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MAJOR ARTICLE

Early Antiretroviral Therapy Not Associated With Higher Cryptococcal Meningitis Mortality in People With Human Immunodeficiency Virus in High-Income Countries: An International Collaborative Cohort Study

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Background. Randomized controlled trials (RCTs) from low- and middle-income settings suggested that early initiation of antiretroviral therapy (ART) leads to higher mortality rates among people with HIV (PWH) who present with cryptococcal meningitis (CM). There is limited information about the impact of ART timing on mortality rates in similar people in high-income settings.

Methods. Data on ART-naive PWH with CM diagnosed from 1994 to 2012 from Europe/North America were pooled from the COHERE, NA-ACCORD, and CNICS HIV cohort collaborations. Follow-up was considered to span from the date of CM diagnosis to earliest of the following: death, last follow-up, or 6 months. We used marginal structural models to mimic an RCT comparing the effects of early (within 14 days of CM) and late (14–56 days after CM) ART on all-cause mortality, adjusting for potential confounders.

Results. Of 190 participants identified, 33 (17%) died within 6 months. At CM diagnosis, their median age (interquartile range) was 38 (33–44) years; the median $CD4^+$ T-cell count, 19/μL (10–56/μL); and median HIV viral load, 5.3 (4.9–5.6) $\log_{10}$ copies/mL. Most participants (n = 157 [83%]) were male, and 145 (76%) started ART. Mimicking an RCT, with 190 people in each group, there were 13 deaths among participants with an early ART regimen and 20 deaths among those with a late ART regimen. The crude and adjusted hazard ratios comparing late with early ART were 1.28 (95% confidence interval, .64–2.56) and 1.40 (.66–2.95), respectively.

Conclusions. We found little evidence that early ART was associated with higher mortality rates among PWH presenting with CM in high-income settings, although confidence intervals were wide.

Keywords. HIV; cryptococcal meningitis; ART; causal inference.

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INTRODUCTION

Cryptococcal meningitis (CM) is a common opportunistic infection (OI) in people with human immunodeficiency virus (HIV) (PWH) and has a high mortality rate. In 2014, there were >200 000 incident cases of CM globally among PWH, with >180 000 deaths, most in sub-Saharan Africa [1].

For antiretroviral therapy (ART)–naive patients presenting with CM, ART should be administered once antifungal treatment has started. However, there is conflicting evidence from randomized controlled trials (RCTs) on the optimal time to initiate ART. Two African RCTs concluded that early ART (within 15 days of starting OI treatment) was associated with higher mortality rates than late ART [2, 3]. A Chinese RCT [4] also showed increased mortality rates with early ART, although that study used different definitions (defining early ART as within 2–5 weeks after the start of OI treatment and late ART as ≥5 weeks after OI treatment). Conversely, the AIDS Clinical Trials Group (ACTG) A5164 trial, conducted in the United States and South Africa [5], found that early ART (within 14 days), resulted in reduced progression to AIDS and fewer deaths than late ART (after completion of OI treatment).

A post hoc analysis, restricted to participants with CM, suggested a beneficial effect of early ART, although the sample size was small. When considering other causes of meningitis, an RCT in Vietnam [6] found that early ART did not decrease the mortality rate in PWH with *Mycobacterium tuberculosis* meningitis. A 2018 Cochrane review found insufficient evidence in support of either early or late ART in PWH with CM [7]. Current World Health Organization advice states that "immediate ART initiation is not recommended for adults, adolescents and children living with HIV who have CM because of the risk of increased mortality" [8]. Because data regarding this issue in high-income settings are lacking, observational data were analyzed using marginal structural models to mimic a clinical trial of when to start ART in PWH with CM diagnosed in high-income settings.

METHODS

Data on ART-naive (no prior ART use) PWH with CM diagnosed between 1994 and 2012 were combined from 3 collaborations of clinical HIV cohorts from Europe and North America: the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) [9], the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) [10], and the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) [11]. To avoid duplication between NA-ACCORD and CNICS, the record from NA-ACCORD was used. Participants were eligible if, at CM diagnosis, they were ≥16 years old and $CD4^+$ T-cell count and viral load (VL) measures were available. In addition, follow-up data were required after CM diagnosis (records present regarding laboratory tests/visits/mortality; blood samples were obtained every 3 months on average across these settings). CM diagnosis was based on the 1993 Centers for Disease Control clinical case definition [12]. The outcome was all-cause mortality.

Variables

The baseline was defined as the date of CM diagnosis. Baseline $CD4^+$ T-cell count and VL were the values closest to CM diagnosis date within a window of 3 months before and 1 week after diagnosis. Baseline $CD4^+$ T-cell counts were low, so were categorized as 0–9, 10–19, 20–49, 50–99, or ≥100 cells/μL. Time-updated $CD4^+$ T-cell counts were higher, and categorized as: 0–49, 50–99, 100–199, 200–349, 350–499, or ≥500 cells/μL. Baseline and time-updated $\log_{10}$VL were categorized as 0–3.99, 4–4.99 and ≥5; and 0–1.69, 1.70–3.99, or ≥4 copies/mL respectively. Other variables included were sex; age; probable mode of HIV acquisition (injecting drug use, sex between men, sex between men and women, or unknown); diagnosis of AIDS before baseline (excluding CM), calendar year of CM diagnosis (1994–1999, 2000–2001, 2002–2004, or 2005 and later) and location (Europe or North America). Follow-up was from CM diagnosis date to the earliest of death, last follow-up, or 6 months after diagnosis. Follow-up was censored at 6 months as an effect of ART timing beyond this was deemed unlikely.

Mimicking an RCT

We used marginal structural models to mimic an RCT of the effect of ART timing on all-cause mortality. We compared regimen A, in which ART was started within 14 days of CM diagnosis (early ART) with regimen B, in which ART was deferred until 15–56 days after CM diagnosis (late ART). We used the 3-stage (clone, censor, weight) approach described by Cain et al [13] and Hernán [14]. First, we replicated (cloned) the data for each participant; 1 clone was assigned to each regimen. Second, data for each clone were censored if the person deviated from the regimen assigned to that clone. For example, a person starting ART on day 10 adhered to regimen A throughout follow-up, so data for the clone assigned to this regimen remained uncensored. Data for the clone assigned to regimen B was censored on day 10, when the person deviated from regimen B. Third, to avoid selection bias caused by the censoring process, the analysis used inverse probability weights, based on the cumulative probability of remaining uncensored. Because censoring was based on being treated with ART, the probability of being censored was estimated from a model for the probability of starting ART over time since CM diagnosis.

To derive weights, $CD4^+$ T-cell counts and VLs were carried forward for a maximum of 6 months in the absence of more recent measures. Inverse probability of treatment weights (IPTWs) were derived using the uncloned data and a pooled logistic regression model for starting ART. We used

multivariable fractional polynomials to allow flexibility in the functional form of time and other continuous covariates. We included all variables listed above.

Using the model described above, we predicted the probability of starting ART for each day each person was in the study, assuming that ART was continued once started. Treatment probabilities were multiplied to derive the probability of each person's observed treatment history on each day. To stabilize the IPTWs, we fitted a further pooled logistic regression model, omitting the time-updated variables. The probabilities of observed treatment history from this model were multiplied by the unstabilized weights.

Fitting the Marginal Structural Model

A pooled logistic regression model, weighted by the stabilized IPTWs, was used to estimate the mortality hazard ratio (HR) comparing late versus early (reference group) ART. The model was adjusted for time (day and day squared), and baseline variables. Robust standard errors allowed for clustering by participant.

Sensitivity Analyses

Missing baseline values for $CD4^+$ T-cell counts or VLs were imputed by modeling their trajectories from baseline to 6 months after diagnosis, for those with and those without baseline measures. Imputation used the 2-fold fully conditional specification algorithm via the 2-fold command in Stata software (version 12.1. Manufacturer StataCorp., College Station, TX) [15]; this imputes missing values at particular time points (at baseline and 2, 4 and 6 months, with a window period of ±4 weeks for each measurement), given data available at that time point and at adjacent time points. $CD4^+$ T-cell counts were square root transformed, and VLs were log-transformed for the imputations. We fitted the model to generate IPTWs and the final marginal structural model for mortality on each of 25 imputed data sets; Rubin's rules [16] were used to combine results over data sets.

RESULTS

Data were available from 30 cohorts across Europe and North America (Supplementary Table 1), with a majority of participants from the United States and Spain. Figure 1 shows a flow chart of PWH included in the analysis, leaving 190 participants with full covariate data. Comparing characteristics of the 190 included PWH with those excluded for reasons other than being ART experienced showed that participants in European cohorts, female participants, those who acquired HIV through sex between men and women, and those with CM diagnosed in earlier calendar periods were more likely excluded (Supplementary Table 2).

Table 1 shows characteristics of those included and compares them by ART and mortality status within 6 months after diagnosis. Most participants were male (83%) and acquired HIV through a sexual route. At CM diagnosis, the median age (interquartile range [IQR]) was 38 (33–44) years; the median $CD4^+$ T-cell count, 19/μL (10–56/μL); and the median VL, 5.3 (4.9–5.6) $\log_{10}$ copies/mL.

Of 190 PWH, 145 (76%) started ART within 6 months of CM diagnosis; most initiated a protease inhibitor (PI)–based regimen, and the median time from CM diagnosis to ART start (IQR) was 23 (6–42) days. Thirty-three people (17%) died

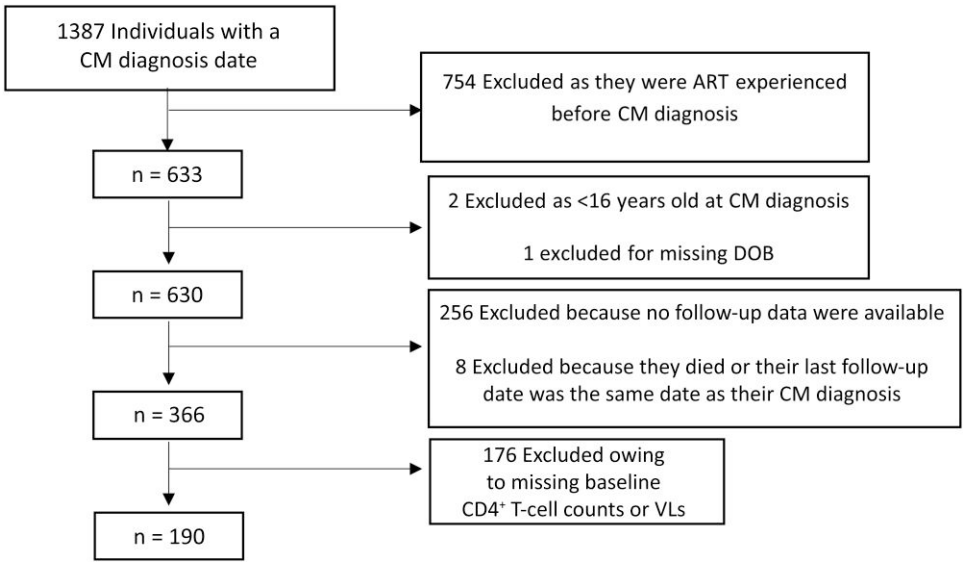

Figure 1. Flow chart of exclusion and inclusion criteria among people with human immunodeficiency virus and a diagnosis of cryptococcal meningitis (CM). Abbreviations: ART, antiretroviral therapy; DOB, date of birth; VLs, viral loads.

Table 1. Demographics, Clinical Characteristics, and 6-Month Outcomes in 190 Eligible People With Human Immunodeficiency Virus and Cryptococcal Meningitis

Characteristic	Category	Participants, No. (%)[a]				Participants, No. (%)[a]		
		Overall (N = 190)	ART by 6 m (n = 145)	No ART by 6 m (n = 45)	*P* Value	Alive at 6 m (n = 157)	Dead at 6 m (n = 33)	*P* Value
Location	Europe	114 (60.0)	94 (64.8)	20 (44.4)	.02	88 (56.1)	26 (78.8)	.02
	North America	76 (40.0)	51 (35.2)	25 (55.6)		69 (43.9)	7 (21.2)	
Sex	Male	157 (82.6)	122 (84.1)	35 (77.8)	.33	129 (82.2)	28 (84.9)	.71
	Female	33 (17.4)	23 (15.9)	10 (22.2)		28 (17.8)	5 (15.2)	
Age, median (IQR), y		38 (33–44)	38 (33–43)	40 (34–44)	.70	38 (34–43)	43 (32–48)	.02
Race	Black	55 (28.9)	37 (25.5)	18 (40.0)	.17	43 (27.4)	12 (36.4)	.45
	White	55 (28.9)	64 (44.1)	16 (35.6)		48 (30.6)	7 (21.2)	
	Other/unknown	80 (42.1)	44 (30.3)	11 (24.4)		66 (42.0)	14 (42.4)	
Mode of HIV acquisition	Sex between men	65 (34.2)	55 (37.9)	10 (22.2)	.26	54 (34.4)	11 (33.3)	.81
	Injecting drug use	28 (14.7)	20 (13.8)	8 (17.8)		24 (15.3)	4 (12.1)	
	Sex between men and women	72 (37.9)	51 (35.2)	21 (46.7)		60 (38.2)	12 (36.4)	
	Other/unknown	25 (13.2)	19 (13.1)	6 (13.3)		19 (12.1)	6 (18.2)	
Year of CM diagnosis	1994–1999	25 (13.2)	19 (13.1)	6 (13.3)	.97	19 (12.1)	6 (18.2)	.59
	2000–2001	42 (22.1)	32 (22.1)	10 (22.2)		35 (22.3)	7 (21.2)	
	2002–2004	67 (35.3)	50 (34.5)	17 (37.8)		54 (34.4)	13 (39.4)	
	2005 and beyond	56 (29.5)	44 (30.3)	12 (26.7)		49 (31.2)	7 (21.2)	
Previous AIDS diagnosis		78 (41.1)	61 (42.1)	17 (37.8)	.61	63 (40.1)	15 (45.5)	.57
$CD4^+$ T-cell count at CM diagnosis, median (IQR), cells/μL		19 (10–56)	20 (10–57)	17 (9–38)	.35[b]	20 (10–61)	15 (9–32)	.22[b]
VL at CM diagnosis, median (IQR), log_{10} copies/mL		5.3 (4.9–5.6)	5.3 (4.9–5.6)	5.4 (5–5.6)	.44[b]	5.3 (4.9–5.6)	5.4 (4.8–5.8)	.32[b]
ART within 6 m of CM diagnosis	No	45 (24)	NA	NA	NA	24 (53)	21 (47)	<.01
	Yes	145 (76)	NA	NA		133 (92)	12 (8)	
Time from CM diagnosis to ART, median (IQR), d		23 (6–42)	NA	NA	NA	23 (5–42)	23 (12–45)	.99[b]
Type of ART received (n = 145)	PI based	82 (56.6)	82 (56.6)	NA	NA	74 (57.4)	8 (50.0)	.84
	NNRTI based	53 (36.6)	53 (36.6)	NA		46 (35.7)	7 (43.8)	
	NRTIs only	3 (2.1)	3 (2.1)	NA		3 (2.3)	0 (0)	
	Other	7 (4.8)	7 (4.8)	NA		6 (4.7)	1 (6.3)	
Causes of death (n = 33 within 6 m)	AIDS-defining events	15 (45.5)	4 (25.0)	11 (64.7)	.055	NA	15 (45.5)	NA
	Non–AIDS-defining events	4 (12.1)	2 (12.5)	2 (11.8)		NA	4 (12.1)	
	Unknown	14 (42.4)	10 (62.5)	4 (23.5)		NA	14 (42.4)	

Abbreviations: ART, antiretroviral therapy; CM, cryptococcal meningitis; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; VL, viral load.

[a]Data represent no. (%) of participants unless otherwise specified.

[b]*P* values based on Wilcoxon rank sum test.

Table 2. Antiretroviral Therapy (ART) and Outcomes at 6 Months According to Receipt of Early or Late ART[a]

Outcome or Characteristic	Category	Participants, No. (%)[b]	
		Early ART (n = 190)	Late ART (n = 190)
Outcome at 6 mo	Artificially censored[c]	126 (66.3)	109 (57.3)
	Administratively censored (database close)	51 (26.8)	61 (32.1)
	Death	13 (6.8)	20 (10.5)
Started ART under this regimen?		56 (29.4)	68 (35.8)
Time from CM diagnosis to start of ART, median (IQR), d		0 (0–7)	31 (23–42)
Type of ART received	PI based	39 (69.6)	35 (51.5)
	NNRTI based	14 (25.0)	29 (42.7)
	NRTIs only	1 (1.8)	1 (1.5)
	Other	2 (3.6)	3 (4.4)
Causes of death	AIDS-defining events	9 (69.2)	9 (45.0)
	Non–AIDS-defining events	2 (15.4)	1 (5.0)
	Unknown	2 (15.4)	10 (50.0)

Abbreviations: ART, antiretroviral therapy; CM, cryptococcal meningitis; HIV, human immunodeficiency virus; IQR, interquartile range; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTIs, nucleoside reverse-transcriptase inhibitors; PI, protease inhibitor.

[a]Findings based on cloning the data for all 190 eligible people, assigning 1 clone to each trial arm, and censoring at the time people deviated from the regimen assigned to that clone.

[b]Data represent no. (%) of participants unless otherwise specified.

[c]In the early ART arm, people were censored if they did not start ART within 2 weeks. In the late ART arm, people were censored if they started ART within 2 weeks or did not start ART within 8 weeks.

within 6 months of CM diagnosis, 16 of 145 (11%) on ART and 17 of 45 (38%) not on ART; 45% of deaths were from CM or other AIDS-defining events and 42% from unspecified causes. Four people died of non–AIDS-defining causes. Characteristics of people who died within 6 months were broadly similar to those who did not, although the former group was older and more likely from European cohort studies.

Table 2 shows characteristics for each arm of the mimicked trial, in which data from all 190 participants were cloned and included in each trial arm, with follow-up censored when they deviated from that arm. Eight deaths were excluded from the mimicked trial because follow-up was censored: 4 in people who started ART after day 56 and 4 in people who died after day 56 without starting ART. Eight deaths that occurred before ART initiation and within 2 weeks of CM were included in both arms, because they occurred in individuals whose follow-up was consistent with both arms. We refer to these as "duplicated deaths."

After censoring, there were 13 deaths under early ART (5 among people who started ART within 2 weeks and died by 6 months and 8 duplicated deaths) and 20 deaths under late ART (5 among people not on ART who died by day 56, 7 among people who started ART within days 15–56 but died by 6 months, and 8 duplicated deaths). In the early ART arm, after censoring, 56 participants started ART within 2 weeks of CM diagnosis, among whom most started ART immediately (median [IQR] time between diagnosis and ART initiation, 0 [0–7] days). In the late ART arm (after censoring), 68 participants started ART between 2 and 8 weeks after diagnosis. Among these, the median (IQR) time to ART initiation was 31 (23–42) days. Participants in the early ART arm were more likely to start a PI-based therapy and to die of an AIDS-defining event than those in the late ART arm. More deaths were from unknown causes in the late ART arm.

Supplementary Table 3 compares longitudinal $CD4^+$ T-cell counts and VLs among participants after imputation of missing values with those with complete data. While baseline values were similar, follow-up VLs were generally higher in the imputed data set than in the complete-case data set, suggesting that those with complete data may represent participants with less advanced HIV.

Figure 2 shows Kaplan-Meier survival estimates from mimicking an RCT by cloning and censoring the data. Survival patterns were similar for the 2 arms, with overlapping confidence intervals (CIs), although by the end of follow-up the estimated mortality incidence was slightly higher among the late ART arm. At 1 month, the estimated survival was 94% (95% CI, 88%–97%) in the early ART arm and 92% (86%–95%) in the late ART arm; the corresponding results at 6 months were 87% (77%–93%) and 82% (73%–88%), respectively.

In constructing marginal structural models, IPTWs were derived by fitting a multivariable fractional polynomials model to predict who starts ART at each time point. Model estimates are in Supplementary Table 4. Supplementary Figure 1 shows a box plot of the stabilized weights. The crude and adjusted mortality HRs comparing late with early ART were 1.28 (95% CI,

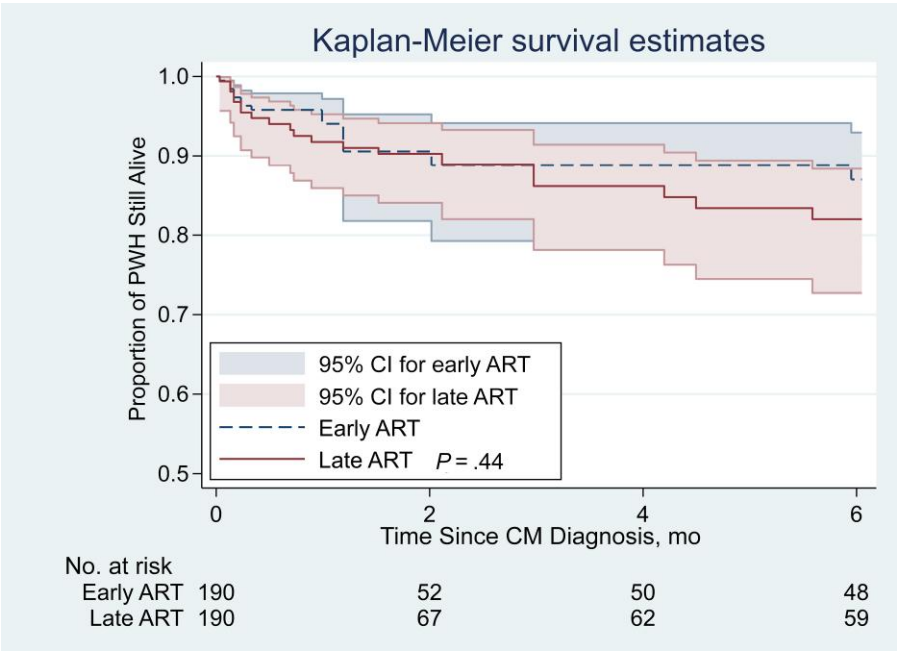

Figure 2. Estimated survival over time in people living with human immunodeficiency virus with cryptococcal meningitis (CM) according to whether they started antiretroviral therapy (ART) early or late, using methods that mimic a randomized controlled trial by cloning the data for each person and censoring at the time of deviation from the assigned regimen. Abbreviation: CI, confidence interval.

.64–2.56) and 1.40 (.66–2.95). Analyses using imputed data gave an attenuated adjusted mortality HR of 1.17 (95% CI, .72–1.91).

Comparisons With Published RCTs

Table 3 compares the present study (further details in Supplementary Table 5) with 3 RCTs on ART timing among PWH with OIs. The Zimbabwean RCT [3] found that early ART was detrimental (HR, 0.35 [95% CI, .14–.91]): mortality risks in participants treated early (<72 hours) and late (>10 weeks) were 82% and 46%, respectively. A potential limitation was that participants were treated with fluconazole, a suboptimal therapy for induction. Furthermore, definitions of early and late ART were different. The COAT (Cryptococcal Optimal ART Timing) trial [2] included PWH with CM in Uganda and South Africa who were treated with amphotericin B plus fluconazole for induction. It found results similar to those in the Zimbabwe trial (HR, 0.26 [95% CI, .09–.71]). Mortality rates in people starting ART within 1–2 weeks and in those deferring ART for 5 weeks after CM diagnosis were 47% and 33%, respectively. Most PWH who died did so within the first 2–5 weeks.

The ACTG A5164 trial [5] combined data from the United States and South Africa. It found that late ART after OI treatment is complete resulted in higher rates of progression to AIDS and death than early ART (within 15 days of starting OI treatment) (HR, 1.96 [95% CI, 1.06–3.06]). Although most participants had Pneumocystis pneumonia (PCP), results of post hoc analysis suggested that the beneficial effect of early ART persisted for CM. No participants in the early ART arm died, compared with 17% in the late ART arm.

DISCUSSION

We found little evidence that early ART after CM was associated with higher mortality rates than late ART in ART-naive PWH living in high-income settings. Mortality rates in this study were markedly lower than those in African RCTs. People in this study and the 3 RCTs were young; the median ages ranged from 35 to 43 years. Women represented 48% of participants in African RCTs but only 16% in our study and the ACTG trial. There is evidence that women with HIV experience higher mortality rates with CM [17] which may partly explain differences in these rates across settings. All African patients reported HIV acquisition through heterosexual routes, whereas in our study 34% of HIV acquisition was through sex between men.

Access to healthcare and severity of CM may be relevant to the effect of early ART. In Africa, contact with healthcare tends to occur later, when CM is more severe with higher deterioration in consciousness and higher fungal load in the central nervous system. These factors, together with the lack of cells in cerebrospinal fluid (CSF), are associated with worse prognosis [6, 18]. Our study did not benefit from clinical or laboratory

Table 3. Comparison of Present Study With Previously Published Randomized Controlled Trials of When to Start Antiretroviral Therapy in People with Human Immunodeficiency Virus and Cryptococcal Meningitis

Characteristic	Category	Participants, No.[a]							
		Present Study (Europe/North America)		ACTG A5164 Trial (US/South Africa)		COAT Trial (Uganda/South Africa)		Zimbabwe Trial	
Study period		1998–2009		2003–2006		2010–2012		2006–2009	
Antifungal therapy		IDSA based		IDSA based		Amphotericin B + fluconazole		Fluconazole	
ART timing		Early (n = 56)	Deferred (n = 68)	Early (n = 13)	Deferred (n = 23)	Early (n = 88)	Deferred (n = 89)	Early (n = 28)	Deferred (n = 26)
Sex	Male	43	58	12	21	46	47	14	14
	Female	13	10	1	2	42	42	14	12
Age, median (IQR), y		38 (34–45)	38 (33–43)	42 (34–43)	43 (29–48)	35 (28–40)	36 (30–40)	37 (8.5*)	37.5 (6.9*)
Race	White	15	23	5	1	0	0	0	0
	Black	14	17	2	11	88	89	28	26
	Other/unknown	27	28	6	11	0	0	0	0
Mode of HIV acquisition	Sex between men	15	27	NA	NA	0	0	0	0
	Sex between men and women	21	26	NA	NA	88	89	28	26
	Injecting drug use	9	7	NA	NA	0	0	0	0
	Other/unknown	11	8	NA	NA	0	0	0	0
Previous AIDS diagnosis		20	31	NA	NA	7	7	NA	NA
$CD4^+$ T-cell count, median (IQR), cells/μL		20 (10–56)	23 (11–63)	32 (18–66)	25 (8–53)	19 (9–69)	28 (11–76)	27 (17–69)	51.5 (25–69)
VL, median (IQR), log_{10} copies/mL		5.4 (4.9–5.7)	5.2 (4.8–5.5)	5.2 (4.9–5.6)	4.9 (4.6–5.1)	5.5 (5.2–5.8)	5.5 (5.3–5.8)	4.97 (.61*)	5.21 (.37*)
Interval between CM diagnosis and ART initiation, median (IQR), d		0 (0–7)	31 (23–42)	0 (0–0)	34 (29–39)	7 (6–7)	35 (34–35)	≤3 d	>70 d
Type of ART	PI based	39	35	13	16	0	0	0	0
	NNRTI based	14	29	0	3	88	89	28	26
	NRTI based	1	1	0	0	0	0	0	0
	Other/unknown	2	3	0	0	0	0	0	0
	Did not start	0	0	0	4	0	0	0	0
Death	Overall	5	7	0	4	41	29	23	12
	At 4 wk	0	0	0	3	33	17	10[b]	7[b]
	At 6 m	5	7	0[b]	1	8	12	NA	NA
Effect measure (deferred vs early ART [reference group])		Adjusted mortality HR, 1.39 (95% CI, .66–2.94).		OR for AIDS progression/deaths, 1.96 (95% CI, 1.06–3.70)		Mortality HR, 0.26 (95% CI, .09–.71)		Adjusted mortality HR, 0.35 (95% CI, .14–.91)	
Causes of death	CM	0	0	0	2	19	10	19	10
	Other AIDS-defining event	2	0	0	1	4	6	1	1
	Non–AIDS-defining event	2	0	1	1	16	10	3	1
	Unknown	1	7	0	0	2	3		

Abbreviations: ACTG, AIDS Clinical Trials Group; ART, antiretroviral therapy; CI, confidence interval; CM, cryptococcal meningitis; COAT, Cryptococcal Optimal ART Timing; HIV, human immunodeficiency virus; HR, hazard ratio; IDSA, Infectious Disease Society of America; IQR, interquartile range; NA, not available; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; VL, viral load.

*Standard deviations around a mean value.

[a]Data represent no. of participants unless otherwise specified.

[b]<2 Weeks.

data, but we know levels of immunosuppression and plasma HIV VL at diagnosis were similar in all 4 studies. The number of $CD4^+$ lymphocytes is inversely proportional to CSF fungal load [19], especially when the $CD4^+$ T-cell count was >100/μL. However, the median $CD4^+$ lymphocyte count in these studies ranged from 19/μL to 51/μL. The plasma HIV VL was about 100 000 copies/mL, implying that participants had advanced HIV disease.

The type of antifungal treatment administered is a likely explanation for mortality rate differences between studies. Since the 1990s, amphotericin B has been the treatment of choice for AIDS-associated CM in the United States, Europe, and other developed settings, and flucytosine has been added during the first 2 weeks whenever there were no contraindications, especially since 2000 [20]. This combination is fungicidal and superior in terms of mortality risk to amphotericin B monotherapy, combined amphotericin B and fluconazole, combined fluconazole and flucytosine, and fluconazole monotherapy [21, 22]. RCTs in high-income settings with amphotericin B and flucytosine induction at 10 weeks had a 9% mortality rate [23], similar to our study. In Africa and other low-income settings with no access to these 2 essential drugs [24], the fungistatic fluconazole was used at induction. Two RCTs in low-income settings [21, 22] compared 10-week mortality across different treatment groups: amphotericin B and flucytosine (30%), fluconazole and flucytosine (35%), amphotericin B and fluconazole (33%), and amphotericin B monotherapy (44%). The Zimbabwean RCT [3] used fluconazole as monotherapy, which may explain the high mortality rate. The COAT trial [2] used amphotericin B and fluconazole at induction and had a mortality rate similar to rates in the 2 African RCTs [21, 22].

Other potential explanations for the mortality rate difference include nonsystematic use of lumbar puncture to reduce intracranial hypertension. This intervention, which reduces mortality rates [25], was practiced only in the COAT trial [2]. Second, immune reconstitution inflammatory syndrome (IRIS) is associated with early ART in high-risk people (low $CD4^+$ T-cell counts, high plasma HIV VLs, high CSF fungal inoculum). Up to 50% of people with CM who start ART early (within <2 weeks) develop paradoxical IRIS, which can worsen the prognosis [26]. The most important predictor of not developing CM-IRIS is a negative CSF culture for *Cryptococcus neoformans* at the start of ART. A South African study showed that the rate of CM-IRIS was reduced by 60% in people with negative CSF culture at ART initiation [27]. Therefore, the CM-IRIS risk is lower in people receiving induction treatment with 2 antifungals. Several studies have shown that the probability of inducing negative CSF culture in the first 2 weeks is higher with combination of amphotericin B and flucytosine [21, 22]. In African studies [5, 6] the most important cause of death was CM itself, whereas CM as a cause of death was rare in high-income settings [7], supporting use of this combination of antifungals.

A third possible explanation is that the type of ART differed across settings. In Africa, people received only ART based on efavirenz or nevirapine, whereas our study and the ACTG trial predominantly used PIs. Although these ART regimens do not influence the risk of IRIS [28], HIV PIs can inhibit in vitro the production of virulence factors of *C. neoformans* and therefore might improve the CM prognosis [29].

Two other relevant factors are subtypes of *C. neoformans* and antifungal resistance. A study sequencing isolates of *C. neoformans* from PWH in Asia and Africa showed an expansion of 3 subclades of the *C. neoformans* VNIa lineage: VNIa-4, VNIa-5, and VNIa-93 [30]. VNIa-93 was most common in Uganda and Malawi and was associated with better prognosis than VNIa-4 and VNIa-5 subclades, which predominated in Southeast Asia. It is unknown which subclades predominate in high-income settings, but the fact that in Africa a subclade with better prognosis predominates does not explain the worse prognosis observed in CM. There is scant data on antifungal resistance in Africa. A Ugandan study [31] showed no resistance to amphotericin B but a loss of sensitivity to fluconazole over time, with 31% of isolates in later years having a fluconazole MIC ≥16/mL.

The current study had certain strengths and limitations. Our sample, while a selected sample of the total population, is representative of PWH in care in high-income settings, whereas current guidelines are based on low-income settings. The main reason for exclusion from analyses was that follow-up data were not available for 256 of 630 potentially eligible PWH. We used statistical methods that mimic a trial using observational data and should avoid biases such as immortal time or lead-time bias. A similar approach was used in observational data from Latin America [32], which similarly found no evidence of a detrimental effect of early ART (<2 weeks).

Although we adjusted for potential confounding factors, unmeasured confounding is always possible in observational studies. We had no information on clinical characteristics (eg, severity of disease or Glasgow coma score), antifungal treatment, intracranial pressure monitoring, use of steroids (the negative impact of steroids emerged only after the trial from Vietnam [6]), reasons for timing of ART initiation other than those accounted for in our analyses, or monitoring of CM progression. The age of our data may be an issue, though antifungal therapy has not changed in 3 decades. Although we collated data from large collaborations, the sample size was small. In conclusion, we did not find evidence that early ART within 2 weeks of CM diagnosis led to higher mortality rates among PWH presenting with CM in high-income settings.

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

Author contributions. **J**. M. M., M. T. M., H. F., and J. A. C. S. conceived and designed the study. S. M. I. combined, checked, cleaned, and verified the data sets. All authors contributed to derivation, cleaning, and provision of cohort data. S. M. I. performed all statistical analyses (with guidance from M. T. M., L. E. C., and J. A. C. S.). S. M. I. and J. M. M. wrote the original draft of the manuscript. All authors interpretated the data and critically revised the manuscript for important intellectual content. S. M. I. and M. T. M. accessed and verified the combined data set. The individual cohort representatives could access the data from their own cohort.

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Data sharing. Owing to the data sharing agreements between individual cohorts and the collaborations (ART-CC, COHERE, NA-ACCORD, and CNICS), the data collected for this study cannot be shared. Data are owned by the individual cohorts, and those wishing to access these data should contact the individual cohorts.

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