Combination Flucytosine and High-Dose Fluconazole Compared with Fluconazole Monotherapy for the Treatment of Cryptococcal Meningitis: A Randomized Trial in Malawi

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(See the editorial commentary by Pappas, on pages 345–6.)

Background. Cryptococcal meningitis is a major cause of human immunodeficiency virus (HIV)–associated morbidity and mortality in Africa. Improved oral treatment regimens are needed because amphotericin B is neither available nor feasible in many centers. Fluconazole at a dosage of 1200 mg per day is more fungicidal than at a dosage of 800 mg per day, but mortality rates remain unacceptably high. Therefore, we examined the effect of adding oral flucytosine to fluconazole.

Methods. From 13 February through 2 December 2008, HIV-seropositive, antiretroviral-naive patients experiencing their first episode of cryptococcal meningitis were randomized to receive (1) 14 days of fluconazole (1200 mg per day) alone or (2) in combination with flucytosine (100 mg/kg per day) followed by fluconazole (800 mg per day), with both groups undergoing 10 weeks of follow-up. The primary end point was early fungicidal activity, derived from quantitative cerebrospinal fluid cultures on days 1, 3, 7, and 14. Secondary end points were safety and 2- and 10-week mortality.

Results. Forty-one patients were analyzed. Baseline mental status, cryptococcal burden, opening pressure, CD4+ cell count, and HIV load were similar between groups. Combination therapy was more fungicidal than fluconazole alone (mean early fungicidal activity \( \pm \) standard deviation, \(-0.28 \pm 0.17 \) log colony-forming units [CFU]/mL per day vs \(-0.11 \pm 0.09 \) log CFU/mL per day; \( P < .001 \)). The combination arm had fewer deaths by 2 weeks (10% vs 37%) and 10 weeks (43% vs 58%). More patients had grade III or IV neutropenia with combination therapy (5 vs 1, within the first 2 weeks; \( P = .20 \)), but there was no increase in infection-related adverse events.

Conclusions. The results suggest that optimal oral treatment for cryptococcal meningitis is high-dose fluconazole with flucytosine. Efforts are needed to increase availability of flucytosine in Africa.

Clinical trials registration. isrctn.org Identifier: ISRCTN02725351.
tries lack the resources to obtain and administer amphotericin B and flucytosine, relying instead on donated fluconazole.

The rate of decrease of *C. neoformans* in cerebrospinal fluid (CSF) provides a rapid and inexpensive comparison of the fungicidal activity of treatment regimens and affords greater statistical power than clinical end points in small cohorts [15]. In addition, the rate of clearance of infection is independently associated with survival at 2 and 10 weeks [16]. Previously used fluconazole dosages (200–400 mg per day) are essentially fungistatic [17], but higher doses are associated with more rapid clearance of infection, and a study from Uganda showed that dosages of 1200 mg per day appeared safe and provided faster cryptococcal clearance, compared with 800 mg per day [12]. Limited data suggest that combining flucytosine with fluconazole improves clinical outcome and time to CSF sterilization [8, 18, 19]. Therefore, in a setting where standard treatment included fluconazole (800 mg per day) since 2004 [20], we conducted an open-label, randomized, controlled trial to determine whether adding flucytosine to high-dose fluconazole (1200 mg per day) during the initial 2 weeks of treatment of cryptococcal meningitis increased the rate of CSF infection clearance.

**METHODS**

The University of North Carolina (UNC) Project (http://id.unc.edu/Malawi/) provides patient care, laboratory facilities, and training and conducts clinical research at Kamuzu Central Hospital, a tertiary referral center in Lilongwe, Malawi, serving a district of ∼230,000 HIV-infected persons. Also located on the Kamuzu Central Hospital campus, the Lighthouse Trust Clinic provides free HIV care to >5000 patients. This study was conducted by the UNC Project and sponsored by St. George’s University of London and the University of North Carolina at Chapel Hill. Approval was obtained from the Malawi National Health Sciences Research Committee, the University of North Carolina Institutional Review Board, and the Research Ethics Committee covering St. George’s University of London. The trial was registered (ISRCTN02725351) at http://www.controlled-trials.com. A data safety monitoring committee reviewed the results and adverse events after analysis of the first 41 patients.

**Participants and procedures.** From 13 February through 2 December 2008, we enrolled HIV-positive adults with their first episode of cryptococcal meningitis, diagnosed by CSF India ink or cryptococcal antigen (Figure 1). We excluded those with an alanine aminotransferase concentration >200 IU/mL, a neutrophil count <500 × 10^3^ cells/mL, a platelet count <50,000 × 10^3^ platelets/mL, pregnancy, breast-feeding, or other contraindications to study drugs. Patients already receiving ART were also excluded because they have lower baseline fungal burden and because of interactions between nevirapine and fluconazole [17, 21, 22]. Written informed consent was obtained from each participant or from the next of kin before randomization. Participants were stratified by Glasgow Coma

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**Figure 1.** Trial profile. ART, antiretroviral therapy; CSF, cerebrospinal fluid.
Scale (GCS) score (score of 15 or <15) and assigned to an intervention group by a random computer-generated list in a block size of 8.

The 2 treatment groups were as follows: (1) 2 weeks of fluconazole (1200 mg per day; Diflucan, Pfizer) or (2) 2 weeks of fluconazole (1200 mg per day) in combination with flucytosine (100 mg/kg per day, rounded down to the nearest gram per day, divided into 4 doses; Valeant Pharmaceuticals). Four patients received intravenous fluconazole as part of their initial 2-week course (3 in the fluconazole monotherapy group, 1 in the combination group); the remainder were treated orally via nasogastric tube if necessary. Patients otherwise received standard inpatient care, including intravenous fluids when indicated. After 2 weeks all patients were given 800 mg of fluconazole per day, unless they were taking rifampicin, in which case fluconazole doses were increased by 50%. When necessary, fluconazole and flucytosine doses were adjusted for renal function. Flucytosine dosage was reduced by 50% for grade III neutropenia or thrombocytopenia, and use of the drug was discontinued for grade IV toxic effects.

After 4 weeks of antifungal therapy, patients attended the Lighthouse Clinic for ART initiation ( stavudine, lamivudine, and nevirapine) according to Malawi national guidelines [23]. The fluconazole dosage was decreased from 800 to 400 mg per day to minimize the theoretical risk of nevirapine toxicity [21, 22]. Participants were observed for 10 weeks after enrollment, when the fluconazole dosage was changed to 200 mg per day indefinitely.

**Evaluation and outcomes.** In addition to the initial diagnostic lumbar puncture, we performed lumbar puncture with opening pressure measurement and quantitative CSF culture on treatment days 1, 3, 7, and 14. Patients with an elevated opening pressure ( >30 cm H2O) had more frequent lumbar punctures according to guidelines [24], and quantitative cultures were also performed on these samples. Quantitative cultures were plated in serial 10-fold dilution, as previously described [15], and the dilution with the least colonies, but at least 30 colony-forming units (CFU) per 200 µL, was used to calculate CFU per milliliter CSF. Laboratory personnel calculating quantitative cryptococcal culture results were masked to the treatment group. Cryptococcal clearance rates were calculated using a summary statistic for each patient, defined as the decrease in log CFU counts using the slope of the linear regression of log CFU counts against time for each patient, as previously described [15]. All data points were analyzed except sterile cultures in the second week if these values lessened the slope because sterility would have been achieved before that day’s lumbar puncture and this value would therefore underestimate the true slope [15].

In addition to clinical assessment, baseline testing included measurement of hematologic components, aspartate aminotransferase, alanine aminotransferase, creatinine, CD4+ cells, and HIV load, performed by a certified laboratory. During the initial 2 weeks, patients underwent at least 3 blood cell counts per week and aspartate aminotransferase, alanine aminotransferase, and chemical analyses once per week. Both aspartate aminotransferase and alanine aminotransferase measurements were performed again at weeks 4, 6, and 10 of study enrollment. Clinical and laboratory adverse events were graded using the toxicity table published by the Division of Acquired Immunodeficiency Syndrome, National Institute of Allergy and Infectious Diseases, National Institutes of Health [25].

The primary outcome measure was the mean rate of decrease in CSF cryptococcal counts or early fungicidal activity for each treatment arm. Secondary outcome measures were serious adverse events, laboratory toxic effects, and mortality at 2 and 10 weeks.

**Statistical analysis.** We compared baseline characteristics of the treatment groups using the Fisher exact test for categorical variables and the Mann-Whitney U test for continuous variables. Linear regression was used to compare early fungicidal activity by treatment group, adjusting where indicated for other variables, giving summary differences with 95% confidence intervals (CIs) and significance levels [12, 15, 17]. CD4+ cell count, opening pressure, and CSF white blood cell count were categorized into equal-sized groups. Mortality was examined using Cox regression. Cox regression was also used to explore the association of rate of clearance of infection with mortality in this study and after adding patients from this study to a previously analyzed combined cohort [16]. Statistical significance was assessed using the likelihood ratio test.

In an earlier trial, addition of flucytosine to amphotericin B was associated with a 74% increase in early fungicidal activity [15]. The original plan was to enroll 80 patients, ensuring 27 evaluable patients per arm, on the basis that this would give 90% power to detect a 60% increase in early fungicidal activity with addition of flucytosine to fluconazole using a 0.05 two-sided significance level. An optimal early fungicidal activity of ~0.25 log CFU/mL per day was assumed for fluconazole monotherapy with a standard deviation (SD) of 0.17 log CFU/mL per day. However, the trial was stopped early after the planned data safety monitoring committee analysis of the first 41 patients found a statistically significant difference (P<.001) among the rates of 14-day CSF fungal clearance, which was the study’s primary outcome.

**RESULTS**

Forty-four patients were randomized, but 3 were later found to meet exclusion criteria (1 was breast-feeding, 1 had been mistakenly diagnosed as having cryptococcosis after a sample error, and 1 had negative CSF cultures despite positive serum antigen test results). Among the remaining 41 patients, baseline
clinical and laboratory characteristics were similar between the groups (Table 1). At the time of enrollment, 24% of patients were receiving concurrent rifampicin therapy for a prior diagnosis of tuberculosis. Overall, 39% had abnormal mental status, defined as a GCS score less than 15. One patient in the fluconazole monotherapy arm was lost to follow-up on day 1, when his family decided to take him home.

**Early fungicidal activity.** A rate of fungal clearance could not be calculated for 4 patients (3 from the fluconazole alone arm and 1 from the combination arm), who died \((n = 3)\) or were lost to follow-up \((n = 1)\) before the second lumbar puncture. The rate of clearance of infection was more rapid in the combination arm compared with fluconazole alone (Figure 2). The mean \(\pm SD\) early fungicidal activity was \(-0.11 \pm 0.095\) log CFU/mL per day for monotherapy and \(-0.28 \pm 0.17\) CFU/mL per day for fluconazole plus flucytosine. The difference in early fungicidal activity was 0.18 log CFU/mL per day (95% CI, 0.085–0.27 log CFU/mL per day; \(P < .001\)). Four patients in the combination arm and 1 in the monotherapy arm had sterile CSF cultures by day 14.

Of the variables examined in this data set (age, sex, weight, altered mental status, concomitant rifampicin, CD4+ cell count, HIV load, baseline organism load, opening pressure, CSF white blood cell count), the only other variable that was associated with early fungicidal activity was concomitant antituberculous therapy; patients taking rifampicin had slower clearance of infection. Adjusting for rifampicin or variables associated with rate of clearance of infection in other, larger data sets (CD4+ cell count and baseline organism load [15, 16]) did not make any difference to the strength of the association between early fungicidal activity and treatment arm: in a model that included any difference to the strength of the association between early fungicidal activity and treatment arm: in a model that included

### Table 1. Baseline Clinical and Laboratory Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients ((n = 41))</th>
<th>Fluconazole monotherapy ((n = 20))</th>
<th>Fluconazole-flucytosine combination therapy ((n = 21))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) of male patients</td>
<td>27 (66)</td>
<td>14 (70)</td>
<td>13 (62)</td>
<td>.41</td>
</tr>
<tr>
<td>Age, years</td>
<td>36 (23–73)</td>
<td>36.5 (27–71)</td>
<td>36 (23–73)</td>
<td>.30</td>
</tr>
<tr>
<td>Weight, mean kg ± SD</td>
<td>54.3 ± 12</td>
<td>53.7 ± 14</td>
<td>54.8 ± 10</td>
<td>.52</td>
</tr>
<tr>
<td>No. (%) of patients with a GCS score &lt;15</td>
<td>16 (39)</td>
<td>8 (40)</td>
<td>8 (38)</td>
<td>.57</td>
</tr>
<tr>
<td>No. (%) of patients taking tuberculosis medication</td>
<td>10 (24)</td>
<td>4 (20)</td>
<td>6 (29)</td>
<td>.39</td>
</tr>
<tr>
<td><strong>Laboratory data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ cell count, ×10^6 cells/L</td>
<td>21 (1–101)</td>
<td>25 (1–66)</td>
<td>19 (3–101)</td>
<td>.07</td>
</tr>
<tr>
<td>HIV load, copies/mL</td>
<td>99,097 (2258–1,145,572)</td>
<td>84,411 (2258–1,606,740)</td>
<td>99,442 (4885–1,145,572)</td>
<td>.96</td>
</tr>
<tr>
<td><strong>CSF data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opening pressure, cm H2O</td>
<td>34 (1–100)</td>
<td>18 (1–100)</td>
<td>35 (7–53)</td>
<td>.24</td>
</tr>
<tr>
<td>White blood cell count, cells/mL</td>
<td>11 (0–1307)</td>
<td>15 (0–318)</td>
<td>8 (0–1307)</td>
<td>.51</td>
</tr>
<tr>
<td>QCC, CFU/mL</td>
<td>185,000 (265–30,950,000)</td>
<td>200,000 (265–30,950,000)</td>
<td>165,000 (1035–4,300,000)</td>
<td>.97</td>
</tr>
</tbody>
</table>

**NOTE.** Data are median (range), unless otherwise indicated. CSF, cerebrospinal fluid; GCS, Glasgow Coma Scale; HIV, human immunodeficiency virus; QCC, quantitative cryptococcal culture; SD, standard deviation.
pressure of 35 cm H\textsubscript{2}O on admission, increasing to 60 cm H\textsubscript{2}O up blood draw without intervention.

Flucytosine monotherapy resolved spontaneously on a follow-up patients receiving combination therapy and the 1 receiving was doing well at 10 weeks. The remaining 2 neutropenia events patient’s neutrophil count recovered by day 19 and the patient resolved with antibiotics and removal of the catheter. This patient's neutrophil count by day 19 and the patient was doing well at 10 weeks. The remaining 2 neutropenia events in patients receiving combination therapy and the 1 receiving fluconazole monotherapy resolved spontaneously on a follow-up blood draw without intervention.

One additional patient with severe meningitis (CSF opening pressure of 35 cm H\textsubscript{2}O on admission, increasing to 60 cm H\textsubscript{2}O on day 14 despite additional lumbar punctures) and a GCS score of 11 throughout hospitalization had normal neutrophil counts, with no reduction in counts, during the 2 weeks of fluconazole therapy. On day 16 the patient developed a urinary tract infection with new grade IV neutropenia and died on day 17 despite appropriate antibiotics. This death was reported as possibly related to fluconazole. There was no increase in infection-related serious adverse events in the combination group (7 vs 8 in the fluconazole arm) and no differences in rates of any other laboratory (Table 3) or clinical adverse events. There were no liver function test abnormalities related to fluconazole.

Assessment of rate of infection clearance and mortality in this study and in a combined cohort that included patients from this study. In this study, rate of clearance of infection was associated with 2-week mortality in univariate analysis (HR for each decrease in rate of clearance quartile, 3.0: 95% CI, 1.1–8.5; \( P = .01 \)). In a recently published combined cohort, rate of clearance of infection was associated with 2- and 10-week mortality, independent of altered mental status and baseline fungal burden, the other major prognostic factors [16]. When data from this trial were added to the combined cohort (now totaling 303 patients) and rate of clearance was fit onto a continuum scale, the HR for death after adjusting for altered mental status and baseline organism count was 1.47 (95% CI, 1.19–1.82; \( P < .001 \)) at 2 weeks and 1.20 (95% CI, 1.07–1.35; \( P = .008 \)) at 10 weeks for each 0.1-log unit decrease in rate of decrease of the organism count.

**DISCUSSION**

The combination of fluconazole (1200 mg per day) and flucytosine (100 mg/kg per day) was associated with a markedly more rapid rate of clearance of infection compared with fluconazole alone. Indeed, accepting the limitations of comparisons between trials, the early fungicidal activity of this combination (−0.28 log CFU/mL per day) is the closest an oral antifungal regimen has come to the fungicidal activity of amphotericin B (−0.31 log CFU/mL per day for amphotericin B [0.7 mg/kg] monotherapy in Thailand [15]). This study was not powered for clinical end points; however, there was a trend toward decreased early mortality in favor of the combination arm. Although this study was too small to conclude a clinical benefit, given the association of early fungicidal activity with survival in this and prior analyses [16], the improvement in fungicidal activity with combination therapy also suggests a survival advantage.

Flucytosine provided an additive effect when combined with fluconazole in murine models of cryptococcal infection [26–28], although not in a study in rabbits [29]. One mouse study evaluated a range of fluconazole and flucytosine doses with amphotericin B and determined the optimal regimen combined high doses of fluconazole with lower doses of flucytosine [28]. A clinical trial combining fluconazole (400 mg per day) with high-dose flucytosine (150 mg/kg per day) for 10 weeks produced a relatively short median time to CSF sterilization of 23 days, but there was no control arm, and adverse effects by 10 weeks were frequent [18]. Two subsequent trials suggested an additive effect when fluconazole was combined with flucytosine. In the first trial, the dosage of fluconazole was low (200 mg per day) [8]. In the second trial, flucytosine (100 mg/kg per day) was given for 4 weeks with increasing doses of flu-
Fluconazole and did have an additive benefit (higher percentage of patients alive with a negative CSF culture at 10 weeks) that was most pronounced with fluconazole (800–1200 mg per day) [19]. As suggested by this latter trial and the earlier mouse data, we used high-dose fluconazole and historically low-dose flucytosine to unequivocally demonstrate the microbiological efficacy of combining flucytosine with fluconazole.

Neutropenia, although more frequent in the combination arm compared with fluconazole alone, was not a clinically significant problem in most instances and rarely limited treatment in this study, suggesting that flucytosine could be used with benefit in resource-limited settings. However, our study alone was too small to adequately address toxicity issues. An earlier study using flucytosine (100 mg/kg per day, but for 4 weeks instead of 2), found grade IV neutropenia occurring in 18% of patients, without evidence of increased infection [19]. In an ongoing study in Cape Town using 2 weeks of flucytosine with amphotericin B, 4.5% of 66 patients developed grade IV neutropenia (J.N.J., S.J., and T.S.H.; unpublished data). In Thailand, the same flucytosine regimen was not associated with significant neutropenia, and no patients discontinued flucytosine therapy before 2 weeks. In that setting, bioavailability of oral flucytosine was 50% that of intravenous flucytosine, and the serum levels with oral flucytosine were well below those associated with bone marrow toxic effects [30]. Analysis of flucytosine and fluorouracil levels in this trial will determine whether bioavailability or gut conversion of flucytosine to fluorouracil [31] is different for patients in Africa. It will be important to continue to monitor the tolerability of flucytosine in Africa because more data will determine the optimal hematologic monitoring needed for safe, expanded use of flucytosine in this setting. Any potential for toxicity must be balanced against the advantage of flucytosine in antifungal efficacy and possibly survival.

Analysis of serum and CSF fluconazole levels in this trial will clarify the effect of rifampicin on the bioavailability of fluconazole. The association of concomitant rifampicin with reduced rates of fungal clearance implies a clinically significant reduction in fluconazole levels and suggests that, even at relatively high doses, fluconazole should be increased when given with rifampicin.

Donation of fluconazole has allowed countries such as Malawi to increase the fluconazole dose recommended in cryptococcal treatment guidelines to 800 mg per day. However, the rate of clearance of infection is unacceptably slow and mortality rates are unacceptably high at this dose [12]. Even with a fluconazole dosage of 1200 mg per day, both in this study and in Uganda [12], the rate of fungal clearance, although more rapid, was well below that achieved with amphotericin B. Although it is impossible to accurately compare the early fungicidal activity slopes among trials in different patient populations, the combination of fluconazole (1200 mg per day) and flucytosine studied in this trial is the most rapidly fungicidal oral regimen to date and, therefore, may be the optimal regimen in the absence of amphotericin B.

### Table 2. Patient Deaths, by Presumed Cause of Death

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>No. of patients</th>
<th>Fluconazole monotherapy group</th>
<th>Fluconazole and flucytosine group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;2 weeks</td>
<td>2–10 weeks</td>
<td>&lt;2 weeks</td>
</tr>
<tr>
<td>Cryptococcus meningitis–related cause</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other infection</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary Kaposi sarcoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 3. Number of Laboratory Adverse Events in the First 2 Weeks, by Grade of Event

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Fluconazole monotherapy group</th>
<th>Fluconazole plus flucytosine therapy group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade III</td>
<td>Grade IV</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Transaminase elevation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

**NOTE.** Cutoffs used to define grade III and grade IV laboratory abnormalities are as follows: platelet count, 25,000–49,999 plates/µL and <25,000 plates/µL, respectively; absolute neutrophil count, 500–749 cells/µL and <500 cells/µL, respectively; hemoglobin concentration, 6.50–7.4 g/dL and <6.5 g/dL, respectively; alanine aminotransferase level, 175–350 IU/L and >350 IU/L, respectively; aspartate aminotransferase level, 190–380 IU/L and >380 IU/L, respectively; sodium level, 121–124 mmol/L and <120 mmol/L, respectively; creatinine level, 2.2–4.1 mg/dL and >4.1 mg/dL, respectively, for men and 2.3–4.4 mg/dL and >4.4 mg/dL, respectively, for women.

*P = .20 for neutropenia.*
In many parts of the developing world, limited resources, personnel, and clinical and laboratory facilities prevent use of the standard 2-week induction course of amphotericin B [32]. Until these problems are resolved, our results argue that wider access to fluconazole should be a priority in resource-limited settings. Fluconazole is a simple molecule that is off-patent and was once registered in South Africa. Additional studies are needed to evaluate regimens that incorporate, in addition, a short course of amphotericin B, which should require minimal additional monitoring and be easier to implement compared with standard 2-week amphotericin B courses.

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Potential conflicts of interest. All authors: no conflicts.

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