Cryptococcal Antigenemia in Severe Immunocompromised HIV Patients in Rural Tanzania: A preventable cause of early mortality

Matthias C. Müller[1,6], Alex J. Ntamatungiro[2], Namvua Kimera[2], Hansjakob Furrer[3], Manuel Battegay[4], Marcel Tanner[1], Christoph Hatz[1], David R. Boulware[5], Tracy R. Glass[1], Emilio Letang[1]

1) Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland 2) Ifakara Health Institute, Ifakara, Morogoro, United Republic of Tanzania 3) University Hospital Bern, Division of Infectious Diseases, Bern, Switzerland 4) University Hospital Basel, Division of Infectious Diseases and Hospital Epidemiology, Basel, Switzerland 5) University of Minnesota, Minneapolis, USA 6) Center for Infectious Diseases and Travel Medicine, Department of Medicine, Medical center - University of Freiburg, Germany

Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

Associated Institute of the University of Basel

Background:

- Cryptococcal meningitis is a leading cause of death in people living with HIV/AIDS in sub-Saharan Africa.[1]
- WHO recommends pre-antiretroviral (ART) cryptococcal antigen (CrAg) screening for persons with CD4 < 100 cells/µl.[2]
- Aim of this study: to explore the potential impact of this strategy in Tanzania by assessing the prevalence and outcome of cryptococcal antigenemia in a rural region of southern Tanzania.

Methods:

- Retrospective study including all patients prospectively enrolled in the Kilombero and Ulanga ART Cohort (KIULARCO) in Tanzania with:
  - Pre-ART visit between Jan 1, 2008 and Dec 31, 2012
  - Age > 5 years old
  - CD4 cell count < 150 cells/µl
  - Availability of cryopreserved pre-ART plasma sample
- Samples were tested for CrAg and titres using lateral flow assay (Immy, Norman, Oklahoma).
- Statistical analysis: logistic and Cox regression to estimate the association between CrAg status and covariates with a composite outcome of death or lost to follow-up (LFU) after one-year follow-up.

Results:

- Of 801 eligible patients, 29 (3.6%) were CrAg+, corresponding to a stratified prevalence of:
  - CD4 < 50 cells/µl: 6.1% (18/293)
  - CD4 51-100 cells/µl: 2.3% (6/263)
  - CD4 101-150 cells/µl: 2% (5/245)
- The median pre-ART CrAg titre among CrAg+ patients was 1:320 (interquartile range 1:20, 1:2560).

Table 1: Baseline Characteristics of individuals included in the analysis

Variables	Total	CrAg –	CrAg +
Age, years - mean (SD)	38.6 (11.5)	38.7 (11.6)	38.1 (8.1)
Female, %	58.5%	59%	41%
BMI, kg/m² - mean (SD)	20.0 (3.6)	20.1 (3.6)	18.7 (2.4)
CD4, cells/µl, median (IQR)	71 (35-109)	71 (35-110)	36 (21-71)
Fluconazole treatment, % (n)	-	-	48% (14)
ART received, %	85.6	88.5	89.6

Table 2: Association with Lost to Follow-up or Death at one year, using a logistic regression model

	Adjusted/ Multivariate model		Unadjusted/ Univariate model	
Variables	OR (95% CI)	P-value	OR (95% CI)	P-value
CrAg+	3.2 (1.35-7.34)	0.008	3.59 (1.30-9.90)	0.014
Age	1.01 (1.00-1.02)	0.139	1.01 (1.00-1.02)	0.345
Female	0.92 (0.68-1.25)	0.615	0.77 (0.58-1.03)	0.075
CD4 <100/µl	1.59 (1.15-2.19)	0.006	1.50 (1.10-2.03)	0.009
No ART	7.73 (4.53-13.18)	<0.001	7.01 (4.19-11.73)	<0.001
Constant	0.39 (0.16-0.90)	0.028		

- Within one year, 72.4% (21/29) of CrAg+ patients died or were LFU compared with 47.2% (364/772) of CrAg-negative patients (p=0.008), with no differences across CD4 strata (p=0.689).
- CrAg+, CD4 count < 100 cells/µl, and not receiving ART independently predicted death or LFU during the first year of follow-up (Table 2).
- Symptoms of cryptococcal meningitis were recorded in 41% (12/29) of CrAg+ patients and cryptococcal meningitis was clinically diagnosed in 10 of them. The remainder showed no pre-ART neurological symptoms, and outcomes were similar between symptomatic and asymptomatic patients (76% vs. 66% death or LFU at one year follow-up respectively, p=0.6).

Contact: emili.letang@unibas.ch
Swiss TPH, Socinstrasse 57, P.O. Box, 4002
Basel, Switzerland. www.swisstph.ch

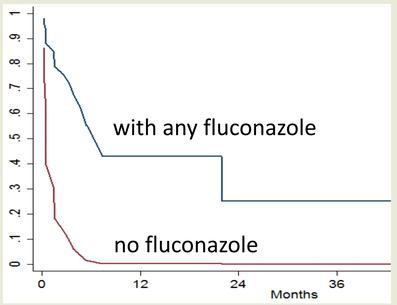


Figure 1.: Survival of asymptomatic, CrAg+ HIV-infected patients starting ART by antifungal treatment status, adjusted for CD4 cell count.

Table 3: Risks of Lost to Follow-up or Death among asymptomatic CrAg+, HIV-infected patients, using a multivariate Cox proportional hazards model

	Adjusted model (n= 15 events)	
Variables	HR (95% CI)	P-value
Fluconazole	0.16 (0.04-0.67)	0.012
CD4 >100/µl	0.28 (0.06-1.33)	0.109
ART	1.03 (0.21-5.11)	0.971

- Fluconazole given at physician discretion decreased the proportion of death/LFU among CrAg+ patients (80% without treatment, 60% with 100-200 mg daily, and none with 800 mg daily, p=0.012).
- In CrAg+, neurologically asymptomatic HIV-infected patients, fluconazole treatment reduced significantly the risk of LFU or death (Table 3, Fig.1).

Conclusions:

- CrAg was prevalent and an independent predictor of LFU/death
- Pre-emptive treatment with fluconazole among CrAg+ persons may reduce early mortality after ART initiation in rural Tanzania.
- CrAg screening and pre-emptive fluconazole would be cost-effective given this prevalence based on previous literature.[3]
- Targeting patients with < 100 CD4 cells/µl may decrease the potential impact of this strategy compared to <150 CD4 cells/µl.

Bibliography:

1) Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. *AIDS*. 2009; 23(4):525-30.
2) Rapid advice: Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Geneva, World Health Organization,2011
3) Rajasingham R, Meya DB, Boulware DR. Integrating cryptococcal antigen screening and preemptive treatment into routine HIV care. *JAIDS* 2012; 59:85-91.