Plasma CD4 Count and Duration ARV as a Predictor of Virological Failure Amongst AIDS Patients

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Abstract

Background: The 90-90-90 strategy to overcome the HIV/AIDS (*Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome)* epidemic in the world still has challenges because 20% of people live with HIV/AIDS (PLWHA) received anti retroviral (ARVs) are at risk of virological failure. This study describes and analyzes the factors that influence the occurrence of virological failure in AIDS patients who have taken ARVs.

Method: A hospital based cross-sectional study and retrospective medical record review in Dr. Soetomo Teaching Hospital Surabaya from January 2017 until December 2018. Virological failure is plasma viral load greater than 1000 copies/ml.

Result: According to data analysis for each variable, we used a CD4 (*Cluster of Differentiation)* cut-off of 134 cells/µl and ≥ 20.5 months for virological failure. There was a statistically significant relationship between CD4 cell count 95% CI (1.33-11,281) p 0.010 and duration of ARV (1,396-11.78) 95% CI p 0.01. Summation of total score from both variables has a p value <0.001 which means the total score of the two variables is significant as a predictor of virological failure. The total area of the ROC curve is 73.6% with a sensitivity of 81.5% and specificity of 44.4%.

Conclusion: The duration of ARV consumption and CD4 cell count have an effect and can be an initial evaluation of the occurrence of virological failure.

Keywords: *Virological Failure, HIV, AIDS, ARV.*

Introduction

Human Immunodeficiency Virus (HIV) is a virus that causes serious health problems in the world. In Indonesia, in 2018 an increase in the prevalence of people with HIV/AIDS (Acquired Immunodeficiency Syndrome) (PLWHA). The strategy in the world to overcome the epidemic is 90-90-90 which means that by the end of 2020 90% of all patients is diagnosed of HIV, get antiretroviral (ARVs), and suppression of viral load (viral load/VL)[(1)]. Yet, Indonesia could only reached 47% to diagnose of HIV status, 31.9% of ARV accesses, and 0.6% suppression of viral load[(2)].

ARVs play an important role in achieving the 90-90-90 target. However, one of the challenges in the management of HIV is virological failure. About 20% of PLWHA experience virological failure despite taking ARVs[(2)]. Meanwhile, virological failure is associated with a 40% risk of death[(3,4)].

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Extensive research on the factors associated with virological failure has been carried out. In a case control study in Ethiopia, CD4 counts <200 cells/mm^3, first-line ARV regimens and adherence had an important role in the occurrence of virological failure[5]. Thus, the existence of other known risk factors in the population from this study is expected to provide a new perspective in the management of PLWHA as well as interventions, especially in Indonesia.

The results of this study are expected to be able to explain the factors that influence virological failure in PLWHA who has received ARVs.

Materials and Method

Study area, design, time,population: A hospital based cross sectional study with a retrospective approach in HIV patients at outpatient clinic UPIPI (Intermediate Care Unit and Infectious Diseases) Dr. Soetomo Hospital Teaching Surabaya. This study is conducted from January 2017 until December 2018.

We collect medical record of HIV/AIDS patients aged ≥21 years who suspicious suffered from virological failure based on the criteria of clinical, immunological, virological failure, and non-compliance with taking ARVs at least for 6 months. We ruled out patients who did not have plasma CD4 count and viral load data at the time of study. Sample was carried out in a consecutive manner from population met the inclusion criteria and there were no exclusion criteria.

Terms of Operational: Virological failure is a condition in PLWHA that shows failure to suppress the amount of virus in the blood after taking ARV for at least 6 months, a viral load of more than 1000 copies/ml. Good adherence is the number of drugs taken compared with the drugs given every month ≥95%.

Result

Sociodemographic Characteristic of Patients: A total of 72 patients met the inclusion and exclusion criteria were included in this study. of these, 51 were men while 21 were women. The average age (SD) of patients in this study was 39.04 (9,964) (range 24-67 years). The average duration of ARV consumption was 29.3 (32.3) (range 6-156 months). 54 patients had primary education (75%) while 18 (25%) patients continued through college. 48 (66.7%) patients received FDC and 24 (33.3%) patients received regimens based on TDF/NVP, ZDV/NVP, ZDV/EFV, ZDV/LPV, TDF/LPV, TDF/RPV, and FTC/LPV. The majority of patients in the study had risk factors for unsafe sex (heterosexual or homosexual) (93%). 55 patients (76%) were in stage III-IV. Opportunistic infections that accompanied the patients in this study were hepatitis C 3 (4%), Toxoplasmosis 8 (11%), PCP 13 (18%) and tuberculosis 13 (18%) **(Table 1).**

Virological failure and Associated Factors: Of the variables associated with virological failure, CD4 cell count and duration of antiretroviral drugs have a significant relationship. The normality test from the CD4 data shows p> 0.05 which means that the CD4 data has a normal distribution while the duration of ARV consumption has an abnormal data distribution (p <0.05). The CD4 test was then continued with Mann Whitney **(Table 2)** data analysis while the duration of ARV consumption used an independent t-test **(Table 2)**.

Using data analysis, the cut-off for CD4 ≤134 cells/ul was obtained while the duration of ARV consumption was ≥ 20.5 months. Statistical analysis for CD4 data and ARV duration using the SPSS 20 program showed a significant relationship between CD4 cell count (p <0.05) and duration of ARV consumption (p <0.05) with virological failure. We use logistic regression analysis to calculate SE and β to formulate a predictive total score **(Table 3)**. From the results of the analysis, each score of 1 was obtained for CD4 cell count and duration of ARV.

Summation scores to each of the research subject variables was described as total scores that passed on to logistic regression analysis. The next assessment is the discrimination of the scoring model obtained p value <0.001 with an area under curve (AUC) of 73.6%. The cut-off of this model shows a sensitivity value of 81.5% and a specificity of 44.4% **(Picture 1)**.

Table 1. Factors Contribute to Virological Failure

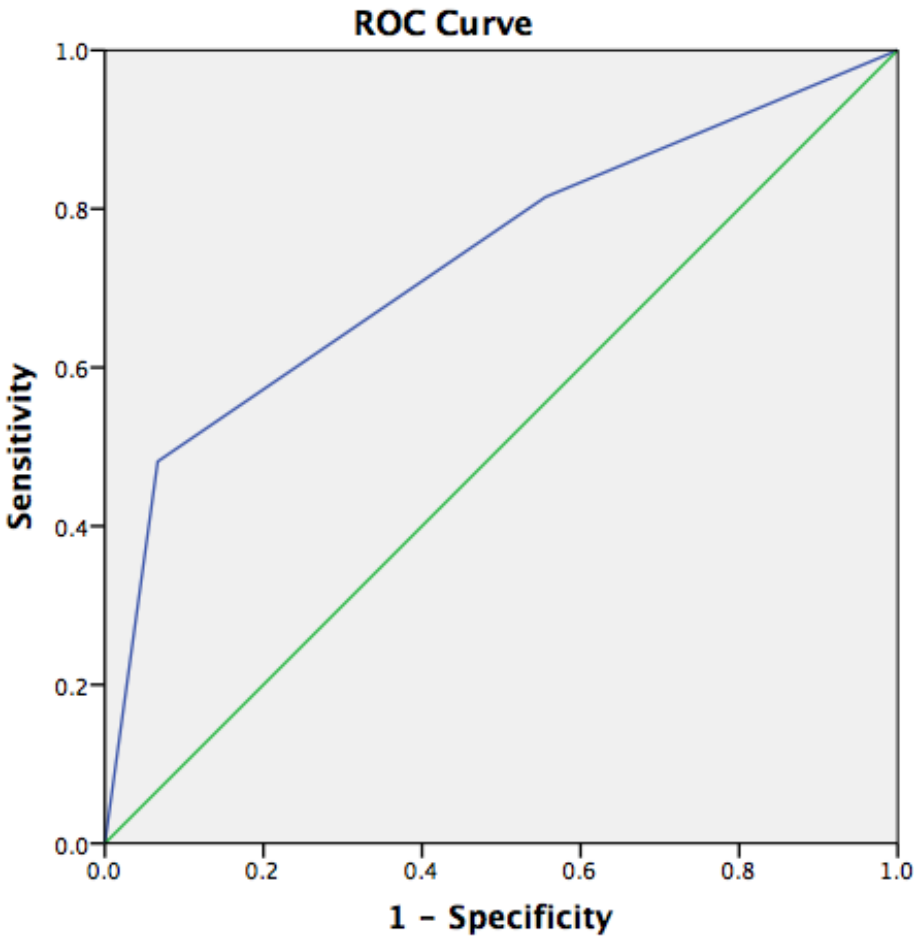
Variable	Group		p-value
	Failure n (%)	Non Failure n (%)	
Gender			
Men	18 (35,2%)	33 (64,8%)	0,598
Woman	9 (42,8%)	12 (57,2%)	
Education			
Primary	21(38,9%)	33 (61,1%)	0,782
College	6 (33,3%)	12 (67,7%)	
ARVs Regimen			
FDC	15 (31,2%)	33 (68,8%)	
Non FDC	12 (50%)	12 (50%)	0,132
Risk Factors			
Unsafe Sex	23 (34,3%)	44 (65,6%)	0,062
Drug injections	4 (80%)	1 (20%)	
Hepatitis C			
Positive	2 (66,67%)	1 (33,3%)	0,136
Negative	5 (19,2%)	21 (80,8%)	
Tuberkulosis			
Positive	7 (53,8%)	6 (46,2%)	
Negative	20 (33,8%)	39 (66,1%)	0,214

Table 2. Statistical Analysis For ARV Duration and CD4 Count

Variable (n=72)	Suppresion VL (n=45)	Virological Failure (n=27)	P value	OR (95%)
ARV duration	21.44±26.05	42.59±37.6	0.01	1.396-11.78
CD4	255.38±190.328	156.36±140	0.01	1.33-11.281

Table 3. Logistic Regression Analysis and Model Scoring for Plasma CD4 count and Duration ARV Consumption

Variabel	b	SE	β/SE	(β/SE)/2.484	Rounded
ARV Duration	1.354	0.545	2.484	1	1
CD4 Count	1.400	0.544	2.573	1.03	1
Total score					**2**



Picture 1. ROC Curve For Total Score of Plasma CD4 Count and Duration ARV Consumption

Discussion

The results of data analysis for each variable that affects virological failure, only CD4 and duration of ARV have a significant relationship. The total predictor scores of the two variables have significant results so that the score model can assist clinicians in evaluating suspicion of virological failure. The assumption of this score is that patients with CD4 counts ≤134 and duration ≥ 20.5 months have a risk of virological failure with a sensitivity of about 81.5%.

CD4 T cells are known as components of the humoral and cellular immune responses to exogenous antigens. HIV binds to CD4 molecules on the surface of helper T cells (Th cells) and replicates on them. This causes damage and decreases in CD4 T cell counts[6].

Several hypotheses in 1980 stated that the decrease in the number of CD4 T cells was caused by rapid damage due to resistance to HIV. Through this theory there is a balance of homeostasis when CD4 T cells are damaged by HIV, it will be offset by T cell production. However, this balance mechanism will be disrupted when there is no production response to T cells due to the burden of T cell production. Therefore, during HIV infection, around one billion HIV particles are produced each day, causing an increase in the number of infected CD4 T cells. Every time a memory CD4 T cell is infected, it will undergo an elimination process that causes a decrease in the number of CD4 T cells. The mechanism of apopotosis of infected CD4 T cells supports this hypothesis but naïve CD8 T cells and uninfected CD4 T cells that participate in elimination in the asymptomatic phase cannot be explained by this process[6].

The second hypothesis that causes CD4 T cell decline in HIV is chronic immune activation under hyperimmune conditions. This condition induces an increase in the division of CD4 cells, CD8 cells, NK cells, and B cells. T cell division also increases the

ability to renew itself which can increase the number of cells. The hypothesis of the number of T cells decreases due to activation because the activated CD4 has a short life and disappears due to apoptosis. HIV causes its targets and increases replication through chronic immune activation. HIV activates immunity through Nef, Tat, Vpr, Vpu and pro-inflammatory cytokines. The presence of HIV DNA in the cytoplasm will activate pro-inflammatory cytokines so that the HIV virus will cause chronic immune activation[6].

Patients with low CD4 cell counts have a nine-fold risk of virological failure than patients with high CD4 cell counts (> 200 cells/mm^3). This finding is consistent with research in Switzerland and Uganda. In theory, there is an inverse relationship between CD4 cell count and replication and viral load. Patients with impaired immune status have a risk of opportunistic infections as well as low immune status and high levels of viral replication. Patients with CD4 counts ≤199 have a risk of virological failure OR 10.09 95% CI (2.47-41.29), CD4 200-349 OR 2.94 95% CI (0.86-10.07), CD4 350 -499 OR 0.83 95% CI (0.18-3.8). CD4$^+$ T cells are the majority of cells infected with HIV. The HIV virus causes adverse effects on the level and proportion of these cells in lymphoid tissue and blood. Some of the mechanisms adopted by viruses that cause a reduction in CD4$^+$ lymphocyte counts include dysregulation of cell proliferation and homeostasis. HIV-1 infection alters CD4 T-cell homeostasis, which is a balance between the rate of production and cell death. This results in a higher rate of cell damage compared to production, contributing to a decrease in CD4$^+$ T cells. HIV infection also interferes with the production of thymic and hematopoietic progenitor cells, causing cell death through the release of the gp120 virus protein. HIV infection causes a cycle that involves activation and death of the immune system then drives HIV replication[7].

Adherence is an important factor for the success of therapy in AIDS patients. Interruption of ARV consumption, especially the NNRTI regimen, causes an increase in virological failure and antiretroviral resistance. This observation reflects the low genetic barrier to antiviral resistance to NNRTIs, such as prolongation of the plasma half-life of NNRTI, which causes the plasma concentration of NRTI therapy to decrease. In areas with limited access to antiretroviral therapy, interruption of therapy causes the total cost of treatment to be more expensive due to difficulty accessing health services, distribution difficulties and drug storage. The risk of non-compliance leads to virological failure OR 3.6 95% CI (1.2-11)[8]. Unfortunately, bivariat analysis of adherence in this study did not show a significant relationship.

When adherence decreases, the dose of the drug becomes intermittent, causing exposure to single and multiple drugs to have a longer half-life. A similar situation occurs when PLWHA stop all antiretroviral drugs[9]. In this study, if the duration of antiretroviral drugs was assessed based on the duration of antiretroviral consumption, a significant relationship was found ($p < 0.001$) which means that the longer the patient took antiretrovirals the lower the adherence to antiretroviral consumption.

Limitation of this study were this research was conducted at the outpatient clinic UPIPI Dr. Soetomo Teaching Hospital Surabaya, which is a tertiary referral health facility so that the exclusion inclusion criteria cannot describe the condition of HIV/AIDS patients extensively, CD4 evaluation data and viral load are not all tested periodically so they cannot describe the tendency of failure and suppression of virological, incomplete medical record data regarding reasons for selection, replacement of antiretroviral drugs and side effects of antiretroviral drugs in patients, unable to evaluate virological failure based on patient adherence every 6 months and the underlying reasons. Furthermore, the total score predictor model shows an area under curve of only 73.6% indicating that there are other variables that can affect virological failure.

Researchers hope that with these findings an evaluation of virological failure can be carried out intensively. This will have an impact on the patient's clinical course, the risk of drug mutations and the mortality of AIDS patients. A study with patient compliance interventions is needed to study the relationship of adherence to virological failure in HIV/ AIDS patients.

Conclusion

Patients with CD4 ≤134 cells/ul and duration of ARV consumption ≥ 20.5 months have a risk of virological failure.

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Ethical Consideration: Ethical clearance was obtained from Ethics Committee Dr. Soetomo Teaching Hospital Universitas Airlangga and official letter was submitted to the Dr Soetomo Hospital administration prior to data collection.

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