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REVIEW ARTICLE

Current trends of HIV disease of the mouth

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HIV infection affects residents of all countries of the world, but the greater majority of affected individuals reside in the developing world. In the past decade there have been substantial changes in the management of HIV disease, particularly the introduction of highly active antiretroviral therapy (HAART). Such agents have reduced significantly the morbidity and mortality associated with HIV disease, however, they are not available for most HIV-infected individuals in the developing world. There is now considerable understanding of the molecular epidemiology, transmission and therapy of the common opportunistic oral infections of HIV disease, and as a consequence of improved anti-HIV strategies, the frequency and severity of oral disease associated with HIV infection have reduced considerably, although HAART may predispose to human papilloma virus infection of the mouth and potentially increase the risk of later oral squamous cell carcinoma. Despite advances in clinical care the majority of individuals with HIV disease worldwide will continue to develop oral disease, as they are resident in the developing world and do not have ready access to even simple therapies.
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Current epidemiological trends of HIV infection

The global AIDS epidemic shows no signs of abating since its first detailed clinical description in 1981 (1). It is now estimated that by the end of 2004 there were about 40 million people alive with HIV infection in the world, of which only 1.6 million live in high income countries, the remaining 95% of infected individuals being resident in low income countries. At the beginning of the 21st century, HIV/AIDS is the most common cause of early death in Africa and the fourth most common of such deaths globally (2, 3). Studies in Africa have shown that HIV/AIDS has reversed the improvement in life expectancy that many countries in sub-Saharan Africa had attained before 1996 (4).

HIV is typically acquired via sexual routes, although in the developed world is still acquired via injecting drug users. Iatrogenic acquisition of HIV has occurred (e.g. via contaminated needle re-use and/or blood products) (5). Intrafamilial transmission – where the route of transmission could not be conclusively determined – has also been described (6). Infection of six patients attending a general dental practitioner with HIV (7) and horizontal transmission from a father to child, possibly via exposure to bleeding skin lesions (8) has been detailed.

Current therapeutic trends

Antiretroviral therapy (ART) principally comprises four classes of antiretroviral agents: nucleoside analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and entry inhibitors. This last class of drug has only become clinically available recently (9) being reserved for the treatment of HIV-1 infection in treatment-experienced patients (10) and represents a new class of antiretroviral agents that block HIV entry into body cells (11). The entry inhibitors are divided into attachment inhibitors, co-receptor inhibitors, and fusion inhibitors (9). Combinations of NRTIs, NNRTIs and PIs are usually termed Highly Active Antiretroviral Therapy (HAART).

Many oral and systemic adverse effects can arise with the various antiretrovirals. Of particular relevance to orofacial disease HIV-associated lipodistrophy syndrome is now considered to be one of the most clinically relevant adverse affects of ART (12). This syndrome is characterized by increased fat around the abdomen, dorsocervical fat pad enlargement (buffalo hump) and possible breast hypertrophy, with loss of fatty tissue in the limbs, buttocks and face. The nasolabial regions and

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temples are the most common sites of facial involvement, although, when severe, orbital fat can also be lost. The fat wasting in the limbs leads to prominence of the subcutaneous veins while that of the face and buttocks leads to marked hollowing and wrinkling of the skin. Some studies demonstrate that both PIs and NRTIs seem to contribute to lipodistrophy, although the former are the more likely cause (12). Other oral adverse oral side effects of HAART are discussed later.

Anti-retroviral therapy is very effective at suppressing viral replication. However, viral rebound with resistance does occur, primarily due to sub-optimal compliance and drug toxicities. It is during the period of failing HAART, when the HIV load may well be high or rising, that the transmission of drug resistant HIV to susceptible individuals occurs (13, 14).

Reported estimates of the prevalence of anti-retroviral resistance in drug-naïve individuals range from 0.8% for NNRTIs, 1.9% for PIs and 3.3% for NRTIs in one European study, to over 25% of patients carrying a virus with at least one primary mutation, in other studies (15). Transmission of anti-retroviral resistance has been documented between: heterosexual partners (16–18), men who have sex with men (MSM) (16, 19), between healthcare workers (HCWs) to their patients (20), from intravenous drug users (IDUs) (16, 21), between donors/recipients of human organs/blood products (16) and from patients to HCWs (22, 23).

HAART is currently not available to all patients in the developing world, where often the treatment of HIV disease is principally directed toward the elimination of opportunistic infection (24).

Classification of oral manifestations of HIV

The oral manifestations of HIV disease in adults (Table 1) and children (Table 2) were classified according to their frequency of association with HIV disease before the advent of effective ART (25–27). Although the EC-Clearinghouse classification was developed over a decade ago, there have been few new infections recognized in HIV-infected persons, this perhaps reflecting the wide availability of HAART in the developed world. The only notable change has been the recognition of *Penicilliosis marneffei* as a potential group 3 disease following reports of its sharp rise in South-East Asia (28). Paralleling the early reports of the oral manifestation of HIV in residents in the developed world, there have now been many reports of the oral lesions of HIV-infected individuals in the developing countries, but despite differences in transmission risk behaviour, geographical location, gender distribution, ethnicity, nutritional status and endemic disease there are few striking differences between the oral disease of HIV infected

Table 1 EC-Clearinghouse classification of the oral manifestations of HIV disease in adults

Group 1 lesions strongly associated with HIV infection	*Group 2 lesions less commonly associated with HIV infection*	*Group 3 lesions seen in HIV infection*
Candidosis	Bacterial infections	Bacterial infections
Erythematous	*Mycobacterium avium-intracellulare*	*Actinomyces israelii*
Pseudomembranous	*Mycobacterium tuberculosis*	*Escherichia coli*
		Klebsiella pneumonia
Hairy leukoplakia	Melanotic hyperpigmentation	Cat-scratch disease
Kaposi's sarcoma	Necrotizing (ulcerative) stomatitis	Drug-reactions
		Ulcerative
		Erythema multiforme
		Lichenoid
		Toxic epydemolysis
Non-Hodgkin's lymphoma	Salivary gland diseases	Epithelioid (bacillary) angiomatosis
	Dry mouth due to decreased salivary flow rate	
	Unilateral or bilateral swelling of major salivary glands	
Periodontal disease	Thrombocytopenic purpura	Fungal infections other than Candida
Linear gingival erythema		*Cryptococcus neoformans*
Necrotizing gingivitis		*Geotrichium candium*
Necrotizing periodontitis		*Histoplasma capsulatum*
		Mucoraceae (mucurmycosis, zygomycosis)
		Aspergillus flavus
	Ulceration NOS (not otherwise specified)	Neurological disturbances
		Facial palsy
		Trigeminal neuralgia
	Viral infections	Viral infections
	Herpes simplex virus	Cytomegalovirus
	Human papillomavirus lesions	Molluscum contagiosum
	Condyloma acuminatum	
	Focal epithelial hyperplasia	
	Verruca vulgaris	
	Varicella zoster virus	
	Herpes zoster	
	Varicella	

Table 2 EC-Clearinghouse and WHO classification of oral manifestations of pediatric HIV disease

Group 1 lesions commonly associated with pediatric HIV infection.	*Group 2 lesions less commonly associated with pediatric HIV infection*	*Group 3 lesions strongly associated with HIV infection but rare in children*
Candidosis	Seborrheic dermatitis	Neoplasms
Erythematous		Kaposi's sarcoma
Pseudomembranous		Non-Hodgkin's lymphoma
Angular cheilitis		
Herpes simplex virus infection	Bacterial infections of oral tissues	Oral hairy leukoplakia
	Necrotizing (ulcerative) stomatitis	
Linear gingival erythema	Periodontal diseases	Tuberculosis-related ulcers
	Necrotizing (ulcerative) gingivitis	
	Necrotizing (ulcerative) periodontitis	
Parotid enlargement	Viral infections	
	Cytomegealovirus	
	Human papilloma virus	
	Molluscum contagiosum	
	Varicella-zoster virus	
	Herpes zoster	
	Varicella	
Recurrent aphthous ulcers	Xerostomia	
Minor		
Major		
Herpetiform		

individuals in the developing world when compared to those of the developed world (28, 29), particularly as regards the prevalence and type of common oral lesions observed.

A number of oral lesions presently not included in the classification of oral manifestations of HIV include: exfoliative cheilitis (30), eruptive cheilitis associated with HAART (31), submucous fibrosis (32), brown hairy tongue (33), petechiae (34), oral erythema (35), ranula (36) and cheilitis glandularis (37). Some of these have only been described in residents in the developing world and may reflect social habits common to a geographic region (e.g. submucous fibrosis – secondary to betel nut use in India). The HAART-related oral lesions seem to be most commonly reported in individuals in the developed world.

Fungal infections

Superficial mycoses

Oral candidosis remains the most prevalent fungal infection in HIV infection (38). In the early stages of HIV infection, candidosis affects mainly the oral mucosa, the esophageal mucosa being affected in more advanced stages of HIV disease (38). Oral candidosis has been associated with a more frequent progression to AIDS, and it has been used as a clinical marker to define the severity of HIV infection (38, 39).

Candidal infection has been reported in adults with a prevalence varying from 1.5 to 56% (32, 38–42), with a higher prevalence in the developing world, although in one study of 60 Malawian pregnant women only one had oral candidosis (43). The widely varying prevalence of oral candidosis may be attributed to a variety of factors, such as the sociodemographic and clinical characteristics of the study group and the diagnostic methods employed (38).

Pseudomembraneous candidosis is the most common clinical presentation (ranging from 55.8 to 69.7% of all candidal infections), followed by erythematous candidosis (EC) (25.7–50%), angular cheilitis (13.7–27.1%) and hyperplastic candidosis (0–1.7%) (32, 38, 40–42). Early studies suggested that EC may indicate a less severely compromised immune system than the presence of pseudomembranous candidosis (PC), the latter occurring in more advanced stages (33, 38, 44). More recent longitudinal studies, however, suggests that EC and pseudomembraneous candidosis are of similar prognostic importance for the progression of HIV disease (45).

In children in the developed and developing world oral candidosis has been described as varying from 22.5 to 83.3% (5, 46–53). Pseudomembranous infection seems to be the most prevalent form in children (46–48, 50–52), followed by the erythematous type (47, 50–52), and angular cheilitis (48, 50–52). However, the erythematous disease has been occasionally reported to be more prevalent than PC (48).

The frequency of oral candidosis is associated with CD4+ T-lymphocyte count and HIV viral load. It has nevertheless been suggested that the CD4+ T-lymphocyte percentage is more accurate than the CD4+ T-lymphocyte count in predicting the likelihood of oral candidosis (38). However, in a group of Italian HIV-infected women, the prevalence of oral candidosis was found to be significantly associated with both the CD4+ cell count and HIV-1 viral load (54, 55), while in Spanish patients the only significant association with oral candidosis was a high HIV viral load (56). A study of Thai patients found that PC was particularly associated with a lymphocyte count of less than <200 cells/ml (39). The improvement of the immune system in patients receiving HAART may explain the reduction in the prevalence of this opportunistic infection in these groups of HIV infected individuals. Other factors that have been implicated in the predisposition of HIV patients to oral candidal infection are age under

35 years, injecting drug use, and smoking more than 20 cigarettes a day (38). In contrast, some recent studies have not revealed any specific feature that may predispose to oral candidosis (57).

Candida albicans is the predominant yeast colonizing the oral cavity of both healthy subjects and HIV-infected individuals in the developed as well as the developing world (38, 58), this yeast being isolated from 10 to 96% of HIV-infected subjects and 10–68% of healthy persons (58–62). Other *Candida* species, such as *C. glabrata*, *C. krusei* and *C. tropicalis* are isolated more commonly from HIV-infected persons (up to 30.7% of all yeasts) than immunocompetent individuals (15.9%) (59, 61, 62). This trend of increased oral carriage of non-*albicans* species has been attributed to the widespread use of fluconazole (63, 64). There has been considerable interest in the isolation of *C. dubliniensis* from the mouth of patients with HIV disease (60, 65–74). This species does occur in adults (60, 65–72) and children (60, 65, 70, 73) with HIV disease, but is not ubiquitous in HIV infection (59) nor is *C. dublininesis* only found in people with HIV disease (60, 75).

Multiple strains, and genetically different isolates of *C. albicans* may be harboured in the mouth of HIV-infected individuals (76, 77). Isolates of *C. albicans* from HIV-positive patients may produce significantly higher amounts of secreted aspartyl proteinase (SAP) than non-HIV infected individuals (78), although high SAP production *C. albicans* may not relate to any specific candidal genotype (76).

A 12-month prospective study of 16 HIV-infected ethnic Chinese individuals with and without symptoms of oropharyngeal candidosis evaluated the phenotype distribution among oral *C. albicans* isolates during disease progression. The major biotypes in the two groups were similar and were in decreasing order of prevalence J1R, J1S, J6S, J6R, J2S, K1S, J10R, K1R and K6R; 48 different biotypes were observed in the two groups, with some uniquely represented in each group, leading to a significant association between the prevalence of the biotypes J1S and J2S and clinical candidal infection (79). In another prospective study the majority (75%) of patients with at least one episode of oropharyngeal candidosis maintained the original *C. albicans* genotype (80).

Reports of oral candidal strain resistance to fluconazole began to be published in 1991 – following the widespread use of fluconazole as treatment and prophylaxis of fungal infection (81). Fluconazole resistance can be accompanied by resistance to other azoles, although there may be continued sensitivity to non-azole antifungals (82). Antifungal drug resistance seems to show geographical variability. Resistant strains are less common in Thailand and Africa than other countries (61). Indeed, antifungal resistance seems to be uncommon in Africa, where susceptibility of oral *Candida* species may be 100% to ketoconazole, 95% to amphotericin B and up to 80% to fluconazole. Susceptibility to nystatin has been found to vary widely from 0 to 100% (24, 83).

Antifungal susceptibility seems also to vary according to the candidal strain. In a study of South African HIV-infected subjects 8.5% of *C. albicans* strains were resistant to amphotericin B, 2.3% were resistant to 5-FM and 0.4% resistant to itraconazole, and no strains were resistant to fluconazole. In this same study 11.1% of *C. glabrata* isolates and 21% of *C. krusei* isolates were itraconazole resistant, while *C. parapsilosis* and *C. tropicalis* were both susceptible to itraconazole. *C. glabrata*, *C. parapsilosis* and *C. tropicalis* were not resistant to fluconazole (58). *Saccharomyces cerevisiae* was susceptible to amphotericin B, 5-flucytosine and fluconazole, but 22.2% of isolates were resistant to itraconazole and, of note, all *Rhodotorula* isolates were resistant to both itraconazole and fluconazole (58). Exposure of *C. dubliniensis* isolates to fluconazole *in vitro* not only causes resistance, but also the resistant isolates have increased adherence to epithelial cells and proteinase secretion (84). There clearly is however considerable variation in resistance to antifungals, at least *in vivo*, for example in a longitudinal study only a minority of *C. dubliniensis* strains exhibited fluconazole resistance (68), and other studies have not found *C. dubliniensis* to be resistant to fluconazole (71, 73). The mechanisms of antifungal resistance are reviewed in detail elsewhere (85, 86).

Systemic mycoses

There remain scant reports of systemic mycotic infections affecting the mouths of patients with HIV disease. The majority of the reported patients have been resident in, or travelled to, regions where systemic mycoses are endemic.

The incidence of histoplasmosis in HIV-infected persons varies from 0.5 to 2.7% in non-endemic, and up to 27% in endemic areas (87, 88) (e.g. Africa and Brazil). However, there remain few reports of oral lesions alone or secondary to disseminated histoplasmosis infection in persons resident in Africa (24) or Brazil (89). Furthermore, the occurrence of histoplasmosis may be decreasing due to the introduction of HAART (90). HIV-related orofacial aspergillosis may manifest as sinusitis but although nasosinusal aspergillosis may be common in Africa, there is only one published report of this in an African patient, although such disease has been reported in patients in the developed world (24).

Blastomycosis is usually a late and fatal complication of HIV infection, and tends to arise in patients from the Americas, but it is rare in Africans (24), and can present as chronic ulcers affecting the oral mucosae or the lip (91).

Mucormycosis (*Zygomycosis*) of the mouth has been reported in HIV-infected individuals from the USA (92, 93) and Europe (94) but has not been reported in Africa (24).

Oral infection by *Cryptococcus neoformans* has been reported in both the developing and developed world (24), manifesting as mucosal and gingival ulceration but its prevalence has declined since the advent of HAART therapy (95).

Paraccocidioidomycosis, caused by *Paracoccidoides brasiliensis*, generally arises in residents of South Amer-

ica, particularly parts of Brazil (96, 97). Oral features of paraccocidioidiomycosis can arise in the presence or absence of HIV infection, and typically give rise to multiple areas of 'moriform' stomatitis and alveolar bone destruction with tooth loss (98), although unusual presentations have also been reported (99).

Viral infections

Herpes simplex 1 (HSV-1)

Although Herpes Simplex virus (HSV) infection has been reported to occur in 1.7–24% of HIV-infected children (27), recent studies from the developing world suggest that such infection is actually very uncommon in both adults, and children in HIV disease (100, 101). The lesions caused by herpes simplex generally comprise both chronic and recurrent ulcerative disease, may progress rapidly to extensive mucocutaneous involvement (53) and/or give rise to atypical presentations (e.g. persistent facial ulceration).

HSV infection is not considered to be a useful indicator of HIV-related immunosuppression or viral burden (102), possibly reflecting the difficulty of being able to delineate infection that would have arisen even in the absence of HIV disease. Resistance by HSV to aciclovir therapy can arise in HIV disease; although cidofovir proved to be clinically effective in a 4-year-old boy with HSV-1 related persistent facial ulceration (103). Alternating aciclovir and cidofovir regimens may be a rational approach for severe HSV infection in immunocompromised hosts, prolonging the effectiveness of both agents by delaying the development of an isolate that is resistant to both therapies (103).

Varicella (Herpes) Zoster virus (VZV)

It has been suggested that herpes zoster infection be considered an indicator of severe HIV-1 infection, but this seems most unlikely, as the majority of patients with orofacial shingles do not have HIV infection. There is still disagreement as to whether the risk of VZV infection rises as the CD4+ cell count decreases (104, 105). However while the frequency of clinically detectable VZV infection may be similar in both HIV-infected and non-HIV infected persons in Africa (104), involvement of the trigeminal nerve may be more common (106) or unique to HIV-infected patients, at least in this geographic region (104).

Of note, cutaneous herpes zoster can be a feature of immune restoration in children and adults (107) and trigeminal herpes zoster infection may occur in 17% of patients with reactivation of mucocutaneous VZV infections (108).

Epstein Barr virus (EBV)

Oral hairy leukoplakia (OHL)

Oral hairy leukoplakia (OHL) is an EBV-associated disease that typically occurs on the lateral border of the tongue of HIV-infected individuals as a consequence of reactivation of the virus (109). The prevalence of OHL in recent studies of HIV-infected adults varies from 0.42 to 38%. In both the developed and developing countries OHL seems to be more common in males than females (39, 41, 54, 61, 110–112), however a recent study observed the peak occurrence of OHL to be at 40–49 years in males, and 70 years in females (112). Alcohol has been shown to be a negative factor for the development of OHL (57, 113), this perhaps reflecting the knowledge that expression of the epithelium EBV receptor depends upon the extent of mucosal differentiation (114).

The increased prevalence of OHL in some but not all (115) groups of HIV-infected MSM, might relate to a higher exposure to EBV (116) but there seems to be no association between number of insertive-oral-sex male partners and incidence of OHL, suggesting that receptive oral sex may not be an effective way of becoming infected or re-infected with EBV. Furthermore, exposure to multiple strains of EBV may not increase the risk of developing OHL. Instead, rather than always arising from recently acquired EBV, OHL may be due to infection or re-infection of the oral epithelium by EBV from an endogenous source (e.g. from EBV-carrying B lymphocytes in the oropharynx) (117).

The occurrence of OHL is associated with a low CD4+ count and high HIV viral load (55, 109, 118–120), but there is conflicting data. Kerdpon et al. (39) observed that OHL was present in individuals in a southern Thailand population who had CD4+ count of more than 500 cells/mm^3, and in a group from northern Thailand there was weak evidence of an association with decreased CD4+ count (39).

Within OHL there is abundant productive EBV replication in oral epithelial cells (121). The current expression model states that EBV may persistently infect oral mucosa without productively replicating; however, recent studies indicate that this process is likely to be more complex *in vivo* (121). In particular, normal oral epithelium supports persistent EBV infection in individuals infected with HIV and productive EBV replication is necessary but not sufficient for the pathogenesis of OLP (122). Oral hairy leukoplakia is characterized by remarkable EBV genetic heterogeneity, and co-infection of OHL with multiple EBV genotypes accelerates the rate of EBV molecular evolution (121).

The intensity of viral replication is proportional to the degree of keratinocyte differentiation, and therefore massive amounts of EBV may be detected in the upper layer of the affected epithelium. Interestingly, the epithelial cells supporting such replicative activity remain intact, whereas typically in permissive herpesvirus infections, abundant virus production results in cell lysis (123).

Attendant to EBV replication is the expression in the keratinocytes of EBV proteins and transcripts associated with lytic replication in B lymphocytes, e.g. those from the BCRF1, BDLF3 and BZLF1 open reading frames (123). The BCRF1 is also known as viral IL-10, and is homologous to human IL-10, a potent anti-inflammatory cytokine. Its high-level production may account for the lack of inflammatory response in OHL. In addition to the expression of replicative proteins, the EBV-carrying keratinocytes also express viral proteins

characteristic of latent infection. It is likely that those both replicative and latent proteins contribute to OHL development, inducing many of the histological features of the disease, such as acanthosis and hyperproliferation (123). The question of whether OHL arises from activation from latency of EBV resident in the basal layer of from superinfection of EBV extraneous to the tongue remains unsolved (123).

As OHL is asymptomatic and has no malignant potential it rarely requires treatment. Nevertheless, aciclovir, and more recently, valaciclovir have been used for the treatment of OHL, but aciclovir resistance can cause lack of clinical resolution of OHL (121). As discussed previously most, but not all, relevant studies have observed that the frequency of OHL falls with HAART, thus further adding to the rationale that there is little, if any, need for active intervention for OHL.

Non-Hodgkin's lymphomas (NHL)

Non-Hodgkin's lymphomas is recognized as an AIDS-defining condition in HIV-infected individuals and is included among the oral lesions associated with HIV infection [EC-Clearinghouse Classification (25)]. Indeed, in population-based studies in the USA, Italy and Australia, the relative risk of NHL in people with AIDS ranged from 15 for low-grade and T-cell NHL to 400 for high-grade NHL (124). Moreover, patients presenting with diffuse infiltrative lymphocytosis syndrome (DILS) have a 44-fold increased risk of developing lymphoma, most often of the MALT type (125).

The prevalence of HIV-related NHL is increasing in the developed world (124, 126–128). Oral NHL gives rise to intra-oral soft tissue masses with or without ulceration and tissue necrosis usually involving the gingival, palatal and alveolar mucosa (129). Although 50% of all HIV-related lymphomas seem to be associated with EBV, oral plasmablastic lymphoma is possibly associated with dual viral infection by HHV-8 and EBV (130, 131).

Hodgkin's disease (HD)

Hodgkin's disease is the most common non-AIDS defining tumour among HIV-infected individuals (131). The majority of recent studies demonstrate an increased incidence of HD in HIV-infected individuals, with a relative risk of HD in HIV disease ranging from 2.5 to 8.5 (132–134). Epstein Barr virus may be of some aetiological significance in HD of HIV disease (135) hence why it may be appropriate to discuss it at this point in the review.

The histological diagnosis of HD is still based upon the presence of classical Reed-Sternberg (RS) cells in an appropriate cellular background. However, HIV-related HD exhibits pathological features different from those of HD in the general population, being characterized by a predominance of unfavourable histological subtypes (136). One of the most peculiar features of HD in the HIV population is the widespread extent of the disease at presentation, the high frequency of systemic 'B' symptoms, with frequent involvement of extranodal sites, these commonly being the bone marrow, liver and spleen (131). Optimal therapy for HD in the HIV-infected population has not been defined yet. A detailed review of possible treatment options can be found elsewhere (131).

Human Herpesvirus 8 (HHV-8) infection

Human Herpesvirus 8 (Kaposi's sarcoma herpesvirus) is a member of the gammaherpesvirus subfamily (30, 137–140), and the causative agent of AIDS-related, classic, endemic and iatrogenic Kaposi's sarcoma (109, 141). In addition HHV-8 is the causative agent of primary effusion lymphoma [also called body cavity-based lymphoma (BCBL)] (142), multicentric Castleman's disease (MCD) (143, 144), and possibly oral plasmablastic lymphoma (130). Detailed reviews of HHV-8 can be found elsewhere (140).

Serological studies have indicated that unlike other human herpesviruses, HHV-8 is not ubiquitous. The seroprevalence of HHV-8 is low in the USA and parts of Europe (ranging from 0 to 20%) (145) rising in Mediterranean countries to reach levels of greater than 50% in some geographic regions of Africa (137, 138). In North America and Europe primary infection with HHV-8 mainly occurs in adulthood, most notably among men having sex with men. In this group the virus is transmitted principally via sexual contact, the HHV-8 seroprevalence being associated with the number of sexual partners and sexual practices (137, 138, 140, 146). Transmission of HHV-8 via saliva has been documented (147). In African populations HHV-8 infection seem to occur largely before puberty through casual family and community contacts, oral secretions being a potential vehicle of non-sexual horizontal spread (vertical transmission of HHV-8 does not seem to be significant) (109, 137, 138, 140). A recent study conducted in Malawi, Africa, has also shown that, apparently, healthy people in regions where HHV-8 is hyperendemic can be infected by multiple strains of HHV-8 (148). However, it is still unclear if this reflects a simultaneous co-infection by several HHV-8 strains, reactivation of latent strains, or superinfection (148).

Kaposi's sarcoma remains the most common AIDS-associated malignancy (30, 32, 109, 139, 149). Oral lesions appear as red to purple macules, papules or nodules that may ulcerate and cause local destruction. The palate and gingiva are the most commonly affected intra-oral sites (30). The oral cavity is commonly involved with KS, being the first clinical sign of KS in 20% of cases and being found to occur concomitantly with skin and visceral involvement in up to 70% of patients (30, 109, 150).

The prevalence of oral Kaposi's sarcoma of the mouth varies from 0 to 12% in Africa, and from 0 to 38% in US and Europe (28, 151, 139). However, differences in the frequency of (both oral and non-oral) KS in HIV disease between the developed and developing world are likely to occur. In the developed world the incidence of HIV-related KS began to decline (152) before HAART became available but became more pronounced thereafter (149). In contrast, the prevalence of KS has risen alarmingly in Africa (149). For example

between 1988 and 1996, the incidence of KS in South Africa increased at least threefold (153) and in Zimbabwe affected 78% of a group of HIV infected subjects (151). Since the advent of AIDS, KS has become more frequent in both genders, the male to female ratio changing from 19:1 to 1.7:1, particularly in East Africa (154).

Recently, the high prevalence of oral KS was demonstrated by the observation that 18.6% of a group of HIV-infected patients in Zimbabwe and from 6 to 14% of another group of patients in the same region had oral KS.

The prognosis of patients with HIV-related KS is often related to factors other than the tumour burden itself. In 1989, the AIDS Clinical Trial Group (ACTG) devised the TIS staging system, based upon the extent of the tumour (T), the status of the immune system in terms of CD4+ cell count (I) and the presence of other systemic HIV-related illness (S) (150).

At present, there is no curative therapy for AIDS-related KS. Treatment is thus directed towards the elimination, or at least reduction of, cosmetically unacceptable lesions, reduction of painful or unsightly oedema or lymphoadenopathy, as well as the relief of symptoms caused by visceral involvement.

Local therapy may be effective for limited disease, but systemic therapy is required for disseminated KS (30). HAART is useful in the management of HIV-related KS, as it will reduce the HIV viral load and raise the CD4+ T-cell count, both of which contribute to the pathogenesis of KS (150, 155–158). In a recent study of 78 patients with AIDS-related KS, who had previously received specific therapy for KS it was shown that the median time to KS treatment failure before commencing HAART was 6 months, but this increased to 1.7 years following commencement of HAART. The absence of PIs from similar protocols still revealed an improvement in patient survival. Of interest, increased HIV viral load (HIV RNA levels >5000 copies/cm^3) was associated with an increased risk of KS, while sudden fall in CD4+ cell count was not (159). Recent reports have described a reduced incidence (160) or regression (155, 161) of KS in HIV-infected individuals treated with HAART that includes at least one PI. Both *in vivo* and *in vitro* studies have demonstrated that PIs have a direct anti-angiogenic, anti-KS and anti-tumour activity at concentrations likely to be present in the blood of treated individuals (162–164). HAART causes a fall in HHV-8 levels in blood (140) presumably because of a reduction in HIV proliferation, HIV/HHV-8-mediated oncogenesis and HIV-induced immunosuppression.

Older approaches of managing oral KS have included local radiation (150, 165, 166), intralesional injections of vinblastine (167) and 3% sodium tetradecyl sulphate (165), laser therapy (168, 169), surgical excision (170), cytotoxic therapy with vinca alkaloids (vinblastine, vincristine and vinorelbine), bleomycin, anthracyclines, paclitaxel (171–174) and liposomal anthracyclines (175, 176). However, only five agents are currently approved by the FDA for the treatment of KS: alitretinoin gel for topical therapy and liposomal daunorubicin and oloxorubucin, paclitaxel and interferon-α for systemic therapy (177).

The strong angiogenic component of KS makes it particularly suitable for treatment with the emerging class of drugs that act as antiangiogenic agents such as thalidomide and newer agents such as matrix metalloproteinases and IM-862 (149, 150, 178–182). Based on the apoptotic and antiproliferative activity of iron chelation on KS cells, it is also suggested that iron withdrawal strategies may be effective (183). Several retinoid compounds have also been tested in clinical trials for KS, with a response rate of 23–37% (150).

Direct antiviral approaches targeting HHV-8 have been proposed. *In vitro* studies have shown that HHV-8 is very sensitive to cidofovir, moderately sensitive to ganciclovir and foscarnet, but only weakly sensitive to aciclovir (184, 185). However, the efficacy of cidofovir *in vivo* has yet to be proven. A prospective randomized trial, aimed at determining optimal maintenance therapy of cidofovir for CMV retinitis indicated that this might have a prophylactic effect upon the development of AIDS-related KS (186). Interferon α (IFN-α) may inhibit infection or reactivation by HHV-8. Single agent therapy with INF-α, is associated with significant toxicity, but when used in combination with antiretroviral agents it may have some application for disseminated, but non-rapidly progressive, KS (149, 150).

Human papilloma virus (HPV)

Until the advent of HAART, HPV infection was uncommon in the mouth of HIV-infected individuals. However, HPV infection has taken on much greater significance in recent years, as the frequency of HPV infection has increased in examined groups following the introduction of HAART, and especially as this virus may be of aetiological significance in the development of oral squamous cell carcinoma (OSCC) [reviewed in detail elsewhere (187)].

Estimates of oral HPV prevalence are highly variable, due to methodological or population differences, prevalence estimates of 9.2–18.6% of HPV in exfoliated oral cells have been reported in studies with disparate specimen collection, methods, study populations and sensitivities of polymerase chain reaction (PCR) (188–190). A recent study demonstrated that the collection method (tonsil brush biopsy vs. oral rinse) could have a significant influence on the HPV detection rate (respectively, 3.1 vs. 12.2%). HIV-infected individuals may be more likely to carry HPV in the mouth than immunocompetent individuals (25.3 vs. 7.6%, respectively), to be infected by more than 1 HPV genotype (5.8 vs. 1.5%) and to carry a high-risk genotype (e.g. HPV-16) (191).

Oral warts are uncommon in immunocompetent individuals (0.5%) (192) but within groups of HPV-infected individuals, oral mucosal abnormalities (e.g. papillomas) are more likely to arise in those with, rather than without, HIV disease (191).

Oral HPV infection (carriage and/or clinical presentation) seems to be associated with male gender, HSV-2 seropositivity and older age in HIV-seronegative individuals (191). In HIV-infected populations the risk

factors for oral HPV infection are still male sex (191, 193) and HSV-2 serostatus but the strongest association is with oro-genital contact. Individuals who reported performing oral sex (i.e. oro-genital contact) with more than one partner during the preceding 12-month period had an estimated 13-fold increase in the odds of having an oral HPV infection (191). An association between HPV oral infection and Hepatitis B seropositivity has also been described (193) again perhaps suggesting a sexual basis for the risk of HPV infection.

The presence of HPV-related oral lesions in HIV disease is sometimes, but not always, related to a decrease in HIV viral load (193) and decreased CD4+ cell count (191, 193). The mechanism by which a reduction in HIV viral load may lead to an increased risk of oral warts is not clear, although the clinical manifestation of HPV infection may represent a form of immune reconstitution syndrome (193, 194). It is possible that the reconstitution of the immune system may be functionally incomplete and its effectiveness might therefore vary with regard to different potentially pathogenic microorganisms. In particular newly generated CD4+ cells are suboptimally immunocompetent, hence permitting replication of HPV and development of oral lesions (195). Indeed, most examined persons who develop HPV related lesions mount a cell-mediated immune response (regulated by CD4 T-cell dependant mechanisms) which, when effective, causes subsequent regression of the lesion (196). Nevertheless failed immunocompetence cannot explain why HPV infection becomes so rapid following HAART, as unlike tuberculosis (and HHV-8 associated KS after HAART) the lesions of HPV infection are not typified by a profound inflammatory response. In contrast to the mouth, HAART-induced reduction in HIV load is associated with a reduced risk of HPV-related cervical cytological abnormalities in HIV-infected women (197). This difference in the two sites may be related to differences in the epithelial cell phenotype between oropharynx and cervix, but has yet to be formally investigated (198).

Oral warts occurring in immunodeficient patients often have an uncharacteristic morphology and may be recalcitrant to therapy (196, 199). In addition, there is little data to suggest that contemporary medical methods of treating HPV infection are consistently effective in the mouth (e.g. interferon-related processes). Of concern, HPV-related lesions in HIV disease may be associated with moderate or severe oral epithelial dysplasia, and similar to OSCC, dysplastic oral warts in HIV disease may have an over expression of Ki-67 (200–202). Nevertheless, there have been a small number of reports of OSCC in HIV disease (202–208), although HPV type 16 (and 51) has been demonstrated within severe oral epithelial dysplasia (209).

The exact relationship between oral HPV infection and HIV disease remains unclear. Of concern if HPV does have an aetiological association with OSCC, it might be expected that patients who receive HAART, have relevant risk factors (e.g. tobacco and alcohol consumption) and are healthy despite HIV disease, may be at significant risk of developing oral epithelial dysplasia and/or squamous cell carcinoma. There may thus be a need to develop effective screening procedures to determine the likely risk of oral carriage of HPV (e.g. by molecular biology or serological methods) to ensure careful clinical follow up of patients at possible risk of potentially malignant or malignant disease of the oral mucosa.

There are a few detailed studies of the therapy of HPV infection in HIV disease. Cryosurgery has been used effectively for the treatment of HPV-related oral lesions in HIV-infected individuals (210). Laser (211), curettage, cautery and oral etretinate are other treatment options (212). Recent studies and reports suggest that may be topical cidofovir 1% may be useful for treating viral cutaneous lesions recalcitrant to traditional treatments (213), but as yet this has not been attempted with oral HPV lesions. Immunomodulatory therapy with imiquimod (Aldara) and alitretinoin gel may offer a new therapeutic approach to the treatment of mucocutaneous viral diseases (208, 214), but there is little data regarding efficacy in the mouth.

HIV-related salivary gland disease

HIV-associated salivary gland disease (HIV-SGD) is characterized by salivary gland swelling in one or both parotid glands with or without xerostomia (109).

Salivary gland enlargement

In some patients, salivary gland enlargement may be the first clinical manifestation of HIV infection (215). The salivary enlargement occurs in approximately 3–10% of reported adult patients infected with HIV, with a higher frequency in children (215, 216). The swelling arises as a consequence of a variety of etiologies, including reactive/inflammatory conditions, infections and neoplasms (215). In particular, it frequently represents a manifestation of diffuse infiltrative CD8+ lymphocytosis syndrome (DILS) (217, 218) or a lymphoepitelial cyst (219). According to some, however, cystic benign lymphoepithelial lesions (BLLs) account for the majority of cases, affecting the parotid rather than the submandibular gland (215, 220). This lesion is also named benign parotid hypertrophy, and can give rise to significant facial deformity (221).

There is some controversy as to the histopathogenesis of the cysts in HIV salivary gland disease. Probably, they originate from glandular epithelium trapped in normally present intraparotid lymph nodes during embryologic development. Following HIV infection, reactive lymphoproliferation results and the embryologically included nodal epithelium may become activated and give rise to a lymphoepithelial cyst. Alternatively, ductal obstruction of the lymphoid proliferation may lead to a ductal dilatation that mimics a true cyst [reviewed by Mandel (216)].

Inflammatory-infectious conditions are the second most common group of salivary gland disorders in HIV disease, followed by neoplastic lesions (215).

McArthur et al. (222) suggested that HIV-associated labial salivary gland swelling may be common in HIV infected individuals, being present, when assessed histo-

pathologically, in 48% of the cases. The prevalence of some degree of salivary ductal epithelial atypia has been shown to be present in 96% of a group of HIV+ Cameroonian individuals (222). Of relevance, cheilitis glandularis has been observed in one HIV infected individual in Brazil (37). As reported previously, HIV-infected patients have a high incidence of non-Hodgkin's lymphoma, the majority of which are high-grade and some of which arise in the salivary glands. Low-grade lymphomas are uncommon in HIV-infected patients and may be difficult to distinguish from a reactive body process. Secondary malignant neoplasms (e.g. Kaposi's sarcoma) account for 10% of malignant salivary gland neoplasms and often involve the parotid gland (215).

The treatment of the salivary gland enlargement of HIV disease remains non-specific. While the frequency of HIV-SGD may increase with HAART, it has been occasionally found to resolve with HAART (220).

Superficial parotidectomy had been advocated to alleviate the parotid swellings associated with HIV, but may be of limited application in view of the possible adverse side effects. Aspiration into cystic lesions may be of some benefit but is transient, and injections of tetracycline and doxycycline are poorly effective due the presence of multiple cysts (220).

Benign parotid hypertrophy in HIV+ infected patients can be treated, with significant improvement in cosmetic control and long-term results, with external radiation therapy with 24 Gy in 1.5 Gy daily fractions. Previous experience with lower doses of irradiation (8–10 Gy) failed to maintain long-term results, with a poor response if the procedure needed to be repeated (221, 223). In addition, higher doses are contraindicated because of the associated morbidity (220).

Xerostomia

The prevalence of xerostomia and salivary gland hypofunction has been reported to be 2–30% in HIV-infected patients [reviewed elsewhere (224, 225)].

Reduced salivary flow may occur as a result of HIV infection, as a side effect of anti-HIV therapies, or in association with significant major salivary gland disease (225). Xerostomia has been reported to occur with HAART particularly with some of the NRTIs and PIs (226). The long-term use of other non-HIV related medications, such as many classes of antidepressants can also lead to oral dryness (225).

The mechanism of salivary gland dysfunction that occurs in the course of HIV disease progression, in the absence of salivary gland disease, is not well understood. Several factors have been suggested to be responsible, including infections of the salivary gland tissues with HIV, CMV or EBV (225), however the exact role of these viruses in the pathophysiology of the xerostomia is unclear; in addition the long term natural history of the disease is not known (109). The literature indicates that both EBV and CMV can be found in latent forms in ductal epithelial cells, but such viral DNA has been found in both healthy and other immunosuppressed patients (109).

Navazesh et al. (224) suggested that HIV-infected women are at risk for salivary gland hypofunction as a result of disease progression and the adverse effects of HAART upon salivary gland function. The mechanism by which HAART causes xerostomia is not completely understood, but such therapy, probably PIs must either have an antisecretory effect upon acinar cells or perhaps lipotrophic changes alter salivary gland structure and function (224).

A recent study reported that flow rates for unstimulated whole, unstimulated submandibular/sublingual, stimulated parotid and stimulated submandibular/sublingual saliva are decreased in the early stages of HIV infection (227). Salivary concentrations of lactoferrin, secretory IgA and chloride may be increased while lysozyme, total protein and potassium are reduced (228). The composition of saliva seems to vary according to the presence of HIV-related oral mucosal disease (229). Saliva of HIV-infected individuals with oral candidosis has significantly higher levels of IFN-γ than that seen in HIV infected individuals without oral mucosal disease and to have significantly higher levels of IL-2, IL-5 and INF-γ than saliva of healthy controls. HIV-infected individuals with OHL have significantly higher levels of both IL-1α and INF-γ compared with those without oral mucosal disease and higher levels of salivary INF-γ than healthy individuals (229). None of these changes have any diagnostic value for the investigation of HIV disease or any associated salivary gland disease. The treatment of xerostomia associated with HIV disease is reviewed elsewhere (230).

Gingival and periodontal disease

The gingival and periodontal diseases associated with HIV may be classified as linear gingival erythema, necrotizing ulcerative gingivitis (NUG) and periodontitis (NUP) and necrotizing stomatitis (231).

Recent reported prevalences of HIV-related gingival and periodontal disease (excluding opportunistic infections and malignancy) vary from 0 to 47% in adults, and from 0 to 20% in children. However, not all the studies specify the type of gingival and periodontal disease observed. When it is specified, linear gingival erythema has prevalence rates of 0–11.9% in adults with HIV infection, although a prevalence of 47% has been described in India. The NUG and NUP have been reported to affect 0–9% of HIV-infected subjects, although a prevalence of 27.7% was observed in Cambodia. Gingival disease seems to affect 4–20% of HIV-infected children, while NUG and NUP are less prevalent, varying from 2.2 to 5% (5, 32, 39–41, 43, 47–52, 54, 57, 151, 231).

Linear gingival erythema has been associated with a CD4+ count of less than 200 cells/mm^3 but not with high viral load, while NUP disease has been found to have no significant association with low CD4+ count or high viral load (151). 'Chronic' periodontal disease has been described as more common and/or more aggressive in HIV-infected patients. The occurrence of possibly specific periodontal disease has been observed in some, but not all, groups of HIV-infected patients (suggesting

perhaps that HIV infection alone does not predispose patients to pocketing, attachment loss or bleeding on probing) (232). Indeed, as with individuals without HIV oral hygiene and compliance have been shown to be key factors in the control of attachment loss in HIV-infected patients (233). Moreover, although aspects of HIV-induced immunosuppression has been advocated as the likely cause of HIV-related gingival and periodontal disease, it has also been demonstrated that HIV-infected patients often have relevant risk habits such as tobacco smoking and poor oral hygiene that can explain the disease (234).

A recent longitudinal study supports the notion that the level of pro-inflammatory cytokine INF-γ in gingival crevicular fluid may be associated with periodontal disease progression in HIV-infected patients (235). An increase in IL-1β, IL-6 and TNF-α in gingival crevicular fluid from periodontal pockets of HIV-infected individuals as compared with non-HIV-infected subjects, and in deep pockets as compared with shallow pockets among HIV-infected patients, suggests a possible role for these pro-cytokines in the development and propagation of HIV-related periodontitis (236). Mast cell matrix metalloproteinases were found significantly higher in marginal periodontitis of HIV-infected people, as compared with healthy gingivae of non-HIV-infected subjects. However, a similar expression of metalloproteinases was found also in healthy gingivae of HIV-infected subjects, hence the significance of this observation is uncertain (237).

The microbiology of HIV-related periodontal disease is generally similar to that expected in otherwise healthy individuals liable to periodontal disease. *Prevotella nigrescens* has been suggested to have a symbiotic relationship with other periodontal flora in HIV-infected patients (238). Microscopic examination of the microbial plaque overlying the necrotic gingival papillae of HIV-infected individuals with NUG, revealed a mixed microbial flora of various morphotype in the majority of specimens, containing mainly spirochetes, but also yeasts and herpes-like viruses (239). There may be a direct association between periodontitis in HIV-seropositive patients and co-infection of EBV and human herpesviruses 6, 7 and 8 (240, 241). In addition, viral infection with CMV, EBV and HSV has been found in 68% of malnourished children with NUG (242). While EBV-1 has been associated with destructive periodontal disease (243), EBV-2 have been found in the gingiva of HIV-infected individuals with HIV-associated periodontitis (240) highlighting a possible important role for herpes viruses in the development of HIV periodontal disease. Of note, mono- or co-infection with herpes viruses appears to be positively associated with elevated levels of periodontopathic bacteria such as *Actinobacillus actinomycetecomitans*, *Porphyromonas gingivalis*, *P. intermedia*, *Bacteroides forsythus*, *P. nigrescens* and *Treponema denticola* (243, 244). Currently, the role of viruses in the pathogenesis of advanced and aggressive periodontal disease is conjectural. However, immunosuppressive factors such as HIV disease could facilitate the selective overgrowth of specific pathogenic bacteria and induce host cells to release tissue destructive cytokines (245).

The periodontal attachment loss in HIV individuals, however, may have an immunogenetic basis, being associated with the haplotype HLA-A1, B8, DR3 (known as the 8.1 ancestral haplotype) which may cause the overproduction of TNF and IL-1, known mediators of periodontal attachment loss (246).

Dental disease in HIV infection

HIV-infected children may be more liable to dental caries, affecting both the deciduous and the permanent dentition, than healthy subjects. However, while the frequency of caries may be higher than in healthy controls, the dmft and DMFT of HIV-infected children is not always higher than that of similarly aged children in the same geographic area (5, 52, 247, 248), in some instances probably reflecting differences in fluoride levels in local water supplies (5). In addition the caries experience of HIV-infected children appears to be broadly similar to that of other chronic sick children of comparable age (247). It has been however speculated that HIV-infected children may display a different decay pattern to that of healthy children, this possibly being related to HIV-associated xerostomia (51).

A greater frequency of caries in HIV-infected children might be attributed to high carbohydrate and sugar intake required to provide sufficient calories in these children after failure to thrive (248), and to the ingestion of sucrose-based medications, particularly antibiotics and antifungals (249), but also antiretrovirals, such as zidovudine (248). Moreover, poor social status and low use of fluoride might also contribute to an increased risk of dental caries in children with HIV disease (249).

Both delayed and accelerated eruption of permanent teeth and over-retention of primary teeth (affecting 25% of patients) were observed in HIV-infected children in Romania (5). The accelerated eruption pattern may be related to concurrent or previous dental and periodontal disease (5). The exact cause of delayed eruption of teeth is unknown, although the poor general health status of some children, particularly when there is malnutrition, may be an important co-factor (5, 48).

Oral aspects of HIV therapy

Since the introduction of specific anti-HIV-therapies there have been striking changes in the frequency and character of the oral complications of HIV disease. Anti-retroviral drugs significantly lessen HIV viral load, increase CD4+ T-cell count and lessen the frequency and severity of opportunistic diseases (250). It would thus be expected that HAART will reduce most HIV related diseases (unless associated with immunological reconstitution) hence it is not surprising that the frequency of disorders such as oral candidosis and OHL lessen with HAART.

A 30% decrease in the frequency of HIV-related oral manifestations was described in Spanish patients receiving HAART (56). Patton et al. (120) reported significant decreases in the prevalence of HIV related oral disease with HAART (from 47.6 to 37.5%) in US patients. In

particular, in that population, HAART decreased the prevalence of OHL (25.8 down to 11.4%) and necrotizing periodontal disease (4.8 down to 1.7%), whilst increased salivary gland disease (1.8–5%) (120). Decreases in oral candidosis, OHL and oral Kaposi's sarcoma were also described in patients in San Francisco, USA following the introduction of HAART (200). Of note, however, the frequency of HIV-related salivary gland disease and oral warts among this group increased, the increase in warts being associated with antiretroviral therapy without PIs (ART), but more particularly, with HAART (sixfold increase) (200). Similarly, Schmidt-Westhausen et al. (195) described a decrease in the prevalence of oral lesions from 21.3 to 8.2% in patients in Germany, 6 months after introduction of HAART (195).

A study on 128 HIV patients in Texas, USA, found a declining rate of oropharyngeal candidosis and overall carriage of *C. albicans* in a year period following the introduction of anti-retroviral therapy (two NRTI or two NRTI plus a protease inhibitor) with stabilization or improvement in the immune status of patients. Of note there was also a reduction in carriage of fluconazole-resistant organisms within the patient group, including those with clinically detectable oropharyngeal candidosis (251). A reduction in fluconazole-resistant strains after HAART therapy was also reported by others (81).

A decrease (47–32.3%) in the frequency of HIV-associated oral lesions was observed over a 7-year period (from 1992 to 1998) in a group of UK patients (199). In particular, the frequency of OHL fell from 44.1 to 12.6%, and the incidence of PC, EC and Kaposi's sarcoma fell by 6.7, 7.8 and 1.3%, respectively (199). As in the USA the frequency of oral squamous papillomata increased from 0 to 4.6%, particularly in patients receiving ART after 1995 (199). EC, PC, OHL and ANUG are significantly higher in patients receiving no therapy – either ART of HAART than in any ART group investigated (252).

Protease inhibitor therapy associated with HAART has been demonstrated to decrease the frequency and recurrence of oral candidosis in HIV-infected patients (120, 253). Moreover, PIs exert an early inhibitory effect upon *C. albicans* virulence in the oral cavity of HIV-infected subjects. This effect is unrelated to the recovery of specific anti-candidal immunity, and is mediated by the inhibition of *C. albicans* SAPs. It is, thus, possible that the impact of HAART may not only lessen the likelihood of candidal infection but also reduce any virulence of opportunistic fungal strains (254). The particular efficacy of PIs in reducing oral lesions has also been suggested by others, stating that 42% of a group of patients receiving ART without PI – will have oral lesions, while only 30% of those receiving HAART will have lesions (252).

There may be a reduction in overall carriage of *C. albicans* and clinical disease after HAART, together with a decrease of fluconazole-resistant yeasts (81, 200, 251), but there are reports that oral candidal carriage may increase with anti-HIV therapies, possibly reflecting the xerostomic effect of some therapy (255). Comparative studies of Italian patients found a significant reduction in resistance to itraconazole and fluconazole (from 37% to the 7% of the *Candida* isolates in the study), in an examined group following HAART. Resistance to ketoconazole remained negligible both before and after HAART (81). It has been suggested that the decreased use of azoles (e.g. for prophylaxis), due to the decreased incidence of fungal infections associated with the use of HAART, accounts for the decrease in azole resistance of the oral *Candida* isolates (81).

HAART therapy seems to increase the incidence of HIV-related salivary gland disease (120, 256). A sharp increase from 5.4 to 14.3% was reported between the pre-ART and the ART era, this decreased again to 6.8% in patients receiving HAART (256). In contrast, however, a USA study reported an increase HIV-related salivary gland disease in patients receiving ART to 5% in patients receiving HAART (120). The changing frequency of oral warts in some groups of patients receiving ART has been discussed previously (120, 199, 200).

HIV-related periodontitis may be less frequent in patients receiving HAART, in particular acute NUG and NUP (120, 252, 256). The aforementioned HAART-related oral disease trends have principally been observed in adults. One group of USA children on HAART was reported to have a decrease in both oral candidosis and (unlike adults) parotid gland enlargement (257). However, HAART did not seem to cause significant change in the oral lesions of HIV-infected children resident in Thailand (48). Thus HAART would seem to have a beneficial effect upon the oral consequences of HIV disease. Indeed, the emergence of HIV-related oral disease may be indicative of failing therapy (199). Nevertheless, as mentioned previously, HAART is not available to the majority of HIV infected persons worldwide, particularly those residents in Africa. In addition, the treatment of opportunistic disease may be limited in such regions of the world as a consequence of the lack of availability of effective therapies (24).

A range of oral diseases can arise as a consequence of HAART. These adverse orofacial side effects are usually not very troublesome, although occasionally they can lead to non-adherence to therapy (258), for example the development of the HIV-associated lipodistrophy syndrome (12).

The oral side effects of some NRTIs are related to the bone marrow suppression, and they can manifest as neutropenic mouth ulcers. Erythema multiforme and toxic epidermal necrolysis have also been described, as well as lichenoid reactions, particularly related to zidovudine. This drug can also give rise to mucocutaneous hyperpigmentation by an, as yet, unknown mechanism (259).

Oral adverse effects seem to be less common with NNRTIs; however, erythema multiforme has been described in association with NNRTIs, particularly Nevirapine (259). Other notable PI-related oral side effects include taste abnormalities, affecting about 10–20% of patients, and oral and perioral paraesthesia.

Ritonavir in particular can give rise to circumoral paraesthesia in over 25% of patients (259, 260). To date there are no reported oral adverse effects of the fusion inhibitors (261).

Conclusion

The oral manifestations of HIV disease are now well described, although occasional new lesions have been described in residents of the developing world. Highly active anti-retroviral therapy generally reduces the frequency and/or severity of most oral lesions associated with HIV disease, other that perhaps warts, although can give rise to a variety of adverse orofacial features, notably facial lipodystrophy. The molecular epidemiology of the common oral infections is now well characterized, however the increased use of high dose of antimicrobials (e.g. antifungals or antivirals) has lead to the emergence of drug resistant oral microbes – that may be transmitted to other individuals. Of greater concern, however, is the realization that HIV disease continues to arise in many persons in the developing world who then do not receive HAART and thus remain liable to frequent and/or severe oral consequences of HIV disease.

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