Oral Manifestations in Hiv Positive Pediatric Patients in Developing Countries: A Systematic Review

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Abstract
HIV positive children are found in high numbers in developing nations. Oral manifestations are prognostic markers of HIV and are considered to be the first sign of HIV in children. This review was undertaken to identify the oral manifestations in HIV positive children in developing nations. Based on the eligibility criteria, 7 studies were found. Oral candidiasis was found to be the most common oral manifestation. Gingivitis was also found to be high in HIV children, but due to the lack of disease-free controls, it cannot be confirmed if the disease was due to poor oral hygiene or due to HIV infection. The introduction of antiretroviral therapy was found to decrease the presence oral lesions. Early identification of oral lesions along with good oral hygiene may help to increase the quality of life in HIV positive children.
Keywords: AIDS, children, HAART, oral manifestations, systematic review

1. Introduction

Over 2.3 million children are living with human immunodeficiency virus (HIIV) below the age of 14 all over the world. It is estimated that approximately 880 children are infected with HIV daily. HIV-positive children experience various health disadvantages and are susceptible to opportunistic and other infectious disease [1].

Oral health is a critical issue for HIV positive children. They are at high risk for oral mucosal disorders due to their defective immune systems. Lower immune status has also been associated with dental caries. Oral manifestations are common in children infected by HIV and are associated with serious immunosuppression and AIDS. They are considered to be indicators for the infection with a predictive value of its progression [2].

The availability of effective treatment for HIV over the past 20 years has resulted in significant improvements and a longer life expectancy for some patients, mainly in the developed world. However, the majority of HIV-positive groups in countries with limited resources continue to endure high rates of morbidity and mortality even after starting antiretroviral therapy. Literature has shown that there has been a significant decrease in the prevalence of the oral manifestations of HIV in response to highly active anti-retroviral therapy (HAART) in developed nations [3]. However, it may not be the same in developing nations. 90% of the children of 2.3 million children infected with HIV below 14 have been found to be living in Africa, many who may not have access to HAART. Without access to HIV care and treatment, every day almost 800 HIV positive children die. Only 28% of children who require treatment are receiving it compared to 37% of adults. In some African countries the disparity between children and adults on treatment is greater [1].Our team has extensive knowledge and research experience that has translated into high quality publications (Choudhari and Thenmozhi, 2016; Govindaraju, Jeevanandan and Subramanian, 2017; Ravi *et al.*, 2017; Vikram *et al.*, 2017; Gupta, Ariga and Deogade, 2018; Hannah *et al.*, 2018; Kavarthapu and Thamaraiselvan, 2018; Pandian, Krishnan and Kumar, 2018; Ramamurthy and Mg, 2018; Ashok and Ganapathy, 2019; Ramesh *et al.*, 2019; Sharma *et al.*, 2019; Venu, Raju and Subramani, 2019; Wu *et al.*, 2019; Samuel, Acharya and Rao, 2020).

In pediatric patients who have been infected by HIV,

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an increase in dental diseases has been documented along with various oral manifestations [4]. This systematic review was undertaken to evaluate the oral manifestations in pediatric patients in developing nations who are infected with HIV.

2. Methods

This systematic review was performed using the Cochrane Handbook for Systematic Reviews of Interventions.

Eligibility criteria

Inclusion and exclusion criteria were determined by discussion and agreed by the investigators based on the population, intervention, comparator, outcome, and study design (PICOS) model as shown in Table 1.

Table 1: Inclusion and exclusion criteria used to assess eligibility of the articles.

Pico Item	Eligibility Criteria
Population	Children below 14 years from developing countries. *
Investigation	oral and dental lesions in HIV positive pediatric patients
Comparison	untreated HIV-positive children and those who underwent ART (antiretroviral therapy) or HAART
Outcome	Identify the most common oral manifestations in HIV-positive children in order to assess the impact on pediatric patients' quality of life
*List of developing nations obtained from https://www.worlddata.info/developing-countries.php	

3. Study selection

An attempt was made to identify all relevant studies, irrespective of the year of publication but language of publication was limited to English only. Database searches were carried out from date of inception to present of MEDLINE (1946–), Scopus (1966–), and Web of Science (1900–) using free text and MeSH terms individually and combined with Boolean operators. The following terms were included in the search: oral lesions, oral manifestations, HIV infection, HIV-positive children, and HIV-positive pediatric patients.

Eligibility for study selection

Titles and abstracts were independently reviewed against inclusion criteria by two investigators. If titles and abstracts met or appeared to meet the inclusion criteria, the full text was obtained to determine eligibility for inclusion in the review. This process was carried out by two researchers independently. If reviewers disagreed on eligibility, they met to discuss and reach a conclusion. Where agreement could not be reached, the opinion of a third reviewer was sought. Studies which did not meet the criteria at this stage were noted along with the reason for exclusion (Figure 1).

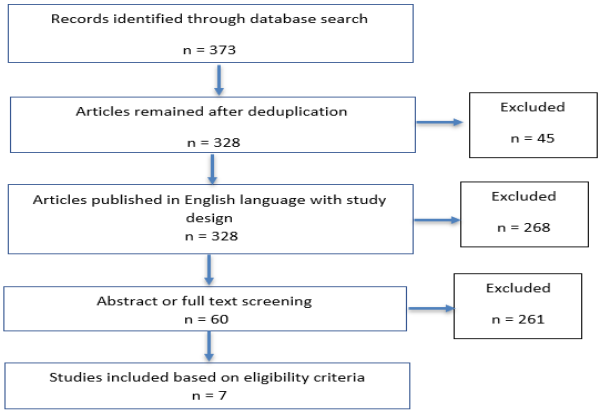

Figure 1: PRISMA Flowchart for selection of articles

Quality assessment

The same teams of two reviewers then independently assessed the quality of included studies using the Quality Assessment Tool for Studies of Diverse Design. Total scores for each paper and the mean score for each criterion met by the included papers were calculated. Disagreements between the reviewers over the quality assessment were resolved by discussion, with a third reviewer invited to resolve issues where necessary.

4. Results

Description of selected studies

7 studies which fulfilled the eligibility criteria were included in the study. Three studies were published from India [2,7,8] while two studies were published from Nigeria [6,10]. The remaining two studies were published in Mozambique [5] and Brazil [9] respectively (Table 2)

The mode of transmission was evaluated in 4 of the studies. Two Indian studies, by Ranganathan et al [2] and Kumar et al [8] reported high prevalence (90%) of vertical transmission. Less than 5% of children were affected by blood transfusion based on the reports of Ranganathan et al [2]and Riberio et al [9].

Disease free controls were seen only in the study conducted by Baghirath et al [7] in India. None of the disease-free children had any mucosal lesions. They also concluded that HAART helped to reduce the prevalence of oral manifestations related to HIV.

The prevalence of oral manifestations varied from 21 % to 73% in all the studies, the highest which was reported by Rwenyonyi et al [5] in Mozambique. The lowest was seen in Nigeria where Adebola et al [6] reported 21% of the patients had at least one oral manifestation while 41% of the patients had multiple manifestations. The most common manifestation was found to be oral candidiasis in all the studies.

Table 2: Characteristics of Selected studies				
S. No	Author:	Country	Sample Size	Characteristics
1.	Ranganathan et al, 2010 [2]	India	212	132 had oral lesions ranging in number from one to three. Oral candidiasis was the most common
2.	Rwenyonyi et al, 2011 [5]	Mozambique	90	One or more oral lesions were recorded in 73% of the children of whom 19.0% experienced discomfort during oral functions. Cervical lymphadenopathy, oral candidiasis and gingivitis were the most common soft tissue oral lesions.
3.	Adebola et al, 2012 [6]	Nigeria	105	21.0% had at least one oral lesion, 41.0% had multiple lesions. The most common lesion was oral candidiasis (79.1%).
4.	Baghirath et al, 2013 [7]	India	100	Nearly 81.3 % of HIV patients receiving long-term therapy did not have any oral lesions. Results demonstrated that ART proved to be effective in reducing the prevalence of HIV-related oral lesions.
5.	Kumar et al, 2013 [8]	India	326	61.65% of the children had oral lesions. Oral Candidiasis was the most common.
6.	Ribeiro et al, 2013 [9]	Brazil	57	69.6% presented one or more oral soft tissue manifestations. More than a half suffered from gingivitis
7.	Oyedeji et al, 2015 [10]	Nigeria	58	63.8% of the children had oral diseases. Enamel hypoplasia, candidiasis, caries, angular chelitis, and herpes labialis were the most common oral lesions found

5. Discussion

All the selected studies in the present review show that HIV infections in children are still a serious problem in developing countries [4]. Vertical transmission continues to be the most common route for transmission of HIV in these countries. Vertical transmissions are observed from pregnant woman to her new-born during pregnancy in utero, intrapartum during labour and delivery or postpartum through breast feeding [11]. About one-fourth of exposed children acquire the virus during childbirth, while one-fifth acquire it during pregnancy and breastfeeding depending on the presence/absence of other maternal and child-related risk factors [12].

The defective immune systems in HIV positive children often make them prone to more systemic infections. The effects on a developing infant may differ from a fully grown adult, and in order to plan for services, interventions, treatment and care, it is important to understand the cognitive abilities and developmental milestones of HIV positive children. [13-15]. The environment within which the children are raised seems to be an important factor in the course of development of oral manifestations. More than 2.3 million children younger than 15 years old are living with HIV, of which 90% are living in Africa alone [1,14].

Seven cardinal lesions are strongly associated with HIV: oral candidiasis, oral hairy leukoplakia, Kaposi's sarcoma, linear gingival erythema, necrotizing ulcerative gingivitis, necrotizing ulcerative periodontitis, and non-Hodgkin's lymphoma. These manifestations involve more than 50% of people with HIV infection and about 80% of those with a diagnosis of AIDS. Similar data have also been found in children, with a very high incidence of oral lesions [3,16]

The introduction of HAART, which is characterized by the association of proteases inhibitors and nucleosides reverse transcriptase or non-nucleoside reverse transcriptase inhibitors, has been one of the main factors in achieving a decrease of the prevalence of HIV-related oral manifestations in pediatric patients. However, their incidence still remains very high [1,15,17]

In the present systematic review, oral candidiasis was the most common oral manifestation to be reported. The highest prevalence was found in Mozambique [5] where 73% of the children had oral candidiasis. Baghirath et al [7] found candidiasis in 32% of children not undergoing HAART while 36.4% of the children receiving HAART had oral candidiasis. None of the controls reported the presence of oral candidiasis.

Enamel Hypoplasia was reported by Oyedeji et al [10] in Nigeria in 44% of the patients. This is an important finding in the perspective of oral hygiene. Children with hypoplastic teeth have high chances for tooth fracture and may result in pain in the future. Though the mechanism for hypoplasia to occur in HIV positive children is not known, we hypothesize that there could be possible relation between the occurrence of enamel hypoplasia and HIV infection, or therapies adopted by the mother and the child during odontogenesis could have resulted in enamel hypoplasia.

Gingivitis was found to be an oral manifestation in most of the studies [2,3] The lack of controls to compare the presence of gingivitis in unaffected children was a drawback as it was difficult to understand the if reason for the presence of gingivitis was due to poor oral hygiene or due to any defects in the body of infected children. Gingivitis, ulcerative necrotizing periodontitis, recurrent aphthous stomatitis, angular cheilitis and oral hairy leucoplakia are lesions that are characterized by a very low incidence in healthy children [2,7].

Nabbanja et al [18] observed that the incidence of oral manifestations in pediatric subjects with poor oral hygiene is significantly higher, while Baghirath et al [7] reported that children living in rural areas and

those with a lower socio-economic status have more lesions than those living in urban areas or belonging to richer social classes.

Children with HIV show a high prevalence of carious lesions in comparison to healthy children [3,7]. The process of HIV infection includes several factors that can cause dental caries: the prolonged use of sugary products and carbohydrates, changes in salivary flow and salivary glands due to medication use, immunosuppression, repeated episodes of hospitalization, poor oral hygiene, and poor competence in terms of oral health promotion [3,19] The present throws light on the lack of studies that compare oral manifestations of HIV positive children with healthy children. Well-designed, long-term studies will help us under the emergence, resolution and characteristics of oral lesions along with the quality-of-life HIV infected children better and help in planning better treatment.

Oral and dental diseases also negatively affect the quality of life of these children: Most seropositive children suffer from an impact of oral problems on their daily activities, reporting many difficulties in eating and other functional limitations. Furthermore, the impact that these problems have on emotional and social well-being, which is inevitably compromised, must be considered. Therefore, the differences between HIV-positive children and adults make it necessary for oral physicians to use a diversified approach. Systemic and oral lesions in HIV infection reflect the immune status of the patients: In particular, the presence of oral lesions may be an early diagnostic indicator of immunodeficiency and could be used as predictor of HIV infection progression. Furthermore, the resolution or the disappearance of oral lesions in HIV-positive patients can serve as indexes of treatment success

6. Conclusion

Oral candidiasis was found to be the most common oral manifestation in our review. HIV iin children represents a difficult challenge in developing countries. The reduced life span of affected children and significantly affecting their quality of life, HIV also leads to the development of various systemic and oral lesions. Oral lesions are the first manifestations of HIV in children and treatment should be initiated immediately

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