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Predicting Time to Achieving Viral Load Less Than 50 Copies/ml in HIV Infected Patients on Antiretroviral Therapy: a Cohort Study

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***Abstract*— Effective HAART reduces blood viral load. This study aims to determine factors which could predict the time to achieve viral load (VL) less than 50 copies/ml in HIV-infected patients on antiretroviral therapy (ART). A bidirectional cohort study was conducted in 2007, with records of patients investigated retrospectively from 1997, and followed prospectively until 2009. The time from starting HAART to achieve VL less than 50 copies/ml date and its associated factors were determined. There were 63.5% (533/840) of HIV patients on ART. Mean age was 36.3 years (SD10.4), 77.9% were males, Chinese (73.0%), sexual route (88.4%) and 79.7% were at clinical stage 3-4 according to WHO staging. Mean CD4 and mean VL were 139.1cell/µl (SD 146.8) and 2.50 x 105 copies/ml (SD 7.82 x 105), respectively. The mean time to achieve VL less than 50 copies/ml was 12.5 months (SD 18). There were 82.7% (441) patients on triple drugs. There was a significant difference in time to achieve VL less than 50 copies/ml by status at start of ART, had opportunistic infection, CD4 at start ART less than 200 cell/ul took longer time to achieve VL less than 50 copies/ml. Significant predictors of the time to achieve VL less than 50 copies/ml was CD4 at start ART. The CD4 at start ART was significant predictors to achieve VL less than 50 copies/ml.**

***Keywords*— HIV, viral load, ART, VL 50 copies, cohort**

I. INTRODUCTION

The first case of HIV infection in Malaysia was reported in 1986 [1] and was initially treated with Zidovudine monotherapy in 1989[2], followed by dual nucleoside analogue therapy in 1990[2]. Highly active antiretroviral therapy (HAART) became the standard treatment for HIV-infected patients in Malaysia in 1997[2]. HAART is considered to be a combination of at least three drugs that typically includes either a protease inhibitor (PI) or a nonnucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors (NRTI) [2]. There are many studies which had showed the efficacy of the drugs HAART with fixed dose combination [3] and what level of immune system T cells (CD4 count) to start [4]. Patients with HIV-1 who have started with HAART, prognosis is strongly associated with CD4 count and baseline viral load [4]. The CD4 count and viral load (VL) also strong predictors of AIDS-defining illnesses (ADI) occurrence [5] and prognostic markers related to progression to AIDS or death [6]. In general, it is now felt that patients with CD4 count < 350 cell/µL should be offered therapy [2]. This recommendation is based on the substantial short term risk of disease progression for untreated patients with CD4 count < 350 cell/µL at all levels of VL. In addition, data from observational cohort suggest that initiation of therapy at CD4 count < 200 cell/ µL is associated with shorter survival compared with initiation of therapy at higher CD4 count [7, 8]. The effect of HAART is to suppress VL below the level of detection and this occurs in the first weeks after start of therapy [9]. Increases in CD4 cell counts during treatment with HAART and reaching undetectable level of VL are also significantly associated with a better prognosis [10]. In another study VL concentration declined quickly in many, but not all, HIV patients with substantial increases in CD4 counts within months of starting HAART [6]. The accuracy of predictions of disease progression might therefore be improved by accounting for early response to therapy, seen in CD4 counts and VL measured some time after HAART is started. This response might allow early identification of patients who are at a high risk of progression and who might benefit from modification or intensification of therapy [6]. The

quantification of VL is a sensitive indicator of the effectiveness of HAART. The successful HAART is generally defined as VL suppression to ≤ 50 copies/ml [2]. Some of the changes over time in number of VL after initiating antiretroviral therapy to achieve VL ≤ 50 copies/ml are less known. There is limited research on HIV/AIDS epidemiology in Malaysia and especially study on the effectiveness of ART. This is the first study in Malaysia to measure the time to achieve VL ≤ 50 copies/ml after initiation of ART. This study aims to determine factors which could predict the time to achieve VL ≤ 50 copies/ml in HIV infected patients on antiretroviral therapy.

II. METHODS

A. Study design

This was a fifteen-year bidirectional cohort study conducted in 2007, with records of patients being investigated retrospectively from 1997, and followed prospectively until 2009. *Setting*: Data were extracted from medical records in the Infectious Disease Clinic. This hospital is a referral centre for HIV patients serving with the population 638,516 and 1,722,500 in 2010 [11]

B. Participant

A total of 533 patients were selected according to inclusion criteria. The study's inclusion criteria were adult HIV infection patients aged 20 years old and above, have baseline CD4 cells count with any value, have baseline viral load ≥ 10000 copies/ml, received initial combination of antiretroviral drugs (NRTI, NNRTI, NRTI + NNRTI, without PI) and first achieved VL ≤ 50 copies/ml. For detection of HIV Ag/Ab Combo (Architect) and anti HIV ½ antibody (Axsym), reactive HIV ½ rapid test and reactive HIV ½ particle agglutination (PA) reactive are used. The second sample test, blood was sent in 2 EDTA tubes for confirmation.

For the first blood test of viral load measured by Amplicor RT-PCR and for molecular test to monitor how many copies/ml of viral load, the Cobas Taqman HIV-1 test was utilized. During follow up antiretroviral therapy, viral load test are usually checked at 3-6 monthly intervals. These tests were done in laboratory of Department Microbiology University of Malaya.

C. Variables

The variables studied were age group (20-29, 30-39, 40-49, 50-59 and 60 years and above), gender (male, female), ethnic group (Malay, Chinese, Indian, Others), exposure risk (heterosexual, homosexual, injection drug user (IDU), Others risk factors), WHO clinical staging (stage 1, 2, 3 and 4) [12], CD4 count at the start of ART, viral load at the start of ART and initial combination ART. All information pertaining variables were obtained from the patients' folders in medical records and for continuous data like age, CD4 count and VL were changed to categorical data.

D. Ethics

Ethical approval was obtained from Medical Ethics Committee (Reference Number 565.22).

E. Statistical analysis

Descriptive statistics were used to describe the baseline characteristics of the sample. The time from initiation ART to VL first achieve to ≤ 50 copies/ml was calculated using the Kaplan-Meier method. Cox regressions were performed to determine the predictors. SPSS soft ware was used for all statistical analyses.

III. RESULT AND DISCUSSION

A total of 533 HIV infected patients during the study period had ART from 1997 to 2009. The baseline characteristics of the sample are shown in Table 1. Majority of patients in aged (20-39 years) was 72.5% and the mean age was 33.6 years (SD 10.4) and the majority (77.9%) were males. Most patients (73.0%) were Chinese and (88.4%) via sexual route. Majority of the HIV infected patients were first seen in the clinic when they were already at late stage (WHO clinical stage 3-4) (79.7%), patients start ART in AIDS status (71.9%) and (82.7%) were initially started on antiretroviral treatment combination of 2 NRTI + NNRTI. The mean CD4 count at the start of ART was 139.1 cell/μL (SD 146.8). The mean VL at the start of ART was 2.50×10^5 (SD $7.82 \times 10_5$) copies/ml. The mean time to achieve VL ≤ 50 copies/ml was 12.5 months (SD 18), as shown in Table 1.

TABLE I
CHARACTERISTICS OF HIV INFECTED PATIENTS IN UMMC

Variable	n (%)
Age (years)	
20-29	157 (29.5)
30-39	229 (43.0)
≥ 40	147 (27.5)
Gender	
Male	415 (77.9)
Female	118 (22.1)
Ethnic group	
Malay	63 (11.8)
Chinese	389 (73.0)
Indian	54 (10.1)
Others	27 (5.1)
Exposure risk	
Sexual	471 (88.4)
Non sexual	62 (11.6)
Come in to clinic	
Early stage (WHO Stage 1-2)	108 (20.3)
Late stage (WHO Stage 3-4)	425 (79.7)
Status at start ART	
ART in HIV	150 (28.1)
ART in AIDS	383 (71.9)
Initial ART combination	
1 NRTI	19 (3.6)
2 NNRTI	73 (13.7)
2 NRTI + 1 NNRTI	441 (82.7)
Mean CD4 at start ART (cell/μL**)**	139.1
Mean Viral Load at start ART (copies/ml**)**	2.50 x 10^5
Mean time to achieve VL < 50 (copies/ml)	12.5 (SD 18)

Note: ART= Antiretroviral therapy;

Table 2 displays the results of the factors associated with the time to achieve VL < 50 copies/ml. The significant factors were status at start ART (p = 0.002), CD4 at start ART less than 200 cell/ul (p = 0.002), have opportunistic infection (p = 0.020). In this study, although the majority of the patients were in age 20-39 years (72.5%) with mean age of 36.3 (SD 10.4), there was a significant difference in the time taken to achieve VL ≤ 50 copies/ml among the age group. The age 40 years and above was observed to take a longer time to achieve VL ≤ 50 copies/ml compared to the age less than 40 years. There was no relationship between the time taken to reach VL ≤ 50 copies/ml in, gender, ethnicity, exposure risk, stage come to clinic and initial ART combination.

TABLE II
MEAN TIME ASSOCIATED FACTORS WITH TIME TAKEN TO ACHIEVE VIRAL LOAD LESS THAN 50 COPIES/ML

Variable	N	Mean time (95% CI)	*Log Rank p* value
Age (years)			
20-29	157	64.12 (44.84-83.39)	0.046
30-39	229	66.79 (54.21-79.38)	
≥ 40	147	131.59 (112.77-150.42)	
Gender			
Male	118	101.98 (84.04-119.92)	
Female	415	95.07 (766.64-113.45)	0.331
Ethnic group			
Malay	63	29.49 (24.75-34.24)	
Chinese	389	108 (91.43-124.83)	
Indian	54	46.16 (35.23-57.09)	
Others	27	106.96 (91.84-122.09)	0.971
Exposure risk	471	82.60 (70.78-94.24)	
Sexual	62	120.26 (87.86-152.66)	0.826
Non sexual			
Come in to clinic	108	45.48 (37.39-53.58)	
Early stage (1-2)	425	106.21 (97.78- 121.65)	0.692
Late stage (3-4)			
Status at start ART	150	67.43 (52.38-82.48)	
ART in HIV	383	131.27 (112.86-149.67)	0.002
ART in AIDS			
Initial ART combination			
1 NRTI	439	82.42 (64.97-99.86)	
2 NNRTI	19	117.75 (84.61-150.89)	
2 NRTI + 1 NNRTI	73	88.54 (74.85-102.22)	0.547
CD4 at start ART	155	69.46 (55.14-83.78)	
≥ 200 cell/ul	378	137.08 (118.28-155.89)	0.002
< 200 cell/ul			
OI	207	77.55 (64.45-90.65)	
Negative	326	127.62 (106.98-148.26)	0.020
Positive			

The final Cox regression is displayed in Table 3. The outcome is the time taken to achieve the first VL ≤ 50 copies/ml in months, and the predictors of the final model are CD4 at start ART.

TABLE III
PREDICTOR TO ACHIEVE VIRAL LOAD LESS THAN 50 COPIES/ML IN HIV INFECTED PATIENTS ON ART

Variable	Hazard Ratio	95% CI	*p* value
CD4 at start ART			
≥ 200 cell/ul	1.00		
< 200 cell/ul	2.13	1.08 – 4.19	0.028

The goal of ART in HIV patients is to limit viral replication, slow the progression of HIV disease and increase the level of CD4 count [2]. Viral replication is measured by the level of HIV viral load and the effectiveness of ART in reducing HIV viral load. In this study from a total of 840 patients receiving ART, 533 patients (63.5%) had achieved VL ≤ 50 copies/ml within the mean time of 12.5 months (SD 18). These findings were lower than the findings in a study done in UK whereby they reported that 482 of 656 (73%) patients had achieved VL ≤ 50 copies/ml within 6 months after the initiation HAART [13].

Similarly, in the European Collaborative study on pregnant women, undetectable viral loads were achieved by 73% (175 of 240 pregnant women at the time of delivery 9.5 months). It was noted that all pregnant women in the study had received PI based HAART 156 (65%) and Nevirapine (NVP) based HAART 84 (35%) [14].

The differences in the duration of time taken to achieve VL≤ 50 copies/ml between the patients in this study and the stated two studies could be attributed to the initial status of ART usage by the patients. The participants of UK study and European Collaborative study were previously antiretroviral naïve individuals who started HAART directly (≥ 3 antiretroviral including at least 2 NRTI+ PI or NNRTI), while in our study the patients started treatment with 2 NRTI or 2NRTI + NNRTI without PI since PI is only used when the first drugs of regiment has failed.

The strength of this study was the bidirectional cohort design and the relatively large sample size (n=533). However, it was limited by the use of first combination of ART without PI in the patients, and the reliance on medical records which had some variables missing. There were also uncertainties on period of HIV infection date and history of prior antiretroviral therapy before treatment was received.

IV. Conclusions

The various factors have been tried as predictor to achieving VL less than 50 copies/ml. This study concluded that only CD4 at start ART is predictor to achieving VL less than 50 copies/ml. It is important for the clinician and medical researchers to be aware of the predictors because the measurement of effectiveness antiretroviral therapy is achieving VL less than 50 copies/ml

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