ClinicalEvidence

Candidiasis (oropharyngeal)

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ABSTRACT

INTRODUCTION: Candida is a fungus present in the mouths of up to 60% of healthy people, but overt infection is associated with immunosuppression, diabetes, broad-spectrum antibiotics, and corticosteroid use. In most people, untreated candidiasis persists for months or years unless associated risk factors are treated or eliminated. In neonates, spontaneous cure of oropharyngeal candidiasis usually occurs after 3 to 8 weeks. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to prevent and treat oropharyngeal candidiasis in: adults undergoing treatments that cause immunosuppression; infants and children; people with dentures; and people with HIV infection? Which antifungal regimens reduce the risk of acquiring resistance to antifungal drugs? We searched: Medline, Embase, The Cochrane Library, and other important databases up to July 2013 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 47 RCTs or systematic reviews of RCTs that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: antifungals (absorbed, partially or topically absorbed, or non-absorbed; for example, imidazole [ketoconazole, clotrimazole, toiconazole, miconazole], polyene [amphotericin B, nystatin], triazole [fluconazole, itraconazole], melaleuca and posaconazole), intermittent or continuous prophylaxis, or treatment, and denture hygiene.

QUESTIONS

What are the effects of interventions to prevent and treat oropharyngeal candidiasis in adults undergoing treatments that cause immunosuppression? 4

What are the effects of interventions to prevent and treat oropharyngeal candidiasis in infants and children? 4

What are the effects of interventions to prevent and treat oropharyngeal candidiasis in people with dentures? 7

What are the effects of interventions to prevent and treat oropharyngeal candidiasis in people with HIV infection? 3

Which antifungal regimens reduce the risk of acquiring resistance to antifungal drugs? 32

INTERVENTIONS

IMMUNOSUPPRESSED ADULTS

Beneficial

Antifungal prophylaxis with absorbed or partially absorbed antifungal drugs in adults having chemotherapy, radiotherapy, or both treatments for cancer (more effective than placebo or non-absorbed drugs) 4

Unknown effectiveness

Antifungal prophylaxis in adults having tissue transplants 8

Antifungal treatment in adults having chemotherapy, radiotherapy, or both treatments for cancer 11

INFANTS AND CHILDREN

Beneficial

Antifungal treatment with miconazole or fluconazole in immunocompetent and immunocompromised infants and children (more effective than nystatin) 15

Likely to be beneficial

Antifungal prophylaxis with fluconazole in immunocompromised infants and children (more effective than oral nystatin or amphotericin B) 14

PEOPLE WITH DENTURES

Likely to be beneficial

Antifungal treatment for denture stomatitis 17

Unknown effectiveness

Denture hygiene 21

PREVENTION/TREATMENT IN HIV

Beneficial

Antifungal prophylaxis (fluconazole or itraconazole) 3

Antifungal treatment 27

REDUCING DRUG RESISTANCE

Unlikely to be beneficial

Intermittent treatment in people with HIV infection and acute episodes of oropharyngeal candidiasis (no reduction in antifungal resistance compared with continuous prophylaxis) 32

Key points

- Opportunistic infection with the fungus *Candida albicans* causes painful red or white lesions of the oropharynx, which can affect taste, speech, and the act of eating.

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Candida is present in the mouth of up to 60% of healthy people, but overt infection is associated with immunosuppression, diabetes, broad-spectrum antibiotics, corticosteroid use, haematinic deficiencies, and denture wear.

- In people with immunosuppression following cancer treatment, absorbed (ketoconazole, itraconazole, or fluconazole) or partially absorbed antifungal drugs (miconazole, clotrimazole) prevent oropharyngeal candidiasis compared with placebo or non-absorbed antifungal drugs. We don't know whether antifungal treatment is effective in this group.

  Non-absorbed antifungal drugs (nystatin or amphotericin B) may be no more effective than placebo at preventing candidiasis.

  We don't know whether antifungal prophylaxis is effective in adults having tissue transplants, as we found few studies.

- CAUTION: there have been drug safety alerts that oral ketoconazole can cause severe liver injury, adrenal gland problems, can lead to harmful drug interactions (www.fda.gov), and that the benefits do not outweigh the risks in treating fungal infections (www.ema.europa.eu/ema). It has been suspended in some countries and restrictions placed on its use in others.
- Prophylaxis with fluconazole is more effective than oral nystatin or amphotericin B at preventing candidiasis in immunocompromised infants and children, while treatment with fluconazole and miconazole increases cure rates compared with nystatin in both immunocompromised and immunocompetent infants and children.
- Antifungal drugs may increase clinical improvement or cure in people with oropharyngeal candidiasis caused by wearing dentures.

  We don't know whether denture hygiene or removing dentures at night reduces the risk of developing oropharyngeal candidiasis.

- Daily or weekly prophylaxis with fluconazole or itraconazole reduces the incidence of candidiasis in people with HIV infection. Prophylaxis with nystatin may not be effective.

  Topical treatments with clotrimazole lozenges and miconazole buccal slow-release tablets may be as effective as oral tablets/suspensions of oral antifungals (fluconazole/itraconazole/ketoconazole) at reducing symptoms of candidiasis in people with HIV infection.

  A single dose of fluconazole (750 mg) may be as effective as a 14-day course of fluconazole in reducing symptoms of candidiasis in people with HIV infection.

- Resistance to antifungal drugs, particularly azole drugs, is an increasing problem. Continuous prophylaxis with antifungal agents may not increase the risk of developing antifungal resistance compared with intermittent prophylaxis, but it may be no more effective at reducing the number of attacks in people with HIV infection, the majority of whom were receiving highly active antiretroviral treatment (HAART).

Clinical context

GENERAL BACKGROUND

Oropharyngeal candidiasis is a common endogenous, opportunistic infection. Candidiasis in primary care is associated with risk factors, such as haematinic deficiency, denture wear, use of corticosteroid inhalers, following broad spectrum antibiotic use, drug induced or autoimmune associated dry mouth, HIV, diabetes and smoking. In secondary care, oropharyngeal candidiasis is a marker of immunosuppression in patients receiving chemotherapy for solid cancers, haematological malignancies and transplant patients. Persistent Candida species carriage in the oral cavity, particularly on the dorsum of the tongue, is observed in up to 65% of patients' mouths, with higher colonisation rates in young children and denture wearers. Therefore, recurrent infections are problematic in patients where the risk factors or underlying disease cannot be readily eliminated or controlled.

FOCUS OF THE REVIEW

Antifungal drugs provide the mainstay of treatment for acute, chronic and recurrent candidiasis. The purpose of this review was to identify the evidence base to support the use of antifungal treatment for the prevention of recurrent candidiasis and treatment of uncomplicated oral and pharyngeal mucosal infections occurring in the recognised at risk groups.

COMMENTS ON EVIDENCE

Oral candidiasis is a common condition in medical and dental primary care, yet we found few RCTs that met our quality criteria for the treatment with antifungals of immunocompetent adults and, in particular, people with diabetes. The evidence we found was restricted to children and denture wearers.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this review was carried out from the date of the last search, August 2011 to October 2013. For more information on the electronic databases searched and criteria applied during assessment of studies

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for potential relevance to the review, please see the Methods section. Searching of electronic databases retrieved 38 studies. After de-duplication and removal of conference abstracts, 21 records were screened for inclusion in the review. Appraisal of titles and abstracts led to the exclusion of 19 studies and the further review of 2 full publications. Of the 2 full articles evaluated, no systematic reviews or RCTs were added at this update.

ADDITIONAL INFORMATION

In resource poor countries, traditional agents such as gentian violet, or lemon juice, have seen resurgence for the management of HIV associated candidiasis due to their low cost, but trials evaluating their use were of insufficient quality to be included in this review. Dentists routinely advise denture wearing patients on denture hygiene and to leave dentures out at night, or to rinse the mouth with water after using steroid inhalers as preventive measures to reduce the risk of recurrent candidiasis. However, given the methodological difficulties of performing robust trials with such behavioural interventions, the available evidence to support these techniques though addressed in this *Clinical Evidence* review is inconclusive.

DEFINITION

Oropharyngeal candidiasis is an opportunistic mucosal infection caused, in most cases, by the fungus *Candida albicans.* It can also be caused by other species such as *C glabrata*, *C tropicalis*, and *C krusei*. The 4 main types of oropharyngeal candidiasis are: (1) pseudomembranous (thrush), consisting of white, curd-like, discrete plaques on an erythematous background that is exposed after the removal of the plaque and found on the buccal mucosa, throat, tongue, or gingivae; (2) erythematous, consisting of smooth red patches on the hard or soft palate, dorsum of tongue, or buccal mucosa; (3) hyperplastic, consisting of white, firmly adherent patches or plaques that cannot be removed, usually bilaterally distributed on the buccal mucosa, tongue, or palate; and (4) denture-induced stomatitis, presenting as either a smooth or a granular erythema confined to the denture-bearing area of the hard palate and often associated with an angular cheilitis, which occurs as red, fissured lesions in the corners of the mouth. [1] Symptoms vary, ranging from none to a sore and painful mouth with a burning tongue and altered taste. Oropharyngeal candidiasis can impair speech, nutritional intake, and quality of life. Oropharyngeal candidiasis is the most common oral manifestation of HIV infection. [1] HIV-seropositive people with recurrent oropharyngeal candidiasis have overall lower levels of oral health as measured by a higher decayed, missing, and filled-teeth index; dry mouth; and taste problems. [2]

INCIDENCE/ PREVALENCE

Candida species are commensals in the gastrointestinal tract. Most infections are endogenously acquired, although infections in neonates can be primary infections. Transmission can also occur directly from infected people or on fomites (objects that can harbour pathogenic organisms). *Candida* is found in the mouth of 18% to 60% of healthy people in high- and middle-income countries. [3] [4] One cross-sectional study in China (77 HIV-seropositive outpatients and 217 HIV-negative students) found no significant difference in the rates of asymptomatic *Candida* carriage reported in healthy and HIV-seropositive people (18% of healthy people *v* 29% of HIV-seropositive people; P = 0.07). [4] Denture stomatitis associated with *Candida* is prevalent in 65% of denture wearers. [3] Oropharyngeal candidiasis affects between 15% and 60% of people with haematological or oncological malignancies during periods of immunosuppression. [5] The prevalence of oral candidiasis during head and neck radiation therapy is similar to that during chemotherapy. [6] Oropharyngeal candidiasis occurs in 7% to 48% of people with HIV infection and in >90% of those with advanced disease. In severely immunosuppressed people, relapse rates are high (30%–50%) and relapse usually occurs within 14 days of stopping treatment. [7]

AETIOLOGY/ RISK FACTORS

Risk factors associated with symptomatic oropharyngeal candidiasis include: local or systemic immunosuppression; haematological disorders; broad-spectrum antibiotic use; inhaled or systemic corticosteroids; xerostomia; diabetes; wearing dentures, obturators, or orthodontic appliances; and smoking. [1] [8] [9] Smoking predisposes to oral carriage of *Candida*. [9] In one study of 2499 men with HIV and a baseline CD4+ cell count >200 cells/microlitre, smoking increased the risk of pseudomembranous candidiasis by 40% (P less than or equal to 0.01). [9] However, another study (139 people with HIV infection) suggested that smoking was not a risk factor for those with a baseline CD4+ cell count <200 cells/microlitre. [10] The exact mechanism of action by which smoking predisposes to *Candida* is not known, but it may involve the impairment of local immunity by inducing cytokine changes and reducing epithelial cell-mediated anticandidal activity. [9] The same *Candida* strain may persist for months or years in the absence of infection. In people with HIV infection, there is no direct correlation between the number of organisms and the presence of clinical disease. Candidal strains causing disease in people with HIV infection seem to be the same as those colonising HIV-negative people, and in most people do not change over time. [4] Symptomatic oropharyngeal candidiasis associated with in-vitro resistance to fluconazole occurs in 5% of people with advanced HIV disease. [11] Resistance to azole antifungal drugs is associated with severe immunosuppression (CD4+ cell count 50 cells/microlitre or less), more episodes treated with antifungal drugs, and longer median duration of systemic azole treatment. [12]

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PROGNOSIS In most people, untreated candidiasis persists for months or years unless associated risk factors are treated or eliminated. In neonates, spontaneous cure of oropharyngeal candidiasis usually occurs after 3 to 8 weeks. Protease inhibitors used in highly active antiretroviral treatment (HAART) regimens in HIV-seropositive people have been shown to directly attenuate the adherence of *Candida albicans* to epithelial cells *in vitro* by inhibiting the action of *Candida* virulence factors. [13]

AIMS OF INTERVENTION To resolve signs and symptoms of oropharyngeal candidiasis; to prevent or delay relapse in immunocompromised people; to minimise drug-induced resistance, with minimum adverse effects.

OUTCOMES **Prevention of oral candidiasis:** rate of occurrence or recurrence on the basis of scoring of signs and symptoms. **Treatment success:** cure; clinical cure; resolution of signs and symptoms of oral candidiasis. Many RCTs report the results of mycological culture but, whenever possible, this review does not use these intermediate outcomes because the relation between the clinical and mycological culture findings is uncertain. **Adverse effects**. For the question on which treatments reduce the risk of acquiring resistance to antifungal drugs, the previously listed outcomes plus **mortality** and **drug-induced resistance to treatment**.

METHODS *Clinical Evidence* search and appraisal July 2013. The following databases were used to identify studies for this systematic review: Medline 1966 to July 2013, Embase 1980 to July 2013, and The Cochrane Database of Systematic Reviews 2013, issue 2 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against pre-defined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against pre-defined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in any language, including open studies, with a minimum of 25 participants. There was no minimum length of follow-up required for included studies, and a maximum of 20% of participants lost to follow-up (except studies involving people with HIV infection that have no minimum follow-up requirement). We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA, the EMA, and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 37). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of interventions to prevent and treat oropharyngeal candidiasis in adults undergoing treatments that cause immunosuppression?**

OPTION **ANTIFUNGAL PROPHYLAXIS IN ADULTS WITH CANCER UNDERGOING CHEMOTHERAPY AND/OR RADIOTHERAPY**

- For GRADE evaluation of interventions for Candidiasis (oropharyngeal), see table, p 37 .
- In people with immunosuppression following cancer treatment, absorbed (ketoconazole, itraconazole, or fluconazole) or partially absorbed antifungal drugs (miconazole, clotrimazole) prevent oropharyngeal candidiasis compared with placebo or non-absorbed antifungal drugs.
- Non-absorbed antifungal drugs (nystatin or amphotericin B) may be no more effective than placebo at preventing candidiasis.
- There have been alerts that oral ketoconazole can cause severe liver injury, adrenal gland problems, can lead to harmful drug interactions, and that the benefits do not outweigh the risks in treating fungal infections. It has been suspended in some countries and restrictions placed on its use in others.

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Benefits and harms

Absorbed antifungal drugs versus placebo or no treatment:

We found one systematic review (search date 2009, 28 RCTs, 4226 people), which grouped antifungal drugs according to gastrointestinal absorption characteristics into: absorbed drugs (ketoconazole, itraconazole, or fluconazole), partially absorbed drugs (miconazole, clotrimazole), and non-absorbed drugs (nystatin, amphotericin B). [14]

Prevention of oral candidiasis

Compared with placebo or no treatment Absorbed antifungal drugs (ketoconazole, itraconazole, fluconazole) are more effective at reducing the proportion of people who develop oral candidiasis at 2 to 10 weeks in people having chemotherapy or radiotherapy for cancer (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Prevention of oral candidiasis					
[14] Systematic review	1153 people having chemotherapy or radiotherapy for cancer 7 RCTs in this analysis	**Oral candidiasis , 2 to 10 weeks** 39/575 (7%) with absorbed antifungal drugs (ketoconazole, itraconazole, or fluconazole) 81/578 (14%) with placebo	RR 0.47 95% CI 0.29 to 0.78	●●○	absorbed antifungal drugs (ketoconazole, itraconazole, or fluconazole)

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[14] Systematic review	871 people having chemotherapy or radiotherapy for cancer 3 RCTs in this analysis	**Adverse effects** 62/437 (14%) with absorbed antifungal drugs (ketoconazole, itraconazole, or fluconazole) 52/434 (12%) with placebo	RR 1.18 95% CI 0.84 to 1.67	↔	Not significant

Partially absorbed antifungal drugs versus placebo or no treatment:

We found one systematic review (search date 2009, 28 RCTs, 4226 people having chemotherapy or radiotherapy for cancer). [14]

Prevention of oral candidiasis

Compared with placebo or no treatment Partially absorbed antifungal drugs (miconazole, clotrimazole) are more effective at reducing the proportion of people who develop oral candidiasis at 3 to 8 weeks in people having chemotherapy or radiotherapy for cancer (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Prevention of oral candidiasis					
[14] Systematic review	292 people having chemotherapy or radiotherapy for cancer 4 RCTs in this analysis	**Oral candidiasis , 3 to 8 weeks** 7/147 (5%) with partially absorbed antifungal drugs (miconazole or clotrimazole) 53/145 (37%) with placebo or no treatment	RR 0.13 95% CI 0.06 to 0.46	●●●	partially absorbed antifungal drugs (miconazole or clotrimazole)

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Adverse effects

No data from the following reference on this outcome. [14]

Non-absorbed antifungal drugs versus placebo or no treatment:

We found one systematic review (search date 2009, 28 RCTs, 4226 people having chemotherapy or radiotherapy for cancer). [14]

Prevention of oral candidiasis

Compared with placebo or no treatment We don't know whether non-absorbed antifungal drugs are more effective at reducing the proportion of people who develop oral candidiasis at 3 to 52 weeks in people having chemotherapy or radiotherapy for cancer (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Prevention of oral candidiasis					
[14] Systematic review	382 people having chemotherapy or radiotherapy for cancer 8 RCTs in this analysis	**Oral candidiasis , 3 to 52 weeks** 85/216 (39%) with non-absorbed antifungal drugs 101/166 (61%) with placebo or no treatment Non-absorbed antifungal drugs in the analysis were nystatin; nystatin plus chlorhexidine; amphotericin B alone; or amphotericin B combined with nystatin, norfloxacin, natamycin, thymostimulin, or chlorhexidine	RR 0.68 95% CI 0.46 to 1.02	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [14]

Absorbed versus non-absorbed antifungal drugs:

We found one systematic review (search date 2009, 28 RCTs, 4226 people having chemotherapy or radiotherapy for cancer) comparing absorbed antifungal drugs (ketoconazole, itraconazole, or fluconazole) versus non-absorbed antifungal drugs (nystatin alone, amphotericin B alone, or amphotericin B plus nystatin), [14] and one subsequent RCT (106 adults with haematological malignancies and neutropenia) comparing itraconazole solution (5 mg/kg twice-daily) versus non-absorbed amphotericin B solution (1000 mg three times daily). [15]

Prevention of oral candidiasis

Absorbed compared with non-absorbed antifungal drugs Absorbed antifungal drugs (ketoconazole, itraconazole, fluconazole) seem more effective than non-absorbed antifungal drugs (nystatin, amphotericin B, amphotericin B plus nystatin) at reducing the proportion of people who develop oral candidiasis at 3 to 12 weeks (moderate-quality evidence).

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Prevention of oral candidiasis					
[14] Systematic review	2014 people having chemotherapy or radiotherapy for cancer 8 RCTs in this analysis	**Oral candidiasis , 3 to 12 weeks** 30/1059 (3%) with absorbed antifungal drugs (ketoconazole, itraconazole, or fluconazole) 81/1044 (8%) with non-absorbed antifungal drugs (nystatin alone, amphotericin B alone, or amphotericin B plus nystatin)	RR 0.40 95% CI 0.21 to 0.76 Significant statistical heterogeneity among RCTs; see further information on studies for full details	●●○	absorbed antifungal drugs (ketoconazole, itraconazole, or fluconazole)
[15] RCT	106 adults with haematological malignancies and neutropenia	***Candida* colonisation rate in the oropharynx , treatments given until neutropenia had resolved** 20% with itraconazole solution (5 mg/kg twice-daily) 41% with non-absorbed amphotericin B solution (1000 mg three times daily) Absolute numbers not reported	P <0.05	○○○	itraconazole solution
[15] RCT	106 adults with haematological malignancies and neutropenia	**Clinical oropharyngeal candidiasis with positive cultures , treatments given until neutropenia had resolved** 2% with itraconazole solution (5 mg/kg twice-daily) 8% with non-absorbed amphotericin B solution (1000 mg three times daily) Absolute numbers not reported	Significance not assessed		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[14] Systematic review	2018 people having chemotherapy or radiotherapy for cancer 6 RCTs in this analysis	**Adverse effects** 67/1011 (6.6%) with absorbed antifungal drugs (ketoconazole, itraconazole, or fluconazole) 67/1007 (6.7%) with non-absorbed antifungal drugs (nystatin alone, amphotericin B alone, or amphotericin B plus nystatin)	RR 0.88 95% CI 0.33 to 2.30	⟷	Not significant

No data from the following reference on this outcome. [15]

Further information on studies

[14] For the comparison of non-absorbed antifungal drugs versus placebo or no treatment, the review found significant heterogeneity in the included RCTs (P <0.001) because of the wide range of drugs and combinations assessed. For all comparisons, adverse effects were documented in 13 of the 28 trials in the review, and ranged from 0% to 18%. However, few data were reported by the RCTs on the nature and severity of the adverse effects. None

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of the RCTs included in the review gave information on general wellbeing or quality of life in people having antifungal prophylaxis. For the comparison of partially absorbed antifungal drugs versus placebo or no treatment, two of the RCTs identified by the review (60 people) reported no treatment-related adverse effects. For the comparison of non-absorbed antifungal drugs versus placebo or no treatment, the RCTs identified by the review gave no information on harms.

[15] The RCT comparing itraconazole solution versus non-absorbed amphotericin B solution reported that a power calculation suggested that 80 people would be needed in each group. However, the RCT did not meet this recruitment target.

Comment: Topical preparations of amphotericin B are no longer available in the UK.

Drug safety alert: oral ketoconazole (July 2013) There have been drug safety alerts that oral ketoconazole may cause severe liver injury, adrenal gland problems, and can lead to harmful drug interactions. In July 2013, the European Medicines Agency's (EMA) Committee on Medicinal Products for Human Use recommended that oral ketoconazole should not be used for the treatment of fungal infections, as the benefits of treatment no longer outweigh the risks (www.ema.europa.eu/ema). The EMA recommended that the marketing authorisations of oral ketoconazole-containing medicines should be suspended throughout the European Union. The final decision is awaited on this recommendation. This recommendation does not apply to topical formulations of ketoconazole (e.g. shampoos containing ketoconazole). Oral ketoconazole may be unavailable or restricted in some countries. The US Food and Drug Administration (FDA) recommend that oral ketoconazole should not be first-line treatment for any fungal infection and should only be used for certain life-threatening fungal infections where alternative treatments are not available or tolerated, and when the potential benefits of treatment outweigh the risks. Its use is contraindicated in people with liver disease (www.fda.gov).

OPTION ANTIFUNGAL PROPHYLAXIS IN ADULTS HAVING TISSUE TRANSPLANTS

- For GRADE evaluation of interventions for Candidiasis (oropharyngeal), see table, p 37 .
- We don't know whether antifungal prophylaxis is effective in adults having tissue transplants, as we found few studies.
- There have been alerts that oral ketoconazole can cause severe liver injury, adrenal gland problems, can lead to harmful drug interactions, and that the benefits do not outweigh the risks in treating fungal infections. It has been suspended in some countries, and restrictions placed on its use in others.

Benefits and harms

Antifungal prophylaxis in people having liver transplant:

We found no systematic review of antifungal prophylaxis specifically for the prevention or treatment of oropharyngeal candidiasis in people having liver transplants. We found two small RCTs in people having liver transplants, comparing the abilities of different antifungal drugs to prevent oropharyngeal candidiasis. [16] [17]

Prevention of oral candidiasis

Different types of antifungal prophylaxis compared with placebo or each other in people having liver transplant We don't know whether different regimens of antifungal prophylaxis differ in their effectiveness at preventing oral candidiasis in people having liver transplants (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Prevention of oral candidiasis					
[16] RCT	143 people having liver transplants	**Oropharyngeal candidiasis , 28 days** 8/76 (11%) with fluconazole 14/67 (21%) with nystatin	Significance not assessed The RCT may have lacked power to detect a clinically important difference between groups		
[17] RCT	34 people having liver transplants	**Oropharyngeal candidiasis , during hospital stay after transplantation**	Significance not assessed		

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		1/17 (6%) with clotrimazole 1/17 (6%) with nystatin	The RCT may have lacked power to detect a clinically important difference between groups		

Adverse effects

No data from the following reference on this outcome. [16] [17]

Different types of antifungal prophylaxis versus placebo or each other in people having bone marrow transplant:

We found no systematic review. We found two RCTs in people with neutropenia who had received bone marrow transplants. [18] [19]

Prevention of oral candidiasis

Different types of antifungal prophylaxis compared with placebo or each other in people having bone marrow transplant
We don't know if different regimens of antifungal prophylaxis differ in their effectiveness at preventing oral candidiasis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Prevention of oropharyngeal candidiasis					
[18] RCT **4-armed trial**	86 adults with leukaemia and bone marrow transplant	**Oropharyngeal candidiasis** with rinse containing saline alone with rinse containing nystatin alone Absolute results not reported Similar rates of development of oropharyngeal candidiasis reported for the two rinses. Chlorhexidine arms not included in this review. The remaining arms evaluated saline alone and nystatin alone	Significance not assessed The RCT was not powered to detect a clinically important difference between groups		
[19] RCT	40 people with a variety of malignancies including lymphoma, breast cancer, multiple myeloma, and testicular cancer, who had neutropenia and who had received bone marrow transplants The RCT was open label	**Clinical signs of oropharyngeal candidiasis** 4/20 (20%) with adding topical amphotericin B 500 mg suspension 8/19 (42%) with adding nystatin suspension 400,000 IU four times daily All people took systemic fluconazole 200 mg/day	P = 0.18 Results may have been affected by compliance: see further information on studies	⟷	Not significant
[19] RCT	40 people with a variety of malignancies including lymphoma, breast cancer, multiple myeloma, and testicular cancer, who had neutropenia and who had re-	**Oral colonisation by *Candida* species** 4/20 (20%) with adding topical amphotericin B 500 mg suspension 5/19 (26%) with adding nystatin suspension 400,000 IU four times daily	P = 0.72 Results may have been affected by compliance: see further information on studies	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	ceived bone marrow transplants The RCT was open label	All people took systemic fluconazole 200 mg/day			

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[19] RCT	40 people with a variety of malignancies including lymphoma, breast cancer, multiple myeloma, and testicular cancer, who had neutropenia and who had received bone marrow transplants The RCT was open label	**Nausea** 16/20 (80%) with adding topical amphotericin B 500 mg suspension 17/20 (85%) with adding nystatin suspension 400,000 IU four times daily All people took systemic fluconazole 200 mg/day	P = 1.00	⟷	Not significant
[19] RCT	40 people with a variety of malignancies including lymphoma, breast cancer, multiple myeloma, and testicular cancer, who had neutropenia and who had received bone marrow transplants The RCT was open label	**Vomiting** 13/20 (65%) with adding topical amphotericin B 500 mg suspension 11/20 (55%) with adding nystatin suspension 400,000 IU four times daily All people took systemic fluconazole 200 mg/day	P = 0.75	⟷	Not significant
[19] RCT	40 people with a variety of malignancies including lymphoma, breast cancer, multiple myeloma, and testicular cancer, who had neutropenia and who had received bone marrow transplants The RCT was open label	**Diarrhoea** 6/20 (30%) with adding topical amphotericin B 500 mg suspension 5/20 (25%) with adding nystatin suspension 400,000 IU four times daily All people took systemic fluconazole 200 mg/day	P = 1.00	⟷	Not significant

No data from the following reference on this outcome. [18]

Further information on studies

[16] **Antifungal prophylaxis in people having liver transplant** The RCT found no increased hepatotoxicity, ciclosporin interaction, or emergence of clinically relevant resistant strains reported in people taking antifungal

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prophylaxis after liver transplantation. However, again, the RCT may have lacked power to detect clinically important increases in adverse effects.

[19] **Antifungal prophylaxis in people having bone marrow transplant** In the second RCT, significantly fewer people taking amphotericin B than nystatin completed the trial (3/20 [15%] with amphotericin B *v* 10/20 [50%] with nystatin; P = 0.04). The difference in trial completion was primarily because of lack of patient compliance with amphotericin B, which was related to its texture (viscosity) and taste.

Comment:

Antifungal prophylaxis in people having liver transplant:
We found one systematic review (search date 2004, 6 RCTs, including 1 RCT described in the benefits section above) [16] comparing systemic antifungal prophylaxis versus control (placebo, no treatment, or oral non-absorbable antifungal treatments such as nystatin) in people having a liver transplant. [20] The systematic review did not distinguish between superficial oral infections and superficial infections at other sites (skin, vagina, gastrointestinal tract, or urinary tract), or distinguish between different types of fungal infection. It found that antifungal prophylaxis reduced superficial fungal infections compared with control (5 RCTs, 679 people; AR: 5.2% with antifungal prophylaxis *v* 19.1% with control; RR 0.27, 95% CI 0.16 to 0.45). It is not clear whether this result is generalisable to oropharyngeal candidiasis.

Drug safety alert: oral ketoconazole (July 2013) There have been drug safety alerts that oral ketoconazole may cause severe liver injury, adrenal gland problems, and can lead to harmful drug interactions (see Drug safety alert, p 4).

OPTION ANTIFUNGAL TREATMENT IN ADULTS WITH CANCER HAVING CHEMOTHERAPY OR RADIOTHERAPY

- For GRADE evaluation of interventions for Candidiasis (oropharyngeal), see table, p 37 .
- We don't know whether antifungal treatment is effective in people with immunosuppression following cancer treatment.
- There have been alerts that oral ketoconazole can cause severe liver injury, adrenal gland problems, can lead to harmful drug interactions, and that the benefits do not outweigh the risks in treating fungal infections. It has been suspended in some countries, and restrictions placed on its use in others.

Benefits and harms

Antifungal drugs versus placebo:

We found one systematic review (search date 2010, 10 RCTs, 940 people with cancer having chemotherapy, radiotherapy, or both). [21]

Treatment success

Antifungal drugs compared with placebo Ketoconazole seems more effective at reducing the proportion of people with oral candidiasis at 14 days in people who have had chemotherapy, radiotherapy, or both for cancer (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Eradication of oral candidiasis					
[21] Systematic review	56 people with cancer having chemotherapy, radiotherapy, or both Data from 1 RCT	**Proportion of people with eradication of oral candidiasis , 14 days** 26/36 (72%) with ketoconazole 4/20 (20%) with placebo	RR 3.61 95% CI 1.47 to 8.88 P = 0.0052	●●○	ketoconazole

Adverse effects

No data from the following reference on this outcome. [21]

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Different doses of the same antifungal drug:

We found one systematic review (search date 2010, 10 RCTs, 940 people with cancer having chemotherapy, radiotherapy, or both). [21]

Treatment success

Different doses of the same antifungal drug compared with each other We don't know whether different doses of clotrimazole differ in their effectiveness at increasing clinical cure rates in people who have had chemotherapy, radiotherapy, or both for cancer. A lower-dose mucoadhesive buccal tablet of the partially absorbed drug miconazole may be as effective as a higher dose of miconazole gel (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Persistence of oral candidiasis					
[21] Systematic review	52 people with cancer having chemotherapy, radiotherapy, or both Data from 1 RCT	**Proportion of people with persistence of oral candidiasis** 1/26 (4%) with clotrimazole 50 mg lozenge 1/26 (4%) with clotrimazole 10 mg lozenge	RR 1.00 95% CI 0.07 to 15.15	⟷	Not significant
[21] Systematic review	282 people with head and neck cancer having chemotherapy or radiotherapy Data from 1 RCT	**Proportion of people with persistence of oral candidiasis** 74/141 (52%) with miconazole mucoadhesive buccal tablets (50 mg) 64/141 (45%) with miconazole gel (125 mg applied four times daily)	RR 1.16 95% CI 0.91 to 1.47	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [21]

Absorbed antifungal drugs versus each other:

We found one systematic review (search date 2010, 10 RCTs, 940 people with cancer having chemotherapy, radiotherapy, or both). [21]

Treatment success

Absorbed antifungal drugs compared with each other We don't know whether fluconazole, ketoconazole, and itraconazole differ in their effectiveness at increasing clinical cure rates in people who have had chemotherapy, radiotherapy, or both for cancer (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinically assessed cure					
[21] Systematic review	293 people with cancer having chemotherapy, radiotherapy, or both 2 RCTs in this analysis	**Clinically assessed cure , 6 weeks** 118/149 (79%) with fluconazole 100/144 (69%) with itraconazole	RR 1.13 95% CI 1.00 to 1.28	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] Systematic review	267 people with cancer having chemotherapy, radiotherapy, or both Data from 1 RCT	**Clinically assessed cure , 4 to 27 days** 15/19 (79%) with fluconazole 14/18 (78%) with ketoconazole	RR 1.02 95% CI 0.72 to 1.42	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [21]

Absorbed versus non-absorbed antifungal drugs:

We found one systematic review (search date 2010, 10 RCTs, 940 people with cancer having chemotherapy, radiotherapy, or both). [21] The review identified three RCTs comparing absorbed and non-absorbed antifungal drugs. [21] The review reported significant heterogeneity among the RCTs. The first RCT identified by the review (186 people) assessed immunocompromised children and is not reported individually here (see antifungal treatment in immunocompetent or immunocompromised infants and children, p 15). [22] However, this RCT is included in the meta-analysis performed by the review. [21]

Treatment success

Absorbed antifungal drugs compared with non-absorbed antifungal drugs Antifungal drugs absorbed from the GI tract may be more effective at increasing clinical cure rates in people who have had chemotherapy, radiotherapy, or both for cancer (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Clinically assessed cure rates					
[21] Systematic review	207 people (including children) 3 RCTs in this analysis	**Proportion of people with eradication of oral candidiasis** 89/105 (85%) with absorbed drugs (fluconazole/ketoconazole) 67/102 (66%) with non-absorbed drugs (amphotericin/nystatin) The review noted significant heterogeneity between trials	RR 1.29 95% CI 1.09 to 1.52 P = 0.0026	●○○	absorbed drugs (fluconazole/ketoconazole)

Adverse effects

No data from the following reference on this outcome. [21]

Further information on studies

[21] Given the heterogeneity of the three RCTs included in the meta-analysis of absorbed versus non-absorbed antifungal drugs, the results may not be robust. The review reported inadequate blinding and allocation concealment in most of the included trials.

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Comment: In assessing outcomes, the review noted that few RCTs described the clinical criteria used. [21] The review concluded that there were insufficient trials to make strong recommendations for patient care, and that further well-designed, placebo-controlled trials were needed to assess the effectiveness of old and new interventions for treating oral candidiasis. [21]

Drug safety alert: oral ketoconazole (July 2013) There have been drug safety alerts that oral ketoconazole may cause severe liver injury, adrenal gland problems, and can lead to harmful drug interactions (see Drug safety alert, p 4).

QUESTION **What are the effects of interventions to prevent and treat oropharyngeal candidiasis in infants and children?**

OPTION **ANTIFUNGAL PROPHYLAXIS IN IMMUNOCOMPROMISED INFANTS AND CHILDREN**

- For GRADE evaluation of interventions for Candidiasis (oropharyngeal), see table, p 37 .
- Prophylaxis with fluconazole is more effective than oral nystatin or amphotericin B at preventing candidiasis in immunocompromised infants and children.
- There have been alerts that oral ketoconazole can cause severe liver injury, adrenal gland problems, can lead to harmful drug interactions, and that the benefits do not outweigh the risks in treating fungal infections. It has been suspended in some countries, and restrictions placed on its use in others.

Benefits and harms

Fluconazole versus oral nystatin or amphotericin B:

We found no systematic review. We found no placebo-controlled RCTs, but found two RCTs comparing antifungal drugs with each other for prevention of oropharyngeal candidiasis. [5] [23]

Prevention of oral candidiasis

Different antifungal regimens compared with each other Antifungal prophylaxis with fluconazole may be more effective than oral polyenes (nystatin, oral amphotericin B, or both) at preventing candidiasis in immunocompromised infants and children aged 6 months to 17 years, about to have initial or repeat courses of chemotherapy or radiotherapy for haematological or oncological malignancies (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Incidence of oropharyngeal candidiasis					
[5] RCT	502 immunocompromised infants and children aged 6 months to 17 years, about to have initial or repeat courses of chemotherapy or radiotherapy for haematological or oncological malignancies Multicentre, open-label trial	**Incidence of oropharyngeal candidiasis** 3/236 (1%) with fluconazole 15/249 (6%) with oral polyenes (nystatin, oral amphotericin B, or both)	RR 0.21 95% CI 0.06 to 0.72 NNT 21 95% CI 18 to 58	●●○	fluconazole
[23] RCT	50 immunocompromised children Subgroup analysis See further information on studies for details on population	**Incidence of oropharyngeal candidiasis** 2/25 (8%) with fluconazole 3/25 (12%) with nystatin	P = 0.63	⟷	Not significant

Adverse effects

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No data from the following reference on this outcome. [5] [23]

Further information on studies

[5] In the RCT, adverse events caused 8/245 (3%) children on fluconazole to withdraw compared with 3/257 (1%) on oral polyenes.

[23] Eighteen of the children from one multicentre RCT [5] were enrolled in this small RCT. The inclusion of pretreated children may have biased results, and the study may have lacked power to detect clinically important differences. In the second RCT, no children were withdrawn from the study, but three children treated with fluconazole reported nausea and abdominal discomfort and one reported pruritus.

Comment: Oral preparations of amphotericin B are no longer available in some countries, such as the UK and the US.

Drug safety alert: oral ketoconazole (July 2013) There have been drug safety alerts that oral ketoconazole may cause severe liver injury, adrenal gland problems, and can lead to harmful drug interactions (see Drug safety alert, p 4).

OPTION ANTIFUNGAL TREATMENT IN IMMUNOCOMPETENT OR IMMUNOCOMPROMISED INFANTS AND CHILDREN

- For GRADE evaluation of interventions for Candidiasis (oropharyngeal), see table, p 37 .
- Treatment with fluconazole and miconazole increases cure rates compared with nystatin in both immunocompromised and immunocompetent infants and children.
- There have been alerts that oral ketoconazole can cause severe liver injury, adrenal gland problems, can lead to harmful drug interactions, and that the benefits do not outweigh the risks in treating fungal infections. It has been suspended in some countries, and restrictions placed on its use in others.

Benefits and harms

Antifungals versus placebo or each other in immunocompetent children:

We found no systematic review or placebo-controlled RCTs. We found two RCTs in immunocompetent infants with oropharyngeal candidiasis comparing miconazole gel, nystatin suspension, and nystatin gel. [24] [25] We found one RCT comparing fluconazole versus nystatin. [26]

Treatment success

Antifungal treatments compared with placebo or each other in immunocompetent infants and children Both miconazole and fluconazole seem more effective than nystatin at increasing rates of clinical cure of oral candidiasis in immunocompetent infants (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure of oral candidiasis					
[24] RCT	183 infants aged <1 year with signs of oropharyngeal candidiasis	**Cure rate , 5 days** 83/98 (85%) with miconazole gel (25 mg four times daily) 18/85 (21%) with nystatin (100,000 units four times daily)	P <0.0001	○○○	miconazole gel (25 mg 4 times daily)
[24] RCT	183 infants aged <1 year with signs of oropharyngeal candidiasis	**Cure rate , 12 days** 97/98 (99%) with miconazole gel (25 mg four times daily)	P <0.0001	○○○	miconazole gel (25 mg 4 times daily)

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		46/85 (54%) with nystatin (100,000 units four times daily)			
[25] RCT	95 infants, mean age 5 months, range 2 to 17 months, with clinical oral thrush	**Clinical cure , 14 days** with miconazole gel with nystatin gel preparation Absolute results not reported	P = 0.0032 Miconazole gel also significantly improved cure rate versus another brand of nystatin gel (P = 0.00068)	○○○	miconazole gel
[26] RCT	47 infants, aged 1 to 12 months, with clinical signs of oral candidiasis and culture positive for *Candida* species	**Clinical cure** 15/15 (100%) with fluconazole (suspension 3 mg/kg once-daily for 7 days) 6/19 (32%) with nystatin (oral suspension 100,000 IU/mL four times daily for 10 days) Absolute results not reported	P <0.0001	○○○	fluconazole (suspension 3 mg/kg once-daily for 7 days)

Adverse effects

No data from the following reference on this outcome. [24] [25] [26]

Antifungals versus placebo or each other in immunocompromised children:

We found no systematic review or placebo-controlled RCTs. We found one multicentre RCT (32 centres, 182 immunocompromised infants and children, aged 5 months to 14 years) comparing fluconazole suspension 3 mg/kg versus nystatin 400,000 units 4 times daily for 14 days. [22]

Treatment success

Antifungal treatments compared with placebo or each other in immunocompromised infants and children Fluconazole may be more effective than nystatin at increasing rates of clinical cure in immunocompromised infants and children aged 5 months to 14 years (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure of oral candidiasis					
[22] RCT	182 immunocompromised infants and children, aged 5 months to 14 years	**Clinical cure rate , 14 days** 78/86 (91%) with fluconazole suspension 3 mg/kg for 14 days 37/73 (51%) with nystatin 400,000 units four times daily for 14 days	RR 1.8 95% CI 1.6 to 1.9 NNT 2 95% CI 2 to 3	●○○	fluconazole suspension 3 mg/kg
[22] RCT	64 children with HIV infection Subgroup analysis	**Clinical cure rate , 14 days** 28/35 (80%) with fluconazole suspension 3 mg/kg for 14 days 6/29 (21%) with nystatin 400,000 units four times daily for 14 days	P <0.001	○○○	fluconazole suspension 3 mg/kg
[22] RCT	92 children with malignancy Subgroup analysis	**Clinical cure rate , 14 days** 49/50 (98%) with fluconazole suspension 3 mg/kg for 14 days	P = 0.001	○○○	fluconazole suspension 3 mg/kg

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		30/42 (71%) with nystatin 400,000 units four times daily for 14 days			
[22] RCT	182 immunocompromised infants and children, aged 5 months to 14 years	**Clinical relapse rate , 14 days after clinical cure** 18% with fluconazole suspension 3 mg/kg for 14 days 24% with nystatin 400,000 units four times daily for 14 days Absolute numbers not reported	Significance not assessed		

Adverse effects

No data from the following reference on this outcome. [22]

Further information on studies

[22] **Immunocompromised infants and children** Adverse events caused 2/94 (2%) children on fluconazole to withdraw compared with 0/88 (0%) children on nystatin (P = 0.04).

[24] **Immunocompetent infants and children** The most common adverse events with both miconazole and nystatin were vomiting and, more rarely, diarrhoea, affecting <4.5% of infants.

[25] **Immunocompetent infants and children** As above, the most common adverse events with both miconazole and nystatin were vomiting and, more rarely, diarrhoea, affecting <4.5% of infants.

Comment:

Immunocompetent infants and children:
The RCTs were not blinded or placebo-controlled. [24] [25] [26] There is potential for observer bias, but the clinical results were corroborated by mycological findings, which were blinded. [24] The larger RCT was carried out in 26 general practices, [24] and so it is representative of the context in which most otherwise healthy infants with oropharyngeal candidiasis would be treated, especially regarding adherence and cure rate.

Immunocompromised infants and children:
Participants included in the RCT were immunocompromised for different reasons: 64 had HIV infection, 92 had a malignancy, and 26 were taking immunosuppressive treatment. [22]

Drug safety alert: oral ketoconazole (July 2013) There have been drug safety alerts that oral ketoconazole may cause severe liver injury, adrenal gland problems, and can lead to harmful drug interactions (see Drug safety alert, p 4).

QUESTION **What are the effects of interventions to prevent and treat oropharyngeal candidiasis in people with dentures?**

OPTION **ANTIFUNGAL PROPHYLAXIS OR TREATMENT IN PEOPLE WITH DENTURES**

- For GRADE evaluation of interventions for Candidiasis (oropharyngeal), see table, p 37 .
- Antifungal drugs may increase clinical improvement or cure in people with oropharyngeal candidiasis caused by wearing dentures.
- We found no clinically important results from RCTs about antifungal prophylaxis in people with dentures.

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- There have been alerts that oral ketoconazole can cause severe liver injury, adrenal gland problems, can lead to harmful drug interactions, and that the benefits do not outweigh the risks in treating fungal infections. It has been suspended in some countries, and restrictions placed on its use in others.

Benefits and harms

Antifungal prophylaxis in people with dentures:

We found no systematic review or RCTs.

Antifungal treatment versus placebo in people with denture stomatitis:

We found no systematic review. We found three small RCTs comparing topical antifungal drugs versus placebo for the treatment of denture stomatitis. [27] [28] [29]

Treatment success

Antifungal treatment compared with placebo Topical fluconazole may be more effective than placebo at increasing the proportion of people with the composite outcome of clinical improvement or cure at 2 and 4 weeks, and topical nystatin and amphotericin B may be more effective than placebo at increasing clinical cure of denture stomatitis (outcome not further defined) in people with denture stomatitis. We don't know whether miconazole dental lacquer (applied to the denture) is more effective than placebo lacquer at improving palatal symptoms (not further defined) at 14 days in people with denture stomatitis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment success					
[27] RCT	46 people with denture stomatitis	**Clinical cure of denture stomatitis , after 4 weeks' treatment** with nystatin with placebo Absolute results not reported	P less than or equal to 0.05	○○○	nystatin
[27] RCT	46 people with denture stomatitis	**Clinical cure of denture stomatitis , after 4 weeks' treatment** with amphotericin B with placebo Absolute results not reported	P less than or equal to 0.01	○○○	amphotericin B
[28] RCT	36 people with denture stomatitis	**Resolution of palatal symptoms , 14 days** 54% with miconazole dental lacquer (applied to the fit surface of an upper denture as a single application) 23% with placebo lacquer Absolute numbers not reported	RR 2.40 95% CI 0.89 to 3.80	⟷	Not significant
[29] RCT	38 people with denture stomatitis	**Clinical improvement or cure rates , 2 weeks** 10/19 (53%) with fluconazole 0/18 (0%) with placebo	P <0.001	○○○	fluconazole
[29] RCT	38 people with denture stomatitis	**Clinical improvement or cure rates , 4 weeks** 5/19 (26%) with fluconazole 0/19 (0%) with placebo	P <0.02	○○○	fluconazole

Adverse effects

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No data from the following reference on this outcome. [27] [28] [29]

Different antifungal treatments versus each other:

We found no systematic review. We found two RCTs. [30] [31]

Treatment success

Different antifungal treatments compared with each other We don't know how fluconazole and amphotericin B treatment differ in their effectiveness at improving cure rates in people with dentures as we found insufficient evidence (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment success					
[30] RCT	29 people with denture stomatitis	**Clinical cure rate** 84% with fluconazole 50 mg daily for 14 days 90% with amphotericin B lozenges plus denture cream for 28 days Absolute numbers not reported	Significance not assessed		
[31] RCT	305 older people with oropharyngeal candidiasis, 176 with dentures Multicentre study	**Clinical cure** with fluconazole 50 mg with amphotericin B 0.5 g Absolute results not reported The RCT reported that it found similar rates of clinical cure in both groups	Significance not assessed		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[31] RCT	305 older people with oropharyngeal candidiasis, 176 with dentures Multicentre study	**Adverse events (including diarrhoea, buccal bitterness, aggravation of pre-existing renal dysfunction, and increased liver transaminases)** 6/150 (4%) with fluconazole 50 mg 0/155 (0%) with amphotericin B 0.5 g	Significance not assessed		

No data from the following reference on this outcome. [30]

Different modes of administration of antifungal drugs:

We found no systematic review. Two RCTs (41 people [32] and 33 people [33]) compared a single application of miconazole dental lacquer versus miconazole gel 2% applied to the denture 4 times daily.

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Treatment success

Different modes of administration of antifungal drugs compared with each other We don't know whether miconazole dental lacquer applied to the denture is more effective than miconazole gel applied to the denture at improving palatal erythema (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment success					
[32] RCT	41 people	**Palatal erythema , 14 days after treatment** 13/20 (65%) with single application of miconazole dental lacquer 16/21 (76%) with miconazole gel 2% applied to the denture 4 times daily	RR 0.85 95% CI 0.42 to 1.20	⟷	Not significant
[33] RCT	33 older people	**Palatal erythema** with single application of miconazole dental lacquer with miconazole gel 2% applied to the denture 4 times daily Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [32] [33]

Further information on studies

[27] The RCT, which exclusively enrolled people with dentures, was not large enough to report reliably on adverse effects.

[28] The RCT, which exclusively enrolled people with dentures, was not large enough to report reliably on adverse effects.

[29] The RCT, which exclusively enrolled people with dentures, was not large enough to report reliably on adverse effects.

[30] Clinical relapse was common in both groups (fluconazole 50 mg daily for 14 days and amphotericin B lozenges plus denture cream for 28 days) at 12 weeks. The RCT, which exclusively enrolled people with dentures, was not large enough to report reliably on adverse effects.

[31] Wearing dentures did not affect the response to antifungal treatment (fluconazole 50 mg or amphotericin B 0.5 g) (clinical cure rate: 151/176 [86%] of denture wearers *v* 102/124 [82%] of non-denture wearers; P value not reported). One person had aggravation of pre-existing renal dysfunction, and withdrew from the RCT. One person had increased liver transaminases, but was not withdrawn from the RCT.

[32] The RCT, which exclusively enrolled people with dentures, was not large enough to report reliably on adverse effects.

[33] The RCT, which exclusively enrolled people with dentures, was not large enough to report reliably on adverse effects.

Comment: Co-interventions included professional cleaning of the dentures at the start of the study, combined with advice on denture hygiene and advice not to wear the dentures while asleep at night. Because the fit surface of the denture may act as a reservoir of primary and recurrent infection, this cleaning and advice may explain the high clinical cure rate in the placebo groups. The RCTs comparing

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different antifungal drugs were not sufficiently powered to detect clinically important differences between treatments.

Drug safety alert: oral ketoconazole (July 2013) There have been drug safety alerts that oral ketoconazole may cause severe liver injury, adrenal gland problems, and can lead to harmful drug interactions (see Drug safety alert, p 4).

OPTION DENTURE HYGIENE

- For GRADE evaluation of interventions for Candidiasis (oropharyngeal), see table, p 37 .
- We found limited evidence that mouth rinsing three times daily plus denture soaking once-daily using an antimicrobial mouth rinse (not specified) may be more effective than the same procedure using a control mouth rinse (not specified) at reducing symptoms of denture stomatitis (outcome not further defined) in people with mild to moderate denture stomatitis.
- We don't know whether denture hygiene or removing dentures at night reduces the risk of developing oropharyngeal candidiasis.

Benefits and harms

Denture hygiene for preventing oropharyngeal candidiasis:

We found one systematic review assessing interventions for cleaning dentures in adults, which included six RCTs; however, none of the interventions used prevention or treatment of oropharyngeal candidiasis as an outcome measure. [34]

Denture hygiene for treating oropharyngeal candidiasis:

We found no systematic review, but found four RCTs. [35] [36] [37] [38]

Treatment success

Denture hygiene regimens for treating oral candidiasis compared with placebo or each other Mouth rinsing three times daily plus denture soaking once daily using an antimicrobial mouth rinse (not specified) may be more effective than the same procedure using a control mouth rinse (not specified) at reducing symptoms of denture stomatitis (outcome not further defined) in people with mild to moderate denture stomatitis; we found insufficient evidence on other regimens compared with placebo or each other (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment success					
[35] RCT	43 people, aged 35 to 73 years with denture stomatitis	**Stomatitis , 4 weeks** with daily soaking of dentures in disinfectant (potassium persulphate 1%) with daily soaking of dentures in placebo (water, peppermint, or dye) Absolute results not reported The results provided for the outcome of stomatitis were difficult to interpret, and therefore no firm conclusions can be drawn	Significance not assessed		
[36] RCT **3-armed trial**	78 people with mild to moderate denture stomatitis The remaining arm evaluated weekly relining of the fit surface of the denture (to improve retention and reduce denture trauma) for 4 weeks	**Symptoms of denture stomatitis , 4 weeks** with mouth rinsing 3 times daily plus denture soaking once-daily using an antimicrobial mouth rinse with mouth rinsing 3 times daily plus denture soaking once-daily using a control mouth rinse Absolute results not reported	P <0.01 for antimicrobial mouth rinse *v* control mouth rinse	○○○	antimicrobial mouth rinse

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[37] RCT	34 people in long-term care with acrylic dentures and a positive test for *Candida albicans*	**Rates of dentures recolonised with *C albicans* , 3 months** with microwave treatment (dentures scrubbed with antibacterial soap and water and then microwaved individually for 1 minute at 850 W on days 1, 5, and 10) with control treatment (dentures soaked in 0.2% chlorhexidine solution overnight for 14 days and scrubbed with antibacterial soap and water on days 1, 5, and 10) Absolute results not reported Both groups also received the same course of topical antifungal medication (nystatin lozenges daily for 14 days)	RR 0.64 95% CI 0.38 to 1.06 The RCT may have lacked power to detect a clinically important difference between groups in this outcome	⟷	Not significant
[37] RCT	34 people in long-term care with acrylic dentures and a positive test for *C albicans*	**Proportion of people with infection of the oral mucosa on cytological smear , 3 months** with microwave treatment (dentures scrubbed with antibacterial soap and water and then microwaved individually for 1 minute at 850 W on days 1, 5, and 10) with control treatment (dentures soaked in 0.2% chlorhexidine solution overnight for 14 days and scrubbed with antibacterial soap and water on days 1, 5, and 10) Absolute results not reported Both groups also received the same course of topical antifungal medication (nystatin lozenges daily for 14 days)	RR 0.25 95% CI 0.06 to 0.59	●●○	microwave treatment
[38] RCT **4-armed trial**	60 people with maxillary complete acrylic dentures and a positive test for *C albicans* and denture stomatitis	**Inflammation severity on Newton scale of 0 to 1 , 30 and 90 days** with microwave treatment (650 W for 6 minutes) 3 times weekly for 30 days with microwave treatment plus topical miconazole gel 3 times daily for 30 days with topical miconazole gel 3 times daily for 30 days with routine dental care (control) The RCT reported absence of *Candida* from palates and dentures in microwave groups at day 30, and from palates at day 90 The RCT reported no response to treatment in the non-microwave groups at day 30; these groups were not followed up at 90 days	P <0.001 for both microwave-treatment arms *v* non-microwave treatment arms The RCT may have lacked power to detect a clinically important difference between groups in this outcome	○○○	microwave treatment

Adverse effects

No data from the following reference on this outcome. [35] [36] [37] [38]

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Further information on studies

[37] In this RCT, exposure time to microwaves was decided arbitrarily. Exposure to microwaves at 850 W for 90 seconds seemed to damage the denture material. The RCT noted that microwave treatment may damage complete dentures that have been relined, repaired, or both, by producing a bubble (pocketing) in the acrylic material; and porcelain teeth with metal retaining pins may cause the microwave to spark and scorch the denture material. It noted that microwave treatment was not suitable for all dentures and should be used with caution. Microwave treatment cannot be used for chrome dentures or dentures with metal clasps.

Comment: Two observational studies found a correlation between the prevalence of denture stomatitis and an unhealthy lifestyle (a global measure including dietary habits, physical activity, alcohol consumption, and smoking), wearing dentures at night, and poor oral hygiene. [39] [40]

QUESTION **What are the effects of interventions to prevent and treat oropharyngeal candidiasis in people with HIV infection?**

OPTION **ANTIFUNGAL PROPHYLAXIS IN PEOPLE WITH HIV INFECTION**

- For GRADE evaluation of interventions for Candidiasis (oropharyngeal), see table, p 37 .
- Daily or weekly prophylaxis with fluconazole or itraconazole reduces the incidence of candidiasis in people with HIV infection. Prophylaxis with nystatin may not be effective.
- There have been alerts that oral ketoconazole can cause severe liver injury, adrenal gland problems, can lead to harmful drug interactions, and that the benefits do not outweigh the risks in treating fungal infections. It has been suspended in some countries, and restrictions placed on its use in others.

Benefits and harms

Fluconazole versus placebo:

We found one systematic review (search date 2009, 33 RCTs, 3445 people), which identified five RCTs that enrolled people with AIDS, AIDS-related complex, or CD4+ cell counts of 300 cells/microlitre or less. [41]

Prevention of oral candidiasis

Compared with placebo Fluconazole is more effective at reducing the proportion of people with oral candidiasis at 1 to 24 weeks compared with placebo in people with AIDS, AIDS-related complex, or CD4+ cell counts of 300 cells/microlitre or less (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Prevention of oral candidiasis					
[41] Systematic review	599 people 5 RCTs in this analysis	**Rate of relapse , 1 to 24 weeks** 100/301 (33%) with fluconazole (either once weekly or once daily) 170/298 (57%) with placebo	RR 0.61 95% CI 0.50 to 0.74	●○○	fluconazole

Adverse effects

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[42] RCT	25 people In review [41]	**Adverse effects** 10/12 (83%) with fluconazole 9/13 (69%) with placebo	P = 0.6	⟷	Not significant
[43] RCT	138 people In review [41]	**Rate of microbial resistance , 37 months** 8/67 (12%) with fluconazole 4/71 (6%) with placebo	P = 0.20	⟷	Not significant

Itraconazole versus placebo:

The systematic review [41] identified one RCT, and we found three additional RCTs. [44] [45] [46]

Prevention of oral candidiasis

Compared with placebo Itraconazole seems more effective at decreasing the proportion of people with oral candidiasis at up to 1 year and at increasing the time to development of oral candidiasis in people with HIV infection, but we don't know whether it is more effective at 32 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Prevention of oral candidiasis					
[41] Systematic review	295 people Data from 1 RCT	**Rate of recurrence , 32 months** 17/149 (11%) with itraconazole 15/146 (10%) with placebo	RR 0.90 95% CI 0.47 to 1.73	⟷	Not significant
[44] RCT	44 men with HIV, successfully treated for oral candidiasis	**Relapse rate , 24 weeks** 5/24 (21%) with daily itraconazole 200 mg for 24 weeks 14/20 (70%) with placebo	ARR 49% 95% CI 19% to 64% NNT 2 95% CI 2 to 5	○○○	itraconazole
[44] RCT	44 men with HIV, successfully treated for oral candidiasis	**Median increase in time to relapse** 10.4 weeks with daily itraconazole 200 mg for 24 weeks 8.0 weeks with placebo	P = 0.001	○○○	itraconazole
[45] RCT	374 people	**Incidence of oral candidiasis , 386 days** 25% with itraconazole 200 mg daily 48% with placebo Absolute numbers not reported	RR 0.33 CI not reported P <0.001	●●○	itraconazole
[45] RCT	374 people	**Time to development of oral candidiasis** 508 days with itraconazole 200 mg daily for a mean duration of 448 days 413 days with placebo for a mean duration of 386 days	P <0.001, log-rank test	○○○	itraconazole
[46] RCT	129 people	**Two or more episodes of oral candidiasis , follow-up 6 to 104 weeks in the itraconazole**	P = 0.04	○○○	itraconazole

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		group and 5 to 104 weeks in the placebo group 6/63 (10%) with itraconazole 200 mg daily 15/66 (23%) with placebo			

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[41] Systematic review	262 people Data from 1 RCT	**Skin rash** 15/149 (10%) with itraconazole 3/113 (2%) with placebo	P = 0.02	○○○	itraconazole
[46] RCT	129 people In review [41]	**Skin rash** 16/63 (25%) with itraconazole 200 mg daily 15/66 (23%) with placebo	P >0.05	⟷	Not significant
[46] RCT	129 people In review [41]	**Mild anaemia** 4/63 (6%) with itraconazole 200 mg daily 5/66 (8%) with placebo	P >0.05	⟷	Not significant
[46] RCT	129 people In review [41]	**Diarrhoea** 3/63 (5%) with itraconazole 200 mg daily 5/66 (8%) with placebo	P >0.05	⟷	Not significant

No data from the following reference on this outcome. [44] [45]

Nystatin versus placebo:

The systematic review identified one RCT (128 men) comparing higher-dose nystatin (400,000 units) and lower-dose nystatin (200,000 units) versus placebo. [41]

Prevention of oral candidiasis

Compared with placebo Nystatin may be no more effective at decreasing the proportion of people with oral candidiasis at 20 weeks in people with AIDS, AIDS-related complex, or CD4+ cell counts of 300 cells/microlitre or less (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Prevention of oral candidiasis					
[41] Systematic review	70 people with recent infection from an RCT of 128 men Data from 1 RCT Subgroup analysis	**Rate of recurrence of oral candidiasis , 20 weeks** 33/47 (70%) with both doses of nystatin (higher-dose nystatin [400,000 units] and lower-dose nystatin [200,000 units]) 20/23 (87%) with placebo	RR 0.82 95% CI 0.65 to 1.04	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[41] Systematic review	48 people with no infection in the preceding year from an RCT of 128 men Data from 1 RCT Subgroup analysis	**Rate of recurrence of oral candidiasis , 20 weeks** 19/38 (50%) with both doses of nystatin (higher-dose nystatin [400,000 units] and lower-dose nystatin [200,000 units]) 10/20 (50%) with placebo	RR 0.99 95% CI 0.52 to 1.89	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [41]

Fluconazole versus clotrimazole:

We found one RCT (428 people from 29 sites) that compared fluconazole 200 mg daily versus clotrimazole 10 mg five times daily over 35 months. [47]

Prevention of oral candidiasis

Fluconazole compared with clotrimazole Fluconazole seems more effective than clotrimazole at decreasing episodes of oral candidiasis in people with HIV infection (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Prevention of oral candidiasis					
[47] Systematic review	428 people from 29 sites Data from 1 RCT	**Rate of recurrence of oropharyngeal candidiasis , 35 months** 6 episodes/100 person-years with fluconazole 200 mg daily over 35 months 38 episodes/100 person-years with clotrimazole 10 mg five times daily over 35 months	P <0.001	○○○	fluconazole

Adverse effects

No data from the following reference on this outcome. [47]

Further information on studies

[41] **Itraconazole versus placebo** In one RCT identified by the review, two people who received itraconazole developed Stevens–Johnson syndrome, one of whom was also taking trimethoprim–sulfamethoxazole. Other adverse effects reported included diarrhoea, nausea, vomiting, and elevated liver enzyme levels.

[44] The RCT found that itraconazole was associated with a widespread itchy rash in 5 people; the rate with placebo was not reported. Concomitant medication and severe underlying disease may have confounded attribution of adverse events.

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[45] The study was terminated because of inadequate power.

[46] One person discontinued treatment with itraconazole because of a skin rash, and concerns about hepatotoxicity resulted in treatment being discontinued in two people (1 with itraconazole, 1 with placebo). There was one case of Stevens–Johnson syndrome in a person taking trimethoprim–sulfamethoxazole as well as itraconazole. Concomitant medication and severe underlying disease may have confounded attribution of adverse events.

[47] The RCT reported that more people discontinued fluconazole due to adverse effects than with clotrimazole, although the difference was not significant (13 with fluconazole *v* 6 with clotrimazole; P = 0.11). Rashes and hepatotoxicity were reported in both groups. Concomitant medication and severe underlying disease may have confounded attribution of adverse events.

Comment:

Clinical guide:
Many of the RCTs were small and not blinded, and most did not adjust for confounding factors such as antiretroviral treatment or other established risk factors for oropharyngeal candidiasis. No RCTs used quality-of-life scores. The optimal dosage schedule and frequency of administration of preventive treatment have not been established. We found no RCTs comparing weekly versus daily regimens of antifungal drugs. We found one RCT that compared two different doses of fluconazole. [48] It found no significant difference between fluconazole 50 mg and 100 mg daily (oropharyngeal candidiasis: 2/18 [11%] with fluconazole 50 mg *v* 4/19 [21%] with fluconazole 100 mg; RR 0.53, 95% CI 0.09 to 2.09). [48] Subgroup analysis in the RCT comparing fluconazole versus placebo found that people with a history of oropharyngeal candidiasis had an absolute benefit of treatment with weekly fluconazole that was higher than in those with no history of infection (ARR: 25.6/100 person-years for those with previous infection *v* 11.2/100 person-years for those with no history of infection). [49]

Drug safety alert: oral ketoconazole (July 2013) There have been drug safety alerts that oral ketoconazole may cause severe liver injury, adrenal gland problems, and can lead to harmful drug interactions (see Drug safety alert, p 4).

OPTION ANTIFUNGAL TREATMENT IN PEOPLE WITH HIV INFECTION

- For GRADE evaluation of interventions for Candidiasis (oropharyngeal), see table, p 37 .
- Clotrimazole lozenges and miconazole buccal slow-release tablets may be as effective as oral tablets/suspensions of oral antifungals (fluconazole/itraconazole/ketaconazole) at reducing symptoms of candidiasis in people with HIV infection.
- Fluconazole, ketoconazole, and posaconazole may be equally effective at increasing cure rates for candidiasis in people with HIV infection, but we don't know whether posaconazole oral suspension is more effective than fluconazole oral suspension.
- A single dose of fluconazole (750 mg) may be as effective as a 14-day course of fluconazole in reducing symptoms of candidiasis in people with HIV infection.
- There have been alerts that oral ketoconazole can cause severe liver injury, adrenal gland problems, can lead to harmful drug interactions, and that the benefits do not outweigh the risks in treating fungal infections. It has been suspended in some countries and restrictions placed on its use in others.

Benefits and harms

Topical antifungal treatment versus placebo:

We found no systematic review or RCTs.

Oral antifungal treatment versus placebo:

We found no systematic review or RCTs.

Topical antifungal treatment versus oral antifungal treatment:

We found one systematic review (search date 2009, 22 RCTs, 1389 people) assessing topical antifungal treatment in people with HIV infection. [41] The review was not restricted to topical treatments and included topical, parenteral,

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and intravenous formulations of antifungals, plus gentian violet, lemon grass, lemon juice, melaleuca, and tea tree oil. The data were pooled for the meta-analysis by type of antifungal, and did not distinguish by method of administration. [41] For most comparisons, the review found only one RCT.

Treatment success

Topical antifungal treatment compared with oral antifungal treatment Fluconazole suspension (directly swallowed) seems more effective than nystatin suspension (used with swish-and-swallow technique) at increasing clinical cure at 14 days, and oral ketoconazole seems more effective than nystatin mouth wash at increasing clinical cure rates in people with HIV infection. Oral fluconazole tablets and clotrimazole lozenges seem equally effective at increasing clinical cure at 14 days, and itraconazole oral solution and clotrimazole lozenges seem equally effective at increasing clinical or mycological cure rates at 7 to 14 days. Oral ketoconazole and topical miconazole slow-release buccal tablets seem equally effective at increasing clinical cure at 14 days (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment success					
[41] Systematic review	167 people Data from 1 RCT	**Clinical cure , 14 days** 60/83 (72%) with fluconazole suspension (directly swallowed) 100 mg daily 36/84 (43%) with nystatin suspension (used with swish-and-swallow technique)	RR 1.69 95% CI 1.27 to 2.23	●○○	fluconazole
[41] Systematic review	150 people with oral candidiasis and HIV Data from 1 RCT	**Clinical cure** 10/45 (22%) with ketoconazole 2/47 (4%) with nystatin mouth wash	RR 5.22 95% CI 1.21 to 22.53	●●●	ketoconazole
[41] Systematic review	358 people 2 RCTs in this analysis	**Clinical cure , 14 days** 151/189 (80%) with oral fluconazole tablets 124/169 (73%) with clotrimazole lozenges	RR 1.14 95% CI 0.92 to 1.42	⟷	Not significant
[41] Systematic review	152 people 2 RCTs in this analysis	**Clinical or mycological cure rates , 7 to 14 days** 43/75 (57%) with itraconazole oral solution 28/77 (36%) with clotrimazole lozenges	RR 1.34 95% CI 0.56 to 3.20	⟷	Not significant
[41] Systematic review	357 people Data from 1 RCT	**Clinical cure , 14 days** 159/179 (89%) with oral ketoconazole 155/178 (87%) with topical miconazole nitrate (10 mg once-daily slow-release mucoadhesive buccal tablet)	RR 1.02 95% CI 0.94 to 1.10	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[41] RCT	Number of people not reported	**Adverse effects** with oral antifungals with topical antifungals			

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute numbers not reported The review did not report adverse effects of oral versus antifungal treatment; for information on overall adverse effects with antifungals; see comment			

Different topical antifungal drugs versus each other:

We found one RCT comparing once-daily bucco-adhesive miconazole tablet with five times daily clotrimazole lozenges. [50]

Treatment success

Different topical antifungal drugs compared with each other A once-daily bucco-adhesive miconazole tablet may be as effective as clotrimazole lozenges five times daily at increasing the proportion of people with clinical cure at 14 days (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment success					
[50] RCT	578 people with oral candidiasis and HIV	**Proportion of people with clinical cure , 14 days** 164/240 (68%) with once-daily miconazole 50 mg bucco-adhesive tablet 175/236 (74%) with 10 mg clotrimazole lozenges five times daily Per-protocol analysis; 476/578 (82%) people completed treatment	Treatment difference –0.059 95% CI –0.140 to +0.022	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[50] RCT	578 people with oral candidiasis and HIV	**Proportion of people with at least 1 adverse event** 161/290 (56%) with once-daily miconazole 50 mg bucco-adhesive tablet 152/287 (53%) with 10 mg clotrimazole five times daily Intention-to-treat analysis 2 people in the miconazole group and 3 in the clotrimazole group withdrew from treatment owing to adverse events	P value not reported Reported as not significant	⟷	Not significant

Different oral antifungals versus each other:

We found one systematic review (search date 2009) assessing oral antifungal treatments versus each other in people with HIV infection; and different doses of fluconazole versus each other. [41]

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Treatment success

Different oral antifungals compared with each other Itraconazole (suspension used in a swish-and-swallow mode) and oral fluconazole tablets seem equally effective at increasing clinical cure at 14 days in people with HIV infection, but we don't know whether posaconazole oral suspension is more effective than fluconazole oral suspension at increasing a composite outcome of clinical success (clinical cure or improvement) (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment success					
[41] Systematic review	434 people 4 RCTs in this analysis	**Proportion of people with clinical cure , 14 days** 118/148 (80%) with fluconazole tablets 214/286 (75%) with topical itraconazole (suspension used in a swish-and-swallow mode)	RR 1.05 95% CI 0.94 to 1.16 P = 0.38	⟷	Not significant
[41] Systematic review	37 people Data from 1 RCT	**Proportion of people with clinical cure , 14 days** 17/18 (94%) with fluconazole 50 mg 12/19 (63%) with ketoconazole 200 mg	RR 1.5 95% CI 1.04 to 2.15 P = 0.029	●○○	fluconazole 50 mg
[41] Systematic review	278 people Data from 1 RCT	**Proportion of people with clinical cure** 130/135 (96%) with fluconazole 139/143 (97%) with posaconazole	RR 1.32 95% CI 0.36 to 4.83	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [41]

Different doses of the same oral antifungal drug:

We found one systematic review (search date 2009), [41] which identified two RCTs comparing different doses of fluconazole versus each other.

Treatment success

Different doses of the same antifungal drug compared with each other A single dose of fluconazole (750 mg or 150 mg) may be as effective as a lower daily dose of the drug (150 mg or 50 mg) for 7 or 14 days at increasing treatment success in people with HIV infection (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment success					
[51] RCT	220 people with HIV and oropharyngeal candidiasis In review [41]	**Proportion of people with clinical cure , 14 days** 105/110 (95%) with fluconazole 150 mg daily for 14 days 105/110 (95%) with fluconazole 750 mg single dose	RR 1.00 95% CI 0.94 to 1.06	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[51] RCT	220 people with HIV and oropharyngeal candidiasis In review [41]	**Proportion of people relapsing , 42 days** 12/100 (12.0%) with fluconazole 150 mg daily for 14 days 12/94 (12.8%) with fluconazole 750 mg single dose	RR 0.94 95% CI 0.44 to 1.99	⟷	Not significant
[41] Systematic review	56 people Data from 1 RCT Non-blinded trial	**Proportion of people with clinical cure , 28 days** 26/28 (93%) with fluconazole 50 mg daily for 7 days 21/28 (75%) with fluconazole 150 mg single dose	RR 1.24 95% CI 0.98 to 1.52	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[51] RCT	220 people with HIV and oropharyngeal candidiasis In review [41]	**Proportion of people reporting adverse effects** 6/110 (5%) with fluconazole 150 mg daily for 14 days 8/110 (7%) with fluconazole 750 mg single dose	Significance not assessed		

Further information on studies

[51] 41/110 (37%) people in the fluconazole single-dose group and 39/110 (35%) people in the fluconazole 14-day group used highly active antiretroviral therapy (HAART). Adverse events were mild. Because most of the trial participants were in an advanced stage of HIV infection and AIDS, abnormalities in full blood count and liver function tests were common, but no clinically significant changes were seen in either arm of the study, except in one person in the single-dose fluconazole group with greatly raised ALT and AST; but the person was asymptomatic and the levels returned to normal.

Comment: Once-daily dosing is likely to increase adherence to treatment. Non-adherence was reported with clotrimazole because of the inconvenience of taking multiple doses.

Adverse effects of antifungal treatment: The most frequently reported adverse effects in the RCTs were gastrointestinal symptoms (nausea, diarrhoea, and vomiting). Altered taste, dry mouth, headache, and rashes were also recorded. [52] [53] [54] [55] [56] There were no withdrawals in two RCTs from adverse effects. [53] [57] Six RCTs (1211 people) reported adverse events with fluconazole (11 people), itraconazole (14 people), clotrimazole (12 people), and nystatin (1 person), resulting in withdrawal from the study. These adverse events were considered to be drug-induced. [52] [54]

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[55] [56] [57] [58] The RCT comparing miconazole nitrate versus ketoconazole found similar rates of adverse effects between the two groups, with the exception of vomiting. [53]
Drug safety alert: oral ketoconazole (July 2013) There have been drug safety alerts that oral ketoconazole may cause severe liver injury, adrenal gland problems, and can lead to harmful drug interactions (see Drug safety alert, p 4).

QUESTION **Which antifungal regimens reduce the risk of acquiring resistance to antifungal drugs?**

OPTION **CONTINUOUS ANTIFUNGAL PROPHYLAXIS VERSUS INTERMITTENT ANTIFUNGAL TREATMENT**

- For GRADE evaluation of interventions for Candidiasis (oropharyngeal), see table, p 37 .
- Continuous prophylaxis with antifungal agents may not increase the risk of developing antifungal resistance compared with intermittent prophylaxis, but it may be no more effective at reducing the number of attacks in people with HIV infection, the majority of whom were receiving highly active antiretroviral treatment (HAART).
- There have been alerts that oral ketoconazole can cause severe liver injury, adrenal gland problems, can lead to harmful drug interactions, and that the benefits do not outweigh the risks in treating fungal infections. It has been suspended in some countries, and restrictions placed on its use in others.

Benefits and harms

Intermittent antifungal treatment versus continuous antifungal prophylaxis:

We found one systematic review (search date 2009, 2 RCT, 891 people). [41]

Mortality

Intermittent antifungal treatment compared with continuous antifungal prophylaxis We don't know whether intermittent fluconazole treatment is more effective than continuous fluconazole prophylaxis at reducing mortality in people with HIV infection who were receiving highly active antiretroviral treatment (HAART) and had a CD4+ cell count <150 cells/microlitre (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[59] RCT	829 people with HIV, CD4+ cell count <150 cells/microlitre, receiving highly active antiretroviral treatment (HAART) In review [41]	**Death** 31/413 (8%) with oral fluconazole (200 mg three times weekly) given continuously 40/416 (10%) with intermittent fluconazole (loading dose 400 mg, followed by 200 mg for 6–13 days)	P = 0.28	⟷	Not significant

No data from the following reference on this outcome. [41]

Drug-induced resistance to treatment

Intermittent antifungal treatment compared with continuous antifungal prophylaxis We don't know whether intermittent fluconazole treatment is more effective than continuous fluconazole prophylaxis at preventing antifungal resistance or at reducing the time to development of fluconazole-refractory oral candidiasis in people with HIV infection, the large majority of whom were receiving highly active antiretroviral treatment (HAART) and had a CD4+ cell count <150 cells/microlitre (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Drug-induced resistance to treatment					
[60] RCT	68 people with oral candidiasis (20 people received continuous prophylaxis with fluconazole; 48 people re-	**Development of acquired resistance , mean of 11 months** 9/16 (56%) with continuous prophylaxis with fluconazole	P = 0.75	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	ceived intermittent treatment with fluconazole 200 mg daily) In review [41]	13/28 (46%) with intermittent treatment with fluconazole 200 mg daily			
[59] RCT	829 people with HIV, CD4+ cell count <150 cells/microlitre, receiving highly active antiretroviral treatment (HAART) In review [41]	**Fluconazole-refractory oropharyngeal candidiasis or oesophageal candidiasis , 42 months** 17/413 (4.1%) with oral fluconazole (200 mg three times weekly) given continuously 18/416 (4.3%) with intermittent fluconazole (loading dose 400 mg, followed by 200 mg for 6–13 days)	Significance not assessed		
[59] RCT	829 people with HIV, CD4+ cell <150 cells/microlitre, receiving HAART In review [41]	**Time to development of fluconazole-refractory oropharyngeal candidiasis or oesophageal candidiasis , after 24 months' treatment** with oral fluconazole (200 mg three times weekly) given continuously with intermittent fluconazole (loading dose 400 mg, followed by 200 mg for 6–13 days) Absolute results not reported	P = 0.88	⟷	Not significant
[59] RCT	829 people with HIV, CD4+ cell count <150 cells/microlitre, receiving HAART In review [41]	**Time to development of fluconazole-refractory oropharyngeal candidiasis or oesophageal candidiasis , after 42 months' treatment** with oral fluconazole (200 mg three times weekly) given continuously with intermittent fluconazole (loading dose 400 mg, followed by 200 mg for 6–13 days) Absolute results not reported	P = 0.97	⟷	Not significant

Prevention of oral candidiasis

Intermittent antifungal treatment compared with continuous antifungal prophylaxis We don't know whether intermittent fluconazole treatment and continuous fluconazole prophylaxis differ in effectiveness at reducing episodes of oral candidiasis in people with HIV infection, the large majority of whom were receiving highly active antiretroviral treatment (HAART) and had a CD4+ cell count <150 cells/microlitre (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Prevention of oral candidiasis					
[41] Systematic review	891 people - the majority (829 people) of whom with HIV with CD4+ cell count <150 cells/microlitre, receiving highly active antiretroviral treatment (HAART) 2 RCTs in this analysis	**Proportion of people relapsing , 11 to 24 months** 22/436 (5%) with continuous fluconazole 40/455 (9%) with intermittent fluconazole There was significant heterogeneity between the 2 studies due to size, fluconazole dosage, and length of treatment period	RR 0.65 95% CI 0.23 to 1.83 P = 0.42	⟷	Not significant

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Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[59] RCT	829 people with HIV, CD4+ cell count <150 cells/microlitre, receiving highly active antiretroviral treatment (HAART) In review [41]	**Discontinued treatment owing to adverse effects** 10/413 (2.4%) with oral fluconazole (200 mg thre times weekly) given continuously 2/416 (0.5%) with intermittent fluconazole (loading dose 400 mg, followed by 200 mg for 6–13 days)	Significance not assessed		
[59] RCT	829 people with HIV, CD4+ cell count <150 cells/microlitre, receiving HAART In review [41]	**Thrombocytopenia (<50,000 platelets/microlitre)** 8/327 (2.4%) with oral fluconazole (200 mg three times weekly) given continuously 1/334 (0.3%) with intermittent fluconazole (loading dose 400 mg, followed by 200 mg for 6–13 days)	P = 0.02	○○○	intermittent fluconazole

Further information on studies

[59] Oropharyngeal candidiasis or oesophageal candidiasis was defined as no response to fluconazole 200 mg daily for 14 days in oropharyngeal candidiasis or 21 days in oesophageal candidiasis.

[60] Antifungal sensitivity testing followed the National Committee for Clinical Laboratory Standards guidelines. [61]

Comment: Optimal treatment regimens to reduce the risk of acquiring resistance have not been adequately evaluated. In a prospective observational study of protease inhibitor treatment, 93 people with HIV infection and a history of recurrent oropharyngeal candidiasis were followed up for 1 year. Oropharyngeal candidiasis was diagnosed in 2/30 (7%) people given protease inhibitors and 23/63 (37%) people given other treatment (P less than or equal to 0.001; CI not reported). [62] In the second RCT, 53% of participants completed treatment. [59] Immunomodulating antiretroviral treatments (e.g., highly active antiretroviral treatment [HAART]) act indirectly as antifungal-sparing agents by reducing the number of recurrences of oropharyngeal candidiasis, thereby reducing exposure to antifungal drugs and the potential risk of resistance. In industrialised nations, the continuous use of fluconazole cannot be recommended except for those individuals experiencing recurrent oropharyngeal candidiasis, given the reduction in fungal infections associated with HAART and the lack of survival benefits associated with continuous fluconazole. [59] [63] In resource-poor settings, where access to HAART is limited, mortality attributable to fungal infections is considerable; therefore, fluconazole prophylaxis may offer greater benefits.

Drug safety alert: oral ketoconazole (July 2013) There have been drug safety alerts that oral ketoconazole may cause severe liver injury, adrenal gland problems, and can lead to harmful drug interactions (see Drug safety alert, p 4).

GLOSSARY

Highly active antiretroviral treatment (HAART) Combination drug treatment used to achieve maximal suppression of HIV replication.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

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Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Antifungal prophylaxis in adults having tissue transplants: Existing evidence re-evaluated. One previously reported RCT excluded. Categorisation unchanged (unknown effectiveness)

Antifungal prophylaxis in people with HIV infection: One previously reported RCT and one pooled analysis excluded. Categorisation unchanged (beneficial).

Antifungal prophylaxis or treatment in people with dentures: Existing evidence re-evaluated. Two previously reported RCTs excluded. Categorisation unchanged (likely to be beneficial).

Antifungal treatment in people with HIV infection: Existing evidence re-evaluated. One previously reported RCT excluded. Categorisation unchanged (beneficial).

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GRADE **Evaluation of interventions for Candidiasis (oropharyngeal).**

Important outcomes	Drug-induced resistance to treatment, Mortality, Prevention of oral candidiasis, Treatment success								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of interventions to prevent and treat oropharyngeal candidiasis in adults undergoing treatments that cause immunosuppression?									
7 (1153) [14]	Prevention of oral candidiasis	Absorbed antifungal drugs versus placebo or no treatment	4	0	0	0	+1	High	Effect-size point added for RR <0.5
4 (292) [14]	Prevention of oral candidiasis	Partially absorbed antifungal drugs versus placebo or no treatment	4	0	0	0	+2	High	Effect-size points added for RR <0.2
8 (382) [14]	Prevention of oral candidiasis	Non-absorbed antifungal drugs versus placebo or no treatment	4	0	–1	–1	0	Low	Consistency point deducted for statistical heterogeneity between RCTs. Directness point deducted for use of co-interventions
9 (2120) [14] [15]	Prevention of oral candidiasis	Absorbed versus non-absorbed antifungal drugs	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (177) [16] [17]	Prevention of oral candidiasis	Antifungal prophylaxis in people having liver transplant	4	–2	0	–1	0	Very low	Quality points deduced for sparse data and incomplete reporting of results. Directness point deducted for small number of comparators
2 (less than 126) [18] [19]	Prevention of oral candidiasis	Different types of antifungal prophylaxis versus placebo or each other in people having bone marrow transplant	4	–2	0	–1	0	Very low	Quality points deduced for sparse data and incomplete reporting of results. Directness point deducted for poor compliance in one RCT
1 (56) [21]	Treatment success	Antifungal drugs versus placebo	4	–1	0	–1	+1	Moderate	Quality point deducted for sparse data. Directness point deducted for unclear definition of outcome. Effect-size point added for RR >2
2 (334) [21]	Treatment success	Different doses of the same antifungal drug	4	–1	0	–1	0	Low	Quality point deducted for methodological weaknesses in some trials (inadequate blinding and allocation concealment). Directness point deducted for unclear definition of outcome
3 (267) [21]	Treatment success	Absorbed antifungal drugs versus each other	4	0	0	–2	0	Low	Directness points deducted for unclear definition of outcome and small number of comparators
3 (207) [21]	Treatment success	Absorbed versus non-absorbed antifungal drugs	4	0	–1	–1	0	Low	Consistency point deducted for heterogeneity among studies. Directness point deducted for inclusion of data from children
What are the effects of interventions to prevent and treat oropharyngeal candidiasis in infants and children?									
2 (502) [5] [23]	Prevention of oral candidiasis	Fluconazole versus oral nystatin or amphotericin B	4	0	0	–2	0	Low	Directness points deducted for inclusion of pretreated children in 1 RCT and open label
3 (325) [24] [25] [26]	Treatment success	Antifungals versus placebo or each other in immunocompetent children	4	0	0	–1	0	Moderate	Directness point deducted for low rate of follow-up in 1 RCT

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Important outcomes	Drug-induced resistance to treatment, Mortality, Prevention of oral candidiasis, Treatment success								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (182) [22]	Treatment success	Antifungals versus placebo or each other in immunocompromised children	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for small number of comparators
What are the effects of interventions to prevent and treat oropharyngeal candidiasis in people with dentures?									
3 (120) [27] [28] [29]	Treatment success	Antifungal treatment versus placebo in people with denture stomatitis	4	–1	0	–2	0	Very low	Quality point deducted for sparse data. Directness points deducted for outcomes not defined in 1 RCT, composite in 1 RCT, and proxy outcome in 1 RCT
2 (334) [30] [31]	Treatment success	Different antifungal treatments versus each other	4	–1	0	-2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for inclusion of non-denture-wearing population and no statistical analysis between groups.
2 (74) [32] [33]	Treatment success	Different modes of administration of antifungal drugs	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for unclear and proxy outcome (palatal erythema)
4 (215) [35] [36] [37] [38]	Treatment success	Denture hygiene for treating oropharyngeal candidiasis	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for use of co-intervention (nystatin), and non-clinical outcomes in 1 RCT
What are the effects of interventions to prevent and treat oropharyngeal candidiasis in people with HIV infection?									
5 (599) [41]	Prevention of oral candidiasis	Fluconazole versus placebo	4	0	0	0	0	High	
4 (842) [41] [44] [45] [46]	Prevention of oral candidiasis	Itraconazole versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for early termination of 1 RCT
1 (128) [41]	Prevention of oral candidiasis	Nystatin versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and combination of 2 different doses in same group in analysis
1 (428) [47]	Prevention of oral candidiasis	Fluconazole versus clotrimazole	4	0	0	–1	0	Moderate	Directness point deducted for small numbers of comparators
7 (1184) [41]	Treatment success	Topical antifungal treatment versus oral antifungal treatment	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of composite outcome (also including mycological cure)
1 (476) [50]	Treatment success	Different topical antifungal drugs versus each other	4	0	0	-2	0	Low	Directness points deducted for high loss to follow up (only 82% completed treatment), and small number of comparators.
at least 4 (434) [41]	Treatment success	Different oral antifungals versus each other	4	0	0	–1	0	Moderate	Directness point deducted for range of interventions in comparison
2 (276) [41]	Treatment success	Different doses of the same oral antifungal drug	4	–1	0	–1	0	Low	Quality point deducted for lack of blinding in 1 RCT. Directness point deducted for highly selected population (>35% using HAART in the largest RCT)

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Important outcomes	Drug-induced resistance to treatment, Mortality, Prevention of oral candidiasis, Treatment success								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
Which antifungal regimens reduce the risk of acquiring resistance to antifungal drugs?									
1 (829) [41]	Mortality	Intermittent antifungal treatment versus continuous antifungal prophylaxis	4	0	0	–2	0	Low	Directness points deducted for highly selected population (majority of people receiving HAART) and low rates of treatment completion
2 (897) [41]	Drug-induced resistance to treatment	Intermittent antifungal treatment versus continuous antifungal prophylaxis	4	0	0	–2	0	Low	Directness points deducted for highly selected population (majority of people receiving HAART) and low rates of treatment completion
2 (891) [41]	Prevention of oral candidiasis	Intermittent antifungal treatment versus continuous antifungal prophylaxis	4	0	–1	–2	0	Very low	Consistency point deducted for heterogeneity between RCTs. Directness points deducted for highly selected population (majority of people receiving HAART) and low rates of treatment completion

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.

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