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## DETERMINANT FACTORS OF LOW COGNITIVE, MOTORIC AND LANGUAGE PERFORMANCE OF HIV-INFECTED CHILDREN

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### ABSTRACT

The effects of HIV infection on children's physical growth, psychological health, and neurodevelopment are essential. This study aims to know the determinants factor low cognitive, motoric, and language performance of HIV-infected children. This study examined 68 HIV-infected children ranged 0 to 36 months selected by simple random sampling. The sample size was determined by simple calculation for cohort design. Cognitive, motoric, and language were assessed using the Cognitive Adaptive Test (CAT) and Clinical Linguistic and Auditory Milestone Scale (CLAMS) score, which are components of the Capute Scale. Data were analyzed using a cross tab, and a significant Pearson chi-square ( $p < 0.05$ ) was used to identify the determinant factors. The result showed that CD4 level, length of antiretroviral treatment, age, stage of HIV infection, socioeconomic status, and family income were determinant factors of low cognitive, motoric, and language performance of HIV-infected children. The performance of cognitive, motoric, and language aspects in HIV children was affected by CD4 level, length of antiretroviral treatment, age, stage of HIV infection, socioeconomic status, and family income. Early intervention in developmental status is needed to prevent HIV-infected children's low cognitive, motoric, and language performance.

**Keywords:** children; cognitive; HIV; language; motoric

### INTRODUCTION

Children with HIV infection are at risk of developmental and behavioral challenges. At the end of 2020, 2.1 million children were living with HIV/AIDS. Two million of them are located in sub-Saharan Africa. Transmission vertically by mother is the most route of infection of these children acquire HIV from HIV mothers during pregnancy, birth, or breastfeeding. The early antiretroviral interventions reduce the risk of mother-to-child HIV transmission. However, the coverage of interventions is still not widely accessible or available in most low-middle-income countries where HIV incidence is high. On the other hand, 1 of 500 children gets new HIV infections per day. The increasing number of children

receiving ART from 75,000 to 200,000 in 2020.

The neurodevelopment aspects of HIV-children commonly affected were growth, gross motoric, social and personal performance, cognitive and language. The main pathogenesis is virus entering the central nervous system (CNS) of foetal during pregnancy through transplacental transmission and mostly affecting glial cells and oligodendrocytes, which results in neuronal injury in the developing brain. This brain injury causes a significant encephalopathy in foetal. Most impairments affect cognitive, language, and motor functions. The prevalence of these delays may be variated by most 60%. Delayed neurodevelopmental are particularly common in countries with limited treatment

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resources.<sup>8</sup> Clinical features include loss or failure to achieve appropriate developmental milestones, impaired brain growth, and global or selective impairments in cognitive, language, motor, attention, behavior, and social skills that may affect day-to-day functioning.<sup>10</sup> Some degrees of cognitive decline may present even in the early and asymptomatic stages of HIV infection. The benefits of antiretroviral treatment for cognitive performance can be detected after only a few weeks of follow-up.<sup>11,12</sup>

The Capute Scales are screening tools that are widely used to assess neurodevelopmental delays, composed of CAT to assess cognitive function and 3. AMS to evaluate language functions. This is an easy and practical screening neurodevelopmental assessment test for HIV-infected children in an outpatient setting.<sup>13</sup> With the ease of this test, we can cooperate it into routine practice and would be able to detect children with delayed development who will benefit from an early stimulation program early.<sup>14</sup> This study aimed to assess determinant factors that affected HIV-infected children's low motoric, cognitive, and language performance.<sup>15</sup>

We recruited 136 subject as sample base on sample calculation of cohort design. The sample was divided into two group, 68 HIV infected group and 68 healthy children as control group.

#### MATERIAL AND METHODS

Samples that meet inclusion criteria was selected as subject. The criteria for HIV group was: confirmed diagnose of HIV infection by serological test positive for HIV antibody and have followed treatment of antiretroviral minimum 6 month. Inclusion criteria for healthy control group was negative for antibody anti HIV test. Exclusion criteria was other comorbid disease such as cerebral palsy, and serious complication of HIV that cause subject difficult to follow the assessment.

The HIV sample was recruited in paediatric policlinic Sanglah hospital, and

health control group was recruited in Taman Kanak-Kanak Werdi Kumara, Sanglah Hospital, Denpasar

The Capute Scales were used to examine the subject's cognitive, motoric, and language performance. The CLAMS consisted of 43 language items, and CAT consisted of 57 visuomotor, nonverbal problem-solving items.<sup>16</sup> The first step, we determine the chronological age and based on age. Then we assess the developmental quotient of each CAT and CLAMS by fulfilling questionnaires based on the subject's ability to pass the task. The Scores of Cat and Clams were categorized as delay under 70, suspect as 70-84, and normal as 85-120.<sup>17</sup> Data was analyzed using a cross tab, and a significant Pearson chi-square ( $p < 0.05$ ) was used to identify the determinant factors.

#### RESULT

A total of 68 HIV-infected children were recruited as research subjects. Several factors affected Cat/Clasm score as a mirror of cognitive, motoric, and language performance. Table 1 explains the factors analyzed by multinomial regression to obtain factors that affect the values of Cat and Clams that have been categorized as suspect 70-84 and normal as 85-120. No delay category was found in the subject because of a history of antiretroviral treatment prior to examination. The Cat / Clams scores were examined at the first meeting and then after six months of observation. The first variable analyzed was gender, both male and female there were no differences in the value of Cat / Clams both in the initial month or the sixth month, evidenced by a  $p$  value  $> 0.05$ , which was not significant. The next variable is CD4 + levels. Most subjects with low Cat and Clams values are subjects with CD4 levels less than 25 cells / mm<sup>3</sup>, as evidenced by  $p$  0.006 in the first month and  $p$  0.003 in the sixth month. The next variable is the length of ARV administration, in which 89.3% - 100% of subjects with low Cat and Clams values have ARV duration of less than 12

months. Based on age classification, age 25-36 months have a lower Cat value compared to other age groups, with a value of p 0.008 in the first month and p 0.01 in the sixth month.

Table 1. Analyses of Determinant Factors of Cat/Clams Score

Variable	First Examination			6 month Examination				
	CAT	p	CLAMS	p	CAT	p	CLAMS	p
	70-84	85-120	70-84	85-120	70-84	85-120	70-84	85-120
<b>Gender</b>								
Male	12 (32.4)	25 (67.6)	12 (32.4)	25 (67.6)	14 (37.8)	23 (62.2)	12 (32.4)	25 (67.6)
Female	15 (48.4)	16 (51.6)	14 (45.2)	17 (54.8)	16 (51.6)	15 (48.4)	14 (45.2)	17 (54.8)
		0.218			0.205		0.329	0.324
<b>CD4 Level</b>								
<25 cells/mm <sup>3</sup>	11 (73.3)	4 (26.7)	10 (66.7)	5 (33.3)	12 (80.0)	3 (20.0)	10 (66.7)	5 (33.3)
>25 cells/mm <sup>3</sup>	16 (30.2)	37 (69.8)	16 (30.2)	37 (69.8)	18 (34.0)	35 (66.0)	16 (30.2)	37 (69.8)
		0.006			0.16			0.016
<b>Length of ARV treatment</b>								
<12 months	27 (96.4)	1 (3.6)	25 (89.3)	3 (10.7)	28 (100)	0 (0)	25 (89.3)	3 (10.7)
>12 months	0 (0)	40 (100)	1 (2.5)	39 (97.5)	2 (5.0)	38 (95)	1 (2.5)	39 (97.5)
		0.000			0.000			0.000
<b>Education</b>								
0-12 months	3 (21.4)	11 (78.6)	4 (28.6)	10 (71.4)	4 (28.6)	10 (71.4)	4 (28.6)	10 (71.4)
13-24 months	9 (29.0)	22 (71.0)	9 (29.0)	22 (71.0)	10 (32.3)	21 (67.7)	9 (29)	22 (71.0)
25-36 months	15 (65.2)	8 (34.8)	13 (56.5)	10 (43.5)	16 (69.6)	7 (30.4)	13 (56.5)	10 (43.5)
		0.008			0.085		0.01	0.085
<b>Stage of HIV infection</b>								
Asymptomatic	6 (15.4)	33 (84.6)	7 (17.9)	32 (82.1)	8 (20.5)	31 (79.5)	7 (17.9)	32 (82.1)
Mild	9 (64.3)	5 (35.7)	8 (57.1)	6 (42.9)	9 (64.3)	5 (35.7)	8 (57.1)	6 (42.9)
Moderate	10 (76.9)	3 (23.1)	9 (69.2)	4 (30.8)	11 (84.6)	2 (15.4)	9 (69.2)	4 (30.8)
Severe	2 (100)	0 (0)	2 (100)	0 (0)	2 (100)	0 (0)	2 (100)	0 (0)
		0.000			0.000			0.001
<b>Nutritional status</b>								
Good	11 (31.4)	24 (68.6)	11 (31.4)	24 (68.6)	12 (34.3)	23 (65.7)	11 (31.4)	24 (68.6)
Undernourish	15 (50.0)	15 (50.0)	14 (46.7)	16 (53.3)	17 (56.7)	13 (43.3)	14 (46.7)	16 (53.3)
Malnourish	1 (33.3)	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)	2 (66.7)
		0.304			0.445		0.180	0.445
<b>Socio-economic status</b>								
Low	17 (68.0)	8 (32.0)	16 (64.0)	9 (36.0)	19 (76.0)	6 (24.0)	16 (64.0)	9 (36.0)
Middle	10 (25.6)	29 (74.4)	10 (25.6)	29 (74.4)	11 (28.2)	28 (71.8)	10 (25.6)	29 (74.4)
High	0 (0)	4 (100)	0 (0)	4 (100)	0 (0)	4 (100)	0 (0)	4 (100)
		0.001			0.002		0.000	0.002
<b>Maternal Education</b>								
Elementary school	1 (100)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)
Junior high school	9 (45)	11 (55)	8 (40)	12 (60)	9 (45)	11 (55)	8 (40)	12 (60)
Senior high school	14 (34.1)	27 (65.9)	14 (34.1)	27 (65.9)	17 (41.5)	24 (58.5)	14 (34.4)	27 (65.9)
Bachelor degree	3 (50)	3 (50.0)	3 (50)	3 (50)	3 (50)	3 (50)	3 (50)	3 (50)
		0.467			0.516		0.688	0.516
<b>Father Education</b>								
Elementary school	3 (100)	0 (0)	3 (100)	0 (0)	3 (100)	0 (0)	3 (100)	0 (0)
Junior high school	9 (42.9)	12 (57.1)	8 (38.1)	13 (61.9)	9 (42.9)	12 (57.1)	8 (38.1)	13 (61.9)
Senior high school	13 (932.5)	27 (67.5)	13 (32.5)	27 (67.5)	16 (40)	24 (60.0)	13 (32.5)	27 (67.5)
Bachelor degree	2 (50)	2 (50)	2 (50)	2 (50)	2 (50)	2 (50)	2 (50)	2 (50)
		0.128			0.131		0.246	0.131
<b>Family income</b>								
<1 milion IDR	2 (7.1)	26 (92.9)	3 (10.7)	25 (89.3)	4 (14.3)	24 (85.7)	3 (10.7)	25 (89.3)
1-2.5 milion IDR	20 (62.5)	12 (37.5)	18 (56.2)	14 (43.8)	20 (62.5)	12 (37.5)	18 (56.2)	14 (43.8)
2.5-5 milion IDR	5 (62.5)	3 (37.5)	5 (62.5)	3 (37.5)	6 (75.0)	2 (25.0)	5 (62.5)	3 (37.5)
		0.000			0.000		0.000	0.000

The stage of HIV infection was also analyzed, and it found that 100% of subjects with a severe stage had a low Cat / Clams value, followed by a moderate stage of 69.2% - 84.6%. Poor nutritional status at most has a low Cat / Clams value compared

to good nutritional status, but the result is insignificant (p> 0.05). Low economic literacy mostly has low Cat / Clams values, which is significant with p <0.05. mothers with an education level only completed primary school as much as 100% had

children with low Cat / Clams grades. Still, these results were not different from subjects with higher maternal education, evidenced by  $p > 0.05$ . This result is also similar to the father's education variable, which is not statistically different from the value of CAT / CLAMS in subjects with fathers with low education or high education. Furthermore, the last but not least is an analysis of family income, where children with a parent's income below 1 million rupiahs have a higher Cat / Clams value, while  $> 1$  million rupiahs have a lower CAT / CLAMS value, and this is statistically significant ( $p = 0.000$ ).

## DISCUSSION

This study found that children with CD4 counts of less than 25 cells/mm<sup>3</sup> had a lower difference in Cat/Clams scores than children who have CD4 levels of more than 25 cells/mm<sup>3</sup>. The results of this study are in accordance with research by Widyadharna et al., 2017 which stated that subjects with CD4 cells less than 200 cells/mm<sup>3</sup> had lower cognitive function than subjects with CD4 levels of more than 200 cells/mm<sup>3</sup>.<sup>18</sup> Another study by Supadma et al., 2020 also stated that there was a relationship between CD4 levels and Capute Scale values in HIV-infected children compared to children who were not infected with HIV.<sup>19</sup>

Research by Ravindran et al., 2014 found that children with HIV tend to suffer cognitive deficits in the domains of attention, language, verbal learning and memory, visuomotor functions, fine motor performance, and executive functions.<sup>17, 20</sup>

Research by Cohen et al., 2015, stated that the cognitive performance of HIV-infected children is poor compared with healthy controls.<sup>21, 22</sup> Gaining insight into these cognitive deficits is essential, as subtle impairments may progress to more pronounced complications that will influence future intellectual performance, job opportunities, and community participation of HIV-infected children.<sup>23, 24</sup>

Research by Kandehwal et al., 2020 on malnourished children stated that the results indicated that children with SAM exhibit

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developmental delay across all domains.<sup>22</sup> Identifying multiple modifiable risk factors for developmental delay in children with Severe Acute Malnutrition will be helpful in devising early interventional strategies in low-middle income countries; In this study, it was found that most of the HIV-infected children were undernourished, although it was not statistically significant.<sup>24</sup> This can be the result of a series of chronic inflammation caused by HIV infection, which requires the HIV-infected child's body to undergo a higher metabolism to break down ATP to fight the virus, coupled with the release of inflammatory mediators which also exacerbate carbohydrate, fat and protein metabolism so that children to lose a lot of energy and protein.<sup>25</sup> This loss of energy and protein, of course, inhibits nerve conduction which plays an important role in the intelligence process.<sup>26</sup>

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According to Ruel et al., 2011, motor and cognitive deficits were significantly found in HIV-infected ART-naive Ugandan children with CD4 cell counts of 350 cells/IL<sup>7</sup> percentages of .15%. Early initiation of ART could prevent or reverse such deficits. In accordance with the results of this study which states that the length of ARV treatment has a significant effect on the value of Cat/Clams, the earlier a child is treated with ARV, the better his neuropsychomotor, cognitive, and language development will be. These results are also supported by Blokhuis et al., 2016 who stated that ART effectively reduces brain injury by intervening viral load and consequent inflammation.<sup>24</sup> Uninfected children from HIV mothers suffered a higher developmental delay than unexposed children in receptive and expressive language.<sup>25</sup>

Other research by Sania et al., 2019 stated that nursing patterns, parental education, stimulating factor, and environmental and nutritional factors contribute to child development. In contrast to this study's results, the family's socioeconomic status greatly affects the cognitive, motor, and language functions of children with HIV. The level of education of

mothers and fathers **in this study** did not significantly affect cognitive, motor, and language functions.<sup>26</sup>

#### CONCLUSION

The CD4 level, length of antiretroviral treatment, age, stage of HIV infection, socio economic status, and family income were determinant factors of low cognitive, motoric, and language performance of HIV-infected children. It can be concluded that internal and external factors affect cognitive, motoric, and language. Further research must be conducted to assess how this factor affects HIV-infected children's cognitive, motoric, and language performance.

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