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Prospective cohort of AIDS patients screened for cryptococcal antigenaemia, pre-emptively treated and followed in Midwest Brazil V.2

PLOS One

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1 Works for me dx.doi.org/10.17504/protocols.io.22fggbn

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ABSTRACT

This is a study carried out in partnership with of the Brazilian Cryptococcosis Network. It is the implementation of cryptococcal antigen (CRAG) screening and preemptive anti-fungal therapy of HIV-infected persons with advanced immunosuppression (CD4<200 cells/μl). It aime to evaluate the prevalence of CrAg antigenemia, its associated factors and to measure outcomes of CrAg positive and negative subjects.

The participants will be recruited from June 2015 to July 2018 and followed through December 2019. Outpatients and inpatients assisted at the Tropical Diseases State Hospital “Dr. Anuar Auad”, in Goiânia, State of Goiás, Brazil, will have a serum CRAG performed by lateral flow assay. The population will be composed by adults, with HIV diagnosis, with a CD4 count ≤200 cells/μL, regardless of symptoms and with no history of cryptococcal disease. Lumbar puncture will be performed in every CrAg-positive individual to rule out cryptococcal disease.

Those who are CRAG-positive and have no CNS involvement will be treated pre-emptively with high dose fluconazole. Six months and 12 months after the end of recruitment period, the medical records will be reassessed for information of survival with retention-in-care in CRAG positive and CRAG negative and comparisons between groups.

EXTERNAL LINK

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THIS PROTOCOL ACCOMPANIES THE FOLLOWING PUBLICATION

Borges MASB, Filho JAdA, Oliveira BdJS, Moreira IS, Paula VVd, Bastos ALd, Soares RdBA, Turchi MD (2019) Prospective cohort of AIDS patients screened for cryptococcal antigenaemia, pre-emptively treated and followed in Brazil. PLoS ONE 14(7): e0219928. doi: 10.1371/journal.pone.0219928

1 **Study Type**: Prospective cohort

2 **Objectives**

Estimate the prevalence of cryptococcal antigenemia in an AIDS population from the Midwest of Brazil
Identify socio-demographic factors potentially associated with CrAg+;
Identify clinical and laboratory aspects potentially associated with the CrAg+
To evaluate the percentage of cryptococcal meningitis among patients with CrAg+
To mesure outcomes of CrAg+ and CrAg- subjects

3 **Outcomes** - **Primary**

Retention in care before/after CRAG screening implementation
Adherence to ART
Resistance to current ARV
Time to undetectable viral load after recruitment
Adherence to treatment (pre-emptive fluconazole or amphotericin regime)

4 **Outcomes - Secondary**

Survival time among CRAG+ vs. CRAG negative persons with CD4<200 cells
Cryptococcal meningitis-free survival time in those who are CRAG positive and treated regularly or irregularly with fluconazole compared to CRAG-negative persons with CD4<200
Cryptococcal meningitis survival time
All-cause discontinuation of fluconazole
Opportunistic diseases during follow up
Cause of death

5 **Inclusion Criteria:**

Laboratory confirmed diagnosis of HIV-1 infection
CD4<200 cells/µL measured in the last 6 months
Age ≥18 years
With or without neurological symptoms
Hospitalized or outpatient
Regardless of antiretroviral therapy (ARV) experience or adherence

6 **Exclusion Criteria:**

Prior known history of cryptococcal disease
Current known pregnancy

7 **Consent Form**

The interviewee will be informed that acceptance or refusal will not interfere with their regular follow-up at the service. After agreeing to participate, the written informed consent will be collected. The individuals allow the use of anonymous data for future scientific publications

8 **Recruitment**

The recruitment of participants will be made by two strategies:
1)Outpatient and in patients who fulfilled inclusion criteria and have no cryptococcal disease previously diagnosed, will be enrolled. A medical appointment will be scheduled. The structured interview will be performed by the assistant physician or a medical researcher.

9 **Recruitment**

2)The Central Laboratory of Public Health confidentially provide researchers with a list of patients with CD4 <200 cells/µL assisted in the service in question.A first chart review will be performed, aiming to clarify history of cryptococcosis or death. A medical appointment will be scheduled with a medical researcher for the interview.

10 **Structured Interview**

During the scheduled visit or assistant physician evaluation, the main purpose of the study will be explained to the participant or legal reponsable. The risk of opportunistic diseases including cryptococcosis because of low cd4 count will be explained. The patients will be informed about the diagnostic test to be performed - serum CrAg using Lateral Flow Aassay (Immuno-Mycologics Inc®).

The structured interview is based on an adapted form from the Brazilian Cryptococcosis Network. Socio-demographic, clinical and laboratory data will be accessed.

FICHA DE COLETA DE DADOS PROJETO CRAG

NOME														
DN	__/___/_____			IDADE (ANOS)			SEXO	1. M	2. F					
PRONTUÁRIO				RG OU CPF										
NATURALIDADE				ESTADO		NACIONALIDADE		1. BRA	2. OUTRO					
DATA ENTRADA NO ESTUDO		__/___/_____												
LOCAL DE ENTRADA NO ESTUDO	1. AMBULATÓRIO		2. ENFERMARIA	3. PS/EMERGÊNCIA		4. OUTRO								
SINTOMAS SISTÊMICOS (PODE MAIS DE 1)	1. SIM	2. NÃO												
	1. FEBRE		2. PERDA DE PESO											
	3. DIARRÉIA		4. SINTOMAS PULMONARES											
	5. LESÕES DE PELE		6. FRAQUEZA/ASTENIA											
	7. MONILÍASE ORAL		8. OUTROS											
SINTOMAS NEUROLÓGICOS (NO MOMENTO DA PESQUISA, PODE MAIS DE 1)	1 . SIM	2. NÃO												
QUAIS	1. CEFALÉIA	2. CONVULSÕES	3. SONOLÊNCIA											
	4. CONFUSÃO MENTAL	5. HEMIPARESIA	6. PARAPARESIA											
	7. ALTERAÇÃO ESFINCTERIANA	8. PARESTESIAS	9. DISESTESIAS											
	10. ALTERAÇÃO VISUAL	11. ALTERAÇÃO AUDITIVA	12. ALTERAÇÃO DE MEMÓRIA											
	13. DISARTRIA	14. TONTURA/VERTIGEM	15. OUTROS											
ANTECEDENTES OUTROS														
DIAGNÓSTICO PRÉVIO DE HIV	1. SIM	2. NÃO	3. NÃO SABE INFORMAR/IGNORADO											
	DATA OU HÁ QUANTO TEMPO	__/___/_____												
JÁ TEVE DOENÇA OPORTUNISTA ASSOCIADA AO HIV?	1. SIM	2. NÃO												
	DATA	3. NÃO SABE INFORMAR/IGNORADO	DATA											
PODE MAIS DE 1	DATA													
1. TB DISSEMINADA	2. CANDIDÍASE ORAL/ LEUCOPLASIA	3. PNEUMOCISTOSE												
4. HISTOPLASMOSE	5. TB PULMONAR	6. HERPES ZOSTER												
7. TOXOPLASMOSE SNC	8. CMV	9. DISFUNÇÃO DO SNC												
10. DIARRÉIA POR MAIS DE 1 MêS	11. PERDA DE PESO/CAQUEXIA	12. ASTENIA > 1 MêS												
13. DERMATITE PERSISTENTE	14. ANEMIA/LINFOPENIA/PLAQUETOPENIA	15. TOSSE PERSISTENTE OU PNM												
16.LINFADENOPATIA > 1CM	17. SARCOMA DE KAPOSI													
OUTRAS:														
CD4+ MAIS PRÓXIMO DA COLETA	ABSOLUTO		PORCENTAGEM	DATA										
CARGA VIRAL	ABSOLUTO		LOG	DATA										
NADIR DE CD4+	ABSOLUTO		PORCENTAGEM	DATA										
INICIOU TARV	1. SIM	2. NÃO	DATA DO 1º ARV NO SICLOM	RETIROU NOS ULTIMOS 3 M?										
ESTÁ EM ABANDONO?	1. SIM	2. NÃO	REINICIOU QUANDO?	1. SIM	2. NÃO									
USO REGULAR	1. SIM	2. NÃO	DATA DA ÚLTIMA RETIRADA	DATA:										
EXAMES LABORATORIAS (DATA MAIS PRÓXIMA À ENTRADA)														
	HB		HT		LEUCO		PLAQUETAS							
	URÉIA		CREAT		NA		K							
	PROT T		ALBUMINA		GLOBULINA									
RESULTADO DO ANTÍGENO CRIPTOCÓCICO SÉRICO	1. REAGENTE	2. NÃO REAGENTE	3. INDETERMINADO											
Se positivo, coletar LCR e fazer CrAg – preencher próxima ficha														
HEMOCULTURA PARA FUNGOS COLETADA	DATA													
1. NEGATIVA	2. POSITIVA PARA CRYPTOCOCCUS		3. POSITIVA PARA HISTOPLASMA											
	4. POSITIVA PARA CANDIDA		5. POSITIVA PARA BACTÉRIA											
OUTROS EXAMES RELEVANTES														
DESFECHO		1. em seguimento	2. abandono, perda de seguimento, ignorado		3. óbito no HDT									

Etapa II- Para pacientes da etapa I que tiveram LFA positivo no soro:

Resultados de punção lombar	LCR 1 (primeiro)	LCR 2	LCR 3	LCR 4	LCR 5	LCR 6	LCR 7 (último)
DATA							
PI / PF (cmH_20)							
Celularidade PMN / MN Eos/Baso/Plasmo							
Glicose							
Glicose LCR / soro							
Proteínas							
Gram							
Látex bacterias							
Cultura bactérias							
LFA (teste CrAg)							
Cultura fungos							
Tinta da China							
VDRL / HÁ, ELISA ou FTA-Abs							
ADA							
BAAR							
Cultura micobact.							
PCR							
Outros							

b-Exames de imagem:

RX/ CT/ RM de tórax:_____

_____Data: ___/___/___

CT / RM de crânio (admissão): _____

_____Data: ___/___/___

CT / RM de crânio (última):_____

_____ Data: ___/___/___

c-Diagnósticos (durante a internação ou avaliação ambulatorial):

Neurológicos: Meningite criptocócica (_) outro/s: _____

Não Neurológicos: Fungemia criptocócica( ) outros:_____

d- Tratamento recebido: Indução: Anfotericina: dose/dia: _____, Dias: _____, Dose Acumulada

Fluconazol: dose/dia: _____, Dias/semanas: _____,

Consolidação: dose/dia: _____, Dias/semanas: _____,

Manutenção: dose/dia: _____, Dias/semanas: _____,

Se foi diagnosticada meningite criptocócica:

Houve hipertensão intracraniana?: (sim) (não) (não informado)

Recebeu punções diárias de alívio?: (sim) (não)

Fez neurocirurgia?: (sim) (não). Se sim, qual?_____ Data ___/____/____

e- Evolução clínica (durante a internação ou acompanhamento ambulatorial):

(melhor) (igual) (pior) (seqüela).

Especificar:_____

f-Desfecho: (alta) (perda de seguimento) (óbito). Causa direta do óbito:_____Data:___/____/____

Variables: age, sex, time of HIV diagnosis, CD4 cell count, HIV viral load, ART history, previous opportunistic infections and current systemic or neurological symptoms.

General symptoms: fever, weight loss, asthenia, pulmonary symptoms, diarrhoea

Neurological symptoms: headache, convulsions, changed mental state, dizziness, and visual or auditory deficit.

11 Recruitment - Chart review

Physical and electronic medical records will be accessed at the beginning of the study, objecting personal and laboratory background.

12 Laboratory exams

The participantswill then referred to the hospital's internal laboratory for venipuncture and laboratory tests.

- serum CrAg, fungal blood culture, blood count, proteinogram, urea, creatinine.
- cerebrospinal fluid (CSF) rotine, fungal culture, India Ink, CrAg in CSF

The CrAg LFA test result will be available in up to 24 hours. The local laboratory will informe the researcher when the CrAg test was positive.

13 Management - CrAg negative

The CrAg negative patients will be referred to the attending physician for follow-up and culture exams will be checked in the first 30 days.

14 **Management - CrAg positive**

Patients with positive antigenemia will be called up to an appointment with the researcher or the attending physician to rule out CNS involvement. A lumbar puncture will be performed with CSF analysed. The risks of the procedure will be clarified.
CSF analysis: biochemistry, cellularity, India ink, direct research and culture for bacteria, fungi and mycobacteria and CrAg by LFA.
When the rachimanometer is available, the intracranial pressure will be measured

15 **Management - CrAg positive**

During couple months after the enrollment date, all positive subjects will be reassessed in at least 2 medical consultations with the researcher: for initial orientation and prescription of preemptive treatment (WHO Guideline 2018) and for assessing adherence.

In the presence of cryptococcal meningitis, subjects receive treatment with amphotericin + fluconazole

16 The follow-up will be maintained according to service routine.
Chart review (physical and electronic medical records) will access outcomes at the end of recruitment period, in 6 and 12 months for follow-up evaluation.