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MAJOR ARTICLE

Alarming Tuberculosis Rate Among People Who Inject Drugs in Vietnam

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Background. The tuberculosis (TB) epidemic is not homogeneous in the general population but presents high-risk groups. People who inject drugs (PWID) are such a group. However, TB among PWID remains largely undocumented. Our goal was to assess the prevalence of TB and the risk factors associated with TB among PWID in Vietnam.

Methods. We implemented a cross-sectional survey among 2 community-based cohorts of human immunodeficiency virus (HIV)-positive and HIV-negative PWID in Hai Phong. Participants were screened for TB using questions on TB symptoms. Those who reported any symptom were accompanied by peers to the TB clinic for chest x-ray. If the latter was abnormal, a sputum was collected to perform an Xpert MTB/RIF test.

Results. A total of 885 PWID were screened for TB. For both cohorts, most PWID were male (>90.0%), with a median age of 42 years. Beside heroin injection, 52.5% of participants reported smoking methamphetamine, and 63.2% were on methadone. Among HIV-positive PWID (N = 451), 90.4% were on antiretroviral therapy and 81.6% had a viral load <1000 copies/mL. Using a complete-case analysis, the estimated TB prevalence was 2.3% (95% confidence interval [CI], 1.0–4.5) and 2.1% (95% CI, 0.8–4.2) among HIV-positive and HIV-negative people, respectively. Living as a couple, arrest over the past 6 months, homelessness, and smoking methamphetamine were independently associated with TB but not HIV infection.

Conclusions. In the context of very large antiretroviral therapy coverage, this extremely high rate of TB among PWID requires urgent actions.

Keywords. drug users; epidemiology; prevalence; risk factors; tuberculosis.

Tuberculosis (TB) remains a major public health threat in Southeast Asia, despite international and national efforts to reach TB elimination. Although widely spread in the general population, the TB epidemic is not homogeneous but consists of high transmission areas and high-risk populations, making the World Health Organization (WHO) zero TB goal difficult to achieve [1]. Among these populations, people who inject drugs (PWIDs) have been identified as a potential important high-risk group [2, 3]. Several reasons contribute to the increased TB risk among PWID. First, they are at a higher risk of human immunodeficiency virus (HIV) infection, which carries its own increased susceptibility to TB [4]. In the United Kingdom, TB incidence among HIV-infected patients was 4.8 times higher among PWIDs [5]. Antiretroviral therapy (ART)-naive patients more often have a bacteriologically confirmed TB test and a history of treatment [6]. In addition to HIV, direct alteration of cell-mediated immune response due to drugs exposure might facilitate the acquisition of TB infection and the development of the disease [7]. Finally, frequent administrative detention, social deprivation, and poor housing, common features of PWID, are also known as risk factors for TB [1, 8].

Overall, very few epidemiological studies have investigated the prevalence of active TB among PWIDs. The available surveys enrolled people who used drugs but with very few injectors (3.6%) [9] or with limited sample size and few TB cases [10]. Others only enrolled HIV-infected PWIDs who were not on ART for the majority of them [6, 11]. Although all of these studies suggest a high TB burden, they only partially reflect the TB prevalence among the overall PWID population. Furthermore, the current context of universal ART, which reduces the TB rate by two thirds [12, 13], may have changed the level of risk. This gap in knowledge prevents us from specifically targeting this

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potentially high-risk group in TB control programs, and it may hamper the efforts towards TB elimination [1].

Among Southeast Asian countries, Vietnam had a high annual TB incidence rate estimated at 176 cases per 100 000 inhabitants in 2019 [14], and it has a long history of heroin use [15]. During the past 10 years, the national HIV program has been supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the President's Emergency Plan for AIDS Relief provided combined interventions to PWIDs in Vietnam. These interventions included harm reduction through Community-Based Organizations (CBOs), free and universal ART, and access to methadone in most provinces and large cities across the country, which led to end the HIV epidemic among this group in the 2 million inhabitants in the harbor city of Hai Phong [16].

In this study, our goal was to assess the prevalence of TB and the risk factors associated with TB infection among PWIDs, with and without HIV infection, in Hai Phong, Vietnam.

METHODS

Study Design and Study Population

We implemented a cross-sectional survey during a follow-up visit of 2 large community-based cohorts of HIV-negative and HIV-positive PWIDs in Hai Phong. Cohort participants were initially selected from 2 large community-based, respondent-driven sampling (RDS) surveys implemented in October 2016 and October 2017 [16]. The survey eligibility criteria were to currently report injecting drugs, which was confirmed by the detection of heroin or methamphetamine in urine and by the presence of recent injection skin marks, being age 18 years or older, and being able to provide informed consent.

Human Immunodeficiency Virus Screening and Participation in the Cohorts

During both RDS surveys, drug use behaviors were first assessed using both urine testing and a face-to-face questionnaire. Then, the HIV serological status was assessed using the national algorithm, which includes a rapid test (SD BIOLINE HIV1/2 3.0; Standard Diagnostic Inc., Gyeonggi, South Korea). The result was then confirmed by 2 other (rapid) tests (Alere Determine 1/2, Alere Medical Co., Chiba, Japan and VIKIA HIV1/2, bioMerieux, Marcy L'Etoile, France). All HIV-positive PWIDs were offered to participate in a cohort with biannual follow-up visits including a similar questionnaire on drug use behaviors, a HIV viral load assay, and a urine drug test. Likewise, consecutive HIV-negative participants not already on methadone and with available contact details were invited to participate in the HIV-negative cohort (first 441 HIV-negative participants of 2016 survey, first 180 HIV-negative participants of 2017 survey), with similar visit content and HIV testing. In addition, 12 HIV-positive and 66 HIV-negative PWIDs who were participating in a former cohort initiated in 2014 from another RDS survey [17, 18] were enrolled in the appropriate cohort. Follow-up visits of both cohorts were scheduled within the same time interval. As part of the cohort activities, CBO members facilitated participants' access to methadone and to ART for those infected with HIV.

Tuberculosis Screening

Between March and May 2018, all participants from both cohorts who attended the planned follow-up visit were proposed a TB screening. The TB screening algorithm started with CBO members questioning participants on the presence of TB symptoms (ie, fever; cough >1 week; night sweats; weight loss; intense fatigue). If participants had at least 1 symptom or a history of TB, then they were invited to have a chest x-ray at the Hai Phong referral TB Hospital. If the chest x-ray was considered as "abnormal", then sputum was collected for an Xpert MTB/RIF assay. The CBO members tracked participants who dropped from the screening cascade. All screening and treating costs were free of charge for the participants as part of the national TB program, and transportation costs were reimbursed. All patients with a positive Xpert MTB/RIF assay were treated according to the national guidelines.

Outcomes

The study primary outcome was confirmed TB, which was defined by a positive Xpert MTB/RIF assay during the visit.

Data Analysis

Cascade of Tuberculosis Screening

For both HIV-negative and HIV-positive cohorts, the number of PWID who attended the follow-up visit, who were screened through a TB questionnaire, who had an abnormal chest x-ray, and who had a positive Xpert MTB/RIF assay was provided. The percentage of participants who had a positive screening at any stage was then calculated.

Prevalence of Active Tuberculosis

After the cascade of TB screening, we calculated the prevalence of active TB as the number of identified PWIDs with TB over those PWIDs over those who have been adequately screened. Finally, we estimated the TB prevalence in the PWIDs population in Hai Phong. For this purpose, we extrapolated our findings of the HIV-negative and HIV-positive cohorts to a PWID population with an HIV prevalence of 27% as estimated at the time of the second RDS survey [16].

Characteristics of the Participants

Sociodemographic information (ie, age, gender, marital status, absence of regular place to stay, employment status), drug use behavior (ie, kind of drugs, frequency), and TB information (ie, previous TB episode, symptoms) were collected. Additional information on HIV treatment and viral load were provided for HIV-positive participants. The data were then compared between each cohort.

Risk Factors Analysis

We determined the risk factors using a multivariable exact logistic regression analysis in which having TB (confirmed by a positive Xpert MTB/RIF assay) was the dependent variable. Participants of the 2 cohorts who completed the diagnostic algorithm were included in this analysis, and we created a combined HIV and CD4 count variable. In addition to the latter, which was forced in the multivariable model, only the independent variables that were significant at a 20% level in an univariable analysis were included in the model.

Statistical Tools

All data were recorded using an electronic case report form solution and analyzed using SAS software (version 9.4 for Windows; SAS Institute Inc., Cary, NC) and STATA software (version 10.0; StataCorp LP, College Station, TX).

Ethical Consideration and Patient Consent Statement

The research protocol of the main study was approved by the Ethical Committee of Hai Phong University of Medicine and Pharmacy. Individual written informed consent was obtained from all participants before participation to the cohort studies.

RESULTS

Among the 672 HIV-negative and 581 HIV-positive cohort participants who were invited to the follow-up visit, 457 (68%) and 484 (83%) PWIDs (941 in total) completed their visit (Figure 1), and 434 (95%) and 451 (93%) PWIDs were screened for TB, respectively. In the HIV-negative and HIV-positives cohorts, 336 (77.4%) and 350 (77.6%) completed the diagnostic cascade, respectively.

Characteristics of the People Who Inject Drugs Enrolled in the Two Cohorts

For both cohorts, most PWIDs were male (>90.0%) and employed (82.0% of HIV-negative participants; 74.5% of HIV-positive participants), with a median age of 42 years (Table 1). Methadone was used by 50.7% of HIV-negative and 75.2% of HIV-positive participants, and only a few (<6.0%) had no regular living place. Among HIV-positive PWIDs, 90.4% were on ART and 81.6% had a viral load ≤1000 copies/mL, with a median CD4 count of 472 cells/μL.

Cascade of Tuberculosis (TB) Screening and TB Prevalence

Overall, 434 (95%) HIV-negative PWIDs and 451 (93%) HIV-positive PWIDs (ie, 885 in total) were screened for TB through a questionnaire on the presence of TB symptoms (Figure 1, Table 1). At the first screening step, 228 (52%) and 308 (68%), respectively, reported having at least 1 symptom. Among the latter, 158 and 253 had a chest x-ray that was abnormal for 46 (29%) HIV-negative participants and 84 (33%) HIV-positive participants. Finally, 18 (39%) HIV-negative participants and 38 (45%) HIV-positive participants had an Xpert MTB/RIF result available, among which 7 (39%) and 8 (21%) had a positive test, respectively. Overall, 3 (20%) of these TB cases were identified as resistant to rifampicin.

After exclusion of PWID who dropped from the diagnostic cascade (N = 121 HIV negative; N = 134 HIV positive), the TB

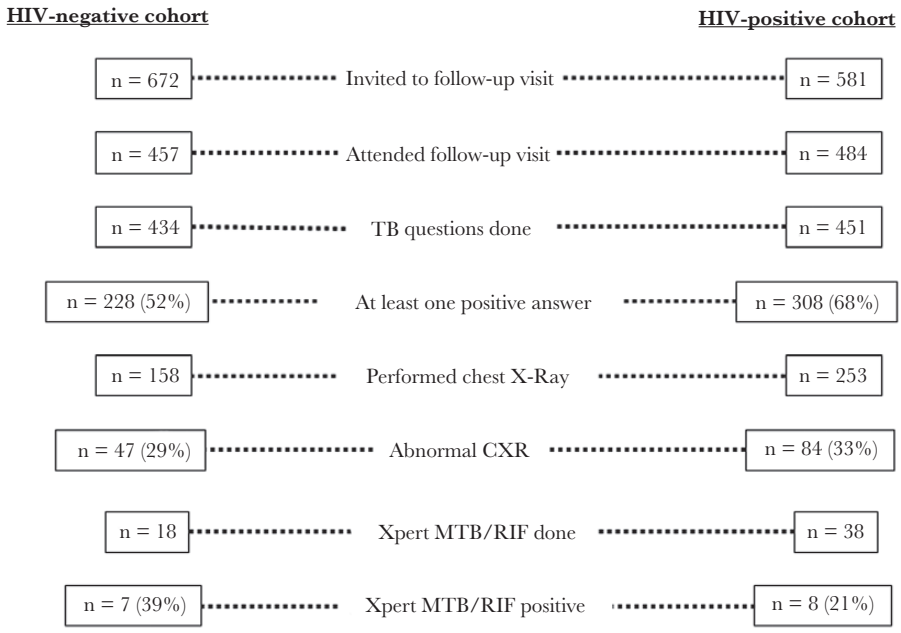

Figure 1. Flow chart of the cohort participants. CXR, chest x-ray; HIV, human immunodeficiency virus; TB, tuberculosis.

Table 1. Characteristics of People Who Inject Drugs Enrolled in the Two Cohorts and Screened for Tuberculosis in Hai Phong, Vietnam

Category	Subcategory	HIV-Negative PWID (N = 434)	HIV-Positive PWID (N = 451)
		No. (%)	No. (%)
Sociodemographic Variables			
Median age (IQR)		42.5 (35.0–50.0)	41.0 (37.0–45.0)
Gender	Female	40 (9.2)	26 (5.8)
	Male	392 (90.3)	425 (94.2)
	Transgender	2 (0.5)	0 (0.0)
Marital status	Divorced/separated/widowed	266 (61.3)	294 (65.2)
	Legally married/living as a couple	168 (38.7)	157 (34.8)
No fixed abode/homeless		25 (5.8)[a]	12 (2.7)[b]
Salaried/employed		356 (82.0)	336 (74.5)
HIV Care			
Taking ART		- -	407 (90.4)[b]
HIV load ≤1000 copies/mL		- -	367 (81.6)[b]
Median CD4 count (IQR)		- -	472 (317–674)[b]
Drug Use Behaviors			
Heroin use last 6 months	No more	166 (38.2)	146 (32.4)
	Sometimes[c]	109 (25.1)	165 (36.6)
	Regular/frequent[d]	159 (36.6)	140 (31.0)
Smoking MET[e]		252 (58.1)	213 (47.2)
On methadone[f]		220 (50.7)	339 (75.2)
Sharing needles/syringes[g]		8 (3.0)	1 (0.3)
TB Questionnaire			
Previous TB episode declared		37 (8.6)[h]	152 (33.7)
Cough >1 week		5 (1.2)	0 (0.0)[b]
Night sweats		125 (28.8)	170 (37.7)
Weight loss		74 (17.1)	104 (23.1)
Chest pain/difficulties in breathing		151 (34.8)	188 (41.7)
Fever		40 (9.2)	58 (12.9)
Fatigue		167 (38.5)	221 (49.0)

Abbreviations: ART, antiretroviral therapy; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; IQR, interquartile range; MET, methamphetamine; PWID, people who inject drugs; TB, tuberculosis.

NOTE: Percentages are rounded and sometimes do not add to 100%.

[a]5 missing values.

[b]1 missing value.

[c]≤15 days within the past 30 days.

[d]>15 days within the past 30 days.

[e]Either self-declaration of smoking methamphetamine in the past 6 months or during a recent cohort visit (at month 12 or 18), or detection of methamphetamine in urine at recent visit.

[f]Mentioned by the participant during the cohort visit.

[g]Among injectors only.

[h]2 missing values.

prevalence was 2.1% (95% confidence interval [CI], 0.8–4.2) for HIV-negative participants and 2.3% (95% CI, 1.0–4.5) for HIV-positive participants. The estimated TB prevalence within the PWID population with a HIV prevalence of 27% was 2.2% (95% CI, 1.8–2.6).

Risk Factors Associated With Tuberculosis

In the final multivariable model, being homeless (odds ratio [OR], 8.7; 95% CI, 1.4–41.8), having been arrested over the past 6 months (OR, 6.6; 95% CI, 1.1–28.5), being engaged in a relationship (OR, 5.1; 95% CI, 1.5–21.4), and smoking methamphetamine (OR, 3.8; 95% CI, 1.0–22.0) were independently associated with active TB (Table 2). It is interesting to note that HIV-infection, whatever the CD4 count, was not associated with TB infection.

DISCUSSION

In this high TB burden country, the estimated prevalence of TB among PWID is alarmingly high, ranging between 1.7% and 5.6%, despite the end of the HIV epidemic [16] and very high coverage of ART. Assuming that this prevalence translates in an annual incidence rate that is probably two times higher (ie, 3400 cases/100 000 per year for the conservative estimate), PWIDs are at least 20 times, and possibly up to 65 times (in the sensitivity analysis), more at risk of active TB than the general population [19].

Table 2. Risk Factors Associated With TB Infection Among PWID in Vietnam (n = 686)

Variable		Number of TB/Total (%)	Crude OR	95% CI	aOR	95% CI
Age	<38	5/208 (2.4)	Ref			
	38–45	3/229 (1.3)	0.5	0.1–2.8		
	≥45	7/249 (2.8)	1.2	0.3–4.8		
Gender	Male	14/639 (2.2)	Ref			
	Female	1/47 (2.1)	1.0	0.0–6.7		
On methadone						
		8/441 (1.8)	0.6	0.2–1.8		
Being a couple		10/250 (4.0)	3.6	1.2–10.6	4.9	1.4–19.8
Employed		11/534 (2.1)	1.3	0.3–4.4		
Arrested in last 6 months		3/30 (10.0)	5.9	1.0–23.8	5.9	1.0–26.6
Heroin use last 6 months	No more	6/243 (2.5)	Ref			
	Sometimes	4/214 (1.9)	0.8	0.2–3.2		
	Frequent	5/229 (2.2)	0.9	0.2–3.5		
Smoking MET[a]		12/359 (3.3)	3.7	1.0–20.8	3.5	0.9–20.5
HIV and CD4 status	HIV-negative	7/336 (2.1)	Ref			
	HIV-positive and CD4 ≤350 cells/μL	4/107 (3.7)	1.8	0.4–7.3	2.9	0.6–13.1
	HIV-positive and CD4 >350 cells/μL	4/242 (1.7)	0.8	0.2–3.2	1.1	0.2–4.5
No fixed abode/homeless		3/30 (10.0)	5.9	1.0–23.6	8.0	1.2–38.5

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; MET, methamphetamine; MTD, methadone; PWID, people who inject drugs; Ref, Reference strata; TB, tuberculosis.

[a]Either self-declaration of smoking methamphetamine in the past 6 months or during a recent cohort visit (at month 12 or 18), or detection of methamphetamine in urine at any visit.

Of note, these figures did not account for asymptomatic TB cases, nor for TB cases with negative Xpert MTB/RIF assay. This likely underestimation of the TB prevalence is also supported by the possibly higher risk of TB for those who missed the cohort visit, because incarceration, a well known "institutional TB amplifier", is a frequent cause of dropout.

Our findings are consistent with the few relevant previous studies reporting TB among people who use drugs (PWUDs), with prevalence rates of 1.8% in Cote d'Ivoire among PWUDs [9], 6.1% among HIV-infected PWIDs in Pakistan [11] or 2.6% among PWUDs on medication-assisted treatment in Tanzania [20]. Contrasting with previous studies reporting TB among subgroups of PWID, our findings are unique in the sense that they provide a good estimation of the TB burden in the overall PWID population, whatever the HIV status, and in the current context of high ART coverage [6, 11].

Role of Human Immunodeficiency Virus in the Tuberculosis Epidemic

Although Vietnam belongs to the top 30 high TB burden countries, these extremely high rates are surprising. It was believed that the high TB burden among PWIDs was largely driven by their high rate of uncontrolled HIV infection. We expected that the remarkable ART coverage in Vietnam, and the documented very low HIV incidence, would have reduced the risk of active TB as reported among non-PWID HIV-infected individuals [21–23], and would possibly have brought it down to the general population level [12]. It is clear that this is not the case, and this was confirmed by our risk factor analysis, which do not show any independent association between HIV status and TB. This finding could potentially be explained by the latent TB treatment (9-month daily isoniazid) proposed to all HIV-positive PWID receiving ART according to Vietnamese guidelines. However, according to local CBO and physicians, the acceptance and adherence of latent TB treatment is deemed very low in routine practice, as reported elsewhere [2].

Individual Factors and High Transmission

In addition to HIV, PWIDs are highly exposed to a combination of other well known TB risk factors, such as tobacco [24], alcohol [25], poor housing conditions [1], and drug-induced immune impairment [7]. Likewise, as reported before [26–29], having no fixed abode or being homeless increased the risk of TB. Together with the high level of air pollution in the city [24], these accumulations of exposure certainly contribute to this alarming situation.

This much higher rate of TB among PWID than among the general population is also certainly fueled by a high TB transmission within this community [1, 23]. The PWIDs are frequently arrested and incarcerated in overcrowded places with poor ventilation, which increase the risk of TB transmission [28–30]. However, our risk factor analysis provides additional clues on these transmission patterns within PWIDs. The association between TB and living as a couple strongly suggests that in-house transmission is important. Given the high HIV prevalence, it is likely that PWID partners are also at a high risk of TB, either through HIV infection or drug use risks. Of note, this finding contrasts with previous studies implemented in very different settings (Eastern Europe, Russia, Africa) showing

that single people who are usually younger and have a different lifestyle than married people are at a higher risk of TB [29, 31, 32]. It is unfortunate that we did not collect any information on the participants' partners such as HIV, history of TB status, or whether they injected drugs.

The association of methamphetamine use with TB is also very informative. It is supported by pathophysiological findings showing that regular exposure to methamphetamine use leads to systemic inflammation [33], important lung injuries [34] consisting of the infiltration of inflammatory cells in lungs, thickened alveolar septum, and reduced number of alveolar sacs [35]. These inflammatory cells likely include macrophages, the cells targeted by *Mycobacterium tuberculosis* (MTB) for infection [36]. In addition to this potential facilitation of methamphetamine for MTB infection in lungs, the conditions of this recreational drug use are also favorable to transmission [3]. According to CBO members and PWIDs, these sessions gather from 5 to 10 persons for several hours in a closed room (to escape police watch), who share water pipes used to smoke crystal methamphetamine. Therefore, these frequent collective methamphetamine sessions stand as a plausible route of TB transmission within PWIDs. It is interesting to note that 2 small TB outbreaks that occurred in the United States more than 10 years ago concerned methamphetamine users, although no facilitating relationship was made at the time between this particular drug and TB [37, 38].

Tuberculosis Interventions for People Who Inject Drugs

There is little awareness among physicians and health policy makers regarding the dramatic TB situation among PWIDs. This is likely due to the paucity of recent epidemiological studies that have quantified the TB burden in this vulnerable group. Given the low access to care of this marginalized population [39, 40], this high TB prevalence likely translates into a high mortality rate. Urgent dedicated combined interventions, including large TB screening, contact tracing of cases, better access, and improved referral to care, and treatment of latent TB are needed to control the disease among PWIDs, not only to reduce morbidity and mortality, but also to impact on the TB dynamics in the rest of the population [1]. In addition, impacting TB transmission through preventive measures will be key to markedly reduce the TB infection rate. Before designing these interventions, we first need to understand further or confirm the drivers of TB transmission among PWIDs, both at the individual and structural levels [41], and then pilot relevant and adequate control measures. The HIV epidemic among PWIDs has been ended by relying heavily on CBO to reach this stigmatized and marginalized population, provide counseling on harm reduction, and facilitate access to care [16]. The same winning strategy should certainly be used to control TB. It is clear that our data showed that the acceptance of TB screening at the community site was very high (>90%). However, this acceptance rate for referral to the health system to continue TB screening with a chest x-ray and Xpert MTB/RIF was much lower. This situation calls for a full collection of sample or data for TB screening at the community level. Sputum collection to be further processed in a TB laboratory, or trucks equipped with a mobile chest x-ray, digitalization, and computer-assisted automatic reading by deep learning systems [42, 43], could be envisaged in community sites. This strategy would first require the elaboration of a screening algorithm with the best balance between TB yield, cost, and logistics allowing scaling-up. Finally, given that most risk factors are not directly related to injection practices, our findings prompt us to estimate the TB burden among the larger population of people who used drugs.

Our study has several limitations. Although its size was important, our sample may not be representative of all PWIDs residing in Hai Phong because it originated from 2 cohort studies. However, these participants were drawn from a RDS survey, a methodology invented to obtain a representative sample of the desired population [44]. Given that our study participants were already part of a cohort, and therefore benefiting from CBO support, the most "hard-to-reach" PWIDs may be underrepresented. We also did not capture asymptomatic TB cases (because the first-line screening algorithm was based on the detection of symptoms). In addition, we could not identify TB cases with negative Xpert MTB/RIF. Finally, because 30% of cohort participants have not been adequately screened, our findings should be interpreted with caution. Taken together, these limitations probably led to underestimation of the true TB prevalence rate. Although these data need to be confirmed in other settings, the high rates reported in the literature among the few available epidemiological studies suggest a similar burden in low- and middle-income countries.

CONCLUSIONS

Our findings highlight the extremely high TB prevalence among the PWID population in Vietnam. This high TB burden is not explained by HIV infection, but rather by an accumulation of individual risk factors. Recreational methamphetamine smoking sessions may represent one such situation of high-risk TB transmission. Specific TB interventions targeting PWIDs should be elaborated and evaluated, to ultimately reach the WHO goal of TB elimination. Peers should play an important role in the design and implementation of these innovative interventions.

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and R. V. coordinated the data entry; N. N., R. V., and J. C. contributed to the design of the data analysis; R.V. and N. N. conducted the data and statistical analyses; N. N., D. L., and J. C. wrote the manuscript, which was then reviewed and approved by all authors.

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