AIDS in Children—Epidemiology, Clinical Course, Oral Manifestations and Management

Meenu Mittal*

HIV/AIDS has gained enormous proportion globally. In 2007, there were an estimated 33 million people living with HIV and an estimated 270,000 HIV infected children younger than 15 years died because of AIDS, HIV/AIDS can manifest in different forms and in present day scenario, it is imperative that dentists know its clinical presentation and management. Oral manifestations are one of the earliest indicators of HIV infection and progression in children, as in adults, although the specific manifestations differ between adults and children. The aim of this paper is to briefly review, on the basis of literature, the AIDS epidemiology, transmission, clinical course, oral manifestations and their management in children.

Keywords: *HIV infection, AIDS, oral manifestations, management*
J Clin Pediatr Dent 34(2): 95–102, 2009

EPIDEMIOLOGY OF AIDS IN CHILDREN

AIDS was first recognized in US in the summer of 1981. In 1983, HIV was isolated from a patient with lymphadenopathy and by 1984 it was demonstrated clearly to be the causative agent of AIDS. By the end of 2007, it was estimated that there were 33 million people living with HIV, of which 2 million were children under 15 years of age. The number of children younger than 15 years living with HIV increased from 1.6 million in 2001 to 2.0 million in 2007 (Figure 1). Figure 2 shows that the number of people newly infected with HIV in 2007 were 2.7 million of which 370, 000 were children. New infections in children appear to have peaked in 2000-2002. This is believed to be due mainly to the stabilization of HIV prevalence among women overall, and to increasing coverage of the programs for preventing mother to child transmission of HIV.[1]

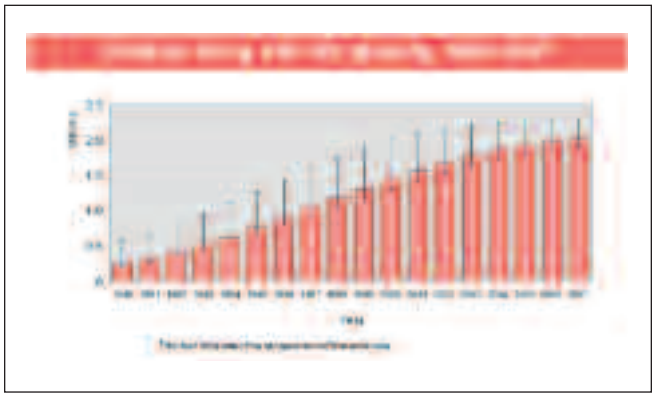

Figure 1. Children living with HIV globally 1990–2007 (Courtesy UN AIDS 2007 Report)

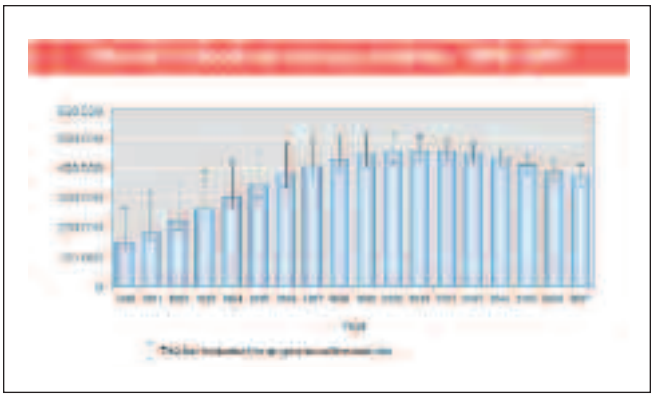

Figure 2. New HIV infections in children 1990–2007 (Courtesy UN AIDS 2007 Report)

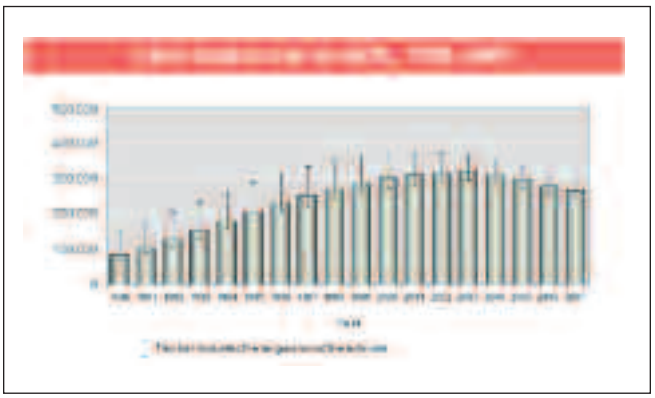

Figure 3. AIDS deaths in children (Courtesy UN AIDS 2007 Report)

Around 2 million people died due to AIDS in 2007, of which 270,000 were children. As seen in Figure 3 showing

* Meenu Mittal, BDS, MDS., Professor, Department of Pedodontics, SGT Dental College, Gurgaon, Haryana, India.

Send all correspondence to: Meenu Mittal, A - 4/ 16, Paschim Vihar, New Delhi - 110063, India.

Phone: +919811840018

E-mail: meenufeb20@hotmail.com

child deaths due to AIDS, the total number of AIDS deaths in children peaked around 2000 and has decreased since. This decline mainly reflects the drop in new infections in children as well as increased access to antiretroviral treatment. Of 7400 new infections a day in 2007, 1000 were children under 15 years of age.[1] Geographic location of pediatric AIDS cases around the world is shown in Table 1.

Table 1. Geographic location of Pediatric cases around the world (Courtesy UN AIDS 2007 Report)

Country	Children (0-14) 2007	Children (0-14) 2001
Sub Saharan Africa	1,800,000	1,400,000
East Asia	7,800	3,500
Oceania	1,100	< 500
South & South East Asia	140,000	98,000
Eastern Europe & Central Asia	12,000	2,800
Western & Central Europe	1,300	2,100
North Africa & Middle East	26,000	20,000
North America	4,400	5,400
Caribbean	11,000	8,200
Latin America	44,000	3,6000

Table 2. EC- Clearinghouse & 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 disease	Group 3 lesions strongly associated with HIV infection but rare in children
Candidiasis -Erythematous -Pseudomembranous -Angular cheilitis	Seborrheic dermatitis	Neoplasms - Kaposi's sarcoma - Non Hodgkins lymphoma
Herpes simplex virus infection	Bacterial infections of oral tissues -Necrotizing (ulcerative stomatitis)	Oral hairy leukoplakia
Linear gingival erythema	Periodontal disease - Necrotizing (ulcerative) gingivitis - Necrotizing (ulcerative) periodontitis	Tuberculosis related ulcers
Parotid enlargement	Viral infections - Cytomegalovirus - Human papilloma virus - Molluscum contagiosum - Varicella zoster virus - herpes zoster - varicella	
Recurrent aphthous ulcers - Major - Minor - herpetiform	xerostomia	

Table 3. Treatment Table

Oral Manifestation	Treatment
Oral candidiasis	**Topical antifungal medications** (when the patient's CD4 cell percentage above 15%) Clotrimazole, 10mg oral troches, dissolved in the mouth 3-5 times *per* day are preferred as initial therapy. For bottle fed infants, vaginal tablet of 100000 U/ml can be placed within the nipple. Nystatin mouth rinses, 1 to 5 ml suspension, also can be used but may be less efficacious than clotrimazole troches. Topical antifungal medications typically contain dextrose, which may be cariogenic with prolonged use, especially in children with reduced salivary flow. **Systemic antifungal medications** (In patients with a CD4 cell percentage below 15%) Fluoconazole 2 to 5 mg/kg and ketaconazole 4 to 6 mg/kg are well tolerated. Hepatotoxicity has been associated with both of these medications, and resistance may develop when these medications are used for prolonged periods of time. Antifungal therapy should continue 2 to 3 days after disappearance of clinical signs.
Gingival & Periodontal disease	**For linear gingival erythema**, scaling of affected areas combined with 0.12% chlorhexidine, 0.5 oz bid rinse for 30 sec and spit can be helpful. **For NUG, NUP & stomatitis**, along with debridement and dental prophylaxis and 0.12% chlorhexidine rinse, systemic antibiotics are to be given. Metronidazole 15-35 mg/kg every 8 hours, or Clindamycin 20 – 30 mg/kg every 6 hours, or Ampicillin/ clavulanate potassium 40 mg/kg every 8 hours can be taken.
Viral Infections	Treatment for **herpes virus infection** is indicated only when the child has profound immune suppression. Antiviral drugs like acyclovir 200 – 400 mg tablet every 6 hours may be administered orally or I/V in severe cases, particularly in a child who refuses to eat or drink. Valacyclovir can also be used. For **varicella zoster**, a higher dose is needed.
HIV related Salivary Gland Disease	Parotid enlargement cannot be treated effectively. Antibiotics and even glucocorticosteroids have been used with mixed success. **Children with decreased salivary flow** can be treated conservatively by stimulating stimulation by chewing of sugar free gum or sucking on sugar free candies. Commercial artificial saliva substitutes and oral lubricants may alleviate some of the symptoms of oral dryness and may, to some degree improve oral functions. Medications such as pilocarpine, 5mg 1 tablet tds before meals, may be considered but only in collaboration with the patient's physician. Patient should be instructed to avoid products containing caffeine and alcohol. Topical fluorides therapy should be undertaken for patients with persistent xerostomia.

ROUTES OF TRANSMISSION

HIV can be transmitted perinatally from a mother to her newborn infant in three ways: (1) transplacentally, during pregnancy; (2) during delivery, as the infant passes through the birth canal (estimated to be 40% of the cases); or postnatally, during breastfeeding.[2] In the absence of breastfeeding, about 30% of infant HIV infections occur in utero and 70% during labour and delivery.[3] The frequency of breast milk transmission is 16% and majority of infections occur early in breastfeeding.[4] A small fraction of HIV infections in children are caused by contaminated injections, the transfusion of infected blood or blood products, sexual abuse, sexual intercourse or scarification.[5,6,7,8,9] The use of antiretroviral therapy, avoidance of breastfeeding and elective caesarian sections have dramatically reduced the risk of perinatal transmission of HIV in developed countries.[10] When HIV infected mothers are treated early and aggressively with zidovudine (AZT), the chance of transmission to the newborn infant decreases from approximately 25% to less than 8%.[11] Another drug used in preventing mother to child transmission is nevirapine.[2]

ETIOPATHOGENESIS AND STRUCTURE OF HIV RETROVIRUS

The etiologic agent of AIDS is HIV which belongs to the family of human retroviruses and the subfamily of lentiviruses. The most common cause of HIV throughout the world is HIV-1, while HIV-2 was first identified in 1986 in West African patients and was originally confined to West Africa.[12]

Electron microscopy shows that HIV virion is an icosahedral structure containing numerous external spikes formed by the two major envelope proteins, the external gp120 and the transmembrane gp41 (Figure 4). HIV is an RNA virus whose hallmark is reverse transcription of its genomic RNA to DNA by the enzyme reverse transcriptase. The replication cycle of HIV (Figure 5) begins with the high affinity binding of its V1 region near the N terminus to its receptor on the host cell surface, the CD4 molecule. The CD4 molecule is a 55-KDa protein found predominantly on a subset of T lymphocytes that are responsible for helper or inducer function in the immune system.

In order for HIV-1 to fuse and enter its target cell, it must also bind to one of a group of co-receptors . The two major co-receptors for HIV-1 are CCR5 and CXCR4. Following binding, fusion with the host cell membrane occurs in a coiled spring fashion via the newly exposed gp41 molecule, the HIV genomic RNA is uncoated and internalized into the target cells. The reverse transcriptase enzyme that is contained in the infecting virion then catalyzes the reverse transcription of the genomic RNA into double stranded DNA. The DNA translocates to the nucleus, where it is integrated randomly into the host cell chromosomes through the action of another virally encoded enzyme, integrase, thus establishing HIV provirus. This provirus may remain transcriptionally inactive (latent) or it may manifest varying levels of gene expression, up to active production of virus. Budding of progeny virus occurs through host cell membrane, where the core acquires its external envelope. The virally encoded protease then catalyzes the cleavage of the gag-pol precursor to yield the mature virion.

DIAGNOSIS

Standard serologic HIV antibody test method consists of screening enzyme immunoassay (ELISA) or confirmatory Western Blot test. HIV test is read as negative, with results returned within 3–4 days if the initially run enzyme immunoassay or ELISA is negative. False negative results are possible in the window period (usually 10-14 days from infection to seroconversion or development of HIV antibodies) but may last up to 6 months in rare instance.[13] A repeatedly reactive enzyme immunoassay or ELISA is the criterion for Western Blot testing. Western Blot detects antibodies to HIV-1 proteins including core, polymerase and envelope with a frequency of false positive of 0.0004%.[14]

CLINICAL COURSE

Most children born with HIV infection are asymptomatic at birth, and time between birth and initial symptoms and signs varies considerably. Symptoms may appear at any time after

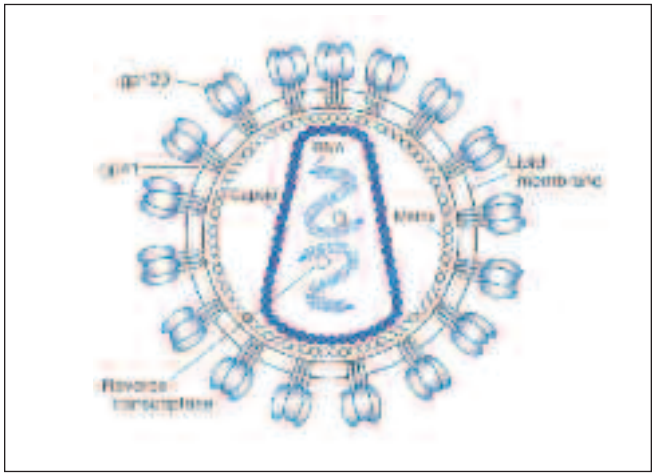

Figure 4. Showing structure of HIV 1 virus. Courtesy Harrisons

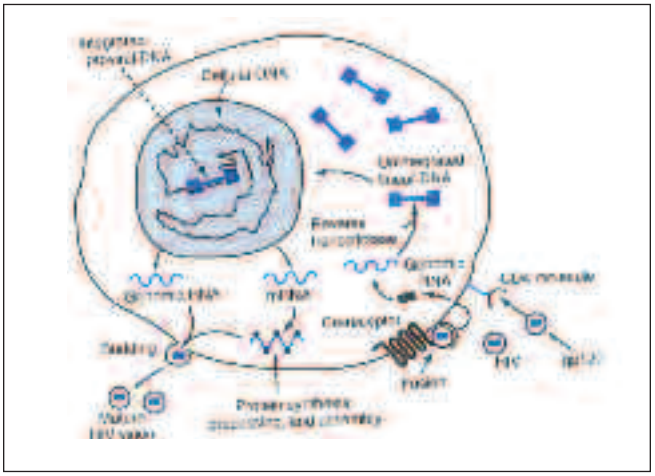

Figure 5. Showing replication cycle of HIV virus. Courtesy Harrisons

viral incubation, however, the median age of pediatric patients at the time of an AIDS diagnosis is 12 months and oral manifestations are the first sign of infection in approximately half of all infected children.[15] HIV infection in children has a clinical course that is similar but not identical to that in adults. Many of the earlier manifestations seen in adults infected with HIV are also seen in children including failure to thrive, fever, chronic or recurrent diarrhea, lymphadenopathy, and recurrent or persistent oral candidiasis.[16] Spira *et al*, 1999[17] reported the initial clinical signs occurring frequently to be failure to thrive (51.9%) and persistent lymphadenopathy (44.4%). One of the striking differences seen in children when compared with adults is the markedly increased susceptibility to bacterial infections, particularly with polysaccharide encapsulated organisms.[18,19,20] This probably results from lack of acquired immunity in infants to most common pathogens.[16] Bacterial infections such as draining otitis media, haemophillus influenza pneumonia and recurrent episodes of sepsis and meningitis are common in children. These infections are distinguished from those occurring in the general population by their persistence and severity. These non specific signs and symptoms may last weeks to months before development of those clinical signs indicative of AIDS (i.e. opportunistic infections, diffuse lymphocytic interstitial pneumonitis, or malignancy). Pulmonary disease is the most common cause of morbidity and mortality in children with HIV infection. According to Scott *et al,*[21] the median age of clinical onset of disease in perinatally infected infants was 8 months, with mortality highest in the first year of life.

Because evidence of HIV disease progression in both adults and pediatric patients is marked by oral manifestations and general periodontal status,[22] oral symptoms and signs may have prognostic value that is independent of CD4 status or other more commonly used markers. Recognition of these early signs during routine examinations and in surgical procedures may allow for early intervention and a reduction in mortality in this population.[23]

Clinical staging

The clinical staging of HIV disease and the relative risk of developing opportunistic infections have historically relied on the CD4 cell count as the principal laboratory marker of immune status.[13] HIV disease is commonly categorized on the basis of three levels of immunodeficiency:- relative immune competence (CD4 cell count > 500/microliter; >=29%), early immune suppression (CD4 cell count between 200-500/micoliter; 14-28%), severe immune suppression (CD4 cell count < 200/microliter; <14%).[24] But the use of disease markers prevalent in adult HIV infection is not necessarily effective in the pediatric AIDS population.[23] CD4 lymphocytes decline with the progression of HIV disease in infected adults; in children however, a CD4 count alone is not as reliable a marker for progressive disease because children tend to have higher and less consistent CD4 levels than do adults.[25,26] Severe opportunistic infection may occur in infants with minimally impaired immunity.[16]

More recently developed technologies allowing determination of HIV viral load reported as HIV RNA copies per milliliter, provide a quantitative measurement of viral replication in the blood that is seen as a harbinger of future CD4 cell destruction.[27] Even the most ultrasensitive assay Amplicor HIV-1 Monitor (Roche Diagnostics, Basel, Switzerland) is unable to detect levels below 50 copies /milliliter. Quantitative plasma HIV RNA is useful in diagnosing acute infection, predicting rate of disease progression and overall progression in chronically infected patients, predicting the probability of transmission and for therapeutic monitoring of patient response to antiretroviral therapy.[28,29]

MEDICAL MANAGEMENT

Medical management[30] of HIV infected patient consists of two primary objectives:

1) Suppression of HIV viremia to maintain immune competence with the use of antiretroviral drugs and management of subsequent drug toxicities.
2) Prevention and treatment of opportunistic diseases that result from immune suppression.

Suppression of HIV viremia

The most recent opinion is that antiretroviral treatment should be offered to persons with a CD4 cell count < 350/microliter or plasma HIV RNA levels of >55000 copies/ml (Center for disease control and prevention). 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 and entry inhibitors

Combination of NRTIs, NNRTIs and PIs are usually used and termed as Highly active antiretroviral therapy (HAART). Regimens generally include at least one protease inhibitor or NRTI in addition to one or more NNRTI in order to target HIV replication at more than one stage in the virus life cycle and to allow more complete suppression of replication.

ORAL MANIFESTATIONS AND THEIR MANAGEMENT

Classification of oral manifestations of HIV

The oral manifestations of HIV disease in adults and children were classified according to their frequency of association with HIV disease before the advent of effective ART[31] (Table 2).

Oral candidiasis

Oral candidiasis is the most common lesion in children with AIDS and often the first manifestation of HIV infection.[32,33,2] In children in the developed and developing world,

oral candidiasis has been described as varying from 22.5% to 45%.[32, 34, 35, 36, 37, 38, 39, 33]

Oral candidiasis may be present as clinically distinct forms including pseudomembranous, erythematous and angular cheilitis. Pseudomembranous candidiasis is characterized by the presence of white or yellow spots or plaques that may be located in any part of the oral cavity and can be wiped off to reveal an erythematous surface that may bleed. Erythematous or atrophic candidiasis appears clinically as red areas usually located on the palate and dorsum of the tongue but occasionally located on the buccal mucosa. Angular cheilitis may appear either alone or in conjunction with either of the other forms. Pseudomembranous infection seems to be the most prevalent form in children[32,34,35,36,37] followed by erythematous type[32,36,37] and angular cheilitis.[35,36,37,32] However, the erythematous disease has been occasionally reported to be more prevalent than pseudomembranous.[35]

In a recent study the presence of oral candidiasis was found to be significantly associated with CD4/ CD8 cells ratio. Those with a CD4/ CD8 ratio less than 0.5 were more prone to development of oral candidiasis.[40] It has also been suggested that CD4+ T lymphocytes percentage is more accurate than CD4+ T lymphocyte count in predicting the likelihood of oral candidiasis.[41] Oral candidiasis and oral hairy leukoplakia have been associated with immune suppression (as measured by high HIV RNA quantity in plasma).[42,30] Margiotta *et al*[43] reported correlation between candidiasis and low CD4 counts and high viral load. While in most cases clinical appearance is adequate to arrive at a diagnosis, simple exfoliative cytology will show characteristic budding yeast and hyphae when the clinical diagnosis is uncertain.[44]Treatment is discussed in Table 3.

Gingival and periodontal disease

The gingival and periodontal disease associated with HIV may be classified as linear gingival erythema, necrotizing ulcerative gingivitis (NUG) and periodontitis (NUP) and necrotizing stomatitis.[46]

Gingival disease seems to affect 4-20% of HIV infected children, while NUG and NUP are less prevalent, varying from 2.2-5%.[47,48,49,36,50,32,46]

HIV associated gingivitis is found to be associated with both the primary and permanent dentition.[16] The lesion is characterized by a linear erythema of the facial and interproximal gingival margins and is unresponsive to improved oral hygiene. In children, particularly in the primary dentition, it may be generalized or localized. In adolescents, the more generalized form seems to occur, comparable to the lesion seen in adult patients. In HIV infected adults, gingivitis can rapidly progress to a destructive periodontal disease in a few months.[16] In developed countries, ANUG has seldom if ever been reported in children under 10 years of age. However, in countries such as Africa and India among malnourished, immunosuppressed children, ANUG and the more severe form NOMA is a relatively common finding.[52]

Viral infections

Herpes simplex virus infection

The most common viral infection seen in children with HIV infection is Herpes simplex virus (HSV) or primary herpetic gingivostomatitis. Although HSV infection has been reported to occur in 1.7–24% of HIV infected children,[52] recent studies from the developing world suggest that such infection is actually very uncommon in both adults and children in HIV disease.[53,22]

This causes both oral lesions and systemic manifestations. Illness is acute, with varying degrees of fever and malaise, cervical lymphadenopathy, and perioral and intraoral lesions. The lesions start as vesicles that rupture and become painful, irregular ulcers. In HIV infected children, severe chronic painful lesions may occur on all mucous membranes and may require hospitalization. Lesions caused by herpes simplex in HIV infected children usually appear in a recurrent and chronic form, able to progress rapidly towards mucocutaneous areas. The most frequent locations are mucosa, lingual dorsum and hard palate (intraoral), lips and adjacent (perioral) cutaneous areas.[54] The lesions appear as crater like ulcers with well defined raised white borders and have a grey–white pseudomembrane. Diagnosis is based on the clinical picture and cytology with immunoassay for HSV specific antigens or culture.

Herpes zoster (VZV) caused by varicella zoster virus

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.[55] The skin lesions are of characteristic unilateral distribution and are often preceded and accompanied by severe pain. If the virus involves the second and third division of the trigeminal nerves, oral lesions will be seen. The early oral lesions are vesicles that rupture to form ulcers. Adult patients with HIV infection who acquire a varicella zoster infection, will in fact develop zoster; however, in children, zoster is an uncommon finding probably related to exposure.

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.[56]

Salivary gland enlargement occurs in approx. 3 – 10% of reported adult patient infected with HIV, with a higher frequency in children.[57] Parotid enlargement occurs in 10 – 30% of HIV infected children.[52,58]

In children, the initial and subsequent manifestations may be of an acute infectious nature that are associated with pain and fever and require antibiotic therapy. The lesions are generally much larger and more disfiguring in pediatric patients than in adults.[16] In most children, xerostomia is not usually associated with the parotid swelling, although in adult patients, it is a fairly common finding.[16] In both adults and children, lesion often occurs in conjunction with generalized

lymphadenopathy. Reasons for the difference between the adult and pediatric manifestations are not yet understood. Parotid enlargement has been associated with slower progression to AIDS in children. The median time to death has been reported as 3–4 years among patients with oral candidiasis and 5.4 years among those with parotid enlargement.[58]

Parotid enlargement cannot be treated effectively. Antibiotics and even glucocorticosteroids have been used with mixed success.

Recurrent aphthous ulceration

These lesions are commonly seen in HIV infected adults are also frequently seen in children.[58] Recurrent aphthous ulceration though classified as group 1 by Ramos Gomez *et al*, were reported in a few cases by Pongsiriwet *et al*[32] and reported to be infrequent by Leggott.[16]

The large solitary or multiple, chronic and painful ulcerations of major aphthae appear identical to those in non-infected patients, but they may last much longer and are less responsive to therapy.

Treatment of oral ulcerations should be based on an accurate diagnosis.[45] Topical corticosteroid applications, such as fluocinonide 0.05% or clobetasol 0.05%, mixed with orabase 1:1 are usually beneficial for localized aphthous ulcers. Dexamethasone elixir, swish and expectorate, can be used for more generalized and multiple lesions. Systemic glucocorticosteroids therapy is indicated for more severe cases.

Other rare conditions in children but common in adults

Oral hairy leukoplakia

Oral hairy leukoplakia is caused by EB virus, is presumptively diagnosed by clinical appearance as asymptomatic, non removable, flat or vertically correlated bilateral whitish/ grey lesions on lateral margins of tongue. These lesions have also been shown to predict progression to AIDS, even independently of CD4 cell count.[59]

This lesion can be treated with acyclovir, but because it usually does not cause any discomfort or undergo any malignant transformation, treatment should be based on patient's desire to have it eliminated.

Oral neoplasms

The most common HIV associated malignancies, Kaposi's sarcoma and non Hodgkin's lymphoma are never seen in children in association with HIV infection.[2] The type of lymphoma most commonly seen in association with HIV infection in adults is non Hodgkin's lymphoma. In the oral cavity the lesion, may present as a firm painless swelling that can occur anywhere.

Kaposi's sarcoma, though uncommon in children, but remains the most common AIDS associated malignancy.[48,56] Oral lesions appear as red to purple macules, papules or nodules that may ulcerate or cause local destruction. The palate and gingiva are the most commonly affected intraoral sites.

Dental disease in HIV infection

HIV infected children may be more liable to dental caries affecting both the deciduous and 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.[32] Baby bottle caries has been associated with anti HIV therapy. Caries prevalence of 28-33% among HIV infected infants and toddlers have been reported.[23] A greater frequency of caries in HIV infected children might be attributed to high carbohydrate and sugar intake required to provide sufficient calories in children after failure to thrive, and to ingestion of sucrose based medications, particularly antibiotics and antifungals, but also antiretrovirals such as zidovudine. Moreover, poor social status and low use of fluoride might also contribute to an increased risk of dental caries in children with HIV disease.

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.[47] The accelerated eruption patterns maybe related to concurrent or previous dental, and periodontal disease.[47] The exact cause of delayed eruption of teeth is unknown, although the poor health status of some children, particularly when there is malnutrition maybe an important co- factor.[47,35] Hauk *et al*[60] reported correlation between the progression from HIV infection to pediatric AIDS and delayed tooth eruption and found the delay to be mostly linked to severity of symptoms and not CD4 depletion. Delayed eruption of primary and permanent teeth has been reported among HIV infected children.[61] The lower teeth counts found at different ages could be due to low socioeconomic status reflecting poor nutrition and /or health.[23]

CONCLUSIONS

Oral manifestations are common and prevalent in pediatric HIV infection and have been found to be the earliest indicators of HIV infection. Since mouth is readily accessible for clinical management, these important oral signs can be utilized to assist in early diagnosis of AIDS in children. This would enhance case management, ensure better health outcomes and improve quality of life for HIV infected children.[23] Care of HIV infected children should include a pro active preventive approach, consistent with the implementation of anticipatory care, guidance with periodic examinations to monitor and treat symptoms of oral infections and dental disease.[2]

REFERENCES

1. UN Aids 2008 Report on the Global AIDS Epidemic.
2. Ramos Gomez F. Dental considerations for the pediatric AIDS/HIV patient. Oral Dis, 8(Suppl 2), 49–54, 2002.
3. DeCock KM, Fowler MG, Mercier E et al. Prevention of mother to child HIV transmission in resource poor countries. J Am Med Assoc, 283: 1175–1182, 2000.
4. McCarthy GM, Ssali CS, Bedranash H, Jorge J et al. Transmission of HIV in the dental clinic and elsewhere. Oral Dis, 8 (Suppl 2), 126–135, 2002.

5. Kengeya-Kayondo JF, Malamba SS, Nunn AJ, Seeley JA, Ssali A, Mulder DW. Human immunodeficiency virus (HIV 1) seropositivity among children in rural population of South-West Uganda: probable routes of exposure. Ann Trop Pediatr, 15(2): 115–20, 1995.
6. Mulder DW, Nunn A, Kamali A, Kengeya- Kayondo JF. Post natal incidence of HIV-1 infection among children in a rural Ugandan population: no evidence for transmission other than mother to child. Trop Med Int Health, 1(1): 81–5, 1996.
7. Hauri AM, Armstrong GL and Hutin YJ. The global burden of disease attributable to contaminated injections given in health care settings. Int J STD AIDS Jan; 15(1): 7–16, 2004.
8. Kiwanuka N, Gray RH, Serwadda D, Li X, Sewankamboo NK, Kigozi G, Lutalo T, Nalugoda F, Wawer MJ. The incidence of HIV-1 associated with injections and transfusions in a prospective cohort, Rakai, Uganda. AIDS, 23; 18(2): 342–4, 2004.
9. Schmid GP, Buve A, Mugyenyi P, Garnett GP, Hayes RJ, Williams BG, Calleja DG, De Cock KM, Whitworth JA et al. Transmission of HIV-1 in sub-Saharan Africa and effect of elimination of unsafe injections. Lancet, 363(9407): 482–8, 2004.
10. Bulterys M and Fowler MG. Prevention of HIV infection in children. Pediatr Clin North Am, 47(1): 241–60, 2000.
11. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, VanDyke R, Bey M, Shearer W, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type1 with zidovudine treatment, New Eng J Med, Vol 331: 1173–1180, 1994.
12. Harrison's Principles of Internal Medicine, 2000, 15th ed., Mc Graw Hills
13. Mylonakis E, Paliou M, Lally M, Flanigan TP, Rich JD. Laboratory testing for infection with human immunodeficiency virus: established and novel approaches. Am J Med; 109(7): 568–76, 2000.
14. Kleinman S, Barsch MP, Hall L, Thomson R, Glynn S, Gallahan D, et al. False positive HIV 1 test results in a low risk screening setting of voluntary blood donation. Retrovirus epidemiology donor study. JAMA, 280(12): 1080–5, 1998.
15. European Collaborative Study. Children born to women with HIV-1 infection: natural history and risk of transmission(letter). Lancet, 337(8736): 253–60, 1991.
16. Leggott PJ. Oral manifestations of HIV infection in children. Oral Surg Oral Med Oral Pathol, 73: 187–92, 1992.
17. Spira R, Lepage P, Msellati P, Van de Perre P, Leroy V, Simmonon A, Karita E, et al. Natural history of human immunodeficiency virus type1 infection in children: A five year prospective study in Rwanda. Pediatrics, 104, No 5: 1–9, 1999.
18. Pahwa S, Kaplon M, Fikrig S,et al. Spectrum of human T cell lymphotropic virus type III infection in children. Recognition of symptomatic, asymptomatic and seronegative patients. JAMA, 255(17): 2299–305, 1986.
19. Wiznia A, Rubinstein A. Pediatric infections and therapy. AIDS, 2 Suppl 1: S195–9, 1988.
20. Krasinski K, Borkowsky W, Bonk S, Lawrence R, Chandwani S. Bacterial infections in human immunodeficiency virus-infected children. Pediatr Infect Dis J, 7(5): 323–8, 1988.
21. Scott GB, Hutto C, Makusch RW, Mastrucci MT, O'Connor T, Mitchell CD, et al. Survival in children with perinatally acquired human immunodeficiency virus type 1 infection. N Eng J Med, 321(26): 1791–6, 1989.
22. Greenspan JS, Greenspan D. The epidemiology of the oral lesions of HIV infection in the developed world. Oral Dis, 8(Suppl.2), 34–39, 2002.
23. Ramos Gomez FJ, Petru A, Hilton JF, Canchola AJ, Wara D & Greenspan JS. Oral manifestations and dental status in pediatric HIV infection. Int J Ped Dent, 10: 3–11. 2000.
24. Centre for disease control and prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep. Dec 18; 41(RR-17): 1–19, 1992.
25. Pizzo PA and Wilfret CM. Markers and determinants of disease progression in children with HIV infection. The Pediatric AIDS Sienna Workshop II. J Acquir Immun Defic Syndr Hum Retrovirol, 8(1): 30–44, 1995.
26. Centre for disease control and prevention. 1995 revised guidelines for prophylaxis against Pneumocystitis carinii pneumonia for children infected with or perinatally exposed to human immunodeficiency virus. MMWR Recomm Rep. Apr 28; 44(RR-4): 1–11, 1995.
27. Patton LL, Shugars DC. Immunologic and viral markers of HIV-1 disease progression: Implications for dentistry. JADA, 130: 1313–1322, 1999.
28. O'Brien WA, Hartigan PM, Martin D, Esinhart J, Hill A, Benoit S, et al. Changes in plasma HIV-1 RNA and CD4+ lymphocyte counts and the risk of progression to AIDS. New Eng J Med, Feb; 334: 426–431, 1996.
29. Quinn TC, Wawer MJ, Sewankamboo N, Serwadda D, LI C, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. New Eng J Med, 342: 921–929, 2000.
30. Patton LL. HIV disease. Dent Clin N Am, 47: 467–492, 2003.
31. EC clearinghouse. Classification and diagnostic criteria for oral lesions in HIV Infection and WHO Collaborating Centre on oral manifestations of the immunodeficiency virus. J Oral Pathol Med, 22(7): 289–91, 1993.
32. Pongsiriwet S, Iamaroon A, Kanjanavanit S, et al. Oral lesions and dental caries status in perinatally HIV infected children in Northern Thailand. Int J Pediatr Dent, 13: 180–185, 2003.
33. Olaniyi TO, Sunday P. Oral manifestations of HIV infection in 36 Nigerian children. J Clin Pediatr Dent, 30(1): 89–92, 2005.
34. Barasch A, Safford MM, Catalanotto FA, Fine DH, Katz RV. Oral soft tissue manifestations in HIV positive vs. HIV negative children from an inner city population: a two year observational study. Pediatr Dent, 22(3): 215–20, 2000.
35. Khongkunthian P, Grote M, Isaratanam W, Piyaworawong S, Reichart PA. Oral manifestations in 45 HIV-positive children from Northern Thailand. J Oral Pathol Med, 30 Issue 9, 549–52, 2001.
36. Magalhaes MG, Bueno DF, Serra E, Goncalves R. Oral manifestations of HIV positive children. J Clin Pediatr Dent, 25(2): 103–6, 2001.
37. Naidoo S, Chikte U. Oro-facial manifestations in pediatric HIV: a comparative study of institutionalized and hospital outpatients. Oral Dis, 10(1): 13–8, 2004.
38. Santos LC, Castro GF, deSouza IP, Oliveira RH. Oral manifestations related to immunosuppression degree in HIV-positive children. Braz Dent J, 12: 135–8, 2001.
39. Kozinetz CA, Carter AB, Simon C, Hicks MJ, Rossmann SN, Flaitz CM, et al. Oral manifestations of pediatric vertical HIV infection. AIDS Patient Care and STDs, 13(2): 89, 2000.
40. Fonseca R, Cardoso AS, Pomarico I. Frequency of oral manifestations in children infected with human immunodeficiency virus. Quintessence Int, 31(6): 419–22, 2000.
41. Campo J, Del Romero J, Castilla J, Garcia S, Rodriguez C, Bascones A. Oral candidiasis as a clinical marker related to viral load, CD4 lymphocyte count and CD4 lymphocyte percentage in HIV-infected patients. J Oral Pathol Med, 31(1): 5–10, 2002.
42. Patton LL, Mckaig RG, Strauss RP, Eron JJ Jr. Oral manifestations of HIV in southeast USA population. Oral Dis, 4(3): 164–9, 1998.
43. Margiotta V, Campisi G, Mancuso S, Accurso V, Abbadessa V. HIV infection: oral lesions, CD4+ cell count and viral load in an Italian study population. J Oral Pathol Med, 28: 173–7, 1999.
44. Sirois DA. Oral manifestations of HIV disease. Google.com.1998 Oct/Nov; No 5 & 6, Vol 65: 322–332.
45. Glick M. Orofacial disorders in children with HIV disease. Dent Clin N Am, 45: 259–271, 2005.
46. 1999 International Workshop for a classification of periodontal diseases and conditions. Papers. Oak Brook, Illinois, October 30–November 2, 1999.
47. Flaitz C, Wullbrandt B, Sexton J, Bourdon T, Hicks J. Prevalence of orodental findings in HIV infected Romanian children. Pediatr Dent, Jan Feb; 23: 44–50, 2001.

48. Ranganathan K, Reddy BVR, Kumaraswamy N, Solomon S, Vishwanathan R, Johnson NW. Oral lesions and conditions associated with human immunodeficiency virus infection in 300 south Indian patients. Oral Dis, 6: 152–157, 2000.
49. Chidzonga MM. HIV/ AIDS orofacial lesions in 156 Zimbabwean patients at referral oral and maxillofacial surgical clinics. Oral Dis, 9: 317–322, 2003.
50. Holmes HK and Stephen LX. Oral lesions of HIV infection in developing countries. Oral Dis, 8(Suppl2): 40–3, 2002.
51. Enwonwu Co. Infectious oral necrosis (cancrum oris) in Nigerian children: a review. Community Dent Oral Epidemiol, 13: 190–4, 1985.
52. Ramos Gomez FJ, Flaitz C, Catapano P, Murray P. Milnes AR, Dorenbaum A. Classification, diagnostic criteria, and treatment recommendations for orofacial manifestations in HIV infected pediatric patients. Collaborative Workgroup on Oral Manifestations of Pediatric HIV infection. J Clin Pediatr Dent, 23(2): 85–96, 1999.
53. Arendorf T, Holmes H. Oral manifestations associated with human immunodeficiency virus (HIV) infection in developing countries – are there differences from developed countries? Oral Dis, 6: 133–135, 2000.
54. Ex Posito-Delagado AJ, Vallejo-Bolanos E, Martos- Cobo EG. Oral manifestations of HIV infection in infants: a review article. Med Oral Pathol Oral Cir Bucal, 9: 410–20, 2004.
55. Frezzini C, Leao JC & Porter S. Current trends of HIV disease of the mouth. J Oral Pathol Med, 34: 513–31, 2005.
56. Lin HC, Corbet EF, Lo EC. Oral mucosal lesions in adult Chinese. J Dent Res, May; 80(5): 1486–90, 2001.
57. Mandel L. Ultrasound findings in HIV-positive patients with parotid gland swellings. J Oral Maxillofac Surg, 59(3): 283–6, 2001.
58. Katz MH, Mastrucci MT, Laggott PJ, Westenhouse J, Greenspan JS, Scott GB. Prognostic significance of oral lesions in children with perinatally acquired human immunodeficiency virus infection. Am J Dis Child, 147(1): 45–8, 1993.
59. Katz MH, Greenspan D, Westenhouse J, Hessol NA, Buchbinder SP, et al. Progression to AIDS in HIV- infected homosexual men with hairy leukoplakia and oral candidiasis. AIDS, 6(1); 95–100, 1992.
60. Hauk MJ, Moss ME, Weinberg GA & Berkowitz RJ. Delayed tooth eruption association with severity of HIV infection. Pediatr Dent, 260–262, 2001.
61. Ramos Gomez FJ. Oral aspects of HIV infection in children. Oral Dis, 3: S31–S35, 1997.