Factors associated to first line antiretroviral therapy (ART) failure among HIV/AIDS patients at Sanglah Hospital, Bali

Cok Istri Sri Dharma Astiti[1,2], A.A Sagung Sawitri[2,3], Tuti Parwati M[2,4]

[1]Bali Provincial Health Office, [2]Public Health Postgraduate Program Udayana University, [3]Department of Community and Preventive Medicine Faculty of Medicine Udayana University, [4]Department of Internal Medicine Faculty of Medicine Udayana University/Sanglah General Hospital
Corresponding author: cokistrisri_dharmaastiti@yahoo.co.id

Abstract

Background and purpose: The incidence of first line ART failure is increasing in the South East Asia region. The main referral hospital in Bali has recorded an increased use of second line ART due to the first line ART failure. This study aims to explore risk factors associated to first line ART failure.
Methods: A case control study was conducted among people living with HIV and AIDS at Sanglah Hospital Denpasar who started first line ART between 2004 and 2013. Cases were those who diagnosed as having clinical treatment failure and still on treatment in 2015. Controls were those with no treatment failure. Sex and year of ART initiation were matched between case and control. Data were obtained from medical records that include initial regiments, HIV mode of transmission, the WHO HIV clinical stage, CD4 count, opportunistic infections, body mass index, hemoglobin level, and drug substitution at the beginning and during treatment. Risk factors were analysed using logistic regression.
Results: Out of 68 HIV/AIDS patients with clinical ART failure, 72.1% were confirmed with immunological and 36.8% were confirmed with virological failure. Median time before treatment failure was 3.5 years. Factors associated to ART failure were HIV clinical stage IV (AOR=3.43; 95%CI=1.65-7.13) and being widow/widower (AOR=4.85; 95%CI=1.52-15.53). Patients with TB co-infection have a lower risk for treatment failure due to early diagnosis and treatment through TB-HIV program (AOR=0.32; 95%CI=0.14-0.70).
Conclusions: Higher HIV clinical stage at ART initiation increases the risk of treatment failure. HIV-TB co-infection indirectly reduces the risk of treatment failure.
Keywords: treatment failure, first-line ART, HIV/AIDS, Bali

Introduction

People living with HIV and AIDS (PLWHA) require a long-life antiretroviral treatment (ART) to reduce viral load and to prevent infections, drug resistance, complications and AIDS-related deaths.[1] Long term ART is associated with lack of treatment adherence which leads to treatment failure and drug resistance.[2] The scalled-up of first line ART globally may contribute to the increase of ART failure.[3] First line ART failure increases the need for second line ART that are more expensive with higher adverse effects and demand more advance healthcare facilities.[4-7] Globally, as many as 14.9 million PLWHA were on ART in 2014 for which 94.8% were on first line ART.[8] The average incidence of ART failure in Sub-Saharan African countries is 2.65 per 100 person years, while in the South East Asian countries is only less than 5%.[9,10] In Indonesia, from 160,138 PLWHA as many as 97.03% were on first line ART in 2014[11] however until now the rate of treatment failure is still unknown.

Studies have revealed that ART failure is associated with factors prior to ART initiation

and during the treatment, however these studies are still inconsistent. Factors prior to ART initiation that contribute to ART failure are HIV clinical stage IV and lower CD4 count.[12-18] During the treatment, lack of adherence and period of treatment contribute to treatment failure.[17-24] Several other studies have evaluated association between treatment failure and clinical indicators such as opportunistic infections (OIs), drug regiments, modes of HIV transmission, haemoglobin level, body mass index (BMI), drug toxicity and first line ARV resistence.[15-16,20,25-26] These studies have also examined relationship between treatment failure and sociodemographic variables such as age, sex, employment, education level and marital status.[12,15,17,21,26-28]

Data from Bali Provincial Health Office in 2015 showed that as many as 96.2% of 1,173 HIV/AIDS patients were on first line ART.[29] In 2015, there were 54 voluntary counselling and testing (VCT) facilities available across Bali Province, seven hospitals/clinics providing first line ART and only three hospitals providing second line ART. One among those health facilities that is able to provide comprehensive care including ART for HIV/AIDS patients is Sanglah General Hospital. Until 2015, a total of 2,431 HIV/AIDS patients had ever accessed ART from this hospital. In addition, a total of 152 clients were on second line ART or 84% of the total second line ART in Bali Province. Until recently, limited studies have been undertaken in Indonesia to explore factors associated with ART failure. An understanding on factors associated to ART failure is essential for designing effective intervention strategies to prevent treatment failure.

Methods

A case control study was conducted at Sanglah Hospital. Primary data source in this study was medical record. Other data sources included pre-ART register, ART register and drug delivery register. Researcher also conducted crosschecking information from nurses and doctors.

Cases were PLWHA and fulfil the following criteria: 1) adult patient who had diagnosed to be ART failure by medical doctor; 2) starting or continuing ART at Sanglah Hospital between August 2004 and December 2013; 3) still on ART between January and December 2015 and 4) having a complete medical record on pre-ART, during ART and follow-up visit until the ART failure occurred. Controls were PLWHA without treatment failure that fulfilled criteria number 2, 3 and 4. Case and control ratio was 1:2. Cases and controls were selected using different sampling methods. Cases were selected from 118 PLWHA who were on second line ART until December 2015. Only 68 patients met the case criteria and the rest were excluded due to several reasons that include child (6 cases), allergic (14 cases), unavailability of prior to ART data (20 cases), and incomplete medical record (10 cases). Controls were conveniently selected from 1,831 medical records. Medical records were reviewed against the control selection criteria. Cases and controls were matched for sex and year of initiating ART. This strategy was implemented until 136 controls were selected.

This study defined ART failure based on the standard operational procedure of Sanglah Hospital. Clinical ART failure is confirmed if first line ART has been taken for at least 6 months with observed clinical improvements followed by clinical deterioration such as the presence of OIs. Immunological examination (CD4 count) was not regularly performed even though it is a routine procedure. Viral load could not either be routinely conducted due to limited access. Immunologically, ART failure is defined if CD4 count remains the same or reduces up to 50% from initial CD4 count, while virologically if viral load count remains the same or increases more than 5,000 copies/ml from initial viral load count. Risk factors that

examined in this study were sociodemographic and clinical variables. Clinical variables included all variables at ART initiation and during ART. Sociodemographic variables included age, level of education, employment and marital status at ART initiation and during ART. Clinical variables at ART initiation were modes of HIV transmission, first line ART regiments, the most frequent OIs, the WHO HIV clinical stage (stage I-IV), CD4 count, haemoglobin level, and BMI. Clinical variable during first line ART was history of drug substitution due to adverse reactions or side effects. Modes of HIV transmission were defined as potential sources for acquiring HIV that included those with high risk sexual behavior, partner of PLWHA, and injecting drug user. OIs in this study included candidiasis (oral and oro-esophageal), tuberculosis, and hepatitis.

Univariate and bivariate analysis were conducted for each identified risk for ART failure to obtain crude odd ratio. Variables with $p<0.25$ on bivariate analysis were included in the multivariate analysis. Prior to multivariate analysis, correlation test between variables was performed. If a strong correlation ($r>0.6$; $p<0.05$) was found, only one variable will be included in the multivariate analysis. Logistic regression using combination of enter and backward methods was performed to calculate adjusted odd ratio (AOR), p-value and 95%CI.

The study protocol has been approved by Human Research Ethics Committee of Faculty of Medicine Udayana University/ Sanglah General Hospital.

Results

Sixty-eight HIV/AIDS patients were confirmed as clinical ART failure with median time of 3.5 years. Forty-nine (72.1%) were confirmed as immunological failure with median time of 3.7 years (95%CI: 2.7-5.1) and 25 (36.8%) were confirmed as virological failure with median time of 4.1 years (95%CI: 3.2-5.1).

Characteristics between cases and controls were comparable for sex (p=1.000), year of initiating ART (p=0.803), religion (p=0.659), place of HIV testing (p=0.178), domicile (p=0.411) and the government insurance ownership (p=0.162).

Table 1. Sociodemographic variables associated to treatment failure at Sanglah Hospital, Denpasar - Bali

Variables	Bivariate				Multivariate	
	Control n (%)	Cases n (%)	Crude OR	p value	Adjusted OR	95%CI
Age						
≤ 25 year	15 (11.0)	9 (13.2)	Ref			
26-35 year	85 (62.5)	45 (66.2)	0.88	0.356[a]		
> 35 year	36 (26.5)	14 (20.6)	0.65			
Marital status						
Married	84 (61.8)	39 (57.4)	Ref		Ref	
Single	46 (33.8)	19 (27.9)	0.89	0.048[a]	0.86	0.42-1.69
Widow/widower	6 (4.4)	10 (14.7)	3.59		3.69	1.21-11.27
Education level						
University	11 (8.1)	10 (14.7)	Ref			
Junior-SeniorHigh	110 (80.9)	46 (67.7)	0.46	0.112[a]		
Primary and under	15 (11.0)	12 (17.7)	0.88			
Employement status						
Employed	104 (76.5)	49 (72.1)	Ref			
Unemployed	32 (23.5)	19 (27.9)	1.26	0.493		

Notes: [a] = p overall value

Table 1 shows the crude OR of sociodemographic variables that include education level, employment status, age, and marital status with treatment failure. Table 2 shows the crude OR of clinical variables and treatment failure. Bivariate analysis revealed that the HIV clinical stage, candidiasis, CD4 count, tuberculosis, and hepatitis were all eligible for multivariate analysis. Correlation test among these factors also showed a weak correlation.

Multivariate analysis showed that HIV/AIDS patients at clinical stage IV were more likely to experience treatment failure than clinical HIV stage I-III (AOR=3.45; 95%CI: 1.65-7.13). HIV/AIDS patients with treatment failure were more likely to be a widow/widower (AOR=3.69; 95%CI: 1.21-11.27) as can be seen in Table 1. In contrast, HIV/AIDS patients with tuberculosis co-infection prior to first line ART initiation were less likely to experience treatment failure than those without tuberculosis infection (AOR=0.32; 95%CI: 0.14-0.70).

Table 2. Clinical risk factors associated to treatment failure at Sanglah Hospital, Denpasar - Bali

Variables	Control n (%)	Bivariate Cases n (%)	Crude OR	p value	Multivariate Adjusted OR	95%CI
Risk for HIV transmission						
Sexual	98 (72.1)	43 (63.2)	Ref			
PLWHA partner	18 (13.2)	12 (17.7)	1.52	0.439[a]		
IDU	20 (14.7)	13 (19.1)	1.48			
First line ART regiment						
Standard	95 (69.8)	49 (72.1)	Ref			
Non-standard	41 (30.2)	19 (27.9)	0.90	0.745		
Candidiasis (OI)						
No	59 (43.4)	21 (30.9)	Ref			
OC	47 (34.6)	18 (26.5)	1.08	0.007[a]		
OEC	30 (22.0)	29 (69.1)	2.72			
Tuberculosis (OI)						
No	84 (65.4)	53 (77.9)	Ref		Ref	
Yes	47 (34.6)	15 (22.1)	0.54	0.069	0.32	0.14-0.70
Hepatitis (OI)						
No	126 (92.7)	58 (85.3)	Ref			
Yes	10 (7.4)	10 (14.7)	2.17	0.102		
Clinical HIV stage						
Stage I-III	94 (69.1)	34 (50.0)	Ref		Ref	
Stage IV	42 (30.9)	34 (50.0)	2.24	0.008	3.43	1.65-7.13
CD4 count						
>200	20 (14.7)	4 (5.9)	Ref			
≤ 200	116 (85.3)	64 (94.1)	2.75	0.075		
Hemoglobin level						
Normal	35 (25.7)	14 (20.6)	Ref			
Anemia	101 (74.3)	54 (79.4)	1.34	0.418		
BMI						
Normal	78 (57.3)	36 (52.9)	Ref			
Overweight	7 (5.2)	5 (7.4)	1.54	0.641[a]		
Underweight	51 (37.5)	27 (39.7)	1.14			
Drugs side effects						
No substitution	97 (71.3)	44 (64.7)	Ref			
Substitution 1 time	27 (19.9)	20 (29.4)	1.63	0.279[a]		
Substitution >1time	12 (8.8)	4 (5.9)	0.73			

Note: [a] = p overall value

Discussion

This study shows that the diagnosis of treatment failure among HIV/AIDS patients was delayed due to limited access. Late HIV/AIDS clinical stage and being widow/widower increase the risk of treatment failure. In contrast, co-infection with tuberculosis reduces the risk of treatment failure.

Diagnosis of treatment failure in this study is based on clinical criteria. Due to limited testing facilities at Sanglah Hospital, immunologic and virologic tests can only be offered to some patients who can afford it. Therefore the median time from ART initiation to the event of immunological failure (3.7 years) and virological failure (4.1 years) were longer than clinical failure (3.5 years). In contrast, existing studies showed that median time for diagnosing clinical failure is shorter than immunological and virological failures (1.4 to 2.5 years).[36-40] Among all clinical failure cases in this study, 72.1% underwent immunologic confirmation test while only 36.8% underwent virologic confirmation test. All these patients were at late HIV/AIDS clinical stage (stage IV), with low CD4 count (46 cells/mm^3) and high viral load (an average of 296.633 copies/ml). Similar situations have also been found in Malawi, Uganda and Zimbabwe that also use clinical diagnosis to determine treatment failure.[39,40] Given the fact that Sanglah General Hospital is the referral centre for HIV/AIDS care in Bali Province, governments should support the provision of immunologic and virologic confirmation tests to prevent the delayed diagnosis.

This study also revealed that HIV/AIDS clinical stage IV increases the risk for treatment failure by 3.43 times than clinical stage I-III. Similar findings have also reported by numerous studies in Asia and Africa.[12,15-18] As many as 39.3% of HIV/AIDS patients at clinical stage IV in this study were diagnosed with severe OIs that include candidiasis esophageal (77.6%), extra-pulmonary tuberculosis (48.7%), severe anemia (39.3%), hepatitis (19.7%), and toxoplasmosis (9.2%). In addition, they had low CD4 count (23.5 sel/mm^3). Previous studies in India and Indonesia reported that patients at HIV/AIDS clinical stage IV presented to hospital with severe OIs, low CD4 count and high viral load.[30,31] Studies in Asia and Africa also showed that patients at late HIV/AIDS clinical stage often presented to health facilities with severe OIs and low CD4 count. Due to these clinical conditions, they required a longer recovery period and a high adherence rate. Therefore they tended to have higher risk of developing treatment failure.[13-16,32]

HIV/AIDS patients co-infected with tuberculosis seem to have a lower risk of treatment failure. The implementation of TB-HIV collaboration leads to an early HIV diagnosis among tuberculosis patients followed by an early ART initiation. HIV-TB co-infection patients receive monitoring from Directly Observed Treatment Short Course (DOTS) program as well as from VCT program – leading to better adherence towards HIV and TB treatments. From all TB-HIV co-infection cases in this study, 40.3% HIV status were confirmed after the TB diagnosis. The majority of these patients (82.3%) received ART at four weeks after the commencement of TB treatment. DOTS program facilitates treatment compliance for both HIV and TB. Studies in Kenya and South Africa have also revealed that TB-HIV collaboration improves compliance towards ART and reduces drop out of TB medication.[33,34] However, previous studies in West Java and South Africa found that HIV-TB co-infection was not associated with treatment failure.[12,20]

Being widow/widower increases the risk of treatment failure when compared to married HIV/AIDS patients. This finding is consistent with study conducted in Brazil,[35] however the proportion of widow/widower in the present study was small (only 7.8% from

total sample). Therefore, this finding should be interpreted with caution.

This study has several limitations. Primary source of data in this study is medical record that is often incomplete and confirmation from other sources is required. This may influence the internal validity of this study. Several key factors associated to treatment failure are unavailable for example data on compliance rate to ART. In this study, drugs could also be taken not directly by patients thus making it difficult to accurately measure patients' compliance. HIV patients only present to the clinic if they experience symptoms associated to treatment failure. Since controls were selected using convenience method, it may not accurately represent the control population.

Conclusion

Clinical diagnosis of treatment failure is delayed. This delay leads to deterioration of patients' clinical conditions. In addition, severe clinical conditions can increase the risk of first line ART failure. TB-HIV co-infection reduces the risk of treatment failure due to early diagnosis and treatment. Monitoring of viral load is essential to prevent ART failure or CD4 count monitoring if viral load test is not available.

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