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

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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/ μ L, 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/ μ L not on ART, and those with CD4<100 cells/ μ L 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/ μ L, 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.

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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/ μ L 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

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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/ μ L) 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/ μ L on ART, and those eligible for ART, we calculated the ART gap (not receiving ART but CD4<350 cells/ μ L). We used UNAIDS and WHO reports for estimates of CD4<100 cells/ μ L,²² CD4 100-200 cells/ μ L, 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/ μ L not on ART, and 2) adults with CD4<100 cells/ μ L 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/ μ L was 22.5% (Range: 19% to 26%) among those with CD4<350 cells/ μ L in LMICs.^{22, 24} In HICs, 18.5% (Range: 16% to 21%) of those with a CD4<350 cells/ μ L were estimated to have a CD4<100 cells/ μ L.^{22, 24} Thus, we estimated the number with CD4<100 cells/ μ L on ART from the ART percent coverage (ART percent coverage x ART eligible (CD4<350 cells/ μ L) x proportion with CD4<100 cells/ μ L, 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

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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/ μ L 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

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The cryptococcal meningitis incidence amongst persons with CD4<200 cells/ μ L 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/ μ L, 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

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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/ μ L) by WHO 2010 guidelines, with 11·3 million actually receiving ART. Globally, 8·2 million people had CD4<350 cells/ μ L 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/ μ L 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/ μ L, with the number with cryptococcal antigenemia (CRAG-

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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)

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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 \$4.00⁴⁹ 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/ μ L 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/ μ L in 2015.⁵¹ We estimated 382,400 South Africans with a CD4<100 cells/ μ L would be at risk for cryptococcal disease. In 2015, the South African National Health Laboratory Service processed 360,000 CD4 counts <100 cells/ μ L (~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/ μ L by country. We used these numbers to estimate CD4<100 cells/ μ L and thereby estimate the population at risk for cryptococcal infection.

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UNAIDS no longer publishes the number with CD4<350 cells/ μ L by country; thus a 2016 estimate would require us to project the number with a CD4<100 cells/ μ L 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/ μ L entering care is still substantial at ~20-25% of those presenting to care.⁵³

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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/ μ L 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.

Contributors:

Literature search: RR

Study design: RR, DB, BP, RS

Data collection: RR DB

Data analysis: RR, DB, RS, BP, JJ, NG, TC, DD, AL

Data interpretation: RR, DB, RS, BP, JJ, NG, TC, DD, AL

Manuscript Writing: RR, DB

Conflicts of Interest: Dr. Denning and family hold Founder shares in F2G Ltd, a University of Manchester spin-out antifungal discovery company, in Novocyt which markets the Myconostica real-time molecular assays. He acts or has recently acted as a consultant to Astellas, Sigma Tau, Basilea, Scynexis, Cidara, Biosergen, Quintilles, Pulmatrix and Pulmocide. In the last 3 years, he

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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.

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Table 1: Model Inputs and Assumptions

	Variable	Estimate	Range of Uncertainty	Source
	Adults living with HIV	31.8 million	30.1 million to 33.7 million	UNAIDS 2013
A	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
	CRAG+ who develop Cryptococcal Meningitis			
J	• 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 risk⁶⁶
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.

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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)

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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.