

## Oral Findings in Children with Human Immunodeficiency Virus Treated with Highly Active Antiretroviral Therapy: an Institutional Study in Indonesia

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### Abstract

The oral findings among human immunodeficiency virus (HIV)-infected children in Indonesia especially treated with highly active antiretroviral therapy (HAART) have never been reported. This study aimed to identify the oral manifestations, dental and oral health status of Indonesian children with HIV infection treated with HAART.

The cross sectional study was conducted at Cipto Mangunkusumo Hospital (CMH) in Jakarta, Indonesia. The children in-patients (aged 1 to 12 years) confirmed to be HIV-positive by Department of Pediatrics were recruited. The sociodemographic data, oral mucosal condition, DMFT, deft, OHIS score, use of HAART and immune status were recorded. Seventy children who were undergoing HAART were included in this study. This study found low prevalence of oral mucosal lesion related to HIV infection.

Gingivitis was the most common oral condition found in 48 (68.6%) children followed by aphthous ulcers, pseudomembrane candidiasis, herpes infection, angular cheilitis, ecchymosis and oral wart lesion. A high caries prevalence were seen in this study with mean score of deft and DMFT were 8.2 + 6.7 and 0.9 + 1.9 respectively and the mean OHIS score was 1.35 + 0.6.

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### Introduction

Infection of HIV in adults and children has become a chronic infectious disease. There has been an improvement in the understanding of the pathogenesis and progress of antiretrovirus treatment of HIV infection in children.<sup>1</sup> The HIV is epidemic in the world including Indonesia.<sup>2-6</sup> It is accounted for more than 34 million people, including 2.5 million infection in children aged less than 15 years. More than 90% of HIV-infected children lived in the Sub Sahara area.<sup>2</sup> The prevalence of HIV-infected children is increasing every year, although the incidence of HIV-infected children is declining after the introduction of HAART therapy.<sup>2,3,7,8</sup>

The number of children younger than 15

years receiving ART in low and middle income countries increased from 566.000 to 630.000 in 2011 and 2012 respectively. In contrast, the increase use was substantially less than for adults.<sup>8</sup> This cause many women with HIV and need ART are missing opportunities to start treatment during pregnancy, including in some countries that have a high burden of HIV infection.<sup>8,9</sup>

According to the data from the Directorate of Disease and Environmental Health, the cumulative number of AIDS cases in Indonesia in 2013 was 1438 cases. The data was limited to the ones that have perinatal transmission as risk factor. However, when the data was presented by the group, there were 234 cases (<1 year), 921 cases (1-4 years), 418 cases (5-14 years), 1710 cases (15-19 years). The number of death by AIDS in Indonesia were 9585 people.<sup>10</sup>

There are various manifestations of oral and dental oral health problems that occur in HIV-infected children. The manifestation can be caused by various factors, both directly and

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indirectly. The causes include HIV infection, opportunistic infections and complications of cancer and side effects of drug use.<sup>3,11</sup> The children with HIV infection could also have dental health problems. The common problems are related to oral hygiene and dental caries affecting deciduous and permanent teeth.<sup>12-14</sup> The presence of oral lesions in HIV infected individuals are also known to be predictors of disease progression and markers for immune suppression and signs of virologic failure in children undergoing HAART.<sup>15,16</sup>

Although there is significant literature on the oral manifestations of HIV infection in the pediatric age group from the rest of the world, there are no studies from Indonesia been reported. Also, it is possible that the spectrum of oral manifestations of pediatric HIV infection in Indonesia may differ from the rest of the world. Hence, we conducted this study which was performed in one of the National Hospital in Indonesia in order to compare our findings with some of the studies previously reported from other countries.

## Materials and methods

### Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki and independently reviewed and approved by the Human Research Ethics Committee of the Faculty of Medicine Universitas Indonesia, Cipto Mangunkusumo Hospital (CMH) (No 211/H2.F1/ETIK/2014).

### Participant and General Approach

This cross – sectional study comprised of HIV – positive children treated with HAART attended to Allergy and Immunology of Pediatric Clinic, CMH, Jakarta during March to May 2014. The investigators followed the ethical principles by obtaining informed consent from the parents or caregivers. This study ensured that the participants would benefit for being part in this study by receive oral examination, oral health educations and dental treatment in Pediatric Dentistry Clinic.

### Medical record

Once the informed consent was gained, the sociodemographic data was recorded. This data included age, gender, caregivers, anthropometric indicators of nutritional status, mode of delivery, and immunosuppression status. This data was extracted from the hospital

medical records. Information was recorded in an interviewer administered questionnaire.

The children who confirmed to be HIV positive by ELISA results were recruited into the study. General examination was carried out and recorded by the Paediatrician. The details taken from the children also include CD4+ T cell count and therapeutic drugs used. The researchers ensure that data was safe and confidentiality was kept.

### Clinical measures

The clinical examination was performed by two trained dental surgeons in a consulting room under natural light. The children were sitting on an ordinary chair or on the mother's or caregiver's lap. The sterile dental mirrors and periodontal probes were used. Both examiners performed the examination together.

The extraoral and intraoral examination were performed on all subjects and documented. The classification for presumptive diagnostic criteria for oral mucosal lesions was based on the EC Clearing House Diagnostic criteria for paediatric patients.<sup>3,11</sup> The data on dental status, DMFT, deft and Oral Hygiene Index Score (OHIS) score were also recorded. After the examination, the patients were referred to the pediatric dentist for dental treatment.

### Data analysis

The dental status of immunosuppression children with HIV oral manifestations, DMFT scores, deft and oral hygiene status based on Oral Hygiene Index Score (OHIS) and the length of HAART were recorded. The descriptive analysis of the data was performed.

## Results

Total of 70 children who met the inclusion criteria were participated in this study. The subjects' profile consisted of age, gender, caregivers, nutritional status, delivery of birth, immunosuppression status, line regimen of ARV, oral mucosa findings, DMFT score, deft score, OHI-S and frequency of tooth brushing are given in Table 1.

The subjects were between 1 to 12 years of age ( $6.3 \pm 3.02$  years). The majority of subjects had normal weight (82.9%) but there was 1 (1.4%) subject who were severely underweight. Vertical route was the most common route of HIV infection (85.7%) and the majority of subjects (87.1%) were receiving first line ARV regimen.

Based on the WHO classification of HIV-associated immunodeficiency using CD4 count for paediatric HIV disease, most of the subjects had normal immune status, while only 13(18.6%) subjects had severe immunosuppression. Lymphadenopathy was found in 16 (22.9%) subjects, which was found majorily in submandibular lymph node. Out of 70 children, 66 children (94.3%) had caries in deciduous and permanent teeth and 48 children (68.6%) had gingivitis.

Sociodemographic		n (%)
Sex	Male	33 (47.1)
	Female	37 (52.9)
Age (years)	mean ± SD	6.3 ± 3
Caregivers	Parents	40 (57.2)
	Family Caregiver	25 (35.7)
	Orphanage	5 (7.1)
Delivery of birth	Normal	60 (85.7)
	Caesarian section	10 (14.3)
Clinical findings		
Nutritional status		
BMI / Age :	Severely wasted	1 (1.4)
	Wasted	9 (12.8)
	Normal	58 (82.9)
	Overweight	2 (2.9)
Body height/ Age	Severly stunted	6 (25)
	Stunted	5 (20.8)
	Normal	13 (54.2)
Line regimen of ARV	First	61 (87.1)
	Second	9 (12.9)
Length of HAART	Median (min and max score)	4 (0 - 12)
Immunosuppression status	Mild	2 (2.8)
	Moderate	7 (10)
	Severe	13 (18.6)
Lymphadenopathy	None/absent	48 (68.6)
	Submandibular	14 (20)
	Submental	1 (1.4)
	Submandibular, cervical and submental	1(1.4)
Oral Mucosal finding	None/absent	54 (77.2)
	Gingivitis	48 (65.6)
	Aphthous ulcers	4 (5.7)
	Pseudomembrane candidiasis	1 (1.4)
	Herpes infection	1 (1.4)
	Oral wart like lesion	1 (1.4)
Caries index (Mean ± SD)	DMFT	0.9 ± 1.9
	deft	8.2 ± 6.7
Oral Hygiene Index Score (OHIS)	Mean +SD	1.35±0.6
	Frequency of tooth brushing per day	
	1	31(43.7)
	2	20 (28.2)
	3	2 (2.8)
	Not regularly	18 (25.4)

**Table 1.** Sociodemographic characteristics of 70 subjects.

Table 2 describes 7 children with oral manifestations and are classified according to age, sex, immunosuppression status, line of ARV regimen, DMFT, deft and OHIS categories. Two children were severe immunosuppressed and 5 children were not immunosuppressed. These subjects had tooth decay in the deciduous and permanent teeth.

Oral Manifestation	Age	Sex	Immunosuppression status	Line of regimen	DMFT	deft	Category OHIS	Weight-Height/ Height - Age
Minor RAS	2 y 10 m	F	Severe	1	14	0	Fair	Wasted/ severely stunted
	6 y 11m	M	Normal	1	10	0	Good	Normal/Normal
	7 y 9 m	M	Normal	2	10	0	Good	Wasted/Normal
	10 y 1 m	M	Severe	1	3	2	Good	Normal/Normal
Pseudomembranous candidiasis	6 y 2 m	F	Normal	1	18	0	Fair	Normal/Normal
Recurrent Intraoral Herpes	11 y 6 m	M	Normal	2	0	4	Good	Normal/Normal
Oral Warts like lesion	3 y 11 m	M	Normal	1	2	0	Fair	Normal/Normal

**Table 2.** Type and number of oral lesions compared with age, sex, immunosuppression status, line of ARV regimen, DMFT, dmft and OHIs categories in the study.

\*M = male; F = female; y = year; m = month; line of ARV regimen: 1 = 2 NRTIs + PI ; 2 = boosted PI + 2 NRTI; AZT+3TC; ABC or TDF+3TC (or FTC).







**Figure 1.** (a,b) Minor aphthous ulcers of dorsal of the tongue and the lower labial mucosa (black arrow); (c) Hutchinson teeth (white arrow); (d) and carious of deciduous dentition.

## Discussion

The administration of anti retroviral drugs is a life long process, expensive and have side effects.<sup>17</sup> The increased of the occurrence of oral lesions in children in the developing countries could be related to the lack of early diagnosis and medical care, poor nutritional status, minimal or sporadic access to ARV, being orphaned or abandoned.<sup>12</sup> This study had explored the oral condition of the children with HIV infection with HAART in the main Indonesian National Hospital. The HAART induction initially related to the clinical presence of oral lesions such as oral candidiasis, since its presence is usually indicated an immunosuppression state and progression of the infection. Therefore, usually HAART is indicated for more severely immunosuppressed patients.<sup>18</sup>

Wide spectrum of oral lesions may vary in severity and were associated by paediatric HIV infection. The decreases of the finding of oral lesions such as oral candidiasis, Kaposi sarcoma, and HIV-related periodontal diseases were reported with the use of HAART, although other studies had reported differently.<sup>3,5,16</sup> The use of HAART also linked to the improved status of patients and increases the findings of lesions related to salivary gland diseases, human papillomavirus (HPV), xerostomia, and recurrent oral ulcers.<sup>16,19-21</sup> In the current study, only 10% of children HIV had oral lesions. This finding was similar with previous study that showed decrease in the prevalence of soft tissue oral lesions. The study showed decreased of oral lesions from 34.4% to 8.2%.<sup>22</sup>

The prevalence of gingivitis was high in this study (68.6%) compared with other previous studies which showed that 18%-40% of the subjects had gingivitis.<sup>11</sup> However, previous research also found that gingivitis is the most common oral manifestation found. Gingivitis could manifest both in patients with and without immunosuppression. In the children with HIV, this is often due to serious immunosuppression, negligence of oral hygiene and the presence of oral lesions causing pain in brushing their teeth.<sup>11</sup> The common lesions found in this study were gingivitis and several minor recurrent aphthous ulcers. There were several oral aphthous ulcers found in the subjects of the study. The prevalence of aphthous ulcers in patients with HIV tend to be painful and larger compare to non HIV infected patients. The precise mechanism of the ulcers is still unknown, however the possible adverse effect of the ARV drugs and possible vital nutrient deficiency might be related.<sup>7</sup> The results of this study were different with other previous studies that found gingivitis, parotid hypertrophy and linear gingival erythema as the most common lesions.<sup>11</sup> Furthermore, this study also different with other study in an industrialized country which found parotid hypertrophy, oral candidiasis and Kaposi sarcoma as the most common lesions.<sup>23</sup>

The prevalence of oral candidiasis (OC) in this study was 1.4% (1 patient) with deft score 18, fair OHIS, first line of HAART regimen (Zidovudine, Lamivudine, Nevirapine) with mean duration 1 year 7 months. The frequency of candidiasis this study was lower than other studies (22% and 24%).<sup>4</sup> Oral candidiasis was more frequent being observed in the patient treated without a PI.<sup>3,4</sup> Studies showed prevalence of OC was declined in children treated with ARV by two mechanism of HAART. Protease inhibitor (PI) may directly inhibit growth of *Candida* by the similarity of PI with secreted aspartic proteinases (SAPs). Patient on HAART for the duration of more than six months had significantly lower prevalence of oral lesions especially oral candidiasis. There still many conflicting results about the relationship between prevalence of oral lesions, immunosuppression and viral load.<sup>20</sup>

This study also found recurrent intraoral herpes, an a wart-like lesion in the minority of the subjects. Although there was only one wart-like lesion found in this study, the increase of HPV

lesions among patient on HAART has been associated with immune reconstitution.<sup>24,25</sup> This study is the first which report the presence of oral wart-like lesion in a child with HIV infection in Indonesia. One of the drawback of the data was that we did not confirm the presence of HPV as the etiology of the lesion with further examination such as immunohistochemistry. It was suggested that the increased of oral warts lesion may be associated with the protease inhibitor effect of the HAART regimens.<sup>26</sup> Therefore, the long-term monitoring of these children is needed.

This study also found high prevalence of dental caries in deciduous and permanent teeth of the children. There were only 6 children (11%) who had no dental caries. The previous longitudinal study discovered that dental caries particularly in the deciduous dentition occur out of proportion in HIV-infected children when compared with uninfected children.<sup>13,27</sup> This indicates that the awareness of children and their caregivers in maintaining healthy teeth and mouth independently was still low. There were several possible causes cause the high dental caries finding in this study. One possible cause was that the respondents were generally aged between 6-8 years, which had a mixed dental age and classified as susceptible to dental caries. Other possible causes were not many children get an education about the importance of maintaining healthy teeth and mouth. In addition, a child's behavior can determine the status of their dental health, including diet and teeth cleaning habits. Diet and high sugar consumption may also cause the score of deft becomes high. In general, children are very fond of sweets like cotton candy, candy, and chocolate. Food is classified cariogenic foods, which when dissolved together with saliva will be attached to the tooth surface as a pellicle and will form dental plaque.<sup>28</sup>

Dental caries, reduced immunological response, painful symptoms in the mouth, decreased salivary function and continuous use of medicines that have been formulated as syrups or sugared solutions are usual characteristics of children with AIDS.<sup>3,4,20,27</sup> These children frequently exhibit lesions on the oral mucosa, resulting in pain that contributes to ineffective or infrequent tooth brushing. All of these conditions imply the risk of a prejudicial impact on oral health, and may affect the quality of life.<sup>29</sup>

The access of paediatric patients who have AIDS or are HIV positive to programs of oral health is made difficult by the stress of parents and guardians, the accumulation of multiple treatment needs, and reduced integration of units of medical and dental care. The insufficient provision of dental services for children with special care needs has been appraised as a chronic public health problem.<sup>29</sup> Strong points of the study were the population of children assessed in the hospital and the completeness of overall coverage, obtained by undertaking the measurements in the hospital. Limitations of the study were that healthy paediatric patient was not examined and determined. The differences in sex, age distribution, maternal nutritional status, inadequate weaning practices and diet, and recurrent episodes of illness biochemical aspect of saliva and socioeconomic status between the groups of children were not measured and included in the analysis. Large scale studies are necessary to determine the oral manifestations related to long-term use of HAART with further investigation of the role of these factors through longitudinal follow up.

However, despite the decrease in the presence of oral lesions following the introduction of HAART, some factors must be considered. Firstly, the long-term effects of HAART - related hyposalivation. Secondly, the increased prevalence of oral warts that are related to HPV.

Thirdly, the correlation between CD4 cell counts and oral manifestation does not always in line. Based on these factors, the dentists should do a thorough examination of the oral health of these patients, mainly for any early signs of cancer. In fact, cancer has been recently linked to HIV infection and pay attention to lesions that are not commonly related to HIV.<sup>30</sup> The examination is relatively simple because the oral cavity can be investigated quickly with a clinical examination.

Therefore, early diagnosis and prompt treatment of the oral lesions which are the important signs of the progression of the infection can be done.

## Conclusions

This study did not find the lesions that were commonly related to HIV infection in children. There has been a considerable

reduction in the frequency and severity of oral disease associated with HIV infection with the use of HAART. However, long-term monitoring of these children should be done, since the CD4 counts and the oral manifestation are not always correlating over time of the treatment. The appearance and treatment of the lesion with close association with the use of HAART should be monitored and treated.

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### Declaration of Interest

The authors report no conflict of interest.

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