MAJOR ARTICLE

Outcomes of Cryptococcal Meningitis in Uganda Before and After the Availability of Highly Active Antiretroviral Therapy

Andrew Kambugu,[1] David B. Meya,[1] Joshua Rhein,[3] Meagan O'Brien,[6] Edward N. Janoff,[7] Allan R. Ronald,[1,8] Moses R. Kamya,[1,2] Harriet Mayanja-Kizza,[1,2] Merle A. Sande,[1,a] Paul R. Bohjanen,[3,4,5] and David R. Boulware[3,5]

[1]Infectious Disease Institute, Makerere University, and [2]Department of Medicine, Makerere University Medical School, Kampala Uganda; [3]Division of Infectious Disease & International Medicine, Department of Medicine, [4]Department of Microbiology, and [5]Center for Infectious Diseases and Microbiology Translational Research, University of Minnesota, Minneapolis; [6]Department of Medicine, Division of Infectious Diseases, New York University School of Medicine, New York; [7]Mucosal and Vaccine Research Program Colorado (MAVRC), Division of Infectious Diseases, Colorado Center for AIDS Research, University of Colorado–Denver School of Medicine, Denver Veterans Affairs Medical Center, Denver, Colorado; and [8]University of Manitoba, Winnipeg, Canada

Background. Cryptococcal meningitis (CM) is the proximate cause of death in 20%–30% of persons with acquired immunodeficiency syndrome in Africa.

Methods. Two prospective, observational cohorts enrolled human immunodeficiency virus (HIV)–infected, antiretroviral-naive persons with CM in Kampala, Uganda. The first cohort was enrolled in 2001–2002 ($n = 92$), prior to the availability of highly active antiretroviral therapy (HAART), and the second was enrolled in 2006–2007 ($n = 44$), when HAART was available.

Results. Ugandans presented with prolonged CM symptoms (median duration, 14 days; interquartile range, 7–21 days). The 14-day survival rates were 49% in 2001–2002 and 80% in 2006 ($P < .001$). HAART was started 35 ± 13 days after CM diagnosis and does not explain the improved 14-day survival rate in 2006. In 2006–2007, the survival rate continued to decrease after hospitalization, with only 55% surviving to initiate HAART as an outpatient. Probable cryptococcal-related immune reconstitution inflammatory syndrome occurred in 42% of patients, with 4 deaths. At 6 months after CM diagnosis, 18 persons (41%) were alive and receiving HAART in 2007. The median cerebral spinal fluid (CSF) opening pressure was 330 mm H_2O; 81% of patients had elevated pressure (>200 mm H_2O). Only 5 patients consented to therapeutic lumbar puncture. There was a trend for higher mortality for pressures >250 mm H_2O (odds ratio [OR], 2.1; 95% confidence interval [CI], 0.9–5.2; $P = .09$). Initial CSF WBC counts of <5 cells/mL were associated with failure of CSF sterilization (OR, 17.3; 95% CI, 3.1–94.3; $P < .001$), and protein levels <35 mg/dL were associated with higher mortality (OR, 2.0; 95% CI, 1.2–3.3; $P = .007$).

Conclusions. Significant CM-associated mortality persists, despite the administration of amphotericin B and HIV therapy, because of the high mortality rate before receipt of HAART and because of immune reconstitution inflammatory syndrome–related complications after HAART initiation. Approaches to increase acceptance of therapeutic lumbar punctures are needed.

Cryptococcal meningitis (CM) is the most common fatal CNS infection in patients with AIDS in sub-Saharan Africa [1], where patients often present with advanced HIV disease. CM is often the initial AIDS-defining illness [2]. The rate of cryptococcal infection in Uganda (40.4 cases per 1000 person-years) was double that reported among HIV-infection patients in North America prior to the HAART era (17–20 cases per 1000 person-years), and it is exponentially higher in Uganda than that in North America during the HAART era (1.5 cases per 1000 person-years) [3–5]. In 2 cohorts from Uganda, 20%–30% of persons with advanced HIV died of CM, with a median duration of survival of 26 days [4, 6]. Although access to antiretrovirals is rapidly expanding in Africa, management of

Received 29 October 2007; accepted 6 January 2008; electronically published 23 April 2008.

[a] Deceased.

Reprints or correspondence: Dr. David R. Boulware, MMC 250, 420 Delaware St. SE, Minneapolis, MN 55455 (boulw001@umn.edu).

Clinical Infectious Diseases 2008; 46:1694–1701

1058-4838/2008/4611-0008$15.00
DOI: 10.1086/587667

opportunistic infections remains a major challenge for HIV/AIDS care.

In North America, the mortality rate for CM is <10% with administration of a combination of amphotericin B (0.7–1.0 mg/kg per day), flucytosine, and aggressive management of increased intracranial pressure [7]. The rate of mortality at 14 days for HIV-associated CM in sub-Saharan Africa after receipt of amphotericin B ranges from 17% to 36%, with a median duration of survival of ~1 month [8–12]. Risk factors for mortality include delay in diagnosis, lack of amphotericin B treatment, lack of HAART, and greater fungal burdens [11]. A prospective study of amphotericin B treatment (0.7 mg/kg per day) from Thailand reported a 14-day CM mortality rate of 16% [13]. In clinical practice in Africa, fluconazole alone is routinely used because of its affordability and ease of use [14–16]. With receipt of fluconazole and without receipt of HAART, the survival rate of HIV-associated CM in Africa at 6 months is dismal (<5%) [14–18].

We conducted 2 prospective observational studies—one before and the other after HAART became available—to determine the clinical presentation and mortality rate for CM among HIV-infected adults receiving amphotericin B treatment.

METHODS

Study design. Two prospective, observational studies of HIV-infected adults who received a diagnosis of CM were conducted in Kampala, Uganda, at Mulago Hospital, the national tertiary referral and teaching hospital. The first observational period was from November 2001 through March 2002, prior to the availability of HAART (table 1). All patients who presented with headache, neck stiffness, photophobia, fever, and/or mental status change were screened for study eligibility in the emergency ward. Patients were enrolled if they were ⩾18 years of age, HIV seropositive (as determined by ELISA), not receiving HAART, and had a qualitative CSF culture that yielded *Cryptococcus neoformans.* Exclusion criteria were as follows: hemoglobin concentration, <5.0 g/dL; creatinine level, >3.0 mg/dL; or being comatose and thus unable to consent.

The second study period was July 2006 through December 2006, after HAART became available in Uganda. Screening and inclusion criteria were identical, except that CM status was considered to be positive if 2 of the following 3 CSF tests yielded positive results: India ink, cryptococcal antigen (CRAG), or *C. neoformans* quantitative culture.

Written informed consent was obtained from each subject. Study protocols were approved by the University of Minnesota (Minneapolis), Makerere University, and Ugandan National committees.

Treatment. Amphotericin B deoxycholate was given for 14 consecutive days at a dosage of 0.7 mg/kg per day. Intravenous fluid of 1 L of normal saline daily was recommended in 2001 and provided in 2006. In 2001, renal function was monitored at baseline, on day 7, and on day 14; in 2006, it was monitored at baseline and 3 times weekly thereafter. Patients who developed acute renal dysfunction (creatinine level, >3.0 mg/dL) received ⩾2 L of normal saline per day and amphotericin B on alternate days and underwent daily measurements of the creatinine level. To manage elevated intracranial pressure (>200 mm H_2O), CSF was drained until the pressure was reduced by 50% and/or the pressure was <200 mm H_2O, and daily lumbar punctures were then recommended; however, subjects often refused to undergo subsequent therapeutic lumbar punctures [19]. At the time of hospital discharge, patients received consolidation therapy with fluconazole (400 mg per day for 8 weeks) at the Infectious Diseases Institute clinic. Thereafter, they received maintenance therapy with fluconazole (200 mg per day) for secondary prophylaxis indefinitely.

In 2006, patients were seen at the Infectious Diseases Institute

Table 1. Differences between the study periods before and after HAART availability.

Characteristic	Period before HAART availability (2001–2002)	Period when HAART was available (2006)	*P*
Age, years	34.5 (29–38)	36 (31–42)	.27
Duration of antecedent symptoms, days	14 (7–21)	14 (7–21)	.43
Opening pressure, mm H_2O[a]	330 (240–476)	330 (191–465)	.42
CSF pressure, percentage of patients			
>200 mm H_2O	84	69	.09
>560 mm H_2O	20	17	.6
Percentage of patients who underwent therapeutic LP	5	5	.9
CSF protein, level, mg/dL	40 (30–40)	70 (40–120)	.002
CSF glucose level, mg/dL	56 (32–65)	37 (28–50)	.008
CSF WBC count, cells/mL	5 (<5 to 62)	10 (<5 to 53)	.9

NOTE. Data are median (interquartile range), unless otherwise indicated. LP, lumbar puncture.

[a] Maximum measurable opening pressure, 560 mm H_2O.

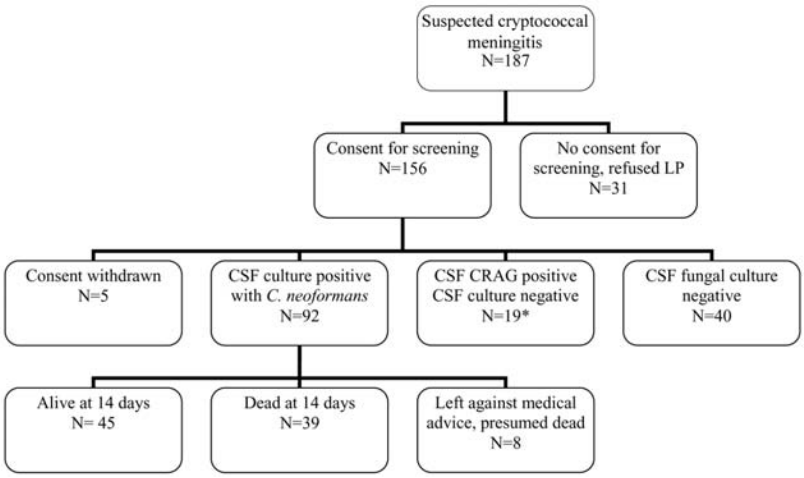


Figure 1. Profile of the study during the pre-HAART era (2001–2002). *C. neoformans, Cryptococcus neoformans;* LP, lumbar puncture. *Patients with positive CSF cryptococcal antigen (CRAG) results but negative culture results were not enrolled in 2001–2002.

clinic ≤1 week after hospital discharge for HAART counseling, and they began taking HAART 1–2 weeks thereafter. Initial HAART regimens were (1) zidovudine, lamivudine, and efavirenz or (2) stavudine, lamivudine, and nevirapine.

Data collection. Medical history was obtained; a physical examination, neurological assessment, and lumbar puncture were performed; and the CSF opening pressure (up to 560 mm H_2O) was measured. CSF specimens were analyzed for protein level, glucose level, and cell count with differential; underwent India ink, Gram, and Ziehl-Neelsen staining for detection of mycobacteria; CSF CRAG by latex agglutination titer (Murex Diagnostics); and *C. neoformans* culture on Sabouraud dextrose agar. Quantitative CSF cultures were performed in 2006 using a calibrated loop, with 10 μL of CSF supernatant cultured on Sabouraud and chocolate agars. Visible colonies were counted on each agar plate by 2 different technicians with the average recorded. CSF specimens were recultured on day 14. Study personnel visited subjects daily and repeated neurologic and laboratory evaluations on days 7 and 14.

After initiation of HAART, patients were evaluated for evidence of immune reconstitution inflammatory syndrome (IRIS). IRIS was defined as an atypical or exaggerated infectious or inflammatory condition temporally related to the initiation of HAART whereby the symptoms cannot be explained by an alternate infection, malignancy, failure of treatment of the opportunistic infection, adverse drug reaction, or complete noncompliance with antiretroviral therapy. When CM-associated IRIS was suspected, subjects underwent lumbar punctures, with India ink staining, qualitative CRAG testing, and repeated quantitative cultures of specimens to exclude CM relapse. The common triad for CM-associated IRIS is as follows: (1) CM is treated, (2) the patient commences HAART, and (3) clinical deterioration with new aseptic meningitis develops.

Statistical analysis. Data were analyzed using SPSS software, version 15.0 (SPSS). The log rank test identified categorical factors associated with risk of death. Logistic regression was used to assess the risk of microbiologic treatment failure and death during the first 2 weeks of amphotericin B therapy. Normally distributed continuous variables are reported as mean values ± SDs and were compared using the *t* test. Nonnormally distributed variables are presented as medians and interquartile ranges (IQRs) and were compared using the Mann-Whitney *U* test. Categorical differences between time periods were compared using the χ^2 test, and survival analysis was performed using Cox proportional hazards regression. Statistical significance was defined as a P value <.05.

RESULTS

Baseline Characteristics

Among the 226 persons who were screened and who had symptoms and signs suggestive of meningitis, 136 had CM (92 persons in 2001–2002, and 44 in 2006) (figures 1 and 2). The median duration of antecedent headache was 14 days (IQR, 7–21 days), and 38% of patients presented with altered mental status. The results of CSF cryptococcal cultures were positive in 122 (90%) of 136 patients, with a mean colony count of 5×10^4 colonies/mL (range, 5×10^2 to 7.5×10^5 colonies/mL); the results of CSF CRAG tests and India ink stains were positive for 100% and 97% of these patients, respectively. The median CSF CRAG titer was 1:2048 (IQR, 1:640–1:4096). The serum CRAG result was positive for 57 (97%) of 59 patients. The mean CSF opening pressure was 350 ± 144 mm H_2O (median, 330 mm H_2O; IQR, 240–476 mm H_2O), with opening pressures greater than the maximum measurable (>560 mm H_2O) present in 20%. Papilledema, which was present in 37% of subjects,

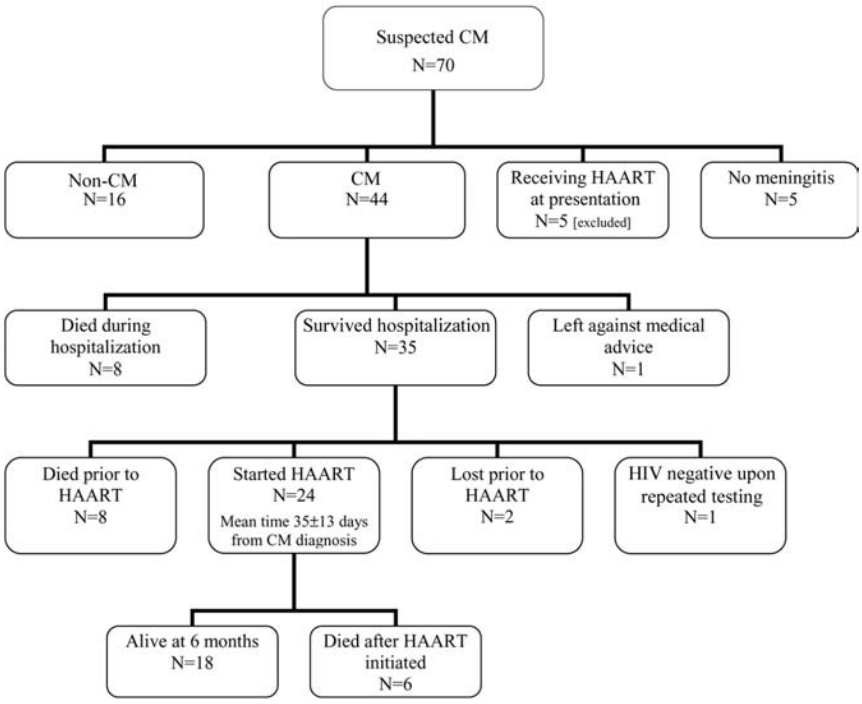


Figure 2. Profile of the study during the HAART era (2006). Subjects who left the hospital against medical advice and who were lost to follow-up were presumed to be dead. The mean time (± SD) from cryptococcal meningitis (CM) diagnosis to the commencement of HAART was 35 ± 13 days, including a mean (± SD) of 18 ± 5 days of hospitalization.

was associated with increasing opening pressure. Each 100-mm increase in CSF pressure increased the odds of papilledema (OR, 2.3; 95% CI, 1.7–3.2; $P < .001$). Comparing the study periods of 2001 to 2006, there were no significant differences in patient demographic characteristics, duration of illness, clinical symptoms, and CSF parameters, including opening pressure.

Outcomes

The pre-HAART era (2001). The CM-related mortality rate was high: 39 (42%) of 92 patients died in the first 2 weeks after presentation. The median time of death was day 4 (figure 3). Eight patients (9%) prematurely left the hospital against medical advice; thus, only 45 (49%) of 92 patients were known to be alive at 14 days. Resolution of headache by day 7 of antifungal therapy occurred in 32% of patients and by day 14 in 69%. For the 45 survivors who completed 2 weeks of amphotericin B treatment, the median CRAG titer was 1:512 (IQR, 1:128–1:1024), and 25 subjects (56%) continued to have *C. neoformans*–positive cultures. In 2001, long-term follow-up was not performed, because HAART was not yet available in Uganda. However, nearly all patients with CM who have been described in the literature died by month 6 without receipt of HAART [14–18].

The HAART era (2006). In 2006, of the 44 antiretroviral-naive patients with CM who were treated with amphotericin B, 35 (80%) survived hospitalization. The rate of survival at 14 days was greater during the HAART era (absolute risk reduction, 31%; 95% CI, 15%–46%; $P < .001$). The 2006 survival benefit persisted when our analysis excluded patients who left the hospital against medical advice and who were presumed to be dead (absolute risk reduction, 28%; $P < .001$).

After hospital discharge, 8 persons died before they could commence HAART; 2 did not return to the clinic for enrollment and were lost to follow-up, despite repeated attempts to reach them by mobile phone (they were presumed to be dead); and 1 was found to be HIV seronegative by repeated ELISA testing. Only 24 patients (55%) started HAART at a mean time from CM diagnosis of 35 ± 13 days (range, 17–78 days). The median CD4 cell count among survivors at the time of HAART initiation was 20 cells/μL (IQR, 7–47 cells/μL; maximum, 77 cells/μL). By month 3 of HAART, the median CD4 cell count had increased to 76 cells/μL (IQR, 33–153 cells/μL), and by month 6, it had increased to 66 cells/μL (IQR, 55–109 cells/μL). Plasma HIV RNA was undetectable (i.e., it was <400 copies/mL) in 8 (44%) of 18 patients at months 3 and in 15 (83%) of 18 at month 6. Only 18 persons (41%) were alive after 6 months of HAART, and each survived >12 months (median duration of antiretroviral therapy, 16 months).

Predictors of survival. Lack of CSF inflammation correlated with poor outcome. An initial CSF WBC count of <5 cells/mL was independently associated with a positive CSF *C. neoformans* culture result after 14 days (23 [74%] of 31 patients

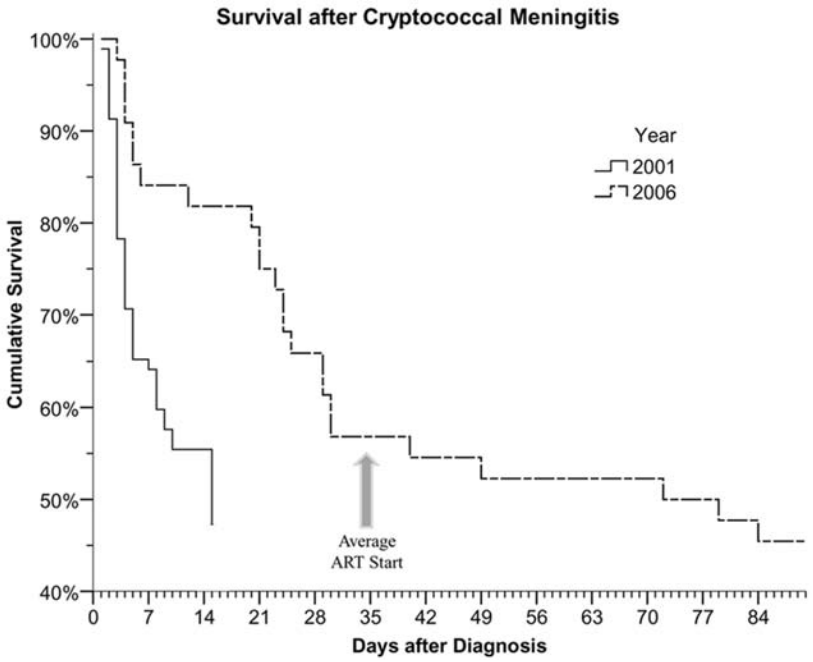


Figure 3. Kaplan-Meier survival curves stratified by time period. The follow-up period in 2001–2002 (i.e., the pre-HAART era) ended at 15 days from cryptococcal meningitis diagnosis. The 2006 follow-up continued for 12 months after commencement of HAART.

vs. 2 (14%) of 14 patients; OR, 17.3; 95% CI, 3.1–94.3; $P <$ .001). A normal CSF protein level (<35 mg/dL) was associated with higher 14-day mortality rate (24 [50%] of 48 patients with a normal CSF protein level vs. 17 [19%] of 88 patients with an abnormal level; adjusted OR, 2.0; 95% CI, 1.2–3.3; $P =$ .007).

More advanced disease, as evidenced by abnormal mental status (mini mental status exam [MMSE], <25) at presentation, was associated with increased mortality (19 [70%] of 27 patients vs. 20 (35%) of 57 patients; adjusted OR, 6.5; 95% CI, 2.1–19.7; $P =$ .001). Higher quantitative colony counts ($>5 \times 10^4$ colonies/mL) trended toward a higher mortality rate ($P =$ .054). In contrast, the initial CSF CRAG titer was not associated with mortality ($P =$ .7) or mycologic failure at 14 days ($P =$ .4). Other baseline clinical and CSF parameters, including opening pressure, were not helpful in predicting survival.

Multivariate Cox regression analysis revealed that the only clinical and laboratory parameters statistically associated with more rapid death were MMSE scores <25 (hazard ratio, 3.0; 95% CI, 1.6–5.8; $P =$ .001), CSF protein level <35 mg/dL (hazard ratio, 2.1; 95% CI, 1.1–4.0; $P =$ .03), and body weight <55 kg (hazard ratio, 2.0; 95% CI, 1.1–3.9; $P =$ .04).

IRIS

Of the 24 patients with CM who started antiretroviral therapy, 7 subsequently developed cryptococcal-related IRIS, which manifested as aseptic meningitis ($n = 5$), generalized lymphadenopathy ($n = 1$), and severe pneumonitis with respiratory failure ($n = 1$), within 2–33 weeks after HAART initiation. Among the 5 subjects with aseptic meningitis, the presenting features were severe headache, vomiting, negative CSF culture results, and high opening pressures (range, 280–320 mm H_2O). One subject experienced sudden onset of transient, bilateral blindness twice after 20 and 25 weeks of HAART in conjunction with aseptic meningitis and normal findings of an ophthalmologic examination without papilledema. Another 3 subjects developed possible cryptococcal-related IRIS events, including chorioretinitis, phlyctenular conjunctivitis, and lobar pneumonitis. IRIS also presented as unmasking of pulmonary tuberculosis in one patient and varicella zoster in another. Thus, suspected IRIS events occurred in 50% of patients with CM (95% CI, 29%–71%). Six persons subsequently died after starting HAART; 4 died of CM-related IRIS, 1 died of possible CM-related IRIS 12 days after commencement of HAART, and 1 died of profound anemia (hemoglobin concentration, 1.4 g/dL) with lactic acidosis after receiving 10 weeks of a zidovudine-lamivudine-efavirenz regimen.

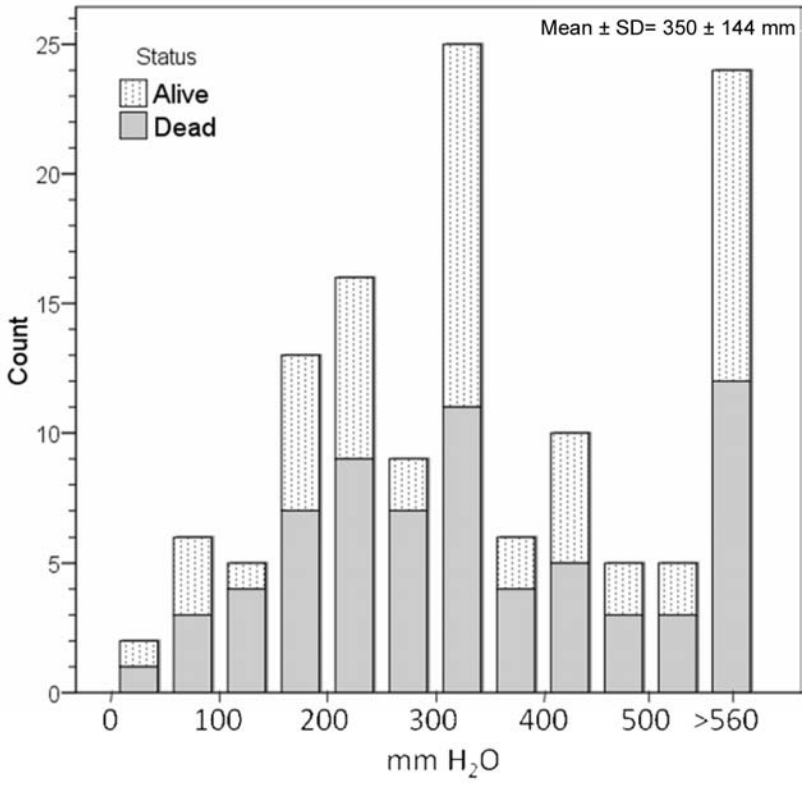
The median time between CM diagnosis and initiation of HAART was 34 days (IQR, 27–41 days) for patients with IRIS and 37 days (IQR, 29–42 days) for those who did not experience IRIS ($P =$ .7). The onset of IRIS occurred a mean ($\pm$SD) of 12.6 $\pm$ 8.6 weeks after commencement of HAART (median, 12 weeks; range 2–33 weeks).

Management of Elevated Intracranial Pressure

Initial opening pressure was measured in 126 (93%) of 136 subjects with CM, of whom 81% had opening pressures ⩾200 mm H_2O (figure 4); 69% met the criterion for therapeutic CSF drainage (pressure, >250 mm H_2O) of the guidelines of the Infectious Diseases Society of America (IDSA) [19]. However, only 5 eligible patients consented for therapeutic lumbar punctures. There is a strong cultural bias against lumbar punctures in Uganda. Considerable efforts to convince patients and their caregivers of the necessity of therapeutic lumbar punctures were unsuccessful. Surprisingly, logistic regression indicated that the initial opening pressure was unassociated with mortality ($P = .7$), even in a comparison of patients with markedly increased CSF pressure (>560 mm H_2O) versus those with normal CSF pressure (OR, 1.9; 95% CI, 0.6–6.1; $P = .3$) at the time of CM diagnosis. Patients who met the IDSA criterion for therapeutic CSF drainage (CSF pressure, >250 mm H_2O) trended toward a higher 14-day mortality rate than did those with lower CSF pressures (OR, 2.1; 95% CI, 0.9–5.2; $P = .09$).

Toxicity

Nausea and vomiting associated with amphotericin B treatment occurred in 17% of patients, and 10% experienced marked rigors associated with amphotericin B treatment. Renal toxicity associated with amphotericin B was uncommon: only 1 person (1%) stopped amphotericin B treatment (on day 7) because of a creatinine level >3 mg/dL, and only 7 (9%) of 80 patients had creatinine levels >3.0 mg/dL at day 14. The median increase in the creatinine level among survivors at day 14 was 0.6 mg/dL (IQR, 0–1.5 mg/dL), but a survival bias may be present. Neither creatinine level at presentation nor change in the level by day 7 was associated with mortality ($P > .9$).



	Baseline Opening Pressure, mm H_2O					Total
	<190	190-249	250-349	350-560	>560	
Total	24	15	31	32	24	126
Alive	19	12	18	22	16	87
Dead*	5	3	13	10	8	39
% Dead	21%	20%	42%	31%	33%	31.0%

$P = .46$, by Fisher exact-test

Figure 4. Distribution of CSF opening pressures among 126 HIV-infected patients with cryptococcal meningitis (2001 and 2006). *Persons who left against medical advice ($n = 9$) were excluded.

In 2006, renal function and electrolytes (sodium and potassium) were measured 3 times per week. An unintended result was that 66% of survivors had amphotericin B treatment withheld temporarily for >1 day and 33% for >2 days because of concerns about renal toxicity. Although these patients missed doses, all but 2 patients completed 14 doses of amphotericin B over 14–18 days.

DISCUSSION

Cryptococcal infection remains a significant problem in patients with AIDS in sub-Saharan Africa. We report a 14-day mortality rate of 20%–42% for HIV-associated CM, despite administration of amphotericin B therapy. This mortality was much higher than the 5.5%-15% mortality rate reported in North American studies [3, 7] but is comparable to that reported elsewhere in sub-Saharan Africa [1, 8, 9]. The 14-day mortality rate improved between 2001 to 2006, likely as a result of increased institutional expertise and better intravenous fluid support. Nevertheless, even with the availability of HAART, the 6-month rate of survival after CM was only 41%. The 1-year survival rate for CM in Uganda with HAART available remains 4-fold worse than that in France and ~2-fold worse than that in Thailand [20, 21].

CM mortality in Africa may remain a problem, because late presentation with advanced CM is common. In this study, the median duration of symptoms was 2 weeks. A significant proportion of patients had altered mental status (38%), similar to the experience in France (33%) but much higher than the 10%–12% rate in reports from the United States [7, 22]. The median CSF opening pressure in this study was also higher than that in the National Institute of Allergy and Infectious Diseases Mycosis Study Group (330 vs. 250 mm H_2O; $P < .001$), as was the proportion of patients with CSF opening pressures >250 mm H_2O (70% vs. 50%), which meet the recommended criterion for therapeutic lumbar punctures [23].

As highlighted by Pappas [24], management of increased intracranial pressure is critical, yet only 6% of patients in our study who had an intracranial pressure >250 mm H_2O consented to undergo therapeutic lumbar punctures. There is a strong cultural bias against lumbar punctures that has been reinforced by the high mortality of meningitis and inconsistent availability of local anesthetic for the procedure. In our experience, patients and their families consented to diagnostic lumbar punctures when they were near death and/or nearly comatose, yet they would refuse later therapeutic lumbar punctures. An additional 36 (24%) of 151 patients refused consent for the initial diagnostic lumbar puncture in 2001 and were not included in this study.

Surprisingly, we did not find a correlation between CSF pressure and mortality. Perhaps this is because most patients presented late and had advanced disease, and a high proportion had elevated pressure. We found that lack of CSF inflammation was associated with poor outcome. For example, low-to-normal protein levels (<35 mg/dL) were associated with increased acute mortality, and low-to-normal CSF WBC counts (<5 cells/mL) were associated with culture positivity at day 14, which is associated with delayed mortality through 10 weeks; these findings are in agreement with other published observations [13, 25].

IRIS is also an emerging problem in Africa, and the magnitude of the problem is poorly characterized. Unlike the cases of CM-associated IRIS from North America that involved no reported mortality [26], in our study, 4 of 10 persons with cryptococcal IRIS died, similar to results from France (3 [30%] of 10) and South Africa (6 [66%] of 9) [27, 28]. However, delaying HAART as a strategy to prevent IRIS in resource-limited areas is not likely the answer, because mortality continues to accrue between the time of hospital discharge and commencement of HAART among persons with very advanced HIV infection or AIDS. In our 2006–2007 cohort, the 21% mortality rate at days 14–28 equaled the initial 14-day mortality rate (20%). Because there was also mortality associated with IRIS after HAART initiation, the optimal timing for initiation of HAART remains unknown, and randomized trials are needed.

Given the high mortality rate for CM in Africa, alternative and complimentary approaches should be considered. Adjunctive flucytosine is unavailable and cost prohibitive (>$120 per day). From a public health perspective, scaling up routine HIV counseling and testing offers the potential to intervene with HAART before AIDS-related opportunistic infections occur. Early HIV care offers the potential of timely screening with a serum CRAG test, because cryptococcal antigenemia precedes CM symptoms by a median of 22 days [4, 29]. Patients with asymptomatic cryptococcal antigenemia have 7-fold higher odds of death after starting HAART, with an 18% attributable risk [30]. Unfortunately, the current cost of CRAG analysis ($15–$25) is prohibitive. Another potential cost-effective approach is primary fluconazole prophylaxis in populations with a high incidence of CM and antiretroviral unavailability [31].

The limitations of this work include unclear reasons for improvement in survival in 2006. Although the amount of intravenous fluid administered was not quantified, in 2001–2002, fluid use was intermittent because of frequent shortages; however, in 2006, fluid use was universal. Basic intravenous fluid management to limit amphotericin B–associated toxicity should not be neglected, and we hypothesize that improved fluid management may improve mortality in resource-limited regions. This requires additional study.

In summary, our study demonstrates a high mortality rate for CM, despite amphotericin B therapy and the availability of HAART. Although use of HAART and early detection of HIV infection may eventually lead to a reduction in opportunistic

infections, including CM, management of opportunistic infections remains a key facet of AIDS care in Africa. Trials to delineate the optimal timing of HAART initiation and treatment for CM-associated IRIS are needed, as are studies to understand the pathophysiology of IRIS.

Acknowledgments

We thank Darlisha Williams and Sarah J. Lee (University of Minnesota) and Vivian Cox (University of Colorado), for assistance with data collection; Emmanuel Okiring and Dr. Henry Kajumbula (Makerere University), for laboratory support in 2006; Henry Wamala (Makerere University), for assistance with data collection in 2000–2001; and Keith McAdam, for institutional support. All authors wish to thank Dr. Merle Sande, who had the vision to establish the Infectious Diseases Institute in Kampala, Uganda, and without whom this project would not have been possible.

Financial support. This work was supported in part by the Academic Alliance Foundation (A.K.), University of Minnesota Academic Health Center (P.R.B. and D.B.M.), National Institutes of Health Fogarty International Center: AIDS International Training and Research Program (AITRP) at Case Western Reserve University (TW000011 to A.K.), National Institute of Allergy and Infectious Diseases (T32AI055433, L30AI066779, and K12RR023247 to D.R.B.), Minnesota Medical Foundation (P.R.B., D.R.B., and D.B.M.), University of Minnesota Office of International Programs (D.R.B.), the Colorado Center for AIDS Research (NIAID P30AI054907 to E.N.J.), and the Veterans Affairs Research Service (E.N.J.).

Potential conflicts of interest. All authors: no conflicts.

References

1. Hakim JG, Gangaidzo IT, Heyderman RS, et al. Impact of HIV infection on meningitis in Harare, Zimbabwe: a prospective study of 406 predominantly adult patients. AIDS **2000**; 14:1401–7.
2. "3 By 5" progress report: December 2003–June 2004. Geneva: World Health Organization, **2004**.
3. Chuck SL, Sande MA. Infection with *Cryptococcus neoformans* in the acquired immunodeficiency syndrome. N Engl J Med **1989**; 321:794–9.
4. French N, Gray K, Watera C, et al. Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. AIDS **2002**; 16:1031–8.
5. Sacktor N, Lyles RH, Skolasky MA, et al. HIV-associated neurologic diseases incidence changes: Multicenter AIDS cohort Study, 1990–1998. Neurology **2001**; 56:257–60.
6. Lara-Peredo O, Cuevas LE, French N, Bailey JW, Smith DH. Cryptococcal infection in an HIV-positive Ugandan population. J Infect **2000**; 41:195.
7. van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. N Engl J Med **1997**; 337:15–21.
8. Schutte CM, Van der Meyden CH, Magazi DS. The impact of HIV on meningitis as seen at a South African Academic Hospital (1994 to 1998). Infection **2000**; 28:3–7.
9. Heyderman RS, Gangaidzo IT, Hakim JG, et al. Cryptococcal meningitis in human immunodeficiency virus–infected patients in Harare, Zimbabwe. Clin Infect Dis **1998**; 26:284–9.
10. McCarthy KM, Morgan J, Wannemuehler KA, et al. Population-based surveillance for cryptococcosis in an antiretroviral-naive South African province with a high HIV seroprevalence. AIDS **2006**; 20:2199–206.
11. Bicanic T, Meintjes G, Wood R, et al. Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviral-naive or antiretroviral-experienced patients treated with amphotericin B or fluconazole. Clin Infect Dis **2007**; 45:76–80.
12. Millogo A, Ki-Zerbo GA, Andonaba JB, et al. Cryptococcal meningitis in HIV-infected patients at Bobo-Dioulasso hospital (Burkina Faso). Bull Soc Pathol Exot **2004**; 97:119–21.
13. Pitisuttithum P, Tansuphasawadikul S, Simpson AJ, Howe PA, White NJ. A prospective study of AIDS associated cryptococcal meningitis in Thailand treated with high-dose amphotericin B. J Infect **2001**; 43:226–33.
14. Collett G, Parrish A. Fluconazole donation and outcomes assessment in cryptococcal meningitis. S Afr Med J **2007**; 97:175–6.
15. Schaars CF, Meintjes GA, Morroni C, Post FA, Maartens G. Outcome of AIDS-associated cryptococcal meningitis initially treated with 200 mg/day or 400 mg/day of fluconazole. BMC Infect Dis **2006**; 6:118.
16. Mwaba P, Mwansa J, Chintu C, et al. Clinical presentation, natural history, and cumulative death rates of 230 adults with primary cryptococcal meningitis in Zambian AIDS patients treated under local conditions. Postgrad Med J **2001**; 77:769–73.
17. Mayanja-Kizza H, Oishi K, Mitarai S, et al. Combination therapy with fluconazole and flucytosine for cryptococcal meningitis in Ugandan patients with AIDS. Clin Infect Dis **1998**; 26:1362–6.
18. Maher D, Mwandumba H. Cryptococcal meningitis in Lilongwe and Blantyre, Malawi. J Infect **1994**; 28:59–64.
19. Saag MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the management of cryptococcal disease. Clin Infect Dis **2000**; 30:710–8.
20. Lortholary O, Poizat G, Zeller V, et al. Long-term outcome of AIDS-associated cryptococcosis in the era of combination antiretroviral therapy. AIDS **2006**; 20:2183–91.
21. Jongwutiwes U, Kiertiburanakul S, Sungkanuparph S. Impact of antiretroviral therapy on the relapse of cryptococcosis and survival of HIV-infected patients with cryptococcal infection. Curr HIV Res **2007**; 5:355–60.
22. Dromer F, Mathoulin-Pélissier S, Launay O, Lortholary O; French Cryptococcosis Study Group. Determinants of disease presentation and outcome during cryptococcosis: the CryptoA/D study. PLoS Med **2007**; 4:e21.
23. Graybill JR, Sobel J, Saag M, et al. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups. Clin Infect Dis **2000**; 30:47–54.
24. Pappas PG. Managing cryptococcal meningitis is about handling the pressure. Clin Infect Dis **2005**; 40:480–2.
25. Siddiqui AA, Brouwer AE, Wuthiekanun V, et al. IFN-gamma at the site of infection determines rate of clearance of infection in cryptococcal meningitis. J Immunol **2005**; 174:1746–50.
26. Shelburne SA 3rd, Darcourt J, White AC Jr, et al. The role of immune reconstitution inflammatory syndrome in AIDS-related *Cryptococcus neoformans* disease in the era of highly active antiretroviral therapy. Clin Infect Dis **2005**; 40:1049–53.
27. Lortholary O, Fontanet A, Memain N, et al. Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococcosis in France. AIDS **2005**; 19:1043–9.
28. Lawn SD, Bekker LG, Myer L, Orrell C, Wood R. Cryptococcal immune reconstitution disease: a major cause of early mortality in a South African antiretroviral programme. AIDS **2005**; 19:2050–2.
29. Micol R, Lortholary O, Sar B, et al. Prevalence, determinants of positivity, and clinical utility of cryptococcal antigenemia in Cambodian HIV-infected patients. J Acquir Immune Defic Syndr **2007**; 45:555–9.
30. Liechty CA, Solberg P, Were W, et al. Asymptomatic serum cryptococcal antigenemia and early mortality during antiretroviral therapy in rural Uganda. Trop Med Int Health **2007**; 12:929–35.
31. Chetchotisakd P, Sungkanuparph S, Thinkhamrop B, Mootsikapun P, Boonyaprawit P. A multicentre, randomized, double-blind, placebo-controlled trial of primary cryptococcal meningitis prophylaxis in HIV-infected patients with severe immune deficiency. HIV Med **2004**; 5:140–3.