A Comparison of Itraconazole Versus Fluconazole as Maintenance Therapy for AIDS-Associated Cryptococcal Meningitis


This study was designed to compare the effectiveness of fluconazole vs. itraconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. HIV-infected patients who had been successfully treated (achieved negative culture of CSF) for a first episode of cryptococcal meningitis were randomized to receive fluconazole or itraconazole, both at 200 mg/d, for 12 months. The study was stopped prematurely on the recommendation of an independent Data Safety and Monitoring Board. At the time, 13 (23%) of 57 itraconazole recipients had experienced culture-positive relapse, compared with 2 relapses (4%) noted among 51 fluconazole recipients ($P = .006$). The factor best associated with relapse was the patient having not received fluconazole during the initial 2 weeks of primary treatment for cryptococcal disease (relative risk = 5.88; 95% confidence interval, 1.27–27.14; $P = .04$). Fluconazole remains the treatment of choice for maintenance therapy for AIDS-associated cryptococcal disease. Fluconazole may contribute to the prevention of relapse if used during the first 2 weeks of primary therapy.

Cryptococcal meningitis occurs in 3%–10% of patients with HIV-1 disease [1]. Primary treatment of acute disease consists of high-dose amphotericin B, with or without flucytosine (5-fluorocytosine, 5-FC), for 2 weeks followed by 8 weeks of oral fluconazole (400 mg/d) [2, 3]. Other treatment modalities exist as well, including use of liposomal amphotericin B and combination therapy with fluconazole and flucytosine [4–6]. Even after successful therapy, defined as achievement of negative CSF culture by week 10, relapse of cryptococcal meningial disease occurs in 25%–60% of patients unless long-term maintenance therapy is used [7, 8].

Oral fluconazole has been established as the treatment of choice to prevent relapse of cryptococcal disease in patients with AIDS. In a large comparative trial of daily oral fluconazole therapy (200 mg/d) vs. weekly intravenous amphotericin B (1.0 mg/[kg · wk]), recurrent disease occurred in 3% of fluconazole recipients vs. 22% of those receiving amphotericin B over 1 year [8]. Toxicity was more common in the amphotericin B group, with 15% of patients requiring discontinuation of therapy because of serious adverse events compared with 5% of fluconazole recipients.

See editorial response by Larsen on pages 297–8.

The most common side effects associated with fluconazole consisted of gastrointestinal symptoms (nausea, vomiting) in 22% of patients, skin rashes in 13%, and moderate hepatotoxicity in 11%. The side effects that led to discontinuation of fluconazole included skin rash in three patients, abnormal liver function tests in two, and nausea in one.

Because of the occurrence of significant adverse events among some fluconazole recipients, and the potential emergence of resistant isolates, alternative oral regimens are sought for patients with this disorder. Itraconazole, another triazole antifungal agent, demonstrates significant in vitro activity against Cryptococcus neoformans, yet does not penetrate the blood-brain barrier well, achieving only minimal drug concentrations in the CSF [3]. Nonetheless, animal model studies have demonstrated in vivo activity comparable to that of fluconazole in the treatment of cryptococcal meningitis in mice and rabbits, and phase I and II studies in humans have confirmed the activity of the drug in the treatment of acute AIDS-associated crypto-
coccoc disease (reviewed in [9]). In three pilot studies of itraconazole, 18 (64%) of 36, 11 (38%) of 29, and 5 (42%) of 12 of HIV-infected patients with cryptococcal meningitis were successfully treated [10–12]; these data are comparable to success rates observed with fluconazole therapy [3]. The role of itraconazole as maintenance therapy for patients with HIV-associated cryptococcal disease has not been evaluated. To address this question, a phase III comparative trial of itraconazole vs. fluconazole was initiated, and the results of this study are presented herein.

Methods

Study design. A randomized, double-blind, controlled clinical trial of fluconazole vs. itraconazole as maintenance therapy was done in HIV-infected patients who had been successfully managed with primary therapy for an acute episode of cryptococcal meningitis. Patients were enrolled at 24 study sites throughout the United States. A listing of participating institutions is provided after the text. Patients were eligible for enrollment if they were HIV-infected; were ≥13 years of age; had been successfully treated for acute cryptococcal meningitis, as judged by a negative CSF culture within the 2 weeks before enrollment, and had no clinical evidence of disease; had received at least 6 weeks of therapy for acute disease with either amphotericin B (with or without flucytosine), fluconazole, or itraconazole (use of intrathecal amphotericin B was not allowed); were not receiving histamine, blockers, antacids, rifampin, rifabutin, phenytoin, or phenobarbitol; had acceptable hematologic, metabolic, hepatic, and renal laboratory parameters; and agreed to participate and signed an informed consent document.

Once entered into the trial, the study participants were randomly assigned to receive, in a blinded fashion, either fluconazole (200 mg/d) or itraconazole (200 mg/d), both administered orally with food, orange juice, or a cola drink, and followed up for 12 months. Randomization was stratified by study site and prior therapy for the acute episode. Clinical and laboratory safety evaluations were done at study entry, every 2 weeks for the first 3 months, and every 4 weeks thereafter. CSF was obtained at baseline, at the end of the study, and at any time a patient presented with signs or symptoms suggestive of clinical relapse of cryptococcal disease.

The primary endpoint of the study was successful outcome, defined as no evident disease at the last study visit. Unsuccessful outcome was defined as culture-positive (CSF or serum) relapse with no clinical disease, clinical evidence of relapse with a CSF culture positive for *C. neoformans*, clinical evidence of cryptococcal meningitis with no culture obtained (confirmed by a blinded review panel of the Mycoses Study Group [MSG]), or death due to cryptococcal disease. Autopsies were not routinely done on study patients. Participants who died of other causes were included in the overall survival analysis but were not included as an unsuccessful outcome if the patients had no evidence of cryptococcal disease at their last visit.

Pharmacologic assays. Fluconazole blood levels were determined by using a gas-liquid chromatography technique [13] and itraconazole levels were assayed by HPLC [14] in the laboratory of Dr. Michael Rinaldi (University of Texas Health Sciences Center, San Antonio). Serum samples were collected at each study visit, stored at −20°C, and shipped to the central laboratory for analysis. CSF concentrations of study drugs were not determined.

Statistical considerations. The objective of this study was to show equivalence between fluconazole and itraconazole. The hypothesis, which we hoped to reject, was that the relapse rate in the itraconazole group would be at least 15% greater than the relapse rate in the fluconazole group (expected to be ≤10%). The ability to detect a 15% difference with a one-sided test \( \alpha = .025 \) (two-sided equivalence, .05) and \( \beta = .20 \) (power of 80%) required 65 patients per group [15].

An intent-to-treat analysis of all patients meeting eligibility criteria is presented. Comparability of the treatment regimens was determined by \( \chi^2 \) analysis (two-tailed) for categorical factors and the Kruskal-Wallis two-sample test for continuous factors [16]. A Kaplan-Meier survival analysis with log-rank test was used to compare the two therapies for time to relapse (culture and/or clinical) [17]. Cox’s proportional hazards model was used to assess the effect of potentially confounding variables on the risk of relapse [18]. Factors assessed for their association with a positive CSF culture relapse included age, race (white/nonwhite), sex, AIDS risk group (homosexual/bi-sexual vs. other), all pretreatment CSF laboratory values, history of *Pneumocystis carinii* pneumonia, serum cryptococcal antigen group, maintenance therapy (fluconazole vs. itraconazole), and acute therapy using flucytosine. Factors with a univariate \( P \) value of ≤.30 initially included in the multivariate model were sex, risk group, serum antigen, acute therapy with flucytosine, and maintenance therapy.

Interim analysis was scheduled at the time that 50% of participants had entered the study to ensure that there was no obvious benefit to one of the treatment regimens and to examine overall treatment safety and trial conduct. The O’Brien-Fleming stopping boundaries were used to determine whether one treatment arm was significantly superior to the other [19] while maintaining an overall significance level of 5%. The National Institute of Allergy and Infectious Diseases MSG Data Safety and Monitoring Board (DSMB) served as interim reviewers of the conduct of this study.

Results

Over the 27 months of the study, 118 patients were enrolled, 10 of whom were ineligible because of a CSF culture positive for *C. neoformans* at baseline (5 assigned to each treatment group). Among the remaining 108 eligible patients, 57 assigned to itraconazole and 51 to fluconazole, no differences in baseline demographics were noted between the two treatment groups (table 1). Primary therapy for the acute episode of cryptococcal meningitis prior to entry into this study was similar.
between the fluconazole and itraconazole groups, with the majority of patients (79%) initially receiving amphotericin B, with or without fluycytosine, followed by “consolidation” therapy with either itraconazole (37%) or fluconazole (40%). Primary monotherapy with fluconazole (17%) or itraconazole (4%) was used in 22 of the 108 evaluable patients, and 10 weeks of amphotericin B was used as initial therapy in 2 patients (2%). The median baseline serum and CSF cryptococcal antigen titers were 1:512 and 1:32, respectively, with no significant difference between the treatment groups. No differences between treatment groups were noted in median values for baseline CSF glucose (median, 51 mg/dL), protein (46 mg/dL), WBC count (1 cell/mm³), or opening pressure (185 mm H₂O). The median CD4 cell count was 10/mm³ in each treatment group.

There was only one formal interim analysis planned on this study. For a typical trial aimed at identifying treatment differences, a stopping boundary of 0.005 would be recommended by the O’Brien-Fleming method. Being that this is an equivalence trial, direct extension of this stopping-rule to apply to the case in which equivalence can be determined was not considered. However, the primary aim of the preliminary analysis was to ensure that there was no obvious benefit to one of the treatment regimens and to examine overall treatment safety and trial conduct. Thus, for this equivalence trial, we concluded that an obvious benefit of a treatment would be determined if the O’Brien-Fleming boundary was crossed. The second boundary was violated.

At the planned interim analysis of the study, the DSMB concluded there was insufficient reason to close the study. However, the DSMB recommended that the study statistician should follow the number of relapses carefully and notify the DSMB should an inordinate number of new relapses occur. Four months later, an increasing number of relapses of cryptococcal meningitis prompted a special meeting of the DSMB. The Board recommended that “‘MSG study #25 be terminated . . . based on the data available which indicates definitive superiority of one of the two treatment arms.” The study was stopped after accruing 118 patients.

At the time the DSMB stopped the trial, 13 (23%) of 57 itraconazole recipients had a CSF culture–positive relapse of cryptococcal disease, compared with 2 (4%) of 51 patients who had a CSF culture–positive relapse while receiving fluconazole (table 2; figure 1). All culture–positive relapses were symptomatic. In addition to the culture-positive relapses, 2 additional patients, 1 in each treatment group, were judged by the blinded MSG review panel to have experienced a clinical relapse of cryptococcal meningitis, although with negative CSF cultures. The differences between treatment groups for relapse estimates for both culture-positive and clinical relapses or culture-positive relapses only were 19% (95% CI, 8%–29%). On the basis of these data, the null hypothesis, which stated that fluconazole would be at least 15% better than itraconazole, could not be rejected for clinical or culture relapse (P = .712) or culture-positive relapse only groups (P = .735). Therefore,

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Maintenance regimen</th>
<th>Comparison*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluconazole</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Total (n = 108)</td>
<td>51</td>
<td>57</td>
</tr>
<tr>
<td>Age, median</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Race, white</td>
<td>25 (49)</td>
<td>25 (44)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>48 (94)</td>
<td>52 (91)</td>
</tr>
<tr>
<td>Serum cryptococcal antigen &lt; 1:512</td>
<td>24 (57)</td>
<td>17 (37)</td>
</tr>
<tr>
<td>CSF cryptococcal antigen &lt; 1:32</td>
<td>19 (39)</td>
<td>25 (49)</td>
</tr>
<tr>
<td>CSF WBC count (cells/mm³), median (range)</td>
<td>1.5 (0–73)</td>
<td>1.0 (0–49)</td>
</tr>
<tr>
<td>CSF glucose (mg/dL), median (range)</td>
<td>51 (20–92)</td>
<td>52 (27–83)</td>
</tr>
<tr>
<td>CSF protein (mg/dL), median (range)</td>
<td>45 (16–250)</td>
<td>47 (25–432)</td>
</tr>
<tr>
<td>CSF pressure (mm H₂O), median (range)</td>
<td>180 (0–480)</td>
<td>190 (0–500)</td>
</tr>
<tr>
<td>CD4 cell count (/mm³), median (range)</td>
<td>10 (1–122)</td>
<td>9 (1–100)</td>
</tr>
</tbody>
</table>

NOTE. AmB = amphotericin B; Flu = fluconazole; 5-FC = fluycytosine; Itr = itraconazole. Data are no. (%) of patients unless otherwise indicated.

*1 Treatment comparison used χ² (two-tailed) for categorical comparisons and the Kruskal-Wallis two-sample test (χ² approximation) for continuous variables.

5-FC during primary therapy; P = .71 for treatment comparisons.
Table 2. Patient status at completion or discontinuation of study medication.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total eligible</td>
<td>51</td>
<td>57</td>
</tr>
<tr>
<td>Completed study</td>
<td>13 (26)</td>
<td>28 (50)</td>
</tr>
<tr>
<td>Successfully treated</td>
<td>10 (20)</td>
<td>14 (25)</td>
</tr>
<tr>
<td>Relapsed (CSF culture-positive)</td>
<td>2 (4)</td>
<td>13 (23)</td>
</tr>
<tr>
<td>Relapsed (clinical only)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Prematurely discontinued</td>
<td>38 (74)</td>
<td>29 (50)</td>
</tr>
<tr>
<td>Administrative*</td>
<td>13 (26)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Death²</td>
<td>8 (16)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Intercurrent illness</td>
<td>7 (14)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Chose to discontinue</td>
<td>5 (10)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Adverse experience</td>
<td>1 (2)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Poor compliance</td>
<td>2 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Abnormal laboratory results</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>2 (4)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients.
* Patients still receiving study medication at the time the study was stopped on recommendation of the Data Safety and Monitoring Board were discontinued from the study for administrative reasons.
² Three more patients died after discontinuation of protocol therapy. None of the deaths were due to cryptococcal disease.

equivalence between the two treatment groups could not be established. None of the patients who relapsed died as a result of cryptococcal disease. Overall mortality was 13%, with deaths occurring in 8 (16%) of 51 fluconazole patients and 6 (10%) of 57 itraconazole patients ($P = .809$).

In a univariate analysis to determine predisposing factors associated with the clinical likelihood of relapse, none of the following factors were associated statistically with relapse: age, race, sex, AIDS risk group, baseline serum or CSF cryptococcal antigen titer or any other CSF laboratory parameter, or consolidation therapy with itraconazole (all $P$ values $> .05$). The only factors associated with relapse of cryptococcal disease were the assigned maintenance treatment regimen, itraconazole vs. fluconazole ($P = .005$), and no use of flucytosine during the initial 2 weeks of primary treatment ($P = .01$). Treatment with other primary regimens, for example, amphotericin B followed by fluconazole or itraconazole for the remainder of the primary treatment period (consolidation therapy) or azole alone, did not influence the risk of later relapse while receiving maintenance therapy. Among the 15 patients who relapsed, 2 were initially treated with amphotericin B plus flucytosine and received itraconazole as consolidation therapy; 5 received amphotericin B alone and received fluconazole as consolidation therapy; 3 received amphotericin B alone followed by itraconazole as consolidation therapy; 4 received fluconazole only; and 1 received only itraconazole. Thus, 13% (2 of 15; 95% CI, 2%–40%) of relapsing patients vs. 48% (45 of 93; 95% CI, 37%–59%) of those not relapsing received flucytosine as primary therapy. Moreover, none (0 of 23) of the patients assigned to receive fluconazole who had been treated previously with flucytosine relapsed, compared with 7% (2 of 28; 95% CI, 4%–24%) of fluconazole recipients who did not receive flucytosine. Similarly, 8% (2 of 24; 95% CI, 1%–27%) of the patients assigned to receive itraconazole who had received flucytosine previously relapsed, compared with 33% (11 of 33; 95% CI, 18%–52%) of itraconazole recipients who did not receive previous flucytosine.

Cox’s proportional hazards analysis was done to determine those risk factors independently associated with relapse while adjusting for the covariate of time on protocol. A high serum cryptococcal antigen level at study entry and assigned treatment group (itraconazole or fluconazole) were both suggestive of an increased risk of relapse (relative risk [RR] = 1.166 [95% CI, 0.98–1.38; $P = .08$] and RR = 4.321 [95% CI, 0.98–19.82; $P = .06$]), respectively. However, the only significant factor associated with value for independent predictive relapse was whether the patient received flucytosine during the initial 2 weeks of primary treatment for acute cryptococcal disease, with an RR of 5.88 (95% CI, 1.27–27.14; $P = .04$) for those not receiving flucytosine.

Drug levels were obtained from 43% of fluconazole recipients and 54% of itraconazole recipients. Serum concentrations of itraconazole were consistently lower than fluconazole concentrations, with mean concentrations of 0.644 µg/mL (range, 0.0–9.3 µg/mL) for itraconazole recipients, compared with

Figure 1. Kaplan-Meier survival curve demonstrating relapse-free survival for patients assigned to receive fluconazole (○) vs. itraconazole (■). The difference for relapse-free survival between the two groups was statistically significant ($P = .006$).
9.38 µg/mL (range, 0–22.57 µg/mL) for those receiving fluconazole. However, within each treatment group, neither itraconazole nor fluconazole serum levels predicted failure of maintenance therapy.

The majority of patients in each treatment group (64% fluconazole and 56% itraconazole) reported no side effects due to their assigned study drug. Adverse experiences for each drug were similar to those published previously. Four patients were discontinued from study drug because of toxicity: two patients with skin rash and one each with severe anemia and gastrointestinal toxicity. No unanticipated or life-threatening adverse events were reported for either drug.

Discussion

The purpose of our study was to assess the relative efficacy of itraconazole vs. fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. At the time of initiation of the study, fluconazole at a dose of 200 mg/day was the treatment of choice for preventing relapse among AIDS patients who had been successfully treated for acute cryptococcal disease [8]. Itraconazole was frequently used by AIDS clinicians in some areas of the world because of the drug’s comparable activity to fluconazole in animal models of cryptococcal meningitis and in smaller phase II studies of cryptococcal disease among HIV-infected patients [9–12]. Because of the high success rate of fluconazole in preventing recurrence of cryptococcal disease (>95% success) and the possibility that itraconazole might achieve a similar success rate and potentially less toxicity, this study was designed as an equivalence trial. The null hypothesis stated that fluconazole was at least 15% better at preventing relapse of AIDS-associated cryptococcal meningitis than was itraconazole; if this hypothesis was rejected, the conclusion of our study would be that the two treatments were similar in efficacy. On the basis of the data from our study, the null hypothesis could not be rejected (P = .735); therefore, at the doses used in this study, itraconazole is not as effective as fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. Indeed, the rate of culture-positive relapse remained low (4%) among fluconazole recipients, consistent with the rates observed in previous studies. Thus, fluconazole should remain the therapy of choice in this setting.

Relapse of cryptococcal disease in this patient population was not associated with any difference in overall survival. Indeed, none of the patients who relapsed died of cryptococcal disease. Nonetheless, relapsing cryptococcal meningitis is associated with significant morbidity. Each culture-positive relapse in this study was symptomatic and commonly associated with recurrent headache and fever and, less commonly, with mental status changes. Current recommendations for the treatment of both acute and recurrent cryptococcal meningitis suggest the use of amphotericin B for at least the initial 2 weeks of primary therapy [1]. Therefore, in addition to the signs and symptoms associated with relapse, patients must also contend with the need for intravenous access and the associated costs of hospitalization or intensive home-based therapy.

Several factors may have contributed to the higher rate of relapse among itraconazole recipients. Itraconazole may be inherently less active against C. neoformans than is fluconazole in vivo, although no significant differences are noted between the two agents in animal studies of cryptococcal meningitis or in vitro studies of susceptibility [9]. Drug concentrations of itraconazole in plasma were uniformly lower than those achieved with fluconazole; this difference could not be explained by the use of concomitant medications that interfere with itraconazole absorption or increased drug metabolism. That fact, combined with the relatively low penetration of itraconazole into the CSF through the blood-brain barrier, indicates that pharmacologic factors may play a role in the decreased efficacy of itraconazole in preventing relapse of cryptococcal disease. Yet, in a recently completed two-step clinical trial of primary therapy for acute AIDS-associated cryptococcal meningitis in which itraconazole and fluconazole were compared as consolidation therapy following an initial 2 weeks of induction therapy with amphotericin B (with or without flucytosine), no significant difference in clinical outcome was observed between the two treatment groups. However, a higher proportion of patients receiving fluconazole were culture-negative at the end of the 10 weeks of study [2].

In the multivariate analysis of patients participating in the present study, previous treatment with fluconazole, itraconazole, or amphotericin B followed by either azole agent was not associated with a higher risk of relapse of cryptococcal disease. However, the use of flucytosine during the first 2 weeks of primary therapy for acute cryptococcal meningitis was associated with an almost six-fold lower risk of relapse, regardless of the assigned maintenance treatment regimen. None of the fluconazole recipients who received flucytosine as part of primary therapy relapsed, and only 2 of 13 with itraconazole failure had received flucytosine. The use of flucytosine in the primary therapy study was associated with a higher rate of culture-negativity (51% without flucytosine vs. 60% with flucytosine) after 2 weeks of therapy [2]. Many possible factors may be responsible for this observation, including a selection bias in favor of healthier patients (e.g., without neutropenia or gastrointestinal disease) assigned to receive flucytosine concomitant with use of more potent antiretroviral therapy (not controlled for in this study). However, the use of flucytosine during the first 2 weeks of primary therapy may lower total body fungal burden of C. neoformans, resulting in both an improvement in culture-negative status achieved during acute therapy and a decreased risk of relapse over time, regardless of whether itraconazole or fluconazole is used as maintenance therapy.

On the basis of previously conducted studies combined with data acquired in our study, fluconazole remains the treatment of choice as maintenance therapy to prevent relapse in AIDS patients who have been successfully treated for acute cryptococcal meningitis. Although itraconazole, at the doses used in
this study, is less effective than fluconazole as maintenance therapy, the drug has demonstrated activity in the treatment of cryptococcal disease [2, 10–12] and may play a role as second-line maintenance therapy for those who are unable to tolerate fluconazole. Evaluation of higher doses of itraconazole as maintenance therapy may be warranted. Perhaps the most striking finding in this study is the association of flucytosine use during primary therapy with a significantly lower likelihood of relapse for the patients enrolled in our study. When combined with the data from the recently completed study of primary therapy for acute cryptococcal meningitis [2], our data indicate that flucytosine should be used routinely as part of the primary treatment regimen for cryptococcal disease in AIDS patients.

Study Group Members

Members of the NIAD Mycoses Study Group, the AIDS Clinical Trials Group, Janssen Research Foundation, and the investigators who contributed to this study are as follows.


AIDS Clinical Trials Group: University of California, San Francisco: M. Jacobson, D. Gray, R. Coleman; Washington University, St. Louis: W. Powderly, J. Voorhees, M. Klebert, M. Royal; Beth Israel Medical Center: D. Mildvan.

Independent sites. San Diego Community Research Group: D. Pearce; University of Kansas School of Medicine: S. Gagnon; Miami VA Medical Center: G. Dickinson; St. Francis Memorial Hospital: T. Chew; Nalle Clinic: J. Jemsek; Denver Community Program for Clinical Research on AIDS: R. Reves; The Permanente Medical Group: J. Fessel; and Austin Infectious Diseases Consultants: J. T. Bagwell.

Janssen Research Foundation. B. L. Moskovitz, B. Wiesinger, D. Cosmetos.

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References