

## Characteristics of HIV-infected children born to HIV-positive mothers in Cipto Mangunkusumo Hospital between 2002 and 2007

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### Abstract

**Background** In 2003, the Joint United Nation Program on HIV/AIDS and the World Health Organisation estimated that there will be 36.2 million people living with HIV/AIDS throughout the world by the end of 2003, and that 2.1 million of them will be children less than 15 years old. The profile of children with HIV in the Department of Child Health, Cipto Mangunkusumo Hospital has not been studied.

**Objective** To identify the characteristics of HIV-infected children born to HIV-positive mothers, and to evaluate the Prevention Programme for Mother-to-Child Transmission at Cipto Mangunkusumo Hospital.

**Methods** This was a cross-sectional study conducted between March and May 2008 based on medical records. The study population consisted of all mother-child pairs who were admitted between January 2002 and December 2007.

**Results** Between 2002 and 2007, 342 children were born to HIV-infected mother, with 201 (58.5%) children contracting HIV. The median age of children was 20 months. There were 121 (35.4%) cases involved in prevention of mother-to-child transmission. Triple-drug antiretroviral therapy was prescribed to 78.1% children. The most frequent morbidities were chronic diarrhea, wasting syndrome, and oropharyngeal candidiasis. Thirty-six children died; mostly due to sepsis (30.5%)

**Conclusion** The majority of cases of HIV were between 1 and 5 years old. The most frequent morbidities were chronic diarrhea, wasting syndrome, and oropharyngeal candidiasis. Thirty-six children died mostly due to sepsis. The preven-

tion program for mother-to-child transmission should be encouraged among pregnant women who are known to be HIV-positive. [*Paediatr Indones.* 2009;49:112-8].

**Keywords:** HIV, AIDS, mother-to-child transmission, antiretroviral therapy

Since the first case of acquired immunodeficiency syndrome (AIDS) in a child was reported in United States in 1982, Human Immunodeficiency Virus (HIV) infection has been one of the most common causes of morbidity and mortality in United States. In 2003, a report from the Joint United Nation program on HIV/AIDS and the World Health Organizations (UNAIDS-WHO) estimated that there will be 36.2 million people living with HIV/AIDS throughout the world by the end of

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2003, and 2.1 million of them were children less than 15 years old.<sup>1</sup> In 2005, there were 2.5 millions death due to AIDS.<sup>2</sup>

In Indonesia, the Ministry of Health reported 3924 cases of HIV/AIDS between September 1987 and September 2003 (2685 HIV cases and 1239 cases of AIDS). Of these patients, 429 died.<sup>3</sup> The cumulative number of cases until 31 March 2007 shown an increase to 5640 cases of HIV infection and 8988 cases of AIDS. The highest cumulative proportion of AIDS cases (54.3%) was found in adults in the reproductive age range of 20-29 years. Therefore, it is suggested that the number of infants born to HIV-positive mothers will increase in Indonesia.<sup>4</sup> Between 1996 and July 2007, 289 infants and children were exposed to HIV according to the Department of Child Health, Cipto Mangunkusumo Hospital. Studies on HIV-infected infants and children at Cipto Mangunkusumo Hospital between 2002 and 2005 revealed that the most common opportunistic infections were diarrhea, followed by failure to thrive, dermatitis, tuberculosis, otitis media, bronchopneumonia and BCG-itis.<sup>5</sup> A study of 17 children with HIV infection at Fatmawati Hospital, Jakarta, showed that the commonest opportunistic infections were oral candidiasis, lung tuberculosis, chronic suppurative otitis media, and hepatitis C.<sup>6</sup> In contrast, at Soetomo General Hospital, Surabaya, Indonesia, the most common causes of morbidity in HIV-infected children were malnutrition, followed by chronic diarrhea, moniliasis, respiratory tract infections (bronchopneumonia, *Pneumocystis carinii* pneumonia, tuberculosis) and lymphadenopathy.<sup>7</sup> Similar clinical manifestations were also reported in four children with HIV infection at Kariadi Hospital, Semarang, Central Java, Indonesia.<sup>8</sup> We aimed to identify the characteristics of HIV-infected children born to HIV-positive mothers, and to evaluate the program for Prevention of Mother-to-Child Transmission (PMTCT) of HIV at Cipto Mangunkusumo Hospital.

## Methods

This was a cross-sectional study using medical record data from HIV infected children born to HIV-positive mothers at the Department of Child Health,

Medical School, University of Indonesia - Cipto Mangunkusumo Hospital. The study population consisted of all mother-child pairs between January 2002 and December 2007. Medical records were retrieved and data were collected for analysis. This study was approved by the Ethical Committee of Faculty of Medicine, University of Indonesia.

The clinical manifestations of HIV infection were categorized clinically according to the Centers for Disease Control and Prevention (CDC) 1994.<sup>9</sup> Data collected included demographic characteristics, i.e., age, birth weight, and nutritional status based on anthropometric measurement. Nutritional status was assessed at the time when HIV diagnosis was made and was categorized as good, reduced, and poor, according to the Waterlow classification.<sup>10</sup> The clinical data recorded was the status of HIV infection, PMTCT program, clinical characteristics of the HIV infection, and laboratory findings. Data are presented descriptively. We analyzed data using Statistical Package for Social Studies (SPSS) software version 13.0 for Windows PC (SPSS Inc., Chicago, Illinois, USA).

## Results

Between January 2002 and December 2007, 342 children were born to HIV-positive mothers. From these cases, 202 (58.8%) were HIV-positive, 46 cases (13.5%) were HIV-negative, and the rest (27.8%) were of unknown status. The number of HIV-positive cases sharply increased from two cases in 2002 to 13 cases in 2003, 31 in 2004, 41 in 2005, 42 in 2006 and 72 cases in 2007.

The age of the patients was not normally distributed; more babies and young children were found compared with the older ones. The median age of HIV-positive children was 20 months, ranging from 0 to 87 months. The largest proportion (61.7%) was children between 1-5 years. More than half of the cases were boys. See **Table 1**.

Most children were born with normal birth weight ( $\geq 2500$  g) with a mean of 3008 g (SD 469.5) g. However, on hospital admission there were 55 (27.4%) and 43 (21.4%) children who presented with low and poor nutritional status, respectively. A parental risk factor as an intravenous drug user

**Table 1.** Characteristics of HIV-positive children (n = 201)

Characteristic	n	%
Age group		
< 1 year old	62	30.8
1 – 5 years old	124	61.7
6 – 12 years old	15	7.5
Gender		
Male	111	55.2
Female	90	44.8
Birth weight		
< 2500 grams	19	9.5
> 2500 grams	140	69.7
No data	42	20.8
Nutritional status at diagnosis		
Good	23	11.4
Low	55	27.4
Poor	43	21.4
No data	80	39.8
Maternal HIV-infection risk factor		
IVDU	38	18.9
MPS	5	2.5
Unknown/ others	158	78.6
Paternal HIV-infection risk factor		
IVDU	121	60.2
MPS	18	9.0
Unknown/ others	62	30.8
Last condition		
Survived	102	50.8
Deceased	36	17.9
Loss to follow-up	63	31.3

(IVDU) was identified in 38 (18.9%) of mothers and 161 (60.2%) of fathers. Transmission risk due to multi-partner sexual (MPS) behavior was identified in 2.5% of mothers and 9% of fathers (Table 1). Both parents were identified as IVDUs in 22 (10.9%) cases, but there was only 1 case where both parents showed MPS behavior. About half of the children were still alive at the end of study.

Approximately 60% of HIV-infected children were in the CDC clinical category C and 51.2% children who had severe immunosuppression. The majority of patients were not tested for viral load; however, among 85 children who were tested, 91.8% had a viral load of more than 100,000 copies/mL (Table 2).

The PMTCT program was followed by 121 from 342 (35.4%) HIV-positive mothers and their children. From these 121 cases, 5 (4.1%) resulted in an HIV-positive child, 40 (33.1%) in an HIV-negative child and 76 (62.8%) cases had an unknown status. From the 221 cases that did not follow the PMTCT program, 196 (88.7%) resulted in an HIV-positive child, 6

**Table 2.** Clinical category, immune category, and viral load in HIV-positive children (n = 201)

Characteristic	n	%
Clinical category (CDC, 1994)		
Category N	5	2.5
Category A	18	9.0
Category B	56	27.8
Category C	121	60.2
Unknown	1	0.5
Immune category (CDC, 1994)		
Mild suppression	25	12.5
Moderate suppression	31	15.4
Severe suppression	103	51.2
CD4 not counted	42	20.9
Viral Load		
< 100.000 copies/mL	7	3.5
> 100.000 copies/ mL	78	38.8
Not tested	116	57.7

(2.7%) cases were HIV-negative and 19 (8.6%) were of unknown status.

The most common morbidities found in HIV-infected children prior to antiretroviral (ARV) treatment were chronic or recurrent diarrhea and wasting syndrome. Each of these conditions occurred in 115 (57.2%) cases. The identified causes of chronic or recurrent diarrhea were *Blastocystis hominis*, *Cryptosporidium*, *Candida albicans*, and *Microsporidia*. Additionally, more than half of the children (54.3%) had persistent oropharyngeal candidiasis. Other morbidities found were anemia (47.8%), lymphadenopathy and hepatomegaly (43.8% each), fever (41.8%), recurrent respiratory infections (37.3%), dermatitis (26.4%), pneumonia (15.4%), splenomegaly (13.4%), otitis media (10%), trombocytopenia (7.5%), sepsis (4.5%), and *Pneumocystis jiroveci* pneumonia (3%). Several rare and very rare morbidities which indicated manifestations of late HIV infection were also found (Table 3).

The PMTCT program included prenatal antiretroviral (ARV) therapy (65 cases), intrapartum ARV therapy (10 cases), postpartum ARV therapy (three cases), caesarean delivery (158 cases), ARV therapy in infants (118 cases), and nonbreastfeeding (186 cases). Only two cases followed the complete PMTCT program. There were 156 children who were breastfed; 137 (87.8%) were HIV-positive. A history of vaginal delivery was identified in 166 children including three that were delivered with vacuum suction; 146 (88.0%) were HIV-positive. Therapy with prenatal ARV was

**Table 3.** Morbidity of HIV-infected children (n = 201)

	n	%
Clinical category A		
Lymphadenopathy	88	43.8
Hepatomegaly	88	43.8
Recurrent upper respiratory tract infections	75	37.3
Dermatitis	53	26.4
Splenomegaly	27	13.4
Otitis media	20	10.0
Clinical category B		
Chronic or recurrent diarrhea	115	57.2
Persistent oropharyngeal candidiasis	109	54.2
Anemia	96	47.8
Fever	84	41.8
Pneumonia	31	15.4
Trombocytopenia	15	7.5
Sepsis	9	4.5
Cardiomyopathy	4	2.0
CMV infection at less than 1 month of age	3	1.5
Herpes zooster	2	1.0
Varicella	2	1.0
Nephropathy	1	0.5
Hepatitis	1	0.5
Clinical Category C		
Wasting syndrome	115	57.2
Lung tuberculosis	68	33.8
HIV encephalopathy	58	28.9
Lymphadenitis BCG	14	7.0
Pneumocystis jiroveci pneumonia	6	3.0
Esophageal or respiratory candidiasis	5	2.5
Cryptosporidiosis or isosporiasis persistent diarrhea	5	2.5
Disseminated or extrapulmonary tuberculosis	5	2.5
CMV infection at more than 1 month of age	3	1.5
Brain toxoplasmosis	2	1.0
Extrapulmonary cryptococcus	0	0

not received by 277 mothers; 199 (71.8%) give birth to HIV-positive children. Three hundred-thirty two women did not receive intrapartum ARV therapy and 200 (60.2%) had HIV-positive children. Postnatal ARV therapy was not given to 339 mothers and 201 (59.3%) had HIV-positive children. ARV therapy was not administered to 224 infants and 196 (87.5%) were HIV-positive (**Table 4**).

Most children received ARV treatment that consisted of first-line and second-line treatments. The most common first line treatment between 2000 and 2004 was AZT+3TC, with a third drug (NVP) being added from 2003 onwards (AZT+3TC+NVP or d4T+3TC+NVP). The number of children who were treated with ARV was 157 children, with 91 children treated during the study period. Patients also received prophylaxis with co-trimoxazole (**Table 5**).

**Table 4.** Results from the PMTCT program in (n = 342)

Program	HIV Status		
	Positive n (%)	Negative n (%)	Unknown n (%)
Breastfeeding			
Yes (n=156)	137 (87.8)	3 (1.9)	16 (10.3)
No (n=186)	64 (34.4)	43 (23.1)	79 (42.5)
Mode of delivery			
Caesarean section (n=158)	39 (24.7)	39 (24.7)	80 (50.6)
Vaginal delivery (n=166)	146 (88.0)	6 (3.6)	14 (8.4)
Unknown (n=18)	16 (88.8)	1 (5.6)	1 (5.6)
Prenatal ARV therapy			
Yes (n=65)	2 (3.1)	23 (35.4)	40 (61.5)
No (n=277)	199 (71.8)	23 (8.3)	55 (19.9)
Intrapartum ARV therapy			
Yes (n=10)	1 (10.0)	1 (10.0)	8 (80.0)
No (n=332)	200 (60.2)	45 (13.6)	87 (26.2)
Postpartum ARV therapy			
Yes (n=3)	0	2 (66.7)	1 (33.3)
No (n=339)	201 (59.3)	44 (13.0)	94 (27.7)
ARV therapy to infant			
Yes (n=118)	5 (4.2)	40 (33.9)	73 (61.9)
No (n=224)	196 (87.5)	6 (2.7)	22 (9.8)

**Table 5.** Management of HIV-infected children (n = 201)

Antiretroviral treatment	n	%
• Yes	157	78.1
• No	44	21.9
First-line treatment		
2002 – 2004		
• AZT + 3TC	32	
2003 – 2007		
• AZT + 3TC + NVP (since the beginning)	87	
• d4T + 3TC + NVP (since the beginning)	39	
• The addition of NVP or EFV	20	
Second-line treatment (after 2006)		
• AZT + ddl + LPPr/r	1	
• 3TC+ddl+LPPr/r	1	
• ddl + TdF + LPPr/r	1	
Cotrimoxazole prophylaxis		
• Yes	148	73.6
• No	53	26.4

Thirty-six (17.9%) HIV-infected children died and 63 (31.3%) subjects were lost to follow-up and are of unknown status. HIV-related death was apparent in 22 (61.1%) cases; this was commonly due to sepsis (usually caused by *Pseudomonas*) or pneumonia. Two children died due to non-HIV-related causes, one in a traffic accident and one by choking on food. There were 12 cases with no data on the cause of death.

## Discussion

Our study shows that HIV infection could be confirmed in more than half of the children born to HIV-positive mothers. This number suggests a lack of awareness of HIV infection among women and therefore missed prevention of mother-to-child HIV transmission. Worldwide, mother-to-child transmission (MTCT) is estimated to be responsible for more than 90% of HIV infections in infants and children. Vertical transmission may occur during late pregnancy or during labor. The exact mechanism is unknown, but it is assumed that HIV could be transmitted when the maternal blood enters fetal circulation or when the mucosa is exposed to the virus during labor. The role of the placenta in HIV transmission is not clear. The risk of MTCT significantly increases if the mother has severe disease, high viral load in the blood or low CD4 T-lymphocyte count.<sup>11</sup> The rate of transmission varies from approximately 15-25% among untreated, nonbreastfeeding, seropositive women to 25-40% among the breastfeeding population.<sup>12,13</sup> Transmission can occur in utero, during labor, and via breastfeeding.<sup>14</sup> Most transmission occurs at birth,<sup>15</sup> and may result from direct contact with maternal blood and genital tract during delivery, ascending infection after membrane rupture, maternal-fetal microtransfusions during uterine contractions, and absorption of the virus through the infant's digestive tract.<sup>14</sup>

The characteristics of subjects in our study were similar with those in the United States before the era of highly active anti-retroviral therapy (HAART). At that time, the number of male children and female children with HIV infection was almost equal. Sixty percent of them were between 0-4 years. After the introduction of the PMTCT program and HAART, there was a sharp reduction (16.9%) in HIV infection in children aged 0-4 years. However, this meant that the number of HIV patients in children aged 10-18 years old reached more than 60%, with most of these patients (60%) being girls.<sup>16</sup> The children's birth weight was normal. However, a case control study by Kuhn *et al*<sup>17</sup> found that the birth weight of children with AIDS was lower compared to that of healthy children (2,816 g vs. 3,144 g,  $P < 0.001$ ).

Our study results suggest that HIV infection should be suspected in a child presenting one of

the three most common co-morbidities (chronic or recurrent diarrhea, wasting syndrome, and oropharyngeal candidiasis) without other obvious disease history or etiology. Severe malnutrition in HIV-infected children is associated with high mortality and poses a great challenge that requires special treatment.<sup>17</sup> We found that a high percentage (60.2%) of subjects were classified as being in clinical category C, and that about half of the patients (51.2%) had severe immunosuppression. These results were comparable to those of a study in South Africa that found 57% of cases were in clinical category C in, 41% in category B in, and 2% in category A. That study also found severe immunosuppression in half of cases, with moderate and mild immunosuppression in 28% and 22% of cases respectively.<sup>18</sup> Another report showed that the most common morbidities in children who died due to HIV infection were lung infection and diarrhea, while early symptoms were failure to thrive (51.9%) and persistent lymphadenopathy (44.4%).<sup>19</sup> Viral load was not routinely checked in our hospital due to financial constraints. A meta-analysis found that in children aged more than 2 years old, the risk of death increased if the CD percentage is less than 10% and within the same CD4 percentage, children aged less than 2 years has worse condition. The risk of disease progression increases when viral load exceeds 100,000 copies/mL.<sup>20</sup>

ARV treatment was not given to all patients. Indications for ARV therapy according to the WHO guidelines for limited resources countries are as follows: stage 3 or 4 disease regardless of CD4 percentage, stage 2 disease with CD4 percentage  $< 25\%$  (for children aged  $\leq 11$  months), CD4 percentage  $< 20\%$  (for children aged 12-35 months), and CD4 percentage  $< 15\%$  (for children aged 36 months or more).<sup>21</sup> The use of triple-drug combinations since 2003 was based on the recommendation of the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children.<sup>22</sup>

A study in Thailand found that 46% (from 68 children) with HIV infection did not survive.<sup>23</sup> In our current study, mortality rate of children receiving ARV therapy was lower (15.3%). However, if lost-to-follow-up patients were not included, then the mortality rate would be 20% for children who received ARV therapy and 52% in ARV therapy. This number is similar to that in rural Uganda,

where diagnosis of HIV in children is difficult, meaning that ARV therapy is not started early.<sup>24</sup> In Africa, the mortality rate of HIV-infected children is nine times higher than the mortality of children without HIV; at two years, more than half of the children had died.<sup>25</sup> These studies emphasized the importance of ARV therapy in HIV-infected children as a live-saving effort in areas with a high risk of HIV transmission.

Our study showed that the most common cause of death was sepsis, which was mostly due to *Pseudomonas* infection. It is known that HIV infection increases the frequency of *Pseudomonas* infection, especially in children with low numbers of CD4 lymphocytes.<sup>26</sup> Another study found that infections are the most common cause of death in HIV-infected children aged less than 6 years (49.2%), and the highest was pulmonary infection (65.6%). In older children, wasting syndrome and *Mycobacterium avium* complex infections were more common causes of death.<sup>27</sup> A study in UK found that 18 out of 22 children who died at less than one year old suffered from PCP, or CMV infection, or both.<sup>28</sup> The mortality rate of HIV-infected children in Cote d'Ivoire was 64% during 1995-2000 and 51% during 2001-2005. The most common cause of death was pneumonia (41%) in the 1995-2000 period and diarrhea in the 2001-2005 (43%) period.<sup>29</sup>

In summary, HIV-positive children born to HIV-positive mothers at Cipto Mangunkusumo had a median age of 20 months, with the majority of cases (65.7%) between 1 and 5 years old. Most children born with normal birth weight but 40% of them had low or poor nutritional status on hospital admission. HIV infection was positive in 58.8% children born to HIV-positive mothers. Antiretroviral therapy was given to 78.1% of children, and the most common drug regimes were triple-drug combinations i.e. AZT+3TC+NVP (37.3%) and d4T+3TC+NVP (16.9%). Prophylaxis for opportunistic infection was given to 73.6% of subjects. Most common morbidities were chronic or recurrent diarrhea and wasting syndrome (57%). The mortality rate was 17.9%, although 31.3% of cases were of unknown status. Death occurred in 20% of children who received ARV and 52% of those who did not receive ARV therapy. The most common cause of death was sepsis due to *Pseudomonas* infection.

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