Prophylaxis with Weekly Versus Daily Fluconazole for Fungal Infections in Patients with AIDS


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We compared the efficacy of a 400-mg once-weekly dosage versus a 200-mg daily dosage of fluconazole for the prevention of deep fungal infections in a multicenter, randomized, double-blind trial of 636 human immunodeficiency virus–infected patients to determine if a less intensive fluconazole regimen could prevent these serious but relatively infrequent complications of AIDS. In the intent-to-treat analysis, a deep fungal infection developed in 17 subjects (5.5%) randomly assigned to daily fluconazole treatment and in 24 (7.7%) given weekly fluconazole during 74 weeks of follow-up (risk difference, 2.2%; 95% confidence interval [CI], −1.7% to 6.1%). Thrush occurred twice as frequently in the weekly versus daily fluconazole recipients (hazard ratio, 0.59; 95% CI, 0.40−0.89), and in a subset of patients evaluated, fluconazole resistance was infrequent. Fluconazole administered once weekly is effective in reducing deep fungal infections in patients with AIDS, but this dosage is less effective than the 200-mg-daily dosage in preventing thrush.

Fungal infections complicating the course of persons infected with HIV cause a broad spectrum of diseases, ranging from asymptomatic mucocutaneous candidiasis to life-threatening cryptococcal meningitis. Fluconazole is effective in preventing thrush, but primary prophylaxis is not routinely utilized because of concern about promoting fluconazole resistance among Candida strains causing this otherwise easily treated infection [1–3]. Fluconazole also prevents the most common serious mycosis, disseminated cryptococcal infection, but is recommended only for secondary prophylaxis or maintenance therapy because of the relatively low risk of primary infection, even in patients with severe immunosuppression [3–6]. In one study of HIV-infected individuals with <200 CD4 cells/mm³, 11,756 doses of fluconazole were given for each case of serious fungal infection prevented [7]. Costs associated with fungal prophylaxis are appreciable; Freedberg et al. estimated costs at $100,000 per quality life-year saved [8].


Substantially reducing the dose of fluconazole would lower overall costs of deep fungal prophylaxis but would be reasonable only if efficacy were preserved and fluconazole resistance among Candida and Cryptococcus strains did not increase. Intermittent fluconazole therapy has been associated with a reduction in the risk of cryptococcal disease in the HIV-infected population but has never been compared to the 200-mg once-daily prophylaxis dosage [9, 10]. Prolonged daily fluconazole exposure appears to select for azole-resistant Candida strains. Less frequent dosing could potentially reduce this risk, although intermittent exposure to antimicrobials may increase the risk of resistance in some situations. We compared the treatment efficacy andazole susceptibility of Candida isolates between two groups of patients, randomized to a 400-mg weekly or 200-mg daily dosage of fluconazole, within the California Collaborative Treatment Group (CCTG) trial of prophylaxis.
Methods

Study Design and Patient Population

This double-blind, randomized, multicenter trial compared weekly to daily fluconazole treatment for the prevention of fungal infections in persons with HIV infection and <100 CD4 cells/mm³. Persons were randomly assigned to receive 400 mg once per week or 200 mg per day, a fluconazole dosage demonstrated to prevent superficial and deep fungal infections in the AIDS Clinical Trials Group (ACTG) 981 study [7]. Subjects in this study represented 94% of patients co-enrolled in the CCTG trial of prophylaxis for MAC infection [11]. All subjects were independently randomized to receive azithromycin (1,200 mg weekly), rifabutin (300 mg daily), or both as prophylaxis for MAC infection, and none of the subjects had disseminated MAC infection or signs or symptoms suggestive of MAC infection at enrollment.

Inclusion criteria for the study were documented HIV infection, a CD4 cell count of <100/mm³, an absolute neutrophil count of >500/mm³, a platelet count of >50,000/mm³, a bilirubin level <3 times the upper limit of normal, a hepatic transaminase level <5 times the upper limit of normal, and a creatinine level <3 times the upper limit of normal. Patients were excluded for active fungal infections (cryptococcosis, histoplasmosis, blastomycosis, aspergillosis, mucocutaneous candidiasis, or aspergillosis) or ongoing chronic therapy with any systemic antifungal agent (fluconazole, ketoconazole, itraconazole, or amphotericin B). Patients with odyphagia were eligible only after candidal esophagitis had been excluded. Subjects who had had prior episodes of mucocutaneous candidal infections could participate even if they were receiving daily fluconazole at study enrollment, if they discontinued receiving open-label fluconazole. Pregnant and nursing females were not allowed to enroll in the study. Approval of institutional review boards and informed consent were required before study enrollment.

Patients were assessed monthly for evidence of fungal infection or drug toxicity and underwent bimonthly laboratory evaluations consisting of complete blood cell counts and liver function tests. Patients developing mucocutaneous candidiasis were treated with topical agents ( clotrimazole or nystatin) while administration of the study medication was continued. For those who failed to respond to topical agents, the study drug dosing was interrupted and treatment with systemic antifungal agents was instituted at the discretion of their primary physician.

Isolates from breakthrough mucosal infections were shipped to a central laboratory for susceptibility testing by means of macro-broth dilution [12]. Candidal isolates for which MICs were ≥64 μg/mL were defined as fluconazole-resistant; isolates for which MICs were ≤8 μg/mL were interpreted as fluconazole-susceptible [13]. Patients developing deep fungal infections discontinued receiving the study medications and were followed for survival data. Adherence to therapy was measured by pill counts when participants returned their study-medication packets at each visit.

Endpoints

The primary endpoint of the study was diagnosis of a deep fungal infection. Cryptococcal disease was defined by a Cryptococcus neoformans-positive culture of blood, spinal fluid, urine, or other sterile-site specimen or by two consecutive cryptococcal antigen titers (in blood or spinal fluid) of >1:8. Candidal esophagitis was classified either as definite (biopsy-proven) or probable (on the basis of clinical symptoms and response to antifungal therapy). Candidemia, coccidioimycosis, histoplasmosis, and blastomycosis documented by a positive culture of a specimen from an infected site or a biopsy sample were study endpoints. Primary endpoints were reviewed by the protocol chairpersons and CCTG study investigators without knowledge of treatment assignment. Secondary endpoints included fluconazole toxicity, survival, and mucocutaneous candidiasis, defined as a compatible clinical picture with either evidence of candidal organisms on microscopic examination of a potassium hydroxide preparation or a culture yielding Candida species.

Statistical Analysis

Because we regarded a doubling of incidence with weekly prophylaxis to be unacceptable, the sample size was selected to provide 80% power to detect an increase in the incidence of deep fungal infections from 5% to 10% at the 0.05 level of significance. Crude risks, failure rates, and risk differences were calculated and compared with use of standard methods. The Kaplan-Meier method was used to estimate the cumulative risk of developing a deep fungal infection and to estimate the risk of developing secondary endpoints of thrush, toxicity, and survival. Cox proportional-hazards models, stratified by study site and M. avium complex prophylaxis and adjusted for baseline CD4 cell count, were used to calculate hazard ratios for the primary and secondary endpoints. All statistical tests were two-tailed.

Both an intent-to-treat analysis and an on-treatment analysis were used to compare efficacy of the two prophylactic strategies. The intent-to-treat analysis compared all events developing during the entire study period between the two arms, according to the initial assignments at randomization. In the on-treatment analysis, events occurring within 30 days of initiation of prophylaxis, >30 days after permanent discontinuation of study treatment, or after 30 days of interrupted therapy because of the need for disallowed medications were not considered prophylaxis failures and were excluded as study endpoints.
A Data and Safety Monitoring Board composed of a statistician and experts in HIV and fungal disease reviewed the incidence of the primary endpoint and toxicity data with use of protocol-specified guidelines.

**Results**

**Patient Population**

Participants were enrolled in the study at 12 sites from December 1992 until April 1994. Subjects received drug for a mean of 335 days in the daily fluconazole arm and 328 days in the weekly fluconazole arm and were followed for a median of 528 and 502 days, respectively.

The baseline characteristics of 636 patients who were randomized and received fluconazole prophylaxis in the two study arms were similar (table 1). The median CD4 cell counts were 41/mm³ and 40/mm³ in the daily and weekly fluconazole arms, respectively. Sixty-two percent of patients had a history of thrush. Forty-two percent of patients had used fluconazole before enrollment in the study, and the median durations of prior fluconazole exposure for these patients were 2 months (daily fluconazole) and 4 months (weekly fluconazole).

**Deep Fungal Infections**

Seventeen subjects (5.5%) receiving daily fluconazole and 24 subjects (7.7%) receiving weekly fluconazole developed a serious fungal infection in the intent-to-treat analysis (table 2). The risk difference between the two arms, 2.2%, had a 95% confidence interval of −1.7% to 6.1%. Candidal esophagitis was the most frequent serious fungal infection, occurring in 12 subjects (3.9%) randomized to receive daily fluconazole and 15 subjects (4.8%) randomized to receive weekly fluconazole (risk difference, 0.9%; 95% CI, −2.2% to 4.2%; *P* = .56). Cryptococcal disease developed in 7 subjects, of whom 2 were randomized to daily and 5 to weekly fluconazole (risk = 0.6% and 1.6%, respectively; risk difference, 1.0%; 95% CI, −0.7% to 2.6%; *P* = .25).

Candidiasis and histoplasmosis were rare events, occurring in three and four subjects, respectively. Seventeen deep fungal infections were included in the on-treatment analysis. Candidal esophagitis was the most common occurrence: four cases occurred with daily fluconazole and seven with weekly fluconazole. Two cases of cryptococcal disease developed in subjects who reported compliance with weekly fluconazole prophylaxis.

The time to onset of deep fungal infection was similar in the two prophylaxis groups (figure 1A). In the Cox regression analysis, the hazard ratio of daily vs. weekly fluconazole dosing for the development of a deep fungal infection was 0.70 (95% CI, 0.38–1.30; *P* = .26) in the intent-to-treat analysis and 0.47 (95% CI, 0.17–1.36; *P* = .17) in the on-treatment analysis. Patients with cryptococcal disease were all treated with a regimen that included amphotericin B, and no deaths were attributed to cryptococcal disease. Susceptibility of the cryptococcal isolates to fluconazole was not tested. Esophageal candidiasis was successfully treated with fluconazole in all cases but three, in which intravenous amphotericin B was used for treatment.

Rates of deep fungal infection were also determined according to prophylaxis for MAC infection to assess the effect of the possible drug interaction between rifabutin and fluconazole. The risk of developing a deep fungal infection did not

**Table 1.** Baseline characteristics of 636 study participants randomized to receive daily or weekly fluconazole prophylaxis for fungal infections.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Daily fluconazole (n = 318)</th>
<th>Weekly fluconazole (n = 318)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>58</td>
<td>63</td>
</tr>
<tr>
<td>Black</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>Hispanic</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>Range</td>
<td>18–60</td>
<td>23–69</td>
</tr>
<tr>
<td>Previous fluconazole use</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>Prior thrush episode</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>No. of CD4 cells/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean count</td>
<td>50</td>
<td>54</td>
</tr>
<tr>
<td>Median count</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>&lt;50/mm³ (% of patients)</td>
<td>59</td>
<td>56</td>
</tr>
</tbody>
</table>

**Table 2.** Deep fungal infections in HIV-infected subjects randomized to receive daily or weekly fluconazole prophylaxis.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Intent-to-treat analysis</th>
<th>On-treatment analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily</td>
<td>Weekly</td>
</tr>
<tr>
<td>Candidal esophagitis</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Probable</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Definite</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Candidemia</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>24</td>
</tr>
</tbody>
</table>

NOTE: Data are percentages unless otherwise indicated.
Superficial Fungal Infections

Thirty-nine subjects (12.3%) receiving daily fluconazole and 63 subjects (19.9%) receiving weekly fluconazole developed thrush (risk difference, 7.5%; 95% CI, −1.8 to 13.2; P = .01).
In the Cox regression model, the hazard ratio for the risk of thrush was 0.59 (95% CI, 0.40–0.89; \( P = .011 \)), favoring daily fluconazole. The time to onset of an initial episode of thrush was significantly shorter in patients receiving weekly vs. daily fluconazole in the Kaplan-Meier analysis (figure 1B). Six (1.9%) of the subjects receiving daily fluconazole and 23 (7.3%) receiving weekly fluconazole had more than one episode of thrush. Rates of thrush were 16.8 per 100 patient-years among patients receiving daily fluconazole and 35.7 per 100 patient-years among patients receiving weekly fluconazole (rate difference, 18.9 per 100 patient-years; 95% CI, 10.5–27.2 [per 100 patient-years]; \( P < .001 \)).

Isolates from 26 (25.5%) of all culture-confirmed thrush episodes were tested for susceptibility to fluconazole at the central laboratory. Although requested, isolates from the other 74.5% of cases were not sent to the central laboratory. Resistance, defined as an MIC of >64 \( \mu \)g/mL, was noted in 1 of 8 isolates from subjects receiving daily fluconazole and 1 of 18 isolates from subjects receiving weekly fluconazole; 5 (63%) of the 8 Candida isolates from the daily arm and 14 (78%) of the 18 from the weekly arm were fluconazole-susceptible (MIC, \( \leq 8 \mu \)g/mL). Only one non-albicans Candida isolate (Candida krusei) was identified, against which the MIC of fluconazole was 8 \( \mu \)g/mL; it was recovered from a subject receiving daily fluconazole. Two patients were treated with intravenous amphotericin B for thrush.

Dermatophyte infections were diagnosed on the basis of clinical findings and were significantly less frequent in subjects receiving daily vs. weekly fluconazole. Forty-nine subjects (15.5%) randomized to the weekly fluconazole regimen developed a dermatophyte infection, compared with 30 subjects (9.5%) randomized to the daily dosing regimen (RR, 0.61; 95% CI, 0.40–0.94).

Adverse Events and Survival

The most frequently reported adverse events during the study were gastrointestinal symptoms, occurring in 72.6% of subjects receiving daily fluconazole and 70.4% of subjects receiving weekly fluconazole. Diarrhea (48%) and nausea (33%) that were mild to moderate in severity were common but seldom necessitated discontinuation of medication. Fluconazole treatment was discontinued because of gastrointestinal symptoms for 6.3% of patients receiving weekly fluconazole and 6.9% of subjects receiving daily fluconazole. Fluconazole was withdrawn because of laboratory abnormalities (increase in liver function test values or hematologic abnormalities) in 3.1% of patients receiving daily and 2.5% of patients receiving weekly fluconazole. The groups were also similar in the Cox regression analysis in terms of time to withdrawal because of drug toxicity (hazard ratio, 1.15; 95% CI, 0.74–1.77).

Survival did not differ between the two fungal prophylaxis groups (hazard ratio, 0.98; 95% CI, 0.76–1.26); 36.7% of patients receiving daily and 37.2% receiving weekly fluconazole died during the course of the study.

Discussion

The protection against serious fungal infection afforded by weekly and daily prophylaxis was similar over nearly 600 patient-years of follow-up. This study complements previous work showing that the 200-mg-daily dosage of fluconazole was effective in reducing the rate of serious fungal infections in HIV-infected patients with significant immunosuppression [7]. Furthermore, we found that intermittent fluconazole dosing was not associated with occurrence of candidal infections refractory to azole therapy.

We observed a 2.2% difference in risk of serious fungal infections between the prophylaxis groups, indicating that one would need to treat 45 patients with 10,961 capsules for each additional case prevented by daily versus weekly dosing. The upper limit of the 95% confidence intervals for the protection afforded by daily compared to weekly dosing was 6%, while the upper limit for the risk of serious fungal infection in those randomized to weekly treatment was 12%. This implies that if we conducted the trial repeatedly, the difference in protection would be no greater than 6% and the absolute risk of serious infection with weekly dosing would be no greater than 12% in 95% of repetitions.

The results of this study can be best appreciated in perspective with the smaller but longer ACTG 981 study. That study, which compared topical therapy with clotrimazole troches to systemic fluconazole at a dosage of 200 mg daily, enrolled 205 subjects with <100 CD4 cells/mm\(^3\) at enrollment. The 12-month cumulative failure rates for serious fungal infections were 15.5% for those randomized to clotrimazole but only 2.0% for those randomized to fluconazole (authors’ unpublished data). Furthermore, the upper limit of the 95% confidence interval for the 12-month cumulative risk of disease in the ACTG 981 fluconazole group, 7.7%, included the observed risk of disease in this study (5.5%). Thus, the similarity between failure rates in the two arms of our study was not likely caused by a spuriously high rate in the daily fluconazole arm.

The potency of fluconazole in this trial for preventing cryptococcal disease in severely immunocompromised patients was striking. In the on-treatment analysis, which included only events involving those subjects without significant interruptions (for >30 days) of fluconazole prophylaxis, there were only two cases of cryptococcal meningitis among 280 subjects. This observation suggests that weekly fluconazole is sufficient to inhibit \( C. \)neoformans replication and subsequent disseminated infection in most subjects. Observations that once-weekly, thrice-weekly, or even any reported use of fluconazole treatment is associated with a reduction in cryptococcal disease are consistent with this finding [5, 9, 10].
Once-weekly fluconazole was relatively less successful than daily dosing in preventing thrush. Although prior placebo-controlled studies have established the efficacy of weekly dosing of fluconazole for oral and vaginal candidiasis, the results of this study are not surprising, given that patients in this study had greater immune suppression [14–16]. A dosing frequency between daily and weekly (e.g., three times weekly) may provide the optimal cost-benefit ratio for protection against thrush, and a clinical trial is currently under way to address this question.

In addition to cost, the potential for selection of fluconazole-resistant organisms has been a major argument against the universal use of fluconazole prophylaxis by patients with AIDS. Thrush refractory to azole therapy is caused by selection of either C. albicans resistant to fluconazole or non-albicans Candida species that are inherently more azole-resistant [17–19]. Cross-resistance to other oral azoles is common and may necessitate treatment with intravenous amphotericin B, which is more toxic [20].

Risk factors for the development of fluconazole resistance include immunosuppression, prior opportunistic infections, and prior cumulative exposure to fluconazole [19, 21–25]. Nevertheless, resistance to fluconazole, as defined by an MIC of $>64 \mu g/mL$, was detected in only two (7.7%) of the isolates tested in this study. Although interpretation is limited by the small proportion (25%) of isolates available for fluconazole susceptibility testing, our findings are consistent with larger prospective studies under way in the United States which suggest that fluconazole resistance rates are $<6\%$ among isolates from patients with $<100$ CD4 cells/mm$^3$ [25]. Furthermore, evidence of clinical resistance was uncommon in the present study, as only five subjects were treated with intravenous amphotericin B for thrush or candidal esophagitis.

The results of this trial were part of a larger trial designed to examine prophylaxis against multiple organisms. While the study design reflected a practical clinical setting, it also complicated the interpretation of the study. We examined whether prophylaxis for MAC infection influenced outcome in this study and found no evidence of any interaction. Gastrointestinal toxicity was frequently reported in this study. In most cases it was difficult to distinguish the relative contribution of fluconazole and the prophylactic medications (azithromycin and rifabutin) against MAC, because all are known to cause nausea, vomiting, abdominal pain, and diarrhea. The finding of gastrointestinal toxic effects in other studies suggests fluconazole infrequently causes these symptoms, and in this study dose-limiting toxic effects were similar between the two fluconazole arms [7, 10].

The availability of potent antiretroviral agents and new prophylactic regimens provides an unprecedented opportunity to increase disease-free survival, even for patients with AIDS and severe immunosuppression [26]. These therapeutic advances also bring complicated choices for patient and provider, because optimal long-term benefit requires frequent administration of multiple agents. Because patients are less likely to adhere to more complicated drug regimens, simplification of prophylactic regimens represents a high priority in the management of HIV-infected patients.

Recently published guidelines for the prevention of opportunistic infections in HIV-infected persons did not recommend fluconazole as primary prophylaxis for cryptococcal disease because of the low incidence of disease, absence of survival benefit, potential for drug interactions, risk of selection of resistant Candida strains, and increased cost [27]. Our data do not contradict these recommendations. Rather, this study provides additional information about the outcome of a daily versus weekly regimen for clinicians choosing to prescribe fluconazole prophylaxis. While efficacy is modestly reduced, the costs of prophylaxis can be reduced by more than two-thirds with use of weekly dosing, and resistance is not increased. These factors should be considered by clinicians selecting prophylactic regimens for their patients.

Acknowledgments

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Appendix

In addition to the authors, the following institutions and investigators participated in this trial.

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