl	1		
≤50 cells/ µl	1.4	0.054	0.99 – 1.9
Gender			
Female	1		
Male	1.1	0.586	0.8 – 1.5

[a] CRAG+ regardless of the presence of meningitis

CONCLUSIONS

- Implementation of routine HIV PITC plus lab-reflex CRAG screening both among out- and hospitalized-patients resulted in a 1.7-fold increased and rapid detection of CRAG and meningitis compared to previous years.
- Six-months mortality did not vary between CRAG+ without meningitis treated with pre-emptive fluconazole and CRAG-negative patients.
- Mortality of cryptococcal meningitis was high but within the reported ranges in the region, further stressing the need for early HIV and CRAG diagnosis. Wide availability and access to first-line antifungals is desperately needed in sub-Saharan Africa.
- These results provide a model of a feasible, highly effective and scalable CRAG screening and treatment strategy integrated into routine care in rural sub-Saharan Africa.

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