

# Sensitivity and Specificity of Linear Gingival Erythema as Immune Suppression Marker in Pediatric HIV-infected at UPIPI Soetomo General Hospital Surabaya, Indonesia

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# Sensitivity and Specificity of Linear Gingival Erythema as Immune Suppression Marker in Pediatric HIV-infected at UPIPI Soetomo General Hospital Surabaya, Indonesia

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## ABSTRACT

**Introduction:** Strikingly, more than 95% pediatric HIV infections worldwide are in developing countries. Although ART can reduce significantly the risk of HIV transmission to children born from HIV-infected mothers, this can be effective only if the women know their HIV status. In many developing countries, such as Indonesia, the lack of access by pregnant mothers to laboratory facilities may deprive them of knowing their HIV status, thus the opportunity to transmit the disease to their children is high, knowing no preventive intervention is attempted. To date, it is estimated that the number of HIV infected children in Indonesia who are left undiagnosed is still high, therefore a study on clinical markers of HIV that can aid in the diagnosis and predict the severity of the disease among children is critical. In this study, Linear Gingival Erythema is assessed on its correlation to degree of immune suppression to be used as HIV clinical marker in laboratory-poor settings in Indonesia. **Method:** HIV-infected children admitted to Soetomo General Hospital between June – October 2017 were screened and examined intraorally for the presence of LGE. Other relevant data were obtained from questionnaire-guided interview to parents/guardians and from patient's medical record. **Results:** LGE was found in 21.43% children and statistical analysis shows significant correlation of LGE to degree of immune suppression. **Conclusion:** Further study with larger study population size is required to analyze the sensitivity and specificity of LGE to be used as HIV marker in predicting a particular degree of immune suppression, specific to Indonesian pediatric population.

**Keywords:** Oral Manifestation, Children with HIV/AIDS, Linear Gingival Erythema, CD4+

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## INTRODUCTION

Human Immunodeficiency Virus (HIV) continues to be a major global health issue. United Nations Program on HIV/AIDS (UNAIDS) estimated 36.7 million people

worldwide were living with the infection in 2016, with an extremely high proportion (95%) resides in developing countries. Despite the discovery of ART decades ago, the growth rate of HIV-infected population is still unacceptably high; 5.000 new infections per day, which 400 among them are children below 15 years.<sup>1,2</sup>

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Most (90%) children were infected with HIV through mother to-child transmission (MTCT).<sup>3</sup> Although the administration of ART during pregnancy and other preventive interventions can significantly lower the risk of MTCT from 45% to less than 2%, this is not the case for many developing countries, such as Indonesia.<sup>4</sup>

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Indonesia does not screen for HIV infection as part of its routine antenatal care due to laboratory limitations in many areas.<sup>5</sup> This concerning condition causes many children born from unaware women of their HIV status do not get the necessary preventive interventions from the outset, thus they are very vulnerable to get vertically infected. This is proven by the drastic increase of reported new HIV infections among Indonesian children below 4 years between 2010-2015 by >230%.<sup>6</sup>

To date, it is estimated that the number of HIV infected children who are left undiagnosed in Indonesia is still high.<sup>1</sup> When no laboratory facilities are available, clinical indicators becomes the solely most important marker in making presumptive diagnosis of HIV infection and predict the severity of the disease.<sup>7,8</sup> Oral manifestations have longed been studied to be used as HIV clinical indicators, however no studies to date have analyzed the correlation of these oral lesions to predict certain degree of immune suppression among Indonesian pediatric population. One of the most commonly found oral lesions in HIV pediatric infection is Linear Gingival Erythema (LGE).<sup>9</sup> The aim of this study is therefore to analyze the correlation of LGE to degree of immune suppression among pediatric patients admitted to Intermediate Care and Infectious Disease Centre (UPIPI), Soetomo General Hospital, Surabaya, Indonesia.

## MATERIAL AND METHOD

A cross-sectional study was carried between June – October 2017 at the outpatient clinic UPIPI, Soetomo General Hospital. The study protocol was approved by Ethics Committee of Dr. Soetomo Hospital (No:326/Panke.KKE/V/2017) and Health Research Ethical Clearance Commission Universitas Airlangga (No:137/HRECC.FODM/VIII/2017). Pediatric patients under 18 years with confirmed HIV diagnosis according to the Indonesian Ministry of Health guidelines and attended the center between the study period were screened. The age limit set for pediatric patients in this study follows the regulations applied by the Indonesian legal system.<sup>10</sup>

Prior to the study, attending parents/guardians of the eligible patients were explained about the study objectives. Approval from parents/guardians regarding the participation of their children in the study was obtained by written consents. Oral mucosal status of

each patient was then assessed by a trained oral medicine specialist using disposable plastic mouth mirrors and sterile gauze pads under artificial lighting. Identification of LGE was based on its clinical features according to EC-Clearinghouse diagnostic criteria as a distinct fiery red band along the margin of the free gingiva, with the amount of erythema is disproportionately intense for the amount of plaque seen.<sup>9</sup>

Other relevant data of the patients were obtained from their respective parents/guardians through questionnaire-guided interview and from their medical records. Data collected include age, gender, use of ART, and latest laboratory result on CD4 values (CD4% or CD4 counts). Viral load counts were not accessible to most patients; thus, this parameter was excluded from the present study. To determine patients' immune status closest to the condition at oral examination, CD4 values were restricted only up to 6 months interval from the date of examination. This time range follows the Indonesian Ministry of Health guidelines on pediatric CD4 monitoring<sup>11</sup>. CD4 value of each patient served as a baseline to determine patient's degree of immune suppression according to classification system of Centers for Disease Control (CDC) (Table 1).<sup>12,13</sup>

Correlation between LGE and degree of immune suppression was analyzed using chi-square test. Statistical Package of Social Sciences (SPSS) 17.0 for windows was used and p values <0.05 were considered significant.

## RESULTS

The study was conducted among HIV-positive children admitted to the outpatient clinic at UPIPI, Soetomo General Hospital, Indonesia. Between June – October 2017, a total of 47 HIV-positive children who attended the center were screened. This number is much lower than the total number of children registered at the center. Although all HIV-positive children are required to pay periodic visit to the center for monitoring, the reality did not seem so. Many parents/guardians did not attend the center with their children, unless their children show any symptoms. Far distance between the center and their homes and the fact that their children need to attend classes at schools were the most-heard reasons from parents/guardians who came to the center to get the prescribed ART for free on behalf of their children.

Out of the 47 children screened, a relatively high proportion (19 children) had to be further excluded. Reasons for exclusion were parental refusal in providing consents, children being not cooperative during examination, and no CD4 values found within 6 months interval from the date of oral examination on patients' medical record. Not all children were routinely get their CD4 tested due to the high laboratory cost. Consequently, the total number of children included in the study is 28 children.

Summary of age range, ART status, and degree of immune suppression of these children are presented in

Table 2. Oral examinations on 28 Indonesian children found LGE in 6 (21.43%) children (Fig 1 & 2). Three (10.71%) children with LGE were on ART while the other 3 (10.71%) were ART naïve (Table 2).

Indonesian children were categorized into several degrees of immune suppression. Two (7.14%) children with LGE were in degree of no immune suppression, while the other 4 (14.29%) children with LGE were in degree of severe immune suppression (Table 2). Statistical analysis to correlate the occurrence of OHL according to child's immune suppression was found to be statistically significant (p value = 0.027) (Table 3).

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**Table 1. Immunologic categories based on age-specific CD4 % and CD4 counts.**

Immunologic category	Age of child				
	< 12 months		1-5 years		> 5 years
	cells/mm <sup>3</sup>	%	cells/mm <sup>3</sup>	%	cells/mm <sup>3</sup>
No immune suppression	≥ 1.500	≥ 25	≥ 1.000	≥ 25	≥ 500
Moderate immune suppression	750 - 1499	15 - 24	500 - 999	15 - 24	200 - 499
Severe immune suppression	< 750	< 15	< 500	< 15	< 200

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**Table 2. Summary of age, ART status, and degree of immune suppression in the study population**

	No. of Patients	
	OHL present	OHL absent
Total	6 (21.43%)	22 (78.57%)
<b>Age</b>		
Age range (years)	1 - 15	
Mean age	6.8 ± 3.1	
<b>HAART</b>		
Yes	3 (10.71%)	21 (75%)
No	3 (10.71%)	1 (3.57%)
<b>Degree of immune suppression</b>		
No	2 (7.14%)	16 (57.14%)
Moderate	-	3 (10.71%)
Severe	4 (14.29%)	3 (10.71%)

**Table 3. Statistical relationship between LGE and immune suppression degree in the study population**

Degree of Immune Suppression	No. of Patients		Chi-square	P value
	LGE present	LGE absent		
No	2 (7.14%)	16 (57.14%)	7.2590	0.027*
Moderate	-	3 (10.71%)		
Severe	4 (14.29%)	3 (10.71%)		

\*statistically significant





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Figure 1. Four years old, ART naïve female patient



Figure 2. Five years old, ART naïve male patient (a) Maxillary LGE (b) Mandible LGE

## DISCUSSION

Oral lesions can not only indicate HIV infection, they are also among the earliest clinical features of the infection that can aid in predicting the course of the disease. EC-Clearinghouse clinical diagnostic criteria, the term of reference for most studies in HIV-associated oral diseases, classified LGE into lesions commonly associated with pediatric HIV infection. LGE was formerly known as HIV-gingivitis and it is the most common form of HIV-associated periodontal disease in infected children.<sup>14</sup>

LGE has been correlated to fungal infection of the *Candida* species, yet the nature etiology of this lesion is still a controversy, as other studies reported different findings.<sup>15</sup> Umadevi et al reported the possibility of certain viruses, such as CMV, EBV, and papillomavirus in initiating and causing LGE progression.<sup>16</sup> On the contrary, Aas et al. found *Saccharomyces cerevisiae*, *Gamella spp.*, *Dialister spp.*, *Streptococcus spp.*, and *Veillonella spp.* as the causative agents of LGE.<sup>17</sup> Despite the discrepancies between studies, it is now widely accepted that *Candida* contributes to the occurrence of LGE as many clinical cases were effectively treated with antifungal treatment.<sup>15,18</sup>

In this study, the prevalence of LGE was found to be 21.43%. This prevalence is higher than other studies in developing countries in Uganda (0.84%)<sup>19</sup> and India (2.27%<sup>20</sup> and 9.05%<sup>21</sup>) yet lower than a study conducted in Venezuela (27.03%)<sup>22</sup>. The varying prevalence of LGE between countries may be due to the distinct characteristics among the populations (proportion of the population on ART, their adherence to ART, immune status of the population, nutritional status, etc.), as well as the influence of cultural and geographical factors of

each country.

Furthermore, EC-Clearinghouse classification has also associated LGE to be more prevalent in children HIV infection than in adults.<sup>18</sup> Comparing this study to another study conducted in 2014 among adult patients at the same centre (UPIPI, Soetomo General Hospital) supports this classification as LGE was found to be much lower in adult patients (5.83%) than among pediatric children in this study.<sup>23</sup>

ART has been widely accepted to be highly effective at inhibiting HIV replication, although it is not curative. Combination of ART can dramatically suppress the number of virus circulating in the plasma, even to a level of undetectable. With the successful viral suppression, immunologic recovery is expected and the number of opportunistic infections to manifest should be lower.<sup>24</sup> In this study, although LGE were also found in children undergoing ART, LGE were found more predominantly in children who had not received treatment as seen in Table 2.

Although LGE in this study were found in children with severe immune suppression yet also in children with no immune suppression, the occurrence of LGE is more notable in children with severe immune suppression (4 children with LGE among 7 children with severe immune suppression) than in children with no immune suppression (2 children with LGE among 18 children with no immune suppression). This trend indicates that LGE will be more likely to manifest when immune status of the host is continuously declining. Statistical analysis between the presence of LGE with degree of immune suppression is also proven to have a solid relationship ( $p$  value = 0.027) (Table 3).

## CONCLUSION

Immune status was significantly correlated with the presence of LGE in this study. However, its sensitivities and specificities to predict a specific degree of immune suppression is yet still need to be assessed. Further study with larger Indonesian pediatric HIV/AIDS population size is thus recommended.

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**Conflict of Interest:** The authors declare no conflict of interest.

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