MAJOR ARTICLE

Dose Response Effect of High-Dose Fluconazole for HIV-Associated Cryptococcal Meningitis in Southwestern Uganda

Nicky Longley,[1,3] Conrad Muzoora,[1] Kabanda Taseera,[2] James Mwesigye,[2] Joselyne Rwebembera,[1] Ali Chakera,[1] Emma Wall,[1] Irene Andia,[1] Shabbar Jaffar,[4] and Thomas S. Harrison[3]

Departments of [1]Medicine and [2]Microbiology, Mbarara University Hospital, Mbarara, Uganda; and [3]Centre for Infection, Department of Cellular and Molecular Medicine, St. George's University of London, and [4]Department of Epidemiology and Population, London School of Hygiene and Tropical Medicine, London, United Kingdom

Background. Therapy for human immunodeficiency virus (HIV)–associated cryptococcal meningitis in many centers in Africa is fluconazole administered at a dosage of 400–800 mg per day. However, higher dosages of fluconazole have been used to treat patients without resulting in serious toxicity. Pharmacokinetic and pharmacodynamic considerations suggest that higher dosages might be associated with greater efficacy.

Methods. Sixty HIV-seropositive, antiretroviral therapy–naive patients with first-episode cryptococcal meningitis in Mbarara, Uganda, were treated with fluconazole: the first 30 patients received 800 mg per day, and the second 30 patients received 1200 mg per day. After 2 weeks, the dosage was reduced to 400 mg per day for an additional 8 weeks. The primary outcome measure was rate of clearance of infection, or early fungicidal activity, as determined by serial quantitative cerebrospinal fluid cryptococcal cultures during the first 2 weeks. Secondary outcome measures were safety and mortality through 10 weeks.

Results. Forty-seven percent of patients had a reduced level of consciousness at presentation. Early fungicidal activity was significantly greater for patients receiving fluconazole at a dosage of 1200 mg per day than it was for patients receiving 800 mg per day (early fungicidal activity $\pm$ standard deviation, -0.18 ± 0.11 vs. -0.07 ± 0.17 log colony-forming units/mL per day; $P = .007$). Fluconazole administered at a dosage of 1200 mg per day appeared to be well tolerated, and no liver function disturbance was observed. Two-week and 10-week mortality were 30% and 54%, respectively, with no statistically significant difference between the groups.

Conclusions. Fluconazole is more rapidly fungicidal when administered at a dosage of 1200 mg per day than when administered at a dosage of 800 mg per day. In resource-limited settings, additional studies are needed to test the addition of flucytosine or short-duration amphotericin B to high-dose fluconazole and to test strategies to facilitate earlier presentation, diagnosis, and treatment of patients with cryptococcal meningitis.

HIV-associated cryptococcal meningitis (CM) is now the most common cause of community-acquired meningitis in many parts of sub-Saharan Africa [1]. In addition, the associated acute mortality remains high [1]. Access to antifungal drugs is an issue in many African countries [2]. Many health care centers do not have the facilities and resources to treat patients with intravenous amphotericin B, and fluconazole, which is available through a donation program, is often the only treatment option.

Evidence suggests that outcomes in patients who are treated with fluconazole therapy at a dosage of 200 or 400 mg per day (as used in earlier trials) are poor [3–5]. In Zambia, the median duration of survival for patients receiving fluconazole at a dosage of 200 mg per day was only 19 days [3]. The 10-week mortality associated with initial fluconazole monotherapy at 200 or 400 mg per day of ~50% that was reported by Schaars et al. [4] in South Africa represents a minimum estimate, given the retrospective nature of the study and incomplete outpatient follow-up. Recent work from Cape Town, South Africa, has demonstrated that, when administered at 400 mg per day, fluconazole is essen-

Received 1 July 2008; accepted 31 August 2008; electronically published 6 November 2008.

N.L. and C.M. contributed equally to this article.

Reprints or correspondence: Dr. Conrad Muzoora, Dept. of Medicine, Mbarara University Hospital, Mbarara, Uganda (conradmuzoora@yahoo.com).

Clinical Infectious Diseases 2008; 47:1556–61
© 2008 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/2008/4712-0010$15.00
DOI: 10.1086/593194

Downloaded from http://cid.oxfordjournals.org/ at Eccles Health Sci Lib-Serials on November 28, 2014

tially fungistatic over the first 2 weeks of treatment [5]. The resulting prolonged period with a high viable organism load may predispose patients to the development of fluconazole resistance. In a recent study [6], such resistance was a significant problem when initial therapy was fluconazole administered at 400 mg per day.

In light of this data, and taking into account the safety and availability of fluconazole, some centers and countries have recently adopted 800 mg as the initial treatment dose [7, 8]. In support of this, and accepting the caveats of comparing across trials and the small numbers of patients in the higher-dose cohorts, there is some suggestion that time to sterilization of CSF decreases as the dosage of fluconazole is increased from 200 to 800 mg per day. Time to CSF sterilization was a median of 64 days in a study in which patients received 200–400 mg of fluconazole per day [9], a mean of 41 days in a study in which patients received 400 mg per day [10], and a median of 21 days and 33 days in 2 studies in which the patients received 800 mg per day [11, 12]. In addition, the recent trial reported by Pappas et al. [13] suggests the superiority of 800 mg of fluconazole per day over 400 mg of fluconazole per day in treating CM in Thailand (in both regimens, fluconazole was administered in combination with amphotericin B).

However, dosages >800 mg per day have also been given to smaller numbers of patients with cryptococcal disease and other severe fungal infections, and no evidence of serious toxicity has been found in patients receiving up to 1600 mg per day [14, 15]; in addition, there has been some suggestion of increased efficacy associated with higher dosage [15]. The plasma concentration–dosage relationship is known to be linear with fluconazole dosages up to 2 g per day [14]. Therefore, in southwest Uganda, where standard treatment before our study was 400 mg of fluconazole per day, we undertook a dose escalation cohort study to determine the effect of increasing the fluconazole dosage from 800 mg per day to 1200 mg per day on the rate of clearance of cryptococcal infection.

PATIENTS AND METHODS

Our study was conducted at Mbarara University Hospital, Mbarara, in southwestern Uganda. It was approved by the Research Ethics Committee of Mbarara University of Science and Technology, the Wandsworth Local Research Ethics Committee (covering St. Georges University of London; London, UK), and the Uganda National Council for Science and Technology.

HIV-infected patients aged ⩾18 years who were hospitalized with a first episode of CM diagnosed by CSF India ink test were eligible for enrollment in the study. The diagnosis of CM was confirmed by a CSF culture positive for *Cryptococcus neoformans*. Patients were excluded if they had alanine transaminase (ALT) levels >5 times the upper limit of normal (>200 U/L), were pregnant, had a previous serious reaction to fluconazole, had received fluconazole within the previous month, or were already receiving antiretroviral therapy (ART). Patients already receiving ART were excluded, because they have a much lower initial fungal burden than do other patients [5], which might make assessment of fungal clearance over a 2-week period less precise in these individuals, and because of concern that receiving ART might affect clearance and, therefore, constitute a confounding factor. Written informed consent was obtained from each patient or from the next of kin for patients with altered mental status.

Interventions. For the first 2 weeks, 30 patients were treated with fluconazole (Diflucan; Pfizer) at a dosage of 800 mg per day, and 30 patients were treated with fluconazole at a dosage of 1200 mg per day. After 2 weeks, all patients received fluconazole at a dosage of 400 mg per day for 8 weeks and 200 mg per day thereafter. The dosage was adjusted for patients with significant renal impairment, and the consolidation and maintenance dosage (after the first 2 weeks) was increased by 50% for patients receiving concomitant rifampicin.

Follow-up lumbar punctures were performed on days 3, 7, and 14. Patients with CSF opening pressure >35 cm water and/or headache or other symptoms attributable to increased pressure underwent additional lumbar punctures [16]. After hospital discharge, participants were counselled and initiated ART (nevirapine or efavirenz, plus stavudine and lamivudine, administered in accordance with Ugandan Ministry of Health guidelines) 1–8 weeks after the start of antifungal therapy (median time to ART initiation, 5 weeks) and were followed up for 6 months from the date of enrollment.

Evaluation and outcomes. At baseline, all participants had complete blood cell counts, $CD4^+$ cell counts, and electrolyte, urea, creatinine, and ALT measurements. The complete blood cell counts and electrolyte, urea, creatinine, and ALT measurements were repeated on days 7 and 14. The final serum ALT level was the last value obtained during the 2-week treatment period. Peak values were the highest values at any point during the treatment course. Percentage change of a value was calculated using the following formula: (final value − baseline value/baseline value) × 100%.

CSF samples were analyzed for cell count and differential cell count, protein level, and glucose level, and India ink tests and quantitative fungal cultures were performed, as described elsewhere [17]. In brief, as soon as possible after lumbar puncture, CSF samples were serially diluted 10-fold, and 100 μL of each dilution was spotted onto each half of a Sabouraud dextrose agar plate. Counts were taken from the plate with the lowest dilution that had at least 30 colonies. Cryptococcal clearance rates were calculated using a summary statistic for each patient, which was defined as the decrease in log colony-forming units (CFU) per mL of CSF per day, by use of the slope

Downloaded from http://cid.oxfordjournals.org/ at Eccles Health Sci Lib-Serials on November 28, 2014

Table 1. Baseline clinical and laboratory characteristics and clinical and laboratory outcomes for patient receiving fluconazole for the treatment of HIV-associated cryptococcal meningitis in southwestern Uganda.

Variable	All patients (n = 60)	Fluconazole dosage group: 800 mg per day (n = 30)	Fluconazole dosage group: 1200 mg per day (n = 30)	P
Male sex	34 (57)	15 (50)	19 (63)	.30
Age, median years (IQR)	34 (29–39)	35 (30–38)	33 (28–42)	.78
Abnormal mental status[a]	28 (47)	10 (33)	18 (60)	.04
Median $CD4^+$ cell count (IQR), 1×10^6 cells/L	12 (4–32)	7 (3–17)	14 (4–33)	.44
CSF data				
OP, median cm water (IQR)	30 (22–40)	30 (27–40)	34 (18–40)	.86
WBC count, median cells/mL (IQR)	15 (7–30)	20 (5–30)	13 (10–21)	.51
Baseline fungal burden, median CFU/mL (IQR)	622,500 (115,625–1,725,000)	510,000 (109,875–1,251,250)	845,000 (211,250–2,950,000)	.33
ALT level				
Baseline	…	22 (14–30)	22 (14–39)	.76
Peak	…	25 (17–39)	25 (18–36)	.82
Final	…	21 (16–34)	21 (15–35)	.92
Deaths				
2 weeks	17/57 (30)[b]	11 (37)	6/27 (22)[b]	.23
10 weeks	31/57 (54)[b]	18 (60)	13/27 (48)[b]	.37

NOTE. Data are no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; CFU, colony-forming units; IQR, interquartile range; OP, opening pressure.

[a] Defined as any reduction in Glasgow Coma Score.

[b] Three patients in the 1200 mg per day dosage group were lost to follow-up.

of the linear regression of log CFU against time for each patient [17].

The primary outcome measure was the mean rate of decrease in CSF cryptococcal CFU, or early fungicidal activity (EFA), for each of the 2 cohorts. Secondary outcome measures were change in ALT level and mortality at 2 and 10 weeks.

Statistics. Linear regression was used to compare mean rates of decrease in CSF cryptococcal CFU (i.e., EFA) by treatment cohort, adjusting for other variables if indicated, giving summary differences with 95% CIs and significance levels [17]. A P value of <.05 was considered to be statistically significant. Baseline characteristics and outcomes in the cohorts were compared by the χ^2 test for categorical variables and by the Mann-Whitney U test or Student's t test for continuous variables. Analyses were performed using Stata software, version 8 (Stata).

RESULTS

From August 2005 through May 2007, 60 patients with India ink test results and CSF cultures positive for *C. neoformans* were enrolled in the study. The first 30 patients received fluconazole at a dosage of 800 mg per day (group 1), and the next 30 patients received fluconazole at a dosage of 1200 mg per day (group 2). Forty-one patients with a positive India ink test result were screened for group 1. Of these, 8 patients were excluded because they had already initiated ART, 2 declined consent, and 1 had received fluconazole within the past month. Fifty-five patients with a positive India ink test result were screened for group 2. Of these, 16 patients were excluded because they had already initiated ART, 4 declined consent, 4 were unable to provide consent and had no next of kin with whom to discuss consent, and 1 had received fluconazole within the past month.

Baseline clinical and laboratory characteristics and clinical outcomes are shown in table 1. At the time of presentation with CM, the overall median $CD4^+$ cell count was 12×10^6 cells/L, and the median baseline fungal burden was 622,500 CFU/mL. Twenty-eight patients (47%) had altered mental status (Glasgow coma scale, <15) at presentation. There were significantly more patients with altered mental status at presentation in group 2 than in group 1.

EFA. All of the enrolled patients were analyzed for rate of clearance of infection, with the exception of 1 patient who died before the first follow-up lumbar puncture and whose infection clearance could not be assessed. The rate of clearance of infection during the first 2 weeks of therapy was more rapid in group 2 than in group 1. EFA ($\pm$SD) was -0.07 ± 0.17 log CFU/mL per day for group 1 and -0.18 ± 0.11 CFU/mL per day for group 2 (figure 1).

The difference in rate of clearance was 0.11 log CFU/mL per day (95% CI, 0.03–0.18 log CFU/mL per day; $P = .006$). In contrast with previous datasets [17, 18], baseline CSF CFU count was not significantly associated with rate of clearance ($r = 0.07$; $P = .6$); there was no statistically significant association between rate of clearance and altered mental status, age, sex, or CSF WBC count. The only other factor that was associated with rate of clearance was $CD4^+$ cell count; patients

Downloaded from http://cid.oxfordjournals.org/ at Eccles Health Sci Lib-Serials on November 28, 2014

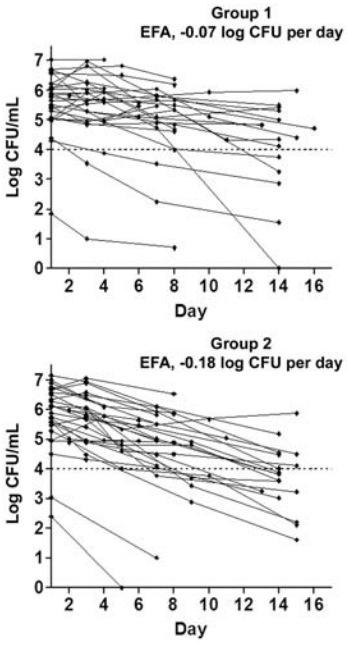

Figure 1. Decrease in CSF *Cryptococcus neoformans* colony-forming units (CFU) over time, by treatment cohort. To aid comparison of the treatment groups, the dotted lines represent a threshold of 1×10^4 CFU/mL. The decrease in log CFU/mL per day was calculated for each patient with use of the slope of the linear regression of log CFU against time. For each cohort, early fungicidal activity (EFA) is shown as the mean rate of decrease in log CFU counts. EFA was statistically significantly greater for patients receiving 1200 mg of fluconazole per day (group 2; $n = 29$) than it was for those receiving 800 mg of fluconazole per day (group 1; $n = 30$; $P = .007$).

with higher $CD4^+$ cell counts had more-rapid clearance (increase in rate of clearance, 0.07 log CFU/mL per day [95% CI, 0.04–0.10 log CFU/mL per day] for each increment in $CD4^+$ cell count quartile; $P < .001$). In a linear regression model that included fluconazole dosage and $CD4^+$ cell count, both of these factors remained independently associated with rate of clearance, and the estimates of effect were little changed. EFA was significantly greater for patients receiving fluconazole at a dosage of 1200 mg per day, compared with those receiving fluconazole at 800 mg per day (difference in EFA, 0.10 log CFU/mL per day; 95% CI, 0.03–0.16 log CFU/mL per day; $P = .007$), and was significantly greater for patients with higher $CD4^+$ cell counts (increase in rate of clearance, 0.07 log CFU/mL per day [95% CI, 0.04–0.10 log CFU/mL per day] for each increment in $CD4^+$ cell count quartile; $P < .001$).

Safety. Fluconazole at both dosages appeared to be well tolerated. No patients discontinued fluconazole therapy because of suspected adverse reactions before completing 14 days of treatment. There was no statistically significant difference between the 2 dosage groups in the percentage change in ALT level during the first 2 weeks of therapy (median percentage change in ALT level [interquartile range], 16% [−8% to 68%] for group 1 vs. 15% [−23% to 36%] for group 2; $P = .62$). Similarly, baseline, peak, and final ALT levels did not differ significantly between the 2 dosage groups (table 1). No patient developed clinical jaundice during the follow-up period.

Mortality. At 6 months after initiation of treatment, 3 patients in group 2 had been lost to follow-up, all within the first 2 weeks of treatment. Overall mortality was 30% at 2 weeks (17 of 57 patients died) and 54% at 10 weeks (31 of 57 patients died); there was no statistically significant difference between the 2 groups at either time point (table 1). At 6 months, 9 (30%) of 30 patients in group 1 and 13 (43%) of 30 patients in group 2 were known to be alive and receiving ART.

DISCUSSION

This study demonstrated a statistically significant increase in EFA when fluconazole dosage was increased from 800 to 1200 mg per day. The difference was not affected by adjustment for other factors that affected rate of clearance in this or other datasets, making it unlikely that the difference was attributable to imbalances between the groups that may have been caused by the cohort nature of the study. When added to data derived from several patients who received treatment in Cape Town, South Africa, with fluconazole at a dosage of 400 mg per day (EFA, −0.02 log CFU/mL per day) [5], these results suggest that the EFA of fluconazole increases approximately linearly with increasing dosage over this dosage range (figure 2). Such an increase would be consistent with the known pharmacokinetics and proposed area under the curve/MIC–dependent pharmacodynamics of fluconazole [19].

No evidence for an increase in toxicity at the higher dosage was observed, although the number of patients studied was small. However, fluconazole at a dosage of 1200 mg per day has been used to treat a variety of serious or refractory fungal infections without evidence for increased serious toxicity [14, 15, 20, 21]. Indeed, in coccidioidal meningitis, some experts routinely administer fluconazole at this dosage [22]. Our study

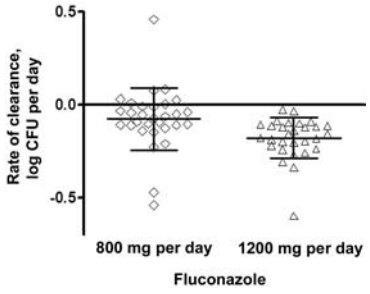

Figure 2. Decreases in CSF *Cryptococcus neoformans* log colony-forming units (CFU) per mL per day, by fluconazole dosage. The mean (± SD) rate of decrease in log CFU count *(bars)* was −0.07 ± 0.17 for patients who received 800 mg of fluconazole per day and −0.18 ± 0.11 for patients who received 1200 mg of fluconazole per day.

Downloaded from http://cid.oxfordjournals.org/ at Eccles Health Sci Lib-Serials on November 28, 2014

was not powered to determine differences in mortality. Nevertheless, there were more known survivors at 6 months in group 2 than in group 1, despite the fact that group 2 included a higher proportion of patients with altered mental status at presentation, which is the most important predictor of poor prognosis in cryptococcal meningitis.

It should be emphasized that this was a minimally selected and severely ill population; the overall proportion of patients with a reduced level of consciousness at presentation and the median baseline organism load were both markedly higher than in previous studies from Thailand and South Africa [5, 17, 18]. This may reflect late presentation, as emphasized by a previous study from the national referral hospital in Kampala, Uganda, that reported a 2-week mortality of 42% in a series of unselected patients with cryptococcal meningitis, despite the availability of amphotericin B therapy [23]. Efforts are needed to promote awareness of the clinical significance of headache in patients with possible late-stage HIV infection, and studies are needed to test strategies to facilitate rapid referral, diagnosis, and initiation of therapy for patients with cryptococcal disease [24] or to screen for early, subclinical disease. Of note, the same group recently reported outcomes for a cohort of patients (excluding comatose patients) treated with amphotericin B during 2006; these outcomes were similar to those of group 2 in our study, with 41% survival 6 months after ART initiation [25], compared with 43% survival at 6 months in group 2.

Quantitative fungal cultures of CSF samples were sometimes helpful in managing the cases of patients who presented to the hospital for a second time soon after their initial hospital admission, at a time when CSF cultures would still be expected to have positive results for most patients. An additional decrease in CFU count, compared with the CFU count for the most recent CSF sample obtained before discharge from the hospital, supported a diagnosis of immune reconstitution in those patients who had started ART, whereas an increase in CFU count despite reported adherence to consolidation or maintenance fluconazole therapy was suggestive of the possibility of developing fluconazole resistance. Maintaining high-dose fluconazole therapy after the first 2 weeks, at least until ART is started, might reduce the risk of developing resistance and improve outcome. Questions remain regarding the safety of high-dose fluconazole when administered in combination with nonnucleoside reverse-transcriptase inhibitors (in particular, nevirapine) [26, 27].

Additional studies are required, building on the work of Larsen et al. [15], to determine a full dose response for fluconazole. However, it seems to be likely, based on these results, that even at optimal dosing, treatment with fluconazole will clear cryptococcal infection less rapidly than will amphotericin B–based regimens, which have been associated with rates of clearance of 0.31–0.56 log CFU/mL per day in earlier studies [5, 17, 18]. Thus, 2 additional strategies need testing urgently in settings in which 2 weeks of amphotericin B–based treatment is not yet feasible: addition of flucytosine to optimized fluconazole in an oral regimen and addition of short course (5–7-day) amphotericin B therapy to optimized fluconazole therapy. An optimized oral regimen also needs to be tested against amphotericin B–based therapy. In the meantime, at African health care centers where fluconazole is currently used, these data would support the use of 1200 mg per day as the initial dosage, with continued vigilance for the possibility of rare drug-related adverse events.

Acknowledgments

We thank all of the doctors and nurses at the Mbarara University Hospital Department of Medicine and HIV Clinic and Robert Wagubi, Nkangi Lwanga, and other staff in the microbiology laboratory, for their relentless support, and Dr. David Bangsberg and the members of the data safety monitoring committee, for their support and assistance in the conduct of this study.

Financial support. Medical Research Council (United Kingdom).

Potential conflicts of interest. All authors: no conflicts.

References

1. Jarvis J, Harrison TS. HIV-associated cryptococcal meningitis. AIDS **2007**; 21:2119–29.
2. Bicanic T, Wood R, Bekker LG, et al. Antiretroviral rollout, antifungal roll-back: access to treatment for cryptococcal meningitis. Lancet Infect Dis **2005**; 5:530–1.
3. 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.
4. 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.
5. 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.
6. Bicanic T, Harrison T, Niepieklo A, et al. Symptomatic relapse of HIV-associated cryptococcal meningitis after initial fluconazole monotherapy: the role of fluconazole resistance and immune reconstitution. Clin Infect Dis **2006**; 43:1069–73.
7. Ministry of Health, Malawi. Management of HIV-related diseases. 2nd ed. Lilongwe, Malawi: Ministry of Health, **2008**:42–3.
8. Guidelines for the prevention, diagnosis and management of cryptococcal meningitis and disseminated cryptococcosis in HIV-infected patients. Southern African J HIV Med **2007**; Spring:25–35.
9. Saag MS, Powderly WG, Cloud GA, et al. Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. The NIAID Mycoses Study Group and the AIDS Clinical Trials Group. N Engl J Med **1992**; 326:83–9.
10. Larsen RA, Leal MA, Chan LS. Fluconazole compared with amphotericin B plus flucytosine for cryptococcal meningitis in AIDS: a randomized trial. Ann Intern Med **1990**; 113:183–7.
11. Haubrich RH, Haghighat D, Bozzette SA, Tilles J, McCutchan JA. High-dose fluconazole for treatment of cryptococcal disease in patients with human immunodeficiency virus infection. The California Collaborative Treatment Group. J Infect Dis **1994**; 170:238–42.
12. Menichetti F, Fiorio M, Tosti A. High-dose fluconazole therapy for cryptococcal meningitis in patients with AIDS. Clin Infect Dis **1996**; 22:838–40.

Downloaded from http://cid.oxfordjournals.org/ at Eccles Health Sci Lib-Serials on November 28, 2014

13. Pappas PG, Nolen T, Chetchotisakd P, Larsen R, Manosuthi W, Filler S; BAMSG3-01 Study Team. Fluconazole plus amphotericin B vs amphotericin B alone for primary treatment of AIDS-associated cryptococcal meningitis: results of a phase II trial [abstract M-626]. In: Program and abstracts of the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago). Washington, DC: American Society for Microbiology, **2007**:436.
14. Anaissie EJ, Kontoyiannis DP, Huls C, et al. Safety, plasma concentrations, and efficacy of high-dose fluconazole in invasive mold infections. J Infect Dis **1995**; 172:599–602.
15. Milefchik E, Leal MA, Haubrich R, et al. Fluconazole alone or combined with flucytosine for the treatment of AIDS-associated cryptococcal meningitis. Med Mycol **2008**; 46:393–5.
16. Saag MS, Graybill RJ, Larsen RA, et al. for the MSG cryptococcal subproject. Practice guidelines for the management of cryptococcal disease. Clin Infect Dis **2000**; 30:710–8.
17. Brouwer AE, Rajanuwong A, Chierakul W, et al. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. Lancet **2004**; 363:1764–7.
18. Bicanic T, Wood R, Meintjes G, et al. High dose amphotericin B with flucytosine for the treatment of cryptococcal meningitis in HIV: a randomized study. Clin Infect Dis **2008**; 47:123–30.
19. Andes D. Pharmacokinetics and pharmacodynamics of antifungals. Infect Dis Clin North Am **2006**; 20:679–97.
20. Duswald K-H, Pemk A, Pittrow L. High-dose therapy with fluconazole >800 mg day−1. Mycoses **1997**; 40:267–77.
21. Voss A, de Pauw BE. High-dose fluconazole therapy in patients with severe fungal infections. Eur J Clin Microbiol Infect Dis **1999**; 18: 165–74.
22. Johnson RH, Einstein HE. Coccidioidal meningitis. Clin Infect Dis **2006**; 42:103–7.
23. Kambugu AD, Kamya M, Mayanja-Kizza H, O'Brien M, Dorsey G. The high mortality of HIV associated cryptococcal meningitis despite high dose amphotericin B therapy in Uganda [abstract 629]. In: Program and abstracts of the 41st Annual Meeting of the Infectious Diseases Society of America (San Diego). Arlington, VA: Infectious Diseases Society of America, **2003**:132.
24. Trachtenberg JD, Kambugu AD, McKellar M, et al. The medical management of central nervous system infections in Uganda and the potential impact of an algorithm-based approach to improve outcomes. Int J Infect Dis **2007**; 11:524–30.
25. Kambugu AD, Meya DB, Rhein J, et al. Outcomes of cryptocccal meningitis in Uganda before and after the availability of highly active antiretroviral therapy. Clin Infect Dis **2008**; 46:1694–701.
26. Geel J, Pitt J, Orrell C, van Dyk M, Wood R. Effect of fluconazole on nevirapine pharmocokinetics [abstract TuPeB4606]. In: Program and abstracts of the XVth International AIDS Conference (Bangkok). **2004**.
27. Manosuthi W, Athichathanabadi C, Uttayamakul S, Phoorisri T, Sungkanuparph S. Plasma nevirapine levels, adverse events and efficacy of antiretroviral therapy among HIV-infected patients concurrently receiving nevirapine-based antiretroviral therapy and fluconazole. BMC Infect Dis **2007**; 7:14.

Downloaded from http://cid.oxfordjournals.org/ at Eccles Health Sci Lib-Serials on November 28, 2014