Pediatric HIV infection and its oral manifestations: a review

Radhika Chigurupati, BDS  Sai Subhasree Raghavan, PhD  Deborah A. Studen-Pavlovich, DMD

This article presents a comprehensive review of the recent literature on the epidemiology, immunopathogenesis, clinical features, and current classification of pediatric HIV infection with special emphasis on oral manifestations, their prognostic significance, and treatment modalities. Infection with HIV results in profound immunosuppression, rendering the host susceptible to the development of various opportunistic infections and neoplasms. Compared with adults, the progression of HIV infection is more rapid and severe in infants and children due to ongoing development of different organ systems and an immature immune system that is less resistant to infection.1

The oral cavity is particularly susceptible to infection since it harbors numerous microorganisms that thrive in conditions of immunosuppression and cause characteristic fungal, viral, bacterial, and neoplastic lesions.2 Oral lesions are frequently among the first symptoms in HIV-infected children.3-5 Early detection of HIV-related oral lesions can be used to diagnose HIV infection, elucidate progression of the disease, predict immune status, and provide timely therapeutic intervention.6,7

Epidemiology of pediatric HIV infection

In their second decade, AIDS and HIV infection continue to spread rapidly affecting an increasing number of women and children worldwide. The World Health Organization (WHO) reported that one million children were infected with HIV by the end of 1992 and estimated that 10 million children will be born infected by the year 2000.5 Consequently, infant and child mortality rates will be 30% greater than previously projected.8,9 Currently, children constitute 2% of the total recognized AIDS cases in the United States, and 15–20% of the total reported AIDS cases in the developing nations.10,11 Vertically acquired HIV infection (transmission from mother to offspring during gestation or parturition or as a result of breastfeeding) accounts for 85% of all reported pediatric cases in the U.S. and worldwide. The remaining 15% who are exposed to the virus include those with hemophilia/coagulation disorders, recipients of blood transfusions and blood/tissue components (prior to 1985), and other unidentified risks.11 The rate of vertical transmission from HIV-infected mother to infant is estimated to be 15–20% in Europe, 16–30% in the U.S., and 25–40% in the developing nations.12-14 Data obtained from studies on vertical transmission imply that both intrauterine and intrapartum transmission occurs. The expression of HIV-related symptomatic disease as early and late HIV infection may reflect the differences in the timing of transmission: infants with in utero infection have a rapid onset of clinical disease and infants with intrapartum or postpartum infection have a slower onset of clinical disease.15

In the U.S., as of December 1994, 6209 pediatric AIDS cases had been reported to the Centers for Disease Control and Prevention (CDC). While drug use and sexual contact with an injection drug-using partner are the major indirect contributing factors for new cases of pediatric HIV/AIDS in the U.S.,16 child-bearing women who are infected via the heterosexual route of transmission constitute the main source of pediatric HIV infection in the developing countries.17,18 Metropolitan areas along the East Coast account for two-thirds of all perinatal cases of HIV infection in the U.S. The cumulative AIDS incidence rates among African-American and Hispanic children are 17 and 7 times higher respectively than the incidence rates among Caucasian children.19 Even with recent advances in preventive and therapeutic interventions, mortality rates of children with AIDS continues to be high, particularly in the 1- to 4-year age group.20

Immunology and pathogenesis

HIV is an RNA retrovirus that has a specific tropism for cells bearing the CD4 (cluster determinant) antigen, including the helper subset of T-lymphocytes (T4), monocytes/macrophages, some B-lymphocytes, and possibly glial cells.21 Since the CD4 lymphocytes (T4 helper cell) play a vital part in the induction and evolution of a normal immune response by other effector cells, a decrease in number or disruption of function of
the CD4 lymphocytes, by direct or indirect cytopathic mechanisms of HIV, is responsible for many immunologic aberrations. Some of the immunologic abnormalities include absolute decrease in CD4+T lymphocytes; a reversal of CD4+/CD8+T lymphocyte ratios; elevated immunoglobulin levels; and deficient production of IL-2 and interferon. These abnormalities result in a greater susceptibility to opportunistic fungal and bacterial infections, an increased propensity toward malignancy, lymphoid interstitial pneumonitis, and thrombocytopenia. The direct effect of the virus on the developing central nervous system (CNS) in the infected child results in progressive encephalopathy with cognitive, behavioral, and motor deficits.

Although many of the immune system abnormalities are similar in pediatric and adult HIV infection, important differences exist. Unlike adults, vertically infected children have an immature immune system and, consequently, a shorter incubation period with a more rapid and fulminant disease process. In pediatric HIV infection, the immunological marker is abnormal B-cell function (poor response to B-cell mitogens, and polyclonal hypergammaglobulinemia), which actually precedes T-lymphocyte decreases. These B-cell defects predispose infants and children to more frequent and severe bacterial infections than those in adults. In infants with vertically transmitted HIV infection there is no striking reversal of CD4+/CD8+ T-lymphocyte ratios in the first year of life. Decreasing CD4+/CD8+ ratios are often initially due to an increase in the number of suppressor CD8+ lymphocytes rather than depletion in CD4+ T-lymphocytes.

Rubenstein and Rogers et al. have reported that roughly half of the infected infants become clinically symptomatic in the first year of life. In children, individual signs and symptoms are often nonspecific and may be seen in a variety of pediatric conditions. Major systemic findings include:

1. Chronic pneumonitis
2. Recurrent bacterial infections including otitis media
3. Persistent oral candidiasis
4. Chronic or recurrent diarrhea
5. Lymphadenopathy
6. Hepatosplenomegaly
7. Failure to thrive
8. Developmental delay
9. Progressive encephalopathy

Certain clinical findings are typical in the pediatric age group, such as:

1. Pulmonary lymphoid hyperplasia
2. Salivary gland enlargement
3. Pyogenic bacterial infections such as otitis media
4. Developmental delay
5. Dysmorphic craniofacial features.

Overall immunologic function in children with HIV infection, as in infected adults, tends to deteriorate over time. Understanding the specific immunopathogenesis of oral lesions facilitates the correlation of oral manifestations to progression of HIV infection. A study by Roilides et al. showed that impairment of the helper T-cell functions correlated with an increased risk of opportunistic infections including oropharyngeal candidiasis. A review by Leggott et al. comparing the oral manifestations of HIV-infected children with similar oral lesions in children afflicted with either primary T-cell or phagocytic cell defects concluded that children with T-cell defects tend to have more oral mucosal candidiasis, herpes simplex virus (HSV) infections, and recurrent aphthous ulcerations. By comparison, children with primary disorders of phagocytosis have rapidly progressive periodontal diseases and parotitis.

### Table 1. Pediatric HIV Classification (CDC, 1994)

<table>
<thead>
<tr>
<th>Immunologic Categories</th>
<th>N: No Signs/ Symptoms</th>
<th>A: Mild Signs/ Symptoms</th>
<th>B: Moderate Signs/ Symptoms</th>
<th>C: Severe Signs/ Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence of suppression</td>
<td>N1</td>
<td>A1</td>
<td>B1</td>
<td>C1</td>
</tr>
<tr>
<td>Evidence of moderate suppression</td>
<td>N2</td>
<td>A2</td>
<td>B2</td>
<td>C2</td>
</tr>
<tr>
<td>Evidence of severe suppression</td>
<td>N3</td>
<td>A3</td>
<td>B3</td>
<td>C3</td>
</tr>
</tbody>
</table>

* Children whose HIV infection status is not confirmed are classified by using the above grid with a letter E (perinatally exposed) placed before the appropriate classification code.

**Recent classification of pediatric HIV infection/AIDS**

In 1994, a revised classification system for HIV infection in children younger than 13 years was presented by Balsley et al. from the National Institutes of Health and replaced the 1987 CDC classification. The new system summarized in Table 1 is based on infection status, immune status, and clinical categories. Table 2 compares 1987's classification with 1994's. Table 3 elaborates the immunologic categories by presenting a summary of age-specific CD4+ T lymphocyte counts.
Oral lesions: types, prevalence and prognostic significance

Candidiasis has been documented in various studies as the most frequently occurring oral manifestation in HIV-infected children, with a prevalence ranging from 20–72%.36 Other lesions encountered include:

1. Parotid enlargement
2. Herpetic stomatitis
3. Oral hairy leukoplakia
4. Petechiae
5. Aphthous stomatitis
6. Linear gingival erythema
7. Cervical lymphadenopathy.

Table 4 lists the prevalence of HIV-related oral lesions in some recent studies.6,36-39 The variations in the prevalence of oral lesions in the reported studies may be due to differences in study methodology:

1. Sample size
2. Stage of illness of the sample children
3. Site of oral examination—hospital/dental clinic setting
4. Length of follow-up period.

Oral candidiasis

Recurrent candidiasis, which is persistent for long periods and often resistant to conventional antifungal therapy, is a frequent oral manifestation in pediatric HIV infection/AIDS.48 Oral thrush/candidiasis is also a finding in healthy infants in the first 6 months of life.47 However, in the immunocompetent child, candidial lesions are often mild, readily amenable to treatment, or regress spontaneously and are rarely seen beyond infancy in the absence of predisposing factors.

The clinical presentation of oral candidiasis in HIV-infected children is variable. It is manifested as creamy white pseudomembranous plaques, erythematous patches, angular cheilitis, or as nonscrappable hyperplastic plaques. In HIV-infected children, lesions are often characteristic of the pseudomembranous and erythematous types. Pseudomembranous candidiasis typically presents as white or yellowish plaques which, when scraped off, reveal a bleeding surface. These patches may occur on the tongue, buccal and labial mucosa, palate, and oropharynx. Erythematous or atrophic form appears as flat or raised red patches noted most often on the dorsum of the tongue, palate, and buccal mucosa. Angular cheilitis manifests as fissures or cracks at the comissures of the lips.45 Once colonization and superficial infection by candida are established, deeper penetration into submucosal tissue may be facilitated by concomitant mucosal infections caused by HSV.52 Chan et al.36 and Moniaci et al.6 found that there were more children with pseudomembranous candidiasis in stage P2 than stage P1 or P0 stages of HIV infection. Ketchem et al.37 noted in their cohort of HIV-seropositive children, that most of the candidial lesions were characteristic of the pseudomembranous type and affected large areas of the oral mucosa.
Candida albicans have been documented. In infants and small children, candidial lesions can be treated by swabbing with nystatin/gentian violet, or administering nystatin suspension (100,000 U/ml) in doses of 1–2 ml, three or four times a day. In older children, the use of nystatin pastilles (200,000 U/pastille) or clotrimazole (10 mg/troche) troches are effective. Lesions may subside or disappear without treatment, but relapses are common due to underlying immunodeficiency. The antifungal therapy should continue for 1–2 weeks after clinical resolution of the symptoms. More severe cases require suppressive maintenance antifungal therapy and may be managed by ketoconazole 5–10 mg/kg/day or parenterally administered amphotericin B. In adults, fluconazole is being used since it has a long plasma half life and achieves high concentrations in multiple tissue sites and cerebrospinal fluid relative to plasma concentrations. However, it has not been approved by the Food and Drug Administration for use in children. Treatment modalities for candidiasis in children are included in Table 5.

**Parotid enlargement**

Parotid enlargement has been recognized as a distinctive feature of HIV infection in children since the first descriptions of the disease. This manifestation has been reported in 10–30% of the children with symptomatic HIV infection. The presence of parotitis is a predictor of positive prognosis and long-term survival in HIV-infected children. Typically, the parotid glands are diffusely swollen and firm and without evidence of inflammation or tenderness. The swelling is chronic with unilateral or bilateral involvement, occasionally accompanied by xerostomia. It is often associated with lymphoid interstitial pneumonitis (LIP) and diffuse lymphadenopathy, which probably represents a lymphoproliferative stage of HIV infection in children. Histologically, the enlarged parotid gland demonstrates lymphocytic infiltration, which may be caused by infection with Epstein-Barr virus (EBV) or HIV or an interaction between the two. Chronic parotid enlargement does not require treatment. Parotitis resolves in many patients being treated with zidovudine; however, recurrence of the lesion may occur. Occasionally, a biopsy may be necessary to rule out an infectious etiology or neoplasm in the presence of atypical findings such as unilateral involvement, acute inflammation, or a rapidly enlarging mass.

**Cervical lymphadenopathy**

Enlargement of the cervical lymph nodes in children with HIV infection is usually a part of generalized lymphadenopathy. Lymphadenopathy is an early nonspecific finding in HIV-infected children, and its presence alone does not meet the CDC criteria for symptomatic HIV infection. Lymphadenopathy is chronic, diffuse, without tenderness or signs of inflammation, and often is accompanied by hepatosplenomegaly and salivary gland enlargement. In a study reported by Chan et al., cervical lymphadenopathy was the most prevalent orofacial manifestation (54.5%) in HIV-infected children in their study. This manifestation was significantly related to a decline in CD4+ T cells and an increase in serum IgG. A recent report from the Italian register of pediatric HIV infection, documented that lymphadenopathy was a nonspecific clinical sign in 91% of the long-term survivors, and 58% of short-term survivors, indicating that the presence of lymphadenopathy was a positive predictor of survival in HIV-infected children.

**Oral hairy leukoplaikia**

Hairy leukoplakia (HL) is rarely manifested in children with perinatally acquired HIV infection. However, it is a common finding in adults and has been documented as a predictor of progression of HIV infection to CDC-defined AIDS. It presents as a nonscrappable, white, finely corrugated lesion along the lateral borders of the tongue. Studies show that this lesion is associated with intraepithelial proliferation of EBV and that multiple strains of the virus often are present in hairy leukoplakia tissues. As exposure to EBV often does not occur until children are older, this lesion may not be an early manifestation in perinatally acquired HIV infection. Among recent studies of oral lesions in HIV-infected children, Katz et al. have reported a 2% prevalence of hairy leukoplakia. Hairy leukoplakia lesions must be distinguished from other white lesions as candidiasis in the oral cavity. A noninvasive diagnostic method—scraping the lesion and using in situ hybridization is particularly useful in children. Hairy leukoplakia lesions may regress with antiretroviral therapy and concurrent improvement of cellular immunity, but recurrence is possible after discontinuing treatment.

**Herpes simplex virus infections**

Herpetic stomatitis caused by herpes simplex virus-1 (HSV) is commonly seen in HIV-infected children and has a tendency to recur (two or more episodes within a year). The primary lesions of HSV infections in children may manifest as gingivostomatitis, and recurrent lesions are seen as vesicles on the vermilion border, which rupture and form ulcers (“cold sores”) on the lips or appear as clusters of small painful ulcers on the palate and gingiva. Primary HSV lesions also are seen in the healthy child between ages 2 to 6 years. However in healthy children, HSV lesions resolve in

---

**Table 5. Treatment of Candidiasis in HIV-Infected Children**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade Name</th>
<th>Dosage Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nystatin</td>
<td>Mycostatin™</td>
<td>100,000 U/ml, 2-4 ml q 6 h (oral)</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>Mycelex™</td>
<td>10 mg troches ≤ 5/day (oral)</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Nizoral™</td>
<td>5-10 mg/kg/day q 24-12h (oral)</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Diflucan™</td>
<td>2-8 mg/kg/day q 24 h (oral)</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Fungizone™</td>
<td>0.25 mg/kg/day (parenteral)</td>
</tr>
</tbody>
</table>
10–14 days and generally require only palliative treatment. In HIV-infected children these lesions are chronic, recurrent, and may progress rapidly to cause extensive mucocutaneous involvement. As immunosuppression increases, an increase in severity and frequency of recurrences of orolabial lesions occurs. Early diagnosis and treatment of lesions with antiviral agents such as acyclovir is important in HIV-infected children with severe, long standing, painful lesions because they may prohibit oral intake. In a study by Katz et al. HSV was manifested in 30% of the children within 5 years from the date of acquiring HIV infection. This lesion was not significantly related to survival time, unlike candidiasis and parotitis. Diagnosis of oral HSV lesions is simple due to typical clinical presentation, but atypical lesions should be scraped and examined for intranuclear inclusions and multinucleated giant cells.

Other viral lesions manifested in the oral cavity include ulcers involving the tongue, palate, buccal mucosa, and pharynx caused by varicella zoster and coxsackie virus. These lesions also are seen in healthy children and are not specific to children with HIV infection.

Gingival and periodontal lesions

Linear gingival erythema (LGE) and necrotizing ulcerative periodontitis (NUP) occur frequently in HIV-infected adults and have been reported occasionally in children with perinatally acquired HIV infection. Ketchem et al. documented gingivitis in HIV-infected children as an intensely erythematous band involving the labial marginal and attached gingivae. Moniaci et al. reported two patients in the P2 stage with gingivitis. Additionally, Jandinski et al. reported a prevalence of 37% for gingivitis and 4.5% for periodontitis in a sample of 67 children infected with HIV.

NUP is characterized by a localized lesion resulting in rapid loss of supporting periodontal structures and loose teeth with no pocket formation. Microbiologic studies revealed the prevalence of Actinobacillus actinomycetemcomitans and Candida albicans from the lesions of LGE and NUP. In one patient, a severe ulceration of the supporting periodontal structures and alveolar mucosa in relation to the mandibular primary central incisors was observed with class 3 mobility of the two teeth.

Other oral lesions

Some of the other oral manifestations include Kaposi sarcoma (KS), recurrent aphthous ulcers, petechiae, and rampant caries. KS as a manifestation of HIV infection in children is rare in western countries. In Kampala, Uganda, KS is being recognized in an increasing number of children. From 1986 to 1990, 25 cases were documented, in at least 25% of those with HIV infection relating to a previous blood transfusion. Thrombocytopenia is reported to occur in 20–30% of HIV-infected patients at any age. It may appear as a result of HIV-induced autoanti-
hand, children having onset of opportunistic infections early in their disease course had poor prognosis.67

Katz et al. in a longitudinal study determined that the median time from the development of lesion to death was shorter for oral candidiasis than for parotid enlargement. They were of the opinion that, because of the strong association between oral lesions and survival outcomes, candidiasis and parotid enlargement should be incorporated into prognostic indices and decisions regarding therapy for HIV-infected children.58

Scott et al. reported that age at diagnosis and patterns of disease (sequence of appearance of clinical manifestations such as LIP, encephalopathy and, recurrent candida esophagitis) are important prognostic factors for survival.68

Ketchem et al., in a survey of oral findings in 47 HIV-seropositive children, found that oral candidiasis was present in 60% of the children in P-2 stages and 23% of the children in P-0 stages. Most candidial lesions were creamy white or yellowish pseudomembranous plaques and usually affected large areas of the oral mucosa in P-2 children, whereas lesions in P-0 children were generally small and localized. When correlating severity and frequency of candidiasis to immunological parameters, their data indicated that as CD4 lymphocyte cell depletion progressed, the frequency and severity of candidiasis increased.69

Diagnosis, treatment modalities, and prevention

Currently, presence of maternal antibody is not a significant confounding factor in establishing an early diagnosis of HIV infection in children because of the availability of more accurate diagnostic tests. In developed countries, a diagnosis using polymerase chain reaction for HIV, viral culture, and acid dissociated p24 antigen assays can be made with certainty in the immediate newborn period in at least 50% of the infants. By 3 months of age, a diagnosis can be made in 95% of the patients. Therefore, it is not necessary to wait until the infant is 9 to 12 months old when the maternal antibody disappears before making a definitive diagnosis.

Therapeutic interventions, particularly administration of zidovudine, appear to have marked benefits in delaying disease progression in some children. Seropositive pregnant women should be treated with zidovudine if they become clinically ill or have evidence of severe immunodeficiency. They should be advised specifically to bottle feed rather than breast feed their infants.

Although the oral candidiasis is present in healthy infants (independent of HIV infection) during the neonatal period, its presence for long periods of time beyond infancy and in the absence of antibiotic therapy in children born to parents at risk for HIV infection, may be predictive of immunodeficiency and potential HIV infection.

Conclusions

1. The presence of oral lesions is useful in selecting antiviral prophylactic and therapeutic interventions.
2. Pediatric dentists can play a role both in the early detection of HIV-related oral lesions and in training pediatricians to recognize these oral lesions.
3. The pediatric dentist should collaborate with other health professionals to correlate oral lesions, immunological parameters, and other clinical findings to provide proper prophylactic therapy and to improve the survival of HIV-infected children.

Further areas to be researched include:

1. More longitudinal studies with sero-reverter control groups in nondental settings are necessary to do prevalence studies of oral lesions in HIV-infected children.
3. The effects of CNS developmental delay on craniofacial growth and in the development of the dentition.

Dr. Chigurupati was a postdoctoral fellow at Columbia University when the review article was initiated. Dr. Raghavan is associate research scientist for the Institute of Human Nutrition at Columbia University in New York, New York. Dr. Studen-Pavlovich is director of undergraduate pediatric dentistry at the University of Pittsburgh.


Illiteracy keeps many from comprehending medical instructions

A study of emergency room and clinic patients at two public hospitals shows many of them are unable to read and understand basic written medical instructions, according to an article in a recent issue of The Journal of the American Medical Association.

The study raises the question of whether the estimated 40-44 million U.S. adults who are functionally illiterate and another 50 million who are marginally literate are leaving doctor's offices without understanding what to do to ensure their good health.

Mark V. Williams, MD, from the Emory University School of Medicine, Atlanta, Ga., and colleagues write: "To our knowledge, no study has used a standardized instrument to measure the ability of patients to perform basic reading tasks required to function in the health care environment, such as reading labels on prescription bottles, understanding information on appointment slips, completing health insurance forms, and following instructions pertaining to diagnostic tests."

The study was conducted in 1993 and 1994 at two urban public hospitals: a large public hospital in Atlanta with a predominantly indigent African-American clientele and a large public hospital in Los Angeles serving a diverse patient population.

In Atlanta, of 1,271 patients invited to participate in the study, 979 completed reading test and initial questionnaire. In Los Angeles, 1,997 patients were invited to participate in the study and 1,680 completed the test and initial questionnaire. In Los Angeles, patients whose primary language was Spanish were given the test in Spanish. The majority of patients at both sites were poor, had no health insurance, and many had not completed high school.

After examining a standard appointment slip, 20.8% (Los Angeles, English) to 31.2% (Los Angeles, Spanish) of patients could not describe when a follow-up appointment was scheduled. From 32.5% (Los Angeles, English) to 59.3% (Atlanta) of patients were unable to determine if they were eligible for financial assistance based on their income and number of children. Between 10.8% (Los Angeles, English) and 33% (Los Angeles, Spanish) of patients could not read well enough to understand standard preparation instructions for an upper gastrointestinal radiographic procedure. In Atlanta, 42.9% of patients could not fully comprehend the Rights and Responsibilities of the Medicaid application.

The older the patients, the poorer were the scores the researchers report. From 47.9 to 80.5% of patients aged 60 years or older had inadequate functional health literacy.

The authors write that the fact patients with limited literacy skills have difficulty reading informed consent forms presents a troubling ethical issue. "The ethical obligation of physicians to explain the risks and benefits of any procedure or treatment is fundamental to the physician-patient relationship."