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## MORTALITY OF HIV/AIDS- INFECTED PEOPLE WITH ANTIRETROVIRAL THERAPY: A GENDER ANALYSIS

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## MORTALITY OF HIV/AIDS-INFECTED PEOPLE WITH ANTIRETROVIRAL THERAPY: A GENDER ANALYSIS

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### Abstract

**Background:** Mortality in people living with HIV/AIDS is one of measures to the success of its treatment. Study related to their deaths seen from gender is still very limited.

**Objective:** The aim of this study was to determine the incidence rate of mortality between men and women living with HIV/AIDS and receiving antiretroviral therapy.

**Methods:** This was a retrospective study using secondary data of HIV/AIDS-infected patients in Buleleng District Hospital in the period of 2006-2015. This research used *Survival analysis, Kaplan-meier, incident rate comparison* and *logistic regression* with STATA SE 12.

**Results:** A total of 1204 HIV/AIDS-infected patients data was included. The incidence of total mortality rates was 27.7 per 1000 person-years. Based on gender, the mortality in men (35 per 1000 person-years) was higher than women (14 per 1000 person-years) with the incidence rate ratio (IRR) of 2.39 (p 0.01). Fifty percent of cases of mortality occurred at 0.15 years of observation. The median time of mortality in men was 0.14 years (1.7 months) and in women was 0.15 years (1.8 months). The poor clinical condition was seen from a body weight <50 kg, which increased the risk of death with aOR 3.85 (p 0.01 CI 2.40-6.16). Nevirapine increased the risk of mortality (aOR 2.18; p 0.01; CI 1.18-4.03). and CD4 cell counts of  $\leq 200$  cells / mm<sup>3</sup> reduced the risk of death by 69% (AOR 0.31; p 0.01; CI 0.18-0.53).

**Conclusion:** The incidence of mortality in men was greater than it in women, which is caused by poor clinical conditions. It is better to evaluate the success of antiretroviral therapy by considering the needs of patients according to their gender. Further research is needed in regard to adherence of treatment and loss to follow-up events.

**Keywords:** HIV/AIDS, gender, mortality, antiretroviral therapy

## INTRODUCTION

HIV / AIDS epidemic is still a global issue that needs special attention. Various programs are developed to achieve the goal of reducing the risk of transmission. The four pillars of HIV/AIDS prevention in Indonesia that lead to a paradigm zero new infection, zero AIDS-related death and zero discrimination include

prevention, care, support and treatment, mitigation of impacts, and preparation of a conducive environment ([MOH, 2010, 2011a](#)). Indicators to measure the success of antiretroviral (ARV) therapy programs in people living with HIV are the mortality rate and loss to follow-up (LTFU) rate. Both measures are very influential in the

continuity of therapy. Bali was the seventh highest province in Indonesia for the mortality of people living with HIV/AIDS (PLHA) in ARV therapy. Although it is still below the national mortality percentage (18.04%), but still far from the target of zero AIDS-related death ([ASEAN Nations, 2011](#)).

Common clinical conditions associated with the incidence of mortality in PLHA are weight, CD4 cell count, clinical stage and functional status. Thus, ARV therapy requires adherence to therapy so that patient compliance must always be monitored and evaluated regularly at each visit. Failure of ARV therapy is often caused by non-adherence patients taking ARV ([Lamb, El-Sadr, Geng, & Nash, 2012](#); [MOH, 2011a](#); [WHO, 2013](#)). And gender is one of variables that greatly determines the pattern of adherence in ARV therapy. Risk of mortality in men tends to be higher (RR 1.19, aSHR 1.7) compared to women ([Hawkins et al., 2011](#); [Mugisha et al., 2014](#)). Men have different adherence than women, and they still have worse treatment. While women have a greater position in matters related to depression, stress, stigmatization, and social roles related to gender ([Applebaum, Richardson, Brady, Brief, & Keane, 2009](#)). In addition, social and cultural stigma is more likely with men and related to the prevention, awareness, and treatment of diseases ([Mitra & Sarkar, 2011](#)). However, the results of gender studies related to ARV therapy are still inconsistent. Studies on gender analysis in the case of mortality in PLHA with ARV therapy in Indonesia, especially in Bali Province are still limited. The aim of this study was to describe the incidence rates of mortality based on gender analysis.

## METHODS

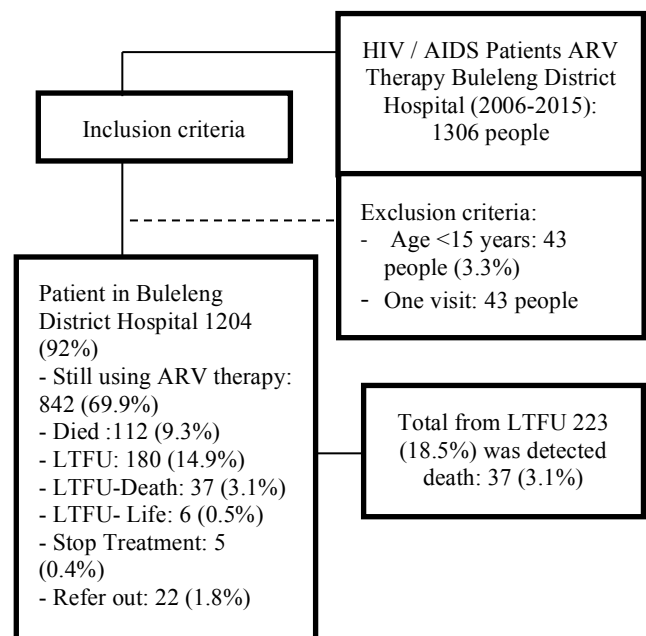
### *Study design*

This was a retrospective study with secondary data of HIV/AIDS-infected

patients receiving ARV therapy at the District General Hospital of Buleleng District from 2006 to 2015. This research was conducted at Edelweis VCT Polyclinic of Buleleng District Hospital from January to August 2017.

### *Sample*

A total sample of 1204 people was retrieved from the medical records based on the inclusion criteria. Surveys via telephone and home visits were made for special patients with lost to follow-up (LTFU) accompanied by field officers from NGOs. The sample research selection procedure is illustrated in **Figure 1** below:



**Figure 1** Selection procedure of sample

### *Ethical consideration*

The study permission was obtained from Buleleng District Hospital. And the ethical clearance was approved by the Ethics Commission of the Faculty of Medicine, Udayana University/Sanglah Hospital Denpasar with approval number: 2611/UN.14.2/KEP/2017.

### *Data analysis*

STATA SE 12 version was used for data analysis. Univariate analysis was used to

obtain the incidence rate of death rate per 100 people according to a year and adjusted odds ratio, in addition to the median time of mortality until the end of the observation year. Bivariate analysis with p-value and survival rate was used to see the significance of the differences between the respective groups. The value of the crude Odds Ratio (cOR), p specific, and p of OR crude from each independent variable to mortality were performed using logistic regression with a 95% confidence level. The parm test was used when the nominal independent variable was for three or more categories, and we used a test for the trends when the ordinal data or

intervals were in two or more categories. Logistic Regression with backward model was used for multivariate analysis. The insignificant variables were removed from the model until the final model was obtained.

## RESULTS

The results of the study from 1204 data on PLHA patients who met the inclusion criteria showed that the percentage of death cases was 9.30%. The proportion of mortality in men was 79.46% and females were 20.54%. The incidence rates of death

**Table 1** Sociodemographic and Clinical Characteristics of PLHAs with ARV Therapy by Gender

Characteristics	Men		Women	
	Life	Death	Life	Death
	f (%)	f (%)	f (%)	f (%)
Age				
< 40 years	535 (79.73)	66 (81.48)	361 (85.34)	21 (91.30)
≥ 40 years	136 (20.27)	15 (18.52)	62 (14.66)	2 (8.70)
Status of supervisors taking medicine				
Presence	584 (86.65)	71 (87.65)	359 (84.27)	18 (78.26)
Absence	90 (15.73)	10 (12.35)	67 (15.73)	5 (21.74)
Weight				
> 50 kg	185 (56.23)	5 (27.78)	84 (35.00)	1 (25.00)
≤ 50 kg	144 (43.77)	13 (72.2)	156 (65.00)	3 (75.00)
CD4 counts				
≥ 200 cell / mm <sup>3</sup>	45 (15.79)	2 (8.00)	54 (30.86)	0 (0)
<200 cell / mm <sup>3</sup>	240 (84.21)	23 (92.00)	121 (69.14)	11 (100)
Functional Status				
Bed rest	198 (31.78)	44 (57.14)	89 (24.12)	11 (52.38)
Ambulatory	287 (46.07)	28 (36.36)	171 (46.34)	8 (38.10)
Work	138 (22.15)	5 (6.49)	109 (29.54)	2 (9.52)
Clinical status				
Stadium 3 & 4	508 (83.55)	68 (94.44)	245 (69.80)	17 (80.95)
Stadium 1 & 2	100 (16.45)	4 (5.56)	106 (30.20)	4 (19.05)
Policy therapy				
Policy before 2011	193 (28.64)	43 (53.09)	89 (20.89)	14 (60.87)
Policy after 2011	481 (71.36)	38 (46.91)	337 (79.11)	9 (39.13)
NRTI				
tenofovir, fdc	128 (18.75)	7 (8.97)	67 (15.80)	2 (9.09)
stavudin	48 (7.14)	11 (14.10)	29 (6.84)	4 (18.18)
zidovudin / duviral	498 (74.11)	60 (76.92)	328 (77.36)	16 (72.73)
NNRTI				
efavirens	195 (29.02)	16 (20.51)	75 (17.73)	3 (13.64)
nevirapine	477 (70.98)	62 (79.49)	348 (82.27)	19 (86.36)
Distance to service center				
≤ 5 km	83 (12.31)	11 (13.58)	43 (10.09)	3 (13.04)
> 5 km	591 (87.69)	70 (86.42)	383 (89.91)	20 (86.96)

nucleoside reverse transcriptase inhibitors (NRTIs)  
non-nucleoside reverse transcriptase (NNRTI)

were 13.1 per 1000 person-years with a median time of death at 0.15 years (1.8 months) of observation. This condition shows that, out of 112 deaths in PLHA receiving ARV therapy, 50% of deaths occurred in 5.25 years after therapy. The incidence rates of mortality in men were 35 per 1000 person-years while in women were 14 per 1000 person-years.

It can be seen from **Table 1** that the mortality in men is higher than it in women in each sociodemographic variable, which was 81.48% of death in terms of age <40 years, 87.65% from the

present of support, and 86.42% from distance to the service center (more than 5 km). Before treatment policy in 2011, the mortality was 53.09%, which was also higher seen from the clinical conditions, such as from body weight  $\leq 50$  kg (72.2%), CD4  $\geq 200$  cell / mm<sup>3</sup> (92%), bed rest functional status (57.14%), stage 3 and 4 (94.4%), zidovudine therapy (76.92%) and nevirapine therapy (79.49%). **Table 2** shows that the incidence rates of mortality in men were 35 per 1000 person-years, which is higher than women with 14 per 1000 person-years (See also **Figure 2**).

**Table 2** Comparison of Incidents Rate Based on Gender

Gender	Rate Per 1000 Person years	Incidence rate ratio (IRR)	p-value
Female	14	2.39	0.01
Male	35		

**Table 3** Bivariate and Multivariate Analysis of Gender Differences in the Death of PLHIV with ARV Therapy

Characteristics of respondents	Bivariate				Multivariate		
	Crude OR	95% CI	p	p (g)	aOR	95% CI	p
Age							
< 40 years	1.00 (ref)						
$\geq 40$ years	0.79	0.43-1.45	0.45				
Status of Supervisor taking medicine (PMO)							
There is	1.00 (ref)						
No	1.18	0.53-2.61	0.69				
Weight							
> 50 kg	1.00 (ref)						
$\leq 50$ kg	3.97	2.37-6.67	0.01 *		3.85	2.40-6.16	0.01 **
CD4 count							
$\geq 200$ cell / mm <sup>3</sup>	1.00 (ref)						
<200 cell / mm <sup>3</sup>	0.35	0.19-0.66	0.01 *		0.31	0.18-0.53	0.01 **
Functional status				0.85			
Bed rest	1.00 (ref)						
Ambulatory	0.96	0.34-2.69	0.94				
Work	1.03	0.35-3.04	0.95				
Clinical status							
Stadium 3 & 4	1.00 (ref)						
Stadium 1 & 2	1.00	0.55-1.83	0.98				
Policy							
Policy before 2011	1.00 (ref)						
Policy after 2011	0.69	0.32-1.50	0.35				
NRTI							
tenofovir, fdc	1.00 (ref)			0.34			
stavudin	0.14	0.01-1.47	0.10 *				
zidovudin / duviral	0.54	0.19-1.48	0.23 *				
NNRTI							
efavirens	1.00 (ref)						
nevirapine	3.67	1.42-9.48	0.01 *		2.18	1.18-4.03	0.01 **
Distance to service center							
5 km	1.00 (ref)						
> 5 km	1.28	0.57-2.92	0.55				

Bivariate analysis seen from Table 3 indicates that only three variables fit with the model. The results show that the absence of adherence support and distance to the service center (>5 km) increased the risk of death, but were not statistically significant. While weight < 50 kg (cOR 3.97; p= 0.01) and nevirapine therapy users (cOR 3.67; p= 0.01) were two variables that increased the risk of death and were statistically significant. And CD4 counts > 200 cells / mm<sup>3</sup> (cOR 0.35; p=0.01) decreased the risk of death and was statistically significant.

The results of multivariate analysis in Table 3 also showed that three variables related to death. Weight <50 kg was 3.85 times increasing death (Adj OR 3.85 95% CI 2.40-6.16 p=0.01). ARV Therapy in NNRTI and Nevirapine were 2.18 times increasing death (Adj OR 2.18 95% CI 1.18-4.03 p=0.01). CD4 with level < 200 cell / mm<sup>3</sup> decreased death until 64 % (Adj OR 0.31 95% CI 0.18-0.53 p=0.01).

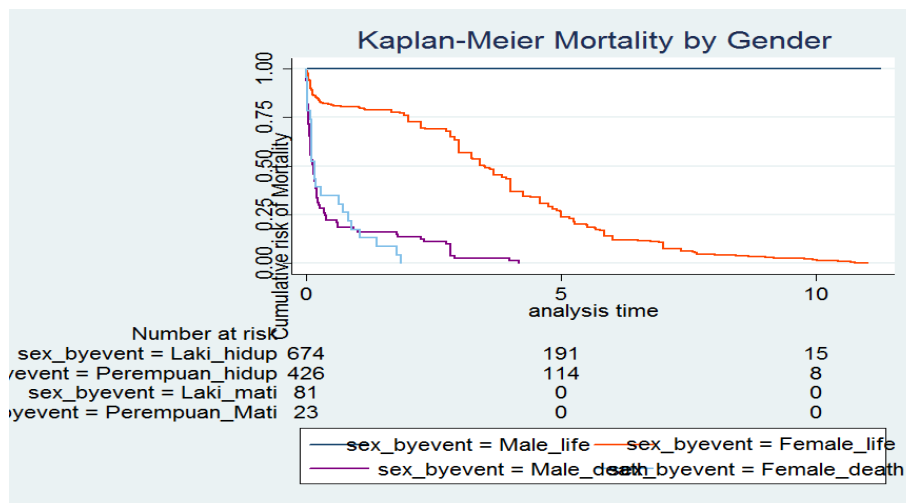


Figure 2 Kaplan Meier Death of PLHAs based on Gender

## DISCUSSION

The incidence rates of mortality in men were 35 per 1000 person-years while in women were 14 per 1000 person-years. This result is in line with several studies, which found that the incidence of mortality rates in men was higher than in women (Hawkins et al., 2011; Taylor-Smith, Tweya, Harries, Schoutene, & Jahn, 2010; Weigel et al., 2012). Non-adherence to treatment contributes to death by up to 50% (Brinkhof, Pujades-Rodriguez, & Egger, 2009; Wubshet, Berhane, Worku, & Kebede, 2013). The incidence rate ratio (IRR) was 2.39 (p 0.01), which showed that the risk of mortality in men was 2.39 times that of women.

The success of ARV therapy requires adherence to therapy for HIV/AIDS patients,

so the adherence of a patient must be monitored and evaluated regularly at each visit. Failure of ARV therapy is often caused by non-adherence to patients taking ARV (Lamb et al., 2012; MOH, 2011a; WHO, 2013). ARV therapy requires maximum adherence.

Men have a tendency to behave worse in adherence to treatment. They tend to come to health services with poor clinical conditions so that the risk of death is greater (Brinkhof et al., 2009; Brinkhof et al., 2010; Gabillard et al., 2013; Weigel et al., 2012; Wilkinson, Skordis-Worrall, Ajose, & Ford, 2015).

Multivariate analysis with backward model shows three characteristics that have been statistically significant to increase the risk of death. Weight less than 50 kg increases the

risk of death by 3.85 times. Body weight was the clinical indicator of the quality of life of PLHA. Body weight is a reference commonly used to assess nutritional status. People with HIV who start therapy weighing less than 45 kg are more at risk of death. Weight loss > 10% is a common symptom experienced when infected with HIV (Dalal et al., 2008). On the contrary, every one kilogram increased in body weight reduced the risk of death in PLHA who experienced LTFU by 6% (HR 0.94; p = 0.035 (CI 0.89-0.99) (Kusuma Dewi & Widiarta, 2018).

ARV regimen consisted of *nucleoside reverse transcriptase inhibitors* (NRTIs) and *non-nucleoside reverse transcriptase* (NNRTI). Nevirapine (NVP) increases the risk of death by 2.18 times. The antiretroviral regimen related to drug characteristics and side effects and the easy of access to ARVs impact on the compliance of PLHA (Ford et al., 2013; MOH, 2011b). NVP has a greater level of toxicity in the general population, where the toxic effects reach 1.5 times (OR 1.5, 95% CI 0.9-2.3) (Ford et al., 2013). Nevirapine also increases the risk of death in PLHA who experienced LTFU by 3.92 (Kusuma Dewi & Widiarta, 2018). Severe side effects certainly contributed to the case of the death of PLHA. When starting therapy with a higher CD4 in 350 cell / mm<sup>3</sup> can reduce the effect of toxicity on PLHAs (Clouse et al., 2013; MOH, 2011a). The rate of CD4 becomes a benchmark for the health status of PLHAs and immunological failure indicators in ARV therapy. CD4 examination completes clinical examinations that can guide in determining the time to start treatment prophylaxis against opportunistic infections (OI) and ARV therapy before the disease continues to worsen. CD4 levels ≤ 200 cells / mm<sup>3</sup> reduced the risk of death by 69% with aOR 0.31 (p 0.01 CI 0.18-0.53). This condition is inversely proportional to research, which states that a low CD4 cell count can increase the risk of death (Clouse et al., 2013; Gabillard et al., 2013).

The limitation in this study is that there are still gaps in CD4 variables that cannot yet be explained in detail so that further research is

needed to link the CD4 count with the risk of death by looking at the magnitude of the effect. Qualitative research is also needed to look at the treatment and loss-to-follow-up by gender-based.

## CONCLUSION

The incidence of mortality in men was 2.39 times greater than women and poor clinical conditions tend to worsen the health condition of PLHA so the risk of death was even greater. The incidence rate of death rates in men was 35 per 1000 PY while in women 14 per 1000 PY. Poor clinical conditions with a body weight below 50 kg increase the risk of death by 3.85 times. The level of nevirapine (NVP) NNRTI toxicity increases the risk of death by 2.18 times. CD4 cell counts less than 200 cells / mm<sup>3</sup> reduce the risk of death by 69%. It is better to evaluate the success of ARV therapy considering the study and differences in needs between women and men. Further research needs to be carried out on the adherence of treatment and loss to follow-up (LTFU) gender-based events.

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