Abstract This paper discusses the importance of oral lesions as indicators of infection with human immunodeficiency virus (HIV) and as predictors of progression of HIV disease to acquired immunodeficiency syndrome (AIDS). Oral manifestations are among the earliest and most important indicators of infection with HIV. Seven cardinal lesions, oral candidiasis, hairy leukoplakia, Kaposi sarcoma, linear gingival erythema, necrotizing ulcerative gingivitis, necrotizing ulcerative periodontitis and non-Hodgkin lymphoma, which are strongly associated with HIV infection, have been identified and internationally calibrated, and are seen in both developed and developing countries. They may provide a strong indication of HIV infection and be present in the majority of HIV-infected people. Antiretroviral therapy may affect the prevalence of HIV-related lesions. The presence of oral lesions can have a significant impact on health-related quality of life. Oral health is strongly associated with physical and mental health and there are significant increases in oral health needs in people with HIV infection, especially in children, and in adults particularly in relation to periodontal diseases. International collaboration is needed to ensure that oral aspects of HIV disease are taken into account in medical programmes and to integrate oral health care with the general care of the patient. It is important that all health care workers receive education and training on the relevance of oral health needs and the use of oral lesions as surrogate markers in HIV infection.

Keywords HIV infections/diagnosis; Acquired immunodeficiency syndrome/diagnosis; Oral manifestations; Antiretroviral therapy, Highly active/ adverse effects; Dental care; Child; Candidiasis/epidemiology/therapy; Oral; Leukoplakia, Hairy/epidemiology/therapy; Sarcoma, Kaposi/epidemiology/therapy; Gingivitis, Necrotizing ulcerative/epidemiology/therapy; Gingivitis/epidemiology/therapy; Lymphoma, Non-Hodgkin/epidemiology/therapy (source: MeSH, NLM).

Mots clés Infection à VIH/diagnostic; SIDA/diagnostic; Manifestation buccale; Thérapie antirétrovirale hautement active/effets indésirables; Soins dentaires; Enfant; Candidose buccale/épidémiologie/thérapeutique; Leucoplasie chevelue/épidémiologie/thérapeutique; Leucoplasie/épidémiologie/thérapeutique; Sarcome de Kaposi/épidémiologie/thérapeutique; Gingivite ulcéro-nécrotique/épidémiologie/thérapeutique; Gingivite/épidémiologie/thérapeutique; Parodontite/épidémiologie/thérapeutique; Lymphome non hodgkinien/épidémiologie/thérapeutique (source: MeSH, INSERM).

Palabras clave Infecciones por VIH/diagnóstico; Síndrome de inmunodeficiencia adquirida/diagnóstico; Manifestaciones bucales; Terapia antirretroviral altamente activa/efectos adversos/terapia; Atención odontológica; Niño; Candidiasis bucal/epidemiología/terapia; Leucoplasia vellosa/epidemiología/terapia; Sarcoma de Kaposi/epidemiología/terapia; Gingivitis ulcerosa necrotizante/epidemiología/terapia; Gingivitis/epidemiología/terapia; Períodontitis/epidemiología/terapia; Linfoma no Hodgkin/epidemiología/terapia (fuente: DeCS, BIREME).

The importance of oral lesions in HIV infection

Oral lesions can not only indicate infection with human immunodeficiency virus (HIV), they are also among the early clinical features of the infection and can predict progression of HIV disease to acquired immunodeficiency syndrome (AIDS). They can therefore be used as entry or end-points in therapy and vaccine trials and can be determinants of opportunistic infection and anti-HIV therapy and be used in staging and classification systems (Box 1). Oral manifestations are the earliest and most important indicators of HIV infection. Seven cardinal lesions: oral candidiasis, hairy leukoplakia, Kaposi sarcoma, linear gingival erythema, necrotizing ulcerative gingivitis, necrotizing ulcerative periodontitis and non-Hodgkin lymphoma are strongly associated with HIV infection and have been identified internationally. These lesions may be present in up to 50% of people with HIV infection and in up to 80% of those with a
diagnosis of AIDS (4). These oral lesions are usually clearly visible and can be diagnosed reliably from the clinical features alone (2). The lesions parallel the decline in numbers of CD4+ cells and an increase in viral load, and are independent indicators of disease progression (3). In cases where a person’s HIV status is unknown, the lesions provide a strong indication of the presence of HIV infection (4). For this reason the presence and development of oral lesions are used as entry criteria and end-points for prophylaxis and therapy (3, 5), which explains the weight given to these lesions in HIV prevention and intervention programmes.

Hairy leukoplakia and pseudomembranous candidiasis are the most common lesions seen in HIV infection and are used in all current classifications of HIV disease. The presence of either of these oral lesions indicates progression to AIDS (2). Other oral lesions strongly associated with HIV infection include erythematous candidiasis, linear gingival erythema, Kaposi sarcoma, necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis (6). This emphasizes the importance of a thorough oral examination at every stage in the diagnosis and management of all HIV-positive patients, as well as those thought to be infected or at risk (3).

HIV infection in children

An important question is whether the epidemiology of HIV-associated oral lesions in children differs from that in adults and whether it differs in children from different continents. Orofacial lesions commonly associated with HIV infection in children in Europe and North America include oral candidiasis, herpes simplex infection, linear gingival erythema, parotid enlargement and recurrent oral ulceration. In contrast, oral lesions strongly associated with HIV infection in adults, but less common in children, include Kaposi sarcoma, non-Hodgkin lymphoma and oral hairy leukoplakia (3). In Europe and North America, oral candidiasis occurs in 67% of children and is the most frequently seen oral health condition among paediatric HIV patients. The next most common oral manifestations are parotid enlargement, periodontal and gingival disease, and herpes simplex (7, 8).

In children in the developing world, the prevalence of these lesions may vary from country to country. In Mexican children oral candidiasis is the most frequently detected HIV-related oral lesion, followed by periodontal disease and herpes simplex infection (9). In Thailand almost 50% of children with HIV infection have one or more HIV-related oral lesions, of which erythematous candidiasis is the most commonly identified (10). In a South African study the figure was higher, with 63% of paediatric outpatients having orofacial lesions associated with HIV disease. Pseudomembranous candidiasis was the most commonly identified lesion; 9% of the children in the sample had oral ulceration and 1% oral hairy leukoplakia. In the same study almost 50% of children in non-hospital institutions had unilateral parotid enlargement (11). The prevalence of oral Kaposi sarcoma and ranula is increasing in HIV-infected children in Zimbabwe (12). Several studies have reported an increase in the number of HIV-infected children with cancrum oris; cases of which have been reported from Lesotho, South Africa and Zimbabwe (11, 13, 14).

The recent world workshop on HIV and oral lesions (15) concluded that oral candidiasis is the most common lesion in children, but there is a lack of data from resource-poor countries. Noma, and possibly other oral lesions, are seen in resource-poor countries, but at present these may be underreported. Oral candidiasis is strongly associated with the progression of HIV disease (i.e. it has prognostic significance). Little is known of the prognostic implications of oral lesions in short- and long-term survival in resource-poor countries. A high prevalence of concomitant dental diseases, especially caries and periodontal disease has been reported in HIV-positive children. There is a need to update and revise the classification criteria for diagnosis of oral manifestations in children with HIV infection to include data from Africa, Asia and India.

Effect of highly-active antiretroviral therapy on oral lesions

With the advent of highly active antiretroviral therapy (HAART), the prevalence of oral candidiasis, oral hairy leukoplakia and HIV-associated periodontal disease have decreased in adults (16–18). The prevalence of Kaposi sarcoma, one of the oral manifestations strongly associated with HIV has not changed (16, 19). There has been an increase in benign human papilloma virus (HPV)-associated oral lesions including papillomas, condylomas and focal epithelial hyperplasia (16, 17, 20) and HIV-related salivary gland disease (16). No change has been observed in the occurrence of HIV-related oral lesions in children receiving HAART (21, 22).

Thus the question arises of how effectively HIV treatment controls oral disease. Overall it would seem that antiretroviral treatment for HIV is very effective in reducing the occurrence of oral candidiasis, presumably in part by the inhibition of candida proteases. There is little evidence of changes in prevalence of hairy leukoplakia, but increasing evidence of an increase in prevalence of oral warts in patients being treated with protease inhibitors (19).

Influence of oral health on general health and quality of life

The presence of oral lesions has a significant impact on health-related quality of life, because oral health is associated with physical and mental health (23). HIV-associated orofacial lesions (and oral diseases secondary to antiretroviral therapy) alter facial appearance, impair speech and make swallowing difficult, which may lead to significant weight loss but, more significantly, may give rise to pain.

In the developing world oral candidiasis is a significant cause of morbidity in patients with HIV disease. Dysphagia in malnourished subjects infected with HIV may result in rapid clinical deterioration. Patients with oral candidiasis, angular cheilitis and oral hairy leukoplakia have a higher decayed, missing and filled teeth index (DMFT), dry mouth and taste problems, and lower oral health-related quality of life. Furthermore,
active dental decay, gingivitis and oral pain have an impact on oral health (24). Poor oral health and HIV-associated oral lesions should be considered debilitating (25). The prevalence, severity and progression of periodontal diseases are all significantly increased in people with HIV infection (26).

**Oral lesions as indicators of HIV infection**

The main factor associated with the development of oral lesions, and especially oral candidiasis, is the CD4+ count (27). The onset of oral candidiasis and oral hairy leukoplakia is heralded by a sustained reduction in the CD4+ blood cell count associated with a sharp increase in viral load (19). Disease progression is characterized by an increased prevalence of oral candidiasis, oral hairy leukoplakia, ulcerative periodontal disease and xerostomia (2). Any reduction in viral load in patients taking HAART is associated with a reduction in the prevalence of oral lesions (28). Cross-sectional studies have associated low CD4+ lymphocyte counts with the presence of oral Kaposi sarcoma (29), non-Hodgkin lymphoma (30) and necrotizing ulcerative periodontitis (29). An oral health care professional diagnosing these lesions in a patient known to be infected with HIV should be alert to the possibility of disease progression (24).

In resource-poor countries the prevalence of oral lesions varies from region to region, but can be used to detect HIV infection. In Mexico oral candidiasis is a predictor of CD4+ counts, changes in CD4+ counts, and the occurrence of AIDS-defining disease. Oral hairy leukoplakia has been found to be predictive of CD4+ counts but not of a change in CD4+ count. The number of episodes of oral candidiasis was the most significant predictor for change in CD4+ count. The presence of concurrent oral diseases, mainly oral candidiasis, also predicted disease progression (19). The repeated use of antifungal drugs as a marker of recurrent candidiasis is an important predictor of progression of HIV disease. The severity of oral hairy leukoplakia does not appear to predict disease progression. The onset of oral candidiasis and oral hairy leukoplakia is heralded by a reduction of CD4+, with an associated sharp increase of viral load (27). The interaction between CD4+ counts and viral load prior to the development of oral candidiasis and oral hairy leukoplakia emphasizes the potential use of oral lesions as early clinical markers of HIV disease progression (19).

**Oral sentinel lesions**

In a study in the United Republic of Tanzania oral mucosal lesions were found to indicate underlying immunosuppression in 85% of people who did not know their HIV status. In the Democratic Republic of the Congo, oral candidiasis was one of several clinical features related to HIV seroconversion; in Nigeria 27% of cases were associated with advanced HIV infection and this condition was highly predictive of low CD4+ counts in adults in India and Thailand. In Zambia erythematous candidiasis was the only lesion significantly associated with CD4+ lymphocyte counts of less than 200 cells/mm³ (24).

A longitudinal study from Mexico showed a rapid progression to AIDS in adults with oral hairy leukoplakia and oral candidiasis. In the United Republic of Tanzania oral candidiasis and oral hairy leukoplakia were strong predictors for HIV infection. In South Africa necrotizing ulcerative gingivitis and periodontitis in apparently healthy individuals was predictive of underlying HIV infection in 69.6% of patients. In Malawi and Uganda clinical signs strongly indicative of HIV infection included oral hairy leukoplakia, Kaposi sarcoma and oral candidiasis. However, oral hairy leukoplakia, which has been used to indicate disease progression in the developed world, is less prevalent in developing countries. In populations where the prevalence of HIV is low, oral mucosal lesions alone are poor predictors of HIV infection. The predictive values increase if oral lesions are used together with a social history to identify risk factors for infection (24, 31).

Most studies reporting the prognostic value of oral lesions in children infected with HIV originate in developed countries. In a cohort study in California, USA, the presence of oropharyngeal candidiasis was significantly associated with failure to thrive, use of antiretroviral agents, lower CD4+ counts and development of AIDS (32). Oral candidiasis and cervical lymphadenopathy suggest disease progression, but are poor predictors of the serious consequences of AIDS or of mortality. Another North American study showed that an increase in the number of oral lesions in children known to be infected with HIV was associated with a decreased CD4+ count, but not with HIV viral load. Parotid enlargement has been recognized as a distinct feature of HIV infection in children since the disease was first described. Parotid enlargement is a predictor of positive prognosis and long-term survival in HIV-infected children. The prevalence of oral lesions in children receiving antiretroviral therapy is less than that in untreated controls; however a low CD4+ count is associated with a greater number of oral lesions (24).

There is a correlation between delayed tooth eruption and the progression of paediatric HIV to AIDS (33). Caries experience in HIV-infected children is reported to be considerably greater than that in the general paediatric population in Romania and the United States. Caries experience increases with a decreasing CD4+ count and moderate-to-severe immune suppression (24).

**Role of health care professionals in prevention of oral manifestations in developed and resource-poor countries**

A consensus meeting of experts of the American Dental Association held in Chicago, USA in 1992 stated that it was both safe and desirable to make regular dental care available to HIV patients (34). No modification of treatment is recommended except when patients have low CD4+ lymphocyte levels that predispose to oral lesions requiring specific treatment. If they have reduced platelet count below 60 000 cells per mm³ this may affect clotting time and patients with reduced neutrophil levels below 500 cells per mm³ may require antibiotic prophylaxis. Patients with late-stage AIDS may require a rolling treatment plan (i.e. frequent treatment evaluation) with regular reviews (34, 35).

An overall treatment strategy, based on the treatment of symptoms or the provision of antiretrovirals, should include the management of oral conditions associated with HIV infection. Enhanced care comprising bimonthly protective treatment and chlorhexidine mouth rinses to treat gingivitis improves oral health. This improvement is associated with an improvement in both physical and mental health, but has no detectable effect on AIDS-related complications, symptoms or mortality (24).
In poor communities where HAART is unavailable and laboratory tests infrequent, the dentist may not know how ill a person with HIV is. Treatment should be prioritized as follows: — firstly, relief of pain and treatment of infection; — secondly, restoration of function; — thirdly, act to prevent further disease; and — finally, consider aesthetics.

The consensus guidelines also advocated a preventive approach for the HIV patient (34). Clinicians are advised to optimize oral hygiene, establish regular review periods, screen for HIV-related oral lesions and treat them if necessary and to screen for xerostomia as a possible symptom of HIV or as a side-effect of HAART. Because the incidence of these oral-hygiene-related diseases in HIV patients is not significantly greater than in the population at large, HIV status alone would not be grounds to modify treatment. Access to HAART has meant that many HIV-positive patients present with a functional immune system and a viral load that is undetectable. Dental care for these patients requires no particular modification (34, 35).

Developing basic inexpensive oral and dental care protocols for underserved communities

A proposal for basic oral health care for underserved communities has been presented (34). The principle of the package is that it should be available for all, with the emphasis on prevention. It includes emergency care, which may involve urgent oral treatment, exposure to appropriate fluoride in the form of affordable fluoride toothpaste and appropriate treatment technology involving atraumatic restorative treatment. This package can be extended to cover regions with a high prevalence of HIV with the added proviso that basic training in the diagnosis and management of the common oral lesions of HIV/AIDS is provided. This protocol needs to be adapted to accommodate the prevailing disease pattern in a region, an oral health care infrastructure, positive community attitudes, perceptions and practices and finance (34, 36; Box 2). Treatment of severe necrotizing periodontitis and noma will require referral to a specialist.

The strategies for the prevention and control of common HIV-related orofacial disease are poorly documented in resource-poor countries where expensive pharmacotherapy is unavailable (24). Many oral lesions are associated with HIV/AIDS and several treatment protocols have been developed for each lesion. For oral candidiasis, which may occur in 50% of HIV-infected subjects and 90% of AIDS patients in the developed world, the antifungals clotrimazole, fluconazole and itraconazole are recommended for outpatient treatment (37). The use of nystatin suspension in HIV/AIDS patients, either children or adults is not recommended (35).

Antifungal medication is generally not widely available for the majority of people infected with HIV in Africa (24). Some less expensive and more readily available alternatives have been tested. The antifungal effect of gentian violet has been documented in clinical trials (38). An oral solution of this oil, which is a cheap alternative to antifungals, has been successfully used to treat fluconazole-resistant oropharyngeal candidiasis in patients with AIDS (41). Many of the traditional antifungal agents used in resource-poor settings warrant further investigation.

Important advances in the treatment of Kaposi sarcoma in Europe and North America have included the use of liposomal anthracyclines and paclitaxel (42, 43), but this treatment has been superseded by the use of HAART (44). However, the use of chemotherapeutic agents is not curative, is associated with cumulative toxicity including bone marrow suppression and is unavailable in the majority of resource-poor environments. Single-agent chemotherapy is intermittently available and may palliate Kaposi sarcoma in resource-poor settings (45). Thalidomide may also be a potentially efficacious and cheap palliative therapy for mucocutaneous paediatric Kaposi sarcoma in settings where resources are limited (46).

Role of the dental profession in the management of HIV-infected individuals

(see Box 3)

Although there are limited studies available to directly guide clinicians in Europe and North America on the risk of complications following dental procedures, dental management is easily accomplished in the outpatient setting (47). Regular dental care of HIV-infected individuals results in better oral health at a cost no greater than that of treating non-infected patients (48). In HIV-infected individuals intensified dental care can result in decreases in mean periodontal pocket depth.
gingival erythema index and caries rate, but it has no effect on systemic AIDS-related complications, symptoms or mortality (25). Periodontal attachment levels (i.e. the levels at which gingiva attaches to the teeth), in HIV-infected subjects can be maintained with supportive therapy, adequate oral hygiene and adherence (49). It is unlikely that such an intensive treatment regimen could be instigated, instituted or maintained in a resource-poor setting.

Future research priorities in oral health care in HIV infection

Future research priorities in oral health care in HIV infection were specifically discussed at the Fifth World Workshop on Oral Lesions and HIV disease held in Phuket, Thailand, in 2004 (50). The workshop concluded that it was clear that there is now a need to retarget research efforts to resource-poor countries, and especially to prioritize research efforts on children with HIV disease in resource-poor countries (see Box 4). The international community has done much to assess commonalities and variations in oral health needs across geographical and cultural boundaries (e.g. by the organization of regional meetings and the creation of regional research centres), but much more needs to be done. There is a need to centralize research efforts in resource-poor countries to support standardized multicentre longitudinal studies to explore the use of oral lesions as surrogate markers for the initiation of antiretroviral therapy and prophylaxis of opportunistic diseases. Alternative therapies for oral candidiasis and other opportunistic infections should be discussed and their efficacy assessed in randomized controlled trials. Further research to assess the impact of oral disease on quality of life, and on access to oral care is needed and it is important to integrate oral health research into other health care research programmes.

Competing interests: none declared.

Résumé

Lésions buccales liées aux infections par le virus de l’immunodéficience humaine

L’article analyse l’importance des lésions buccales en tant qu’indicateurs d’infection par le virus de l’immunodéficience humaine (VIH) et comme facteurs prédictifs de la progression de la maladie à VIH vers le syndrome d’immunodéficience acquise (SIDA). Les manifestations buccales font partie des indicateurs les plus précoces et les plus importants d’infection à VIH. On a identifié et calibré au niveau international sept lésions cardinales (candidose orale, leucoplasie orale chevelue, sarcome de Kaposi, érythème gingival linéaire, gingivite ulcéro-nécrosante, pérodontite ulcéro-nécrosante et lymphome non hodgkinien), présentant une forte association avec les infections à VIH. Ces lésions se rencontrent dans les pays développés, comme dans les pays en développement. Elles peuvent constituer une indication forte d’infection à VIH et s’observent chez la majorité des personnes infectées par ce virus. Le traitement antirétroviral peut influer sur la prévalence des lésions liées au VIH. La présence de lésions buccales peut avoir un impact important sur la qualité de vie liée à l’état de santé. La santé buccodentaire est fortement associée à la santé physique et mentale et on relève une augmentation importante des besoins en matière de soins bucco-dentaires chez les personnes contaminées par le VIH, en particulier les enfants, et dans le cas des adultes lorsqu’il s’agit notamment de parodontolyses. Une collaboration internationale s’impose pour garantir la prise en compte des aspects buccaux de la maladie à VIH dans les programmes médicaux et l’intégration des soins bucco-dentaires dans la série de soins généraux administrés au patient. Il est important que tout le personnel de santé reçoive une éducation et une formation concernant l’opportunité des soins bucco-dentaires et l’utilisation des lésions buccales comme marqueurs de remplacement pour détecter les infections à VIH.
Resumen

Lesiones bucodentales en la infección por el virus de la inmunodeficiencia humana

En este artículo se analiza la importancia de las lesiones bucodentales como indicadores de la infección por el virus de la inmunodeficiencia humana (VIH) y como factores predictivos de la progresión de la infección por VIH al síndrome de inmunodeficiencia adquirida (SIDA). Las manifestaciones bucodentales son uno de los indicadores más tempranos e importantes de la infección por el VIH.

Se han identificado y evaluado internacionalmente siete lesiones fundamentales -candidiasis oral, leucoplasia vellosa, sarcoma de Kaposi, eritema gingival lineal, gingivitis ulcerativa necrotizante, periodontitis ulcerativa necrotizante y linfoma no hodgkiniano- que aparecen estrechamente asociadas a la infección por VIH y se dan tanto en los países desarrollados como en los países en desarrollo. Esas lesiones son un importante indicio de infección por VIH, y afectan a la mayoría de los afectados por el virus. La terapia antirretroviral puede alterar la prevalencia de las lesiones relacionadas con el VIH. Las lesiones bucodentales pueden tener un impacto importante en la calidad de vida relacionada con la salud. La salud bucodental está claramente asociada a la salud física y mental, y las personas infectadas por el VIH tienen más necesidades de salud bucodental, especialmente los niños, y los adultos en lo que respecta a las periodontopatías. Se requiere colaboración internacional para garantizar que las manifestaciones orales de la infección por VIH se tengan en cuenta en los programas médicos, así como para integrar la atención de salud bucodental en la atención general del paciente. Es preciso formar a todos los agentes de salud para que comprendan la importancia de las necesidades de salud bucodental y sepan usar las lesiones orales como marcadores indirectos de la infección por VIH.

Referencias

Special Theme – Oral Health

Mouth lesions and HIV infection


