TITLE OF THE ARTICLE: CIGARETTE SMOKING AND ITS ASSOCIATION WITH HIV VIRAL LOAD AMONG HIV-POSITIVE OPIOID USERS IN VIETNAM

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The study aimed to determine the smoking prevalence and explore the association between smoking and viral load among people living with HIV who are drug users (HIV+ PWID) in Vietnam. We used secondary data from a descriptive cross-sectional study of 280 HIV+ PWID in an open-label, non-inferiority trial from July 2015 to February 2018 at six HIV clinics in Northern Vietnam. The results showed that 82.1% of the participants reported daily smoking, and among them, 53.5% were classified as heavy smokers. After controlling for confounding factors, using non-smokers as the reference group, we found no association between cigarette smoking and HIV viral load. However, the study also revealed a large number of patients with co-infections such as HBV, HCV, TB, STIs (81.3%), and over half of the patients (51.4%) reported depression ranging from mild to severe. Considering the adverse health effects of smoking, it is crucial to integrate tobacco cessation programs and specialized treatments for other health issues in this key population. More longitudinal studies are needed to better understand this relationship.

Keywords: Cigarette smoking, viral load, HIV positive, people who inject drugs.

I. INTRODUCTION

Cigarette smoking is a hazardous behavior for all population and the adverse health effects of cigarette smoking have been well-documented.[1,2] Despite these health risks, recent estimates from a nationally representative survey in Vietnam named "the Vietnam GATS", in 2015, the prevalence of smoking was 22.5% over the population. Alarmingly, the prevalence of smoking is significant higher in certain population subgroups, including persons living with HIV/AIDS. Up to 2022, the number of HIV-infected people in Vietnam was approximately 250,000 (UNAIDS, 2022), along with a smoking rate of 36.1%.[3] In recent years, the highest incidence rate is in the group of men who have sex with men, accounting for about 12.5%.[4] However, it is still concerning that despite implementing preventive measures for drug users, the HIV infection rate in this group remains relatively high at 12.1%.[4]

Among HIV+ population, the HIV viral load, also known as the "level of HIV infection" is the amount of HIV virus present in the blood or other biological samples of an HIV-infected individual. This is a critical indicator in assessing disease progression and the effectiveness of treatment. The HIV viral load reflects the quantity of virus in the body, and when the viral load is high, the person with HIV has a higher potential for transmitting the virus. PWID with uncontrolled viral load often engages in high-risk behaviors, such as unsafe sex and needle-sharing practices, make it easier to transmit HIV within the community.[5] To limit the risk of

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spreading the virus to others, preventative and interventional measures are needed to achieve and maintain viral suppression below detectable levels. Smoking is also a prevalent behavior among injecting drug users, with 93.5%[6] are smokers, which is four times higher than the general population. Some studies in the field of smoking has focused on understanding the relationship between smoking behavior and biological features of HIV/AID, including viral load. However, it remains inconsistent, some researchers agreed that smoking increases the viral load and is associated with the high viral load of PLWH.[7,8] This could be explained that smoking can directly lead to the negative biological effects on the efficacy of specific antiretroviral (ARV) medication[9] or smoking even boost susceptibility of the HIV-infected people to opportunistic infection.[10] Furthermore, smokers with HIV are more likely to develop psychosocial synergies including depression and substance abuse that affect the viral load suppression.[11] On the other hand, there were some studies that did not find a relation between smoking and viral load.[12,13]

Therefore, further researches are needed to ensure a comprehensive understanding of the relationship. HIV clinic-based buprenorphine plus naloxone versus referral for methadone maintenance therapy for treatment of opioid use disorder in HIV clinics in Vietnam (BRAVO)[14] is an open-label, non-inferiority trial with the sample size of those group of patients. Based on that study, we conducted this research to characterize smoking prevalence and examine the relationship between smoking pattern and viral load among HIV-infected people who are drug users in Vietnam.

II. METHODS

1. Study population

A total of 280 patients were recruited from the baseline of BRAVO. The study was conducted at six HIV clinics in northern Vietnam (four HIV clinics in Hanoi, one in Thanh Hoa Province, and one in Bac Giang Province) from July 27, 2015 to Feb 12, 2018. The eligible criteria for inclusion were:

(1) confirmed HIV infection,

(2) age ≥ 18 years old,

(3) had current moderate-to-severe opioid use disorder (as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition).

Patients were excluded if they had a known hyper sensitivity to buprenorphine or naloxone, had an aspartate aminotransferase or alanine aminotransferase greater than five times the upper limit of normal, had a serious medical or psychiatric illness in the past 30 days that was deemed by the study physician to preclude safe participation, received methadone maintenance therapy within the past 30 days, or were currently pregnant or breastfeeding.

2. Measures

At the baseline visit, eligible participants were invited to take the survey. Research assistants administered surveys assessing self-reported demographics, smoking frequency, poly-drug use, alcohol use, history of co-infection and mental health symptoms, HIV care in confidential settings using secured, web-based electronic data entry (REDCap). All survey instruments were administered in Vietnamese and adapted for regional dialects where needed.

Exposure variable:

To assess cigarette smoking, subjects were asked about current smoking frequency using the following categories:

(1) everyday,

(2) some-days

(3) no smoking.

Due to the small number of individuals in the some-days group which was combined into no-smoking group and based on the measurement was previously used by Okuyemi et al.[15] , the everyday group would be separated into 2 sub-groups: Light/Moderate Smoker (smoked 1 to less than 20 cigarettes per day) and Heavy smoker (smoked 20 or more cigarettes per day). Finally, smoking status of subjects was categorized as follow:

(1) Non-smokers,

(2) Light/Moderate Smokers (< 20 cigarettes/day),

(3) Heavy smokers (≥ 20 cigarettes/day). By using this classification, we retained all cases in the analysis and ensured the number of subjects in each group, rather than arbitrarily excluding participants who did not smoke a certain number of cigarettes per day.

Outcome variable:

Blood specimens for HIV viral load were collected at HIV clinics at baseline then sent to the National Hospital for Tropical Diseases in Hanoi. The study outcome was VL non-suppression defined as an HIV-1 RNA level of 200 copies per mL or higher on PCR (suppression: ≤ 200 copies/ml, non-suppression: > 200 copies/ml)

Covariates:

- Demographics:

We collected data on age, ethnic, education level, marital status, employment status, average monthly income in Vietnam dong.

- Poly-drug use:

We conducted urine tests after the participants self-reported using at least one of those illicit drugs: heroin, ecstasy, sedatives, methadone, cocaine, amphetamine, marijuana in the last 30 days in the interview questionnaire.

- Alcohol use:

To assess alcohol use, we performed Alcohol Use Disorder Identification Test – Consumption (AUDIT-C)[16] scale and since most of our participants were male, a score of 4 points or more is considered positive, optimal for identifying hazardous drinking or active alcohol use disorders. Therefore, we classified the subjects as follows: (1) Lower risk (0-4 points), (2) Higher risk/Possible Dependence (5-12 points)

- History of co-infection and depression:

History of co-infection was evaluated by asking whether they had history of at least one of those diseases: HBV, HCV, TB, STIs.

To figure out depressive symptoms of the patients, we only took depressive emotional state score from Depression, Anxiety and Stress Scale – 21 Items (DASS-21).[17]latent structure and convergent validity of the Depression, Anxiety and Stress Scale-21 (DASS-21 Participants were then divided into 2 groups (1) No depression (0-9 points), (2) Depression (>9 points).

- HIV care:

Participants had their blood drawn for CD4+ lymphocyte count and reported whether they received ART, percentage of ART adherence.

3. Statistical analysis

We performed descriptive statistics to characterize the study sample. Chi-square or ANOVA-based F test statistics are used to compare proportions and means between or among smoking groups, respectively. Multivariable logistic regression model was performed in steps by including cigarette smoking, followed by adding demographics and finally by other covariates considered as confounding

factors, including age (continuous variable), gender, education level (under highschool vs. highschool and above), employment status (employment vs. unemployment), monthly income (<5 million vs. ≥ 5 million), alcohol use (low risk vs. high risk/possible dependence), poly-drug use, co-infection, depression, ART status (on medication vs. not on medication). All confounders were then added sequentially in the models according to the magnitude of their impact on the association between cigarette smoking and viral load.

The changes in regression parameters of cigarette smoking before and after adding each of those groups of variables were also assessed. To assess whether ART modifies the effect of smoking, subgroups were analyzed for subjects not on ART and for subjects on ART. All analysis was performed by using Stata/MP 14 (Stata Corporation, College Station, TX). The model fit was assessed based on likelihood ratio Chi2 test statistics ($p<0.05$), Hosmer-Lemeshow criteria ($p>0.05$), and no multicollinearity among independent variables and confounders.

4. Research Ethics

The study was approved by institutional review boards at Oregon Health & Science University (IRB00000471), Hanoi Medical University (IRB00003121), and Vietnam's Ministry of Health Ethics Review Committee (IORG0006396).

III. RESULTS

Table 1 displays the demographic and clinical characteristics of the research participants. The demographic and clinical characteristics of the study subjects are shown in Table 3.1. In total, 280 patients were enrolled in this study, with most of the patients were over 30 years old. The majority of the participants (96.8%) were male and Kinh (98.9%). 166 patients (59.3%) reported never been to school or high shool educated. 112 patients (40%) were single and one fifth of the patients were divorced, separated or widows. More than half of the participants were employed with most of their monthly income (70.6%) less than 5 million dong. Two hundred patients (81.3%) reported ever had one of the following diseases: Hepatitis B, Hepatitis C, Tuberculosis, STIs. In addition to heroin use, there were 71 patients using at least one of the following illicit substances, such as: ecstasy, cocaine, amphetamine, methadone, methamphetamine, sedative. Most participants (80.4%) were at low risk for alcohol and only 4 subjects were possibly dependent on alcohol. Almost a half of subjects (51.4%) suffered from mild to severe depression. 89 patients (31.8%) reported that they had never been on ART, the remaining 75% had any prior exposure to ART. About one-fifth of patients had a CD4 cell count less than 200 and the viral load of 189 patients (67.5%) reached the suppressed threshold.

On bivariate analysis, there was no difference in some characteristics between the groups of patients in term of smoking pattern. However, monthly income was different between these groups and the difference was statistically significant.

Table 1. Clinical and sociodemographic characteristics of HIV positive patients who are opioid users by smoking pattern (N = 280)

Characteristics	Total (N = 280)	Non-smokers (n = 50)	Light/Moderate smokers (n = 107)	Heavy smokers (n = 123)	p* value
Age group (yrs)					
18 – 29	14 (5.0)	1 (2.0)	6 (5.6)	7 (5.7)	0.08
30 – 39	161 (57.5)	22 (44.0)	61 (57.0)	78 (63.4)	
≥ 40	105 (37.5)	27 (54.0)	40 (37.4)	38 (30.9)	
Gender					
Male	271 (96.8)	49 (98.0)	102 (95.3)	120 (97.6)	0.664
Ethnic					
Kinh	277 (98.9)	50 (100)	106 (99)	121 (98.4)	-
Education level					
Under highschool	112 (40.0)	31 (62.0)	59 (55.1)	76 (61.8)	0.540
Highschool and above	109 (38.9)	19 (38.0)	48 (44.9)	47 (38.2)	
Marital status					
Single	112 (40.)	18 (36.0)	39 (36.5)	55 (44.7)	0.303
Married	109 (38.9)	22 (44.0)	48 (44.9)	39 (31.7)	
Divorced/Separate/ Widows	59 (21.0)	10 (20.0)	20 (18.7)	29 (23.6)	
Employment status					
Unemployment	129 (46.1)	23 (46.0)	50 (46.7)	56 (45.5)	0.983
Monthly income (n = 269)					
< 5 million dong	190[a] (70.6)	40 (85.1)	74 (71.1)	76 (64.4)	0.031
History of co-infection (n = 246)					
Yes	200[b] (81.3)	35 (79.6)	74 (81.3)	91 (82.0)	0.940
Poly-drug use					
Yes	71 (25.4)	14 (28.0)	26 (24.3)	41 (33.3)	0.317
Alcohol use					
Lower risk	225 (80.4)	43 (86.0)	80 (74.8)	102 (82.9)	0.162
Higher risk/Possible Dependence	55 (19.6)	7 (14.0)	27 (25.0)	21 (17.1)	

Characteristics	Total (N = 280)	Non-smokers (n = 50)	Light/Moderate smokers (n = 107)	Heavy smokers (n = 123)	p* value
Depression					
Yes	144 (51.4)	22 (44.0)	59 (55.1)	63 (51.2)	0.428
Viral load (copies/ml)					
≤ 200	189 (67.5)	33 (66.0)	64 (59.8)	74 (60.2)	0.732
CD4 (cells/ mm^3)					
< 200	56[c] (20.1)	13 (26.0)	19 (17.8)	25 (20.3)	0.490
Currently on ART					
Yes	191 (68.2)	37 (74.0)	75 (70.1)	79 (64.2)	0.397
ART adherence					
Yes	160 (83.8)	33 (89.2)	63 (89.2)	64 (81.0)	0.537

[a]: 11 missing values/refuse to answer

[b]: 34 missing values

[c]: 1 missing value

*p value based on Chi-square/ANOVA-based F test statistics

The results of multivariable analysis are shown in Table 2. After controlling for all variables considered as confounding factors and using non-smoker as the reference group, the odds of having high HIV viral load among heavy smokers was 2.25 times higher than non-smokers, but not significant (OR: 2.25; 95% CI: 0.74 – 6.88). Similarly, being light and/or moderate smokers was not associated with a likelihood of 2.20 more than being non-smokers (OR: 2.20; 95% CI: 0.68 – 7.10).

Generally, when stratified by ART status, there was no conclusive evidence that cigarette smoking and HIV viral load are related. We found that among patients who receive ART, heavy smokers and light/moderate smokers were respectively 2.27 and 2.94 times more likely to have experienced high viral load compared with non-smokers. In another group of patients who did not receive ART, we still observed no substantial outcome differences, the adjusted differences were: 3.23 (95% CI: 0.67 – 15.75; p = 0.15) for heavy smokers and 1.41 (95% CI: 0.25 – 7.82; p = 0.69) for light/moderate smokers.

Table 2. The association between cigarette smoking and HIV viral load

	HIV viral load non-suppression	
	All subjects combined (n=279)[a,b]	
Smoking pattern	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Non-smokers	Reference	Reference
Light/Moderate smokers	1.20 (0.57 – 2.50)	2.20 (0.68 – 7.10)
Heavy smokers	1.38 (0.67 – 2.84)	2.25 (0.74 – 6.88)
	On ART (n=190)[c]	
Non-smokers	Reference	Reference
Light/Moderate smokers	0.79 (0.26 – 2.38)	2.94 (0.52 – 16.63)
Heavy smokers	0.50 (0.16 – 1.62)	2.27 (0.38 – 13.70)
	Not on ART (n=89)[c]	
Non-smokers	Reference	Reference
Light/Moderate smokers	1.87 (0.47 – 7.41)	1.41 (0.25 – 7.82)
Heavy smokers	2.81 (0.73 – 10.90)	3.23 (0.67 – 15.75)

[a]: 1 missing value was alcohol use

[b]: Adjusted analysis controlled for age, gender, education level, employment status, monthly income, alcohol use, poly-drug use, depression, co-infection, ART status

[c]: Stratified on ART status

IV. DISCUSSION

This study showed a high prevalence of cigarette smoking, 82.14% patients reported daily smoking which is over 3.5 times higher than the national rate (22.5%) according to Vietnam GATS, 2015. This prevalence is similarly high compared to a previous study conducted in Thai Nguyen province in 2009-2013 with current daily smokers are 86.4%.[6] Co-infections and depression were also prevalent in our study population. Eight out of every ten HIV positive PWID had at least one of the transmitted diseases: HBV, HCV, TB or STIs, which is relatively consistent with a research[18] of 979 HIV patients in Northern Vietnam, where PWID made up about 50% of the HCV coinfected group and nearly 60% of the HBV/HCV dually coinfected group. Because these viruses can be efficiently transmitted via percutaneous exposure to blood, PWID are at an especially high risk for infection and co-infection with these viruses, as well as for transmission to others through unsafe needle sharing or sex practices.

Compared with a research[19] on depressive symptoms among 455 HIV+ PWID in Thai Nguyen, Vietnam, the proportion of patients with mild to severe depression in our study is lower (~51% vs. 69%). It could be due to the differences in depression scales; however, this rate is relatively high, explained by the

fact that many people living with HIV face a high-risk behavior, stigma, legal constraints, and discrimination when disclosing their HIV positive status.

Initially, after adjusting for all potential confounding factors, we observed no substantial differences in VL between non-smokers, light/moderate smokers and heavy smokers. Our results are in line with other research that did not discover a connection between smoking and high viral load.[12,13] However, according to a study of 250 HIV Russian woman,[7] the researcher has highlighted that adherence to ART may have hindered the capacity to detect differences by smoking status as a potential mediator. Therefore, we decided to stratify the model by ART status.

When subgroups are analyzed separately for subjects not on ART and for subjects on ART and still maintain adjustment for potential confounding factors, in the group of patients on ART, we did not find an association between smoking and high viral load. It could be explained by the small sample size or by the fact that patients have already started ART and a high percentage of patients have undetectable viral loads and high CD4 cell counts (>200) consistent with viral suppression. In addition, reporting high levels of adherence (83.8% of patients reported adherence ≥90%) may have limited the detection of an association between smoking and viral load.[20]

Among the group of non-ART patients, although we observed an uptrend in increase the odds of having high HIV viral load in the group of heavy smokers, we still found no association between cigarette smoking and HIV viral load. Perhaps, our comparison group was relatively small (n=89), so the detection ability was quite low. Eventually, this study did not provide evidence that cigarette smoking is associated with an increase in VL among HIV+ PWID. This result is similar to the finding from a research of 462 subjects in two HIV-infected cohorts in Massachusetts[12] when using mean viral load as a primary outcome. As a result, this study's findings does not directly link smoking to signs of disease progression. Additional research using longitudinal designs may be able to provide more light on the long-term effects of smoking on symptoms and disease development.

Our findings should be interpreted in light of its strengths and limitations. The strengths of this study included study population of a trial which was well-defined within the confines of strict qualifying requirements and a reduction in bias and confounding. Nevertheless, the cross-sectional design might not be able to assess the temporal relationship between cigarette smoking and VL. In addition, our participants were individuals with opioid use disorders so it may limit the generalizability of the findings, but in the context of Vietnam, where the main route of HIV transmission is heroin injection, these findings still have important implications in the data on HIV-infected patients. In recent years, as the HIV transmission route shifts to sexual intercourse, especially male homosexuality, more studies are needed on the association between smoking and viral load in this group of patients.

Our study also had some limitations. First, self-reported cigarette smoking was also subject to biases due to patients' recall or influences of health workers. Second, the lack of assessment of other tobacco forms (e.g., e-cigarette, pipe tobacco). That leads to underestimate the actual smoking dosage. However, we had other potential predictors of cigarette smoking in our assessment such as depression and other behavioral factors. Additionally, by grouping

smokers into the appropriate categories and using measures (AUDIT-C or DASS-21) to assess how frequently people drink alcohol and experience depression, both of which have demonstrated excellent measurement properties in numerous studies as well as in the Vietnamese context. The findings of this study can therefore be used to create comprehensive HIV/AIDS care and treatment for drug users throughout the nation, it may also serve as a beneficial model for other injection-driven HIV epidemics.

V. CONCLUSION

Our study has shown a significantly high proportion of HIV+ PWID smoke cigarettes and half of them are heavy smokers. The study also revealed a majority of population has either experienced or currently have co-infections. Notably, more than half of the patients reported having mild to severe depression. Although we did not find a direct correlation between smoking and viral load, the research suggests the need for smoking cessation services to reduce the prevalence and intensity of smoking. Additionally, HIV treatment facilities should strengthen screening and referral services for patients with co-infections, including depression. Identifying and addressing these co-occurring health issues is crucial for providing comprehensive care and improving the overall well-being of HIV patients. We suggest that additional longitudinal studies are needed to better understand the long-term relationship between cigarette smoking and HIV viral load.

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