A systematic review of the effectiveness of antifungal drugs for the prevention and treatment of oropharyngeal candidiasis in HIV-positive patients

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Authors' objectives
To determine the strength of evidence for the effectiveness of antifungal drugs (nystatin, clotrimazole, amphotericin B, fluconazole, ketoconazole, and itraconazole) in the prevention and treatment of oral candidiasis in human immunodeficiency virus (HIV)-positive patients.

Searching
MEDLINE and EMBASE were searched from 1966 to April 2000, and the contents of the Cochrane Library were manually reviewed. Key search terms were: 'HIV', 'AIDS', 'oral candidiasis', 'antifungal agents', 'nystatin', 'clotrimazole', 'amphotericin B', 'ketoconazole', 'fluconazole', 'itraconazole' or 'drug therapy'. For the prevention group, the search was further limited by the terms: 'primary prevention', 'prevention', 'preventive medicine', 'health promotion', 'disease prevention', 'dental prophylaxis' or 'prophylaxis'. For the treatment group, the original search was further limited by the terms: 'drug therapy', 'therapy', 'intervention studies', 'intervention', 'treatment outcome' or 'treatment'. The searches did not include unpublished (grey) literature and were restricted to English language publications. The references in review articles were reviewed for additional relevant studies. In addition, the contents of five journals that had contributed a large number of the articles identified in the searches were examined for the 12 months prior to May 2000.

Study selection
Study designs of evaluations included in the review
Randomised placebo-controlled trials (RCTs) were eligible for the question of preventive efficacy, while randomised drug comparisons were eligible for the question of treatment effectiveness. Studies without a concurrent control group or comparison group were excluded. Prophylactic treatments lasted from 12 weeks to more than one year (17 months) with follow-up evaluation intervals varying according to the study. Treatments in the majority of the study arms lasted 14 days; a few evaluated a 28-day course, a 7-day course, or a single dose. The evaluation intervals selected varied according to the study.

Specific interventions included in the review
Studies of antifungal drugs (nystatin, clotrimazole, amphotericin B suspension, fluconazole, ketoconazole, and itraconazole) were eligible for inclusion. Aqueous gentian violet was also included in the treatment studies. In the prophylactic trials, the doses were 150 mg/week, 200 mg/week, 50 mg/day and 100 mg/day for fluconazole, and 200,000 or 400,000 u/day for nystatin pastilles. In the treatment trials, the most commonly used drug for effectiveness or equivalence comparisons was fluconazole at varying doses in capsule form and as an oral suspension. Studies comparing only different formulations of the same drug (i.e. no other active drug) were excluded from the treatment group of trials.

Participants included in the review
HIV-positive patients with oral candidiasis drawn from private practice, community clinic or hospital settings were eligible for inclusion. Non-HIV/AIDS patients were excluded. Studies of mixed-site candidiasis in which the results for oropharyngeal candidiasis were not reported separately were excluded. Studies without laboratory confirmation of oral candidiasis were excluded from both the treatment and prevention groups of trials.

Outcomes assessed in the review
The prophylactic trials had to assess the prevention of initial infection or recurrence of oropharyngeal candidiasis to be eligible for inclusion. The end points for new oral candidiasis diagnosis typically required new signs and/or symptoms of oral candidiasis, confirmed by microbiological evidence such as positive Candida culture, positive potassium hydroxide fungal smear, or additional colony-forming units in oral washings. The outcome measures found for the treatment of oral candidiasis included both clinical cure (the absence of signs and/or symptoms of oral candidiasis) and
mycological cure (evidence such as negative Candida culture or negative potassium hydroxide microscopic preparation).

How were decisions on the relevance of primary studies made?
Two authors independently reviewed the articles for inclusion. The reviewers were not blinded to authors or affiliations.

Assessment of study quality
Each article received a summary quality score comprised of the following attributes (maximum points): research design (8 points), data analysis (5 points), and measurement and validity (12 points). The resulting scores (0 to 25) were rescaled on a scale of 0 to 100 for clarity of presentation. The assessment of study quality also took the CONSORT criteria (see Other Publications of Related Interest) into consideration. No studies were excluded on the basis of their quality score. The authors do not state how many of the reviewers performed the quality assessment.

Data extraction
One author extracted the data into data abstraction forms. Another author then independently reviewed the extracted data against the original article. The abstracted data pertained to the study design, sampling and characteristics of the study group, interventions, and the reported outcomes and statistics.

Methods of synthesis
How were the studies combined?
Quality scores, the number of studies reported on a question, and the strength and consistency or homogeneity of the findings across the studies, were used to evaluate the overall strength of the literature base. The level of evidence was assessed as either, good, fair, poor or insufficient.

How were differences between studies investigated?
The authors do not state how differences between the studies were assessed.

Results of the review
Eighteen RCTs were included in the review. Six RCTs (5 double-blind and 1 open) were included in the prevention review. The total sample size ranged from 14 to 323 participants. Twelve RCTs (3 double-blinded, 5 examiner blinded, and 4 open-label with no blinding) were included in the treatment effectiveness review. The total sample size ranged from 37 to 344 participants.

Quality: the quality score ranged from 44 to 84 points for the prevention trials, and from 44 to 92 points for the treatment effectiveness trials.

Prophylaxis: there was insufficient evidence from which to draw conclusions about the efficacy of nystatin, clotrimazole, amphotericin B suspension, ketoconazole and itraconazole with regard to oral candidiasis prevention. Few side-effects were reported for nystatin. No studies were reviewed for the other antifungals. The evidence was good with respect to fluconazole (n=5), which was significantly more effective at preventing recurrences and new infections than placebo over a range of 3 to 17 months, when studied at doses from 50 to 100 mg/day and from 150 to 200 mg/week. Nausea was the most common side-effect, but this was reported to be tolerable.

Treatment: there was no evidence about the effectiveness of amphotericin B suspension because it was not assessed in any of the included studies. Fluconazole appeared to be from 87 to 100% effective in obtaining a complete clinical response after 14 days of therapy, and from 53 to 87% effective in obtaining a culture negative for Candida species. Fourteen-day therapy with itraconazole (71 to 97% clinical response rates) appeared to be equivalent to fluconazole, while ketoconazole (43 to 81% clinical response rates) achieved the same or slightly lower response rates. Fluconazole and itraconazole appeared to be more effective with respect to the management of oropharyngeal candidiasis than nystatin (9 to 52% clinical response rates) or clotrimazole (65 to 85% clinical response rates), particularly when taking mycologic response rates and relapse rates into account.
For any given drug, not all individuals with complete clinical response achieved a complete mycologic response. The rates of relapse within 28 to 31 days tended to be lower when mycologic cure was obtained.

Two studies assessed drug efficacy in infants and children. However, drug efficacy did not appear to be affected by patient age and the levels of immune suppression, when reported, were similar between the groups. Adverse events rarely resulted in discontinuation of therapy. The side-effects were generally mild and typically involved the gastrointestinal system. The proportion of participants dropping out because of side-effects was 0.5% with nystatin, 1.8% with fluconazole, 2.8% with ketoconazole, 4.6% with clotrimazole, and 6.1% with itraconazole.

**Authors’ conclusions**
The evidence for the prophylactic efficacy of fluconazole was good, although insufficient to draw conclusions about the other antifungals. The evidence for the treatment effectiveness was insufficient for amphotericin B but good for nystatin, clotrimazole, fluconazole, ketoconazole and itraconazole. The authors also made several suggestions for strengthening the evidence base.

**CRD commentary**
The authors stated their research question and the inclusion and exclusion criteria. The literature search appears to have been thorough although the search was restricted to English publications. There was no assessment of possible publication bias. The authors reported who and how many of the authors performed the study selection and data extraction processes, but have not reported who performed the quality assessment. Only one author extracted the data.

A narrative synthesis of the evidence was presented since statistical pooling was inappropriate. Differences between the trials were not formally assessed; however, there was a discussion on the limitations of the evidence base for both the prevention and treatment groups of trials.

The conclusions appear to follow from the results.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors made suggestions about gathering prevention and treatment evidence. Future research should use larger, more well-defined groups; control for immunologic status, viral load, history of oral candidiasis, past exposure to antifungals, baseline oral Candida carriage, drug interactions, and antiviral therapy; and use compliance monitors, fungal speciation and susceptibility testing consistently.

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