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Effect of antifungal treatment on the prevalence of yeasts in HIV-infected subjects

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Oral candidiasis, the most common opportunistic infection in patients with HIV infection, is usually associated with *Candida albicans*. Several factors may influence the carriage of *Candida*, including immunocompromised conditions and HIV infection, colonization by yeasts from different geographical areas and antimycotic treatment. This study investigated the *Candida* carrier rate, level and types of yeast in HIV-positive and -negative subjects, and the effect of previous exposure to antifungal drugs on the level of yeasts in HIV-positive patients in Gauteng, South Africa. Unstimulated saliva was collected from 332 HIV-positive patients and 100 HIV-negative subjects and cultured for yeasts. The number and species of yeast were determined. HIV-positive patients who carried yeasts were divided into two groups depending upon their previous antifungal drug exposure, and the level of *Candida* carriage in each group was compared. The *Candida* carrier rate in the HIV-positive patients (81·3 %) was slightly higher than previously reported and significantly higher ($P<0{\cdot}001$) than in the HIV-negative group (63 %). The carrier rate in the HIV-negative group was also higher than in earlier studies. Fourteen per cent of the HIV-positive patients carried more than 10 000 c.f.u. ml^{-1} whereas none of the HIV-negative subjects carried this large a number of yeasts ($P<0{\cdot}001$). Seventy per cent of the yeasts were identified as *C. albicans* and approximately 30 % as non-*albicans* species. In conclusion, the *Candida* carrier rate is higher in the South African population than elsewhere. HIV-positive patients carry more and a greater variety of yeasts than HIV-negative subjects. Exposure to antifungal drugs has no effect on the level of yeast carriage in HIV-positive patients.

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INTRODUCTION

Oral candidiasis is the most frequently encountered opportunistic infection in patients with HIV and AIDS (Patton *et al.*, 2002). Several studies have shown that asymptomatic carriage of oral *Candida* species varies geographically in healthy and compromised individuals (Table 1). Reports vary in different regions of South Africa. In the Western Cape, a province of South Africa, the rate was higher, with 68 % of HIV-negative subjects and 75 % of HIV-positive patients carrying yeasts (Hauman *et al.*, 1993). In this paper, only 28 HIV-positive patients were investigated, while the level of carriage was unclear. Most of the yeasts were identified as *Candida albicans*. In patients whose HIV status was unknown, a rate of 30·4 % was reported in the Kalahari in a rural area of South Africa and 58 % in the semiurban region of Gauteng province (Blignaut *et al.*, 1995; Masipa *et al.*, 1992).

C. albicans is the most common species of yeast isolated from patients with oral candidiasis (Fidel, 2006). There are several reports that non-*albicans* yeasts including *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, *Candida tropicalis*, *Candida guilliermondii*, *Candida dubliniensis* and *Saccharomyces cerevisiae* have been isolated from the oral cavity of immunocompromised patients (Powderly, 1992; Pfaller, 1996). Recent studies have shown that non-*albicans* species may become pathogenic in HIV-negative patients. For example, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *S. cerevisiae* have been isolated from infections in neonates, secondary sepsis in bone marrow transplant patients, and fungaemia (Roilides *et al.*, 2003; Cherifi *et al.*, 2004; Henry *et al.*, 2004; Redding *et al.*, 2004a). This information may change the perception of non-*albicans* yeasts from opportunistic to exogenous infective agents that can be transmitted readily from person to person and be easily acquired by immunocompromised people (Pfaller, 1996; Sanchez *et al.*, 1993; Doebbeling *et al.*, 1991).

Candida carriage and candidiasis may also be affected by several factors including HIV infection (Diamond, 1991), immunosuppressive drug therapy, cytotoxic therapy, intensive care treatment, iron status of the host and the prolonged use of antibiotics (Bodey *et al.*, 1992; Paya, 1993; Pfaller, 1996; Blignaut *et al.*, 1995; Pendrak *et al.*, 2004). The emergence of less common yeasts could be caused by the selection of resistant species by the pressure of antifungal agents such as fluconazole (Price *et al.*, 1994; Wingard *et al.*, 1991; Wingard, 1994).

Table 1. Reports of *Candida* carrier rate in HIV-positive and HIV-negative subjects in Asia, Europe and Africa

Country	Sampling method	*Candida* carrier rate (%)		Reference
		HIV-positive	HIV-negative	
Thailand (adults)	Oral rinse	66·6 ($n=45$)	10·8 ($n=74$)	Teanpaisan & Nittayananta (1998)
Thailand (children)	Oral rinse/swab	70 ($n=40$)	40 ($n=15$)	Pongsiriwet *et al.* (2004)
Hong Kong	Oral rinse	54·8 ($n=73$)	ND	Tsang & Samaranayake (2000)
Italy	Oral rinse	61·9 ($n=42$)	29·3 ($n=41$)	Campisi *et al.* (2002)
Germany	Oral swab	73·8 ($n=73$)	13·8 ($n=58$)	Schmidt-Westhausen *et al.* (1991)
India	Swish	65·3 ($n=150$)	ND	Gugnani *et al.* (2003)
South Africa	Oral rinse	75 ($n=28$)	68 ($n=28$)	Hauman *et al.* (1993)

ND, Not determined.

The aim of this study was to compare the prevalence and level of yeast species in HIV-positive patients and HIV-negative subjects in South Africa. In addition the effect of previous antifungal treatment on the carrier rate of yeasts in HIV-positive patients was investigated.

METHODS

Subjects and collection of saliva. The study population was selected from patients attending the HIV clinic at the New Johannesburg and Chris Hani Baragwanath Hospitals, Gauteng, a single geographical locale. The HIV-negative patients were healthy individuals who volunteered to participate in an ongoing HIV vaccine trial at Chris Hani Baragwanath Hospital and were screened for their HIV status. The first 332 HIV-positive and 100 HIV-negative subjects who volunteered were included in the study regardless of their gender. The population consisted of 332 HIV-positive patients (88 males with a mean age of 38·7 years, range 21–62; 244 females mean age 34·9 years, range 16–57) and 100 HIV-negative subjects (55 males with a mean age of 27·2 years, range 18–59; 45 females mean age 26·1, range 18–41). Ethical clearance was obtained from The Committee for Research on Human Subjects, University of the Witwatersrand. Written consent was obtained from the subjects. Ten minute unstimulated saliva samples were collected, cultured on Sabouraud dextrose agar and incubated at 37 °C for 48 h. Yeast counts were determined by colony morphology and the Gram stain. Previous treatment with antifungal agents was recorded for 255 HIV-positive patients. Of these patients, 177 had never been exposed to antifungal agents while 78 had been treated with either fluconazole, nystatin, myconazole or amphotericin B within the last year. Amphotericin B lozengers and miconazole gel were applied topically 10 times a day for 1 week while nystatin and fluconazole were used systemically for the same period.

Yeast identification. Isolates from 150 HIV-positive patients carrying $\geqslant$1000 c.f.u. (ml saliva)$^{-1}$ and 63 HIV-negative patients were identified to species level using the germ tube technique, chlamydospore production and the API 32 C sugar assimilation tests (bioMèrieux). Four colonies with different colony morphology per patient were identified.

Germ tube and chlamydospore formation, β-glucosidase activity and growth at 45 °C were used to differentiate between *C. albicans* and *C. dubliniensis* (Staib & Morschhauser, 1999; Pinjon *et al.*, 1998; Boerlin *et al.*, 1995). Counts of individual species were not performed.

Statistical analysis. The yeast carrier rate among HIV-positive and HIV-negative groups and the number of yeast in both study groups were compared using the chi-square test. In addition the chi-square test was used to compare *Candida* counts in HIV-positive patients who had been previously exposed to antifungal agents to *Candida* counts in patients with no previous exposure to antimycotics.

RESULTS AND DISCUSSION

Carriage rate

The *Candida* carriage rate (Table 2) in the HIV-positive patients (81·3 %) was significantly higher ($P<0·001$) than in the HIV-negative group (63 %). This carrier rate was higher than in studies from Thailand (adults 66·6 % and children 70 %), Hong Kong (54·8 %), Italy (61·9 %),

Table 2. Viable yeast counts in the whole saliva of HIV-positive and HIV-negative patients

Values are the number of patients (%).

Study group	Carrier rate (%)	Yeast count (c.f.u. ml^{-1})			
		0	1–1000	1000–10 000	>10 000
HIV-positive	270 (81·3)*	62 (18·7)	116 (43)†	115 (42·6)	39 (14·4)†
HIV-negative	63 (63)*	37 (37)	45 (71·4)†	18 (28·6)	0 (0)†

*$P<0·001$
†$P=0·001$

Germany (73·8 %) and India (65·3 %) (Teanpaisan & Nittayananta, 1998; Pongsiriwet *et al.*, 2004; Tsang & Samaranayake, 2000; Campisi *et al.*, 2002; Schmidt-Westhausen *et al.*, 1991; Gugnani *et al.*, 2003).

Several factors may have contributed to this high carrier rate. Diet could be important because a recent study has shown that malnourished HIV-positive children in Nigeria carried more yeasts than a similar population in the United States (Jabra-Rizk *et al.*, 2001). A study in Turkey showed that different populations and age groups carry different levels of yeasts, while the type of diet may affect the frequency of carriage (Kadir *et al.*, 2005). Our subjects were African adults whose diet is usually high in carbohydrates. However, carbohydrate intake varied according to regions. For example people living in the Kalahari region are nomads and their main diet is animal protein and occasionally carbohydrate, while in the Western Cape province and Gauteng the population is urbanized and their carbohydrate intake is usually high (MacKeown & Faber, 2004). This could explain the differences between results among the South African studies. The carrier rate was 30·4 % in Kalahari, 58 % in the semiurban area of Gauteng and 68 % in the urbanized Western Cape region. In our study the population was urbanized and their carbohydrate intake was probably high. This enhances the proliferation of *Candida* (Knight & Fletcher, 1971), adhesion to epithelial cells (Pizzo *et al.*, 2000) and the production of acidic proteases (Samaranayake *et al.*, 1984). Carriage rate could also be related to the method of sample collection (Table 1). For example using oral swabs and unstimulated saliva may not detect as many *Candida* as using an oral rinse. In our study, even though unstimulated saliva was tested, the carrier rate was high.

The level of carriage in HIV-positive subjects was significantly higher ($P<0·001$) than in HIV-negative patients (Table 2). These differences may be related to the level of $CD4^+$ cells, because our patients did not have access to HAART and probably had low $CD4^+$ cell counts. This is supported by Fidel (2006), who suggests that *Candida*-specific T cells do not become defective with immunosuppression, but a threshold number of $CD4^+$ cells is required to protect the oral cavity against infection by this normal commensal. Out of the 39 patients who had more than 10 000 *Candida* (ml saliva)$^{-1}$ only 16 patients had oral lesions. Of these 16 patients with oral candidiasis 3 carried other yeasts in addition to *C. albicans*. The rest of the patients with high *Candida* counts and oral candidiasis at the time of sampling carried only *C. albicans*.

This study showed that 63 % of HIV-negative subjects carried *Candida* (Table 2). This was higher than reports from Europe (13·8–29 %), Thailand (10·8 %) and from a Saudi population (52 %) (Teanpaisan & Nittayananta, 1998; Pongsiriwet *et al.*, 2004; Campisi *et al.*, 2002; Schmidt-Westhausen *et al.*, 1991; Darwazeh *et al.*, 2002). A recent study reported that oral yeast colonization among AIDS household contacts is high (Milan *et al.*, 2001), which suggests that transfer and colonization of strains can occur readily. The transfer may not be related to HIV status but to exposure to AIDS patients with high counts because 63 % of HIV-negative subjects carried *Candida* and live in South Africa where more than 5·0 million of the population are living with AIDS (Dorrington *et al.*, 2004). The HIV-positive and -negative patients came from the same low socioeconomic densely populated area, where several families may live in one house and general hygiene is poor.

Species isolated

C. albicans was the most common species isolated in our study and comprised 78·6 % of the isolates whereas 21·4 % were non-*albicans* species (Table 3). The percentage of non-*C. albicans* was higher than in reports from Thailand (3·4 %) and Germany (13·2 %) (Teanpaisan & Nittayananta, 1998; Schmidt-Westhausen *et al.*, 1991). Non-symptomatic oral cavity carriage of non-*C. albicans* is well established (Kadir *et al.*, 2005; Qi *et al.*, 2005; Torres *et al.*, 2003; Gugnani *et al.*, 2003; Reichart *et al.*, 2002; Belazi *et al.*, 2004; Redding *et al.*, 2004a). A recent epidemiological trend is the emergence of less pathogenic species of non-*albicans Candida* as significant opportunistic pathogens. Species isolated in our study included *C. glabrata*, *C. tropicalis*, *C. krusei*, *C. parapsilosis*, *S. cerevisiae* and the newly characterized species *C. dubliniensis* (Table 3). *C. glabrata* sepsis has been observed in bone marrow transplant patients and oropharyngeal candidiasis in head and neck cancer patients (Redding *et al.*, 2004a, b). Fungaemia due to *C. parapsilosis*, *C. tropicalis* and *C. glabrata* has been reported in neonates (Roilides *et al.*, 2003) whereas oral candidiasis due to *C. glabrata* has been reported (Hoegl *et al.*, 1998). *S. cerevisiae*

Table 3. Species of yeast isolated from 150 HIV-positive and 63 HIV-negative patients

Yeast isolate	No. of isolates (%)	
	HIV-positive	HIV-negative
C. albicans	136 (78·6)	45 (70·3)
C. dubliniensis	11 (6·3)	3 (4·7)
C. glabrata	9 (5·2)	0
C. parapsilosis	3 (1·7)	1 (1·6)
C. lusitaniae	3 (1·7)	0
S. cerevisiae	3 (1·7)	1 (1·6)
C. sake	2 (1·2)	3 (4·7)
C. tropicalis	1 (0·6)	2 (3·1)
C. krusei	1 (0·6)	0
C. famata	1 (0·6)	0
C. pelliculosa	1 (0·6)	0
C. utilis	1 (0·6)	0
C. kafyr	0	1 (1·6)
C. holmii	0	1 (1·6)
Unidentifiable	1 (0·6)	7 (10·8)
Total	**173**	**64**

has become an opportunistic pathogen causing fungaemia in immunocompromised patients (Cherifi *et al.*, 2004; Henry *et al.*, 2004). Three strains of *S. cerevisiae* were accompanied by *C. albicans*. The transient presence of *S. cerevisiae* in the oral cavity has been observed but the genetic heterogeneity of the isolates and rapid clearance suggest that the presence of *S. cerevisiae* is the result of colonization by orally adapted strains (Sweet *et al.*, 2002). Twenty-one patients carried two species of yeasts, two patients carried three species and one patient harboured four different species of yeasts. Occurrence of multiple yeasts could not be linked to candidiasis; however, three patients who carried other yeasts with *C. albicans* had oral candidiasis at the time of sampling.

In addition to the above well-documented species, four non-*albicans* species, *Candida sake*, *Candida famata*, *Candida pelliculosa* and *Candida utilis*, were isolated from the oral cavity of the HIV-infected subjects (Table 3). The large variety of yeasts harboured by the South African population could be attributed to life in a rural environment where there is exposure to a large variety of yeasts. The pathogenic role of these rare non-*albicans* yeasts in the oral cavity of HIV-positive patients needs further investigation.

Effect of antifungal agents

Another factor that could influence *Candida* carriage is the use of antimycotic agents. Nystatin, amphotericin B and fluconazole have been used for many years for long-term therapy in patients with HIV infection (Greenspan, 1994). The development of fluconazole resistance is an emerging trend. In 1995, 40 % of patients on long-term therapy carried resistant strains, 43 % in 1997 and 45 % in 2000 (Magaldi *et al.*, 2001; Tumbarello *et al.*, 1997; Johnson *et al.*, 1995), which threatens its clinical effectiveness. In our study, we examined the effect of previous antifungal treatment with nystatin, amphotericin B, fluconazole or miconazole on the number of viable *Candida* cells carried by HIV-positive patients. Overall there was no significant difference ($P=0{\cdot}05$) between patients who had been treated previously with antimycotic drugs and those who had not been exposed (Table 4). However, 25 of the 45 patients who were treated with nystatin required further treatment while only 7 of the 37 patients treated with amphotericin B required more than one treatment. Seven of the eight patients with yeast counts of greater than 10^4 had received amphotericin treatment previously while one patient was treated with miconazole and fluconazole.

These findings suggest that some patients carry large numbers of yeast that are resistant to several antifungals, do not respond to treatment and are prone to candidiasis. This also suggests that the resident yeast population is stable and occupies a specific niche in the oral cavity. With treatment the level of yeast declines but is restored to the original level after treatment is discontinued. This may not apply to several non-*albicans* species because there are numerous reports describing the colonization and infection of compromised patients taking long-term oral antifungal agents. Primary resistance to the antifungal agent has been reported in *C. krusei* and *C. glabrata* (Wingard *et al.*, 1991, 1993; Wingard, 1994) with *C. krusei* being universally resistant to fluconazole (Wingard *et al.*, 1991). For this reason, all oral lesions with a presumptive diagnosis of candidiasis should be subjected to microscopy and culture. Isolated cultures should be identified to species level, antifungal sensitivity should be determined and primary resistance should be kept in mind during treatment.

In conclusion, this study has shown that the carrier rate of *Candida* is higher in South Africa than elsewhere in the world. In addition, HIV-positive patients carry more and a greater variety of yeasts than HIV-negative subjects. This may be related to several factors, including diet, oral hygiene, the number of HIV-positive patients in the population and the large number of patients who do not have access to HAART. Exposure to antifungal drugs has no effect on the level of yeast carriage in HIV-positive patients.

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Table 4. Viable yeast counts in the whole saliva of HIV-positive subjects with no previous antimycotic therapy or who had antimycotic drugs previously

Values are the number of patients (%).

Study group	Yeast count (c.f.u. ml^{-1})		
	1–1000	1000–10 000	>10 000
No previous antimycotic treatment ($n=177$)	96 (54·2)	60 (33·9)	21 (11·9)
Previous antimycotic treatment ($n=78$)	36 (46·1)	34 (43·6)	8 (10·3)

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