A Controlled Trial of Itraconazole as Primary Prophylaxis for Systemic Fungal Infections in Patients with Advanced Human Immunodeficiency Virus Infection in Thailand

Suwat Chariyalertsak,1 Khuanchai Supparatpinyo,1 Thira Sirisanthana,1 and Kenrad E. Nelson2

1Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; and 2Department of Epidemiology, Johns Hopkins University, School of Hygiene and Public Health, Baltimore, Maryland

Cryptococcal meningitis and *Penicillium marneffei* infection are common serious fungal infections in patients infected with human immunodeficiency virus (HIV) in Southeast Asia. In a prospective, double-blind trial, 63 patients with HIV infection and CD4+ lymphocyte counts of <200 cells/μL were randomized to receive oral itraconazole (200 mg per day), and 66 similar patients received a matched placebo. Both groups were monitored for evidence of invasive fungal infections. Baseline characteristics and the CD4+ cell counts of the 2 groups were similar. In the intent-to-treat analysis, a systemic fungal infection developed in 1 patient (1.6%) assigned to receive itraconazole (*P. marneffei*) and in 11 patients (16.7%) given placebo (7 patients had cryptococcal meningitis, and 4 patients had *P. marneffei* infection; \( P = .003 \), by the log-rank test). The incidence of recurrent or refractory mucosal candidiasis was significantly reduced in the itraconazole group. The 2 groups did not differ with regard to adverse effects. Primary prophylaxis with oral itraconazole is well tolerated and prevents cryptococcosis and penicilliosis marneffei in patients with advanced HIV infection, especially those with CD4+ lymphocyte counts of <100 cells/μL. However, prophylaxis with itraconazole was not found to be associated with a survival advantage when it was given to patients with advanced HIV disease.

Fungal infections are an important complication of HIV infection and AIDS. They vary in severity from mild to moderate discomfort, which is associated with mucosal candida infections, to life-threatening systemic mycoses. The incidence of severe and life-threatening fungal infections increases as the immune system becomes more compromised. Cryptococcal infection, which is the most common invasive fungal infection among patients with AIDS, occurs in 3% to 18% of different populations of patients with AIDS [1–4]. Furthermore, it is important for clinicians to recognize the possibility of other endemic mycoses, such as histoplasmosis in the midwestern United States [5, 6], coccidioidomycoses in the southwestern United States [7], and penicilliosis in Southeast Asia [8, 9]. These fungal infections are common AIDS-related infections for patients living in these areas but can also be seen in persons who have lived in these areas previously or in HIV-infected patients who are only exposed during travel to these endemic areas.

Although these invasive fungal infections are treatable, therapy is not curative and must be followed by lifelong receipt of suppressive therapy, to prevent relapses in the absence of highly effective antiretroviral therapy [10–13]. The role of primary prophylaxis to
prevent opportunistic fungal infections in patients with advanced HIV infection remains controversial [14]. Fluconazole has been shown to be effective as primary prophylaxis of cryptococcosis in patients with advanced HIV infections in prospective and retrospective clinical trials [15, 16]. Itraconazole has also been recommended as primary prophylaxis for histoplasmosis in patients who live in the endemic region in the midwestern United States, especially those individuals with CD4+ counts of <100 cells/μL [17].

*Penicillium marneffei* is one of the most common systemic mycoses in HIV-infected patients; it is second only to cryptococcosis among patients with AIDS in northern Thailand. A recent study described the nationwide distribution and regional variation of AIDS-defining illnesses among >100,000 persons with AIDS who were reported through the National AIDS surveillance system from 1994 through 1998 [4]. Cryptococcosis was reported in ~20% and *P. marneffei* infections were reported in 7% of patients with AIDS in northern Thailand. Cryptococcosis was also the most common mycosis in the other regions, but penicilliosis occurred in <1% of patients in areas outside of northern Thailand. Treatment with oral itraconazole at a dosage of 200 mg once per day is highly effective in preventing a relapse of penicilliosis, and it has been recommended as the standard of care for patients with AIDS and *P. marneffei* infection [13]. Itraconazole is commonly used in Thailand for the treatment and prophylaxis of systemic fungal disease; however, the cost of the drug is a barrier for some patients. We conducted a study to evaluate the efficacy and safety of itraconazole as primary prophylaxis for cryptococcosis penicilliosis and other serious fungal infections in patients with advanced HIV infection who live in northern Thailand, where *P. marneffei* infection is endemic [9, 13].

**PATIENTS AND METHODS**

**Study design.** A prospective, randomized, placebo-controlled, double-blind study was conducted to compare the safety and efficacy of itraconazole (200 mg per day) with that of placebo, which was identical in appearance to the study drug, in the prevention of penicilliosis and other serious fungal infections in HIV-infected patients who had absolute CD4+ lymphocyte counts of <200 cells/μL. Itraconazole was administered as capsules to be taken with food.

The study design was approved by the Human Experimentation Committee of Chiang Mai University. Patients enrolled in the study were seen at Chiang Mai University hospital and gave their written informed consent. Appropriate informed consent was obtained and clinical research was conducted in accordance with guidelines as specified by the US Department of Health and Human Services and the authors’ institutions.

Eligibility criteria included the following characteristics: age of 18–60 years, documented HIV infection, Karnofsky score of >70 (normal activity possible with effort), absolute CD4+ lymphocyte count of <200 cells/μL, and residence in the Chiang Mai area. Exclusion criteria included the following characteristics: history of systemic fungal infections, use of systemic antifungal therapy within 2 weeks before study entry, history of active tuberculosis, pregnancy or breast-feeding, a history of intolerance to triazole compounds, failure to use a medically approved and effective method of birth control, inability to take oral medications, use of a medication with a known interaction with itraconazole, and serum aminotransferase levels at >5 times the upper limit of normal. Patients with mucosal *Candida* infection could receive treatment with topical antifungal agents and remain eligible for enrollment in the study after they were in clinical remission.

The patients were randomly assigned to receive itraconazole or placebo in a 1:1 ratio. Randomization was performed by the drug manufacturer (Janssen Pharmaceutical) with a computerized randomization list based on a block size of 6. The medication was packaged in sequentially numbered boxes that were dispensed to successive patients. All patients in both study groups received 2 single-strength tablets of trimethoprim-sulfamethoxazole (80 mg/400 mg taken orally once per day) for prophylaxis against *Pneumocystis carinii* pneumonia throughout the study period. Patients who developed a drug allergy to trimethoprim-sulfamethoxazole during the study period were switched to dapsone (50 mg per day).

Clinical and laboratory assessments were undertaken at baseline and every 4 weeks for the remainder of the study. At each visit, all patients were evaluated by history and physical examination. The blood examination included performance of complete blood counts, blood chemistry studies, and blood cultures for fungus, which were performed at baseline and at every other visit. All episodes that suggested possible invasive mycoses were investigated by cultures of samples of body fluids and tissues, histopathological studies, and cryptococcal-antigen measurements. Patients with symptoms between scheduled visits were encouraged to come to the clinic for evaluation. If a patient had visited another clinical facility because of relevant symptoms, the records were obtained and reviewed with the patient’s permission. Adherence to the study regimen was assessed by calculating the proportion of doses reportedly missed at each visit and using that value to estimate the number of days each week that study drugs were taken. If a patient missed a follow-up visit, 1 member of the study personnel visited the patient at home and scheduled a new visit. During the follow-up period, topical therapy for oropharyngeal or vaginal candidiasis was permitted. Administration of oral ketoconazole (200 mg given once per day for up to 2 weeks) was allowed when topical therapy was not effective. While they were re-
ceiving ketoconazole, patients were asked to stop taking the trial drug for 2 weeks.

End points. The primary end points were the completion of 104 weeks of follow-up, development of *P. marneffei* infection or other invasive fungal infection (diagnosed by fungal culture, a histopathological examination, or buffy coat smear), and death. The secondary end points included oropharyngeal or vaginal candidiasis that required >2 weeks of treatment with ketoconazole and esophageal candidiasis that required >4 weeks of treatment with a systemically active antifungal drug. Mucocutaneous *Candida* infection was diagnosed on the basis of compatible clinical signs and symptoms and a response to specific antifungal therapy. A diagnosis of esophageal candidiasis was based on the presence of oropharyngeal thrush and esophageal symptoms with abnormal findings on an endoscopic evaluation or a response to appropriate therapy.

Patients were withdrawn from the study if they developed the following abnormal laboratory values: hemoglobin, <10.5 g/dL (6.52 m/M); WBC count, <4000 cells/mm³; and alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase values >5 times the upper limit of normal. Patients who missed 2 consecutive appointments were considered lost to follow-up.

Statistical analysis. We estimated that the incidence of invasive fungal infections would be 20% in the placebo recipients. To detect a 50% reduction, with 80% power and a 5% significance level (1-sided), 161 patients were required per treatment group. To account for a 20% dropout rate, a total of 402 patients were included in the analysis. The treatment groups were similar with respect to demographic variables and baseline laboratory values, including CD4⁺ lymphocyte counts (*P* ≥ .05). The percentages of patients in the 2 treatment groups who had received 1 or 2 antiretroviral drugs at baseline were similar (*P* ≥ .05; table 1). The median duration of follow-up was 40 weeks in the itraconazole arm (range, 6–104 weeks) and 35 weeks in the placebo arm (range, 5–104 weeks; table 2).

Clinical end points. Invasive fungal infections developed in 1 (1.6%) of the patients randomized to receive itraconazole and 11 (16.7%) of the patients randomized to receive placebo (*P* = .003, by the log-rank test; table 2; figure 1). No patient experienced more than 1 invasive fungal infection. Of the 12 patients with invasive fungal infections, 7 had *C. neoformans* infection (all 7 patients were in the placebo group) and 5 had *P. marneffei* infection (4 patients in the placebo group and 1 patient in the itraconazole group). Two cases of esophageal candidiasis were diagnosed (1 in each study group). The total number of person-weeks of follow-up was 3013.1 for the placebo group and 2906.1 for the itraconazole group. The incidence rates of all invasive fungal infections were 36.5 cases per 100 person-weeks in the placebo group and 3.4 cases per 100 person-weeks in the itraconazole group. Histoplasmosis and other invasive fungal infections were not found in any patient.

### Table 1. Baseline characteristics of 129 HIV-infected patients randomized to receive itraconazole prophylaxis or placebo.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients who received</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Itraconazole (n = 63)</td>
</tr>
<tr>
<td>Sex, no. male/no. female</td>
<td>24/39</td>
</tr>
<tr>
<td>Age, mean years (range)</td>
<td>33.4 (22–51)</td>
</tr>
<tr>
<td>CD4⁺ cell count, cells/µL</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>77.7</td>
</tr>
<tr>
<td>Median</td>
<td>60</td>
</tr>
<tr>
<td>1–99</td>
<td>40 (63.5)</td>
</tr>
<tr>
<td>100–200</td>
<td>23 (36.5)</td>
</tr>
<tr>
<td>Antiretroviral therapy</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>60 (96.2)</td>
</tr>
<tr>
<td>Monotherapy or combination</td>
<td>3 (4.8)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless otherwise indicated. Combination, 2 nucleoside reverse-transcriptase inhibitors.
Table 2. Outcomes of the study among 129 HIV-infected patients randomized to receive itraconazole prophylaxis or placebo.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients who received Itraconazole (n = 63)</th>
<th>Placebo (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive mycoses</td>
<td>1 (1.6)</td>
<td>11 (16.7)</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>0 (0)</td>
<td>7 (10.6)</td>
</tr>
<tr>
<td>Penicilliosis</td>
<td>1 (1.6)</td>
<td>4 (6.1)</td>
</tr>
<tr>
<td>Candida esophagitis</td>
<td>1 (1.6)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Death</td>
<td>12 (19.0)</td>
<td>11 (16.7)</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>48 (76.2)</td>
<td>43 (65.2)</td>
</tr>
<tr>
<td>1 episode</td>
<td>9 (14.3)</td>
<td>8 (12.1)</td>
</tr>
<tr>
<td>&gt;1 episode</td>
<td>6 (9.5)</td>
<td>15 (22.7)</td>
</tr>
<tr>
<td>Discontinuation of therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>2 (3.2)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Patient’s decision</td>
<td>14 (22.2)</td>
<td>9 (13.6)</td>
</tr>
<tr>
<td>Drug interaction with rifampicin</td>
<td>3 (4.8)</td>
<td>3 (4.5)</td>
</tr>
<tr>
<td>Drug resistance</td>
<td>1 (1.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Interim analysis</td>
<td>29 (46.0)</td>
<td>30 (45.5)</td>
</tr>
<tr>
<td>Duration of follow-up, weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>40.3</td>
<td>34.6</td>
</tr>
<tr>
<td>Mean</td>
<td>46.1</td>
<td>45.7</td>
</tr>
<tr>
<td>Range</td>
<td>6–104</td>
<td>5–104</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless otherwise indicated.

Two or more episodes of oral candidiasis occurred in 15 (22.7%) of the patients randomized to receive placebo and in 6 (9.5%) of those who received itraconazole. (P = .04, by the χ² test). No patients developed vaginal candidiasis.

Among the 12 patients with invasive fungal infections, all of those with cryptococcosis and penicilliosis had the diagnoses confirmed by culture. Two cases of esophageal candidiasis were considered probable on the basis of clinical symptoms. Ten invasive fungal infections (6 cases of cryptococcosis in the placebo group, 3 cases of penicilliosis in the placebo group, and 1 case of penicilliosis in the itraconazole group) occurred in patients who had CD4⁺ lymphocyte counts of <100 cells/μL. One patient with esophageal candidiasis in the placebo group had a CD4⁺ lymphocyte count of <100 cells/μL, and another patient in the itraconazole group had a CD4⁺ lymphocyte count of >100 cells/μL. When we stratified the patients according to their CD4⁺ counts, the benefit of itraconazole prophylaxis to prevent all invasive fungal infections was seen only in the subset of patients with CD4⁺ lymphocyte counts of <100 cells/μL (P = .008, by the log-rank test).

Survival. Twelve patients (19.0%) in the itraconazole arm and 11 patients (16.7%) in the placebo arm died during the study (P > .05, by the log-rank test). A total of 13 (20.6%) of the patients in the itraconazole group and 22 (33.3%) in the placebo group either had an invasive fungal infection or died (P = .14, by the log-rank test; figure 2). In the itraconazole group, 3 patients died of P. carinii pneumonia, 2 patients died of chronic diarrhea, and 6 patients died of a wasting disease. One patient with a history of a convulsion died at home, but the blood cultures performed before death were negative for C. neoformans. In the placebo group, 2 patients died of P. carinii pneumonia, 2 patients died of chronic diarrhea, and 6 patients died of a wasting disease. One patient committed suicide and died at home.

Adverse events and compliance. Adverse events that were...
possibly attributed to protocol drugs are shown in table 3. The two treatment groups were similar with respect to the rate of occurrence of symptoms and abnormalities in laboratory measurements ($P > .05$, by the $\chi^2$ test). The most frequently reported adverse events were skin rash, which occurred in 16 (25.4%) of the patients who received itraconazole and 15 (22.7%) of the patients who received placebo. Protocol therapy was discontinued in 1 patient (in the itraconazole arm) because of a skin rash. Concern about hepatotoxicity resulted in the discontinuation of treatment in 2 patients (1 in each study group). There was 1 case of Stevens-Johnson syndrome in the itraconazole group. This patient was also receiving trimethoprim-sulfamethoxazole, which may have been the cause of the adverse event. The patient was asked to stop taking the study drug and trimethoprim-sulfamethoxazole for 3 weeks and was then restarted on the study drug but without trimethoprim-sulfamethoxazole; the rash did not recur.

The overall rate of compliance with study treatment for at least 6 days per week during the follow-up period was 92% in the itraconazole group and 85% in the placebo group ($P > .05$). No patients were lost to follow-up. The study was terminated after the interim analysis because antifungal prophylaxis was highly effective. Eleven cases of invasive mycosis occurred in the placebo group, whereas only 1 case of invasive mycosis occurred in the itraconazole group, which resulted in a significant difference between the treatment groups ($P = .003$, by the log-rank test; power, 84.6%, with a

DISCUSSION

Invasive fungal infections are an important cause of morbidity and mortality in patients with advanced HIV disease. Prospective trials have established that fluconazole, in dosages ranging from 400 mg per week to 200 mg per day, is very effective in preventing invasive cryptococcal infections, especially in patients with CD4$^+$ counts of $<50$–100 cells/μL [16, 18, 19]. The widespread use of fluconazole has probably been a major factor in the observed reduction in the incidence of cryptococcosis in patients with AIDS. However, probably because of the relative infrequency of invasive fungal infections in the United States and European countries, antifungal prophylaxis, unlike prophylaxis for P. carinii pneumonia [20], disseminated Mycobacterium avium complex infection [21], and toxoplasmosis [22], has not been shown to be associated with a survival advantage when it is given to patients with advanced HIV disease [23]. Itraconazole has also been considered to be the primary prophylaxis for histoplasmosis in patients who live in an area where it is endemic, especially those individuals with CD4$^+$ counts of $<100$ cells/μL [17].

Disseminated P. marneffei infection is a common opportunistic fungal infection in patients with advanced HIV infection who live in Southeast Asian countries and southern China [8]. The incidence of this systemic mycoses continues to increase in parallel with the increasing number of cases of HIV infection in these areas [4, 8, 9, 24]. Also, many cases of P. marneffei mycoses have been reported among visitors to Southeast Asia from countries outside of the region [25, 26]. Itraconazole has been recommended as lifelong suppressive therapy in patients infected with HIV who have completed successful treatment of P. marneffei infection [13].

The study was terminated after the interim analysis because antifungal prophylaxis was highly effective. Eleven cases of invasive mycosis occurred in the placebo group, whereas only 1 case of invasive mycosis occurred in the itraconazole group, which resulted in a significant difference between the treatment groups ($P = .003$, by the log-rank test; power, 84.6%, with a
and among HIV-infected patients who had CD4⁺ lymphocyte counts of <100 cells/µL.

The treatment arms in our study did not differ with regard to the occurrence of esophageal candidiasis. This was similar to the results of an itraconazole study published elsewhere [17], but it was different from a study of fluconazole, which showed that prophylaxis was effective in the prevention of esophageal candidiasis [16]. The other itraconazole study showed no reduction of the occurrence of recurrent or refractory oropharyngeal candidiasis, whereas our study showed a significant reduction. One patient in the itraconazole group developed oral candidiasis, but he did not recover after the application of topical antifungal therapy followed by 2 weeks of oral ketoconazole. This patient was discontinued from the study because of resistance to antifungal treatment. Other invasive mycoses, such as histoplasmosis or aspergillosis, were not diagnosed in the subjects in our study.

Several factors might explain these differences between our results and those of the other studies. Our study was restricted to patients with CD4⁺ lymphocyte counts of <200 cells/µL, which is similar to the fluconazole study [16], whereas the other itraconazole study included patients with CD4⁺ counts of <150 cells/µL [17]. The median CD4⁺ lymphocyte count of the group that received itraconazole in our study was 60 cells/µL; in the previous itraconazole study, it was 57 cells/µL. However, in the fluconazole study the median CD4⁺ count was 90 cells/µL. Our study was restricted to 1 city in Thailand where P. marneffei and C. neoformans infections are endemic [4]. The fluconazole study was conducted throughout the United States, and the other itraconazole study was conducted in the southwestern United States, which are areas where histoplasmosis is endemic. In addition, the differences in protocol design may have influenced the outcome of these 3 clinical trials. In the 2 itraconazole trials, itraconazole was compared with a blinded placebo, whereas, in the fluconazole trial, fluconazole was compared with clotrimazole in a nonblinded fashion [16].

Itraconazole was well tolerated by our patients. Serious adverse reactions were rare, and there was no serious hepatotoxicity attributable to the drug. Skin rash and dermatitis appear to be the most common side effects, but the rates of their occurrence were not significantly different between the treatment groups. Most of the skin rashes were related to the use of trimethoprim-sulfamethoxazole to prevent P. carinii pneumonia. In fact, most of the patients improved when trimethoprim-sulfamethoxazole was discontinued or when the patients were desensitized. Our study did not detect a survival benefit associated with itraconazole prophylaxis. However, the study was not powered to detect a survival advantage. This finding is consistent with the results of other studies of primary prophylaxis for systemic fungal infections in patients with advanced HIV infection [16–18]. This may reflect the relatively

### Table 3. Adverse events among 129 HIV-infected patients randomized to receive itraconazole prophylaxis or placebo.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No. (%) of patients who received</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Itraconazole (n = 63)</td>
</tr>
<tr>
<td>None</td>
<td>37 (58.7)</td>
</tr>
<tr>
<td>Skin rash</td>
<td>16 (25.4)</td>
</tr>
<tr>
<td>Mild anemia</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (4.8)</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Alkaline phosphatase level at &gt;5 times the upper limit of normal</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Mild elevated level of aspartate aminotransferase</td>
<td>7 (11.1)</td>
</tr>
<tr>
<td>Mild elevated level of alanine aminotransferase</td>
<td>4 (6.3)</td>
</tr>
</tbody>
</table>

1-sided α level of 0.05). The median duration from the initial treatment to the occurrence of systemic mycoses was 21 weeks (range, 5–56) in the placebo group and 37 weeks in the itraconazole group. At the interim analysis, 29 patients in the itraconazole arm and 30 patients in the placebo arm were being followed up.

The present study shows that penicilliosis and cryptococcosis can be prevented with 200 mg of itraconazole per day. Ours is the third controlled clinical trial of primary prophylaxis for systemic fungal infection that has been reported. In 1 study, the incidence of systemic mycoses was reduced from 10.9%, among the patients who received clotrimazole, to 4.1%, among those who received fluconazole daily, during a median observation period of 35 months, for an overall rate of reduction of 62% [16]. Another study compared itraconazole with placebo and found an incidence of systemic mycoses of 13.0% among patients who received placebo and 4.1% among those who received itraconazole over a median observation period of 16 months, for an overall rate of reduction of 68% [17]. In the present study, itraconazole reduced the incidence of systemic mycoses from 17.5% to 1.5%—a 91% rate of reduction—over a median follow-up period of 9 months.

The estimated rate of invasive fungal infections after 1 year of therapy in the present study was 1.8% in the itraconazole group and 19% in the placebo group, whereas the estimated 1-year rate of invasive fungal infections in the fluconazole study published elsewhere was 1.4% in the fluconazole group and 4.6% in the placebo group [16]. The higher rate of systemic fungal infections in untreated patients with HIV/AIDS in Thailand suggests that the cost benefit of prophylaxis is greater in Thailand than it is in developed countries in Europe and North America. The benefit seen with itraconazole prophylaxis mainly resulted from the reduction in the incidence of cryptococcosis.
low rate of mortality directly attributable to fungal infections compared with other serious opportunistic illnesses in patients with AIDS.

The widespread use of combination antiretroviral therapy, including protease inhibitors, has led to a dramatic decrease in the incidence of new opportunistic infections, including systemic fungal infections [27]. The incidence of esophageal candidiasis has decreased significantly [28]. In addition, oropharyngeal candidiasis is less common and clears rapidly in patients who receive antiretroviral therapy that includes protease inhibitors [29]. Discontinuation of primary prophylaxis for *P. carinii* pneumonia and toxoplasma encephalitis in HIV-infected patients whose CD4+ lymphocyte counts increase to >200 cells/mm3 while they were receiving highly active antiretroviral therapy was suggested by 3 recent studies [30–32]. However, it is important to note that our study was conducted in a developing country where highly active antiretroviral therapy is rarely used to treat HIV-infected patients, which is in contrast to the experience in developed countries.

In conclusion, itraconazole (200 mg per day) was safe, effective, and well tolerated as primary prophylaxis for penicilliosis and cryptococcosis in patients with advanced HIV infection. It is reasonable to consider primary prophylaxis with itraconazole in HIV-infected patients with CD4+ lymphocyte counts of <100 cells/µL who live in developing countries, especially if the patients cannot be treated with highly active combination antiretroviral therapy.

**Acknowledgments**

We are indebted to the Epidemiology Unit, Faculty of Medicine, Khon Kaen University (Khon Kaen, Thailand), for the data management and analysis, and to supporting nurses Kanokporn Panchareon, Jutharat Praparatanapan, and Juthamarth Inchai of the Faculty of Medicine, Chiang Mai University.

**References**


