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Complete List of Authors:	Do, Huyen; Queensland University of Technology School of Public Health and Social Work Nguyen, Long; School of Medicine and Pharmacy, Vietnam National University Nguyen, Nhung; Hanoi University of Pharmacy Chau, Ngo; Johns Hopkins University Bloomberg School of Public Health Nguyen, Lan Huong; Duy Tan University, Institute for Global Health Innovations Le, Giang; Authority of HIV/AIDS Control, Ministry of Health Nguyen, Linh; School of Economics, Vietnam National University Nguyen, Cuong; Institute for Global Health Innovations, Duy Tan University Xuan Bach, Tran; Institute for Preventive Medicine and Public Health, Hanoi Medical University, Health Economics Thi Huong, Le; Institute for Preventive Medicine and Public Health, Hanoi Medical University Vu, Minh Thuc; Department of Immunology and Allergy, National Otolaryngology Hospital Phan, Huong; Authority of HIV/AIDS Control, Ministry of Health Tho, Tran; Department of Hepatobiliary Surgery, Vietnam-Germany Hospital, Hanoi, Vietnam Latkin, Carl; Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA Michael, Dunne; Queensland University of Technology School of Public Health and Social Work
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Lower nicotine dependence amongst Vietnamese opiate drug users on longer methadone maintenance treatment

Huyen Phuc Do[9], Long Hoang Nguyen[6], Nhung Phuong Thi Nguyen[7], Chau Ngo[2], Huong Lan Thi Nguyen[9§], Giang Tong Le[5], Linh Khanh Nguyen[8], Cuong Nguyen Tat[9], Bach Xuan Tran[2,3], Huong Thi Le[3], Vu Thi Minh Thuc[4], Huong Thi Thu Phan[5], Tran Dinh Tho[10], Carl A Latkin[2], Michael Dunne[1]

[1] School of Public Health and Social Work, The Queensland University of Technology, Australia
[2] Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America
[3] Institute for Preventive Medicine and Public Health, Hanoi Medical University, Vietnam
[4] Department of Immunology and Allergy, National Otolaryngology Hospital, Hanoi, Vietnam
[5]Authority of HIV/AIDS Control, Ministry of Health, Hanoi, Vietnam
[6]School of Medicine and Pharmacy, Vietnam National University, Hanoi, Vietnam
[7] Hanoi University of Pharmacy, Hanoi, Vietnam
[8]School of Economics, Vietnam National University, Hanoi, Vietnam
[9]Institute for Global Health Innovations, Duy Tan University, Vietnam
[10]Department of Hepatobiliary Surgery, Vietnam-Germany Hospital, Hanoi, Vietnam

[§] Corresponding author:
Huong Lan Thi Nguyen, Msc.
Institute for Global Health Innovations,
Duy Tan University, Da Nang, Vietnam, 550000
+84974638867 | nguyentlanhuong5@duytan.edu.vn

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ABSTRACT

Objectives: Smoking is associated with adverse health outcomes among drug users. However, there has been a scarcity of evidence about smoking patterns among people receiving opioid dependence treatment in developing countries. We sought to explore self-reported nicotine dependence and determine associated factors in a large sample of opioid-dependent patients receiving methadone maintenance treatment (MMT) in Northern Vietnam.

Setting: Five clinics in Hanoi (urban area) and Nam Dinh (rural area)

Participants: Patients receiving MMT in the settings during the study period

Primary and secondary outcome measures: We collected data about smoking patterns, levels of nicotine dependence and other covariates such as socioeconomic status, health status, alcohol use and drug use. The Fagerström test was used to measure nicotine dependence (FTND). Logistic regression and Tobit regression were employed to examine relationships between the smoking rate, nicotine dependence, and potentially associated variables.

Results: Among 1,016 respondents, approximately 87.2% of drug users taking methadone were current smokers. The mean FTND score was 4.5 (SD=2.4). Longer duration of MMT (OR=0.98; 95%CI=0.96-0.99) and HIV-positive (OR=0.46, 95% CI=0.24-0.88) were associated with lower likelihood of smoking. Being employed, higher age at first drug injection and having long duration of MMT treatment were inverse factors for FTND scores. Whereas, higher age and drug and alcohol abuse were significantly associated with higher FTND score.

Conclusion: Smoking prevalence is high among methadone maintenance drug users. Despite the decrease of smoking over the course of MMT, smoking cessation support should be integrated into MMT program in Vietnam along with controlling risk factors associated with cigarette smoking.

Strengths and limitations of this study:

- Including a large sample size in multiple clinics in various areas
- Employing validated instruments to increase the comparability of the study.
- The causal relationships were unable to establish due to cross-sectional design.
- All data were assessed by retrospective self-reporting without biochemical confirmation, which might result in under-reporting of ongoing drug use due to recall and disclosure bias.
- Convenience sampling strategy limited the generalization of findings

INTRODUCTION

Despite the reduction of smoking worldwide, cigarette smoking rates remain high among opiate-dependent individuals – three or four times higher than that prevalence in general population [1-4]. A systematic review of Guydish et al. in 2011 indicates that the smoking rates among patients in addiction treatment were from 65% to 87.2% [5]. Smoking is concerned as a primary cause of morbidity and mortality in illicit drug users [6 7]. Previous evidence indicates that the death rates of smokers were four times greater than that of their counterparts [8]. Additionally, smoking increases the likelihood of suffering from disability, diminishing daily function and the quality of life among opioid abusers compared to their non-smoking peers [6 8 9].

Methadone maintenance treatment (MMT) is an effective method to reduce opiate use and improve health status [10 11]. However, empirical evidence suggested that short-term MMT may possibly increases the smoking rates in a dose-dependent relationship, with higher dose of MMT associated with greater nicotine dependence [12-14]. Nicotine appears to make methadone or other opiates more efficaciously reinforced [15]; therefore, MMT patients are more likely to smoke when taking methadone to counteract the sedating effects of methadone, or to produce more pleasurable experience when tobacco and methadone are accompanied [1 16].

Nonetheless, the long-term effect of MMT on smoking is unclear. A study of Helena et al. showed that people with a long duration of MMT were likely to change their smoking habits, reducing nicotine dependence and cigarette smoking [17]. In addition, some prior studies also suggested a high level of motivation to quit smoking among long-term MMT patients [18 19]. Other findings indicated that there is no significant association between ongoing MMT and smoking levels or quitting attempt [20].

Globally, Vietnam is one of the countries with the highest prevalence of tobacco smoking, with approximately 23.8% adults being current cigarette smokers [21]. Smoking is one of the major risk factors for disease burden in Vietnam, attributing to 6.2% of total deaths [22]. Currently, there has been several evidences regarding sexual activities [23], concurrent drug use [24 25], quality of life [23] and health service utilization [26] among MMT patients. However, evidence of smoking behavior in this population in Vietnam remains limited. This study aimed to explore the prevalence of smoking and level of nicotine dependence, and determines associated factors among MMT patients in Vietnam. Our study is among the first to provide evidence on the pattern of smoking cigarettes during opioid dependent treatment in Vietnam. Therefore, it would partly contribute to the implemetation of smoking cessation service for drug users in Vietnam, reducing smoking behavior and eventually, improving the outcomes of methadone treatment.

MATERIALS AND METHODS

Survey design and sampling

We conducted a cross-sectional study from June to August 2013 at five clinics in Hanoi and Nam Dinh. These two provinces have a high prevalence of HIV-positive patients in the Northern region of Vietnam, with 19,987 and 3,577 people living with HIV/AIDS, respectively [27]. A sampling strategy was employed to select clinics based on the following criteria: (1) clinics at central-, provincial-, and district-level and (2) having an adequate number of MMT patients. The characteristics of the study sites are listed in **Table 1**.

Table 1: Study settings and sample size

Level	Settings	Site Name	Type of services	Sample size
District (urban)	Nam Dinh City	Provincial AIDS Centre	MMT+ VCT	270
District (rural)	Xuan Truong District	District Health Centre	MMT+ VCT + ART + GH	151
District (urban)	Tu Liem District	District Health Centre	MMT+ VCT + ART + GH	201
District (urban)	Long Bien District	District Health Centre	MMT+ VCT + ART + GH	184
District (urban)	Ha Dong District	Regional Polyclinic	MMT+ GH	210

**MMT: Methadone maintenance treatment; VCT: Voluntary counselling and testing; ART: Antiretroviral therapy; GH: General healthcare*

Participant recruitments

Participants were eligible if they 1) received daily methadone; 2) ages 18 years or above, and 3) agreed to provide written informed consent. Patients were excluded if they had any health problems that prevented them answering the questionnaire.

Eligible patients were invited when they visited the clinics. If they agreed to enroll, they would be asked to give their written informed consent. A private room in each clinic was arranged to ensure confidentiality and to create a comfortable atmosphere during the interview. A sample of 1,016 patients was enrolled in the study, accounting for 90% of MMT patients in five clinics.

Data collectors did not engage in the provision of care or treatment. No health care providers were involved in the interview or handling of data. Interviewers were well-trained Master of Public Health students from Hanoi Medical University.

Measures and instruments

Smoking related variables

The primary outcome was current smoking status, categorized into three groups: current smoker, former smoker, and never-smoker. Participants were classified as a current cigarette smoker if they have ever smoked at least 100 cigarettes in their life and have smoked in the last 30 days. Participants who have smoked 100 cigarettes but have been abstinent in the last 30 days were categorized as former cigarette smokers. Those who have never smoked 100 cigarettes and not currently smoking were considered as never smokers. Nicotine dependence was measured by the *Fagerström test for nicotine dependence* (FTND) [28 29]. FTND instrument has been applied elsewhere in the context of Vietnam [30]. The total scores range from 0 to 10. The higher the Fagerström score indicates the greater nicotine dependence. Regarding FTND score, patients were categorized into five groups: 0-2: very

low, 3-4: low, 5: moderate, 6-7: high and 8-10: very high.

Covariate variables

In this study, covariate variables were selected based on the conceptual framework that was built via prior literature [30-39].

Socio-demographic variables consisted of sex, age, monthly income, employment status, educational attainment, residential area, and marital status. Monthly household income included all sources of income for each household member and was collected via self-reported information by patients Based on income information, patients were classified into five quintile groups: poorest, poor, middle, rich, and richest.

Health status was self-reported by employing the five-level EQ-5D (EQ-5D-5L) instrument [40]. This instrument invested in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The EQ-5D-5L instrument has been validated in Vietnamese context in a previous research [41]. Those experienced from "Slightly" to "Extremely" were categorized as "currently having pain or anxiety". Those who reported no pain or anxiety were categorised "no pain/ anxiety". Additionally, health conditions examined included HIV-infected status and whether they received antiretroviral treatment (ART).

Alcohol use was assessed using the Alcohol Use Disorders Identification Test - Consumption (AUDIT-C), a brief version of the 10-question AUDIT instrument [42 43]. The AUDIT-C score ranges from 0-12, where 4 or more in men and 3 or more in women are considered at-risk drinking [44]. The higher score means the greater alcohol dependence. The AUDIT-C instrument has been validated for Vietnamese populations elsewhere [45 46].

Drug use characteristics were assessed regarding of history of drug use, age at on set of drug use and drug injection and number of episodes of drug rehabilitation [45]. Participants who reported using any substance (heroin, cocaine, methamphetamine, etc.) at least once within the past month were considered concurrent drug users during MMT. Duration of MMT was assessed by self-reported.

Statistical analysis

Data were analysed using Stata version 12.0 for Windows. One-way analysis of variance (ANOVA), Kruskal-Wallis and Chi-squared tests were applied to identify the differences amongst socio-demographic, drug and alcohol-related and health-related characteristics regarding smoking status (never, former, and current smokers).

Multivariate logistic regression, combining with polynomial fractions for the duration of MMT treatment, was employed to determine associated factors with being the current smoker. Variables associated with the outcome in bivariate analysis with a $p < 0.25$ were evaluated for inclusion in the multivariate model manually in a forward stepwise manner. Only statistically significant variables with a $p < 0.05$ were retained in the final model.

Because the FTND score was censored from 0 to 10, we used Tobit regression to examine the relationships between FTND scores and potentially related factors [47]. We also utilized a stepwise backward strategy, which is based on the log-likelihood ratio test. The threshold of p-value < 0.1 was used to include variables. All potential interactions were examined. The Hosmer-Lemeshow goodness-of-fit test was employed to assess model calibration. A p-value less than 0.05 was considered statistically significant.

RESULTS

Table 2 indicates the characteristics of respondents. Most of patients (85.1%) were from the urban area. The mean age was 36.8 years old (SD=7.6). Most of respondents had less than a high school education (55.3%). The majority was married or lived with their partners (67.7%). One-fifth of respondents were employed. The average monthly income was 5.2 million VND, approximately 250 USD (SD=4.2).

One-third of participants were hazardous drinkers (29.6%). Patients with a history of heroin injection accounted for more than 70% of the sample. Only five in one hundred patients reported current illicit drug use during substance abuse treatment (4.8%). The average length of MMT was 16.5 months (SD=11.1). Overall, 17.7% and 20.7% of participants reported currently feeling pain and anxiety, respectively. Respondents with morbidity and self-care problem were 7.3% and 3.9%, respectively. Half of the participants enrolled in MMT clinics with comprehensive packages (including MMT, HIV testing and counselling services, ART and general health care (GH)).

In addition, the results of **Table 2** show that the proportion of MMT patient who currently smoked, formerly smoked and never smoked were 87.2%, 4.5%, and 8.3%, respectively. Smoking status was significantly different among groups regarding age, history of drug injection, age at initiation of drug use, and currently in pain ($p<0.05$).

Table 2: Characteristics of study participants by smoking status

	Never smokers	Former Smokers	Current Smokers	Total	p-value
N (%)	84 (8.3)	46 (4.5)	886 (87.2)	1016 (100)	
Socio-demographics					
Age in years, mean years (sd)	39.9 (9.2)	36.2 (5.7)	36.5 (7.5)	36.8 (7.6)	<0.01
Annual income (million VND), mean (sd)	5.0 (4.0)	4.6 (3.3)	5.2 (4.2)	5.2 (4.2)	0.55
Marital status (n, %)					
Single/Divorced/separated/widowed	18 (21.4)	17 (37.0)	293 (33.1)	328 (32.3)	0.07
Live with spouse/partner	66 (78.6)	29 (63.0)	593 (66.9)	688 (67.7)	
Education (n, %)					
Less than high school	55 (65.5)	25 (54.3)	482 (54.4)	562 (55.3)	0.3
High school	23 (27.4)	17 (37.0)	347 (39.2)	387 (38.2)	
More than high school	6 (7.1)	4 (8.7)	57 (6.4)	67 (6.5)	
Location (n, %)					
Urban	64 (76.2)	40 (87.0)	761 (85.9)	865 (85.1)	0.05
Rural	20 (23.8)	6 (13.0)	125 (14.1)	151 (14.9)	
Employment status (n, %)					
Unemployed	21 (25.0)	18 (39.1)	222 (24.8)	261 (25.5)	0.32
Self-employed	44 (52.4)	20 (43.5)	478 (54.0)	542 (53.4)	
Employed	19 (22.6)	8 (17.4)	186 (21.2)	213 (21.1)	
Substance use, n (%)					
Hazardous drinking (n, %)	27 (32.1)	8 (17.4)	266 (30.0)	301 (29.6)	0.38
History of drug injection (n, %)	50 (59.5)	31 (67.4)	665 (75.1)	746 (73.4)	0.01
Current drug use (n, %)	4 (4.8)	0	45 (5.1)	49 (4.8)	0.29
Age of drug use, mean age (sd)	26.4 (8.6)	24.5 (6.2)	24.4 (6.6)	24.5 (6.7)	0.03
Age of drug injection, mean age (sd)	27.6 (8.9)	25.4 (6.7)	26.8 (7.2)	26.8 (7.3)	0.44
Number of drug rehabilitation, mean episode (sd)	4.4 (4.2)	7.0 (11.8)	4.8 (6.0)	4.8 (6.3)	0.87
MMT duration, mean months (sd)	18.5 (12.3)	17.0 (11.7)	16.3 (10.8)	16.5 (11.0)	0.21
Health-related characteristics					

Current ARV treatment, n (%)	7 (8.3)	6 (13.0)	53 (5.9)	66 (6.5)	0.13
Currently feeling pain, n (%)	21 (25)	3 (6.5)	156 (17.6)	180 (17.7)	0.03
Currently feeling anxiety, n (%)	22 (26.2)	6 (13.4)	182 (20.5)	210 (20.7)	0.20
Currently perceive morbidity problem, n (%)	5 (6.0)	3 (6.5)	66 (7.5)	74 (7.3)	0.86
Currently perceive self-care problem, n (%)	4 (4.8)	3 (6.5)	33 (3.7)	40 (3.9)	0.59
Currently perceive usual activity problem, n (%)	3 (5.8)	4 (8.7)	53 (6.0)	60 (5.9)	0.48
MMT service delivery model					
MMT+ VCT	17 (20.2)	15 (32.6)	238 (26.9)	270 (26.6)	0.04
MMT + GH	10 (11.9)	7 (15.2)	193 (21.8)	210 (20.7)	
MMT+ VCT + ART + GH	57 (67.9)	24 (52.2)	455 (51.4)	536 (52.8)	

Smoking pattern of MMT patients is revealed in **Table 3**. Mean age of initial smoking was 17.2 years (SD=3.5), with mean duration of regular smoking being 14.1 years (SD=8.5). A total of 306.3 thousand VND per month were spent for cigarettes (=15 USD). Among smokers, mean FTND score was 4.5 (SD=2.4), and most of them were in low (27.0%) and very low dependence (26.1%) groups.

Table 3 – Smoking pattern of Vietnamese MMT patients

Characteristic	N (%)
Lifetime smoking (Current and former smoking)	932 (91.7)
Age at smoking initiation, mean years (sd)	17.2 (3.5)
Duration of regular smoking, mean years (sd)	14.1 (8.5)
Expense for smoking (VND per month), mean (sd)	306.3 (289.4)
FTND score, mean (sd)	4.5 (2.4)
Nicotine dependence scale, n (%)	
Very low	231 (26.1)
Low	239 (27.0)
Moderate	115 (12.9)
High	184 (20.8)
Very high	117 (13.2)
Number of cigarette per day, n (%)	
<=10	409 (46.2)
11-20	407 (45.9)
21-30	49 (5.5)
>30	21 (2.4)

Figure 1 indicates that the smoking rate and FTND score were high in the early phase of treatment, then significantly decreased afterward.

The reduced multivariate model in **Table 4** revealed that patients high school education (OR=2.29, 95%CI=1.28-4.07) were more likely report current smoking than others. Being HIV-positive (OR=0.46, 95% CI=0.24 – 0.88) was negative factors for currently smoking. Notably, individuals having longer duration of MMT were less likely to smoke than others (OR=0.98; 95%CI=0.96-0.99).

Table 4 also shows the findings from Tobit model. Being employed, higher age at first drug injection and having long duration of MMT treatment were inverse factors for FTND scores.

Whereas, higher age and having other single or multiple substance abuse (illicit drug, alcohol drinking) were significantly associated with higher FTND score.

Table 4: Associated factors of smoking status among study participants

Characteristics	Current smoking (Yes/No)			FTND score		
	OR	95% CI		Coef	95% CI	
Age				0.04**	0.01	0.08
Education (vs < High school)						
• High school	2.29**	1.28	4.07			
Occupations (vs Unemployed)						
• Employed				-0.55**	-1.07	-0.03
Income quintile (vs Poorest)						
• Rich				0.52*	-0.03	1.07
• Richest				0.63*	0.10	1.17
HIV status (vs Negative)						
• Positive	0.46**	0.24	0.88	-0.44	-1.11	0.22
• Unknown				-0.76	-1.76	0.24
Age of first drug injection				-0.07**	-0.11	-0.02
Substance use						
Interaction between current drug use and alcohol drinking (vs No use drug + No drink hazardously)						
• Only drink hazardously	1.51	0.82	2.78	0.83**	0.37	1.30
• Only use drug				1.61**	0.23	3.25
• Both use drug + drink hazardously				1.75**	0.24	3.25
No. of drug rehabilitation (vs None)						
• 1-5 times				-0.33	-0.75	0.09
Duration of MMT (months)	0.98**	0.96	0.99	-0.03**	-0.05	-0.01
MMT delivery model (vs MMT+VCT)						
• MMT + GH	2.11*	0.98	4.56			
• MMT+ VCT + ART + GH				-0.30	-0.73	0.13

MMT: Methadone maintenance treatment; VCT: voluntary counselling and testing service; GH: General health care

**p<0.01; ** p<0.05*

DISCUSSION

We observed the high smoking rate among MMT patients with nearly 90% - three times higher than that of the Vietnamese general population (23.8%) [21]. The result is consistent with research in other countries namely Switzerland, United States, Australia, Canada, Mexico, and England [8 48-52]. The prevalence of current smokers among MMT patients in this study appeared to be consistent with the statistic in both developed (e.g. United States and Australia) and developing countries (e.g. China) [53-56]. This result can be explained by the interaction between nicotine and methadone, that smoking eases the craving for heroin and cocaine consumption [15]. A study by McCool et al. suggested that MMT patients smoked to counteract the sedating effects of methadone and experience the pleasing effect when cigarettes and methadone are taken together [1 16]. Furthermore, we observed the difficulty of accessing smoking cessation support among MMT patients due to a lack of cessation services. To date, in Vietnam, only two official smoking cessation clinics, one in Hanoi and one in Ho Chi Minh city, have been operated. Therefore, further plans for scaling-up MMT program should consider integrating with smoking cessation services, which might help to diminish the smoking epidemic in the MMT population.

Notably, our result shows that longer duration of MMT was disproportionate with the likelihood of being smokers or higher nicotine dependence. We found that the smoking rates increased gradually in the first 30 months (but not significantly), and remarkably decrease afterwards. We suppose that in the initial stage of treatment, smoking helped patients to counter the aftertaste of MMT and improved the pleasing effect [57]. Consequently, they were more likely to smoke cigarette until they could feel comfortable with the side-effects of MMT. A study of Abbott (2010) on 189 MMT patients showed that after 12 months of treatment, smoking support cessation was the fourth most requested and important service although very few patients requested this service at baseline [58].

Likewise, we observed a dramatic increase of FTND score in the first 5 months before a steady decline afterwards. It can be explained that in the first few months, patients would require a high dose for substantial treatment, which led to more severity of nicotine dependence (displayed by FTND score) [14 59]. When patients treated MMT in the long time, they tended to receive stable or lower methadone doses, which diminished nicontine dependence and promoted the intention to quit smoking [3]. This result is consistent with previous study of Okruhlica et al., which suggested that level of nicotine dependence was reduced after 12 months of treatment when the MMT dose was stabilized [60].

Respondents with multiple substance abuse (alcohol and illicit drug use) were associated with higher nicotine dependence, especially among those who currently used illicit drug. The complex relationships between smoking, alcohol and drug use have been well-documented in global settings, that people having one risk behavior (such as drug use) tended to engage in other behaviors (such as smoking and alcohol) [31 38 39 57 61]. Therefore, these relationships during the course of MMT are clinically important that should be carefully monitored and controlled, which could help to identify who may need to receive specific cessation interventions at MMT sites.

This study also found significant associations between smoking and socio-demographic factors such as age, education, and employment. We have found that higher age was a predictor for higher nicotine dependence (higher FTND score). This finding was consistent with the results of other studies in Korea and China, which suggested the positive correlation between age and FTND [62 63]. Additionally, people with high school education were more likely to smoke compared with lower education group, which was supported by prior study

[31]. This point needs further investigation; however, it might anticipate that highly educated respondents are more likely to have higher income to spend more for tobacco consumption. Notably, patients who were employed had lower FTND scores than that of unemployed respondents. With about 25% sample being unemployed, this finding proposes the necessity of employment orientation for MMT patients to diminish the negative effects of cigarette smoking.

Results of multivariable regression indicated that HIV-positive drug users was less likely to be current smokers, which could be explained by the belief of health risk. Perceiving the deficit immunization and/or facing poor physical health condition due to HIV/AIDS could encourage patients to avoid risky behaviors such as smoking and alcohol use[37]. However, empirical evidence worldwide noted that people undertaking both ART and MMT, might relapse and smoking more often [30 36]. Furthermore, when they believe that they will not live long enough to suffer from smoking related illnesses; or perceived that they are at a lower health risk for continued smoking especially during a stable stage of ART, they will smoke more [37]. Therefore, special attention shoud be paid on patients living with HIV in order to help them avoid risk behaviors such as smoking, and promote a healthier lifestyle.

This study has strengths that included a large sample size (1,016 MMT patients), collaboration with multiple clinics in various areas and validated instruments (e.g. FTND, AUDIT-C, EQ-5D-5L). Nonetheless, several limitations should be considered. First, the causal relationships were unable to establish due to cross-sectional design. Additionally, all data were assessed by retrospective self-reporting without biochemical confirmation. This may have resulted in under-reporting of ongoing drug use due to recall and disclosure bias. Finally, due to the convenience sampling strategy to address confidentiality issues of drug use and HIV-positive patients, the generalization of our results is limited. Therefore, the results should be careful to be interpreted to the whole MMT population.

CONCLUSION

The findings from this study revealed that smoking is highly prevalent among MMT patients, putting them at a high risk of smoking-related illnesses. Despite the decrease of smoking over the course of MMT, smoking cessation support, along with concerning multi-substance use, employment and health status, should be integrated into MMT program in Vietnam in order to diminish smoking-related adverse outcomes.

Ethics, consent and permissions
The protocol of this study was reviewed and approved by the IRB of Vietnam Authority of HIV/AIDS Control. Written informed consent was obtained from all participants. Patients could withdraw at any time without the influence on their current treatment.

Consent to publish
Not applicable

Availability of Data and Materials
Data are available from the Authority of HIV/AIDS Control (VAAC). Requests for data on this study may be submitted to VAAC and go through a review process by the Scientific and Ethical Research Committee. The contact for requesting data use is Dr. Phan Thi Thu Huong, email: huongphanmoh@gmail.com, Deputy Director in Research of the Vietnam Authority of HIV/AIDS Control, Ministry of Health, Vietnam.

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Competing interests
The authors declare that they have no competing interests.

Authors' Contributions
BXT, HLTN, CL, MD, HPD and HTTP conceived of the study, and participated in its design. HPD, LHN, NPTN, CN, HLTN, GTL, LKN, CNT, BXT, HTL, VTMT, HTTP, TDT, CAL, MD implemented the survey and compiled the data. HPD, LHN, NPTN and BXT analyzed the data. HPD, LHN, NPTN, CN, HLTN, GTL, LKN, CNT, BXT, HTL, VTMT, HTTP, TDT, CAL, MD helped to draft the manuscript. All authors have read and approved the final manuscript

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FIGURE CAPTIONS

Fig 1. Smoking pattern of MMT patients regarding the duration of MMT
(A) Prevalence of cigarette smoker; (B) FTND score

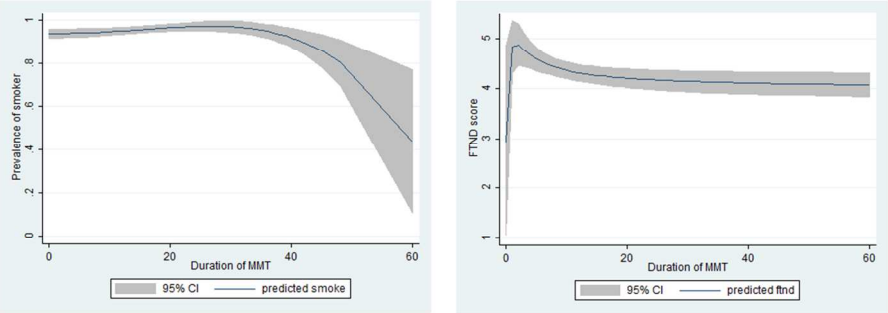

Fig 1. Smoking pattern of MMT patients regarding the duration of MMT
(A) Prevalence of cigarette smoker; (B) FTND score

190x107mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Page	Recommendation
Title and abstract	1	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		2	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	2	3	Explain the scientific background and rationale for the investigation being reported
Objectives	3	3	State specific objectives, including any prespecified hypotheses
Methods			
Study design	4	4	Present key elements of study design early in the paper
Setting	5	4	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	4	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
			(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	4, 5	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	4, 5	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	5	Describe any efforts to address potential sources of bias
Study size	10	4	Explain how the study size was arrived at
Quantitative variables	11	5	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	2	5	(*a*) Describe all statistical methods, including those used to control for confounding
		5	(*b*) Describe any methods used to examine subgroups and interactions
		5	(*c*) Explain how missing data were addressed
			(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
			(*e*) Describe any sensitivity analyses

	Item No	Page	Recommendation
Results			
Participants	13*	6	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
			(b) Give reasons for non-participation at each stage
			(c) Consider use of a flow diagram
Descriptive data	14*	6	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		6, 7	(b) Indicate number of participants with missing data for each variable of interest
			(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*		*Cohort study*—Report numbers of outcome events or summary measures over time
			Case-control study—Report numbers in each exposure category, or summary measures of exposure
		7, 8	*Cross-sectional study*—Report numbers of outcome events or summary measures
Main results	16	7, 8	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
			(*b*) Report category boundaries when continuous variables were categorized
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17		Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			
Key results	18	9	Summarise key results with reference to study objectives
Limitations	19	10	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	9, 10	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	10	Discuss the generalisability (external validity) of the study results
Other information			
Funding	22	11	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association of nicotine dependence and duration of methadone maintenance treatment for opioid users: findings from multi-site survey

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Association of nicotine dependence and duration of methadone maintenance treatment for opioid users: findings from multi-site survey

Huyen Phuc Do[1,9], Long Hoang Nguyen[6], Nhung Phuong Thi Nguyen[7], Chau Ngo[2], Huong Lan Thi Nguyen[9§], Giang Tong Le[5], Linh Khanh Nguyen[8], Cuong Nguyen Tat[9], Bach Xuan Tran[2, 3], Huong Thi Le[3], Vu Thi Minh Thuc[4], Huong Thi Thu Phan[5], Tran Dinh Tho[10], Carl A Latkin[2], Michael Dunne[1]

[1] School of Public Health and Social Work, The Queensland University of Technology, Australia
[2] Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America
[3] Institute for Preventive Medicine and Public Health, Hanoi Medical University, Vietnam
[4] Department of Immunology and Allergy, National Otolaryngology Hospital, Hanoi, Vietnam
[5]Authority of HIV/AIDS Control, Ministry of Health, Hanoi, Vietnam
[6]School of Medicine and Pharmacy, Vietnam National University, Hanoi, Vietnam
[7] Hanoi University of Pharmacy, Hanoi, Vietnam
[8]School of Economics, Vietnam National University, Hanoi, Vietnam
[9]Institute for Global Health Innovations, Duy Tan University, Vietnam
[10]Department of Hepatobiliary Surgery, Vietnam-Germany Hospital, Hanoi, Vietnam

[§] Corresponding author:
Huong Lan Thi Nguyen, Msc.
Institute for Global Health Innovations,
Duy Tan University, Da Nang, Vietnam, 550000
+84974638867 | nguyentlanhuong5@duytan.edu.vn

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ABSTRACT

Objectives: Smoking is associated with adverse health outcomes among drug users. However, there has been a scarcity of evidence about smoking patterns among people receiving opioid dependence treatment in developing countries. We sought to explore self-reported nicotine dependence and determine associated factors in a large sample of opioid-dependent patients receiving methadone maintenance treatment (MMT) in Northern Vietnam.

Setting: Five clinics in Hanoi (urban area) and Nam Dinh (rural area)

Participants: Patients receiving MMT in the settings during the study period

Primary and secondary outcome measures: We collected data about smoking patterns, levels of nicotine dependence and other covariates such as socioeconomic status, health status, alcohol use and drug use. The Fagerström test was used to measure nicotine dependence (FTND). Logistic regression and Tobit regression were employed to examine relationships between the smoking rate, nicotine dependence, and potentially associated variables.

Results: Among 1,016 respondents, approximately 87.2% of drug users taking methadone were current smokers. The mean FTND score was 4.5 (SD=2.4). Longer duration of MMT (OR=0.98; 95%CI=0.96-0.99) and HIV-positive (OR=0.46, 95% CI=0.24-0.88) were associated with lower likelihood of smoking. Being employed, higher age at first drug injection and having long duration of MMT treatment were inverse factors for FTND scores. Whereas, higher age and drug and alcohol abuse were significantly associated with higher FTND score.

Conclusion: Smoking prevalence is high among methadone maintenance drug users. Despite the decrease of smoking over the course of MMT, smoking cessation support should be integrated into MMT program in Vietnam along with controlling risk factors associated with cigarette smoking.

Strengths and limitations of this study:

- Including a large sample size in multiple clinics in various areas
- Employing validated instruments to increase the comparability of the study.
- The causal relationships were unable to establish due to cross-sectional design.
- All data were assessed by retrospective self-reporting without biochemical confirmation, which might result in under-reporting of ongoing drug use due to recall and disclosure bias.
- Convenience sampling strategy limited the generalization of findings

INTRODUCTION

Despite the reduction of smoking worldwide, cigarette smoking rates remain high among opiate-dependent individuals – three or four times higher than that prevalence in general population [1-4]. A systematic review of Guydish et al. in 2011 indicates that the smoking rates among patients in addiction treatment were from 65% to 87.2% [5]. Smoking is concerned as a primary cause of morbidity and mortality in illicit drug users [6 7]. Previous evidence indicates that the death rates of smokers, who had received opioid abuse treatment, were four times greater than that of their counterparts [8]. Additionally, smokers with a range of other substance abuse problems were more likely to die due to smoking related illnesses compared to their non-smoking peers [6 8 9].

Methadone maintenance treatment (MMT) is an effective method to reduce opiate use and improve health status [10 11]. However, empirical evidence suggested that short-term MMT may possibly increases the smoking rates in a dose-dependent relationship, with higher dose of MMT associated with greater nicotine dependence [12-14]. Nicotine appears to make methadone or other opiates more efficaciously reinforced [15]; therefore, MMT patients are more likely to smoke when taking methadone to counteract the sedating effects of methadone, or to produce more pleasurable experience when tobacco and methadone are accompanied [1 16].

Nonetheless, the long-term effect of MMT on smoking is unclear. A study of Helena et al. showed that people with a long duration of MMT were likely to change their smoking habits, reducing nicotine dependence and cigarette smoking [17]. In addition, some prior studies also suggested a high level of motivation to quit smoking among long-term MMT patients [18 19]. Other findings indicated that there is no significant association between ongoing MMT and smoking levels or quitting attempt [20].

Globally, Vietnam is one of the countries with the highest prevalence of tobacco smoking, with approximately 23.8% adults (with 47.4% of men, 1.4% of women) being current cigarette smokers [21]. Smoking is one of the major risk factors for disease burden in Vietnam, attributing to 6.2% of total deaths [22]. Currently, there has been several evidences regarding sexual activities [23], concurrent drug use [24 25], quality of life [23] and health service utilization [26] among MMT patients. However, evidence of smoking behaviour in this population in Vietnam remains limited. This study aimed to explore the prevalence of smoking and level of nicotine dependence, and determines associated factors among MMT patients in Vietnam. Our study is among the first to provide evidence on the pattern of smoking cigarettes during opioid dependent treatment in Vietnam. Therefore, it would partly contribute to the implementation of smoking cessation service for drug users in Vietnam, reducing smoking behaviour and eventually, improving the outcomes of methadone treatment.

MATERIALS AND METHODS

Survey design and sampling

We conducted a cross-sectional study from June to August 2013 at five clinics in Hanoi and Nam Dinh. These two provinces have a high prevalence of HIV-positive patients in the Northern region of Vietnam, with 19,987 and 3,577 people living with HIV/AIDS, respectively [27]. A sampling strategy was employed to select clinics based on the following criteria: (1) clinics at central-, provincial-, and district-level and (2) having at least 150 MMT patients. The characteristics of the study sites are listed in **Table 1**.

Table 1: Study settings and sample size

Level	Settings	Site Name	Type of services	Sample size
District (urban)	Nam Dinh City	Provincial AIDS Centre	MMT+ VCT	270
District (rural)	Xuan Truong District	District Health Centre	MMT+ VCT + ART + GH	151
District (urban)	Tu Liem District	District Health Centre	MMT+ VCT + ART + GH	201
District (urban)	Long Bien District	District Health Centre	MMT+ VCT + ART + GH	184
District (urban)	Ha Dong District	Regional Polyclinic	MMT+ GH	210

**MMT: Methadone maintenance treatment; VCT: Voluntary counselling and testing; ART: Antiretroviral therapy; GH: General healthcare*

Participant recruitments

Participants were eligible if they 1) received daily methadone; 2) ages 18 years or above, and 3) agreed to provide written informed consent. Patients were excluded if they had any health problems that prevented them answering the questionnaire.

Eligible patients were invited when they visited the clinics. If they agreed to enroll, they would be asked to give their written informed consent. A private room in each clinic was arranged to ensure confidentiality and to create a comfortable atmosphere during the interview. A sample of 1,016 patients was enrolled in the study, accounting for 90% of MMT patients in five clinics.

Data collectors did not engage in the provision of care or treatment. No health care providers were involved in the interview or handling of data. Interviewers were well-trained Master of Public Health students from Hanoi Medical University.

Measures and instruments

Smoking related variables

The primary outcome was current smoking status, categorized into three groups: current smoker, former smoker, and never-smoker. Participants were classified as a current cigarette smoker if they have ever smoked at least 100 cigarettes in their life and have smoked in the last 30 days. Those who have never smoked 100 cigarettes and not currently smoking or participants who have smoked 100 cigarettes but have been abstinent in the last 30 days were categorized as non- smokers [28]. Among current smokers, nicotine dependence was measured by the *Fagerström test for nicotine dependence* (FTND) [29 30]. FTND instrument has been applied elsewhere in the context of Vietnam [31]. The total scores range from 0 to 10. The higher the Fagerström score indicates the greater nicotine dependence. Regarding FTND score, patients were categorized into five groups: 0-2: very low, 3-4: low,

5: moderate, 6-7: high and 8-10: very high.

Covariate variables

In this study, covariate variables were selected based on the conceptual framework that was built via prior literature [31-40].

Socio-demographic variables consisted of sex, age, monthly income, employment status, educational attainment, residential area, and marital status. Monthly household income included all sources of income for each household member and was collected via self-reported information by patients Based on income information, patients were classified into five quintile groups: poorest, poor, middle, rich, and richest.

Health status was self-reported by employing the five-level EQ-5D (EQ-5D-5L) instrument [41]. This instrument invested in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The EQ-5D-5L instrument has been validated in Vietnamese context in a previous research [42]. Those experienced from "Slightly" to "Extremely" were categorized as "currently having pain or anxiety". Those who reported no pain or anxiety were categorised "no pain/ anxiety". Additionally, health conditions examined included HIV-infected status and whether they received antiretroviral treatment (ART).

Alcohol use was assessed using the Alcohol Use Disorders Identification Test - Consumption (AUDIT-C), a brief version of the 10-question AUDIT instrument [43 44]. The AUDIT-C score ranges from 0-12, where 4 or more in men and 3 or more in women are considered at-risk drinking [45]. The higher score means the greater alcohol dependence. The AUDIT-C instrument has been validated for Vietnamese populations elsewhere [46 47].

Drug use characteristics were assessed regarding of history of drug use, age at on set of drug use and drug injection and number of episodes of drug rehabilitation [46]. Participants who reported using any substance (heroin, cocaine, methamphetamine, etc.) at least once within the past month were considered concurrent drug users during MMT. Duration of MMT was assessed by self-reported.

Statistical analysis

Data were analysed using Stata version 12.0 for Windows. T-test, Mann-Whitney test and Chi-squared tests were applied to identify the differences amongst socio-demographic, drug and alcohol-related and health-related characteristics regarding smoking status (never, former, and current smokers).

Multivariate logistic regression, combining with polynomial fractions for the duration of MMT treatment, was employed to determine associated factors with being the current smoker. Additionally, this model controlled for nesting of participants within each of the 5 clinic sites. Variables associated with the outcome in bivariate analysis with a $p < 0.25$ were evaluated for inclusion in the multivariate model manually in a forward stepwise manner. Only statistically significant variables with a $p < 0.05$ were retained in the final model.

Because the FTND score was censored from 0 to 10, we used Tobit regression to examine the relationships between FTND scores and potentially related factors [48]. We also utilized a stepwise backward strategy, which is based on the log-likelihood ratio test. The threshold of p-value < 0.1 was used to include variables. All potential interactions were examined.

The Hosmer-Lemeshow goodness-of-fit test was employed to assess model calibration. A p-value less than 0.05 was considered statistically significant.

RESULTS

Table 2 indicates the characteristics of respondents. All participants were men. Most of patients (85.1%) were from the urban area. The mean age was 36.8 years old (SD=7.6). Most of respondents had less than a high school education (55.3%). The majority was married or lived with their partners (67.7%). One-fifth of respondents were employed. The average monthly income was 5.2 million VND, approximately 250 USD (SD=4.2).

One-third of participants were hazardous drinkers (29.6%). Patients with a history of heroin injection accounted for more than 70% of the sample. Only five in one hundred patients reported current illicit drug use during substance abuse treatment (4.8%). The average length of MMT was 16.5 months (SD=11.1). Overall, 17.7% and 20.7% of participants reported currently feeling pain and anxiety, respectively. Respondents with mobility and self-care problem were 7.3% and 3.9%, respectively. Half of the participants enrolled in MMT clinics with comprehensive packages (including MMT, HIV testing and counselling services, ART and general health care (GH)).

In addition, the results of **Table 2** show that the proportion of MMT patient who currently smoked, and non-smoked were 87.2% and 12.5%, respectively. Smoking status was significantly different among groups regarding age, history of drug injection, age at initiation of drug use, and MMT clinic models ($p<0.05$).

Table 2: Characteristics of study participants by smoking status

	Current smoker		Total	p-value
	No	Yes		
N (%)	130 (12.8)	886 (87.2)	1016 (100)	
Socio-demographics				
Age in years, mean years (sd)	38.6 (8.3)	36.5 (7.5)	36.8 (7.6)	<0.01
Annual income (million VND), mean (sd)	4.8 (3.8)	5.2 (4.2)	5.2 (4.2)	0.29
Marital status (n, %)				
Single/Divorced/separated/widowed	35 (10.7)	293 (89.3)	328 (32.3)	0.16
Live with spouse/partner	95 (13.8)	593 (86.2)	688 (67.7)	
Education (n, %)				
Less than high school	80 (14.2)	482 (85.8)	562 (55.3)	0.18
High school	40 (10.3)	347 (89.7)	387 (38.2)	
More than high school	10 (14.9)	57 (85.1)	67 (6.5)	
Location (n, %)				
Urban	104 (12)	761 (88)	865 (85.1)	0.08
Rural	26 (17.2)	125 (82.8)	151 (14.9)	
Employment status (n, %)				
Unemployed	39 (14.9)	222 (85.1)	261 (25.5)	0.46
Self-employed	64 (11.8)	478 (88.2)	542 (53.4)	
Employed	27 (12.7)	186 (87.3)	213 (21.1)	
Substance use, n (%)				
Hazardous drinking (n, %)	35 (11.6)	266 (88.4)	301 (29.6)	0.88
History of drug injection (n, %)	81 (10.9)	665 (89.1)	746 (73.4)	<0.01
Current drug use (n, %)	4 (8.2)	45 (91.8)	49 (4.8)	0.32
Age of drug use, mean age (sd)	25.7 (7.8)	24.4 (6.6)	24.5 (6.7)	0.04
Age of drug injection, mean age (sd)	26.8 (8.2)	26.8 (7.2)	26.8 (7.3)	0.97
Number of drug rehabilitation, mean episode (sd)	5.3 (7.8)	4.8 (6.0)	4.8 (6.3)	0.98
MMT duration, mean months (sd)	18.0 (12.1)	16.3 (10.8)	16.5 (11.0)	0.20
Health-related characteristics				

Current ARV treatment, n (%)	13 (19.7)	53 (80.3)	66 (6.5)	0.08
Currently feeling pain, n (%)	24 (13.3)	156 (86.7)	180 (17.7)	0.81
Currently feeling anxiety, n (%)	28 (13.3)	182 (86.7)	210 (20.7)	0.60
Currently perceive mobility problem, n (%)	8 (10.8)	66 (89.2)	74 (7.3)	0.79
Currently perceive self-care problem, n (%)	7 (17.5)	33 (82.5)	40 (3.9)	0.36
Currently perceive usual activity problem, n (%)	7 (11.7)	53 (88.3)	60 (5.9)	0.79
MMT service delivery model				
MMT+ VCT	32 (11.9)	238 (88.1)	270 (26.6)	0.03
MMT + GH	17 (8.1)	193 (91.9)	210 (20.7)	
MMT+ VCT + ART + GH	81 (15.1)	455 (84.9)	536 (52.8)	

Smoking pattern of MMT patients is revealed in **Table 3**. Mean age of initial smoking was 17.2 years (SD=3.5), with mean duration of regular smoking being 14.1 years (SD=8.5). A total of 306.3 thousand VND per month were spent for cigarettes (=15 USD). Among smokers, mean FTND score was 4.5 (SD=2.4), and most of them were in low (27.0%) and very low dependence (26.1%) groups.

Table 3 – Smoking pattern of Vietnamese MMT patients

Characteristic	N (%)
Age at smoking initiation, mean years (sd)	17.2 (3.5)
Duration of regular smoking, mean years (sd)	14.1 (8.5)
Expense for smoking (VND per month), mean (sd)	306.3 (289.4)
FTND score, mean (sd)	4.5 (2.4)
Nicotine dependence scale, n (%)	
Very low	231 (26.1)
Low	239 (27.0)
Moderate	115 (12.9)
High	184 (20.8)
Very high	117 (13.2)
Number of cigarette per day, n (%)	
<=10	409 (46.2)
11-20	407 (45.9)
21-30	49 (5.5)
>30	21 (2.4)

Figure 1 indicates that the smoking rate and FTND score were high in the early phase of treatment, then significantly decreased afterward.

The reduced multivariate model in **Table 4** revealed that patients high school education (OR=2.29, 95%CI=1.28-4.07) were more likely report current smoking than others. Being HIV-positive (OR=0.46, 95% CI=0.24 – 0.88) was negative factors for currently smoking. Notably, individuals having longer duration of MMT were less likely to smoke than others (OR=0.98; 95%CI=0.96-0.99).

Table 4 also shows the findings from Tobit model. Being employed, higher age at first drug injection and having long duration of MMT treatment were inverse factors for FTND scores.

Whereas, higher age and having other single or multiple substance abuse (illicit drug, alcohol drinking) were significantly associated with higher FTND score.

Table 4: Associated factors of smoking status among study participants

Characteristics	Current smoking (Yes/No)			FTND score		
	OR	95% CI		Coef	95% CI	
Age				0.04**	0.01	0.08
Education (vs < High school)						
• High school	2.29**	1.28	4.07			
Occupations (vs Unemployed)						
• Employed				-0.55**	-1.07	-0.03
Income quintile (vs Poorest)						
• Rich				0.52*	-0.03	1.07
• Richest				0.63*	0.10	1.17
HIV status (vs Negative)						
• Positive	0.46**	0.24	0.88	-0.44	-1.11	0.22
• Unknown				-0.76	-1.76	0.24
Age of first drug injection				-0.07**	-0.11	-0.02
Substance use						
Interaction between current drug use and alcohol drinking (vs No use drug + No drink hazardously)						
• Only drink hazardously	1.51	0.82	2.78	0.83**	0.37	1.30
• Only use drug				1.61**	0.23	3.25
• Both use drug + drink hazardously				1.75**	0.24	3.25
No. of drug rehabilitation (vs None)						
• 1-5 times				-0.33	-0.75	0.09
Duration of MMT (months)	0.98**	0.96	0.99	-0.03**	-0.05	-0.01
MMT delivery model (vs MMT+VCT)						
• MMT + GH	2.11*	0.98	4.56			
• MMT+ VCT + ART + GH				-0.30	-0.73	0.13

MMT: Methadone maintenance treatment; VCT: voluntary counselling and testing service; GH: General health care

**p<0.1; ** p<0.05*

DISCUSSION

We observed the high smoking rate among MMT patients with nearly 90% - three times higher than that of the Vietnamese general population (23.8%) [21]. The result is consistent with research in other countries namely Switzerland, United States, Australia, Canada, Mexico, and England [8 49-53]. The prevalence of current smokers among MMT patients in this study appeared to be consistent with the statistic in both developed (e.g. United States and Australia) and developing countries (e.g. China) [54-57]. This result might be explained by the interaction between nicotine and methadone, that smoking eases the craving for heroin and cocaine consumption [15]. A study by McCool et al. suggested that MMT patients smoked to counteract the sedating effects of methadone and experience the pleasing effect when cigarettes and methadone are taken together [1 16]. This might play as a motivation factor for keeping smoking or in other words, might be a barrier for smoking cessation among MMT patients. To date, in Vietnam, only two official smoking cessation clinics, one in Hanoi and one in Ho Chi Minh city, have been operated. Therefore, further plans for scaling-up MMT program should consider integrating with smoking cessation services, which might help to diminish the smoking epidemic in the MMT population.

Notably, our result suggests sensitive stages of smoking change among MMT patients. The current study shows that longer duration of MMT was disproportionate with the likelihood of being smokers or higher nicotine dependence. We found that the smoking rates increased gradually in the first 30 months (but not significantly), and remarkably decrease afterwards. We suppose that in the initial stage of treatment, smoking helped patients to counter the aftertaste of MMT and improved the pleasing effect [58]. Consequently, they were more likely to smoke cigarette until they could feel comfortable with the side-effects of MMT. A study of Abbott (2010) on 189 MMT patients showed that after 12 months of treatment, smoking support cessation was the fourth most requested and important service although very few patients requested this service at baseline [59].

Likewise, we observed an association of higher FTND score among the first 5 month MMT patients and then steadily decrease afterwards . It can be explained that in the first few months, patients would require a high dose for substantial treatment, which led to more severity of nicotine dependence (displayed by FTND score) [14 60]. When patients treated MMT in the long time, they tended to receive stable or lower methadone doses, which diminished nicotine dependence and promoted the intention to quit smoking [3]. This result is consistent with previous study of Okruhlica et al., which suggested that level of nicotine dependence was reduced after 12 months of treatment when the MMT dose was stabilized [61].

Respondents with multiple substance abuse (alcohol and illicit drug use) were associated with higher nicotine dependence, especially among those who currently used illicit drug. The complex relationships between smoking, alcohol and drug use have been well-documented in global settings, that people having one risk behaviour (such as drug use) tended to engage in other behaviours (such as smoking and alcohol) [32 39 40 58 62]. Therefore, these relationships during the course of MMT are clinically important that should be carefully monitored and controlled, which could help to identify who may need to receive specific cessation interventions at MMT sites.

This study also found significant associations between smoking and socio-demographic factors such as age, education, and employment. We have found that higher age was a predictor for higher nicotine dependence (higher FTND score). This finding was consistent with the results of other studies in Korea and China, which suggested the positive correlation

between age and FTND [63 64]. Additionally, people with high school education were more likely to smoke compared with lower education group, which was supported by prior study [32]. This point needs further investigation; however, it might anticipate that highly educated respondents are more likely to have higher income to spend more for tobacco consumption. Notably, patients who were employed had lower FTND scores than that of unemployed respondents. With about 25% sample being unemployed, this finding proposes the necessity of employment orientation for MMT patients to diminish the negative effects of cigarette smoking.

Results of multivariable regression indicated that HIV-positive drug users were less likely to be current smokers, which could be explained by the belief of health risk. Perceiving the deficit immunization and/or facing poor physical health condition due to HIV/AIDS could encourage patients to avoid risky behaviours such as smoking and alcohol use [38]. However, empirical evidence worldwide noted that people undertaking both ART and MMT, might relapse and smoking more often [31 37]. Furthermore, when they believe that they will not live long enough to suffer from smoking related illnesses; or perceived that they are at a lower health risk for continued smoking especially during a stable stage of ART, they will smoke more [38]. Therefore, special attention should be paid on patients living with HIV in order to help them avoid risk behaviours such as smoking, and promote a healthier lifestyle.

This study has strengths that included a large sample size (1,016 MMT patients), collaboration with multiple clinics in various areas and validated instruments (e.g. FTND, AUDIT-C, EQ-5D-5L). Nonetheless, several limitations should be considered. First, the causal relationships were unable to establish due to cross-sectional design. Additionally, all data were assessed by retrospective self-reporting without biochemical confirmation. This may have resulted in under-reporting of ongoing drug use due to recall and disclosure bias. Finally, due to the convenience sampling strategy to address confidentiality issues of drug use and HIV-positive patients, the generalization of our results is limited. Therefore, the results should be careful to be interpreted to the whole MMT population.

CONCLUSION

The findings from this study revealed that smoking is highly prevalent among MMT patients, putting them at a high risk of smoking-related illnesses. Despite the decrease of smoking over the course of MMT, smoking cessation support, along with concerning multi-substance use, employment and health status, should be integrated into MMT program in Vietnam in order to diminish smoking-related adverse outcomes.

Ethics, consent and permissions
The protocol of this study was reviewed and approved by the IRB of Vietnam Authority of HIV/AIDS Control. Written informed consent was obtained from all participants. Patients could withdraw at any time without the influence on their current treatment.

Consent to publish
Not applicable

Availability of Data and Materials
Data are available from the Authority of HIV/AIDS Control (VAAC). Requests for data on this study may be submitted to VAAC and go through a review process by the Scientific and Ethical Research Committee. The contact for requesting data use is Dr. Phan Thi Thu Huong, email: huongphanmoh@gmail.com, Deputy Director in Research of the Vietnam Authority of HIV/AIDS Control, Ministry of Health, Vietnam.

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Competing interests
The authors declare that they have no competing interests.

Authors' Contributions
BXT, HLTN, CL, MD, HPD and HTTP conceived of the study, and participated in its design. HPD, LHN, NPTN, CN, HLTN, GTL, LKN, CNT, BXT, HTL, VTMT, HTTP, TDT, CAL, MD implemented the survey and compiled the data. HPD, LHN, NPTN and BXT analyzed the data. HPD, LHN, NPTN, CN, HLTN, GTL, LKN, CNT, BXT, HTL, VTMT, HTTP, TDT, CAL, MD helped to draft the manuscript. All authors have read and approved the final manuscript

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FIGURE CAPTIONS

Fig 1. Smoking pattern of MMT patients regarding the duration of MMT
(A) Prevalence of cigarette smoker; (B) FTND score

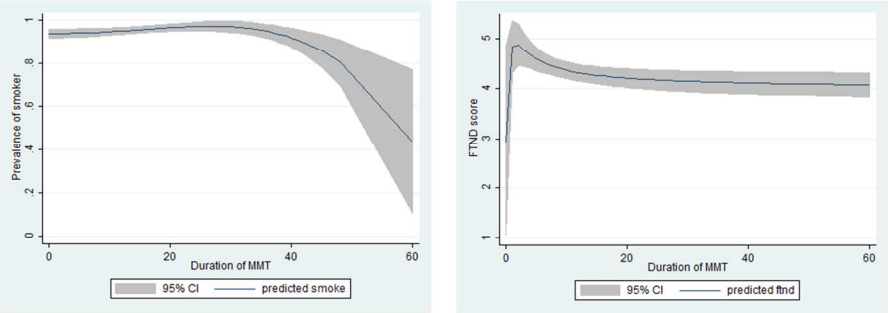

Fig 1. Smoking pattern of MMT patients regarding the duration of MMT
(A) Prevalence of cigarette smoker; (B) FTND score

190x107mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Page	Recommendation
Title and abstract	1	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		2	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	2	3	Explain the scientific background and rationale for the investigation being reported
Objectives	3	3	State specific objectives, including any prespecified hypotheses
Methods			
Study design	4	4	Present key elements of study design early in the paper
Setting	5	4	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	4	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
			(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	4, 5	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	4, 5	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	5	Describe any efforts to address potential sources of bias
Study size	10	4	Explain how the study size was arrived at
Quantitative variables	11	5	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	2	5	(*a*) Describe all statistical methods, including those used to control for confounding
		5	(*b*) Describe any methods used to examine subgroups and interactions
		5	(*c*) Explain how missing data were addressed
			(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
			(*e*) Describe any sensitivity analyses

	Item No	Page	Recommendation
Results			
Participants	13*	6	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
			(b) Give reasons for non-participation at each stage
			(c) Consider use of a flow diagram
Descriptive data	14*	6	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		6, 7	(b) Indicate number of participants with missing data for each variable of interest
			(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*		*Cohort study*—Report numbers of outcome events or summary measures over time
			Case-control study—Report numbers in each exposure category, or summary measures of exposure
		7, 8	*Cross-sectional study*—Report numbers of outcome events or summary measures
Main results	16	7, 8	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
			(*b*) Report category boundaries when continuous variables were categorized
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17		Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			
Key results	18	9	Summarise key results with reference to study objectives
Limitations	19	10	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	9, 10	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	10	Discuss the generalisability (external validity) of the study results
Other information			
Funding	22	11	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Factors associated with nicotine dependence during methadone maintenance treatment: findings from a multi-site survey in Vietnam

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Complete List of Authors:	Do, Huyen; Queensland University of Technology School of Public Health and Social Work Nguyen, Long; School of Medicine and Pharmacy, Vietnam National University Nguyen, Nhung; Hanoi University of Pharmacy Chau, Ngo; Johns Hopkins University Bloomberg School of Public Health Nguyen, Lan Huong; Duy Tan University, Institute for Global Health Innovations Le, Giang; Authority of HIV/AIDS Control, Ministry of Health Nguyen, Linh; School of Economics, Vietnam National University Nguyen, Cuong; Institute for Global Health Innovations, Duy Tan University Xuan Bach, Tran; Institute for Preventive Medicine and Public Health, Hanoi Medical University, Health Economics Thi Huong, Le; Institute for Preventive Medicine and Public Health, Hanoi Medical University Vu, Minh Thuc; Department of Immunology and Allergy, National Otolaryngology Hospital Phan, Huong; Authority of HIV/AIDS Control, Ministry of Health Tho, Tran; Department of Hepatobiliary Surgery, Vietnam-Germany Hospital, Hanoi, Vietnam Latkin, Carl; Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA Michael, Dunne; Queensland University of Technology School of Public Health and Social Work
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Factors associated with nicotine dependence during methadone maintenance treatment: findings from a multi-site survey in Vietnam

Huyen Phuc Do[1,5], Long Hoang Nguyen[2], Nhung Phuong Thi Nguyen[3], Chau Ngo[4], Huong Lan Thi Nguyen[5§], Giang Tong Le[6], Linh Khanh Nguyen[7], Cuong Nguyen Tat[5], Bach Xuan Tran[4,8], Huong Thi Le[8], Vu Thi Minh Thuc[9], Huong Thi Thu Phan[6], Tran Dinh Tho[10], Carl A Latkin[4], Michael P Dunne[1,11]

[1] School of Public Health and Social Work, the Queensland University of Technology, Australia
[2]School of Medicine and Pharmacy, Vietnam National University, Hanoi, Vietnam
[3] Hanoi University of Pharmacy, Hanoi, Vietnam
[4] Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America
[5]Institute for Global Health Innovations, Duy Tan University, Vietnam
[6]Authority of HIV/AIDS Control, Ministry of Health, Hanoi, Vietnam
[7]School of Economics, Vietnam National University, Hanoi, Vietnam
[8] Institute for Preventive Medicine and Public Health, Hanoi Medical University, Vietnam
[9] Department of Immunology and Allergy, National Otolaryngology Hospital, Hanoi, Vietnam
[10]Department of Hepatobiliary Surgery, Vietnam-Germany Hospital, Hanoi, Vietnam
[11]Institute for Community Health Research, Hue University of Medicine and Pharmacy, Hue, Vietnam

[§] Corresponding author:
Huong Lan Thi Nguyen, Msc.
Institute for Global Health Innovations,
Duy Tan University, Da Nang, Vietnam, 550000
+84974638867 | nguyentlanhuong5@duytan.edu.vn

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ABSTRACT

Objectives: Smoking is associated with adverse health outcomes among drug users, including those in treatment. To date however, there has been little evidence about smoking patterns among people receiving opioid dependence treatment in developing countries. We examined self-reported nicotine dependence and associated factors in a large sample of opioid-dependent patients receiving methadone maintenance treatment (MMT) in Northern Vietnam.

Setting: Five clinics in Hanoi (urban area) and Nam Dinh (rural area)

Participants: Patients receiving MMT in the settings during the study period

Primary and secondary outcome measures: We collected data about smoking patterns, levels of nicotine dependence and other covariates such as socioeconomic status, health status, alcohol use and drug use. The Fagerström test was used to measure nicotine dependence (FTND). Logistic regression and Tobit regression were employed to examine relationships between the smoking rate, nicotine dependence, and potentially associated variables.

Results: Among 1,016 drug users undergoing MMT (98.7% male), 87.2% were current smokers. The mean FTND score was 4.5 (SD=2.4). Longer duration of MMT (OR=0.98; 95%CI=0.96-0.99) and being HIV-positive (OR=0.46, 95% CI=0.24-0.88) were associated with lower likelihood of smoking. Being employed, older age at first drug injection and having long duration of MMT were inversely related with FTND scores. Higher age and continuing drug and alcohol use were significantly associated with higher FTND scores.

Conclusion: Smoking prevalence is high among methadone maintenance drug users. Enhanced smoking cessation support should be integrated into MMT programs in order to reduce risk factors for cigarette smoking and improve the health and well-being of people recovering from opiate dependence.

Strengths and limitations of this study:

- Included a large sample in multiple clinics in urban and rural areas
- Employed validated instruments to increase the comparability of the study.
- The causal relationships could not be established due to the cross-sectional design.
- All data were gathered by retrospective self-report without biochemical confirmation, which might may mask under-reporting of ongoing drug use.
- The convenience sampling strategy limited the generalizability of findings

INTRODUCTION

Despite the reduction of smoking worldwide, cigarette smoking rates remain high among opiate-dependent individuals – three or four times higher than in the general population [1-4]. A systematic review of Guydish et al. in 2011 indicated that smoking rates among patients in addiction treatment ranged from 65% to 87.2% [5]. Smoking is a primary cause of morbidity and mortality in illicit drug users [6 7]. Evidence indicates that the death rates of smokers who had received opioid abuse treatment were four times greater than that of their counterparts [8]. Additionally, smokers with a range of other substance abuse problems were more likely to die due to smoking related illnesses compared to their non-smoking peers [6 8].

Methadone maintenance treatment (MMT) is an effective method to reduce opiate use and improve health status [9 10]. However, some evidence suggests that short-term MMT may increase smoking in a dose-dependent relationship, with higher dose of MMT associated with greater nicotine dependence [11-13]. Nicotine appears to make methadone or other opiates more efficaciously reinforced [14]; therefore, MMT patients may be more likely to continue to smoke, and to smoke heavily, when taking MMT to counteract the sedating effects of methadone, or to produce a more pleasurable experience when tobacco and methadone are used together [1 15].

In contrast, a study by Helena et al. found that people with a long duration of MMT were likely to change their smoking habits, reducing nicotine dependence and cigarette smoking [16]. In addition, some prior research suggests a high level of motivation to quit smoking among long-term MMT patients [17]. However, other research indicates that there is no significant association between ongoing MMT and smoking levels or quitting attempts [18].

Globally, Vietnam is one of the countries with very high prevalence of tobacco smoking. Approximately 23.8% of adults smoke, and there is a major gender difference, with 47.4% of men and 1.4% of women being current cigarette smokers [19]. Smoking is a major contributor to disease burden in Vietnam, accounting for 6.2% of total deaths [20]. Health surveys of people with opioid dependence have described sexual activities [21], concurrent drug use [22 23], quality of life [21] and health service utilization [24], but there has been little analysis of smoking behaviour in this population in Vietnam. This study explored the prevalence of smoking and levels of nicotine dependence, and associated factors among MMT patients. Our study is among the first to provide evidence on the pattern of smoking cigarettes during opioid dependence treatment in Vietnam. The purpose was to contribute evidence to support implementation of dedicated smoking cessation services for opiate users in treatment in Vietnam.

MATERIALS AND METHODS

Survey design and sampling

We conducted a cross-sectional study from June to August 2013 at five clinics in Hanoi and Nam Dinh. These two provinces have a high prevalence of HIV-positive patients in the Northern region of Vietnam, with 19,987 and 3,577 people living with HIV/AIDS, respectively [25]. Sampling was undertaken at clinics at central-, provincial-, and district-levels that had at least 150 MMT patients. The characteristics of the study sites are shown in **Table 1**.

Table 1: Study settings and sample size

Level	Settings	Site Name	Type of services	Sample size
District (urban)	Nam Dinh City	Provincial AIDS Centre	MMT+ VCT	270
District (rural)	Xuan Truong District	District Health Centre	MMT+ VCT + ART + GH	151
District (urban)	Tu Liem District	District Health Centre	MMT+ VCT + ART + GH	201
District (urban)	Long Bien District	District Health Centre	MMT+ VCT + ART + GH	184
District (urban)	Ha Dong District	Regional Polyclinic	MMT+ GH	210

**MMT: Methadone maintenance treatment; VCT: Voluntary counselling and testing; ART: Antiretroviral therapy; GH: General healthcare*

Participant recruitments

Participants were eligible if they 1) received daily methadone; 2) were aged 18 years or above and 3) agreed to provide written informed consent. Patients were excluded if they had any health or communication problems that prevented them answering the questionnaire.

Eligible patients were invited when they visited the clinics. If they agreed to enroll, they were asked to give written informed consent. A private room in each clinic was arranged to ensure confidentiality and to create a comfortable atmosphere during the interview. A sample of 1,016 patients was enrolled in the study, accounting for 90% of MMT patients in five clinics.

Data collectors did not engage in the provision of care or treatment. No direct health care providers were involved in the interview or handling of data. Interviewers were well-trained Master of Public Health students from Hanoi Medical University.

Measures and instruments

Smoking related variables

The primary outcome was current smoking status, categorized into two groups: current smoker (Y/N). Participants were classified as a current cigarette smoker if they have ever smoked at least 100 cigarettes in their life and have smoked in the last 30 days. Those who have never smoked 100 cigarettes and not currently smoking or participants who have smoked 100 cigarettes but have been abstinent in the last 30 days were categorized as non-smokers [26]. Among current smokers, nicotine dependence was measured by the *Fagerström test for nicotine dependence* (FTND) [27 28]. The FTND instrument has been applied elsewhere in Vietnam [29]. The total scores range from 0 to 10. The higher the Fagerström score indicates the greater nicotine dependence. Regarding FTND score, patients were categorized into five groups: 0-2: very low, 3-4: low, 5: moderate, 6-7: high and 8-10:

very high.

Study covariates

Socio-demographic variables consisted of sex, age, monthly income, employment status, educational attainment, residential area, and marital status. Monthly household income included all sources of income for each household member and was collected via self-reported information by patients. Based on income information, patients were classified into five quintile groups: poorest, poor, middle, rich, and richest.

Health status was self-reported by employing the five-level EQ-5D (EQ-5D-5L) instrument [30]. This includes five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The EQ-5D-5L has been validated in Vietnamese context[31]. Respondents who experienced from "Slightly" to "Extremely" on an item were categorized as "currently having pain or anxiety". Those who reported no pain or anxiety were categorised "no pain/ anxiety". Other health conditions examined included HIV-infection status and whether they received antiretroviral treatment (ART).

Alcohol use was assessed using the Alcohol Use Disorders Identification Test - Consumption (AUDIT-C), a brief version of the 10-question AUDIT instrument [32 33]. The AUDIT-C score ranges from 0-12, where 4 or more in men and 3 or more in women are considered at-risk drinking [34]. The higher score means the greater alcohol dependence. The AUDIT-C instrument has been validated for Vietnamese populations elsewhere [35 36].

Drug use characteristics were assessed regarding of history of drug use, age at onset of drug use and drug injection and number of episodes of drug rehabilitation [35]. Participants who reported using any substance (heroin, cocaine, methamphetamine, etc.) at least once within the past month were considered concurrent drug users during MMT. Duration of MMT was assessed by self-reported.

Statistical analysis

Data were analysed using Stata version 12.0 for Windows. T-tests, Mann-Whitney tests and Chi-squared tests were applied to identify differences amongst socio-demographic, drug and alcohol-related and health-related characteristics by current smoking status (Yes/No).

Multivariate logistic regression, combined with polynomial fractions for the duration of MMT treatment, was employed to determine factors associated with being a current smoker. Additionally, this model controlled for nesting of participants within each of the 5 clinic sites. Variables associated with the outcome in bivariate analysis with a $p < 0.25$ were included in the multivariate model manually in a forward stepwise manner. Only statistically significant variables with a $p < 0.05$ were retained in the final model.

Because the FTND score was censored from 0 to 10, we used Tobit regression to examine the relationships between FTND scores and potentially related factors [37]. We also utilized a stepwise backward strategy, which is based on the log-likelihood ratio test. The threshold of p-value < 0.1 was used to include variables. All potential interactions were examined. The Hosmer-Lemeshow goodness-of-fit test was employed to assess model calibration. A p-value less than 0.05 was considered statistically significant.

RESULTS

Table 2 indicates the characteristics of respondents. Most participants were men (98.7%) compared to just 1.3% of women, and they mainly came from urban areas (85.15). The mean age was 36.8 years (SD=7.6). Most respondents had less than a high school education (55.3%). The majority were married or lived with their partners (67.7%). One-fifth of respondents were employed. The average monthly income was 5.2 million VND, approximately 250 USD (SD=4.2).

One-third of participants were hazardous drinkers (29.6%). Patients with a history of heroin injection accounted for more than 70% of the sample. Only five in one hundred patients reported current illicit drug use during treatment (4.8%). The average length of MMT was 16.5 months (SD=11.0). Overall, 17.7% and 20.7% of participants reported currently feeling pain and/or anxiety, respectively. Respondents with mobility and self-care problem were 7.3% and 3.9%, respectively. Half of the participants were enrolled in MMT clinics that had comprehensive packages (including MMT, HIV testing and counselling services, ART and general health care (GH)).

Table 2 shows that the proportion of MMT patient who currently smoked was 87.3% of men and 76.9% of women. The difference between male and female smokers was not statistically significant (p=0.26), probably because of the very small number of females in this study. Smoking status was significantly different between groups regarding age, history of drug injection, age at initiation of drug use, and MMT clinic models (p<0.05).

Table 2: Characteristics of study participants by smoking status

	Current smoker		Total	p-value
	No	Yes		
N (%)	130 (12.8)	886 (87.2)	1016 (100)	
Socio-demographics				
Age in years, mean years (sd)	38.6 (8.3)	36.5 (7.5)	36.8 (7.6)	<0.01
Gender, n (%)				
Female	3 (23.1%)	10 (76.9%)	13(1.3)	0.26
Male	127 (12.7%)	876 (87.3%)	1003 (98.7)	
Monthly income (million VND), mean (sd)	4.8 (3.8)	5.2 (4.2)	5.2 (4.2)	0.29
Marital status (n, %)				
Single/Divorced/separated/widowed	35 (10.7)	293 (89.3)	328 (32.3)	0.16
Live with spouse/partner	95 (13.8)	593 (86.2)	688 (67.7)	
Education (n, %)				
Less than high school	80 (14.2)	482 (85.8)	562 (55.3)	0.18
High school	40 (10.3)	347 (89.7)	387 (38.2)	
More than high school	10 (14.9)	57 (85.1)	67 (6.5)	
Location (n, %)				
Urban	104 (12)	761 (88)	865 (85.1)	0.08
Rural	26 (17.2)	125 (82.8)	151 (14.9)	
Employment status (n, %)				
Unemployed	39 (14.9)	222 (85.1)	261 (25.5)	0.46
Self-employed	64 (11.8)	478 (88.2)	542 (53.4)	
Employed	27 (12.7)	186 (87.3)	213 (21.1)	
Substance use, n (%)				
Hazardous drinking (n, %)	35 (11.6)	266 (88.4)	301 (29.6)	0.88
History of drug injection (n, %)	81 (10.9)	665 (89.1)	746 (73.4)	<0.01
Current drug use (n, %)	4 (8.2)	45 (91.8)	49 (4.8)	0.32

Age of drug use, mean age (sd)	25.7 (7.8)	24.4 (6.6)	24.5 (6.7)	0.04
Age of drug injection, mean age (sd)	26.8 (8.2)	26.8 (7.2)	26.8 (7.3)	0.97
Number of drug rehabilitation, mean episode (sd)	5.3 (7.8)	4.8 (6.0)	4.8 (6.3)	0.98
MMT duration, mean months (sd)	18.0 (12.1)	16.3 (10.8)	16.5 (11.0)	0.20
Health-related characteristics				
Current ARV treatment, n (%)	13 (19.7)	53 (80.3)	66 (6.5)	0.08
Currently feeling pain, n (%)	24 (13.3)	156 (86.7)	180 (17.7)	0.81
Currently feeling anxiety, n (%)	28 (13.3)	182 (86.7)	210 (20.7)	0.60
Currently perceive mobility problem, n (%)	8 (10.8)	66 (89.2)	74 (7.3)	0.79
Currently perceive self-care problem, n (%)	7 (17.5)	33 (82.5)	40 (3.9)	0.36
Currently perceive usual activity problem, n (%)	7 (11.7)	53 (88.3)	60 (5.9)	0.79
MMT service delivery model				
MMT+ VCT	32 (11.9)	238 (88.1)	270 (26.6)	0.03
MMT + GH	17 (8.1)	193 (91.9)	210 (20.7)	
MMT+ VCT + ART + GH	81 (15.1)	455 (84.9)	536 (52.8)	

Smoking behaviour and nicotine dependence among MMT patients are revealed in **Table 3**. Mean age of initial smoking was 17.2 years (SD=3.5), with mean duration of regular smoking being 14.1 years (SD=8.5). A total of 306.3 thousand VND per month were spent for cigarettes (=15 USD). Among smokers, mean FTND score was 4.5 (SD=2.4), and most of them were in low (27.0%) and very low dependence (26.1%) groups.

Table 3 – Smoking pattern of Vietnamese MMT patients

Characteristic	N (%)
Age at smoking initiation, mean years (sd)	17.2 (3.5)
Duration of regular smoking, mean years (sd)	14.1 (8.5)
Expense for smoking (VND per month), mean (sd)	306.3 (289.4)
FTND score, mean (sd)	4.5 (2.4)
Nicotine dependence scale, n (%)	
Very low	231 (26.1)
Low	239 (27.0)
Moderate	115 (12.9)
High	184 (20.8)
Very high	117 (13.2)
Number of cigarette per day, n (%)	
<=10	409 (46.2)
11-20	407 (45.9)
21-30	49 (5.5)
>30	21 (2.4)

Figure 1 indicates that the smoking rate and FTND score were high in the early phase of treatment, and then significantly decreased afterward.

The reduced multivariate model in **Table 4** shows that patients with high school education (OR=2.29, 95%CI=1.28-4.07) were more likely report current smoking than others. Being HIV-positive (OR=0.46, 95% CI=0.24 – 0.88) was negatively associated with current

smoking. Individuals having longer duration of MMT were less likely to smoke than others (OR=0.98; 95%CI=0.96-0.99).

Table 4 shows the findings from the Tobit model. Being employed, higher age at first drug injection and having long duration of MMT treatment were inverse factors for FTND scores. Further, higher age and having other single or multiple substance abuse (illicit drug, alcohol drinking) were significantly associated with higher FTND score.

Table 4: Factors associated with smoking status

Characteristics	Current smoking (Yes/No)			FTND score		
	OR	95% CI		Coef	95% CI	
Age				0.04**	0.01	0.08
Education (vs < High school)						
• High school	2.29**	1.28	4.07			
Occupations (vs Unemployed)						
• Employed				-0.55**	-1.07	-0.03
Income quintile (vs Poorest)						
• Rich				0.52*	-0.03	1.07
• Richest				0.63*	0.10	1.17
HIV status (vs Negative)						
• Positive	0.46**	0.24	0.88	-0.44	-1.11	0.22
• Unknown				-0.76	-1.76	0.24
Age of first drug injection				-0.07**	-0.11	-0.02
Substance use						
Interaction between current drug use and alcohol drinking (vs No use drug + No drink hazardously)						
• Only drink hazardously	1.51	0.82	2.78	0.83**	0.37	1.30
• Only use drug				1.61**	0.23	3.25
• Both use drug + drink hazardously				1.75**	0.24	3.25
No. of drug rehabilitation (vs None)						
• 1-5 times				-0.33	-0.75	0.09
Duration of MMT (months)	0.98**	0.96	0.99	-0.03**	-0.05	-0.01
MMT delivery model (vs MMT+VCT)						
• MMT + GH	2.11*	0.98	4.56			
• MMT+ VCT + ART + GH				-0.30	-0.73	0.13

MMT: Methadone maintenance treatment; VCT: voluntary counselling and testing service; GH: General health care

**p<0.1; ** p<0.05*

DISCUSSION

The smoking rate among MMT patients was very high, with 87.3% of men and 79.6% of women being current smokers. Smoking prevalence among the mostly male MMT clients was twice the national average for men (about 47%) in the general population. [19]. This is consistent with research in other countries, such as Switzerland, United States, Australia, Canada, Mexico, and England [8 38-42]. The high persistence of smoking might be explained by the interactive effects of addictive substances such as methadone, narcotics and nicotine [14]. Consequently, patients during MMT may be more vulnerable to smoking than in general populations. Some evidence indicates that smoking helps drug users to cope with cravings [43 44]. Additionally, methadone use might contribute to high consumption of cigarettes because MMT patients smoke to counteract the sedating effects of methadone. It is also possible that there are pleasing effects when cigarettes and methadone are taken together [1 15]. Together, these effects might be a barrier for smoking cessation among MMT patients. To date, in Vietnam, only two official smoking cessation clinics for opiate users in treatment, one in Hanoi and one in Ho Chi Minh City, have been in operation. Therefore, plans to scale up MMT nationally should consider integrating smoking cessation services to diminish the smoking epidemic in this population.

The current study shows that longer duration of MMT was associated with lower likelihood of current smoking and less nicotine dependence. Notably, smoking increased gradually in the first 30 months (but not significantly), and decreased remarkably afterwards. It is possible that in the initial stage of treatment, smoking helped patients to counter the aftertaste of MMT and may have enhanced the pleasing effects [45]. Consequently, they may have been more likely to smoke cigarettes until they could feel comfortable with the side-effects of MMT. A study by Abbott (2010) with 189 MMT patients found that after 12 months of treatment, smoking support cessation was the fourth most requested and important service although very few patients requested this service at baseline [46].

Likewise, we observed higher FTND scores among patients in the first 5 month of MMT and then a steady decrease afterwards. It may be that in the first few months, patients would require a high dose for effective treatment, which leads to more severe nicotine dependence (as indicated by FTND score) [13 47]. In contrast, patients treated with MMT for a long time tend to receive stable or lower methadone doses, which may diminish nicotine dependence and promote the intention to quit smoking [3]. The evidence from Vietnam is consistent with a study in Slovakia by Okruhlica et al., which suggested that level of nicotine dependence was reduced after 12 months of treatment when the MMT dose was stabilized [48].

Respondents with multiple substance abuse (alcohol and illicit drug use) had higher nicotine dependence, especially among those who concurrently used illicit drugs during MMT. The complex relationships between smoking, alcohol and drug use have been well-documented in global settings. People having one risk behaviour (such as drug use) tend to engage in other behaviours (such as smoking and alcohol) [45 49-52]. Therefore, these relationships during the course of MMT are clinically important that should be carefully monitored and controlled, which could help to identify who may need to receive specific cessation interventions at MMT sites.

This study also found significant associations between smoking and socio-demographic factors such as age, education, and employment. Older age was correlated with higher nicotine dependence (higher FTND score). This is consistent with studies in Korea and China [53 54]. Additionally, people with high school education were more likely to smoke

compared to those with lower education. This is somewhat counter-intuitive given the inverse relationship between education and smoking in many countries [30], but could be explained by an associated factor such as income. It might be anticipate that the highly educated respondents are more likely to have higher income to spend more on tobacco consumption.

Results of multivariable regression indicated that HIV-positive drug users were less likely to be current smokers, which could be related to perceptions about health risks. Fears about impending poor physical health due to HIV/AIDS could encourage patients to avoid risky behaviours such as smoking and alcohol use [55]. However, empirical evidence worldwide suggests that people undertaking both ART and MMT often relapse and smoke more often [29 56]. Furthermore, when they believe that they will not live long enough to suffer from smoking related illnesses; or perceive that they are at a lower health risk for continued smoking especially during a stable stage of ART, they may smoke more [55]. Therefore, special attention should be paid to MMT patients living with HIV in order to help them avoid risk behaviours and promote a healthier lifestyle.

This study has strengths that included a large sample size (1,016 MMT patients) and high response rate, collaboration with multiple clinics in various areas and validated instruments (e.g. FTND, AUDIT-C, EQ-5D-5L). Nonetheless, several limitations should be considered. First, the causal relationships could not be established due to the cross-sectional design. Additionally, all data were gathered via retrospective self-report interviews without biochemical confirmation. This may have resulted in under-reporting of ongoing drug use due and introduce recall and disclosure bias. Finally, due to the convenience sampling strategy at clinics in just two geographical areas, the generalization of our results is limited.

CONCLUSION

This study revealed that smoking is highly prevalent among MMT patients, putting them at a high risk of smoking-related illnesses. Despite the decrease of smoking over the course of MMT, smoking cessation support should be integrated into MMT programs in Vietnam in order to diminish smoking-related adverse outcomes.

Ethics, consent and permissions

The protocol of this study was reviewed and approved by the IRB of Vietnam Authority of HIV/AIDS Control. Written informed consent was obtained from all participants. Patients could withdraw at any time without the influence on their current treatment.

Consent to publish

Not applicable

Availability of Data and Materials

Data are available from the Authority of HIV/AIDS Control (VAAC). Requests for data on this study may be submitted to VAAC and go through a review process by the Scientific and Ethical Research Committee. The contact for requesting data use is Dr. Phan Thi Thu Huong, email: huongphanmoh@gmail.com, Deputy Director in Research of the Vietnam Authority of HIV/AIDS Control, Ministry of Health, Vietnam.

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Competing interests

The authors declare that they have no competing interests.

Authors' Contributions

BXT, HLTN, CL, MPD, HPD and HTTP conceived of the study, and participated in its design. HPD, LHN, NPTN, CN, HLTN, GTL, LKN, CNT, BXT, HTL, VTMT, HTTP, TDT, CAL, MD implemented the survey and compiled the data. HPD, LHN, NPTN and BXT analyzed the data. HPD, LHN, NPTN, CN, HLTN, GTL, LKN, CNT, BXT, HTL, VTMT, HTTP, TDT, CAL, MPD helped to draft the manuscript. All authors have read and approved the final manuscript.

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FIGURE CAPTIONS

Fig 1. Smoking pattern of MMT patients regarding the duration of MMT
(A) Prevalence of cigarette smoker; (B) FTND score

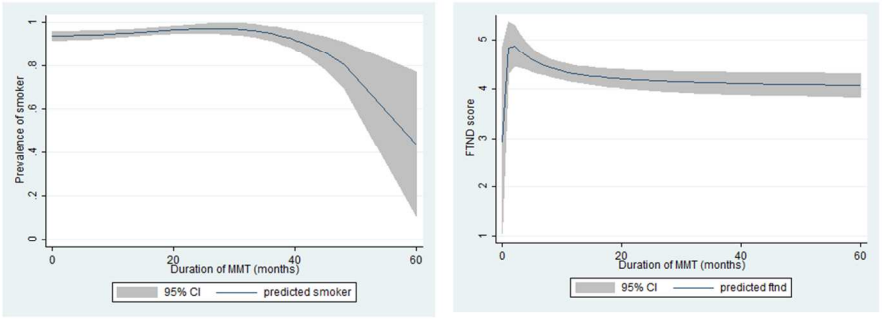

Fig 1. Smoking pattern of MMT patients regarding the duration of MMT‼ ┼ (A) Prevalence of cigarette smoker; (B) FTND score

190x107mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Page	Recommendation
Title and abstract	1	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		2	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	2	3	Explain the scientific background and rationale for the investigation being reported
Objectives	3	3	State specific objectives, including any prespecified hypotheses
Methods			
Study design	4	4	Present key elements of study design early in the paper
Setting	5	4	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	4	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
			(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	4, 5	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	4, 5	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	5	Describe any efforts to address potential sources of bias
Study size	10	4	Explain how the study size was arrived at
Quantitative variables	11	5	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	2	5	(*a*) Describe all statistical methods, including those used to control for confounding
		5	(*b*) Describe any methods used to examine subgroups and interactions
		5	(*c*) Explain how missing data were addressed
			(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
			(*e*) Describe any sensitivity analyses

	Item No	Page	Recommendation
Results			
Participants	13*	6	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
			(b) Give reasons for non-participation at each stage
			(c) Consider use of a flow diagram
Descriptive data	14*	6	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		6, 7	(b) Indicate number of participants with missing data for each variable of interest
			(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*		*Cohort study*—Report numbers of outcome events or summary measures over time
			Case-control study—Report numbers in each exposure category, or summary measures of exposure
		7, 8	*Cross-sectional study*—Report numbers of outcome events or summary measures
Main results	16	7, 8	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
			(*b*) Report category boundaries when continuous variables were categorized
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17		Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			
Key results	18	9	Summarise key results with reference to study objectives
Limitations	19	10	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	9, 10	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	10	Discuss the generalisability (external validity) of the study results
Other information			
Funding	22	11	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.