

Cryptococcal Meningitis and Clinical Outcomes in Persons With Human Immunodeficiency Virus: A Global View

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

Methods. In this retrospective cohort study, we investigated CM incidence and all-cause mortality in PWH in the International Epidemiology Databases to Evaluate AIDS cohort from 1996 to 2017. We estimated incidence using quasi-Poisson models adjusted for sex, age, calendar year, CD4 cell count (CD4), and 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 3857 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. In total, 2478 (64%) were diagnosed with CM after ART start with a median of 253 days from ART start to CM diagnosis. Older age (hazard [HR], 1.31 for 50 vs 35 years), lower CD4 (HR, 1.15 for 200 vs 350 cells/mm³), and earlier year of CM diagnosis (HR, 0.51 for 2015 vs 2000) 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.

Cryptococcal meningitis (CM) is a major cause of morbidity and mortality in persons with human immunodeficiency virus (HIV; PWH), both before and after the advent of combination antiretroviral therapy (ART). Mortality rates from CM in several studies are approximately 40% [1–3], representing a significant burden to the individual patient as well as healthcare systems and resources worldwide. Estimates range from 181 000 to 625 000 annual deaths 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 1 clinic in North America) reported an overall mortality of 42% among 340 individuals with CM from 1985 to 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 with 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

Received 28 November 2022; editorial decision 06 February 2023; published online 23 February 2023

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Clinical Infectious Diseases® 2023;76(12):2116–25

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https://doi.org/10.1093/cid/ciad076

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

In this retrospective, observational, cohort study, we investigated CM incidence and all-cause mortality after CM diagnosis in the International Epidemiology Databases to Evaluate AIDS (IeDEA) cohort from 1996 to 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 aged ≥ 16 years and enrolled at IeDEA sites between 1 January 1996 and 31 December 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 [Supplementary Material](#)). 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 lost to follow-up, 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 [Supplementary 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 were used to estimate 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 vs not), and country-level income (gross domestic product [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 and timing of CM diagnosis (before/after ART initiation) and age, calendar year, and CD4 (square-root transformed) at CM diagnosis. The model was stratified (ie, 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 (1 fewer knot than for incidence analyses because of the fewer number of events).

RESULTS

Incidence per Region

A total of 518 852 PWH, followed for a median of 3.4 years (interquartile range [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, and 51% of patients were male. At enrollment, median age was 36 years, median CD4 was 261 cells/mm³, and 71% were ART-naive. 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 3857 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 (2.17/1000 person-years) compared with East Africa (2.08/1000 person-years), South Africa (1.69/1000 person-years), North America (0.89/1000

Table 1. Characteristics of Patients by International Epidemiology Databases to Evaluate AIDS Region and Across all Regions

Characteristic	Asia-Pacific (N = 8319)	Latin America (N = 20 324)	East Africa (N = 289 159)	North America (N = 157 370)	South Africa (N = 43 680)	Overall (N = 518 852)
Age at enrollment, y						
Median (IQR)	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 (IQR)	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)	191 161 (66.1)	25 071 (15.9)	28 644 (65.6)	252 355 (48.6)
Male	5713 (68.7)	15 451 (76.0)	97 998 (33.9)	132 297 (84.1)	15 031 (34.4)	266 490 (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 (IQR)	269 (133–427)	242 (86–436)	245 (99–443)	354 (169–562)	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)	98 334 (34.0)	41 005 (26.1)	11 721 (26.8)	156 028 (30.1)
VL at enrollment, copies/mL ^a						
Median (IQR)	644 (400–75 001)	49 300 (5118–190 000)	792 (400–58 538)	8562 (400–72 680)	70 350 (4399–308 662)	10 900 (400–84 439)
< 400	2288 (48.2)	2056 (14.9)	1461 (40.0)	36 890 (32.5)	598 (18.5)	43 293 (31.2)
< 200	1949 (41.1)	1864 (13.5)	1364 (37.4)	34 489 (30.4)	586 (18.2)	40 252 (29.0)
Missing (%)	3572 (42.9)	6550 (32)	285 509 (99)	43 944 (28)	40 452 (93)	380 027 (73)
ART-naïve at enrollment, N (%)	2866 (34.5)	16 659 (82.0)	230 705 (79.8)	97 834 (62.2)	19282 (44.1)	367 346 (70.8)
Follow-up, y						
Median (IQR)	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, d	0	26	47	5	50	31
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 (IQR)	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, copies/mL ^a						
Median (IQR)	99 660 (400–211 665)	75 000 (400–397 086)	5918 (400–112 720)	29 100 (400–157 449)	18 600 (400–210 833)	26 641 (400–186 484)
< 400	5 (35.7)	46 (25.6)	48 (29.6)	197 (28.9)	61 (34.4)	357 (29.4)
< 200	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)	26 432 (68.5)
ART-naïve at CM diagnosis, N (%)	3 (9.1)	98 (37.8)	907 (39.6)	190 (21.3)	181 (46.9)	1379 (35.8)

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

^aPercentage is among those with nonmissing values.

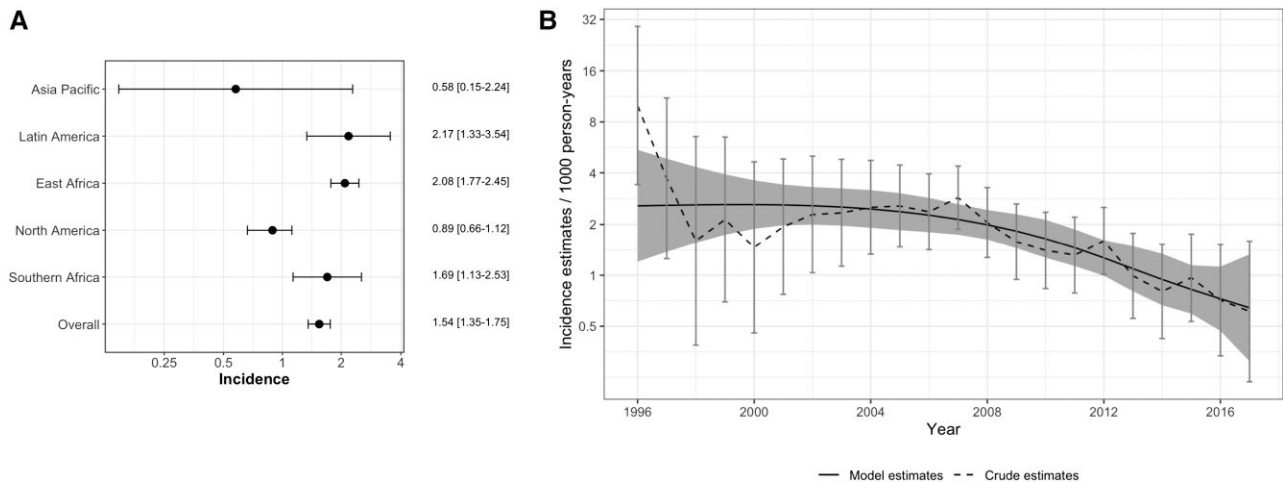


Figure 1. Incidence of cryptococcal meningitis (CM) diagnosis. A, Unadjusted incidence of CM diagnosis per 1000-person years (95% CIs) according to region and overall. B, Incidence (95% CI) of CM diagnosis across all sites according to calendar year; dashed line represents crude estimates for that year,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

person-years), and Asia-Pacific (0.58/1000 person-years; Figure 1A). Both overall and per region incidence during the first year of follow-up was substantially higher (overall, 5.66/1000 person-years; Supplementary 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 with 0.97 (95% CI, .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. Median age at enrollment and CM diagnosis were 36.8 and 38.5 years, respectively. Median CD4 at CM diagnosis was 64 cells/mm³ (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; Table 3). Median year of enrollment for those without vs with a CM diagnosis was 2009 (IQR, 2005–2012) vs 2007 (IQR, 2004–2010), respectively. Median CD4 at enrollment for those with a CM diagnosis was 59 cells/mm³ (IQR, 20–163 cells/mm³) vs 262 cells/mm³ (IQR, 106–469 cells/mm³) for those without a CM diagnosis. The median CD4 for those diagnosed with CM before starting ART was 47 cells/mm³ (IQR, 16–118) vs 77 cells/mm³ (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/mm³ was 3.89 times higher than for a patient with CD4 = 350 cells/mm³ (95% CI, 3.13–4.84). Being on ART was also highly protective of CM, with an estimated IRR of 0.33 (95% CI, .24–.44). The risk of CM tended to be lower in more recent years (IRR, 0.23; 95% CI, .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 of 33) among those with CM diagnosis, followed by East Africa at 26.5% (607 of 2289), South Africa at 28.2% (109 of 386), Latin America at 42.5% (110 of 259), and North America at 43% (383 of 890). However, the proportions lost to follow-up 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

Table 2. Characteristics of Patients Stratified by Cryptococcal Meningitis Diagnosis

Characteristic	No CM (N = 514 995)	CM (N = 3857)	Overall (N = 518 848)
Age at enrollment, y			
Median (IQR)	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, y			
Median (IQR)	...	38.5 (32.3–45.6)	...
Range	...	16.3–90.2	...
Missing (%)	...	0 (0.0)	...
Year of enrollment			
Median (IQR)	2009 (2005–2012)	2007 (2004–2010)	2009 (2005–2012)
Range	1996–2017	1996–2017	1996–2017
Year of CM diagnosis			
Median (IQR)	...	2008 (2005–2012)	...
Range	...	1996–2017	...
Sex			
Female	250 688 (48.7)	1667 (43.2)	252 355 (48.6)
Male	264 300 (51.3)	2190 (56.8)	266 490 (51.4)
Missing (%)	7 (0.0)	0 (0.0)	7 (0.0)
CD4 at enrollment, cells/mm³			
Median (IQR)	262 (106–469)	59 (20–163)	261 (105–468)
Range	0–4868	0–1963	0–4868
Missing (%)	154 530 (30.0)	1498 (38.8)	156 028 (30.1)
CD4 at CM diagnosis, cells/mm³			
Median (IQR)	...	64 (20–168)	...
Range	...	0–3695	...
Missing (%)	...	1066 (27.6)	...
VL at enrollment, copies/mL^a			
Median (IQR)	10 712 (400–83 500)	87 387 (12 381–312 096)	10 900 (400–84 439)
< 400	43 199 (31.3)	94 (13.1)	43 293 (8.2)
< 200	40 165 (29.1)	87 (12.2)	40 252 (7.7)
Missing (%)	376 885 (73.2)	3142 (81.5)	380 027 (3.2)
VL at CM diagnosis, copies/mL^a			
Median (IQR)	...	26 641 (<400–186 484)	...
< 400	...	357 (29.4)	...
< 200	...	320 (26.3)	...
Missing (%)	...	2642 (68.5)	...
ART-naive at enrollment	364 572 (70.8)	2774 (71.9)	367 346 (70.8)
ART-naive at CM diagnosis	...	1379 (35.8)	...

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

^aPercentage is among those with nonmissing values.

diagnosed before ART initiation and after ART initiation, respectively, the estimated probabilities of death were 0.35 (95% CI, .32–.38) and 0.33 (95% CI, .35–.31); the estimated probabilities of death or LTFU were 0.62 (95% CI, .60–.65) and 0.49 (95% CI, .47–.51); and the estimated cumulative incidences of death treating LTFU as a competing event were 0.27 (95% CI, .25–.30) and 0.28 (95% CI, .26–.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, .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/mm³; 95% CI, 1.03–1.30), and earlier year of CM diagnosis (HR, 0.51 for 2015 vs 2000; 95% CI, .37–.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 (Supplementary Appendix 2). In total,

Table 3. Characteristics of Patients Diagnosed With Cryptococcal Meningitis by Timing of Antiretroviral Therapy

Characteristic	Diagnosis Before ART (N = 1379)	Diagnosis After ART (N = 2478)	Overall (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, y			
Median (IQR)	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, y			
Median (IQR)	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 (IQR)	2008 (2005–2011)	2006 (2003–2010)	2007 (2004–2010)
Range	1996–2017	1996–2017	1996–2017
CM diagnosis year			
Median (IQR)	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/mm³			
Median (IQR)	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/mm³			
Median (IQR)	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, copies/mL^a			
Median (IQR)	147 865 (38 562–475 134)	70 850 (6356–235 777)	87 387 (12 381–312 096)
< 400	14 (1.0)	80 (3.2)	94 (2.4)
< 200	13 (0.9)	74 (3.0)	87 (2.3)
Missing (%)	1176 (85)	1966 (79)	3142 (81)
VL at CM diagnosis, copies/mL^a			
Median (IQR)	145 740 (39 091–438 590)	7076 (400–106 123)	26 641 (400–186 484)
< 400	20 (1.5)	337 (13.6)	357 (9.3)
< 200	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, d			
Median (IQR)	–	253 (56–1064)	–
Range	–	1–6604	–
Follow-up after CM diagnosis, y			
Median (IQR)	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
Loss to follow-up			
	530 (38.4)	591 (23.8)	1121 (29.1)
Mortality status: dead			
	424 (30.7)	793 (32.0)	1217 (31.6)
Time to death, y			
Median (IQR)	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

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

^aPercentage is among those with nonmissing values.

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

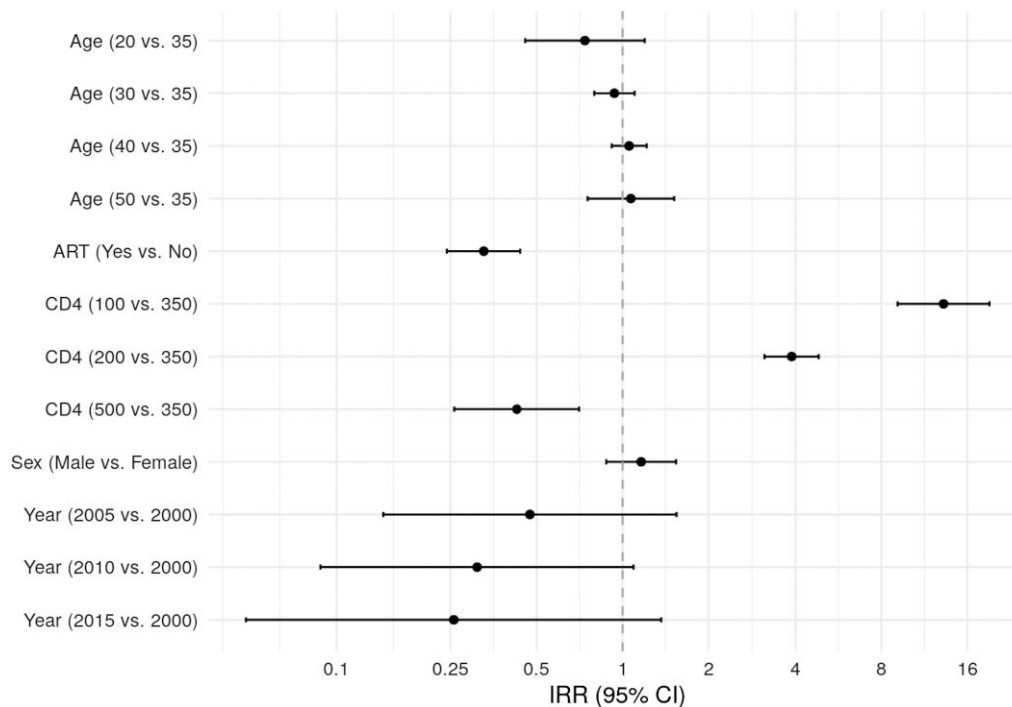


Figure 2. Estimated IRR (95% CI) of risk factors for cryptococcal meningitis combined across all regions, in adjusted analyses. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; IRR, incidence rate ratio.

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 LTFU 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- to 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 that from past studies [10, 11]. Regional differences in mortality shown in our study may be due to ascertainment but also to variability in the 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 with amphotericin and fluconazole, or non-flucytosine-containing regimens [1, 12]. At that time, the World Health Organization’s

(WHO’s) first-line recommended regimen and 1 of the 2 alternative regimens included 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 central nervous system penetration (such as voriconazole) [14] have been little studied against CM in the global south. In the randomized, controlled Advancing Cryptococcal Meningitis Treatment for Africa (ACTA) trial of 721 patients with CM and HIV in Africa, it was found that 1 week of AmB plus 5-FC and 2 weeks of fluconazole plus 5-FC were effective regimens for induction therapy for CM in resource-limited settings [1]. Based on these results, the 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 AMBisome Therapyinduction Optimization (AMBITION) trial, an open-label, phase 3, 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

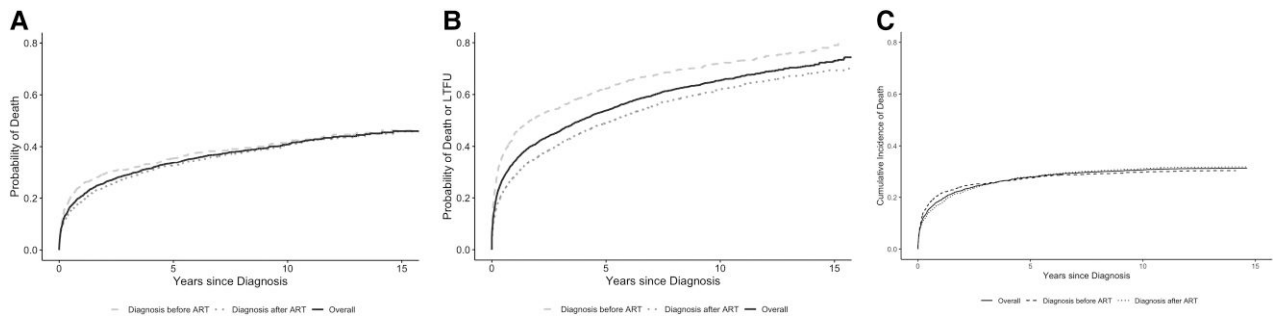


Figure 3. All-cause mortality after diagnosis of cryptococcal meningitis, overall and stratified by whether diagnosis was before or after ART initiation. *A*, Estimated probabilities based on Kaplan–Meier curves. *B*, Estimated probability of death or loss to follow-up based on Kaplan–Meier curves. *C*, Estimated cumulative incidence of death treating loss to follow-up as a competing event. Abbreviation: ART, antiretroviral therapy.

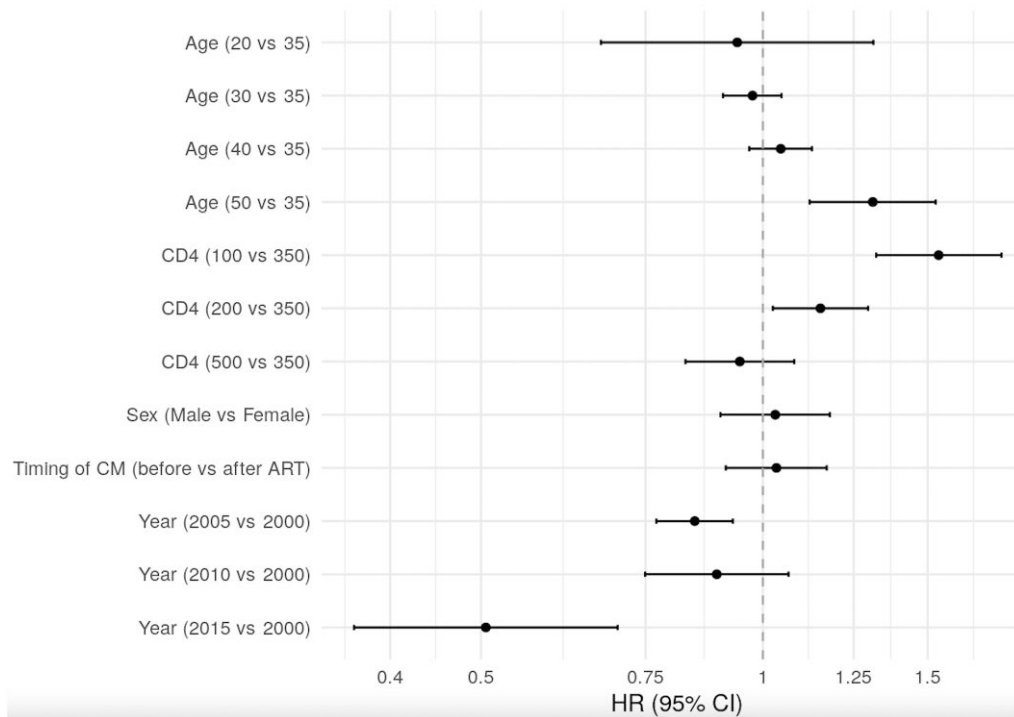


Figure 4. Estimated HRs (95% CIs) of risk factors for all-cause mortality after diagnosis of CM combined across regions, in adjusted analyses. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; CM, cryptococcal meningitis; HR, hazard ratio.

treatment for HIV-associated CM and was associated with fewer adverse events [15]. Based on results from the AMBITION trial, the WHO further updated their guidance in 2022 [16], recommending that a single dose of liposomal AmB 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. 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 a

high level of missingness, the median viral load at CM diagnosis after ART start was 7076 copies/mL. This high rate of CM diagnosis after ART start as well as a detectable viral load around the time of CM diagnosis hint at CM as a complication of virologic failure.

Our study has important limitations. First, because of diagnostic limitations that 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 who are lost to follow-up might be expected to have higher mortality than those who remain 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, so our estimates may not be generalizable to all PWH. There may also be differences in definitions of variables (eg, 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.

CONCLUSIONS

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.

Supplementary Data

[Supplementary materials](#) are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. This work is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions listed here.

Financial support. The International Epidemiology Databases to Evaluate AIDS is supported by the National Institutes of Health's (NIH's) National Institute of Allergy and Infectious Diseases; the Eunice Kennedy Shriver National Institute of Child Health and Human Development; the 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; Caribbean, Central and South America network for HIV epidemiology (CCASAnet), U01AI069923 (A. K. P. is listed as an investigator); East Africa, U01AI069911; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), U01AI069918; Southern Africa, U01AI069924. Informatics resources are supported by the Harmonist Project, R24AI24872. REDCap support was provided by UL1 TR000445 from National Center for Advancing Translational Sciences (NCATS)/NIH.

Potential conflicts of interest. M. J. G. reports an NIH subgrant from JSPHU to the University of Calgary and honoraria for participation as an ad hoc member of HIV Canadian advisory boards to Merck, ViiV Healthcare, and Gilead. G. W. reports unrestricted research grants from Roche Diagnostics and Gilead Sciences and honoraria for advisory board participation and/or travel grants from MSD, Gilead Sciences, and ViiV Healthcare, all paid to their institution. A. K. P. reports participation on the HIV Medicine Association Board of Directors and receipt of support for attending meetings and/or travel including Vanderbilt continuing medical education funds. C. C. M. reports support for attending meetings and/or travel from NIH paid to their institution. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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