

Comparative Efficacy of Topical Therapy With a Slow-Release Mucoadhesive Buccal Tablet Containing Miconazole Nitrate Versus Systemic Therapy With Ketoconazole in HIV-Positive Patients With Oropharyngeal Candidiasis

Jens Van Roey, MD,* Myriam Haxaire, DDS,* Moses Kanya, MD,† Isaac Lwanga, MD,†
Elly Katabira, MD†

Abstract: This randomized comparative study assessed the efficacy and safety of a 10-mg once-daily topical regimen of miconazole nitrate mucoadhesive buccal tablet (n = 178) versus a 400-mg once-daily systemic regimen of ketoconazole (n = 179) in HIV-positive patients with oropharyngeal candidiasis. A total of 357 patients were treated for 7 or 14 days depending on response after 7 days of treatment. Clinical response was the primary outcome variable, and secondary outcomes included microscopy, time to cure, symptom scores, and safety outcomes. A per-protocol analysis of 332 patients demonstrated that miconazole nitrate was not statistically significantly inferior to ketoconazole treatment. At day 7, the clinical response rate was 135 of 156 (87%) for miconazole nitrate and 137 of 153 (90%) for ketoconazole (90% confidence interval of the treatment difference: [-9%; 3%]). At the end of treatment, dysphagia was 1% in both groups. Microscopic findings paralleled the clinical results. The mucoadhesive tablet was generally well tolerated. A higher incidence of gastrointestinal disorders and drug-related adverse events was seen during ketoconazole treatment. The low-dose 10-mg miconazole mucoadhesive tablet is not inferior to systemic antifungal treatment with ketoconazole in the treatment of AIDS-related oropharyngeal candidiasis with and without dysphagia. It provides the first and only once-daily topical treatment option and should therefore be considered in first-line therapy for this condition, particularly in resource-poor settings, where ease of use can help to guarantee the success of therapy.

Key Words: miconazole nitrate; oropharyngeal candidiasis; mucoadhesive tablet

(*J Acquir Immune Defic Syndr* 2004;35:144–150)

HIV/AIDS represents a major health challenge, with an estimated worldwide incidence of 5 million (as of 2001) infections, 3.5 million of which are on the African continent alone.¹ Oral lesions cause considerable morbidity in HIV-

positive patients. Oropharyngeal candidiasis is the most common oral manifestation of HIV infection, reflecting progressive immunodeficiency. Oral *Candida* infections are observed in more than 90% of HIV-positive patients at some time during their disease, particularly in advanced immunosuppression.^{2–8} Among hospitalized African AIDS patients, point prevalences of 45% have been reported.^{9,10} The most common causative pathogen is *Candida albicans*, but other species such as *C. glabrata*, *C. tropicalis*, and *C. krusei* are also found.

In the *Guidelines for the Clinical Management of HIV Infection in Adults*, the World Health Organization (WHO) Global Project on AIDS (GPA) recommended 100,000 IU of nystatin orally 3 times daily for 7 days or gentian violet as a first-line treatment for oropharyngeal candidiasis.^{11,12} Ketoconazole at a dose of 400 mg daily for 2 weeks is recommended in cases of suspected esophageal candidiasis.^{11,12} In further revisions to the WHO essential drug list, fluconazole is listed as a model “azole” compound, with various drugs serving as alternatives. The following topical agents are listed as alternatives: nystatin (tablet, lozenge, or pessary), griseofulvin (capsule or tablet), and complementary drugs (flucytosine and potassium iodide).

Other topical therapies for the treatment of oropharyngeal candidiasis include miconazole (in the form of buccal gels or tablets), clotrimazole (in the form of lozenges or troches), and amphotericin B (in the form of lozenges or rinses). The treatment regimen for all topical forms is repeated administration (ie, 3–5 times per day). The requirement for multiple applications is related to the relatively short intraoral exposure to topical antifungal agents as a result of rapid drug clearance via salivary production. The intraoral pharmacokinetics were documented for a miconazole-containing buccal gel, which provided maximal miconazole salivary concentrations immediately after application, followed by rapid clearance from the oral cavity.^{13–15}

To prolong the residence time of miconazole and to maintain fungicidal levels throughout the day, a mucoadhesive buccal tablet with slow-release properties was developed.¹⁵ Despite the reduction in drug dose, the intraoral exposure in-

Received for publication July 7, 2003; accepted November 6, 2003.

From *Tibotec BVBA, Mechelen, Belgium; and †Makerere University, New Mulago Hospital, Kampala Uganda.

Funded by the Tibotec Pharmaceuticals Limited, Dublin, Ireland.

Reprints: Jens Van Roey, Tibotec BVBA, Gen. De Wittelaan 11B-3, 2800 Mechelen, Belgium (e-mail: jvroey@tibbe.jnj.com).

Copyright © 2004 by Lippincott Williams & Wilkins

creased more than 5 times with 1 application of the mucoadhesive tablet versus 4 applications of the buccal gel. It is anticipated that ease of use associated with once-daily administration will facilitate patient compliance. Furthermore, the enormous reduction in drug dose (8.69 mg of miconazole compared with 240 mg associated with application of gel 4 times daily) precludes the risk of systemic exposure or systemic drug-drug interactions with drugs commonly used in HIV patients.¹⁶

This study assessed the efficacy of a topically active mucoadhesive buccal slow-release tablet containing 10 mg of miconazole nitrate compared with systemic treatment with ketoconazole tablets (400 mg) once daily in the treatment of oropharyngeal candidiasis in patients with HIV infection. Although nystatin has been recommended as first-line therapy, ketoconazole was selected as a comparator based on the standard of care at the study location (Uganda).

METHODS

Male and female presumed HIV-seropositive patients with clinical signs of oropharyngeal candidiasis who were aged at least 18 years, had a life expectancy of >6 months, and were living within 10 km from the study sites were eligible. Consistent with the standard of care on site, oropharyngeal candidiasis was diagnosed by clinical examination. Additionally, the presence of mycelia as observed by microscopic evaluation was documented. Patients who had received antifungal therapy within 2 weeks of entry (except Gyno-Daktarin, nystatin cream, or pessaries applied locally for the treatment of vaginal candidiasis), pregnant female patients, and patients with a history of known allergy or intolerance to the trial drugs were excluded. Concomitant use of rifampicin, rifabutin, isoniazid, phenobarbital, phenytoin, carbamazepine, methylprednisolone, terfenadine, astemizole, or cisapride was not allowed. Patients with a history of significant hepatic abnormalities as judged by the principal investigator or with clinical evidence of hepatic disease within 2 months before beginning protocol-specific procedures could not be entered. Concomitant use of all broad-spectrum antibiotics was allowed, because treatment of opportunistic infections in this patient population is common (approximately 70% of patients were taking antibiotics during the study period).

The study was approved by an independent ethics committee (the AIDS Research Committee), and all patients provided written informed consent.

Mucoadhesive tablets containing 10 mg of miconazole nitrate were manufactured by Janssen Pharmaceutica (batch number 98L09/109) and packed in blisters of 7 tablets each. Ketoconazole tablets containing 200 mg of ketoconazole per tablet (batch number 99D20/322) were packed in blisters of 14 tablets each.

Patients were selected at visit 1 (day 1) and were randomized to 1 of the 2 treatment groups; treatment was initiated

immediately. Each of the treatments was used once daily for 7 to 14 days. Subjects were provided with a single blister containing a 1-week supply for the first week of treatment. Those described as not cured at day 7 were allowed to continue treatment for a further 7 days; in such cases, a second blister of tablets was provided and the subject returned on day 14. Patients who failed treatment after 14 days were provided with fluconazole rescue medication (200 mg once daily for 7 days). All subjects were evaluated at 14 days after treatment.

Administration of the mucoadhesive buccal tablet took place about 30 minutes after breakfast (if taken). The mucoadhesive tablet was applied to the left or right gingiva in the upper region of the upper canine. The tablet was secured with slight manual pressure.

Baseline assessments were made on day 1, and subjects returned for assessment on days 3, 7, and 14 (if the subject was not cured at day 7) after treatment. At all visits, the severity of oropharyngeal candidiasis was scored by means of a signs-symptoms score composed of signs and 3 symptoms. The total maximum score of 10 was the sum total of points given for each symptom and sign. The relapse of oropharyngeal candidiasis was determined based on the signs and symptoms scores as reported by the investigator.

Signs and symptoms were scored by the same physician at each visit. Symptoms, defined as the presence (2) or absence (0) of dysphagia, oral pain, and loss of taste, provided a maximum score of 6. The signs (extent of oral lesions [erythema or removable white plaques]) were scored as 0 = no lesions, 1 = minimal lesions covering less than 1 cm², 2 = mild lesions covering more than 1 cm², 3 = moderate lesions covering more than 1 cm² and involving both buccal mucosa and palatal or peritonsillar regions, and 4 = severe lesions with extensive involvement of buccal mucosa and palatal peritonsillar regions and pharyngeal mucosa. At all visits, oral scrapings were examined by microscopy (potassium hydroxide [KOH]) and expressed as positive or negative for mycelium. Clinical cure was defined as an absence of signs and symptoms (score of 0) as confirmed by the investigator. Unused trial medication or empty blisters were returned at follow-up visits to assess patient compliance.

Based on an expected cure rate of 85% with a clinically relevant difference of 10%, a sample size of 158 subjects for each treatment arm was required to have 80% power to demonstrate no inferiority of miconazole compared with ketoconazole (α level of 5%, 1-sided). A total of 352 subjects (176 per group) were required for recruitment, considering a 10% dropout rate. All demographic data and baseline disease characteristics were compared by means of χ^2 tests for nominal data and by means of the Wilcoxon rank sum test for the ordered (and continuous) data for both treatment groups.

The primary outcome variable was clinical response after 1 week of treatment (ie, the percentage of subjects who were cured [total score of 0 for signs and symptoms] at the

“week 1” evaluation). Cure rates for both treatment groups were compared by means of the Blackwelder 1-sided equivalence test at the 5% significance level.¹⁷ A 90% 2-sided confidence interval (CI) of the difference between both groups was calculated. The primary population for the efficacy evaluation was the per-protocol population—specifically, all subjects with at least 1 trial medication intake, excluding the major protocol deviators.

A subgroup analysis on clinical response rate was performed by baseline CD4 count, absence/presence of dysphagia at baseline, concurrent use of broad-spectrum antibiotics during the treatment phase, and α level (5%, 1- or 2-sided). Signs and symptoms scores and microscopy results were tabulated and graphically presented. A 90% 2-sided CI of the differences in cure rate between the 2 groups was calculated. Relapse, defined as recurrence of at least 1 sign or symptom during the follow-up phase, was calculated and tabulated.

The intent-to-treat population—all subjects with intake of at least 1 trial medication—was the primary population for the safety analysis. Type and incidence of all adverse events (AEs) and HIV events were tabulated per treatment group.

RESULTS

Patients were recruited by 6 investigators at 4 hospitals in Kampala over a 7-month period. In total, 357 subjects were recruited, of whom 178 were assigned to 10-mg miconazole nitrate tablets and 179 were assigned to and treated with 400 mg of ketoconazole. The 357 subjects in the intent-to-treat population included all subjects receiving trial medication at least once. The per-protocol population (excluding all major protocol violators) was composed of 332 subjects (167 in the miconazole group and 165 in the ketoconazole group). There were 154 subjects in both groups who completed treatment and 152 subjects in each group who completed follow-up. Patient demographics are summarized in Table 1. There were 14% early terminations in both groups (the majority were lost to follow-up or withdrew because of an HIV event). HIV serology was documented via recent source documents containing HIV serology, or an HIV antibody test plus a confirmatory test were performed. Of the 357 patients, 299 (84.2%) had docu-

mented HIV serology, 51 (14.4%) had a positive screening test confirmed by Western blot analysis, and 5 (1.4%) had a negative screening test (4 in the ketoconazole group and 1 in the miconazole group). The median CD4 count was 36 cells/mm³, indicative of an extremely immune-suppressed patient population.

At the end of the treatment phase, the clinical response rates were 155 of 167 (92.8%) for miconazole nitrate and 159 of 165 (96.4%) for ketoconazole. The treatment difference [90% CI] was -3.5% (-7.6%; 0.5%). At this time point, miconazole nitrate was not statistically significantly inferior to ketoconazole, taking into account the 10% maximal clinically allowable difference ($P = 0.005$). In Table 2, the clinical response rates at day 7, at the end of treatment, and at the end of follow-up are presented for the per-protocol population.

The clinical response rate at the end of treatment was also analyzed by subgroup (see Table 2). Subgroups were defined by baseline CD4 count, by absence/presence of dysphagia at baseline, by both baseline CD4 count and absence/presence of dysphagia at baseline, and by the concurrent use of broad-spectrum antibiotics during the treatment phase. None of these factors appeared to have an influence on the clinical response rate.

At baseline, dysphagia, loss of taste, and oral pain were present in 126 (75%), 129 (77%), and 146 (87%) subjects in the miconazole nitrate group and in 127 (77%), 119 (72%), and 140 (85%) subjects in the ketoconazole group. For all 3 symptoms, a shift from presence at baseline to absence at day 7, at end of treatment, and at end of follow-up was seen in the majority of the subjects for both treatment groups. At end of treatment, dysphagia was reduced from 75% at baseline to 1% in the miconazole nitrate group and from 77% at baseline to 1% in the ketoconazole group.

For patients who were defined as clinically cured at the end of treatment, relapse was defined as recurrence of a sign or symptom 14 days later. The relapse rate was 30.8% (45/146) in the miconazole nitrate group and 23.0% (34/148) in the ketoconazole group. This difference was not statistically significant ($P = 0.148$). Besides a slightly higher relapse rate in the miconazole nitrate group for baseline CD4 count of less than

TABLE 1. Demographics

Baseline Characteristics Subject Disposition	Miconazole Nitrate	Ketoconazole	<i>P</i>
Number of subjects entered (M/F)	178 (41/137)	179 (41/138)	0.977
Age: median (minimum–maximum), years	32 (20–58)	34 (19–62)	0.793
CD4 count (mean \pm SE), cells/mm ³	102.3 \pm 14.15	109.5 \pm 12.88	0.199
CD4 count (CI), cells/mm ³	31 (23–42)	47 (27–67)	

F, female; M, male; SE, standard error of the mean.

TABLE 2. Clinical Response

Efficacy*	Miconazole Nitrate (n = 167)†	Ketoconazole (n = 165)†	Treatment Difference‡	90% CI of the Treatment Difference	P
Primary variable					
Clinical cures at day 7, n/N (%) (95% CI of the response rate)	135/156 (87%) (81; 92)	137/153 (90%) (85; 94)	-3%	(-9; 3)	0.029
Secondary variables					
Clinical cures, n/N (%) (95% CI)			-4%	(-8; 1)	0.005
At end of treatment	155/167 (93%) (89; 97)	159/165 (96%) (94; 99)			
At end of follow-up	102/147 (70%) (62; 77)	114/148 (77%) (70; 84)	-8%	(-16; 1)	0.323
Additional secondary variables at end of treatment					
Clinical response by baseline CD4 count					
<50 cells/mm ³	93/101 (92%)	79/83 (95%)			
50-200	39/40 (98%)	52/52 (100%)			
≥200	23/26 (89%)	24/26 (92%)			
Clinical response by baseline dysphagia					
With dysphagia	117/126 (93%)	122/127 (96%)			
Without dysphagia	38/41 (93%)	37/38 (97%)			

*If not specified otherwise, all efficacy results discussed in the synopsis are the results of the per-protocol population.

†Number of subjects (per-protocol population) with efficacy data (miconazole nitrate and ketoconazole) at baseline (167 and 165), day 7 (156 and 153), end of treatment (167 and 165), and end of follow-up (148 and 147). One subject in ketoconazole group had no "loss of taste" score at end of follow-up (and thus no Clinical Global Impression (CGI) and no total signs and symptoms score).

‡Blackwelder test for no inferiority of miconazole nitrate versus ketoconazole with 10% maximal clinically relevant difference (at 5%, 1-sided significance level).

50 cells/mm³, there did not seem to be a relationship between the relapse rates and baseline CD4 count.

Microscopic results from KOH smears were comparable between the groups, although not statistically significant. At baseline, 23% of the subjects in the miconazole nitrate group (128/167) and the ketoconazole group (127/165) had a negative microscopic result. At day 7 and at end of treatment, the percentage of subjects with a negative microscopic examination increased to approximately 70% in the miconazole nitrate group and to approximately 75% in ketoconazole group. During the follow-up period, the microscopic results were generally maintained.

Safety results are reported in Table 3. There were no severe or unexpected AEs related to the use of the miconazole nitrate mucoadhesive tablet. The incidence of the most frequently reported AEs under treatment (fever, malaria, coughing, headache, abdominal pain, anorexia, chest pain, and vomiting) was similar in the 2 groups, except for vomiting, which had an incidence of 1% in the miconazole nitrate group and 8% in the ketoconazole group. In addition, there were fewer drug-related AEs in the miconazole nitrate group. No signs of local irritation were reported in the miconazole nitrate group. The

most frequently reported HIV events during treatment were diarrhea, fever, rash, coughing, vomiting, anorexia, and tuberculosis (TB) infection, again reported in similar frequencies.

DISCUSSION

The design of this study was based on the design of a previous WHO GPA study conducted at the same clinical site in Uganda. The WHO GPA study was meant to compare various topical and systemic antifungal treatments (nystatin, miconazole gel, ketoconazole, and ketoconazole plus acid) and to mimic "real-world" use of antifungals in developing countries. In the current open randomized, comparative, phase IIIb trial in presumed HIV-seropositive subjects with oropharyngeal candidiasis, subjects were randomized to receive either topical therapy using a 10-mg miconazole nitrate mucoadhesive buccal tablet once daily or systemic therapy using 400 mg of ketoconazole once daily for 7 consecutive days.

The clinical response rate at day 7 and at the end of treatment demonstrated that miconazole nitrate was not significantly inferior to ketoconazole. At the end of treatment, the clinical response rate was 155/167 (93%) for miconazole nitrate and 159/165 (96%) for ketoconazole. Signs and symp-

TABLE 3. Safety Data

Safety: AEs during treatment most frequently reported AE (>4 subjects per treatment group)	Miconazole Nitrate (n = 178)*	Ketoconazole (n = 179)*
Fever	9 (5)	7 (4)
Malaria	8 (5)	7 (4)
Coughing	7 (4)	10 (6)
Headache	7 (4)	8 (5)
Abdominal pain	6 (3)	6 (3)
Anorexia	6 (3)	5 (3)
Chest pain	6 (3)	2 (1)
Vomiting	2 (1)	14 (8)
HIV events during treatment: most frequently reported HIV event (>4 subjects per treatment group)		
Diarrhea	13 (7)	12 (7)
Fever	9 (5)	8 (5)
Rash	9 (5)	7 (4)
Coughing	8 (5)	7 (4)
Vomiting	6 (3)	5 (3)
Anorexia	6 (3)	5 (3)
Infectious TB	6 (3)	2 (1)

*Number of subjects (intent-to-treat population) with safety data (miconazole nitrate and ketoconazole) in treatment phase (178 and 179).

toms improved greatly and to an equal extent in the 2 treatment groups. Some authors have reported that treatment of oral candidiasis in HIV-positive subjects with low CD4 counts is more difficult and may require higher doses of antifungal agents. A degree of a functioning immune system is generally required for fungistatic antifungals to be effective, and HIV populations are considered a worst-case scenario versus other underlying conditions, such as cancer chemotherapy, in terms of ability to respond to treatment, time to response, and rate of relapse. The clinical response rate in the present trial following administration of miconazole nitrate in a mucoadhesive slow-release tablet was well within the range seen in studies with other systemic antifungal treatment approaches in patients with advanced immune suppression of approximately 80% to greater than 90%.^{18,19} There was no influence of baseline CD4 count, baseline dysphagia score, or concurrent use of broad-spectrum antibiotics on the treatment responses. This contrasts with findings by others, where an association between CD4 count and treatment response has been identified.³

Although topical antifungal therapies are generally positioned as first-line therapies for oropharyngeal candidiasis, their utility in daily practice has been limited by bitter taste (in the case of nystatin) and reduced compliance associated with onerous treatment regimens, possibly also leading to lower efficacy.¹⁸ The administration of the miconazole mucoadhesive

tablet represents a breakthrough in topical therapy by combining the user-friendliness of a tasteless once-daily regimen with the effectiveness of a systemic antifungal.

Approximately 75% of the subjects in the miconazole nitrate and ketoconazole groups had dysphagia at baseline, which was virtually eliminated at the end of treatment in both groups. In resource-poor settings, the noninvasive diagnosis of esophageal candidiasis in HIV-seropositive subjects is accepted as the standard of care and is based on a combination of signs and symptoms (dysphagia) together with a CD4 count below 50 cells/mm³.²⁰ The study results support the use of the miconazole mucoadhesive buccal tablet in this important subgroup of patients, although in general, topical antifungals are considered of limited value in the treatment of esophageal candidiasis. It is likely that the continuous intraoral presence of fungicidal concentrations resulting from the 0-order delivery of miconazole from the buccal tablet throughout the day contributed to effects on esophageal pathology observed in this study. A study in laryngectomized patients similarly evaluated the effects of miconazole delivered from the mucoadhesive tablet on the growth of *Candida* on the deeper anatomic structures in the throat area, including the oropharynx, the voice prosthesis (valve part), and the tracheo-esophageal shunt.²¹ A significant reduction in yeast colonization and longer device lifetime were observed in patients

treated with the miconazole buccal tablet versus those using placebo tablets.

Given the severely immunocompromised status of the study population (median CD4 count of 36 cells/mm³), relapse at 2 weeks following termination of therapy was anticipated. At the follow-up visit, the relapse rate was not significantly different in the 2 groups: 31% (45/146) for miconazole nitrate and 23% (34/148) for ketoconazole. Overall relapse rates in AIDS populations with CD4 counts below 200 cells/mm³ range between 35% and 53%.^{2-8,22} Relapse tends to depend on the duration of therapy, degree of immunosuppression, and type of treatment.¹⁸ The most appropriate long-term strategy for antifungal prophylaxis in HIV populations has not yet been established. Antiretroviral treatment will undoubtedly decrease the incidence of oropharyngeal candidiasis in HIV-infected patients.²³

There were no serious or unexpected AEs related to the use of the miconazole nitrate mucoadhesive tablet. The incidence of AEs in both treatment groups was comparable, except for vomiting, which was more frequent in the ketoconazole group versus the miconazole group (8% vs. 1%). In addition, a higher incidence of drug-related AEs was seen in the ketoconazole group compared with the miconazole nitrate group. No signs of local irritation were reported in the miconazole nitrate group.

The low dose and resultant negligible systemic exposure is of particular interest in patients dually infected with HIV and TB. Currently used TB drugs as well as antiretroviral drugs such as protease inhibitors and nonnucleoside reverse transcriptase inhibitors all use the cytochrome P450 monooxygenase system for biotransformation. The same cytochrome P450 enzyme is involved in the metabolism of ketoconazole and fluconazole; hence, interactions between systemic antifungals and TB drugs may be expected. The resulting metabolite may be pharmacologically inactive, less active, or occasionally more active or more toxic. The Centers for Disease Control and Prevention (CDC) recommend the use of alternative therapies in such cases of expected drug interactions, given the overlapping toxicities between rifampicin and ketoconazole, itraconazole, or fluconazole.²⁴

In this trial, the use of tuberculostatic agents before the trial was an exclusion criterion and forbidden during the trial in the ketoconazole group. Nevertheless, 4.2% of the subjects reported use of TB drugs during the study duration. The incidence of TB seen over the 6-week study period in the current HIV-infected population highlights the significance of dual infection and is consistent with literature estimates of 30% prevalence rates for dual infection.^{25,26} For HIV-seropositive subjects diagnosed with TB, the miconazole nitrate mucoadhesive buccal tablet represents an attractive alternative to systemic treatment, particularly given the ease of use associated with once-daily dosing.

The 10-mg mucoadhesive tablet is not inferior to systemic antifungal treatment with ketoconazole in the treatment of AIDS-related oropharyngeal candidiasis with and without dysphagia. It is a particularly useful alternative to systemic therapy in a heavily medicated HIV population, where drug-drug interactions should be avoided. It provides the first and only once-daily topical treatment option and should therefore be considered in first-line therapy for this condition, particularly in resource-poor settings, where ease of use can help to guarantee the success of therapy.

REFERENCES

- UNAIDS. *Report on the Global HIV/AIDS Epidemic*. Geneva, UNAIDS; 2002.
- Hunter KD, Gibson J, Lockhart P, et al. Fluconazole-resistant *Candida* species in the oral flora of fluconazole-exposed HIV-positive patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998;85:558-564.
- Diz Dios PD, Alvarez Alvarez J, Fernadéz Feijoo J, et al. Fluconazole response patterns in HIV-infected patients with oropharyngeal candidiasis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1995;79:170-174.
- Greenspan D. Treatment of oropharyngeal candidiasis in HIV-positive patients. *J Am Acad Dermatol*. 1994;31(Suppl):S51-S55.
- Powderly W-G, Gallant J-E, Ghannoum M-A, et al. Oropharyngeal candidiasis in patients with HIV: Suggested guidelines for therapy. *AIDS Res Hum Retroviruses*. 1999;15:1619-1623.
- Silverman S, Gallo JW, McKnight ML, et al. Clinical characteristics and management responses in 85 HIV-infected patients with oral candidiasis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1996;82:402-407.
- MacPhail LA, Hilton JF, Dodd L, et al. Prophylaxis with nystatin pastilles for HIV-associated oral candidiasis. *J Acquir Immune Defic Syndr Human Retrovirol*. 1996;12:470-476.
- Hoepelman IM, Dupont B. Oral candidiasis: the clinical challenge of resistance and management. *Int J Antimicrob Agents*. 1996;6:155-159.
- Colebunders R, Mann JM, Francis H, et al. Evaluation of a clinical case definition of AIDS in Africa. *Lancet*. 1987;1:492-494.
- Sonnet J, Taelman H. Clinical and biological profile of African AIDS. In: Stacquet M, Hemmer R, Baert A, eds. *Clinical Aspects of AIDS and AIDS Related Complex*. Oxford: Oxford University Press; 1986:78-89.
- Global Programme on AIDS. Guidelines for the Clinical Management of HIV Infection in Adults*. Geneva: WHO; 1991. Order number 1930036.
- Nyst MJ, Perriens JH, Lusakamunu K, et al. Gentian violet, ketoconazole and nystatin in oropharyngeal and oesophageal candidiasis in Zairian AIDS patients. *Ann Soc Belge Méd Trop*. 1992;72:45-52.
- Odds FC. Persistence of miconazole in saliva after a single oral dose. *J Clin Res Rev*. 1981;1:231-232.
- Turner A, Warnock DW. Determination of miconazole in human saliva using high-performance liquid chromatography. *J Chrom*. 1982;227:229-232.
- Bouckaert S, Schauttee H, Lefebvre RA, et al. Comparison of salivary miconazole concentrations after administration of a bioadhesive slow-release buccal tablet and an oral gel. *Eur J Clin Pharmacol*. 1992;43:137-140.
- Janssen P, Symoens J. Hepatic reactions during ketoconazole treatment. *Am J Med*. 1983;74:80-85.
- Blackwelder WC. Proving the null hypothesis in clinical trials. *Control Clin Trials*. 1982;3:345-353.
- Vazquez JA. Options for the management of mucosal candidiasis in patients with AIDS and HIV infection. *Pharmacotherapy*. 1999;19:76-87.
- Powderly WG, Mayer KH, Perfect JR, et al. Diagnosis and treatment of oropharyngeal candidiasis in patients infected with HIV: a critical reassessment. *AIDS Res Hum Retroviruses*. 1999;15:1405-1412.

20. Odynophagia and Dysphagia. In: *Clinical AIDS Care Guidelines for Resource-Poor Settings*. 1st ed. Belgium-Luxemburg: Médecins Sans Frontières; 2001:11.6.
21. Van Weissenbruch R, Bouckaert S, Remon JP. Chemoprophylaxis of fungal deterioration of the Provox silicone tracheoesophageal prosthesis in postlaryngectomy patients. *Ann Otol Rhinol Laryngol*. 1997;106:329–337.
22. Phillips P, De Beule K, Frechette G, et al. A double-blind comparison of itraconazole oral solution and fluconazole capsules for the treatment of oropharyngeal candidiasis in patients with AIDS. *Clin Infect Dis*. 1998; 26:1368–1373.
23. Diz Dios P, Ocampo A, Miralles C, et al. Frequency of oropharyngeal candidiasis in HIV-infected patients on protease inhibitor therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1999;87:437–441.
24. Kaplan JP, Gayle HD, Castro KG. Prevention and treatment of tuberculosis among patients infected with HIV. Principles of therapy and revised recommendation. *MMWR*. 1998;47:34.
25. Harries AD, Hargreaves NJ, Kemp J, et al. Deaths from tuberculosis in sub-Saharan African countries with a high prevalence of HIV-1. *Lancet*. 2001;357:1519–1523.
26. *STOP TB News*. The Newsletter of the Global Partnership to Stop TB. 2001;4:1–12. Available at: www.stoptb.org.