

Magnitude of *Cryptococcus* among HIV patients in sub-Saharan Africa countries: a systematic review and meta-analysis

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Abstract

Background: *Cryptococcus* is encapsulated opportunistic yeast that causes life threatening meningoencephalitis of patients with human immunodeficiency virus (HIV). The magnitude of *Cryptococcus* among HIV patients varies from 1-10% in Western countries as opposed to almost a one third of HIV-infected individuals in sub-Saharan Africa where it is associated with high mortality.

Methodology: By using key terms “*Cryptococcus* among HIV patients in sub-saharan Africa countries”, articles that published in different journals from 2010-2017 searched on Pub-Med and Google scholar database. Those freely accessible and included the prevalence of *Cryptococcus* in the result section, their PDF file was downloaded and the result extracted manually and presented in table. Articles that did not report the prevalence of *Cryptococcus*, with a study design other than cross sectional, or a sample size less than 100, and those duplicated in the same study area and period by the same authors were excluded. The article selection followed the PRISMA guidelines and meta-analysis was performed using OpenMeta(Analyst).

Results: The overall pooled magnitude of *Cryptococcus* among HIV patients in sub-Saharan African countries was 8.3% (95%CI 6.1-10.5%). The highest prevalence was from Uganda (19%) and the least was from Ethiopia at 1.6%. There was 87.2 % of substantial heterogeneity among the studies with p -value < 0.001. The symmetry of the forest plot showed that there was little publication bias. The most commonly used method for diagnosis of *Cryptococcus* was lateral flow assay and latex agglutination test and culture was the least method employed.

Conclusion: The overall pooled magnitude of *Cryptococcus* is high among HIV patients in sub-Saharan African countries. The studies showed substantial heterogeneity, and little publication bias. Most of the studies relied on LFA & LA that showed the scarcity of facilities for fungal culture. Therefore, paying attention to screening HIV patients; those with signs and symptoms of meningitis may help to reduce the loss of HIV patients.

Keywords: *Cryptococcus*, sub-Saharan African, HIV, meta-analysis.

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Introduction

Cryptococcus is an encapsulated opportunistic yeast that

causes life threatening meningoencephalitis of patients with the Human Immunodeficiency Virus (HIV)¹. It is dangerous and leads to death in nearly all patients who are not treated. Nevertheless, the treatment is efficacious². This *basidiomycete* fungus was first isolated in 1894 by Sanfelice in fruit juices and subsequently recovered from the tibial lesion of a patient by Busse and Buschke³. *Cryptococcus* is caused by two species in the genus *Cryptococcus*, *Cryptococcus neoformans* (CN) and *C. gattii*. CN (serotypes A, D, and AD) is found worldwide and causes *Cryptococco-*

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sis most frequently in HIV patients. *C. gattii* (serotypes B and C) is geographically restricted and is infrequently diagnosed in HIV patients except in some areas of Africa⁴.

The magnitude of *Cryptococcus meningitis* among HIV patients varies from 1-10% in Western countries as opposed to almost a third of HIV-infected individuals in sub-Saharan Africa and SouthEast Asia where it is associated with high mortality⁵. Since the introduction of highly active antiretroviral therapy (HAART), the national HIV surveillance programs implemented in Western countries have reported a sharp decrease in the incidence of HIV cases and the estimated number of deaths among HIV patients. While the number of persons living with HIV has increased, the incidence of opportunistic infections like CM has decreased⁵. Meningoencephalitis is the most common clinical manifestation of CN infection, and it is usually incurable, despite antifungal therapy⁶. In the pre-ART era, lifelong fluconazole was recommended after a presentation with CM, but it now appears that late relapse is unlikely during successful ART. International guidelines state that immune restoration by ART permits discontinuation of maintenance therapy. However, evidence to support cessation of secondary prophylaxis is weaker when induction/consolidation therapy is not fungicidal (e.g., fluconazole monotherapy), and isolated CM relapses have been described in patients on ART with CD4 counts up to 495 cells/ μ L⁶⁻⁸. Despite antifungal treatment, acute mortality in low income countries remains between 24% and 43% and *Cryptococcus meningitis* (CM) accounts for 10-20% of all HIV-related deaths in sub-Saharan Africa⁹.

Although effective treatment for HIV disease has decreased the incidence of CM significantly in high income countries, it remains a common cause of morbidity and mortality especially among patients living in sub-Saharan Africa and South East Asia³. The causative organism, *Cryptococcus*, is a facultative intracellular pathogen that has developed numerous strategies allowing it to survive and replicate inside macrophages^{10,11}. In the context of impaired adaptive immune responses, the ability of *Cryptococcus* to evade macrophage killing leads to dissemination, disease and ultimately death¹². The primary immune defect leading to development of CN is impairment of CD4+ T-cell responses, usually secondary to HIV infection¹³.

As far as we know, there is no systematic review and meta-analysis about *cryptococcosis* among HIV patients in sub-Saharan African countries, Therefore, this study can be used as a basis for policy makers, clinicians and researchers.

Literature search method

PubMed and Google Scholar database were searched for potential articles published in the English language, by using key words “*Cryptococcosis* among HIV patients in Sub-Saharan Africa countries”. A total of 144 related articles were retrieved. After carefully examining the title, uniformity of study design, study subjects, sample size and study period, 16 articles were selected for systematic review and meta-analysis¹⁴⁻²⁹.

Eligibility

Articles that reported the magnitude of *Cryptococcus* among HIV patients; those with a cross sectional study design, published in the English language, with sample size of more than 100 and published after 2010 were included.

Data analysis

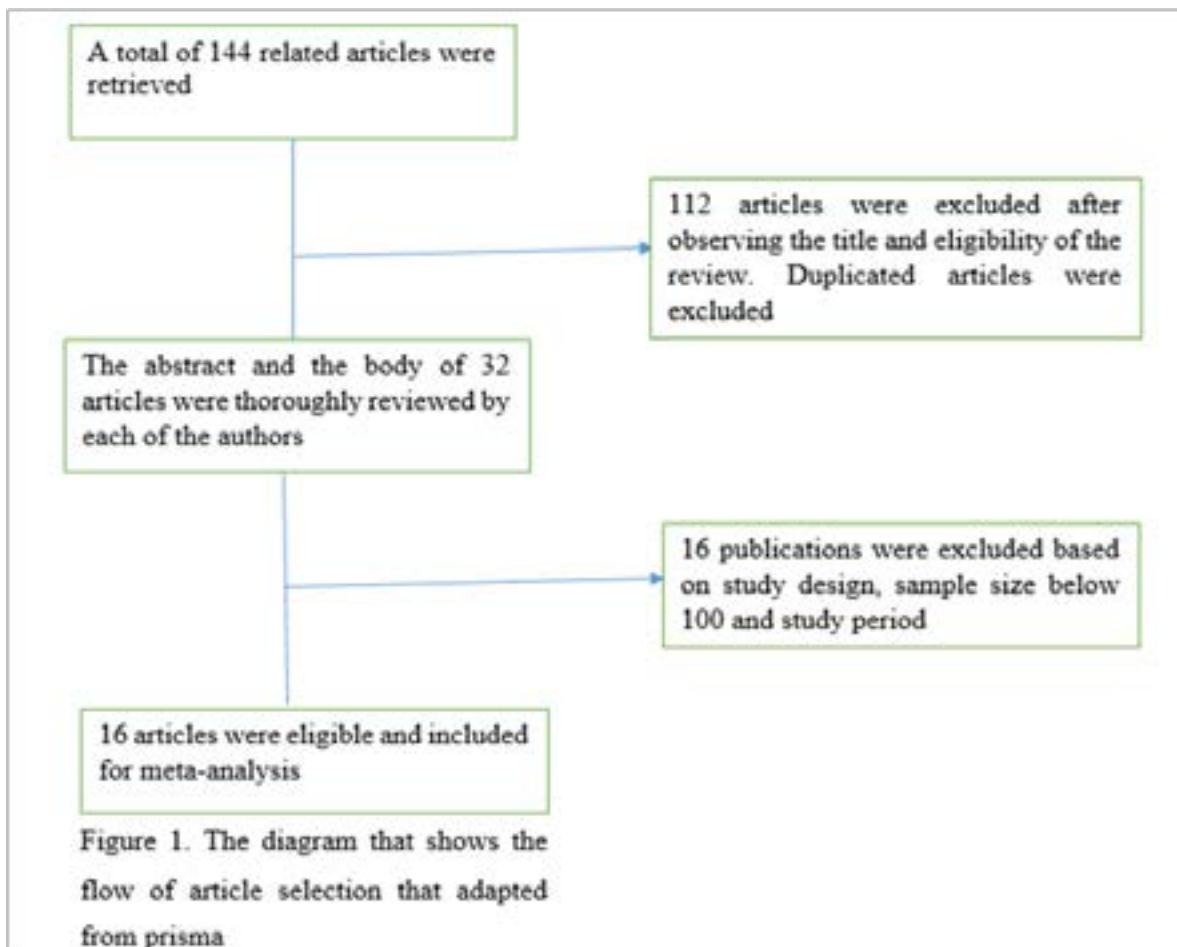
A Systematic review was performed according to the PRISMA protocol. A data extraction tool was used for abstraction of data from each article selected for review and presented in a table. The data analysis was performed using OpenMeta (analyst) software and presented in forest plot. Random effect model was used to calculate the pooled prevalence and heterogeneity of the study were identified by using I² at 95% CI and p-value <0.05.

Data quality

The quality of data was checked by each of individual authors for the similarity of study design, sample size greater than 100 and the inclusions/exclusions criteria was strictly followed.

Results

Based on our inclusions criteria five articles from Ethiopia^{14,19,20,23,28}, four from Nigeria^{16,24,27,29}, three from Tanzania,^{15,21,26} two from Uganda^{18,22} and one from each Cameroon and Malawi^{17,25} respectively were selected and included for the review and meta-analysis.



A different category of HIV patients was enrolled for the respective studies as we tried to present in Table 1. Most of the studies were conducted on adult HIV patients in studies from Uganda^{18,22}, Malawi²⁵, Tanzania²⁶, and Nigeria²⁷. The rest of the studies were conducted on all HIV patients from Cameroon¹⁷, Ethiopia²⁰ and Nigeria²⁴; on

Adolescent & adult HIV admitted patients from Tanzania¹⁵, on ART naïve patients in a study from Nigeria¹⁶, ≥18 years old HIV patients <200 cells/μl CD4 from Ethiopia¹⁹, ≥18 years ART naïve patients <200 cells/μl CD4 from Tanzania²¹, ≥18 years ART-naïve²³, admitted HIV patients from Ethiopia²⁸, ART naïve HIV patients from Nigeria²⁹.

Table 1: Characteristic of 16 articles on Cryptococcosis among HIV patients in sub-Saharan African countries from 2010-2017.

| Authors, Country | Year | Study population | Study Design | Sample Size | Sample Type | Lab. Method | Median CD4cells/ μ l | N ^o (%) of Cryptococcosis |
|---|-------|--|-----------------|-------------|-------------------|------------------------|--------------------------|--------------------------------------|
| Seboxa T, <i>et al</i> , Ethiopia14 | 2010, | Admitted HIV Pts | Cross sectional | 375 | CSF | Indian ink and culture | NA | 30(8) |
| John A. <i>et al</i> , Tanzania15 | 2011, | Adolescent & adult HIV admitted pts | Cross sectional | 161 | CSF, serum | LA | 98 | 17(10.6) |
| Favour O. <i>et al</i> , Nigeria16 | 2012, | ART naïve HIV pts | Cross sectional | 150 | CSF, serum | LA | NA | 19(12.7) |
| Dzoyem J. <i>et al</i> , Cameroon17 | 2012, | All HIV pts | Cross sectional | 294 | CSF, urine, Serum | Indian ink, culture | NA | 21(7.14) |
| Jacinta O. <i>et al</i> , 2012,Uganda18 | | Adult HIV pts | Cross sectional | 367 | CSF/serum | LA | 23 | 69(19) |
| Abere S. <i>et al</i> , Ethiopia19 | 2013, | ≥ 18 yrs. HIV pts and CD4 ≤ 200 cells/ μ l | Cross sectional | 369 | Serum | LA | NA | 31(8.1) |
| Tafese B. <i>et al</i> , Ethiopia20 | 2013, | All HIV pts | Cross sectional | 254 | Serum | LA | NA | 26(10.2) |
| Kinanga A. <i>et al</i> , Tanzania21 | 2014, | ≥ 18 yrs ART naïve pts, < 200 cells/ μ l CD4 | Cross sectional | 140 | urine, serum | LFA | 97 | 10(7.1) |
| Manabe Y, <i>et al</i> , 2014,Uganda22 | | Adult HIV pts | Cross sectional | 351 | Urine | LFA | 57 | 25(7) |
| Anton R. <i>et al</i> , Ethiopia23 | 2015, | ≥ 18 yrs ART-naïve | Cross sectional | 129 | CSF, serum | LA | 21 | 2(1.6) |
| Ogba O. <i>et al</i> , Nigeria24 | 2015, | All HIV patients | Cross sectional | 272 | Serum | LA | 100.7 | 14(5.1) |
| Chifundo C. <i>et al</i> , Malawi25 | 2015, | Adult HIV patients | Cross sectional | 113 | Whole blood | LFA | NA | 2(1.8) |
| Joan R. <i>et al</i> , Tanzania26 | 2015, | Adult HIV Pts | Cross sectional | 213 | Serum | LA&LFA | 19 | 7(3) |
| Christopher A. <i>et al</i> , 2015, Nigeria27 | | Adult HIV Pts | Cross sectional | 333 | Serum | LA | NA | 33(9.91) |
| Admasu T. <i>et al</i> , Ethiopia28 | 2016, | Admitted HIV pts | Cross sectional | 198 | Serum | LFA | 98 | 16(8.1) |
| Baba W <i>et al</i> , Nigeria29 | 2017, | ART naïve HIV patients | Cross sectional | 215 | Serum | LFA | 58 | 37(16.7) |

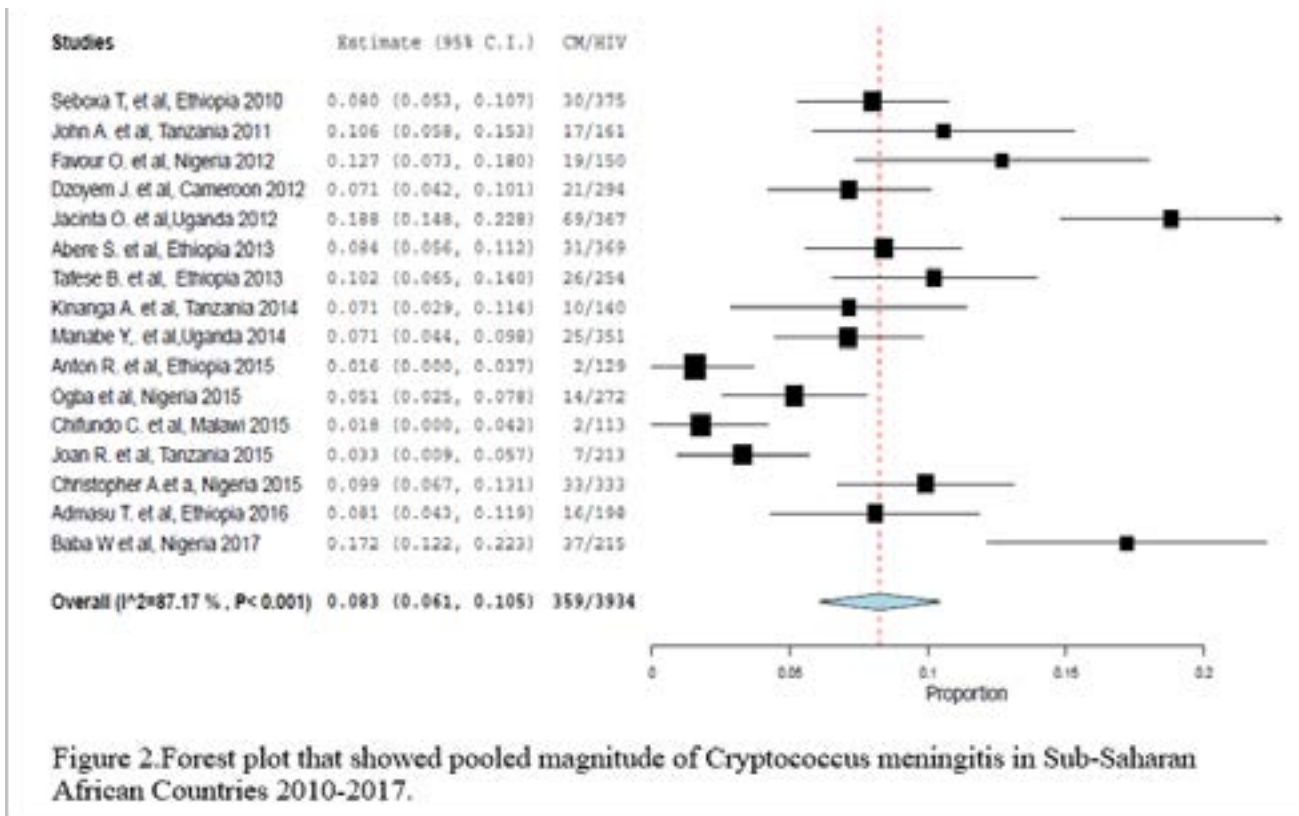
All the studies were conducted using a cross sectional design. The largest sample size was from Ethiopia is 375 participants¹⁴ and the smallest was from Malawi with 113 participants²⁵. Different types of samples were used to diagnosis the presence of *Cryptococcus* infection. None the less, most of the studies were conducted using serum^{19,20,24,26-29}, both cerebrospinal fluid (CSF)/serum^{15,16,18,23}, CSF¹⁴, urine and serum²¹, CSF, urine & serum¹⁷, urine²² and whole blood²⁵. More than 50% of the studies used latex agglutinations (LA) laboratory method and the rest of the studies used Lateral flow assay (LFA), both LFA & LA, and two studies used both Indian ink and fungal culture method.

The highest of *Cryptococcosis* magnitude were reported

from Uganda which was 19.0% in 2012¹⁸ and the least was from Ethiopia in 2015 which was (1.6%)²³. The median CD4 count was reported in more than 50% of studies in which the highest was reported from Nigeria that is 101 cells/ μ l²⁴ and the lowest count was reported from Tanzania 19 cells/ μ l²⁶.

Outcome of interest

According to our meta-analysis presented on the forest plot on figure below the pooled magnitude of *Cryptococcosis* in sub-Saharan African countries was 8.3 % (95%CI 6.1-10.5%, P<0.001). The random effect model showed that there is substantial heterogeneity among the studies which is I² = 87.17% with p value <0.001.



Discussion

Cryptococcus a cosmopolitan fungus that causes human disease mainly in patients infected with HIV that is mainly presented as *Cryptococcosis* worldwide³⁰. However, the condition is more serious in low income countries, especially in sub-Saharan African countries where HIV/AIDS is more prevalent and resources for diagnosis CM are scarce.³¹

According to our study the overall pooled prevalence of *Cryptococcosis* was 8.3 % (95% CI, 6.1-10.5%, P<0.001) which is higher than a study conducted in USA (2.8 %)³². It is also comparable with a report on global burden of CM that is 6.0% in HIV patients with CD4 count lower than 100 cells/ μ l³³ and one meta-analysis study in the world population with HIV that is 6.5%³⁴. Even if there is lack of meta-analysis data for each continent, the prevalence of *Cryptococcosis* high in sub-Saharan African countries when compared to the rest of the world. Even though the prevalence is comparable with the external world *Cryptococcosis* is a neglected disease in sub-Saharan African countries that need immediate attention especially for those with low CD4 counts.

Since the study population is from different countries the random effect model was used to determine the effect size. The random effect model showed that there is higher heterogeneity among the studies which is mostly considered. If $I^2 > 75\%$, this indicates higher heterogeneity. In our case $I^2 = 87.17\%$, p-value <0.001 that showed substantial heterogeneity and it is also statistically significant. The symmetry of forest plot funnel showed that some studies caused insignificant publication bias since the study is conducted with the same study design and study populations even though there is a difference between study area and period.

Cryptococcus is a fungus that lives in the environment throughout the world. People can become infected with *Cryptococcus* after breathing in the microscopic fungus, although most people who are exposed to the fungus never get sick from it. *Cryptococcus* infections are extremely rare in people who are otherwise healthy; most cases occur in people who have weakened immune systems, particularly those who have advanced HIV/AIDS³⁵. In sub-Saharan Africa countries since there is lack of facilities for diagnosis of *Cryptococcus* which is based on Indian ink if available, it may lead false positive or negative results since there is lack of culture facility, relying on availability of

LFA & LA tests for confirmation. As we tried to present in Table 1 from our systematic review most of the studies rely on LFA and LA test in which only one study used fungal culture that supported our idea.

Conclusion

The overall pooled magnitude of *Cryptococcosis* is high among HIV patients in sub-Saharan African countries. The studies showed substantial heterogeneity with little bias. Most of the studies relied on LFA & LA that showed the scarcity of facility for fungal culture. Even though our meta-analysis showed results comparable to the rest of the world, attention to screening the HIV patients especially those with signs and symptoms of meningitis may help to reduce the loss of HIV patients. LFA & LA is helpful for the diagnosis *Cryptococcus* as point of care test.

Authors' contribution

TA: Conceived the idea, searched the articles, extracted the data performed systematic review and Meta-analysis and prepared the manuscript. SA, TA, and DD: Participated on article selection, advised and editing of the manuscript. All authors have read the final manuscript.

Ethical approval

Ethical clearance was not required and was not necessary for this study.

Conflicts of interest

We authors declare that they have no conflicts of interest

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