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ORIGINAL ARTICLE

A cohort study revealed high mortality among people who inject drugs in Hai Phong, Vietnam

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Abstract

Objective: To estimate the residual mortality rate among people who inject drugs (PWID) in a Low-Middle Income Countries context where the HIV epidemic has been controlled and methadone coverage is high.

Study design and setting: PWID from Haiphong, Vietnam, were recruited through three annual respondent-driven sampling surveys that fueled two cohorts of PWID with HIV ($n = 761$) and without HIV ($n = 897$), with bi-annual follow-up. Presumed causes of death were ascertained from medical records and/or interviews of participants family.

Results: Among the 1658 participants with a median follow-up of 2 years, 67 and 36 died in the HIV-positive and HIV-negative cohort, respectively, yielding crude mortality rates of 4.3 (95% Confidence interval (CI): 3.3–5.4) per 100 person-years of follow-up (PYFU) and 1.9 (CI: 1.4–2.6) per 100 PYFU. In the HIV-positive cohort, in which 81% of participants had undetectable viral load, the two main causes of death were tuberculosis and HIV-related diseases. In the HIV-negative cohort, the two main causes of death were liver-related diseases and overdose. In a time-dependent multivariable model, “unsuppressed viral load” was associated with increased risk of mortality, whereas “being on methadone” or “being employed” was associated with a lower risk.

Conclusion: Despite a very successful HIV and methadone program, the mortality remains high among PWID in Vietnam, largely due to curable infectious diseases such as tuberculosis and viral hepatitis. © 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Keywords: People who inject drugs; Mortality; HIV; Tuberculosis; Viral hepatitis

1. Introduction

Increased mortality rate among people who inject drugs (PWID) has been well documented [1–3]. In a recent meta-

analysis, the pooled crude mortality rate (CMR) worldwide was 2.71 per 100 person-years and the pooled standardized mortality ratio (SMR) was 16.4 [3]. A former meta-analysis showed that the CMR varied from 0.5 to 7.8 across different settings, with higher rates in low- and middle-income countries (LMIC) [1]. HIV-related diseases and overdose were the commonest causes of death in PWID [4,5]. Other infectious diseases, such as viral hepatitis and tuberculosis, were also frequently described [6,7].

The authors declare no conflict of interest.

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What is New?

- Despite full HIV control, mortality remains very high among PWID in Vietnam.
- Avoidable liver diseases (including hepatitis) and tuberculosis are leading causes.
- Methadone and successful HIV treatment reduced the risk of death.
- Urgent plans for tuberculosis and viral hepatitis control among PWID are needed.

Combined prevention and care, including needle/syringe programs (NSP), medication-assisted treatment (MAT) for substance use disorders and antiretroviral treatment for HIV infection, has reduced the mortality among PWID in many high-income countries [8–10]. In Canada, the scale-up of a large “seek-and-treat” campaign was associated with a significant reduction of mortality among PWID living with HIV from 6.0 per 100 person-years in 1996–2003 to 3.0 in 2010–2014 [11].

In LMIC, mainly from Asia, scarce mortality data among PWID date back from about 10 years ago, before the implementation of universal ART and the emergence of MAT scale-up [1,4,7]. In these countries, a meta-analysis reported a CMR of 5.25 per 100 person-years, with a standardised mortality ratio of 14.5 [1]. The residual mortality rate among PWID after ART and MAT scaling-up remains unknown.

Hai Phong, a port city in Vietnam with more than 2 million inhabitants, was home of about 5,000 (range 4,000–6,000) currently injecting PWID in 2016 [12]. The HIV burden has been extremely high among PWID in this city with more than 60% prevalence in 2005 (Integrated HIV bio-behavioural surveillance survey) but now down to 27%. Indeed, the city has pioneered interventions among PWID [13,14], including a needle syringe program (NSP) in 2005, followed by a MAT program in 2008 which rapidly expanded with 13 clinics providing MAT in the city by 2014. In addition, free universal antiretroviral treatment was provided to PWID since 2005. Altogether, these interventions led to reduce the HIV incidence down to 0.085/100 person-years (95%CI, 0.02–0.25) [15]. This incidence is below the threshold set at 0.5/100 person-years that we previously defined for ending the HIV epidemic among PWID in LMIC [16–19]. In this context of high ART and MAT coverage, we primarily aimed at assessing the residual mortality rate among PWID. We also investigated the factors associated with mortality and the likely causes of deaths.

2. Methods

2.1. Participant recruitment and follow-up

The DRIVE project is an international research program that evaluated a community-based intervention com-

binning mass HIV screening, and peer case-management for support and referral to HIV care and MAT, among currently injecting PWID in Hai Phong, Vietnam. . Currently injecting PWID were recruited through three annual community-based respondent-driven sampling (RDS) surveys starting in September 2014, 2015 and 2016 for about 3 months each. The study design and participant enrollment were described elsewhere [17]. In brief, persons were eligible if they were 18 years or older, capable of giving informed consent, self-reporting injecting drugs currently, confirmed by presence of recent skin injection marks and positive urinalysis for heroin and/or methamphetamine (Nal Von Minden, Germany). A fingerprint reader identified unique participants and prevent multiple enrollments and to identify persons at successive interviews. Data on demographic characteristics, drug use and sexual behavior, a psychological assessment, use of HIV-related services were collected by a standardised interview. All study activities were carried out at community-based organizations (CBO) sites where CBO staff were actively involved in research procedures and data collection. All participants were tested for HIV using first SD BIOLINE® HIV1/2 3.0 rapid test (Standard Diagnostic Inc., South Korea), with confirmation using two other rapid tests: Alere Determine 1/2 (Alere Medical Co., Japan) and VIKIA®HIV1/2 (Biomerieux, France); and for HCV using HCV ELISA 3.0 (SD Bioline, South Korea). HIV-positive participants were tested for CD4 cell count (BD Biosciences, US) and HIV viral load (Roche, Switzerland).

Nearly 1,500 PWID participants were enrolled per RDS survey. At each survey, all HIV-positive RDS participants were eligible to the cohort enrolment. In addition, consecutive HIV-negative RDS participants with confirmed contact details and presumably not receiving MAT were enrolled in the cohort until completion of the sample size (400 for the 1st survey, 200 for the 2 others). The sample size of the HIV positive cohort was determined to estimate the proportion of participants with undetectable HIV viral load. The sample size of the HIV-negative cohort was determined to estimate the HIV incidence. Cohort participants were invited to come to the study site every six months for a follow-up visit consisting in the same standardized interview and blood testing as those used at the enrolment visit. CBO members supported cohort participants (30–40 participants per CBO member) for harm reduction activities and administrative or social issues in a case-management approach, and linked them to HIV clinic and to MAT program when appropriate. The frequency of contact was about once a month. HIV seroconverters were switched from the HIV-negative cohort to the HIV-positive cohort.

2.2. Outcomes

Deaths were registered by CBO members either directly or through participants’ family declaration. Home visits were then performed by CBO members in order to collect

information related to participants' death. If the participant was hospitalised before death, the medical records were checked by the study group physicians. Thereafter, the causes of death were reviewed independently by three clinicians and categorised into 8 groups: HIV-related conditions, overdose, suicide, liver-related conditions, tuberculosis, accidental causes, others, and unknown (definitions given in Supplemental Appendix Table S2).

2.3. Statistical analysis

We restricted our analyses to PWID with any known vital status after enrolment.

The end-point date was the M36 visit. The follow-up time was calculated between enrolment and the date of death, or the date of last known vital status.

CMR were calculated for 100 person-years of follow-up and presented with confidence interval (CI) using Poisson distribution (Garwood exact central). In order to describe mortality in the overall population of PWID, weighted estimates have been calculated using the HIV prevalence among PWID in Hai Phong in 2014, i.e. 27%.

To compare the observed mortality rates among PWID with the general population, we applied the 2019 national age- and sex- specific death rates among the general population in Vietnam to our population and calculated the standardised mortality ratio (SMR). The SMR were calculated by HIV serology at baseline and presented with profile likelihood confidence intervals. The survival curves from the 2 cohorts were elaborated using Kaplan-Meier methods and compared with a log rank test.

The independent predictors of death among all cohort participants were determined using extended cox proportional hazard model. We built a variable with three categories: HIV negative, HIV-positive with viral load ≤ 1000 copies/mL [20] and HIV-positive with viral load > 1000 copies/mL, according to the WHO guidelines [20]. The time-dependent variables (updated at each 6-month visit) were: age in 5 categories, drugs used (e.g. methamphetamine, frequency of methamphetamine use, heroin, cannabis, and ketamine), HIV status and viral load, being on methadone, hazardous and binge drinking which was assessed using AUDIT-C questionnaire [21,22]. In addition, we used the RDS survey number, gender, marital status, having a regular salary, housing and duration of heroin injection at baseline as fixed variables. We adopted a complete case analysis strategy for missing data as they represented less than 5% of all data. In addition, very few participants ($< 1\%$) had missing data, for both fixed and time-dependent variables. All variables which were significantly linked to death in univariate analysis ($p < 0.20$) were included in the multivariate analysis. Then, we used a backward selection based on the p value and the Akaike Information Criterion to select the final model.

The final model was validated by bootstrapping ($n=100$; using validate function in the rms package). All statistical

tests were bilateral. Analyses were done using SAS software (Version 9.4 for Windows; SAS Institute Inc., Cary, NC, USA) and R (version 3.6.3; The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Characteristics of participants

Between 2014 and 2016, 766 and 926 participants (1692 overall) from three successive RDS surveys were enrolled in the HIV-positive and HIV-negative cohort, respectively (Figure 1). We excluded 34 participants without any follow-up visits and with no known vital status (5 HIV-positives and 29 HIV-negatives).

Overall, participants were mostly male (93.4%), they had a median age of 40 years and were all injecting heroin at enrollment (Table 1). Due to misreport from participants, 354 (21.4%) turned out to be on MAT at baseline. Overall, 694 (41.9%) participants were referred to a MAT clinic during the study follow-up.

A third of participants reported injecting heroin for more than 15 years; this proportion reached 45% in the HIV-positive cohort. Smoking methamphetamine was common with 67.8% of participants reporting ever smoking and 43.0% reporting smoking in the last 30 days (injection of methamphetamine was extremely rare).

3.2. Mortality rates

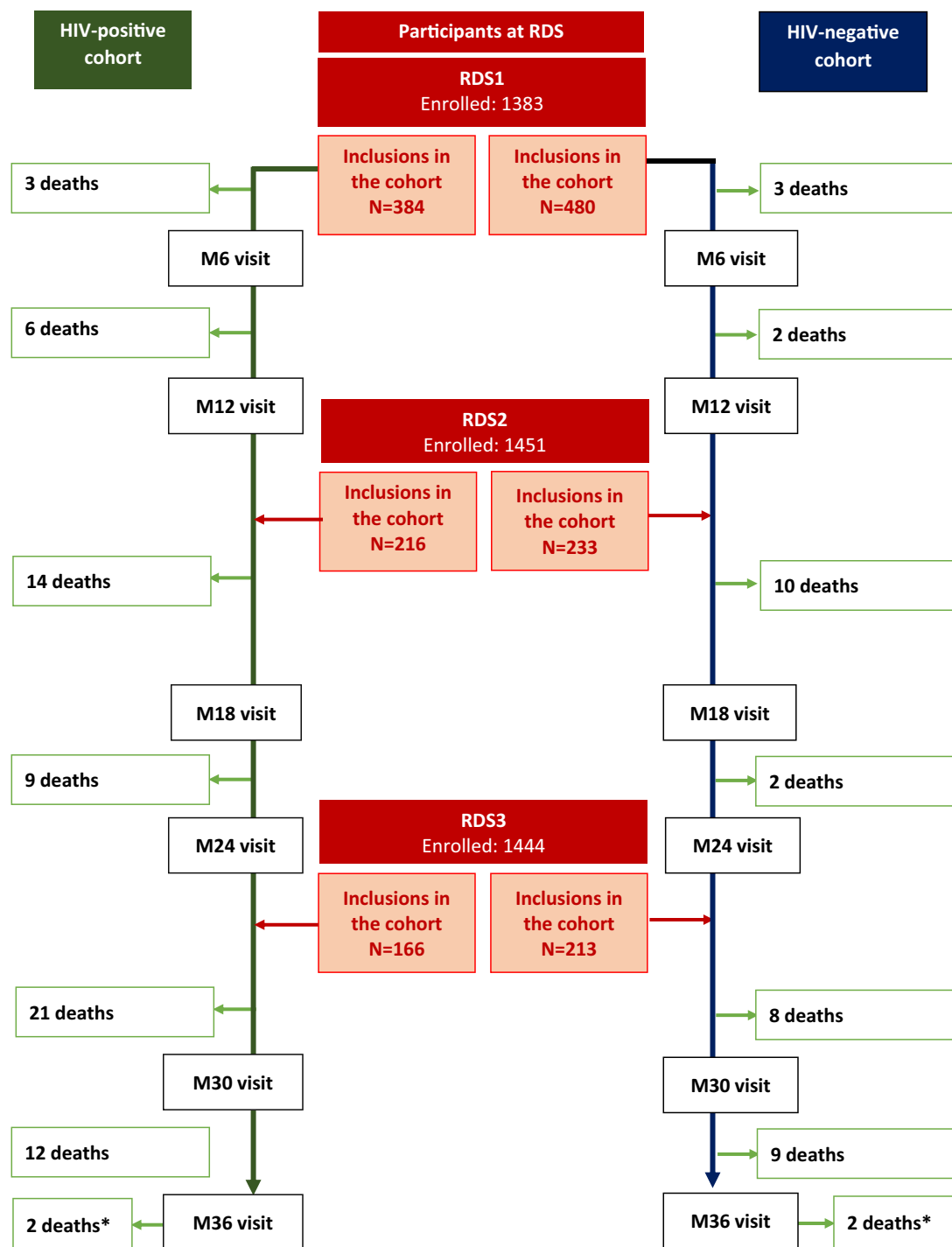
The participants of the HIV-negative cohort were followed for a median of 2.0 years (interquartile range (IQR): 1.0; 2.9) and contributed to 1888 person-years. The median follow-up was similar in the HIV-positive cohort (2.0 years, IQR: 1.2; 2.9) for 1562 person-years.

Of the 1692 participants of both cohorts, 71 (4.2%) were censored at their last visit because their vital status could not be assessed at that time, including 13 (1.7%) from the HIV-positive cohort and 58 (6.3%) from the HIV-negative cohort.

A total of 103 deaths were reported during the study period, 36 in the HIV-negative cohort and 67 in the HIV-positive cohort, resulting in CMR of 1.9 (95% CI: 1.3; 2.6) and of 4.3 (95% CI: 3.3; 5.4) per 100 person-years, respectively (Figure 2 & Table 2). Among the HIV-infected PWID who died, 44% had a viral load > 1000 copies/mL, and amongst them, 44% were on ART.

The age- and gender-SMR was 4.2 (95% CI: 3.0; 5.8) among PWID without HIV infection and 12.0 (95% CI: 9.3; 15.1) among PWID with HIV infection.

The HIV prevalence among all distinct RDS participants was 28% (data not shown). When reconstituting a population of PWID which would have a HIV prevalence of 28%, the CMR was 2.5 (95% CI: 2.0-3.1) per 100 person-years and the age- and gender-SMR was 5.8 (95% CI: 4.3-7.7) per 100 person-years.



*Deaths during M36 period

Figure 1. Participant study design and flow chart. Three annual RDS surveys recruited about 1500 PWID each. In parallel, a cohort study was implemented with bi-annual visits. Out of RDS participants, all HIV-positive PWID and consecutive HIV-negative PWID up to 400 for the RDS1 and 200 for the subsequent RDS were invited to participate to the cohorts.

Table 1. Baseline characteristics of study participants in HIV- negative and HIV-positive cohorts

	HIV negative (n = 897)	HIV positive (n = 761)	P value
	N (%)	N (%)	
Age in years, median (IQR)	40.0 (33.0; 47.0)	40.0 (36.0; 44.0)	0.26
Male gender	829 (92.4)	718 (94.5) ⁻	0.09
Marital status			
Single	261 (29.1)	309 (40.7) ⁻	< 0.01
Married/living with partner	355 (39.6)	264 (34.7)	
Divorced/separated/widowed	281 (31.3)	187 (24.6)	
Salaried/employed	732 (81.6)	559 (73.6) ⁻	< 0.01
Regular place to stay	862 (96.1)	736 (96.8) ⁻	0.42
Duration of heroine injection, years			
<5	261 (29.1)	50 (6.6) ⁻	< 0.01
5-<10	242 (27.0)	169 (22.2)	
10-<15	200 (22.3)	202 (26.6)	
≥15	194 (21.6)	339 (44.6)	
Regular use of heroin ^a	825 (92.0)	684 (90.0) ⁻	0.16
Use of methamphetamine			
Ever injected	10 (1.1) ⁻	8 (1.1) ⁻	0.90
Ever smoked	647 (72.1)	478 (62.9) ⁻	< 0.01
Frequency of smoked methamphetamine use (last 30 days)			
No consumption	460 (51.3)	483 (63.6) ⁻	<0.01
Occasional use ^b	367 (40.9)	245 (32.2)	
Regular use ^a	70 (7.8)	32 (4.21)	
Other drugs used (last 6 months)			
Cannabis	121 (13.5) ⁻	132 (17.4) ⁻	0.03
Ketamine	53 (5.9) ⁻	30 (4.0) ⁻	0.07
Cocaine	6 (0.7) ⁻	10 (1.3) ⁻	0.18
On methadone treatment	99 (11.1) ⁺	255 (33.6) ⁺	<0.01
Consumption of alcohol (last 6 months)	301 (33.6) ⁻	223 (29.4) ⁺	0.07
At-risk consumption	119 (13.3)	66 (8.7) ⁻	<0.01
Binge drinking			
HIV-positive			
Suppressed viral load		608 (80.6) ^{&}	
On ART		639 (85.5) ^{\$}	
CD4 cell count (median, IQR)		463 (299 ; 637) ⁻	
HCV-positive serology	550 (61.3)	683 (89.8)	<0.01

Values are number and percentage unless otherwise specified. -: 1 missing value, +: 2 missing values, *: 3 missing values, &: 7 missing values, \$: 14 missing values. IQR, interquartile range; ART, antiretroviral treatment; HCV, hepatitis C virus.

Note: in all Tables, totals may not exactly match the sums of items because of rounding.

^a More than one time every 2 days,

^b 1 time or less every 2 days

3.3. Cause of death and predictors of all-cause mortality

The likely most common causes of death were liver-related conditions and overdose among HIV-negative PWID, and tuberculosis and HIV-related conditions among HIV-infected PWID (Table 2). Treatable infectious diseases contributed to a large part of mortality in this population. Indeed, tuberculosis- and liver-related deaths together rep-

resented up to 31% and 40% of deaths in PWID without and with HIV infection, respectively, with mortality rates of 0.6 (95% CI: 0.3-1.0) and 1.7 (95% CI: 1.1-2.5) per 100 person-years (Table 2).

Older age and HIV infection were independent risk factors of mortality whereas being employed and being on MAT were protective factors. Being on MAT was associated with a 40% reduction of mortality (adjusted hazard

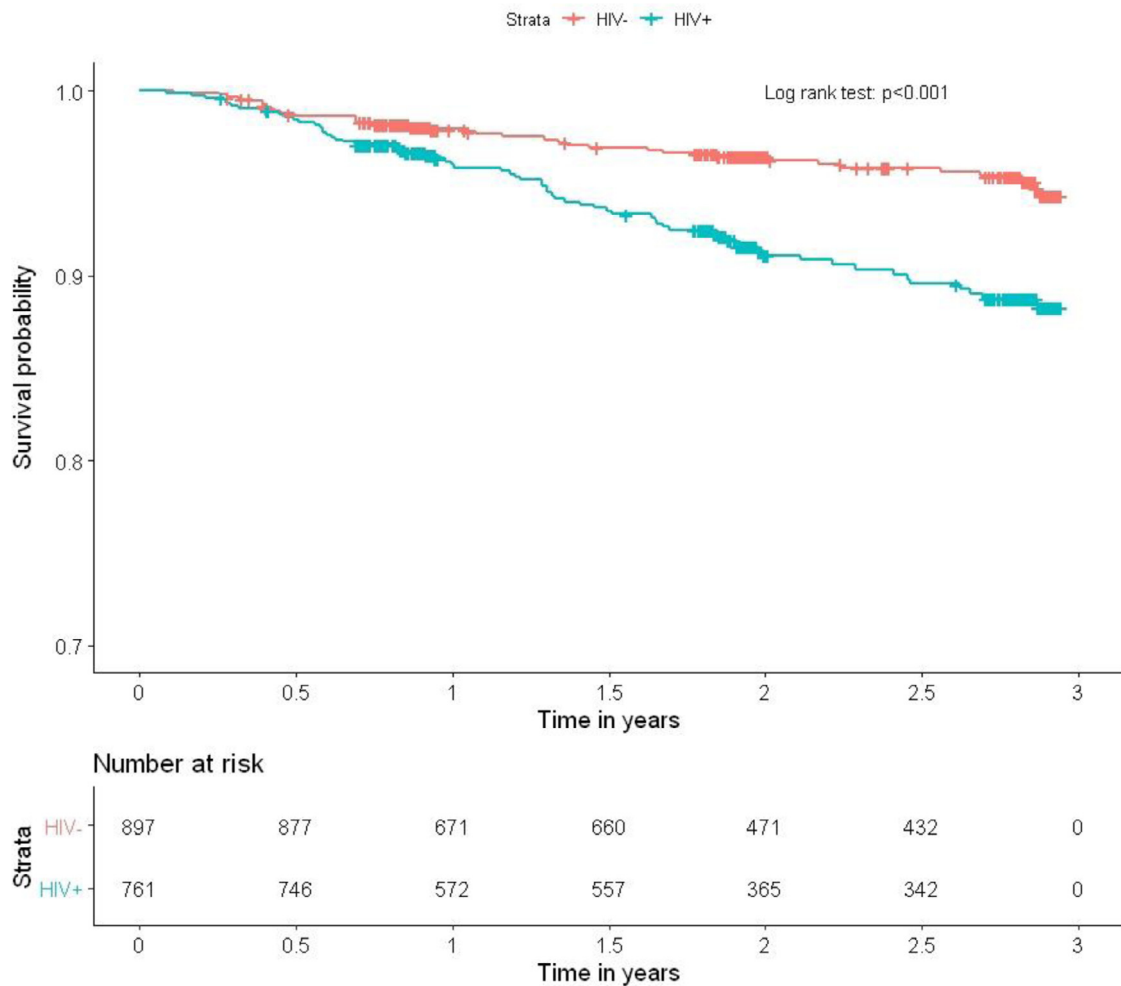


Figure 2. Kaplan-Meier survival curves by HIV status among study participants in the HIV-negative and HIV-positive cohorts.

ratio (aHR): 0.6 (95% CI: 0.4–0.9)). Among HIV-positive participants, those with viral load above 1000 copies/mL also had higher risk of mortality than those who had suppressed viral load (Table 3).

4. Discussion

Hai Phong has pioneered many PWID interventions in Vietnam and South-East Asia, which results today in a remarkable coverage of MAT, above 50% [15], a higher achievement than in most high-income settings [23,24]. Even more impressive is the ART coverage in this hard-to-reach and stigmatised population, which exceeded the expectations of 90/90/90 and which certainly contributed greatly to ending the HIV epidemic in this high-risk group [15]. In addition, our study population benefited from close case-management from experienced CBO members for harm-reduction activities and access to care, on top of the research program. Despite this very favorable context, the overall mortality remains about 6 times higher than an

age-sex-HIV standardised general population, and it is not explained by overdoses.

Nonetheless, the large coverage of universal ART has certainly contributed greatly to reducing mortality among PWID in Northern Vietnam. Between 2005 and 2007, the latter was estimated at 6.3 /100 person-years (95% CI: 4.6; 8.5), with a similar 23% prevalence of HIV infection among PWID [7]. Of note, the high rate of lost to follow-up rate at 1 year (30%) certainly underestimated the mortality rate estimation, which may be compensated by the much younger age of the participants (median 32 years vs. 40 years in our study).

The mortality rate in Hai Phong among PWID is now close to those reported in North America in the last decade, which ranged from 1.6 per 100 person-years among HIV-negative PWID to 4.6 among HIV-positive PWID [5,11,25–27] but somewhat higher than those reported in Western Europe or Australia, rarely exceeding 1.5 per 100 person-years [6,28–31].

When compared with high-income settings, the higher mortality among PWID from Asian countries was classi-

Table 2. Mortality rates (per 100 person-years) and likely causes of death among study participants in HIV-negative and HIV-positive cohorts

Cause of death	HIV negative (n = 897)			HIV positive (n = 761)			Overall	
	n	CMR	95% CI ^a	N	CMR	95% CI ^a	Weighted mortality rate ^b	95% CI ^a
All causes	36	1.9	1.4–2.6	67	4.3	3.4–5.4	2.5	2.0–3.1
Liver-related	8	0.4	0.2–0.8	8	0.5	0.3–1.0	0.4	0.3–0.8
Tuberculosis	3	0.2	0.1–0.5	19	1.2	0.8–1.9	0.4	0.3–0.7
Overdose	8	0.4	0.2–0.8	5	0.3	0.1–0.8	0.4	0.2–0.8
Unknown	5	0.3	0.1–0.6	11	0.7	0.4–1.3	0.4	0.2–0.7
Others	7	0.4	0.2–0.8	5	0.3	0.1–0.8	0.4	0.2–0.7
HIV-related death				15	1.0	0.6–1.6	0.2	0.1–0.4
Suicide	3	0.2	0.1–0.5	2	0.1	0.0–0.5	0.2	0.1–0.5
Accident	2	0.1	0.0–0.4	2	0.1	0.0–0.5	0.1	0.0–0.5

^a Poisson confidence interval

^b Weighted mortality rate estimates were calculated using the proportion of people with HIV among PWID in Hai Phong. CMR, crude mortality rate per 100 person-years; CI, confidence interval

cally attributed to the higher underlying mortality in the general population. This statement was supported by similar SMR in the different regions of the world, averaging 14.7 in studies conducted before 2010 [1], and 16.4 in a more recent review [3]. In the latter, the SMR for people who use opioids extra-medically was 13.4 in South-East Asia. In line with the reduction of mortality, one can also note a substantial decrease in SMR in some countries. In Hai Phong, we reported a SMR of 5.8, much lower than the former estimation of 13 in Northern Vietnam one decade ago [7]. Of note, ART was not available in 2010 for PWID in Vietnam, and our population was older (median age 40 years vs. 32 years), injected for longer (71% of participants injected for 5 years or more, vs. 54%), and with much more frequent methamphetamine use (quasi null in 2010)". This suggests that the mortality gap between PWID and general population is narrowing in those setting as a result of specific interventions including harm reduction, MAT services and improved access to universal ART.

The pooled CMR for AIDS related deaths was 0.59/100py among people who use opioids extra-medically in the recent review from Larney et al [3], i.e. 3 times higher than in Hai Phong. This comparison, although not quite in the same population and region, suggests the high ART and MAT coverage lowered the AIDS-related mortality in Hai Phong. Yet, the overall mortality rate remains high among PWID, still mainly driven by HIV, despite 81% of participants having suppressed viral load. The proportion of HIV-positive PWID not in care is very small, almost irreducible. If HIV treatment management was very good overall, better addressing ART resistance may reduce deaths among those with unsuppressed viral load. Overdoses represent a usual important cause of deaths, despite local naloxone rescue initiatives.

The main gaps in reducing mortality further among PWID are curable viral hepatitis and tuberculosis. Tuberculosis mortality was unexpectedly high, accounting for

almost one third of all deaths in the HIV-positive cohort and around 8% of deaths among PWID without HIV. Our findings confirm the high burden of TB among PWID we reported in Hai Phong [32], but also reported from several other settings [33–35]. In addition, Vietnam belongs to the top 30 countries most affected by TB in the world, representing a major cause of death in the general population [36]. Low socio-economic status including poor housing, poor nutritional status, very frequent smoking and frequent indoor gathering for sharing drugs likely contributed to this excess risk of TB. Importantly, the high death rate likely due to TB, potentially underestimated since 'HIV-related deaths' could be due to undiagnosed TB, highlights the limited access to TB care of this population. These findings support the need for adapted and dedicated TB interventions for PWID, from large TB screening coverage to successful care. Clearly, these TB interventions should also include regular and systematic TB screening in MAT and HIV outpatient clinics [37]. There is certainly much value for TB control in learning from the successful HIV program among PWID in Hai Phong. In particular, the major engagement of CBO in community information, testing and linkage to care was key in this success.

Liver disease also contributed substantially to mortality. It was one of the two main causes of death among PWID without HIV. With a HCV seroprevalence of 60% to 90%, the role of HCV in these liver diseases is certainly predominant. Urgent studies are needed to implement direct-acting antivirals in these high-risk groups in LMIC, defining the appropriate level of care, delivery and follow-up modalities, prevention of re-infection and associated morbidities (alcohol, HBV infection, etc.). Again, CBO will certainly be pivotal to this implementation.

As expected, MAT was a protective factor for mortality [8,10,38]. MAT has a beneficial impact on ART uptake and adherence, which could mediate the impact on mortality [39]. However, our study strongly suggests that MAT had an effect on mortality independently of HIV.

Table 3. Factors associated with all-cause mortality among PWID in Vietnam

	Crude HR (95%CI)	P value ^a	Adjusted HR ^b
<i>RDS survey of inclusion</i>			
RDS survey 1	Ref.	0.16	
RDS survey 2	1.4 (0.9–2.2)		
RDS survey 3	1.8 (0.9–3.6)		
<i>Age in years^c</i>			
[19;35[Ref.	<0.001	Ref.
[35;39[0.5 (0.2–1.2)		0.4 (0.2–1.0)
[39;43[0.9 (0.4–1.9)		0.9 (0.4–1.9)
[43;48[1.8 (1.0–3.3)		1.7 (0.9–3.2)
[48;74[2.2 (1.2–3.9)		2.5 (1.4–4.5)
Male gender	1.8 (0.7–4.9)	0.20	
<i>Marital status</i>			
Single	1.0 (0.6–1.6)	1.00	
Married/living with partner	1.0 (0.6–1.6)		
Divorced/separated/widowed	Ref.		
Salaried/employed	0.5 (0.4–0.8)	0.006	0.5 (0.3–0.8)
Regular place to stay	0.5 (0.2–1.2)	0.17	
<i>Duration of heroine injection, years</i>			
<5	Ref.	0.55	
5–<10	0.8 (0.5–1.6)		
10–<15	1.2 (0.7–2.1)		
≥15	1.2 (0.7–2.1)		
Use of heroin (last 6 months) ^c	0.7 (0.4–1.1)	0.10	
<i>Frequency of heroin use (last 30 days)^c</i>			
No consumption	Ref.	0.25	
Occasional use ^d	0.6 (0.4–1.1)		
Regular use ^e	0.7 (0.4–1.1)		
<i>Frequency of smoked methamphetamine use (last 30 days)^c</i>			
No consumption	Ref.	0.14	
Occasional use ^d	0.8 (0.5–1.2)		
Regular use ^e	1.8 (0.9–3.6)		
<i>Other drugs use (last 6 months)^c</i>			
Cannabis	1.6 (0.9–2.7)	0.13	
Ketamine	1.9 (0.8–4.3)	0.17	
At-risk alcohol consumption	0.8 (0.5–1.3)	0.37	
Binge drinking	1.3 (0.7–2.4)	0.46	
On methadone treatment ^c	0.7 (0.4–1.0)	0.04	0.6 (0.4–0.9)
<i>HIV status</i>			
HIV-negative	Ref.	<0.001	Ref.
HIV-positive with VL < 1000cp/mL ^c	1.5 (0.9–2.3)		1.8 (1.1–3.0)
HIV-positive with VL > 1000cp/mL ^c	6.2 (3.8–10.1)		7.5 (4.6–12.3)
HCV-positive serology	1.0 (0.7–1.6)	0.95	

^a Log-rank test,^b Multivariable final cox model,^c Time-dependent variable,^d Less or equal to one time every 2 days),^e More than one time every 2 days. HR, hazard ratio; RDS, respondent-driven sampling; VL, viral load; HCV, hepatitis C virus. Note: HIV-negative and HIV-positive cohorts were pooled together in this analysis.

Finally, employment was also independently associated with a reduction of mortality. This finding highlights the important role of resocialisation through work, leading to better socio-economic conditions, which are an important health determinant in general.

Our study has several limitations. First, the follow-up was relatively short. Second, although the proportion of lost-to follow-up was low (4%), mortality could have been underestimated if most of these participants died during the study period. This is unlikely, given the main reason of lost contact was a move to another region. Similarly, PWID who did not agree to participate in the cohorts may have had more risk factors (for example, viral suppression was lower among those who did not participate). Finally, the lack of formal verbal autopsies to ascertain the causes of death may have contributed to misclassification.

4.1. Methodological challenges, opportunities, and lessons learned

In this hard to reach and stigmatised population, the first methodological challenge was to reduce the lost to follow-up rate to very low level. It was overcome by the major involvement of CBO on the study procedures, data collection and participant follow-up, to eventually reach less than 5% of participants with unknown vital status. The second methodological challenge was related to the implementation of robust verbal autopsies to better ascertain the causes of deaths. It proved very difficult to implement, given most deaths occurred outside health centres. The consideration of the past medical history collected in the cohort interviews, and the circumstances of death as reported by CBO after interviewing in detail their family or their drug user network, turned out an efficient procedure to reach a consensual likely cause of death among three clinicians. Well aware of the limitations of this approach, we decided to use a broad and adapted categorisation to minimise the misclassification bias. The high TB mortality rate certainly highlights a large TB burden among PWID, which should prompt their consideration as a priority population in TB control programs, which is not currently the case. Similarly, the high mortality rate due to liver diseases, certainly primarily due to HCV infection, provides an opportunity to stress the urgent need for free DAA in LMIC, along with mass HCV screening. The successful strategy to end the HIV epidemic, based on the great mobilisation and involvement of the PWID community itself for reaching, testing and facilitating access to care should also be used for both TB and HCV control. Finally, an important lesson learned is the need to monitor mortality and likely causes of death among PWID, as it can remain high and require targeting specific interventions. For this purpose, relying on CBO through their case-management approach with PWID is the key.

In conclusion, despite the very successful MAT and HIV programs among PWID in Vietnam, the mortality rate in

this group remains unacceptably high. The large proportion of avoidable TB and liver-related deaths calls for urgent specific interventions.

Conflict of Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.jclinepi.2021.07.007](https://doi.org/10.1016/j.jclinepi.2021.07.007).

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