Cryptococcal antigenemia and its predictors among HIV infected patients in resource limited settings: a systematic review

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Abstract

Background : Cryptococcosis is an opportunistic fungal infection that primarily affects people with advanced Human immunodeficiency virus (HIV) disease and is an important cause of morbidity and mortality around the globe. By far the most common presentation of the disease is cryptococcal meningitis (CM), which leads to an estimated 15-20% of all HIV related deaths worldwide, 3/4 of which are in sub-Saharan Africa. However, to the best of our knowledge there is quite limited reviewed data that on the epidemiology of cryptococcal antigenemia in a large HIV-infected population in resource limited settings.

Methods : Articles published in English irrespective of the time of publication were systematically searched using comprehensive search strings from PubMed/Medline and SCOPUS. In addition, Google Scholar and Google databases were searched manually for grey literature. Two reviewers independently assessed study eligibility, extracted data, and assessed risk of bias. The magnitude of cryptococcal antigenemia and its predictors were presented with descriptive statistics and summary measures. The pooled prevalence of cryptococcal antigenemia was also determined with 95% confidence interval (CI).

Result: Among 2941 potential citations, we have included 22 studies with a total of 8,338 HIV positive individuals. The studies were reported in ten different countries during the year (2007-2018). Most of the articles reported the mean CD4 count of the participants <100 cells/ μ l. The pooled prevalence of cryptococcal antigenemia at different CD4 count and ART status was at 8% (95%CI: 6-10%) (ranged between 1.7% and 33%). Body mass index (BMI) <18.5kg/m², CD4 count <100 cells, presenting with headache and male gender were reported by two or more articles as an important predictors of cryptococcal antigenemia.

Conclusions : Implementing a targeted screening of HIV patients with low BMI, CD4 count <100 cells, having headache and males; and treatment for asymptomatic cryptococcal disease should be considered. Additional data is needed to better define the epidemiology of cryptococcal antigenemia and its predictors in resource limited settings in order to design prevention, diagnosis, and treatment strategies.

Background

According to the latest report of the United Nations Programme on acquired immunodeficiency syndrome (UNAIDS), some 36.9 million people globally were living with HIV in 2017. In the same year, about 940, 000 people died from AIDS-related illnesses [1]. Cryptococcosis is one of the most important opportunistic infections among people living with advanced human immunodeficiency virus (HIV) disease having defective cellular immune component and is a major contributor to AIDS-related mortality worldwide [2]. In spite of the increasing availability of antiretroviral treatment (ART), cryptococcal disease continues to be a leading cause of death among HIV infected patients in the developing world [3-5]. Considerable number of HIV-infected population still presents late to care with advanced AIDS [6].

Disseminated cryptococcal infection is a serious opportunistic infection that commonly occurs in patients with untreated HIV infection [7]. It is primarily caused by *Cryptococcus neoformans*

and *Cryptococcus gattii* species [8, 9]. *C. neoformans* is encapsulated yeast that can be found in pigeon droppings which causes mild infections, from airway colonization or asymptomatic ones in laboratory workers to severe infections like meningitis or disseminated disease in individuals with impaired immune system [10]. There are several well-characterized virulence factors that contribute to the success of infection. To mention the common one; tolerance to mammalian body temperature at 37°C, owning a polysaccharide capsule that protects the yeast from phagocytosis, and a thick cell wall with the deposition of phenolic melanin, which has been proposed to protect the yeast from oxidation [11, 12].

The burden of the disease is greatest in middle and low-income countries with a high incidence of HIV infection [13]. Patients taking immunosuppressive drugs and some immunocompetent hosts are also at risk [14]. Although the infection begins in the lungs, certainly the most common presentation of cryptococcal disease, representing 70–90% of HIV-related cryptococcal disease, is cryptococcal meningitis (CM), which accounts for 15%–20% of all AIDS-related deaths globally, three quarters of which are in sub-Saharan Africa. An estimated 223, 100 cases of cryptococcal meningitis resulted in 181, 100 deaths among people living with HIV in 2014 [2, 4, 7, 13, 15]. Many of these deaths are preventable. Screening patients for subclinical cryptococcal infection at the time of entry into ART programs using point-of-care tools like, cryptococcal antigen (CrAg) immunoassays is highly effective in identifying patients at risk of developing CM, allowing these patients to then be targeted with pre-emptive antifungal therapy to prevent the development of severe disease [16].

There are three categories of methods that can be used to diagnose CM: 1) India ink microscopy for encapsulated yeasts, which can be used on cerebrospinal fluid (CSF); 2) culture, which can be done on CSF or blood; and 3) immunoassay for CrAg detection. While the gold standard for diagnosis of cryptococcal disease is *culture from bodily fluids*, CrAg is used to presumptively diagnose cryptococcal disease with sensitivity and specificity near 100%. There are several methods to detect cryptococcal antigen in CSF or plasma/serum: latex agglutination (LA), enzyme immunoassay (EIA), and lateral flow assay (LFA) [6]. Recent advances in the diagnosis and management of cryptococcal meningitis are promising and have been improving long-term survival. Point-of-care testing, like CrAg test, has made diagnosing CM rapid, practical, and affordable. Targeted screening and treatment programs for cryptococcal antigenemia are a cost effective method for reducing early mortality [17].

Some of the independent predictors of positive serum cryptococcal antigenemia includes; CD4(+) T cell counts of ≤ 100 cells/mm, low body mass index, neck pain, signs of meningeal irritation, and a recent diagnosis of HIV infection [18–21]. Routine screening of such category of patients may detect cryptococcosis, and hence provide an opportunity for early intervention.

Despite the high burden of cryptococcal meningitis related morbidity and mortality in resource limited settings compiled data on magnitude of cryptococcal antigenemia with its epidemiological predictors is missing [22, 23]. Hence, data is required on this field to inform policy makers for input to tailor public health intervention measures. Therefore, this systematic review was conducted aimed at determining the magnitude of cryptococcal antigenemia and its predictors in resource limited settings.

Methods

Protocol registration In accordance with the PRISMA guidelines, this systematic review protocol was registered by the International Prospective Register of Systematic Reviews (PROSPERO) on 01 Feb 2019

with a registration number 'CRD42019119970'. Eligible criteria Studies were selected according to the following criteria; Study design: observational quantitative studies, like cross-sectional and cohort studies that reported the magnitude of cryptococcal antigenemia and its predictors. Participants: We included studies that employed HIV infected people irrespective of gender and the age group who were tested for cryptococcal antigenemia. Interventions: our interests were 1) the level of cryptococcal antigenemia, which was defined as the presence of cryptococcal Ag (CrAg) in the blood (serum or plasma) and 2) its predictors, which are to mean factors that are statistically associated with the positive cryptococcal Ag test in the blood. Setting: we included studies with the outcome of interest reported in resource-limited settings (countries, listed as low and middle income economic status based on the 2018/19 World Bank report) [24]. Language and publication: We considered peer-reviewed journal articles, governmental documents and unpublished articles (thesis) reported in English language irrespective of the year of publication. Information sources and search strategy This review was done following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA) Guidelines [25]. Research papers were systematically searched in PubMed/Medline and SCOPUS, the last search was conducted on 22th of Dec, 2018. Manual search from Google scholar and Google databases was also done for grey literature. The search terms were developed in line with the Medical Subject Headings (MeSH) thesaurus using a combination of the big ideas (or 'key terms') which derived from the research question. The reference lists of retrieved articles were probed (forward and back ward searching) to identify articles that were not retrieved from databases and our manual search. The first two authors; AD and DM searched the articles independently. The domains of the search terms were Cryptococcus, cryptococcal antigenemia, cryptococcal meningitis, cryptococcosis, cryptococcal antigen/CrAg, associated factors/risk factors (or predictors), HIV, AIDS and resource-limited setting/countries. We combined cryptococcal antigenemia, cryptococcal meningitis, cryptococcosis with the Boolean operator "OR", and the result was combined with the other terms with "AND". Full search strategy for the two databases is presented in Supplement 1. Study selection Research papers that reported the level of cryptococcal antigenemia and its epidemiological predictors in the stated settings were included. Searched articles were directly imported and handled using EndNote X5 citation manager (Thomson Reuters, New York, USA). Based on the PRISMA protocol, duplicated articles were excluded and the titles and abstracts of the remaining papers were screened independently for inclusion in full text evaluation by the first two authors. Differences between the reviewers were resolved through discussion. In case of disagreements the decision was determined by the last author. Data collection process and data items The Joanna Briggs Institute (JBI) data extraction tool was adopted for data extraction. Data such as the name of the first author, data collection period and year of publication, country where the study was conducted, mean/median age of the study participants, proportion of male participants, type of the study design, the total number of the study participants, the type of specimen (serum/plasma) used for the CrAg test, the proportion of cryptococcal Ag test result, reported statistically significant predictors (like, mean CD4 count, ART status...) for CrAg positive test were extracted from the included articles. Quality appraisal To assess the risk of bias, the two authors independently used the nine items (each score one point) based on the Joanna Briggs Institute (JBI) Critical Appraisal tools [26] for prevalence studies. We assumed that papers that scored >50% (i.e >5 of 9 scores) of the weighted value of the tool considered as

good quality. Data synthesis The data extracted from the included studies were fed into a Microsoft Excel and were presented in terms of 1) the proportion of cryptococcal antigenemia from each study; 2) meta-analysis was done to determine the pooled prevalence of cryptococcal antigenemia. A systematic narrative synthesis was provided in which summary results were presented using text, table and figures. Descriptive statistics, such as: simple counts, ranges and percentages were used to describe the synthesized data.

Results

Search results

From the systematically searched databases and other sources, a total of 2941 articles were retrieved and sequentially screened. After removing the duplicate, 2930 were screened by title then 2865 were removed. Consequently, 36 were removed by abstract and 7 by full text with justifiable reasons. Lastly, a total of 22 studies met our inclusion criteria and included in this review for analysis. Screening was based on the PRISMA flow chart which was adapted from the PRISMA guidelines [27] (Figure 1).

Figure 1: The PRISMA flow diagram of literature selection.

Study characteristics

The description of each study is presented in (Table 1). The studies were reported in the last decade (2007-2018) in ten different countries. All but three studies [28-30] were conducted in Africa including. All the included articles were published in peer-reviewed journals. Some 19 (86.4%) of the articles used cross-sectional study design; while the remaining three papers were cohort type. The primary interest of most the included papers were to determine the prevalence of cryptococcal antigenemia among HIV infected patients using rapid CrAg test kits.

In this review, data of 8,338 HIV positive individuals (male gender 25%-76.3% and median age range 30-40 years) were included.

Table 1: Characteristics of the included studies

<i>Author (s)</i>	<i>*Pub. Year</i>	<i>Country</i>	<i>Study period</i>	<i>Study design</i>	<i>Sample size</i>	<i>Gender, male (%)</i>	<i>Median/ Mean/ age</i>
Vidal et al. [28]	2016	Brazil	2014-15	CS*	163	61	38.3
Ganiem et al. [29]	2014	Indonesia	2014	CS	810	76.3	30
Cheryl et al. [31]	2007	Uganda	2003-7	CS	377	29.4	38
Beyene et al. [32]	2013	Ethiopia	2011-12	CS	254	45.3	33
Meya et al. [33]	2010	Uganda	2004-6	CS	609	31	no data
Rugemalila et al. [34]	2013	Tanzania	2011-12	CS	218	43	39
Longley et al. [35]	2016	S. Africa	2011-14	Cohort	645	47	36
Hailu et al. [36]	2017	Ethiopia	2016-7	CS	267	49	38
Letang et al. [37]	2015	Tanzania	2008-12	Cohort	750	40	38
Christopher et al. [38]	2015	Nigeria	2010-11	CS	333	46.8	33
Williams et al. [39]	2015	Uganda	2013-14	CS	207	60.3	36
Alemu et al. [40]	2013	Ethiopia	2011	CS	369	44	36
Derbie et al. [41]	2018	Ethiopia	2016	CS	137	45.3	32
Mamuye et al. [42]	2016	Ethiopia	2013-14	CS	198	53	36.7
Oyella et al. [43]	2012	Uganda	2009-10	CS	367	48	32
Ogouyemi et al. [18]	2016	Benin	2015	CS	355	42.3	40
Drain et al. [44]	2015	S. Africa	2011-13	CS	432	60	36.1
Mdodo et al. [45]	2010	Kenya	2008-9	CS	340	47.5	35
Micol et al. [30]	2007	Cambodia	2004	CS	327	55	35
Jarvis et al. [46]	2009	South Africa	2002-5	CS	707	25	33.5
Wajanga et al. [47]	2011	Tanzania	2009-10	Cohort	333	46.2	38.5
Magambo et al. [48]	2014	Tanzania	2012-13	CS	140	42.1	36

*CS: Cross-sectional study design.

Risk of bias

The nine domain-based JBI Critical appraisal tool[26] for prevalence studies was used to test outcome level risk of bias of each studies. Each domain had a score of 1 point. The risk of bias for each individual domain was measured as 'yes', 'no', 'unclear' and 'not applicable'. In this study, 'yes' scored 1 and 'no' 'unclear' and 'not applicable' scores zero. The total score is summarized below in Table 2. The score therefore ranges from zero to nine, with higher scores indicating higher quality of outcome. Based on our assumption, all the included articles scored above 50% positive score. Hence, we considered all as good quality articles.

Table 2: Risk of bias summary result: review authors' judgements about each risk of bias item for the included studies, 2007-18.

Author (s)	Overall score of the JBI Critical Appraisal Checklist
Vidal et al. [28]	7
Ganiem et al.[29]	6
Cheryl et al.[31]	7
Beyene et al.[32]	6
Meya et al.[33]	5
Rugemalila et al.[34]	6
Longley et al.[35]	7
Hailu et al.[36]	6
Letang et al.[37]	7
Christopher et al.[38]	6
Williams et al.[39]	5
Alemu et al.[40]	5
Derbie et al.[41]	5
Mamuye et al.[42]	6
Oyella et al.[43]	7
Ogouyemi et al.[18]	5
Drain et al.[44]	5
Mdodo et al.[45]	6
Micol et al.[30]	7
Jarvis et al.[46]	5
Wajanga et al.[47]	7
Magambo et al. [48]	6

The tables showed that the overall score ranged 5-7 which is > 50%.

Magnitude of Cryptococcal antigenemia

The reported median CD4 count was between 23 and 123cell/. Except one study[40] that reported mean CD4 count at 123 cells/ μ l, the rest reported the mean CD4 count of the participants <100 cells. With regard to ART status of the participants, twelve studies[18, 29-31, 33, 35, 37, 43, 44, 46-48] included those who were ART naïve. In contrast, two studies [38, 41] used all participants on ART. The remaining articles reported different proportion of ART status of the participants. On top of this, at least one or more indicative sign and symptoms for cryptococcal meningitis were reported from some of the papers. Consequently, almost half of them reported, 10%-80.6% proportion of headache and WHO clinical stage IV proportion was between 17.9% and 100% (Table 3). The overall reported prevalence of cryptococcal antigenemia was between 1.7% and 33%. Running meta-analysis, the pooled prevalence was at 8% (95%CI: 6-10%) (Table 3 and Figure 2).

Predictors of Cryptococcal antigenemia

The statistically significant predictors of positive cryptococcal antigen test are depicted below in (Table 4). Body mass index<18.5kg/m2, CD4 count <100 cells and male gender were reported by two or more articles as an important predictors of cryptococcal antigenemia.

Table 3: The proportion of cryptococcal antigenemia and distribution of other clinical features of the study participants, 2007-2018

<i>Author (s)</i>	<i>Median CD4 count (cells/μl)</i>	<i>ART status</i>	<i>WHO stage IV (%)</i>	<i>Had headache (%)</i>	<i>+ CrAg test, n (%)</i>
Vidal et al. [28]	25	74% on ART	66	No data	5 (3.1)
Ganiem et al. [29]	20	All naïve	no data	No data	58(7.1)
Cheryl et al. [31]	50	All naïve	36.2	No data	22 (5.8)
Beyene et al. [32]	.*	47.6% on ATR	36.2	45.7	26 (10.2)
Meya et al. [33]	79	All naïve	No data	45.7	50(8.2)
Rugemalila et al. [34]	96	44% on ART	No data	66	7 (3)
Longley et al. [35]	55.5	All naïve	No data	No data	28(4.3)
Hailu et al. [36]	.**	52% on ART	45	33	9 (3.4)
Letang et al. [37]	71	All naïve	No data	No data	28 (3.7)
Christopher et al. [38]	.***	All on ART	No data	No data	33 (9.9)
Williams et al. [39]	25	51% on ART	No data	No data	149 (72)^
Alemu et al. [40]	123	74% on ART	100	28	31(8.4)
Derbie et al. [41]	51.8	All on ART	No data	No data	16(11.7)
Mamuye et al. [42]	93	51% on ART	36%	39	18(9.1)
Oyella et al. [43]	23	All naïve	No data	37.1	69(19)
Ogouyemi et al. [18]	.**	All naïve	No data	No data	6 (1.7)
Drain et al. [44]	75	All naïve	No data	No data	39 (9)
Mdodo et al. [45]	72	30.6% on ART	No data	80.6	111(33)
Micol et al. [30]	24	All naïve	28%	52.5	59 (18)
Jarvis et al. [46]	97	All naïve	No data	No data	46 (7)
Wajanga et al. [47]	68	All naïve	17.9%	No data	17 (5.1)
Magambo et al. [48]	97	All naïve	66	10	10 (7.1)

* Those who had CD4 <100 account at 59 (23.2%); ** All CD4 counts were <100; *** those who had CD4<200 account at 121(36.3%); ^ **Outlier:** subjects were HIV patients suspected for meningitis who were admitted to a hospital. The figure is excluded from the pooled prevalence analysis.

Figure 2: The pooled prevalence of cryptococcal antigenemia in resource limited settings, 2007-2018.

Table 4: Reported factors associated with cryptococcal antigenemia among HIV infected patients in resource limited settings, 2007-2018.

<i>Author (s)</i>	<i>Reported predictors for positive CrAg test</i>
Vidal et al. [28]	No data
Ganiem et al. [29]	No data
Cheryl et al. [31]	No data
Beyene et al. [32]	Being ART naive and ART-defaulter
Meya et al. [33]	A cryptococcal diagnosis during follow-up
Rugemalila et al. [34]	No data
Longley et al. [35]	No data
Hailu et al. [36]	Being male, living in rural areas, being hospitalized
Letang et al. [37]	No data
Christopher et al. [38]	Female gender, CD4 count of <200 cell/ μ L
Williams et al. [39]	No data
Alemu et al. [40]	An increasing age, self-reported fever, CD4 count <100 cells and site of screening.
Derbie et al. [41]	Gender
Mamuye et al. [42]	Lower median CD4, history of cryptococcal disease, having symptoms of headache, head stiffness
Oyella et al. [43]	Low body mass index, CD4+ count of less than 50 cells/mm ³ , recent diagnosis of HIV infection and meningeal signs
Ogouyemi et al. [18]	Body mass index<18.5kg/m ² , an alteration of the general condition with a CD4 lymphocyte counts<50cells/ μ L
Drain et al. [44]	CD4 counts < 50 cells/ μ L
Mdodo et al. [45]	male sex, headache, blurred vision and previous antifungal drug use
Micol et al. [30]	Countryside residence, headache, body mass index <15.4 kg/m ² , CD4+ count <50 cells/mm ³ , male gender
Jarvis et al. [46]	Baseline CD4 cell count, incident cryptococcal meningitis, history of cryptococcal disease
Wajanga et al. [47]	CD4 counts of < 100 cells, altered mental status, neck stiffness, fever
Magambo et al. [48]	Age, body mass index, CD4 count and WHO stage

Discussion

Cryptococcal meningitis, a deadly opportunistic fungal infection, is one of the most common form of meningitis and a leading cause of death among people with advanced HIV in resource limited settings [15, 49, 50]. Coupled with loose adherence to ART and retention in HIV care, cryptococcal disease contributes for about 20% of HIV related mortality in these settings every year [15]. However, it is one of the neglected topics by public health authorities while most deaths from the diseases are avoidable [23].

In the year 2018 the WHO released a guideline on the diagnosis, management, and prevention of HIV associated cryptococcosis to reduce the high mortality in resource limited settings where there is high prevalence of HIV: 1) optimized combination therapies for confirmed cryptococcal meningitis cases and 2) CrAg screening for ambulatory individuals living with HIV who could access care[2]. Testing for cryptococcal antigen, which is present in the blood several weeks before overt clinical symptoms of meningitis, provides a golden opportunity to detect infections as early as possible [6, 51].

Over the past few years, advances have been made in rapid point-of-care diagnostics and early detection of CrAg both in the blood and CSF which enabled screening and pre-emptive treatment to prevent clinical infections in patients with advanced HIV disease[49]. However, due to a number of factors; like limitation in resource, these strategies are not well implemented in a number of high HIV burden countries [50] where the disease seems neglected at all [52, 53].

There is quite few data regarding the prevalence of cryptococcosis in resource limited settings for public health measure. Therefore, in this systematic review data of some 8,338 HIV positive individuals is described to uncover the magnitude of cryptococcal antigenemia and its possible predictors. The median age of the patients in the included studies range 30-40 years which implies that HIV infection continue affecting the productive segment of the population.

In this review the reported median CD4 count of the HIV patients was between 23 and 123cell/ μ l. Except a study[40], the rest articles reported mean CD4 count of the participants below 100 cells (range 23-97 cells/ μ l). On top of this twelve studies [18, 29-31, 33, 35, 37, 43, 44, 46-48] reported that all the participants were ART naïve. Consequently, low CD4 count coupled with not starting ART would expose HIV infected patients for higher risk of different opportunistic infections including, cryptococcosis.

Our review result showed the overall prevalence of cryptococcal antigenemia between 1.7% and 33%; the pooled prevalence was at 8% (95%CI: 6-10%). A review by Firacative et al. (2018) on the status of cryptococcosis in Latin America reported prevalence of 10%-21% [22] which is in line with our report. Similarly, based on Rajasingham et al. (2017) review report on the Global burden of HIV-associated cryptococcal meningitis, the estimated global cryptococcal antigenaemia prevalence was at 6% (95%CI 5.8-6.2%) among people with a CD4 cell count of less than 100 cells per μ L in 2014. This finding is in line with our pooled estimate at (8%). In addition, according to this report the Sub-Saharan Africa accounted for 73% of the estimated cryptococcal meningitis cases in 2014. Moreover, the report also highlighted that there might be an ongoing burden of HIV-associated cryptococcal disease, primarily in sub-Saharan Africa[54].

Another review by Park et al. (2009) aimed at estimating the current global burden of cryptococcal meningitis among persons living with HIV showed an incidence ranged from 0.04 to 12% per year. Sub-Saharan Africa had the highest yearly burden estimate (median incidence at 3.2%). In contrast, the median incidence was lowest in Western and Central Europe and Oceania ($\leq$ 0.1% each)[5]. This implies that the reported incidence joined with the existing cryptococcal cases, the overall prevalence of the disease would be much

higher, may be close to or greater than our pooled report at (8%), in poor settings. In contrast, the prevalence of cryptococcosis in the developed world has decreased as there is quite low burden of HIV and is also being diagnosed earlier, but is still significant, and the problem in resource-limited settings is exceedingly high [55] in which over half of patients die within 10 weeks of diagnosis compared to as few as 10% of patients from developed nations [56].

Our sub-group analysis also showed that the prevalence of cryptococcal antigenemia in Ethiopia varied between 3.4% and 11.7%. The pooled prevalence was at 7% (95%CI: 3-11%) among HIV infected patients at different ART status and CD4 count. Comparable reports have been released in Ethiopia and overseas; Bite et al. (2016) had reported (8.5%) positive cryptococcal antigenemia proportion in Addis Ababa, Ethiopia [57]. Thomsen et al. (2018) reported that, of HIV patients included in a study in Guinea-Bissau, (10%) had a positive cryptococcal antigen test [58].

On top of this, in our review the pooled prevalence of cryptococcal antigenemia was 11% (Uganda), 4% (Tanzania) and 7% (South Africa). As the HIV patients had different CD4 count, ART status and other background variables, i.e due to clinical variability, minor variation in the prevalence of cryptococcal antigenemia is likely to happen in different settings. On top of this as most of the participants had CD4 count less than 100 cells/ μ l, relatively higher proportion of Cryptococcal antigenemia is more likely to be reported among these immunosuppressed HIV patients in these settings [43]. In contrast to our result, a relatively lower prevalence (2.9%) of CrAg positivity among HIV/AIDS patients was reported in United States in 2012[21]. Difference in ART adherence and HIV care might contribute for the lower prevalence of Cryptococcal antigenemia in the US than the African countries.

With regard to the possible predictors of cryptococcal antigenemia, in this review apart from the magnitude of cryptococcal antigenemia some of the included studies also reported different associated factors that could potentially be utilized for public health measures. Body mass index <18.5kg/m², CD4 count <100 cells, had headache and male gender were reported by two or more articles as an important predictors of cryptococcal antigenemia. These all might directly or indirectly contributed for reduced immune status of individuals that could put them at risk for different opportunistic infections, including cryptococcosis.

Specifically, lower CD4 count has strong correlation with severe immune depletion, hence risk of opportunistic infections. Liechty et al. (2007) reported that among HIV-infected individuals with CD4 cell count < 100 cells/ μ l, cryptococcal antigenemia was associated with a higher risk of death than CrAg negative participants [31]. Other studies in different settings also reported that lower CD4 count (usually <100 cells/mm), low body mass index, having neck pain and signs of meningeal irritation were an important predictors of cryptococcal antigenemia [18-21]. Thomsen et al. (2018) reported that self-reported headache and fever were also predictors of a positive CrAg test [58].

In our review at least one or more indicative sign and symptoms for cryptococcal meningitis were reported from some of the included articles. Among their study participants almost half of the papers reported 10%-80.6% proportion of headache and 17.9% and 100% proportion of clinical stage IV HIV disease. Few of other the included papers reported these variables as an important predictor cryptococcal antigenemia [30, 45, 47, 48]. Therefore, concerned stakeholders and policy makers should consider target screening and management of HIV patients coming-up with such associated factors might decrease the morbidity and mortality associated with cryptococcal infection in resource limited settings.

Strength and limitations

To the best of our knowledge, this systematic review represents the first to present the magnitude of cryptococcal antigenemia and its predictors among HIV patients in resource limited settings. The other strong suit of this review is that it includes studies from different settings: Africa, Asia and Latin America that allowed incorporating a better representation of data for policy making.

However, our review should be interpreted in light of a couple of drawbacks including but not limited to the small number of included studies despite the setting covers large number of countries. As a result, the absence of data from some countries might compromise the overall picture of the magnitude of cryptococcal antigenemia and its predictors for clear understanding of the problem for further considerations. The review didn't provide data on the CrAg titer and specific cryptococcal species involved in positive CrAg tests. The other possible pitfall of this review is the variation in demographic characteristic of the study subjects (clinical variability). Finally, the other limit relates to the point in time analysis of studies with cross-sectional study designs, as majority of the articles were this type, which inherently could affect the overall picture of the magnitude of cryptococcal antigenemia. Restricting our inclusion criteria to include only articles published in English languages may have missed relevant studies and reduced the precision of our results.

Conclusions

The pooled prevalence of cryptococcal antigenemia among HIV infected patients at different CD4 count and ART status was at 8%. Body mass index < 18.5 kg/m², CD4 count < 100 cells, presenting with headache and male gender were reported by two or more articles as an important predictors of cryptococcal antigenemia. Therefore, it will be good to consider routine screening for CrAg among HIV infected patients specifically those presenting with these predictors. Policy makers should consider the implementation of targeted screening and treatment interventions for asymptomatic cryptococcal antigenemia patients in resource limited settings. Meningitis associated with cryptococcosis might be a reflection of HIV treatment programme failure; therefore timely HIV testing and rapid linkage to care will have paramount importance for patients. Finally, further work is needed to better define the scope of the problem and track the epidemiology of this infection, in order to prioritize prevention, diagnosis, and treatment strategies.

Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ART	Anti-Retroviral Therapy (or Treatment)
<i>C. neoformans</i>	<i>Cryptococcus neoformans</i>
CD	Cluster of Differentiation
CI	Confidence Interval
CM	Cryptococcal Meningitis
CNS	Central Nervous System
CrAg	Cryptococcal Antigen
CSF	Cerebrospinal Fluid
EIA	Enzyme Immunoassay
HIV	Human Immunodeficiency Virus
JI	Joanna Briggs Institute
LFA	Lateral Flow Assay
UNAIDS	United Nations Programme on HIV/AIDS

Declarations

- **Ethical Approval and Consent to participate:** Not applicable in this section
- **Consent for publication:** Not applicable in this section
- **Availability of data and material:** All the generated data in this review are included in the manuscript.
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References

1. UNAIDS. *Global HIV & AIDS statistics — 2018 fact sheet*. 2018 [cited 2019 3 Jan]; Available from: <http://www.unaids.org/en/resources/fact-sheet>.
2. WHO. *Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. 2018 [cited 2018 15 Dec]; Available from: <http://apps.who.int/iris/bitstream/handle/10665/260399/9789241550277-eng.pdf;jsessionid=3DD47D6B4F06AFA32280E2048900A316?sequence=1>.
3. Meyer, A.C. and M. Jacobson, *Asymptomatic cryptococcemia in resource-limited settings*. *Curr HIV/AIDS Rep*, 2013. **10**(3): p. 254-63.
4. Lawrence, D.S., T. Boyer-Chammard, and J.N. Jarvis. *Emerging concepts in HIV-associated cryptococcal meningitis*. *Curr Opin Infect Dis*, 2018. **30**(10): p. 0000000000000514.
5. 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): p. 525-30.
6. Rajasingham, R., D.B. Mehta, and D.R. Boulware, *Integrating cryptococcal antigen screening and pre-emptive treatment into routine HIV care*. *J Acquir Immune Defic Syndr*, 2012. **59**(5).
7. Uptodate. *Microbiology and epidemiology of Cryptococcus neoformans infection*. 2018 17 Ju 2018 [cited 2018 15 Dec]; Available from: <https://www.uptodate.com/contents/microbiology-and-epidemiology-of-cryptococcus-neoformans-infection>.
8. Kwon-Chung KJ, Fraser JA, Doering TL, Wang Z, Janbon G, Idnurm A et al. *Cryptococcus neoformans and Cryptococcus gattii, the etiologic agents of cryptococcosis*. *Cold Spring Harb Perspect Med*, 2014. **4**(7).

9. Lortholary, O. *Management of cryptococcal meningitis in AIDS: the need for specific studies in developing countries*. Clin Infect Dis. 2007 Jul 1;45(1):81-3. doi: 10.1086/518583. Epub 2007 May 25.
10. Pescador Ruschel, M.A. and B. Thapa, *Meningitis, Cryptococcal*. Available from <https://www.ncbi.nlm.nih.gov/books/NBK525986/>. Accessed 15 June 2019.
11. Liu, T.B., D.S. Perlin, and C. Xue. *Molecular mechanisms of cryptococcal meningitis*. Virulence, 2012. **3**(2): p. 173-81.
12. Hamilton, A.J. and J. Goodley. *Virulence factors of Cryptococcus neoformans*. Curr Top Med Mycol, 1996. **7**(1): p. 19-42.
13. Jackson, A. and M.C. Hosseini. *Management of cryptococcal meningitis in sub-saharan Africa*. Curr HIV/AIDS Rep, 2010. **7**(3): p. 134-42.
14. Sloan, D.J. and V. Parris. *Cryptococcal meningitis: epidemiology and therapeutic options*. Clin Epidemiol, 2014. **6**: p. 169-82.
15. Loyse A, Thangaraj H, Easterbrook P, Ford N, Roy M, Chiller T et al. *Cryptococcal meningitis: improving access to essential antifungal medicines in resource-poor countries*. The Lancet Infectious Diseases, 2013. **13**(7): p. 629-637.
16. Jarvis JN, Govender N, Chiller T, Park BJ, Longley N, Meintjes G et al. *Cryptococcal Antigen Screening and Preemptive Therapy in Patients Initiating Antiretroviral Therapy in Resource-Limited Settings: A Proposed Algorithm for Clinical Implementation*. Journal of the International Association of Physicians in AIDS Care, 2012. **11**(6): p. 374-379.
17. Abassi, M., D.R. Boulware, and J. Rhein. *Cryptococcal Meningitis: Diagnosis and Management Update*. Curr Trop Med Rep, 2015. **2**(2): p. 90-99.
18. Ogouyemi-Hounto A, Zannou DM, Ayihounton G, Ahouada C, Azon-Kouanou A, Acakpo J et al. *Prevalence and factors associated with cryptococcal antigenemia in HIV-infected patients in Cotonou/Benin*. J Mycol Med, 2016. **26**(4): p. 391-397.
19. Oyella J, Meya D, Bajunirwe F, Kamya MR. *Prevalence and factors associated with cryptococcal antigenemia among severely immunosuppressed HIV-infected adults in Uganda: a cross-sectional study*. J Int AIDS Soc, 2012. **15**(1): p. 1758-2652.
20. Magambo KA, Kalluvya SE, Kapoor SW, Seni J, Chofle AA, Fitzgerald DW et al. *Utility of urine and serum lateral flow assays to determine the prevalence and predictors of cryptococcal antigenemia in HIV-positive outpatients beginning antiretroviral therapy in Mwanza, Tanzania*. J Int AIDS Soc, 2014. **17**(19040).
21. McKenney J, Bauman S, Neary B, Detels R, French A, Margolick J et al. *Prevalence, correlates, and outcomes of cryptococcal antigen positivity among patients with AIDS, United States, 1986-2012*. Clin Infect Dis, 2015. **60**(6): p. 959-65.
22. Firacative C, Lizarazo J, Illnait-Zaragoz MT, Castaeda E. *The status of cryptococcosis in Latin America*. Memorias do Instituto Oswaldo Cruz, 2018. **113**(7): p. e170554-e170554.
23. Bongomin F, Gago S, Oladele RO, Denning DW. *Global and Multi-National Prevalence of Fungal Diseases-Estimate Precision*. J Fungi, 2017. **3**(4).
24. Group, T.W.B. *World Bank Country and Lending Groups*. 2018 [cited 2018 18 Dec]; Available from: <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>
25. Shamseer L, Moher D, Clarke M, Gherzi D, Liberati A, Petticrew M et al. *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation*. Bmj, 2015. **2**(350).
26. Institute, T.J.B. *The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews: Checklist for Prevalence Studies*. 2017 [cited 2018 1 Aug]; Available from: <http://joannabriggs.org/research/critical-appraisal-tools.html>.

27. Moher D, Liberati A, Tetzlaff J, Altman DG. *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement*. PLoS Med, 2009. **6**(7): p. 21.
28. Vidal JE, Toniolo C, Paulino A, Colombo A, Dos Anjos Martins M, da Silva Meira C et al. *Asymptomatic cryptococcal antigen prevalence detected by lateral flow assay in hospitalised HIV-infected patients in Sao Paulo, Brazil*. Trop Med Int Health, 2016. **21**(12): p. 1539-1544.
29. Ganiem AR, Indrati AR, Wisaksana R, Meijerink H, van der Ven A, Alisjahbana B et al. *Asymptomatic cryptococcal antigenemia is associated with mortality among HIV-positive patients in Indonesia*. Journal of the International AIDS Society, 2014. **17**(1): p. 18821.
30. Micol R, Lortholary O, Sar B, Laureillard D, Ngeth C, Dousset JP et al. *Prevalence, determinants of positivity, and clinical utility of cryptococcal antigenemia in Cambodian HIV-infected patients*. J Acquir Immune Defic Syndr, 2007. **45**(5): p. 555-9.
31. Liechty CA, Solberg P, Were W, Ekwaru JP, Ransom RL, Weidle PJ et al. *Asymptomatic serum cryptococcal antigenemia and early mortality during antiretroviral therapy in rural Uganda*. Tropical Medicine & International Health, 2007. **12**(8): p. 929-935.
32. Beyene T, Woldeamanuel Y, Asrat D, Ayana G, Boulware DR. *Comparison of Cryptococcal Antigenemia between Antiretroviral Naïve and Antiretroviral Experienced HIV Positive Patients at Two Hospitals in Ethiopia*. PLoS One, 2013. **8**(10): p. e75585.
33. Meya DB, Manabe YC, Castelnovo B, Cook BA, Elbireer AM, Kambugu A et al. *Cost-Effectiveness of Serum Cryptococcal Antigen Screening to Prevent Deaths among HIV-Infected Persons with a CD4+ Cell Count ≤ 100 Cells/ μ L Who Start HIV Therapy in Resource-Limited Settings*. Clinical Infectious Diseases, 2010. **51**(4): p. 448-455.
34. Rugemalila J, Maro VP, Kapanda G, Ndaro AJ, Jarvis JN. *Cryptococcal antigen prevalence in HIV-infected Tanzanians: a cross-sectional study and evaluation of a point-of-care lateral flow assay*. Trop Med Int Health, 2013. **18**(9): p. 1075-1079.
35. Longley N, Jarvis JN, Meintjes G, Boule A, Cross A, Kelly N et al. *Cryptococcal Antigen Screening in Patients Initiating ART in South Africa: A Prospective Cohort Study*. Clinical Infectious Diseases, 2016. **62**(5): p. 581-587.
36. Hailu K, Niguse S, Hagos K, Abdulkader M. *Cryptococcal antigenemia and associated risk factors among ART-naïve and ART-experienced HIV-infected peoples at selected health institutions of Mekelle, Northern Ethiopia*. Microbiologyopen, 2018. **2**(10): p. 746.
37. Letang E, Müller MC, Ntamatungiro AJ, Kimera N, Faini D, Furrer H et al. *Cryptococcal Antigenemia in Immunocompromised Human Immunodeficiency Virus Patients in Rural Tanzania: A Preventable Cause of Early Mortality*. Open Forum Infectious Diseases, 2015. **2**(2): p. ofv046-ofv046.
38. Christopher, A.E., O. Richard, and A.-I. Otiabor. *Cryptococcus neoformans infection among human immunodeficiency virus patients on highly active antiretroviral therapy in Benin City, Nigeria*. NZ J Med Lab Science, 2015. **69**(1): p. 21-23.
39. Williams DA, Kiiza T, Kwizera R, Kiggundu R, Velamakanni S, Meya DB et al. *Evaluation of Fingerstick Cryptococcal Antigen Lateral Flow Assay in HIV-Infected Persons: A Diagnostic Accuracy Study*. Clinical Infectious Diseases, 2015. **61**(3): p. 464-467.
40. Alemu AS, Kempker RR, Tenna A, Smitson C, Berhe N, Fekade D et al. *High prevalence of Cryptococcal antigenemia among HIV-infected patients receiving*

antiretroviral therapy in Ethiopia. PLoS One, 2013. **8**(3): p. 4.

41.   Derbie A, Ayalew W, Mekonnen D, Alemu M, Mulugeta Y. *Magnitude of Cryptococcal Antigenemia among HIV Infected Patients at a Referral Hospital, Northwest Ethiopia* Ethiop J Health 2018. **28**(4): p. 6.
42.   Mamuye AT, Bornstein E, Temesgen O, Blumberg HM, Kempker RR. *Point-of-Care Testing for Cryptococcal Disease Among Hospitalized Human Immunodeficiency Virus-Infected Adults in Ethiopia*. Am J Trop Med Hyg, 2016. **95**(4): p. 786-792.
43.   Oyella J, Meya D, Bajunirwe F, Kamya MR. *Prevalence and factors associated with cryptococcal antigenemia among severely immunosuppressed HIV-infected adults in Uganda: a cross-sectional study*. Journal of the International AIDS Society, 2012. **15**(1): p. 15.
44.   Drain PK, Kleene JM, Coleman SM, Losina E, Katz JN, Giddy J et al. *Prevalence of cryptococcal antigenuria at initial HIV diagnosis in KwaZulu-Natal*. HIV Med, 2015. **16**(10): p. 640-4.
45.   Mdodo R, Brown K, Omonge E, Jaoko W, Baddley J, Pappas P et al. *The prevalence, clinical features, risk factors and outcome associated with cryptococcal meningitis in HIV positive patients in Kenya*. East Afr Med J, 2010. **87**(12): p. 481-7.
46.   Jarvis JN, Lawn SD, Vogt M, Bangani N, Wood R, Harrison TS. *Screening for Cryptococcal Antigenemia in Patients Accessing an Antiretroviral Treatment Program in South Africa*. Clinical Infectious Diseases, 2009. **48**(7): p. 856-862.
47.   Wajanga BM, Kalluvya S, Downs JA, Johnson WD, Fitzgerald DW, Peck RN. *Universal screening of Tanzanian HIV-infected adult inpatients with the serum cryptococcal antigen to improve diagnosis and reduce mortality: an operational study*. J Int AIDS Soc, 2011. **14**(48): p. 1758-2652.
48.   Magambo KA, Kalluvya SE, Kapoor SW, Seni J, Chofle AA, Fitzgerald DW et al. *Utility of urine and serum lateral flow assays to determine the prevalence and predictors of cryptococcal antigenemia in HIV-positive outpatients beginning antiretroviral therapy in Mwanza, Tanzania*. Journal of the International AIDS Society, 2014. **17**(1): p. 19040.
49.   Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A et al. *Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy*. Nat Rev Neurol, 2017. **13**(1): p. 13-24.
50.   Oladele RO, Bongomin F, Gago S, Denning DW. *HIV-Associated Cryptococcal Disease in Resource-Limited Settings: A Case for "Prevention Is Better Than Cure"?* J Fungi, 2017. **3**(4).
51.   Roy, M. and T. Chiller. *Preventing deaths from cryptococcal meningitis: from bench to bedside*. Expert Review of Anti-infective Therapy, 2011. **9**(9): p. 715-717.
52.   Antinori, S. *New Insights into HIV/AIDS-Associated Cryptococcosis*. Isrn Aids, 2013. **25**(471363): p. 471363.
53.   Molloy SF, Chiller T, Greene GS, Burry J, Govender NP, Kanyama C et al. *Cryptococcal meningitis: A neglected NTD?* PLoS Neglected Tropical Diseases, 2017. **11**(6): p. e0005575-e0005575.
54.   Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM et al. *Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis*. The Lancet Infectious Diseases, 2017. **17**(8): p. 873-881.
55.   Spec A, Powderly WG. *Cryptococcal meningitis in AIDS*. Handb Clin Neurol, 2018. **152**: p. 139-150.
56.   Tenforde MW, Wake R, Leeme T, Jarvis JN. *HIV-Associated Cryptococcal Meningitis: Bridging the Gap Between Developed and Resource-Limited Settings*. Curr Clin Microbiol Rep, 2016. **3**: p. 92-102.

57. Adane B, Mulu H, Tigist G, Surafel F. *Prevalence of Cryptococcal Infection in Patients Clinically Diagnosed to Have Meningitis in Ethiopia*. Clinical Medicine Research, 2016. **5**(4): p. 73-76.
58. Thomsen D, Hviid CJ, Hønge BL, Medina C, Te DDS, Correia FG et al. *Increased mortality among HIV infected patients with cryptococcal antigenemia in Guinea-Bissau*. Pan Afr Med J, 2018. **29**(18).

Figures

Figure 1

The PRISMA flow diagram of literature selection process.

Figure 2

Frost plot for the pooled prevalence of cryptococcal antigenemia in resource limited settings.

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