Global Burden of Disease of HIV-Associated Cryptococcal Meningitis: an Updated Analysis

Radha Rajasingham, MD [1]
Rachel M Smith, MD [2]
Benjamin J Park, MD [2]
Joseph N Jarvis, MRCP [3,4,5,6]
Nelesh P Govender, MMed [7]
Tom M Chiller, MD [2]
Prof David W Denning, FRCP [8]
Angela Loyse, MD (Res) [9]
David R Boulware, MD[1]

[1] Division of Infectious Diseases and International Medicine, Department of Medicine, University of Minnesota, Minneapolis, MN, USA

[2] Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, CDC, Atlanta, GA, USA

[3] Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK

[4] Botswana-University of Pennsylvania Partnership, Gaborone, Botswana

[5] Division of Infectious Diseases, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, PA, USA

[6] Botswana-Harvard AIDS Institute Partnership, Gaborone, Botswana

[7] National Institute for Communicable Diseases –Centre for Opportunistic, Tropical and Hospital Infections, Johannesburg, South Africa; Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

[8] University of Manchester, Manchester Academic Health Science Centre and the National Aspergillosis Centre, University Hospital of South Manchester, Manchester, UK

[9] Cryptococcal Meningitis Group, Research Centre for Infection and Immunity, Division of Clinical Sciences, St. George's University of London, London, UK

Keywords: Cryptococcus, cryptococcal meningitis, epidemiology, Global Burden of Disease, HIV/AIDS, AIDS-Related Opportunistic Infections, cryptococcosis

Corresponding Author:
Radha Rajasingham, MD
Address: 420 Delaware St SE, MMC 250, Minneapolis, MN, USA 55455
Email: radha@umn.edu   Phone: +1.612.626.8171

Abstract

Background: *Cryptococcus* is the most common cause of meningitis amongst adults living with HIV in sub-Saharan Africa. Global burden estimates are critical to guide prevention strategies and determine treatment needs.

Methods: We used 2014 Joint United Nations Programme on HIV/AIDS estimates of adults with HIV and antiretroviral therapy (ART) coverage. Estimates of CD4<100 cells/μL, virologic failure incidence, and loss-to-follow up were from published multinational cohorts in low- and middle-income countries. We calculated those at risk for cryptococcal infection, specifically those with CD4<100 cells/μL not on ART, and those with CD4<100 cells/μL on ART but lost-to-follow up or with virologic failure. Cryptococcal antigenemia (CRAG) prevalence by country was derived from 46 studies globally. Based on CRAG prevalence in each country/region, we estimated the annual numbers developing and dying from cryptococcal meningitis.

Findings: We estimated an average CRAG prevalence of 6·0% among CD4<100 cells/μL, with 278,000 (95% CI 195,500 to 340,600) CRAG+ persons globally and 223,100 (95% CI 150,600 to 282,400) incident cryptococcal meningitis cases globally in 2014. Sub-Saharan Africa accounted for 73% of the estimated cryptococcal meningitis cases (162,500 cases; 95% CI 113,600 to 193,900). Cryptococcal-related deaths were estimated at 181,100 (95% CI 119,400 to 234,300) globally, with 135,900 (75%) (95% CI 91,000 to 161,000) deaths in sub-Saharan Africa. Globally, *Cryptococcus* was responsible for 15% of AIDS-related mortality (95% CI 10% to 19%).

Interpretation: Our analysis highlights the substantial ongoing burden of HIV-associated cryptococcal disease, primarily in sub-Saharan Africa.

Introduction

Cryptococcus is the most common cause of meningitis among adults living with human immunodeficiency virus (HIV) in sub-Saharan Africa.[1-3] Despite antiretroviral therapy (ART) expansion, prevalence of cryptococcal infection remains largely unchanged in low- and middle-income countries (LMICs), unlike high-income countries (HICs).[4-7] Estimates of national, regional, and global burden of cryptococcal meningitis are critical to guide prevention strategies and determine needs for diagnostic tests, antifungal medicines, and medical supplies, such as lumbar puncture needles and manometers.

In 2008, the global annual incidence of cryptococcosis was estimated as 957,900 cases per year (range, 371,700-1,544,000 cases).[8] This estimate was based on published cohorts from the pre-ART era, and the wide confidence interval (CI) indicates the high level of uncertainty of these estimates. Since then, extensive ART expansion has occurred; acquired immunodeficiency syndrome (AIDS)-related deaths have declined by 45% from 2.0 to 1.1 million deaths.[9] The significance of asymptomatic cryptococcal antigenemia (CRAG) as a precursor to symptomatic meningitis and death has been further defined,[10-13] and more CRAG prevalence data have been published (Figure 1).

Recently, the World Health Organization (WHO), U.S. President's Emergency Plan for AIDS Relief (PEPFAR), and U.S. Department of Health and Human Services have recommended CRAG screening among those with CD4+ T-cell count <100 cells/μL who are not receiving effective ART.[14-16] CRAG screening coupled with preemptive antifungal therapy has proven survival benefit,[10, 12, 17] and has been incorporated into HIV national guidelines in Botswana, Kenya, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, U.S., and Zimbabwe with consideration elsewhere. Estimating the cryptococcal disease burden helps stakeholders weigh the costs and resources required for hospital-based meningitis treatment versus investment of resources into preemptive CRAG screen-and-treat strategy.[18]

We provide an updated estimate of the global incidence of HIV-associated cryptococcal disease using published Joint United National Programme on HIV and AIDS (UNAIDS) data on HIV incidence, ART access, retention-in-care, and published CRAG prevalence data.

Methods

Burden of Cryptococcus

Global Estimates of HIV Infection

We used UNAIDS 2014 country-level estimates of global incidence and cases of HIV infection (Table 1); specifically published estimates of adults living with HIV, adults (age 15+) receiving ART, and percent receiving ART among adults eligible for ART per WHO 2010 guidelines (CD4 <350 cells/µL) via UNAIDS 2014 Spectrum Estimates,[19] UNAIDS GAP Report,[20] and WHO Global Health Observatory database.[21] Each UNAIDS and WHO estimate was originally published with a low and high estimate range as a measure of uncertainty. Using the estimates of those with a CD4<350 cells/µL on ART, and those eligible for ART, we calculated the ART gap (not receiving ART but CD4<350 cells/µL). We used UNAIDS and WHO reports for estimates of CD4<100 cells/µL,[22] CD4 100-200 cells/µL, virologic failure,[23] and loss to follow up.[23] See Table 1, and Appendix (p2 to 8) for further details.

For each point estimate a 95% CI was obtained. To further account for bias and limitations of the primary literature, the 95% CI was widened by adding/subtracting 1.5 times the difference between the right and left limits respectively. Thus, the uncertainty ranges described in the Methods below and in Table 1 are conservatively wider than 95% CI from the published literature.

Estimate of persons at risk for Cryptococcal Disease

We defined the total number of persons *at risk* for cryptococcosis by country and region, defined as: 1) adults with CD4<100 cells/µL not on ART, and 2) adults with CD4<100 cells/µL on ART but either lost to follow up or with virologic failure. Those who start ART but do not have virologic failure, and are CRAG negative, have no risk of developing cryptococcal infection. The estimate of adults with a CD4 <100 cells/µL was 22·5% (Range: 19% to 26%) among those with CD4<350 cells/µL in LMICs. [22, 24] In HICs, 18·5% (Range: 16% to 21%) of those with a CD4<350 cells/µL were estimated to have a CD4<100 cells/µL.[22, 24] Thus, we estimated the number with CD4<100 cells/µL on ART from the ART percent coverage (ART percent coverage x ART eligible (CD4<350 cells/µL) x proportion with CD4<100 cells/µL, accounting for uncertainty around those estimates (*Appendix pages 2 and 3*).

Based on a UNAIDS systematic review, we assumed 16% (Range: 12% to 20%) of persons initiating ART retained-in-care had virologic failure at 12 months.[23] After completing one year on ART, we assumed the virologic failure incidence to be one-third of that in the first year at

Burden of Cryptococcus

5·3% (95% CI 4·0% to 6·6%).[23, 25-27] This review cites observational data from Canada, the U.S., and the United Kingdom with similar frequencies of viral suppression at 12 months.[28-30] Retention-in-care is based on country level estimates from UNAIDS,[19] and where missing, we used continental mean estimates.

CRAG Prevalence

We then estimated the total number of persons with CRAG using blood CRAG prevalence studies from 1989 to 2016, either in the published literature, or posters presented at conferences, among outpatient populations for 17 African countries, 5 Asian countries, 5 Latin American countries, the U.S., and United Kingdom (Figure 1). CRAG prevalence studies of solely inpatient populations were excluded, as prevalence may be higher in those presenting to the hospital, and not representative of the asymptomatic outpatient population that is ideal for CRAG screening. For countries with available data, CRAG prevalence amongst persons with a CD4<100 cells/µL was used for that specific country along with the associated 95% CI by Fisher's Exact test (see *Appendix p4, p10*). For countries without CRAG prevalence data, we used the pooled, weighted continental mean estimate. Thereafter, we estimated the number with prevalent CRAG by country and region by multiplying persons *at risk* for cryptococcal disease by the CRAG prevalence of the country/region (described above and in Table 1).

CRAG-positive persons who develop Cryptococcal Meningitis

Not all CRAG-positive patients develop cryptococcal meningitis. Estimates of CRAG-positive adults who go on to develop symptomatic cryptococcal meningitis were from published cohort studies.[10-12, 31-33] We estimated 70% (Range: 56% to 84%) of CRAG+ persons progressed to develop cryptococcal disease or died without diagnosis, unless treated with ART and/or preemptive fluconazole (*Appendix p5*). Without ART or preemptive fluconazole therapy, we assumed 95% (Uncertainty Range: 90% to 100%) progression in all regions (expert opinion of authors) with a 5% competing risk of death from other causes or comorbid conditions.[10, 11, 34-36]

CRAG-negative persons at risk for Cryptococcal Infection

Burden of Cryptococcus

The cryptococcal meningitis incidence amongst persons with CD4<200 cells/µL who were initially blood CRAG-negative, before initiating ART is 5·14 per 100 person-years.[33] This is estimated from the only publication available for estimating incidence of cryptococcal meningitis *before initiation of ART* in Uganda, and for this we assumed an incidence range of 2·6 to 9 cryptococcal events per 100 person-years. In high-income countries, we assumed the risk of development of cryptococcal meningitis was 50% lower, due to more intensive monitoring and additional second-line ART options.   For those persons with CD4<200 cells/µL, initially prevalent CRAG-negative status and not receiving ART, we assumed a competing risk of starting ART or death of 50% (i.e. 500/1000 person-years).

Annual Incidence of Cryptococcal Meningitis

Annual incidence of cryptococcal meningitis includes the estimation of those CRAG-positive persons who developed symptomatic meningitis, both in care newly initiating ART with unmasking disease and those not in care and/or not on ART with AIDS progression.

Cryptococcal Meningitis Deaths

We estimated 1-year mortality in low-income countries (LICs) as 70% (Uncertainty Range: 59% to 81%) after cryptococcal meningitis for those in care and 100% for those not in care (*Appendix p5*).[30, 47-52] For middle-income countries, we presumed 1-year mortality of 40% (Uncertainty Range: 34% to 46%), based on summary statistics of outcomes of those receiving amphotericin B and fluconazole, and 60% for those not originally in care (i.e., not receiving ART).[37, 38] In Europe (including Eastern Europe and Russia), we estimated 1-year mortality to be 30% for those in care and 45% for those not in care (*expert opinion of authors*). In North America, we estimated 1-year mortality to be 20% for those in care and 30% for those not in care.[39]

Uncertainty Analysis

To account for parameter uncertainty in the primary data, we used probability distributions to describe a range for each point estimate of interest. We varied each value in our model simultaneously with, sampled from *a priori* defined probability distributions. The outputs from

this uncertainty analysis generated CIs for each parameter. Full details of each parameter and distribution are available in the *Appendix (pages 7 and 8)*.

We used empirical data, when available, to define distributions (*Appendix p7 and 8*). We used standard beta distributions for binomial data, and normal distribution for continuous estimates. Using Microsoft Excel 2013, we randomly selected a value for each parameter within the appropriate distribution, and used the combination of these values to estimate the number of CRAG-positive persons, annual incidence of cryptococcal meningitis, and number of deaths from cryptococcal meningitis for each region. Using 50,000 iterations, we obtained empirical distributions corresponding to posterior distributions calculated by Monte Carlo simulations. These distributions were used to generate a point estimate (posterior mean) and Monte Carlo CIs from the lower 2·5% and higher 97·5% for the estimates of CRAG, meningitis, and fatality from cryptococcal disease.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In December 2013, 31·8 million (range 30·1 to 33·7 million) adults were living with HIV globally, with 21·7 million (20·7 to 23·0 million) living in sub-Saharan Africa. Globally, 19·5 million adults were eligible for ART (CD4<350 cells/μL) by WHO 2010 guidelines, with 11·3 million actually receiving ART. Globally, 8·2 million people had CD4<350 cells/μL but not receiving ART, with 5·2 million of these individuals in sub-Saharan Africa. We estimated 4·3 million adults have a CD4<100 cells/μL globally, and of these, 1·8 million (42%) were not on ART. This group is at particularly high risk for opportunistic infections, including cryptococcosis. In 2013, there were an estimated 1·4 million (range 1·1 to 1·6 million) AIDS-related deaths globally, per UNAIDS estimates.

We estimated an average global CRAG prevalence of 6·0% (95% CI 5·8% to 6·2%) among persons with CD4<100 cells/μL, with the number with cryptococcal antigenemia (CRAG-

positive) to be 278,000 (95% CI 195,500 to 340,600) persons globally in 2014 (**Figure 2**). Annually, we estimate there are 223,200 (95% CI 150,600 to 282,400) cases of cryptococcal meningitis globally, with 73% of cases (n=162,500, 95% CI 113,600 to 193,900) occurring in sub-Saharan Africa (*Supplemental Figure 2, Appendix p9*). The region with the second highest incidence was Asia & Pacific (20% of total), with an annual incidence of 43,200 (95% CI 25,300 to 64,700) cases of cryptococcal meningitis. Annual fatalities from cryptococcal meningitis are estimated at 181,100 (95% CI 119,400 to 234,300) deaths globally, with 135,900 (75%) (95% CI 93,900 to 163,900) deaths occurring in sub-Saharan Africa. Globally, cryptococcal meningitis results in 15% of AIDS-related mortality (95% CI 10% to 19%). Table 2 highlights the countries with the highest incidence of cryptococcal meningitis. Table 3 specifies cryptococcal infection burden by region. *Supplemental Table 1* provides country-level listing of data for all parameters considered in the model.

Discussion

We estimated the global incidence of cryptococcal meningitis to be substantial at 223,100 cases annually (95% CI 150,600 to 282,400), resulting in 181,100 (95% CI 119,400 to 234,300) annual deaths in 2014. Sub-Saharan Africa continues to bear the brunt of this burden. We estimated cryptococcal meningitis causes 15% (95% CI 10% to 19%) of AIDS-related deaths globally. Although the absolute number of cryptococcal deaths has decreased since the prior 2008 estimate,[8] the proportion of AIDS-related mortality remains similar. Our estimates, and others, imply that cryptococcosis remains the second most common cause of AIDS-related mortality, only narrowly behind tuberculosis.[40,41-45] These updated accurate disease estimates enable appropriate ordering of essential antifungals, diagnostics, and medical supplies.

Importantly, prevention of cryptococcal disease has demonstrated survival benefit and is cost-saving to healthcare systems.[18, 38, 46, 47] The cost of CRAG screening programs needs to be appreciated in the context of the treatment costs for cryptococcal meningitis patients in LMICs. For example, the per patient cost of cryptococcal meningitis treatment in Uganda with amphotericin B and fluconazole is $510 for two weeks.[38] Consolidation and maintenance therapy with fluconazole for one year costs $60 per meningitis survivor ($0·15 per 200mg fluconazole)

Burden of Cryptococcus

in LMICs.[48] Thus, with an annual estimated incidence of 12,200 meningitis cases in Uganda, $6·2 million would be required for initial meningitis diagnosis and treatment. Conversely, if CRAG screening costs $4·00 [49] plus $24·60 for the WHO-recommended preemptive treatment regimen,[9] screening those 110,500 persons at risk for cryptococcal disease in Uganda with CD4<100 cells/μL and preemptively treating those 15,500 CRAG+ costs $822,600, which is 13% of the cost of meningitis treatment with >40% better long-term survival.[50]

Evaluation of results

Compared with prior 2008 estimates,[8] our 2014 estimates are lower, as the HIV/AIDS landscape has changed with rapid ART expansion and a 45% decrease in AIDS-related mortality from 2005 to 2013 in sub-Saharan Africa.[9] We also used a different methodologic approach using CRAG prevalence, as CRAG+ status is a known predictor of progression to cryptococcal meningitis. Country-specific CRAG prevalence data were less available previously.

Additionally, we compared our estimates to the few published estimates of the national incidence of cryptococcal meningitis. Our model estimated 2,945 U.S. cases of cryptococcal meningitis annually. In the U.S., an estimated 3,400 recognized cryptococcal meningitis hospitalizations were identified by ICD-9 hospital billing codes, of which two-thirds were HIV-related.[39] In South Africa during 2015, the national reported laboratory-confirmed cryptococcal meningitis cases were 6174 and an additional 4295 CRAG+ persons without documented meningitis.[5] We estimated 21,400 cases in South Africa for 2014. This discrepancy likely reflects a proportion of persons living with AIDS not in care, undiagnosed, and lost-to-follow-up who do not receive a *reported* laboratory-confirmed diagnosis. An estimated 554,990 South Africans are living with AIDS,[5] and the median CD4 count among ART-naïve persons entering care was 150 cells/μL in 2015.[51] We estimated 382,400 South Africans with a CD4<100 cells/μL would be at risk for cryptococcal disease. In 2015, the South African National Health Laboratory Service processed 360,000 CD4 counts <100 cells/μL (~10% of nationwide total) of which ~80% are estimated to be from unique individuals.[51]

One limitation of this estimate is our use of UNAIDS 2014 data, when 2016 data are available. The most recent figures were not used, as the 2014 UNAIDS estimates have published numbers of those with CD4<350 cells/μL by country. We used these numbers to estimate CD4<100 cells/μL and thereby estimate the population at risk for cryptococcal infection.

Burden of Cryptococcus

UNAIDS no longer publishes the number with CD4<350 cells/µL by country; thus a 2016 estimate would require us to project the number with a CD4<100 cells/µL based on the proportion of HIV-infected, thereby adding more uncertainty to our estimates. At the time of this publication, 2016 data were also missing in several critical country estimates.

Further limitations of our analysis are related to lack of UNAIDS country data for HICs. A second limitation is that many countries do not have any CRAG prevalence data available, so estimates were extrapolated from countries in the region with CRAG data available. There is also significant heterogeneity in studies reporting CRAG prevalence. Solely inpatient CRAG prevalence studies were excluded; however, some studies included symptomatic and asymptomatic persons, which may overestimate point estimates for CRAG prevalence and yet underestimate the progression to symptomatic meningitis, if already symptomatic. CRAG prevalence studies used different testing methods (latex agglutination vs. lateral flow assay) with different sensitivities for detection. There are relatively few studies which assess progression of asymptomatic CRAG+ to symptomatic meningitis or death.[10-12, 31, 32] Our estimate of asymptomatic cryptococcal antigenemia progression to symptomatic meningitis was based on a weighted average of mixed studies where many were not treated at all.[11] Thus progression to meningitis/death may be an underestimate and will vary with access to timely ART. To account for bias and limitations of the primary data, we performed a probabilistic sensitivity analysis that generated Monte Carlo CIs according to the probability distribution of possible outcomes. Given the limited high quality source data, we broadened our estimates of uncertainty of the primary data by widening our CIs to use 99.7% CI with three standard deviations above and below the weighted averages of included studies. Furthermore, our estimates of meningitis incidence and death are based on point-prevalence data over the past 10 years. These estimates do not reflect averages of historic trends nor are they based on dynamic disease models to predict future disease incidence. However, CRAG prevalence data has been relatively constant by country over time.[10, 13, 52] Notably, the proportion of AIDS-related mortality due to cryptococcosis has remained stable from prior estimates.[8] However with improvements in ART access and retention-in-care, estimates of incidence of cryptococcal meningitis should correspondingly decrease over time.

Despite global improvement in access to ART, the number HIV-infected persons with a CD4 count <100 cells/µL entering care is still substantial at ~20-25% of those presenting to care.[53]

Burden of Cryptococcus

Thus, the annual number with cryptococcal infection remains high at 278,000 globally. Cryptococcal meningitis is an excellent metric of HIV treatment program failure. In 2016, no HIV-infected person *should* develop cryptococcal disease, yet due to challenges with: late diagnosis, linkage to care, ART access, retention in care, and virologic failure on ART,[24, 53, 54] the often final event in a failed cascade of HIV care is the development of cryptococcal meningitis. Until linkage to comprehensive HIV care can be improved, cryptococcal screening programs are a worthy investment that identify populations at high risk for death. In order to reduce AIDS-related deaths, ensuring that those with CD4 counts <100 cells/µL are CRAG screened, preemptively treated (if CRAG+), and initiated on ART remains critical.

Our analysis highlights the ongoing substantial burden of HIV-associated cryptococcal disease, primarily in sub-Saharan Africa but also in Asia. Ensuring timely HIV testing and rapid linkage-to-care remains an urgent priority. CRAG screening and preemptive fluconazole treatment should be part of a routine package of enhanced care for those presenting late with AIDS at time of entering into HIV care.

has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck and Pfizer. He is a longstanding member of the Infectious Disease Society of America Aspergillosis Guidelines group, the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines group and the British Society for Medical Mycology Standards of Care committee. In addition, Dr. Denning has a patent Assays for fungal infection licensed. Dr. Govender reports grants from NIH, another from MSD , personal fees from Fujifilm Pharma, personal fees from Astellas, grants from CDC, grants from NHLS Research Trust, outside the submitted work. Dr. Boulware reports grants from NIH, and grants from UK MRC, during the conduct of the study. Dr. Jarvis reports grants from Gilead Sciences Europe, outside the submitted work.

References:

1.   Durski KN, Kuntz KM, Yasukawa K, Virnig BA, Meya DB, Boulware DR. Cost-effective diagnostic checklists for meningitis in resource-limited settings. Journal of acquired immune deficiency syndromes. 2013; **63**(3): e101-8.

2.   Jarvis JN, Meintjes G, Williams A, Brown Y, Crede T, Harrison TS. Adult meningitis in a setting of high HIV and TB prevalence: findings from 4961 suspected cases. BMC Infect Dis. 2010; **10**: 67.

3.   Siddiqi OK, Ghebremichael M, Dang X, Atadzhanov M, Kaonga P, Khoury MN, et al. Molecular diagnosis of central nervous system opportunistic infections in HIV-infected Zambian adults. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014; **58**(12): 1771-7.

4.   Jarvis JN, Boulle A, Loyse A, Bicanic T, Rebe K, Williams A, et al. High ongoing burden of cryptococcal disease in Africa despite antiretroviral roll out. AIDS. 2009; **23**(9): 1182-3.

5.   National Institute for Communicable Diseases. GERMS-South Africa Annual Report 2015. [cited 2016 25 Oct]; Available from: www.nicd.ac.za/?page=publications&id=196

6.   Mirza SA, Phelan M, Rimland D, Graviss E, Hamill R, Brandt ME, et al. The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large

metropolitan areas, 1992-2000. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2003; **36**(6): 789-94.

7.   Wall EC, Everett DB, Mukaka M, Bar-Zeev N, Feasey N, Jahn A, et al. Bacterial meningitis in Malawian adults, adolescents, and children during the era of antiretroviral scale-up and Haemophilus influenzae type b vaccination, 2000-2012. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014; **58**(10): e137-45.

8.   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 (London, England). 2009; **23**(4): 525-30.

9.   UNAIDS. Gap Report, Fact Sheet. 2014 [cited 21 Dec 2014]; Available from: http://www.unaids.org/en/resources/campaigns/2014gapreport

10.   Meya DB, Manabe YC, Castelnuovo 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 < or = 100 cells/microL who start HIV therapy in resource-limited settings. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2010; **51**(4): 448-55.

11.   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 : an official publication of the Infectious Diseases Society of America. 2009; **48**(7): 856-62.

12.   Letang E, Muller MC, Ntamatungiro AJ, Kimera N, Faini D, Furrer H, et al. Cryptococcal antigenemia in immunocompromised HIV patients in rural Tanzania: A preventable cause of early mortality. Open Forum Infect Dis. 2015; **2**(2): ofv046.

13.   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): 959-65.

14.   World Health Organization. Rapid advice: Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. 2011 December [cited 2015 1 Nov]; Available from: www.who.int/hiv/pub/cryptococcal_disease2011

15.   PEPFAR. The President's Emergency Plan for AIDS Relief: FY 2013 Technical Considerations. 2013 [cited July 26, 2013]; Available from: www.pepfar.gov/documents/organization/199147.pdf

16.   Masur H, Brooks JT, Benson CA, Holmes KK, Pau AK, Kaplan JE. Prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Updated Guidelines from the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association of the Infectious Diseases Society of America. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014; **58**(9): 1308-11.

17.   Mfinanga S, Chanda D, Kivuyo SL, Guinness L, Bottomley C, Simms V, et al. Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial. Lancet. 2015; **385**(9983): 2173-82.

18.   Jarvis JN, Harrison TS, Lawn SD, Meintjes G, Wood R, Cleary S. Cost effectiveness of cryptococcal antigen screening as a strategy to prevent HIV-associated cryptococcal meningitis in South Africa. PloS one. 2013; **8**(7): e69288.

19.   UNAIDS. Spectrum. 2013 [cited 2015 1 Nov]; Available from: www.unaids.org/en/dataanalysis/datatools/spectrumepp

20.   Chan-Tack KM, Chengappa KS, Wolf JS, Kao GF, Reisler RB. Immune reconstitution inflammatory syndrome presenting as sinusitis with inflammatory pseudotumor in an HIV-infected patient: a case report and review of the literature. AIDS Patient Care STDS. 2006; **20**(12): 823-8.

21.   World Health Organization. Global Health Observatory (GHO) data 2015 [cited 2015 1 Nov]; Available from: www.who.int/gho/en/

22.   UNAIDS. Access to Antiretroviral Therapy in Africa: Status report on progress towards the 2015 targets. 2013 Geneva. 2013; **www.unaids.org/en/resources/documents/2013**.

23.   McMahon JH, Elliott JH, Bertagnolio S, Kubiak R, Jordan MR. Viral suppression after 12 months of antiretroviral therapy in low- and middle-income countries: a systematic review. Bulletin of the World Health Organization. 2013; **91**(5): 377-85E.

24.   Avila D, Althoff KN, Mugglin C, Wools-Kaloustian K, Koller M, Dabis F, et al. Immunodeficiency at the start of combination antiretroviral therapy in low-, middle-, and high-income countries. Journal of acquired immune deficiency syndromes (1999). 2014; **65**(1): e8-16.

25.   Castelnuovo B, Kiragga A, Mubiru F, Kambugu A, Kamya M, Reynolds SJ. First-line antiretroviral therapy durability in a 10-year cohort of naive adults started on treatment in Uganda. Journal of the International AIDS Society. 2016; **19**(1): 20773.

26.   Castelnuovo B, Kiragga A, Musaazi J, Sempa J, Mubiru F, Wanyama J, et al. Outcomes in a Cohort of Patients Started on Antiretroviral Treatment and Followed up for a Decade in an Urban Clinic in Uganda. PloS one. 2015; **10**(12): e0142722.

27.   Sanne IM, Westreich D, Macphail AP, Rubel D, Majuba P, Van Rie A. Long term outcomes of antiretroviral therapy in a large HIV/AIDS care clinic in urban South Africa: a prospective cohort study. Journal of the International AIDS Society. 2009; **12**: 38.

28.   Bansi L, Sabin C, Gilson R, Gazzard B, Leen C, Anderson J, et al. Virological response to initial antiretroviral regimens containing abacavir or tenofovir. The Journal of infectious diseases. 2009; **200**(5): 710-4.

29.   Uy J, Armon C, Buchacz K, Wood K, Brooks JT. Initiation of HAART at higher CD4 cell counts is associated with a lower frequency of antiretroviral drug resistance mutations at virologic failure. Journal of acquired immune deficiency syndromes (1999). 2009; **51**(4): 450-3.

30.   Moore DM, Mermin J, Awor A, Yip B, Hogg RS, Montaner JS. Performance of immunologic responses in predicting viral load suppression: implications for monitoring patients in resource-limited settings. Journal of acquired immune deficiency syndromes (1999). 2006; **43**(4): 436-9.

31.   Govender N, Roy M, Mendes J, Zulu T, Chiller T, Karstaedt A. Evaluation of screening and treatment of cryptococcal antigenaemia among HIV-infected persons in Soweto, South Africa. HIV medicine. 2015.

32. Pongsai P, Atamasirikul K, Sungkanuparph S. The role of serum cryptococcal antigen screening for the early diagnosis of cryptococcosis in HIV-infected patients with different ranges of CD4 cell counts. The Journal of infection. 2010; **60**(6): 474-7.

33. Parkes-Ratanshi R, Wakeham K, Levin J, Namusoke D, Whitworth J, Coutinho A, et al. Primary prophylaxis of cryptococcal disease with fluconazole in HIV-positive Ugandan adults: a double-blind, randomised, placebo-controlled trial. Lancet Infect Dis. 2011; **11**(12): 933-41.

34. Mwaba P, Mwansa J, Chintu C, Pobee J, Scarborough M, Portsmouth S, et al. Clinical presentation, natural history, and cumulative death rates of 230 adults with primary cryptococcal meningitis in Zambian AIDS patients treated under local conditions. Postgraduate medical journal. 2001; **77**(914): 769-73.

35. Mayanja-Kizza H, Oishi K, Mitarai S, Yamashita H, Nalongo K, Watanabe K, et al. Combination therapy with fluconazole and flucytosine for cryptococcal meningitis in Ugandan patients with AIDS. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 1998; **26**(6): 1362-6.

36. Letang E, Muller MC, Ntamatungiro AJ, Kimera N, Faini D, Furrer H, et al. Cryptococcal antigenemia in immunocompromised HIV patients in rural Tanzania: A preventable cause of early mortality. Open Forum Infect Dis. 2015; **2**: ofv046.

37. Vidal JE, Penalva de Oliveira AC, Dauar RF, Boulware DR. Strategies to reduce mortality and morbidity due to AIDS-related cryptococcal meningitis in Latin America. The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases. 2013; **17**(3): 353-62.

38. Rajasingham R, Rolfes MA, Birkenkamp KE, Meya DB, Boulware DR. Cryptococcal meningitis treatment strategies in resource-limited settings: a cost-effectiveness analysis. PLoS medicine. 2012; **9**(9): e1001316.

39. Pyrgos V, Seitz AE, Steiner CA, Prevots DR, Williamson PR. Epidemiology of cryptococcal meningitis in the US: 1997-2009. PloS one. 2013; **8**(2): e56269.

40. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; **380**(9859): 2095-128.

41. Castelnuovo B, Manabe YC, Kiragga A, Kamya M, Easterbrook P, Kambugu A. Cause-specific mortality and the contribution of immune reconstitution inflammatory syndrome in the first 3 years after antiretroviral therapy initiation in an urban African cohort. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2009; **49**(6): 965-72.

42. French N, Gray K, Watera C, Nakiyingi J, Lugada E, Moore M, et al. Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. AIDS (London, England). 2002; **16**(7): 1031-8.

43. 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. Trop Med Int Health. 2007; **12**(8): 929-35.

44.   Lawn SD, Bekker LG, Myer L, Orrell C, Wood R. Cryptococcocal immune reconstitution disease: a major cause of early mortality in a South African antiretroviral programme. AIDS (London, England). 2005; **19**(17): 2050-2.

45.   Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. AIDS (London, England). 2008; **22**(15): 1897-908.

46.   Rajasingham R, Boulware DR. Reconsidering cryptococcal antigen screening in the U.S. among persons with CD4 <100 cells/mcL. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012; **55**(12): 1742-4.

47.   Mfinanga S, Chanda D, Kivuyo SL, Guinness L, Bottomley C, Simms V, et al. Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial. Lancet. 2015.

48.   Joint Medical Store. Product Catalogue. November 27, 2015 [cited 2016 25 Oct]; Available from: http://www.jms.co.ug/resources

49.   Rajasingham R, Meya DB, Boulware DR. Integrating cryptococcal antigen screening and pre-emptive treatment into routine HIV care. Journal of acquired immune deficiency syndromes (1999). 2012; **59**(5): e85-91.

50.   Butler EK, Boulware DR, Bohjanen PR, Meya DB. Long term 5-year survival of persons with cryptococcal meningitis or asymptomatic subclinical antigenemia in Uganda. PloS one. 2012; **7**(12): e51291.

51.   National Health Laboratory Service. National Health Laboratory Services Annual Report 2015/2016. [cited 2016 15 Oct]; Available from: http://www.nhls.ac.za/?page=annual_report&id=45

52.   Morawski BM, Boulware DR, Nalintya E, Kiragga A, Kakooza F, Rajasingham R, et al. Pre-ART cryptococcal antigen titer associated with preemptive fluconazole failure. Abstract 159. Conference on Retroviruses and Opportunistic Infections. Boston; 2016.

53.   Siedner MJ, Ng CK, Bassett IV, Katz IT, Bangsberg DR, Tsai AC. Trends in CD4 count at presentation to care and treatment initiation in sub-Saharan Africa, 2002-2013: a meta-analysis. Clin Infect Dis. 2015; **60**(7): 1120-7.

54.   Lahuerta M, Wu Y, Hoffman S, Elul B, Kulkarni SG, Remien RH, et al. Advanced HIV disease at entry into HIV care and initiation of antiretroviral therapy during 2006-2011: findings from four sub-saharan African countries. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014; **58**(3): 432-41.

55.   Late presentation for HIV care across Europe: update from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study, 2010 to 2013. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2015; **20**(47).

56.   European Centre for Disease Prevention and Control, WHO Regional Office for Europe. HIV/AIDS Surveillance in Europe, 2014. 2015 [cited 2015 1 Dec]; Available from: http://ecdc.europa.eu/en/healthtopics/aids/surveillance-reports/Pages/surveillance-reports.aspx

57.   Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas—2013. HIV Surveillance Supplemental Report 2015. 2015; **20**(2).

58.   Jarvis JN, Bicanic T, Loyse A, Namarika D, Jackson A, Nussbaum JC, et al. Determinants of mortality in a combined cohort of 501 patients with HIV-associated Cryptococcal meningitis: implications for improving outcomes. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014; **58**(5): 736-45.

59.   Gaskell KM, Rothe C, Gnanadurai R, Goodson P, Jassi C, Heyderman RS, et al. A prospective study of mortality from cryptococcal meningitis following treatment induction with 1200 mg oral fluconazole in Blantyre, Malawi. PloS one. 2014; **9**(11): e110285.

60.   Lessells RJ, Mutevedzi PC, Heller T, Newell ML. Poor long-term outcomes for cryptococcal meningitis in rural South Africa. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2011; **101**(4): 251-2.

61.   Baldassarre R, Mdodo R, Omonge E, Jaoko W, Baddley J, Pappas P, et al. MORTALITY AFTER CLINICAL MANAGEMENT OF AIDS-ASSOCIATED CRYPTOCOCCAL MENINGITIS IN KENYA. East African medical journal. 2014; **91**(5): 145-51.

62.   Rothe C, Sloan DJ, Goodson P, Chikafa J, Mukaka M, Denis B, et al. A prospective longitudinal study of the clinical outcomes from cryptococcal meningitis following treatment induction with 800 mg oral fluconazole in Blantyre, Malawi. PloS one. 2013; **8**(6): e67311.

63.   Kendi C, Penner J, Koech J, Nyonda M, Cohen CR, Bukusi EA, et al. Predictors of outcome in routine care for Cryptococcal meningitis in Western Kenya: lessons for HIV outpatient care in resource-limited settings. Postgraduate medical journal. 2013; **89**(1048): 73-7.

64.   Jongwutiwes U, Kiertiburanakul S, Sungkanuparph S. Impact of antiretroviral therapy on the relapse of cryptococcosis and survival of HIV-infected patients with cryptococcal infection. Current HIV research. 2007; **5**(3): 355-60.

65.   Lortholary O, Poizat G, Zeller V, Neuville S, Boibieux A, Alvarez M, et al. Long-term outcome of AIDS-associated cryptococcosis in the era of combination antiretroviral therapy. AIDS (London, England). 2006; **20**(17): 2183-91.

66.   Resch S, Ryckman T, Hecht R. Funding AIDS programmes in the era of shared responsibility: an analysis of domestic spending in 12 low-income and middle-income countries. The Lancet Global health. 2015; **3**(1): e52-61.

Burden of Cryptococcus

Table 1: Model Inputs and Assumptions

	Variable	Estimate	Range of Uncertainty	Source
A	**Adults living with HIV**	31·8 million	30.1 million to 33.7 million	UNAIDS 2013
	Adults with CD4<350	19·5 million	18.5 million to 20.7 million	UNAIDS 2013
B	**CD4<100 cells/µL of those CD4<350 cells/µL**			
	Low/Middle-Income Countries	22·5%	19% to 26%	[22, 24, 55-57]
	High-Income Country	18·5%	16% to 21%	[22, 24, 55-57]
	CD4 100-200 cells/µL of those CD4<350 cells/µL			
	• **Low/Middle-Income Countries**	27·5%	24% to 31%	[22, 24, 55-57]
	• **High-Income Countries**	31·5%	29% to 34%	
C	**Adults receiving ART**	11·3 million	10·4 million to 12·7 million	UNAIDS 2013
	New Initiation of ART	2·3 million	1·8 million to 2·8 million	UNAIDS 2013, 2014
	Retention in Care (year 1)	Country-specific, regional estimate, weighted pooled average. Total LTFU estimated at 1.1 million in 2014.		UNAIDS 2015
D	**Virologic failure (year 1)**	16%	12% to 20%	UNAIDS 2015, [23]
	Virologic failure (year 2+)	5·33%	4·0% to 6·6%	[25-27]
E	**At risk for cryptococcal infection**	1. CD4 < 100 cells/µL not on ART 2. CD4 < 100 cells/µL on ART but LTFU or virologic failure 3. CD4 100-200 cells/µL not on ART, LTFU, or virologic failure		
F	**CD4 100 to 200 cells/µL no ART, LTFU, or virologic failure**	25% of those with CD4<100 cells/µL not on ART, or LTFU, or virologic failure		[10, 33]
G	**CRAG prevalence for countries with multiple sources**	Weighted average of all sources	Computed 95% CI	Figure 1
H	**CRAG prevalence for countries without sources**		Regional weighted average	Computed 95% CI
I	**CRAG negative progression to CRAG+ (without effective ART) CD4<200 cells/µL**			
	Low/Middle-Income Countries	5·14 events per 100 person-years	2·6 to 9·0 events per 100 person-years	[33]
	High-Income Country	2·57 events per 100 person-years	1·3 to 4·5 events per 100 person-years	50% of [33]
J	**CRAG+ who develop Cryptococcal Meningitis**			
	• **In care without preemptive treatment**	70%	56% to 84%	[10-12, 31, 32]
K	• **Not in care**	95%	90% to 100%	[10-12, 31, 32]
L	**Deaths from Cryptococcal Meningitis (1 year mortality)**			
	• **Low-Income Country**	70%	59% to 81%	[50, 58-63]
	• **Middle-Income Country**	40%	34% to 46%	[37, 38, 58, 64]
	• **North America**	20%	12·5 to 27·5%	[39, 65]
	• **Europe**	30%	25% to 35%	
M	**Death not in care (all regions)**	1·5x higher	N/A	[34]

ART: antiretroviral therapy. LTFU: Lost to follow up.
* Retention-in-care and virologic failure in years 2+ are assume to be 33% of their year 1 value. † Refer to Supplemental Methods for further details. Boxed letters correspond to Supplemental Figure 1

Table 2: Countries with the Highest Incidence of Cryptococcal Meningitis

Country	Annual incidence of CM	Number at Risk (CD4<100 cells/μL)	Cost of screening all at risk*	% of HIV budget to screen all at risk[66]
1. **Nigeria**	27,100	325,900	$1,303,437	0·23%
2. **South Africa**	21,400	382,400	$1,529,685	0·09%
3. **Mozambique**	18,600	184,300	$737,228	0·28%
4. **India**	18,300	209,900	$839,502	0·06%
5. **Uganda**	12,200	110,500	$441,933	0·08%
6. **Ethiopia**	9,600	60,600	$242,561	0·06%
7. **Kenya**	9,000	84,700	$329,138	0·08%
8. **Tanzania**	8,400	117,200	$468,959	0·15%
9. **Democratic Republic of Congo**	8,400	51,200	$204,889	0·24%
10. **Zimbabwe**	8,100	92,400	$369,621	N/A
11. **Indonesia**	6,600	58,900	$235,564	0·27%
12. **Zambia**	5,000	66,200	$264,611	0·10%

*Based on presumed cost of CRAG Lateral Flow Assay test of $3 per test delivered price for resource-limited areas, with an additional $0·50 added for laboratory labor, and $0·50 for profit/overhead costs. Although not every person at risk will present to care, this gives an estimate of the magnitude of budgetary resources necessary to start screening.

Table 3: Burden of cryptococcal infection by region

	Total CRAG+	Annual Burden of Cryptococcal Meningitis	Deaths from Cryptococcal Meningitis
Sub-Saharan Africa	204,300 (148,400 to 237,800)	162,500 (113,600 to 193,900)	135,900 (93,900 to 163,900)
Asia & Pacific	52,300 (32,900 to 74,100)	43,200 (25,300 to 64,700)	39,700 (20,600 to 59,700)
Caribbean	1,800 (1,300 to 2,200)	1,400 (1,000 to 1,800)	700 (500 to 900)
Latin America	7,000 (3,600 to 11,100)	5,300 (2,600 to 8,900)	2,400 (1,100 to 4,400)
North America	3,700 (3,000 to 4,600)	3,000 (2,300 to 3,700)	700 (500 to 1,000)
North Africa & Middle East	3,600 (2,600 to 5,000)	3,300 (2,400 to 4,500)	1,900 (1,300 to 2,700)
Europe	5,200 (4,000 to 6,500)	4,400 (3,400 to 5,600)	1,800 (1,300 to 2,400)
Global	278,000 (195,500 to 341,000)	223,100 (150,600 to 282,400)	181,100 (119,400 to 234,300)

Figure legends:

Figure 1: CRAG Prevalence studies among HIV-infected outpatient populations from 1989 to 2016. Estimates of US and UK were not included in final summary estimate of low and middle income countries. Studies of hospitalized populations were not included. For full details of population and reference, see *Appendix p10*.

Figure 2: Annual Incidence of cryptococcal infection by country. Annual number with cryptococcal antigenemia (CRAG-positive) estimated at 278,000 (95% CI 195,500 to 340,600) persons globally in 2014.