



# High Prevalence of Cryptococcal Antigenemia among HIV-infected Patients Receiving Antiretroviral Therapy in Addis Ababa, Ethiopia

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**INDEPTH Network**  
Better Health Information for Better Health Policy

**ISC 2015 Addis Ababa**

**11 - 13 November 2015**



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# OUTLINE

Introduction

Objective

Methods

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Conclusion & Recommendations





# Introduction

- Cryptococcosis is caused by an encapsulated yeast
  - *Cryptococcus neoformans*
- The portal of entry is the respiratory tract
  - Resulting in a pulmonary cryptococcosis- inapparent clinical course



# Introduction cont'd

- Preconditions for haematogenously dissemination to other organs, especially to CNS
  - Primary diseases that weaken the immune defenses
- Despite limited data, it is estimated there are > 700,000 cases of Cryptococcal Meningitis (CM) in SSA annually resulting in > 500,000 deaths with ~70% case fatality rate



# Introduction cont'd

- Cryptococcal antigenemia preceded symptoms by a median of 22 days add to the scientific rationale of a screen and treat strategy (French, N., et al., 2002)
  - WHO guideline recommend screening in high prevalence RLS among those with  $CD4 < 100$  cells/ $\mu$ l (WHO, 2011)
- ART alone is insufficient treatment for CRAG-positive persons (Meya, D.B., et al., 2010)
- Immune-mediated clearance, becomes less likely as antigen titer increases (Jarvis N, et al., 2009)



# Introduction cont'd

- Despite these facts **CRAG screening is not routine** in Ethiopia
- There is lack of published data on the rate of cryptococcal antigenemia in HIV-infected patients in Ethiopia
- ❖ Provide **baseline data** on the rate of cryptococcal antigenemia for further studies on the clinical impact of using cryptococcal antigenemia screening

# Objective



- To determine the prevalence of Cryptococcal antigenemia and to assess associated factors among HIV-Infected patients attending Black Lion and ALERT Hospital ART clinics in Addis Ababa, Ethiopia





# Methods

- Study Design and Patients

- A **cross sectional study** was conducted among adult HIV-infected patients with  **$CD_4 \leq 200/\mu l$** - irrespective of ART status

- Consecutive patients were enrolled between May and August 2011 from the outpatient ART clinics of both Black Lion and ALERT hospital



# Methods cont'd

- **Inclusion Criteria**

- CD<sub>4</sub> count  $\leq 200/\mu\text{l}$

- **Exclusion Criteria**

- Treated for Cryptococcal infection in last 3 months

- Taking systemic antifungal agent at time of visit



# Methods cont'd

- **Ethical Considerations**

- Written informed consent was obtained from all study participants
- Approved by
  - AHRI/ALERT IRB
  - Emory university IRB
  - AAU Medical Faculty research and ethics review board
- Result was communicated to the treating physician



# Methods cont'd

## ■ Data Collection

- Patient interview, physical examination and medical chart review
  - Demographics
  - Clinical signs and symptoms
  - Medical history (opportunistic infection, ART use, most recent CD4 count)
- Laboratory Testing
  - A Cryptococcal Antigen Latex Agglutination Test (CALAS Meridian) was performed (according to the Insert)



# Methods cont'd

- **Data Analysis**

- Data was entered into an **online REDCap** database and analyzed using SAS version 9.3
- Univariate & multivariate logistic regression analyses were performed to assess risk factors for a positive cryptococcal Ag test result
- Risk factors with possible significance or those with biologic plausibility and known to be associated with cryptococcal disease were included in the model

# Result & Discussion



- **Patients and antigen screening**
  - A total of 369 HIV-infected patients were enrolled
  - The mean age was 36 years and 56% were female
  - Majority of patients were on ART (74%) and had been receiving for a mean duration of 34 months
  - The mean CD<sub>4</sub> count was 123 cells/ $\mu$ l and 31% had a CD<sub>4</sub> count less than 100 cells/ $\mu$ l
  - 25% of them had history of prior pulmonary and extra pulmonary tuberculosis (9%)



## Patients and Ag screening...

- Of the 369 patients, 31(8.4%) were positive for cryptococcal antigen test (CrAg)
  - The overall prevalence of 8.4% is in line with results from Uganda (5-9%), South Africa (13%), and Kenya (6%)
  - Limited data despite its similar mortality rate with TB in SSA HIV patients ([Park BJ et al., 2009](#))



# Patients and Ag screening...

- All antigen titers were  $\geq 1:8$ 
  - May indicate the possibility for the development of symptomatic cryptococcal disease
  - Higher Ag titers were predictor for the development of CM & IRIS after commencement of ART (Jarvis N, et al., 2009; Jarvis N, Harrison TS, 2007; Pongsai P, et al., 2010)





## Patients and Ag screening...

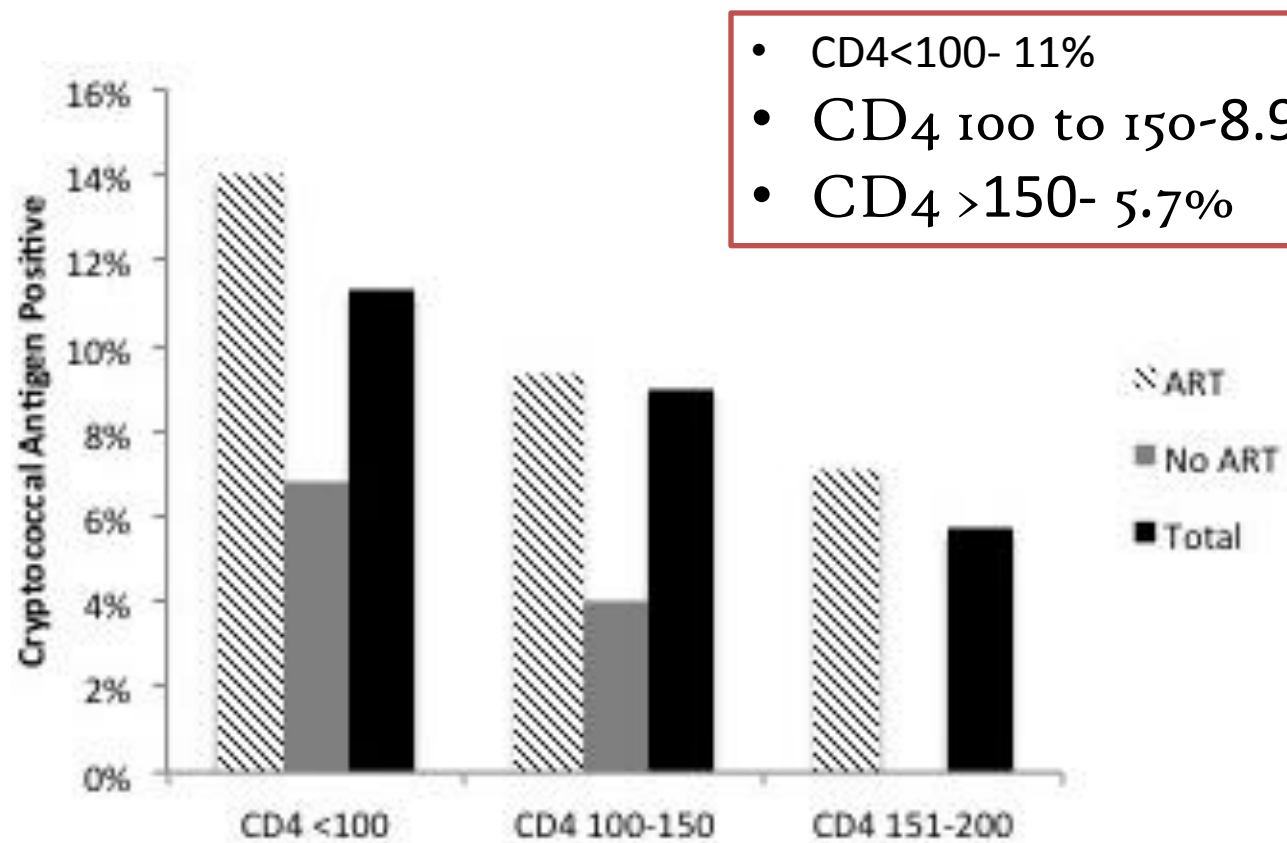
- 26 (84%) of 31 patients with a positive CrAg test were receiving ART for a mean duration of 37 months
  - Lack of HIV viral load data on these patients may limit to base screening recommendations on ART response



# Result & Discussion cont'd

- In contrast to prior studies done in SSA (Jarvis JN et al, 2009; Liechty CA et al, 2007), high prevalence **18(7.1%)** was found among patients with CD4 counts 100-200 cells/ $\mu$ l
  - Which calls into question whether screening recommendations should be expanded to include patients with CD4 counts <200 cells/ $\mu$ l
  - But inclusion of patients already on ART in our study might be a factor

# Result & Discussion cont'd



- CD4<100- 11%
- CD4 100 to 150-8.9%
- CD4 >150- 5.7%

Figure 1. Percentage of HIV Infected Patients with Cryptococcal Antigenemia by CD4 count and Antiretroviral Use



**Table 1. Univariate and Multivariate Analysis of Risk Factors for Cryptococcal Antigenemia among HIV infected patients in Addis Ababa, Ethiopia (n=369)**

| Characteristic                       | Univariate Analysis |      | Multivariate Analysis |              |
|--------------------------------------|---------------------|------|-----------------------|--------------|
|                                      | OR (95% CI)         | P    | OR (95% CI)           | P            |
| Age, per year                        | 1.05 (1.01-1.09)    | 0.02 | 1.05 (1.002-1.09)     | <b>0.04</b>  |
| Male                                 | 2.12 (1.00-4.51)    | 0.05 |                       |              |
| <b>Site 1 vs. 2</b>                  | 4.05 (1.20-13.63)   | 0.02 | 5.49 (1.57-19.16)     | <b>0.01</b>  |
| <b>BMI &lt;18.5 kg/m<sup>2</sup></b> | 0.39 (0.13-1.13)    | 0.08 | 0.32 (0.10-0.98)      | <b>0.046</b> |
| Currently employed                   | 1.33 (0.62-2.87)    | 0.46 | -                     | -            |
| On ART                               | 1.91 (0.71-5.10)    | 0.20 | 2.60 (0.91-7.45)      | 0.08         |
| <b>CD4 count status</b>              |                     |      |                       |              |
| <b>&lt;100</b>                       | 2.08 (0.83-5.21)    | 0.34 | 2.81 (1.06-7.47)      | <b>0.04</b>  |
| 100-150                              | 1.60 (0.61-4.20)    | 0.11 | 1.81 (0.65-5.04)      | 0.26         |
| 151-200                              | 1.00                | -    | 1.00                  | -            |
| <b>Symptoms</b>                      |                     |      |                       |              |
| <b>Fever</b>                         | 2.14 (0.98-4.67)    | 0.06 | 2.95 (1.26-6.87)      | <b>0.01</b>  |
| Headache                             | 1.04 (0.46-2.35)    | 0.56 | -                     | -            |
| Photophobia                          | 1.46 (0.41-5.18)    |      |                       |              |
| <b>Signs</b>                         |                     |      |                       |              |
| Fever (≥ 38.3 °C)                    | 1.22 (0.45-3.33)    | 0.70 | -                     | -            |
| Meningismus                          | 3.71 (0.37-36.79)   | 0.27 |                       |              |

BMI, body mass index; ART, antiretroviral therapy; OI, opportunistic infection



# Result & Discussion cont'd

- After controlling for ART use and CD<sub>4</sub> count
  - Patients at site 1 as compared to site 2 were more likely to have cryptococcal antigenemia (aOR 5.49, 95% CI 1.57-19.16)
- Catchment area of site one- more verdant areas on the outskirts of Addis compared to site two
  - Favorable ecological habitat of *C. neoformans*- rotting wood and trees (including eucalyptus) and soil contaminated by bird guano ([Chowdhary A et al., 2012](#); [Ellis H et al., 1990](#))



# Result & Discussion cont'd

- Persons who reported a fever were more likely to have cryptococcal antigenemia (aOR 2.95, 95% CI 1.26-6.87)
- But 64% of positive patients reported no fever and 48% reported a lack of any symptoms
  - Consistent with other SSA studies (Liechty et al., 2007, Jarvis et al., 2009)- indicated relatively high rates of asymptomatic cryptococcosis



**Table 2. Predicting Cryptococcal Antigenemia Based on the Presence of Individual or Combination of Clinical Symptoms (n=369)**

| Symptom(s)                       | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|----------------------------------|-----------------|-----------------|---------|---------|
| Fever                            | 36              | 80              | 14      | 93      |
| Headache                         | 29              | 72              | 9       | 92      |
| Photophobia                      | 10              | 93              | 12      | 92      |
| Night Sweats                     | 23              | 81              | 10      | 92      |
| Fever, Headache, or Photophobia  | 42              | 62              | 10      | 92      |
| Fever, Headache, and Photophobia | 9               | 97              | 3       | 92      |

- **Poor sensitivity:**
  - Individual symptom (10-36%), combination of symptoms (9-42%)
- **Less than optimal specificity:**
  - Individual (72-93%), combinations of symptoms (62-97%)



# Result & Discussion cont'd

- Our findings are similar to results from a prior study conducted in Uganda ([French N et al., 2002](#))
  - Adult HIV infected patients with low CD4 counts in high burdened settings should be **screened for cryptococcal antigenemia regardless of symptoms**
- Meya et al. demonstrated pre-emptive therapy with fluconazole in asymptomatic CrAg positive patients as cost effective intervention ([Meya DB, et al., 2010](#))





# Limitations

- Viral load testing was not available
- There was absence of lumbar puncture for CrAg positive patients
- The study took place at only two hospital HIV clinics in Addis Ababa

# Conclusion & Recommendations



- We found a previously unreported high prevalence of cryptococcal antigenemia with CD4 counts  $\leq 200$  cells/ $\mu$ l, including those on ART
- No utility of symptom screening in disease detection



# Recommendations Cont'd

- It indicates **the need to scale up cryptococcal disease screening** among HIV-infected persons and suggest it may be beneficial to expand current cryptococcal screening recommendations
- Further large-scale studies of cryptococcal disease are currently underway in South Africa and are needed in Ethiopia to better understand the true extent of disease burden



# Acknowledgement

- Sponsors
  - AHRI/ALERT
  - Emory University Global Health Institute
  - AAU-ALIPB
- INDEPTH Network
- ISC-2015 Scientific Programme Committee
- Haramaya University

# Thank You!



**Semen Mountain**



**Bule Nile Fall**



**Awash National Park**



**Dallo Depressio**



**Axum Obelisk**



**Lalibella**



**Fasil Castel: Gondar**



**Lucy: Australopithecus afarensis**



**Ephany**



**Easter and Christ-Mas**



**Finding of the True Cross**



Natural & old civilization Heritages

Religious festivals

20 nicity



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