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Most common oral manifestations in pediatric patients HIV positive and the effect of highly active antiretroviral therapy

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Abstract *This integrative literature review aims to identify the main oral lesions affecting pediatric patients with HIV, and describe the effect of highly active antiretroviral therapy (HAART) on these injuries, comparing it to antiretroviral therapy (ART). A search was conducted in PubMed and Scielo databases, following predetermined inclusion and exclusion criteria. 19 papers were selected and the main information on the prevalence and frequency of oral manifestations in HIV-positive pediatric patients and effect of therapy applied were extracted. The most frequent injuries were oral candidiasis, gingivitis, parotid gland enlargement and linear gingival erythema. The use of HAART shown to reduce the prevalence of oral manifestations in pediatric patients with HIV and be more effective than ART. The findings of this study suggest that the most frequent oral manifestation in HIV-infected children is oral candidiasis, followed by changes such as gingivitis and enlargement parotid glands. The use of HAART appears to reduce the prevalence of these oral lesions, showing more effective results than ART.*

Key words *Child, Acquired Immunodeficiency Syndrome, Oral manifestations, Antiretroviral therapy*

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Introduction

Acquired Immunodeficiency Syndrome (AIDS) is a systemic disease caused by the Human Immunodeficiency Virus (HIV), which affects the individual's immune system and makes him/her more susceptible to other diseases of systemic origin, such as oral lesions[1].

First cases of AIDS were reported in the mid-1980s and its heterosexual transmission has grown over time, affecting a large number of women of childbearing age and capable of transmitting HIV virus to their children[2]. This vertical transmission, from mother to child,is considered the main factor for the increasing prevalence of this disease in pediatric patients[2-4] and it can occur during pregnancy, childbirth or through breastfeeding[5,6].

HIV infection currently affects more than 2 million children under the age of 15 years old worldwide and it is associated with numerous life-long comorbidities for this population[6,7]. Early identification of oral manifestations, which usually are the first signs of this infection or its progression in children[2], may assist in choosing appropriate therapy and reducing its morbidity[6].

Immunosupressed patients are more susceptible to opportunistic infections, especially those that affect the oral cavity, such as oral candidiasis[8]. This problem becomes worse when it comes to HIV-positive pediatric patients because they present an immature immune system that makes them more prone to severe immunosuppression and rapid disease progression[2,6].

Some oral manifestations in pediatric patients present a different prevalence of adult patients[9]. The prevalence of oral lesions is, on average, 63%[1,10], ranging from 20% to 80%[11]. This variation may occur according to the region or country and type of treatment instituted, such as whether patients have access to more potent antiretroviral drugs[4] or not.

Introduction of antiretroviral therapy (ART) regarding the treatment of HIV-infected patients brought enhancements in their oral health quality of life, reducing frequency of the disease's oral manifestations[6]. Subsequently, it was created a combination therapy known as highly active antiretroviral therapy (HAART). This one delivered more effective results, altering the prevalence of some oral lesions caused by HIV, besides improving the immune function, which reduced opportunistic infections, morbidity and mortality[10,12].

A wide variety of oral lesions in HIV-infected pediatric patients are reported in the literature, such as: candidiasis[8,10-12], gingivitis[12-14], oral hairy leukoplakia[9,13],Kaposi's sarcoma[5,10,15],parotid enlargement[1,4,14,16], herpes simplex[1,2].This data also reveal divergence of information regarding which ones are the most frequent oral manifestations and how the antiretroviral therapies act on them. For this reason, this present study aims to identify the main oral lesions affecting pediatric patients with HIV, as well as the effects of ART and HAART on said lesions.

Methodology

This integrative review consisted of a bibliographic survey in the PubMed and SciELO databases. Adopting "advanced search" mode, the following keywords were used blended and standalone: "oral manifestations", "HIV", "children", "childhood", "prevalence", "HAART", "antiretroviral therapy" in both Portuguese and English.

Inclusion criteria for the articles were: descriptive, cross-sectional, and comparison studies reporting oral manifestations in HIV-infected children published in Portuguese or English between 2004 and 2014.

After the initial selection, repeated articles were excluded from the sample, along with those which did not include at least three keywords in the title or abstract, were not published in full and did not present the investigated issue as main subject. Last selection step consisted of reading the texts in full, followed by the construction of tables using most relevant information of each selected article.

Results

A total of 367 articles were identified in the databases searched. After excluding duplicate articles and those that did not meet predetermined inclusion and exclusion criteria, there were 24 articles left for full reading. After analyzing the content of each one of them, 19 scientific articles that addressed investigated issues were selected for this review. Most relevant subjects raised were:

- Identification of oral manifestations affecting HIV-positive pediatric patients, highlighting the most frequent ones;
- ART and HAART effects on oral lesions of HIV-positive children, especially HAART in the prevalence of these oral manifestations.

Most frequent lesions in HIV-positive pedi-

atric patients were oral candidiasis, gingivitis, parotid enlargement and linear gingival erythema, being oral candidiasis considereda predictor of disease progression. The use of HAART has been shown to decrease the prevalence of oral manifestations in pediatric patients with HIV and to be more effective than ART. Main information contained in each article were described in the form of Charts 1 to 4 and sorted according to their publication year.

Discussion

Cross-sectional and prospective studies have shown that pediatric HIV-infected patients will present some type of oral lesion in non-specific phases of their childhood, which will help to identify the correct diagnosis of the syndrome[1,2,17] and, consequently, to find the most suitableantiretroviral therapy treatment[4,9,11].

Chart 1. Integrative review consolidation.

Author/ Year	Methods	Purpose	Results	Conclusions
Vaseliu et al. 2005	Longitudinal study	To evaluate the presence of oral manifestations associated with HIV infection in children.	Most common oral lesions: gingivitis (49%), enlargement of the parotid glands (13%), oral candidiasis (11%), hairy leukoplakia (3%), herpes simplex (2%).	Gingivitis was the most prevalent lesion. Oral candidiasis and hairy leukoplakia were positive predictors for progression of the disease.
Glick 2005	Literature review	To discuss over the classification, prevalence and treatment of oral manifestations in HIV-positive children.	Oral lesions serve as markers for the deterioration of the immune system and progression of HIV.	The prevalence differs between regions. Three common orofacial lesions in children: oral candidiasis, enlargement of the parotid glands and lymphadenopathy. There is a significant association between the occurrence of oral lesions and immune suppression.
Miziara et al. 2006	Retrospective cohort study	To assess whether HAART changes the patterns and prevalence of oral lesions in HIV-positive children.	Lesions commonly associated with HIV: oral candidiasis, herpes simplex, linear gingival erythema, parotid enlargement, recurrent oral ulcerations.	Oral candidiasis was the most prevalent lesion. HAART use may be associated with a lower prevalence of oral lesions (especially oral hairy leukoplakia) compared to the use of ART.
Miziara e Weber 2008	Cross-sectional study	To assess the accuracy of oral lesions related to HIV to predict the immunologic and virologic failure in HIV-infected children on HAART.	31.6% of children had oral lesions.	Oral manifestations of HIV may be important markers for immunological suppression and for virological failure in Brazilian children on HAART.
Leao et al. 2009	Literature review	To discuss the oral manifestations associated with HIV infection in adults and children, and, in addition, current trends of antiretroviral therapy and its effect on those lesions.	Most prevalent lesions: oral candidiasis, enlargement of the parotid glands and angular cheilitis.	Pseudomembranous candidiasis was considered to be the most common oral manifestation, often associated with the disease progression.

Chart 2. Integrative review consolidation.

Autor/Ano	Methods	Purpose	Results	Conclusions
Sowole et al. 2009	Cross-sectional study	To assess oral manifestations, oral health status and treatment needs of pediatric patients with HIV.	Most common oral lesion was oral candidiasis (27%). 25.5% presented gingivitis and 3.6% presented enlargement of the parotid glands.	Candidiasis was the most common manifestation and could be used as a marker for early detection of HIV in children.
Pinheiro et al. 2009	Literature review	To review current epidemiological trends of oral manifestations in HIV-positive children on HAART.	Most common lesion: oral candidiasis. HAART use decreased the severity and/ or frequency of the lesions. Observe the Immune reconstitution inflammatory syndrome (IRIS) because some unusual manifestations may occur after the use of HAART.	HAART typically reduces the frequency and/or severity of most oral lesions associated with HIV infection, but SRI is resurfacing and modifying the injury presented.
Gaitán-Cepeda et al. 2010	Cross-sectional study	To assess the prevalence of HIV-related oral lesions in HIV-positive adolescents and the differences between them and HIV-positive children infected in the perinatal period.	Oral candidiasis was the most prevalent oral lesion in both groups. There is association ($p < 0.05$) between a high prevalence of HIV and oral candidiasis with a high viral load.	Adolescents infected with HIV in the perinatal period have a high prevalence of HIV-related oral lesions, oral candidiasis being the most frequent lesion in both groups.
Ranganathan et al. 2010	Cross-sectional study	To document and study the most common oral lesions in HIV-positive children and its connection to diseases in other parts of the body.	62.2% had oral lesions. Most frequent lesions: oral candidiasis (56.1%) and gingivitis (10.8%). Most common systemic lesion: lymphadenopathy (74.1%). Enlargement of the parotid glands was observerd in 36.8% of the children.	Oral and systemic lesions were significant characteristics in HIV-positive children. Oral candidiasis was the most common lesion associated with the degree of immunosuppression.
Domaneschi et al. 2011	Cross-sectional study	To assess the prevalence of factors associated with the colonization of Candida albicans in pediatric AIDS patients.	Prevalence of 62% candida colonization in patients with HIV. Inverse association between colonization by Candida and the use of antiretrovirals.	Despite the high evidence of colonization by candida, manifestations in oral candidiasis were reduced, probably due to the use of antiretroviral drugs.

In all the studies analyzed, although they occurred in different regions and countries, oral manifestations were highlighted as a common feature in children infected with HIV virus. Most commonly found lesions were oral candidiasis in various forms[3,7,14,18], gingivitis[2,13,14,16], acute herpetic gingivostomatitis[2], linear gingival erythema[1,10,17], oral hairy leukoplakia[5,9,13], Kaposi's sarcoma[1,5,15] and parotid enlargement[4,13,15,19]. However, almost all of them reported oral candidiasis as the most frequent manifestation, corroborating with the findings in literature. This fact can be ob-

Chart 3. Integrative review consolidation.

Author/Year	Methods	Purpose	Results	Conclusions
Ogunbosi et al. 2011	Cross-sectional study	To estimate the prevalence, clinical pattern of HIV infection and the results amongst new patients aged <15 years, using age-specific diagnostic methods.	A significant proportion (p = 0,000) of HIV-infected children presented oral candidiasis (13.3%). In the logistic regression analysis, candidiasis was considered a predictive characteristic of HIV (OR = 0,223; p = 0,026).	The prevalence rate of HIV infection in patients submitted to the PITC test was high
Rosendo et al. 2011	Longitudinal study	To assess oral conditions in HIV-positive children.	The frequency of oral lesions was 61.6%. Gingivitis was the most prevalent with 57.5%, followed by oral candidiasis with 19.1% and primary herpetic gingivostomatitis with 17%.	Oral manifestations are very common in children affected by the HIV virus, and gingivitis is the most prevalent oral manifestation.
Ponnam et al. 2012	Cross-sectional study	To adentify the oral manifestations in HIV-positive children on HAART.	Children on HAART had fewer oral manifestations than those who did not receive the therapy. Gingivitis and oral candidiasis were the most common lesions in patients on HAART.	HAART use increased the disease-free status in HIV-positive children, which increases the life span. Oral candidiasis and ulcerative stomatitis were significantly less prevalent in children on HAART.
Sales-Peres et al. 2012	Cross-sectional study	To assess oral manifestations in HIV-infected children on or not on ART.	Total lesions in the buccal mucosa: 13.3%. Enlargement of the parotid glands was seen in 23% of patients. Oral lesions observed: oral candidiasis, gingivitis and herpetic stomatitis. Children who were not on ART were more affected by oral lesions.	Patients on ART are less likely to have lesions on the oral mucosa. The most frequent oral lesion was candidiasis (5.5%).

served in the analysis of Charts 1 to 4 and it will be further discussed in the course of this article.

Regarding periodontal conditions, it can be observed that when it comes to immunosuppressed patients, gingivitis can occur even when the patient is well hygienised and there is no biofilm, which does not happen with healthy children[2].

In a longitudinal study, Vaseliu et al.[13] found that gingivitis was the most frequent oral lesion (49%), however, the authors suggest that the relevance of gingivitis in pediatric infection scenario

Chart 4. Integrative review consolidation.

Author/ Year	Methods	Purpose	Results	Conclusions
Kumar et al. 2013	Cross-sectional study	To assess the prevalence rate of oral lesions in HIV infected children treated in antiretroviral therapy clinics.	The most frequent oral lesions were oral candidiasis (20.86%), angular cheilitis (16.56%), necrotizing ulcerative gingivitis (8.28%), linear gingival erythema (5.53%) and aphthous ulcers (2.76 %).	61.65% had oral lesions, and the age group of 9-12 years was the most affected (28.53%). Oral candidiasis was the most prevalent lesion (20.86%).
Tonelli et al. 2013	Systematic reviews	To investigate the main oral manifestations in pediatric patients infected with HIV.	Average prevalence of oral manifestations in children: 63%. Main lesions found in the articles: oral candidiasis, angular cheilitis, linear gingival erythema, xerostomia, enlargement of the parotid glands, Kaposi's sarcoma, herpes simplex, recurrent aphthous ulcers (RAUs).	Oral lesions are common in pediatric patients infected with HIV. Most common lesion: oral candidiasis, with a prevalence of up to 90%, being an important marker of immune compromise. Linear gingival erythema has been found with a prevalence of 27%.
Konstantyner et al. 2013	Retrospective cohort study	To verify the factors associated with time spent free of oral candidiasis in children living with HIV, using the technique of survival analysis for recurrent events.	Associated factors: mono, double or triple therapy with HAART, immunosuppression, hospitalization and malnutrition lead to more time without oral candidiasis in children with HIV.	HAART has a beneficial effect in the prevention of oral candidiasis. Other factors are associated with the reduction of the prevalence of this oral manifestation.
Jose et al. 2013	Cross-sectional study	To evaluate the prevalence of oral manifestations in HIV patients receiving on or not on HAART.	Candidiasis was the most frequent oral manifestation in both groups, on or not on HAART (33% in total), followed by linear gingival erythema with 16%. Patients with HIV on HAART present moderate oral manifestations.	Oral candidiasis was the most frequent lesion. Lymphadenopathy was the most prevalent systemic condition (85%). HAART decreased the rate of oral manifestations. Only recurrent aphthous ulcerations (RAU) were greater in patients with HAART.
Meless et al. 2014	Cross-sectional study	To estimate the prevalence of oral mucosal diseases and dental caries in children with HIV on ART.	Lesions of the oral mucosa were rare in children with HIV on ART, occurring in only 8.3% of them. The most frequent lesion was oral candidiasis (24 lesions of 42 found).	Enlargement of the parotid glands seems to be common even on ART (16.4%). The most frequent lesion was oral candidiasis (52.6%).

is still unknown. On the other hand, Sowole et al.[16] found gingivitis (25.5%) as the second most prevalent lesion, followed by enlargement of parotid glands (3.6%).

Linear gingival erythema has also been described by some authors as a common oral manifestation in these patients[1,17], besides also being considered as a unique feature of seropositive

patients by Tonelli et al.[1]. These characteristics reinforce the need for a careful clinical evaluation of periodontal condition for a possible early diagnosis ofthe HIV virus' presence in pediatric patients.

Oral candidias is and its pseudomembranous, angular cheilitis, erythematous and oropharyngeal variants were reported in most studies[1,2,16,17,19]. The first three variants have been described as the types known to be associated with HIV infection nowadays[11].

Thus, it is possible to affirm that the opportunistic lesion most commonly associated with HIV-infected patients is oral candidiasis and that this finding is fundamental for the early diagnosis of AIDS[1-3,10,14,16,18,19]. In addition, this oral manifestation may serve as a marker of disease progression and immunosuppression[2,5,13,15]since its prevalence is related to lower values ofTCD4+ lymphocytes[1].

According to Konstantyner et al.[8], candidias is has a considerable importance in the clinical prognosis of HIV infection, besides being a good indicator to show the non-efficacy of antiretroviral treatment. In their study, antiretroviral therapy (mono, double or triple/highly active) proved to be a significant protective factor against oral manifestations and the latter (triple/highly active) demonstrated a better beneficial effect to prevent candidias is in HIV-positive pediatric patients.

According to Pinheiro et al.[11], the use of HAART significantly reduces oral manifestations associated with AIDS, because an improvement in the immune systemoccurs and consequently a decrease in the incidence and prevalence of opportunistic infections. Such finding was reported in other studies that compared oral manifestations in HIV-positive children with or without the use of this therapy, where those who received the medication had a lower prevalence of oral disorders than children who did not receive said treatment[9,10,12].

Corroborating with the affirmative protective action of antiretroviral drugs, Meless et al.[19] observed in their study a low prevalence of oral lesions, possibly because all the children in the study were being treated with this type of medication. Jose et al.[6] compared patients that used and did not use HAART and observed that those on this medication had oral manifestations with moderate intensity, with a lower occurrence of oral candidiasis. In addition, there was a significant reduction in the presence oflesions when the treatment time with HAART was longer, especially in periods that exceed five months.

Ogumbosi et al.[3] study showed that the high number of deaths was related to pre-antiretroviral era and that lower mortality rates were observed when ART was instituted. On the other hand, Ponnamet al.[12] observed that the administration of HAART increased thedisease's free time, with a consequent raise in patients' survival rates. However, it is important to point out that unusual clinical manifestations of oral lesions may appear due to the immune response restoration, known as immune reconstitution syndrome (IRS). This may occur a few weeks after starting the treatment[11] and professionals involved should watch out for this adverse effect.

It is important to highlight that the use of HAART may be associated with a lower prevalence of oral lesions compared to the use of ART[9]. Therefore, it is possible to say that HAART plays a key role in reducing the prevalence of oral manifestations in HIV-positive pediatric patients, contributing substantially to give saidimmunosuppressed patients a better quality of life[11,18].

Final Considerations

The findings of this study suggest that the most frequent oral manifestation in HIV-infected children is oral candidiasis, followed by alterations such as gingivitis and parotid glandsenlargement, being candidiasis regarded as a marker of disease progression. It is relevant to point out that oral manifestations are common in seropositive pediatric patients and treating them is fundamental to improve these children quality of life. In addition, HAART seems to reduce the prevalence of said oral lesions, making its use beneficial for patients.

Collaborations

JF Araújo worked on the conception, design, research, analysis and interpretation of data and writing of the article; FRVO Roma worked on the analysis and interpretation of data and writing of the article; HLCC Carvalho worked on the design and writing of the article; AEF Oliveira and FF Lopes worked on the critical review and approval of the version to be published.

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