Itraconazole Prophylaxis for Fungal Infections in Patients with Advanced Human Immunodeficiency Virus Infection: Randomized, Placebo-Controlled, Double-Blind Study


In a prospective, randomized, double-blind trial, 149 patients with advanced human immunodeficiency virus (HIV) infection were randomized to receive itraconazole capsules (200 mg daily) and 146 to receive a matched placebo. Both groups were monitored for evidence of fungal infections. Baseline characteristics of the two groups were similar. Failure of prophylaxis occurred in 29 (19%) of the itraconazole recipients and 42 (29%) of the placebo recipients ($P = .004$; log-rank test). There were 6 invasive fungal infections in the itraconazole group (4, histoplasmosis; 1, cryptococcosis; 1, aspergillosis) and 19 in the placebo group (10, histoplasmosis; 8, cryptococcosis; 1, aspergillosis) ($P = .0007$; log-rank test). Itraconazole significantly delayed time to onset of histoplasmosis ($P = .03$; log-rank test) and cryptococcosis ($P = .0005$; log-rank test). Prophylaxis failure due to recurrent or refractory mucosal candidiasis occurred with similar frequency in the two groups (itraconazole, 15%; placebo, 16%). A survival benefit was not demonstrated. Itraconazole generally was well tolerated. Primary prophylaxis with itraconazole capsules prevents histoplasmosis and cryptococcosis in patients with HIV infection.

Administration of primary prophylaxis for selected opportunistic infections has become standard medical care for patients with advanced HIV infection. Prevention of *Pneumocystis carinii* pneumonia and disseminated *Mycobacterium avium* complex (MAC) infection prolongs survival [1, 2], and effective prophylaxis for toxoplasmosis and tuberculosis has been documented [3, 4]. Although opportunistic fungal infections are among the leading causes of death for persons with advanced HIV infection [5], the role of primary antifungal prophylaxis remains controversial [6–8].

Fluconazole has been shown to be effective primary prophylaxis for cryptococcosis in prospective and retrospective clinical trials [9–11]; however, fluconazole prophylaxis has not been associated with a reduction in the incidence of histoplasmosis, which is one of the most common opportunistic infections in regions where *Histoplasma capsulatum* is endemic [12]. Itraconazole is an orally administered triazole antifungal drug with excellent in vitro activity against *Cryptococcus neoformans*, *H. capsulatum*, and several other opportunistic fungal pathogens [13]. Its improved activity for histoplasmosis offers a potential advantage over fluconazole for primary prophylaxis. Accordingly, we undertook a prospective, randomized, placebo-controlled, double-blind study of patients with advanced HIV infection living in cities with high rates of endemic histoplasmosis to assess the efficacy of itraconazole primary prophylaxis for histoplasmosis and other serious fungal infections.

**Patients and Methods**

The primary objective was to assess the safety and efficacy of itraconazole capsules (200 mg daily) vs. placebo in the prevention of histoplasmosis in those HIV-infected subjects who had absolute CD4 lymphocyte counts <150/mm$^3$ and who...
resided in an area with endemic histoplasmosis. Secondary objectives were to assess the safety and efficacy of itraconazole in the prevention of other fungal infections and to assess the impact of prophylaxis on in vitro susceptibility of selected fungal pathogens to itraconazole and fluconazole.

Subjects were eligible for participation if they met the following criteria: age of \( \geq 13 \) years; HIV infection, documented by positive enzyme immunoassay and western blot tests; life expectancy of \( \geq 1 \) year; no life-threatening infection or malignancy other than cutaneous Kaposi’s sarcoma; absolute CD4 lymphocyte count \( <150/\text{mm}^3 \) within 1 year prior to study enrollment; and residence in a city with a high prevalence of histoplasmosis. Exclusion criteria included the following: use of an investigational drug concurrently or within 1 month prior to initiation of the study (with the exception of drugs available under a U.S. Food and Drug Administration–authorized expanded-access program); pregnancy, lactation, or (among women) failure to use a medically approved and effective method of contraception; history of intolerance of imidazole or triazole compounds; inability to take oral medications; history of active histoplasmosis; active fungal infection (cryptococcosis, aspergillosis, coccidioidomycosis, or oropharyngeal, vaginal, esophageal, or disseminated candidiasis); use of a medication with a known interaction with itraconazole; and elevated liver function test values (\( >5.0 \) times the upper limit of normal for aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase or \( >2.5 \) mg/dL for total bilirubin).

Endpoints

The study endpoints included (1) toxicity necessitating discontinuation of study medication and (2) failure of prophylaxis, defined as development of histoplasmosis, cryptococcosis, aspergillosis, or other proven or probable systemic fungal infection; oropharyngeal or vaginal candidiasis requiring \( >2 \) weeks of treatment with a systemically active antifungal drug or requiring such treatment on more than one occasion; or esophageal candidiasis requiring \( >3 \) weeks of treatment with a systemically active antifungal drug or more than one course of treatment.

Confirmed histoplasmosis was defined as a compatible clinical syndrome consistent with signs and symptoms of pulmonary or disseminated fungal infection, along with either a positive culture for \( H. \) capsulatum or a histopathologically positive tissue biopsy specimen or buffy coat smear. Probable histoplasmosis was defined as a compatible clinical syndrome and both detection of Histoplasma polysaccharide antigen in body fluids and initiation of specific antifungal treatment, unless further evaluation identified a nonfungal pathogen or cause. Other fungal infections were classified as confirmed or probable on the basis of previously established criteria [11].

Laboratory Tests

Serum specimens were obtained at baseline, every 6 months, and when breakthrough fungal infections were suspected, and these were frozen at \( -70^\circ C \). Specimens were obtained at random times following itraconazole dosings. After completion of the study, itraconazole concentrations in banked serum specimens were measured by bioassay, with use of a method modified from a procedure by Bodet et al. [15], at the Histoplasmosis Reference Laboratory. Samples were tested in duplicate, and concentrations were calculated by comparison to a standard curve ranging from 0.62 \( \mu \)g/mL to 20.0 \( \mu \)g/mL [15]. Culture specimens were obtained from patients who had clinical evidence of mucosal or systemic fungal infections and were processed at local hospital laboratories. Isolates were subcultured once, and the freshly grown cultures were suspended in lactase glycerol freezing medium and stored frozen in liquid nitrogen. \( H. \) capsulatum isolates were evaluated in vitro for susceptibility to itraconazole and fluconazole with use of a macrobroth method slightly modified from the M27-T method of the National Committee for Clinical Laboratory Standards (NCCLS) [16]. The MIC was defined as the concentration of drug required to inhibit 80% of the organism’s growth, as detailed in the NCCLS methodology [16].

Statistical Considerations

The study hypothesis was that itraconazole would reduce the annual incidence of histoplasmosis from 15% to 5% or less.
among HIV-infected patients who had absolute CD4 lymphocyte counts of <150/mm³ and who lived in an area where histoplasmosis is endemic. The study was designed to assess this hypothesis with 80% power at a two-sided type 1 error level of 0.05. Assuming that the probability of developing histoplasmosis in such a group of patients could be approximated by an exponential distribution, we calculated the sample size to be 220 patients, with 110 in each arm of the study [17]. On the basis of an anticipated dropout rate of ~20% in each treatment group, it was estimated that 130 patients should be accrued in each arm, for a total enrollment of 260 patients.

All analyses were performed on an intention-to-treat basis. These included data from all subjects who met the eligibility criteria and were enrolled in the study, given that they received at least one dose of test medication (either itraconazole or placebo). Analyses were conducted on the basis of assigned treatment, regardless of actual treatment received. The primary measure of effectiveness was the duration of time to development of histoplasmosis, determined by means of the Kaplan-Meier (product-limit) method with the log-rank test [18].

Secondary efficacy analyses considered a broader classification of treatment failure, including other systemic fungal infections or refractory mucosal fungal infections. Independent factors that may have affected development of fungal infections were investigated by the Wilcoxon test for continuous variables and by the chi² analysis for categorical variables and by the Wilcoxon test for continuous variables [19]. The Cox proportional hazards model was not utilized to investigate concomitant factors related to development of systemic mycoses because of an insufficient number of meaningful clinical events. Interim analyses were reviewed by an independent data-safety monitoring board and maintained an overall type 1 error of 0.05.

### Results

#### Study Population

Two hundred ninety-eight patients were enrolled, of whom 3 were ineligible (2 withdrew consent before receiving study medication, and 1 was taking disallowed medications and never received study drug) and 295 were evaluable. The data-safety monitoring board requested that enrollment exceed the originally planned sample size because of a lower than anticipated incidence of invasive fungal infections during the early phase of the study. Among evaluable cases, 146 were randomized to the placebo arm and 149 to the itraconazole arm. Baseline characteristics of the two treatment groups, including CD4 lymphocyte counts, were comparable (table 1). The study began in June 1993, enrollment ended in April 1995, and follow-up evaluations were concluded in April 1996. The median duration of follow-up was 16 months (range, 1–34 months). Thirty-seven percent of subjects were enrolled in Kansas City, 33% in Indianapolis, 18% in Nashville, and 12% in Memphis.

#### Prophylaxis Failure

Prophylaxis failure occurred for 29 (19%) of the subjects randomized to receive itraconazole and 42 (29%) of those randomized to receive placebo ($P = .004$; log-rank test) (table 2). There were 6 invasive fungal infections among itraconazole recipients (4, histoplasmosis; 1, cryptococcosis; 1, aspergillosis) and 19 among placebo recipients (10, histoplasmosis; 8, cryptococcosis; 1, aspergillosis) ($P = .0007$; log-rank test).

---

### Table 1. Baseline characteristics of 295 HIV-infected patients randomized to receive itraconazole prophylaxis or placebo.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo ($n = 146$)</th>
<th>Itraconazole ($n = 149$)</th>
<th>Total ($n = 295$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (y)</td>
<td>36</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Race: no. (%) of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>117 (80)</td>
<td>116 (78)</td>
<td>233 (79)</td>
</tr>
<tr>
<td>Black</td>
<td>27 (19)</td>
<td>30 (20)</td>
<td>57 (19)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (1)</td>
<td>3 (2)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Male: no. (%) of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (no./mm³)</td>
<td>63</td>
<td>57</td>
<td>61</td>
</tr>
<tr>
<td>&lt;100/mm³: no. (%) of patients</td>
<td>103 (71)</td>
<td>101 (68)</td>
<td>204 (69)</td>
</tr>
<tr>
<td>Antiretroviral therapy: no. (%) of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>92 (63)</td>
<td>97 (65)</td>
<td>189 (64)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>73 (50)</td>
<td>79 (53)</td>
<td>150 (52)</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>19 (13)</td>
<td>18 (12)</td>
<td>37 (13)</td>
</tr>
</tbody>
</table>

### Table 2. Outcomes among 295 HIV-infected patients randomized to receive itraconazole prophylaxis or placebo.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Itraconazole ($n = 149$)</th>
<th>Placebo ($n = 146$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis failure</td>
<td>29 (19.5)*</td>
<td>42 (28.8)</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>4 (2.7)'</td>
<td>10 (6.8)</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>1 (0.7)†</td>
<td>8 (5.5)</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Oropharyngeal candidiasis (recurrent or refractory)</td>
<td>17 (11.4)</td>
<td>15 (10.3)</td>
</tr>
<tr>
<td>Esophageal candidiasis (recurrent or refractory)</td>
<td>6 (4.0)</td>
<td>8 (5.5)</td>
</tr>
<tr>
<td>Discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>13 (8.7)§</td>
<td>5 (3.4)</td>
</tr>
<tr>
<td>Patient’s decision</td>
<td>27 (18.1)</td>
<td>36 (24.7)</td>
</tr>
<tr>
<td>Death</td>
<td>32 (21.5)</td>
<td>21 (14.4)</td>
</tr>
</tbody>
</table>

* $P = .004$ (log-rank test).
† $P = .03$ (log-rank test).
§ $P = .0005$ (log-rank test).
§ $P = .04$ (chi² test).
of cryptococcosis were confirmed (7 of 8 in the placebo group and the single case in the itraconazole group). Both cases of aspergillosis were confirmed. Thirty-nine of 46 cases of mucosal candidiasis (11 of 14 esophageal and 28 of 32 oropharyngeal) also were confirmed.

Only 1 of the 4 itraconazole recipients who developed histoplasmosis was taking study medication at the time of diagnosis; among the other 3 subjects, 2 discontinued the itraconazole therapy because of adverse events (skin rash; headache and dizziness) and a third required a disallowed medication, necessitating discontinuation of study medication. The one itraconazole recipient who developed cryptococcosis discontinued study medication 4 weeks prior to diagnosis because of a skin rash. The itraconazole recipient who developed aspergillosis was taking study medication when the infection occurred. Thus, there were only two patients who were taking itraconazole at the time of onset of systemic fungal infection. One of 6 itraconazole recipients who developed recurrent or refractory esophageal candidiasis was receiving study medication when the prophylaxis failure occurred, and 10 of 17 itraconazole recipients who had recurrent oropharyngeal candidiasis were taking study medication at the time of diagnosis.

In total, 93 (63.7%) of 146 patients in the placebo arm, vs. 91 (61.1%) of the 149 in the itraconazole arm, were still taking study medication at the time of either prophylaxis failure or conclusion of the protocol. If only those patients who continued with the assigned treatment are considered, prophylaxis failure occurred in 28 (30%) of 93 placebo recipients and in 13 (14%) of 91 itraconazole recipients when they completed the study.

Itraconazole significantly delayed time to onset of histoplasmosis ($P = .031$; log-rank test) (figure 1), cryptococcosis ($P = .0005$; log-rank test) (figure 1), and all systemic fungal infections ($P = .0007$; log-rank test). At least one episode of mucosal candidiasis occurred in 74 (51%) of the patients randomized to receive placebo and in 51 (34%) of those who received itraconazole ($P = .004$; $\chi^2$ test). Twenty-three itraconazole recipients’ prophylaxis failed because they had 2 or more episodes of mucosal candidiasis (17, oropharyngeal; 6, esophageal) requiring systemic antifungal therapy; likewise, 23 placebo recipients’ regimens failed for the same reason (15 had oropharyngeal candidiasis and 8 had esophageal candidiasis) ($P = .27$; $\chi^2$ test). There were no prophylaxis failures due to vaginal candidiasis.

Among 25 invasive fungal infections, 22 were confirmed and 3 were considered probable. Twelve of 14 cases of histoplasmosis were confirmed, including all 4 cases in the itraconazole arm and 8 of 10 in the placebo arm. Eight of the 9 cases of cryptococcosis were confirmed (7 of 8 in the placebo group and the single case in the itraconazole group). Both cases of aspergillosis were confirmed. Thirty-nine of 46 cases of mucosal candidiasis (11 of 14 esophageal and 28 of 32 oropharyngeal) also were confirmed.

Only 1 of the 4 itraconazole recipients who developed histoplasmosis was taking study medication at the time of diagnosis; among the other 3 subjects, 2 discontinued the itraconazole therapy because of adverse events (skin rash; headache and dizziness) and a third required a disallowed medication, necessitating discontinuation of study medication. The one itraconazole recipient who developed cryptococcosis discontinued study medication 4 weeks prior to diagnosis because of a skin rash. The itraconazole recipient who developed aspergillosis was taking study medication when the infection occurred. Thus, there were only two patients who were taking itraconazole at the time of onset of systemic fungal infection. One of 6 itraconazole recipients who developed recurrent or refractory esophageal candidiasis was receiving study medication when the prophylaxis failure occurred, and 10 of 17 itraconazole recipients who had recurrent oropharyngeal candidiasis were taking study medication at the time of diagnosis.

In total, 93 (63.7%) of 146 patients in the placebo arm, vs. 91 (61.1%) of the 149 in the itraconazole arm, were still taking study medication at the time of either prophylaxis failure or conclusion of the protocol. If only those patients who continued with the assigned treatment are considered, prophylaxis failure occurred in 28 (30%) of 93 placebo recipients and in 13 (14%) of 91 itraconazole recipients when they completed the study ($P = .01$; $\chi^2$ test).

Among 149 patients randomized to receive itraconazole, serum concentrations were measured during the course of the study for 128 (once for 114 and twice or more for 14). The median itraconazole concentration was $1.07 \mu g/mL$ (range, $0–32.6 \mu g/mL$), and the mean ($\pm$ SE) level was $2.86 \pm 0.39 \mu g/mL$. Fifty-one levels (39.8%) were undetectable, 12 (9.4%) were between zero and 1 $\mu g/mL$, and 65 (50.8%) were $>1 \mu g/mL$. Among the 14 patients who had multiple concentrations measured, at least one concentration was undetectable in 12 cases; however, 8 of these 12 patients had detectable concentrations on other occasions.

The benefit of itraconazole prophylaxis was seen only in the subset of patients with lower baseline CD4 lymphocyte counts. Among patients with CD4 lymphocyte counts $>100/mm^3$, itraconazole did not significantly decrease the incidence of histoplasmosis ($P = .46$; log-rank test) or any other fungal infections ($P = .71$; log-rank test). Forty-three placebo recipients had baseline CD4 counts $>100/mm^3$. Three cases of histoplasmosis (7.0%) and one case of cryptococcosis (2.3%) occurred in this group. Among the 48 patients with CD4 lymphocyte counts $>100/mm^3$ randomized to receive itraconazole, there were two cases of histoplasmosis (4.2%) and one case of cryptococcosis (2.1%). In the subset with counts $<100/mm^3$, itraconazole pro-
Itraconazole prophylaxis significantly decreased the incidence of histoplasmosis ($P = .02$; log-rank test) and all invasive fungal infections ($P = .0009$; log-rank test). Seven (7.0%) of the 103 placebo recipients with CD4 lymphocyte counts <100/mm$^3$ developed histoplasmosis, 7 (7.0%) developed cryptococcosis, and 1 (1.0%) developed aspergillosis. Histoplasmosis occurred in 2 (2.0%) of the 101 itraconazole recipients with CD4 lymphocyte counts <100/mm$^3$ and aspergillosis occurred in 1 (1.0%); there were no cases of cryptococcosis in this group.

Survival

Thirty-two patients (21.5%) in the itraconazole arm died, vs. 21 (14.4%) in the placebo arm ($P = .72$, log-rank test). There were 3 deaths due to fungal infection, including those of 2 patients with cryptococcosis (1 in the placebo arm and 1 in the itraconazole arm; the latter patient had not taken study medication for 4 weeks prior to death) and 1 with histoplasmosis (who was in the itraconazole arm of the study).

Adverse Events

Adverse events that were possibly attributed to protocol therapy are reviewed in table 3. Protocol therapy was discontinued due to presumed adverse events in 18 cases, 5 in the placebo group (3.4%) and 13 in the itraconazole group (8.7%) ($P = .04$; $\chi^2$ test). Skin rash occurred more frequently in patients who received itraconazole ($P = .02$; $\chi^2$ test) and was the reason for discontinuation of protocol therapy for six of 13 itraconazole recipients. There were two cases of Stevens-Johnson syndrome among itraconazole recipients, although one of these patients also was receiving trimethoprim-sulfamethoxazole, which may have been the cause of this disorder. Gastrointestinal toxicities were reported by a large number of subjects but were relatively evenly distributed between the two regimens.

**Table 3. Adverse events during itraconazole prophylaxis.**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Itraconazole (n = 149)</th>
<th>Placebo (n = 146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>96 (64.0)</td>
<td>113 (77.0)*</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (5.4)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9 (6.0)</td>
<td>9 (6.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (4.7)</td>
<td>5 (3.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (2.7)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Elevated liver enzyme level</td>
<td>7 (4.7)</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>Rash</td>
<td>15 (10.1)</td>
<td>3 (2.1)*</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>2 (1.3)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

* $P < .05$ ($\chi^2$ test).

### Factors Associated with Prophylaxis Failure

The median CD4 lymphocyte count at baseline was 60/mm$^3$ (range, 0–162/mm$^3$) among patients who did not develop systemic fungal infections and 71/mm$^3$ (range, 11–144/mm$^3$) among those who did ($P = .51$; Wilcoxon’s test). Among the patients randomized to receive itraconazole, the last serum itraconazole concentrations determined were not significantly different between the prophylaxis successes (median concentration, 1.065 µg/mL; range, 0–22.6 µg/mL) and the prophylaxis failures (median concentration, 2.2 µg/mL; range, 0–11.6 µg/mL) ($P = .80$; Wilcoxon’s test). The percentages of patients in the two treatment arms who received two or more antiretroviral drugs at baseline were similar (table 1); the percentage of prophylaxis successes was significantly greater among those receiving combination antiretroviral therapy at the completion of the study.

Among the 14 patients who developed histoplasmosis, only 1 (7%) had a reactive histoplasmin skin test at baseline, and 6 (2%) of 277 who did not acquire histoplasmosis had reactive skin tests ($P = .24$; $\chi^2$ test). CF antibodies to *Histoplasma* yeast or mycelial antigens (at a titer of $\geq 1:8$) were present at baseline in 3 (21%) of 14 patients who developed histoplasmosis and in 37 (20%) of 185 who did not ($P = .37$; $\chi^2$ test).

Among 46 patients whose prophylaxis failed because of recurrent or refractory oropharyngeal or esophageal candidiasis, the median baseline CD4 lymphocyte count was 42/mm$^3$ (range, 0–151/mm$^3$), compared with 63/mm$^3$ (range, 0–162/mm$^3$) among 249 whose prophylaxis did not fail ($P = .05$; Wilcoxon’s test). At initiation of the study, similar proportions of patients in the 2 groups were receiving $\geq 2$ antiretroviral drugs, but at study completion 4 (9%) of 46 patients whose prophylaxis failed, vs. 58 (23%) of 249 successfully treated patients, were receiving combination antiretroviral therapy ($P = .03$; Wilcoxon’s test). Median serum itraconazole concentrations were 1.4 µg/mL (range, 0–32.6 µg/mL) and 1.065 µg/mL (range, 0–20.5 µg/mL) in the mucosal candidiasis prophylaxis-failure and prophylaxis-success groups, respectively ($P = .94$; Wilcoxon’s test). Further analyses of the *Candida* species isolated and their susceptibilities to azole antifungal agents are under way [20].

Only two *H. capsulatum* isolates from patients whose itraconazole prophylaxis failed were available for analysis; for neither of these isolates were the MICs of itraconazole or fluconazole significantly higher than for those of the three available *H. capsulatum* isolates from placebo recipients. For both isolates from itraconazole recipients, the MIC of itraconazole was 0.0025 µg/mL and the MIC of fluconazole was 1.0 µg/mL. The MICs for the three isolates from subjects who received placebo were 0.0025, 0.0025, and 0.005 µg/mL of itraconazole and 1.0, 1.0, and 2.0 µg/mL of fluconazole.

### Discussion

Our results show that primary prophylaxis with itraconazole capsules is effective in the prevention of histoplasmosis and...
cryptococcosis. Although four patients in the itraconazole group developed histoplasmosis, only one was still taking the medication at the time the infection occurred. Similarly, the one patient in this group who developed cryptococcosis had stopped taking the drug 1 month prior to the onset of infection. Itraconazole was more effective in the prevention of systemic mycoses than noted in prior studies with fluconazole [9, 11]. A prospective placebo-controlled study of daily fluconazole prophylaxis demonstrated a significant reduction in incidence of cryptococcosis, especially among patients with CD4 lymphocyte counts < 50/mm³ [11]. Fluconazole prophylaxis also was associated with decreased incidence of cryptococcosis in a prospective uncontrolled study [9], in a prospective trial with historical controls [10], and in a case-control study [21]. However, fluconazole prophylaxis was not associated with a reduction in the incidence of histoplasmosis in these studies [10, 11]. Only the current trial was designed primarily to assess prophylaxis of histoplasmosis.

In the AIDS Clinical Trials Group (ACTG) study by Powderly and co-workers, the incidence of systemic mycoses was reduced from 10.9% among the patients receiving clotrimazole to 3.3% among those receiving daily fluconazole, over a median observation period of 35 months, an overall reduction of 62% [11]. In our study itraconazole reduced the incidence of systemic mycoses from 13.0% to 4.1%, a 73% reduction, over a median follow-up period of 16 months. Comparison of the two studies by expression of the efficacy as numbers of cases prevented per 100 patient-years reveals that 2.2 cases were prevented by fluconazole, vs. 8.1 cases by itraconazole.

Several factors other than the choice of study drug might explain these differences. Our study was restricted to patients with CD4 lymphocyte counts < 150/mm³, while the ACTG fluconazole study included patients with counts < 200/mm³; the median CD4 lymphocyte count of the group receiving itraconazole was 57/mm³, while that of the group receiving fluconazole was 90/mm³. In addition, our prophylaxis study was restricted to four cities with high attack rates of histoplasmosis, while the ACTG fluconazole study was conducted throughout the United States. Other important considerations may be that fluconazole is less effective than itraconazole for treatment of histoplasmosis in HIV-seronegative and HIV-seropositive patients [22, 23] and that H. capsulatum has been shown to acquire resistance to fluconazole [24], whereas acquired resistance to itraconazole has not been demonstrated.

Although itraconazole was highly effective in preventing histoplasmosis and cryptococcosis in our study and fewer patients who received itraconazole had documented oropharyngeal candidiasis, it did not reduce the incidence of recurrent or refractory oropharyngeal or esophageal candidiasis. A previous ACTG study showed that fluconazole prophylaxis decreased the incidence of mucosal candidiasis [11]. Differences in protocol design may have influenced the outcome of these two clinical trials. Whereas fluconazole was compared with clotrimazole in a nonblinded fashion in the ACTG study [11], itraconazole was compared with a blinded placebo in the current study. This difference may have had an impact on the voluntary discontinuation rates in the two clinical trials. During the period this study was conducted, use of chronic suppressive therapy with fluconazole for mucosal candidiasis was a widespread practice, so physicians may have been more likely to discontinue prophylaxis and initiate fluconazole therapy for oropharyngeal or esophageal candidiasis.

The disparity between the efficacy of itraconazole for prevention of histoplasmosis and cryptococcosis and its relative lack of efficacy for prevention of recurrent mucosal candidiasis may be related to differences in drug concentrations at the sites of infection. Concentrations of itraconazole in blood and lung may be most important in preventing acquisition of infection with C. neoformans and H. capsulatum, whereas candidiasis is almost always a mucosal infection in patients with AIDS. Itraconazole capsules, which were utilized in our study, are partially dependent on an acidic gastric pH for absorption and are variably absorbed in HIV-infected patients [25]. Development of mucosal candidiasis could not be attributed to impaired drug absorption, however, since serum itraconazole concentrations were comparable between the patients in the candidiasis prophylaxis-failure and prophylaxis-success groups. Mucosal concentrations of itraconazole may be inadequate to suppress infection, even when the drug is well absorbed.

Although high salivary concentrations of itraconazole are attained after administration of itraconazole oral solution, the metabolite hydroxyitraconazole is undetectable in saliva despite twofold higher plasma concentrations of hydroxyitraconazole than of the parent compound [26]. This finding supports the hypothesis that the low efficacy of the capsule formulation for prevention of recurrent or refractory oropharyngeal and esophageal candidiasis was caused by inability to achieve therapeutic concentrations at the mucosal surface. Use of itraconazole oral solution, which has efficacy against mucosal candidiasis similar to that of fluconazole [27–29], might be expected to reduce the incidence of recurrent candidiasis as a cause of prophylaxis failure.

It is important to note that this study was conducted immediately before the era when highly active antiretroviral therapy (HAART) became available. Despite the fact that none of our patients received HAART, those who were being treated with two or more antiretroviral drugs at the completion of the study were significantly less likely to have prophylaxis fail. Thus, even suboptimal antiretroviral therapy was associated with a reduction in the incidence of opportunistic fungal infections.

In summary, our data show that itraconazole (200 mg daily) is effective primary prophylaxis for histoplasmosis and cryptococcosis in patients with advanced HIV infection and generally is well tolerated. Itraconazole prophylaxis should be considered for those patients with CD4 lymphocyte counts ≤ 100/mm³ who reside in areas where there is a high incidence of histoplas-
mosis. This form of prophylaxis may be most useful for patients who cannot take highly active antiretroviral therapy or whose HIV infections have not been effectively controlled.

Acknowledgments

This article is dedicated to the memory of Laura Lancaster, M.D. The authors thank S. Heyse, M.D., for reviewing the manuscript and K. Wilcox (Kansas City, MO) for manuscript preparation.

Contributors

Other contributors to this study, by site, include the following. Infectious Disease Associates of Kansas City: D. Smith, B. Lee, and M. Driks; Indiana University School of Medicine: P. Connolly, H. Nixon, and S. Ryan; Mycoses Study Group: C. Flanagan; Vanderbilt University: J. Richardson and J. McKinsey; Infectious Disease of Indiana: S. Norris, T. Slama, R. Yates, B. Baker, and J. Fraiz; University of Missouri—Kansas City and Kansas City AIDS Research Consortium: D. Simpson and J. Larkin; JanssenPharmaceutica: B. Weissinger, A. Baruch, and A. Dine; Methodist Hospital System: D. Lancaster and D. Ray; and Infectious Disease Associates of Memphis: M. Threlkeld.

Authors’ Current Affiliations

Dr. McKinsey: Research Medical Center, 2316 East Meyer Boulevard, Kansas City, Missouri 64132.

Dr. Wheat: Wishard Memorial Hospital, OPW 430, 1001 West 10th Street, Indianapolis, Indiana 46202-2879.


Dr. Pierce: Box 1734, Kampala, Uganda.

Dr. Black: Infectious Disease of Indianapolis, 1633 North Capitol, Suite 700, Indianapolis, Indiana 46202.

Dr. Bamberger: University of Missouri—Kansas City School of Medicine, Red 4 Unit, 2411 Holmes Street, Kansas City, Missouri 64108-2792.

Dr. Goldman: Wishard Memorial Hospital, OPW 430, 1001 West 10th Street, Indianapolis, Indiana 46202-2879.

Ms. Thomas: University of Alabama at Birmingham, MS Center, DERB 335, 1808 7th Avenue South, Birmingham, Alabama 35294-0012.

Ms. Gutsch: Veterans Affairs Medical Center, Room 839-A, 2215 Fuller Road, Ann Arbor, Michigan 48105.

Dr. Moskovitz: Janssen Pharmaceutica, P.O. Box 200, 1125 Trenton-Harbourton Road, Titusville, New Jersey 08560-0200.

Dr. Dismukes: University of Alabama at Birmingham, THT 299, 1900 University Boulevard, Birmingham, Alabama 35294-0006.

Dr. Kaufman: Veterans Affairs Medical Center, Room 839-A, 2215 Fuller Road, Ann Arbor, Michigan 48105.

References


