

Adherence to ARV, Clinical Stages of AIDS, and Self-Perceived Risk of HIV Infection are Predictors of Immunologic Success on PLHIV in Surabaya and Sidoarjo, East Java

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Abstract

Background

People living with HIV (PLHIV) are very dependent on the antiretroviral therapy (ART) during their lifetime, and CD4 cell count is an indicator of ART effectiveness. The objective of this study is to determine the predictors of the immunologic success on PLHIV at Dr. Ramelan Naval Hospital, Surabaya and Sidoarjo Regency General Hospital. **Methods:** This research was conducted on 29 PLHIV at Dr. Ramelan Naval Hospital, Surabaya and Sidoarjo Regency General Hospital. All subjects had taken ART for six months. CD4 count, ART card and questionnaires were used in the study. The data was analysed using multiple linear regression with SPSS version 21.0. **Results:** 92.9% subjects were from the key population aged 20-54 years. 73.9% subjects were in the second clinical stage of AIDS, 68.9% subjects reported high adherence ($\geq 95\%$) to ART, 24.1% subjects were not aware of the risk of getting HIV infection when having sexual intercourse without using a condom. The results of the multiple linear regression analysis showed there were six predictors of immunologic success: adherence to ART ($p = 0.047$), clinical stages of AIDS ($p = 0.004$) and the awareness of getting HIV infection when having sexual intercourse without using a condom ($p = 0.045$). **Conclusion:** Monitoring adherence to ART, clinical condition and condom use were very important to achieve immunologic success.

Keywords: PLHIV, absolute CD4 cell count, adherence to ART, clinical stages of AIDS, condom use

1. Introduction

As of 2012, it was estimated that HIV prevalence on Indonesian adults aged 15-45 years was 0.4%. However, Indonesia is a country in SEARO with increase rate of HIV new cases, in contrast with other countries which had stable or decrease rate. ⁽¹⁾ The mortality rate of PLHIV in developing countries is higher than that in developed countries due to delays in diagnosis, delays in the provision of ART, lack of knowledge, stigma, discrimination, and lack of access to health services. ^(2,3)

Until now PLHIV are dependent on ART, as it suppresses HIV replication, ⁽⁴⁾ thus improving health and reduce mortality of people living with HIV, ^(3,5,6) improving quality of life, ^(7,8) and reducing the risk of HIV transmission through sexual intercourse. ^(9,10) Care and treatment services for

PLHIV in Indonesia has the biggest proportion in the national HIV and AIDS strategy and action plan 2010-2014, between 55% and 60% of the total funding that is equivalent to US\$1.1 billion. ⁽¹¹⁾ Despite the funding, Indonesia was among 30 countries where 90% of PLHIV had unmet need of ART. ⁽¹²⁾

In Indonesia ART are given to PLHIV who met the criteria written in the National guideline for clinical management of HIV and antiretroviral therapy in adults 2011 (Pedoman nasional tatalaksana klinis HIV dan terapi antiretroviral pada orang dewasa tahun 2011). First-line ART consists of a combination of two nucleoside reverse transcriptase inhibitor (NRTI) and one non nucleoside reverse transcriptase inhibitor (NNRTI). Immunologic (CD4 count), virologic (viral load) and clinical condition are indicators of the success or failure of therapy. ⁽¹³⁾ It is therefore necessary to determine predictors of immunologic success on PLHIV at hospitals that provide care and treatment services.

2. Methods

2.1 Research Design

This cross-sectional study was conducted on 29 PLHIV at Dr. Ramelan Naval Hospital, Surabaya and Sidoarjo Regency General Hospital from September to October 2014. This research used quantitative methods to measure clinical condition, absolute CD4 cell count, and quality of life using WHO-QoLBREF questionnaire.

2.2 Research Subjects

Included in the study were PLHIV aged 17 years and over, met the eligibility criteria for receiving ART in the previous six months, had been taking ART for six months, voluntarily agreed to participate in the study and signed informed consent, were not taking other medications or supplements except those prescribed by Dr. Ramelan Naval Hospital, Surabaya and Sidoarjo Regency General Hospital.

2.3 Data Collection

The absolute CD4 cell count was measured using BD FACSCalibur flow cytometer, liver function tests and routine haematological tests were measured using Dimension® RxL® Max, Siemens at the Pathology Clinic Laboratory, Dr. Soetomo General Hospital, Surabaya. ART card, demographic questionnaire and Sarason's Social Support Questionnaire (SSQ) were used to collect data from the research subjects.

2.4 Data Analysis

SSQ consisted of 27 items designed to measure perceptions of social support and satisfaction with that social support. (14) The score of social support was then categorized into six groups: poor (<128.996 point), fair (128.996-152.996), and good (>152.996). There was only one subject at the clinical stage 4 of AIDS, therefore clinical stage 3-4 was categorized into one group.

Normality and correlation tests were used in the analysis. Multiple linear regression was used to determine predictors of immunologic success using SPSS version 21.0.

2.4 Ethical Clearance

The research ethics approvals were obtained from the Human Research Ethics Committee at Hang Tuah University, Dr. Ramelan Naval Hospital Surabaya and Sidoarjo Regency General Hospital.

3. Results

Based on the Table 1, it was showed that majority (75.9%) of our research subjects were males; 48.3% completed 12 years education; 79.3% were on the second clinical stage of AIDS (13); 96.5% were from key population; 75.9% reported that they were aware of getting HIV infection while having sex without using a condom; 65.5% had good knowledge of HIV and AIDS (the cause, transmission and prevention); 69.0% had fair and good support from family, friends, NGO or health care staff; 79.3% always use a condom after being diagnosed with HIV infection.

The mean age of our research subjects was 32.2 years (SD 9.37); and the means of absolute CD4 cell count before and after six months of ART were 207.3 cells / mm³ and 266.4 cells / mm³, respectively (Table 2).

The absolute CD4 cell count after six months of ART showed normal distribution with Shapiro-Wilk test ($p = 0.936$). The absolute CD4 cell count after six months was used as a dependent variable and factors in the Table 1 were used as independent variables in a multiple linear regression.

The adjusted R² of the final model was 0.673, meaning that the linear regression explained 67.3% of the variance in the data. The Durbin-Watson $d = 1.714$, which was between the critical values of $1.5 < d < 2.5$ and therefore it was assumed that there was no first order linear auto-correlation in the multiple linear regression data. The F-ratio in the ANOVA test showed $F = 3.698$, $p = 0.008$, meaning that there was a linear relationship between the variables in the model or the independent variables statistically significantly predicted the dependent variable. As the Goldfeld-Quandt test was not supported in SPSS, therefore checking the homoscedasticity and normality of residuals was conducted by using the Q-Q-Plot of z^* -pred and z^* -presid. The plot indicated that in the multiple linear regression analysis there was no tendency in the error terms. If that happened, the graph would look like a staircase. Moreover, there was no multicollinearity in the multiple linear regression, which was showed by tolerance > 0.1 and variance inflation factor (VIF) < 10 for all variables (Table 3).

Based on the significance (p) of each independent variable in the multiple linear regression in the Table 3, it was obvious that clinical stages of AIDS, awareness of HIV risk while having sex without using a condom and adherence to ART were significant predictors of immunologic success (The absolute CD4 cell count after six months of ART).

Table 3 also showed the unstandardized coefficients, which indicated how much the dependent variable varied with an independent variable when all other independent variables were held constant. It was shown that subjects with clinical stage 3-4 of AIDS decreased the mean of the absolute CD4 cell count after six months of ART by 122.823 cells/mm³ ($p = 0.004$, 95% CI -202.145, -43.502), compared to that of the subjects with clinical stage 2 of AIDS. It was also shown that subjects who were aware of getting HIV infection while having sex without using a condom (self-perceived risk) increased the mean of the absolute CD4 cell count after six months of ART by 96.071 cells/mm³ ($p = 0.045$, 95% CI 2.189, 189.952), compared to that of the subjects who were not aware of the risk. The last, subjects with good adherence to ART increased the mean of the absolute CD4 cell count after six months of ART by 98.607 cells/mm³ ($p = 0.047$, 95% CI 1.581, 195.634), compared to that of the

subjects with poor adherence to ART.

4. Discussion

HIV primarily targets CD4⁺ T-lymphocytes, and studies have shown that during primary HIV infection, HIV viral replication in CD4⁺ T-lymphocytes results in significant drop of CD4⁺ T-lymphocyte and an accompanying nonspecific immune activation.⁽¹⁵⁾ Subsequent CD4 counts recover after a few months to values within the normal range, though pre-infection values are rarely reached. During the progressive course of HIV infection a gradual decrease of CD4 T cells is observed. The risk for AIDS-defining illnesses increases with time when CD4 T cells decrease below 200. Given the central role of CD4⁺ T-lymphocytes in HIV pathogenesis, CD4⁺ T-lymphocyte determination during the course of HIV infection is one of the most reliable predictors of prognosis for AIDS-defining illnesses.^(16, 17)

To evaluate the success or failure of ART, CD4 count that was taken before PLHIV start ART should be compared with the count after six months of therapy. The possibility of failure of therapy typically had immunologic patterns as follows: persistent CD4 levels below 100 cells/mm³, CD4 count fell to the baseline or below, CD4 count was 50% of the highest level ever achieved for therapy.⁽¹³⁾

Overall, the mean of CD4 count before ART of all subjects in this study was 207.3 cells/mm³ (SD 84.2), and it increased to 266.4 cells/mm³ (SD 108.7) after six months of ART.

In this study adherence to ART was reviewed using the ART card that was brought home by the subjects. This was in accordance with a study conducted in 1982 PLHIV who received ART in nine countries in southern Africa. This study evaluated adherence to antiretroviral therapy based on the record on the drug card and connect it with the effectiveness of antiretroviral based on examination of the absolute CD4 cell count and the number of HIV RNA (viral load). The study concluded that the use of ART card to review adherence to ART was an accurate measurement, and compliance with therapy was a predictor of success of antiretroviral therapy.⁽¹⁸⁾

However, a study conducted by Smith et al (2006) indicated that adherence to therapy was not enough to be judged based on the percentage of 95% or how many missed dose is not taken, but must be taken into account to timekeeping (hours) taking antiretroviral drugs. The study reported that the dose limit of forgotten taking medicine but still be tolerable depended on the type of antiretroviral drugs. If the drugs are oblivious taken exceeds the threshold, then the blood levels will drop, allowing the occurrence of resistance. For example, people with HIV should not be delayed more than 16 hours to take Zalcitabine, but a person with HIV could still miss up to 40 tablets (20 days) for taking Nevirapine. However, PLHIV who missed taking the medicine must demonstrate compliance up to 99% during the following days to prevent resistance.⁽¹⁹⁾

Besides having a role as a predictor of success of ART, adherence to therapy was also associated with HIV transmission. Research conducted on 226 male PLHIV in Atlanta, US, reported that people with HIV who did not adhere to ART reported that they had more sexual partners and anal sexual intercourse without using a condom. People with HIV who do not adhere to this therapy believe that if they are taking antiretroviral drugs then they are protected, so they did not need to use a condom during sexual intercourse because they would be less likely to transmit HIV.⁽⁴⁾

A prospective cohort study conducted for 24 months in 416 PLHIV who received ART in Cambodia reported that advanced stage of AIDS and low CD4 counts at the beginning of therapy increased the AIDS mortality in the first year of ART. This was due to delays in diagnosis and the provision of antiretroviral therapy, the difficulty of providing management of opportunistic infections, immune recovery syndrome, or poor nutritional status.⁽²⁰⁾

A cross-sectional study conducted on 3,831 men and 3,986 women aged 15-24 years in Mozambique, Africa, reported that men and women who were aware of the risk of HIV infection when having sex without condoms were significantly associated with the prevalence of condom use during intercourse (30% in males and 16% for women) compared with the prevalence of condom use among male respondents (14%) and women (6%) who were not aware of their risk for HIV infection. Therefore, awareness of the risk of HIV infection might be a preventive factor for getting HIV infection.⁽²¹⁾

A research conducted in South Africa found that male respondents who were aware of the risk of HIV infection when having sexual intercourse without using a condom showed higher adherence to ART compared to men who were not aware of the risk of HIV infection.⁽²²⁾ So in other study, awareness of the risk of HIV infection was not an independent predictor, but it was the moderator of the effectiveness of ART.

The small number of subjects was a limitation of this study. It was quite difficult to find a newly-infected HIV adult who met the inclusion criteria but not met the exclusion criteria in both Dr. Ramelan Naval Hospital and Sidoarjo Regency General Hospital. Therefore, researcher had a collaboration with NGO that assisted PLHIV and five Community Health Centers who provide VCT service. The future study should be conducted on the larger sample size and should use a cohort or clinical trial design.

5. Conclusion

There were six predictors of the immunologic success (CD4 count after six months of therapy): adherence to ART, which had the highest impact on CD4 count after six months of ART ($\beta = 0.427$), awareness of HIV risk while having sex without using a condom ($\beta = 0.385$) and clinical stage of AIDS ($\beta = -0.578$). Accordingly, the six factors had to be carefully monitored to achieve immunologic success of ART.

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Table 1. Characteristics of research subjects

Characteristics	n	%
Sex		
Males	22	75.9
Females	7	24.1
Education		
Elementary school	6	20.7
Junior high school	6	20.7
Senior high school	14	48.3
College / university	3	10.3
Clinical stages of AIDS		
2	23	79.3
3 - 4	6	20.7
Key population		
No	1	3.5
Sex workers	6	20.7
High risk men	9	31.0
Man who have sex with man	9	31.0
Transverstitute	4	13.8
Self-perceived risk of HIV infection while having sex without a condom		
Yes	22	75.9
No	7	24.1
Knowledge about HIV and AIDS		
Good	19	65.5
Poor	10	34.5
Score of social support		
Poor (<128,996 point)	9	31.0
Fair (128,996-152,996 point)	10	34.5
Good (>152.996 point)	10	34.5
Adherence to ART		
Good ($\geq 95\%$)	20	69.0
Poor ($< 95\%$)	9	31.0
Condom use		
Always	23	79.3
Sometimes - rarely	6	20.7

Table 2. Age and laboratory test results

Age & laboratory tests	mean	SD
Age	32.2	9.37
CD4 count before ART	207.3	84.2
CD4 count after six months of ART	266.4	108.7

Table 3. The coefficients table of the multiple linear regression

Model	Unstandardized		Standardized		t	Sig	95% CI for B	
	B	SE	Coefficient Beta				Lower	Upper
(Constant)	322.846	165.726			1.948	0.067	-25.332	671.025
Knowledge	24.512	51.444	0.113		0.476	0.639	-83.567	132.591
SSQ	1.159	20.993	0.009		0.055	0.957	-42.946	45.265
Adherence	98.607	46.183	0.427		2.135	0.047	1.581	195.634
Sexual practice	-49.858	59.957	-0.189		-0.832	0.417	-175.823	76.108
Sex	-23.274	81.588	-0.093		-0.285	0.779	-194.683	148.135
Level of education	-26.669	19.009	-0.233		-1.403	0.178	-66.605	13.268
AIDS clinical stage	-122.823	37.756	-0.578		-3.253	0.004	-202.145	-43.502
Self-perceived risk	96.071	44.686	0.385		2.150	0.045	2.189	189.952
Age	1.339	2.553	0.115		0.525	0.606	-4.025	6.703
Type of key population	37.581	32.604	0.371		1.153	0.264	-30.918	106.080