MAJOR ARTICLE

Single-Dose Fluconazole versus Standard 2-Week Therapy for Oropharyngeal Candidiasis in HIV-Infected Patients: A Randomized, Double-Blind, Double-Dummy Trial

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Background. Oropharyngeal candidiasis is the most common opportunistic infection affecting patients with human immunodeficiency virus (HIV) infection. Because of convenience, cost, and reluctance to complicate antiretroviral treatment regimens, single-dose fluconazole may be a favorable regimen for treatment of moderate to severe oropharyngeal candidiasis. We conducted a prospective, randomized, double-blind, placebo-controlled trial to compare the clinical and mycological responses, relapse rates, and safety of a single 750-mg dose and a 14-day course of treatment with fluconazole.

Methods. A total of 220 HIV-infected patients with clinical and mycological evidence of oropharyngeal candidiasis were randomly assigned in a 1:1 ratio to receive either a 750-mg single dose of orally administered fluconazole (110 patients) or 150 mg of orally administered fluconazole once per day for 2 weeks (110 patients). The primary efficacy analysis was based on clinical and mycological responses at the end of treatment. Secondary parameters were safety and relapse rate.

Results. Single-dose fluconazole was equivalent to a 14-day course of fluconazole in achieving clinical and mycological cure, with clinical cure rates of 94.5% and 95.5%, respectively (odds ratio, 0.825; 95% confidence interval, 0.244–2.789; $P = .99$), and mycological cure rates of 84.5% and 75.5%, respectively (odds ratio, 1.780; 95% confidence interval, 0.906–3.496; $P = .129$). Drug-related adverse events were uncommon and were not different between the treatment groups.

Conclusion. A single dose of 750 mg of fluconazole was safe, well tolerated, and as effective as the standard 14-day fluconazole therapy in patients with HIV infection and acquired immunodeficiency syndrome who had oropharyngeal candidiasis coinfection.

Trial registration. ClinicalTrials.gov identifier: NCT00553137.

Oropharyngeal candidiasis (OPC) has been reported to occur in up to 90% of subjects infected with HIV; therefore, OPC is the most commonly encountered opportunistic infection in these patients [1, 2]. As a result of HAART, the incidence and prevalence of most opportunistic infections has greatly decreased [3, 4]. However, OPC remains the most frequent HIV-associated oral disease in sub-Saharan Africa, where access to HAART is still limited [5, 6].

The occurrence of OPC is associated with low CD4 T lymphocyte numbers, high viral loads, and disease progression [1, 4, 7], but at the same time, OPC tends to be one of the first opportunistic infections seen in patients with CD4 T lymphocyte levels <200 cells/mm^3.

In Tanzania, fluconazole, at a dose of 150 mg once per day for 2 weeks, is included in the guidelines for

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the treatment of OPC in HIV-infected patients [8]. Treatment with fluconazole achieved complete clinical response in 87%–100% of patients and was effective in obtaining a mycological cure in 53%–87% of patients after a 7-, 14-, or 28-day course of therapy [9– 14]. Single-dose fluconazole (150 mg) therapy has been reported to lead to complete clinical response in 75%–100% of patients and mycological eradication of *Candida* species in 6%–41%, whereas 30%–38.5% of patients experienced relapse during follow-up after treatment [15–17]. However, the single-dose fluconazole studies involved a limited number of patients, may have been performed with a suboptimal fluconazole dose, and did not make use of a randomized study design. Because of convenience, cost, and reluctance to complicate antiretroviral treatment regimens, single-dose fluconazole may be a more favorable regimen for treatment of HIV-associated OPC than the recommended dose of 150 mg of fluconazole once per day, administered orally, for 2 weeks [8]. The aim of our study was to determine whether a single dose of 750 mg of fluconazole was as effective as the standard 14-day course of fluconazole for the treatment of OPC in HIV-infected patients.

PATIENTS AND METHODS

Patients. Participants were recruited at the HIV clinic of the Muhimbili National Hospital (Dar es Salaam, Tanzania) from November 2006 through December 2007. Patients were eligible for the study if they met the following criteria: ⩾18 years of age, with documented HIV infection (as determined by positive ELISA results and confirmed by Western-blot analysis); clinical symptoms of OPC; characteristic visual lesions; and microbiological confirmation.

Patients were excluded from study participation for any of the following reasons: ongoing or previous topical or systemic antifungal therapy within 3 days before study enrollment; a history of allergy to azole derivatives; abnormal results of liver function tests, defined as alanine aminotransferase (ALT), aspartate aminotransferase (AST), or direct or total bilirubin levels >3 times the upper limit of normal; evidence of significant hepatic or renal disease within 2 months before study enrollment; inability to tolerate oral drug administration; current pregnancy or breast feeding; life expectancy of <4 weeks; current participation in another clinical trial; current treatment with drugs that are known to interact with fluconazole; documented systemic fungal infection; and symptoms suggestive of esophageal candidiasis. Also, patients with a history of alcohol abuse, drug addiction, psychiatric disorders, inability to cooperate, and poor motivation were excluded from the study.

The study was performed in accordance with good clinical practices and the principles set forth in the World Medical Assembly Declaration of Helsinki. The Ethics Committee of the Muhimbili University of Health and Allied Sciences and Muhimbili National Hospital approved the study protocol, and each patient signed a written statement of informed consent before enrollment and receipt of study medication.

Study design and procedures. We conducted a prospective, randomized, double-blind, double-dummy trial to compare the clinical and mycological responses, relapse rates, and safety of 2 regimens of fluconazole therapy for treatment of OPC in HIV-infected patients. Eligible patients were randomized in a 1:1 ratio to 1 of the 2 treatment groups on the basis of a predefined randomization code. The pharmacist, who dispensed the medicine, held the randomization code, and neither the evaluator nor the patients had knowledge of what treatment was given. Patients were randomized to receive oral treatment of a single dose of 750 mg (5 tablets of 150 mg) of fluconazole and 1 placebo tablet once per day for 2 weeks or a standard regimen of orally administered fluconazole (1 tablet of 150 mg) once per day for 2 weeks [8]. These patients also received 5 placebo tablets on the first day of therapy. After the baseline visit on day 0, visits were scheduled for day 3 or 4, day 6 or 7, day 14 (end of therapy), and day 42 (follow-up). At baseline, a structured standard questionnaire was used to systematically collect demographic information, medical history, treatment history, concomitant illness(es), and current treatments. General and oral examinations were performed at baseline and at subsequent visits, with use of a standard oral examination method [18]. On days 3 or 4, 6 or 7, and 14, patients were examined and assessed for signs and symptoms, adverse drug effects, and compliance with the regimen. Clinical adverse effects were recorded at each visit and were graded as mild, moderate, or severe. Patients were asked to bring the remaining study medication during follow-up visits, and pill count was performed by a pharmacist and the result was recorded. Follow-up examinations in both treatment groups were performed on day 42 or earlier if patients experienced relapse. A single examiner evaluated all patients throughout the trial.

Oral swab specimens were obtained at baseline for diagnosis, on day 14 for mycological evaluation, and on day 42 or earlier when there was evidence of a relapse of OPC. Specimens were obtained by firmly swabbing the lesion site with a sterile cotton-wool swab [19]. The swabs were sent immediately to the laboratory for microbiological confirmation. Isolates were identified to the species level, and antifungal susceptibility to fluconazole was assessed according to the guidelines of the Clinical and Laboratory Standards Institute [20].

Blood samples were obtained at baseline for determination of basic hematology, for biochemical tests, and to assess CD4 and CD8 cell counts. Blood samples were also obtained at the end of treatment (day 14) for hematology and biochemical tests. Also, blood samples from 25 randomly selected patients (13 patients receiving a single-dose and 12 receiving standard therapy) were obtained at baseline, on day 1, on day 4 or 5, on day 7, and on day 14, for determination of fluconazole plasma

concentrations. Fluconazole plasma concentrations were measured by means of protein precipitation followed by tandem–mass spectrometric detection, with use of internal standard and spiked-pool serum samples as controls.

Efficacy evaluations. The efficacy of each of the 2 treatment regimens was assessed by comparison of primary outcome measures that included clinical and mycological responses at the end of treatment. The severity of signs and symptoms at baseline and at the end of therapy and the extent of lesions were graded and scored. Lesions were monitored with assistance of oral-cavity diagrams for estimating lesion sizes and locations. The overall OPC clinical score based on signs, symptoms, and extent of lesions was graded as absent (no symptoms or lesions present), mild (scattered, nonconfluent lesions >2 mm in size), moderate (multiple lesions >2 mm in size), and severe (extensive, confluent lesions). Clinical responses were defined as cured (complete resolution of lesions, signs, and symptoms of OPC), improved (a reduction in the number of lesions and symptoms but persisting typical oropharyngeal lesions), or failed (no resolution of signs and symptoms; i.e., either no change or OPC that has progressed). In evaluation of results of mycological cultures on day 14, any growth of *Candida* species was classified as mycological treatment failure.

Secondary outcome measures included relapse of OPC and safety of the 2 fluconazole regimens. Relapse was defined as an initial cure followed by reappearance of symptoms, clinical signs of OPC, and/or confirmation by positive yeast culture during a follow-up period of 4 weeks after the end of treatment. Patients with a clinical evaluation of "cured" on day 14 were considered to have a successful outcome and were eligible for the follow-up phase.

Safety evaluations. Safety and tolerability were assessed by the observation of adverse events. Baseline and posttreatment blood investigations included biochemical tests and full blood count and were compared between the 2 regimens.

Statistical analysis. This trial was designed to have 80% power to demonstrate equivalence (within 20%) in clinical response between the 2 fluconazole regimens, and 95% CIs of the difference in response rates were used in determination of equivalence. Data were analyzed using SPSS, version 14.0 (SPSS). Comparisons between the 2 treatment groups were performed using Student's *t* test whenever continuous variables were normally distributed; for skewed distributions, the Mann-Whitney *U* test was used. Noncontinuous categorical and ordinal variables were analyzed using Fisher's exact test. The results of posttreatment liver function test and full blood count were compared (between the 2 fluconazole regimens) by analysis of covariance, with the pretreatment test result as a covariate. All statistical tests were 2 tailed, and exact probabilities were reported for each test.

RESULTS

Demographic baseline and clinical characteristics. A total of 220 patients were randomized to either the single-dose fluconazole group (110 patients) or the 14-day fluconazole group (110 patients). The baseline clinical and demographic characteristics were similar in both treatment groups (table 1). The median CD4 cell count, World Health Organization HIV clinical stage, and OPC clinical score were similar in all treatment groups. More than one-half of patients in both treatment groups were not receiving antiretroviral therapy at baseline. Eighty (36.4%) of 220 patients were receiving HAART, which comprised combinations as follows: stavudine, lamivudine, and nevirapine in 57 patients (71.3%); zidovudine, lamivudine, and efavirenz in 20 patients (25.0%); and zidovudine, lamivudine, and nevirapine in 2 patients (2.5%). One patient (1.3%) was receiving stavudine, didanosine, and ritonavir-lopinavir. More than one-half of the patients (40 patients; 55%) had received HAART for <3 months. With regard to previous exposure to azole antifungal agents, the proportions were also equal between the 2 treatment groups. As measured by the pill counts, all 220 patients were highly compliant with the study treatment regimens.

Baseline mycological findings and susceptibility testing. *Candida albicans* comprised 90% of pretreatment isolates, and there were no statistically significant differences in species distribution and MICs of fluconazole between the treatment groups at baseline ($P = .823$).

Efficacy Analysis

All 220 enrolled patients were evaluable for clinical and mycological responses.

Clinical efficacy. In the 14-day fluconazole group, 105 patients (95.5%) were considered to be clinically cured, 4 patients (3.6%) had improved clinically, and 1 (0.9%) experienced treatment failure. In the single-dose fluconazole group, 104 patients (94.5%) were considered to be clinically cured, 2 patients (1.8%) had improved clinically, and 4 patients (3.6%) experienced treatment failure. The difference in clinical success between the 2 treatment groups was not significant (OR, 0.825; 95% CI, 0.244–2.789; $P = .99$). There was a significant association between higher MICs for fluconazole at baseline and poor clinical outcome ($P = .016$). There were no significant associations between clinical outcome and CD4 cell count and previous azole exposure ($P = .089$ and $P = .805$, respectively). Ninety patients with recurrent OPC at baseline (72.2%) had a history of 1 previous episode of OPC, and the range of recurrences was 1–4 episodes. There were no statistically significant associations between clinical outcome and number of previous OPC episodes.

Mycological efficacy. At baseline, all enrolled patients had positive results of both microscopy and culture. At the end of

Table 1. Patient demographic and baseline characteristics.

Variable	Fluconazole treatment group			P[a]	Test
	14 Days (n = 110)	Single dose (n = 110)	All patients (n = 220)		
Sex					
Male	27 (24.5)	26 (23.6)	53 (24.1)	.99	F
Female	83 (75.5)	84 (76.4)	167 (75.9)		
Mean age, years ± SD (range)	35 ± 8.1 (22–75)	34 ± 7.9 (19–63)	34.8 ± 8.0 (19–75)	.130	*t*
Body mass index,[b] mean ± SD (range)	20.9 ± 4.0 (13.1–38.1)	21.0 ± 3.3 (13.6–32.4)	20.9 ± 3.7 (13.1–38.1)	.908	*t*
Median CD4 cell count, cells/mm^3 (range)	100 (3–689)	88 (2–614)	100 (2–689)	.578	MW
World Health Organization stage					
III	86 (78.2)	94 (85.5)	180 (81.8)	.221	F
IV	24 (21.8)	16 (14.5)	40 (18.2)		
OPC clinical score					
Mild	6 (5.5)	4 (3.6)	10 (4.5)	.835	F
Moderate	73 (66.4)	76 (69.1)	149 (67.7)		
Severe	31 (28.2)	30 (27.3)	61 (27.7)		
History of OPC					
Primary	66 (60.0)	64 (58.2)	130 (59.1)	.891	F
Recurrent	44 (40.0)	46 (41.8)	90 (40.9)		
Pretreatment isolates					
Candida albicans only	100 (90.9)	98 (89.1)	198 (90.0)	.823	F
Candida krusei only	4 (3.6)	2 (1.8)	6 (2.7)		
Candida glabrata only	2 (1.8)	3 (2.7)	5 (2.3)		
Candida tropicalis	1 (0.9)	4 (3.6)	5 (2.3)		
Candida kefyr	2 (1.8)	…	2 (0.9)		
C. albicans and *C. krusei*	…	2 (1.8)	2 (0.9)		
C. glabrata and *C. krusei*	1 (0.9)	1 (0.9)	2 (0.9)		
Prior azoles antifungal exposure	56 (50.9)	56 (50.9)	112 (50.9)	.99	F
Use of HAART					
Yes	39 (35.5)	41 (37.3)	80 (36.4)	.889	F
No	71 (64.5)	69 (62.7)	140 (63.6)		

NOTE. All data are no. (%) of patients, unless otherwise indicated. F, Fisher's exact test; MW, Mann-Whitney *U* test; OPC, oropharyngeal candidiasis; *t*, Student's *t* test.

[a] A 14-day course of fluconazole compared with a single dose of fluconazole.

[b] Calculated as weight in kilograms divided by the square of height in meters.

treatment, mycological cure was achieved in 83 patients (75.5%) in the 14-day fluconazole group and in 93 patients (84.5%) in the single-dose fluconazole group. Mycological failure was observed in 27 patients (24.5%) in the 14-day fluconazole treatment group and in 17 patients (15.5%) in the single-dose fluconazole group. There was no significant difference in mycological cure rates between patients receiving the 2 fluconazole regimens (OR, 1.780; 95% CI, 0.906–3.496; $P = .129$). The mean MICs of fluconazole for these isolates were not significantly different between the 2 treatment groups ($P = .318$). Overall, in 11 patients, clinical cure was not achieved, and for all of these, *Candida* species were isolated from patient specimens at baseline and on day 14. In 33 patients (15.0%), clinical cure was obtained despite persistent positive culture results on day 14 (mycological failure).

Relapse. Relapse was analyzed in the 194 patients who completed the follow-up phase of the study. The reasons for discontinuation during the follow-up phase were death related to advanced stage of HIV infection and AIDS (4 patients), loss to follow-up (11 patients), and administration of additional treatment for OPC because of failure of the primary therapy (11 patients). No difference was observed in relapse rates between the evaluable patients from the 14-day and single-dose fluconazole groups (OR, 1.073; 95% CI, 0.456–2.523; $P = .99$) (table 2). The average time to relapse after clinical cure was 20 days (range, 7–30 days) in the 14-day fluconazole group, compared with 18 days (range, 14−30 days) in the single-dose fluconazole group. Twenty-two (91.7%) of 24 patients who experienced relapse during follow-up had CD4 cell counts <200 cells/mm^3, 16 (66.7%) had CD4 cell counts <100 cells/mm^3, 17 (70.8%) were not receiving HAART, and 14 (58.3%) had had previous episodes of OPC.

Fluconazole plasma concentrations. The mean plasma fluconazole concentrations on days 1, 4 or 5, 7, and 14 in the 14-day fluconazole group were 4.18, 6.88, 7.94, and 7.62 mg/L, respectively; for the single-dose fluconazole group, the concentrations were 13.35, 5.46, 1.37, and 0.32 mg/L, respectively (figure 1). There were statistically significant differences in mean plasma concentrations between the 2 treatment groups on days 1, 7, and 14 but not on day 4 or 5 (figure 1). Fluconazole exposure was greater for patients who received the single dose of fluconazole, at least until day 4 or 5, compared with those who received the 14-day course.

Safety analysis. Overall, adverse events were mild, and no differences in frequency of adverse events were noted between patients in the 2 treatment regimens. Adverse events were reported in 6 patients (5.5%) in the 14-day fluconazole group; all events were gastrointestinal. In the single-dose fluconazole group, adverse events were reported in 8 patients (7.3%); 6 reported nausea, vomiting, abdominal pain, and/or diarrhea, 1 patient had headache, and 1 patient had heart palpitations and dizziness. Because most of the study patients were in an advanced stage of HIV infection and AIDS, abnormalities in full blood count and liver function tests were common (table 3). However, no clinically significant changes in full blood count and liver function parameters were observed after treatment in either of the 2 treatment groups, with the exception of 1 patient (0.9%) in the single-dose fluconazole group in whom ALT and AST levels increased to 262 U/L and to 377 U/L, respectively, without symptoms; later, ALT and AST levels returned to normal. This patient was taking the study drug while HAART (stavudine, lamivudine, and nevirapine) was initiated concomitantly. None of the patients discontinued therapy because of adverse events related to the study drug.

DISCUSSION

The results of the present study demonstrate that a single-dose regimen of 750 mg was as effective as a standard 14-day fluconazole regimen in achieving clinical and mycological cure in the treatment of OPC in patients with HIV infection and AIDS.

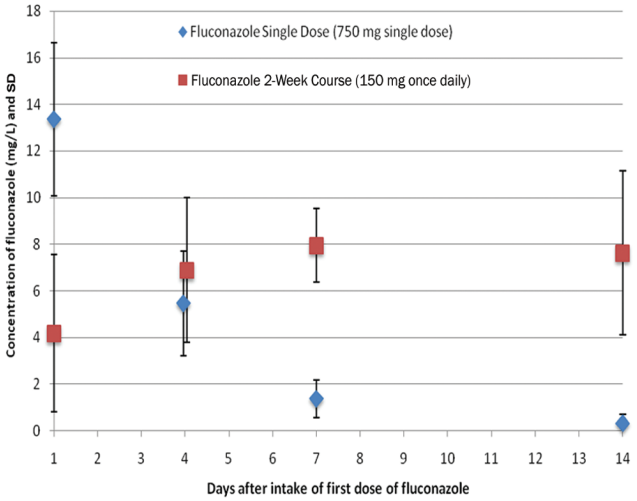

Figure 1. Plasma fluconazole concentrations in HIV-positive patients with oropharyngeal candidiasis who received treatment with a single dose (750 mg) or a 14-day course (150 mg once per day) of fluconazole. Plasma concentrations were significantly different on days 1, 7, and 14 ($P < .01$) but not on day 4 ($P = .23$).

These results are in agreement with previous studies conducted to assess the clinical and mycological efficacy of 14-day fluconazole for management of OPC in patients with HIV infection and AIDS, which demonstrated 87%–100% effectiveness in obtaining a complete clinical response [9–14]. The mycological cure rate, with a single-dose treatment of 750 mg fluconazole, was much higher (84.5%) than the 6%–41% mycological cure rates reported elsewhere [15–17] that made use of a single dose of 150 mg of fluconazole. *C. albicans* was the species most commonly isolated at baseline, at the end of therapy, and during OPC recurrence for both treatment groups. In addition, plasma fluconazole concentrations on day 1 were significantly higher in patients receiving single-dose fluconazole; however, until day 4 or 5, fluconazole exposures were similar in both treatment groups. In this trial, similar efficacy was found in maintaining a symptom-free period after the end of therapy in both treatment groups. OPC relapses were observed

Table 2. Evaluation of oropharyngeal candidiasis (OPC) relapse during the follow-up period after fluconazole treatment.

	No. (%) of patients		
Variable	14-Day course of fluconazole ($n = 100$)	Single dose of fluconazole ($n = 94$)	Full cohort ($n = 194$)
OPC relapse	12 (12)	12 (12.8)	24 (12.4)
No relapse	88 (88)	82 (87.2)	170 (87.6)

NOTE. *n* Values are numbers of evaluable patients. OR, 1.073; 95% CI, 0.456–2.523; $P = .99$ (Fisher's exact test) for the difference in OPC relapse rates between patients receiving a 14-day course (150 mg once per day) and patients receiving a single dose (750 mg) of fluconazole.

Table 3. Baseline and posttreatment hematology and biochemical test results of HIV-positive patients with oropharyngeal candidiasis treated with a single dose (750 mg) and a 14-day course (150 mg once per day) of fluconazole.

	Mean results by fluconazole treatment group				
	14 Days		Single dose		
Variable	Baseline	Day 14	Baseline	Day 14	P^a
Hematology					
Leukocytes, μL $\times 10^3$	5.04	4.61	5.05	4.52	.612
Erythrocytes, μL $\times 10^6$	3.99	4.04	4.03	4.08	.893
Hemoglobin, g/dL	10.49	10.76	10.51	10.91	.740
Platelets, μL $\times 10^3$	292.1	286.4	303.6	300.4	.428
ESR, mm/h	72	49	68	51	.260
Biochemical					
ALP, U/L	109.7	109.3	97.7	102.8	.955
ALT, U/L	24.1	27.6	23.5	31.3	.134
AST, U/L	33.2	33.6	33.7	36.6	.320
BilD, mmol/L	3.7	3.1	3.23	3.4	.185
BilT, mmol/L	7.4	6.4	7.14	6.39	.987
LD, U/L	277.8	279.3	281.7	275.4	.535
Urea, mmol/L	3.6	3.4	3.7	3.6	.109
Uric acid, mmol/L	0.29	0.24	0.27	0.26	.360

NOTE. ALP, alkaline phosphatase; AST, aspartate aminotransferase; BilT, total bilirubin; BilD, direct bilirubin; ESR, erythrocyte sedimentation rate; LD, lactate dehydrogenase.

[a] Based on the *F* test, which is based on the linearly independent pairwise comparisons among the estimated marginal means.

(12.4%) in both treatment groups, with the majority occurring among patients who had low CD4 cell counts (<200 cells/mm^3), had previous episodes of OPC, and were not receiving HAART. Antifungal prophylaxis for these patients may be considered in addition to the provision of HAART [12, 21]. In addition, both treatments had acceptable treatment tolerability and safety. However, it was demonstrated that ALT and AST levels after initiation of HAART among HIV-infected patients who concurrently received nevirapine and fluconazole were not different from levels of those who received nevirapine-based HAART without fluconazole [22]. The elevation of ALT and AST levels that was observed in 1 patient in the single-dose group in the present study could be attributable to the effect of the nevirapine component of the regimen, because liver toxicity caused by nevirapine is well known [23, 24].

In the present study, reduced susceptibility to fluconazole at baseline was found to be a significant factor associated with treatment failure, irrespective of the treatment regimen used. For fluconazole, several studies have shown a correlation between in vitro susceptibility and treatment outcome [25–27], and interpretative breakpoints have been established [28]. Our study also indicates that MIC testing of isolates at the time of OPC diagnosis might be useful in patient management for identification of those patients with an increased probability of experiencing treatment failure.

The high percentage of patients receiving HAART who presented with OPC may suggest that the HAART regimens were not effective. However, a recent study that was conducted at the same hospital as our study and that involved some of our patients found high patient compliance to therapy and extremely low rates of resistance to HAART [29]. The most plausible explanation is that more than one-half of the patients (55%) were receiving HAART for <3 months, and the majority (86.3%) had low CD4 cell counts (<200 cells/mm^3).

The use of a single high dose of fluconazole for the treatment of OPC in patients with HIV infection and AIDS presents the advantages of simplicity and convenience, thus improving compliance and reducing the cost of therapy. A single dose of five 150-mg tablets is less costly than fourteen 150-mg tablets taken over a 14-day course and, therefore, could be used, especially in resource-limited settings like in sub-Saharan Africa. In addition, adminstration of the single-dose therapy can be observed directly by medical personnel, thereby assuring patient compliance.

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