Major changes are occurring in the epidemiology of opportunistic infections (OI) in patients with acquired immune deficiency syndrome (AIDS) and treated with highly active antiretroviral therapy (HAART). A marked decrease of minor and major OI was observed and clinical resistance of thrush to antifungal agents became extremely rare. Primary and secondary prophylaxis against *Pneumocystis carinii* infections can be stopped; however, the situation is less clear for other OI such as cryptococcosis or endemic mycoses. The epidemiology is dramatically different in the countries which cannot afford the cost of HAART for the majority of patients, such as South Africa. These topics will be discussed in this paper.

**Keywords** antifungal prophylaxis, cryptococcosis, endemic mycosis, fluconazole-resistant *Candida*

What has happened to fluconazole-resistant oropharyngeal candidiasis?

Prior to the widespread usage of highly active antiretroviral therapy (HAART), 50–70% of human immunodeficiency virus (HIV)-infected patients developed at least one episode of mucosal candidiasis during the course of their disease [1,2]. Although azoles in general and fluconazole in particular provided effective therapy for this condition, it soon became apparent that the relapsing nature of this opportunistic infection and the need to treat it with repeated courses of therapy provided a perfect scenario for induction of resistance. As illustrated in many reports, *Candida albicans* isolates with high minimal inhibitory concentration (MIC) to fluconazole were frequently recovered from the oropharynx of these patients [3–8]. For example, one survey found that the point prevalence carriage of *Candida* resistant to fluconazole (MIC ≥ 64 µg ml⁻¹) was 21% in HIV-infected patients with oropharyngeal candidiasis (OPC) and 14% in asymptotically colonized patients [9]. Epidemiological studies found that advanced HIV infection and extensive exposure to fluconazole were the major risk factors for the development of resistance [10,11]. While the clinical expression of both sensitive and fluconazole-resistant candidiasis is similar, patients with resistant infection tend to have a more progressive and recurrent disease due to the poor response to antifungal therapy.

Recently, however, the widespread use of HAART to treat HIV infection has led to an interesting change in the pattern of OPC. In addition to producing (i) partial improvement of immune function [12–14], (ii) decreased prevalence of opportunistic infections [15–23], (iii) lower rates of hospital admissions and (iv) reduced mortality [24–27], HAART seems to have altered the behavior of OPC.
An early hint that this would occur came with a case report in which Zingman [16] described resolution of OPC following initiation of combination antiretroviral therapy in an HIV-infected patient. We have observed this in a larger study population. Between August 1995 and February 1996, we enrolled a cohort of 128 HIV-infected patients in a prospective observational study of OPC. At the time these patients were enrolled, monotherapy was the standard of care to treat HIV infection. However, in February of 1996 the initial release of information describing the value of combination therapy radically altered the approach to treat HIV. Over the next year, our patients went from being on an average of 0.5 antiretroviral agents to 1-8 drugs. Of the 70 HIV-infected patients who were still available for follow-up one year later, we found (i) reduced rates of OPC (from 30% to 4%; \( P < 0.001 \)), (ii) reduced oral carriage of \( C.\) albicans (from 61% to 39%; \( P < 0.008 \)) and (iii) a trend toward less frequent \textit{in vitro} resistance to fluconazole [28]. Similar events following introduction of HAART have been reported by others [29,30].

The recovery of host immunity that follows the use of HAART is thought to be the main factor attributed to the declining rates of OPC in general [31] and fluconazole-resistant candidiasis in particular [30]. Supporting this concept, our observational study showed a decline in the carriage rate for resistant isolates, but not for susceptible isolates. When taken with the long-known ability of susceptible strains of \( C.\) albicans to behave as normal oral commensals in man and the observation that resistant strains of \textit{Candida} are often slightly less virulent than their susceptible counterparts [32], these data suggest the possibility that enhanced immune function reduced the ability of the less fit resistant strains to survive without altering the behavior of the more fit susceptible strains.

However, other mechanisms for resolution of OPC are also possible and recent studies postulate that at least two other mechanisms may be operative. First, protease inhibitors (PIs) may have directly interfered with \textit{Candida} infection by inhibiting the fungal secretory aspartyl protease (Sap) enzymes. Some of these enzymes are similar to HIV proteases [33,34] and had been shown to play a pathogenic role in mucosal invasion [35–37]. The antifungal activity of PIs has been recently demonstrated in \textit{in vitro} and \textit{in vivo} studies [38,39], and is also supported by the fact that resolution of candidiasis has been observed soon after initiation of PI therapy and before any obvious immune reconstitution was achieved [40,16]. Additionally, the PI effects on \textit{Candida} in a rat vaginitis model were found to be comparable to the well known curative effects of fluconazole [38].

Second, low plasma HIV-1 RNA levels were found to significantly correlate with low oropharyngeal carriage of \textit{Candida} and reduction of symptomatic OPC [41]. These findings were observed independently of CD4+ T-cell count recovery and history of fungal infection. These observations are somewhat similar to the ones found in patients that developed OPC during acute HIV-1 infection, when viral loads are usually very high and CD4+ T-cell counts are relatively preserved [42]. These data suggest that HIV-1 replication may directly promote the interaction between \textit{Candida} and buccal mucosa by interfering with local host responses [43,44]. Therefore, lowering plasma viral replication may result in a partially restored local immune function.

In summary, the incidence of fluconazole-resistant candidiasis has clearly decreased in the HAART era. Whether due to immunorestitution, low levels of HIV-1 replication, the antifungal activity of PIs, or other as-yet-unidentified factors, the clinical benefit to the patients is unambiguous. Indeed, it could be stated that the single best therapy for OPC in the HIV-infected patient is adequate antiretroviral therapy.

### Antifungal prophylaxis in HIV-infected patients at the time of HAART

HAART consists of the combination of at least three drugs that contain a minimum of one protease inhibitor and/or one non-nucleoside reverse-transcriptase inhibitor. These drugs are able to markedly decrease human immunodeficiency virus (HIV) replication and increase the CD4-cell count. In the HIV-infected population, HAART has demonstrated its capacity to reduce acquired immune deficiency syndrome (AIDS)-related deaths and the number of new AIDS cases [45]. Simultaneously, a dramatic change in the epidemiology of fungal infections has been observed in HIV-infected patients, with a reduced number of OPC episodes [9], as well as the control of azole-resistant OPC [30]. Such effects have been attributed to the immune restoration, but also potentially to the inhibition of aspartyl protease activity and production in \( C.\) albicans [38]. Similar epidemiological trends have been observed for other fungal infections such as \textit{Pneumocystis carinii} pneumonia (PCP) or \textit{Cryptococcus neoformans} (Cn) meningitis [24,46].

Over the past years, results of a series of clinical trials have defined which antifungal prophylactic regimens were the most appropriate in HIV-infected patients. Such results will be briefly reviewed as well as more recent ones which reassess the role of some primary or secondary antifungal prophylaxes in selected patients who have sustained responses to HAART.
Primary antifungal prophylaxis has been shown to be effective for the prevention of PCP (CD4 < 200 cells mm\(^{-3}\)) [47] and for infections caused by *Histoplasma capsulatum* (Hc) (CD4 < 100 cells mm\(^{-3}\)) [8] or Cn (CD4 < 50 cells mm\(^{-3}\)) [48,49]. However, because of potential drug interactions, development of azole-resistant *Candida* sp. and cost, only the prevention of PCP is routinely recommended. The preferred regimen consists of the daily administration of cotrimoxazole at either one double-strength or single-strength tablet [7]. Several alternatives, such as atovaquone (1500 mg day\(^{-1}\)), dapsone (100 mg day\(^{-1}\)) or monthly aerosolized pentamidine (300 mg), can be used in patients who are intolerant of trimethoprim or sulfonamides [47]. However, it should be noted that the use of pentamidine is not recommended for HIV-infected patients whose CD4-cell count is below 100 cells mm\(^{-3}\) [50]. Combinations of dapsone and pyrimethamine, using various protocols, are also effective [47]. Whether or not the increase in the frequency of mutations in the gene encoding *P. carinii* dihydropteroate synthase [51] will have any influence on the effectiveness of the large-scale use of cotrimoxazole remains to be documented. Interestingly, in patients responding to HAART and having a CD4-cell count > 200 cells mm\(^{-3}\) for at least 3–6 months, results of several recent studies have demonstrated that primary PCP prophylaxis could be safely discontinued [52–55]. Indeed, in these studies, no PCP relapse was noted during a median follow-up of 11–18 months. The utility of primary prophylaxis has not been demonstrated for other systemic fungal infections, although results of a recent study suggested that HIV-infected patients living in Arizona and treated with an antifungal azole had a reduced risk of developing coccidiodomycosis than their matched controls [56]. Finally, no routine prophylaxis is recommended for mucosal infections caused by *Candida* sp.

The prevention of PCP relapse is based on one of the regimens used for primary prophylaxis [47]. Interestingly, two recent studies have now shown that secondary prophylaxis might also be safely discontinued in patients who restored their immune defenses [47]. Life-long prophylaxis of Cn infection relapse is based on fluconazole (200 mg day\(^{-1}\)) which showed a greater efficacy than placebo, weekly intravenous amphotericin B or daily itraconazole, in three multicenter clinical trials [47]. Results of only one preliminary study have suggested that secondary Cn prophylaxis might be withdrawn in asymptomatic compliant patients after 1 year of fluconazole therapy and prolonged antiretroviral treatment [57]. As we are aware that some physicians belonging to the French Cryptococcosis Study Group have already stopped fluconazole in several HIV-infected patients who had a history of documented cryptococcosis, we will characterize this subgroup of non-relapsing individuals through a nationwide-based survey. For Hc and *Penicillium marneffei* infections, itraconazole is the preferred secondary prophylactic regimen [58,59], but no study has yet reported the possibility of withdrawing it in either disease. Although a prophylaxis against relapse is also recommended for other endemic mycoses (coccidiodomycosis, blastomycosis, paracoccidioidomycosis and sporotrichosis), no study has documented which regimen would be the most appropriate. Fluconazole might be preferred for coccidiodomycosis [47], while itraconazole might be used for other endemic fungal diseases [60]. No prevention of relapse is advocated for *Candida* mucosal infections except in patients experiencing frequent recurrences of esophagitis. In case of episodes caused by a fluconazole-resistant strain, itraconazole solution may be administered. Finally, the co-administration of most of the PIs with itraconazole should be cautiously started and necessitates a close pharmacokinetic follow-up.

In conclusion, recent studies have demonstrated that PCP prophylactic regimens can be safely discontinued in selected compliant HIV-infected patients who have a sustained immunological restoration with HAART (i.e. above the CD4 thresholds for initiating prophylaxis). However, a careful follow-up of these patients should be performed to detect virological/immunological failures to HAART as early as possible and thus eventually discuss the need for restarting antifungal prophylaxis. At present, there are no convincing data to stop secondary prophylaxis of potentially life-threatening fungal infections such as those caused by Cn or Hc.

On the other hand, a vigorous focus on the adherence to prophylactic guidelines remains necessary in the group of HIV-infected patients with profound immunodeficiency. Finally, other prophylactic measures such as the reduction of exposure to fungal pathogens in areas of endemicity (*H. capsulatum, C. immitis* and *P. marneffei*) or in the hospital setting (*P. carinii*) should not to be forgotten in the era of HAART.

**Impact of HAART on management of the endemic mycoses**

In endemic areas in the USA, *H. capsulatum* and *C. immitis* commonly cause infection in AIDS patients [61–68]. In this population, these infections are frequently disseminated and often life-threatening. Treatment for severe histoplasmosis is amphotericin B followed by itraconazole, and for severe coccidiodomycosis, amphotericin B followed by either itraconazole or fluconazole [60,61]. Patients with mild to moderate histoplasmosis are
generally treated with itraconazole [64,69], and those with coccidioidomycosis with either itraconazole or flucona-azole [61,67]. Response rates for histoplasmosis are higher than those for coccidioidomycosis. For both infections, life-long maintenance therapy is required to prevent relapse [58,70,71].

Since the introduction of HAART, there have been few studies addressing the epidemiology and treatment of these endemic mycoses. This report highlights current practices among those physicians caring for AIDS pa- tients who have histoplasmosis or coccidioidomycosis.

A questionnaire was sent to members of the Mycoses Study Group who practiced in those areas endemic for histoplasmosis or coccidioidomycosis and who cared for large numbers of AIDS patients. The five sites queried in regard to coccidioidomycosis were located in Los Angeles, Bakersfield and San Jose, California, San Antonio, Texas, and Tucson, Arizona. The respondent at one of the five sites noted that he saw too few patients with HIV infection to provide meaningful data. The nine sites queried in regard to histoplasmosis were located in Houston, Texas; Kansas City, Missouri; Birmingham, Alabama; Indianapolis, Indiana; Columbus, Ohio; St. Louis, Missouri; and Memphis, Tennessee. The sample included physicians whose practices were in private, city/county, university, and veterans affairs medical centers. Physicians were asked about the numbers and types of patients they currently were seeing compared with 5 years ago when HAART therapy was not widespread; their preferred treatment for histoplasmosis and coccidioidomycos- is; whether they used maintenance therapy for prevention of relapse or discontinued this at a certain CD4 level in patients on HAART; and whether they have noted relapses in patients on HAART, irrespective of maintenance therapy.

**Histoplasmosis**

Prior to HAART, histoplasmosis was estimated to occur in approximately 5% of patients with HIV infection who lived in endemic areas [61], but rates as high as 25% were noted in areas experiencing outbreaks of histoplasmosis [64]. In the HAART era, there has been a marked decline in newly diagnosed cases of histoplasmosis in patients with HIV infection. All of the respondents, except one, noted that they were now seeing fewer AIDS patients with histoplasmosis compared with 5 years ago. In a large Kansas City cohort, the rate of infection has fallen from 12 cases per 100 AIDS patient years in 1990–1993 to zero in 1998–1999 [D. McKinsey, personal communi- cation]. Similar data from Houston show a decline from 9.6 cases per 1000 AIDS patients in 1993 to approxi- mately 2.3 cases per 1000 AIDS patients in 1998 [R. Hamill, personal communication].

It has clearly been shown that HIV-infected patients at most risk for developing histoplasmosis are those whose CD4 counts are < 150 cells μl⁻¹ [63]. Most patients with histoplasmosis continue to have this infection as their presenting manifestation of HIV infection, and many of these patients have severe disseminated disease. None of the physicians who were queried had seen histoplasmosis develop in patients who remained compliant with HAART. The patients who did develop histoplasmosis had refused to take antiretroviral agents or were known to be non-compliant with HAART. Thus, it currently appears that almost all cases of histoplasmosis observed in AIDS patients occur in those who are not receiving antiretroviral therapy, many of whom are not receiving any medical care for HIV infection.

Treatment for severe histoplasmosis in AIDS patients remains amphotericin B [60,61,64]. A recent study ther- apy of moderately severe to severe histoplasmosis found enhanced efficacy and lessened toxicity when liposomal amphotericin B (Ambisome; Fujisara and Nexstar, Boulder, CA, USA) was compared with standard formulation amphotericin B [72]. Patients with mild-to-moderate disease can be treated with itraconazole [69]. Fluconazole is not as effective as itraconazole [73]. For most patients in whom histoplasmosis is the AIDS-defining illness, anti- fungal therapy is started first, and HAART is given only after the fungal infection is controlled.

The greatest impact of HAART appears to be on the need for maintenance therapy to prevent relapse of histo- plasmosis. Life-long maintenance therapy with once or twice daily itraconazole has been shown to reduce relapse rates to < 5% [58,70]. Given the numerous drug interac- tions of itraconazole and the difficulties inherent in achieving full compliance with chronic dosing regimens, the discontinuation of maintenance therapy is attractive to both physicians and patients. One-third of the physi- cians polled do not stop maintenance therapy, one-third stop when CD4 counts are > 200 cells μl⁻¹, and another one-third are part of an ongoing AIDS Clinical Trials Group (ACTG) study in which itraconazole therapy is stopped after 1 year of therapy if CD4 counts are > 150 cells μl⁻¹. Those physicians who have stopped maintenance therapy have not noted any relapses to date in patients who have remained compliant with HAART. One physician reported seeing a patient who experienced a flare of the symptoms of histoplasmosis, but without a positive culture, after starting HAART, raising the issue of reconstitution syndrome related to histoplasmosis.

HAART appears likely to make an impact on the need for antifungal prophylaxis to prevent histoplasmosis. It
has been shown that itraconazole is effective at preventing histoplasmosis in those patients whose CD4 counts are $< 150$ cells $\text{mL}^{-1}$ and who live in a highly endemic area [48]. However, with the virtual disappearance of infection in those patients effectively treated for their HIV infection and with almost all disease occurring in those who are not receiving medical care and who present with histoplasmosis as their initial manifestation of HIV infection, antifungal prophylaxis does not appear to be an effective tool for the prevention of histoplasmosis.

**Coccidioidomycosis**

Few data are available on the incidence of coccidioidomycosis in those with HIV infection. Prior studies from Tucson showed an incidence of 6-5% among AIDS patients living in Arizona [71]. Further studies in the southwestern endemic area showed that the incidence was highest in Arizona, in which 5-2% of AIDS patients developed disseminated coccidioidomycosis, compared with all other areas, in which only 0-5-1-4% of AIDS patients were reported to have disseminated coccidioidomycosis [68]. Patients at most risk for development of coccidioidomycosis have been shown to be those with CD4 counts of $< 250$ cells $\text{mL}^{-1}$ [66].

All physicians queried noted that they were seeing fewer AIDS patients with coccidioidomycosis than 5 years ago. Patients who were seen with coccidioidomycosis were mostly those presenting with coccidioidomycosis as their AIDS-defining illness in two centers, those non-compliant with HAART in one center, and patients on HAART in one center.

No trials have been conducted in AIDS patients to establish the superiority of one azole over another or amphotericin B over an azole for the treatment of coccidioidomycosis. Among those physicians who were queried, treatment regimens varied. Two primarily used fluconazole, one used amphotericin B followed by itraconazole or fluconazole, and one used both fluconazole and itraconazole simultaneously.

Prior recommendations were to give life-long maintenance therapy with an azole to prevent relapse of coccidioidomycosis [71]. All physicians who were queried agreed with that recommendation and continued to use life-long maintenance therapy with fluconazole or itraconazole and, in one case, with both agents. None were willing to stop antifungal therapy in patients on HAART. None had seen relapses in those patients who were on HAART and who remained on maintenance therapy.

In summary, the greatest impact noted with HAART appears to be on the long-term management of histoplasmosis. Life-long maintenance therapy may not be required in all patients. Further data will be available after the ACTG trial is completed. HAART has had little impact on the management of coccidioidomycosis, possibly reflecting the overall poorer response of this fungal infection to antifungal agents.

**Mycoses and AIDS in South Africa**

The AIDS epidemic is continuing to escalate in most of our provinces in South Africa. Currently, approximately four million people are infected (about 10% of our population) and an estimated 1600 new infections are acquired each day. The majority of the population are not able to afford antiretroviral therapy and the government is financially unable to provide it.

HIV seroprevalence studies are carried out annually on groups of antenatal patients in our nine provinces. The recently released 1999 report of the Department of Health indicates that seroprevalence rates vary from 32-5% in KwaZulu Natal, 27-9% in the Free State, 27-3% in Mpumalanga, 23-9% in Gauteng, 23% in North West, 11% in Northern Province, 10-1% in Northern Cape and 7-1% in Western Cape [74]. The seroprevalence rates prior to 1990 were lower than 1%. No increase was observed in KwaZulu-Natal or Mpumalanga in the past year before the death rate due to AIDS is increasing.

The information provided in this paper is mainly a reflection of experience on mycoses and AIDS obtained in the past few years at Chris Hani Baragwanath Hospital (CHBH, Soweto, Gauteng), a 2600-bed tertiary care academic institution and the largest hospital in Africa.

Candidiasis, particularly oropharyngeal candidiasis, occurs very commonly, present in more than 80% of patients seen at our AIDS clinics during the course of their disease. Pseudomembranous candidiasis is seen more often than the erythematous form and angular cheilitis may occur. Therapy with nystatin drops has not been very effective and amphotericin B lozenges are commonly used. Some patients require ketoconazole, fluconazole or itraconazole for recurrent infections.

Most *C. albicans* isolates remain susceptible to fluconazole as observed in the National Biome Susceptibility study conducted in 1998 and 1999, which included isolates from HIV-positive patients. Of 4058 isolates tested, 99-4% were susceptible, 0-3% susceptible but dose dependent and 0-3% resistant [75].

Symptomatic *Candida* esophagitis may be seen more commonly in South Africa than in the Americas, due to late presentation of some patients. On esophagoscopy at CHBH, asymptomatic infection is observed in about 50%, and symptomatic infection with dysphagia in
10–20% of cases [R. Alli, personal communication]. In a study on HIV-positive adults with dysphagia, in whom C. albicans esophagitis was confirmed by culture and histology, patients were found to have multisystem disease. More than half had tuberculosis, 23% had pneumonia and 28% had chronic diarrhoea; 23% of women had pelvic inflammatory disease. The male to female ratio (M:F) was reversed (1:1·4). Half the patients were anemic and 28% neutropenic; CD4 cell counts were low with a mean of 169 cells mm$^{-3}$ in males and 106 cells mm$^{-3}$ in females. Mortality was high with 28% dying within 3 weeks, despite fluconazole therapy [76].

Candida vulvovaginitis has increased in frequency and may occur early in HIV infection. In studies on the etiology of vaginal discharge, C. albicans was an etiological agent in 19% of cases in Cape Town, 45% in Johannesburg and 51% in Durban, reflecting increases in HIV seropositivity in those areas [77]. Recurrent infection is common and problematic to treat.

Cryptococcosis, particularly cryptococcal meningitis, is the most life threatening fungal infection in AIDS patients in South Africa. Rates have increased progressively throughout the 1990s in many hospitals. In a study at King Edward VIII Hospital in Durban, cryptococcal meningitis was found to be the initial AIDS-defining illness in 84% of patients. Higher rates of neurological complications were seen than in the developed world, possibly due to lateness of presentation, and 64% of HIV-positive patients died while receiving therapy in hospital [78]. In 1999, 220 cases were diagnosed at the hospital. At the CHBH, numbers increased from one to three cases per year in the 1980s to 149 cases per year in 1999. The proportion of infected women increased, with a M:F ratio of 1:1·3 in 1999. Patients presented late in the course of disease, as more than half had altered mental state, CD4 cell counts of 50 cells mm$^{-3}$ and a high cryptococcal antigen load in cerebrospinal fluid with a titer of >1:1024. Cryptococcus neoformans var. neoformans serotype A was the most common serotype. Six cases of C. neoformans var. gattii were seen in the period 1995–1998, four of which were due to serotype C in HIV-positive patients [79]. An unusual presentation occurred at the CHBH in which Kaposi sarcoma and cutaneous cryptococcosis were observed in the same skin lesions [80].

In an autopsy study on men who had worked in a gold mine, cryptococcosis was the most frequent pulmonary finding in 31 of 119 (26%) men autopsied, and was extensive in 28 of these cases. Nineteen of 31 had cryptococcal meningitis; 21/31 had been on treatment for pulmonary tuberculosis, and in about 90% of these the diagnosis of tuberculosis had been confirmed on sputum culture. Five patients also had mixed infections, three with P. carinii pneumonia [J. Murray, personal communication].

Therapy of cryptococcal disease is problematic because of cost. Some hospitals are only able to treat the acute stage with amphotericin B or fluconazole or are unable to treat patients at all. Fluocytosine is not available in South Africa. At the CHBH, fluconazole therapy is associated with about 40% mortality in hospital, but maintenance therapy is continued on discharge.

Clinically significant histoplasmosis is uncommon in immunocompetent individuals in South Africa. Many of the caves around the country harbor bats and also contain H. capsulatum conidia. Speleologists have in the past been shown to have positive histoplasmin skin tests. Cave associated and other cases of histoplasmosis have occurred. The first AIDS associated case of histoplasmosis was identified in the Transvaal in 1984 in a male homosexual with unusual skin lesions [81]. Disseminated cases were reported in association with AIDS in two adults in the Cape and one in the Free State [82], and also in an 8-year-old child in KwaZulu-Natal [83]. Several AIDS-related disseminated infections have been seen in Durban in the past 5 years, with certain histopathological differences in skin lesions [84]. Most of the AIDS-associated cases have not followed entry into caves. H. duboisii which occurs in Central Africa, has not yet been reported in AIDS patients as far south as South Africa.

Sporotrichosis due to Sporothrix schenckii was a problem in the South African mines in 1927 and again during 1941–1944 when a large outbreak, involving 2825 miners, occurred due to the use of untreated timber poles underground. After treatment of the timber, cases ceased to occur [85]. No increase has been noted in the mines in recent years. At the CHBH, up to four cases per year of the cutaneous and lymphocutaneous forms of sporotrichosis occur in adults, with a M:F ratio of 1:3·1. No increase in numbers of cases has been observed. However, two cases of AIDS-associated disseminated infection with more widespread skin involvement occurred in the past 3 years. Lesions presented as chronic crusted ulcerations, with unusual distribution, i.e. face and trunk as well as arms bilaterally in a male patient and on arms and legs bilaterally in a female. These infections responded to itraconazole therapy.

A number of mycoses in South Africa have not been associated with an obvious increase in infection, e.g. zygomycosis, eumycetoma, blastomycosis. Chromoblastomycosis occurs occasionally; in 1999 diagnosis was confirmed in an adult male with extensive skin lesions and AIDS at the Johannesburg Hospital. Certain mycoses are not endemic to South Africa, e.g. coccid-
iodomycosis, paracoccidioidomycosis and \textit{P. marneffei} infection and have not been reported in AIDS patients in our country.

The incidence of various dermatophytic infections is not considered to have increased in HIV infected patients but the severity and variability of presentation is increased. In tinea corporis, clinical lesions may lack the elevated borders and central clearing that is usually observed. Diffuse tinea corporis may occur at any stage of HIV disease \cite{86}.

Although rare in HIV-negative adults, tinea capitis is sometimes seen in those who are HIV-positive. Onychomycosis is common in HIV disease, especially advanced disease. Tinea unguium, particularly due to \textit{Trichophyton rubrum} may occur in up to 50\% of cases. Proximal white subungual onychomycosis often with bilateral involvement of the fingernails is the most common presentation. Terbinafine or itraconazole therapy is useful. Seborrheic dermatitis is very common and pruritis may be severe. Pityriasis versicolor may be more extensive in AIDS patients and occur in different skin areas.

In the absence of antiretroviral therapy for the majority of patients, the numbers of opportunistic infections including fungal infections will continue to increase in our hospitals and clinics, with consequent increase in morbidity and mortality.

**Contributors**

The contributors to this symposium were: M. D. Martins & J. H. Rex, \textit{What has happened to fluconazole-resistant oropharyngeal candidiasis?}; O. Lortholary & B. Dupont, \textit{Antifungal prophylaxis in HIV-infected patients at the time of HAART; C. A. Kauffman, Impact of HAART on management of the endemic mycoses; H. H. Crewe Brown & K Westermann, Mycoses and AIDS in South Africa.} The co-convenors were B. Dupont and H. H. Crewe-Brown.

**References**


