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Outcomes of HIV-positive patients with cryptococcal meningitis in the Americas

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ABSTRACT

Background: Cryptococcal meningitis (CM) is associated with substantial mortality in HIV-infected patients. Optimal timing of antiretroviral therapy (ART) in persons with CM represents a clinical challenge, and the burden of CM in Latin America has not been well described. Studies suggest that early ART initiation is associated with higher mortality, but data from the Americas are scarce.
Methods: HIV-infected adults in care between 1985–2014 at participating sites in the Latin America (the Caribbean, Central and South America network (CCASAnet)) and the Vanderbilt Comprehensive Care Clinic (VCCC) and who had CM were included. Survival probabilities were estimated. Risk of death when initiating ART within the first 2 weeks after CM diagnosis versus initiating between 2–8 weeks was assessed using dynamic marginal structural models adjusting for site, age, sex, year of CM, CD4 count, and route of HIV transmission.
Findings: 340 patients were included (Argentina 58, Brazil 138, Chile 28, Honduras 27, Mexico 34, VCCC 55) and 142 (42%) died during the observation period. Among 151 patients with CM prior to ART 56 (37%) patients died compared to 86 (45%) of 189 with CM after ART initiation ($p = 0.14$). Patients diagnosed with CM after ART had a higher risk of death ($p = 0.03$, log-rank test). The probability of survival was not statistically different between patients who started ART within 2 weeks of CM (7/24, 29%) vs. those initiating between 2-8 weeks (14/53, 26%) ($p = 0.96$), potentially due to lack of power.
Interpretation: In this large Latin-American cohort, patients with CM had very high mortality rates, especially those diagnosed after ART initiation. This study reflects the overwhelming burden of CM in HIV-infected patients in Latin America.

Introduction

Cryptococcal meningitis (CM) is associated with substantial morbidity and mortality worldwide among HIV-infected patients. Mortality in settings across low, middle, and high income countries has ranged from 10–43%, despite availability of appropriate treatment (Jarvis and Harrison, 2007). In studies from Brazil and Argentina, mortality rates among those with CM have been as high as 30–63% (Bamba et al., 2012). However, other reports from Peru and Brazil demonstrate that when intracranial pressure is aggressively managed, mortality rates are lower, at 19% and 26%, respectively (Vidal et al., 2013). In many resource-constrained settings however, performing serial lumbar punctures or placing ventriculo-peritoneal shunts to manage intracranial pressure may not be possible. Additionally, the gold standard of effective induction therapy for CM requires potent fungicidal drugs such as flucytosine (5-FC) with amphotericin B (lipid formulation) (Perfect et al., 2010), which may be unavailable in resource-constrained settings such as some countries in Latin America.

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Further, without reconstitution of the immune system in patients with acquired immunodeficiency syndrome (AIDS), as well as consolidation and maintenance therapy after induction, relapse of CM may be as high as 15% (Perfect et al., 2010). Moreover, correctly timed introduction of antiretroviral therapy (ART) represents a clinical challenge given the risk for immune reconstitution inflammatory syndrome (IRIS) and fatal outcomes (WHO, 2011; Bisson et al., 2013; Department of Health and Human Services, 2016) A prospective randomized controlled trial from Zimbabwe found that patients who received ART within 72 h of diagnosis of CM had mortality rates of 88% versus 54% in those who delayed ART initiation to 10 weeks; all participants received 800 mg of fluconazole daily for CM induction therapy (Makadzange et al., 2010). Another randomized controlled trial in Uganda and South Africa demonstrated that patients who received early ART (within 2 weeks of diagnosis of cryptococcal meningitis) were at higher risk of mortality than those in whom ART initiation was deferred until 5 weeks after diagnosis (45% vs 30% at 26 weeks) (Boulware et al., 2014). The majority of studies of HIV-associated CM have been conducted in Sub-Saharan Africa, whereas studies of CM outcomes in HIV-infected patients in the Americas (which have a mix of low, middle, and high-income countries) are scarce. We investigated mortality and timing of ART initiation among patients with CM at study sites in South (3), Central (1), and North `America (2).

Methods

Data collaboration

The Caribbean, Central and South America network for HIV epidemiology (CCASAnet) cohort (www.ccasanet.org) has been described elsewhere (McGowan et al., 2007). The collaboration was established in 2006 as Region 2 of the International Epidemiologic Databases to Evaluate AIDS (IeDEA; www.iedea.org) with the purpose of collecting retrospective clinical HIV data to describe the unique characteristics of the epidemic in Latin America and the Caribbean. Five CCASAnet sites that routinely collect clinical endpoints contributed patient data to this study: Centro Medico Huesped/Hospital Fernandez, Buenos Aires, Argentina (CMH/HF-Argentina); Instituto de Pesquisa Clinica Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil (FC- Brazil); Fundación Arriarán, Santiago, Chile (FA-Chile); Instituto Hondureño de Seguridad Social and Hospital Escuela, Tegucigalpa, Honduras (IHSS/HE-Honduras); and Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico (INCMNSZ-Mexico). Data were also obtained from the Vanderbilt Comprehensive Care Clinic in Nashville, Tennessee, U.S.A. (VCCC-US), which provides care to HIV-infected individuals in a large region of the southeastern United States.

Table 1
Patient characterstics by site.

	CMH/FH-Argentina (n = 58)	FC-Brazil (n = 138)	FA-Chile (n = 28)	IHSS/HE-Honduras (n = 27)	INCMNSZ-Mexico (n = 34)	VCCC-United States (n = 55)	CCASAnet (n = 285)	Combined (n = 340)	p-value*
Patient age at enrollment (years)	35 (31–39)	35 (29–41)	34 (28–43)	37 (31–43)	35 (29–44)	41 (36–45)	35 (29–41)	36 (30–43)	<0.001
Male sex	51 (88%)	105 (76%)	26 (93%)	16 (59%)	29 (85%)	44 (80%)	227 (80%)	271 (80%)	1.000
CD4 at enrollment	46 (19–75)	111 (40–242)	46 (4–104)	50 (45–110)	37 (13–96)	29 (8–58)	51 (21–132)	46 (15–105)	<0.001
Missing CD4 at enrollment, n (%)	34 (59%)	92 (67%)	19 (68%)	10 (37%)	1 (3%)	0 (0%)	156 (55%)	156 (46%)	
CD4 at diagnosis of CM	22 (13–45)	83 (31–182)	86 (10–142)	65 (45–150)	28 (10–51)	38 (11–69)	47 (17–112)	45 (16–100)	0.065
Missing CD4 at diagnosis of CM, n (%)	26 (45%)	61 (44%)	14 (50%)	8 (30%)	1 (3%)	21 (38%)	110 (39%)	131 (39%)	
CD4 at ART initiation	30 (14–65)	110 (43–251)	30 (7–88)	50 (32–102)	31 (13–51)	56 (17–90)	51 (24–128)	51 (22–124)	0.495
Missing CD4 at ART initiation, n (%)	25 (43%)	68 (49%)	16 (57%)	3 (11%)	9 (26%)	20 (36%)	121 (42%)	141 (41%)	
Route of HIV transmission, n (%)									0.442
Heterosexual	16 (28%)	50 (36%)	9 (32%)	16 (59%)	13 (38%)	24 (44%)	104 (36%)	128 (38%)	
MSM	18 (31%)	53 (38%)	18 (64%)	1 (4%)	20 (59%)	16 (29%)	110 (39%)	126 (37%)	
Other	19 (33%)	9 (7%)	1 (4%)	0 (0%)	0 (0%)	8 (15%)	29 (10%)	37 (11%)	
Unknown	5 (9%)	26 (19%)	0 (0%)	10 (37%)	1 (3%)	7 (13%)	42 (15%)	49 (14%)	
Deaths	11 (19%)	85 (62%)	6 (21%)	9 (33%)	13 (38%)	18 (33%)	124 (44%)	142 (42%)	0.182
Never started on ART	1 (2%)	14 (10%)	3 (11%)	2 (7%)	4 (12%)	3 (5%)	24 (8%)	27 (8%)	0.636
CM before ART initiation	27 (47%)	29 (21%)	9 (32%)	15 (56%)	10 (29%)	34 (62%)	90 (32%)	124 (36%)	<0.001
Days from diagnosis of CM to ART initiation[a]	29 (22–72)	31 (13–61)	59 (24–76)	39 (11–106)	40 (32–51)	58 (32–214)	33 (14–73)	40 (23.5–94.5)	0.002
CM after ART initiation	30 (52%)	95 (69%)	16 (57%)	10 (37%)	20 (59%)	18 (33%)	171 (60%)	189 (56%)	<0.001
Days from ART initiation to diagnosis of CM[b]	1025 (168–2383)	832 (125–2404)	986 (215–1822)	69 (40–546)	363 (80–2806)	734 (122–1997)	743 (97–2282)	743 (98–2274)	0.888
Follow-up after CM (years)	4 (0.8–8)	3 (0.2–6)	6.6 (3–9)	6.3 (1.6–8.4)	1.3 (0.3–4.5)	3.5 (1.4–7)	3.5 (0.5–7.5)	3.5 (0.7–7.5)	0.39

Continuous variables are reported as medians (interquartile range).
CMH/FH-Argentina – Centro Medico Huesped/Hospital Fernandez, Buenos Aires, Argentina.
FC-Brazil – Instituto de Pesquisa Clinica Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil.
FA-Chile – Fundación Arriarán, Santiago, Chile.
IHSS/HE-Honduras – Instituto Hondureño de Seguridad Social and Hospital Escuela, Tegucigalpa, Honduras.
INMNSZ-Mexico – Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.
VCCC – US Vanderbilt Comprehensive Care Clinic, Nashville, Tennessee, U.S.A.
CM Cryptococcal meningitis.
MSM – Men who have sex with men.
* p-values between CCASAnet and Vanderbilt.
[a] Time to ARV estimated only in patients with a cryptococcosis event reported before ARV initiation.
[b] Time since ARV initiation to cryptococcosis event estimated only in patients with a cryptococcosis event reported after ARV initiation.