Original Article

Time to Treatment Initiation and Retrospective Analysis of Antiretroviral Therapy Outcomes among HIV-positive Methadone Maintenance Therapy Clients in Primary Health-care Centers, Kuantan, Pahang

Aida Roziana Ramlan1,2, Nor Ilyani Mohamed Nazar3, Afidalina Tumian1, Norny Syafinaz Ab Rahman1, Dzawani Mohamad4, Mat Sharii Abdul Talib1, Khairul Faizan M. Zakaria5, Muhammad Azzim Izuddin6, Syarifah Syafiqah T. Syed Manso9, Wan Nur Khairiyah Wan Hassan10

1Kulliyyah of Pharmacy, International Islamic University Malaysia, Kuantan, Pahang, Malaysia, 2Department of Pharmacy, Hospital Tengku Ampuan Afzan, Ministry of Health Malaysia, Kuantan, Pahang, Malaysia, 3Kulliyyah of Engineering, International Islamic University Malaysia, Gombak, Selangor, Malaysia, 4Medical Department, Hospital Tengku Ampuan Afzan, Ministry of Health Malaysia, Kuantan, Pahang, Malaysia, 5Pharmacy Unit, Kurnia Health Clinic, Kuantan, Pahang, Malaysia, 6Pharmacy Unit, Paya Besar Health Clinic, Kuantan, Pahang, Malaysia, 7Pharmacy Unit, Bandar Kuantan Health Clinic, Kuantan, Pahang, Malaysia, 8Pharmacy Unit, Bukit Goh Health Clinic, Kuantan, Pahang, Malaysia, 9Pharmacy Unit, Beserah Health Clinic, Kuantan, Pahang, Malaysia

Address for correspondence: Dr. Nor Ilyani Mohamed Nazar, Department of Pharmacy Practice, International Islamic University Malaysia (IIUM), Jalan Sultan Ahmad Shah, Bandar Indera Mahkota Campus, 25200 Kuantan, Pahang, Malaysia. E-mail: norilyani@iium.edu.my

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Abstract

Introduction: Methadone maintenance therapy (MMT) program helped to improve access to antiretroviral therapy (ART) among people who inject drugs (PWID) with human immunodeficiency virus (HIV). However, the time to treatment initiation (TTI) and outcomes of ART intervention in this population have scarcely been analyzed. Objectives: The aim of this study was to analyze the TTI and outcomes of ART among MMT clients in primary health-care centers in Kuantan, Pahang. Materials and Methods: This was a retrospective evaluation of MMT clients from 2006 to 2019. The TTI was calculated from the day of MMT enrolment to ART initiation. The trends of CD4 counts and viral loads were descriptively evaluated. Cox proportional hazard model was used to analyze the survival and treatment retention rate. Results: A total of 67 MMT clients from six primary health-care centers were HIV-positive, of which 37 clients were started on ART. The mean TTI of ART was 27 months. The clients who were given ART had a mean CD4 count of 119 cells/mm³ at baseline and increased to 219 cells/mm³ after 6 months of ART. Only two patients (5.4%) in the ART subgroup had an unsuppressed viral load. The initiation of ART had reduced the risk of death by 72.8% (hazard ratio = 0.27, P = 0.024), and they are 13.1 times more likely to remain in treatment (P < 0.01). Conclusion: The TTI of ART was delayed in this population. MMT clients who were given ART have better CD4 and viral load outcomes, helped reduced death risk and showed higher retention rates in MMT program.

Keywords: Antiretroviral therapy treatment outcomes, HIV positive, methadone maintenance therapy, time to treatment initiation

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**INTRODUCTION**

Injecting drug use is listed among the significant contributing factors for human immunodeficiency virus (HIV) transmission in many countries. The initiation of antiretroviral therapy (ART) is crucial to restore the immunity system of the HIV-infected patient and further overcome the disease progression of acquired immune deficiency syndrome (AIDS). In Malaysia, the introduction of methadone maintenance therapy (MMT) program in 2005 is one of the harm reduction approaches meant to control the HIV transmission among people who inject drugs (PWID). A local study showed that older age and HIV diagnosis were among the predictors of poor quality of life among the MMT clients.[1] However, the time to treatment initiation (TTI) and outcomes of ART intervention in this population, especially in Malaysia, have scarcely been analyzed. Studies have shown that the combination of ART and MMT improves adherence to both therapies.[2-4] The combination plays a vital role in ensuring the success of the harm reduction program. It is evident that the combination can reduce the spread of a new HIV infection by decreasing the HIV risk behavior, as well as suppressing the viral load in HIV-infected PWID. Hence, this study was designed to identify the time taken for HIV treatment initiation in this population, and to compare the mortality and the retention rate between ART-initiated and -noninitiated subgroup for HIV-positive MMT clients in Kuantan. The study also examined the effectiveness of ART in terms of restoring the CD4+ T-cell count and suppressing the viral load.

**SUBJECT AND METHODS**

The study conducted has been registered and received approval from the Malaysian Medical Research and Ethics Committee (ID: [NMRR]-18-3067-43939). It was a retrospective study where all clients’ profiles from six MMT clinics in Kuantan district were screened. Clients’ informed consent for MMT enrolment, details on addiction habits, and other related data such as viral screenings were obtained by the physicians and medical staff responsible in the MMT clinic. This step is essential to ensure that the clients were voluntarily enrolled in MMT program. The diagnosis of opioid dependence should be clearly stated by using standard medical criteria such as those listed in the DSM-5.[5] The inclusion criteria of this study were all HIV-positive MMT clients enrolled from January 2006 to July 2019 with complete baseline data and relevant laboratory monitoring for objective measurement of the study outcomes. MMT clients with missing data and files or have been transferred out to the other treatment centers were excluded. All subjects who received at least 1 month of ART or methadone were included as exposure to ART or methadone. The subjects were divided into two subgroups for the analysis, depending on whether they received MMT-only or MMT plus ART at any time during the study period. Data on the exact date of HIV diagnosis were also recorded. Subjects’ profiles were reviewed from the start of the MMT program until the endpoint of the study, which was HIV-related death, default from treatment, or until July 2019 (end of the study). The compliance to ART was self-reported by the patients as recorded in the file. The methadone dose and compliance toward MMT were recorded based on the dispensed record in MMT clinics. A total of 95% days of methadone intake in a calendar month were considered as compliance to MMT. Subjects were considered as a discontinued treatment or lost to follow-up when there were no follow-up data for 3 months or when they defaulted the appointment date.

The calculation of TTI was determined from the MMT enrolment date to the time when ART was started. The improvement of CD4+ T cell and suppressed viral load was the indicator of a successful HIV treatment. In this case, the CD4+ T-cell recovery (CD4+ T cell of more than 350 cells/mm³ or an increment of more than 100 cells/mm³ per year) and viral load less than 50 copies/mL was an indicator of a good outcome.[6] Another important primary endpoint for HIV-related outcomes was the mortality rate among MMT clients who were HIV positive. The survival time of the subjects was calculated from the time of diagnosis to the endpoint of the study. Retention in the MMT program was determined at the end of the study. Kaplan–Meier curves and log-rank analyses were used to compare the survival probability. Both mortality and retention rate among the MMT clients were analyzed through Cox proportional hazard regression. The observation time was presented in person-years.

**RESULTS**

A total of 125 MMT program clients had been diagnosed with HIV from 2006 to 2019 in six MMT clinics of primary health-care centers in Kuantan district. Eighteen (14.4%) of them were transferred out to the other facilities, and another 40 (32%) were excluded from the study because of incomplete data and missing records and files. A final total of 67 MMT clients were included in this study. The clients’ characteristics are listed in Table 1. In the ART-initiated subgroup, the TTI was 27 months (mean).
Table 1: Characteristics of HIV-positive methadone maintenance therapy (MMT) clients in six primary health-care centers in Kuantan, Pahang

| Characteristics                              | Number, n (%) of participants |
|----------------------------------------------|--------------------------------|
|                                              | Total 67 (100%) | MMT only, 30 (44.8%) | MMT + ART, 37 (55.2%) | P value |
| **Age**                                      |                  |                      |                        |         |
| Mean (SD), years                            | 36.10 (4.38)    | 37.53 (3.95)         | 34.9 (4.42)            | 0.150*  |
| Marital status                               |                  |                      |                        |         |
| Single                                       | 34 (50.7)        | 13 (43.3)            | 21 (56.8)              | –       |
| Married                                      | 23 (34.3)        | 12 (40.0)            | 11 (29.7)              | –       |
| Divorced                                     | 8 (11.9)         | 4 (13.3)             | 4 (10.8)               | –       |
| Widow                                        | 2 (3.0)          | 1 (3.3)              | 1 (2.7)                | –       |
| **Job status**                               |                  |                      |                        |         |
| Odd jobs                                     | 27 (40.3)        | 12 (40.0)            | 15 (40.5)              | –       |
| Unemployed                                   | 18 (26.9)        | 7 (23.3)             | 11 (29.7)              | –       |
| Laborer                                      | 10 (14.9)        | 4 (13.3)             | 6 (16.2)               | –       |
| Others                                       | 12 (17.9)        | 7 (23.3)             | 5 (13.5)               | –       |
| **Home placement**                           |                  |                      |                        |         |
| Family                                       | 58 (86.6)        | 28 (93.3)            | 30 (81.1)              | –       |
| Alone                                        | 6 (9.0)          | 2 (6.7)              | 4 (10.8)               | –       |
| NGO shelter home                             | 2 (3.0)          | –                    | 2 (5.4)                | –       |
| Partner                                      | 1 (1.5)          | –                    | 1 (2.7)                | –       |
| Alcohol                                      | 3 (4.5)          | –                    | 3 (8.1)                | –       |
| **History of illicit drugs use**             |                  |                      |                        |         |
| Heroin                                       | 64 (95.5)        | 28 (93.3)            | 36 (97.3)              | 0.123** |
| Amphetamine-type stimulants                  | 44 (65.7)        | 22 (73.3)            | 22 (59.5)              | 0.236** |
| Cannabis                                     | 20 (29.9)        | 12 (40.0)            | 8 (21.6)               | 0.112** |
| Benzodiazepines                              | 20 (29.9)        | 10 (33.3)            | 10 (27.0)              | 0.582** |
| Morphine                                     | 19 (28.4)        | 9 (30.0)             | 10 (27.0)              | 0.792** |
| Codeine                                      | 8 (11.9)         | 6 (20.0)             | 2 (5.4)                | 0.870** |
| Kratom leaves (ketum)                        | 7 (10.4)         | 5 (16.7)             | 2 (5.4)                | 0.160** |
| Cocaine                                      | 1 (1.5)          | –                    | 1 (2.7)                | 0.372** |
| **Hepatitis cases**                          |                  |                      |                        |         |
| HCV                                          | 67 (100)         | 30 (100)             | 37 (100)               | –       |
| HCV treatment                                | 1 (1.5)          | –                    | 1 (2.7)                | –       |
| HBV                                          | 4 (6.0)          | –                    | 4 (10.8)               | –       |
| HBV treatment                                | 4 (6.0)          | –                    | 4 (10.8)               | –       |
| Opportunistic infections cases               | 27 (40.3)        | 10 (33.3)            | 17 (45.9)              | 0.302** |
| Tuberculosis                                 | 22 (32.8)        | 6 (20.0)             | 16 (43.2)              | 0.040** |
| Candidias                                     | 10 (14.9)        | 2 (6.7)              | 8 (21.6)               | 0.076** |
| *Pneumocystis jirovecii*                     | 2 (3.0)          | –                    | 2 (5.4)                | 0.160** |
| **PCP**                                      |                  |                      |                        |         |
| toxoplasmosis                                 | 2 (3.0)          | –                    | 2 (5.4)                | 0.160** |
| Cytomegalovirus                              | 1 (1.5)          | –                    | 1 (2.7)                | 0.372** |
| Histoplasmosis                               | 1 (1.5)          | –                    | 1 (2.7)                | 0.372** |
| Isoniazid prophylaxis therapy                | 30 (44.8)        | 10 (33.3)            | 20 (54.1)              | <0.001**|
| **Other treatment-related parameters**       |                  |                      |                        |         |
| ART counseling sessions                      | 29 (43.3)        | 4 (13.3)             | 25 (67.6)              | <0.001**|
| Compliance to MMT                           | 21 (31.3)        | 6 (20.0)             | 15 (40.5)              | 0.068** |
| Ever had positive urine test                 | 49 (73.1)        | 21 (70.0)            | 28 (75.7)              | 0.609** |
| Ever been detained/prison                    | 25 (37.3)        | 9 (30.0)             | 16 (43.2)              | 0.268** |
| **MMT in mean (SD)**                         |                  |                      |                        |         |
| Duration (years)                             | 4.79 (3.27)      | 3.43 (2.70)          | 5.89 (3.32)            | 0.002*  |
| MMT dose (mg)                                | 80 (34.76)       | 65 (28.57)           | 90 (35.29)             | 0.004*  |
| **ART regime**                               |                  |                      |                        |         |
| Tenofovir + emtrictabine + efavirenz         | –                | –                    | 15 (40.5)              | –       |
| Zidovudine + lamivudine + efavirenz          | –                | –                    | 15 (40.5)              | –       |
The MMT clients who were initiated on ART had a mean CD4+ T-cell count of 119 cells/mm³ and after 6 months of ART, the CD4+ T-cell count increased to a mean of 219 cells/mm³. Only two patients (5.4%) in the MMT plus ART subgroup had an unsuppressed viral load. A total of 13 deaths occur over 514 person-years, which showed the overall mortality rate of 2.5 per 100 person-years. The mortality rate for MMT plus ART subgroup was 1.4 per 100 person-years as compared to MMT-only subgroup 4.7 per 100 person-years. The rate of death is 3.3 times larger in MMT-only subgroup. Kaplan–Meier curves Figure 1 shows a better survival probability in MMT plus ART subgroup as compared to MMT-only subgroup (P<0.01). The univariate Cox’s proportional hazards regression analysis showed that the initiation of ART reduced the risk of death by 72.8% (hazard ratio = 0.27, P = 0.024), and they were 13.1 times more likely to remain in the MMT treatment (P < 0.001).

**DISCUSSION**

Only 37 (55.2%) of the MMT clients received ART despite clinical eligibility. The TTI of ART was 27 months long. For the HIV treatment, the latest 2017 guideline in Malaysia is to start ART regardless of the CD4+ T-cell count. Between 2008 and 2011, the count was below 200 cells/mm³ and less than 350 cells/mm³ after 2011. From the Malaysia Country Progress Report 2019, in 2017, 13.5% from 72,399 people living with HIV/AIDS (PLHIV) were PWID, but only 34.6% of them received ART.[7] It is still far from the target of 90% PLHIV to be treated with ART. On the basis of the Integrated Biological and Behavioural Surveillance survey in 2017, a significant proportion of PWID refused to start ART because of stigma, negative feeling, shame, and guiltiness.[8] Criminalization of illicit drug use most likely to cause them to lose their jobs and also delay ART initiation.[9] New regulation and consideration to reduce the criminalization of the PWID population are needed to increase access to the MMT program and helped scale-up ART initiation. It will reduce the morbidity and mortality, and curb the new HIV transmission.

In Malaysia, the physicians tend to delay ART in the PWID population, especially those with criminal records and imprisonment history, regardless of the
patients’ CD4+ T-cell count. This practice leads to a low-rate of ART coverage among PWID in Malaysia. In this study, five clients in the MMT-only subgroup were already eligible for ART based on CD4+ T-cell count but was not initiated on the treatment. The compulsory detention for drug use as part of the rehabilitation program had also halted the PWID to come forward and seek treatment for HIV infection. PWID who were infected with HIV always experienced suboptimal outcomes or delayed HIV care and treatment. They are the key population who needed intervention to prevent the spreading of new HIV infections and to reduce the number of HIV-related death. Strategies that are holistic and comprehensive, including evidence-based prevention and treatment intervention, are required to achieve good target outcomes.

A total of 13 clients from the MMT-only subgroup did not have CD4+ T-cell count test results, and 29 of them did not have any CD4+ cell count tests repeated after the initial test. Delay in CD4+ cell count tests and results, offsite HIV clinics, an untrained and a limited number of staff in MMT clinics, and stigma were some of the factors that delayed the ART initiation. The onsite CD4+ cell count test, peer support, and one-stop center (HIV treatment and MMT program in the same clinic) reduced the barrier to ART initiation among MMT clients. Lack of knowledge among MMT clients and to start ART only when sick were also the reasons for late ART. Our study showed that counseling sessions were high in the MMT plus ART subgroup. Trained staff for counseling and intervention using motivational interviewing methods to improve adherence and knowledge had shown beneficial to start the patient on ART and increase the retention rate. Persistent and continuous monitoring of MMT clients were crucial to make sure they remain in the program. MMT discontinuation was independently associated with the risk of ART discontinuation and ART interruption. It may lead to treatment failure and, eventually, death.

This study showed that the MMT clients who were given ART had an increment of CD4+ T-cell count of 100 cells/mm³ (mean) in 6 months, with 94.5% of them had suppressed viral load. These good outcomes were related to 95% adherence to ART. Engagement in MMT not only helps to initiate ART but also reduces the risk of ART discontinuation and associated with HIV viral Ribonucleic acid suppression and improved clinical outcome. However, a high dose of methadone was necessary due to drug–drug interaction, and it had proved to retain patients in the MMT program. An adequate dose of methadone is important to improve adherence to ART among MMT clients. In this study, the mean dose of methadone among the MMT plus ART subgroup is 90 mg per day. A few other studies also proved that those receiving higher doses of methadone were more likely to achieve more than 95% adherence to ART. Studies in Malaysia have shown that methadone dose of at least 80 mg per day increases the retention rate of MMT clients. The mortality rate was significantly lower, and the retention rate in MMT was higher in the MMT plus ART subgroup. It is supported by a few studies that showed that the mortality rate in HIV-positive MMT clients was low with early ART initiation, and the combined treatment increased the retention rate in the MMT program.

Receiving hepatitis C virus (HCV) treatment was also an important factor for MMT clients’ good clinical outcomes. Most of the patients with HIV–HCV coinfection did not seek treatment due to inadequate knowledge and lack of screening, and without treatment, it may lead to liver disease progression and death. Intervention through knowledge sharing sessions and counseling had proven to improve overall knowledge and lead to treatment interest. The latest HCV treatment, daclatasvir plus sofosbuvir with or without ribavirin were well tolerated and showed no drug interaction with ART, thus, no change in ART needed and opioid substitution therapy can be continued without interruption.

**Conclusion**

This study showed that the risk of death reduced and the retention rate was higher with the combination of MMT and ART, but the numbers of MMT clients who received ART were very low. The MMT clients who were given ART had better CD4+ T-cell count outcomes and suppressed viral loads. Better outcomes and lower mortality rates may be expected if the TTI was not delayed in this population. Future research needs to be conducted to identify factors associated with the treatment delay among MMT clients.

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**Conflicts of interest**

There are no conflicts of interest.

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