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*Brief Original Article*

# Immunological outcomes after six months with first line antiretroviral therapy: a lesson from Yogyakarta, Indonesia

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## Abstract

Introduction: More than 1,300 children aged 0-14 years were infected with HIV in Indonesia by 2016. Adequate antiretroviral therapy (ART) can increase nutritional and immunological status, reduce incidence of opportunistic infection and mortality caused by HIV infection. After ART initiation, the children's treatment response needs to be monitored with $CD4^+$ cell count and Viral Load (VL) evaluation. In resource-limited setting, clinical and immunological parameters can be used to evaluate ART outcomes. The aimed of this study to know immunological status of the patient after 6 months ART in Dr. Sardjito Hospital in Yogyakarta, Indonesia.

Methodology: A retrospective study was conducted from January 2010 to May 2016. HIV-infected children aged 0-18 years who were given first-line ART at least 6 months were included in this study. Age when ART initiation, gender, residence, nutritional status, clinical staging based on WHO criteria, incidence of hospitalization, baseline $CD4^+$ cell count and $CD4^+$ cell count after 6 months of therapy, tuberculosis treatment, and ART regimens were collected from medical records. Data were entered and analyzed using SPSS version 20.0

Results: Thirty-five subjects were included in this study. Median $CD4^+$ T cell percentage increased from 3.16 (IQR 1-18) % to 11.0 (IQR 2-32) %, whereas median $CD4^+$ absolute cell count increased from 9.5 (IQR 3-176) cell/$mm^3$ to 419.5 (IQR 202-1428) cell/$mm^3$.

Conclusion: Immunologic conditions could improve even with very low levels of $CD4^+$ T cell percentage and $CD4^+$ absolute cell count. Monitoring immunologic conditions and adherence of children with ART are essential to improve treatment outcomes.

**Key words:** $CD4^+$; HIV; children; antiretroviral therapy; Yogyakarta, Indonesia.

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## Introduction

More than 1,300 children aged 0-14 years are infected with human immunodeficiency virus (HIV) in Indonesia by 2016. This number increases about 65% when compared with total number of children who were infected in 2011 [1]. Adequate antiretroviral therapy (ART) can increase nutritional and immunological status, reduce the incidence of opportunistic infections [2-4], and decrease mortality caused by HIV infection [5-7]. Before 2014, according to national guidelines, ART is given to all children who are in clinical stages 3 and 4 based on the World Health Organization (WHO) clinical staging. Also, ART is given to all children who are in clinical stages 1 and 2 accompanied with severe immunosuppressive conditions [8]. Currently, ART is given to all children less than 5 years old who are diagnosed with HIV and to all children more than 5 years old who are in clinical stages 3 and 4 based on the WHO clinical staging. While for all children older than 5 years who are in clinical stages 1 and 2, ART is given if $CD4^+$ absolute count is less than age-related thresholds [9].

The fulfillment of ART requirements for adult and child patients, from 2012 to 2013, has increased by 27% [10]. In line with these conditions, monitoring of treatment response and drug side effects is essential after ART is started. WHO (2013) recommends evaluation of $CD4^+$ cell counts every 6 months and Viral Load (VL) testing 6 months after ART initiation and every 12 months after first VL evaluation [11]. In rural areas which are resource-limited, clinical and immunological parameters can be used as parameters to evaluate ART therapy [12,13]. Immunological response after ART initiation occurs within the first 6 months and this response continues within 3 years thereafter [3,14]. Until now, no data have been reported on immunological responses in HIV-infected children who are treated with first-line ART in Yogyakarta. This study aimed to determine the immunological status of the patient 6 months after ART initiation in Dr. Sardjito Hospital in Yogyakarta, Indonesia.

## Methodology

A retrospective study was conducted to determine the immunological status of HIV-infected children who were treated with first-line ART at Dr. Sardjito Hospital Yogyakarta. This hospital is one of the teaching hospitals and the main referral hospital for Yogyakarta Special Province. Patient data were collected from medical records from January 2010 to May 2016. Inclusion criteria included HIV-infected children and adolescents younger than 18 years who have had first-

**Table 1.** Demographic and baseline clinical characteristics.

| Characteristics | Subject N = 35 |
|---|---|
| **Gender** | |
| Male | 22 |
| Female | 13 |
| **Age ART initiation, median (IQR), months** | 45 (13-102) |
| **Residence** | |
| Yogyakarta region | 23 |
| Outside Yogyakarta region | 12 |
| **Nutritional status** | |
| Good nutritional status | 8 |
| Undernutrition | 16 |
| Severe malnourished | 10 |
| Stunted | 1 |
| **WHO stage** | |
| Stadium 1-2 | 8 |
| Stadium 3-4 | 27 |
| **Primary care taker** | |
| Parents | 27 |
| Caregiver | 8 |
| **Parental status** | |
| Known | 18 |
| Not known | 17 |
| **Health insurance** | |
| Yes | 16 |
| No | 19 |
| **Regimen NRTI started at initiation of ART** | |
| AZT + 3TC backbone | 21 |
| D4T + 3TC backbone | 14 |
| **Regimen NNRTI started at initiation of ART** | |
| NVP | 30 |
| EFV | 5 |
| **Adherence** | |
| Yes | 17 |
| No | 18 |
| **Rehospitalization** | |
| Maximum once | 24 |
| More than once | 11 |
| **Baseline $CD4^+$ percentage, median (IQR), cell/%** | 3.16 (1-18) |
| **Baseline $CD4^+$ absolute count, median (IQR) cell/$mm^3$** | 9.5 (3-176) |
| **Immunosuppression at initiation of ART** | |
| No immunosuppression | N/A |
| Mild immunosuppression | N/A |
| Advanced immunosuppression | N/A |
| Severe immunosuppression | 35 |
| **Tuberculosis treatment** | |
| Yes | 17 |
| No | 18 |

ART: Antiretroviral therapy, AZT: Zidovudine, 3TC: Lamivudine, d4T: Stavudin, NVP: Nevirapine, EFV: Efavirenz, IQR: Interquartile range, N/A: not available.

line ART for at least 6 months. Ethics approval for conducting this study was obtained from the institutional review board at Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada Yogyakarta, Indonesia.

*Data/measures*

Collected data were age when ART initiation, gender, residence, nutritional status, clinical staging based on WHO criteria, incidence of hospitalization, baseline $CD4^+$ cell count and $CD4^+$ cell count after 6 months of therapy, tuberculosis treatment, and ART regimens. $CD4^+$ absolute cell count values which we used were the closest to the 6 months evaluation after ART was started. Immunosuppressive status of children aged ≤ 59 months was grouped by percentage of $CD4^+$ T cell by age-related thresholds. $CD4^+$ T cell percentage was used because it is more stable, not affected by the change of total and differential leucocyte count, and presenting only slight differences during re-measurements [15]. Immunosuppressive status of children aged > 59 months was grouped according to absolute levels of $CD4^+$ absolute cell count. Severe immunodeficiency was defined if $CD4^+$ T cell percentage < 25%, < 20%, < 15% for children aged ≤ 11 months, 12-35 months, and 36-59 months respectively and if children aged > 5 years, severe immunodeficiency was defined if the absolute $CD4^+$ absolute cell count ≤ 200 cell/$mm^3$ [9]. Nucleoside Reverse Transcriptase (NRTI) regimens used were zidovudine (AZT) and lamivudine (3TC) or stavudine (d4T) and 3TC. Nucleoside Reverse Transcriptase (NNRTI) regimens were nevirapine (NVP) or efavirenz (EFV). Adherence assessment was assessed based on the adherence to schedule of visits to the outpatient clinic visiting schedule every month. High adherence, more than 95%, needed to got viral suppression [16]. Subject categorized not adhere if they missed at least one of the outpatient clinic visiting schedule. During this period, VL examination was not available, so it was not used in monitoring patient condition. Data were entered and analyzed using SPSS version 20.0.

## Results

Of 64 children who went to the outpatient clinic in Dr. Sardjito Hospital, there were 29 subjects excluded because of relocation (1 subject), lost to follow up (9 subjects), and incomplete data (19 subjects). Two of excluded subjects used presumptive diagnosis without VL examination. Based on our national guidelines, HIV diagnosis for children less than 18 months used DNA PCR examination [9]. WHO presumptive criteria didn't use because of low sensitivity [17,18]. Baseline characteristics of 35 subjects included in the study were as in Table 1, 22 subjects were male, with median age at ART initiation 45.0 (IQR 18-102) months. Most subjects were in WHO 3 and 4 clinical stages. Twenty-six subjects were undernutrition and severe malnutrition. At the time of ART initiation, median baseline of $CD4^+$ T cell percentage was 3.16 (IQR 1-18) %, with median $CD4^+$ absolute cell count 9.5 (IQR 3-176) cell/$mm^3$. All subjects were in severe immunodeficiency condition. One subject who was in mild immunosuppression was 87 months old. After 6 months of therapy, median $CD4^+$ T cell percentage level became 11.0 (IQR 2-32) %, with median $CD4^+$ absolute cell count 419.5 (IQR 202-1428) cell/$mm^3$. The evaluation of the immunosuppressive condition after 6 months of ART is summarized in Table 2. No serious adverse effects were found, and 3 subjects' regimens were switched to d4T and 3 TC backbone due to anemia.

## Discussion

In our study, immunological status increased after receiving 6 months of ART. Median $CD4^+$ T cell percentage increased from 3.16 (IQR 1-18) % to 11.0 (IQR 2-32) %, whereas median $CD4^+$ absolute cell count increased from 9.5 (IQR 3-176) cell/$mm^3$ to 419.5 (IQR 202-1428) cell/$mm^3$. Baseline level of $CD4^+$ cell count in our study was very low compared with other studies [15,19-22], but this result was not much different from baseline levels from 8 sites in Asia [14]. After ART initiation, $CD4^+$ cell count could increase more than two-fold [15,19,21]. Five subjects in our

**Table 2.** Immunosuppressive condition after six months of ART.

| Age (months) | Immunosuppression (n) | | | |
|---|---|---|---|---|
| | No immunosuppression | Mild | Advanced | Severe |
| ≤ 11 | N/A | N/A | N/A | N/A |
| 12-35 | 1 | 1 | 1 | 8 |
| 36-59 | N/A | 3 | 1 | 8 |
| ≥ 60 | 4 | 2 | 4 | 2 |

N/A: not available.

study could achieve immune recovery within 6 months. Immune recovery is associated with thymus activity [23-24], so that children with severe immunodeficiency conditions when they start ART, can still achieve their normal value [24]. Almost a half of subjects got tuberculosis therapy but this immunologic status changed was not affected by tuberculosis therapy [25-26].

ART initiation may reduce opportunistic infection incidence [27-28]. This condition directly reduced rehospitalization incidence. In our study most of the subjects (68.6%) only had one time hospitalization period. A cohort study in Uganda found decrease of sick visits 48 weeks after ART initiation [29]. More than half of the subjects were categorized as non-adherence. Adherence to outpatient clinic visit is required for ART medication including evaluation of therapy. One community-based clinic study suggested low $CD4^+$ cell levels are associated with non-adherence to clinic visits [30].

There are several limitations in our study. We used descriptive methods to evaluate immunologic outcomes of our subject, but this is the first study to be conducted in Yogyakarta. Some subjects could not be included in our study because of incomplete data. Until now in our study site, there was no agreement to assess adherence in HIV-infected children who are on ART, so in this study we only based adherence measurement by outpatient clinic visits.

## Conclusion

In conclusion, immunologic conditions could improve even with very low levels of $CD4^+$ T cell percentage and $CD4^+$ absolute cell count. Monitoring immunologic conditions and adherence of children with ART are essential to improve treatment outcomes.

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