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Mucosal and Systemic Fungal Infections in Patients with AIDS

Prophylaxis and Treatment

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Abstract

In countries where highly active antiretroviral therapy (HAART) is widely available, a decrease in the incidence of fungal infections has been observed in the last 5 years compared with countries that cannot afford this treatment. Even refractory fungal infections may be controlled when HAART is given to patients, and end-stage AIDS infections, such as aspergillosis, are now only infrequently seen. In contrast, fungal infections in certain regions, such as penicilliosis in Southeast Asia or cryptococcosis in Sub-Saharan Africa, are a growing problem.

Antifungal therapy for documented infections has not changed very much during recent years; however, new drugs such as caspofungin and voriconazole may be more effective in the treatment of opportunistic fungal infections, in particular, those involving resistant organisms.

Secondary antifungal prophylaxis for many opportunistic pathogens can now be temporarily or even permanently discontinued in many HIV-positive patients

who have a marked improvement in immune function parameters, such as CD4+ cell counts, after initiation of HAART. The link between effective virustatic control of HIV infection and a decreasing incidence of fungal infections has been recognised; and so, despite the availability of very effective new antifungal drugs, the cornerstone of treatment and prevention of opportunistic fungal infections in patients with HIV infection is effective antiretroviral therapy including protease inhibitors.

The course of infection with the human immunodeficiency virus (HIV-1, HIV-2) is characterised by the occurrence of opportunistic infections and opportunistic malignancies. In Europe and the US, with *Pneumocystis jiroveci* (previously *P. carinii*) pneumonia and oesophageal candidiasis, two invasive fungal infections are among the leading AIDS-defining illnesses. In addition, in industrialised countries, these two diseases most commonly lead to the diagnosis of AIDS before other opportunistic diseases. In tropical and subtropical countries, infections by *Cryptococcus neoformans* and endemic fungi such as *Histoplasma capsulatum* or *Penicillium marneffei* may be more frequent, but exact data are rare for many rural areas. Other fungal diseases (mostly superficial fungal infections such as oral or vaginal candidiasis, dermatomycosis and onychomycosis) are more prevalent but are not regarded as AIDS-defining illnesses. Indicator (fungal) conditions in the case definition of AIDS in adults are candidiasis of the oesophagus, trachea, bronchi or lungs, extrapulmonary coccidioidomycosis, extrapulmonary cryptococcosis, extrapulmonary histoplasmosis and *Pneumocystis* pneumonia.[1] However, candidiasis of the trachea and lungs are not common in HIV-positive patients anywhere in the world, whereas, in contrast, disseminated infection with the endemic fungus *P. marneffei* is the most frequent opportunistic fungal infection in Southeast Asia together with cryptococcosis (and tuberculosis). Penicilliosis is not included in the case definition of AIDS proposed by the Centers for Disease Control and Prevention in the US, but is regarded as an AIDS-defining illness in that endemic area.[2,3]

Diseases such as invasive aspergillosis,[4-8] zygomycosis, mucormycosis and sporotrichosis have been reported with decreasing incidence since the early 1990s,[4,9] as have case reports on various rare fungal infections such as fusariosis or trichosporonosis.[10,11] A summary of fungal infections in patients with HIV infection is shown in table I.

In HIV-infected patients, the occurrence of fungal infections depends largely on the degree of CD4+ T-cell depletion; however, exposure to dimorphic fungi in endemic areas is also a key factor. Until recently, recommendations have emphasised the need to continue primary or secondary prophylaxis for life for some invasive fungal infec-

Table I. Diseases caused by fungal infections in patients with HIV infection

Pathogen	Disease
Aspergillus spp.	Tracheobronchitis, invasive pulmonary/disseminated aspergillosis
Blastomyces dermatitidis	Pulmonary and/or disseminated infection, and meningitis
Candida spp. (predominantly *C. albicans*)	Mucocutaneous candidiasis, oesophageal candidiasis, fungaemia, pulmonal candidiasis (children)
Coccidioides immitis	Pulmonal and/or disseminated disease
Cryptococcus neoformans	Meningitis, pneumonia, disseminated infection
Histoplasma capsulatum	Pneumonia, disseminated infection
Paracoccidioides brasiliensis	Pneumonia, skin lesions, orolaryngeal lesion
Penicillium marneffei	Skin lesions, disseminated infection (mostly Thailand/Southeast Asia)
Pneumocystis jiroveci (previously *P. carinii*)	Pneumonia, in advanced disease and with prophylaxis atypical presentation (e.g. multiorgan involvement)
Sporothrix schenckii	Diffuse skin lesions, polyarthritis

Table II. Drug-drug interactions between antifungal agents and drugs used in HIV-positive patients; effect on serum drug concentrations

Potentially interacting drug	Antifungal				
	ketoconazole (KET)	fluconazole (FLU)	itraconazole (ITR)	voriconazole (VOR)	caspofungin (CAS)
Rifampin	KET↓	FLU↓	ITR↓	VOR↓	CAS↓
Rifabutin	KET↓	FLU↓	ITR↓	VOR↓	CAS↓
Phenytoin (Phen)	Phen↑– KET↓	Phen↑– FLU↓	Phen↑– ITR↓	Phen↑– VOR↓	CAS↓
Carbamazepine	KET↓	FLU↓	ITR↓	VOR↓	NA
Efavirenz (EFV)	NA	EFV↑	NA	NA	CAS↓
Nevirapine (NVP)	NVP↓	NA	NA	NA	CAS↓
Delavirdine	DLV↑	NA	NA	NA	NA
Indinavir (IDV)	IDV↑	IDV↑	IDV↑	NC	NA
Ritonavir (RTV)	NA	RTV↑	RTV↑	NA	NA
Saquinavir	NA	NA	NA	NA	NA
Nelfinavir	NA	NA	NA	NA	NC
Didanosine	KET↓	NA	ITR↓	NA	NA
Zidovudine (ZDV)	NA	ZDV↑	NA	NA	NA

NA = not available; **NC** = no change; ↑ indicates serum drug concentrations increase; ↓ indicates serum drug concentrations decrease.

tions (e.g. cryptococcosis), even when the primary fungal infection has been cured.[10] If the institution of highly active antiretroviral therapy (HAART) restores CD4+ cell counts to levels at which opportunistic infection rarely occurs, newer data suggest that secondary prophylaxis may be discontinued not only for *Pneumocystis* pneumonia but for cryptococcal meningitis or penicilliosis as well.[12] However, fungal diseases other than *Pneumocystis* pneumonia are much less studied. Although *Pneumocystis* pneumonia is regarded as a fungal infection, it does not respond to most antifungals (except caspofungin, which was extremely potent against *P. jiroveci* in models of immune-compromised animals[13]) and is not further considered in this review. The aim of this review is to outline the current strategies for prophylaxis and treatment of the most common mucosal and systemic fungal infections other than *P. jiroveci* in patients with HIV infection or AIDS.

Importantly, drug-drug interactions between antifungal agents and antiretroviral therapy occur and could be an important issue when therapy is given concomitantly for a longer period of time. The most common interactions are described in table II and need to be considered when deciding on treatment and prevention strategies for fungal infections in patients with HIV infection (table II).

1. Candidiasis

At the beginning of the AIDS epidemic in 1981, the very first reports linked the occurrence of oral candidiasis with *Pneumocystis* pneumonia in HIV-infected persons.[14] Since then numerous publications have found a strong correlation between the occurrence of mucocutaneous candidiasis (either oral, vaginal or oesophageal) and the progression to AIDS. Oral candidiasis was found as an independent parameter of advanced immunodeficiency in HIV-infected people.[15]

The most common *Candida* species isolated from mucous membranes in HIV-infected patients is *Candida albicans*. Other species such as *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, *C. krusei* or the 'new' species *C. dubliniensis* are frequently cultured and have been found concomitantly with *C. albicans*. These non-*C. albicans* species rarely cause infections without simultaneous presence of *C. albicans*.

Before the introduction of protease inhibitors as part of treatment for HIV infection (i.e. HAART), the incidence of oral candidiasis in HIV-infected individuals varied from 7% to 93% depending on the methodology of the study and the degree of immunosuppression of the study population.[16] In asymptomatic HIV-infected individuals the incidence varied from 0% to 63%, in individuals with AIDS-related complex from 43% to 78%, and in persons with AIDS from 54% to 93%.[17] The most

common type presents as pseudomembranous candidiasis (thrush), but erythematous candidiasis has also been described frequently and may be readily overlooked and left untreated.[18] A recent study reported that elevated plasma HIV-1 RNA levels was found to be associated with the baseline prevalence of oral candidiasis, and appeared to be a better predictor of HIV-related oral disease than CD4+ cell count at early stages of HIV disease.[19] In HIV-infected women, vaginal candidiasis often precedes oropharyngeal candidiasis.[20] The attack rate and recurrence of oropharyngeal candidiasis in HIV-infected women is the same as in men. However, despite several studies showing higher rates of vaginal colonisation with *Candida* spp. among HIV-infected women, a higher attack rate of vaginal candidiasis compared with in HIV-negative women is anticipated but not definitely proven.[21]

1.1 Prophylaxis

In general, primary prophylaxis is not routinely recommended against fungi (*Candida* spp., *C. neoformans*, *H. capsulatum*, *P. marneffei* and *Coccidioides immitis*).[12,22] However, long-term secondary prophylaxis in patients with recurrent oral candidiasis can prevent recurrences and may be indicated in some patients with HIV infection (fluconazole 100–200 mg/week).[23-26] The development of resistance to fluconazole has been studied in a comparative trial giving continuous (200 mg/day) or intermittent (only for relapse) therapy as prophylaxis for oral candidiasis in HIV-positive patients with a CD4+ cell count <350 cells/μL.[27] Continuous therapy was highly effective in preventing relapses and the development of resistance did not differ between the continuous and the intermittent group after 1 year. The 1999 US Public Health Service (USPHS)/Infectious Disease Society of America (IDSA) Guidelines for prevention of opportunistic infections in persons infected with HIV recommend secondary antifungal prophylaxis for oropharyngeal, vaginal or oesophageal candidiasis only if subsequent episodes are frequent or severe.[22] Fluconazole 100–200 mg/day is recommended as the first choice and as alternatives itraconazole solution 200 mg/day or ketoconazole 200 mg/day are recommended for all indications.

1.2 Treatment

Most patients with mucocutaneous candidiasis respond well to antifungal therapy (table III lists available therapies). For oropharyngeal candidiasis topical non-absorbed therapy using the 'swish and swallow' principle is usually effective, and is often used in patients with a single occurrence of disease as first-line therapy for 10–14 days. Local therapy may consist of amphotericin B suspension or tablets, nystatin lozenges or clotrimazole troches. A small study in 29 patients found clotrimazole troches (10mg five times daily) produced equivalent results to itraconazole oral solution.[28] A comparative study of itraconazole capsules (200mg once daily) and clotrimazole troches (10mg five times daily) produced similar results at the end of therapy but a significantly faster response to itraconazole and a faster relapse rate with clotrimazole.[29] However, fluconazole capsules have proven to be superior to nystatin and at least equivalent to clotrimazole for thrush therapy.[30,31] Clinical response rates between topical and systemic treatment are often similar, but signs and symptoms of mucosal disease respond more rapidly with systemic treatment.

Treatment for oesophageal candidiasis is essentially the same as for oral candidiasis, but because oesophageal candidiasis is considered as an invasive fungal infection, treatment with fluconazole or itraconazole is given in most patients. In patients with HIV infection and chronic recurrent oral disease, fluconazole has now became the drug of choice in many patients (for adults: 100 mg/day, oral loading

Table III. Therapeutic options for oropharyngeal and oesophageal candidiasis

Drug	Formulation	Dosage
Clotrimazole[a]	Troche	5 × 10 mg/day
Nystatin[a]	Lozenges	6 × 1mL ≈ 6 × 100 000 IE/day
Amphotericin B[a]	Suspension	5 × 100 mg/day
Fluconazole	Capsule, suspension	100 (–400[b]) mg/day
Itraconazole	Capsule, suspension	100–200 (–400[b]) mg/day
Voriconazole	Capsule	200mg twice daily[b]
Caspofungin	Intravenous infusion	50 mg/day[b]
Amphotericin B	Intravenous infusion	0.3–0.7 mg/day[b]

a Drug is only recommended for oropharyngeal candidiasis.

b Dosage for oesophageal candidiasis.

Table IV. Selection of studies on therapy of invasive fungal infections in patients with AIDS

Indication (no. of patients)	Drug	Response	Significance	References
Aspergillosis	No prospective studies in HIV+ patients Amphotericin B/itraconazole (descriptive)	18% if >7 days' therapy	Unknown	8
Blastomycosis	No prospective comparative studies in HIV+ patients		Unknown	32,33
(15)	Amphotericin B (descriptive)	60%[a]		
(48)	Itraconazole	90%		
Candidiasis [oesophageal]	Fluconazole 100mg vs	91%	$p < 0.001$	34
(143)	Ketoconazole 200mg	52%	(95% CI 24, 52%)	
Candidiasis [oesophageal]	a) Fluconazole 3mg/kg/day vs	69%	$p = 0.772$ (a vs b)	35
(85)	b) Itraconazole 3 mg/kg/day + flucytosine 100 mg/kg/day vs	72%	$p < 0.001$ (a or b vs c)	
	c) Placebo	23 (partial)		
Candidiasis [oesophageal]	Fluconazole 200mg vs	81%	$p < 0.001$	36
(2213)	Itraconazole 200mg	66% (endoscopic cure at 2 wks)		
Candidiasis [oesophageal]	Fluconazole 100mg vs	91%	95% CI –0.074,	37
(126)	Itraconazole 100mg (solution)	94%	0.16%	
Candidiasis [oral/	Caspofungin 35mg vs	65%	95% CI 'similar' for	38
oesophageal] (140)	Caspofungin 50mg vs	90%	all groups	
	Caspofungin 70mg vs	82%		
	Amphotericin B 0.5 mg/kg	57%		
Candidiasis [oesophageal]	Fluconazole 200 mg/day vs	90%	95% CI –1.0, 7.5%	39
(391)	Voriconazole 200mg bid	95%		
Coccidioidomycosis (198)[b]	Fluconazole 400 mg/day vs	57%	$p = 0.05$	40
	Itraconazole 200mg bid	72% (by 12mo)	(95% CI 0.003, 30%)	
Cryptococcosis (14)	Fluconazole 800–1000 mg/day	54.5%	$p = 0.11$[c]	41
Cryptococcosis (21)[d]	Amphotericin B 0.7 mg/kg/day + flucytosine 150 mg/kg/day vs	100%	$p = 0.04$	42
	Fluconazole 400 mg/day	42%		
Cryptococcosis (194)	Amphotericin B 0.4–0.5 mg/kg/day vs	40%	$p = 0.40$	43
	Fluconazole 200 mg/day	34%		
Cryptococcosis (381)	Amphotericin B 0.7 mg/kg/day + flucytosine 100 mg/kg/day vs	60%	$p = 0.06$	44
	Amphotericin B 0.7 mg/kg/day	51%		
Cryptococcosis (100)	Amphotericin B 0.3 mg/kg/day + flucytosine 150 mg/kg/day + itraconazole 400 mg/day vs	100%	$p = 0.03$	45
	Amphotericin B 0.3 mg/kg/day + flucytosine 150 mg/kg/day	90%		
Cryptococcosis (28)[e]	Liposomal amphotericin B 4.0 mg/kg/day vs	66%	$p = 0.01$	46
	Amphotericin B 0.7 mg/kg/day	11% after 14 days (negative culture)		
Histoplasmosis (37)	Itraconazole 200–400 mg/day for 9mo	86% (>2mo therapy)	Open, noncomparative trial	33

Continued next page

Table IV. Contd

Indication (no. of patients)	Drug	Response	Significance	References
Histoplasmosis (49)	Fluconazole 800 mg/d for 12 wks + 400 mg/day up to 1y	74%	95% CI 59, 85%	47
Histoplasmosis (59)	Itraconazole 300mg bid for 3 days then 200mg bid for 12 wks	85%	95% CI 73, 93%	48
Histoplasmosis (110)[f]	Itraconazole 300mg bid for 3 days then 200mg bid for 12 wks	85%	Clinical efficacy not different	49
	Liposomal amphotericin B 3 mg/kg/day for 2 wks + itraconazole 200mg bid for 10 wks	86%		
Penicilliosis (74)	Amphotericin B 0.6 mg/day for 2 wks then itraconazole 400 mg/day	97%	Open, noncomparative trial	50

a Nine out of 15 patients responded to amphotericin B.

b Only seven patients with HIV infection/AIDS included in this study.

c p-Value related to the median time to first negative CSF culture with an isolate for which the minimum inhibitory concentration was 4 μg/mL was 56 days as compared with 16 days with an isolate <4 μg/mL.

d Only six patients treated with combination amphotericin B plus flucytosine, but all six responded; only 14 patients treated with fluconazole and 6 of 14 responded.

e From 15 patients, ten responded to AmBisome B; from nine patients, one patient responded to amphotericin B.

f Evaluation of two separate trials in one analysis; blood cultures after 2 weeks negative in 85% of liposomal amphotericin B group vs 53% of itraconazole group ($p = 0.0008$).

bid = twice daily; **CSF** = cerebrospinal fluid; **HIV+** = HIV positive.

dose of 200mg on day 1; or for children: 3 mg/kg/day), either as capsules or liquid suspension (≈10–20 mL/day) for a duration of 5–14 days, because the clinical response is usually apparent within 1–2 days and adverse effects with therapy are uncommon.[51] A single dose of 150mg may be effective as well.[52] In oral candidiasis, two studies comparing fluconazole capsules (100mg once daily for 14 days) with variable dosages of itraconazole suspension (from 100mg once daily to 100mg twice daily for 7 or 14 days) produced similar results, but the highest clinical (97%) and mycological (88%) efficacy was observed with itraconazole (100mg twice daily) for 14 days.[53,54]

In oesophageal candidiasis, a large double-blind, randomised trial comparing capsules of fluconazole 200 mg/day with itraconazole 200 mg/day involving 2213 HIV-positive patients showed superior endoscopic and clinical cure after 14 days therapy with fluconazole (endoscopic 81% versus 66% and clinical cure 82% versus 75%, respectively) [see table IV].[36] Therefore, a higher dosage of at least 200 mg/day fluconazole should be used for oesophageal disease compared with oral disease. If itraconazole is used, the solution is preferred because of better resorption of the drug compared with capsules.[55] Duration of antifungal therapy should be 14–21 days.[56]

Recently, two new antifungals (caspofungin and voriconazole) became licensed in the US and Europe. In a double-blind, randomised study, 140 patients received either caspofungin 35, 50 or 70mg or amphotericin B 0.5 mg/kg intravenously for 7–14 days for oral and/or oesophageal candidiasis.[38] The proportion of patients with oesophageal disease with a favourable endoscopic response was greater in the caspofungin groups (67%, 90% and 77% for the 35, 50 and 70mg dose levels, respectively) than in the amphotericin B group (61%). The role of caspofungin is probably for second-line use in oesophageal candidiasis which is refractory to fluconazole.[57] Another randomised, double-blind, multicentre trial compared voriconazole 200mg twice daily and fluconazole 400 mg/day in 391 patients with proven candidal oesophagitis.[39] Efficacy analysis revealed success rates of 98.3% with voriconazole and 95.1% with fluconazole. As shown in a small series of patients, voriconazole 400 mg/day may be an appro-

priate alternative to intravenous amphotericin B for treatment of fluconazole-refractory oral/oesophageal candidiasis (FROC).[58]

FROC has been defined as a progressive disease or lack of improvement after treatment with intravenous or oral fluconazole 200 mg/day for at least 7 days.[59] Alternatively, itraconazole as the hydroxypropyl-β-cyclodextrin solution 200mg once daily may be given,[60] and itraconazole solution 200mg two times daily for >14 days has proven to be effective in patients with FROC.[61] Furthermore, intravenous amphotericin B 0.3–0.5mg/kg for 7–14 days could be tried, but efficacy has not been established in this situation.[62] It is more reasonable to switch to caspofungin or voriconazole because of the good *in vitro* activity as well as good clinical activity of the newer agents against non-*C. albicans* species.[38,39]

1.3 Candidiasis in the Era of HAART

The pattern of oral opportunistic infections is now changing in the era of HAART. The overall prevalence of all oral lesions significantly decreased in one study from early (1995 until beginning of 1996) to late (end of 1996 until 1999), 47.6% to 37.5%, respectively (p = 0.01), with some variation by lesion type. However, changes in the prevalence of oral candidiasis (20.3–16.7%) were not statistically significant.[63] Another study found a much greater decline, from 30% to 4%, in an observation period of only 1 year together with a trend toward reduction in the frequency of fluconazole-resistant *C. albicans* isolates.[64] In an observational study of 99 patients with advanced HIV infection where a protease inhibitor (ritonavir) was added to pre-existing antiretroviral therapy, a significant reduction in plasma viral load together with a significant decrease in oral candidiasis was observed.[65] In a study of 1115 patients from Spain (most of whom were intravenous drug users), a protecting effect of antiretroviral treatment against oesophageal candidiasis was also observed; however, the authors argued this effect was probably caused by better adherence to prophylaxis, rather than only good adherence to HAART.[66] More interestingly, resolution of FROC after the initiation of HAART has been observed in some patients.[67,68] Fluconazole therapy for suppression of oral candidiasis may be safely discontinued in the majority of patients receiving protease inhibitors. However, combination antiretroviral regimens containing protease inhibitors do have little impact on oral candidiasis recurrence rates if it is not accompanied by a significant decrease of viral load and a sustained rise in CD4+ cell counts.[69,70] Bringing these observations together, it should be considered that effective control of HIV virus load with HAART may contribute considerably to the overall response when treating mucocutaneous candidiasis with antifungals.

2. Cryptococcosis

Infection of the lungs may be the initial manifestation of cryptococcosis and serve as a port of entry for disseminated disease in patients with HIV infection. In patients with HIV infection, therapy for disseminated disease should be given as for cryptococcal meningitis which is the most common presentation of cryptococcosis in this patient population.[10] However, cryptococcosis may be restricted to the lungs and present as atypical pneumonia without meningitis, but there are no controlled trials describing the outcome of therapy for AIDS-related cryptococcal pneumonia. One of the important features of cryptococcal infections in patients with HIV infection, compared with those without, is that the former has a very high rate of relapse after treatment (30–50%). Because of the likelihood of relapse, the management of cryptococcosis in patients with AIDS routinely involves lifelong antifungal therapy but with the introduction of HAART these concepts are now changing.

2.1 Immune Reconstitution Inflammatory Syndrome and Cryptococcosis

In some HAART-treated patients paradoxical deterioration in their clinical status occurs despite satisfactory control of viral replication and improvements in CD4+ cell counts. This clinical deterioration, known as the immune reconstitution inflammatory syndrome (IRIS), is a result of an exuberant inflammatory response towards previously diagnosed or incubating opportunistic pathogens (mostly atypical mycobacteria). Such manifestations of IRIS have been described for *C. neoformans* infections, mostly as paradoxical exacerbations of meningitis.

Table V. Studies on prophylaxis and/or maintenance therapy of invasive fungal infections in patients with AIDS

Disease	Patients	Drug	Indication	Response	Reference
Cryptococcosis	151	Fluconazole 400 mg/day	Maintenance after	72% negative cultures at 10 wks vs	44
	155	Itraconazole 400 mg/day	AmB + 5-FC	60% negative cultures at 10 wks	
Histoplasmosis	46	Itraconazole 200–400 mg/day	Maintenance	1 year relapse free rate 95.3% (95% CI 85.3, 99.7%)	78
Histoplasmosis	42	Itraconazole 200mg bid	Maintenance	Two relapsed, two withdrawn (95% CI 0.5, 16%)	79
Histoplasmosis	76	Fluconazole 100–400 mg/day	Maintenance	Nine relapses	80
Penicilliosis	72	Itraconazole vs placebo	Maintenance	0 vs 20 relapses ($p < 0.001$)	81
Penicilliosis	63	Itraconazole vs placebo	Primary prophylaxis	1 vs 11 breakthrough fungal infection ($p = 0.003$)	82
Fungal infections	149	Itraconazole vs	Primary prophylaxis	6 vs	83
	146	Placebo		19 breakthrough fungal infection ($p = 0.007$)	

5-FC = flucytosine; **AmB** = amphotericin B; **bid** = twice daily.

Treatment for this disorder includes continuation of primary therapy against the fungal pathogen as well as continuation of effective HAART and other supportive measures. In a recent report, five of ten patients who started successful HAART for HIV-1 infection concurrent with or soon after a diagnosis of cryptococcal infection experienced clinical events characterised by sterile inflammation. These events occurred 2–11 months after initiation of HAART.[71,72]

2.2 Prophylaxis

As stated for mucosal candidiasis (section 1.1), primary prophylaxis is not routinely recommended against *C. neoformans*.[12,22] However, secondary prophylaxis is recommended as a standard of care using either fluconazole or itraconazole.[22] Fluconazole has been shown to prevent more relapses than amphotericin B when given as secondary prophylaxis and is recommended as lifelong suppressive therapy at a dosage of ≥200 mg/day in patients with AIDS.[73] Itraconazole 400 mg/day may be an alternative to fluconazole for maintenance therapy but is less effective (see table V).[44] In a survey from The Netherlands, an overall decline in the number of patients with cryptococcosis has been observed since the introduction of HAART.[74] The discontinuation of secondary prophylaxis for cryptococcal meningitis in HIV-infected patients responding to HAART has been described as safe in a report of six patients who were treated with any HAART regimen for at least 6 months and experienced an increase of CD4+ cells counts to >100/μL and a viral load reduction.[75] Another study observed that in 16 individuals who stopped antifungal prophylaxis, after a median follow-up of 13.4 months there were no relapses of cryptococcosis despite the fact that seven of these patients remained serum cryptococcal antigen positive; three of the 16 had negative viral loads.[76] The same group observed in a retrospective analysis that maintenance therapy with fluconazole 400 mg/day was superior to fluconazole or itraconazole 200 mg/day in a group of 38 patients.[77] The recent IDSA Guidelines for cryptococcosis recommend oral fluconazole 200 mg/day as the most effective maintenance therapy.[10]

2.3 Treatment

Cryptococcal disease that develops in patients with HIV infection always warrants therapy. For the treatment of HIV-associated cryptococcal pneumonia, fluconazole 200–400 mg/day appears to be the best choice in patients with mild-to-moderate symptoms or who are asymptomatic with a positive culture from the lung, with itraconazole 400 mg/day as an alternative.

Recommendations for therapy of cryptococcal meningitis do not differ whether a *C. neoformans var. neoformans* (= serotype A or D) or *C. neoformans var. gattii* (serotype B or C) infection is treated.[84]

For AIDS-related cryptococcal meningitis, induction therapy with amphotericin B 0.7–1 mg/kg/

day plus flucytosine 100 mg/kg/day for 2 weeks followed by fluconazole 400 mg/day for a minimum of 10 weeks or until sterilisation of the cerebrospinal fluid (CSF) is the treatment of choice for the majority of patients. An alternative regimen for AIDS-associated cryptococcal meningitis is amphotericin B 0.7–1 mg/kg/day plus flucytosine 100 mg/kg/day for 6–10 weeks, followed by fluconazole maintenance therapy as stated in the IDSA practice guidelines.[10,44]

With the combination of amphotericin B and flucytosine as induction therapy plus fluconazole or itraconazole as maintenance therapy, 72% of the 151 fluconazole recipients and 60% of the 155 itraconazole recipients had negative CSF cultures at 10 weeks and the overall death rate at 10 weeks was 3.9% (table IV).[44] In a subsequent study using the combination of amphotericin B plus flucytosine in 236 patients, just 129 (55%) patients were alive with negative CSF cultures at 10 weeks, which suggests that two-combination therapy may be not enough.[85]

The addition of fluconazole 400 mg/day to amphotericin B plus flucytosine has been studied in a smaller series of 22 patients with cryptococcal meningitis.[86] Cure with this triple therapy without recurrence using fluconazole as secondary prophylaxis has been observed in 19 of 22 patients. This approach is supported by a study from Thailand. In an open, randomised trial, 50 patients received amphotericin B 0.3 mg/kg/day plus flucytosine 150 mg/kg/day plus itraconazole capsules 400 mg/day until mycological cultures became negative, followed by oral itraconazole for a total of 6 weeks, and were compared with a control group of 50 patients receiving intravenous amphotericin B plus flucytosine for 6 weeks.[45] Treatment was considered successful in the study group with 100% cure (no deaths) compared with 90% (five deaths) in the control group. Monotherapy with a higher dose of fluconazole (800–1000 mg/day) has been studied in a small series of 14 patients with HIV-associated cryptococcal meningitis. Clinical success at 10 weeks was 54.4% with an overall mortality of 18.2%.[41] Of significance in this study appears to be the importance of the minimum inhibitory concentration (MIC) value of the pathogen in relation to the time to first negative CSF culture. The median time to the first negative CSF culture for patients with an isolate for which the MIC was ≥4 μg/mL was 56 days compared with 16 days for patients with an isolate for which the MIC was <4 μg/mL ($p = 0.11$). Furthermore, a recent study concluded that the clinical outcome after fluconazole maintenance therapy may be better when the infecting *C. neoformans* strain is inhibited by lower concentrations of fluconazole for eradication (MIC <16 μg/mL) than when the patients are infected with strains that require higher fluconazole concentrations (MIC ≥16 μg/mL).[87] These data would support the use of MIC testing the infecting *C. neoformans* strain.

Liposomal amphotericin B (AmBisome® [1] 3–4 mg/kg/day) produced a more rapid sterilisation of CSF as well as fewer relapses compared with conventional amphotericin B.[46,88] In general, single drug therapy with either amphotericin B, fluconazole or liposomal amphotericin B is an effective therapy in only 30–40% of patients and should be considered only in mild cases (defined as no signs of CNS or disseminated disease) or patients without AIDS.[43]

Clinical data to support the use of caspofungin in cryptococcosis are not available. However, preclinical data showed *in vitro* resistance against isolates of *C. neoformans*.[89] *In vitro*, voriconazole was more active than either itraconazole or fluconazole against 566 clinical isolates of *C. neoformans*.[90] Some clinical information about the efficacy of voriconazole for cryptococcal meningitis come from salvage therapy data. In a recent report, a satisfactory response was observed in 7 of 18 patients (39%), but 11 patients recorded an unsatisfactory outcome, with stable disease in ten patients at end of therapy.[91]

According to the recently published practice guidelines for the management of cryptococcal disease, initial combination therapy of amphotericin B plus flucytosine and then fluconazole 400 mg/day for a total of 10 weeks is recommended, but initial triple therapy may be superior.[10] An alternative regimen with longer duration of induction therapy is amphotericin B 0.7 mg/kg/day plus flucytosine 100 mg/kg/day for 6–10 weeks, followed by fluconazole

1 The use of trade names is for product identification purposes only and does not imply endorsement.

maintenance therapy, but toxicity with this regimen is higher than with the 2-week induction regimen.[10]

2.4 Cryptococcosis in the Era of HAART

In a recent study conducted during 1992–2000 in Atlanta, Georgia, USA and Houston, Texas, USA, 89% (1322 cases) of cryptococcosis occurred in HIV-infected individuals.[92] Because less than one-third of all HIV-infected individuals with cryptococcosis were receiving antiretroviral therapy before diagnosis it was suggested that HIV-infected individuals who continue to develop cryptococcosis in the era of HAART in these cities are those with limited access to healthcare. In a prospective, randomised study in patients who were successfully treated for cryptococcal meningitis, the role of secondary prophylaxis with or without fluconazole 200 mg/day together with HAART was studied. Patients were randomised to continue or discontinue secondary prophylaxis when CD4+ cell count had increased to >100 cells/μL and an undetectable HIV RNA level had been sustained for 3 months.[93] At a median of 48 weeks there were no recurrences of cryptococcal meningitis in either group. Although the ultimate impact from HAART is currently unclear, cessation of maintenance therapy in patients with stable immune reconstitution (CD4+ cell count >100–150 cells/μL and undetectable HIV viral load) appears to be safe and preferable to continuing maintenance therapy for life.[76,94]

3. Coccidioidomycosis

Within the disease-epidemic area of rural south-central valley of California and the low deserts of southern Arizona, coccidioidomycosis is an important opportunistic fungal infection which disproportionately affected people with HIV infection between 1990 and 1995.[95] Most cases are presently concentrated in regions highly endemic for the fungus, but for patients with AIDS it is important to be aware of even distant exposure to endemic regions because late recrudescence of latent infection is possible. For example, 46% of reported infections cause by *C. immitis* in patients with AIDS were identified in persons outside the endemic regions.[96]

Infection in patients with HIV most frequently involves the lungs and diffuse reticulonodular infiltrates are typical.[97] In an earlier report, 42% of patients died despite antifungal therapy.[97] Disseminated disease may develop in many patients involving extrapulmonary sites including the meninges, peritoneum, skin, soft tissue or bones. When progressive disease occurs, most patients already have CD4+ cell counts <250 cells/μL.[97]

3.1 Prophylaxis

Similar to the other fungal infections (see sections 1.1 and 2.1), primary prophylaxis is not routinely recommended against *C. immitis*.[12,22] However, secondary prophylaxis is recommended as standard of care when patients respond to initial treatment using either fluconazole 400 mg/day (first choice) or itraconazole 200mg twice daily for life.[22] It is unclear whether antifungal secondary prophylaxis for coccidioidomycosis in HIV-positive patients may be stopped safely after initiation of HAART. A single case report suggests that even after a significant rise in CD4+ cell count (>300 cells/μL), recurrence may occur after discontinuation of fluconazole as secondary prophylaxis.[98]

3.2 Treatment

Comparative trials regarding the therapy of coccidioidomycosis in HIV-positive patients have not been done. Recently, a randomised, double-blind, placebo-controlled trial comparing fluconazole 400mg/day and itraconazole 200mg twice daily in 198 patients, primarily not infected with HIV, with chronic pulmonary, soft tissue or skeletal coccidioidal infections was published (table IV).[40] By 12 months, 57% of patients had responded to fluconazole and 72% had responded to itraconazole. Relapse rates after discontinuation of therapy were higher in the fluconazole-treated group but not significantly (28% after fluconazole and 18% after itraconazole). The currently preferred treatment of coccidioidal meningitis is oral fluconazole 400–800 mg/day but only very limited data are available from studies in HIV-infected patients with meningitis.[99,100] In a noncomparative study, 37 of 47 (79%) evaluable patients (only 9 patients with HIV infection) responded to treatment.[101]

The role of the new drugs such as caspofungin and voriconazole has not been studied in humans,

but *in vitro* data and some animal experiments (caspofungin) as well as case reports suggest activity of both drugs against *C. immitis*.[102-104]

The treatment of choice for severe disease such as diffuse reticulonodular pneumonia is amphotericin B 0.5–0.7 mg/kg/day. Duration of therapy is not clearly defined, but resolution of signs and symptoms of infection should be achieved which leads to several weeks of therapy.[100]

4. Histoplasmosis

Histoplasmosis is caused by infection due to *Histoplasma capsulatum var. capsulatum* and less frequently due to *H. capsulatum var. duboisii*. The infection due to *H. capsulatum var. capsulatum* is concentrated in the eastern part of the US but is also found in the Caribbean as well as in Central and South America and Southeast Asia; however, infection due to *H. capsulatum var. duboisii* is only described in Africa. Histoplasmosis occurs in 2–5% of patients with AIDS from endemic areas and in up to 25% of those from selected cities such as Indianapolis, Indiana, USA.[105,106] Furthermore, in certain parts of the endemic areas histoplasmosis is reported to be among the most frequent opportunistic infections. However, many cases of histoplasmosis in HIV-infected people have now been reported in patients living outside the recognised histoplasmosis endemic areas.

In patients with AIDS, histoplasmosis presents as a disseminated infection in 95% of cases. Patients with disseminated disease usually have fever, malaise and weight loss over a period of several weeks. These non-specific symptoms are accompanied by respiratory complaints in about 50% of patients. Some patients present with septic shock. CNS involvement with meningitis, local or generalised lymphadenopathy, gastrointestinal lesions, and skin and oral ulcers may occur in some patients.[105] Eighty-five percent of cases occur in patients with CD4+ cell counts of <100 cells/μL. According to a multivariable analysis, receipt of antiretroviral therapy and of azole drugs were independently associated with a decreased risk of histoplasmosis.[107]

4.1 Prophylaxis

Primary prophylaxis using itraconazole capsules 200 mg/day prevents histoplasmosis in patients with HIV infection and CD4+ cell counts <150 cells/μL.[83] Even though no survival benefit was demonstrated, itraconazole (but not fluconazole) is recommended as primary prophylaxis in HIV-positive patients living in regions experiencing high rates of histoplasmosis (more than five cases per 100 patient-years) according to recent guidelines.[108]

Suppressive therapy is required in all patients with AIDS as the relapse rate without suppression is >50%. An AIDS clinical trial group study found that itraconazole 200mg twice daily prevented relapse in 40 (95%) of 42 patients followed up to 2 years after primary therapy with amphotericin B (table V).[79] In this study antigen clearance from blood and urine correlated with clinical efficacy. Itraconazole 200–400 mg/day is now regarded as the suppressive therapy of choice in patients with AIDS. Fluconazole ≥200 mg/day has been found to be a reasonable alternative for chronic suppressive therapy but at least 400 mg/day should be given.[80] However, based on historical comparison, fluconazole 400 mg/day is assumed to be less effective than itraconazole 200–400 mg/day or amphotericin B 50mg given weekly as maintenance therapy to prevent relapse and is not recommended according to recent recommendations.[108] Amphotericin B 50mg intravenously once weekly was effective as suppressive therapy and may be an alternative but in general is not well tolerated.[109] Ketoconazole is regarded as ineffective as suppressive therapy and should no longer be given for this indication.

4.2 Treatment

Therapy consists in general of an initial 12-week therapy phase to induce remission of histoplasmosis and then a long-term maintenance phase to prevent relapses. In disseminated or severe histoplasmosis in patients with AIDS, as well as for histoplasma meningitis, amphotericin B is considered the drug of choice.[108] Clinical findings of severe histoplasmosis include hypotension, hypoxia, mental status changes, evidence of rhabdomyolysis with high creatine kinase levels, or coagulopathy. Amphotericin B was effective in 74–88% of patients with AIDS,

which is similar to itraconazole with 85% efficacy[48,108] (table IV). The recommendation to use amphotericin B as the first choice for moderately severe or severe histoplasmosis may be reconsidered with more recent data, where a clinical response after 2 weeks of therapy has been observed in 88% of patients receiving liposomal amphotericin compared with 64% of patients receiving standard amphotericin B.[49] Itraconazole is an appropriate alternative in mild or moderately severe histoplasmosis using a loading dosage of 200mg three times daily for 3 days, followed by 200mg twice daily for 12 weeks. The clinical response to therapy is slower with itraconazole than with amphotericin B and treatment failures have been described in patients with moderately severe disease.[108] Recently, clearance of fungaemia was shown to be more rapid with liposomal amphotericin B than with itraconazole for treatment of disseminated histoplasmosis in patients with AIDS. The clinical response rates were similar; 86% with liposomal amphotericin B (n = 51) versus 85% with itraconazole (n = 59). Liposomal amphotericin B may be an appropriate alternative for initial treatment of moderately severe or severe histoplasmosis.[49] Other lipid associated amphotericin formulations (e.g. amphotericin B lipid complex) may be used as well but have not been studied in patients with AIDS.[110]

Ketoconazole was associated with successful outcomes for patients without AIDS, but was found to be associated with a high failure rate for induction therapy in patients with AIDS.[111] In a study using fluconazole in AIDS-related disseminated histoplasmosis, 74% of patients responded to 800mg once daily. The authors concluded that fluconazole 800 mg/day is a well tolerated and moderately effective induction therapy for mild or moderately severe disseminated histoplasmosis. However, patients who entered maintenance therapy with fluconazole 400 mg/day had a high relapse rate of 30.5%.[47] Fluconazole 400 mg/day is less effective than itraconazole 200–400 mg/day or amphotericin B 50mg weekly as maintenance therapy to prevent relapse, and should not be given for this indication according to the IDSA guidelines.[108]

The role of newer agents such as caspofungin or voriconazole has not yet been defined. In contrast to amphotericin B, caspofungin did not reveal significant activity in an animal model of pulmonary histoplasmosis.[112] Voriconazole was found to have lower MICs in isolates of *H. capsulatum* than amphotericin B and itraconazole, which supports further clinical studies.[113,114]

5. Penicilliosis

Disseminated infection with *P. marneffei* is an important disease among HIV-infected people in Southeast Asia. The number of cases of penicilliosis has increased remarkably over the past 10 years and the majority of those reported have been from Thailand. Between 1991 and 1997, penicilliosis was diagnosed in 1173 HIV-infected people in a single city (Chiang Mai) in the north of Thailand.[2] Penicilliosis was reported in 6.8% of patients from the northern part of Thailand but less frequently from other parts of the country.[115] Since 1988 several cases of penicilliosis have been reported in HIV-infected people from other countries after exposure to the fungus in an endemic region.[116,117]

In the majority of patients with AIDS, penicilliosis presents as a disseminated infection, and symptoms are usually chills, persistent fever, malaise, cough, lymphadenopathy, hepatosplenomegaly, skin lesions and weight loss. Penicilliosis occurs late in the course of HIV infection when CD4+ cell counts are <100 cells/μL.[2]

5.1 Prophylaxis

A double-blind, placebo-controlled trial of itraconazole 200mg once daily to prevent relapse of *P. marneffei* infection after successful response to initial treatment with the combination of amphotericin B and itraconazole for 12 weeks was performed in Thailand.[81] None of the 36 patients assigned to itraconazole had a relapse within 1 year, whereas 20 of 35 patients assigned to placebo had relapses. Therefore, secondary prophylaxis may be regarded as standard of care in HIV-infected people. A second, double-blind, placebo-controlled trial with itraconazole given as primary prophylaxis for systemic fungal infections was performed in 63 patients with HIV-infection and CD4+ cell counts <200 cells/μL[82] (table V). Systemic fungal infection developed in one patient (penicilliosis) assigned to itraconazole and 11 patients (four with penicil-

liosis, seven with cryptococcal meningitis) assigned to placebo. Primary prophylaxis with itraconazole may prevent systemic fungal infections but a survival advantage was not observed in that study. An observation from Taiwan suggested that discontinuation of secondary prophylaxis in AIDS responding to HAART is safe. In nine patients who received secondary prophylaxis with itraconazole after *P. marneffei* infection, treatment was discontinued after CD4+ cell count increased to 85 cells/μL (mean; range 45–120 cells/μL) and no relapse occurred within 15 months' follow up.[118]

5.2 Treatment

P. marneffei infection is a potentially fatal disease in the absence of antifungal treatment, and a relapse rate of 50% is reported. Treatment with amphotericin B as induction therapy followed by itraconazole as maintenance therapy has been successful in most patients. An open-label, nonrandomised study in 74 HIV-infected patients investigated treatment with amphotericin B 0.6 mg/kg/day intravenously for 2 weeks followed by itraconazole 200mg capsules twice daily for 10 weeks.[50] Of patients treated with this regimen, 97.3% responded and fungaemia cleared after 2 weeks in all patients. Because no other studies have been performed, this regimen is considered as first choice.

6. Aspergillosis

Aspergillosis is an infrequent but commonly fatal fungal infection in HIV-infected people. In a review of 342 cases of invasive pulmonary aspergillosis, major predisposing risk factors were described as CD4+ cell counts <50 cells/μL, neutropenia and corticosteroid treatment.[8] Additional risk factors such as cigarette and marijuana use were suggested in an earlier study but not confirmed in a later study.[5,119] The overall incidence of aspergillosis was calculated to be 3.5 cases per 1000 person-years. Median survival time after diagnosis of aspergillosis in HIV-infected people was 3 months and only 26% survived ≥1 year in an analysis of 228 cases.[120] Two major patterns of disease were observed: invasive pulmonary aspergillosis and obstructing bronchial aspergillosis or necrotising tracheobronchitis.[5,6] Disseminated disease with involvement of the brain, heart, kidneys, sinuses or skin has also been described.[7,120]

6.1 Prophylaxis

Because invasive aspergillosis is a rare complication of AIDS, no primary or even secondary prophylaxis is established.

6.2 Treatment

The conventional formulation of amphotericin B is still regarded as the standard antifungal therapy for invasive aspergillosis.[121] However, in most reports, death was the usual outcome in AIDS patients with invasive aspergillosis, despite treatment with amphotericin B or itraconazole. In one observational study from France, the use of amphotericin B 0.5 mg/kg/day and/or itraconazole 200–600 mg/day was unsuccessful in 29 of 33 patients.[6] The poor response to either amphotericin B or itraconazole was confirmed by other reports with an overall response of no more than 18% in patients who received at least 7 days treatment.[5,8,122] Because of the limited number of patients with invasive aspergillosis, prospective studies with antifungal treatment are difficult to perform. Whether the new agents such as voriconazole or caspofungin play a role in this patient population remains to be established. With voriconazole, a response was documented in only one of five patients with AIDS-related invasive aspergillosis.[123] In immunocompromised patients with underlying diseases other than AIDS, initial therapy with voriconazole led to better responses and improved survival than initial therapy with amphotericin B.[124] If invasive aspergillosis is diagnosed early, it may be treated successfully and voriconazole can be regarded as the drug of choice.

7. Other Fungal Infections

Infections with *Blastomyces dermatitidis* have been described in patients with HIV infection, but are still unusual infections even in the endemic midwestern area of the US. The overall incidence of severe blastomycosis in patients with AIDS is not known. The clinical presentation of the disease in patients with HIV infection is characterised by either localised cavitary pulmonary lesions, or disseminated blastomycosis including skin lesions and

involvement of the CNS, or adult respiratory distress syndrome.[32] Blastomycosis may be a rapidly fatal illness with 40% mortality in the first 30 days in patients with AIDS. Treatment options include amphotericin B, ketoconazole, itraconazole and fluconazole, although no comparative trials of these agents have been performed.[125] Amphotericin B (1.5–2.5g total dose) is regarded as the treatment of first choice in disseminated disease, followed by life-long suppressive therapy with itraconazole 200–400 mg/day.[125]

AIDS-associated paracoccidioidomycosis has been reported from Brazil, Venezuela and Colombia.[106] The estimated incidence in Brazil is assumed to be 0.02%. According to data on 39 cases, infection by *Paracoccidioides brasiliensis* was a late event in advanced HIV infection in patients with CD4+ cell counts <100 cells/μL. The clinical presentation of disease in patients with HIV infection is characterised by fever, weight loss, fatigue, anorexia, lymphadenopathy, skin lesions, pulmonary lesions and orolaryngeal lesions. Amphotericin B is considered the treatment of choice but mortality may be as high as 23% despite treatment. Long-term secondary prophylaxis should be considered in all patients who respond to induction therapy. Azoles and cotrimoxazole[126] may be used for this indication, but definite recommendations have yet to be established.[106]

Even more rare, fungaemia due to *Candida* spp. or *Trichosporon* spp. have been observed in some adult patients with late-stage HIV disease or HIV-infected children.[11,127,128] Mostly, candidaemia was nosocomially acquired and associated with a central venous catheter. The attributable mortality from candidaemia did not differ from other patient groups and treatment should be given according to recent recommendations.[56] Therefore, candidaemia should not be considered as an opportunistic HIV-related infection. Similarly, fungaemia without pneumonia or meningitis exclusively due to *C. neoformans* is uncommon even in endemic areas and is not discussed separately.[129]

Sporotrichosis is a chronic granulomatous mycosis caused by a dimorphic fungus, *Sporothrix schenckii*. Infection with *S. schenckii* causes a localised lymphocutaneous disease in the immunocompetent host, while it frequently presents with diffuse cutaneous lesions and is associated with polyarticular arthritis and results in disseminated disease in the immunocompromised patient. There are a growing number of reports of *S. schenckii* infection in the HIV-infected population with severe CD4+ T-cell depletion, where the disease usually starts as a localised cutaneous lesion and subsequently disseminates. Overall, meningeal and disseminated forms of sporotrichosis in HIV-positive patients are rare and usually require treatment with amphotericin B. AIDS patients most often have disseminated infection and require life-long suppressive therapy with itraconazole after initial use of amphotericin B.[4,130-132]

8. Conclusion

This review has highlighted frequent and unusual fungal pathogens that may cause invasive fungal infections in patients with HIV infection. Antifungal therapy for documented infections has not changed very much during recent years, but new drugs such as caspofungin and voriconazole may help to treat opportunistic fungal infections even more effectively, especially when dealing with resistant organisms. Secondary antifungal prophylaxis for many opportunistic pathogens may now be temporarily or permanently discontinued in many HIV-positive patients who showed a marked improvement in immune function parameters, such as CD4+ cell counts, as well as maintaining undetectable HIV RNA levels several months after initiation of HAART. The concept of discontinuation of secondary antifungal prophylaxis appears to be safe after successful treatment of cryptococcal meningitis, penicilliosis or recurrent oral/oesophageal candidiasis, but not necessarily other invasive fungal infections (e.g. coccidioidomycosis). In some HAART-treated patients paradoxical deterioration in their clinical status will be exhibited, despite satisfactory control of viral replication and improvements in CD4+ cell counts. This clinical deterioration, known as IRIS, is a result of an exuberant inflammatory response towards previously diagnosed or incubating opportunistic pathogens. Such manifestations of IRIS have been described for *C. neoformans* infections but potentially may be observed with other fungal pathogens as well.

It can be concluded that the epidemic of HIV infection still continues, and clinicians need to be vigilant for various frequent invasive fungal infections, in particular in patients with limited access to healthcare. The link between effective virustatic control of HIV infection and decreasing incidence, as well as effective control of opportunistic fungal infections, is essential for understanding of the pathogenesis of these infections.

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