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# Risk Factor Of Substitution ARV First Line People Living With HIV/AIDS In General Hospital Buleleng Bali

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**ABSTRACT**
Substitution is still a threat to the failure of ARV therapy so that no matter how small it must be noted and monitored in ARV therapy. The aims was analysis risk factor substitution ARV first line in therapy ARV. This study was an analytic longitudinal study with retrospective secondary data analysis in a cohort of patients receiving ARV therapy at the District General Hospital of Buleleng District for the period of 2006-2015 and secondary data from medical records of PLHA patients receiving ART. Result in this study that the percentage of first-line ARV substitution events is 9.88% (119/1204) who received ARV therapy for the past 11 years. Risk factors that increase the risk of substitution in ARV therapy patients are zidovudine (aOR 4.29 CI 1.31 -2.65 p 0.01), nevirapine (aOR1.86 CI 2.15 - 8.59 p 0.01) and functional working status (aOR 1.46 CI 1.13 - 1.98 p 0.01).

**Keyword** : Substitution, First Line, Buleleng

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## INTRODUCTION

The issue of consistency and scope of ARV therapy becomes a problem in the response to HIV / AIDS both nationally and globally. Stigma and discrimination that have not been overcome cause many effects and impacts, especially on the therapeutic process carried out. Global conditions occur that gaps in access to ARV therapy still occur (UNAIDS, 2013a). The problem of death, loss of treatment and drug substitution is still a priority in the handling of HIV / AIDS. National guidelines for antiretroviral treatment in Indonesia are continually updated periodically referring to WHO guidelines and recommendations in accordance with the development of scientific evidence in the form of clinical studies and observational studies on the efficacy, side effects of drugs and experience of using antiretroviral drugs by programs in countries with limited resources, such as drugs and costs (RI Ministry of Health, 2011). Coverage of ARV treatment in Indonesia from 2013 to 2017 continues to increase, indicated by the absolute number of PLHAs who still receive ARV increased from 34,961 to 79,833 people with the trend of first-line substitution decreasing 25.36% to 18.41% in 2017. (Ministry of Health Republic of Indonesia, 2013 , 2014; RI, 2017). Although the percentage of substitution shows a decrease but it has not reached the maximum because it shows that toxicity, side effects and other factors still occur in patients receiving ARV therapy. Reasons for ARV drug substitution include toxicity and treatment failure which is most common in the stavudine regimen (Castelnuovo et al., 2019). Substitution is still a threat to the failure of ARV therapy so that no matter how small it must be noted and monitored in ARV therapy (Ababa, 2018; Castelnuovo et al., 2019; Ndakala et al., 2017; WHO, 2018). ARV substitution is a replacement for ARV drugs that are still classified as the original first-line group. Substitution is one of the toxicity monitoring benchmarks determined by WHO, because the risk of treatment failure is very likely to occur in those who experience substitution (Enderis et al., 2019; Lenjiso et al., 2019; Shearer et al., 2014; WHO, 2018 ).
Monitoring ARV drug toxicity is an important component of a patient monitoring system (WHO, 2018).
First-line ART failure is a public health problem and early detection of treatment failure is very important to manage (Enderis et al., 2019). History of drug use, lack of disclosure status, time since HIV diagnosis, advanced WHO clinical stage, low CD4 cell count, opportunistic infections, functional status, non-adherence to HAART and malnutrition affect the time to first-line treatment failure among adult patients living with HIV ( Enderis et al., 2019). The average time of failure of first-line ARV substitution is 21 months and the first year of therapy (Enderis et al., 2019; Ndakala et al., 2017).

## METHODS

This study was an analitic longitudinal study with retrospective secondary data analysis in a cohort of patients receiving ARV therapy at the District General Hospital of Buleleng District for the period of 2006-2015. This study used secondary data from medical records of PLHA patients receiving ART and ARV registers contained in the VCT Polyclinic of Buleleng Hospital.
The first step taken before the data extraction is the permit application to the Buleleng District Hospital. The first is to make permits for data collection and to conduct research in RSUD Buleleng. Then take care of study permit in National Unity and Politics Board and take care of Ethical Clearance in ethics commission R & D FK UNUD / Sanglah Hospital Denpasar. Data were collected by medical record extraction and ARV registers of each PLHIV antiretroviral period 2006 to December 2015 at the VCT service Edelweies RSUD

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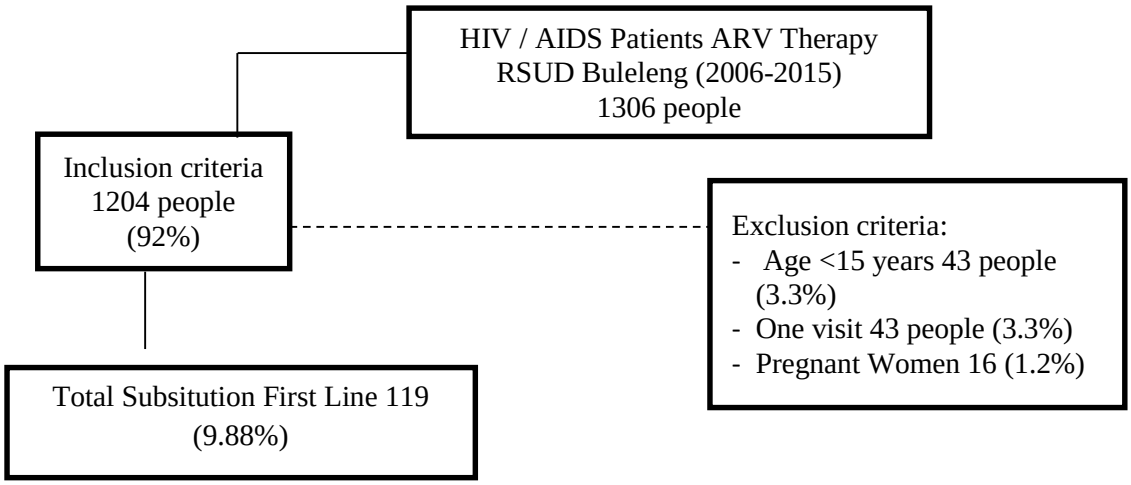
Buleleng meeting the inclusion criteria. Further data on the data collection form is still in hard copy form made into soft copy (in the form of microsoft excel) to facilitate the analysis.

This research was conducted in VCT Eldeweies clinic of Buleleng District Hospital during April 2017 - November 2017 period. Dependent variable is substitution first line ARV data on medical records. The independent variable consists of sociodemographic and clinical characteristics. Characteristics of sociodemography consist of sex and drug conservator. Clinical characteristics include WHO stage/stadium,functional status, type of NRTI ARV, NNRTI ARV type and reason subsitution. Reason of substitution just analysis with univariate analysis.

The total population in the study until July 31, 2014 was 1306 patients. This population is limited in the inclusion criteria of HIV / AIDS patients receiving ARV therapy under substitution ARV first line. The exclusion criteria established in this study were pregnant women, <15 years of age and unrandom identities.

The sample research selection procedure is illustrated in Figure 1 below :




The calculation of the sample size used is as follows: (Lwanga, S. K. Lemeshow, 1991)

$$n = \frac{\left((Z_\alpha \sqrt{(1+k)}\lambda 2 + Z_\beta \sqrt{k\lambda_1^{\,2} + \lambda_2^{\,2}}\right)}{k(\lambda_1 - \lambda_2)^2}$$

Information :
Zα = derivate alpha standard
Zβ = raw beta derivate
k = the ratio of groups not exposed to the exposure group in the population
λ 2 = the proportion of LTFU in a known group (control group)
λ 1 = proportion of LTFU group to be tested

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The analysis in this study used survival analysis using STATA SE 12 software. Univariate analysis to obtain the percentage of substitution. The value of adjusted Odds Ratio (OR), p specific, and p of OR crude from each independent variable to subsitution were performed with Logistic Regresion with 95% confidence level. Multivariate analysis with Logistic Regression with the selection method used is the backward method where one by one insignificant variable is removed from the model until the final model is obtained. The propotional hazard test is performed on the last multivariate model which aims to check the proportional model produced where the model is said to be proportional when it has a p> 0,05.

## RESULTS

### Univariate Analysis

Table 1. Univariate Analysis Characteristic Subject with Subtitution ARV Fisrt Line

| Characteristic | Subtitution ARV Fisrt Line | | |
|---|---|---|---|
| | Yes f(%) | No f (%) | p |
| 1 | | 2 | 4 |
| Sex | | | 0.11* |
| Female | 52 (11.66) | 394(88.34) | |
| Male | 67 (8.84) | 691(91.16) | |
| Stadium Klinis | | | 0.34* |
| Stadium 1 dan 2 | 24 (11.21) | 190(88.79) | |
| Stadium 3 dan 4 | 76(9.07) | 762(90.93) | |
| NRTI | | | 0.01* |
| Tenofovir | 6(2.97) | 196(97.03) | |
| Stavudine | 9(9.78) | 83(90.22) | |
| Zidovudine | 104(11.53) | 798 (88.47) | |
| NNRTI | | | 0.01* |
| *Evapirine* | 9 (3.11) | 280(96.89) | |
| Nevirapine | 110 (12.14) | 796(87.86) | |
| Functional Status | | | 0.01* |
| Bes Rest | 22(6.43) | 320(93.57) | |
| Ambulatory | 47(9.51) | 447(90.49) | |
| Doing | 34(13.39) | 220(86.61) | |
| Adherence Support | | | 0.78* |
| Yes | 103(9.98) | 929(90.02) | |
| No | 16(9.30) | 156(90.70) | |
| Reason Subsitusi | | | 0.01* |
| No reason | 62(5.41) | 1085(94.59) | |
| Anemia | 17(100) | 0(0) | |
| Side effect | 40(100) | 0(0) | |

Based in table 1 in top describe that the proportion of characteristics based on sex, NRTI regimen, NNRTI regimen, functional status, and reasoning substitution have statistically significant difference with p value, 0.05.

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Table 2. Multivariate Analysis Risk Factor of Subtitution ARV Fisrt Line

| Characteristic | Subtitution ARV Fisrt Line | |
|---|---|---|
| | aOdds Ratio | CI (P value) |
| 1 | 2 | 3 |
| Sex | | |
| Female | 1.00 | |
| Male | 0.73 | 0.50-1.07 (0.11) |
| Stadium Klinis | | |
| Stadium 1 dan 2 | 1.00 | |
| Stadium 3 dan 4 | 0.73 | 0.52-1.03 (0.11) |
| NRTI | | |
| Tenofovir | 1.00 | |
| Stavudine | 1.00 | |
| Zidovudine | 4.29 | 1.31 -2.65 (0.01*) |
| NNRTI | | |
| *Evapirine* | 1.00 | |
| Nevirapine | 1.86 | 2.15 – 8.59 (0.01*) |
| Functional Status | | |
| Bes Rest | 1.00 | |
| Ambulatory | 1.00 | |
| Working | 1.49 | 1.13 – 1.98 (0.01*) |
| Adherence Support | | |
| Yes | 1.00 | |
| No | 0.93 | 0.53 – 1,61 (0.78) |

Based on the table. 2 above shows that there are three variables which are risk factors for first-line ARV substitution, namely patients who use the NRTI zidovudine regimen have a 4.29 times risk of substitution compared to other NRTI types. Users of the Nevirapine NNRTI 1.86 time risk of substitution compared to other NNRTI types. Similarly, for patients who come in the condition of functional status of working have a risk of 1.49 times to experience substitution compared to other functional status conditions.

## DISCUSSION

The first line of antiretroviral drugs prescribed by the government is 2 NRTIs (nucleoside reverse transcriptase inhibitors) accompanied by 1 NNRTI (non-nucleoside reverse transcriptase inhibitors, for example zidovudin given with lamivudine and nevirapin (Ministry of Health Republic of Indonesia, 2011). encountered in the administration of antiretroviral therapy.The level of toxicity arising from antiretroviral drugs is often a major factor for the act of substitution, substitution is a replacement procedure for one of the NRTI or NNRTI regimens that are still in the original first-line group (Kemenkes RI, 2011). anemia, toxicity, rash, failure of immunity are the most common reasons for ARV substitution (Castelnuovo et al., 2019; Enderis et al., 2019; Mulisa et al., 2019). The rates of clinical or virology failure (VF) were 1.48 / 100 person years (95% CI 1.14 to 1.91) in the minor substitution group (Jung et al., 2017) Substitution in this study was conducted. report that 9.88% (119/1204) of patients receiving ARV therapy, when compared with TAHOD (TREAT Asia HIV Observational Database) data, this figure is still smaller,

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where TAHOD 1170 (37.5%) underwent a minor substitution regimen (Boettiger et al. , 2014; Jung et al., 2017).

This study shows that the risk of substitution is 4 times higher in those who use the NRTI regimen, zidovudine (AZT). Side effects of the use of zidovudine are anemia with low hemoglobin levels <10g% (HR 2.72; 95% CI 1.02-7.21). Besides the ARV therapy policy in Indonesia after 2012 which started ARVs with CD4> 350 cell / mm3, this also increased the risk of zidovudine substitution reaching HR 3.83; 95% CI 2.19-6.70 (Adnyani et al., 2016). When compared with tenofovir (TDF), the risk of toxicity driven substitution was 5 times higher in AZT (AHR = 5.07, 95% CI (1.4-18.33), P = 0.013) (Ababa, 2018). The NNRTI regimen of nevirapine has been shown to be 1.86 times more at risk of substitution. Nevirapine is reported to cause liver toxicity called hepatotoxins which is indicated by the SGPT value of patients increasing up to five times from the previous condition (Ministry of Health RI, 2011). The hazard of composite outcome on nevirapine compared with efavirenz was AOR 1.02 -2.77 (95% CI: 0.52-6.28) (Awoke et al., 2016; Mulisa et al., 2019). Nevirapine has been shown to increase the risk of failure of antiretroviral therapy (Mulisa et al., 2019). Research in Johannesburg, South Africa shows that patients initiating NVP-based regimens experienced more virologic failure than patients initiating EFV-based regimens (Shearer et al., 2014). Nevirapine metabolism is more sensitive to induction of hepatic enzymes than that of Efavirenz; therefore, Efavirenz-based regimens are advocated as the first-line treatment in HIV-TB co-infected patients (Shearer et al., 2014; Sinha et al., 2017).

Another finding from this study is that patients who come with functional "work" status tend to be 1.46 times more likely to experience substitution compared to lying and ambulatory conditions. Different conditions found in other studies that lying and ambulatory functional beds increase the risk of treatment failure (AHR = 2.71 95% CI = 1.33 to 5.51, P = 0.006), although this does not directly increase the risk of ARV substitution (Enderis et al., 2019). Likewise in other studies that ambulatory / bedridden functional status at the last visit on ART (AOR: 2.41, 95% CI: 1.22–4.75) in cases of failure of ARV therapy (Lenjiso et al., 2019).

## CONCLUSION

The results of this study indicate that the percentage of first-line ARV substitution events is 9.88% (119/1204) who received ARV therapy for the past 11 years. Risk factors that increase the risk of substitution in ARV therapy patients are zidovudine (aOR 4.29 CI 1.31 -2.65 p 0.01), nevirapine (aOR1.86 CI 2.15 - 8.59 p 0.01) and functional working status (aOR 1.46 CI 1.13 - 1.98 p 0.01). supervision of those receiving AZT and NVP therapy needs to be increased to anticipate substitution which will have an impact on the failure of ARV therapy.

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