Original Article

Prevalence and Factors Associated with Cryptococcosis among Human Immunodeficiency Virus-Infected Patients of a Tertiary Hospital in Northwestern Nigeria

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Abstract

Background: Cryptococcosis is an important opportunistic infection and major contributor to mortality in human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) patients. There have been increasing reports of varied prevalence for cryptococcosis among HIV patients in Nigeria. **Aims:** The aim of this study was to determine the prevalence and factors associated with risk of cryptococcosis among HIV/AIDS patients from Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto. **Materials and Methods:** A descriptive cross-sectional study at HIV clinic of UDUTH, Sokoto, Nigeria, was conducted. The participants were HIV positive enrolled by systematic random sampling. Information on sociodemographics and clinical features of the participants was recorded. Blood was collected to determine the CD4 count/presence of cryptococcosis among the participants. Their CD4 counts were determined, and the presence of cryptococcal antigen was detected in the blood sample using IMMY CrAg LFA (cryptococcal antigen lateral flow assay test kit). Statistical analysis using Epi Info version 7.2/SPSS version 20.0 was done. Univariate, bivariate, and multivariate analyses were done. **Results:** Of 326 HIV-positive patients recruited, 36 of them were positive to cryptococcal antigen (prevalence of 11%). The highest proportion of patients positive to cryptococcosis (13 [36.1%) had CD4 values <50 cells/μL. Weight loss was the most common presenting symptom (11 [30.6%]) among those who were *Cryptococcus* positive. **Conclusions:** This study demonstrates that cryptococcosis is a burden among HIV patient in Sokoto, and its occurrence is associated with decreasing levels of CD4.

Keywords: *Cryptococcus*, diagnosis, factors, human immunodeficiency virus, prevalence

Introduction

Cryptococcosis is the most common fungal infection affecting the central nervous system (CNS) globally. The disease presents as a space-occupying lesion, meningitis, and meningoencephalitis or it can even affect the respiratory system to cause an atypical pneumonia.[1] Cryptococcosis is caused by a fungus known as *Cryptococcus neoformans*. It belongs to the category of opportunistic fungi. It is an encapsulated, round-to-oval yeast measuring 4–6 microns with a surrounding polysaccharide capsule.[2] Cryptococcosis is acquired via inhalation of aerosolized particles from the environment. After inhalation, it is believed to lie dormant for many years with reactivation occurring predominantly among immunosuppressed individuals such as persons with human immunodeficiency virus infection (HIV)/acquired immune deficiency syndrome (AIDS).[1]

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Cryptococcus is distributed worldwide and exists in high concentrations in avian guano, particularly pigeons and chickens.[3] Diagnosis of cryptococcosis is by isolation of *C. neoformans* from a sterile body site, histopathologic analysis, or by detection of cryptococcal capsular antigen.[2] Indian ink staining method is also employed to outline the polysaccharide capsule on direct examination of the cerebrospinal fluid. The antifungal agent, fluconazole,

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is highly effective in preventing cryptococcal infection in HIV-infected patients.[1]

Early in the HIV epidemic, cryptococcosis was the AIDS-defining illness in 60%–70% of HIV-infected patients.[3] However, currently, there is considerable reduction to only 15%–30% depending on the part of the world affected. This reduction was attributed to the use of the protease inhibitors and nucleoside analogs that are components of the highly active antiretroviral therapy (HAART) and also the antifungal agent azole.[3]

A report by the global HIV/AIDS pandemic in 2015 showed that approximately 60% of world populations living with HIV are in Sub-Saharan Africa. In Nigeria, a total of 3.4 million people were living with HIV by the end of 2014, and about 300,000 new infections occur annually.[4] In Nigeria, despite the availability of HAART in most HIV treatment centers, cryptococcosis is not routinely sought for and azole antifungals are usually not part of HIV/AIDS management.[3]

A prevalence of 12.7% for cryptococcosis among ART-naïve HIV patients was reported in Benin city, Nigeria.[5] Another study from Calabar city, Nigeria, by Ofonime *et al*. to detect cryptococcal antigenemia among HIV-seropositive patients accessing care in antiretroviral therapy clinics in Calabar detected a prevalence of 5.1%.[6]

The World Health Organization recommends screening for cryptococcosis among HIV patients.[7,8] Implementation of cryptococcal screening programs has begun in several countries in Sub-Saharan Africa, particularly in South Africa, Rwanda, and Mozambique. Certainly, Nigeria is among those countries that have not started.[9] Consequently, many patients die of cryptococcosis shortly after the initiation of antiretroviral therapy.[10,11] There is good treatment success rate for cryptococcosis among HIV patients if identified early.[8]

It is against this background that this study was taken to determine the seroprevalence of cryptococcosis and factors associated with occurrence of cryptococcosis among HIV/AIDS-infected patients in Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto. It is intended that the study would help provide a guide that may influence decision-making for policy-makers to improve cryptococcosis screening, detection, and HIV management in Nigeria.

Materials and Methods

The study was carried out in UDUTH, Sokoto, Northwestern Nigeria, a tertiary hospital, with a 500-bed capacity.[12] The HIV clinic had about 4820 registered HIV patients as at May 2016. The study was descriptive cross-sectional carried out over a period of 3 months (December 2016–February 2017). The study population was all HIV-positive patients attending the HIV Clinic in UDUTH. Patients who were bedridden with incapacitation (i.e., those with coma or on life support) due to ethical considerations were excluded from the study. A sample size of 326 was determined using the Fischer's formula[13] based on a prevalence of 5.1% from a previous study.[10] Finite correction and adjustment for nonresponse rate were done, respectively. Systematic random sampling was used to enroll the study participants.

The study instruments used were questionnaire, laboratory recording forms, cryptococcal antigen detection kit, and the CyFlow CD4 machine. The questionnaire was a structured interviewer-administered questionnaire. It was structured into the following subheadings: demographic information, clinical history, antiretroviral regimen, comorbid conditions, and therapy for opportunistic infections. The questionnaire was adapted from the previous studies. The questionnaire was pretested at a similar site to the study area, and corrections were made thereafter where necessary. A laboratory result recording form was used as a template for recording all patients' result generated in the laboratory. Three trained research assistants were recruited for data collection. Data were entered independently at two separate occasions using Microsoft Excel 2016. Double data entry analysis was done to ensure data quality**.** Blood samples were taken in an ethylenediaminetetraacetic acid -containing tube for the cryptococcal antigen detection and for the determination of the CD4 count. The samples were subsequently taken to the virology laboratory at UDUTH, where samples were analyzed for cryptococcal antigen as well as CD4 cell count. Cryptococcal antigen detection was done with the cryptococcal antigen lateral flow assay test kit (IMMY CrAg LFA). The test was performed by the addition of 1 drop of specimen diluent to a test tube. Thereafter, 40 μL of the test specimen was added. The test strip was put into the mix and allowed to incubate for 10 min. The test was then read as positive if two lines appear on the strip and negative if only 1 line appears. The CD4 count levels of each patient were determined by flow cytometry using the "Partec" CyFlow fluorescent-activated cell sorter based on the manufacturers' instruction.

Statistical analysis was done with Microsoft Excel 2016, Epi InfoTM version 7.2 (Atlanta, USA, CDC) and IBM SPSS version 20.0 (Armonk, NY: IBM Corp). Data were double entered and checked for the quality. The independent variables were: sociodemographic factors, risk factors, and levels of CD4 categorized into five (from I to V). The levels were as follows: I (>350 cells/μL), II (200–350 cells/μL), III (101–199 cells/μL), IV (50–100 cells/μL), and V (<50 cells/μL). The dependent variable was the presence or absence of cryptococcosis. Univariate analysis was done to show the prevalence of cryptococcosis using frequencies and proportions. Distribution of the variables was shown using mean/standard deviation for normally distributed quantitative data, and tables and charts were used for qualitative data. Bivariate analysis was done to show the association between categorical variables via Chi-square test or Fisher's exact, where the expected value of any cell is below five. A significance level of $P < 0.05$ was used. Multivariate analysis using logistic regression and odds ratio/confidence interval (OR/CI) was used for any factor that had a bivariate $P < 0.05$. Standard precautions were adhered to at all times.

Ethical approval (UDUTH/HREC/2016/No. 511) was obtained from the Ethics and Research Committee of UDUTH, Sokoto.

Results

A total of 326 HIV-positive patients were recruited during the study period. They consist of 176 females with a female-to-male ratio of 1.2:1. The mean age of the study participants was 35.8 years (±10.7 years' standard deviation). The highest proportion of the study participants of 131 (40.2%) were in the age category of 30–39 years. Hausa was the predominant ethnic group accounting for 187 (57.4%) of the study participants, whereas 121 (37.1%) were not gainfully employed [Table 1].

A total of 265 (81.3%) of the HIV-positive patients were already on antiretroviral regimen (treatment experienced), whereas 51 (18.7) were not on antiretroviral regimen (treatment naive) during the study period. However, 36 (11.0%) of the study participants were found to be positive to the cryptococcal antigen. This implies a prevalence of 11%.

The CD4 levels in HIV-positive patients versus their status to cryptococcosis are shown in Figure 1. The highest proportion of 13 (36.1%) patients positive to cryptococcosis had CD4 <50 cells/μL, whereas the lowest proportion of 5 (13.9%) had CD4 >200 cells/μL. The clinical features among HIV patients with and without the cryptococcal antigen are shown in Figure 2. Weight loss was the most common presenting complaint with a proportion of 11 (30.6%) among those who were *Cryptococcus* positive followed closely by patients presenting with loss of consciousness with 8 (22.2%).

There was a significant association between the level of CD4 count and the status of *Cryptococcus* using Chi-square test with a chi value of 128.7 and $P = 0.00$. This is shown in Table 2. There was no significant association ($P > 0.05$) between the sociodemographic characteristics of the participants and the presence of *Cryptococcus* among the study participants using the Chi-square test [Table 3]. There was a statistically significant association between cryptococcosis and clinical features ($\chi^2 = 62$, $P = 0.00$) among HIV patients using the Chi-square test [Table 4].

The predictors for acquisition of cryptococcosis among HIV patients from our study using logistic regression were shown in Table 5. Using CD4 level, the study participants with CD4 level IV (50–100 cells/μL) were found to be 16 times more likely to have cryptococcosis (OR: 16.476, 95% CI: 4.2960–63.110), whereas the study participants with CD4 level V (<50 cells/μL) were 101 times more likely to acquire cryptococcosis (OR: 101.833, 95% CI: 27.432–378.028) compared to those with other CD4 levels. However, in the clinical features, the study participants with cryptococcosis were 29 times more likely to present with headache (OR: 29.102, 95% CI: 1.010–57.5070) than with other symptoms.

Table 1: Sociodemographic characteristics of the study participants at Usmanu Danfodiyo University Teaching Hospital, Sokoto

Variables	Frequency ($n=326$), *n* (%)
Gender	
Male	150 (46.1)
Female	176 (53.9)
Age group (years)	
0-9	8 (2.5)
10-19	4 (1.2)
20-29	74 (22.7)
30-39	131 (40.2)
40-49	78 (23.9)
50-59	27 (8.3)
≥60	4 (1.2)
Educational status	
No formal education	109 (33.1)
Primary	98 (30.1)
Secondary	74 (23.0)
Tertiary	45 (13.8)
Address	
Rural	102 (31.3)
Urban	224 (68.7)
Ethnic group	
Hausa	187 (57.4)
Fulani	81 (24.9)
Yoruba	15 (4.6)
Igbo	21 (6.4)
Others	22 (6.7)
Occupation	
Civil servant	61 (18.7)
Self-employed	23 (7.1)
Farmer	18 (5.5)
Artisan	44 (13.5)
Business person/trader	59 (18.1)
Not gainfully employed	121 (37.1)

Discussion

This study found a prevalence of 11% for cryptococcosis among HIV/AIDS patients from UDUTH, Sokoto. This is consistent with the findings of a recent study in Southeastern Nigeria done by Chukwuanukwu *et al*.[14] in 2013, where a prevalence of 13% was determined; even though their study populations were mainly pregnant women utilizing the prevention of mother-to-child transmission of HIV/AIDS at their center. Similarly, a prevalence of 12.7% was found by Osazuwa *et al*.[5] in a study conducted in Benin city, Nigeria. Even though their study was done among only ART-naive individuals, our study has for the first time highlighted the burden from our center. This relatively high prevalence from our center is comparable across different centers in Nigeria highlighting the needs for the institution of a National Screening Program for HIV patients.

Findings from this study also showed that the majority of the study populations were in the age group of 30–39 years. This is similar to the 2015 report[15] on the quality of care among HIV/AIDS patient by the National Agency for the Control of AIDS where they determined that age group of 30–34 years has

Table 2: CD4 level and *Cryptococcus* status among patients in Usmanu Danfodiyo University Teaching Hospital, Sokoto

CD4 levels (cells/μl)	*Cryptococcus* (present), count (%)	*Cryptococcus* (absent), count (%)	Total, count (%)	χ^2	df	*P*
I (>350)	5 (13.9)	235 (81.0)	240 (73.6)	128.7	4	0.0000*
II (200-350)	5 (13.9)	38 (13.1)	43 (13.2)			
III (101-199)	7 (19.4)	6 (2.1)	13 (3.9)			
IV (50-100)	6 (16.7)	5 (1.7)	11 (3.4)			
V (<50)	13 (36.1)	6 (2.1)	19 (5.9)			
Total	36 (100)	290 (100)	326 (100)			

*Significant value (i.e., $P<0.05$)

Table 3: Association between sociodemographic characteristics of the participants and cryptococcosis at Usmanu Danfodiyo University Teaching Hospital, Sokoto

Variables	*Cryptococcus* (present), count (%)	*Cryptococcus* (absent), count (%)	Total, count (%)	χ^2	*P*
Sex					
Male	22 (61.1)	128 (44.1)	150 (53.9)	3.7	0.0539
Female	14 (38.9)	162 (55.9)	176 (46.1)		
Total	36 (100)	290 (100)	326 (100)		
Age group (years)					
<20	0 (0.0)	12 (4.1)	12 (3.7)	2.4	0.6660
20-29	8 (22.2)	66 (22.8)	74 (22.7)		
30-39	15 (41.7)	116 (40.0)	131 (40.2)		
40-49	8 (22.2)	70 (24.1)	78 (23.9)		
>50	5 (13.9)	26 (9.0)	31 (9.5)		
Total	36 (100)	290 (100)	326 (100)		
Educational status					
No formal education	12 (33.3)	97 (33.4)	109 (33.4)	1.0	0.9970
Primary	10 (27.7)	88 (30.3)	98 (30.1)		
Secondary	9 (25.1)	65 (22.4)	74 (22.7)		
Tertiary	5 (13.9)	40 (13.9)	45 (13.8)		
Total	36 (100)	290 (100)	326 (100)		
Address					
Rural	15 (41.7)	87 (30.0)	102 (31.3)	2.0	0.1820
Urban	21 (58.3)	203 (70.0)	224 (68.7)		
Total	36 (100)	290 (100)	326 (100)		
Ethnic group					
Fulani	8 (22.2)	73 (25.2)	81 (24.8)	5.4	0.2360
Hausa	18 (50.0)	169 (58.3)	187 (57.4)		
Igbo	2 (5.6)	19 (6.6)	21 (6.4)		
Others	4 (11.1)	18 (6.2)	22 (6.7)		
Yoruba	4 (11.1)	11 (3.7)	15 (4.7)		
Total	36 (100)	290 (100)	326 (100)		
Occupation					
Artisan	8 (22.2)	36 (12.4)	44 (13.5)	6.1	0.2950
Trader	5 (13.9)	54 (18.6)	59 (18.1)		
Civil servant	9 (25.0)	52 (17.9)	61 (18.7)		
Farmer	3 (8.3)	15 (5.2)	18 (5.5)		
Not employed	10 (27.7)	111 (38.3)	121 (37.1)		
Self-employed	1 (2.9)	22 (7.6)	23 (7.1)		
Total	36 (100)	290 (100)	326 (100)		

the highest burden. However, it is in contrast to a study done in Central Nigeria on patients' satisfaction with ART services by Osungbade[16] in 2013, which showed that majority (27.1%) of all the clients assessing ART services were young people aged 15–24 years old. Coincidently, the 2008 United Nations Human Development report on Nigeria has in the past indicated that the burden of HIV infection in Nigeria is borne by young people with more females affected than males.[17]

The findings from this study showed that more than half of the HIV-positive patients were already on ART regimen and

Table 4: Factors associated with the occurrence of Cryptococcosis among human immunodeficiency virus patients in Usmanu Danfodiyo University Teaching Hospital, Sokoto

Variables	*Cryptococcus* (present), count (%)	*Cryptococcus* (absent), count (%)	Total, count (%)	χ^2	df	*P*
Clinical features						
Cough	3 (8.3)	33 (11.4)	36 (11.0)	62	8	0.0000*
Diarrhea	5 (13.9)	21 (7.2)	26 (8.0)			
Fever	4 (11.1)	40 (13.8)	44 (13.5)			
Weight loss	11 (30.6)	8 (2.8)	19 (5.8)			
Headache	5 (13.9)	0 (0.0)	5 (1.5)			
Seizures	0 (0.0)	9 (3.1)	9 (2.8)			
Convulsions	0 (0.0)	10 (3.5)	10 (3.2)			
Loss of consciousness	0 (0.0)	7 (2.4)	7 (2.1)			
Nil	8 (22.2)	162 (55.9)	170 (52.1)			
Total	36 (100)	290 (100)	326 (100)			
Status of ART						
Yes	20 (55.6)	245 (84.5)	265 (81.3)	3.5	1	0.0610
No	16 (44.4)	45 (15.5)	61 (18.7)			
Total	36 (100)	290 (100)	326 (100)			
Antiretroviral regimen type						
ABC/3TC/LPVr	0 (0.0)	1 (0.3)	1 (0.3)	11.4	8	0.2520
ABC/3TC/NVP	0 (0.0)	1 (0.3)	1 (0.3)			
AZT/3TC/LPVr	0 (0.0)	1 (0.3)	1 (0.3)			
TDF/3TC/EFV	14 (38.9)	55 (19.0)	69 (21.2)			
TDF/3TC/LPVr	3 (8.3)	12 (4.1)	15 (4.6)			
TDF/3TC/NVP	4 (11.1)	31 (10.7)	35 (10.7)			
ZDV/3TC/EFV	1 (2.8)	36 (12.4)	37 (11.3)			
ZDV/3TC/NVP	9 (25.0)	97 (33.4)	106 (32.5)			
Nil	5 (13.9)	56 (19.5)	61 (18.8)			
Total	36 (100)	290 (100)	326 (100)			
Comorbidities						
Diabetes	6 (16.7)	26 (8.9)	32 (27.3)	3.6	3	0.3074
Hypertension	4 (11.1)	28 (9.7)	32 (27.3)			
Tuberculosis	8 (22.2)	37 (12.8)	45 (13.8)			
Nil	18 (50.0)	199 (68.6)	217 (31.6)			
Total	36 (100)	290 (100)	326 (100)			
Type of OIs therapy						
Co-trimoxazole	18 (50.0)	101 (34.8)	119 (36.5)	4.1	3	0.2160
Nystatin	0 (0.0)	11 (3.8)	11 (3.8)			
Dapsone	0 (0.0)	1 (0.3)	1 (0.3)			
Nil	18 (50.0)	177 (61.0)	195 (59.4)			
Total	36 (100)	290 (100)	326 (100)			

*Significant value (i.e., $P<0.05$). d4T: Stavudine, 3TC: Lamivudine, EFV: Efavirenz, ZDV: Zidovudine, TDF: Tenofovir, ART: Antiretroviral therapy, ABC: Abacavir, LPVr: Lopinavir/Ritonavir, NVP: Nevirapine, AZT: Zidovudine, OIs: Opportunistic infections

greater than half of the *Cryptococcus* burden was shared by them. However, the literature reveals that while the majority of those who present with cryptococcosis are ART naive, an increasing population are being diagnosed within the first 3 months after ART initiation.[18,19]

The distribution of cryptococcal antigenemia from this study varied highly with the CD4 cell levels. Several studies that had evaluated the prevalence of cryptococcosis in HIV patients have reported a consistently higher prevalence of cryptococcosis in HIV patients with lower CD4 cell counts.[5,20]

Our study also demonstrated that CD4 values <100 cells/μL were predictors for cryptococcosis. The implication of this finding is that once our HIV patients have a low CD4 count, it becomes necessary for us to screen for cryptococcosis.

This finding is also supported by a retrospective study in South Africa, where stored plasma from 7% of patients who had initiated HAART was positive for cryptococcal antigen. Cryptococcal antigenemia was detected in all the subset of patients with CD4 count <100 cells/μL of blood.[21] The results from this study show that there is no association between gender or age and cryptococcosis. This is similar to other studies that examined predictors for cryptococcosis.[22,23]

Several studies have shown that with the commencement of HAART therapy among HIV patients, the incidence of

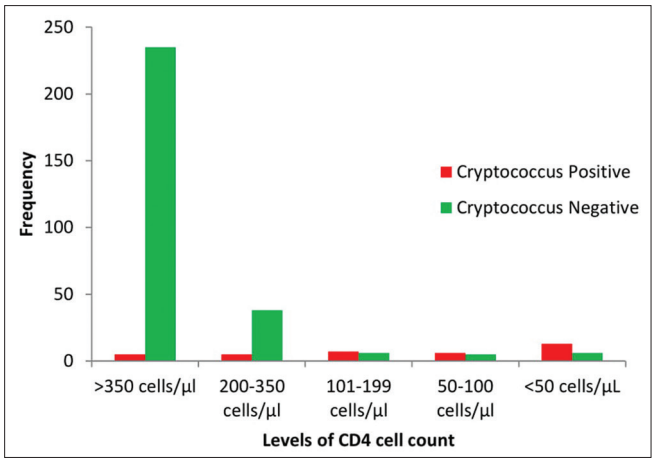

Figure 1: CD4 levels in human immunodeficiency virus-positive patients versus their status to cryptococcosis

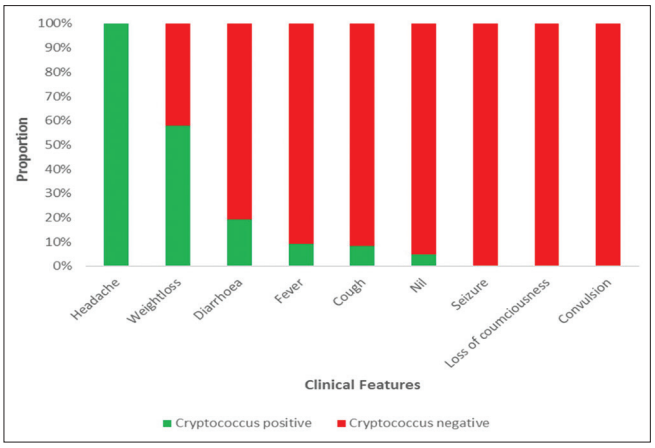

Figure 2: Clinical features among human immunodeficiency virus-infected patients with and without the cryptococcal antigen

Table 5: Predictors of Cryptococcosis among human immunodeficiency virus patients in Usmanu Danfodiyo University Teaching Hospital, Sokoto

Variables	*P*	Adjusted OR	95% CI
CD4 level (cells/µL)			
I (>350)	0.1870	1.8060	0.3910-8.3480
II (200-350)	0.0690	1.608	0.3420-4.8341
III (101-199)	0.4050	1.8570	0.4050-7.9780
IV (50-100)	0.0000*	16.476	4.2960-63.110
V (<50)	0.0000*	101.833	27.432-378.028
Clinical features			
Cough	0.3270	0.5200	0.1230-2.1890
Diarrhea	0.7630	0.1980	0.0560-0.7090
Fever	0.5300	0.4720	0.1270-1.7580
Weight loss	0.2320	1.4260	0.0340-0.0100
Headache	0.0000*	29.102	1.010-57.5070
Seizures	0.0800	0.0710	0.0110-0.1170
Convulsions	0.3270	0.0941	0.0190-0.4731
Loss of consciousness	0.1780	1.2170	0.0198-0.4730
Nil	0.1780	0.992	0.1930-5.1041

*Significant value (i.e., $P<0.05$). OR: Odds ratio, CI: Confidence interval

cryptococcosis and other opportunistic infections reduced globally.[24,25] The clinical features of cryptococcosis have also been reported to be highly variable but generally include CNS-localizing symptoms.[24] Cryptococcal antigen can be detected weeks before the onset of symptoms, and those who are asymptomatic but positive to cryptococcal antigen have a high risk of subsequent cryptococcal meningitis and mortality.[8]

This study was able to show that about one-fifth of the study population with cryptococcosis had no obvious symptoms at presentation. This study also demonstrated that among those HIV populations who were positive to *Cryptococcus* antigen; weight loss, headache, and diarrhea were the most common presenting symptoms. However, only headache was a predictor for cryptococcal infection among the clinical features from this study. This finding is similar to several other studies that reported headache as the predominant symptom in this group of patients.[26-28]

The present study was able to determine a relatively high prevalence of cryptococcosis among HIV patients and has also determined that lower CD4 counts and headache are predictors for HIV/AIDS in UDUTH, Sokoto. Several studies have shown that the integration of fluconazole prophylaxis at the initiation of HAART therapy reduces mortality from cryptococcosis even at CD4 <50 cells/µL by several studies.[29-31]

Conclusions

This study shows that in Sokoto, the decreasing levels of CD4 count are associated with a higher incidence of cryptococcosis, with the lower values predicting for cryptococcosis. Furthermore, HIV-infected patients presenting with weight loss were likely to have cryptococcosis.

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Conflicts of interest

There are no conflicts of interest.

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