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Predictors of discontinuation of antiretroviral therapy among HIV-infected adults at Hospital Sungai Buloh: A 10-year retrospective cohort study

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ABSTRACT

Aims: Discontinuation from antiretroviral therapy (ART) lowers the immunological advantages of human immunodeficiency virus (HIV) treatment and increases the problems related to HIV. Therefore, this study determined the predictors of discontinuation among HIV-infected adults at Hospital Sungai Buloh.

Methods: We carried out an institutional-based retrospective cohort study and reviewed the medical records of ART-naïve patients with HIV in Hospital Sungai Buloh, Selangor, Malaysia from January 2007 through December 2016. Discontinuation was defined as not attending the follow-up for 90 days or longer. Simple and multiple logistic regression was used to identify the predictors.

Results: Out of 339 patients, 63 (18.6%) experienced discontinuation. Among them, 63.5% were younger than 39 years, 81.0% were male and 62.0% were of Malay ethnicity. Sexual transmission via homosexual and heterosexual routes was the commonest mode of HIV transmission (76.7%). Patients with Malay ethnicity [adjusted Odds ratio (AOR): 2.5, confidence interval (CI): 1.4-4.5, p=0.002], tuberculosis co-infection (AOR: 2.0, CI: 1.1-3.7, p=0.025) and a history of ART regimen switch (AOR: 5.3, CI: 2.2-13.1, p<0.001) were significantly associated with ART discontinuation.

Conclusions: The proportion of patients who discontinued ART in our observation presents a challenge to the long-term success of the treatment program. There is a need for special attention to patients with HIV who are Malay, had tuberculosis co-infection, and history of switching to other regimens to avoid discontinuation of therapy.

Introduction

The human immunodeficiency virus (HIV) is a major public health issue and affects the whole world. In 2017, over 36.9 million people were living with HIV (PLHIV). Africa is one of the most affected continents with 25.7 million (70%) of PLHIV (1). Asia also had no exception for the HIV epidemic where Malaysia is a country with the highest number of PLHIV.

According to Malaysia Global AIDS Report 2020, a total of 77,903 PLHIV were reported in 2019, with 77,602 (99.6%) aged above 15 years old and 301 (0.4%) aged below 15 years old. There were 3,564 newly infected individuals with HIV in 2019,

slightly less than the estimated cases of new HIV infection in 2019 (2). The epidemic is higher in Selangor (30.4%), Kuala Lumpur (12.6%), Johor (9.5%), Sarawak (8.1%), and Penang (8.1%), which contributed to more than 50% of new HIV cases in Malaysia (2).

In the beginning most efforts to combat the AIDS epidemic mainly focused on access to antiretroviral drugs. Antiretroviral therapy (ART) coverage escalated progressively from 7% in 2005 to 59% in 2017. ART has significantly extended the life expectancy of patients with HIV (1,3). However, a major challenge of ART is treatment discontinuation.

ART should be continued to show its benefits, requiring a lifelong commitment. Discontinuation from ART contributed to the slow destruction among patients and lead to poor quality of life and death (4). Besides, it shows a negative effect on the immunological benefit of treatment, increases the complications of HIV, and results in severe consequences such as treatment failure due to poor adherence to ART, drug toxicity, and drug resistance (1,5).

Past studies reported different factors to influence the discontinuation of ART. Socio-demographic factors such as gender (6,7), age (8,9), educational level (10), marital status (11), occupation status (12,13), disclosure status (6,10), distance from the health facility (14), caregiver (15,16) and clinical- and treatment-related factors such as baseline stage (11,17), baseline CD4 count (13), history of opportunistic infection at enrollment (18), baseline functional status (8,15), opportunistic prophylaxis (8) and type of ART regimen after initiation of their medication (13,17).

Previous authors defined discontinuation as the interruptions to ART treatment due to loss to follow-up, defaulting, transferring out, and stopping the medications while remaining in care (19). However, the current study defined ART discontinuation as not attending the scheduled follow-up for more than three months. Therefore, this study determined the factors that influence the discontinuation of ART among the population with HIV in Malaysia.

Methods

This retrospective cohort study included all PLHIV registered in Hospital Sungai Buloh, Malaysia, between January 1, 2007, and December 31, 2016, with the addition of 20 months of follow-up from January 1, 2017, and August 31, 2018. Hospital Sungai Buloh was chosen as the study location because it was a center of excellence for infectious diseases in Malaysia. It is one of the biggest tertiary hospitals under the Ministry of Health Malaysia. Also, this hospital is in the Selangor state, with the highest number of PLHIV in Malaysia.

We reviewed the medical records in the electronic Hospital Information System. The sampling frame was obtained based on an internal database called Malaysian Antiretroviral Treatment Cohort (MATCH). This database was developed by the Infectious Disease Unit of Hospital Sungai Buloh and updated in the first quarter of every year by the unit staff. Using the MATCH database, patient name, registration number, ART initiation date, and the latest status (on treatment or transferred out) were collected.

The patients were included if they were above 15 years old at the time of ART initiation, diagnosed with HIV using enzyme-linked immunosorbent assay and particle agglutination test, and ART-naïve. We excluded the patients transferred from Hospital Sungai Buloh to other hospitals or clinics during the study period.

Between 2006 and 2016, 7090 HIV-infected patients were newly started with ART in Selangor. However, 931 patients were transferred out, and 6159 patients were eligible as the reference population. Among 6159 patients, 385 patients were treated with ART at Hospital Sungai Buloh. Following exclusions, 339 patients were eligible for the analysis.

The study outcome was the discontinuation of ART. Discontinuation was defined as not attending the scheduled follow-up for more than three months. If a patient showed up more than three months after the appointment date, he or she would be considered as having a history of defaulting from follow-up.

The required information was extracted from the MATCH and e-HIS databases, using a data collection form. The information included was patients-related characteristics (age, gender, ethnicity, smoking status, alcohol intake, history of illicit drug use, transmission mode) and clinical-related characteristics (time between first HIV positive test and ART initiation, baseline CD4 cell count, baseline viral load, World Health Organization clinical staging, tuberculosis co-infection, hepatitis B co-infection, hepatitis C co-infection, opportunistic infection, underlying liver disease, renal disease, cardiovascular disease, and diabetes mellitus).

The information for the treatment-related characteristics included the year of ART initiation, the first non-nucleoside reverse transcriptase (NNRTI) background regimen, number of regimen substitutions, regimen switch, and default history. Anemia was defined as a hemoglobin level of less than 11 g/dL.

Universiti Sains Malaysia Research Ethics Committee (ref: USM/JEPeM/18060287) and the National Medical Research and Ethics Committee of the Ministry of Health Malaysia (NMRR; Ref: KKM.NIHSEC. P18-1703(6)) approved the study.

We recorded the data on a password-protected computer with limited access. All data were anonymous; thus, there were no unique identifiers. All the data were kept strictly confidential.

Statistical Analysis

Data entry and analysis were conducted using the Statistical Package for Social Sciences (SPSS) version 24 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Continuous variables were expressed as a mean and standard deviation or as a median and interquartile range, depending on the normality of distribution. The categorical variables were presented as frequency (n) and percentage (%). Simple and multiple logistic regression analyses were used to determine the predictors of discontinuation of ART among patients with HIV. The results are tabulated as crude and adjusted Odds ratio (OR), 95% confidence interval (CI), and p-value. Statistical significance was set at $p < 0.05$.

Results

Baseline findings

A total of 385 patients with HIV were evaluated. However, 46 patients were ineligible to include in this study (7 patients had their ART planned but it was not started, eight were not treatment naïve, 30 were transferred out and one subject had incomplete information). As a result, 339 patients were included in the final analysis and of these, 63 patients (18.6%) had discontinued ART treatment.

Socio-demographic characteristics

The details of the socio-demographics are summarized in Table 1. Most HIV-infected patients who discontinued the ART treatment were in the age group below 30 years old (33.3%) and 81.0% were male. Malay ethnicity constituted 62.0% of

all patients who discontinued the ART treatment, followed by Chinese (19.0%) and other ethnicities (19.0%). Other ethnicities consisted of Indians, Sabahan, and Sarawakian, and non-Malaysians include Myanmar, Indonesia, the Philippines, and Nigeria.

The most common HIV transmission mode reported among patients who discontinued the ART was via the homosexual/bisexual route with 17 patients (28.3%) and the heterosexual route with 29 patients (48.3%). Only 14 patients (23.4%) were infected with HIV via the parenteral route including patients who were parenteral drug users, needlestick injury, blood transfusion, and via tattooing.

Of the subjects who discontinued ART, 41.2% had a history of illicit drug use such as heroin and methamphetamine. Information on alcohol intake was largely missing (41.6%). Of

Table 1. Socio-demographic characteristics of HIV-infected patients in Hospital Sungai Buloh (n=339)

Variables	Discontinuation of ART	
	No Frequency (%)	Yes Frequency (%)
Age (years)		
<30	75 (27.2)	21 (33.3)
30-39	104 (37.6)	19 (30.2)
40-49	62 (22.5)	16 (25.4)
≥50	35 (12.7)	7 (11.1)
Gender		
Male	238 (86.2)	51 (81.0)
Female	38 (13.8)	12 (19.0)
Ethnicity		
Malay	108 (39.1)	39 (62.0)
Chinese	115 (41.7)	12 (19.0)
Others*	53 (19.2)	12 (19.0)
Smoking status		
Non-smoker	103 (49.8)	19 (42.2)
Ex-smoker	15 (7.2)	5 (11.1)
Active smoker	89 (43.0)	21 (46.7)
Alcohol intake		
Non-drinker	103 (62.4)	24 (72.7)
Social drinker	53 (32.1)	6 (18.2)
Heavy drinker	9 (5.5)	3 (9.1)
History of illicit drug		
No	184 (82.1)	30 (58.8)
Yes	40 (17.9)	21 (41.2)
Mode of transmission		
Homo/bisexual	117 (45.9)	17 (28.3)
Heterosexual	107 (42.0)	29 (48.3)
Parenteral route	31 (12.1)	14 (23.4)

*Others included Indians, Sabah and Sarawak and non-Malaysians (Myanmar, Indonesia, Philippines and Nigeria).
HIV: Human immunodeficiency virus

those 33 patients who reported the discontinuation of the ART, 24 patients (72.7%) were non-drinkers, six patients (18.2%) were social drinkers and three patients (9.1%) were heavy drinkers. Also, information on smoking status was not available for 87 patients (25.7%). Concerning the smoking status, 42.2% was non-smoker, 46.7% was active smokers and 11.1% was ex-smoker.

Clinical characteristics

Half of the patients who discontinued ART (56.7%) started ART after six months after the first HIV-positive test as in Table 2. A total of 31 patients (53.4%) had less than 200 cells/ μ L in their baseline CD4 cell count. Information on the baseline viral load was not available for 129 patients (38.1%). Of the remaining 210 patients, 25 patients who discontinued ART treatment (59.5%) had more than 100,000 copies/mL of HIV/RNA as the baseline. There were 14 (26.4%) patients who were anemic.

HIV clinical staging was not available in almost half of the patients (45.7%). However, the patients were categorized into clinically advanced stages, with 15 patients (39.5%) having clinically advanced HIV and 23 patients (60.5%) who did not. Less than half (34.8%) of the patients had experienced at least one episode of opportunistic infection.

A total of 24 patients (38.1%), five patients (8.6%), and 16 patients (25.4%) were diagnosed with tuberculosis, hepatitis B, and hepatitis C co-infection, respectively. As the underlying disease at ART initiation, only a minority, 4 (6.3%), 1 (1.6%), and 4 (6.3%) patients had underlying liver, renal and cardiovascular diseases, respectively. Liver diseases included fatty liver and liver hemangioma. Only 6.3% of the patients had diabetes mellitus.

Treatment characteristics

Among patients with HIV who discontinued ART, 26 (41.3%) patients had initiated ART between 2007 and 2010. The remaining 22 patients (34.9%) and 15 patients (23.8%) were from the years between 2011 and 2013 and 2014 and 2016, respectively. When we stratified according to the year, a greater proportion of patients had ART in the later years. This trend was consistent with the increasing number of patients who started ART at Hospital Sungai Buloh from 2007 to 2016. Since we applied systematic random sampling, more patients were recruited from the later years.

The commonest NNRTI in the first ART was efavirenz (65.6%) and the commonest first NNRTI background was the combination of zidovudine and lamivudine (57.1%). Less than half of the patients had their ART substitution; 15 patients (23.8%) had it once and 14 patients (22.2%) had it more than two. Even lesser for regimen switch, only 12 patients (19.0%) had their regimen switch to a second-line ART. During the study period, 26 patients (41.3%) experienced at least one adverse

drug reaction (ADR). Table 3 shows the details of treatment-related characteristics.

Simple logistic regression

There were 25 clinically important variables to be tested for univariable analysis using simple logistic regression. Ethnicity, history of illicit drugs, mode of transmission, baseline viral load, tuberculosis co-infection, hepatitis C and history of ART regime switch were significant factors as the p-value was less than 0.05 (Table 4).

Multiple logistic regression

Ethnicity, tuberculosis co-infection, and history of ART regime switch were associated with the discontinuation of ART. Malay patients (adjusted OR: 2.5, 95% CI: 1.4-4.5, $p=0.002$), had tuberculosis co-infection (adjusted OR: 2.0, 95% CI: 1.1-3.7, $p=0.025$) and history of ART regime switch (adjusted OR: 5.3, 95% CI: 2.2-13.1, $p<0.001$) had higher risk to discontinue the ART as presented in Table 4.

Malay patients had 2.53 higher Odds of discontinuing the ART compared with non-Malay patients after controlling for tuberculosis co-infection and history of ART regime switch. Tuberculosis co-infection proved to be significant in the model. There were 2.01 higher odds of discontinuing ART in subjects with tuberculosis co-infection controlling for ethnicity and history of ART regime switch. The history of ART regime switches was also associated with the discontinuation of ART. Those who switched to the ART regime had 5.31 higher odds of discontinuing the ART compared to those without a switch to the ART regime after controlling for ethnicity and tuberculosis co-infection.

Discussion

Discontinuation occurred in 63 (18.6%) patients. It was not uncommon that a proportion of lost to follow-up patients in Hospital Sungai Buloh returned to the clinic several months or years after defaulting follow-up. Some female patients came back on subsequent pregnancy a few years after defaulting follow-up. Among them, 63.5% were younger than 39 years, 81.0% were male and 62.0% were of Malay ethnicity. Sexual transmission via homosexual and heterosexual routes was the commonest mode of HIV transmission (76.7%).

The current finding was comparably lower compared to the studies conducted in Southwest Ethiopia (22.3%) (20), Nigeria (28%) (21), the United States (45.1%) (22), Guinea-Bissau (51.1%) (23) and a multi-clinic study from the Republic of Congo, Cameroon and Burundi (83%) (24). Access to HIV care facilities (25), variations in measurement, innovation, adoption and implementation of cost-effective retention strategies may explain the differences in the prevalence numbers between the current study and others (1).

Table 2. Clinical-related characteristics of HIV-infected patients in Hospital Sungai Buloh (n=339)

Variables	Discontinuation of ART	
	No Frequency (%)	Yes Frequency (%)
Duration of the first HIV-positive test to ART initiation (months)		
0-6	153 (62.4)	26 (43.3)
>6	92 (37.6)	34 (56.7)
Baseline CD4 cell count (cells/ μ L)		
0-49	80 (29.7)	16 (27.6)
50-199	74 (27.5)	15 (25.9)
\geq 200	115 (42.8)	27 (46.5)
Baseline viral load (copies/mL)		
<10 000	25 (14.9)	10 (23.8)
10 000-100 000	64 (38.1)	7 (16.7)
>100 000	79 (47.0)	25 (59.5)
Baseline hemoglobin		
No anemia	192 (75.0)	39 (73.6)
Anemia	64 (25.0)	14 (26.4)
WHO clinical staging		
Class I	96 (63.2)	17 (53.1)
Class II	20 (13.2)	5 (15.6)
Class III	24 (15.8)	7 (21.9)
Class IV	12 (7.8)	3 (9.4)
Clinically advanced HIV		
No	118 (83.7)	23 (16.3)
Yes	71 (82.6)	15 (17.4)
Opportunistic infections		
No	147 (53.2)	31 (49.2)
Yes	129 (46.8)	32 (34.8)
Tuberculosis		
No	215 (77.9)	39 (61.9)
Yes	61 (22.1)	24 (38.1)
Hepatitis B		
No	254 (92.0)	58 (92.1)
Yes	22 (8.0)	5 (7.9)
Hepatitis C		
No	242 (87.7)	47 (74.6)
Yes	34 (12.3)	16 (25.4)
Underlying liver disease		
No	262 (94.9)	59 (93.7)
Yes	14 (5.1)	4 (6.3)
Underlying renal disease		
No	275 (99.6)	62 (98.4)
Yes	1 (0.4)	1 (1.6)
Underlying cardiovascular disease		
No	261 (94.6)	59 (93.7)
Yes	15 (5.4)	4 (6.3)
Diabetes mellitus		
No	261 (94.6)	59 (93.7)
Yes	15 (5.4)	4 (6.3)

HIV: Human immunodeficiency virus, ART: Antiretroviral therapy, WHO: World Health Organization

Table 3. Treatment-related characteristics of HIV-infected patients in Hospital Sungai Buloh (n=339)

Variables	Discontinuation of ART	
	No Frequency (%)	Yes Frequency (%)
Year of ART initiation		
2007-2010	62 (22.5)	26 (41.3)
2011-2013	93 (33.7)	22 (34.9)
2014-2016	121 (48.8)	15 (23.8)
First NNRTI in the first ART		
Efavirenz	208 (75.6)	40 (65.6)
Nevirapine	67 (24.4)	21 (34.4)
First NNRTI background		
ZDV/3TC	146 (52.9)	36 (57.2)
TDF/FTC	84 (30.4)	13 (20.6)
D4T/3TC	43 (15.6)	13 (20.6)
ABC/3TC	3 (1.1)	1 (1.6)
Number of regimen substitution		
0	158 (57.2)	34 (54.0)
1	75 (27.2)	15 (23.8)
≥2	43 (15.6)	14 (22.2)
Regimen switch		
No	264 (95.7)	51 (81.0)
Yes	12 (4.3)	12 (19.0)
Adverse drug reaction		
No	188 (68.1)	37 (58.7)
Yes	88 (31.9)	26 (41.3)

ART: Antiretroviral therapy, NNRTI: Non-nucleoside reverse transcriptase, ZDV/3TC: Zidovudine/lamivudine, TDF/FTC: Tenofovir/emtricitabine; D4T/3TC stavudine/lamivudine, ABC/3TC: Abacavir/lamivudine

Table 4. The associated factors of discontinuation of ART among HIV-infected patients in Hospital Sungai Buloh (n=339)

Variables	Simple logistic regression			Multiple logistic regression		
	b	Crude Odds ratio (95% CI)	p-value	b	Adjusted Odds ratio (95% CI)	p-value
Ethnicity						
Non-Malay	-	1.00	-	-	1.00	-
Malay	0.93	2.53 (1.44, 4.44)	0.001	0.93	2.53 (1.41, 4.54)	0.002
History of illicit drug						
No	-	1.00	-	-	-	-
Yes	1.17	3.22 (1.67, 6.19)	<0.001	-	-	-
Mode of transmission						
Home/bisexual	-	1.00	-	-	-	-
Heterosexual	0.62	1.87 (0.97, 3.59)	0.062	-	-	-
Parenteral route	1.13	3.11 (1.38, 6.91)	0.006	-	-	-
Tuberculosis co-infection						
No	-	1.00	-	-	1.00	-
Yes	0.77	2.17 (1.21, 3.88)	0.009	0.70	2.01 (1.09, 3.72)	0.025
Hepatitis C						
No	-	1.00	-	-	-	-
Yes	- 0.89	0.41 (0.21, 0.81)	0.010	-	-	-
Regime switch						
No	-	1.00	-	-	1.00	-
Yes	1.64	5.18 (2.20, 12.17)	<0.001	1.67	5.31 (2.16, 13.07)	<0.001

b regression coefficient; CI: Confidence interval, Forward LR and Backward LR variable selection were applied; Multicollinearity and interaction term were checked and not found; Assumptions were met.
ART: Antiretroviral therapy, HIV: Human immunodeficiency virus

Discontinuation of ART is a major predictor of the success of HIV treatment. So this study aimed to determine the factors associated with the discontinuation of ART among patients with HIV in Malaysia. The current study found that the Malay ethnicity had tuberculosis co-infection and had a history of ART regimen switch and had a higher risk for discontinuation of ART.

Malay ethnicity was associated with the discontinuation of ART. The result was not surprising since, among Malaysian citizens, the Malays were the predominant ethnic group in Peninsular Malaysia. Furthermore, stigma and discrimination regarding HIV as a 'humiliating disease' among Malaysian citizens may contribute to the discontinuation of the treatment among Malay citizens. Patients with HIV were often stigmatized by society and even by their family members. Particularly, before the ART is initiated, their HIV status was easy to keep secret. However, dose-taking of ART or such treatments that need to be followed according to the schedule could expose their illness to other individuals and thus, create personal or family humiliation.

HIV-infected patients with tuberculosis co-infection were significantly associated with discontinuation of ART, similar to the previous study (20). The intimate linkage between HIV and tuberculosis speeds up the progression of HIV disease to the advanced stage rapidly and thereby disallowing patients from regular treatment intake (26). Additionally, the double stigma related to tuberculosis/HIV co-infection and the double burden of having to take multiple pills for both conditions (pill effect) could be a compounding factor for discontinuation within this cohort.

We also found regimen switches as one of the significant factors for the discontinuation of ART among HIV-infected patients. During the lifelong treatment of HIV, certain patients commonly experience switches in ART regimens. The current study reported that only 12 patients had their regimen changed to a second-line ART, which was attributable to the higher percentage of patients on ART who have suppressed the viral load. Moreover, the availability and accessibility of second-line ART such as raltegravir are limited, and not freely provided by the Malaysian government. Other reasons for ART regimen change include drug toxicity, anticipated drug-drug interactions, viral suppression, increasing drug availability, simplification of a current regimen, treatment failure, tuberculosis treatment, and pregnancy were reported in previous studies (27,28).

Study Limitations

The study was conducted at one of the biggest hospitals under the Ministry of Health Malaysia. Hence, the results can be translated to the other hospitals in Malaysia, as all facilities under the Ministry of Health share the same system and support. All patients included in this study were treatment naïve, therefore the results were not confounded by previous ART.

Considering the retrospective study design of the current study, there were missing data for a few of the variables of interest such as clinical staging and lifestyle factors such as smoking and alcohol intake. Some of the information such as employment status and underlying disease were collected only at baseline during ART initiation and not after enrollment into the study. This could cause misclassification bias.

Conclusion

The proportion of patients who discontinue ART presents a challenge to the long-term success of the treatment program. There is a need for special attention to patients with HIV who are Malay, had tuberculosis co-infection, and with a history of regimen, switches to avoid discontinuation of therapy. The ID team in hospitals, comprised of doctors, nurses, and other allied staff, should take the initiative to lower the rate of ART discontinuation and avoid the circumstances that cause ART discontinuation. They can assist by identifying the patients who have ART discontinuation predictors.

Ethics

Ethics Committee Approval: Universiti Sains Malaysia Research Ethics Committee (ref: USM/JEPeM/18060287) and the National Medical Research and Ethics Committee of the Ministry of Health Malaysia (NMRR; Ref: KKM.NIHSEC. P18-1703(6)) approved the study.

Informed Consent: This was a retrospective cohort study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.H.S-A., B.N., K.C.S., Concept: A.H.S-A., B.N., S.C.L., K.C.S., Design: A.H.S-A., B.N., K.C.S., Data Collection and Processing: S.C.L., K.C.S., W.A.W-N-A., Analysis and Interpretation: A.H.S-A., B.N., S.C.L., W.A.W-N-A., Literature Search: A.H.S-A., S.C.L., W.A.W-N-A., Writing: S.C.L., W.A.W-N-A.,

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