

CLINICAL-IMMUNOLOGICAL ASSESSMENT FAILURE ON INITIAL COMBINATION USE OF ZIDOVUDINE-LAMIVUDINE-NEVIRAPINE IN CHILDREN WITH HIV/AIDS AT SANGLAH HOSPITAL BALI

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Background: Assessing clinical progression and CD4⁺ level were important in determining the efficacy of antiretroviral (ARV) and switching to other regimens, especially when viral-load data were not available. This research aims to assess combination of zidovudine-lamivudine-nevirapine (Co-ZLN) failure using WHO 2010 criteria on clinical failure (CF) and immunological failure (IF), single or together, to determine correlation between CF and IF; and to evaluate two failure categories (CF alone and combination of CF-IF) in making decision to switch to second-line of ARV. **Methods:** Children at Sanglah General Hospital, who gain initial treatment of Co-ZLN in period of March 2006–March 2013 were selected. Cross-sectional study was applied. The ARV response was assessed twice. First period (P1) and second period (P2) of evaluation were conducted after patients received the Co-ZLN at least 6 and 12 months. **Results:** Forty five patients were included in this study. After at least 6 and 12 months of therapy, more patients showed IF (10 and 9 children in P1 and P2) than those in CF (4 and 2 patients in P1 and P2). Only one child met to CF-IF category in P2. The low clinical condition (HIV stage 4) did not always associate with deteriorating immunologic marker in the treatment-failure (TF). The patients who fit on CF and CF-IF based decision to switch regimen criteria were different. In resource-limited hospital, CF-IF based decision could give a better picture of patients' condition and be used as an indicator to assess TF compared to single CF criteria.

Keywords: first-line ARV, failure, children

INTRODUCTION

HIV/AIDS in children were commonly vertically transmitted from their mother. The majority pediatric patients were found under 5 years old (66%), then it was followed by 26% in between of 5-10 years old, and 7.9% above 10 years old.¹

The first choice at Sanglah Hospital was first-line ARV (combination of Zidovudine-Lamivudine-Nevirapine / Co – ZLN). Determining failure-response to these medicines was crucial and it could be indicator to switch to another ARV-regimens. Therefore, it was able to increase the quality of life and reduce the morbidity and mortality rate.^{2,3}

ARV-failure can be detected by viral load (VL) testing. However, it is expensive to do in Indonesia. If VL data is not available, World Health Organization (WHO) recommend to evaluate treatment-failure (TF) by monitoring clinical progression or using combination between clinical and CD4⁺ measurement.³

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The aims of this research was (1) to assess the ARV-failure using WHO clinical failure (CF) criteria, immunological failure (IF) criteria, and combination of both; (2) to determine correlation between CF and IF; and (3) to evaluate two failure categories (CF alone and CF-IF parameter) in making decision to switch to 2nd line ARV.

PATIENTS AND METHOD

This cross-sectional research was approved by Local Ethics Committee, Faculty of Medicine Udayana University/Sanglah General Hospital. All pediatric patients who were diagnosed with HIV/AIDS (6 months - 12 years of age, when started ARV) at Sanglah General Hospital in period of March 2006 – March 2013, who were initially prescribed with and stayed on Co-ZLN for at least 12 months; and had complete data of HIV-stage and CD4⁺ (before starting the therapy, and during the treatment at least 6 and 12 months after receiving the drugs) were included.

TF and consideration on ARV switching was based on CF and IF WHO 2010 Criteria for Children. The result will be descriptively presented in two periods of evaluations. First period (P1) and second period (P2) of assessments were conducted after patients received the treatment at least 6 and 12

months. Contingency coefficient test was used to analyze the correlation between CF and IF. P-value <0.05 was considered statistically significant.⁴

RESULTS

Characteristics and Nutritional Status of Patients

Forty five patients, who fit the sample criteria, become the subjects of this research. Patient characteristics (sex and age), duration of ARV therapy, and progressing of nutritional status during the treatment showed in Table 1, Table 2 and Figure 1. Percent ideal body weight (IBW), were used to determine the nutritional status, which was classified into obesity (>120%), overweight (110-120%), normal (90-100%), mild wasting (80-90%), moderate wasting (70-80%), and severe wasting (< 70%).⁵

Table 1
 Patients Characteristics (N total=45)

Characteristic	N ₁	N ₂
Sex		
Female	23	23
Male	22	22
Age	a	b
1-2 years old (y.o)	11	6
>2 -3 y.o	5	7
>3-4 y.o	7	7
>4-5 y.o	11	6
>5-6 y.o	5	10
>6-7 y.o	4	5
>7-8 y.o	1	3
>8-9 y.o	1	1

N₁ and N₂ : total subjects in P1 and P2
 a, b :age in P1 and P2

Table 2
 Duration of ARV Therapy in 45 Subjects

Period	Range (months)	Median (months)	Mean (months)
P1 ^c	6-11	7	7.9
P2 ^d	12-20	14	14.4

c, d: not all patients tested the CD⁺ level just after 6 and 12 months therapy, thus duration of therapy was counted from the beginning of treatment until the first CD⁺ measurement at or after 6 months (c) /12 months (d) of ARV use.

Based on Shapiro Wilk normality test, data of ARV duration was not normal distributed p=0.07 (P1) and p=0.002 (P2), p<0.005.⁴

Figure 1 showed that there was an improvement of nutritional status of the patients. More patients were in a good nutrition, which was on the range of normal body weight, during the longer time of therapy.

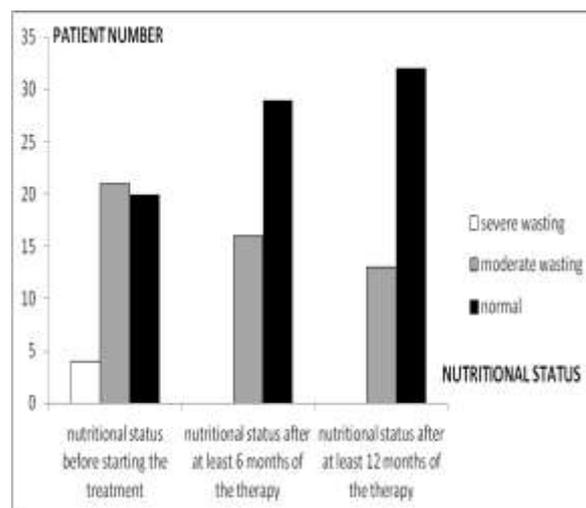


Figure 1
 Progression of Nutritional Status
 During the ARV Therapy

Therapeutic Response

The ARV-failure was evaluated using WHO CF and IF with result as indicated on Table 3. Clinical condition was improved with the longer time of therapy. It was determined by decreasing CF patients, which was 4 of 45 pediatric-patients in P1, and only 2 children in P2. Slightly better immunologic progression was observed in the second period. However, there was one child fit to both CF and IF in P2. He had HIV stage-4 and also performed a deteriorating percentage of CD4⁺.

Table 3
 Monitoring of ARV-Failure Event
 in 45 Children

Parameter	N ₁	N ₂
CF(stage 4)	4	2
IF	10	9
Both (stage-4 and IF)	0	1

N₁ and N₂: total subjects who met the failure-criteria in at least 6 and 12 months of therapy

Correlation between CF and IF

Contingency coefficient (CC) test was applied on the data of 45 subjects to analyze association between CF and IF, with the result r=0.165 and p= 0.263 in P1; and r=0.160 and p= 0.278 in P2 (p>0.05). There was no significant correlation between CF and IF.⁴ It showed that a fall of CD4⁺ was not always followed by a decrease of clinical condition.

CF and CF-IF Based Consideration and Recommendation in changing to second line ARV regimen

Based on WHO guideline 2010¹³, there were two parameters of making decision to switch to second-line drugs in the absence of VL, which were using CF

(stage-4); and combination both CF-IF (any HIV-stage with IF), with the result on Table 4.

Table 4
Decision Making Based on CI Alone and Combined with IF (N total = 45 patients)

Changes	CF based decision		CF-IF based decision	
	n	Patient Code**	n	Patient Code**
P1				
Recommend to change	4	AN, YS, BR, MR	2	SM, PY
No change	41		45	
P2				
Recommend to change	2	AN*, YS	3	AN*, SM, JY
No Change	43		42	

* : a patients who met CF and CF-IF criteria
** : each patient had a different code

There was a discrepancy on selected patients to consider in switching regimen. The children, who should switch the drugs, were nearly different in both categories.

DISCUSSION

Indonesian Health Department suggested checking CD4⁺ every 3-6 months.² However in Sanglah General Hospital, due to the financial constraints, CD4⁺ test was not always be done regularly in that period. In this study, first and second evaluation (P1 and P2) were conducted on the range of 6-11 (median: 7) months and 12-20 (median: 14) months after therapy (Table 2). In general, a better clinical progression was found by longer duration of treatment. Fewer children with CF or IF was found in P2 than those in P1 (Table 3).

In this study, HIV stage 4 was not associated with IF. It was showed by CC correlation tests in P1 and P2 with $p > 0.05$ and $r < 0.2$. Clinical response to ARV was not always correlated with immunological indicator⁶. Moreover, CD4⁺ level may decrease faster than clinical condition.² It was showed by only one child with stage 4 and IF on P2. This child, who was remaining on stage 4 from baseline, had a deteriorating CD4⁺ level in P2. On this child, VL was tested and it showed that the virus was still detected. Combination of these three ARVs should inhibit HIV replication, thus a fall of CD4⁺ percentage or count can be avoided.^{3,7} A decline of CD4⁺ level may be happened through several mechanisms, such as (1) immune response dysfunction that eliminated the infected cells and the surrounding normal cells; (2) direct cell death because of loss of plasma membrane integrity (3)

fusion between HIV infected membrane cell and uninfected lymphocyte T-CD4⁺; (4) autoantibody producing from autoimmune mechanism that eliminated the uninfected cell, and (5) apoptosis^{8,9}. A failing of VL could be caused by poor adherence-behavior, unsuccessful retention HIV medical care, ARV resistance, intolerance to the present therapy, and drug interaction.¹⁰ Besides CF and a drop of CD4⁺ below the age threshold, the child also had severe wasting at a baseline-condition and moderate wasting during the 13-months of therapy. One of the factors in contributing of a CD4⁺ fall was nutrient deficiency. Malnutrition may reduce the functional capacity, and cause immune response dysfunction. This condition may increase morbidity and mortality.⁷

Regarding to the lack of affordability in checking VL at Sanglah General Hospital, the decision-making to switch ARV-regimen, using CF alone and combination with IF based on WHO guideline in children with HIV/AIDS 2010,³ were applied. The data showed that there was a different in amount and selected patients who were able to continue the treatment between two categories (Table 4). In P1, all stage-4 HIV patients had CD4⁺ level above their age-threshold, thus they could stay on the drug regimen based on CF-IF indicator. However, in P1, two children, who need to change regimen, was stage-3 patients because their %CD4⁺ were below their age-threshold. In P2, fewer patients were fit to CF based decision, because of improvement on the clinical condition. However, the total patients, who considered to change the drugs based on CF-IF criteria, was increased, because % CD4⁺ of one child, who was on stage-4, deteriorated to the level under his age threshold in P2 although he showed a high % CD4⁺ in P1. This boy could switch to the next line of ARV regimen.

Based on the CC test, CF and IF was not significantly correlated. The switching ARVs should not only rely on CF only. Health and survival was improved in CF-IF based monitoring than in CF only.¹¹ Furthermore, clinical-CD4⁺ based monitoring was more cost-effective than symptom-based evaluation alone.¹²

However this combination criterion had lower performance in monitoring ARV-failure in children compared to alone.^{13,14} Thus it may lead to misclassification on response-monitoring and contribute to the health-impact. If it is too early switching ARV, it will make a major public impact through the rising cost of ARV programs. Another consequent, if HIV pediatric patients stay too long in a failing-regimen, it is able to increase ARV-resistance mutations. By the time the decision of changing ARVs is made; the choices are limited or even completely no drug-choices. Comparing to VL measurement, the ARV resistance test was less available.¹⁵

Combination of CF-IF based decision for changing regimen can be an initial indicator to assess a failing ARV therapy before testing VL. This is due to

accessibility and cost-barrier in resource limited hospitals or clinics, conducting even infrequently viral monitoring gave clinical benefits to children with HIV and it was more cost-effective.¹⁶

CONCLUSION

From 45 patients, after at least 6 and 12 months of therapy, more patients showed IF (10 and 9 children in P1 and P2) than those in CF (4 and 2 patients in P1 and P2). Only one child fit to both CF-IF category in P2. The low clinical condition (HIV stage-4) did not always associate with deteriorating immunologic marker in the treatment-failure patients. The amount and selected patients on CF and CF-IF based decision to switch regimen were different. In resource-limited clinics, CF-IF based decision could give a better picture of patients' condition and be used as an indicator to assess TF compared to single CF criteria.

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