Clinical Infectious Diseases

MAJOR ARTICLE

Cryptococcal Meningitis and Clinical Outcomes in Persons with HIV: A Global View

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Background: Cryptococcal meningitis (CM) is a major cause of morbidity and mortality in persons with HIV(PWH). Little is known about CM outcomes and availability of diagnostic and treatment modalities globally.

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Methods: This retrospective cohort study investigated CM incidence and all-cause mortality after CM diagnosis in PWH in the IeDEA cohort from 1996-2017. We estimated overall and region-specific incidence and incidence rate ratios using quasi-Poisson models adjusted for sex, age, calendar year, time-updated CD4, and time-updated antiretroviral therapy (ART) status. Mortality after CM diagnosis was examined using multivariable Cox models. A site survey from 2017 assessed availability of CM diagnostic and treatment modalities.

Results: Among 518,852 PWH, there were 3,857 diagnosed cases of CM with an estimated incidence of 1.54 per 1000 person-years. Mortality over a median of 2.6 years of post-CM diagnosis follow-up was 31.6%, with 29% lost to follow-up. 2,478 (64%) were diagnosed with CM after ART start with a median of 253 days from ART start to CM diagnosis. Older age (HR 1.31 for 50 vs 35 years; 95%CI 1.12-1.53), lower CD4 (HR 1.15 for 200 vs 350 cells/mm^3; 95%CI 1.03-1.30), and earlier year of CM diagnosis (HR 0.51 for 2015 vs 2000; 95%CI 0.37-0.70) were associated with higher mortality. Of 89 sites, 34% reported access to amphotericin B; 12% had access to flucytosine.

Conclusions: Mortality after CM diagnosis was high. A substantial portion of CM cases occurred after ART start, though incidence and mortality may be higher than reported due to ascertainment bias. Many sites lacked access to recommended CM treatment.

Keywords: HIV, AIDS, cryptococcal meningitis, global health

BACKGROUND:

Cryptococcal meningitis (CM) is a major cause of morbidity and mortality in persons with HIV (PWH), both before and after the advent of combination antiretroviral therapy (ART). Mortality rates from CM in several studies are approximately 40%[1,2,3], representing a significant burden to the individual patient as well as health care systems and resources worldwide. Estimates range from 181,000 to 625,000 annual deaths annually due to CM[2,4]. Further, mortality varies significantly according to country income[5]. Although there have been several studies of CM in resource limited settings, particularly in sub-Saharan Africa, there are gaps in our knowledge regarding the full impact of CM on PWH globally. Few studies have investigated the burden of CM after global availability of ART, recognizing that access to ART varied worldwide. Additionally, although there has been some study of this in sub-Saharan Africa[6], global data of CM incidence in relation to ART start are scarce. Further, lack of access to certain diagnostic and treatment modalities may lead to variance from recommended guidelines and impact patient outcomes, even in today's era.

These knowledge gaps warrant further exploration. The largest study to date of CM outcomes in PWH from Latin America (and one clinic in North America) reported an overall mortality of 42% among 340 individuals with CM from 1985-2014. In that cohort, the majority developed

CM *after* initiating ART, with a median time to CM diagnosis of 2 years, and 76% of patients had documented virologic failure preceding CM diagnosis[7]. Those with CM after ART start had a 28% higher risk of death compared to those with CM prior to ART start. This study highlighted the need to consider CM as a possible complication even months to years after starting ART, especially in those with virologic failure. It also underscored the high mortality associated with CM, even at the North American site (33%), despite access to state-of-the-art diagnostic and treatment modalities.

We therefore conducted an observational study to examine CM incidence, including before and after ART initiation, and all-cause mortality rates in a large global cohort of PWH. We also sought to describe current practices for treating CM across these global regions.

METHODS:

This retrospective observational cohort study investigated CM incidence and all-cause mortality after CM diagnosis in the International Epidemiology Databases to Evaluate AIDS (IeDEA) cohort, from 1996-2017. IeDEA is a research consortium established by the National Institute of Allergy and Infectious Diseases to provide globally diverse HIV/AIDS data (www.iedea.org). This study used data from the North America, Latin America, Asia-Pacific, East Africa, and Southern Africa IeDEA regions. The IeDEA regions of West Africa and Central Africa did not participate as they do not routinely collect data on opportunistic infections. Data were collected from clinical records at local sites; harmonized, cleaned and merged by each region's data coordinating center; and then merged across regions for analysis. All data collection and analyses were approved by local and regionally centralized institutional review boards, and all study activities adhered to the Declaration of Helsinki standards.

PWH who were 16 years or older and enrolled at IeDEA sites between January 01, 1996 and December 31, 2017 were included. Patients were followed from enrollment until the first occurrence of death, loss to follow-up (LTFU), or site-specific database closing date (see Appendix 1). All-cause mortality was used to define death. LTFU was defined as no clinic or laboratory visit within 12 months prior to the site-specific database closing date; for those LTFU, the date of last visit marked the end of follow-up. Baseline was defined as the date of enrollment in the cohort.

Baseline CD4 cell count (CD4) and plasma HIV-1 RNA level (viral load) were defined as the measurements closest to but no more than 180 days before or 30 days after enrollment. CD4 and viral load at CM diagnosis were defined as the measurements closest to but no more than 90 days before or after date of CM diagnosis. Viral load at enrollment could be undetectable as some patients on ART transferred into care.

CM diagnosis was as noted in the clinical record; most IeDEA data are obtained from routine patient care. Information on site-level capacity in treatment and diagnosis of CM was obtained from the 2017 IeDEA Site Assessment Survey (see Appendix 2) [8].

We estimated incidence of CM diagnosis and incidence rate ratios (IRRs) using univariate and multivariable quasi-Poisson models with time at risk included as an offset. Univariate models estimated incidence (and 95% confidence intervals [CIs]) of CM diagnosis within regions, across all regions, and as a function of calendar year across all regions. Multivariable models were adjusted for sex, baseline age, calendar year, time-updated CD4 (square-root transformed), time-updated ART status (initiated versus not), and country-level income (GDP per capita in 2010). No adherence data were available for analyses. We did not assess HIV exposure category or viral load as risk factors because of high levels of missingness. To relax linearity assumptions, continuous covariates (age, calendar year, and CD4) were included in models using natural splines with 5 knots[9]. Missing data for variables included in multivariable models were imputed separately within regions using multiple imputation by chained equations with 20 replications. Multivariable analyses using multiply imputed data were performed within IeDEA region with standard errors calculated using Rubin's rules; results were then combined across regions using random-effects meta-analysis techniques.

Mortality after CM diagnosis was examined using Kaplan-Meier curves, cumulative incidence curves that accounted for LTFU as a competing risk, and univariate and multivariable Cox proportional hazards models. The multivariable Cox model included sex, timing of CM diagnosis (before/after ART initiation), and age, calendar year, and CD4 (square-root transformed) at CM diagnosis. The model was stratified (i.e., separate 'baseline' hazards estimated) by IeDEA region. ART start date (or first ART date in cohort for patients who transferred in) was used to determine timing of CM diagnosis relative to ART initiation. Missing data were multiply imputed with 20 replications and continuous variables (age, CD4, and calendar year) were expanded using natural splines with 4 knots (one fewer knot than for incidence analyses because of the fewer number of events).

RESULTS:

Incidence per Region

518,852 PWH, followed for a median of 3.4 years (IQR 0.9-7.7) from enrollment were included. Patient characteristics by IeDEA region and across all regions are shown in Table 1. Median year of enrollment was 2009, 51% of patients were male, and at enrollment, median age was 36 years, median CD4 was 261 cells/mm^3, and 71% were ART naïve. Of the total follow-up time, 78% was after ART initiation, and the median time from enrollment to ART initiation was 31 days.

There were 3,857 diagnosed cases of CM (0.7%) during follow-up, for an incidence of 1.54 per 1000 person-years (95% CI 1.35-1.75). Within the regions, Latin America had the highest unadjusted incidence (2.17 per 1000 person years), compared with East Africa (2.08/1000 person-years), South Africa (1.69/1000 person-years), North America (0.89/1000 person-years), and Asia-Pacific (0.58/1000 person-years) (Figure 1A). Incidence, both overall and per region, during the first year of follow-up was substantially higher (overall, 5.66/1000 person-years; Supplemental Material). The incidence of CM diagnosis across all sites by calendar year is shown including both crude year-specific estimates and smoothed estimates across years (Figure 1B). In general, the incidence of CM diagnosis decreased over time; for example, the incidence was 2.56/1000 person-years (95% CI 1.47-4.46) in 2005 compared to 0.97 (95% CI 0.54-1.75) in 2015.

Characteristics of Diagnosed CM Cases

Characteristics of patients with and without a diagnosis of CM are shown (Table 2). Of the 3857 CM cases, the median year of diagnosis was 2008, 56.8% were male, and median age at enrollment and CM diagnosis were 36.8 and 38.5 years, respectively. Median CD4 at CM diagnosis was 64 cells/mm^3 (interquartile range [IQR] 20-168) and median viral load at CM diagnosis was 26,641 copies/mL, though 68.5% were missing viral load at CM diagnosis. Seventy-two percent of patients with CM diagnosis were ART naïve at enrollment, but only 36% were ART naïve at CM diagnosis. Of those diagnosed with CM after ART start, the median time to CM diagnosis was 253 days (IQR 56-1064 days; Table 3). Median year of enrollment for those without versus with a CM diagnosis 2009 (IQR, 2005-2012) versus 2007 (IQR, 2004-2010), respectively. Median CD4 at enrollment for those with a CM diagnosis was 59 cells/mm^3 (IQR: 20-163 cells/mm^3) versus 262 cells/mm^3 (IQR: 106-469 cells/mm^3) for those without a CM diagnosis. The median CD4 for those diagnosed with CM before starting ART was 47 cells/mm^3 (IQR: 16-118) versus 77 cells/mm^3 (IQR: 24-195) for those diagnosed after starting ART.

Figure 2 shows risk factors associated with CM diagnosis, combining estimates across all regions. Current CD4 was highly predictive of CM: in adjusted analyses, the incidence rate for a patient with CD4=200 cells/mm^3 was 3.89 times higher than for a patient with CD4=350 cells/mm^3 (95% CI 3.13-4.84). Being on ART was also highly protective of CM, with an estimated incidence rate ratio (IRR) of 0.33 (95% CI 0.24-0.44). The risk of CM tended to be lower in more recent years (IRR 0.23, 95% CI 0.04-1.28, comparing 2015 vs. 2000), although this was quite variable across regions. Age and sex were not statistically associated with CM diagnosis in adjusted models.

Timing of CM Diagnosis and All-Cause Mortality

Overall mortality for those diagnosed with CM was 31.6% (95% CI 30.1-33.0) over a median follow-up of 2.6 years after CM diagnosis (IQR 0.3-7.0); 1121 (29%) were lost to follow-up

(Table 3). Mortality differed by region; Asia-Pacific had a mortality of 24.2% (8/33) among those with CM diagnosis, followed by East Africa at 26.5% (607/2289), South Africa at 28.2% (109/386), Latin America at 42.5% (110/259), and North America at 43% (383/890). However, the proportions LTFU were high and inversely correlated with mortality rates by region: Asia-Pacific 36.4%, East Africa 32.3%, South Africa 37.6%, Latin America 19.3%, and North America 19.6%. LTFU was higher for those who were diagnosed with CM before ART initiation: 38.4% vs. 23.8%. Figure 3 shows over time after CM diagnosis the estimated probability of death (Figure 3A), the estimated probability of death or LTFU (Figure 3B), and the cumulative incidence of death treating LTFU as a competing event (Figure 3C), both overall and stratified by whether the diagnosis was before or after ART initiation. At 5 years after CM diagnosis, for those diagnosed before ART initiation and after ART initiation, respectively, the estimated probabilities of death were 0.35 (95% CI 0.32-0.38) and 0.33 (95% CI 0.35-0.31); the estimated probabilities of death or LTFU were 0.62 (95% CI 0.60-0.65) and 0.49 (95% CI 0.47-0.51); and the estimated cumulative incidences of death treating LTFU as a competing event were 0.27 (95% CI 0.25-0.30) and 0.28 (95% CI 0.26-0.30).

Risk factors for Mortality

In unadjusted analyses, the cause-specific hazard of death was higher for those diagnosed with CM before ART initiation (hazard ratio [HR] 1.16, 95% CI 1.03-1.30), but this association was not significant (HR=1.03, 95% CI 0.91-1.17) adjusting for CD4 at CM diagnosis, sex, age, and year of CM diagnosis and stratifying by IeDEA region. Figure 4 shows the association between these other variables and all-cause mortality. Older age (HR 1.31 for 50 vs 35 years; 95% CI 1.12-1.53), lower CD4 (HR 1.15 for 200 vs 350 cells/mm^3; 95% CI 1.03-1.30), and earlier year of CM diagnosis (HR 0.51 for 2015 vs 2000; 95% CI 0.37-0.70) were associated with higher risks of mortality (Figure 4).

Site survey results

Eighty-nine sites across all 5 geographical regions responded to questions in 2017 regarding availability of diagnostic testing and treatment for CM (Appendix 2). 53% of sites reported access to serum cryptococcal antigen testing in 2017, and 37% had access to lateral flow assays for detection of cryptococcal antigen. Nearly two-thirds of sites reported access to fluconazole, with 8% responding that they did not have access to fluconazole in 2017 (29% had missing data). Only 34% of sites reported access to amphotericin B, with 37% responding that it was not available. Only 11 of 89 (12%) sites reported they had access to 5-flucytosine (5-FC) in 2017.

DISCUSSION:

This study highlights several key findings with implications for clinical care of CM globally. First, the incidence of CM diagnosis decreased over time and varied across regions. Second,

diagnosis of CM occurred frequently after ART initiation. Third, mortality after CM diagnosis was high but varied across regions, and loss to follow up was also high. Finally, CM testing/screening and currently recommended CM treatment regimens that are safe and effective are often out of reach for many in low-middle income settings.

This study documents the ongoing high mortality rate associated with CM and raises the question as to why survival has not improved more substantially over time. We report an overall mortality similar to past studies.[10,11] Regional differences in mortality shown in our study may be due to ascertainment, but also to variability in ability to diagnose and treat CM. Lack of access to "gold standard" treatment regimens may be one possible explanation. Even in 2017, only 12% of sites reported access to 5-FC, which has been shown to lower mortality when used in combination treatment of CM compared to amphotericin and fluconazole, or non-flucytosine-containing regimens[1,12]. At that time, the World Health Organizations' first line recommended regimen and one of the two alternative regimens include flucytosine[13]. In our survey, 38% of sites reported no access to amphotericin and 8% reported no access to fluconazole. These data, and the ongoing high mortality repeatedly demonstrated in global cohorts of PWH diagnosed with CM, highlight an urgent need for health equity in access to CM diagnostic tools and standard of care treatments.

It is significant that in the 4 decades since recognition of HIV/AIDS and accompanying opportunistic infections, research on new CM treatments has been scarce. Antifungal agents with improved ease of administration and favorable CNS penetration (such as voriconazole)[14], have been little studied against CM in the global south. In the randomized controlled ACTA trial of 721 patients with CM and HIV in Africa, it was found that one week of AmB plus 5-FC and 2 weeks of fluconazole plus 5-FC were effective regimens for induction therapy for cryptococcal meningitis in resource-limited settings[1]. Based on these results, the World Health Organization (WHO) in 2018 recommended induction therapy with the less toxic and more efficacious 1-week regimen of AmB and 5-FC in resource-limited settings.[13] In the AMBITION trial, an open-label phase III randomized controlled trial conducted in Africa among 814 PWH with CM, single-dose liposomal AmB combined with 5-FC and fluconazole was noninferior to the WHO-recommended treatment for HIV-associated CM and was associated with fewer adverse events.[15] Based on AMBITION, the WHO further updated their guidance in 2022[16], recommending that a single dose of liposomal amphotericin B with 14 days of flucytosine and fluconazole is the recommended regimen for induction. Alternative induction regimens are listed for situations in which amphotericin or flucytosine is not available[16]. However, these regimens may not be available in most affected regions, as our survey data show. While more randomized controlled trials for the treatment of CM in PWH are needed, they must be paired with emphatic calls for access to the medications proven safer and more effective.

One of the most surprising findings of this analysis (as reported in our Latin America cohort[7]), was the high rate of CM diagnosis after ART start, representing 64% of all diagnosed CM cases. Here, the median time to CM diagnosis from ART start was 8 months, suggesting that most

often, this did not reflect an "unmasking" of CM after ART start or immune reconstitution syndrome (IRIS). Indeed, in the Latin America cohort, 76% of those with CM after ART start had evidence of virologic failure[7]. Although we were limited by high level of missingness, the median viral load at CM diagnosis after ART start was 7,076 copies/mL. This high rate of CM diagnosis after ART start, as well as a detectable viral load around the time of CM diagnosis hints at CM as a complication of virologic failure.

Our study has important limitations. First, because of diagnostic limitations which varied across time and clinical sites, there may have been differential ascertainment of CM. We did not have data on availability of diagnostic tools for CM over time in all regions. Hence, it is possible that in certain regions, the incidence of CM may be higher than our reported estimates. Our study had high rates of LTFU, including after CM diagnosis; those lost to follow-up might be expected to have higher mortality than those remaining in care. Additionally, the study is limited by high rates of missing data at the time of CM diagnosis, particularly missing viral load data and measures of adherence. Other limitations include potential measurement errors in other analysis variables, in part due to harmonizing clinical data collected differently at multiple sites. The use of GDP in 2010 was a crude measure of socioeconomic differences between countries within regions. Furthermore, our study only captured CM diagnoses among individuals engaged in care while they were in care, so our estimates may not be generalizable to all PWH. There may also be differences in definitions of variables (e.g., LTFU) when comparing our results with other studies. Despite these potential shortcomings, an important strength of this study is the pooling of data from clinical cohorts across multiple sites globally, resulting in a rich source of data with diversity of clinical and patient characteristics analyzed using robust methods and including adjustment for important confounders.

CONCLUSION:

Our large study across 5 IeDEA regions straddles the ART era and represents CM outcomes in low-, middle-, and high-income countries. We describe an ongoing high, albeit decreasing, incidence of CM in PWH, with substantial immediate and delayed all-cause mortality in PWH and CM. Moreover, providing data on global availability of testing and treatment capacity for CM highlights inequities in resources that could contribute to poor clinical outcomes. Further studies are needed to identify novel and accessible diagnostic modalities and improved treatment regimens that are readily accessible to resource-rich and resource-poor regions alike.

NOTES

National Cancer Institute, the National Institute of Mental Health, the National Institute on Drug Abuse, the National Heart, Lung, and Blood Institute, the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Fogarty International Center: *Asia-Pacific*, U01AI069907; *CCASAnet*, U01AI069923 (**A.K.P.** is listed as an investigator); *East Africa*, U01AI069911; *NA-ACCORD*, U01AI069918; *Southern Africa*, U01AI069924. Informatics resources are supported by the Harmonist project, R24AI24872. This work is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above. REDCap support was provided by UL1 TR000445 from NCATS/NIH.

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FIGURE LEGENDS:

Figure 1. Incidence of cryptococcal meningitis (CM) diagnosis. A. Unadjusted incidence of CM diagnosis per 1000-person years [95% confidence intervals, CI] according to region and overall. B. Incidence [95% CI] of CM diagnosis across all sites according to calendar year; dashed line represents crude estimates for that year, dark line represents model-based estimates smoothing across calendar years.
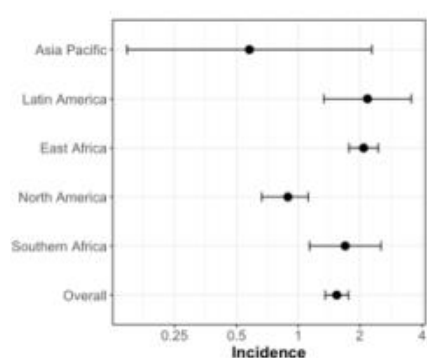
Figure 1A
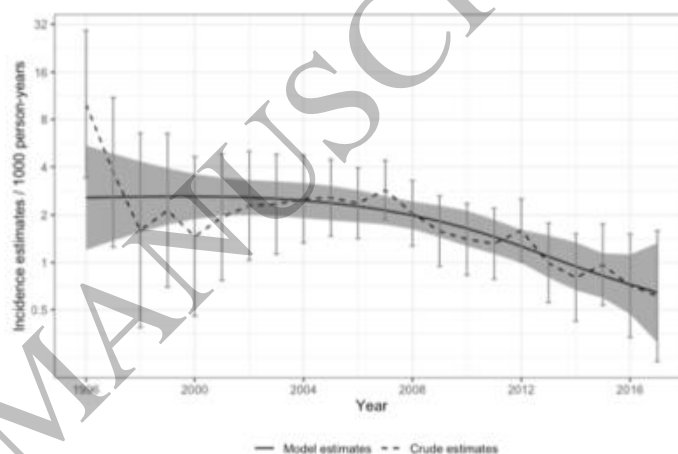
Figure 1B

Figure 2. Estimated incidence rate ratios (IRR) [95% confidence intervals, CI] of risk factors for cryptococcal meningitis combined across all regions, in adjusted analyses.
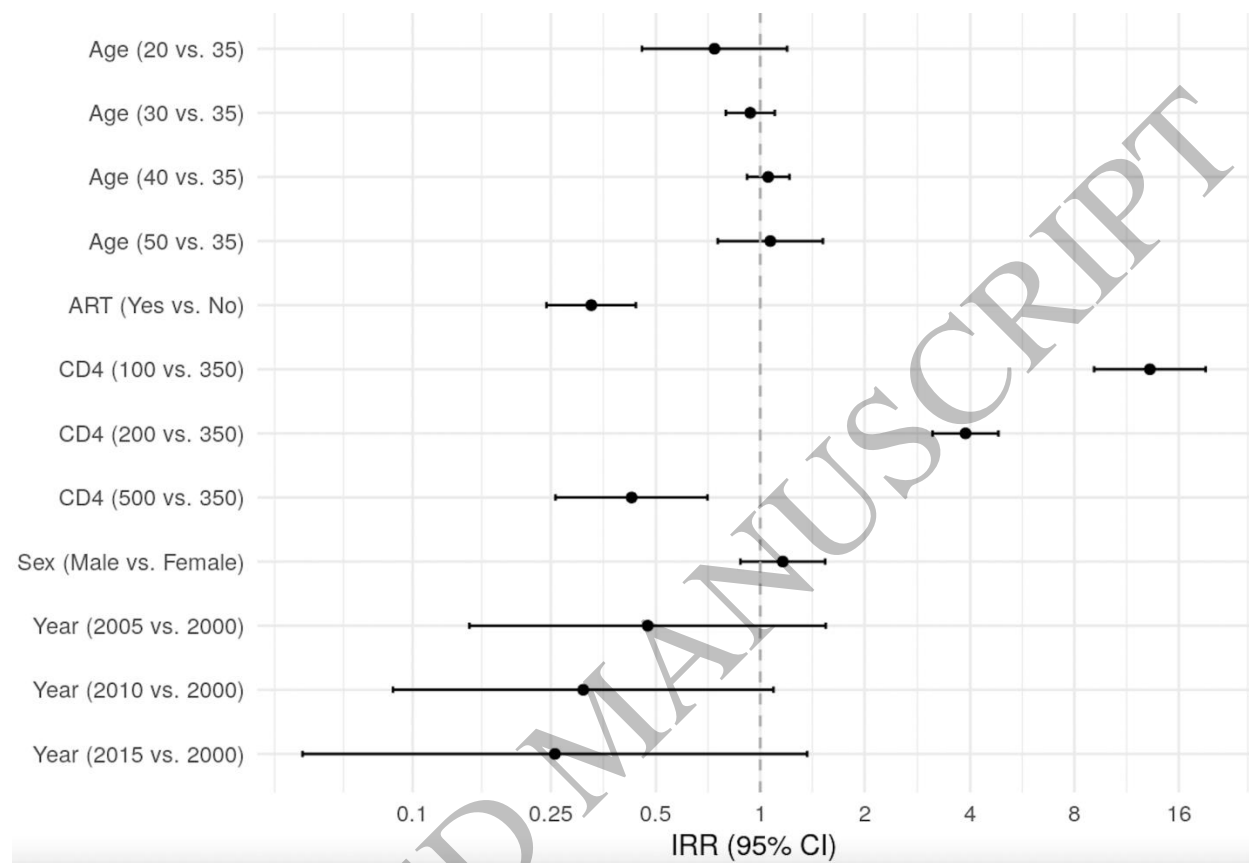
Figure 3. All-cause mortality after diagnosis of cryptococcal meningitis, overall and stratified by whether diagnosis was before or after ART initiation. A. Estimated probabilities based on Kaplan-Meier curves. B. Estimated probability of death or loss to follow-up based on Kaplan-Meier curves. C. Estimated cumulative incidence of death treating loss to follow-up as a competing event.

Figure 3A   Figure 3B   Figure 3C

Figure 4. Estimated hazard ratios (HR) [95% confidence intervals, CI] of risk factors for all-cause mortality after diagnosis of cryptococcal meningitis combined across regions, in adjusted analyses.
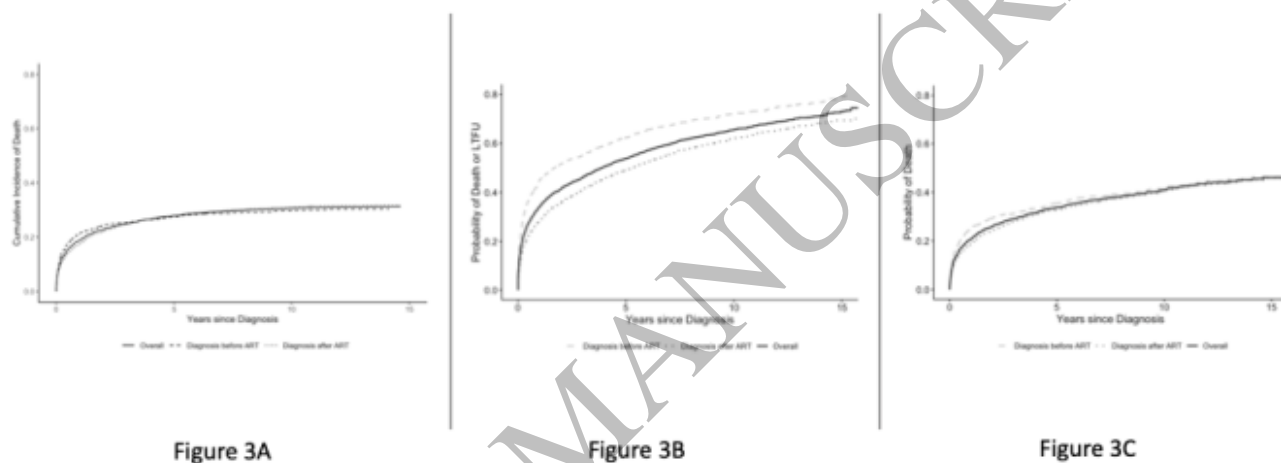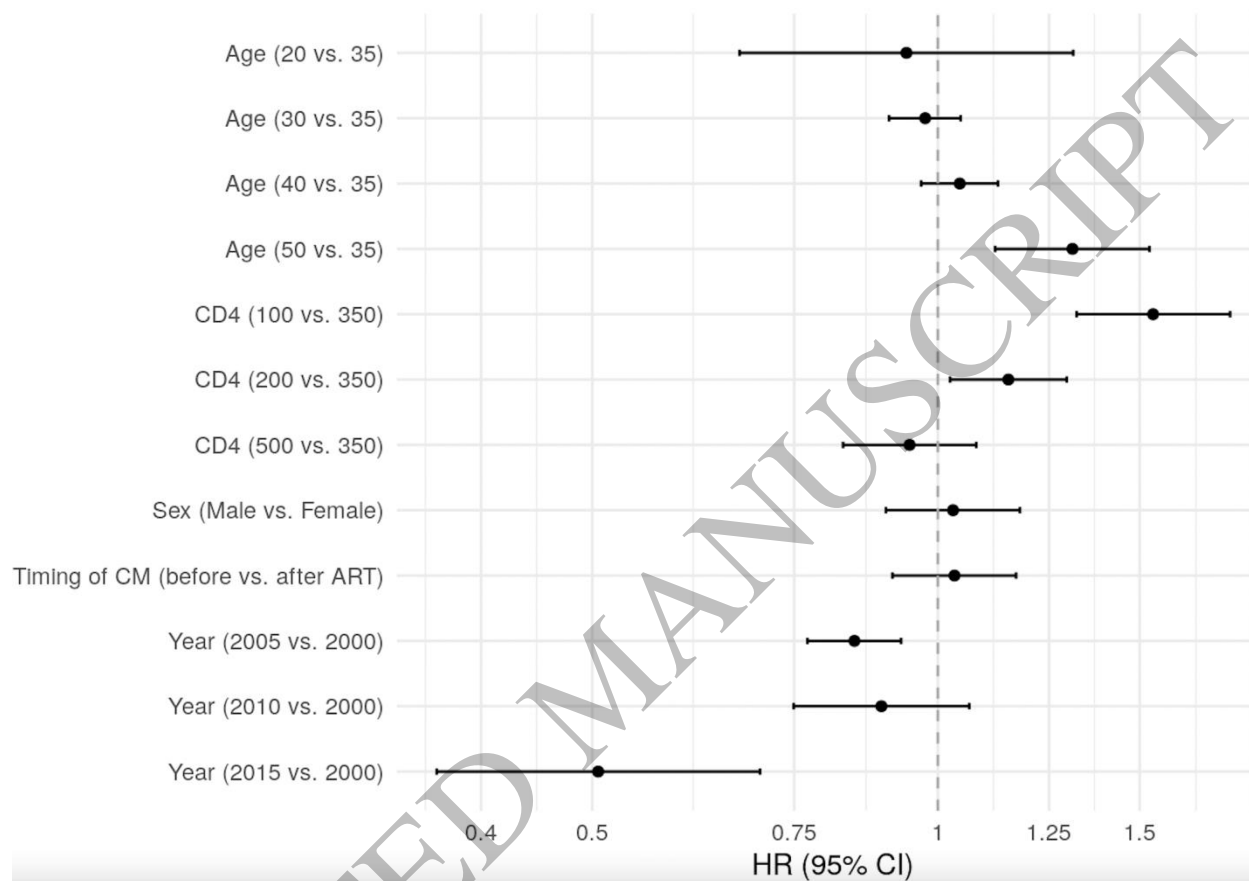
Table 1. Characteristics of patients by IeDEA region and across all regions.

	Asia-Pacific (N=8319)	Latin America (N=20324)	East Africa (N=289159)	North America (N=157370)	South Africa (N=43680)	Overall (N=518852)
Age at enrollment (years)						
Median (interquartile range)	35.8 (30.5-42.4)	33.8 (27.3-41.8)	34.0 (27.9-41.4)	42.0 (34.0-49.2)	33.7 (28.6-40.3)	36.1 (29.2-44.4)
Range	16.0—83.3	16.0—89.0	16.0—100.5	16.6—99.0	16.0—108.8	16.0—108.8
Missing (%)	0 (0.0)	0 (0.0)	4 (0.0)	0 (0.0)	0 (0.0)	4 (0.0)
Year of enrollment						
Median (interquartile range)	2008 (2005—2011)	2010 (2005—2014)	2010 (2007—2013)	2004 (2000—2010)	2008 (2006—2011)	2009 (2005—2012)
Range	1997—2017	1996—2017	1998—2017	1996—2017	1996—2017	1996—2017
Sex, N (%)						
Female	2606 (31.3)	4873 (24.0)	191161 (66.1)	25071 (15.9)	28644 (65.6)	252355 (48.6)
Male	5713 (68.7)	15451 (76.0)	97998 (33.9)	132297 (84.1)	15031 (34.4)	266490 (51.4)
Missing (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	5 (0.0)	7 (0.0)
CD4 at enrollment (cells/mm^3)						
Median (interquartile range)	269 (133—427)	242 (86—436)	245 (99—443)	354 (168—562)	125 (51—217)	261 (105—468)
Range	0—4022	0—2505	0—4600	0—4868	0—3210	0—4868
Missing (%)	889 (10.7)	4079 (20.1)	98334 (34.0)	41005 (26.1)	11721 (26.8)	156028 (30.1)
VL at enrollment						

Median (interquartile range)	644 (400-75001)	49300 (5118-190000)	792 (400-58538)	8562 (400-72680)	70350 (4399-308662)	10900 (400-84439)
<400 copies/mL[*]	2288 (48.2)	2056 (14.9)	1461 (40.0)	36890 (32.5)	598 (18.5)	43293 (31.2)
<200 copies/mL[*]	1949 (41.1)	1864 (13.5)	1364 (37.4)	34489 (30.4)	586 (18.2)	40252 (29.0)
Missing (%)	3572 (42.9)	6550 (32)	285509 (99)	43944 (28)	40452 (93)	380027 (73)
ART naive at enrollment, N (%)	2866 (34.5)	16659 (82.0)	230705 (79.8)	97834 (62.2)	19282 (44.1)	367346 (70.8)
Follow-up in years						
Median (interquartile range)	6.8 (3.4—9.6)	4.6 (1.5—9.5)	2.4 (0.5—6.4)	4.7 (1.7—10.0)	4.6 (1.5—8.1)	3.4 (0.9—7.7)
Range	0.0—15.4	0.0—22.0	0.0—19.0	0.0—21.8	0.0—21.9	0.0—22.0
Percent of follow-up time on ART	94	85	76	76	86	78
Median, enrollment to ART start	0 days	26 days	47 days	5 days	50 days	31 days
CM diagnosis, N (%)	33 (0.4)	259 (1.3)	2289 (0.8)	890 (0.6)	386 (0.9)	3857 (0.7)
CM diagnosis year						
Median (interquartile range)	2009 (2006—2011)	2008 (2004—2012)	2010 (2007—2012)	2004 (2000—2009)	2008 (2005—2011)	2008 (2005—2012)
Range	2003—2017	1996—2017	1998—2017	1996—2017	2000—2017	1996—2017
VL at CM diagnosis						
	99660	75000	5918	29100	18600	26641
Median (interquartile range)	(400—211665)	(400—397086)	(400—112720)	(400—157449)	(400—210833)	(400—186484)
<400 copies/mL[*]	5 (35.7)	46 (25.6)	48 (29.6)	197 (28.9)	61 (34.4)	357 (29.4)
<200 copies/mL[*]	5 (35.7)	37 (20.6)	42 (25.9)	175 (25.7)	61 (34.3)	320 (26.3)

Missing (%)	19 (57.6)	79 (30.5)	2127 (92.9)	209 (23.5)	208 (53.9)	26432 (68.5)
ART naive at CM diagnosis, N (%)	3 (9.1)	98 (37.8)	907 (39.6)	190 (21.3)	181 (46.9)	1379 (35.8)

[*] Percentage is among those with non-missing values.

Abbreviations: VL, viral load; ART, antiretroviral therapy; CM, cryptococcal meningitis.

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Table 2. Characteristics of patients stratified by cryptococcal meningitis (CM) diagnosis.

	No CM (N=514995)	CM (N=3857)	Overall (N=518848)
Age at enrollment (years)			
Median (interquartile range)	36.1 (29.2—44.5)	36.8 (30.8—43.6)	36.0 (29.1—44.4)
Range	16.0—108.8	16.0—88.0	16.0—108.8
Missing (%)	4 (0.0)	0 (0.0)	4 (0.0)
Age at CM diagnosis (years)			
Median (interquartile range)	—	38.5 (32.3—45.6)	—
Range	—	16.3—90.2	—
Missing (%)	—	0 (0.0)	—
Year of enrollment			
Median (interquartile range)	2009 (2005—2012)	2007 (2004—2010)	2009 (2005—2012)
Range	1996—2017	1996—2017	1996—2017
Year of CM diagnosis			
Median (interquartile range)	—	2008 (2005—2012)	—
Range	—	1996—2017	—
Sex			
Female	250688 (48.7)	1667 (43.2)	252355 (48.6)
Male	264300 (51.3)	2190 (56.8)	266490 (51.4)
Missing (%)	7 (0.0)	0 (0.0)	7 (0.0)
CD4 at enrollment (cells/mm^3)			
Median (interquartile range)	262 (106—469)	59 (20—163)	261 (105—468)
Range	0—4868	0—1963	0—4868
Missing (%)	154530 (30.0)	1498 (38.8)	156028 (30.1)
CD4 at CM diagnosis (cells/mm^3)			

Median (interquartile range)	—	64 (20—168)	—
Range	—	0—3695	—
Missing (%)	—	1066 (27.6)	—
VL at enrollment			
Median (interquartile range)	10712 (400—83500)	87387 (12381—312096)	10900 (400—84439)
<400 copies/mL[*]	43199 (31.3)	94 (13.1)	43293 (8.2)
<200 copies/mL[*]	40165 (29.1)	87 (12.2)	40252 (7.7)
Missing (%)	376885 (73.2)	3142 (81.5)	380027 (3.2)
VL at CM diagnosis			
Median (interquartile range)	—	26641 (<400—186484)	—
<400 copies/mL[*]	—	357 (29.4)	—
<200 copies/mL[*]	—	320 (26.3)	—
Missing (%)	—	2642 (68.5)	—
ART naive at enrollment	364572 (70.8)	2774 (71.9)	367346 (70.8)
ART naive at CM diagnosis	—	1379 (35.8)	—

[*] Percentage is among those with non-missing values.

Abbreviations: VL, viral load; ART, antiretroviral therapy.

Table 3. Characteristics of patients diagnosed with cryptococcal meningitis (CM) by timing of antiretroviral therapy (ART).

	Diagnosis before ART	Diagnosis after ART	Overall
	(N=1379)	(N=2478)	(N=3857)
Region			
Asia-Pacific	3 (0.2)	30 (1.2)	33 (0.9)
Latin America	98 (7.1)	161 (6.5)	259 (6.7)
East Africa	907 (65.8)	1382 (55.8)	2289 (59.3)
North America	190 (13.8)	700 (28.2)	890 (23.1)
South Africa	181 (13.1)	205 (8.3)	386 (10.0)
Age at enrollment			
Median (interquartile range)	36.5 (30.9—43.2)	36.8 (30.8—43.8)	36.8 (30.8—43.6)
Range	16.8—88.0	16.0—73.2	16.0—88.0
Age at CM diagnosis			
Median (interquartile range)	37.0 (31.4—43.6)	39.3 (32.9—46.3)	38.5 (32.3—45.6)
Range	16.8—90.2	16.3—77.5	16.3—90.2
Year of enrollment			
Median (interquartile range)	2008 (2005—2011)	2006 (2003—2010)	2007 (2004—2010)
Range	1996—2017	1996—2017	1996—2017
CM diagnosis year			
Median (interquartile range)	2008 (2005—2012)	2009 (2005—2012)	2008 (2005—2012)
Range	1996—2017	1996—2017	1996—2017
Male sex	745 (54.0)	1445 (58.3)	2190 (56.8)
CD4 at enrollment (cells/mm^3)			
Median (interquartile range)	52 (18—143)	66 (21—170)	59 (20—163)

Range	1—1175	0—1963	0—1963
Missing (%)	621 (45.0)	877 (35.4)	1498 (38.8)
CD4 at CM diagnosis (cells/mm^3)			
Median (interquartile range)	47 (16—118)	77 (24—195)	64 (20—168)
Range	1—1308	0—3695	0—3695
Missing (%)	464 (33.6)	602 (24.3)	1066 (27.6)
VL at enrollment			
Median (interquartile range)	147865 (38562—475134)	70850 (6356—235777)	87387 (12381—312096)
<400 copies/mL*	14 (1.0)	80 (3.2)	94 (2.4)
<200 copies/mL*	13 (0.9)	74 (3.0)	87 (2.3)
Missing (%)	1176 (85)	1966 (79)	3142 (81)
VL at CM diagnosis			
Median (interquartile range)	145740 (39091—438590)	7076 (400—106123)	26641 (400—186484)
<400 copies/mL*	20 (1.5)	337 (13.6)	357 (9.3)
<200 copies/mL*	18 (1.3)	302 (12.2)	320 (8.3)
Missing (%)	1088 (79)	1554 (63)	2642 (68)
ART naive at enrollment	1379 (100.0)	2063 (83.3)	3442 (89.2)
Time to CM from ART start in days			
Median (interquartile range)	—	253 (56—1064)	—
Range	—	1—6604	—
Follow-up after CM diagnosis (years)			
Median (interquartile range)	1.3 (0.2—6.2)	3.2 (0.6—7.4)	2.6 (0.3—7.0)
Range	0.0—21.5	0.0—19.5	0.0—21.5

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LTFU	530 (38.4)	591 (23.8)	1121 (29.1)
Mortality status: Dead	424 (30.7)	793 (32.0)	1217 (31.6)
Time in years to death			
Median (interquartile range)	0.3 (0.1—1.6)	0.7 (0.1—2.6)	0.5 (0.1—2.3)
Range	0.0—17.6	0.0—18.8	0.0—18.8

[*] Percentage is among those with non-missing values.

Abbreviations used: VL, viral load; LTFU, loss to follow-up.