EXPLORING THERAPY OUTCOMES AMONG HIV POSITIVE PEOPLE WHO INJECT DRUGS (PWID) IN MALAYSIA

BY

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A thesis submitted in fulfilment of the requirement for the degree of Master in Pharmaceutical Sciences (Pharmacy Practice)

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ABSTRACT

The role of Methadone Maintenance Therapy (MMT) with antiretroviral therapy (ART) initiation among HIV-positive people who inject drugs (PWID) is not widely studied in Malaysia. This study aims to compare the treatment outcomes and time to treatment (TTT) between HIV-positive PWID enrolled in the MMT program compared to those who were not. This retrospective study involves HIV infected PWID in Kuantan from the year of 2006 to 2019. The Kaplan Meier survival curve and the Cox proportional hazard model was used to compare the mortality rate and to measure the outcome. The TTT was calculated from the day of ART eligibility to ART initiation. A total of 141 PWID from 6 health clinics in Kuantan and Infectious Disease Clinic of Hospital Tengku Ampuan Afzan were included in this study. They were categorized into MMT only group (29 subjects), MMT + ART group (41 subjects), and ART only group (71 subjects). From the Kaplan Meier test, the 5-year cumulative survival probabilities were at 60.9% in the MMT only group, 94.1% in the MMT + ART group, and 98.5% in the ART only group. The cumulative mortality incidence was significantly different between MMT only group compared to MMT + ART group, and MMT only group compared to ART only group with p-value < 0.001 and 0.003. A total of 94 subjects had their viral load test available for both MMT + ART group (n=32) and ART only group (n=62). More than 95% of the subjects in the MMT + ART group (n=31) and ART only group (n=60) achieved good viral load suppression (defined as viral load <1000 copies/ml). Both groups showed good CD4 cells count recovery with increment of >50ccells/mm^3 within 6 months. The time to treatment for ART only group was 2 months and 5.5 months in the MMT + ART group. The occurrence of opportunistic infection and low CD4 cells count baseline influenced earlier ART initiation in the ART only group. From the cox proportional hazard regression, the factors that reduced the mortality risk among PWID were the initiation of ART, HIV related counselling, and living with family with p value <0.05. The MMT program's 5-year cumulative retention probability for MMT + ART group compared to MMT only group was 93.6% and 41.2%. In conclusion, the initiation of ART improved PWID survival probability and clinical outcomes. Although the MMT program in this research was not associated with earlier ART initiation or a better outcome, it was evident that ART and MMT combination improved PWID retention in the healthcare system compared to PWID given MMT alone.

خلاصة البحث

علاج المداومة بالميثادون (MMT) مع العلاج المضاد للفيروسات القهقرية (ART) ودورهما كالعلاج الأساسي لمتعاطي المخدرات المصابين بفيروس نقص المناعة البشرية أو الإيدز (PWID) لم يتم دراسته على نطاق واسع في ماليزيا. هدفت هذه الدراسة إلى مقارنة نتائج العلاج ووقت العلاج بين الأشخاص المصابين بالإيدز الذين تم علاجهم بالـ MMT مع أولئك الذين لم يعالجوا به. تضمنت هذه الدراسة الرجعية الـ PWID المصابين بالإيدز في كوانتان من عام 2006 إلى 2019. تم استخدام منحنى البقاء على قيد الحياة لكابلان ماير ونموذج كوكس للخطر التناسبي لمقارنة احتمالية البقاء على قيد الحياة وقياس النتائج. تم حساب وقت العلاج بالـ ART من تاريخ أهلية المريض للخضوع لعلاج ART حتى تاريخ البدء بالمعالجة. تم في هذه الدراسة اشراك 141 شخصًا من الـ PWID من ستة مراكز للرعاية الصحية الأولية في مدينة كوانتان ومن عيادة الأمراض المعدية في مستشفى تونجكو أمبوان أفزان. تم تصنيف المشاركين إلى مجموعة الـ MMT فقط (29 مشاركا) ومجموعة الـ ART+MMT (41 مشاركا) ومجموعة الـ ART فقط (71 مشاركا). كانت احتمالات البقاء على قيد الحياة التراكمية لمدة 5 سنوات بنسبة 60.9٪ في مجموعة الـ MMT فقط، و 94.1% في مجموعة الـ ART+MMT، و98.5% في مجموعة الـ ART فقط.كان معدل الوفيات التراكمي مختلفا بشكل ملحوظ بين مجموعة الـ MMT فقط مقابل مجموعة الـ ART+MMT، ومجموعة الـ MMT فقط مقابل مجموعة الـ ART فقط بقيمة p < 0.001 و 0.003. أكثر من 95% من المشاركين في مجموعة الـ ART+MMT ومجموعة الـ ART أظهروا تثبيطا جيدًا للحمل الفيروسي. أظهرت كلا المجموعتين أيضًا استشفاء جيدا لعدد الـ CD4. كان وقت العلاج لمجموعة الـ ART فقط شهرين و 5.5 شهرًا في مجموعة الـ ART+MMT، وقد أثر حدوث حالات للعدوى الانتهازية وانخفاض عدد خلايا الـ CD4 على البدء المبكر للعلاج بالـ ART. العوامل التي قللت من خطر الوفيات بين الـ PWID كانت بدء العلاج بالـ ART، والاستشارات المتعلقة بالإيدز، والعيش مع الأسر. بلغت نسبة احتمال الالتزام التراكمي لمدة 5 سنوات لبرنامج الـ MMT لمجموعة الـ ART+MMT 93.6٪، مقابل 41.2٪ لمجموعة الـ MMT فقط. في الختام ، أدى بدء العلاج بالـ ART إلى تحسين احتمالية التزام الـ PWID والنتائج السريرية. على الرغم من أن برنامج الـ MMT في هذا البحث لم يكن مرتبطًا بالبدء المبكر في الـ ART أو بنتائج أفضل، فقد كان من الواضح أن الجمع بين الـ ART والـ MMT قد أدى إلى تحسين التزام الـ PWID في نظام الرعاية الصحية مقارنةً بـ PWID مع الـ MMT وحده.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion, it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master in Pharmaceutical Sciences (Pharmacy Practice)

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DECLARATION

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LIST OF ABBREVIATION

ART	Antiretroviral therapy
DOT	Direct Observational Therapy
DSM	Diagnostic and Statistical Manual of Mental Disorder
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HTAA	Hospital Tengku Ampuan Afzan
ID	Infectious disease
IPT	Isoniazid prophylaxis therapy
IRIS	Immune reconstitution inflammatory syndrome
IVDU	Intravenous drug users
MMT	Methadone maintenance Therapy
MSM	Men who have sex with men
NSEP	Needle syringe exchange program
OI	Opportunistic infections
PJP	*Pneumocystis Jirovecii Pneumonia*
PLHIV	People living with HIV
PWID	People who inject drugs
STI	Sexually transmitted infection
TB	Tuberculosis

CHAPTER ONE

INTRODUCTION

1.1 HUMAN IMMUNODEFICIENCY VIRUS (HIV)

The human immunodeficiency virus (HIV) destroys the cells of the immune systems and weakens the ability to fight pathogens, thus increasing the risk and effect of disease and infection. An absence of antiretroviral therapy (ART) will lead the infected individual progressing to the advanced stage of HIV called acquired immune deficiency syndrome (AIDS).

The main target of HIV is the T helper cells (T cell) of the CD4 glycoprotein, the white blood cells that play an important role in the immune system of a human body. These white blood cells pass across the body to detect cells anomalies or the presence of infections. The body loses its ability to combat infections and diseases once HIV reaches these target cells hence increases the risk of cancer and opportunistic infection (OI) in the patient.

OI commonly occur and affecting people with compromised immune systems, including HIV. There are two ways to diagnose AIDS among HIV-positive individuals namely the patients presented with one or more OI (further elaboration of this topic will be discussed in Chapter Five) and the CD4 cells count is less than 200 cells/mm^3. In the initial stage, prophylaxis therapy for common OI is crucial. Some asymptomatic individuals might be an HIV carrier, which could be unnoticed.

HIV is transmitted through bodily fluids such as blood, semen, vaginal secretion, anal fluids, and breastmilk. It is important to recognize the risks and routes

of transmission in an infected individual to target the specific intervention and prevention method.

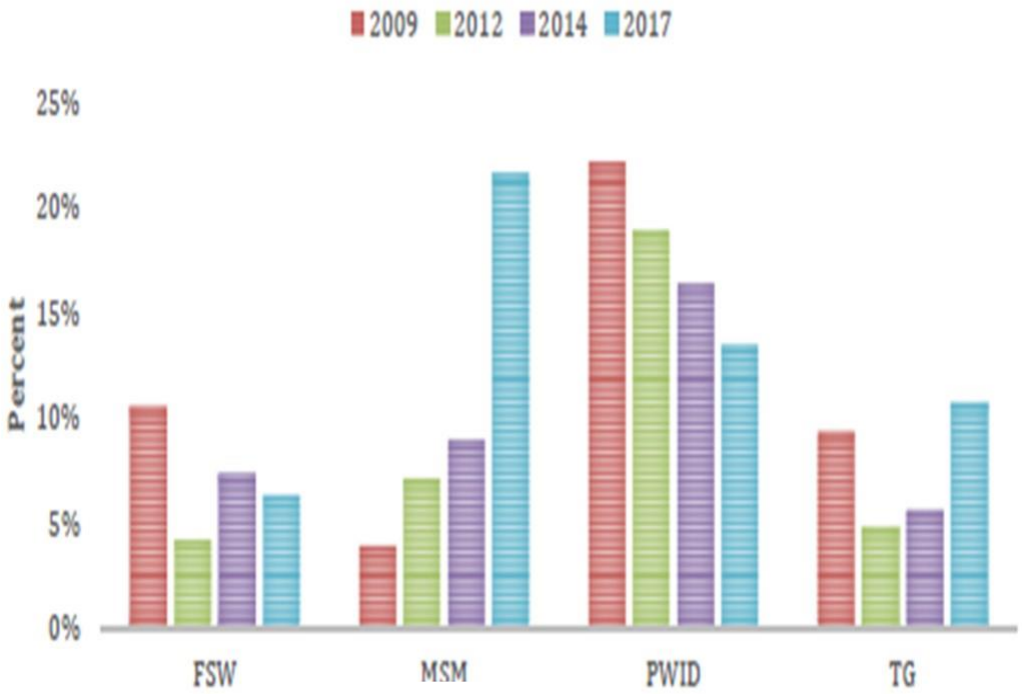
1.2 HIV KEY POPULATION

The key populations are people known to be at a greater risk for HIV infections due to risky behaviors that placed them at a higher risk of HIV infection. Initiatives and specific HIV prevention that target each key population should be tailored to each population depending on the activities that put them at risk of HIV infection for a successful HIV epidemic prevention.

There are 4 common key populations that are at high risk of HIV infection in Malaysia. They are categorized as people who inject drugs (PWID), female sex workers (FSW), transgender women (TG), and men who have sex with men (MSM). A PWID is referring to a drug user who used devices for self-injection, mainly opioids. Transgender people are sometimes referred to as 'Mak Nyah' in Malaysia's scenario. These are people who identified their gender differently from their original sex at birth. Homosexual or MSM are men who have sex with another men, usually with multiple sexual partners and had sexual intercourse through anal.

Throughout the early years of the HIV outbreak, it was thought that the disease only affecting the western countries and spread among the homosexual population, typically in MSM. In the United States during 1981, the first clusters of AIDS were reported among gay men infected with PJP (*Pneumocystis Jirovecii Pneumonia*) and Kaposi's Sarcoma (Nakashima & Fleming, 2003). The pattern then changed from the MSM population to PWID and heterosexual transmission. However, as shown in Figure 1.1, the trend of HIV transmission then reverted to the MSM population with a yearly

increment from 2009 to 2017, and HIV transmission through IVDU showed a decreasing trend.



Source: Malaysia Integrated Biological and Behavioral Surveillance (IBBS) 2017

Figure 1.1 HIV prevalence among the key population in Malaysia from 2011 – 2017

The Malaysia Integrated Biological and Behavioral Surveillance (IBBS) survey showed the highest prevalence of HIV infection in 2009 was among the PWID (22.1%) followed by FSW (10.5%), TG (9.3%), and MSM (3.9%). According to the Malaysia IBBS in 2017, the rate of HIV infection in 2009 exceeded 5% with PWID was the highest contributing population (Suleiman, Ramly, Ahmad Hafad, & Chandrasekan, 2017) (Figure 1.1).

In 2017, the MSM population HIV prevalence rate peaked to more than 20% (Figure 1.1). An intervention was needed to be done promptly and one of the crucial

steps to stop a further spread of HIV infection among this population was to introduce ART. The coverage of ART for the MSM population was the highest (62.6%) compared to the other key population, PWID, FSW, and TG with only 34.6%, 22.5%, and 34.0%, respectively (Table 1.1). This percentage was far behind the target set of 90% of the key population received ART by the year of 2020.

Table 1.1
Overview of Global AIDS Monitoring indicators, Malaysian Integrated Bio-Behavioral Surveillance (IBBS) 2017

Indicators (%)	**PWID**	**Female sex worker**	**Transgender women**	**MSM**
Percentage of key population (KP) who are living with HIV	13.5	6.3	10.9	21.6
Percentage of KP who tested for HIV in the past 12 months or who know they are living with HIV	38.9	35.1	43.0	43.3
Percentage of KP living with HIV receiving ART in the past 12 months	34.6	22.5	34.0	62.6
Percentage of KP reporting using a condom with their most recent client	25.7	83.5	78.2	65.4
Percentage of Overview of Global AIDS Monitoring indicators, 2016 - 2018 who report receiving HIV prevention services from an NGO, health-care provider or other sources	1.4	40.0	57.9	36.7

Source: Malaysia Integrated Biological and Behavioral Surveillance (IBBS) 2017

It was reported that only 25% of PWID used condoms during sex while FSW (83.5%), TG (78.2%), and MSM (65.4%) showed a higher percentage (Table 1.1). The data indicate that the PWID key population are able to actively be transmitting HIV to the other population through heterosexual transmission. ART should be combined with

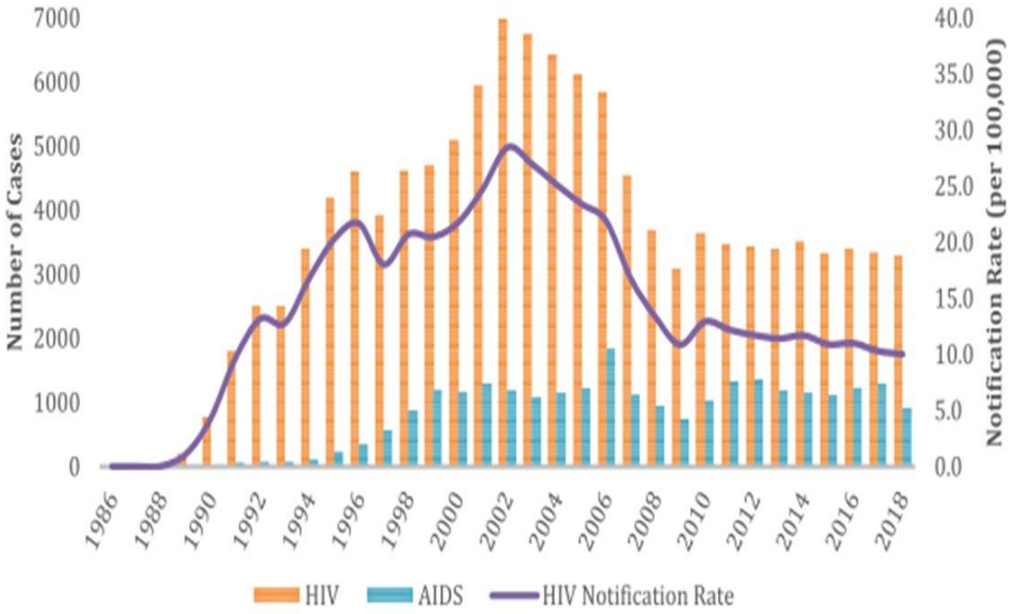
other harm reduction programs to reduce and curb HIV infection from infecting other Malaysian population.

1.3 HIV IN MALAYSIA

The first AIDS case in Malaysia was reported in 1986 involving a Chinese man who has been residing abroad for 30 years. He was first diagnosed with *Pneumocystis Jirovecii Pneumonia* (PJP) and later was confirmed positive for HIV (Goh, Chua, Chiew, & Soo-Hoo, 1987).

In Malaysia, the preparation for HIV/AIDS was initiated a year before the first case was reported in Kuala Lumpur Hospital. The National AIDS Task Force, which was established in 1985, was a joint committee from the government and multiple agencies that helped the country to stop and curb the epidemic by developing and implementing standard policies. In the same year of establishment, HIV/AIDS was recognized as a notifiable disease. In the early 1990s, HIV Screening Program started for inmates, residents of drug rehabilitation centers, tuberculosis (TB), sexually transmitted infection (STI) patients, sex workers, and pregnant mothers (Ngadiman, Sulaiman, Abd Aziz, Yuswan, & Md Taib, 2015).

To further stop the spread of HIV infection, the harm reduction program was implemented in 2005. In 2006, the provision of free first-line ART to all Malaysian was one of the policies included in the first National Strategic Plan for HIV and AIDS (2006 – 2010) (Ngadiman, Sulaiman, et al., 2015).



Source: Country Progress Report 2019 - Malaysia

Figure 1.2 Reported HIV and AIDS cases in Malaysia from 1986 – 2018

Since the first diagnosed case, the number of HIV infected individuals increased to almost 7000 people 8 years later (refer to Figure 1.2) (Suleiman & Chai, 2019). There were various reasons for the rapid increase in the prevalence of HIV. One of the factors was mandatory testing of all intravenous drug users (IVDU) admitted to drug rehabilitation centers and prisons (Ismail, 1995). Needle sharing was one of the risks of HIV transmission. HIV screening for all IVDU detained in the center was the fastest and easiest way to test the key population who has the risk of HIV infection.

Screening for HIV among the key population is crucial. However, stigma and prejudice can result from compulsory testing if conducted without a proper HIV pre-test counselling. It is essential to ensure that all inmates who have been confirmed positive are provided with the necessary interventions related to HIV care and treatment services.

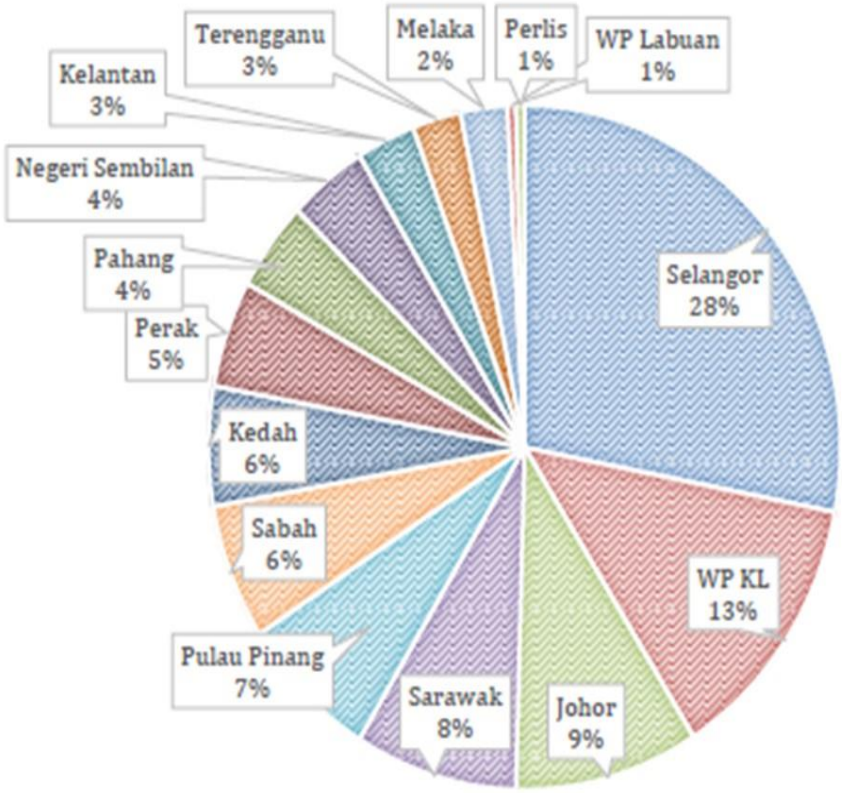
According to the Country Progress Report on HIV/AIDS 2019, Malaysia (Suleiman & Chai, 2019), the number of people living with HIV (PLHIV) has been estimated to be 87,000. Approximately, 75,000 of the PLHIV have been alerted through a national surveillance system made available since 1985 (Table 1.2).

Since 2002, the number of new HIV infections decreased with 50% drop case reduction (Figure 1.2). In 2002, the overall number of HIV infections was 6,978 and eventually decreased to 3,293 cases in 2018. In the same analysis, 55% of 75,000 PLHIV received ART at the end of 2017.

Table 1.2
Overview of HIV epidemic, Malaysia 2018

Indicator	Number
Cumulative number of reported HIV	118,883
Cumulative number of reported AIDS	25,925
Cumulative number of deaths related to HIV/AIDS	43,843
Estimated people living with HIV (Spectrum 2018)	87,041
Total number of people living with HIV (surveillance data)	75,040
Reported new HIV infections	3,293
HIV notification rate (per 100,000)	10.0
People living with HIV receiving ART as of December 2017	41,430

Source: Country Progress Report 2019 - Malaysia



Source: Country Progress Report 2019 - Malaysia

Figure 1.3 PLHIV in Malaysia by state, 2018

The highest percentage of PLHIV was in Selangor followed by Kuala Lumpur. This study was conducted in Kuantan, Pahang with a total of 4% of the estimated 87,000 PLHIV live in Pahang (Figure 1.3).

1.3.1 The Malaysian 'Ending AIDS' Target

Although the infection rate decreases, the goal to stop and halt HIV infection would not be achievable if the planned and specific intervention was not carried out. For each identified key population, the intervention strategy should be uniquely prepared.

As stated in the 2016 United Nations General Assembly Political Declaration on Ending AIDS, Malaysia is committed to ending AIDS by 2030. The plan and related

policies were developed in the 2016-2030 Malaysian National Strategic Plan for Ending AIDS (NSPEA). The most recent NSPEA is consistent with the Sustainable Development Goals (SDGs) by the United Nations.

The SDGs are the goals set and accepted by the members of the United Nations to end hunger and poverty, to protect the world and improve everybody's lives and opportunities, everywhere in this world. There are 17 goals targeted in the 2030 Sustainable Development Agenda including to end AIDS by 2030. The 15-year timeline was set to accomplish the targeted goals.

The word 'Ending AIDS' refers to the elimination of AIDS as a public health issue by the end of 2030. This aim is to be attained by preserving the effects of 'fast-tracking' and achieving the goals of screening and obtaining the results of 95% of the key populations. This is including 95% of those identified as HIV-positive initiated on ART and 95% of those provided with ART achieved undetectable viral load. Another goal is to have an effective prevention program covering at least 80% of the main population (Ngadiman, Sulaiman, et al., 2015).

The 'fast-tracking' concept refers to the achievement of these goals by 2020. The aims are the 90% of the main populations screened for HIV aware of their status, 90% of the population who were tested positive for HIV were given ART, and 90% of the HIV-positive individual given ART have a suppressed viral load (Ngadiman, Sulaiman, et al., 2015).

Malaysia aims to meet the 'getting to zero' NSPEA target by 2020. The zero goals defined as zero new HIV infections, zero discrimination due to HIV and AIDS, and zero death. The four key NSPEA goals are in place. The first goal is to test and treat, followed by the second goal, which is to improve the quality and coverage of the prevention programs tailored to each key population. The third goal is to decrease the

stigma and prejudice that HIV-infected individuals and other key populations frequently encountered. The fourth and final strategy is to ensure the decision-makers and planners use quality strategic knowledge through monitoring, assessment, and research analysis.

1.4 PEOPLE WHO INJECT DRUGS AND HARM REDUCTION PROGRAM

Harm reduction is an approach or intervention that alters human conduct of behavior, especially among the PWID population who are potentially harmful to himself or their circle of community. The goal of the intervention was not to stop or decrease drug use, however, it is intended to minimize risky behavior that could impact health, social or economic effects. The main goal of this initiative was to modify the risky behavior of the PWID that do not wish to stop taking illicit drugs.

In the harm reduction program, 3 core preventions and strategies may be implemented. The interventions include needle syringe exchange program (NSEP) that provides clean needles and syringes. The second intervention is opioid substitution therapy (OST) such as the Methadone Maintenance Therapy (MMT) to assist users with withdrawal and concurrently reducing or stopping the illicit opioid intakes mainly via injections. Another approach in the harm reduction program is to initiate ART in HIV-positive PWID to reduce the risk of transmitting the virus to the other PWID population or through heterosexual transmission in the other key or general population such as the spouses or their sexual partners.

In Malaysia, a National Task Force of the harm reduction program comprises of officials from Ministries of Health, National Anti-Drugs Agency, Royal Malaysian Police, Prisons Department, academicians, and representatives of NGOs. Each representative played an important role in ensuring a successful harm reduction program to be carried out (Kamarulzaman, 2009).