

University of Alberta

Cost - Effectiveness of Integrating Methadone Maintenance with
Antiretroviral Treatment in Injection-Driven HIV Epidemics

by

Tran Xuan Bach

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DEDICATION

For Ingeborg, my mum, my wife, and my brilliant daughter - Pé Kem!

ABSTRACT

In the household survey, Health-Related Quality of Life (HRQL) of patients on antiretroviral treatment (ART) was profoundly reduced and significantly lower among drug users (DUs) than that of non-DUs, especially in the psychological and social dimensions. Drug use is known to negatively affect HIV/AIDS treatment outcomes; that made it essential to integrate drug dependence treatment into HIV/AIDS treatment policies in Vietnam's injection-driven HIV epidemics.

The effectiveness and cost-effectiveness of Methadone Maintenance Treatment (MMT) were assessed using secondary data of the first MMT cohort in Vietnam. The findings showed that the rates of concurrent drug use during MMT among HIV-positive DUs rapidly decreased at the first trimester (18.1%), and then stabilized during the next 2 trimesters (11.8% and 14.4%). Improvements in HRQL were large over 9 month follow-up and highest in the psychological dimension. However, MMT patients with ongoing drug use (30.5%) and injection (20.5%) reported large decrements in all HRQL dimensions compared to those abstinent to drug. A social ecological model was applied to explore multilevel predictors of ongoing drug use, and it revealed higher likelihood in those patients who had higher levels of prior opioid dependence, peer pressure, took ART or tuberculosis treatment, and had more health concerns. The subsequent economic evaluation determined that MMT was cost-effective for HIV-positive DUs in term of gains in Quality-Adjusted Life Years; however, it might not be cost-effective for those patients who continued to inject drug.

The modeling study sought to assess the potential integration of ART and MMT for HIV-positive DUs. A decision analytical model was developed to compare the costs and consequences of 3 ART strategies: 1) only ART model 2) the separated ART-MMT model as currently delivered in Vietnam, and 3) direct administered ART-MMT where patients took methadone and ART regimens under supervisions of health workers. The findings indicated that integrating ART and MMT services for HIV-positive DUs facilitated the use of directly observed therapy that can bring about clinically important improvements in health outcomes. This approach was also incrementally cost-effective in this large injection-driven HIV epidemic.

PUBLICATIONS

1. Tran BX, Ohinmaa A, Nguyen LT, Nguyen TA, Nguyen TH. Determinants of health-related quality of life in adults living with HIV in Vietnam. *AIDS Care*. 2011 Oct;23(10):1236-45.
2. Tran BX, Ohinmaa A, Duong AT, Do NT, Nguyen LT, Nguyen QC, Mills S, Jacobs P, Houston S. Changes in drug use are associated with health-related quality of life improvements among methadone maintenance patients with HIV/AIDS. *Quality of Life Research*. Jul 6 2011.[Epub ahead of print]
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4. Tran BX, Ohinmaa A, Duong AT, Nguyen LT, Mills S, Houston S, Jacobs P. Cost - effectiveness of methadone maintenance treatment for HIV-positive drug users in Vietnam. *AIDS Care*. Sep 22 2011.[Epub ahead of print]
5. Tran BX, Ohinmaa A, Duong AT, Nguyen LT, Houston S, Jacobs P. Cost-effectiveness of integrating methadone maintenance and antiretroviral treatment for HIV-positive DUs in an injection-driven HIV epidemic. *BMC Health Services Research (under review)*.

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LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
ART - MMT	Antiretroviral Treatment and Methadone Maintenance Treatment provided in separated sites
CEAC	Cost-Effectiveness Acceptability Curve
DAART-MMT	Directly Administered Antiretroviral Treatment integrated with Methadone Maintenance Treatment
DOT	Directly Observed Therapy
DU	Drug User
EQ-5D	EuroQOL five-dimension questionnaire
GEE	Generalized Estimating Equations
HIV	Human Immunodeficiency Virus
HRQL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
MMT	Methadone Maintenance Treatment
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Years
VAAC	Vietnam Authority of HIV/AIDS Control
VAS	Visual Analog Scale
WHOQOL-BREF	World Health Organization Quality of Life – Brief Version

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1. Introduction

Three decades after the first AIDS case reported in the USA, HIV has rapidly spread and become one of the world's leading causes of death. Following Sub-Saharan Africa, Asia has the second largest HIV epidemic in the world. It is estimated that 9 million people in Asia have been infected with HIV, and millions of them have died of AIDS-related illness¹. The burden of HIV infection is rapidly increasing, fuelled by poverty, social vulnerability, gender inequalities and poor healthcare systems¹⁻³. Effective and contextualized interventions are urgently needed to support the governments to meet targets on Universal Access for prevention, treatment, care and support by 2010, as well as the Millennium Development Goal 6 to halt and reverse the epidemic by 2015¹.

HIV transmission in Asia is primarily driven by most-at-risk behaviors, including unprotected commercial sex, injecting drug use, and unprotected sex between men. These sizable high-risk populations have been a challenge to prevent HIV transmission as well as manage HIV/AIDS care and treatment services. As seen in many studies, HIV/AIDS treatment has been less effective in injecting drug users (DUs) compared to other patient groups⁴⁻⁶. DUs were seen to have severe co-morbidities, delayed access to health care services, and more importantly, poor compliance with HIV/AIDS treatment^{5, 7}. In addition, some of them might have complex social status, such as criminal histories or sex-trade involvement, which have been accompanied by high stigma and discrimination¹. As a result, this "twin epidemic" of HIV and drug injection shapes the biological and social vulnerability of people living with HIV/AIDS in Asia.

Vietnam has a growing HIV epidemic that was initially emerged in drug using populations^{1, 8}. The estimated HIV prevalence rate among adults aged 15-49 was 0.5-0.7% in 2010⁹, classifying the country as still in a concentrated phase. Approximately 320,000 people have contracted HIV/AIDS, among those 70% have a history of drug injection, and 20% are at an advanced HIV/AIDS stage and requiring treatment with antiretroviral drugs¹⁰. Treatment for large HIV populations in Vietnam, like other developing countries, is mainly dependant on funding from international donors^{1, 11}. This substantial support has significantly enhanced the capacity of the health system to respond to the burden of HIV epidemic¹¹⁻¹³. However, unstable future funding increases the uncertainty on the coverage and expansion of services. Therefore, defining cost-effective interventions and setting priorities for scaling up HIV/AIDS services is crucial to inform the financial decisions of governments as well as major international donors.

Globally, the introduction of antiretroviral therapy (ART) has dramatically reduced HIV-related mortality and morbidity, and has improved quality of life of HIV/AIDS patients receiving treatment¹⁴⁻¹⁶. With substantial support from global health initiatives, free ART services have been rapidly scaled up in low-income settings¹⁷⁻¹⁹. However, the current regimens require that patients remain on life-long treatment. In addition, a strict compliance of patients is central to prevent drug resistance to achieve treatment success. Because of this, adherence support models have been highly recommended as an important component of ART services and prioritized when it is possible.

In the fight against tuberculosis (TB), Directly Observed Therapy (DOT) has been widely recommended as an effective model to deliver the service²⁰⁻²². DOT seeks to improve adherence to TB treatment through health workers who are directly observing the patients taking their anti-TB drugs. In practice, DOT is capable to prevent TB relapses occurring and drug resistance developing²². The advantage of DOT includes a close monitoring of TB treatment which in turn improve patients' adherence. However, the resources needed for such a policy are substantial, particularly in low-income countries where the case load is high²². Moreover, the benefits associated with DOT short-course treatment for TB may be attributable to other factors apart from the direct observation. The application of DOT for other diseases, therefore, is still limited.

There has been an introduction of adherence support using facility-based or community-based DOT for the delivery of ART²³. The facility-based DOT aims at the supervision of patients taking medications in any clinic visits. This adopts the traditional approach applied in TB treatment. Noticeably, researchers have started to explore the effects of a combination of medical, social, and economic supports during the ART²⁴⁻²⁶. Community-based DOT for ART is one model that helps address daily obstacles to adherence, provides emotional and informational support, and serves as a liaison with formal health services^{25, 26}. Nonetheless, whether these strategies should be implemented in resource-poor settings remains controversial. First, both facility-based and modified community-based DOT is resource-intensive. Moreover, a recent meta-analysis of randomized controlled trials by Ford et al. showed that DOT may not offer incremental benefits for the general patient population²⁷. Therefore, taking the advantage of the DOT approach and confining it to certain subpopulations would

be helpful for the HIV/AIDS care and treatment program in Vietnam as well as in other low-income settings^{20, 22}.

Recent studies have expressed considerable interest in the role of methadone maintenance treatment (MMT) for HIV-positive DUs. The recognition of MMT included its high efficacy in treatments for opiate addiction that could lead to significantly reduced criminal activities and other high-risk behaviors²⁸⁻³². Providing MMT for HIV-positive DUs helps release them from drug dependence that facilitate better adherence to ART. Moreover, scaling up MMT may enhance the feasibility of using DOT for ART. In the literature, several randomized controlled trials have showed high virologic success in patients taking antiretroviral drugs and MMT under direct supervision of health workers during MMT clinic visits³³⁻³⁸. However, it is important to notice that these evaluations were carried out with a small number of patients and in resource-rich settings. Meanwhile, evidence in low-income settings where large drug using populations exist is not available.

Since 2008, the Vietnam Ministry of Health has been piloting the first national MMT program. Up to now, there has been little experience with how MMT benefits HIV/AIDS care and treatment for DUs in the Vietnamese context^{5, 39}. Moreover, the benefit of expanding this intervention for HIV-positive DUs in such a large injection population like Vietnam is uncertain. First, a high drop-out rate was observed in other countries. For instance, the retention rate was only 56% after 14 months in China⁴⁰. Noticeably, the long-term retention rate in British Columbia, Canada was just 20%-25% after 3 years⁴¹. Moreover, results of economic evaluations, which have compared costs with outcomes of this

intervention, have been heterogeneous across international settings, ranging from 1,501 USD to as much as 48,575 USD per 1 quality-adjusted life year (QALY) gained⁴²⁻⁴⁸. The purpose of this thesis is to identify the determinants of the HRQOL of the HIV/AIDS population; and to evaluate the impact and cost-effectiveness of MMT and its potential integration with ART services for HIV-positive DUs in Vietnam. Specifically, it consists of the following five studies:

The first study aims to evaluate the HRQL of adults with HIV/AIDS, and explore determinants of their HRQL. This could inform services development and programmatic decisions. Comparing health outcomes under ART between DUs and non-DUs, this study seeks to identify health care needs of DUs in each HIV/AIDS stage classified according to the World Health Organization's clinical staging guidelines.

Building upon the first study, the second study aims to examine the role of MMT as a component of HIV/AIDS care and treatment for DUs. It assessed changes in drug use behaviors under MMT, and the way by which these changes were correlated with HRQL of HIV-positive DUs in a longitudinal cohort. Gains in health outcomes were then tested for different HIV/AIDS stages and concurrent drug use during MMT.

The purpose of the third study is to analyze the responses of HIV-positive DUs to MMT. It utilized the social ecological model to explore longitudinal predictors of concurrent drug use during MMT with the purpose of identifying changes that might enhance program efficacy. Multilevel predictors of ongoing drug use,

including individual, interpersonal, community and service influences, were examined.

Drawing on findings from the second and third studies, the fourth study attempted to evaluate the cost-effectiveness of the pilot MMT program for HIV-positive DUs in terms of incremental cost over gains in QALYs from the perspective of health service providers.

The fifth study aims to evaluate the cost-effectiveness of different ART and MMT services delivery models for HIV-positive DUs in Vietnam. It utilized a decision analytical model comparing the cost and consequences of 3 strategies: 1) the ART model where DUs were offered only ART, 2) the ART-MMT model which provided ART and MMT in separated sites as currently delivered in Vietnam, and 3) the DAART-MMT which integrated ART with MMT services that facilitate direct administration of ART regimens and methadone at the same time during clinic visits.

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2. Determinants of health-related quality of life in adults living with HIV in Vietnam

2.1. Introduction

Vietnam has one of the fastest growing HIV epidemics in Asia, which was largely driven by unsafe sex and drug injection^{1, 2}. In 2009, the national surveillance system revealed that injecting drug users (DUs) accounted for 50.6% of newly detected HIV cases³. Approximately 254,000 people are thought to have contracted HIV in the country, among those 25% are at an advanced stage and in need of antiretroviral treatment (ART)⁴.

With substantial support from global health initiatives, ART services have been rapidly scaled up in Vietnam⁵⁻⁷. In 2008, there were 27,000 HIV/AIDS patients receiving ART that accounted for 45% of people in need of ART. However, the effectiveness of ART might be confined given the majority of treated patients were IDUs⁸. Drug use was related to a rapid HIV disease progression⁹, delayed access to ART¹⁰, and more importantly, adherence difficulties once ART had been started⁸. Therefore, to develop health care policies and services for adults with HIV/AIDS in Vietnam, evaluation of health outcomes and their predictors are essential.

Health-related quality of life (HRQL) indicators have been widely applied in the sphere of HIV/AIDS as a crucial complement to more objective outcomes such as co-morbidities or death¹¹⁻¹³. HRQL is associated with physiological and biomedical status of HIV/AIDS patients. It is shown continuously deteriorate by

HIV infection over time, and been related to treatment adherence and viral load¹⁴⁻¹⁶. Moreover, HRQL has been capable to reflect non-medical aspects of living with HIV/AIDS^{17, 18}. Poorer HRQL has been observed among HIV+ people perceiving less psychosocial supports¹⁷, experiencing depressive symptoms^{17, 19}, or injecting drug²⁰. As a result, measuring HRQL has the potential to assess the impact of health interventions, identify the need for health services improvements, and monitor changes in health status of HIV+ patients over time.

There has been a growing body of evidence in various aspects of HRQL in HIV populations^{12, 21}. Nevertheless, very few of the studies were conducted in developing countries where large HIV populations live²¹. Moreover, given the life-long treatment, psychosocial aspects are becoming important in evaluating and developing comprehensive HIV care and treatment services for HIV/AIDS patients. The purpose of this study was to measure and compare HRQL of HIV+ adults with that of the general population, and to explore the determinants of HRQL in HIV+ population.

2.2. Methods

Study settings and sampling

A cross-sectional household-based survey was conducted between October 2008 and April 2009. Six provinces involved in the study represented the differences in ecological regions and progressions of HIV epidemics (both mature and recent epidemics). Since HIV status in Vietnam is confidential, we constructed sample frame of HIV population using the total number of reported HIV+ cases in each district. HIV-affected households were sampled with

probability-proportional-to-size, following the random selection of rural and urban districts in target provinces. In one district with a small sample size, a minimum of 30 subjects were recruited.

The study populations consisted of HIV+ individuals 18 years and older and a comparison group of HIV- adults in general population. HIV-affected households were conveniently referred to by peer-HIV educators. These included both HIV+ people at an advanced stage of HIV infection and receiving ART when CD4 counts < 200 cells/ μ L and/or WHO stage 4 AIDS (56.3 %), and those who not yet required ART (43.7 %). There were no HIV+ individuals in need of but not taking ART in this sample. If there were more than 1 HIV+ person in a household, all of them were interviewed. For each HIV-affected household involved, there was one purposefully selected adult in a surrounding household with similar living standard and family size.

The number of subjects needed for each population was estimated assuming a difference between arms of 5% units for HRQL scores and corresponding standard deviation of 15%. Requiring a power of 90% and a significance level of 5%, the necessary number was about 190 per arm. Inflating the size by two times to compensate for design effects, we got about 400 patients per arm.

Instruments

Respondents were interviewed face-to-face using structured questionnaires by well-trained investigators with regular and ad-hoc supportive supervisions. Information on socio-demographic characteristics, HIV-related status and HRQL were then collected.

HRQL was measured using the EuroQOL five-dimension questionnaire (EQ-5D), and a visual analog scale (VAS). The EQ-5D consists of a weighted sum of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, which provided a simple descriptive profile and a single index value for health status²². Each dimension contains one question. Each question is divided in three levels: no problems, some problems and severe problems that enable the EQ-5D to define 243 health states. For example, in mobility, participants were asked to indicate which statements best describe their own current health state: “1) I have no problems in walking about; 2) I have some problems in walking about; and 3) I am confined to bed”. Each state was then assigned a preference weight using scoring algorithm of general populations based on the time trade-off or the visual analogue scale valuation techniques²²⁻²⁷. Although the EQ-5D single index reflects full health and death as 1 and 0, in some severe health states, it results in negative values, which indicate that the health states are considered to be worse than death. This study applied the UK scoring algorithm which has a possible score range of (-0.59; 1)²². In addition, the VAS recorded respondent’s self-rated health on a vertical, 20-cm scale resembling a thermometer where the endpoints (0, 100) were labeled “Best imaginable health state” and “Worst imaginable health state”²². The Vietnamese version of EQ-5D instruments was provided by the EuroQOL Group.

Data analysis

Stata version 11 was used for analyzing the data²⁸. HRQL was measured by both: (1) EQ-5D single index score calculated using UK scoring algorithm; (2)

VAS score; and (3) frequency of reported problems in each EQ-5D dimension²⁹⁻

31 .

Population weights were constructed based on the selection probabilities and the sampling weights of each stratum. Descriptive statistics were used to describe the health status, socio-demographic and HIV-related characteristics of respondents. Proportions and means were calculated with 95% confidence intervals. Chi-square test, Wald test, and Student's t-test were used to examine the differences between proportions and means. Using analysis of covariance technique, the means of HRQL scores were compared across groups adjusting for age, sex and disease progression. Kruskal-Wallis rank test was used to compare the equality of populations.

Multivariate linear regression was used to identify independent factors associated with overall single index of HRQL and VAS in statistical models. Candidates for multivariate analysis included those variables that met one of the following three criteria: (1) biological association with the outcome of interest; (2) previously shown to be associated with the HIV-specific quality of life among Vietnamese population; and (3) significant difference between groups when screened by univariate analysis. The significance level was set at $p < 0.05$.

Logistic regression analysis was performed to determine the association of reported problems in each dimension of HRQL controlling for the effect of potential confounders. The independent variables were assessed in five different mathematical models using each of the above outcomes in one model. The

likelihood ratio test was performed to compare the reduced model (without the variable of interest) with the larger model (with the variable of interest).

Internal consistency reliability of HRQL measurement, an average inter-item correlation of the five dimensions, was estimated using Cronbach's alpha. Spearman's rank correlation was estimated to test for correlation between EQ-5D Index score and VAS score. Cross-sectional construct validity was evaluated by testing an 'a priori' hypothesis that the measure was able to distinguish HRQL of HIV+ individuals at different disease progression and their HRQL was lower than that of the general population.

Ethical consideration

The study protocol was reviewed and approved by the Vietnam Authority of HIV/AIDS Control. Written informed consent of all the participants was sought after explaining the purpose of the study. Respondents were able to withdraw from the study at any time. Confidentiality was assured using codes for patient in a computerized procedure.

2.3. Results

Characteristics of the study participants

Of the 413 HIV-affected and 438 non-HIV-affected households asked to participate in the study, 400 HIV+ and 420 HIV- people (96%) accepted to enroll and were interviewed. Among all respondents, 61.3% were male and 61.8% were living in an urban area. The percentages of respondents having a job were 73.1% and 84.0% in HIV+ and general population, respectively. Although, households involved in this

study had the same socioeconomic characteristics, the HIV+ population and general population were not completely identical. A total of 41.7% of HIV+ people were living with their spouse or partner although it was 82.7% in the comparison group ($p < 0.001$). In addition, HIV+ population was younger and had a lower level of education than the comparison group. (Table 2-1).

Stages of HIV infection and social supports structure

Of the HIV+ population, 56.3% were taking ART, and 43.8% were asymptomatic and/ or had not yet met the criteria for treatment. Mean length of living with HIV diagnosis was five years (95% confidence interval (CI) = [4.7; 5.3]), and ART patients having longer time (5.3 years) than those at an earlier HIV stage (4.7 years) ($p < 0.05$). Among HIV+ individuals, 52.3% reported historically injecting drug use.

The percentage of HIV+ respondents receiving social support services, such as loan, tuition fee for children, health care, food, medicine, was significantly higher in those with ART (89.2%) than among others (76.0%) ($\text{Chi}^2 = 12.3$, $p < 0.01$). Peer-group involvement was reported to be similar (44%) in the HIV+ people taking or not yet taking ART.

Health-related quality of life

Adjusting for age and gender, the EQ-5D index and VAS score in early HIV stage people (0.90, 69.3) and ART patients (0.88, 65.2) was significantly lower than those of the general population (0.96, 81.6) ($p < 0.001$). The frequency of reported problems across EQ-5D dimensions in the HIV population (2.5% to 32.5%) was significantly higher than in the general population (0.7% to 12.1%) in every

dimension. Compared to ART patients, those at earlier HIV stages reported having problems at similar proportions across four HRQL dimensions (Table 2-2), except pain/discomfort, where ART patients had a significantly higher proportion of problems (Chi² test, p = 0.027).

Table 2-3 compared HRQL between HIV+ individuals with and without history of injecting drug. At an early HIV stage, both EQ-5D index score and VAS score were not different between the 2 groups. However, during ART, IDUs reported significantly lower VAS score than non-IDUs (p=0.01).

Predictors of HRQL among HIV+ population

Multivariate analysis was carried out to examine the influence of socio-demographic variables, HIV-related factors, and social support structure on HRQL in adults with HIV. Social support included any referral and utilization of services respondents have had, such as: loan; vocational training; and self-help groups. As for health services, accessibility was assessed by the difficulties participants experienced in last 3 months in terms of geography, availability and quality of the service. Linear regression results determined that unemployment (p<0.001), and having difficulties in accessing to health services (p<0.001) were significant independent predictors for lower scores in both EQ-5D index and VAS. Moreover, drug injection and disease progression were also associated with lower VAS score in HIV+ population (Table 2-4).

Table 2-5 shows the odd ratios of having problems in various HRQL dimensions. Similarly to HRQL index and VAS score, unemployment and having barriers to health care services were strongly associated with almost all HRQL domains.

Besides, disease-related progression was also found to influence HRQL dimensions. For every one more year living with HIV, the risk of having problems in self-care, usual activities, and anxiety/ depression increased by 122%, 107% and 29% respectively. In addition, the HIV+ patients taking ART were about 2 times more likely to have poorer physical health as compared to those who had not yet met the criteria for ART. Furthermore, those without self-help group involvements were five times more likely to have problems in usual activities than others (Table 2-5).

Validity of EQ-5D instruments

Cronbach's alpha for the EQ-5D items was 0.86 for HIV+ population and 0.81 for general population, indicating a good internal consistency of the five EQ-5D dimensions. The correlation of EQ-5D index score and VAS score was good with Spearman' rank coefficient for HIV+ and general population was 0.53 and 0.41 respectively. EQ-5D instrument demonstrated a good cross-sectional construct validity which distinguished patients at different HIV progression (Table 2-2).

2.4. Discussion

This study, for the first time, measured HRQL in a nationally representative sample of adults living with HIV, and compared it with HRQL of a convenient sample of the general population in Vietnam. We identified substantial impacts of HIV/AIDS on physical and psychological well-being in adults living with HIV. Particularly, compared with the general population, the results indicated a considerable negative influence of HIV infection on psychological functioning, starting from the early stage of the HIV infection.

Several studies have found that physical functioning is worse in AIDS patients compared to those who have less advanced HIV disease³²⁻³⁴. Our findings were consistent with these prior works. In addition, we found that ART patients who had a history of injecting drugs perceived lower HRQL score than non-IDUs. Although problems in physical functioning were much higher at advanced HIV stage, we observed reported psychological problems at similar proportions across different HIV stages. This highlights the demand for early psychosocial support interventions and health care services for adults with HIV/AIDS, particularly IDUs, in Vietnam

Although ART has been rapidly scaled up in the country, it is necessary to make this service accessible to all those requiring treatment, which in turn improves quality of life of patients as well as treatment outcomes. In our study, barriers of access to health care services were identified as significant predictors of decreases in HRQL. This was in line with previous studies in Vietnamese settings where perceived stigma and access to HIV-related information influenced health seeking behaviors³⁵⁻³⁷. Popular HIV testing have been introduced in the country through friendly HIV voluntary testing and counseling (VCT) services^{7, 38}. In fact, scaling up ART services has the potential to encourage an earlier detection of HIV cases as the accessibility to ARV encourages testing for HIV infection. For the efficiency of HIV care and treatment programs, it is crucial to improve the quality of VCT services with particular focus on post-counseling and referrals^{37, 39}.

It is also important to notice that HRQL was influenced by concerns of individual's daily life such as job and educational opportunities of their affected children. This was consistent to the other observations in Vietnam^{35, 40, 41}. It somewhat reflected the stigmatization and discrimination of community against HIV-infected and -affected adults and children. In our study, involvements in self-help groups reduced the risk of having problems in usual activities. Literature revealed that self-help groups potentially increased health care utilization and reduced perceived stigma among HIV+ people^{35, 42-44}.

The limitation of our study included the recruitment of respondents which was referred by peer-HIV-educators. Because of that, we were not able to reach people who had not disclosed their HIV status, and those who were being at in-patient clinics. Several clinics-based surveys have showed a lower HRQL score among patients initiating treatment and/ or having severe opportunistic infections⁴⁵. However, given the fact that advanced HIV patients require life-long ART like other chronic illness, after treatment for opportunistic infections, most of them will be taking drugs at home. Besides, data collection methods included face-to-face interview might be subject to information bias. Finally, the lack of clinical indicators, such as CD4 and viral load, does not sufficiently reflect the disease progression of participants.

The EQ-5D instrument was shown to be able to measure population health in Vietnam. This study provides an initial norm of HRQL in general population in Vietnam that can be useful for identifying health-related problems in specific population such as HIV/AIDS. Nevertheless, the EQ-5D items showed a relatively high ceiling effect which is the percentage of "no-problem" responses.

This implies that the instrument might not have sufficient room to measure health improvements over time. Consequently, application of EQ-5D for measuring changes in health status in longitudinal assessment should, therefore, be considered.

As the first household survey on the HRQL in HIV+ population in Vietnam, this study provided comparable and helpful evidences for developing health care services and conducting economic evaluations of HIV care and treatment alternative strategies in Vietnam as well in other large-populations in low-income settings.

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2.6. Tables

Table 2-1. Socio-demographic profile of respondents

Characteristics	HIV+ (N=400)	Non HIV (N=420)	Total (N=820)	Statistic Z^a	p
Age (years)					
Median (IQR)	30 (27 - 33)	44 (35 - 54)	34 (29 - 45)	17.2	<0.001
	% (n)	% (n)	% (n)	Chi2^b	
Sex					
Male	62.8 (251)	60.0 (252)	61.3 (503)	0.7	0.42
Female	37.3 (149)	40.0 (168)	38.7 (317)		
Residence					
Urban	63.5 (254)	60.24 (253)	61.83 (507)	0.924	0.34
Rural	36.5 (146)	39.76 (167)	38.17 (313)		
Ethnics					
Kinh people	87.9 (369)	92.4 (388)	92.3 (757)		0.60
Others	7.4 (31)	7.6 (32)	7.7 (63)		
Marital status					
Living alone	58.3 (224)	17.2 (71)	37.1 (295)	143.9	<0.001
Living with spouse/ partner	41.7 (160)	82.8 (341)	62.9 (501)		
Level of education					
Secondary school and lower	69.5 (278)	49.8 (209)	59.4 (487)	34.1	<0.001
High school and upper	30.5 (122)	50.2 (211)	40.6 (333)		
Occupation					
Having a job	73.1 (285)	84.0 (351)	78.7 (636)	109.2	<0.001
Retired	0.3 (1)	11.7 (49)	6.2 (50)		
Unable to work	5.4 (21)	2.9 (12)	4.1 (33)		
Unemployed	21.3 (83)	1.4 (6)	11.0 (89)		

^aMann Whitney test

^bChi-square test

Table 2-2. Comparison of health-related quality of life between HIV+ population and general population

	HIV+ population			General population (N=420)	p-value
	Taking ART (N=225)	Not yet required ART (N=175)	All (N=400)		
EQ-5 Dimensions	n (%)	n (%)	n (%)	n (%)	
Mobility					
No problems	205 (91.1)	165 (94.3)	370 (92.5)	411 (97.9)	<0.001 ^a
Have problems	20 (8.8)	10 (5.7)	30 (7.5)	9 (2.1)	
Self-care					
No problems	217 (96.4)	173 (98.9)	390 (97.5)	417 (99.3)	0.051 ^a
Have problems	8 (3.5)	2 (1.1)	10 (2.5)	3 (0.7)	
Usual activities					
No problems	208 (92.4)	166 (94.9)	374 (93.5)	410 (97.6)	0.006 ^a
Have problems	17 (7.6)	9 (5.1)	26 (6.5)	10 (2.3)	
Pain/discomfort					
No problems	182 (80.9)	156 (89.1)	338 (84.5)	395 (94)	<0.001 ^a
Have problems	43 (19.1)	19 (10.9) ^b	62 (15.5)	25 (6.0)	
Anxiety/depression					
No problems	151 (67.1)	119 (68)	270 (67.5)	369 (87.9)	<0.001 ^a
Have problems	74 (32.9)	56 (32.0)	130 (32.5)	51 (12.1)	
EQ-5D Index score					
Mean (95% CI)	0.88 (0.85 - 0.91)	0.90 (0.88 - 0.93)	0.89 (0.87- 0.91)	0.96 (0.94 - 0.97)	<0.001 ^c
Median (IQR)	1.00 (0.85 - 1.00)	1.00 (0.85 - 1.00)	1.00 (0.85- 1.00)	1.00 (1.00 - 1.00)	<0.001 ^d
VAS score					
Mean (95% CI)	65.2 (63.3 - 67.1)	69.3 (66.9 - 71.8)	67.0 (65.5- 68.5)	81.6 (80.3 - 82.9)	<0.001 ^c
Median (IQR)	70 (50 - 75)	70 (60 - 80)	70 (60 - 80)	80 (75 - 90)	<0.001 ^d

^a 2x2 Khi-square Fisher's exact test for the difference in percentages of reported problems between HIV+ population and general population

^b Compared to HIV+ patients taking ART, Khi-square test gave p < 0.05

^c Adjusted Wald test

^d Kruskal-Wallis equality-of-populations rank test

Table 2-3: Health-related quality of life of HIV+ adults with and without history of injecting drug

Groups	N	EQ-5D Index score			VAS score		
		Mean	95% CI	p-value	Mean	95% CI	p-value
Taking ART	225						
non IDU	107	0.88	0.84 0.91	0.67 ^a	66.9	63.4 69.4	0.01 ^a
IDU	118	0.89	0.85 0.92		63.6	61.3 65.9	
Not yet on ART	175						
non IDU	84	0.90	0.86 0.93	0.14 ^a	71.0	68.1 73.9	0.85 ^a
IDU	91	0.91	0.88 0.93		67.8	64.9 70.7	
Overall	400						
non IDU	191	0.88	0.86 0.91	0.61 ^b	68.7	66.5 70.9	0.04 ^b
IDU	209	0.89	0.87 0.92		65.4	63.4 67.5	

^a Analysis of covariance to compare means adjusted for age and sex

^b Analysis of covariance to compare means adjusted for age, sex and disease progression

Table 2-4: Determinants of HRQL score in HIV+ populations

Predictors	EQ-5D Index score		VAS score	
	Coef.	95% CI	Coef.	95% CI
Predisposing factors				
Jobless vs. Working	-0.11 ^c	(-0.16; -0.07)	-9.90 ^c	(-13.44; -6.36)
Female vs. Male	-0.01	(-0.05; 0.03)	0.67	(-2.51; 3.85)
Single vs. married/ live with partners	-0.03	(-0.07; 0.01)	-1.93	(-5.07; 1.20)
Secondary school and below vs. higher	-0.02	(-0.06; 0.02)	-4.84 ^b	(-8.16; -1.52)
Age (years)	0.00	(-0.01; 0.00)	-0.12	(-0.36; 0.13)
HIV-related factors				
Years of living with HIV/AIDS	-0.02	(-0.04; 0.00)	0.72	(-1.16; 2.60)
Taking ART vs. not yet required ART	-0.02	(-0.06; 0.02)	-4.19 ^b	(-7.27; -1.11)
Historically injecting drug vs. Non	0.01	(-0.03; 0.05)	-3.33 ^a	(-6.40; -0.26)
Social support structure				
Have social supports vs. Non	0.01	(-0.06; 0.09)	2.16	(-3.85; 8.17)
Involve in self-help groups vs. Non	0.05	(-0.10; 0.00)	2.48	(-1.96; 6.92)
Difficulties in health care access:				
No vs. Yes	0.14 ^c	(0.07; 0.21)	6.42 ^a	(0.35; 12.49)
Barriers in education for children:				
No vs. Yes	0.13 ^a	(0.03; 0.22)	0.56	(-7.76; 8.87)

^a: p<0.05; ^b: p<0.01; ^c: p<0.001

Table 2-5: Predictors of having problems in each dimension of HRQL in HIV population

Predictors	Mobility	Self-care	Usual activities	Pain/discomfort	Anxiety/depression
Predisposing factors					
	4.8 ^c	13.4 ^b	2.9 ^a	3.0 ^c	2.5 ^c
Jobless vs. Working	(2.1; 10.9)	(2.6; 67.9)	(1.2; 6.7)	(1.7; 5.4)	(1.5; 4.1)
Female vs. Male	0.6 (0.2; 1.5)	1.1 (0.3; 4.5)	1.0 (0.4; 2.5)	1.3 (0.7; 2.3)	1.3 (0.8; 2.1)
Living alone vs. married/ live with partners	0.8 (0.3; 1.9)	1.6 (0.4; 6.1)	0.9 (0.4; 2.2)	1.4 (0.8; 2.5)	1.4 (0.9; 2.3)
Secondary school and below vs. higher	2.0 (0.7; 5.1)	0.5 (0.1; 1.7)	1.5 (0.6; 3.9)	1.5 (0.8; 2.9)	1.2 (0.7; 1.9)
Age (years)	1.0 (1.0; 1.1)	1.0 (0.9; 1.1)	1.0 (0.9; 1.1)	1.0 (1.0; 1.1)	1.0 (1.0; 1.1)
HIV-related factors					
Years of living with HIV/AIDS	1.5 (0.9; 2.4)	2.2 (0.9; 5.5)	2.1 ^a (1.2; 3.6)	1.1 (0.8; 1.5)	1.3 (1.0; 1.7)
Taking ART vs. not yet required ART	1.6 (0.7; 3.5)	3.1 (0.6; 14.7)	1.4 (0.6; 3.3)	1.9 ^a (1.1; 3.5)	1.0 (0.7; 1.6)
Historically injecting drug vs. Non-injecting	1.3 (0.6; 2.9)	1.3 (0.3; 4.6)	0.7 (0.3; 1.5)	1.2 (0.7; 2.1)	0.7 (0.5; 1.1)
Social support structure					
Have social supports vs. Not	1.7 (0.2; 14.1)	1.9 (0.2; 23.5)	1.6 (0.2; 14.5)	2.6 (0.6; 12.1)	0.5 (0.2; 1.2)
Involve in self-help groups vs. Not	1.9 (0.5; 7.3)	0.3 (0.1; 3.6)	6.3 ^a (1.2; 32.3)	1.8 (0.7; 4.1)	1.3 (0.7; 2.6)
Difficulties in health care access:	0.2 ^a		0.2 ^a	0.3 ^a	0.2 ^c
No vs. Yes	(0.1; 0.8)	-	(0.1; 0.8)	(0.1; 0.8)	(0.1; 0.4)
Barriers in education for children:	0.3		0.8	0.3 ^a	0.2 ^c
No vs. Yes	(0.1; 1.5)	-	(0.1; 7.1)	(0.1; 1.0)	(0.1; 0.6)

- : variable dropped; ^a: p<0.05; ^b: p<0.01; ^c: p<0.001

3. Changes in drug use are associated with health-related quality of life improvements among methadone maintenance patients with HIV/AIDS

3.1. Introduction

Antiretroviral treatment (ART) has dramatically reduced HIV-related mortality and morbidity, and has improved quality of life of HIV/AIDS patients receiving treatment¹⁻³. However, the effect of ART is less in injecting drug users (DUs) than in other patient groups⁴. Drug use is associated with severe co-morbidities, delayed access to ART, and more importantly, adherence difficulties once ART is started^{4,5}. Treatment of opioid dependence has, therefore, become an important component of HIV care in injection-driven HIV epidemics.

Vietnam has one of the fastest growing HIV epidemics in Asia, largely driven by drug injection^{5, 6}. According to the National Committee for AIDS, Drugs and Prostitution Prevention and Control, 146,731 DUs were recorded and managed in 90% of districts in the country⁷. Although HIV prevalence among DUs moderately decreased over the last decade, from 29.4% in 2002 to 18.4% in 2009, DUs remained the largest HIV risk group accounting for 44% of prevalent HIV cases⁷⁻⁹, and 50.6% of 15,713 newly detected HIV cases in 2009¹⁰. Approximately 254,000 people are thought to be living with HIV/AIDS; among those, 25% are at WHO HIV stage III/ IV or have a CD4 count < 250 cells/ μ L, and require ART¹¹. Comprehensive HIV/AIDS care and treatment were prioritized as a cost-effective intervention in the National HIV/AIDS Strategic Plan^{6, 12}. With

substantial supports from international donors, free-of charge HIV care and treatment services with antiretroviral drugs have rapidly scaled up in Vietnam¹²⁻¹⁴. However, the effectiveness of these interventions might be reduced as close to half of HIV patients were opioid dependent⁴. Since 2008, the Vietnam Ministry of Health created the first national Methadone Maintenance Treatment (MMT) program for DUs. Until then, the medical community had little experience with how opioid substitution benefits HIV care and antiretroviral treatment for HIV-positive DUs in the Vietnamese context¹⁵⁻¹⁷.

The health-related quality of life (HRQL) indicators are widely applied in the sphere of HIV/AIDS. HRQL complements more objective outcomes that incorporate virologic and immunologic measures, co-morbidities and death [20-22]. HRQL is associated with physiological and biomedical status of HIV patients. In addition, HRQL has a good correlation to the patient's compliance with ART, particularly if adherence was sustained¹⁸. In MMT patients, Winklbaaur et al. (2008) observed that even short-term opioid maintenance was significantly related to higher HRQL scores¹⁹. HRQL, therefore, could be used to predict the impact of MMT on care and treatment for HIV-positive DUs.

This study assessed the changes in drug use and HRQL during MMT; examined if these changes were different between DUs at early HIV stage and those at later HIV stages and receiving ART; and determined the impact of ongoing heroin use during MMT on HRQL among HIV-positive DUs in Vietnam.

3.2. Methods

Study setting

Two metropolitan areas with significant injection-driven HIV epidemics in Hai Phong and Ho Chi Minh City (Vietnam) were selected for the first national pilot MMT program. These cities represent geographical areas with established HIV epidemics in large populations of injecting DUs, and settings where comprehensive HIV interventions have been implemented in the country. The first 6 pilot MMT clinics were organized as standalone sites. Participants were first informed about the availability of MMT services by the local authority of HIV/AIDS control and then selected on voluntary basis.

Hai Phong is a port city of about 1.8 millions citizens on the Red River Delta in northern Vietnam. It has a DU population of approximately 9,500, among whom 75% are injecting drugs and 40-50% are currently living with HIV/AIDS^{14, 20}. The first 3 MMT pilot clinics in Hai Phong were established in 2008 in Le Chan, Ngo Quyen, and Thuy Nguyen Districts.

Ho Chi Minh City is the largest southern metropolitan centre in Vietnam with over 8 million residents. There are approximately 45,000 DUs in the city; 99% of whom are heroin users, mainly by injection²¹. Ho Chi Minh City has the largest HIV-positive population in Vietnam with 41,193 prevalent HIV-positive cases, and had 23.1% of total newly detected HIV cases in the country in 2009⁷. The MMT interventions in Ho Chi Minh City were piloted at District 4, District 6 and Binh Thanh District from May 2008.

Study design and participant recruitment

The Vietnam Administration of HIV/AIDS Control conducted a longitudinal cohort study of DUs recruited from January 2009 to October 2009. At baseline, patients were methadone-naïve, presented with drug use history, and did not have any severe health condition. After informed consent was obtained from volunteer participants, participants were tested for HIV at baseline. Repeated assessments were conducted at baseline, 3 months, 6 months and 9 months. We used structured questionnaires in interviews where respondents documented self-reported drug use behaviors. Opioid (heroin) confirmation urine tests were done every 3 months. A self-administered questionnaire was used to measure HRQL. In this pilot program, DU individuals (N=968) were recruited through 6 clinics. All participants received daily methadone free-of-charge under direct observation of health workers. Patients were not excluded from MMT if they continued opioid use as reported during interviews or confirmed by urine tests. The present study is a secondary analysis of the longitudinal assessments that included all participants who were HIV-infected at baseline (n=370).

This evaluation of the MMT program for HIV-positive DUs is a component of an overall project by the Vietnam Administration of HIV/AIDS Control. Its focus is to develop a framework for economic evaluation of HIV/AIDS interventions in Vietnam ²². A cost-benefit analysis of the overall project indicated significant societal benefits including cost savings from opioid abstinence, decrease in health care needs of DUs, and substantial reduction in risk of HIV transmission ²². These findings, among others, provided evidence to support the Government's decision to scale-up MMT services for 80,000 DUs by 2020 in Vietnam.

Health-related quality of life instrument

The HRQL instrument used in this study was WHOQOL-BREF, an abbreviated version of the WHOQOL-100 ²³. This instrument has 26 items covering 4 domains (Physical, Psychological, Social and Environment) and 2 general items (overall HRQL and General Health). The respondents answered each item using a five-points Likert scale ranging from 1 (Not at all) to 5 (Completely). For example, patients were asked to think about their life in the last 2 weeks in this question: “Do you get the kind of support from others that you need?” Answering options would be: “1- Not at all; 2- Not much; 3- Moderately; 4- A great deal; and 5-Completely”. Most items were scaled in a positive direction, where a value of one indicates low or negative perception, and five indicates high or positive perception. Negative items were reverse scored. For example, 5 for “Not at all” decreases to 1 for “Completely”; this band score was reversed using the formula: New Score = 6 - Original Score. Thus, the higher summary scores denote more favourable HRQL. In the morbidity domain, a higher score reflects a lower morbidity. Each item should contribute equally to the domain score, therefore, the ranges of raw domain scores are: Physical (7-35), Psychological (6-30), Social (3-15), and Environment (8-40). To improve the comparability of the measurement, we converted the domain scores of the original and modified instruments into a 0-100 scale using the formula:

$$\text{Transformed Scale} = \left(\frac{\text{Actual raw score} - \text{lowest possible raw score}}{\text{Possible raw score range}} \right) \times 100 \quad (1)$$

The Vietnamese version of the original WHOQOL-BREF instrument was developed following the protocol provided by the WHOQOL- Group ²⁴. In the preparation phase, a research group was formed and included health economists, infectious diseases physicians, preventive medicine specialists, and

linguistics expert. Another group of DUs with and without HIV/AIDS was also formed and included in the preparation phase. The Vietnamese version was created using forward-backward translation with subsequent reviews and discussions within and between the 2 groups. Patient cognitive debriefing forms were used to accelerate the process. In focus groups, participants were asked about additional socio-cultural or biomedical variables that should be included in the instrument. However, no new items emerged from these focus group interviews. Consequently, the Vietnamese version of 26 items was piloted in a conveniently selected small group of DUs for final amendments prior to data collection. Validation and psychometric properties of the measurement were tested following data collection. Methods are presented in the statistical analysis.

Statistical analysis:

Descriptive statistics were used for health status, socio-demographic and drug use-related characteristics of respondents. Chi-square and ANOVA tests were used to examine the differences between proportions or means.

Psychometric properties of WHOQOL-BREF: Confirmatory factor analysis was used to examine the construct validity of the Vietnamese-version. Six factors were extracted by the principle component analysis at an eigenvalue of 1.0. Orthogonal Varimax rotation with Kaisers' normalization was used to increase the interpretability of these factors. Spearman's correlations between domain scores, overall quality of life and general health status indicators were estimated for convergent validity. Internal consistency reliability of HRQL measurement, an average inter-item correlation, was estimated using Cronbach's alpha. In measuring groups' HRQL, a desirable Cronbach's alpha was set to be 0.7.

Evaluating the changes in HRQL during MMT:

Changes in the overall HRQL and domains scores were quantified using Cohen's effect size, which is defined as the magnitude of changes divided by standard deviations of the baseline measurements [28]. We also examined if the changes in HRQL would distinguish early HIV-positive patients from later stage (ART) patients using the etiological analysis described as below.

Examining the association of ongoing drug use and HIV stages with HRQL:

- **Propensity score:** In multivariate models, we examined the association of our exposures of interest, ongoing heroin use and HIV stages, and changes in HRQL. We assumed that the number of participants was disproportionate between exposure and non-exposure groups; thus, estimation would be biased. In addition, there might have been small numbers of patients with some certain characteristics that influenced the estimability of the models. Because of this, *propensity scores* were employed to minimize the potential effect of pre-existing differences between different groups of exposure ²⁵. A propensity score is defined as the conditional probability of belonging to a particular exposure group given a vector of observed covariates which summarizes information across potential confounders ²⁶. Propensity scores were estimated using logistic regression with exposures of interest as dependent variables. Predictors included socio-demographic characteristics, drug use history, and HIV stage and treatment status, adjusting for the longitudinal structure of data. A stepwise forward model building strategy ²⁷ was applied where variables were selected based on the log-likelihood ratio test. We adopted a p-value <0.05, and excluded variables at p-values >0.3. The equations are expressed as follows:

$$\text{LOGIT}[P(\text{DrugUse}|\text{SES}, \text{HIST}, \text{ART})] = \alpha + \sum_i \beta_{1i} \text{SES}_i + \sum_i \beta_{2i} \text{HIST}_i + \sum_i \beta_{3i} \text{ART}_i \quad (2a)$$

$$\text{LOGIT}[P(\text{ART}|\text{SES}, \text{HIST}, \text{DrugUse})] = \alpha + \sum_i \beta_{1i} \text{SES}_i + \sum_i \beta_{2i} \text{HIST}_i + \sum_i \beta_{3i} \text{DrugUse}_i \quad (2b)$$

Where:

- DrugUse: continued heroin use during MMT which was self-reported heroin use during the previous 3 months, self-reported heroin injection, or a positive opioid (heroin) confirmation urine test.
- ART = 1 means that patients were at a more advanced stage of HIV infection, and that they took both ART and MMT. ART=0: early HIV stages.
- SES represents socio-demographic characteristics of respondents,
- HIST represents a drug use history.

Propensity score is calculated as follows:

$$\text{PROPENSITY} = \text{Predict}[P(\text{DrugUse}|\text{SES}, \text{HIST}, \text{ART})] \quad (3)$$

- **The Generalized Estimating Equations (GEE) models** were estimated for longitudinal data on the association of changes in HRQL with ongoing heroin use and HIV stages using autoregressive working correlations structure within clusters or subjects^{28, 29}. The models adjusted for *propensity scores* with these exposures of interest.

$$\text{QOL}_{ij}(\text{Exposure}|\text{PROPENSITY}_i) = \alpha + \sum_{k=1}^6 \beta_{ijk} \text{PROPENSITY}_{ijk} + \lambda_{ij}(\text{Druguse})_{ij} + \varepsilon_{ij} \quad (4a)$$

$$\text{QOL}_{ij}(\text{Exposure}|\text{PROPENSITY}_i) = \alpha + \sum_{k=1}^6 \beta_{ijk} \text{PROPENSITY}_{ijk} + \lambda_{ij}(\text{ART})_{ij} + \varepsilon_{ij} \quad (4b)$$

Where:

- QOL: the overall HRQL or domains scores
- PROPENSITY is the propensity score stratified into 6 categories.
- Indices i, j represent the i^{th} measurement of the j^{th} subject.
- The symbol λ_{ij} : represents the differences in HRQL scores between patients with and without exposures of interest, adjusting for 6 strata of propensity scores and the longitudinal data structure.

Ethical consideration

The study protocol of the original cohort study was reviewed, and ethical approval was granted by Hanoi School of Public Health, Vietnam. Written informed consent was obtained from all participants. Respondents were able to withdraw from the cohort study at any time, and this did not affect their continuation of MMT. Our secondary data analysis was reviewed and approved by the Vietnam Ministry of Health, Administration of HIV/AIDS Control. Ethical approval was also granted by the Hanoi School of Public Health and the University of Alberta's Health Research Ethics Board.

3.3. Results

Socio-demographic characteristics of participants

All 370 patients diagnosed with HIV at baseline were selected for further analysis in this study. After 9 months, the number of patients decreased to 342 (92.4% of baseline). 337 patients received 4 repeated measurements (89.9%). Most of these patients were male (95.7%) and completed high school or below (97%). Mean age was 29.5 years (Table 3-1). Respondents' employment changed over

time with a decrement in the proportion of jobless from 39.7% at baseline to 31.3% in the third trimester ($\text{Chi}^2=6.24$, $p=0.013$). The proportion of persons having a stable job, however, did not improve significantly ($\text{Chi}^2=0.01$, $p=0.94$). Respondents living with other DUs accounted for 7.8% of the respondents at baseline and 4.2% during the follow-up.

Psychometric properties of HRQL measures

Table 3-2 shows the construct validity, convergent validity and reliability of the WHOQOL-BREF Vietnamese version for HIV-positive DUs. In factor analysis, six selected major factors accounted for 56.9% of the variance. The first factor, the Psychological dimension, accounted for 29.7% of the variance. All major factors had at least 3 items. Four original domain names were maintained in 4 parallel major factors. Two new domains (“Morbidity” and “Performance”, individual performance of functional and cognitive activities) were created based on factor loadings, the square root of domains’ variance explained by factors. Consequently, these 6 modified domains were used for examining the associations between the changes in HRQL and drug use behaviors.

Convergent validity for overall HRQL and general health were moderate or good (Table 3-2). Cronbach’s alpha of all domains was 0.81, indicating a good internal consistency reliability of the instrument. Cronbach’s alpha was moderate for Performance, Social Relationship and Performance domains, and acceptable for Morbidity, Physical and Psychological Health domains.

Drug use patterns, changes and magnitude of changes in HRQL over time

With their first opioid use at the age of 20.6 (95% CI = 20.1; 21.2), participants had used drugs for an average period of 6.7 years prior to entering the MMT

program (95% CI = 6.3; 7.1) (Table 3-1). The proportion of respondents with self-reported opioid use and positive heroin confirmation urine tests were initially 99.7% and 98.2%. This significantly decreased in the 2nd and 3rd trimesters of follow-up to 14.6% and 14.4%, respectively (Table 3-3). The kappa statistic (0.71) indicated a substantial agreement between reported heroin use and urine test.

Table 3-3 describes the changes in HRQL and subscale scores of HIV patients during MMT. The overall HRQL and domains scores rapidly increased over the first trimester, from 46.5 to 76.4, and then stabilized during the second and third trimesters. There were parallel variations in 6 domains' scores over the course of the study. Morbidity domain score was the highest (76.4 – 88.1), whereas the Social Relationships domain was the lowest (51.5 - 60.6). In the third trimester, scores slightly decreased, but this change was not significant (paired-t test, $p>0.05$, data not shown).

Figure 3-1 illustrates the magnitude of changes in HRQL and subscales over time using Cohen's effect size. Compared to baseline, Physical and Psychological domains had large improvements over the course of study. Measures of individual performance and social relationships moderately increased, while the morbidity and environment measures demonstrated small increments within the sample group.

Associations between drug use behaviors and HIV stages and HRQL

Results of the GEE models are shown in Table 3-4. Adjusting for propensity scores and intra-individual correlations, there were large decrements in overall

HRQL and all subscales' scores, especially in the psychological status among patients who continued to use heroin. During MMT, the overall HRQL of more advanced HIV patients who were also taking ART did not significantly differ from those not yet in need of ART. Across 6 domains, there was only a slight decrease in the morbidity domain among those patients who were taking ART (95% CI of difference = [-5.9; -1.2]).

3.4. Discussions

In this study, we observed a high retention rate in MMT among HIV-positive DUs over 9 month follow-up. The percentage of continued drug use and frequency of opioid use decreased along with significant improvements in HRQL of DUs at both advanced HIV-stages with ART and earlier HIV stages. Except morbidity, ART patients benefited from MMT to the same degree as early HIV-positive DUs. During MMT, patients with ongoing heroin use reported substantially lower scores in overall HRQL and specific HRQL domains.

We developed and validated a Vietnamese version of the WHOQOL-BREF. This was then administered to a sample of HIV-positive DUs. Using factor analysis, items of the Vietnamese version was reclassified into 4 corresponding domains and 2 emerging domains ("Morbidity" and "Performance"). This approach has also been applied in previous studies³⁰⁻³³. In practice, the reclassification of items using factor analysis helps create subsets of items that measure the same underlying factor. It also increases the measures' reliability and constructs validity^{34, 35}.

In many injection-driven HIV epidemics in Asia, drug use is illegal and characterized as “a social evil”^{36, 37}. Opioid users might be stressed by the financial burden of addiction, loss of their jobs, involvement in crime, and worrying about being arrested or having an overdose^{37, 38}. In addition, they may have experienced stigma and discrimination by family and community against DUs. Some were ashamed, self-stigmatized or lost their self-esteem^{38, 39}. In the first trimester of the study, changes in psychological health were initially rapid and then maintained over time. This could be explained by the release from the economic and social burden of addiction, and by the fact that those patients who were opioid abstinent could continue to be economically productive. In addition, DUs had supports from health care workers and family members, which might reduce DUs’ perceived stigma and improve their psychological status^{19, 38, 40, 41}. This could also be part of the explanation for an exceptionally high retention rate in this cohort of the pilot MMT program.

Focusing on HIV-positive DUs, we established the potential effectiveness of MMT on HIV care and treatment outcomes. The traditional approach in Vietnam for treating opioid dependence, which is compulsory detention in rehabilitation centers, may prevent HIV/AIDS patient’s access to ART in a timely manner or interrupt the treatment. HIV-positive DUs, who were opioid abstinent during MMT, might have better access and utilization of ART services^{16, 42}. A previous study reported lower perceived HRQL, particularly in mental health, among DUs compared to other HIV-positive groups in Vietnam. In this study, HRQL was also related to poor access to health care and psychosocial support services⁴³. In our current study, we observed the largest improvement in the Psychological domain. Scaling up MMT for DUs, therefore, could be an effective entry point for HIV

testing and other HIV care and treatment services in Vietnam. Several studies have also shown the impact of MMT retention on adherence to ART, viral suppression, and treatment outcomes ^{17, 44-47}. Our findings confirmed that if the patients were in compliance with MMT and did not continue to use heroin, their HRQL would significantly increase. Changes in HRQL domain scores were independent of ART, except for a minor decrement in “Morbidity”. This supports the recommendation for injection-driven HIV epidemics: integrating both MMT and ART services for drug abusers could improve the HIV care and treatment outcomes and HRQL in the Vietnamese setting.

Among 6 modified HRQL domains, Social Relationships had a modest improvement and lowest scores compared to other domains. We hypothesize that DUs could have complex social backgrounds ³⁷. Indeed, during the follow-up in the current study, very few of these DUs obtained stable jobs. This result highlights the need to provide vocational training services and livelihood supports for DUs to sustain the effectiveness of opioid substitution interventions. In contrast to the large early improvements in HRQOL, we observed slight decrements in the third trimester. Although these changes were not significant, they were consistent over all domains. It implies that efforts to maintain the initial achievements of this intervention are essential. Future studies that explore long-term impacts of MMT and identify predictors of ongoing heroin use would be helpful.

The strength of this study was the longitudinal assessments of a sufficient sample that supports the causal inference of changes in drug use and HRQL over time. In practice, the 9 months duration of follow-up might not be sufficient

to assess the sustainability of this intervention. Another limitation of this design was that we did not have a comparison group of those who were HIV-positive DUs without MMT. Continued opioid use during the previous month were self-reported by patients and might be biased; however, the Kappa statistics showed a good correlation of reported opioid use with urine tests during clinics visits. In addition, patients' report on their ongoing opioid use and positive urine test result were not disclosed, and patients were not treated differently. Notwithstanding these limitations, as the first national pilot MMT program, the results of this may be useful towards developing future services and interventions for HIV-positive DUs in Vietnam, as well as other injection-driven HIV epidemics. This experience could prove useful to other programs in resource limited settings.

MMT improved the HRQL among HIV-positive DUs in Vietnam. Changes in drug use behaviors are significant predictors of HRQL. The study supports the recommendation that integrating MMT to HIV care and treatment services could be beneficial for comprehensive HIV care and treatment for DUs.

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3.6. Tables

Table 3-1: Socio-demographic characteristics of participants

	Baseline		3 months		6 months		9 months		Chi ² / F statistic	p
	N	%	N	%	N	%	N	%		
Socio-demographics										
Age (years) mean (sd)	29.5	(5.9)	29.5	(5.9)	29.5	(5.9)	29.5	(6.0)	0.01	0.99
Gender										
Male	354	(95.7)	353	(95.7)	348	(95.9)	328	(95.9)	0.04	0.99
Female	16	(4.3)	16	(4.3)	15	(4.1)	14	(4.1)		
Marital status										
Single	218	(58.9)	193	(53.9)	203	(58.5)	196	(58.3)	6.50	0.69
Married/live w partner	120	(32.4)	131	(36.6)	117	(33.7)	113	(33.6)		
Divorced	30	(8.1)	33	(9.2)	27	(7.8)	24	(7.1)		
Widow/ widower	2	(0.5)	1	(0.3)	0	(0.0)	3	(0.9)		
Occupation										
Jobless	147	(39.7)	142	(38.5)	128	(35.3)	107	(31.3)	11.00	0.28
Freelancer	95	(25.7)	105	(28.5)	113	(31.1)	105	(30.7)		
Stable jobs	43	(11.6)	36	(9.8)	45	(12.4)	36	(10.5)		
Others	85	(23.0)	86	(23.3)	77	(21.2)	94	(27.5)		
Religion										
Buddhism	157	(42.4)	156	(42.3)	153	(42.2)	143	(41.8)	0.27	0.99
Others	42	(11.4)	42	(11.4)	40	(11.0)	36	(10.5)		
None	171	(46.2)	171	(46.3)	170	(46.8)	163	(47.7)		
Education										
Illiterate	3	(0.8)	3	(0.8)	3	(0.8)	3	(0.9)	0.18	0.99
Primary (Grade 1-5)	41	(11.1)	40	(10.9)	39	(10.8)	38	(11.1)		
Secondary (Grade 6-9)	187	(50.7)	187	(50.8)	185	(51.1)	172	(50.4)		
High school(Grade 10-12)	127	(34.4)	127	(34.5)	125	(34.5)	119	(34.9)		
Vocational/ College/University	11	(3.0)	11	(3.0)	10	(2.8)	9	(2.6)		
History of drug use										
Age of 1st drug use	20.6	(5.3)	20.6	(5.3)	20.6	(5.4)	20.8	(5.5)	0.05	0.98
Length of drug use (years) mean (sd)	6.7	(3.6)	6.7	(3.6)	6.7	(3.7)	6.8	(3.7)	0.05	0.98
Living with other drug user	29	(7.8)	15	(4.2)	15	(4.3)	14	(4.2)	7.30	0.06

Table 3-2: Factor loading, convergent validity and reliability of the WHOQOL-BREF in HIV+ drug users

Original domain	Items	Psychological	Physical health	Morbidity	performance	Social relationships	Environment
Physical health	Sleep and rest		0.54				
	Activities of daily living		0.80				
	Work Capacity		0.78				
	Pain and discomfort			0.85			
	Dependence on medicinal substances and medical aids			0.86			
	Energy and fatigue					0.61	
	Mobility					0.54	
Psychological	Thinking, learning, memory and concentration	0.43			0.46		
	Positive feelings	0.83					
	Spirituality / Religion / Personal beliefs	0.83					
	Bodily image and appearance					0.48	
Social relationships	Self-esteem		0.65				
	Negative feelings			0.59			
	Social support					0.69	
	Personal relationships					0.54	
	Sexual activity					0.60	
Environment	Freedom, physical safety and security	0.68					
	Physical environment (pollution / noise / traffic / climate)				0.50		
	Transport						0.51
	Financial resources		0.40				
	Opportunities for acquiring new information and skills				0.48		
	Participation in and opportunities for recreation / leisure activities					0.41	
	Home environment						0.61
	Health and social care: accessibility and quality						0.82
Convergent reliability	Overall HRQL	0.57	0.47	0.25	0.42	0.42	0.31
	General health	0.46	0.49	0.36	0.44	0.43	0.25
Reliability	Cronbach's alpha	0.82	0.80	0.74	0.68	0.62	0.61
	% floor	1.4%	0.0%	0.0%	0.0%	0.0%	0.0%
	% ceiling	0.5%	0.9%	56.1%	0.2%	0.1%	1.2%

Table 3-3: Changes in drug use patterns and HRQL in HIV+ patients over 9 months MMT

Drug use and HRQL	Baseline (370 patients)		3 months (369 patients)		6 months (361 patients)		9 months (342 patients)	
Changes in drug use	N	(%)	N	(%)	N	(%)	N	(%)
Drug use last 30 days	369.0	(99.7)	53	(14.4)	34.0	(9.4)	50	(14.6)
Frequency of use (times/ day (sd))	3.4	(1.3)	1.0	(1.2)	0.5	(0.8)	0.7	(1.3)
Drug administration methods								
- Drink	9	(2.3)	2	(3.6)	0	(0.0)	1	(2.0)
- Smoked	44	(11.4)	19	(34.5)	11	(34.4)	11	(21.6)
- Muscular injection	4	(1.0)	0	(0.0)	0	(0.0)	2	(3.9)
- Intravenous injection	329	(85.2)	34	(61.8)	21	(65.6)	37	(72.5)
Type of drug								
- Heroin	368	(95.1)	45	(84.9)	32	(94.1)	43	(82.7)
- Others	19	(4.9)	8	(15.1)	2	(5.9)	9	(17.3)
Opioid urine test (+)	362	(99.2)	167	(18.1)	105	(11.8)	125	(14.4)
Changes in HRQL	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Psychological health	46.5	(20.1)	63.9	(13.4)	65.0	(14.0)	63.2	(14.0)
Physical health	54.4	(14.8)	68.1	(12.1)	68.5	(12.4)	66.1	(13.0)
Morbidity	76.4	(23.5)	88.1	(17.7)	87.7	(18.2)	84.7	(20.1)
Performance	63.8	(13.3)	70.8	(12.7)	72.4	(12.4)	70.4	(12.7)
Social relationships	51.5	(12.3)	59.7	(11.5)	60.6	(11.8)	60.3	(12.2)
Environment	65.7	(12.8)	69.2	(11.8)	70.7	(10.8)	68.8	(11.5)
Overall composite score	59.7	(10.5)	70.0	(9.2)	70.8	(9.4)	68.9	(9.8)

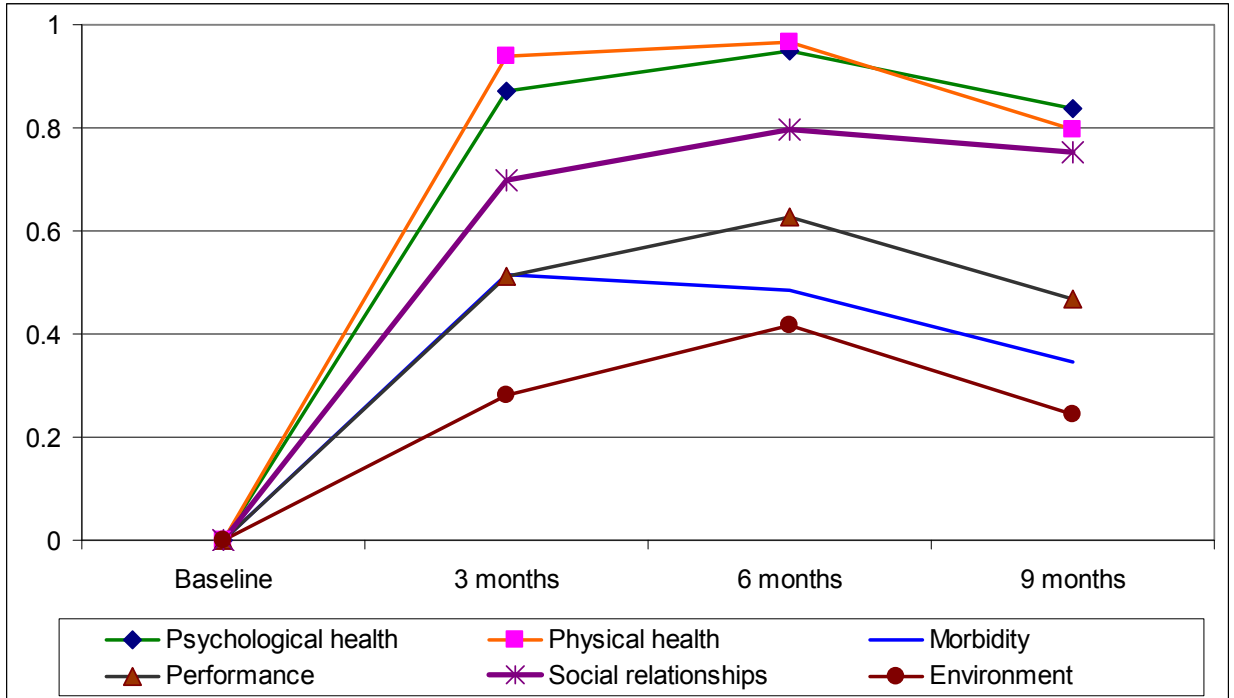
Table 3-4: Differences in HRQL with regards to drug use behaviors and HIV stages over 9 month MMT

	Coefficient*	Standard error	95% Confident interval		p value
Opioid confirmation test: Positive vs. Negative (n= 375; 525 events ~ 37.6%)					
Psychological health	-12.9	0.9	-14.7	-11.1	<0.001
Physical health	-10.1	0.8	-11.5	-8.6	<0.001
Morbidity	-7.5	1.1	-9.7	-5.3	<0.001
Performance	-5.3	0.7	-6.8	-3.9	<0.001
Social relationships	-7.0	0.7	-8.3	-5.7	<0.001
Environment	-2.8	0.7	-4.1	-1.5	<0.001
Average	-7.6	0.6	-8.7	-6.4	<0.001
Reported drug use: Positive vs. Negative (n= 375; 506 events ~ 35.0%)					
Psychological health	-14.1	0.9	-15.9	-12.4	<0.001
Physical health	-10.8	0.8	-12.3	-9.3	<0.001
Morbidity	-8.8	1.1	-11.0	-6.7	<0.001
Performance	-6.2	0.7	-7.6	-4.7	<0.001
Social relationships	-7.3	0.7	-8.6	-6.0	<0.001
Environment	-3.5	0.7	-4.8	-2.2	<0.001
Average	-8.4	0.6	-9.5	-7.3	<0.001
Reported injecting drug: Yes vs. No (n= 375; 420 events ~ 29.1%)					
Psychological health	-14.9	1.0	-16.8	-13.0	<0.001
Physical health	-11.6	0.8	-13.1	-10.0	<0.001
Morbidity	-9.7	1.2	-12.0	-7.4	<0.001
Performance	-6.5	0.8	-8.0	-5.0	<0.001
Social relationships	-7.5	0.7	-8.9	-6.1	<0.001
Environment	-3.9	0.7	-5.3	-2.6	<0.001
Average	-8.9	0.6	-10.1	-7.8	<0.001
ART patients: Yes vs. No (n= 375; 638 events ~ 44.2%)					
Psychological health	0.7	1.0	-1.2	2.7	0.45
Physical health	-0.3	0.8	-1.9	1.3	0.72
Morbidity	-3.5	1.2	-5.9	-1.2	<0.001
Performance	-0.2	0.8	-1.8	1.3	0.77
Social relationships	-0.3	0.7	-1.7	1.1	0.68
Environment	0.9	0.7	-0.4	2.3	0.18
Average	-0.5	0.6	-1.7	0.7	0.40

*The coefficients show the differences in domain scores and overall average scores comparing those with and without exposures of interest over 9 months adjusting for propensity score and longitudinal data structure.

3.7. Figure

Figure 3-1: Effect size of changes in overall HRQL and domains over time



4. Multilevel predictors of ongoing drug use during methadone maintenance treatment among HIV-positive patients in Vietnam

4.1. Introduction

Scaling up HIV/AIDS care and treatment services in large injection-driven HIV epidemics has been challenged by multiple problems ¹. Several studies have found a significant association between opioid dependence and delayed access, poor adherence and worse outcomes of antiretroviral treatment (ART) in HIV-positive drug users (DUs) ²⁻⁴. Therefore, opioid dependence treatment has become an essential component of HIV/AIDS Strategic Plans globally ^{5,6}.

Medication assisted treatment using methadone has been recognized as one of the most efficacious treatments for opiate addiction ⁷. Regular Methadone Maintenance Treatment (MMT) was associated with reductions in illicit drug use, criminal activity, and high-risk behaviors; and improvements in ART adherence, and quality of life of DUs ^{6, 8-11}. Efficacy of MMT has been found to be similar across culturally diverse settings, and between developed and developing countries ⁹. Nonetheless, relapses and ongoing drug use remain a primary problem in treating opioid dependence ^{6, 12}. Substantial relapse and drop-out rates in MMT cohorts have been observed in various settings, due to multiple causes, including patients' attributes, therapeutic process, environmental influences and program characteristics ¹³⁻¹⁷. A better understanding of these

barriers could guide program changes to improve retention and outcomes of MMT services^{18, 19}.

The social ecological model is a helpful tool to recognize, explore and address multiple influences which shape health behaviors²⁰. The model describes influences of health behaviors at various levels, from individual, interpersonal, community to society²¹. These factors interact with each other to impact health behaviors. Notwithstanding, few researchers have applied this model in the study of ongoing drug use during MMT, and little is known about injection-driven HIV epidemics in low-income settings.

Vietnam has a large injection-driven HIV epidemic with an estimated number of 254,000 people living with HIV/AIDS²². According to the National Committee for AIDS, Drugs and Prostitution Prevention and Control, 146,731 DUs have been recorded and managed in 90% of districts in the country²³. Although HIV prevalence among DUs moderately decreased over the last decade, from 29.4% in 2002 to 18.4% in 2009, DUs remained the largest HIV risk group. In 2009, 44% of prevalent HIV cases^{1, 23, 24}, and 50.6% of 15,713 of newly detected HIV cases were drug users²⁵. Since 2008, the Vietnam Ministry of Health has been piloting the first national MMT program for DUs. This service was developed in Vietnam during a transition of HIV/AIDS care and treatment policies globally, with a call for earlier ART and more comprehensive interventions in drug using populations²⁶⁻²⁸. It became important to determine how HIV-positive DUs would respond to MMT, and which factors may influence the impact of MMT program on HIV/AIDS care and treatment in Vietnam. Understanding these concerns is necessary if one is to develop effective intervention packages for DUs and make

programmatic decisions ⁹. In this analysis, we described changes in drug use behaviors, and applied the social ecological model to identify longitudinal predictors of continued drug use during MMT among HIV-positive DUs in Vietnam.

4.2. Methods

Study design and participants

We conducted a secondary data analysis of the pilot MMT cohort in Vietnam. Two metropolitan areas with largely injection-driven HIV epidemics, Hai Phong and Ho Chi Minh City, were first selected for implementing the MMT program. They represent geographical areas with established HIV epidemics in large populations of injecting DUs, and settings where comprehensive HIV interventions have been implemented. Both Hai Phong and Ho Chi Minh City had interventions and projects supported by the National HIV/AIDS Program, The U.S. President's Emergency Plan for AIDS Relief (PEPFAR), the Global Fund to fight AIDS, TB and Malaria, the World Bank/ DFID HIV project, and other global health initiatives. In 2009, Hai Phong had 31 harm reduction sites in 11 out of 14 districts targeting injecting drug users, sex workers and men who have sex with men; and 13 ART sites for adults, children and 9 antenatal care clinics for HIV-positive women. Meanwhile, Ho Chi Minh City had 80 harm reduction, 31 ART and 30 antenatal care sites, which were being operated in all 24 districts ²⁹. Since 2009, the Vietnam Administration of HIV/AIDS Control has conducted a multi-site longitudinal cohort study of all DUs recruited from January 2009 to October 2009 in 3 MMT clinics in Ho Chi Minh City (District 4, District 6 and Binh Thanh District), and 3 clinics in Hai Phong City (Le Chan, Ngo Quyen, and Thuy Nguyen

District). These clinics provided daily methadone for eligible DUs free-of-charge under direct observation of health workers. Patients at baseline were methadone-naïve, had a history of drug use, and did not have any severe health condition. All of them volunteered and gave informed consent to participate in the cohort study. Participants were tested for HIV at baseline. Repeated assessments of recruited DUs were conducted at baseline, 3 months, 6 months and 9 months. Self-reported drug use behaviors of respondents were obtained in interviews using structured questionnaires. Opioid (heroin) confirmation urine tests were done every 3 months. Among 968 patients recruited to the cohort, 370 (38.2%) were diagnosed with HIV at baseline and selected for further analysis.

Instruments and measures

Drug use behavior information was self-reported. In addition, heroin confirmation urine tests were conducted every 3 months. The primary outcomes of interest were continued drug use in repeated assessments. This could be determined by either self-reported drug use in the last month or positive heroin confirmation urine test at clinic visits.

The themes of the interview covered various levels of determinants influencing drug use behaviors. We used the social ecological model as the framework to explain predictors of ongoing drug use during MMT. This model classifies influential factors into 4 fundamental levels: individual, interpersonal, community and society. The idea of this model emphasizes on continuous interactions between individuals with their physical and social environment that helps understand health behaviors as well as develop comprehensive health promotion interventions³⁰.

- *Individual level* included biological and personal history factors that may increase the likelihood of ongoing drug use. Socio-economic characteristics included age, gender, marital status, ethnicity, religion, education level, income, employment and ability to work. Morbidity included Hepatitis B and C Virus (HBV and HCV) co-infections, opportunistic infections including TB, antiretroviral treatment, and other significant health concerns. History of opioid use included length of opioid dependence, age at the first opioid use, and frequency of use, overdose, drug detoxification and reasons of continued drug use prior to MMT.
- *Interpersonal level* included influences of family members, peers, and intimate partners and their drug use behaviors on individuals.
- *Community and societal factors* were those related to settings, infrastructure and broader social policies. In this study, we were interested in health care access through referral system, and availability and utilization of health and community support services, such as loans, legal support, education supports.

Statistical analysis

Descriptive statistics analysis was used to describe health status, socio-demographics, drug use behaviors, access and utilization of health care and social services. Associations between potential explanatory variables and continued drug use were first explored by univariate regression. In longitudinal assessments, patients' responses were repeatedly collected, therefore, independence assumptions of parametric models were violated, and parameter estimates would be biased. To accommodate the correlated nature of data, we used generalized estimating equations (GEE) for binary outcomes with a logit link

to estimate the population-average effects of covariates on the mean outcomes

31.

Since estimation of parameters in GEE is performed on quasi-likelihood, standard model selection such as stepwise techniques and the Akaike Information Criteria, which are based on likelihood methods, were not applicable³². Hence, in multivariate analysis, we used an 'a priori' defined model building strategy which considered candidates for GEE models if they had statistical significance of 0.30 or below in univariate analyses. In addition, we applied the Quasi-likelihood Information Criteria to select "autoregressive" and "exchangeable" data working structures for GEE models of having positive heroin confirmation urine test and self-reported drug use, respectively.

Ethical consideration

Our secondary data analysis was approved by the Vietnam Ministry of Health, Administration of HIV/AIDS Control, the Hanoi School of Public Health and the University of Alberta Research Ethics Board.

4.3. Results

Socio-demographic characteristics of participants

After 9 month follow-up, the remaining number of patients was 342 (92.4% of baseline), of those 337 (89.9%) received all 4 repeated assessments. Percentages of HBV and HCV positive individuals were 22.4% and 61.5%, respectively. With their first opioid use at a mean age of 20.6 (95% CI = 20.1; 21.2), participants had used drugs for an average period of 6.7 years (95% CI =

6.3; 7.1) prior to entering the MMT program (Table 4-1). Frequency of use was 3.2 times per day prior to MMT, and 20.3% had experienced an overdose. Heroin was the most common type of drug (95.1%), and 85.2% of respondents had a history of drug injection (data not shown). Almost all participants had been through some forms of structured detox programs (98.4%), such as compulsory drug rehabilitation centers for compulsory drug rehabilitation, and inpatient- or outpatient- detoxification; however, they reported relapsing because of craving for opioid (67.9%), feeling sadness and disappointment (45.1%), and peer influences (58.2%) (Table 4-1).

Changes in drug use behaviors during MMT

The proportion of self-reported drug use last month and positive urine tests was initially 99.7% and 98.2%. During MMT, these indicators rapidly decreased to 18.1% and 14.4% after 1 trimester, and then plateaued over the next 2 trimesters. The kappa statistic of self-reported drug use and heroin confirmation urine test showed an inter-rater agreement of 0.71 (86.7% agreement), indicating a substantial agreement between reported drug use and urine test. Percentage of reported drug injection also changed accordingly, from 88.7% to 10.8% after 9 months (Figure 4-1).

Changes in access to and utilization of health and social services

Table 4-2 describes the changes in selected characteristics of respondents over 9 month MMT cohort. We observed a large reduction in the number of hospital admissions among respondents, but only a small change in the proportion having health concerns. A high proportion of participants had been referred over 9 months to health services, such as: voluntary HIV testing and counseling (VCT)

(69.1%), treatment of opportunistic infections (OI) (47.9%), and tuberculosis (TB) treatment (51.2%). However, referrals to social support services such as social integration (40.2%), loan, housing (17.9%) or legal services (13.7%) were small. Noticeably, during the 3rd trimester only 5.1% participants utilized social integration services, including vocational and skills training, and job referrals and placement services.

Factors associated with ongoing drug use during MMT in HIV-positive DUs

Table 4-1 and 4-2 present crude odd ratios of the associations between continued drug use and potential predictors in univariate GEE analysis. Having a positive urine test was significantly positively associated with: taking ARV (OR=1.55), higher frequency of drug use in the past (OR=1.76 for increased 1 time/day), peer pressure and enticement (OR=1.71), whereas negatively associated with: being referred to TB treatment (OR=0.61), OI treatment (OR=0.72), mental health care (OR=0.61), peer-education (OR=0.64), social services (OR=0.48), and legal services (OR=0.48). Significant positive predictors of reported ongoing drug use included: taking ARV (OR=1.27), peer pressure (OR=1.22), craving (OR=1.55), having health concerns (OR=1.61), and receiving TB treatment (OR=2.36). Besides referrals to health care and social services, protective factors of reported drug use also included marriage (OR=0.65), living with wife or husband (OR=0.63) and children (OR=0.59), and having economic dependent (OR=0.40),

Table 4-3 shows the adjusted odds ratios (AOR) in GEE models with multilevel predictors including individuals, interpersonal, family, health care, and social services. Participants who had economic dependents (AOR=0.33), or been

referred to TB clinics (AOR= 0.53) were less likely to report ongoing drug use over 9 month MMT. Significant positive predictors of reporting continued drug use were: having health concerns (AOR= 1.54), and had TB treatment (AOR= 3.11). Craving (OR=1.54) and taking ARV (AOR= 1.43) positively predict drug use, however, this association had “borderline” statistical significance with p-value = 0.06 and 0.08, respectively. As for having positive urine tests, its significant predictors included: taking ARV (AOR= 2.05), frequency of drug use prior to MMT (AOR= 1.62 for increased 1 time/ day), and induced by peers (AOR= 1.79).

4.4. Discussion

This study determined the changes in drug use patterns and multilevel predictors of continued drug use during MMT in HIV-positive DUs. We observed a high response rate (89.9%) and substantial reduction in drug use over 9 month MMT. We identified multilevel predictors of ongoing drug use during MMT including morbidity (taking ART, TB treatment, had health concerns), pre- MMT drug use behaviors (frequency of use and craving), interpersonal and familial attributes (peer pressure and cohabitants), and access and utilization of health care and social services.

Individual characteristics positively associated with ongoing drug use, such as higher historical frequency of opioid use and relapse prior to MMT, are consistent with findings of other studies in drug treatment ^{12, 33, 34}. In addition, significant predictors emerged from this analysis were interpersonal and social interactions at family, community and service delivery levels. We observed protective factors

to drug use including marriage, living with wife or husband and children, access to health care, peer education, social integration and legal services. Meanwhile, factors with strong positive association with continued drug use were: peer pressure and enticement and living with sexual partners. Those patients who have unstable family and social status showed greater likelihood of continued heroin use. This finding underlines the importance of the social context and drug network to the provision and success of addiction treatment ³⁵.

In Vietnam, the HIV epidemic is concentrated on high-risk groups including injecting DUs and commercial sex workers, and a large proportion of sex workers are also using drugs. These high-risk behaviors are illegal and characterized as “social evils” in Vietnamese society. Thus, there might be hidden networking to facilitate illicit drug use. This can lead to group pressure on MMT patients to continue their drug behaviors if they do not develop a more stable social status. The impact of MMT programs, therefore, could be limited if other social supports services were not in place ^{36, 37}. It is important to enable patients to adopt new healthy behaviors, and improve their social functioning by integrating them into the workforce and education system ⁶. Vocational training and livelihood support services for those who are taking MMT may also be interventions that provide long-term achievements.

The large proportion of respondents with self-reported health concerns and co-morbidities indicated higher health care needs of HIV-positive DUs than HIV-negative ones. Poor health status in this population was indicated both by reported health concerns and by antiretroviral therapy since official policy during the study period recommended ART initiation only for patients whose absolute

CD4 cell count was <250 cells/ml. The causal relationship between drug use and deterioration in health status could be bidirectional--drug use would be expected to lead to more severe deterioration in health status. It is also possible that advanced disease stage could increase the risk for continued drug use, which would explain the observed association between continued heroin use and ART use. Our analysis showed a greater likelihood of continued drug use in patients taking ART or having TB treatment. Both NNRTI antiretroviral drugs and even more, rifampin, lower serum methadone levels through induction of hepatic sector, enzymes. As for TB patients, service referral was a protective factor, but TB treatment was a significant predictor of ongoing drug use, The contradictory associations indicates that the disease doesn't contribute to ongoing drug use, but the treatment of TB might increase its likelihood. These effects could be an important part of the explanation for the observed association between ART use or TB treatment on one hand and opiate relapse^{38, 39}. The program training and implementation should systematically incorporate awareness of potential drug interactions and anticipate the need for methadone dose adjustment in patients on ART or TB therapy.

The strength of this study was the longitudinal assessments of a sufficient sample that supports the causal inference of multilevel predictors of ongoing heroin use. Several limitations of this study should be acknowledged. First, the drug use behaviors were recalled and self-reported, which might lead to information biases. However, previous studies showed that reported drug use of those recruited through community-based or out-reach program to be both accurate and reliable^{12, 40} and these findings were confirmed in our study by the good correlation with objective urine opiate testing. Secondly, the 9 month follow-

up might not be sufficient to assess the sustainability of this intervention. Besides, we did not have information on severity of ongoing drug use given the limitation of secondary data use. Finally, in this analysis, we did not have a comparison group of those who were HIV-positive DUs without MMT. Notwithstanding, as the first national pilot MMT program, the results of this study are useful for developing comprehensive HIV/AIDS care and treatment for HIV-positive DUs in Vietnam, as well as in other injection-driven HIV epidemics. This experience could prove useful to other programs in resource limited settings.

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4.6. Tables

Table 4-1: Baseline individual and familial characteristics of respondents and crude odd ratios for drug use relapse in univariate GEE models

Characteristics	(N=370)		Crude OR of Drug Use Relapse	
			(+) Urin Test	Reported
I. Individual				
1.1. Demographic				
	Mean	(95% CI)		
Age	29.5	(28.9; 30.1)	0.98	0.98*
Income per month	5.78 ^b	(5.16 ^b ; 6.40 ^b)	1.06 ^a	1.01 ^a
	N	(%)		
Male sex	354	(95.7)	0.74	1.13
Ethnicity: - Kinh people	348	(94.0)	0.73	0.58
Religion: - Buddhism	351	(94.9)	0.74	0.39*
Under High school education	231	(62.6)	1.34*	0.97
Married	120	(32.4)	0.87	0.65**
1.2. Morbidity				
Taking ARV	180	(48.7)	1.55**	1.27*
HBV	82	(22.4)	1.04	1.12
HCV	225	(61.5)	0.76	0.89
1.3. History of drug use				
	Mean	(95% CI)		
Age at first drug use	20.6	(20.1; 21.2)	0.99	0.99
IDU length	6.7	(6.3; 7.1)	1.02	0.98
Frequency of drug use (times/day)	3.2	(3.1; 3.4)	1.76***	n/a
	N	(%)		
History of drug detoxification	364	(98.4)	0.49*	0.59
Reason for drug relapsing:				
- Peer pressure and enticement	212	(58.2)	1.71**	1.22*
- Desire, craving for drug	247	(67.9)	1.14	1.55**
- Sad and disappointed	164	(45.1)	1.12	0.92
History of overdose	75	(20.3)	1.13	1.06
II. Family				
Have economic dependents	10	(2.7)	1.30	0.40**
Cohabitants:				
- Parents	316	(85.4)	0.70*	1.08
- Husband or wife	100	(27.0)	0.81	0.63**
- Children	99	(26.8)	0.94	0.59**
- Sibling	213	(57.6)	0.88	1.19
- Relatives	44	(11.9)	0.64*	1.07
- Partners	13	(3.5)	1.86*	1.26
- Alone	4	(1.1)	0.96	n/a

Note: * p < 0.3; ** p < 0.05; ***p < 0.01

^a Odd ratio of higher income,

^b Million Vietnamese dong in 2009 (1 USD = 17,800 dong)

n/a: not applicable.

Table 4-2: Changes in individual, interpersonal and services-related predictors of drug use relapse in univariate GEE models (N=370)

Characteristics	Baseline		3 months		6 months		9 months		Crude OR	
	<i>n (%)</i>		<i>n (%)</i>		<i>n (%)</i>		<i>n (%)</i>		(+) Urin Test	Reported
I. Individual										
1.1. Demographic										
Employment										
Unemployed:	147	(39.7)	142	(38.5)	128	(35.3)	107	(31.3)	1.00	1.20
- Unworkable due to illness	64	(17.3)	32	(8.9)	29	(8.4)	19	(5.7)	1.27	1.21
- Can't get a job	39	(10.5)	21	(5.9)	9	(2.6)	13	(3.9)	0.59*	1.11
1.2. Morbidity										
Had hospital admission last 3 months	131	(35.4)	9	(2.4)	12	(3.3)	15	(4.4)	1.20	1.12
Had health concerns	61	(16.5)	96	(26.8)	63	(18.2)	71	(21.1)	0.91	1.61**
III. Interpersonal										
Not satisfied with cohabitants	15	(4.1)	5	(1.4)	8	(2.3)	3	(0.9)	0.95	0.46
Have conflicts with others	79	(21.4)	24	(6.7)	24	(6.9)	16	(4.8)	1.14	1.32
Have IDU cohabitant	29	(7.8)	15	(4.2)	15	(4.3)	14	(4.2)	0.94	1.11
Had injected partners	45	(32.4)	15	(8.1)	18	(10.7)	21	(13.0)	0.98	1.00
IV. Services access and utilization										
4.1. Referral										
VCT	253	(68.8)	253	(70.7)	225	(64.8)	232	(69.1)	0.86	0.80*
OI treatment	106	(28.7)	140	(39.1)	149	(42.9)	161	(47.9)	0.72*	0.83
TB treatment	133	(36.0)	161	(45.0)	162	(46.7)	172	(51.2)	0.61**	0.64**
Mental health care	35	(9.5)	82	(22.9)	81	(23.3)	105	(31.3)	0.61**	0.59**
Other health service	32	(8.7)	28	(7.8)	13	(3.8)	15	(4.5)	1.32	1.29
Social integration services	71	(19.2)	93	(26.1)	125	(36.0)	135	(40.2)	0.74*	0.90
Peer-education	79	(21.4)	122	(34.1)	128	(36.9)	132	(39.3)	0.64**	0.73*
Social services (loan, housing,)	20	(5.4)	40	(11.2)	49	(14.1)	60	(17.9)	0.48**	0.40***
Legal services	10	(2.7)	27	(7.5)	33	(9.5)	46	(13.7)	0.48**	0.47**
4.2. Utilization										
VCT	222	(60.2)	220	(61.5)	119	(34.4)	131	(39.0)	1.01	1.19
OI treatment	20	(5.4)	16	(4.5)	18	(5.2)	44	(13.1)	0.97	1.19
TB treatment	26	(7.1)	12	(3.4)	10	(2.9)	24	(7.1)	1.31	2.36**
Mental health care	0	(0.0)	1	(0.3)	2	(0.6)	0	(0.0)	n/a	n/a
Other health service	15	(4.1)	12	(3.4)	6	(1.7)	10	(3.0)	0.90	1.21
Social integration services	13	(3.5)	21	(5.9)	22	(6.4)	17	(5.1)	1.08	1.37
Peer-education	28	(7.6)	33	(9.2)	25	(7.2)	27	(8.0)	0.50*	0.58*
Social services (loan, housing,...)	3	(0.8)	3	(0.8)	5	(1.5)	5	(1.5)	0.49	n/a
Legal services	1	(0.3)	3	(0.8)	0	(0.0)	3	(0.9)	n/a	1.29

Note: * p < 0.3; ** p < 0.05; ***p < 0.01

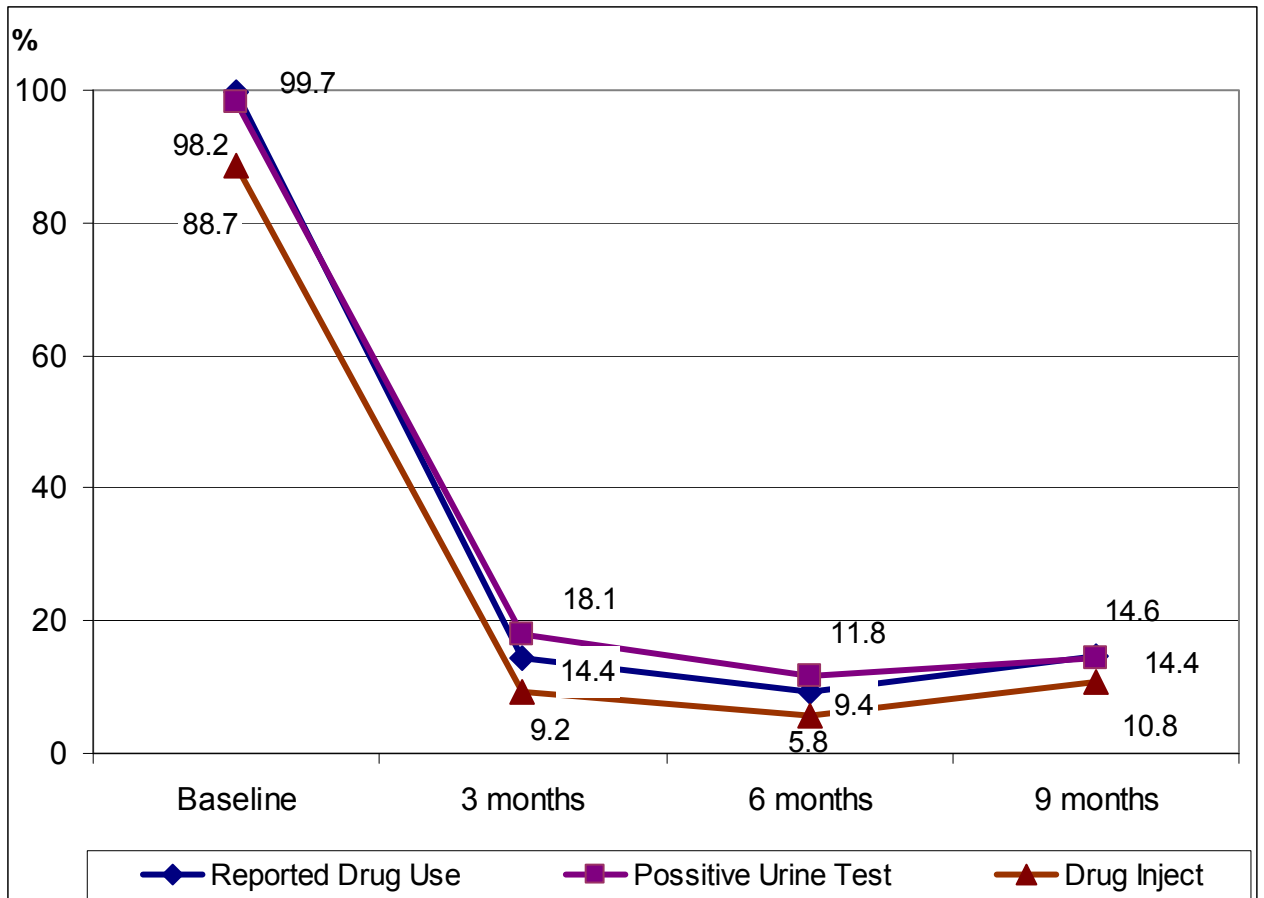
n/a: not applicable.

Table 4-3: Multivariate GEE analysis of predictors for drug relapse during 9 month MMT in HIV+ drug users

	Reported Drug Use			(+ Urine Test		
	AOR (95% CI)		p	AOR (95% CI)		p
I. Individual						
1.1. Demographic						
Age	0.97	(0.94; 1.00)	0.06			
Religion: - Buddhism	0.41	(0.13; 1.28)	0.13			
Under High school education				1.30	(0.84;2.02)	0.24
Married	0.88	(0.36; 2.16)	0.78			
Employment:						
- Can't get a job				0.46	(0.19; 1.13)	0.09
1.2. Morbidity						
Taking ARV	1.43	(0.96; 2.13)	0.08	2.05	(1.36; 3.09)	<0.001
Had health concerns	1.54	(1.01; 2.37)	0.05			
1.3. History of drug use						
Frequency of drug use (times/day)				1.62	(1.18; 2.23)	<0.001
History of drug detoxification						
Reason for drug relapsing:						
- Induced by peers	1.32	(0.89; 1.98)	0.17	1.79	(1.16; 2.74)	0.01
- Desire, craving for drug	1.53	(0.99; 2.37)	0.06			
II. Family						
Have economic dependents	0.33	(0.12; 0.88)	0.03			
Cohabitants:						
- Parents				0.84	(0.53; 1.34)	0.46
- Husband or wife	0.86	(0.33; 2.22)	0.76			
- Children	0.81	(0.41; 1.62)	0.56			
- Relatives				0.65	(0.32; 1.33)	0.24
- Partners				2.00	(0.94; 4.25)	0.07
III. Interpersonal						
Had injected partners	4.93	(0.66; 36.79)	0.12	2.94	(0.59; 14.59)	0.19
IV. Services access and utilization						
4.1. Referral						
VCT	0.97	(0.62; 1.52)	0.89			
OI treatment				1.29	(0.69; 2.44)	0.43
TB treatment	0.53	(0.31; 0.91)	0.02	0.55	(0.30; 1.00)	0.05
Mental health care	0.91	(0.50; 1.65)	0.75	0.80	(0.45; 1.42)	0.45
Social integration services				0.99	(0.61; 1.62)	0.98
Peer-education	1.19	(0.71; 2.01)	0.51	0.77	(0.44; 1.34)	0.35
Social services (loan, housing)	0.59	(0.25; 1.43)	0.25	0.77	(0.35; 1.70)	0.51
Legal services	0.78	(0.29; 2.10)	0.63	0.77	(0.32; 1.84)	0.55
4.2. Utilization						
TB treatment	3.11	(1.46; 6.60)	<0.001			
Peer-education	0.62	(0.26; 1.50)	0.29	0.61	(0.28; 1.35)	0.22

4.7. Figure

Figure 4-1: Percentage of drug use relapse in HIV+ drug users over 9 month MMT cohort



5. Cost - effectiveness of methadone maintenance treatment for HIV-positive drug users in Vietnam

5.1. Introduction

Over the last decade, Vietnam experienced one of the fastest growing HIV epidemics among drug injection populations in Asia¹⁻³. There are an estimated 170,000 illicit opioid users who constitute approximately 50.6% of newly detected and 67.0% of cumulative HIV cases in the country^{1, 4, 5}. Drug use has been recognized not only as the driver of the spread of HIV, but also a major barrier to access to and utilization of antiretroviral treatment (ART) services¹.

Both biological nature and socioeconomic impacts of drug dependence have been challenging the scale-up of ART services towards universal access goals. A recent review by Wolfe (2010) showed that internationally injecting drug users had considerably low access to ART, only 25% of them in 2008¹. Moreover, ART was found to be less effective in HIV-positive patients with history of drug use than other patients groups. Drug dependence negatively affects treatment adherence, and increases the development of drug resistance^{6, 7}. In Vietnam, illicit opioid use is attached to “social evils” that shapes stigma and discrimination of family and community against drug abusers^{8, 9}. Huge cost of addiction and health care, unemployment, involvement in crime, and the fear of being arrested or overdose are burdening those households affected by both addiction and HIV/AIDS^{9, 10}. Treatment of opioid dependence has, therefore, become an integral component of ART services for HIV-positive drug users.

Opioid substitution using methadone has been recognized as one of the most efficacious therapies for opiate addiction¹¹. Effectiveness of methadone maintenance treatment (MMT) has been found to be similar across culturally diverse settings, and between developed and developing countries¹². However, economic evaluations have shown heterogeneous cost-effectiveness ratios ranging from 1,501 USD to as much as 48,575 USD per quality-adjusted life year (QALY) gained^{1, 7, 13}. In addition, very few of them were conducted in resource-scarce settings where large injection-driven HIV epidemics exist. Since the introduction of MMT in 2008, there has been little experience how it benefits HIV care and treatment for drug users in the Vietnamese context¹⁴⁻¹⁶. This study assessed the incremental cost-effectiveness of a multi-site MMT program for HIV-positive drug users in Vietnam from the health service provider perspective.

5.2. Methods

Study population and data source

The first national MMT pilot program was implemented in Hai Phong and Ho Chi Minh City, two metropolitan areas with large injection-driven HIV epidemics. Six standalone MMT clinics were established in District 4, District 6, Binh Thanh District, Le Chan, Ngo Quyen, and Thuy Nguyen District in 2008. Since 2009, the Vietnam Administration of HIV/AIDS Control has been conducting a multi-site longitudinal study of all drug users recruited from January to October 2009. The cohort included 968 patients who were methadone-naïve, had a history of drug use, and did not have any severe health condition. Patients received daily methadone free-of-charge under direct observation of health workers. Recruited drug users were assessed at baseline, 3 months, 6 months and 9 months. Self-

reported drug use behaviors were obtained in patient interviews using structured questionnaires. Opioid (heroin) confirmation urine tests were done every 3 months. Findings of the overall project have been recently published in Vietnam¹⁷. In this secondary data analysis, we selected a sub-group of all 370 patients who were diagnosed HIV-positive at the baseline. Cost-effectiveness of MMT was analyzed over a 9-month period.

Health Services Costs

The costs of providing MMT services in these pilot clinics in 2008 have been analyzed and made available¹⁸. Both capital and recurrent costs were collected:

- *Capital costs*: were those associated with the establishment of standalone MMT clinics, including house renovation, equipments, initial training for health workers, and others. These costs were not depreciated over years in the cost analysis; instead, they were divided by the number of patients. Since this pilot study has been financially supported by international donors, and it was their policy to subsidize one-time establishment costs, these costs might not incur in other settings where integration to existing health facilities is possible. In addition, the allocation of costs for building facilities or lands was not applied. Therefore, recurrent costs would be more of interest if the government wants to scale-up the service, and used for this economic evaluation.
- *Recurrent variable costs*: were usual output-related costs including salary for staffs, daily methadone dose, urine tests and consumables.
- *Recurrent fixed costs*: included site operation and maintenance, medication import and distribution, and allocation of management costs at provincial and central levels.

The unit costs and components, evaluated for the year 2008, were inflated to 2009 Dollars by the change in the Consumer Price Index (1.069). We used the annual average exchange rate of 1 USD = 18,120 Vietnamese Dong in 2009.

Measuring health outcome

In the MMT cohort, health-related quality of life (HRQL) was measured at baseline and every 3 months of the follow-up using the WHOQOL-BREF (World Health Organization Quality of Life – Brief Version), an abbreviated version of the WHOQOL-100¹⁹. It has a profile of 26 items covering 4 domains (namely physical, psychological, social and environment) and 2 general items (overall HRQL and general health). The respondents answered each item using a Likert scale. For example, patients were asked to think about their life in the last 2 weeks in this question: “Do you get the kind of support from others that you needs?” Answering options would be: “1- Not at all; 2- Not much; 3- Moderately; 4- A great deal; and 5-Completely”. Measurement properties and development of the Vietnamese version of this tool have been reported elsewhere²⁰.

Quantifying the effectiveness

Effectiveness of MMT intervention on HIV care and treatment for drug users was quantified in QALY gained over 9 months. QALY is a composite outcome indicator which takes into account both the length of life and HRQL. A QALY places a weight on time in different health states in which a year of perfect health is worth 1, and a year of less than perfect health is worth less than 1. Death is considered to be equivalent to 0, however, some health states are given negative scores as worse than death.

The major component of QALY is the assignment of preference values, or “utilities”, to different health states. Utilities could be measured using preference-based quality of life instruments, such as EQ-5D (Euroqol – 5 dimensions) or HUI (Health Utility Index) ²¹. In Vietnam, Tran et.al. assessed utilities of HIV-positive patients and general populations in 2009 using EQ-5D and a visual analogue scale, making it possible for comparing health outcomes across interventions in this population ²².

Since the WHOQOL-BREF is a generic health profile measure, it does not yield preference weights. Therefore, we derived utility from WHOQOL-BREF using a conversion approach^{21, 23}. Tran et al. compared the performance of WHOQOLHIV-BREF and EQ-5D in 155 Vietnamese patients with HIV/AIDS, and developed a model to estimate the coefficients of 6 domains in the modified WHOQOL-BREF in predicting EQ-5D score ²⁴. We applied these coefficients to convert changes in HRQL domains scores of patients in the MMT cohort into the changes in QALYs. Firstly, average changes in domains scores of the WHOQOL-BREF in our MMT intervention were calculated. These changes were then converted to utilities using derived coefficients. Consequently, QALYs of each patients group were estimated using the utilities over 3 repeated assessments multiplied by the length of follow-up. The equations are expressed as follows:

$$QALYs = 0.25 \times \sum_{i=1}^3 (\beta_1 \times PSY_i + \beta_2 \times PHY_i + \beta_3 \times MOR_i + \beta_4 \times PER_i + \beta_5 \times SOC_i + \beta_6 \times ENV_i)$$

Where:

- QALYs is the total QALYs gained over 9 month follow-up.

- $\beta_1=0.0229$, $\beta_2=0.0122$, $\beta_3=0.0127$, $\beta_4=0.0050$, $\beta_5=0.0114$, $\beta_6=-0.0106$: The derived coefficients of Psychological, Physical, Morbidity, Performance, Social Relationships and Environment domains of the Vietnamese WHOQOL-BREF in predicting EQ-5D score.
- PSY_i , PHY_i , MOR_i , PER_i , SOC_i , ENV_i : the changes in Psychological, Physical, Morbidity, Performance, Social Relationships and Environment domains of the Vietnamese WHOQOL-BREF over the trimester i^{th} .
- 0.25: the duration between 2 assessments (year).

Cost - Effectiveness Analysis

We assessed the intervention by comparing differences in costs of MMT compared to non-MMT over the increments in effectiveness. Assuming that other health care costs remained the same over MMT intervention, we used MMT service costs as the difference in costs. Incremental Cost-Effectiveness Ratio (ICER) was determined, and then compared with the cost-effectiveness thresholds defined by the World Health Organization ^{25, 26}. Interventions with incremental cost per 1 QALY gained less than a country's GDP per capita are considered as “very cost-effective”, and interventions with the corresponding ratios between 1 and 3-times the GDP per capita are “cost-effective”. According to the National General Statistics Office, the GDP per-capita of Vietnam in 2009 was 1113.4 USD ²⁷.

Statistical Analysis:

Descriptive statistics were used to describe the health status, socio-demographic and drug use-related characteristics of respondents. HRQL and QALYs are presented as mean and 95% confidence intervals. A Student t-test was used to

examine the differences between means of incremental effects in different patients groups.

To adjust for time-dependent confounding in longitudinal data analysis, we applied a recently introduced technique, the inverse probability-of-treatment weights, to estimate the effect of MMT on HRQL ^{28, 29}. This method uses propensity score-based weighting estimator to adjust follow-up assessments to represent the entire population, and provides unbiased treatment effect ²⁸. We first constructed the propensity score of responses to treatment during MMT. A propensity score was defined as the conditional probability of belonging to a particular exposure group given a vector of observed covariates which summarizes information across potential confounders ³⁰. Propensity scores were estimated using logistic regression with responses to MMT as dependent variables. Predictors included socio-demographic characteristics, drug use history, and HIV stage and treatment status, family structure and support, adjusting for the longitudinal structure of data. A stepwise forward model building strategy was applied where variables were selected based on the log-likelihood ratio test ³¹. We adopted a p-value <0.05, and excluded variables at p-values >0.3. The equations are expressed as follows:

$$\text{LOGIT}[P(\text{MMT} | \text{SES}, \text{HIST}, \text{DrugUse}, \text{FAM})] = \alpha + \sum_i \beta_{1i} \text{SES}_i + \sum_i \beta_{2i} \text{HIST}_i + \sum_i \beta_{3i} \text{DrugUse}_i + \sum_i \beta_{4i} \text{FAM}_i$$

Where:

DrugUse: continued heroin use during MMT which was self-reported heroin use during the last 3 months, self-reported heroin injection, or a positive opioid (heroin) confirmation urine test.

MMT= 1: means that patients were taking MMT at the follow-up assessment. MMT=0: patients were lost-to-follow up or died.

SES: represents socio-demographic characteristics of respondents,

HIST: represents a drug use history.

FAM: represents familial structure and supports.

Propensity score is calculated as follows:

$$\text{PROPENSITY} = \text{Predict} [P(\text{MMT} | \text{SES}, \text{HIST}, \text{ART}, \text{FAM})]$$

The inverse probability-of-treatment weight is constructed and then used as a frequency weight:

$$\text{Inverse Probability Weight (IPW)} = \frac{1}{\text{Inverse Logit (PROPENSITY)}}$$

5.3. Results

Characteristics of respondents

Of 370 HIV-positive patients, 95.7% were male; mean age was 29.5 (95% CI = 28.9 - 30.1). Mean age at the first drug use was 20.6 (95% CI = 20.1- 21.2), and participants had used drug for an average period of 6.7 years (95% CI = 6.3 - 7.1) prior to MMT. Heroin was the most common type of drug (95.1%), and 85.2% of respondents had a history of drug injection. There were 180 (48.7%) patients at an advanced HIV stage and taking ART; 65 (17.6%) patients were diagnosed as tuberculosis positive. During the follow-up, the percentage of patients who ever reported ongoing drug use or injection in the previous month

was 30.5% and 20.5%, respectively. At clinic visits, 32.7% patients were tested at least once positive for heroin.

Unit costs of the MMT services

The monthly recurrent unit cost of MMT services in 2009 was 21.0 USD per patient¹⁸. Variable and fixed costs accounted for 82.6% and 17.4%, respectively.

The cost of methadone dose was 18.8% of the total recurrent costs.

Effects of MMT on HRQL and QALYs

Table 5-1 describes the changes in HRQL domain scores in HIV-positive drug users who were taking or not-yet-required ART over 9 month-MMT. Comparing the increments in domain scores to the standard deviation at baseline, we observed large increments in the physical and psychological health, small rises in the environment, and moderate changes in 3 remaining domains. The number of QALYs gained for non-ART patients was 0.075 (95% CI = 0,062- 0.088), and for ART patients 0.077 (0,064- 0.090).

Figure 5-1 and 5-2 describe the variation in QALYs gained by drug use during MMT. Ongoing drug use, especially continued injection, was largely limiting the improvements in QALYs of both ART and non-ART patients. Among those ART-patients with drug abstinence, we observed stabilized improvements in QALY over the course of the study.

Cost-effectiveness and sensitivity analysis

Over 9 month MMT, the overall ICER per 1 QALY gained was \$ 3,550.5, approximately 3.2 times GDP per capita, classifying MMT for HIV-positive drug

users as a “borderline” cost-effective intervention. Table 5-2 presents the variation of incremental effects by selected characteristics. The underlying assumption was that MMT interventions possibly enabled patients to cease substance abuse, and then improved their health status. However, ongoing drug use during MMT were found to be negatively associated with HRQL improvements²⁰. In addition, higher likelihood of ongoing drug use was seen in those patients taking ART or TB treatment along with MMT³². In the one-way sensitivity analysis, patients who ever received a positive heroin confirmation urine test, and those reported using drug or injecting had smaller increments in QALYs than others. In addition, incremental effect of women was significantly lower than that of men, and, having ART or TB treatment was not likely to change the incremental effects of MMT intervention. ICER varied as high as 4,636.9/QALY (~4.2 times GDP per capita /QALY) in female groups, and as low as 3,364/QALY (~3.0 times GDP per capita /QALY) in those without continued drug injection (Table 5-2).

5.4. Discussion

These findings suggest that providing MMT for HIV-positive drug users in Vietnam was accompanied by QALY improvements, and may be cost-effective from the health service provider perspective. MMT improved QALYs of both early HIV-positive and ART patients by 0.076 QALY over 9 months, approximately 0.101 QALY per year. This increment equals 0.52 standard deviation of the utility of HIV-positive population in Vietnam, indicating the potential of MMT to bring about clinically important changes in HIV-positive drug users²²

To date, this is the first cost-effectiveness analysis of providing MMT for HIV-positive patients in large injection-driven HIV epidemics in the developing world ¹. The ICER in our study was equivalent to 3 times Vietnam GDP per capita, a threshold recommended by WHO to identify cost-effective interventions. In addition, this ratio was very much lower than cost-effectiveness thresholds of developed countries, for example, 50,000 USD/QALY in the United States, 20,000 - 30,000 GBP/QALY in the United Kingdom, or 20,000 - 100,000 CDN/QALY in Canada ²¹. Sensitivity analysis determined that this result was relatively robust against changes in various patients groups; however, high attention should be paid on those patients who reported ongoing drug use or injection.

The number of QALYs gained in our study was higher than those observed in other studies ^{13, 33}. This could be explained by the large increase in psychological dimension measured using the modified WHOQOL-BREF, which in turn substantially contributed to QALY. Tran et. al (2011) explained the way by which MMT benefits drug users in Vietnam that included the release from social and economic burden of addiction, and supports from health care givers and family members ²⁰. The outcomes of MMT programs, however, have been challenged by the continuation of drug abuse ²⁰. In this study, we confirmed that patients continuing drug use or injection had smaller health benefits, which underlines the importance of maintaining drug abstinence during MMT.

Treatment of opioid dependence is critical in sustaining the impact of ART on HIV-positive drug users. Lucas (2006) found better virologic and immunological outcomes among those patients receiving ART at MMT clinics. In addition, by integrating MMT and ART services, patients' adherence to ART treatment could

be sustained by direct supervisions of health workers ³⁴. In our analysis, we found similar impacts of MMT for advanced HIV-positive patients taking ART. If these patients are drug abstinent, QALYs improvements during MMT will be stable. This finding supports the recommendation that in injection-driven HIV epidemics, integrating both MMT and ART services for drug users could improve HIV care and treatment outcomes.

The strength of this study involved the analysis of empirical data to estimate the changes in health outcomes of HIV-positive patients during MMT. In addition, we employed a longitudinal study design with repeated assessments of a sufficient sample that increase the measurement properties and causality inference. In practice, the 9 months duration of follow-up, however, might not be sufficient to assess the sustainability of this intervention. The latter decrease observed in early HIV-positive groups suggests that longer follow-up study would be of interest in the future. Another limitation of this design was that we did not have a comparison group of those who were HIV-positive drug users without MMT. Notwithstanding, as the first national pilot MMT program, results of this study are useful for developing services and interventions for drug users in Vietnam, as well as other injection-driven HIV epidemics.

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5.6. Tables

Table 5-1: Changes in WHOQOL-BREF domain scores and QALYs gained over 9 month MMT

Domains (Band score)	Baseline Mean (SD)	Changes in domain scores			QALYs gained Mean (95% CI)
		3 rd month	6 th month	9 th month	
Not yet required ART (N=190; 51.4%)					
					0.075 (0.062; 0.088)
Psychological (3; 15)	8.64 (2.36)	2.02	2.23	1.96	0.031 (0.025; 0.037)
Physical (4; 20)	12.66 (2.36)	2.44	2.44	1.83	0.018 (0.015; 0.022)
Morbidity (3; 15)	12.42 (2.86)	1.26	1.24	0.66	0.009 (0.005; 0.013)
Performance (6; 30)	21.50 (3.18)	1.45	2.19	1.39	0.006 (0.004; 0.008)
Social relationship (5; 25)	15.33 (2.44)	1.54	2.12	1.67	0.014 (0.010; 0.017)
Environment (3; 15)	10.79 (1.60)	0.48	0.70	0.45	-0.004 (-0.006; -0.002)
ART patients (N=180; 48.6%)					
					0.077 (0.064; 0.090)
Psychological (3; 15)	8.46 (2.47)	2.19	2.31	2.11	0.034 (0.028; 0.041)
Physical (4; 20)	12.83 (2.43)	1.83	1.98	1.88	0.016 (0.012; 0.019)
Morbidity (3; 15)	12.01 (2.86)	1.42	1.33	1.14	0.012 (0.008; 0.015)
Performance (6; 30)	21.29 (3.15)	1.70	1.69	1.75	0.006 (0.004; 0.007)
Social relationship (5; 25)	15.36 (2.51)	1.57	1.57	1.94	0.013 (0.009; 0.016)
Environment (3; 15)	11.05 (1.46)	0.36	0.50	0.25	-0.003 (-0.005; -0.001)

Table 5-2: Sensitivity analysis of the ICER of 9 month MMT intervention

Characteristics	N (%)	Incremental Effects (QALY)			ICER	~ times GDP per capita, 2009
		Mean	95% CI	p-value		
All participants	370	0.076	(0.067; 0.085)		3,550.5	3.2
Taking ART						
- Not yet required	190 (51.4)	0.075	(0.062; 0.088)	0.78	3,609.7	3.2
- Yes	180 (48.5)	0.077	(0.064; 0.090)		3,490.5	3.1
Ever had (+) urine test						
- No	249 (67.3)	0.077	(0.066; 0.088)	0.65	3,485.2	3.1
- Yes	121 (32.7)	0.073	(0.057; 0.088)		3,694.2	3.3
Ever reported drug use						
- No	257 (69.5)	0.078	(0.067; 0.089)	0.52	3,462.1	3.1
- Yes	113 (30.5)	0.071	(0.055; 0.087)		3,773.1	3.4
Ever reported drug injection						
- No	294 (79.5)	0.080	(0.070; 0.090)	0.06	3,364.0	3.0
- Yes	76 (20.5)	0.059	(0.041; 0.078)		4,535.8	4.1
Study settings						
- Ho Chi Minh City	126 (34.1)	0.070	(0.056; 0.084)	0.38	3,825.3	3.4
- Hai Phong	244 (65.9)	0.079	(0.067; 0.090)		3,428.8	3.1
Ever diagnosed TB						
- No	305 (82.4)	0.076	(0.066; 0.086)	0.94	3,542.5	3.2
- Yes	65 (17.6)	0.075	(0.054; 0.096)		3,587.8	3.2
Sex						
- Male	354 (95.6)	0.077	(0.067; 0.086)	0.36	3,513.5	3.2
- Female	16 (4.3)	0.058	(0.020; 0.097)		4,636.9	4.2

5.7. Figures

Figure 5-1: Incremental QALYs in ART patients with and without ongoing drug use during MMT

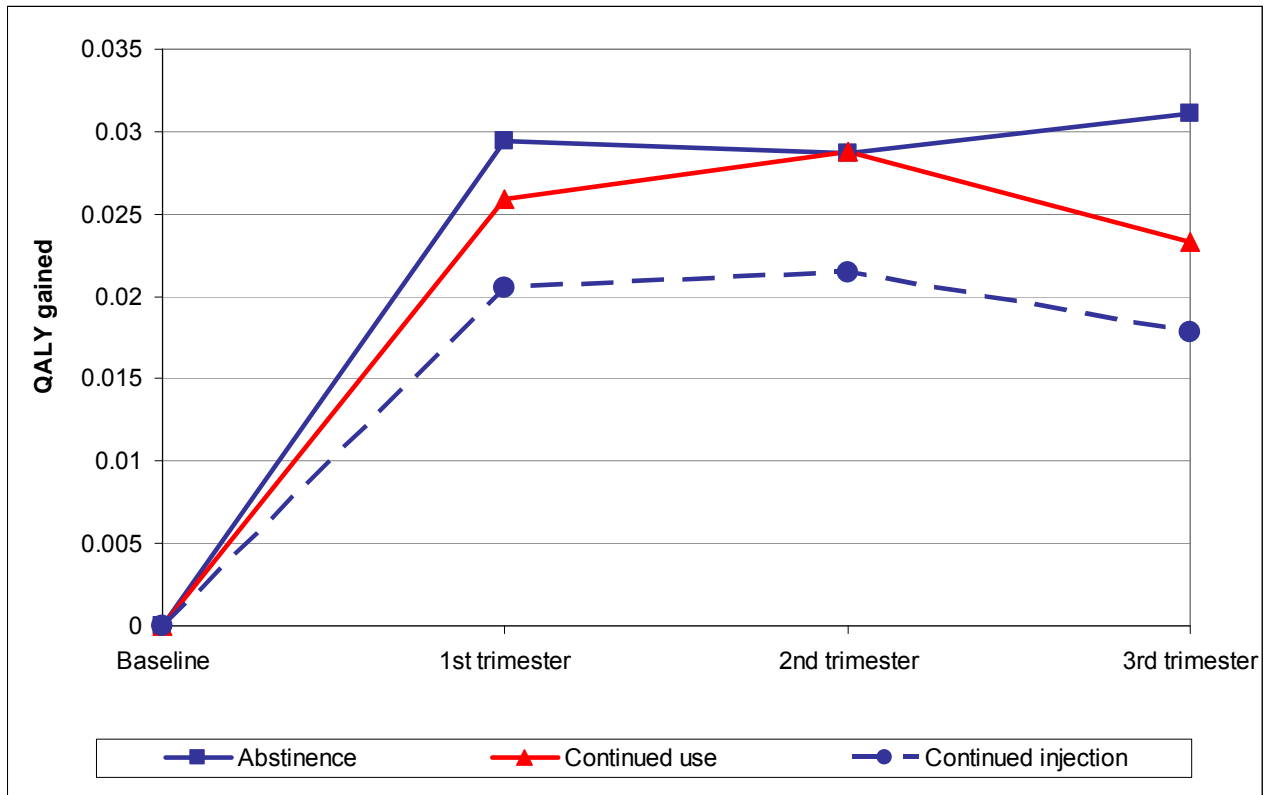
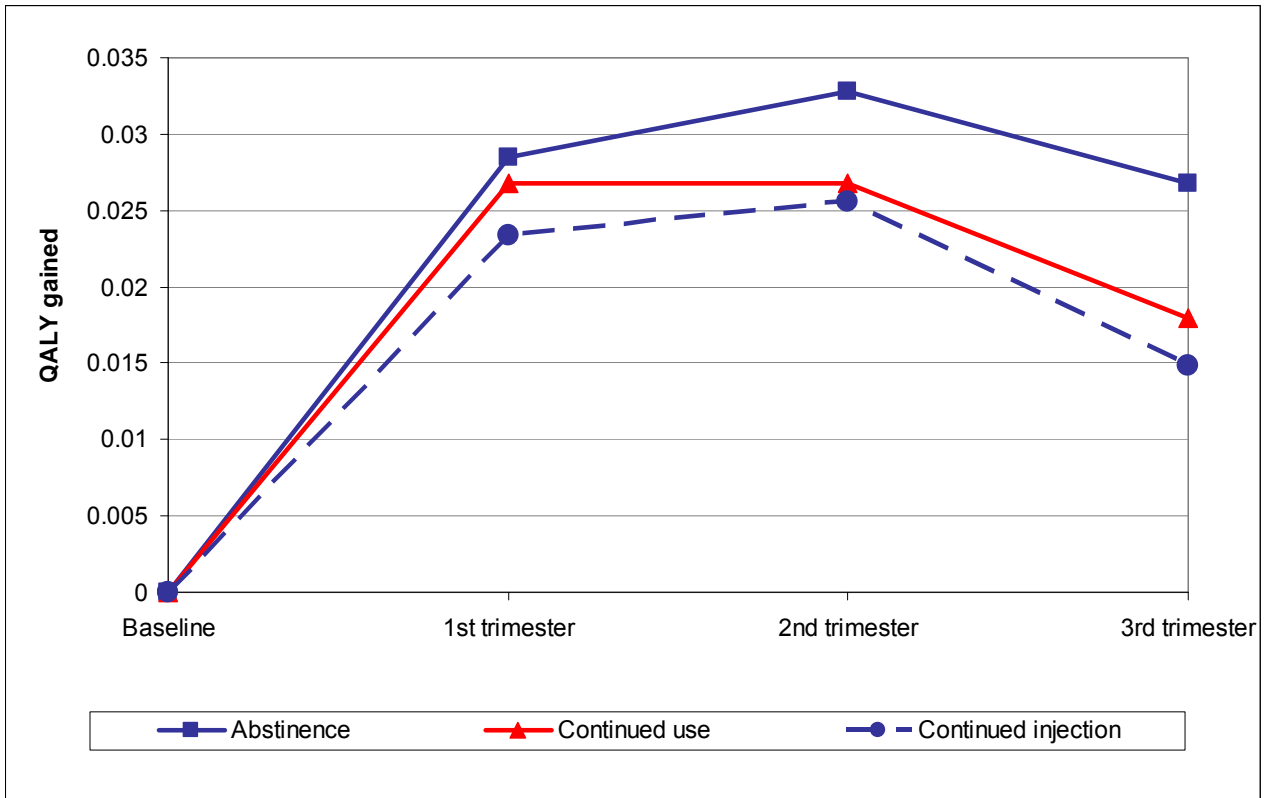


Figure 5-2: Incremental QALYs in non-ART patients with and without ongoing drug use during MMT



6. Cost-effectiveness of integrating methadone maintenance and antiretroviral treatment for HIV-positive DUs in an injection-driven HIV epidemic

6.1. Introduction

Asia and the Pacific has experienced the second highest burden of the HIV epidemic, which is largely driven by drug injection¹. In this region, there are about 3.9 million drug users (DUs) accounting for more than a half of the total DUs in the world². Among Asian countries, Vietnam has a typical course of the regional HIV epidemics, which emerged in drug injecting populations, and then concentrated in high-risk groups³. According to the Ministry of Labor, Invalids and Social Affairs, there were 146,731 DUs recorded in 90% districts, and 70% HIV cases were DUs^{4, 5}. Social and biological barriers associated with illicit drug use have substantially confined the government's efforts to halt the epidemic as well as achieve the goal of Universal Access to HIV/AIDS treatment³.

Globally, antiretroviral treatment (ART) has dramatically reduced HIV-related mortality and morbidity, and has improved quality of life of HIV/AIDS patients receiving treatment⁶⁻⁸. With substantial supports from international donors, free-of-charge HIV care and treatment services with antiretroviral drugs have rapidly scaled up in Vietnam⁹⁻¹¹. However, the effect of ART has been smaller in injecting DUs than in the other patient groups^{2, 12}. Drug dependence is a major obstacle to ART adherence, which is central for achieving virologic treatment success^{13, 14}. Moreover, Tran et al. (2011) found that during ART, DUs had

significantly lower Health-Related Quality of Life (HRQL) than non-DU patients, particularly in the psychological and social functioning. Consequently, there has been an increasing interest to examine the role of opioid dependence treatment in HIV/AIDS care and treatment for DUs ^{15, 16}.

Methadone maintenance treatment (MMT) has been widely recommended as an efficacious therapy for drug addiction treatment. Since 2009, the Vietnam Ministry of Health has piloted the first national MMT program for DUs. Tran et al. (2011) have shown that MMT is associated with changes in drug use behaviors that improved health outcomes among DUs ¹⁷. However, in the Vietnamese context, there is little experience with how MMT benefits ART for DUs ^{2, 18}. Besides, for long-term sustainability of the health system, it is necessary to identify alternatives to integrate MMT with the current health services delivery system. The purpose of this study was to evaluate the cost-effectiveness of integrating MMT with ART for HIV-positive DUs in Vietnam.

6.2. Methods

Antiretroviral treatment services and scope of analysis

The Vietnam National HIV/AIDS care and treatment guideline, adopt from the WHO (2006), determined the eligibility criteria for antiretroviral therapy (ART) at WHO HIV stage 3 and 4, or a CD4 count less than 250 cells/ μ l ^{19, 20}. The management of HIV-positive DUs is not significantly different from that of other patient groups. HIV-positive DUs, eligible for ART, are provided first line regimens including Zidovudine/ Stavudine + Lamivudine + Nevirapine for main regimens, and Zidovudine/ Stavudine + Lamivudine + Efavirenz for alternatives.

The guideline recommends the use of Directly Observed Therapy (DOT) to support patients' adherence if it is feasible or required ¹⁹.

The pilot MMT program in Vietnam included a sub-group of 370 HIV-positive DUs (age: mean \pm SD:29.5 \pm 5.9years; 95.7% male). Impact of the pilot program on HIV-positive DUs has been published elsewhere. In this study, subjects included HIV-positive DUs who were eligible for but not yet received both ART and MMT. We used the conventional ART service for DUs as the reference group, namely "ART", in which patients did not receive any drug substitution therapy during ART. We compared it with 2 other strategies: 1) the ART-MMT strategy where patients received ART and MMT in standalone clinics, as currently delivered in Vietnam; and 2) the integrated DAART-MMT model, where patients were taking ART regimens under the direct supervision of health workers together with methadone during daily clinic visits.

Model structure and assumptions

To evaluate the costs and consequences of each ART strategy, we developed a decision-tree model to represent patient's transitions over different health states during the course of intervention ²¹. In each stage of the model, patients were assigned a transition probability to different health states where they were likely to move. These states then incurred corresponding services costs and health outcomes, such as viral suppression, loss-to follow up and survival. We adhered to guidelines on Decision Modeling in Economic Evaluation of Health Technologies to develop the model and calibrated its parameters against current HIV epidemic trends and policy interests in Vietnam ²²⁻²⁴.

Figure 6-1 illustrates the decision tree and its progression stages. The conceptual framework for evaluating changes in health states of these patients groups included the hypotheses that ongoing drug use negatively affects HIV care and treatment outcomes, such as increased probability of virological failure, and that MMT supports drug abstinence among HIV-positive DUs^{17, 25}. In addition, by integrating ART and MMT services, direct supervision of health workers could sustain patients' adherence to ART regimens and improve virologic outcomes of ART²⁶⁻²⁸.

In the model, hypothetical DUs had an unsuppressed viral load prior to ART. During ART, patients might achieve one of the following states: virologic suppression, progressing to virologic rebound, or death. Virological treatment failure was defined as patients experienced virologic rebound of more than 400 copies/ mL^{26, 27}. These patients then required regimen switches. In Vietnam, approximately 9.0% patients had 1st line ART failure after the 1st year, while 2nd line regimens accounted for only 2.44% of all patients who are currently taking ART^{1, 29-31}. Therefore, we assumed that the coverage of 2nd line regimens was 27.1% among those patients who needed it. However, this might be misleading since treatment failure is only reliably diagnosed by viral load measurement and this is not routinely done in follow up in Vietnam. Since 3rd line ART regimens are not available in Vietnam, patients with 2nd line treatment failure principally discontinued ART³¹.

The "Stop ART" state included those patients who had virological failure without other treatment options, loss-to-follow up, or who chose to discontinue ART. We

assumed that patients who had virologic suppression, but then discontinued ART would develop virologic rebound rapidly. As a result, all patients in “Stop ART” group had unsuppressed viral loads.

The DAART - MMT was expected to improve patients’ compliance to ART and then support virologic treatment ²⁷. We assumed that the percentage of ongoing drug use during MMT were similar between the MMT-ART and the MMT-DAART strategies ¹⁷. However, patients in each service delivery model were assumed to adhere differently to ART; hence, the likelihood of developing virologic rebound or death was different ²⁷. The decision tree did not take into account switches between ART regimens in the same line, changes or discontinuations of ART because of treatment-related toxicity, or potential interactions of methadone and ART drugs since the impact of these attributes to MMT responses and outcomes were unavailable. However, we take into account the changes in costs of different regimens by weighting them in the average unit costs.

Perspective and time frame

The costs and outcomes of these strategies were analyzed from the perspective of the Vietnamese health care system. Time frame for comparison was 1-year follow-up. This period was sufficient to detect the impacts of interventions on changes in ART outcomes. In addition, there has been little experience on either virologic response of Vietnamese patients during ART over 1 year or long-term impacts of MMT^{32, 33}. We used annual discounting rate of 5% for costs and health outcomes.

Health Services Costs

Unit costs of MMT and ART services are described in table 6-1. The ART costs were based on a recent ART costing study by the Vietnam Authority of HIV/AIDS Control³⁴. The study surveyed a nationally representative sample of 17 ART clinics in different geographical regions (north, south and central), levels (central, provincial and district), including their financing sources (e.g. PEPFAR, Global Fund or National HIV/AIDS Program). The costing methods included both step-down costing for overhead and depreciation costs, and micro costing for labor, drugs, materials, and diagnostic services. The average unit cost was weighted using the proportion of different regimens and costs for each regimen.

The costs of MMT services were analyzed for the first 5 pilot sites in Hai Phong and Ho Chi Minh City, including both capital and recurrent costs of MMT services in 2008³⁵. We extracted their *recurrent costs*, including *variable costs* (salary for staffs, daily methadone dose, urine tests and consumables), and *fixed costs* (site operation and maintenance, medication import and distribution, and allocation of management costs at provincial and central levels)^{35, 36}. The MMT costs, evaluated for the year 2008, were converted to US dollars and inflated to 2009 Dollars using in the Consumer Price Index (1.069). The average 2009 exchange rate of 1 USD was 18,120 Vietnamese Dongs³⁷. Co-located integrative MMT and ART model was supposed to decrease the service costs by reducing the fixed costs, such as facility and staff costs, We used the same unit service costs for both MMT-ART and MMT-DAART models since in the pilot MMT program, the donor offered one-time establishment costs, and did not cover costs associated with housing or land.

Model parameters

The model was parameterized using empirical data of MMT and ART cohort and other country-level epidemic characteristics and health outcomes^{1, 30, 31, 34, 36, 38}. The ART retention, mortality, and loss-to-follow up rates at 1 year (Table 6-1) were derived from the ART cohort of 31 ART sites nationwide in 2009^{1, 31}. Probability of drug injection during MMT and health utilities of patients taking both MMT and ART were estimated from the MMT cohort published elsewhere^{17, 25, 36}. The model also utilized international parameters, such as the probability of viral suppression of each ART strategies, and outcomes of the patients who had virological treatment failure, loss-to-follow up, or stopped ART^{26-28, 39, 40}. Eligible patients who received ART would have an increment of 0.144 in health utility over 1 year⁴¹.

Cost - Effectiveness and Sensitivity Analysis

We assessed the three ART strategies by comparing services costs to the improvements in health outcomes, which were quantified into QALYs. We assumed that ART services costs remained the same for all 3 strategies; the cost for MMT was considered as an incremental cost. In addition, we used the same services costs for both DAART-MMT and ART-MMT strategies, and varied the fixed costs in a sensitivity analysis to compensate the potential changes while integrating ART with MMT. The Incremental Cost-Effectiveness Ratio (ICER) was determined, and then compared across interventions. We adapted the cost-effectiveness thresholds for low-income countries defined by the World Health Organization^{42, 43}. Interventions with ICERs that fall into (< 1) or (1 - 3) times the country's GDP per capita (GDPpc) are considered “very cost-effective” and “cost-

effective”, respectively. According to the National General Statistics Office, the GDP per-capita of Vietnam in 2009 was 1113.4 USD ³⁷.

A probabilistic sensitivity analysis (PSA) was performed to examine the robustness of the results against uncertainties in all model parameters simultaneously ⁴⁴. In PSA, the uncertainty in each probability and utility was assumed to possess a probability distribution. Beta and normal distributions were used for health outcomes parameters, and a gamma distribution was used for costs inputs. Using a Monte Carlo technique, each probability and utility was randomly assigned a value within its distribution in 10,000 simulations of the decision tree. PSA presented cost-effectiveness of strategies in a cost-effectiveness plane (CE-plane), cost-effectiveness acceptability curves (CEACs), and frequencies with which each strategy is optimal.

6.3. Results

Table 6-2 presents the average costs and QALYs generated from the model in deterministic and probabilistic analysis. At base-case values of all parameters, the cost-effectiveness ratio of ART, ART-MMT, and DAART-MMT strategies was 1,358, 1,328, and 1,118 (USD/ QALY), equivalent to 1.2, 1.2, and 1.0 times GDPpc. Compared to the ART strategy, providing MMT for HIV-positive DUs in either standalone sites or integrated model, such as DAART-MMT, incurred higher costs but significantly better outcomes. The ICER for ART-MMT and DAART-MMT versus ART strategy was 1,234 and 570, approximately 1.1 and 0.5 times GDPpc/ QALY, classifying MMT with ART strategies as cost-effective or very cost-effective interventions. The potential use of DOT in DAART - MMT

also added benefits to the care and treatment for HIV-positive DUs. The DAART-MMT dominated ART-MMT since it was associated with lower costs and higher QALYs. In the base-case analysis, DAART-MMT saved USD 56 compared to ART-MMT, while it created an increment of 0.048 QALY. The probabilistic results were relatively similar to deterministic results that indicated the robustness of this model against variations of input parameters (Table 6-2).

Figure 6-2 and 6-3 presents the results of 10,000 simulations in probabilistic sensitivity analysis using Monte-Carlo technique. We compared the incremental costs and QALYs of the DAART-MMT strategy with ART and ART-MMT, respectively. Using the threshold of 3 times GDPpc (USD 3340/ QALY gained), the simulations showed that DAART-MMT was more cost-effective than ART-MMT in 58.3% of hypothetical samples. However, 25.8% of the estimates fell in the northwest quadrant of the incremental cost-effectiveness plane with higher costs and lower QALYs (Figure 6-2). In figure 6-3, all hypothetical samples for DAART-MMT incurred gains or remained the same QALYs compared to ART-MMT. There were 42.2% of the times when the ICER for DAART-MMT versus ART-MMT was less than the threshold and 36.8% of the times when these 2 strategies were not different in terms of incremental costs and effectiveness.

The cost-effectiveness acceptability curves showed that if the society is willing to pay USD 3340 per 1 QALY, the probability of DAART-MMT, ART-MMT, and ART being cost-effective is 50.2%, 13.9%, and 35.9% (Figure 6-4). As the willingness-to-pay increases, the probability of being a cost-effective intervention increases in MMT strategies, while it decreases in ART strategy.

6.4. Discussion

We developed a decision analytical model to evaluate the cost-effectiveness of HIV care and treatment strategies for DUs that involved both MMT and ART services. The results indicated that providing MMT along with ART for HIV-positive DUs is incrementally cost-effective from the perspective of health services providers. In addition, the hypothetical model, which integrates ART with MMT and adapts the DOT, brought about an extra 0.048 QALY - approximately 0.5 times standard deviation of health utility of ART patients. In clinical studies these changes are considered clinically important changes in health outcomes measured using health-related quality of life indicators ³⁶. The sensitivity analyses showed that the incremental cost-effectiveness of the DAART-MMT versus ART-MMT model is robust against variations of model parameters.

Findings of this study support previous analyses that MMT is effective not only in the prevention of HIV transmission but also for the care and treatment for HIV-positive DUs ^{26, 27, 36, 45}. Roux (2009) determined that retention in MMT was a significant predictor of virological success in ART for HIV-positive DUs ⁴⁵. Lucas (2006) identified that patients in DAART-MMT were more likely to have virologic suppression than those in ART-MMT and MMT models ²⁷. This analysis confirmed the incremental effectiveness of providing MMT for ART patients in terms of QALYs gained. In the literature, there is little evidence on the cost-effectiveness of integrating MMT with ART services, especially in large injection-driven HIV epidemics. Only a study of Alistar (2011) has estimated the ICER of scaling up ART for 80% and MMT for 25% of HIV-positive DUs in the Ukraine, and found a similar ICER of USD 1120 per QALY gained ¹⁵. Our study analyzed

for the first time the potential integration of DAART-MMT services and found it more cost-effective than the current ART and MMT services delivery models.

Improving adherence to ART regimens is the ultimate goal of treatment support interventions for HIV-positive DUs. The association between adherence and drug use has been well-recorded^{2, 16, 18}. Tran et al. (2011) identified that ongoing drug use was a negative predictor of HIV/AIDS treatment outcomes, and that MMT significantly reduced drug use among HIV-positive DUs¹⁷. Although a higher rate of virologic suppression was observed in other studies, effects of MMT on adherence to ART might not be stable⁴⁵. Firstly, very high drop-out rates (75-80%) of MMT patients were seen over long follow-up periods in resource-rich settings⁴⁶. In addition, ongoing drug use and injection were relatively high (20-30%) among HIV-positive patients in the MMT program in Vietnam^{17, 36}. The sensitivity analyses results showed the lowest probability of being cost-effective for ART-MMT, and the highest one for DAART-MMT model clearly illustrated this uncertainty. It is important to notice that providing MMT in separate clinics from where DUs are taking ART might not causally result in adherence improvements. In practice, scaling up MMT in this injection-driven HIV epidemic facilitates the use of DOT in ART, and promotes an integration model for delivering comprehensive HIV/AIDS-related care and treatment services for HIV-positive DUs.

The strengths of this study included the inclusion of parameters that were derived from recent assessments of costs and longitudinal effectiveness of MMT and ART services in Vietnam^{17, 25, 31, 34, 35}. These parameters reflect the current responses to HIV epidemics in the country, thus, support the validity of the

model. In addition, we used probabilistic sensitivity analyses which took into account variations of various probabilities, costs, and utilities of the model. This method helped inform decision makers on the probability that MMT integration strategies are incrementally cost-effective. Moreover, scaling up MMT may result in substantial societal benefits, such as reduced criminal activities and increased work productivity, although these types of societal and personal benefits have not been included in this analysis. Other cost savings, such as reversed HIV cases or reduced health care utilization and service costs, were significant though not included in the model.

Also some limitations of this study should be acknowledged. First, we used linear likelihood of having virologic outcomes in each strategy that simplified the dynamic and complex process of drug resistance development and virological treatment failure. This assumption did not involve the underlying changes in treatment adherence and its impact on virologic success by different types of antiretroviral regimens¹³. In addition, the time frame for the analysis was 1 year that might not fully capture the long-term impact of MMT and ART services on health outcomes of HIV-positive patients.

In conclusion, providing MMT for HIV-positive DUs during ART is incrementally cost-effective. Moreover, direct observations of health workers for drug taking during patients' visits are potentially useful HIV/AIDS care and treatment outcomes. The results of this study support the scale-up and integration of MMT services with ART for HIV-positive DUs in Vietnam.

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6.6. Tables

Table 6-1: Model parameters

Parameters	Mean	SD	Distribution	Source
I. Probabilities				
1st year ART				
- Retention rate	81.2%	9.5%	Beta	[31]
- LTFU/ Stop ART	7.0%	5.7%	Beta	[31]
Mortality rate during ART				
- Viral suppression	11.8%	7.4%	Beta	[31]
- Viral rebound/ LTFU/ Stop ART	47%			[39]
Probability of viral suppression after 1st year ART				
- ART	33%			[26, 27]
Odd ratios of having viral suppression				
- ART - MMT vs. ART	3.66			[45]
- ART - MMT vs. DAART-MMT	0.40			[26, 27]
- Drug injection vs. Non-injection	0.68			[47]
Viral suppression in 2nd line	83.0%			[40]
Probability of ongoing drug injection	32.7%	47.0%	Normal	[17]
II. Cost (USD, 2009)				
- ART - 1 st line regimen, 1 st year	432.4	95.2	Gamma	[34]
- ART - 2 nd line regimen, 1 st year	1,477.3	191.4	Gamma	[34]
- MMT	252.0	26.7	Gamma	[35]
III. Utilities				
- Increments in Utilities over 12 months ART	0.144			[41]
- ART	0.667	0.112	Normal	[17, 48]
- ART-MMT/ DAART-MMT, ongoing drug use	0.726	0.053	Normal	[17, 36]
- ART-MMT/ DAART-MMT, drug abstinence	0.746	0.070	Normal	[17, 36]

Table 6-2: Cost-effectiveness of 3 ART strategies

Strategy	Cost	Incremental cost	QALYs	Incremental QALYs	CER	ICER
Deterministic						
ART	535.4		0.394		1,358.1	
ART - MMT (vs. ART)	690.1	154.6	0.520	0.125	1,328.3	1,234.4
DAART - MMT (vs. ART)	633.9	98.4	0.567	0.173	1,117.9	569.7
DAART - MMT vs. ART - MMT		-56.2		0.048		-1,182.8
Probabilistic						
ART	590.1		0.433		1,361.5	
ART - MMT (vs. ART)	771.4	236.0	0.547	0.153	1,410.5	1,545.8
DAART - MMT (vs. ART)	719.0	183.5	0.597	0.203	1,204.4	905.3
DAART - MMT vs. ART - MMT		-52.5		0.050		-1,048.2

6.7. Figures

Figure 6-1: Decision tree model

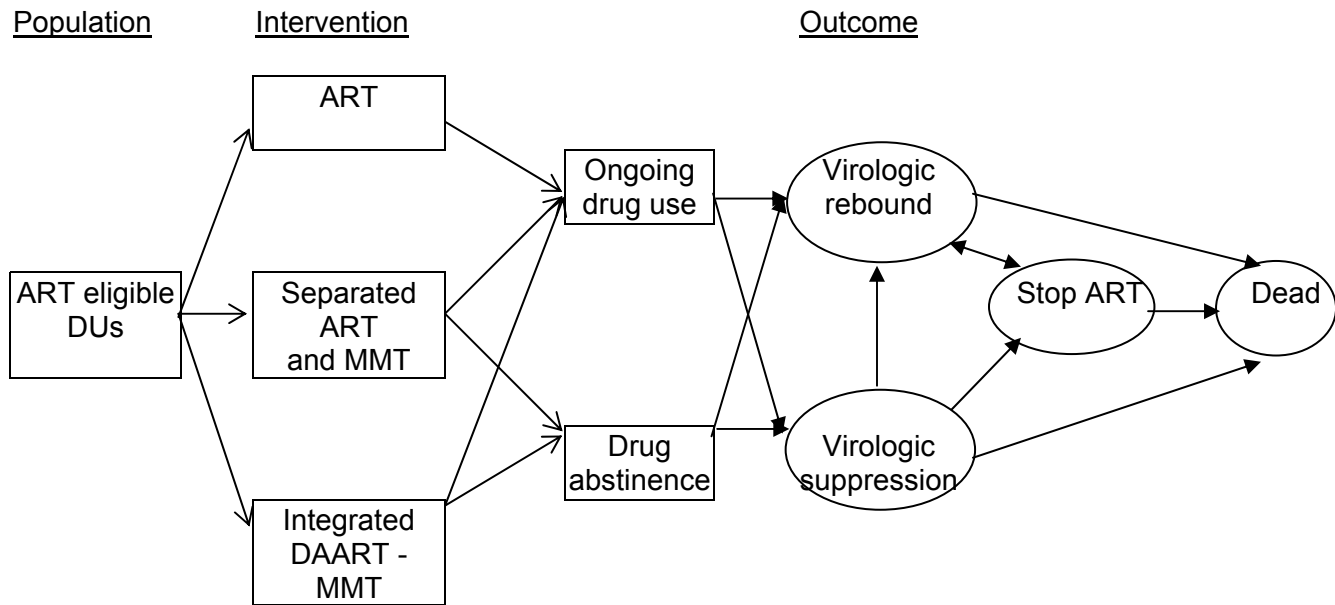


Figure 6-2: Incremental cost-effectiveness plane for DAART-MMT versus ART

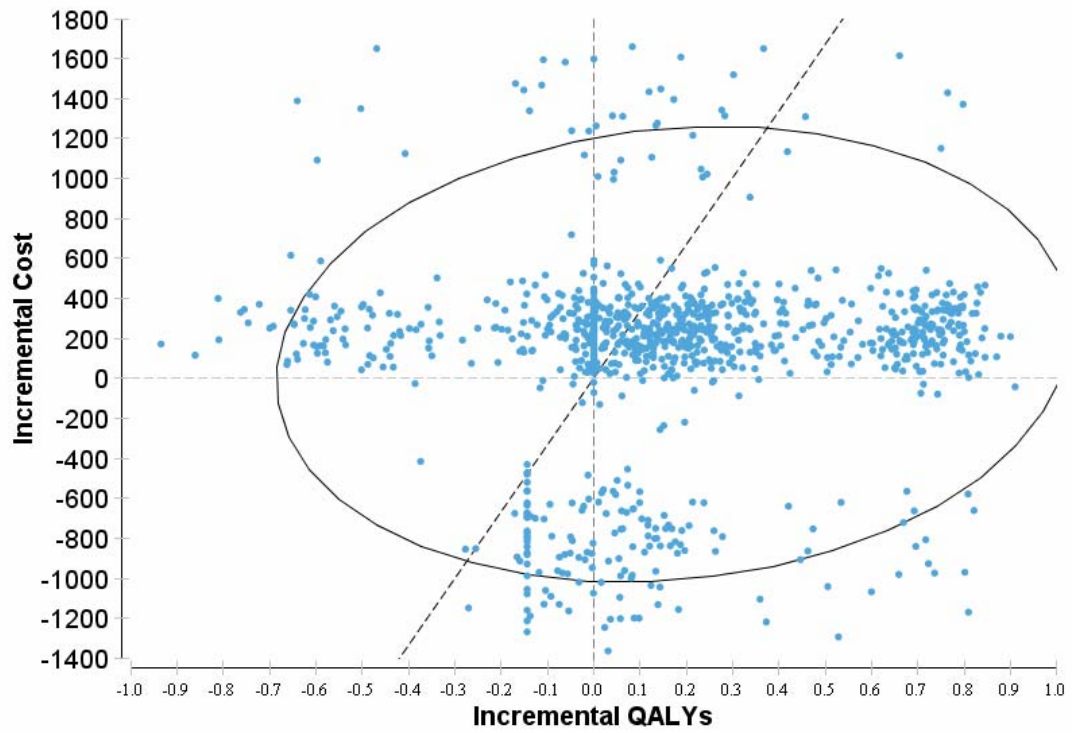


Figure 6-3: Incremental cost-effectiveness plane for DAART-MMT versus ART-MMT

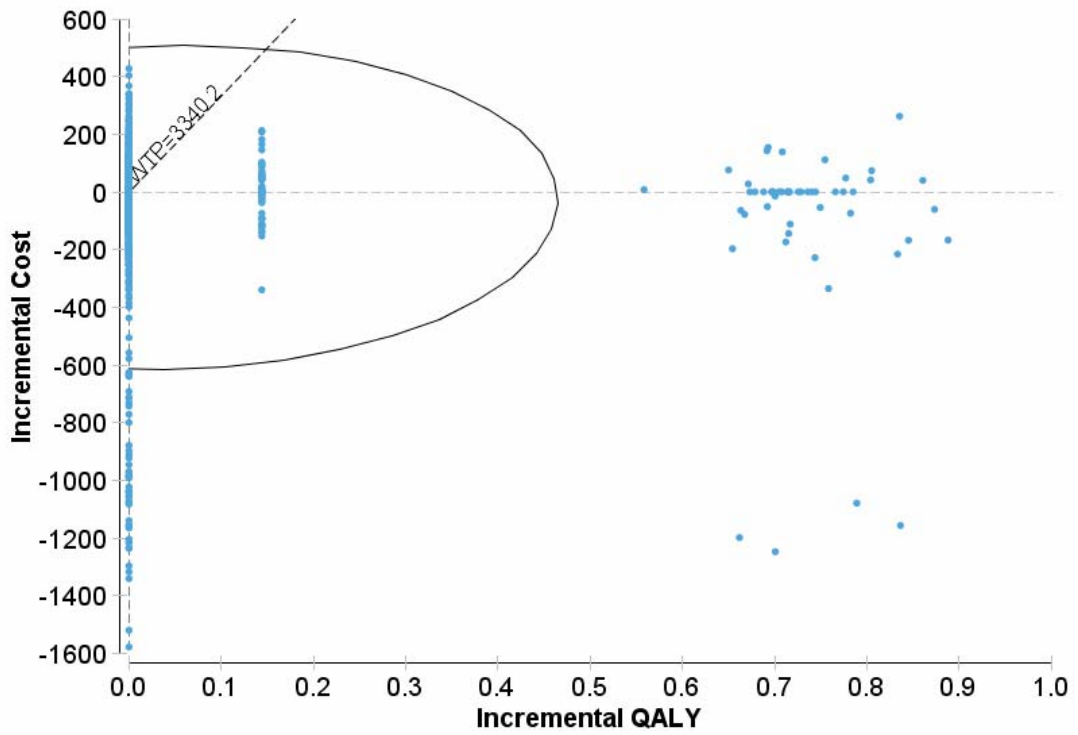
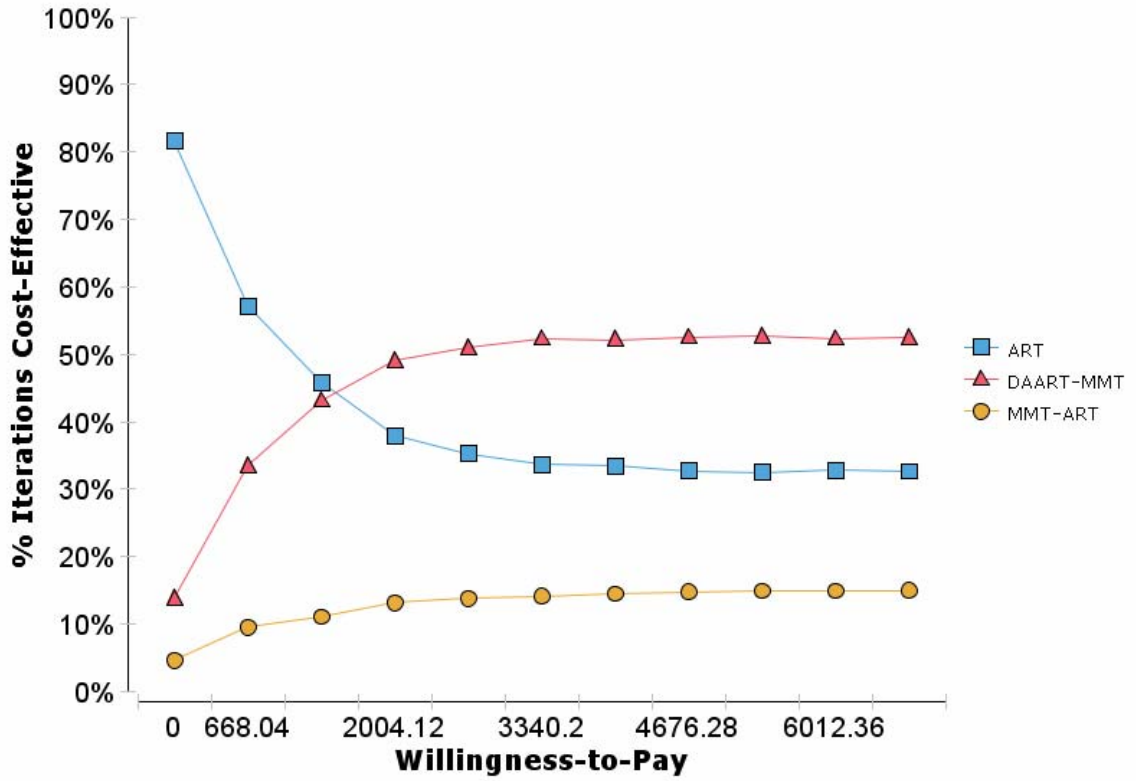


Figure 6-4: Cost-effectiveness acceptability curve for 3 ART strategies



7. DISCUSSION AND CONCLUSIONS

This thesis consists of five, sequential papers, which explored the determinants of health outcomes in ART patients, examined the role of MMT in HIV/AIDS care and treatment, and evaluated the cost-effectiveness of different ART and MMT services delivery strategies. The study found that early care and treatment supports for HIV/AIDS patients were needed to improve their psychological and social functioning. As treatment of opioid dependence became essential in HIV/AIDS care and treatment policies, MMT was found to be a cost-effective intervention for HIV-positive DUs. MMT helped them reduce drug use, improve HRQL, and increase access to health care and social services. Integrating MMT and ART services could facilitate the use of directly observed therapy to support treatment adherence¹⁻⁴, which in turn brought about clinically important improvements in health outcomes. Moreover, integrated services delivery models may support drug abstinence by offering better individualized care, managing drug-interactions, and co-morbidities. This approach was also incrementally cost-effective in this large injection-driven HIV epidemic.

The study one analyzed for the first time HRQL of the Vietnamese general and HIV/AIDS populations; this measurement is a nationally representative reference for comparing sub-groups to identify their health problems and health care demands.

Although ART have been rapidly scaled-up in the country, the current HIV/AIDS treatment policy suggests ART initiation when CD4 count <250 cells/ml, hence,

covered only those patients with considerable deterioration in health status. Consistently, the household survey showed a poorer physical health in ART patients compared to the early HIV-positive group and the general population. Moreover, from the early stage of HIV infection, HIV/AIDS patients reported having problems in psychological and social functioning. Most noticeably, the highest decrements in these HRQL dimensions were experienced by DUs who accounted for approximately 70% of current ART patients. Therefore, it is necessary to develop DU-focused interventions and enhance psychological and social supports for patients from early stages of HIV infection. This strategy can serve larger patients groups, and might be effective even before ART services created an increment in health outcomes of HIV/AIDS populations.

Another interesting result of the study one was the identification of determinants of health outcomes in the HIV-positive population. Unemployment and inaccessibility to health and social services were outstanding predictors which negatively affected the HRQL of HIV-positive patients. In addition, it is important to notice that during the time of this research project, drug use was illegal in Vietnam, thus, HIV-positive DUs might hide their status, and did not commonly access to health care services until very late HIV/AIDS stages. Besides, it was evident that DUs had more adherence difficulties and less virologic success under ART than other patient groups⁵⁻⁷. Therefore, addressing these social and biological barriers associated with drug use is critical to develop sound policies in HIV/AIDS care, treatment and impact mitigation in large injection-driven epidemics.

The second phase of this research project sought to determine the effectiveness and cost-effectiveness of providing MMT for HIV-positive DUs using secondary data analyses of the MMT cohort. A high response rate to MMT over a 9 month follow-up was observed in Vietnam (89.9%). In addition, MMT dramatically reduced the proportion and frequency of drug use which was known to be associated with poor ART adherence^{3, 8-10}. The changes in drug use behaviors were accompanied by large improvements in HRQL of HIV-positive DUs, especially, in the psychological dimension. Besides, MMT also helped improve referrals and access to health care and social services (e.g. self-help groups and peers education). However, utilization of social integration services, such as vocational training, job replacements, was small. From the perspective of health service providers, the economic evaluation results showed that MMT is a cost-effective intervention for HIV-positive DUs in terms of cost per QALYs gained.

Although MMT was shown to be effective, concurrent drug use remained a major challenge to making decisions to expand MMT services for HIV-positive DUs¹¹. There were about 30% who ever-used and 20% who ever-injected drugs during MMT among these patients. Concurrent drug use during MMT resulted in large decrements in all HRQL dimensions that made the MMT intervention become much less cost-effective with higher uncertainty.

To get insights on the responses of HIV-positive DUs to MMT, the social ecological model was applied to explore multilevel predictors of ongoing drug use, including individual, interpersonal, community and service influences¹². Consistent with common knowledge of drug-related problems, higher likelihood of concurrent opioid use was found in those patients who had a higher level of

prior drug abuse, peer pressure, and unstable social and familial status^{13, 14}. More importantly, there was a higher risk of continuing drug use in patients who were on ART, had TB treatment, and had more health problems. Disease stage and drug interactions between antiretroviral or TB drugs and MMT may explain some of the observed predictors of ongoing heroin use; these findings could inform changes in MMT program design and implementation.

The findings of the second phrase implied that providing MMT could generate substantial improvements in health outcomes, and facilitate the success of ART for HIV-positive DUs. However, benefits of MMT might be limited if other interventions addressing social and structural barriers associated with drug use and HIV/AIDS are not in place. Familial and social supports, vocational training, peer-educators, job referrals and placements, and loans are some examples of possible impact mitigation programs for HIV-positive DUs¹⁵⁻¹⁷. As for HIV/AIDS care and treatment policy, a more comprehensive services delivery model is necessary for the treatment of HIV/AIDS and drug dependence in Vietnam.

The modeling part of this thesis attempted to develop a decision analytical model to compare the cost-effectiveness of 3 ART strategies: 1) only ART, 2) providing ART and MMT in separated sites as currently delivered in Vietnam, and 3) integrating ART and MMT with direct administration (DAART-MMT). The findings indicated that providing MMT along with ART is a cost-effective intervention in care and treatment for HIV-positive DUs in Vietnam. However, providing MMT in separate clinics for DUs taking ART might not causally result in better adherence and ART outcomes^{18, 19}. In practice, scaling up MMT would create a chance for supporting ART adherence by using direct observations of health workers^{1, 18-20}.

The integrated model brought about clinically important improvements in health outcomes and was a cost-effective strategy for HIV/AIDS care and treatment in DUs.

The strengths of these studies includes that it is based on a nationally representative survey and a longitudinal cohort study in large injection-driven HIV epidemics of two metropolitan areas in Vietnam. These designs support the causality inference and the generalizability of research findings. Moreover, these cost-effectiveness analyses are very first studies in the developing world which experienced the greatest burden of HIV/AIDS. Therefore, findings of these studies could serve as a good reference in other resource-scare settings. In addition, the validity of economic modeling has been improved given the comprehensive synthesis of costing and empirical epidemiological data in Vietnam. Using these parameters, the economic model provides a framework for evaluating the cost-effectiveness of HIV/AIDS interventions in Vietnam. Engaging scholarship with the involvement of policy makers throughout the process, findings of this thesis have been rapidly translated into HIV/AIDS policies in Vietnam.

Besides, some limitations of this thesis should be acknowledged. Typically, it lacked a comparison group in the longitudinal cohorts and clinical data, such as viral load and CD4. In addition, the impact of MMT was assessed over 9 month that might not capture important long-term changes. This short duration is also observed in the literature that confined the economic model with short-term MMT impacts. Nevertheless, these potential biases have been justified in statistical analysis and the inferences of research findings.

In conclusion, results of this thesis suggest the following policy implications:

1. Strengthening the quality of HIV/AIDS counseling and services referrals at VCT sites as well as other health care services.
2. While expanding the coverage of ART services, it is necessary to improve early care and treatment supports, focusing on impact mitigation programs. Self-help groups and peer-educators could be helpful facilitators of these programs.
3. Vocational training, job replacements, and economic empowerments are critical to support HIV/AIDS patients in the lifelong fight against HIV/AIDS.
4. MMT services are cost-effective and should be rapidly scaled-up in large injection-driven epidemics. MMT could be offered for HIV-positive DUs regardless of their HIV/AIDS stages. In addition, MMT services should play a role as a primary care for DUs from early stages of HIV infection; that also enable DUs to get access and use social and health services.
5. It is important to manage MMT services in line with other health care problems of HIV-positive DUs. Interactions between antiretroviral or TB drugs and methadone, and dosing adjustments should be appreciated in clinical practice.
6. Integrating MMT and ART as well as other HIV-related care and treatment services, such as TB and infectious diseases, to facilitate the use of DOT should be highly prioritized.

This work also inspires numerous questions that might be addressed in future research:

1. Although the economic evaluation showed that DAART-MMT is cost-effective, there has not been such a model implemented in Vietnam as well as low-income countries. It would be of great interest for Vietnam to pilot this model and then explore the operational issues and feasibility of this strategy.
2. Recently, the World Health Organization has recommended that ART should start sooner, at a CD4 threshold below 350 cells/mL. This change promises incredible clinical benefits, both in extending lives and in lowering infection rates. However, patients did not access to ART services until they got into a severe health status; average CD4 count at ART initiation in Vietnam was 80 cells/ mL. Further research may examine the role of MMT in supporting earlier access, initiation, and retention of pre-ART and ART services among HIV-positive DUs.
3. Evaluation of the MMT program for general drug users, including its impacts on HIV risk behaviors and prevention of HIV/AIDS transmission, cost-effectiveness, and cost-benefits of the MMT programs in Vietnam are the next analyses of this project.
4. Comprehensive model for prevention, care, and treatment for DUs in injection driven epidemics would be of great interest. DUs should also have access to and utilization of prevention services such as condom, clean needles, methadone, and other health care services. Multilevel and networking approaches are good guidance for developing such an intervention.

5. The policy makers and program managers are usually interested in the resource demands for implementing a new health technology. A budget impact analysis of expanding MMT as well as other HIV-related services would address this concern and support making program decisions.
6. Financing sustainability and efficiency of the health system is one priority identified by international donors, such as the U.S. President's Emergency Plan for AIDS Relief phase II (PEPFAR - II). Evidence on ability to pay and willingness to pay for HIV-related services, such as MMT and ART, and the potential expansion of health insurance for HIV-positive DUs are essential for resource mobilization in the coming years when international funding for HIV/AIDS is going to decrease.

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