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/µl. 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/m 2, 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 is 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’. Eligibly 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) the-saurus 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 ar-ticles 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 de-sign, 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
| Author(s) | *Pub. Year | Country | Study period | Study design | Sample size | Gender, male (%) | Median/ Mean/ age |
|-----------|------------|---------|--------------|--------------|-------------|------------------|------------------|
| Vidal et al. | 2016 | Brazil | 2014-15 | CS* | 163 | 61 | 38.3 |
| Ganiem et al. | 2014 | Indonesia | 2014 | CS | 810 | 76.3 | 30 |
| Cheryl et al. | 2007 | Uganda | 2003-7 | CS | 377 | 29.4 | 38 |
| Beyene et al. | 2013 | Ethiopia | 2011-12 | CS | 254 | 45.3 | 33 |
| Meya et al. | 2010 | Uganda | 2004-6 | CS | 609 | 31 | no data |
| Rugemalila et al. | 2013 | Tanzania | 2011-12 | CS | 218 | 43 | 39 |
| Longley et al. | 2016 | S. Africa | 2011-14 | Cohort | 645 | 47 | 36 |
| Hailu et al. | 2017 | Ethiopia | 2016-7 | CS | 267 | 49 | 38 |
| Letang et al. | 2015 | Tanzania | 2008-12 | Cohort | 750 | 40 | 38 |
| Christopher et al. | 2015 | Nigeria | 2010-11 | CS | 333 | 46.8 | 33 |
| Williams et al. | 2015 | Uganda | 2013-14 | CS | 207 | 60.3 | 36 |
| Alemu et al. | 2013 | Ethiopia | 2011 | CS | 369 | 44 | 36 |
| Derbie et al. | 2018 | Ethiopia | 2016 | CS | 137 | 45.3 | 32 |
| Mamuye et al. | 2016 | Ethiopia | 2013-14 | CS | 198 | 53 | 36.7 |
| Oyella et al. | 2012 | Uganda | 2009-10 | CS | 367 | 48 | 32 |
| Ogouyemi et al. | 2016 | Benin | 2015 | CS | 355 | 42.3 | 40 |
| Drain et al. | 2015 | S. Africa | 2011-13 | CS | 432 | 60 | 36.1 |
| Mdodo et al. | 2010 | Kenya | 2008-9 | CS | 340 | 47.5 | 35 |
| Micol et al. | 2007 | Cambodia | 2004 | CS | 327 | 55 | 35 |
| Jarvis et al. | 2009 | South Africa | 2002-5 | CS | 707 | 25 | 33.5 |
| Wajanga et al. | 2011 | Tanzania | 2009-10 | Cohort | 333 | 46.2 | 38.5 |
| Magambo et al. | 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 123 cell/μl. Except one study[40] that
reported mean CD4 count at 123 cells/μl, 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 < 18.5 kg/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
| Author (s) | Median CD4 count (cells/μl) | ART status | WHO stage IV (%) | Had headache (%) | + CrAg test, n (%) |
|-----------|-----------------------------|------------|----------------|-----------------|-------------------|
| 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 ART | 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.

| Author(s) | Reported predictors for positive CrAg test |
|-----------|------------------------------------------|
| 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/μL |
| 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/mm3, recent diagnosis of HIV infection and meningeal signs |
| Ogouyemi et al. [18] | Body mass index<18.5kg/m2, an alteration of the general condition with a CD4 lymphocyte counts<50cells/μL |
| Drain et al. [44] | CD4 counts < 50 cells/μL |
| 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/m2, CD4+ count <50 cells/mm3, 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 |
Cryptococcal meningitis, a deadly opportunistic fungal infection, is one of the most common forms 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 123 cell/μl. Except a study[40], the rest articles reported mean CD4 count of the participants below 100 cells (range 23-97 cells/μl). 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 μL 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 (</=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/µl, 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 sever immune depletion, hence risk of opportunistic infections. Liechty et al. (2007) reported that among HIV-infected individuals with CD4 cell count < 100 cells/µl, 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<18.5kg/m$^2$, 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

| Acronym      | Definition                                      |
|--------------|-------------------------------------------------|
| AIDS         | Acquired Immunodeficiency Syndrome              |
| ART          | Anti-Retroviral Therapy (or Treatment)          |
| C. neoformans| *Cryptococcus neoformans*                      |
| 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                    |
| JBI          | 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.
- **Competing interests:** Authors declare that they have no competing interests.
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- **Authors’ contributions:** AD and TA conceived the review topic and objectives. AD and DM participated in the study selection and data extraction. TM and YM reviewed the manuscript critically for its scientific content. All authors reviewed and approved the manuscript.
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**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.

Supplementary Files

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