British HIV Association guidelines on the management of opportunistic infection in people living with HIV: The clinical management of candidiasis 2019 (2022 interim update)

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Keywords: *Candida albicans*, candidiasis, non-*albicans Candida*, oesophagitis

1 Methods

1.1 Guideline development process

Full details of the guideline development process, including conflict of interest policy, are outlined in the BHIVA guideline development manual which was last updated in 2014 (see https://www.bhiva.org/file/jgCacHqmuxZFL/GuidelineDevelopmentManual.pdf). The scope, purpose and guideline topics were agreed by the writing group. Questions concerning each guideline topic were drafted and a systematic literature review undertaken by an independent information scientist (Jacoby Patterson). The search questions (the populations, interventions, comparators and outcomes [PICOs]), are outlined in Appendix 1, and the search strategy in Appendix 2. Details of the methodology can be found on the BHIVA website (https://www.bhiva.org/file/5d514ec9b503d/OI-guidelines-methods-general.pdf). For the current guidelines, PubMed, Medline, Embase and the Cochrane Library were searched for English language publications between January 2010 and March 2018, the period since the last candidiasis guidelines published by BHIVA. Searches were conducted using the following terms: HIV or AIDS and candidosis, candidiasis, *Candida* spp., *Candida albicans*, non-*albicans Candida*, oropharyngeal candidiasis, candida (o)esophagitis, vulvo(-)vaginal candidiasis or mucosal candidiasis. Abstracts from selected conferences (BHIVA, Conference on Retroviruses and Opportunistic Infections, Interscience Conference on Antimicrobial Agents and Chemotherapy and Infectious Diseases Society of America) were also searched for the same period. Articles already cited in the 2011 BHIVA/British Infection Association (BIA) guidelines for the treatment of opportunistic infection in HIV-seropositive individuals were also considered for the current guidelines. Definitions used are summarised in Appendix 3.

Appendix 4 outlines the literature selection process. In total, 1133 abstracts were initially screened by the information scientist and 355 identified on the basis of clinical relevance, match to the PICO questions and level of detail. Exclusion factors were non-human studies, case reports and insufficient detail to allow thorough assessment. The 355 identified abstracts were assigned to PICO questions and subsequently reviewed by at least three members of the writing group. Each PICO question was initially reviewed by one member of the writing team, with expertise in the field, who reviewed the papers for relevance, prioritising meta-analyses and randomised control trials where available. They provided an initial summary, compiling evidence and combining this with evidence collected in the last guideline. The individual summaries were then formatted into an initial draft guideline and all authors then reviewed the recommendations against the evidence and also had the opportunity to review the data and add additional evidence having reviewed the assembled abstracts. For each topic and healthcare question, summated evidence was then evaluated by all writing group members. Using the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (see BHIVA website: https://www.bhiva.org/BHIVA-guideline-development), writing group members were responsible for assessing and grading the quality of evidence for predefined outcomes across studies and developing and grading the strength of recommendations. All writing group members received training in the use of the modified GRADE criteria.

Before final approval by the writing group, the guidelines were published online for public consultation and external peer reviews were commissioned. As part of this process, input was sought from BIA and from patient groups. The writing group responded to all points raised in the consultation and review.

2 Summary of recommendations

6 Diagnosis

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

7 Treatment

- ***Fluconazole remains the preferred treatment option for oropharyngeal candidiasis on the basis of an updated Cochrane database systematic review [55] (Grade 1A, high quality of evidence).***
- ***Fluconazole and topical treatment are equally clinically effective at treating oropharyngeal candidiasis with azole-sensitive strains, but azole therapy is associated with a lower risk of relapse. Topical therapy can be considered as an***

alternative to fluconazole for mild oropharyngeal candidiasis when there is a low risk of relapse (Grade 1B, moderate quality of evidence).

- ***Fluconazole is the recommended treatment for people living with HIV with moderate–severe oropharyngeal candidiasis or with oesophageal candidiasis and azole-sensitive strains (Grade 1A, high quality of evidence).***
- ***Topical therapy or oral fluconazole can be used to treat uncomplicated vulvovaginal candidiasis with regimens similar to those used for HIV-negative populations (Grade 1A, high quality of evidence).***

8 Prophylaxis and impact of cART

- ***Routine prophylaxis for mucosal candidiasis is not recommended (Grade 1B, moderate quality of evidence).***
- ***cART is the major intervention that reduces the incidence of mucosal candidiasis (Grade 1A, high quality of evidence).***

3 Auditable outcomes

- Percentage of patients with persistent recurrent candidiasis on whom microbiological testing has been arranged.
- Percentage of patients with persistent recurrent candidiasis on whom susceptibility testing has been performed.
- Percentage of patients with oral candidiasis treated with fluconazole at 50–100 mg for 7–14 days.

4 Epidemiology of candidiasis

Candida spp. are common commensals in the general population and may be cultured from the oral cavity, gastrointestinal tract and genital tract of up to 75% of individuals [1]. Surveillance studies have consistently identified higher rates of mucosal carriage of *Candida* in men and women with HIV [2,3], with mucosal candidiasis representing the primary pathological manifestation. Oropharyngeal candidiasis is the commonest opportunistic infection to affect individuals with HIV and occurred in 80–90% of patients in the era prior to combination antiretroviral therapy (cART) [4,5]. In recent cohort reviews, the relative frequency of oropharyngeal candidiasis has remained high compared to other opportunistic infections despite reduction in the overall prevalence in association with cART [6,7]. According to NA-ACCORD cohort data from North America, oesophageal candidiasis was the leading opportunistic infection by 2010 with an incidence of 0.34 (0.29-0.38) events per 100 person-years in 2008–2010 [7].

In studies conducted from the era prior to cART to the current era, oesophageal candidiasis has been reported as the AIDS-defining indicator illness in 11–51% of cases [5,8-11]. The most recent of these studies, which examined late presenters with HIV, defined as those with CD4 counts <350 cells/mm^3 or with an AIDS-defining illness, reported the highest contribution of oesophageal candidiasis [11].

Although vaginal colonisation by *Candida* occurs more frequently in women living with HIV, vulvovaginitis occurs sporadically, and is similar in nature to that observed in immunocompetent people [5]. Some studies have shown an increase in vulvovaginal candidiasis with HIV, but severity or recurrence is not increased and, unlike oropharyngeal candidiasis, there is no relationship with CD4 T cell count [12,13]. Therefore, the impact of HIV appears to be less for vulvovaginal than for oropharyngeal candidiasis.
Invasive candidiasis (candidaemia) represents a growing nosocomial threat attributable to individual host factors (e.g. immunosuppression) and healthcare-related risk factors. People living with HIV are increasingly at risk in the context of undergoing intensive treatments for emerging comorbidities that expose them to HIV-independent candidaemia risk factors (e.g. central venous catheter placement or intensive care admission). Studies have not demonstrated good evidence of a further increased risk in people living with HIV in the presence of these HIV-independent risk factors, and management is recommended as for HIV-seronegative individuals [5,14-17]. Several reviews and guidelines cover management of this condition [14,16,17].

4.1 *Candida* spp. causing *Candida* infections in people living with HIV

Candida albicans remains the leading cause of *Candida* infections globally but the distribution of non-*albicans Candida* spp. shows geographical variation [18]. Non-*albicans Candida* spp. occur particularly in association with previous azole therapy and advanced immunosuppression [5]. HIV-specific data for oropharyngeal or vulvovaginal infections reflect the trends in international surveillance data; *C. albicans* remains most prevalent. The rates of non-*albicans Candida* spp. continue to rise to approximately 30% in many cohorts, influenced by geographical location and resource setting [3,19-21]. Recent US data suggest that *C. albicans* is responsible for 62–68% of oropharyngeal *Candida* spp. infections and 73% of vulvovaginal *Candida* spp. infections [2,22]. *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 [22-24].

Antifungal azole resistance may be an intrinsic feature, as observed for fluconazole in *C. krusei,* or may be the result of evolution during recurrent drug exposure, as for fluconazole in *C. albicans* or *C. dublinensis* [5,16]. For some species such as *C. glabrata,* azole resistance may be induced by drug exposure but background resistance to fluconazole is also prevalent. Therefore, detection of *C. glabrata* should prompt treatment with an alternative agent unless fluconazole susceptibility is microbiologically demonstrated [16]. The increased prevalence of innately fluconazole-resistant *Candida* spp. and *Candida* spp. with reduced-susceptibility to echinocandins and many other antifungals highlights the need for accurate speciation and susceptibility testing [25-28]. *C. auris*, an inherently multidrug-resistant new *Candida* spp., has recently emerged as a cause of candidaemia; it is an infection control challenge, particularly in intensive care units and after surgery, but has not yet been linked with particular problems in HIV [29].

Guidance on supporting patients living with HIV with opportunistic infections, including *Candida* infections, can be found on the BHIVA website (https://www.bhiva.org/file/6225e44b53c49/OI-guidelines-supporting-patients.pdf).

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

The immunological response against *Candida* spp. at the gastrointestinal mucosa or on skin surfaces is highly dependent on T helper (Th)17 T cells [30]. This T cell subset is disproportionately depleted during the early stages of HIV-associated T cell decline and this disrupts host surveillance, favouring pathogenicity [31,32]. This in part reflects the fact that the *Candida*-specific Th17 T cells are highly permissive to HIV infection [31]. Vulvovaginal candidiasis may be less influenced by Th17 T cell function and more influenced by dysbiosis and alterations in the vaginal pH. The oral microbiome also shows reduced diversity and increased *Candida* spp. colonisation in association with HIV-related immunosuppression, but these changes are at least partially reversible with cART [19,33,34]. Individuals receiving cART who have oesophageal candidiasis show evidence of impaired T cell responses to *C. albicans* even after 2 years of therapy. Thus, increased susceptibility due to impaired immunity may remain despite cART [35]. Clinical risk factors for oropharyngeal candidiasis other than immunosuppression in people living with HIV include injection drug misuse and tuberculosis. Other more general predisposing factors, not specifically related to HIV, include the presence of multispecies biofilms due to poor oral hygiene, dental caries, diabetes mellitus, use of inhaled/topical or systemic corticosteroids and poorly controlled gastro-oesophageal reflux disease (GORD), since *Candida* spp. thrive in an acidic environment. However, *Candida* spp. have also been found in the presence of proton pump inhibitors in some studies suggesting there may be an optimal pH level to inhibit growth [21,23,36].

5 Presentation

5.1 Clinical manifestations of mucosal candidiasis in people living with HIV

Oropharyngeal candidiasis is associated with worsening immunodeficiency [37] and in the absence of cART predicts the development of AIDS at a median of 25 months [38]. The most familiar clinical appearance of oropharyngeal candidiasis is of easily removable, curd-like white plaques, underneath which lies raw or bleeding mucosa (so-called ‘pseudomembranous’ candidiasis). Other oral presentations include: an erythematous form, with patchy reddening of the mucosa and depapillation of the dorsal surface of the tongue [39]; hyperplastic candidiasis, with white plaques that cannot be scraped away; and angular cheilitis with painful fissuring of the commissures. The predominant symptoms are sore mouth and throat, though the presentation may be asymptomatic with just the clinical appearance of oral candidiasis.

Vulvovaginal candidiasis in women living with HIV presents with similar features to that in women without HIV (vulvovaginitis with itching and curd-like exudate) [5,13,14,40]. Symptoms are non-specific and failure to respond to clinical treatment, associated with failure to detect *Candida* spp. on microbiological testing, should raise the possibility of an alternative diagnosis.

Most commonly the patient with oesophageal candidiasis complains of dysphagia and/or odynophagia. Respiratory symptoms such as increased phlegm production, chronic cough and hoarseness of voice are also common. With widespread use of cART and the decline in

opportunistic infections, the main differential consideration for upper gastrointestinal symptoms in people living with HIV is not erosive oesophagitis due to GORD. Oesophageal candidiasis and GORD can also coexist; GORD is a risk factor for oesophageal candidiasis since *Candida* spp. thrive in acidic environments and can more easily invade damaged mucosa. In a prospective study, people living with HIV who underwent endoscopy to investigate upper gastrointestinal symptoms generally reported higher symptom scores for a range of upper gastrointestinal symptoms, but neither odynophagia nor dysphagia were predictive of oesophageal candidiasis [41]. Heartburn and acid regurgitation were in fact more predictive of erosive oesophagitis in people living with HIV. Dysphagia, especially when not responsive to treatment of oesophageal candidiasis or associated with weight loss, should also raise the possibility of oesophageal carcinoma [42]. Although oesophageal carcinoma is not an AIDS-associated malignancy, people living with HIV who present with dysphagia, and in particular those with weight loss or factors associated with oesophageal cancer in people living with HIV, such as GORD, heavy alcohol use and cigarette smoking [42], should have investigations to exclude oesophageal carcinoma.

Oesophageal candidiasis without oropharyngeal evidence of plaques is uncommon and occurs in only a small number of cases in most studies [43]. Therefore, where a patient complains of typical symptoms in the absence of oropharyngeal candidiasis, other diagnoses such as GORD and malignancy must be considered. However, one recent study, conducted in the cART era, demonstrated that 55% of patients with oesophageal candidiasis had no manifestations of oropharyngeal *Candida*, 57% were deemed asymptomatic, and 31% had CD4 T cell counts >200 cells/mm^3. This implies that some of the clinical features traditionally associated with oesophageal candidiasis in the era before widespread use of cART may be changing in an era of greater antiretroviral therapy coverage and lower degrees of immunosuppression [44].

6 Diagnosis

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

6.1 Role of microbiological confirmation of *Candida* spp. infection

Oropharyngeal 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 candidiasis with 81–90% sensitivity and 92% specificity, which approaches the performance

of microbiological detection [45]. This suggests that this approach is still reasonable for mucosal infections caused by *Candida* spp. There is increasing recognition that empiric antimicrobials and low-dose prophylaxis in settings of minimal risk promote resistance in fungi [46].

Candida cultures should be requested for individuals with persisting signs and symptoms of infection despite antifungal therapy or who experience recurrent infection. This will serve to identify the possibility of an azole-resistant infection or, in the context of negative cultures/ poor response despite susceptible strains, will indicate the possibility of alternative or additional diagnoses. Recurrent oropharyngeal candidiasis occurs in the context of failure to establish immune reconstitution or the presence of persistent non-HIV-related risk factors and has represented a primary driver for the selection of non-*albican*s *Candida* and of fluconazole-resistant species due to repeated antifungal exposure [24,28,47,48].
The goal of culture should be to speciate the *Candida* spp. to inform selection of antifungal therapy and to derive a sample for susceptibility testing. *C. krusei* is always fluconazole resistant and may be cross-resistant to itraconazole and other azoles. *C. glabrata* fluconazole sensitivity is more variable but *C. glabrata* infection emerges following antifungal exposure with many strains demonstrating fluconazole non-susceptibility [49].

6.2 Techniques used to establish microbiological diagnosis of *Candida* spp.

There are national standards for microbiological investigations providing detailed standard operating procedures for laboratories (see https://www.gov.uk/government/collections/standards-for-microbiology-investigations-smi). In brief, a swab of an active lesion from a typical oral site such as the palate or buccal mucosa or a vaginal swab will usually establish the diagnosis [50]. A wet-mount vaginal specimen with use of normal saline and 10% potassium hydroxide should be examined by microscopy for the presence of yeast cells and pseudohyphae. In cases of recurrent symptoms or poor or partial response, specimens should also be sent for culture. A vaginal self-swab is also an effective sample with high acceptance rates in studies of HIV-negative individuals [51]. In symptomatic patients without obvious lesions to swab, oral or vaginal rinse will establish the identity of colonising species to guide initial therapy [52,53]. In rare cases the absence of obvious lesions or failure to respond to initial therapy may suggest diagnostic uncertainty. This should prompt biopsy to exclude other diagnoses such as lichen planus. However, these biopsy specimens should be examined by microscopy with special fungal stains and also sent for culture.

Candida spp. may be cultured on selective media, although they are frequently detected on blood agar. Culture and reporting should follow national standards for microbiology investigation. Automated phenotypic analysis systems such as Vitek-2 are most often used for speciation but may have limitations against some non-*albicans Candida*. MALDI-TOF mass spectrometry-based proteomics techniques may be more rapid and increasingly are being used as alternatives. Candidaemia is diagnosed by blood culture and the presence of *Candida* in blood culture always indicates invasive disease. In all cases with invasive disease and for superficial swabs with unresponsive or recurrent infection the *Candida* isolate should be speciated and anti-fungal sensitivities performed [14]. Techniques used to supplement the diagnosis of invasive candidiasis, such as β-1,3-D-glucan detection, have no role for mucosal disease [50].

6.3 The role of endoscopy in the diagnosis of oesophageal candidiasis

Suspected oesophageal candidiasis 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 which fail to respond to initial therapy, cases without concomitant oropharyngeal candidiasis, or cases where an alternative oesophageal condition is suspected, such as oesophageal carcinoma in cases with dysphagia, where barium swallow may have been the initial investigation.

Endoscopy should reveal typical appearances such as white patches. Directed brushings or biopsy specimens can be sent for laboratory analysis as outlined above [54,43].

7 Treatment (Table 1)

- ***Fluconazole remains the preferred treatment option for oropharyngeal candidiasis on the basis of an updated Cochrane database systematic review [55] (Grade 1A, high quality of evidence).***
- ***Fluconazole and topical treatment are equally clinically effective at treating oropharyngeal candidiasis with azole-sensitive strains, but azole therapy is associated with a lower risk of relapse. Topical therapy can be considered as an alternative to fluconazole for mild oropharyngeal candidiasis when there is a low risk of relapse (Grade 1B, moderate quality of evidence).***
- ***Fluconazole is the recommended treatment for people living with HIV with moderate–severe oropharyngeal candidiasis or with oesophageal candidiasis and azole-sensitive strains (Grade 1A, high quality of evidence).***
- ***Topical therapy or oral fluconazole can be used to treat uncomplicated vulvovaginal candidiasis with regimens similar to those used for HIV-negative populations (Grade 1A, high quality of evidence).***

7.1 Treatment of oropharyngeal candidiasis

An important component of therapy is to address any modifiable risk factors to prevent recurrence and this should be combined with specific therapy. Good oral hygiene and meticulous regular removal of oral biofilms (dental plaque) is a key component of the management of oral infection as biofilms are inherently resistant to antimicrobial therapy alone. The findings of an updated Cochrane database systematic review in 2010 support the conclusion that fluconazole therapy is consistently associated with superior rates of mycological cure when compared to topical therapy for the treatment of oropharyngeal candidiasis [55]. Fluconazole (100–200 mg/day) is the most commonly selected orally absorbable systemic azole against oropharyngeal candidiasis and should be prescribed for 7–14 days [56-59]. Fluconazole 100 mg can be used for 7 days in first episodes with the higher dose or more prolonged duration reserved for severe disease with a fluconazole-sensitive strain or cases of relapse after previous fluconazole treatment. In the latter cases, culture and sensitivity should exclude fluconazole resistance thereby supporting ongoing fluconazole therapy.

Topical therapy may be used in mild oropharyngeal candidiasis. It is associated with slower clearance of yeast from the mouth, a higher relapse rate and reduced tolerability [60,61]. Therefore, we recommend this as an alternative option to fluconazole only in mild cases without a history of frequent recurrence and when there may be reasons to consider an alternative to fluconazole, such as in the setting of fluconazole intolerance or fluconazole-refractory *C. albicans*. Topical treatment is usually administered as nystatin (oral suspension of 100,000 units/mL, 5 mL four times daily for 7–14 days). Alternative topical agents where available through specialist pharmacies, include amphotericin (10 mg lozenges four times daily, or oral solution) [62], clotrimazole pessaries (100 mg, sucked rather than swallowed [Cartledge JD, personal communication]) and clotrimazole troches (i.e. small dissolvable lozenges, 10 mg five times daily) [60,61], all administered for 7–14 days. A recent randomised clinical trial demonstrated that a miconazole buccal adhesive formulation, 50 mg applied over the canine fossa once daily, was non-inferior to clotrimazole troches [63]. However, there is a lack of data on drug–drug interactions or the effects on QT interval with agents such as clotrimazole and they should only be used with expert advice when benefits are considered to outweigh potential risks.

Clinical response rates (using a range of definitions) in these studies with topical therapy ranged from 61–94% and, where directly compared, have been comparable to rates with fluconazole. However, as above, the therapies have been associated with lower rates of mycological cure and greater relapse rates [60-63]. In addition to topical or systemic antifungal therapy, emerging evidence regarding the role of biofilm formation in oropharyngeal candidiasis emphasises the need for mechanical disruption through good brushing and the use of 0.2% chlorhexidine mouthwash [64]. This is especially important for denture wearers who are at particular risk of fluconazole resistance due to biofilm formation which can promote resistance development [22,64].

Empiric treatment should be limited to cases with clear clinical features together with associated risk factors. Fluconazole or topical therapy remain the choices for initial empirical therapy. Other agents discussed below should only be used after consultation with an infectious disease or clinical microbiology specialist and in specific circumstances.

7.2 Treatment of oesophageal candidiasis

As with oropharyngeal candidiasis, attention should focus on any modifiable risk factors in addition to specific therapy for candidiasis. Both fluconazole and itraconazole have demonstrated efficacy in the treatment of oesophageal candidiasis, with fluconazole providing greater short-term response (2-week cure rates of approximately 80% in the era prior to cART) [65,66]. Fluconazole 200–400 mg once daily for 14–21 days remains the preferred option, with 14-day courses of 200 mg used for milder disease [66].
Although itraconazole has been used as an alternative, better bioavailability and fewer drug–drug interactions ensure fluconazole remains the preferred option. When itraconazole is used it should be administered as cyclodextrin (oral) solution, because the bioavailability of capsules is less than that of the oral solution and is more dependent on gastric acid to facilitate absorption. Achlorhydria, which is associated with advanced HIV disease, impairs the absorption of the capsule formulation and unpredictable drug levels reduce efficacy [67,68]. Itraconazole oral solution has better bioavailability than the capsule formulation,

but still shows variability in levels, as its absorption is also facilitated by gastric acidity and its bioavailability is reduced in comparison to fluconazole [69]. Therefore, even with oral solution itraconazole absorption is unpredictable, especially in patients with low CD4 T cell counts and those requiring systemic antacid preparations, and treatment with fluconazole is the preferred option in most cases. Proton pump inhibitors commonly prescribed empirically for oesophageal symptoms also inhibit the activity of fluconazole in cell culture models and withholding these during treatment of the acute stages of oesophageal or severe oropharyngeal candidiasis should be considered [70]. If a short period without acid suppression is not an option, shorter-acting treatment such as antacid therapy or use of an H2-receptor antagonist (e.g. ranitidine) may be an option.

Itraconazole is metabolised 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 azole preparation, in patients with liver disease, although treatment with an echinocandin can also be considered (see below). In exceptional circumstances in patients who cannot tolerate an oral preparation, fluconazole 400 mg once daily intravenously is an option, although this requires discussion with an infection specialist.

7.3 Treatment of fluconazole-refractory oropharyngeal or oesophageal candidiasis

In cases where the patient has not developed a symptomatic response and where follow-up cultures are negative, alternative diagnoses should be considered rather than repeated courses of therapy. Where there is clinical or microbiological persistence of oropharyngeal candidiasis, poor adherence to therapy, dry mouth with poor local drug penetration for oral therapy or poor absorption of oral therapy may be considerations. The anti-fungal agents discussed below should only be used in consultation with an infectious disease or other infection specialist. These are reserved for refractory disease or special circumstances including intolerance to multiple agents or inability to take oral therapy. Itraconazole, voriconazole and posaconazole have variable bioavailability. Although there may be some topical effects of oral suspensions of itraconazole or posaconazole, the contribution of this is unknown in oropharyngeal or oesophageal candidiasis. Therapeutic drug monitoring is therefore usually required to check for therapeutic levels of itraconazole, voriconazole and posaconazole. A newer sustained release tablet formulation of posaconazole increases bioavailability but will not allow for any topical effects that the oral solution may have and its role in the therapy of oropharyngeal candidiasis is unknown. The capsule formulation of itraconazole should not be used as outlined above. Itraconazole, posaconazole and voriconazole have increased drug–drug interactions in comparison with fluconazole which also limits their use and mandates checking for drug–drug interactions via the Liverpool HIV Drug Interactions website (https://www.hiv-druginteractions.org/checker) or similar websites.

Itraconazole oral solution (200 mg twice daily) has demonstrated efficacy against oropharyngeal candidiasis [71-73]. It is reserved for a minority of cases due to poorer bioavailability and greater drug–drug interactions, in comparison with fluconazole (as mentioned above). It is reserved for use when fluconazole resistance is demonstrated but the strain is susceptible to itraconazole, when there is recurrence/fluconazole refractory

disease in the absence of documented fluconazole resistance (e.g. when theoretical concerns about local drug levels might warrant a trial of an oral solution, as might arise in a patient with dry mouth), or in rare cases where there is intolerance to fluconazole. Clinical response rates for fluconazole-refractory disease with itraconazole oral solution were greater than 50% in the pre-cART era [73]. Posaconazole oral suspension is an alternative and has been associated with improved sustained mycological responses in comparison with fluconazole [74]. The duration of therapy can be extended to 28 days in refractory disease.

All azole regimens, other than low-dose fluconazole (100 mg daily or less), require regular monitoring of liver function tests, initially in the first week and then monthly or bi-monthly if prolonged beyond 14 days. Reports of congestive heart failure in patients receiving itraconazole (but not fluconazole) mean this therapy should be avoided in patients with congestive heart failure [75]. Therapeutic drug monitoring is required when using itraconazole, voriconazole or posaconazole, as outlined above.

Occasionally patients may be intolerant to both topical therapy and oral fluconazole or demonstrate lack of response to oral fluconazole or other azoles because of poor adherence to or poor absorption of treatment. In these cases options can include fluconazole 400 mg once daily intravenously or the intravenous therapies outlined below for fluconazole-refractory oesophageal candidiasis.

There are a number of antifungal drugs that can be considered for the treatment of fluconazole-refractory oesophageal disease [76]. As is the case for oropharyngeal candidiasis, non-response should raise concerns about an alternative diagnosis and should lead to early endoscopy if not already performed. Alternatives to fluconazole should be used only with the input of an appropriate infection specialist. Alternatives to itraconazole (discussed above) for refractory oesophageal candidiasis include the azoles posaconazole, voriconazole and isavuconazole. Use of posaconazole and voriconazole requires therapeutic drug monitoring to limit toxicity and to check for adequate systemic absorption when used for oesophageal candidiasis [76], while the role of therapeutic drug monitoring for the newer agent isavuconazole is still being determined. As outlined above there are many drug–drug interactions between these azoles and antiretroviral agents (Table 2) or other agents administered to people living with HIV. The potential for drug–drug interactions involving these azoles and other agents should always be checked prior to administration (https://www.hiv-druginteractions.org/checker).

Posaconazole has demonstrated efficacy against oropharyngeal/oesophageal candidiasis, including candidiasis refractory to fluconazole/itraconazole [74,77]. More recently isavuconazole orally in regimens of 200 mg loading dose followed by 50 mg once daily or 400 mg loading dose followed by 400 mg once weekly have been shown to be non-inferior to fluconazole 100 mg once daily with comparable tolerability in patients with uncomplicated oesophageal candidiasis [78]. In comparison with voriconazole and posaconazole, isavuconazole has fewer drug–drug interactions, although it is still a CYP3A4 substrate and a moderate CYP3A4 inhibitor [79]. Isavuconazole may increase the exposure of medicines that are P-gp substrates, particularly those with a narrow therapeutic index which may require dose adjustment of colchicine, dabigatran, digoxin or other P-gp substrates with a narrow therapeutic index

(https://www.medicines.org.uk/emc/product/5069/smpc). Isavuconazole may also be better tolerated than some of these other azoles and is not known to cause the photosensitivity or neurotoxicity associated with voriconazole [79]. Voriconazole is also active against azole-resistant strains [80] and was found in a randomised controlled trial to be as effective but more toxic than fluconazole [81]. Its greater toxicity profile means it should typically be reserved for cases where isavuconazole or posaconazole are not used. However, the broader spectrum of agents such as voriconazole, posaconazole and isavuconazole and the associated antimicrobial stewardship concerns combined with the greater potential for drug–drug interactions as compared to fluconazole, variability in drug levels and the potential for drug side effects means these azoles should only be used in exceptional circumstances with specialist input.

In other circumstances, such as azole resistance or intolerance, hepatotoxicity or inability to take an oral medication or an intravenous azole, it may be necessary to choose an intravenous non-azole formulation. In these unusual circumstances, options subject to susceptibility may include the echinocandins, caspofungin, micafungin and anidulafungin (see Table 1 for dosing information) or intravenous liposomal amphotericin B (3 mg/kg intravenously once daily) [76]. Treatment duration with these agents should be 14–21 days for oesophageal candidiasis with the 14-day regimen used as first line and longer durations reserved for slow response or relapse.

These agents have all demonstrated efficacy in randomised clinical trials in oesophageal candidiasis, although antimicrobial stewardship and the need to limit the use of broader spectrum antifungal therapies and intravenous formulations means their use should be reserved for specific cases. Examples would include cases where fluconazole therapy is ineffective or not tolerated, oral therapy cannot be administered, or where infection is due to organisms with reduced susceptibility to first-line agents (Grade 2B, moderate quality of evidence). In clinical trials of oesophageal candidiasis, caspofungin was as effective but less toxic than amphotericin B [82] and was active against fluconazole-resistant strains [83]. Caspofungin, micafungin and anidulafungin have shown efficacy (variously defined as endoscopic response with or without improvement in clinical symptoms) comparable to fluconazole in the treatment of oesophageal candidiasis [82-86]. Only micafungin has resulted in a relapse rate comparable to that of fluconazole; caspofungin demonstrated a trend towards, and anidulafungin was significantly associated with, a higher relapse rate [82,85,86]. Of note, interpretation of these differences is hampered by the different doses of fluconazole used in the different studies [76].

For fluconazole-refractory/non-susceptible oropharyngeal candidiasis a typical approach would initially involve the use of itraconazole followed by an alternative azole or an echinocandin if there are no azole options. For oesophageal candidiasis the approach would utilise itraconazole, posaconzole or isavuconazole (or possibly voriconazole) followed by an echinocandin.

7.4 Treatment of vulvovaginal candidiasis

Vulvovaginal candidiasis is classified as acute or recurrent. Vulvovaginal candidiasis is treated in the same way in people living with HIV as it is in the HIV-negative population. Topical azole therapy has been shown to be equivalent to oral therapy in a systematic

review of uncomplicated vulvovaginal candidiasis [87]. The preferred topical agent is clotrimazole pessary 500 mg intravaginally. Oral therapy can be administered as a single dose of 150 mg fluconazole and is preferred in some guidelines (e.g. the British Association for Sexual Health and HIV [BASHH]: https://www.bashhguidelines.org/current-guidelines/all-guidelines/) with topical therapy listed as an alternative. For severe disease with extensive erythema, oedema, excoriation or fissuring the oral dose can be repeated after 72 hours. For recurrent disease the oral fluconazole dose can be administered every 72 hours for three doses and then weekly for 6 months. Vulvovaginal candidiasis due to non-*albicans Candida* spp. with reduced fluconazole susceptibility (e.g. *C. glabrata*) may be treated with nystatin pessaries 100,000 units (unlicensed, but may be obtained through pharmaceutical importers) vaginally for 14 days. Alternatives to nystatin therapy for non-*albicans Candida* are vaginal cream containing 5 g 5-flucytosine combined with nystatin pessaries (as above), amphotericin pessaries 50 mg for 14 days, or topical boric acid 600 mg in gelatin capsules (not licensed). These data derive from HIV-seronegative individuals and small series only [88-90] (Grade 2B recommendation, moderate quality of evidence). Further information is available in the BASSH guidelines for vulvovaginal candidiasis (https://www.bashhguidelines.org/current-guidelines/all-guidelines/).

7.5 Treatment of invasive candidiasis in people living with HIV

There are no clinical trial data to guide the treatment of invasive candidiasis in individuals living with HIV. In general, invasive candidiasis should be treated with systemic antifungal therapy as in other patient groups without neutropenia (Grade 1C, low quality of evidence). International guidelines (e.g. from the European Society of Clinical Microbiology and Infectious Diseases and from the Infectious Disease Society of America) have proposed standards of care for invasive candidiasis in this setting and should be consulted to determine treatment duration which is influenced by patient factors and specific sites of deep-seated infection [14,91]. There are also no specific data on the treatment of *C. auris* in people living with HIV and *C. auris* infections should also be treated in line with emerging guidance for HIV-negative populations.

8 Prophylaxis and impact of cART

- ***Routine prophylaxis for mucosal candidiasis is not recommended (Grade 1B, moderate quality of evidence).***
- ***cART is the major intervention that reduces the incidence of mucosal candidiasis (Grade 1A, high quality of evidence).***

8.1 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 cART prevents relapses of symptomatic oropharyngeal or oesophageal candidiasis. Thus, the most successful strategy for managing patients with candidiasis is to commence cART [6,7]. Drug–drug interactions should be considered with regard to antiretroviral and antifungal agents (see Table 2). Systematic review and meta-analysis of the impact of cART on opportunistic infections in low- and middle-income countries confirms that cART dramatically reduces the incidence of mucosal

candidiasis with oral candidiasis being one of the opportunistic infections with the greatest impact [6]. A case–control study in a high-income setting examining the risk of oesophageal candidiasis showed that cART is associated with a reduced odds ratio of oesophageal candidiasis [92]. There are rare reports of candidiasis associated with immune reconstitution inflammatory syndrome, including a case of *Candida* meningitis leading to fatal vasculitis [93]. Despite the dramatic decline in candidiasis (oesophageal and oropharyngeal) with cART, there remains a residual level in people living with HIV above that in HIV-seronegative individuals [7,11].

8.2 Role of continuous azole therapy

Ongoing prescription of azole antifungals between episodes of recurrent oropharyngeal candidiasis is not recommended, as this may be associated with emergence of azole-resistant candidiasis [94-96] (Grade 1C, low quality of evidence). In the pre-cART era, azole-unresponsive candidiasis was increasingly common in patients who had received prolonged prophylaxis with azole antifungals and was due to infection with either species other than *C. albicans* [97-99], such as *C. krusei* and *C. glabrata*, or resistant strains of *C. albicans* [100-103]. 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 this approach to episodic treatment in people living with HIV with access to cART [104].

8.3 Azole prophylaxis in malignancy

The role of azole therapy to limit fungal infection, including candidiasis, during treatment of malignancy is discussed in the BHIVA malignancy guidelines [105].

Table 1 Antifungal therapies for selected *Candida* infections

Candidiasis	Antifungal agent	Comment
Oropharyngeal	Fluconazole 100–200 mg once daily Topical therapies (various, see text)	Preferred therapy. Duration 7–14 days Mild disease only
Vulvovaginal	Fluconazole 150 mg single dose	Severe or complicated infection: fluconazole 150 mg every 72 hours x 3 doses
Oesophageal	Fluconazole 200–400 mg once daily	Preferred therapy. Duration 14–21 days
Fluconazole refractory/resistant/intolerant oropharyngeal	Itraconazole oral solution 200 mg twice daily Posaconazole oral suspension 400 mg twice daily for refractory, then 400 mg once daily Isavuconazole orally 200 mg loading dose then 100 mg once daily or 400 mg loading dose with 400 mg weekly orally	Duration for all therapies typically 14 days Avoid itraconazole in congestive heart failure Therapeutic drug monitoring with itraconazole, posaconazole and voriconazole Liver function test monitoring with itraconazole, posaconazole and voriconazole Note: posaconazole sustained release tablets have better bioavailability than oral solution but there are no specific data on its use in mucocutaneous candidiasis and if used doses differ from those used for oral solution
Fluconazole refractory/resistant/intolerant oesophageal	Itraconazole oral solution 200 mg twice daily Posaconazole oral suspension 400 mg twice daily on day 1 then 400 mg once daily orally Voriconazole 200 mg twice daily orally or 4 mg/kg intravenously twice daily Isavuconazole orally 200 mg loading dose then 100 mg once daily or 400 mg loading dose with 400 mg weekly	Posaconazole oral suspension should be taken with a meal to increase absorption Note: posaconazole tablets and suspension have different bioavailability and doses are not interchangeable Although bioavailability is superior with the oral tablet (300 mg twice daily on day 1 then 300 mg daily thereafter); there are limited data on its use in mucocutaneous candidiasis

	Caspofungin 70 mg intravenous loading, then 50 mg intravenously once daily Micafungin 150 mg intravenously once daily Anidulafungin 200 mg intravenous loading then 100 mg once daily	Maintenance dose 70 mg intravenously once daily if body weight >80 kg

Table 2 *Candida* infection treatment and antiretroviral drug interactions

Antifungal drug	**Interaction with antiretroviral agent**	**Action required**
Amphotericin	Tenofovir disoproxil fumarate	Caution – increased risk of renal toxicity with concurrent or recent use
Caspofungin	Efavirenz and nevirapine levels reduced	Maintenance caspofungin dose 70 mg once daily, if body weight >80 kg
Fluconazole	Zidovudine levels increased	Caution – monitor for adverse effects
	Nevirapine levels increased	Caution – monitor for adverse effects
	Rilpivirine levels likely to increase	Caution – monitor for adverse effects
	Cobicistat	Concentrations of fluconazole increase. Therapeutic monitoring should be considered
	Tenofovir alafenamide	Fluconazole may increase tenofovir alafenamide levels but dose tenofovir alafenamide according to concomitant antiretroviral agents
Isavuconazole	Tenofovir alafenamide levels may increase	Dose tenofovir alafenamide according to concomitant antiretroviral agents
	Lopinavir/ritonavir levels may decrease, isavuconazole levels may increase	Use with caution
	Efavirenz levels may be decreased	Not recommended to be used together
	Etravirine may decrease isavuconazole	Not recommended to be used together
Itraconazole	Ritonavir- or cobicistat-boosted protease inhibitors or integrase inhibitors may increase itraconazole and protease or integrase inhibitor exposure	Avoid high doses of itraconazole (>200 mg) Monitor for side effects
	Efavirenz, etravirine and nevirapine reduce itraconazole levels	Consider alternative, or increase dose Monitor clinical effect
	Maraviroc levels increased	Reduce maraviroc dose (150 mg twice daily)
	Rilpivirine levels likely to increase	Avoid co-administration
	Cobicistat increases itraconazole	Therapeutic monitoring required Itraconazole dose should not exceed 200 mg once daily
	Tenofovir alafenamide levels predicted to increase due to P-gp inhibition by itraconazole	Dose emtricitabine/tenofovir alafenamide at 200/10 mg once daily
Posaconazole	Efavirenz reduces posaconazole levels	Avoid combination unless benefit to patient outweighs risk
	Atazanavir unboosted, boosted with cobicistat or ritonavir – levels	Caution – additional monitoring for toxicity (bilirubin levels)

	potentially increased	
	Other protease inhibitors – levels possibly increased	Monitor for signs of increased toxicity
	Rilpivirine levels likely to increase	Caution – monitor for adverse effects
	Cobicistat increases posaconazole levels	Therapeutic monitoring required
Voriconazole	Efavirenz levels increased and voriconazole levels decreased	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 and other ritonavir-boosted protease inhibitors reduce voriconazole levels	Not recommended to be used together. Seek HIV specialist pharmacist advice
	Rilpivirine levels likely to increase	No dosage adjustment required – monitor
	Cobicistat may increase or decrease voriconazole levels	Co-administration is not advised unless the potential benefits are considered to outweigh the risks of unpredictable drug levels

Antiretroviral drugs, especially the non-nucleoside reverse-transcriptase inhibitors (NNRTIs) and boosted protease inhibitors (PIs), have several important drug–drug interactions. This table lists some examples of drug–drug interactions between antiretroviral and antifungal drugs. As the azole antifungal compounds are metabolised 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. Several azoles are predicted to inhibit P-gp which may increase levels of tenofovir alafenamide. As data and advice change frequently, this information should always be interpreted in conjunction with the manufacturer's information (https://www.medicines.org.uk/). Other useful online reference sources include the Liverpool HIV Drug Interactions (https://www.hiv-druginteractions.org/) and the Toronto General Hospital (https://hivclinic.ca/drug-information/drug-interaction-tables/) websites.

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10 Acknowledgements

The writing group thanks Ms Rosy Weston, Senior Lead Pharmacist for Sexual Health and HIV at Imperial College Healthcare NHS Trust, for performing a pharmacy review, Dr Jacoby Patterson for conducting independent literature searches and Dr Catherine Nieman Sims for supporting manuscript preparation. The writing group also thanks the HIV community, professional colleagues who contributed to the consultation and the reviewers for helpful comments.

Appendix 1: PICO questions

2 What is the epidemiology of candidiasis in individuals living with HIV?
2.1 What are the main *Candida* spp. causing *Candida* infections in recent surveys of people living with HIV?
2.2 What are the main risk factors for *Candida* infection in people living with HIV?
3.1 What are the clinical manifestations of mucosal candidiasis in people living with HIV?
4.1 When is it appropriate to request microbiological confirmation of *Candida* infections?
4.2 What are the preferred techniques for microbiological diagnosis of *Candida* spp.?
4.3 When should endoscopy be used to diagnose suspected oesophageal candidiasis?
5.1a What are the preferred treatments for oropharyngeal candidiasis?
5.1b What is the role of topical therapy?
5.2. What are the preferred treatments for oesophageal candidiasis?
5.3 How should fluconazole-refractory candidiasis be treated?
5.4 What are the preferred treatments for vulvovaginal candidiasis?
5.5 How should invasive candidiasis be treated in people living with HIV?
6.1 Is prophylaxis to prevent mucosal candidiasis recommended for people with advanced HIV infection?
6.2 Is continuous azole therapy recommended?

Appendix 2: Search strategy

1. Candida and HIV

1	exp “Candida”/ [MESH, all subheadings]
2	Candida or “Candidiasis” [text]
3	1 or 2
4	HIV (MESH and text)
5	3 and 4
6	Limit to dates: 2010 to date of search (March 2018)

2. Candida and diagnostics

1	exp “Candida”/ [MESH, explode]
2	HIV (MESH and text)
3	exp "Diagnosis"/
4	1 and 2 and 3
5	Limit to dates: 2010 to date of search (March 2018)

3. Candida and treatment

1	exp “Candida”/ [MESH, explode]
2	HIV (MESH and text)
3	exp "Treatment"/
4	1 and 2 and 3
5	Limit to dates: 2010 to date of search (March 2018)

Appendix 3: Definitions

Person living with HIV: an individual with a positive serological test for HIV

Oropharyngeal candidiasis: clinical appearance of candidiasis in the mouth or throat with non-adherent or adherent plaques, areas of erythema or cracking or erythema at the angles of the mouth in the presence or absence of symptoms such as pain and burning. Where microbiological testing has been performed it should reveal *Candida* spp. or in their absence fail to identify an alternative micro-organism

Oesophageal candidiaisis: pain or difficulty swallowing, usually in the presence or with features of oropharyngeal candidiasis with or without endoscopic confirmation. Where microbiological testing has been performed it should reveal *Candida* spp. or in their absence fail to identify an alternative micro-organism

Vulvovaginal candidiasis: a clinical diagnosis of redness, itching or curd-like discharge from the vulva with or without associated symptoms such as dyspareunia and external dysuria in association with identification of yeasts on microscopy or culture

Invasive candidiasis: microbiological identification of *Candida* spp. by culture from a normally sterile site such as the blood

Prophylaxis: an intervention performed to prevent development of a clinical syndrome associated with disease

Appendix 4: Summary of selection of literature