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Original Research Article

Factors associated with zidovudine substitution in HIV/AIDS patients attending Badung Hospital, Bali, Indonesia between 2006-2014

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ABSTRACT

Background: Zidovudine (AZT) is the most commonly used drug in first line antiretroviral therapy (ART) in Indonesia; however, substitution due to its side effect is common. The majority of HIV positive patients in Badung Hospital Bali are treated with AZT yet no longitudinal studies in Bali have investigated the number of substitutions or the factors associated with it.
Methods: A retrospective cohort study of HIV positive persons aged >15 years, receiving AZT between 1st January 2006 – 31st August 2014 was conducted. Persons were included from their date of starting AZT. Cox proportional hazard models were applied to estimate the risk and time to substitution. Substitution was defined as single drug change due to side effects and initiating another drug of the same class.
Results: During our study 260 patients started AZT, of which 77 (29.6%) experienced substitution. The risk of substitution was 19 per 100 person years. Of those 77, the median time to AZT substitution was 69 days (IQR 25-178). Factors significantly associated with an increased risk of AZT substitution included women (HR 1.79; 95% CI 1.09-2.94), having low hemoglobin levels <10g% (HR 2.72; 95% CI 1.02-7.21), clinical stage III and IV (HR 3.53; 95% CI 1.26-6.19) at the time of starting AZT, and starting ART after 2012 (HR 3.83; 95% CI 2.19-6.70).
Conclusions: Present study identified individuals that may be at a high risk of AZT substitution who should be monitored more closely or consideration given to initiating them on another treatment regimen.

Keywords: Antiretroviral therapy, Indonesia, Toxicity, Zidovudine

INTRODUCTION

The introduction of antiretroviral therapy (ART) had a major impact on the treatment of people with HIV/ AIDS.[1] Zidovudine (AZT) was the first antiretroviral drug approved for the treatment of HIV and remains a component of combination ART.[2]

Three quarters of patients on ART in Indonesia receive an AZT containing regimen as part of first line therapy. It is also safe for use in pregnant women and children.[2] However, treatment failure on AZT containing regimens is common, with 29.6% of patients on first line AZT containing regimens requiring drug substitution.[3] Substitution of AZT often occurs in the first year of ART, frequently in the second month of treatment.[4] If the side effects of the drug are not detected and treated early, the impact can be severe.[5]

Previous studies examining predictors of AZT substitution have found inconsistent results. Several studies have reported that AZT substitution is related to the patient's age, sex, clinical stage, hemoglobin levels and HIV transmission route.[4-6] However, there is

inconsistent evidence around the relationship between AZT substitution and the patients weight or CD4 cell count at the time of starting treatment.[4,7-9]

A longitudinal study of AZT substitution has not been conducted in district level ART services in Indonesia. Given the relatively high incidence of AZT substitution and the impact treatment side effects can have on a person's quality of life, this study aimed to use longitudinal data from a public HIV treatment hospital in Indonesia to determine the risk of AZT substitution and the factors associated with it in HIV/AIDS patients starting AZT based ART.

METHODS

Badung hospital is one of the largest public hospitals in Badung Regency. It is also a referral hospital for the Bali Medica Clinic which provides sexual health services aimed at men who have sex with men (MSM).

Study design and population

This was a retrospective cohort study using data extracted from medical records at Badung hospital between 1st January 2006 to 31st August 2014. All treatment naïve patients initiating AZT based ART at Badung General Hospital were included. Patients who were treatment experience at study entry, aged-less than 15 years old or who had only one hospital visit, and therefore no follow-up data, were excluded from the analysis.

Time to substitution of AZT was defined as single drug discontinuation of AZT, because of side effects or toxicity, and substitution to another antiretroviral from the same class.[2] Changes of two or more drugs due to virological failure were describe as a switch in therapy.[9] Substitution status was set to be a substitution and non-substitution.

Patient were included in the study from their date of starting AZT containing ART and followed until the date of AZT substitution, death or the end of the observation period. Patients on ART who were not seen at the hospital for more than 3 months were defined as lost to follow-up. Patients who died, patient who had switch therapy due to virological failure, moved away or were lost to follow-up were censored at their last clinic visit.

Data analysis method

Demographic variables included sex, HIV transmission risk group (heterosexual, homosexual or bisexual, and injecting drug use (IDU), age and year of starting ART (<2012 or ≥ 2012). Clinical characteristics at the time of starting ART included hemoglobin level (normal (>12gr%), moderate (10-12gr%) and low (<10 gr%), HIV TB status, clinical stage ('I and II' or 'III and IV', weight, first-line NNRTI (efavirenz or nevirapine) and CD4 cell count. The policy for the provision of ART in Indonesia changed in 2011, prior to 2012 initiation of ART was recommended at CD4 counts <200 cells/mm3 and from 2012 onwards at CD4 counts <350 cells/mm3. Therefore, year of ART initiation was categorized as <2012 and ≥2012 to reflect the changes in policy.

Kaplan-Meier survival analysis and Cox proportional hazard models were used to estimate the risk of AZT substitution and to identify factors associated with AZT substitution. Variables that had p-value <0.25 in univariate analysis were included in the multivariate model.

The model was built using backward elimination (p value <0.05 for retention in the model). All analysis was conducted using Stat SE 12. This study has received approval of the Research Ethics Committee of the Faculty of Medicine, Udayana University.

RESULTS

Between January 2006 and August 2014, among 671 patients initiating ART, 284 initiated an AZT based first line ART regimen.

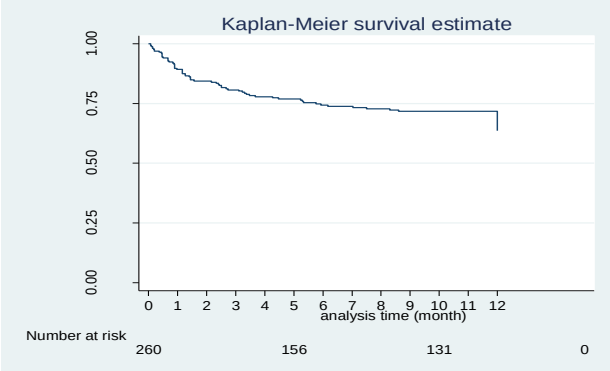

Figure 1: Kaplan-Meir curve of AZT substitution over 12 months of AZT initation.

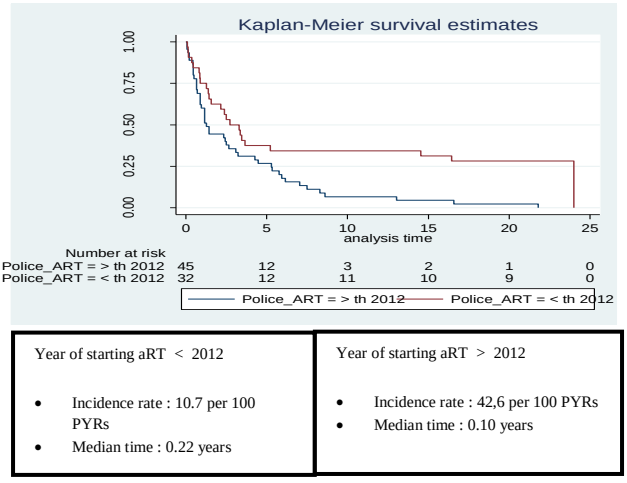

Figure 2: Kaplan-Meier at curve over 2 years (24 months) ART policy.

Of these, 11 patients were excluded as they only had one recorded hospital visit and 13 patients were excluded because they were less than 15 years old at the time of ART initiation.

Resulting in 260 patients included in this study of 77 experienced AZT substitutions and 183 did not substitute AZT. During the study period 5.7% patients died, 2.6% were lost to follow-up, 4.3% moved away and were censored at their last visit.

Table 1: Demographic and clinical characteristics of patients starting AZT based HAART in clinic Sekar Jepun Badung Hospital Bali in 2006–2014.

Characteristic	Total n (%)
Total (% total)	**260 (100)**
Sex	
Women	70 (27.0)
Men	190 (73.0)
Transmission risk group	
Heterosexual	201 (77.3)
Homosexual/Bisexual	46 (17.7)
Injecting Drug Use (IDU)	13 (5.0)
Age (per 1 years) at starting ART	
(Median, IQR)	32 (26.,0-38.0)
First-line NNRTI	40 (15.4)
Efavirenz (EFV)	220 (84.6)
Nevirapine (NEV)	
Year of starting AZT	
< 2012	148 (56.9)
≥ 2012	112 (43.1)
Hemoglobin at stating ART	
Normal (> 12 gr%)	130 (50.8)
Moderate (10 - 12 gr%)	116 (45.3)
Low (< 10 gr%)	10 (3.9)
TB Status at starting ART	
TB Negative	228 (87.7)
Suspect TB	18 (6.8)
TB treatment	(5.4)
Clinical stage at starting ART	
I &II	114 (43.8)
III & IV	6 (56.2)
Weight (kg) at starting ART	
(Median, IQR)	(46-60)
CD4 Count (cell/mm$^{3)}$ at starting ART	66 (16.5-228)
(Median, IQR)	

Table 1 gives the demographic and clinical characteristic of the patients included in our study. Of the 260 patients included the majorities were heterosexual (77.3%), men (73.0%) and the median age at ART initiation was 32 years (IQR: 26-38). The majority initiated AZT in combination with nevirapine (NEV) (84.6%).

A little over half (56.9%) started ART prior to 2012 (56.9%). In terms of clinical conditions, 3.9% of patient start ART with low haemoglobin level (<10gr%).

18 (6.8%) had suspected TB and 14 (5.4%) were receiving TB treatment. A little over half (56.2%) of the patients were diagnosed with clinical stage III and IV. The median weight of patients was 53 kg (IQR: 46-60) and median CD4 was 66 cell/mm3 (IQR: 16.5-228) at the time of starting ART.

Among these 260 patients, 77 (29.6%) experienced AZT substitution. The incidence of AZT substitution among patients attending Badung Hospital was 19 per 100 person years (PYRs) followed for median of 7.70 years.

Among those who made an AZT substitution, the median time to substitution was 69 days (IQR: 25-178) after the initiation of AZT-based first line ART. The estimated probability survival rate of AZT substitution was 80.2%, 74.4% and 71.8% at 3, 6 and 12 months after AZT initiation (Figure 1).

The results of the Cox Proportional Hazards Models are shown in Table 2; In univariate analysis seven variables were significantly associated with AZT substitution; sex, hemoglobin level at starting ART, clinical stage of III and IV, CD4 count <200 cell/mm3 at starting ART, initial weight (per 1 kg increase), age (per 1 year increase and starting ART ≥2012.

All independent variables with p value <0.25 (sex, hemoglobin level, clinical stage of III and IV, CD4 count, initial weight, and starting ART after the year 2012) were included in the multivariate analysis; of these, four were found to be statistically significantly associated with AZT substitution after adjustment for other variables (sex, hemoglobin at starting ART, clinical stage III and IV at starting ART and time of starting ART) and retained in the final model.

Women had almost double the risk of AZT substitution compared to men (Hazard Rate [HR] =1.79; 95% CI: 1.09-2.94; p=0.021). Patients starting ART with low hemoglobin (<10 g%) had almost three times greater risk of AZT substitution than those who had hemoglobin >12 g% (HR=2.72; 95% CI: 1.02-7.21; p=0.002) and for haemoglobin 10-12 gr% (HR 2.21; 95% CI: 1.34-3.66; p= 0.002).

Patients who had clinical stage III and IV had 3.5 times greater risk of AZT substitution than those who had clinical stage I and II (HR=3.53; 95% CI: 1.26-6.19; p=<0.001).

Patients starting ART ≥2012 had almost four times greater risk of experiencing an AZT substitution than those who started ART prior to 2012 (HR=3.83; 95% CI: 2.19-6.70; p≤0.001). The kaplan-Meir graph in Figure 2 shows initially the AZT substitution survival rate in both groups was similar.

Moreover, the two-month survival rate of substitution AZT in person who started ART <2012 was 87.8%

higher those who started ART ≥2012 (80.5%). Those starting ART ≥ 2012 had a maximum follow-up period of two years as all follow-up was censored in 2014.

Table 2: Univariate and Multivariate Analysis of Predictors of Zidovudine Substitution in patients in Clinic VCT Sekar Jepun at Badung Hospital 2006 - August 2014.

Variable	Univariat Analysis				Multivariat Analysis			
	Hazard Ratio	95% CI	P value	P (g)	Ajust Hazard Ratio	95% CI	P value	P (group)
Sex								
Men	**1 (*ref*)**				**1 (*ref*)**	1.09 – 2.94	0.021	
Women	1.5	0.98-2.50	0.06	-	1.79			-
Transmission risk group	**1 (*ref*)**							
Heterosexsual	0.58	0.23-1.47	0.52	-	-			
Homosexual/Bisexsual	0.96	0.38-2.48						
IDU								
Age (per 1 year increase) (Median,IQR)	1.03	1.01-1.06	0.007	-	-			
First-line NNRTI								
EFV	**1 (*ref*)**							
NEV	0.89	0.50-1.59	0.704	-	-			
Year of starting AZT				-		2.19 – 6.70	<0.001	
< 2012	**1 (*ref*)**	1.18-3.23	0.009		**1 (*ref*)**			-
≥ 2012	1.95				3.83			
Weight (per 1 kg increase)	0.96	0.94-0.99	0.006	-	-			
CD4 Count (cell/mm^3) (Median,IQR)	0.023	0.95-0.99	0.023	-	-			
Hemoglobin								
Normal (> 12 gr%)	**1 (ref)**				**1 (*ref*)**			
Moderate (10-12 gr%)	1.84	1.14-2.96	0.012	0.009	2.21	1.34-3.66	0.002	0.002
Low (< 10 gr%)	2.12	0.87-5.17	0.098		2.72	1.02-7.21	0.044	
Clinical stage								
I & II	**1 (*ref*)**				**1 (*ref*)**			
III & IV	2.25	1.34-3.79	0.002	-	3.53	1.26 – 6.19	< 0.001	-
TB Status								
TB Negative	**1 (*ref*)**				-			
Suspect TB	1.07	0.43-2.67	0.88	0.96				
TB treatment	0.89	0.32-2.45	0.83					

* Multivariate analysis was conducted using backward method by gradually removing variables that step 1; CD4 count, step 2; weight, and step 3; age

DISCUSSION

This study of 260 treatment naïve patients starting AZT based ART aimed to look at to substitution of AZT. 77 patients experienced AZT substitution with an IR of 19 per 100 person years (PYRs). The main factors associated with AZT substion included sex, hemoglobin, clinical stage and year of starting ART. Compared with other studies the median time to AZT substitution in our study was shorter. One study study in Cambodia showed the median time to AZT substitution was 94 days (IQR 63-155) with an incidence rate of 13.8 per 100 PYRs.[4]

Another study in Indonesia using a cross sectional design found that median time AZT substitution occurs within five months therapy.[10] In multicenter study found that rate of substitution of AZT in the first 6 months was occurred 8.7 per 100 PYRs (95% CI; 5.2-14.7).[5]

However, compared with Cambodia, the patients in this study started treatment with lower CD4 count (median CD4 40 cells/mm³ (IQR: 13.0-107.0) vs. 288 cells/mm³ (IQR: 186-413), weight (median 49 kg (IQR: 45-56) vs. 51 kg (IQR: 45-58)) and lower hemoglobin (median 11.6 g/dl (IQR: 11-13.1) vs. 12.7 gr% (IQR: 11.7-13.9).[4] This may be due to a delay in diagnosing HIV status and therefore starting ART in present cohort.[2]

This study found women had a greater risk of AZT substitution than men, which has been reported in other studies.[5,8] Several studies have found that anemia (hemoglobin <10 g%), due to the use of AZT, was more predominant in women than men.[11,12] Women might be more vulnerable to AZT substitution because they are more likely to suffer from anemia, due to menstruation, pregnancy and childbirth and therefore women initiating an AZT based regimen may require closer monitoring.[8]

Hemoglobin (Hb) levels in this study were also significantly associated with an increased risk of AZT substitution. Patients with an initial Hb level <10 g% were almost three times more likely to experience AZT substitution than those with an initial Hb level >12 g%. This finding is also consistent with previous studies.[12,4,13] One cross-sectional study in Indonesia found that there was an early decrease in mean Hb levels after starting AZT from 12.3 to 11.4 g% thus increasing the risk of substitution AZT.[10] Another study in Cambodia also showed an association between discontinuation of AZT and initial Hb <10 g% when starting ARV.[4] Low hemoglobin is a measure of anemia, which previous studies have shown to be aserious side effect associated with AZT.

Substitution of AZT was three times more likely to occur in patients with clinical stage III and IV compared with those with initial clinical stage I and II. This result is consistent with a previous study in South Africa that stated that patients in clinical stage III and IV had a higher risk of AZT substitution.[9] This finding may indicate that the presence of secondary infections may increase the risk of substitution zidovudine.[14]

This study showed that patients starting ART after the policy change in 2012, to recommend starting ART in all patients with a CD4 <350 cells / mm^3, had a greater risk of AZT substitution compared to those starting ART before 2012 where the recommendation was to start in once the CD4 count dropped to CD4 < 200 cells / mm^3.

However, patients starting ART after the policy change ≥2012 had a shorter observation period, one and a half years compared with five years in those starting ART prior to 2012 and also patients were monitored more closely in the more recent time period increasing the likelihood of toxicity to be detected early. Several previous studies have showed inconsistent results. Research in South Africa found that lower CD4 at the beginning therapy was associated with AZT substitution however, a study conducted in Indonesia showed there was no significant relationship between CD4 at baseline with AZT therapy (p=0.62).[9] It is therefore important to conduct further research with longer follow-up.

Our study is not without limitations. As with all data there may be some recording errors. Furthermore there may be some unmeasured or unknow confunding that we could not account for. This study was performed in one big general hospital in Badung Hospital, the second big district in Bali Province and therefore, these findings should be relevant to a the broader population of HIV patients in Indonesia.

CONCLUSION

In conclusion present study identified individuals that may be at a high risk of AZT substitution who should be monitored more closely or consideration given to initiating them on another treatment regimen. Research with a prospective design may need to address the limitation of using retrospective data.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. UNAIDS. UNAIDS World AIDS Day Report 2012. 2012.
2. Kemenkes. Pedoman Nasional Tatalaksana Klinis Infeksi HIV dan Terapi Antiretroviral pada orang Dewasa. 2011.
3. Report HM. HIV AIDS Progress Report Second Quarter, 2014. 2014;2.
4. Phe T, Thai S, Veng C, Sok S, Lynen L, van Griensven J. Risk factors of treatment-limiting anemia after substitution of zidovudine for stavudine in HIV-infected adult patients on antiretroviral treatment. PLoS One. 2014;8(3):e60206.
5. Velen K, Lewis JJ, Charalambous S, Grant AD, Churchyard GJ, Hoffmann CJ. Comparison of tenofovir, zidovudine, or stavudine as part of first-line antiretroviral therapy in a resource-limited-setting: a cohort study. PLoS One. 2014;8(5):e64459.
6. Jarrett OD, Wanke CA, Ruthazer R, Bica I, Isaac R, Knox TA. Metabolic syndrome predicts all-cause

mortality in persons with human immunodeficiency virus. AIDS Patient Care STDS. 2013;27(5):266-71.
7. Willig JH, Echevarria J, Westfall AO, Iglesias D, Henostroza G, et al. No Title. Durab Initial Antiretrovir Ther a Resour setting potential need zidovudine Weight dosing. J Acquir. 2010;1:215-21.
8. Sumantri R, Wicaksana R, Ariantana AR, Supandiman IP. Anemia in Patients with HIV-AIDS in Teratai Policlinic Hassan Sadikin Hospital-Bandung Province. 2009;10(3).
9. Boulle A, Orrell C, Kaplan R, Cutsem G Van, Mcnally M, Town C, et al. Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort. 2007;753-60.
10. Wibawa KR, Merati TP, Somia ASU. Factors Related to Macrocytosis in Patient HIV/AIDS with Zidovudine Therapy in Sanglah General Hospital. 2010;11.
11. Sullivan BPS, Hanson DL, Chu SY, Jones JL, Ward JW. Epidemiology of Anemia in Human Immunodeficiency Virus (HIV)-Infected Persons: Results From the Multistate Adult and Adolescent Spectrum of HIV Disease Surveillance Project. 2015.
12. Agarwal D, Chakravarty J, Chaube L, Rai M, Agrawal NR, Sundar S. High incidence of zidovudine induced anaemia in HIV infected patients in eastern India. Indian J Med Res. 2010;132:386-9.
13. Curkendall SM, Richardson JT, Emons MF, Fisher AE, Everhard F. Incidence of anaemia among HIV-infected patients treated with highly active antiretroviral therapy. HIV Med. 2007;8(8):483-90.
14. Spiritia Y. AZT (Zidovudine) [Internet]. 2014. Available from: http://spiritia.or.id/ li/ bacali.php?lino=411
15. Nasronudin. HIV and AIDS Pendekatan Biologi Molekuler, Klinis, dan Sosial. Surabaya: Airlangga University Press. 2007.

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