

## A RANDOMIZED TRIAL COMPARING FLUCONAZOLE WITH CLOTRIMAZOLE TROCHES FOR THE PREVENTION OF FUNGAL INFECTIONS IN PATIENTS WITH ADVANCED HUMAN IMMUNODEFICIENCY VIRUS INFECTION

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**Abstract Background.** Cryptococcal meningitis and other serious fungal infections are common complications in patients infected with the human immunodeficiency virus (HIV). Fluconazole is effective for long-term suppression of many fungal infections, but its effectiveness as primary prophylaxis had not been adequately evaluated.

**Methods.** We conducted a prospective, randomized trial that compared fluconazole (200 mg per day) with clotrimazole troches (10 mg taken five times daily) in patients who were also participating in a randomized trial of primary prophylaxis for *Pneumocystis carinii* pneumonia.

**Results.** After a median follow-up of 35 months, invasive fungal infections had developed in 4.1 percent of the patients in the fluconazole group (9 of 217) and in 10.9 percent of those in the clotrimazole group (23 of 211; relative hazard, as adjusted for the CD4+ count, 3.3; 95 percent confidence interval, 1.5 to 7.6). Of the 32 invasive fungal infections, 17 were cryptococcosis (2 in the flucon-

azole group and 15 in the clotrimazole group; adjusted relative hazard, 8.5; 95 percent confidence interval, 1.9 to 37.6). The benefit of fluconazole was greater for the patients with 50 or fewer CD4+ cells per cubic millimeter than for the patients with higher counts. Fluconazole was also effective in preventing esophageal candidiasis (adjusted relative hazard, 5.8; 95 percent confidence interval, 1.7 to 20.0; P=0.004) and confirmed and presumed oropharyngeal candidiasis (5.7 and 38.1 cases per 100 person-years of follow-up in the fluconazole and clotrimazole groups, respectively; P<0.001). Survival was similar in the two groups.

**Conclusions.** Fluconazole taken prophylactically reduces the frequency of cryptococcosis, esophageal candidiasis, and superficial fungal infections in HIV-infected patients, especially those with 50 or fewer CD4+ lymphocytes per cubic millimeter, but the drug does not reduce overall mortality. (N Engl J Med 1995;332:700-5.)

**P**ROPHYLAXIS against opportunistic infections is a major part of the care of patients with advanced human immunodeficiency virus (HIV) infection. Prophylactic treatment of *Pneumocystis carinii* pneumonia has been clearly shown to prevent initial episodes, as well as relapse, and to prolong survival.<sup>1-4</sup> The effectiveness of preventive therapy for *Mycobacterium avium* infection has also been demonstrated.<sup>5</sup> Invasive fungal infections, especially with *Cryptococcus neoformans*, occur in 5 to 10 percent of patients with the acquired immunodeficiency syndrome (AIDS).<sup>6,7</sup> In addition, mucocutaneous candidiasis is almost ubiquitous in patients with advanced HIV disease, and recurrent infection causes considerable morbidity.

Fluconazole is an orally active triazole antifungal agent that is effective in preventing a relapse of cryptococcal meningitis.<sup>8</sup> Several small studies have sug-

gested that this agent is also effective in preventing a recurrence of oropharyngeal candidiasis.<sup>9,10</sup> Until recently, the true incidence of fungal infections was unclear, however, and there was no reported experience with primary prophylaxis against serious fungal infection. The effectiveness of fluconazole was also unknown, and there was concern about its long-term toxic effects (especially hepatotoxicity), the possibility of drug interactions, the cost of the drug, and the potential for antifungal resistance to develop over time. The AIDS Clinical Trials Group (ACTG) conducted a randomized, prospective clinical trial (ACTG 981) to evaluate the use of fluconazole as prophylactic therapy against fungal infections in patients with advanced HIV disease.

### METHODS

#### Study Design

ACTG 981 compared fluconazole (200 mg per day) with clotrimazole troches (10 mg five times daily) for the prevention of invasive fungal infections in patients with advanced HIV infection. Clotrimazole was chosen for the control group rather than placebo in order to provide patients with effective local therapy for oropharyngeal candidiasis and thus allow an examination of the safety and effectiveness of the long-term use of fluconazole in preventing invasive fungal disease. Eligible participants were already enrolled in ACTG 081.<sup>11</sup>

Patients were excluded from participation in ACTG 981 if they had a history of systemic fungal infection or allergy or intolerance to imidazoles or azoles, if they had serum aminotransferase levels higher than five times the upper limit of normal or a positive serum cryptococcal antigen titer at any dilution during screening, or if they were receiving maintenance therapy with systemic antifungal agents or required multiagent therapy for mycobacterial infection. Patients with a history of oropharyngeal, vaginal, or cutaneous candidiasis were eligible to participate. Patients were ineligible if they had active muco-

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sal fungal infection at the time of enrollment; however, those with mucosal candida infection could receive treatment with topical antifungal agents and be eligible for enrollment once they were in clinical remission. Patients with dermatophyte infections (e.g., tinea pedis) were eligible, provided cultures for candida were negative. The study design was approved by the institutional review board at each participating institution; all patients gave written informed consent before enrollment.

Patients were randomly assigned to treatment with fluconazole or clotrimazole troches in a 1:1 ratio within strata defined according to the study center and treatment assignment in ACTG 081. Study participants underwent clinical and laboratory evaluations at base line, every two weeks for the first month, and monthly thereafter. Cultures of normally sterile body fluids and tissues, histopathological studies, and cryptococcal-antigen measurements were used to evaluate all episodes that suggested possible fungal infection. Prophylaxis was to be continued until an invasive fungal infection developed, the patient withdrew from the trial or the parent study, or the patient died. Follow-up evaluations were performed one month after the discontinuation of prophylaxis for patients who had invasive infection or withdrew from the study. Adherence to the study regimen was assessed by calculating the proportion of doses reportedly missed each month and using that value to estimate the number of days each week that study drugs were taken.

Patients in whom superficial mucocutaneous fungal infections developed (including oral thrush but not esophageal candidiasis) were initially given local therapy. Nystatin suspension (10 ml of a suspension of 100,000 U per milliliter) was given four times daily for the initial treatment of thrush. For vaginal and cutaneous candidiasis, local therapy of the investigator's choice was used. If local therapy failed after a 7-day trial, patients could be treated systemically for up to 30 days.

### End Points

The primary end point of the study was the time to the development of an invasive fungal infection. Secondary end points included survival, the time to the development of a serious fungal infection (invasive fungal infections and esophageal candidiasis), and the time to the development of a superficial fungal infection. Invasive infections included cryptococcosis; the endemic mycoses, including histoplasmosis and coccidioidomycosis; and other fungal infections with evidence of systemic invasion. Cryptococcosis was diagnosed on the basis of a positive culture for *C. neoformans* or biopsy results consistent with cryptococcosis and a positive titer of serum cryptococcal antigen. A diagnosis of presumed cryptococcal infection required a compatible clinical syndrome, with a positive titer of cryptococcal antigen from either serum or cerebrospinal fluid. A diagnosis of other invasive fungal disease was established either by culture or by biopsy.

Candida esophagitis was diagnosed by the demonstration of tissue invasion by candida. A presumptive diagnosis was based on the presence of oropharyngeal thrush and esophageal symptoms with abnormal findings on endoscopy or barium swallow, a response to appropriate therapy, or both. Mucocutaneous candida infection was diagnosed on the basis of a compatible clinical syndrome and microscopic evidence of candida infection (positive potassium hydroxide preparation). A presumptive diagnosis required a compatible clinical syndrome and a response to specific antifungal therapy.

All end points were confirmed at each study center and subsequently reviewed by the protocol chairs without knowledge of specific treatment assignments; the single disagreement was resolved by the vote of a third member of the protocol team.

### Statistical Analysis

The data were analyzed on the basis of the treatment to which the patients were randomly assigned, regardless of whether the treatment was modified or discontinued during the follow-up period (intention-to-treat principle). Although the study was designed to evaluate the one-sided null hypothesis that fluconazole was no better than clotrimazole, more conservative two-sided P values are reported. The initial target sample size of 240 was chosen to ensure that there would be at least 80 percent power to detect a difference of 7.5

percent (10 percent vs. 2.5 percent), with a one-sided alpha level of 0.05, in the 18-month rate of invasive fungal infections. Enrollment was later expanded so that the trial would have sufficient power to detect a treatment difference of at least 4.5 percent (6 percent vs. 1.5 percent) in the 18-month rate of cryptococcosis. Measures were compared by a chi-square test, Fisher's exact test, the Wilcoxon-Mann-Whitney test, or Student's t-test, as appropriate. The end points (time to the occurrence of a fungal infection, a first episode of grade 3 or higher toxic effects [according to the standard ACTG grading system<sup>2</sup>], treatment discontinuation, and death) were summarized as Kaplan-Meier curves and compared by a log-rank test stratified with the use of prerandomization criteria. Multivariate regression models were fit with the proportional-hazards model to adjust for covariates such as the CD4+ lymphocyte count and to derive hazard ratios with confidence intervals.

## RESULTS

### Study Population

A total of 428 patients were enrolled at 29 sites from September 1989 through September 1992; only 7 patients were enrolled after December 31, 1991. The follow-up period ended on June 30, 1993. The median follow-up for the entire cohort was 35 months. A total of 78 patients were lost to follow-up. The treatment groups were balanced with regard to the numbers of patients available for follow-up.

Of the 428 patients enrolled in the study, 217 were assigned to receive fluconazole and 211 to receive clotrimazole troches. All patients are included in the analysis. The treatment groups were similar with respect to demographic variables and base-line laboratory values, with the exception of the median CD4+ cell count, which was lower, although not significantly so, in the fluconazole group than in the clotrimazole group (90 vs. 114 cells per cubic millimeter) (Table 1).

### Clinical End Points

Invasive fungal infections developed in 9 patients assigned to fluconazole and in 23 assigned to clotrimazole (relative hazard, 2.6; 95 percent confidence interval, 1.2 to 5.6; P=0.02) (Table 2). Of the 32 invasive fungal infections, 17 were cryptococcosis (2 in the flu-

Table 1. Base-Line Characteristics of 428 Patients with HIV Infection Assigned to Prophylaxis with Fluconazole or Clotrimazole.

CHARACTERISTIC	FLUCONAZOLE GROUP (N = 217)	CLOTRIMAZOLE GROUP (N = 211)
Median age — yr	36	37
Race — no. of patients (%)		
White	178 (82)	188 (89)
Black	35 (16)	19 (9)
Other	4 (2)	4 (2)
Male sex — no. of patients (%)	207 (95)	200 (95)
<i>P. carinii</i> prophylaxis — no. of patients (%)		
Aerosolized pentamidine	78 (36)	77 (36)
Dapsone	71 (33)	67 (32)
Trimethoprim-sulfamethoxazole	68 (31)	67 (32)
CD4+ count — cells/mm <sup>3</sup>		
Mean	122	141
Median	90	114
CD4+ count ≤50 cells/mm <sup>3</sup> — % of patients	32	28
CD4+ count >150 cells/mm <sup>3</sup> — % of patients	33	42

conazole group and 15 in the clotrimazole group; relative hazard, 7.4; 95 percent confidence interval, 1.7 to 32.2;  $P=0.004$ ). The other invasive fungal infections included eight cases of histoplasmosis (three in the fluconazole group and five in the clotrimazole group), four cases of aspergillosis (three in the fluconazole group and one in the clotrimazole group), and one case each of coccidioidomycosis (in the clotrimazole group), fusarium infection (in the fluconazole group), and aureobasidium fungemia (in the clotrimazole group). The estimated two-year risk of invasive fungal infection was 2.8 percent in the fluconazole group and 9.1 percent in the clotrimazole group (difference in risk, 6.3 percent;  $P=0.02$ ). After adjustment for the base-line CD4+ lymphocyte count, the estimated relative hazard for invasive fungal infection was 3.3 (95 percent confidence interval, 1.5 to 7.6) and the estimated relative hazard for cryptococcosis was 8.5 (95 percent confidence interval, 1.9 to 37.6) among the patients randomly assigned to clotrimazole.

The differences in treatment efficacy were most pronounced among the patients with lower base-line CD4+ lymphocyte counts. In the clotrimazole group, the adjusted relative hazard for invasive fungal infections in patients with base-line counts of 50 or fewer CD4+ cells per cubic millimeter was 4.1 (95 percent confidence interval, 1.3 to 13.0;  $P=0.02$ ), whereas the adjusted relative hazard for patients with base-line counts higher than 50 cells per cubic millimeter was 2.6 (95 percent confidence interval, 0.8 to 8.1;  $P=0.10$ ). Similarly, the estimated two-year cumulative risk of cryptococcosis for patients with base-line CD4+ lymphocyte counts of 50 or fewer cells per cubic millimeter was 1.6 percent in the fluconazole group and 9.9 percent in the clotrimazole group (difference in risk, 8.3 percent;  $P=0.02$ ), as compared with 0.8 percent and 4.3 percent, respectively, for patients with higher base-line counts (difference in risk, 3.5 percent;  $P=0.04$ ). In addition, most patients had profound immunosuppression by the time invasive fungal infections actually developed; 78 percent of such infections occurred in patients whose most recent CD4+ lymphocyte count was 50 or fewer cells per cubic millimeter. The base-line CD4+ lymphocyte counts in patients with subsequent cryptococcal infection were only slightly lower than the base-line counts in those who remained free of such infection, but almost all cases of cryptococcosis

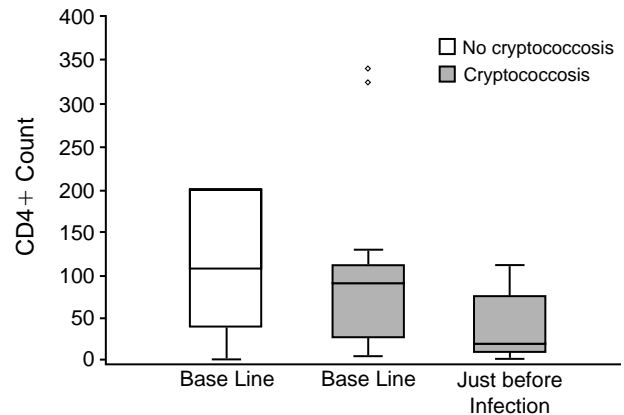


Figure 1. Relation between CD4+ Lymphocyte Count and the Development of Cryptococcosis.

The top and bottom lines of the boxes represent the 75th and 25th percentiles, respectively, and the horizontal lines within the boxes represent the 50th percentiles (medians); the bars above and below the boxes represent the range of outlying values, if any, and the two diamonds at the top represent the two extreme outlying values.

actually occurred after the CD4+ count had become very low (Fig. 1).

There were 20 cases of esophageal candidiasis (3 in the fluconazole group and 17 in the clotrimazole group; relative hazard, as adjusted for the CD4+ count, 5.8; 95 percent confidence interval, 1.7 to 20.0;  $P=0.004$ ). Thus, there were 12 cases of serious fungal infection (invasive disease plus esophageal candidiasis) among the patients assigned to fluconazole, as compared with 40 among those assigned to clotrimazole (adjusted relative hazard, 4.7; 95 percent confidence interval, 2.3 to 9.5;  $P<0.001$ ).

There were 46 confirmed cases of superficial fungal infection (10 in the fluconazole group and 36 in the clotrimazole group) and 87 presumed cases (23 in the fluconazole group and 64 in the clotrimazole group) (relative hazard of a confirmed or presumed infection, 3.1; 95 percent confidence interval, 2.2 to 4.4;  $P<0.001$ ). Oropharyngeal candidiasis accounted for most of these superficial infections. The number of episodes of confirmed or presumed oropharyngeal candidiasis per 100 patient-years of follow-up was 5.7 for patients assigned to fluconazole and 38.1 for those assigned to clotrimazole ( $P<0.001$ ). An insufficient number of women were enrolled in this study to assess the effect of fluconazole on vaginal candidiasis.

### Survival

Ninety-eight patients randomly assigned to fluconazole and 89 randomly assigned to clotrimazole died ( $P=0.26$  by the log-rank test). The unadjusted relative risk of death in the fluconazole group was 0.9 (95 percent confidence interval, 0.6 to 1.1). After adjustment for the base-line CD4+ lymphocyte count with

Table 2. Relative Hazard of Fungal Infection or Death among Patients Assigned to Fluconazole, as Compared with Those Assigned to Clotrimazole.\*

END POINT	FLUCONAZOLE GROUP	CLOTRIMAZOLE GROUP	RELATIVE HAZARD	RELATIVE HAZARD ADJUSTED FOR CD4+ COUNT
	(N = 217)	(N = 211)		
	<i>no. of events</i>			
Invasive mycoses	9	23	2.6 (1.2–5.6)	3.3 (1.5–7.6)
Cryptococcal infection	2	15	7.4 (1.7–32.2)	8.5 (1.9–37.6)
Other invasive mycoses	7	8	1.1 (0.4–3.2)	1.3 (0.5–3.8)
Candida esophagitis	3	17	5.8 (1.7–20.0)	5.8 (1.7–20.0)
Death	98	89	0.9 (0.6–1.1)	0.9 (0.7–1.3)

\*All analyses are stratified according to treatment assignment in ACTG 081 (i.e., according to type of prophylaxis against *P. carinii* pneumonia). Values in parentheses are 95 percent confidence intervals.

the use of a Cox proportional-hazards model, the relative risk of death in the fluconazole group was 0.9 (95 percent confidence interval, 0.7 to 1.3;  $P=0.7$ ). A total of 102 patients in the fluconazole group and 96 in the clotrimazole group either had an invasive fungal infection or died ( $P=0.57$  by stratified log-rank test) (Fig. 2). Five patients in each group died within one month after the diagnosis of invasive fungal infection; three of the deaths in the fluconazole group and four of those in the clotrimazole group were attributed to the fungal infection by the site investigators. Seven of the 10 patients were infected with *C. neoformans*.

#### Interaction with *P. carinii* Prophylaxis

Fluconazole was more effective than clotrimazole in preventing superficial fungal infections in patients assigned to trimethoprim-sulfamethoxazole, dapsone, or aerosolized pentamidine according to the protocol for ACTG 081. The number of patients in each subgroup was too small to detect statistically significant differences between fluconazole and clotrimazole in the prevention of invasive fungal disease, although there was a consistent trend in favor of fluconazole. The observed differences in mortality between the fluconazole and clotrimazole groups were more pronounced among the patients receiving aerosolized pentamidine ( $P=0.17$ ) than among those receiving dapsone ( $P=0.82$ ) or trimethoprim-sulfamethoxazole ( $P=0.5$ ).

#### Toxic Effects

The two treatment groups were similar with respect to the rate of occurrence of most symptoms and abnormalities in laboratory measurements (Table 3). Site investigators discontinued treatment in 19 patients (13 in the fluconazole group and 6 in the clotrimazole group,  $P=0.11$ ) because of probable or possible drug-related side effects. Therapy was discontinued in three patients because of rashes attributed to fluconazole. Concern about hepatotoxicity resulted in the discontinuation of treatment in eight patients (six in the fluconazole group and two in the clotrimazole group,  $P=0.6$ ); however, the overall incidence of severe (grade 3 or higher) abnormalities in the results of liver-function tests was similar in the two groups.

Because common side effects of systemic prophylaxis against *P. carinii* pneumonia could potentially obscure the toxic effects of antifungal therapy, toxic effects were analyzed in the subgroup of patients receiving aerosolized pentamidine. More of the patients assigned to fluconazole required transfusions (7.4 percent, vs. 2.8 percent in the clotrimazole group;  $P=0.03$ ) and had at least one episode of severe nausea (14.1 percent, vs. 3.9 percent in the clotrimazole group;  $P=0.03$ ) or abdominal pain (18.0 percent, vs. 6.5 percent in the clotrimazole group;  $P=0.03$ ). The incidence of severe abnormalities in the results of liver-function tests did not differ between the two groups.

#### Treatment Compliance

Patients receiving clotrimazole discontinued antifungal medication significantly earlier than those receiving

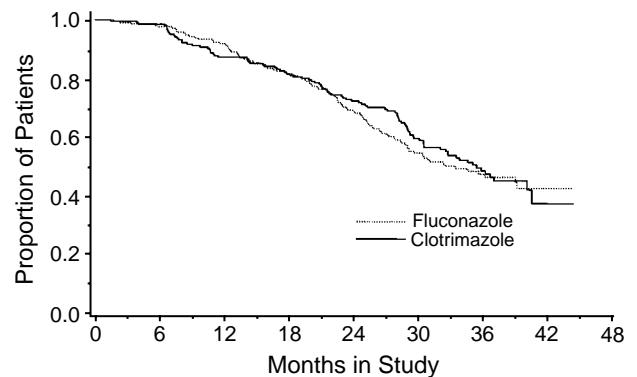


Figure 2. Kaplan-Meier Estimates of the Cumulative Risk of Death or Invasive Fungal Infection among Patients Assigned to Receive Fluconazole or Clotrimazole Troches.

fluconazole ( $P=0.03$ ). In the fluconazole group, patients reported adhering to the regimen for at least six days per week during 95 percent of the patient-months of follow-up, whereas adherence to clotrimazole for at least six days per week occurred during only 50 percent of patient-months ( $P<0.001$ ). Ten patients assigned to clotrimazole (4.7 percent) reported taking systemic antifungal agents for three or more months during the course of the study.

#### DISCUSSION

Invasive fungal infection is an important cause of morbidity and mortality in patients with advanced HIV disease. Disseminated cryptococcosis occurs in 5 to 10 percent of patients with AIDS in the United States and is associated with a mortality rate of 10 to 20 percent.<sup>6,7</sup> Histoplasmosis and coccidioidomycosis are common in the endemic areas and are seen sporadically elsewhere. All require intensive initial therapy, typically with parenteral amphotericin B and lifelong suppressive treatment.<sup>8,12-14</sup>

This study clearly shows that many such infections can be prevented with 200 mg of fluconazole daily. The estimated two-year rate of invasive fungal infections

Table 3. Rate of Severe Abnormalities in Laboratory Measurements during Antifungal Prophylaxis.\*

TOXIC EFFECT	FLUCONAZOLE GROUP	CLOTRIMAZOLE GROUP
	event rate†	
<b>Hematologic</b>		
Hemoglobin $\leq 8$ g/dl	24.8	17.2
Granulocytes $\leq 750/\text{mm}^3$	61.6	64.5
Platelet count $\leq 50,000/\text{mm}^3$	12.2	18.3
Any of the above	93.7	98.3
<b>Hepatic‡</b>		
Serum aspartate aminotransferase $>5$ times ULN	27.5	35.4
Serum alanine aminotransferase $>5$ times ULN	22.2	23.4
Alkaline phosphatase $>5$ times ULN	23.6	17.3
Bilirubin $>2$ times ULN	1.7	1.2
Any of the above	61.9	56.2

\*Severe abnormalities were those classified as grade 3 or higher on the ACTG toxicity scale.

†Number of events per 100 person-years of follow-up.

‡ULN denotes upper limit of normal.

was 2.8 percent in the fluconazole group and 9.1 percent in the clotrimazole group. The benefit seen with fluconazole was almost entirely due to the reduction in the risk of cryptococcosis. The incidence of other invasive fungal infections was too low to determine whether fluconazole provided effective prophylaxis against them. However, fluconazole has been found to be ineffective against aspergillosis and may be inadequate (at the doses used in this study) against histoplasmosis.<sup>15,16</sup> The benefit of antifungal prophylaxis was greater in patients with base-line CD4+ lymphocyte counts of 50 or fewer cells per cubic millimeter. The incidence of invasive fungal infections in the fluconazole group was quite low regardless of the initial CD4+ count, whereas in the clotrimazole group, such infections were uncommon only among patients with initial counts that were higher than 50 cells per cubic millimeter.

Superficial fungal infection due to candida species is ubiquitous in patients with HIV disease and causes considerable morbidity. Our data also show that fluconazole is effective in the prevention of candida infections in patients with advanced HIV disease; however, 10.6 percent of the patients assigned to fluconazole still had at least one episode of proved or presumed candidiasis during the study. These breakthrough infections raise the possibility of the development of a resistance to fluconazole, a phenomenon that is increasingly recognized in patients with advanced HIV infection and that has been linked to the use of fluconazole.<sup>17,18</sup> Unfortunately, data on resistance are not available from this study.

Fluconazole was well tolerated by our patients. Serious adverse reactions were rare, and there was no serious hepatotoxicity attributable to the drug. Gastrointestinal symptoms appear to be the most common side effects of fluconazole. Although the trial was not specifically designed to evaluate mortality, we could detect no survival advantage associated with fluconazole. The lack of an effect on survival, in spite of the clear-cut prophylactic effectiveness of fluconazole, a finding consistent with the results of many other trials of prophylaxis in HIV-infected patients,<sup>3,5,12</sup> reflects the relatively low rate of mortality directly attributable to fungal infections.

In this study, episodes of disease attributable to candida and *C. neoformans* were six to eight times less common among the patients assigned to fluconazole than among those assigned to clotrimazole. Since the overall incidence of serious fungal infections was low, however, the absolute differences in the risk of these infections were small, and the efficiency of prescribing fluconazole for primary prophylaxis against serious fungal infection is uncertain. In fact, we estimate that 11,756 doses of fluconazole were given to prevent each case of invasive fungal infection in the study population. However, this calculation does not consider the benefit of preventing superficial fungal infections or the possibility of reserving therapy for subgroups at particularly high risk. For example, the absolute and differential risk for all fungal infections was much higher among the patients with initial CD4+ lymphocyte

counts of 50 or fewer cells per cubic millimeter, and the prevention of one case of invasive fungal infection required less than one third as many doses of fluconazole in this group as in the group with higher CD4+ counts.

In summary, fluconazole was safe, effective, and well tolerated as prophylaxis against superficial, serious, and invasive fungal infections, especially those caused by candida and *C. neoformans*. Further studies are needed to determine the net benefit of preventing these infections, the population at highest risk for them, the potential for the development of resistance to antifungal azoles, and the cost effectiveness of prophylaxis with fluconazole as compared with careful monitoring. For now, it is reasonable to consider primary prophylaxis with fluconazole in patients with advanced HIV infection, particularly those at higher risk of fungal infection, such as patients with CD4+ lymphocyte counts of 50 or fewer cells per cubic millimeter.

We are indebted to Lucinda Phillips for her meticulous attention to data management and to the many volunteers who participated in the trial, without whom it could not have been completed.

#### APPENDIX

The following institutions and investigators participated in the trial: *University of Cincinnati School of Medicine* — J. Leonard, P. Daniel, M. White, and W. Cotton; *Washington University School of Medicine* — M. Klebert, J. Voorhees, and T. Bailey; *University of California, San Diego* — R. Haubrich, D.D. Richman, and J. Coffman; *Ohio State University* — R.J. Fass, M.F. Para, and C. Jackson; *Johns Hopkins University School of Medicine* — R.L. Becker, L. Grue III, and D.A. Wright; *Case Western Reserve University Medical School* — M. Chance, M. Wallace, and V. Cargill; *Pennsylvania State University College of Medicine* — M.C. Ehman and J. Zurlo; *Duke University Medical Center* — J.A. Bartlett and K. Shipp; *Tulane University and Louisiana State University* — J.A. Zachary and D. Mushett; *University of Washington* — A.C. Collier and L. Corey; *Harvard Medical School* — C.S. Crumpacker, J.D. Allan, and D.E. Craven; *Northwestern University Medical School* — R. Murphy and R. Hirschtick; *Rush–Presbyterian–St. Luke's Medical Center* — C. Benson and J. Pottage; *State University of New York, Buffalo* — R. Hewitt and N. Rzepkowski; *State University of New York, Syracuse* — D.C. Blair; *University of Minnesota* — R. Nelson, C. Jones, and F.S. Rhame; *Mt. Sinai Medical Center* — D. Mildvan, A. Fox, and C. Sanders; *University of North Carolina School of Medicine* — R. Whitten and B. Longmire; *Indiana University Medical School* — J. Craft and L.J. Wheat; *University of California, San Francisco* — S. Safran, R. Mah, and R. Coleman; *St. Luke's–Roosevelt Hospital Center* — M. Grieco; *Stanford University* — J. Fessel, T. Merigan, and S. Kirk; *University of California, Los Angeles* — M.B. Goetz and B.P. Manchester; *Albert Einstein College of Medicine* — R. Soeiro, G. Krienik, and J. Shilozberg; *University of Massachusetts* — S.H. Cheeseman, C.A. Bova, and J. Avata; *Memorial Sloan-Kettering Cancer Center* — D. Armstrong and M. White; *Frontier Science and Technology Research Foundation, Buffalo* — L. Phillips; *Division of AIDS, NIAID* — R. Hafner, M. Power, and B. Landry; and *Pfizer Central Research, Groton, Conn.* — P. Robinson.

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