Antimycotic Agents in Oral Candidosis: An Overview: 1. Clinical Variants

ARJUNA N.B. ELLEPOLA AND LAKSHMAN P. SAMARANAYAKE

Abstract: The advent of the human immunodeficiency virus and the increasing prevalence of immunocompromised individuals in the community have resulted in a resurgence of opportunistic infections, including oral candidoses. Despite the availability of a number of effective antimycotics for the management of oral candidoses, therapeutic failure is not uncommon. Further, the presence of many clinical variants of oral candidosis, both new and old, may confound the unwary clinician and complicate its management. These problems have been partly circumvented by the introduction of the triazole group of antimycotics, which initially appeared to be highly effective. However, an alarming increase in organisms resistant to triazoles has been reported recently. In this paper we provide an overview of clinical variants of oral candidosis. A second paper will discuss recent advances in the usage of antimycotics in the management of this condition.

***Dent Update* 2000; 27: 111-116**

Clinical Relevance: Classically, oral candidosis presents as white patches of 'thrush' especially in the protected mucosal niches such as buccal vestibules. However, a red crythematous variant is now defined as a new manifestation of the disease. These together with the least common, white, hyperplastic variant form the classic 'triad' of oral candidal infections.

The frequency of life-threatening fungal infections is rising worldwide. Candidosis is by far the commonest oral fungal infection in humans and manifests in a variety of clinical guises including pseudomembranous (thrush) and erythematous variants, *Candida*-induced denture stomatitis, linear gingival erythema associated with HIV infection and median rhomboid glossitis and angular stomatitis, possibly of multi-factorial origin.

***Arjuna N.B. Ellepola**, BDS (Hon.), PhD, Lecturer, Department of Oral Medicine & Periodontology, Faculty of Dental Sciences, University of Peradeniya, Sri Lanka and Faculty of Dentistry, The Prince Philip Dental Hospital, University of Hong Kong, and **Lakshman P. Samaranayake**, BDS, DDS, FRCPath, FHKCPath, CBiol, MIBiol, FHKAM (Dental Surgery), FHKAM (Pathology), Chair Professor of Oral Microbiology, Faculty of Dentistry, The Prince Philip Dental Hospital, University of Hong Kong.*

The main reason for the high incidence of oral candidosis appears to be the multiplicity of predisposing factors, which facilitates the conversion of commensal *Candida* to a parasitic existence.[1] All forms of oral candidosis are considered opportunistic. For instance, the advent of the human immunodeficiency virus (HIV) has resulted in a resurgence of oral candidal infections. More than 90% of HIV-infected individuals develop oral candidosis, which is by far the most frequent oral manifestation in these patients.[2] Since the first clinical definition of AIDS, the CDC/WHO have recognized candidosis of the mouth as one of the major opportunistic infections and an important indicator of the disease. The increasing prevalence of other compromised patient groups in the community, usage of broad-spectrum antibiotics, cytotoxics and corticosteroids, common endocrine disorders such as diabetes mellitus, and severe nutritional deficiencies have resulted in a resurgence of oral candidosis (Table 1).

A number of effective antifungal agents, administered either topically or systemically, are available for the management of oral candidosis.[3] These range from the classic polyenes to the azole-group antimycotics, which includes the imidazoles and the newer triazoles. However, despite the availability of such a multiplicity of agents, therapeutic failure is not uncommon: in oral environmental niches the diluent effect of saliva and the cleansing action of the oral musculature often tend to reduce the availability of the antifungals below effective therapeutic concentrations. *Candida* biofilms on mucosal and inert surfaces such as prostheses may also contribute to failure of drug therapy. Poor patient compliance due to frequent drug administration and associated adverse effects, coupled with possible underlying immunodeficiency, can also impair

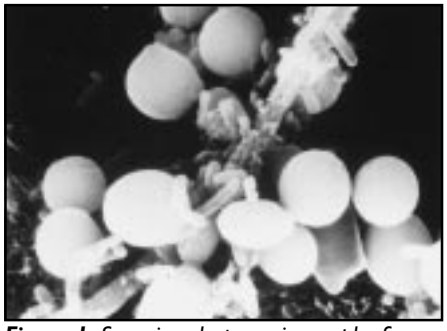

***Figure 1.** Scanning electron micrograph of denture plaque from a patient with* Candida*-induced denture stomatitis, showing* C. albicans *blastospores.*

Physiological	Old age, infancy, pregnancy
Local trauma	Mucosal irritation, poor denture hygiene
Antibiotics	Particularly broad-spectrum antibiotics
Corticosteroids	Steroid inhalers, systemic steroids
Malnutrition	High-carbohydrate diet, iron, folate and vitamin B_{12} deficiencies
Endocrine disorders	Hypoendocrine states (e.g. hypothyroidism, Addison's disease), diabetes mellitus
Malignancies	Including blood disorders (e.g. acute leukaemia, agranulocytosis)
Immune defects	AIDS, thymic aplasia
Xerostomia	Due to irradiation, drug therapy, Sjögren's syndrome, cytotoxic drug therapy

Table 1. *Factors that predispose the host to oral candidosis.*

therapy, resulting in chronic recurrence of the disease.

The fungal infections of the oral mucosa most frequently encountered are those due to species of the genus *Candida*. *C. albicans* is the principal species associated with this infection (Figure 1) and is the most virulent among pathogenic *Candida* species. One possible reason for this may be its ability to transform from the yeast phase to the hyphal phase. Germ tubes, which mark the onset of hyphal growth of the organism, are especially incriminated in the pathogenesis of candidosis (Figure 2), as these cylindrical extrusions are known to facilitate yeast adherence to epithelial cells, and impart resistance to phagocytic killing. Furthermore, germ tubes tend to promote aggregation of yeast cells and bridging of adjacent hyphal elements, thereby bringing many organisms into intimate contact with the epithelium. However, non-*albicans* species, such as *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. guillermondii* and *C. krusei*, are also pathogenic to humans (Figure 3). *C. dubliniensis*, a recently described species, was first isolated from oral lesions in HIV-infected individuals.

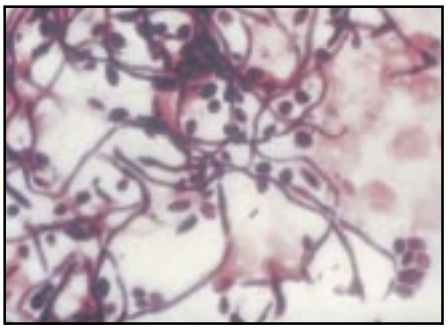

Figure 2. *A Gram-stained smear of denture plaque from a patient with* Candida*-induced denture stomatitis, showing predominance of hyphal elements produced by* C. albicans.

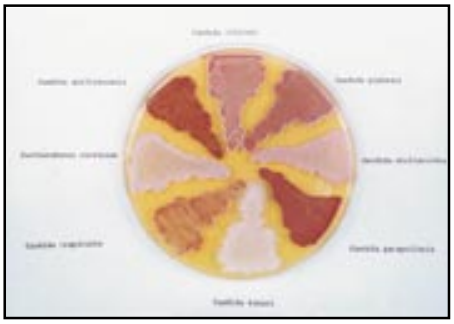

Figure 3. *The appearance of different candidal species grown on Pagano Levin Agar for 48 hours at 37°C. Note the different colours elicited by growing colonies.*

Classification of oral candidal infections is fraught with difficulties due to the varied manifestations of the disease. It is generally accepted that oral candidosis can be divided into two broad categories: primary and secondary (Table 2).[4,5]

- Candidal infections confined to oral and perioral tissues are considered primary oral candidoses.
- Disorders where oral candidosis is a manifestation of generalized systemic candidal infections are categorized as secondary oral candidosis.

The primary oral candidoses are sub-classified into three major variants—pseudomembranous, erythematous and hyperplastic—each of which may manifest as acute or chronic lesions. Despite attempts to discriminate between disease variants, some conditions (such as cheilo-candidosis and chronic multifocal candidosis) do not fall strictly into any of these categories: the former presents as a chronic, ulcerative granulating lesion of the vermilion of the lower lip; the latter causes chronic, erythematous plaque-like lesions in two or more sites in the mouth, palate or dorsum of the tongue.

PSEUDOMEMBRANOUS CANDIDOSIS

Pseudomembranous candidosis or thrush is classically an acute infection, but may recur for many months or even years in patients using corticosteroids topically or by aerosol, in HIV-infected individuals, and in other immunocompromised patients. It may also be seen in neonates and among the terminally ill, particularly in association with serious underlying

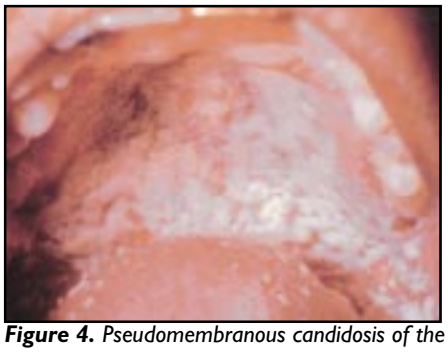

Figure 4. *Pseudomembranous candidosis of the hard palate in a patient using steroid inhalers.*

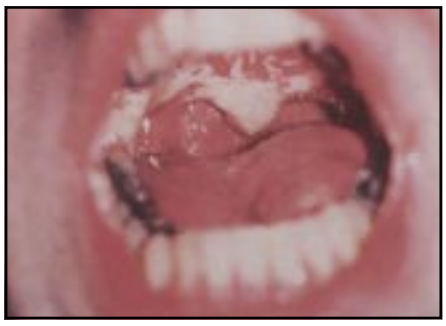

Figure 5. *Pseudomembranous candidosis of the soft palate in HIV infection.*

Primary oral candidoses*	Secondary oral candidoses
Acute forms: Pseudomembranous Erythematous **Chronic forms:** Hyperplastic: Nodular Plaque-like Erythematous Pseudomembranous ***Candida*-associated lesions:** Denture stomatitis Angular cheilitis Median rhomboid glossitis **Keratinized primary lesions superinfected with *Candida*:** Leukoplakia Lichen planus Lupus erythematosus	Oral manifestations of systemic mucocutaneous candidosis as a result of diseases such as a thymic aplasia and candidosis endocrinopathy syndrome
**Candida* may also contribute to the development of linear gingival erythema and necrotizing periodontal disease in HIV infection.	

Table 2. *Classification of oral candidosis as proposed by Samaranayake (1991) and modified by Axell* et al.[5]

conditions such as leukaemia and other malignancies.

Thrush is characterized by white patches on the surface of the buccal and labial mucosa, tongue and the soft palate (Figures 4 and 5). The lesions form confluent plaques that resemble milk curd and can be wiped off to reveal a raw, erythematous and sometimes bleeding base.

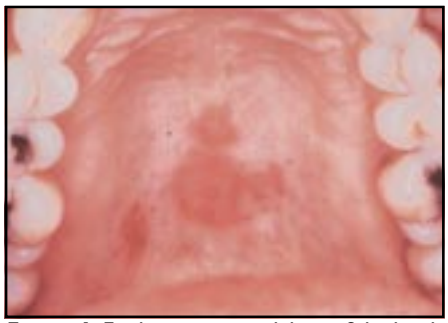

Figure 6. *Erythematous candidosis of the hard palate in an HIV-infected patient.*

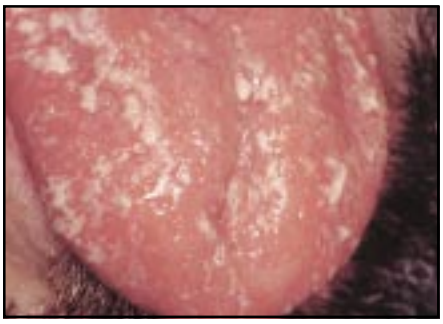

Figure 7. *Mixed pseudomembranous and erythematous candidosis of the dorsum of the tongue in a patient on tetracycline therapy.*

ERYTHEMATOUS CANDIDOSIS

Erythematous candidosis (previously known as antibiotic sore mouth) is associated with corticosteroids, broad-spectrum antibiotics and recently with HIV disease. It may arise as a consequence of persistent acute pseudomembranous candidosis—when pseudomembranes are shed, may develop *de novo*, or (in HIV infection) may precede pseudomembranous candidosis. It is the most common variant of candidosis seen in HIV disease.

Clinically, erythematous areas are seen on the dorsum of the tongue, palate or buccal mucosa (Figures 6 and 7). Lesions on the dorsum of the tongue present as depapillated areas. Red areas are commonly seen in the palate in HIV disease. There can be an associated angular stomatitis.

HYPERPLASTIC CANDIDOSIS

Hyperplastic candidosis or candidal leukoplakias are chronic, discrete raised lesions that vary from small, palpable, translucent, whitish areas to large, dense, opaque plaques, hard and rough areas on palpation (plaque-like lesions). They may also present as homogeneous or speckled lesions (nodular lesions) which do not rub off. Candidal leukoplakias usually occur on the inside surface of one or both cheeks at the commissural areas (Figures 8 and 9) and, less often, on the tongue. The condition is premalignant and shows varying degrees of dysplasia. The risk of carcinoma developing in candidal leukoplakia will depend on:

- whether the lesion is speckled or homogeneous;
- the presence and degree of epithelial dysplasia; and
- the management adopted.

Thus, biopsy is important in its overall management. In a minority of cases, the condition has been associated with iron and folate deficiency and with impaired

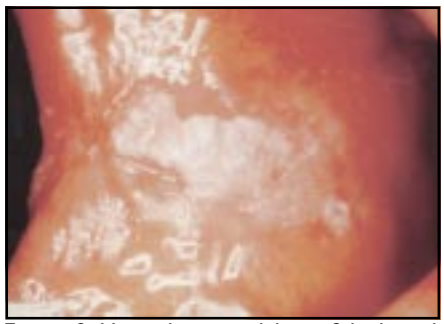

Figure 8. *Hyperplastic candidosis of the buccal mucosal commissures.*

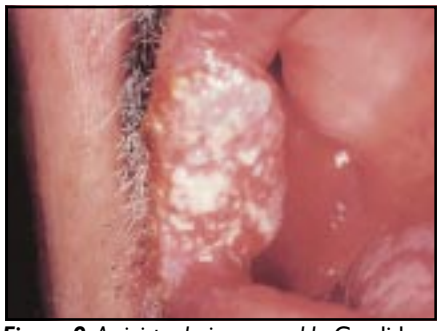

Figure 9. *A sinister lesion caused by* Candida *(hyperplastic candidosis), which was resolved by antifungal therapy alone. (Courtesy of Dr M. Lewis.)*

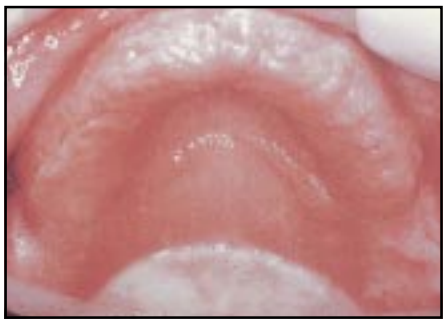

Figure 10. Candida-*induced denture stomatitis of the hard palate (Newton's type II).*

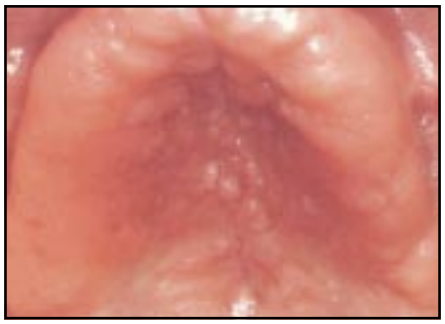

Figure 11. Candida-*induced denture stomatitis of the hard palate (Newton's type III).*

cell-mediated immunity.

OTHER LESIONS ASSOCIATED WITH CANDIDAL INFECTION

Candida-associated Denture Stomatitis

In this condition the characteristic presenting feature is chronic erythema and oedema of the mucosa in contact with the fitting surface of the denture. Denture-induced stomatitis has been classified into three clinical types (Figures 10 and 11):

- type I—a localized simple inflammation or a pinpoint hyperaemia;
- type II—an erythematous or generalized simple type presenting as more diffuse erythema involving a part of, or the entire, denture-covered mucosa;
- type III—a granular or papillary type commonly involving the central part of the hard palate and alveolar ridge.[6]

It was thought that the papillary types of lesions are essentially due to the presence of the prostheses. However, a recent report of similar lesions in HIV-infected individuals implies that the denture is not the prime aetiological factor for the condition (see Figure 12). It occurs mainly due to the overgrowth of commensal *Candida* between the denture surface and the palate where natural salivary flow is restricted. The mucosa beneath the mandibular dentures is hardly ever involved.

Apart from occasional soreness this condition is usually symptomless. However, patients may suffer an associated angular stomatitis and burning or tingling sensation beneath the denture.

Denture-induced stomatitis is not exclusively associated with *Candida*: other factors, such as bacterial infection, mechanical irritation or (rarely) an allergic reaction to the denture base material, have also been implicated.

Angular Stomatitis

Angular stomatitis is characterized by soreness, erythema and fissuring, affects the angle of the mouth and is commonly associated with denture-induced stomatitis (Figure 13). Both yeasts and bacteria (especially *Staphylococcus aureus*) are involved as interacting and predisposing factors.

Angular stomatitis may present as an isolated initial feature of anaemia or vitamin deficiency, such as vitamin B_{12} deficiency, and will resolve once the underlying disease has been treated. Iron-deficiency anaemia and other vitamin deficiencies may predispose to angular stomatitis. Interestingly, in conditions such as orofacial granulomatosis, up to 20% of individuals have angular stomatitis, although *Candida* is not often isolated. The lesion may also be a result of maceration due to deep, occlusive folds of the skin at the angles of the mouth in individuals with reduced facial height caused by old age or ill-fitting dentures. However, it is seen in young individuals with HIV disease, possibly due to impaired immunity. Exfoliative cheilitis, predominantly of the lower lip, may also be associated with *Candida*, especially in HIV infection, and could be considered another variant of candidosis in AIDS.[7]

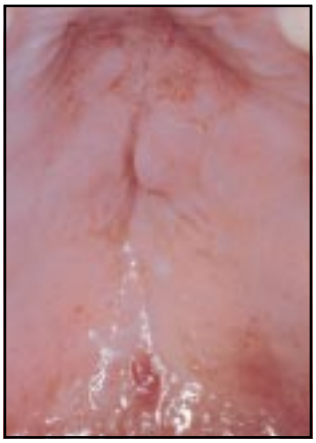

Figure 12. *Papillary hyperplasia of the hard palate in HIV*

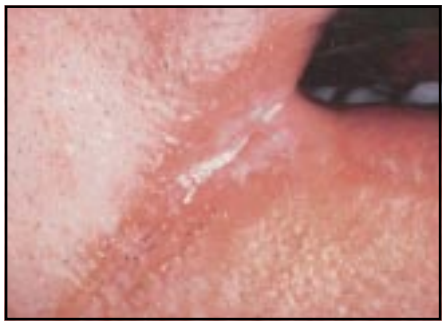

Figure 13. *Typical appearance of angular stomatitis.*

Median Rhomboid Glossitis

This is characterized by an area of papillary atrophy that is elliptical or rhomboid in shape, symmetrically placed

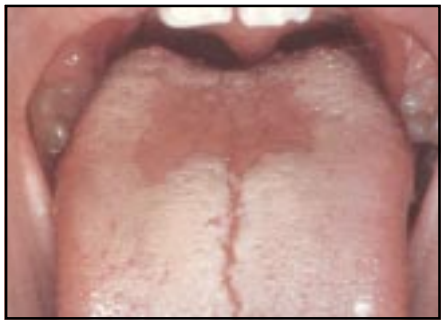

Figure 14. *Median rhomboid glossitis of the tongue.*

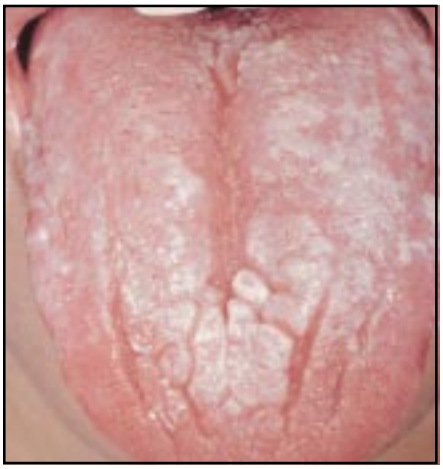

Figure 15. *Chronic mucocutaneous candidosis of the tongue in a 14-year-old girl.*

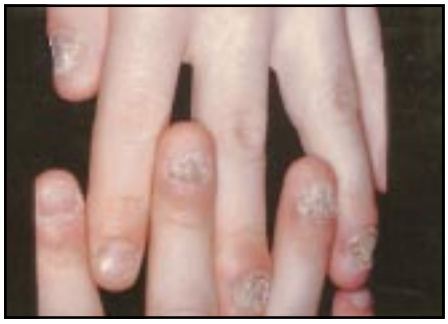

Figure 16. *Chronic mucocutaneous candidosis affecting the nails (koilonychia) of the patient shown in Figure 15.*

centrally at the midline of the tongue, anterior to the circumvallate papillae (Figure 14). Occasionally it presents with a hyperplastic exophytic or even lobulated appearance. The relevance of *Candida* to the aetiology of median rhomboid glossitis has been controversial, as a mixed bacterial and/or fungal flora is associated with the condition.

CANDIDOSIS AND IMMUNOCOMPROMISED HOSTS

Candidosis is usually restricted to the skin and mucous membranes but may occasionally spread. It is also important to recognize that oral candidal infection can manifest as a result of systemic candidosis. However, most of these complications are uncommon (with the exception of patients with AIDS), candidosis remains superficial and immunocompromised patients usually do not die from disseminated candidosis. Oropharyngeal candidosis does, rarely, disseminate to cause *Candida*-associated osteomyelitis in HIV infection, and sometimes in patients with diabetes.[8]

Chronic mucocutaneous candidosis (Figures 15 and 16) is the term given to the group of rare syndromes, sometimes with a definable immune defect, in which there is persistent mucocutaneous candidosis that responds poorly to topical antifungal therapy. In general, the more severe the candidosis, the greater the likelihood that immunological defects can be identified.

Since the first clinical definition of AIDS in 1981, the CDC/WHO have recognized oropharyngeal candidosis and candidal infection of the oesophagus, trachea, bronchi and lungs as major opportunistic infections and important indicators of the disease. The main cause of oral candidosis in HIV infection is the immune impairment. However, *Candida* itself may also induce immunosuppression, and this can influence the prognosis of HIV infection.[9] The manifestations of candidal infections in HIV infection are usually restricted to superficial candidosis with varying degrees of severity. The major clinical variants of oral candidosis (pseudomembranous, erythematous and hyperplastic) have all been described in HIV infection, thrush (pseudomembranous candidiasis) and the erythematous variants being the most common. They may manifest for a variable period before development of other life-threatening opportunistic infections. Papillary hyperplasia similar to denture-induced lesions may occasionally be seen in the palate, although whether candidal infection is involved in its aetiopathology is unclear (Figure 12).[10]

Candida may also contribute to the development of linear gingival erythema or necrotizing ulcerative periodontitis in HIV-infected persons. For instance, a statistically significant relationship between the presence of intra-oral candidosis and these conditions in HIV positive homosexual men, heterosexual men and women has been reported.[11,12]

REFERENCES

1. Samaranayake LP. *Essential Microbiology for Dentistry*. London: Churchill Livingstone, 1996.
2. Arendorf TM, Bredekamp B, Cloete CAC, Sauer G. Oral manifestations of HIV infection in 600 South African patients. *J Oral Pathol Med* 1998; **27:** 176-179.
3. Greenspan D. Treatment of oropharyngeal candidosis in HIV-positive patients. *J Am Acad Dermatol* 1994; **31:** S51-S55.
4. Samaranayake LP, Yaacob HB. Classification of oral candidosis. In: Samaranayake LP, MacFarlane TW, eds. *Oral Candidosis*. Oxford: Wright, 1990; pp. 124-132.
5. Axell T, Samaranayake LP, Reichart P, Olsen I. A proposal for reclassification of oral candidosis. *Oral Surg Oral Med Oral Pathol* 1997; **84:** 111-112.
6. Newton AV. Denture sore mouth: a possible aetiology. *Br Dent J* 1962; **112:** 357-360.
7. Reichart PA, Weigel D, Schmidt-Westhausen A, Pohle HD. Exfoliative cheilitis (EC) in AIDS: association with *Candida* infection. *J Oral Pathol Med* 1997; **26:** 290-293.
8. Arranz-Caso JA, Lopez-Pizarro VM, Gomez-Herruz P, Garcia-Altozano J, Martinez-Martinez J. *C. albicans* osteomyelitis of the zygomatic bone. A distinctive case with a possible peculiar mechanism of infection and therapeutic failure with fluconazole. *Diagn Microbiol Infect Dis* 1996; **24:** 161-164.
9. Samaranayake LP, MacFarlane TW, eds. *Oral Candidosis*. Oxford: Wright, 1990.
10. Reichart PA, Schmidt-Westhausen A, Samaranayake LP, Philipsen HP. *Candida*-associated palatal papillary hyperplasia in HIV-infection. *J Oral Pathol Med* 1994; **23:** 403-405.
11. Gribic JT, Mitchell-Lewis DA, Fine JB *et al*. The relationship of candidiasis to linear gingival erythema in HIV-infected homosexual men and parenteral drug users. *J Periodontol* 1995; **66:** 30-37.
12. Klein RS, Quart AM, Small CB. Periodontal disease in heterosexuals with acquired immunodeficiency syndrome. *J Periodontol* 1991; **62:** 535-540.

Self-Assessment Answers

1. A, B, D	**6.** B, C
2. A,B,D	**7.** B, D
3. B	**8.** A, B, C, D
4. B, C	**9.** A, B, D
5. A, D	**10.** B