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Predictor Factors for Treatment Failure among Patients on Second Line Antiretroviral Therapy

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***Abstract*—**Second line antiretroviral therapy (ART) regimen is used when patients fail their first line regimen. There are many factors such as non-adherence, drug resistance as well as virological and immunological failure that lead to second line highly active antiretroviral therapy (HAART) regimen treatment failure. This study was aimed at determining predictor factors to treatment failure with second line HAART and analyzing median survival time.

An observational, retrospective study was conducted in Sungai Buloh Hospital (HSB) to assess current status of HIV patients treated with second line HAART regimen. Convenience sampling was used and 104 patients were included based on the study's inclusion and exclusion criteria. Data was collected for six months i.e. from July until December 2013. Data was then analysed using SPSS version 18. Kaplan-Meier and Cox regression analyses were used to measure median survival times and predictor factors for treatment failure.

The study population consisted mainly of male subjects, aged 30-45 years, who were heterosexual, and had HIV infection for less than 6 years. The most common second line HAART regimen given was lopinavir/ritonavir (LPV/r)-based combination. Kaplan-Meier analysis showed that patients on LPV/r demonstrated longer median survival times than patients on indinavir/ritonavir (IDV/r) based combination ($p<0.001$). The commonest reason for a treatment to fail with second line HAART was non-adherence. Based on Cox regression analysis, other predictor factors for treatment failure with second line HAART regimen were age and mode of HIV transmission.

***Keywords*—**Adherence, antiretroviral therapy, second line, treatment failure.

I. Introduction

THE human immunodeficiency virus (HIV) made its debut in Malaysia 28 years ago. From 1986 until 2013, the Ministry of Health Malaysia (MOH) reported a cumulative figure of 16,340 deaths which were related to acquired immunodeficiency syndrome (AIDS)-defining conditions. As of 2013, the number of people living with HIV (PLHIV) in the country was estimated at 86,832 [1].

Numbers of new HIV infections have been reduced from 24.8 to 11.4 per 100,000 persons between the year 2000 and 2013 [2]. This was directly attributed to the introduction of harm reduction programmes, implementation of screening programmes, as well as the provision of more affordable first and second line antiretroviral therapy (ART) [2]. Malaysia has made available first line ART treatment at no cost and subsequent second line ART at a highly subsidised rate [3].

Many research findings revealed that patients on prolonged Highly Active Highly Active Antiretroviral Therapy (HAART) could fail treatment because of insufficient drug potency, development of resistance, pharmacological incompatibilities and poor adherence [4]. Most patients who were unable to tolerate first line regimen or failed their treatment i.e. suboptimal response to therapy leading to loss of viral control, were started on second line ART. In consultation with PLHIV, they more unlikely to adhere to second line regimen as the regimen was reported to induce various side effects; it's dosings were complicated; it's costing was higher; and special storage conditions were required [5].

Understanding predictor factors which can lead to ART failure can assist clinicians and healthcare workers so they are able to focus on monitoring treatment for susceptible patients. This can also prevent patients from resorting to third line regimen or salvage therapy that are both more expensive as well as have a higher profile of adverse effects [6].

Generally, there is a lack of published data on HIV management and outcomes of second-line antiretroviral therapy (ART) in resource-limited settings in Asia [7]-[9]. To the best of our knowledge, there is no published study on a Maritime Southeast Asian population investigating predictor factors of treatment failure in individuals with HIV infection treated with second line HAART regimen. Our study is focused on adults and is aimed at 1) determining predictor factors for treatment failure with second line ART, and 2) comparing median survival time of patients treated with two different second line regimens.

II. Methods

The study was observational and retrospective in nature. Data collection was conducted at Sungai Buloh Hospital (HSB) in the Malaysian state of Selangor, which is a state surrounding the federal territory of Kuala Lumpur. HSB was chosen as the study site because it is the referral centre in the western and central region of peninsular Malaysia for adults with HIV and AIDS. The hospital also plays a major role for HAART provision in Malaysia. Prior to conducting the study, approval from the Medical Research Registry (NMRR), and Medical Research Ethics Committee (MREC) of the MOH were obtained. Data were collected for 6 months from July until December 2013.

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A convenience sampling approach was utilised in this study. Inclusion criteria for participation in the study were 1) age 18 and above, 2) patients on second line HAART regimen for at least 12 months, 3) patients with documented immunological and/ or virological failure (in some cases, also supported by clinical failure), 4) patients must have been started by a HIV specialist in HSB, and 4) patients under HSB follow-up until the last date of data collection. Patients whose data were missing were excluded from the study. Definitions of documented treatment failures were based on MOH Guidelines for the Management of Adult HIV infections with Antiretroviral Therapy [2] and WHO Guidelines on Antiretroviral therapy for HIV infection [10].

Data were extracted from the hospital's electronic medical records which is known as electronic Hospital Information System (e-HIS). Information collected include age, gender, race, status of employment, mode of HIV transmission, and types of second line regimen, CD4 count and HIV-1-RNA prior to starting second-line regime. Details on occurrence of adverse drug reactions (ADR) and other reasons for treatment failure were also obtained. Data was analysed using SPSS version 18. Kaplan-Meier was used to measure and compare median survival times between patients on the different types of second line regimen. Cox regression analysis was used to determine predictor factors for treatment failure.

TABLE I
DEMOGRAPHIC PROFILE

Characteristics	N (%)	X^2 (df)[a]	P value
Gender		5.538 (1)	0.019
Male	64 (61.5%)		
Female	40 (38.5%)		
Age group		24.08 (3)	<0.001
< 30	20 (19.2%)		
30 – 45	58 (55.8%)		
> 45	26 (25.0%)		
Race		45.15 (3)	<0.001
Malay	48 (46.2%)		
Chinese	37 (35.6%)		
Indian	13 (12.5%)		
Others	6 (5.8%)		
Employment		11.15 (1)	0.001
Employed	69 (66.3%)		
Unemployed	35 (33.7%)		
Mode of HIV Transmission		98.39 (3)	<0.001
Heterosexual	69 (66.3%)		
Homosexual	17 (16.3%)		
IDU	14 (13.5%)		
Others	4 (3.8%)		
Number of Years since Diagnosis		28.04 (1)	<0.001
< 6	79 (76.0%)		
≥ 6	25 (24.0%)		
Mean (SD)	5 (1.66)		

[a]Chi square test for goodness of fit; SD = standard deviation, IDU = intravenous drug users.

III. RESULTS

A total of 104 patients on second line ART regimen were included in the study. The social demographic characteristics of the patients are presented in Table I. A majority of the patients were male representing 61.5% of total sample size. Mean age of patients was 39 years with 55.8% of them belonging to age group 30-45 years old. In term of races, 46.2% of the patients were Malay, while the Chinese, Indians and other race categories comprised 35.6%, 12.5% and 5.8% respectively.

Most of the patients were employed (66.3%) while 33.7% were unemployed. Patients' data on mode of transmission revealed that heterosexuals comprised 66.3% of the total sample size and this was followed by 16.3% of homosexuals, and 13.5% of intravenous drug users (IDU). Mean number of years since diagnosis was 5.

TABLE II
UPTAKE OF SECOND LINE HAART REGIMEN

Characteristics	N (%)
Distribution	
IDV/r-based combinations	24 (23.1%)
LPV/r-based combinations	80 (76.9%)
Period on ART (months, mean (SD))	
IDV/r-based combinations	20 (7.55)
LPV/r-based combinations	21 (4.95)
Overall	21 (5.64)
Initial viral load	
< 100,000 copies/ml	23 (22.1%)
≥ 100,000 copies/ml	81 (77.9%)
< 100 cells/μL	37 (35.6%)
≥ 100 cells/μL	67 (64.4%)

HAART = highly active antiretroviral therapy; IDV/r = indinavir boosted with ritonavir, LPV/r = lopinavir boosted with ritonavir, SD = standard deviation.

TABLE III
OCCURRENCE OF ADR WITH SECOND LINE HAART REGIMEN

Characteristics	IDV/r N (%)	LPV/r N (%)
ADR		
Renal impairment	1 (4.2)	2 (2.5)
Hyperlipidemia	0 (0)	3 (3.8)
Lipodysthropy	1 (4.2)	0 (0)
GI intolerance	1 (4.2)	0 (0)
None	21 (87.5)	75 (93.8)
Length of ADR occurrence [month, mean (SD)]	10.00 (2.828)	5.48 (8.376)
Overall length of ADR occurrence [month, mean (SD)]	5.87 (8.115)	

ADR = adverse drug reactions; IDV/r = indinavir boosted with ritonavir, LPV/r = lopinavir boosted with ritonavir, SD = standard deviation.

Second line HAART regimen given was either lopinavir boosted with ritonavir (LPV/r) or indinavir boosted with ritonavir (IDV/r) combinations (Table II). LPV/r combination was given to 76.9% patients. Up until the last date of data collection, a mean of 21 months were recorded in terms of the length of treatment on second line HAART regimen. The majority of the patients (77.9%) had an initial viral load (VL) of more than 100,000 copies/ml and 64.4% of patients had an

initial cluster of differentiation 4 (CD4) count of more than 100 cells/μL prior to starting second line HAART regimen.

Table III summarizes ADR occurrence during treatment with second line HAART regimen. Following the initiation of a second line HAART regimen, numbers of occurrences of an ADR were 3 instances related to renal impairment, 3 instances which were hyperlipidemia-related, 1 instance of lipodysthropy and 1 instance of gastrointestinal (GI) intolerance. ADR occurrence with IDV/r-based combinations in this study were renal impairment, lipodystrophy and GI intolerance. ADR occurrences with LPV/r-based combinations were renal impairment and hyperlipidemia. Mean overall length of an ADR occurrence was 5.9 months. Length ofADR occurrence in IDV/r-based combinations was 10 months and in LPV/r-based combinations was 5.5 months.

The reasons for treatment failure with second line HAART regimen were non adherence (25%) and ADR (2.9%). This information was verified by physician in-charge of each patient (Table IV).

TABLE IV
REASONS FOR SECOND LINE HAART REGIMEN FAILURE

Reason for failure	N (%)
Non Adherence	26 (25.0%)
Adverse Drug Reaction	3 (2.9%)
None	75 (72.1%)

TABLE V
KAPLAN- MEIER ANALYSIS TO ESTIMATE PROBABILITIES OF TIME TO TREATMENT FAILURE

2nd line	Median (SE)	95% CI	[a]Log rank P value
IDV/r	20 (3.715)	12.72, 27.28	<0.001
LPV/r	-	-	
Overall	37 (0.000)	17.77, 20.23	

[a]P value derived from using log-rank test; IDV/r = indinavir boosted with ritonavir, LPV/r = lopinavir boosted with ritonavir, SE = standard error, CI = confidence interval.

The median survival time to treatment failure with IDV/r-based combinations was 20 months as shown in Table V. Fig. 1 highlights that there was no median survival time to treatment failure with LPV/r-based combinations because the cumulative proportion surviving was still high (70.8%) at the end of data collection. A majority of patients (75%) on LPV/r-based combinations were estimated to survive with no treatment failure for up to 23 months. In contrast, 75% of subjects on IDV/r-based combinations were estimated to survive for only 15 months with no treatment failure.

In addition, there was a statistically significant difference in the median survival time to treatment failure between IDV/r-based combinations and LPV/r-based combinations ($p< 0.001$). This was indicated by the two survival curves (IDV/r based combination vs. LPV/r based combination) which differed significantly and had a significant influence on survival time.

Social demographic, laboratory and clinical variables which affected survival time are summarized in Table VI. Age group, mode of HIV transmission, and years of having HIV significantly affected an occurrence of treatment failure ($p <0.05$). Age group '30 to 45 years old' had the highest instances (21) of treatment failure compared to age group 'below 30 years old' and 'more than 45 years old'. Patients who had HIV for less than 6 years (27 instances) and initial VL of more than 100,000 copies/ml (20 instances) were more at risk of a treatment failure.

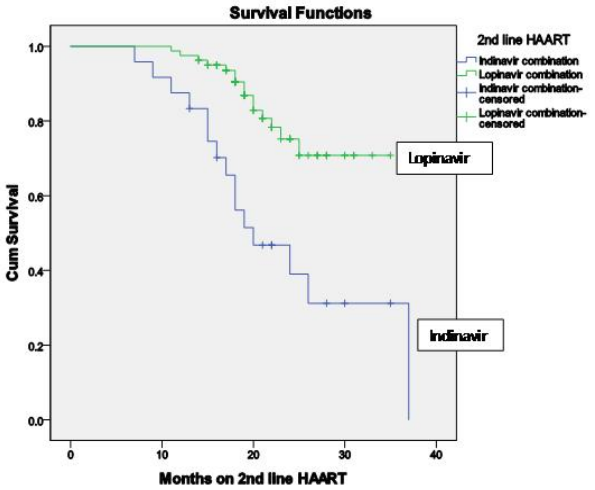

Fig. 1 Kaplan-Meier analysis to estimate probabilities of time to treatment failure between IDV/r and LPV/r combinations

TABLE VI
ASSOCIATION BETWEEN OCCURRENCE OF TREATMENT FAILURE WITH SOCIO-DEMOGRAPHIC, LABORATORY AND CLINICAL VARIABLES

Characteristics	N	[a]Log rank p value
Gender		
Male	21	0.289
Female	9	
Age group		
< 30	9	*0.001
30 – 45	17	
> 45	4	
Race		
Malay	14	0.726
Chinese	10	
Indian	3	
Others	3	
Mode of HIV Transmission		
Heterosexual	18	*0.015
Homosexual	5	
IDU	4	
Others	3	
Employment		
Employed	21	0.663
Unemployed	9	
Years of Having HIV		
< 6	27	*0.007
≥ 6	3	
Initial Viral Load Group		
< 100,000 copies/ml	10	0.072
≥ 100,000 copies/ml	20	
Initial CD4 count Group		
< 100 cells/μL	9	0.224
≥ 100 cells/μL	21	

[a]p value derived using log-rank test; * = statistically significant i.e. p≤0.05; p = probability.

TABLE VII
PREDICTOR FACTORS FOR SECOND LINE HAART REGIMEN SURVIVAL

Variable	Crude HR 95% (CI)	Adjusted HR 95% (CI)	Wald Statistics (df)	[a]p value
Age group				
< 30	1.0	1.0		
30 – 45	0.325 (0.139, 0.758)	0.245 (0.093, 0.648)	8.052 (1)	*0.005
> 45	0.112 (0.029, 0.433)	0.055 (0.012, 0.252)	14.003 (1)	*<0.001
Mode of HIV Transmission				
Others	1.0	1.0		
IDU	0.193 (0.042, 0.879)	0.193 (0.041, 0.911)	4.316 (1)	*0.038
Homosexual	0.281 (0.067, 1.184)	0.068 (0.013, 0.344)	10.533 (1)	*0.001
Heterosexual	0.166 (0.048, 0.577)	0.092 (0.025, 0.340)	12.733 (1)	*<0.001

[a]p value derived usingCox regression analysis; *statistically significant i.e. p≤0.05; HR=hazard ratio, CI= confidence interval, df = degree of freedom, p = probability.

Cox Regression analysis was used to analyze predictor factors such as social demographic, laboratory and clinical variables which affected survival (Table VII). From the analyses done, only age groups and mode of HIV transmissions had statistical significance as predictors of treatment failure with second line HAART regimen.

Hazard Ratio (HR) of treatment failure with second line HAART regimen among age groups were 0.245 in age group '30-45 years old' and 0.055 (p<0.001) in age group 'more than 45 years old'. HR of treatment failure stratified by mode of HIV transmission were 0.193 (p=0.038) in IDU, 0.068 (p = 0.001) in homosexuals and 0.092 (p <0.001) in heterosexuals. The risk of treatment failure with second line HAART regime is increased 0.25 times in age group '30 to 40 years old' compared to those with age less than 30 years. In addition, risk of treatment failure with second line HAART regime is increased 0.193 times if the HIV mode of HIV transmission is IDU compared to others.

IV. DISCUSSION

In our study, most of the patients who failed first line HAART regime were given LPV/r based combinations. It must be noted however that the only protease inhibitors available in HSB were indinavir, lopinavir and ritonavir. LPV based combinations were more popularly prescribed and consumed by patients because the combination drugs were presented as one pill (Kaletra®) which have been considered to ease patients' burden and therefore associated with increased adherence. Meanwhile, IDV was presented as two pills (indinavir and ritonavir). IDV also reportedly posed higher risks of toxicity compare to other protease inhibitors [10].

Randomized trials comparing LPV/r with atazanavir/ ritonavir, darunavir/ritonavir or fosamprenavir/ ritonavir in HAART- naive patients showed that there was non-inferiority at 48 weeks with all three boosted protease inhibitors [11]-[13]. However, another study concluded that darunavir/ ritonavir was superior to LPV/r at 96 weeks [14]. In a Mexican healthcare setting, atazanavir/ritonavir regimen was a preferred option compared to LPV/r regimen [15]. In contrast, concluded that LPV/r based regimen was cost saving through the first 10 years of survival and was a cost effective means of using public resources for Brazilian patients compared to ATV/r based regimen [16].

In this study, we observed that ADR occurrence with second line HAART regimen was in concordance with the warnings stated in the product leaflets. A higher rate of ADR occurrence was observed with IDV/r-based combinations. One study supported our findings where a comparison between IDV/r and LPV/r was done for ADR occurrence and the authors demonstrated that IDV/r had induced higher increases in serum cholesterol and triglyceride at 12 month [17]. The study had also reported that IDV/r had induced renal impairment, nausea, diarrhoea and increases in liver enzymes.

One major reason for treatment failure with second line HAART regimen that identified in our study was non-adherence to treatment. Within 4 weeks, patients reportedly missed>80% doses; optimal adherence to HAART was identified as crucial to achieve immunologic recovery, improve survival and decrease morbidity [18], [19]. Suboptimal adherence resulted in inadequate drug exposure and increased the likelihood of immunological and virological failure, resistance and led to disease progression [19].

Our statistical findings reveal that LPV/r-based combinations had lower risks of treatment failure compared to IDV/r-based combinations. This indicates patients on IDV/r were quicker at to failing treatment in comparison to patients on LPV/r combinations. A similar study which utilised Kaplan-Meier analysis showed that the probability to obtain virological success at 12 months was 88.2%in patients on LPV/r and 73.1% in patients on IDV/r [20].At 12 months, 11.8% had treatment failure with LPV/r and 26.9% with IDV/r [20].Authors of another study reported that at 24 weeks, only 23% subjects on IDV/r achieved virological success compared to 48% in subjected on LPV/r [21]. This showed that IDV/r had less virological success compared to LPV/r, indicating that patients on IDV/r were more prone to treatment failure than those on LPV/r.

We found that the following high risk groups: 1) age between 30 to 45 years old, 2) heretosexuals, 3) infected with HIV for less than 6 years and 4) patients with an initial VL of >100,000 copies/ml were more likely to fail their treatment. An observational cohort study showed that patients who were younger, who had low CD4 cell count at start of therapy, who were heterosexual, and those who had AIDS diagnosed before HAART was started, were significantly associated with a raised rate of extensive triple class failure [22]. We similarly identified that predictors to treatment failure were age younger age group and patients who were heterosexual.

Based on the analysis done, the risk of treatment failure with second line HAART regimen was increased 0.25 times amongst age group of 30 to 40 years and increased 0.19 times amongst IDU. One study reported that non-IDU subjects had a lower risk of discontinuing LPV/r for toxicities compared to IDU subjects. [20] IDU was more likely to experience treatment failure.

V. Conclusion

Predictor factors are important determinants that will influence the outcome of a second line HAART regimen. Clinicians and other healthcare professionals have a crucial role in monitoring patients who are within the riskier group such as patients who were IDU, and those who were on IDV/r regimen as well as patients who had higher levels of CD4 count at baseline. Providing adequate support in ensuring that patients are involved in their treatment process and ensuring adherence are key to preventing treatment failure among patients on second line antiretroviral therapy. Studies on resistance testing are pivotal to differentiate between treatment failure due to non adherence versus drugs resistance.

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