

7 Candidiasis

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7.1 Methods

The PubMed database was searched under the following headings: HIV or AIDS and candidosis, candidiasis, *Candida* spp., *Candida albicans*, non-albicans *Candida*, oropharyngeal candidiasis and mucosal candidiasis. PICO questions were set and the literature reviewed to address each question. Evidence was assessed and graded using the GRADE system

7.2 Epidemiology of Candidiasis

Candida species are common commensals in the general population and may be cultured using selective media from the oral cavity and genital tracts of up to 75% of individuals [1]. Such cultures are not clinically meaningful.

Surveillance studies consistently identify higher rates of mucosal carriage of *Candida* in HIV-seropositive men and women [2-3], with mucosal candidiasis representing the primary pathological manifestation. Oropharyngeal candidiasis is the commonest opportunistic infection to affect HIV-seropositive individuals, occurring in 80–90% of patients in the pre-HAART era [4-5]. The high burden of mucosal candidiasis is substantiated in recent cohort reviews, however overall prevalence has been substantially reduced by virtue of cART availability [6-7]. Oesophageal candidiasis in the pre-HAART era was the AIDS-defining illness in 11% of cases, however rates up to 23% have been reported in differing cohorts [5, 8-10]. More recent data concerning patients diagnosed at advanced stages of disease have identified a prevalence of oesophageal candidiasis of up to 50% [11]. *Candida* vulvovaginitis occurs sporadically, similar in nature to that observed in the immunocompetent, however can be more recurrent or refractory.

Invasive candidiasis (Candidemia) represents a growing nosocomial threat in healthcare experienced patients. Patients living with HIV are increasingly at risk in the context of undergoing intensive treatments for emerging co-morbidities. Numerous updated guidance documents provide references to managing this serious condition [12-15]. Particular to those living with HIV is the risk of non-albicans species and the concern for residual immunological risk even following immune restitution (see below).

7.2.1 *Candida* species causing *Candida* infections in people living with HIV infection.

Candida albicans remains the most frequent cause of *Candida* infections globally but the distribution of non-albicans *Candida* species shows geographical variation [16]. HIV-specific data for oropharyngeal or vulvovaginal infections reflects the trends in international surveillance data. *Candida albicans* remains most prevalent. The rates of non-albicans species continues to rise approximating 30% in many cohorts, being influenced by

geographic location and resource setting [3,17-19]. Recent US data suggests *C. albicans* is responsible for 62-68% of oropharyngeal candida and 73% of vulvovaginal candida [2,20]. *C. glabrata* (17-21% of cases) and *C. dublinensis* (6-12%) are leading causes of non-albicans candida infections in US and South African populations and are strains that are often azole resistant [20-22]. Further to the shift in prevailing *Candida* species and azole resistance is the evolving theme of Echinocandin non-susceptibility and multi-drug resistant species, placing emphasis on the advances in accurate speciation and susceptibility testing [23-26]. *C. auris*, an inherently multi-drug species, has recently emerged as an infection control challenge colonising patients in intensive care units, particularly after surgery, but has not yet been linked with particular problems in HIV [27].

7.2.2 Risk factors for *Candida* infection in people living with HIV infection

Immunity against *Candida* species at mucosal surfaces is critically dependent on Th17 T-cells [28]. This subset is disproportionately depleted during the early stages of HIV-associated T-cell decline and this disrupts host surveillance, favouring pathogenicity [29-30]. This in part reflects the fact that the *C. albicans* specific Th17 T cells are highly permissive to HIV infection [31]. The oral microbiome also shows reduced diversity and increased candida colonisation in association with HIV-associated immunosuppression, but these changes are reversible with antiretroviral therapy [17, 32-33]. Despite this patients receiving antiretroviral therapy who have oesophageal Candidiasis show evidence of impaired T-cell responses to candida after two years of therapy, demonstrating that increased susceptibility may remain despite antiretroviral therapy [34]. Clinical risk factors other than immunosuppression include injection drug misuse, and tuberculosis, in addition to more general predisposing factors such as dental caries, Diabetes mellitus or corticosteroid use [19,21,35].

7.3 Presentation

7.3.1 Clinical manifestations of mucosal *Candida* infection in people living with HIV

Oral candidiasis is associated with worsening immunodeficiency [36] and in the absence of HAART predicts the development of AIDS at a median of 25 months [37]. The most familiar clinical appearance of oral candidiasis is of easily removable curdy white plaques, underneath which lies raw or bleeding mucosa (pseudomembraneous). Other presentations include an erythematous form, with patchy reddening of the mucosa, and depapillation of the dorsal surface of the tongue [38]; hyperplastic candidiasis, where there are white plaques that cannot be scraped away; and angular cheilitis with painful fissuring of the commissures. The symptoms are of pain in the tongue or surrounding structures or the presentation may be asymptomatic with just the clinical appearance of oral candidiasis. Vaginal candidiasis is common in HIV-seropositive women and presents with vaginitis with itching and curd-like exudate. [5,14,39].

Most commonly the patient with oesophageal candidiasis complains of dysphagia and/or odynophagia. Since the advent of antiretroviral therapy and the decline in opportunistic infections the main differential consideration for upper gastrointestinal symptoms has become erosive oesophagitis due to gastro-oesophageal reflux. In a prospective endoscopy study people living with HIV reported higher symptom scores for a range of upper gastrointestinal symptoms, and neither odynophagia or dysphagia were predictive of candida oesophagitis [40]. In contrast heartburn and acid regurgitation were predictive of

erosive oesophagitis in people living with HIV. Oesophageal candidiasis without oral evidence of plaques is infrequent and where a patient complains of typical symptoms in the absence of oral candidiasis other diagnoses must be considered. However, in a minority of cases oesophageal candidiasis may occur without oral involvement [41] and one recent study in the era of cART found 55% of patients had no oral candida, 57% were asymptomatic and 31% had CD4 T-cell counts >200 cells/ μ L [42].

7.4 Diagnosis

- **Oral and oesophageal candidiasis are clinical diagnoses (Grade 2B, moderate quality of evidence).**
- **Microbiological confirmation and susceptibility testing of *Candida* species is required when symptoms of candidiasis persist or recur during antifungal therapy (Grade 1B moderate quality of evidence).**
- **Endoscopic diagnosis should be undertaken in patients with oesophageal symptoms without oropharyngeal candida and in patients who do not respond to initial treatment or relapse (Grade 1C, low quality of evidence)**

7.4.1 Role of microbiological confirmation of candida infection

Oral and oesophageal candidiasis are clinical diagnoses, and microbiological confirmation has traditionally not been advised due to the likelihood of positive cultures in the absence of clinical disease. Recent studies highlight that even in the era of widespread antiretroviral therapy non-oral health specialists can accurately identify oropharyngeal candida with 81-90% sensitivity and 92% specificity, a sensitivity that approaches microbiological detection [43]. This suggests this approach is still reasonable for mucosal infections caused by *Candida*. The increasing recognition that empiric antimicrobials should be limited to avoid resistance in fungi [44] and the increasing rates of infection with non-albicans and azole resistant *Candida* species means that this approach will increasingly be scrutinised.

Candida cultures should be requested in individuals with candida infection that persists despite antifungal therapy or with recurrent infection. Recurrent oropharyngeal Candidiasis occurs in the context of failure to establish immune reconstitution and has represented a primary driver for the selection of non-albicans and of fluconazole resistant species secondary to repeated antifungal exposure [22, 26, 45, 46].

The goal of culture should be to speciate the candida to guide initial antimicrobial therapy and to provide a sample for antifungal susceptibility testing. *C. krusei* is always fluconazole-resistant and may be cross-resistant to itraconazole and other azoles. *C. glabrata* sensitivity is more variable but emerges after antifungal exposure with many strains showing fluconazole resistance [47]. Susceptibility testing is recommended for patients with clinical disease from whom *Candida* species are isolated, since in these patients where culture is indicated with recurrent infection, or candida infection that is not responsive to initial therapy, the likelihood of azole resistance is increased.

7.4.2 Techniques used to establish microbiological diagnosis of *Candida* species?

Candida species are cultured on selective media. Automated phenotypic analysis systems e.g. Vitek-2 are most often used for speciation but may have limitations against some non-albicans *Candida*. MALDI-TOF based proteomics and PCR-based molecular techniques may be more rapid and increasingly are being used as alternatives. Techniques used to

supplement the diagnosis of invasive candidiasis, such as use of β -1,3-D-glucan have no role for mucosal disease [48].

7.4.3 The role of endoscopy in the diagnosis of oesophageal candidiasis

Suspected oesophageal candida can be treated empirically when other opportunistic infections or non-AIDS related oesophageal syndromes are believed to be less likely diagnoses. Confirmation by endoscopy should be used in cases with symptoms of oesophageal candidiasis who fail to respond to initial therapy, do not have concomitant oropharyngeal candidiasis, or those in which an additional oesophageal condition is suspected

Endoscopy should reveal white patches. The main value of endoscopy is to exclude other causes of oesophageal symptoms that may be present with or without oesophageal candidiasis or obtain samples for susceptibility testing if response to therapy is not detected.

7.5 Treatment

- ***Azoles and topical treatment are equally effective at treating oropharyngeal candidiasis but azole therapy is associated with a lower risk of relapse (Grade 1B, moderate quality of evidence).***
- ***Azoles are the mainstay of treatment for HIV-seropositive patients with oral or oesophageal candidiasis. Fluconazole remains the preferred treatment option for oropharyngeal or vaginal candidiasis on the basis of an updated Cochrane database systematic review [49] (Grade 1A, high quality of evidence).***

7.5.1 Treatment of oropharyngeal, oesophageal and vaginal candidiasis?

Fluconazole (50–100 mg/day) is the most commonly selected orally absorbable systemic azole against oropharyngeal candidiasis and is prescribed for 7–14 days [50-53].

Itraconazole also has efficacy [54-55] and may be used in select cases when fluconazole resistance has been demonstrated but cross resistance is common.

Both fluconazole and itraconazole have demonstrated efficacy in the treatment of oesophageal candidiasis with fluconazole providing greater short-term response and fluconazole is therefore the preferred option [56].

Itraconazole capsules, a preparation no longer available, required gastric acid to facilitate absorption, and achlorhydria, which is associated with advanced HIV disease, impaired the efficacy of these agents [57-58]. Itraconazole oral solution has better bioavailability but shows variability in levels and lacks the bioavailability of fluconazole [59]. Therefore patients with low CD4 T-cell counts are thus best treated those requiring systemic antacid preparations are unsuitable for itraconazole. Proton pump inhibitors commonly prescribed empirically for oesophageal symptoms inhibit the activity of fluconazole in cell culture models and with-holding these during treatment of oesophageal or severe oropharyngeal candida should be a consideration [60].

Itraconazole is metabolized via cytochrome P450 enzymes and therefore should not be co-prescribed with hepatic enzyme-inducing agents such as rifamycins. Fluconazole is excreted predominantly unchanged in the urine and is therefore the azole of choice in patients requiring treatment with such enzyme inducers. It is advisable to use fluconazole, as the least hepatotoxic agent, in patients with liver disease.

7.5.2 Role of topical treatment

Topical nystatin or amphotericin are of little benefit for oesophageal candidiasis and are associated with slower clearance of yeast from the mouth, a higher relapse rate and reduced tolerability [61]. Individuals with fluconazole-refractory candida or intolerant to fluconazole may respond to itraconazole cyclodextrin (oral) solution 200 mg bd [62-63]. Where this is not possible, clotrimazole pessaries (100mg) have been used orally (sucked rather than swallowed) or clotrimazole troches (10 mg), available in the US, may be effective (Cartledge JD, personal communication). A recent randomised clinical trial also found a miconazole buccal adhesive formulation was non-inferior to clotrimazole troches [64]. Alternatively, amphotericin B oral solution or lozenges may be used [65].

Recurrent vulvovaginal candidiasis, especially if due to non-albicans species, may be treated using topical boric acid in gelatin capsules (not licensed), if azole treatment is unsuccessful. [66] (Grade 2B recommendation, moderate quality of evidence).

7.5.3 Treatment of fluconazole-refractory candidiasis

There are a number of antifungal drugs that can be considered for the treatment of fluconazole-refractory disease [67]. These include intravenous amphotericin B, the azoles, voriconazole and posaconazole, and the echinocandins, caspofungin, micafungin and anidulafungin. These have all demonstrated efficacy in randomised clinical trials in oesophageal candidiasis, although cost means their use should be reserved for cases where fluconazole therapy is ineffective, not tolerated or where infection is due to organisms with altered susceptibility to first-line agents (Grade 2B, moderate quality evidence). In clinical trials of oesophageal candidiasis caspofungin was as effective but less toxic than amphotericin B [68] and was active against fluconazole-resistant strains [69]. Caspofungin, micafungin and anidulafungin have shown efficacy comparable to fluconazole in treatment of oesophageal candidiasis [70-72]. Only micafungin has resulted in a relapse rate comparable to fluconazole; caspofungin shows a trend towards, and anidulafungin is associated with a significantly higher relapse rate [68,71,72]. However, interpretation of these differences is hampered by the different doses of fluconazole used in the different studies [67]. Voriconazole is also active against resistant strains [73] and was as effective but more toxic than fluconazole [74], and posaconazole also showed efficacy against oropharyngeal/oesophageal candidiasis [75] including candidiasis refractory to fluconazole/itraconazole [76].

7.5.4 Treatment of invasive candidiasis in patients with HIV infection

There are no clinical trial data to guide the treatment of invasive candidiasis in HIV-seropositive individuals. In general, they should be treated with systemic antifungal therapy as in other immunocompromised patients (Grade 1C, low quality evidence). International guidelines (e.g. those from the Infectious Disease Society of America) have proposed standards of care for invasive fungal infections, including *Candida* [77].

7.6 Prophylaxis and impact of cART

Routine prophylaxis for mucosal candidiasis is not recommended (Grade 1B, moderate quality of evidence).

cART is the major intervention which reduces the incidence of mucosal candidiasis (Grade 1A, high quality of evidence).

7.6.1 Strategies to prevent mucosal candidiasis in patients with advanced HIV infection

Routine prophylaxis is not warranted and is associated with the emergence of resistance). As with other opportunistic infections, effective combination antiretroviral therapy (cART) prevents relapses of symptomatic candidiasis. Thus, the most successful strategy for managing patients with candidiasis is to commence cART [6-7], but drug-drug interactions should be considered with some antiretrovirals and antifungal agents (see Table 7.1). Systematic review and meta-analysis of the impact of cART on opportunistic infections in low and middle income countries confirms cART dramatically reduces the incidence of mucosal candida with oral candida being one of the opportunistic infections showing the greatest impact [6]. A case control study in a high income setting examining the risk of oesophageal candidiasis shows cART is associated with a reduced odds ratio of [78]. There are rare reports of candidiasis associated with IRIS, including a case of *Candida meningitis* leading to fatal vasculitis [79].

7.6.2 Role of continuous azole therapy recommended

Ongoing prescription of azole antifungals between episodes of recurrent candidiasis is not recommended, as this may be associated with emergence of azole-resistant candidiasis [80-82] (Grade 1C, low quality evidence). In the pre-cART era, azole-unresponsive candidiasis was increasingly common in patients who had received prolonged prophylaxis with azole antifungals, and was either due to infection with species other than *C. albicans* [83-85], such as *C. krusei* and *C. glabrata*, or resistant strains of *C. albicans* [86-89]. However, continuous thrice weekly fluconazole treatment did not lead to a significant increase in fluconazole-refractory oropharyngeal or oesophageal candidiasis in an open label trial comparing it to episodic treatment in HIV patients with access to cART [90].

TABLE 7.1 CANDIDA INFECTION TREATMENT AND ANTIRETROVIRAL DRUG INTERACTIONS

Antifungal drug name	Interaction with antiretroviral	Action required
Amphotericin	Tenofovir	Caution – increased risk of renal toxicity with concurrent or recent use.
Itraconazole	Ritonavir increases itraconazole	Avoid high doses of itraconazole Caution with boosted PIs – some PI

	exposure	levels increased
	Efavirenz, etravirine and nevirapine reduce itraconazole levels	Consider alternative, or increase dose Monitor clinical effect
	Maraviroc levels increased	Reduce maraviroc dose (150 mg bd)
Voriconazole	Efavirenz levels increased and voriconazole levels reduced	Not recommended to be used together. Seek HIV specialist pharmacist advice
	Etravirine and voriconazole levels are both increased	No dose adjustment required – monitor
	Lopinavir/ritonavir reduces voriconazole levels	Not recommended to be used together. Seek HIV specialist pharmacist advice
Fluconazole	Zidovudine levels increased	Caution – monitor for adverse effects
	Nevirapine levels increased	Caution – monitor for adverse effects
Posaconazole	Efavirenz reduces posaconazole levels	Avoid combination unless benefit to patient outweighs risk
	Atazanavir levels increased	Caution – additional monitoring for toxicity (bilirubin levels)
	Other PIs – levels possibly increased	Monitor for signs of increased toxicity
Caspofungin	Efavirenz and nevirapine reduce levels.	Increase caspofungin dose to 70 mg od, for those <80 kg

Antiretroviral drugs, especially the NNRTIs and boosted PIs, have several important drug–drug interactions. This table lists some examples of drug–drug interactions between antiretrovirals and antifungals. As the azole antifungal compounds are metabolized via the cytochrome P450 enzyme system they are likely to interact with both NNRTIs and PIs. There are few published data on potential drug interactions with the newer antifungal agents. As data and advice changes frequently, this information should always be interpreted in conjunction with the manufacturer’s information (www.medicines.org.uk). Other useful web-based reference sources include the Liverpool HIV drug information website (www.hiv-druginteractions.org) and the Toronto Clinic (www.hivclinic.ca/main/drugs_interact.html).

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Appendix 1

PICO questions

7.2 What is the epidemiology of candidiasis in individuals living with HIV?

7.2.1 What are the main *Candida* species causing Candida infections in recent surveys of people living with HIV infection?

7.2.2 What are the main risk factors for *Candida* infection in people living with HIV infection?

7.3.1 What are the clinical manifestations of mucosal Candida infection in people living with HIV?

7.4.1 When is it appropriate to request microbiological confirmation of candida infections?

7.4.2 What are the preferred techniques for microbiological diagnosis of *Candida* species?

7.4.3 When should endoscopy be used to diagnose suspected oesophageal candidiasis?

7.5.1 What are the preferred treatments for oropharyngeal, oesophageal and vaginal candidiasis?

7.5.2 When may topical treatment be used?

7.5.3 How should fluconazole-refractory candidiasis be treated?

7.5.4 How should invasive candidiasis be treated in patients with HIV infection?

7.6.1 Is prophylaxis to prevent mucosal candidiasis recommended for patients with advanced HIV infection?

7.6.2 Is continuous azole therapy recommended?