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ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: patients with HIV infection or AIDS

O. Lortholary[1,2†], G. Petrikkos[3†], M. Akova[4], M. C. Arendrup[5], S. Arikan-Akdagli[6], M. Bassetti[7], J. Bille[8], T. Calandra[9], E. Castagnola[10], O. A. Cornely[11], M. Cuenca-Estrella[12], J. P. Donnelly[13], J. Garbino[14], A. H. Groll[15], R. Herbrecht[16], W. W. Hope[17], H. E. Jensen[18], B. J. Kullberg[13], C. Lass-Flörl[19], W. Meersseman[20], M. D. Richardson[21], E. Roilides[22], P. E. Verweij[13], C. Viscoli[23] and A. J. Ullmann[24†] for the ESCMID Fungal Infection Study Group (EFISG)

1) *Université Paris Descartes, Service des Maladies Infectieuses et Tropicales, Hôpital Necker-Enfants malades, APHP, Centre d'Infectiologie Necker-Pasteur, IHU Imagine,* 2) *Institut Pasteur, Centre National de Référence Mycoses Invasives et Antifongiques, Unité de Mycologie Mole'culaire, CNRS URA3012, Paris, France,* 3) *4th Department of Internal Medicine, School of Medicine, National and Kapodistrian University of Athens, "ATTIKON" Hospital, RIMINI 1 - Haidari, Athens, Greece,* 4) *Department of Medicine, Hacettepe University School of Medicine, Ankara, Turkey,* 5) *Statens Serum Institut, Copenhagen, Denmark,* 6) *Department of Medical Microbiology, Hacettepe University School of Medicine, Ankara, Turkey,* 7) *Santa Maria Misericordia University Hospital, Udine, Italy,* 8) *Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland,* 9) *Infectious Diseases Service, Department of Medicine, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland,* 10) *Instituto Giannina Gaslini, Children's Hospital, Genova, Italy,* 11) *Department I of Internal Medicine, Clinical Trials Centre Cologne, ZKS Köln, BMBF 01KN1106, Center for Integrated Oncology CIO KölnBonn, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), German Centre for Infection Research, University of Cologne, Cologne, Germany,* 12) *Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain,* 13) *Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands,* 14) *University Hospitals Geneva, Geneva, Switzerland,* 15) *Department of Pediatric Hematology/Oncology, Center for Bone Marrow Transplantation, University Children's Hospital, Muenster, Germany,* 16) *Hôpital de Hautepierre, University of Strasbourg, Strasbourg, France,* 17) *Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK,* 18) *University of Copenhagen, Frederiksberg, Denmark,* 19) *Division of Hygiene & Medical Microbiology, Innsbruck Medical University, Innsbruck, Austria,* 20) *University Hospital Gasthuisberg, Leuven, Belgium,* 21) *Mycology Reference Centre, University Hospital of South Manchester and Manchester Academic Health Science Centre, University of Manchester, Manchester, UK,* 22) *Third Department of Pediatrics, Aristotle University School of Medicine and Hippokration Hospital, Thessaloniki, Greece,* 23) *University of Genoa, IRCCS San Martino-IST, Genoa, Italy and* 24) *Department of Internal Medicine II, Julius-Maximilians-University, Würzburg, Germany*

Abstract

Mucosal candidiasis is frequent in immunocompromised HIV-infected highly active antiretroviral (HAART) naive patients or those who have failed therapy. Mucosal candidiasis is a marker of progressive immune deficiency. Because of the frequently marked and prompt immune reconstitution induced by HAART, there is no recommendation for primary antifungal prophylaxis of mucosal candidiasis in the HIV setting in Europe, although it has been evidenced as effective in the pre-HAART era. Fluconazole remains the first line of therapy for both oropharyngeal candidiasis and oesophageal candidiasis and should be preferred to itraconazole oral solution (or capsules when not available) due to fewer side effects. For patients who still present with fluconazole-refractory mucosal candidiasis, oral treatment with any other azole should be preferred based on precise *Candida* species identification and susceptibility testing results in addition to the optimization of HAART when feasible. For vaginal candidiasis, topical therapy is preferred.

Keywords: Candidiasis, Europe, guideline, HIV AIDS
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Corresponding authors: O. Lortholary, Université Paris Descartes, Hôpital Necker-Enfants malades, Centre d'Infectiologie Necker-Pasteur 149, rue de Sèvres, 75743 Paris Cedex 15, France
E-mail: olivier.lortholary@nck.aphp.fr
and
A. J. Ullmann, Infectious Diseases, Department of Internal Medicine II, Julius-Maximilians-University, Oberdürrbacher Str. 6, 97080 Würzburg, Germany
E-mail: andrew.ullmann@uni-wuerzburg.de

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†Members of the subgroup committee mainly responsible for this manuscript.

Introduction

Oropharyngeal (OPC) and oesophageal (OEC) candidiasis are by far the most common fungal infections among patients with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) [1]. This guideline focuses on patients with HIV infection or AIDS with *Candida* diseases. The same grading system for the strength of recommendation and its documented quality of evidence are used throughout of this guideline as in the majority of the ESCMID *Candida* guidelines. The explanations and abbreviations used in this document are given in Table 1 [85].

Before the era of highly active antiretroviral therapy (HAART), OPC occurred in as many as 90% of patients, at some point during the course of HIV infection [1]. Although the incidence of mucosal *Candida* colonization and infection has been dramatically reduced with the introduction of HAART, it remains a common opportunistic infection in those HIV-infected patients without access to HAART or those in whom antiviral therapy is started late.

Oesophageal candidiasis was the leading opportunistic infection before the HAART era [2] and remains the second AIDS-defining illness in Europe [3]. In addition, mucosal candidiasis is still problematic in patients with poor adherence to treatment and/or multiple virological–immunological failures. The occurrence of OPC and OEC are indicators of profound immune suppression, and these syndromes are most often observed in patients with CD4+ counts <200 cells/μL with OEC being found in a more advanced stage of AIDS than OPC [1]. OPC and OEC are more difficult infections to treat in the context of HIV infection compared with other immunocompromised patients [4].

TABLE 1. Strength of the ESCMID recommendation and quality of evidence

Strength of a recommendation	
Grade A	ESCMID strongly supports a recommendation for use
Grade B	ESCMID moderately supports a recommendation for use
Grade C	ESCMID marginally supports a recommendation for use
Grade D	ESCMID supports a recommendation against use
Quality of evidence	
Level I	Evidence from at least one properly designed randomized, controlled trial
Level II*	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case–controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

*Added index:
$_r$: Meta-analysis or systematic review of randomized control trials.
$_t$: Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation.
$_h$: Comparator group is a historical control.
$_u$: Uncontrolled trial.
$_a$: Published abstract (presented at an international symposium or meeting).

Candida albicans is the most prominent pathogen. This organism can be found in the oral cavity of up to two-thirds of healthy individuals [5]. No particular strains have a preponderance to cause mucosal candidiasis. Acquired fluconazole (or pan triazole) resistance is related to previous exposure to fluconazole (or other triazoles), particularly if repeated and prolonged exposure in the context of profound immunosuppression [6–8]. Fluconazole resistance is associated with the cumulative exposure to fluconazole; patients failing fluconazole have received larger cumulative dosages of fluconazole (mean value, 8.7 g) [9]. The transmission of isolates (including those resistant to fluconazole) has been documented between HIV-infected partners [10]. Therefore, examination of partners is recommended.

In this setting, *C. albicans* resistance has also been accompanied by an emergence of non-*albicans Candida* species with intrinsic reduced azole susceptibility in the oral cavity (particularly *C. krusei* and *C. glabrata* [11]) and in the vagina [12]. *C. glabrata* may cause refractory mucosal candidiasis, particularly in patients with advanced immunosuppression [13].

Candida dubliniensis was first associated with OPC in HIV-infected patients [14]. The introduction of HAART with immunological reconstitution has led to a dramatic decline in the incidence of refractory disease and of infections caused by resistant *Candida* isolates. Barchiesi *et al.* [11] found that 93% of *Candida* collected from oral cavities among 102 HAART-treated patients remained susceptible to fluconazole, despite many of these patients receiving repeated courses of triazoles.

Clinical manifestations

Three clinical patterns of OPC have been described: erythematous, pseudo-membranous and angular cheilitis. OPC can occur at any stage of HIV infection (primary infection, chronic asymptomatic phase and AIDS), but erythematous (erythematous patches without white plaques visible on the anterior or posterior upper palate or diffusely on the tongue) and pseudomembranous (creamy white, plaque-like lesions of the buccal or oropharyngeal mucosa or tongue surface) forms are predictive of progressive immunodeficiency [15].

Oesophageal symptoms include retrosternal burning pain, altered taste and odynophagia. Endoscopic examination reveals whitish plaques similar to those observed with OPC that might progress to superficial ulceration of the OEC mucosa, with central or surface whitish exudates.

As relapse of OPC and OEC is common, it is often associated with recurrence of intense pain that contributes to weight loss because of poor nutrition.

In contrast, vulvovaginal candidiasis is common among healthy adult women and is often unrelated to HIV status. Consequently, recurrent vulvovaginal candidiasis alone cannot be ascribed to advanced HIV disease.

Candida vulvovaginitis may be mild to moderate in severity and sporadic (similar to normal hosts). This syndrome is characterized by a white adherent vaginal discharge that is associated with burning and itching. In patients with advanced immunosuppression, episodes may be more severe and more frequently recurrent. Compared with OPC, vaginal candidiasis is frequently more responsive to triazole therapy.

Diagnosis of oropharyngeal candidiasis and oesophagitis

A diagnosis of OPC is usually made on clinical grounds. Lesions can be readily scraped with a tongue depressor or other instrument to obtain samples for a microbiological diagnosis. Fungal selective media should be used to avoid overgrowth by colonizing bacteria [16]. Identification to species level and susceptibility testing are recommended in recurrent cases of OPC and for patients repeatedly exposed to fluconazole (and/or other triazoles). If an upper endoscopy is performed, a biopsy may enable infection to be distinguished from colonization or other mucosal diseases [16].

The diagnosis of OEC requires endoscopic visualization of lesions with histopathologic demonstration of characteristic *Candida* yeast forms in tissue and culture confirmation of the presence of *Candida* species.

The diagnosis of vulvovaginal candidiasis is made with a combination of characteristic clinical appearances combined with standard microbiological investigations. The detection of serum biomarkers such as mannan/antimannan or ß-D-glucan is not required to confirm a diagnosis of mucosal candidiasis.

Primary prophylaxis of mucosal candidiasis

Despite the demonstrated efficacy of fluconazole, primary antifungal prophylaxis for the prevention of OPC and OEC is not recommended in Europe (DI). Fluconazole (200 mg/day) is superior to clotrimazole troches in a large randomized multicentric unblinded trial for the prevention of both OEC and OPC with a greatest benefit in patients with less than 50 CD4/mm^3 [17]. In addition, in a double-blind trial, Havlir *et al.* [18] observed double the rate of OPC among patients receiving 400 mg fluconazole weekly compared with those treated with 200 mg daily. Fluconazole 200 mg/week in a randomized double-blind placebo-controlled trial involving HIV-infected women prevented OPC and vaginal candidiasis but not OEC [19]. In a retrospective study, Manfredi *et al.* [20] demonstrated that fluconazole 100 mg/day every 3 weeks prevented the occurrence of OEC vs. no therapy. Finally, other triazoles such as itraconazole are more effective than placebo in the prevention of superficial *Candida* sp. infections [21] (Table 2).

While OPC may be associated with significant morbidity, the disadvantages of primary prophylaxis include the potential for drug–drug interactions between triazoles and HAART, the development of fluconazole resistance and/or cross-resistance to azoles, the availability of effective antifungal therapy for OPC and the cost and potential toxicity of triazole antifungal agents. Thus, the best prophylaxis of both OPC and OEC is the appropriate compliance to HAART (AII).

Treatment of first OPC episodes due to triazole susceptible isolates

More than 20 years after its introduction, fluconazole remains the leading antifungal drug that is used for OPC. Fluconazole is fungistatic against *Candida* spp. with an oral bioavailability of over 80%, which is not influenced by concomitant food intake or gastric pH. Penetration into saliva is excellent. Tablets, oral solution and intravenous formulation can all be used to treat OPC. Because of hepatic metabolism via the CYP450 enzyme complex, many drug interactions with fluconazole have been described. Fluconazole is well tolerated within the recommended range of doses for mucosal candidiasis. Side effects increasingly occur with doses in excess of 400 mg per day, which are not usually necessary for treatment of mucosal candidiasis [22]. Finally, EUCAST and CLSI susceptibility breakpoints have been defined for fluconazole and *C. albicans, C. parapsilosis* and *C. tropicalis:* susceptible, MIC ≤2 mg/L; and resistant, MIC >4 mg/L according to both EUCAST and CLSI (http://www.eucast.org).

Fluconazole at a dosage of 100 mg/day for 7–14 days is recommended for the first-line agent for the treatment of OPC for adults [23–28] and children (AI) [29,30] (Table 2). The majority of patients with OPC that is caused by fluconazole-susceptible isolates will respond to therapy within 72 h. Approximately 80% of patients are cured, and a further 10% experience significant improvement in their symptoms [31]. OPC is a mandatory indication of HAART's initiation (AII). No long-term suppressive triazole therapy should be used (DIII).

Potential alternatives to fluconazole include (i) miconazole as a mucoadhesive tablet 10 or 50 mg once daily for 7–14 days (approved in Europe since 2008 in its 50 mg for-

TABLE 2. Recommendations made for patients with HIV infection or AIDS and Candida disease

Intention	Intervention	SoR	QoE	Reference/Commentary
Primary prophylaxis of mucosal candidiasis (OPC/OEC)	Primary antifungal prophylaxis of OPC/OEC	D	I	[17][19][18][20][21] although effective [interactions/ acute therapy effective/induction of resistance/no mortality related to OPC/cost)
	Best prophylaxis is appropriate compliance to HAART	A	II	[80][81][82][83][84]
Treatment of first episodes of oropharyngeal candidiasis (OPC) due to azole susceptible isolates	HAART should be initiated	A	II	[80][81][82][83][84]
	Fluconazole (100 mg/day in adults, at least 7 days)	A	I	[23][11][26,27][25][28][29][30]
	Miconazole mucoadhesive tablet	B	I	[32][33]
	Itraconazole oral solution	B	I	[35][36]
	Posaconazole (100 mg/day)	C	I	[4]
	Voriconazole	–	–	No published data
	Topical agents	D	I	[27][29]
	Ketoconazole	D	I	[23][11][45][42]
	Itraconazole capsules	D	III	Because of poor absorption [39]
	Echinocandins and any amphotericin B formulation	D	III	No published data
	Chronic suppressive therapy	D	III	No published data
Treatment of oesophageal candidiasis	Start treatment without endoscopy	A	III	In case of oesophageal symptoms and OPC, endoscopy is not indicated.
	Oral fluconazole (200 mg/day for 14–21 days) (or i.v. for those who cannot swallow)	A	I	[23][48][46][47]
	Itraconazole solution	B	I	[49][46][47]
	Echinocandins can be used in patients who cannot swallow but not better than Fluconazole	C	I	[55][56][57][53][54] Higher relapse rate with caspofungin and anidulafungin vs fluconazole
	Ketoconazole	D	I	[48][42]
	Any i.v. amphotericin B formulation	D	III	No role for the management of OEC due to azole susceptible isolates
	Local treatments	D	III	Less effective than fluconazole
Treatment of refractory OPC/OEC	Itraconazole oral solution (≥200 mg/day)	A	II	[64][63][65]
	Posaconazole (400 mg twice daily)	A	II	[66][67]
	Voriconazole (200 mg twice daily)	C	II	[68]
	Any echinocandin	A	II	[70][71][72] All echinocandins may be considered equivalent here
	Any amphotericin B formulation	C	III	No published data
Suppressive therapy	Fluconazole 100–200 mg 3×/week	A	I	[75][76][77][78][19][18][9][79]

HAART, highly active antiretroviral; OEC, oesophageal.

mulation) (BI). Miconazole was studied in a randomized trial vs. ketoconazole (similar efficacy but reportedly had more episodes of vomiting in patients on ketoconazole) and in a large phase III double-blind double dummy trial vs. clotrimazole (similar efficacy and acceptable tolerability), but not to the reference drug fluconazole [32–34]; (ii) itraconazole oral solution. Itraconazole solution for 7–14 days (100 or 200 mg/day) is equivalent to fluconazole for 14 days [35,36] (BI). Itraconazole solution may be beneficial even without the attainment of detectable serum levels because of its direct effect if swished in mouth for few seconds before swallowing [37]. Itraconazole solution is associated with a 30% increase in itraconazole absorption in comparison with the capsule formulation [38] and with a comparable rate of side effects compared with fluconazole [35,36] for OPC. Itraconazole has a higher incidence of erratic oral bioavailability and drug–drug interactions compared with fluconazole. The use of itraconazole may be complicated by cross-resistance to fluconazole. Indeed, in one study, 30% of fluconazole-resistant isolates were cross-resistant to itraconazole, and itraconazole solution has been shown effective during OPC in this context against itraconazole susceptible isolates [39]; (iii) voriconazole has not been studied for fluconazole-susceptible OPC; (iv) posaconazole (200 mg on day 1 then 100 mg daily) is also an alternative to fluconazole [40]. Posaconazole is better tolerated and has fewer interactions compared with both itraconazole and voriconazole, but has a broad spectrum of activity for treating initial episodes of OPC and is considered an option for therapy in cases with fluconazole-resistant *Candida* sp. (CI).

Topical agents (e.g. amphotericin B lozenges or nystatin) should not be used for the treatment of OPC because of suboptimal tolerability (bitter taste, gastro-intestinal side effects, frequent dosing) and lower efficacy [27] (DI). Furthermore, a recommendation for clotrimazole was not considered because this agent is not available in Europe. While clotrimazole is effective, it is less efficacious and associated with a higher rate of relapses in comparison with fluconazole at least in some studies [25,26,28]. Finally, acquired resistance to clotrimazole has been documented in *Candida* isolates in OPC [41].

Ketoconazole is efficacious in comparison with fluconazole and itraconazole but its use is limited by hepatotoxicity, drug–drug interactions, limited oral bioavailability in the set-

ting of hypochlorhydria and appears to select for triazole cross-resistance [11,23,42–45]. Ketoconazole is thus not recommended for the management of OPC (DI).

Echinocandins should not be considered for OPC episodes caused by isolates that are susceptible to triazoles due to their parenteral availability and cost in comparison with fluconazole (DIII). Finally, any intravenous formulation of amphotericin B is also not recommended for the management of OPC due to numerous adverse events and associated nephrotoxicity (DIII).

Treatment of oesophageal candidiasis due to triazole susceptible isolates

Antifungal therapy for OEC should be initiated without endoscopy, especially if patients have signs and symptoms of OEC and oropharyngeal lesions are suggestive of mucosal candidiasis (AIII). Topical agents are not effective enough and should be avoided (DIII). Oral fluconazole (200 mg/day for 14–21 days) is the treatment of choice [46–48] (AI). Intravenous formulation can be used in case of severe oesophagitis (Table 2).

Itraconazole (oral solution) is an alternative agent that has been shown to be as effective clinically and mycologically as fluconazole, but endoscopic cure was found less frequently especially during short-term therapy in the itraconazole arm [46,47,49] (BI). Itraconazole capsules are not recommended because of limited oral bioavailability (DII) The addition of flucytosine to itraconazole is not superior to fluconazole and is not recommended [50] (DI).

Voriconazole 200 mg twice daily for 14–21 day is equally as efficacious as fluconazole, but associated with a higher incidence of adverse events [51] and more potential drug–drug interactions, visual abnormalities and phototoxicity in ambulatory patients (BI).

Oral flucytosine alone was tested against fluconazole but was proven less effective [52], in addition to potential side effects (DI). Oral ketoconazole was tested against fluconazole in a large double-blind trial, and endoscopic and clinical cure rates were inferior in the ketoconazole arm [48].

Ketoconazole was also tested in a small trial against itraconazole with a higher efficacy than itraconazole [42] (DI). Finally among azoles, posaconazole has not been specifically studied in the context of primary treatment of oesophagitis in azole susceptible isolates and should be reserved for refractory or resistant disease.

The echinocandins have been evaluated for the treatment of AIDS-associated OEC mostly in comparison with fluconazole. However, these antifungals are only available parenterally and are much less convenient to use than oral azoles (CI). Caspofungin is associated with similar response rates and tolerability compared with fluconazole although higher relapse rates were observed with caspofungin [53]. Caspofungin has been shown superior (74–91% efficacy) to amphotericin B (63%) in one study [54]. Micafungin (50–150 mg/day) produces a dose-dependent response rate in OEC [55]. The use of 150 mg/day regimen was comparable both in terms of efficacy, relapse rate and tolerance compared with fluconazole (200 mg/day) in a large double-blind study [56]. The currently licensed dosage is 150 mg/day. Similarly, anidulafungin [100 mg/day after loading dose] produces comparable response rates to fluconazole, but the rate of relapse 2 weeks after cessation of therapy was higher [57].

Intravenous formulations of amphotericin play no role for the management of OEC due to azole susceptible *Candida* isolates (DII).

Management of refractory OPC and or OEC

Refractory OPC or OEC is defined by symptoms that persist after more than 14 days of fluconazole ≥200 mg/day. This syndrome is reported in approximately 5% of HIV-infected patients and typically in those with CD4+ counts <50 cells/μL who have received multiple and prolonged courses of antifungals/triazole agents for a high number of OPC episodes [6–8]. The clinical impact of refractory mucosal candidiasis has been well documented [58]. In this situation, careful identification to species level and *in vitro* susceptibility testing to fluconazole and other triazoles are mandatory. Detection of resistance based on *in vitro* established breakpoints is indeed of major importance as mucosal candidiasis is one of the clinical settings where the correlation between *in vitro* results and *in vivo* outcome has been established [59,60].

Any use of a topical antifungal agent such as amphotericin B [61] should be avoided because of low efficacy rates (DIII). The use of fluconazole at a higher daily dosage may be beneficial at least transiently, particularly with the suspension, which provides increased salivary concentrations [62] (BIII). Itraconazole solution (up to 600 mg/day) is an alternative and is associated with a 55–75% response rate, but relapses occur subsequently [63–65] (AII).

Posaconazole oral suspension [400 mg twice daily (i.e. a higher dosage than that used for nonrefractory mucosal infections) for 28–90 days] can also be used and is efficacious in up to 86% of patients with fluconazole and/or itraconazole refractory oropharyngeal and/or OEC candidiasis. It has been approved by EMA in such context. In addition, the use of posaconazole is well tolerated up to 90 days of therapy, but relapses do also occur during the follow-up [66,67] (AII).

Voriconazole appears to be active against fluconazole-resistant *Candida* isolates isolated from mucosal infections [68] although cross-resistance has also been demonstrated [69]. Voriconazole has been shown effective in a limited number of refractory OEC cases [68] (CII). If prolonged azole therapy is anticipated, periodic monitoring of liver enzymes should be considered (BIII).

Caspofungin can be used for HIV-infected patients with clinically fluconazole-refractory OEC or microbiologically resistant disease. A favourable response is obtained in 83% and 79% of cases, respectively [70]. Caspofungin can also be used for patients with refractory OPC/OEC who have experienced failure or intolerance to polyenes [71] (AII). Anidulafungin can also be used in this setting. An open-label clinical trial also studied anidulafungin in fluconazole-resistant OPC/OEC in 19 patients with a 95% successful clinical response, including 11/12 patients with OEC who had endoscopic cure (92%). Tolerance was acceptable [72] (AII). In addition, azole-refractory mucosal candidiasis can also be treated with micafungin 150 mg/day although it has not been specifically studied in that setting (AII).

Amphotericin B deoxycholate, amphotericin B lipid complex and liposomal amphotericin B may also be effective in such setting, but their toxicity profiles should receive considerable attention (CII). Preliminary studies have suggested a potential benefit of adjunctive GM-CSF therapy [73] (CII). Finally, any perspective of a new HAART regimen appears crucial in this context [74] (AIII).

Vulvovaginal candidiasis

Vulvovaginal candidiasis usually responds readily to topical agents (AII). Short-course oral azole therapy although effective should be avoided (fluconazole (DII), itraconazole oral solution (DII)). In case of multiple episodes, oral fluconazole (150 mg/week) should be used to prevent recurrences as evidenced outside the HIV setting (AI).

Prevention of recurrences

Maintenance therapy or secondary prophylaxis to prevent recurrences is usually not recommended (DIII). However, when relapses are frequent and/or severe, long-term oral triazole use may be considered providing cost and toxicity are acceptable. Fluconazole maintenance therapy has been well documented as effective in several randomized studies performed during the pre-HAART era. It should be reserved for patients with relapsing OPC/OEC caused by a fluconazole-susceptible isolate after HAART optimization (or failing HAART therapy). The range of dosages is large: 50–200 mg/day or 150–400 mg/week] (BI) [9,18,19,75–78] (Table 2).

Maintenance therapy with fluconazole 100–200 mg 3×/week should be considered for the case of recurrent infections to prevent further relapse (AI), but daily administration of fluconazole should be favoured (BI). A more recent randomized clinical trial has documented that fluconazole (200 mg three times a week) vs. episodic treatment of recurrences therapy was significantly associated with fewer cases of OPC or OEC and fewer invasive fungal infections, but not with improved survival in HIV patients with CD4+ count <150 cells/μL. In the latter study, no difference in the rate of fluconazole-refractory candidiasis was noticed provided that patients received HAART [79]. Oral posaconazole 400 mg twice daily can be proposed in case of relapsing OEC due to fluconazole-resistant *Candida* isolates (BII). Triazole therapy is precluded in pregnancy (AIII). Clinical experience, but no specific study, suggests that maintenance therapy is not required in the context of immune reconstitution to CD4-positive cells >200/μL (AIII).

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J.B. has nothing to declare.

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E.C. has participated as invited speaker to symposia organized by Gilead, Pfizer, Astellas, Merck, Novartis and he has been member of advisory boards for Astellas, Pfizer.

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M.C.E. has received in the past 5 years grant support from Astellas Pharma, bioMerieux, Gilead Sciences, Merck Sharp and Dohme, Pfizer, Schering Plough, Soria Melguizo SA, Ferrer International, the European Union, the ALBAN program, the Spanish Agency for International Cooperation, the Spanish Ministry of Culture and Education, The Spanish Health Research Fund, The Instituto de Salud Carlos III, The Ramon Areces Foundation and The Mutua Madrileña Foundation. He has been an advisor/consultant to the Panamerican Health Organization, Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering Plough. He has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering Plough.

J.P.D. has received grant support from, Astellas, Gilead Sciences, Merck Sharp and Dohme, Pfizer and Schering Plough. He has been a consultant or on an advisory board for Astellas, Gilead Sciences, Merck Sharp and Dohme and Pfizer. He has received remuneration for giving lectures on behalf of Gilead Sciences, Merck and Pfizer.

J.G. has nothing to declare.

A.H.G. has received research support from Gilead, Merck and Schering. He has acted as speaker and/or consultant for Astellas, Cephalon, Gilead, Merck, Pfizer, Schering and Vicuron.

R.H. has been a consultant or at the advisory board for Astellas pharma, Basilea, Gilead Sciences, Merck Sharp and Dohme, Novartis, Pfizer and Schering Plough. He has also received investigator fees for a clinical trial for Pfizer and travel support from Pfizer and Gilead. He has received grant support and/or has been paid for talks on behalf of Astellas, Gilead Sciences, Merck Sharp and Dohme, Pfizer, and Schering Plough.

W.W.H. has received grant support from National Institute of Health Research (NIHR), Medical Research Council, National Institute for the Replacement, Refinement and Reduction, of Animals in Research, Pfizer, Gilead, Schering Plough, Merck and Astellas, and has served as a consultant for Pfizer, Astellas, Gilead, F2G, Vectura, and Schering Plough.

H.E.J. has nothing to declare.

B.J.K. has received research grants from Bio-Mérieux and Cephalon. He is a consultant to Pfizer and is a member of the Gilead, MSD and Pfizer speaker bureaus.

C.L.-F. has received grant support in the past 5 years from Astellas Pharma, Gilead Sciences, Pfizer, Schering Plough and Merck Sharp and Dohme. She has been an advisor/consultant to Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering Plough. She has received travel support from and/or been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering Plough.

W.M. has received grant support from MSD and Pfizer. He had been an advisor to MSD and Pfizer. He has received honoraria for presentations on behalf of MSD/Schering Plough and Pfizer.

M.D.R. has received grants, speaker's honoraria and travel support from ESCMID, Pfizer, Astellas, MSD and Gilead Sciences. He has also received royalties from Blackwell Publishing.

E.R. has received research support from Pfizer, Gilead, Enzon, Schering, Merck and he has made contributions in advisory boards of Gilead, Astellas, Schering, Merck, Pfizer.

He has been paid for talks on behalf of Gilead, Cephalon, Pfizer, Wyeth, Schering, Merck, Aventis and Astellas.

P.E.V. has received research grants from Pfizer, Astellas, Cephalon, Gilead Sciences, Merck and Schering-Plough.

C.V. received grants as speaker/moderator in meetings sponsored by Pfizer, Gilead, MSD, Astellas, Abbott, BMS and received grants for participation in advisory boards by Gilead, Astellas, MSD, Pfizer. Further, he obtained research grants for his institution from Pfizer, MSD, Gilead, Abbott, Jansen, BMS, Novartis- He is member of the SAG (Scientific Advisory Group) for antibacterials and antifungals of CHMP-EMA and consultant for Italian Medical Drug Agency Member of various levels of local Infection Control, Antibiotic Stewardship, Vaccine and HIV Committees (Genoa, Liguria, Italy). He has received payment for education materials for Nadirex International (Pavia, Italy).

A.J.U. has received research grants from MSD (Schering-Plough) and is/was an advisor or received lecture honorarium from Astellas, Aicuris, Basilea, Gilead, MSD and Pfizer.

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