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Low Prevalence of Cryptococcal Antigenemia among Patients Infected with HIV/AIDS in Haiti

Frantz Jean Louis[1]*, Jocelyne Alboth Andre[2], Georges Perrin[1], Jean Wysler Domercant[1], Kesner Francois[2], Daniella Azor[2], Josiane Buteau[2], Jacques Boncy[2], Robert Burris[1], David W Lowrance[1] and Barbara J Marston[3]

[1]*Centers for Disease Control and Prevention, Port-au-Prince, Haiti*
[2]*Government of Haiti, Port-au-Prince, Haiti*
[3]*Centers for Disease Control and Prevention, Atlanta, Georgia, USA*

Abstract

Cryptococcal meningitis is a common opportunistic infection among persons with advanced HIV-associated immunosuppression and is associated with high mortality. The prevalence of asymptomatic cryptococcal antigenemia (CrAg) can inform the potential utility of screening and pre-emptive treatment prevention strategies. We assessed CrAg prevalence in a cohort of patients infected with HIV at 28 health facilities from February to September 2014 in order to inform Haitian national clinical guidelines. Of 13,000 patients that underwent CD4 cell count, 1,025 (7.9%) had a count ≤200 cells/mm^3. Of these, 11 (1.1%) were CrAg positive. The CrAg positivity rate among patients with CD4 cell counts <100 cell/mm^3 was 1.8%. Patients with CD4 cell counts <50 cells/mm^3 had the highest CrAg rate (2.3%). CrAg prevalence was low but still warranted a CrAg screening and pre-emptive therapy approach for people infected with HIV with CD4 cell counts <100 cell/mm^3 in Haiti.

Keywords: Cryptococcal meningitis; Cryptococcal antigen; Lateral flow assay; CD4 cell count; Test and treat

Introduction

Cryptococcosis usually manifests as meningitis (CM) and is generally seen in persons with advanced HIV infection and CD4 cell counts <200 cells/mm^3 [1]. Global estimates suggest that there were about 1 million new cases and at least 500,000 deaths worldwide due to HIV-associated cryptococcosis in 2009 [2]. In developing countries, clinical outcomes are very poor for persons with CM, even when the best available therapy is provided [1,3-5]. Cryptococcosis accounts for between 13% and 44% of deaths among people living with HIV (PLHIV) in resource-limited countries (RLC) [4,6,7]. Limited information is available on the prevalence of cryptococcosis in the Latin American and Caribbean region. The only population-based estimated incidence of cryptococcosis in the Caribbean, reported in 2007, assumed the incidence in the Caribbean to be the same as in Latin America (3.4% per year) [2]. In 2000, Deschamps et al., found a prevalence of CM of 4% in a small cohort of 42 patients infected with HIV in Haiti [8].

Early detection and treatment may be the most cost-effective and easily implemented approach to improve clinical outcomes of CM [9]. Overt cryptococcosis is frequently preceded by asymptomatic cryptococcal infection, which is easily diagnosed by detection of cryptococcal antigen (CrAg) in the serum or cerebrospinal fluid (CSF). Asymptomatic antigenemia has been documented in 4-12% of PLHIV initiating ART [5,10,11]. A substantial proportion of patients with asymptomatic antigenemia later develop overt CM or other evidence of systemic disease, even when ART is provided [11,12]. CrAg is detectable in serum a median of three weeks before the onset of CM symptoms [7]. CrAg screening can help identify individuals who would benefit from pre-emptive treatment of cryptococcal infection prior to ART initiation [13]. A FDA-approved lateral flow immunoassay (LFA) (Immuno-Mycologics, Inc., Norman, OK, USA; ABACUS ALS, Australia) to detect CrAg in serum and plasma has been widely used with reported high sensitivity and specificity [14]. Routine screening of asymptomatic patients with CD4 cell counts <100 cells/mm^3 at ART initiation coupled with preemptive therapy for positive CrAg in Cambodia and Kenya was shown to be cost-effective in reducing the incidence of cryptococcosis, preventing CM and increasing life expectancy [11,15].

The World Health Organization (WHO) recommends to consider the implementation of CrAg screening and pre-emptive anti-fungal therapy in patients with a positive test among pre-ART adults with a CD4 cell count <100 cell/mm^3 in areas with a prevalence of cryptococcal disease >3% (conditional recommendation, low-quality evidence)[16,17]. Studies on cost-effectiveness of a test and treat approach have found such an intervention effective even at prevalence levels as low as 0.6% [9,11,18]. To inform national application of international normative guidance, it was essential to define the burden of cryptococcal infection during the current phase of HIV treatment scale-up. This is particularly relevant as a substantial proportion of CM has been shown to occur among patients already receiving ART [19,20] in RLC.

In this study, we sought to determine the prevalence of CrAg among PLHIV during routine HIV care and treatment enrollment and monitoring visits in Haiti.

Methods

Study design and patient selection

We performed a cross sectional study of patients with advanced HIV (CD4 cell counts <200 cells/mm^3) within health facilities providing HIV care and treatment across five of the 10 administrative departments

***Corresponding author:** Frantz Jean Louis, MPH, Laboratory Team Lead, Centers for Disease Control and Prevention, American Embassy, Tabarre 41, Port-au-Prince, Haiti, Tel: (509) 31703488; E-mail: wso0@cdc.gov, yjeanlouis@cdc.gov

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of Haiti (West, North, Nippes, Artibonite and South). Laboratories with adequate physical and electrical infrastructure in the selected departments had been established as testing hubs for decentralized CD4 testing for surrounding laboratories with less capacity [21]; these hubs also served as CrAg testing hubs for this study. Pre-ART and ART adults (≥18 years old) were enrolled during routine visits at 28 health facilities from February to September 2014. CD4 cell counts were measured at the testing hubs. Patients with CD4 cell count ≤200 cells/mm^3 were tested for CrAg. Patients previously treated for cryptococcal infection in the three months preceding enrollment or currently taking an antifungal agent were excluded from study. Demographic data and tests results (CD4 and CrAg) were collected using a standardized form.

Laboratory testing

A blood sample was obtained from each study participant and sent to a hub for CD4 testing. Every sample with a CD4 cell count <200 cells/mm^3 was reflex tested for cryptococcal antigen using the IMMY Cryptococcal lateral flow assay (LFA), according to the manufacturer's instructions for serum and CSF [14]. In summary, one drop of LFA specimen diluent, then 40 µL of specimen were added to a disposable test tube and mixed. Subsequently, a CrAg LFA test strip was inserted into the tube and read at 1-min intervals for up to 10 minutes. A single control line indicated a valid negative test and a control and test line indicated a valid positive test. All positive samples and 10% of negative samples were retested by technicians at the Haitian National Public Health Laboratory for quality control.

Data analysis

CrAg positivity rates, at different CD4 thresholds (<50, 50-100, <100, 100-200) and ART status was analyzed using SPSS (SPSS, v20.0 Chicago, IL: SPSS Inc.). Bivariate and multivariable logistic regression analyses were performed to assess risk factors for positive CrAg. Predictive factors such as gender, age, ART status and CD4 level were analyzed by stepwise regression with forward entry of variables. A p value <0.05 was considered statistically significant.

Ethics statement

Informed consent was obtained from all study participants and the study was approved by the Institutional Review Boards of the Haitian Ministry of Health and the U.S. Centers for Disease Control and Prevention. All samples were de-identified of personal identifiers for data entry and analysis.

Results

From February to September 2014, a total of 13,000 patients presenting for enrollment or follow-up at the 28 selected health facilities were tested for CD4 cell counts, of which 1,025 (7.9%) had a CD4 cell count <200 cells/mm^3. Forty-one percent (399/982) were male and 59% (581/982) female (data on gender missing from 45 people) and the median age was age 39 years (range 18 to 83 years old). The median CD4 cell count was 87 cells/mm^3 and 585 patients (57.3%) had a CD4 cell count <100 cells/ mm^3 (data missing from 4 patients). The majority of the patients (793/991 (80%), (data missing from 34 patients) were on ART (Table 1).

Overall, the CrAg positivity rate was 1.1% (95% confidence interval 0.4-1.7). In bivariate analysis there was no significant difference between patients positive or negative for CrAg by age, gender or ART status. The CrAg positivity rate in patients with CD4 level <100 cells/mm^3 was 1.8% (Figure 1). Patients with CD4 cell counts <50 cells/mm^3 had significantly higher CrAg rate (2.3%), compared to patients with CD4 level between 50 and 100 cells/mm^3 (1.1%) and those with a CD4 cell count >100 cells/mm^3 (0.2%) (p value=0.02). Patients with a positive CrAg test were much more likely to have a CD4 cell count <100 cells/mm^3 (OR=7.6, 95% Confidence Interval (CI) 0.9-59.6). There was no significant difference between the CrAg positivity rate among ART patients (1.2%) who represent the vast majority of participants and the rate among pre-ART patients (1.0%) (p value >0.05). However, among 11 patients with a positive CrAg, 9 (82%) were on ART. In multivariable logistic regression analysis only CD4 cell counts <50 cells/mm^3 were significantly associated with positive CrAg (OR=9.8, 95% CI 1.2-81.3). There were no significant differences between age, sex and ART status with positive CrAg.

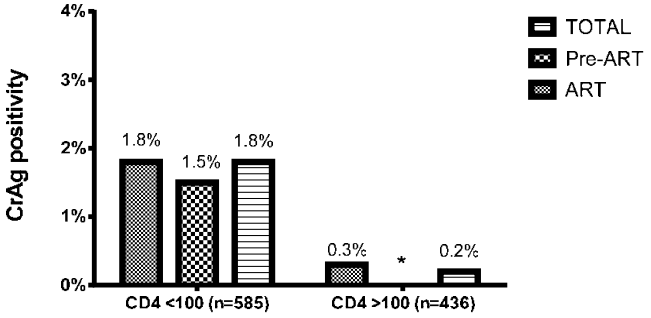
Discussion

This is the first study evaluating the CrAg positivity rate among PLHIV with CD4 cell counts <200 cell/mm^3 in Haiti. CrAg prevalence among patients with CD4 cell counts <200 cell/mm^3 from 28 health facilities providing HIV care and treatment was low (1.1%). In light of the 2011 WHO Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV infected adults, adolescents and children [16], routine CrAg screening and treatment may not be warranted on the basis of these findings. However, several reports, including more recent evidence, have indicated that a screen and treat approach may be cost-effective at a prevalence as low as 0.6%. New guidelines from WHO will update the prevalence cut-of for routine CrAg screening in ART-naïve adults since the 2011 recommendations were based on latex agglutination assay and data from LFA suggest test and treat approach might be effective at prevalence levels as low as 0.6% [9,11,18]. In other RLC, asymptomatic antigenemia has been documented from between 4 to 12% of PLHIV initiating ART [5,10,11] which is quite high compared to our findings. During the eight month study period, only 7.9% (1,025 out of 13,000) of the patients met the criteria of a CD4 count <200 cells/mm^3 to participate in the study. The high proportion of PLHIV with CD4 cell counts >200 cells/mm^3 suggests that PLHIV in Haiti tend to initiate ART at early stages of infection, thus lowering their risk for cryptococcal infection.

Variable	Result
Patient samples included, #	1025
Gender, #, [% (95% CI)][a]	
Female	581, [59.3 (56.2 – 62.4)]
Male	399, [40.7 (37.6 – 43.8)]
Age, median (min - max) (IQR) years[b]	39 (18 - 83) (31 - 47)
Age group, #, [% (95% CI)]	
18-28 years	170 [17.4 (15 – 19.8)]
1-39 years	336 [34.4 (31.4 – 37.4)]
40-50 years	296 [30.3 (27.4 – 33.2)]
>50 years	174 [17.8 (15.4 – 20.2)]
ART status #, [% (95% CI)][c]	
Pre-ART	198 [20.0 (17.5 – 22.5)]
ART	793 [80.0 (77.5 – 82.5)]
CD4 result, median (IQR) cells/ **mm^3**[d]	87 (39 - 150)
CD4 result strata, #, [% (95% CI)]	
<100 cells/ **mm^3**	585, [57.3 (54.3 -60.3)]
100 - 200 cells/ **mm^3**	436, [42.7 (39.7 – 45.7)]

[a]data on gender missing from 45 patients
[b]data on age missing from 49 patients
[c]data on Antiretroviral treatment (ART) status missing from 34 patients
[d]data on CD4 result missing from 4 patients

Table 1: Patient demographic and clinical characteristics.



*There were no CrAg positive patient on pre-ART with a CD4 cell count>100 cells/mm^3.

Figure 1: Percentage of PLHIV with positive CrAg by CD4 cell count and ART status.

It is also clear that early access to ART is unlikely to entirely explain the low prevalence of CrAg observed in this study. CrAg screening and pre-emptive treatment with fluconazole in PLHIV who are CrAg positive has primarily targeted ART-naïve patients, but some reports have demonstrated high prevalence of CrAg among patients receiving ART and at higher CD4 cell count ranges [19,22]. WHO recommends to consider routine serum or plasma CrAg screening in ART-naïve adults[16], but it might be worthwhile to establish the prevalence of cryptococcus in patients already on ART who are failing therapy with low CD4 cell count (<100 cells/mm^3) [19]. These findings also reinforce the fact that ART alone is insufficient treatment for CrAg positivity [5,10,23]. In September 2015, WHO issued new HIV treatment guidelines recommending treatment for all, regardless of CD4 cell count [24]. These early-release guidelines don't address cryptococcus infection among PLHIV, but updates should be provided to clarify the role of CD4 testing and CrAg screening and pre-emptive treatment in the HIV test and treat era.

Conclusion

Further research based on nationally representative sampling of patients with CD4 cell count <100 cells/mm^3 is needed to determine the national prevalence of serum CrAg among PLHIV or to determine if there is geographic variation, to further inform national policies on CrAg screening. Cost-effectiveness studies are needed to inform and update international normative guidance. Ideally, these will be carried out within a HIV "test and treat" model.

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