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# Mortality and HIV transmission among male Vietnamese injection drug users

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# Abstract

**Aims**—To estimate all-cause mortality rate and to assess predictors of all-cause mortality among injection drug users (IDUs) in Thai Nguyen province, Vietnam between 2005 and 2007.

Design—Prospective cohort study.

**Setting**—Community-dwelling IDUs were enrolled and followed at 3-month intervals for up to 2 years.

**Participants**—894 male IDUs (median age of 32 years, 22.8% HIV-positive, all having injected opioid).

**Measurements**—Deaths were confirmed by family members and by reviewing government records. Marginal Cox proportional hazards models for clustered data were constructed to determine the independent predictors of all-cause mortality, using both fixed baseline measurements and time-dependent repeated measurements.

**Findings**—During 710.1 person-years of follow-up, 45 (5.0%) drug injectors died. The causes of deaths were aids-related death (14 cases, 31%), drug overdose (12, 27%), suicide (3, 7%), traffic accident (3, 7%), violence (2, 4%), pneumonia (2, 4%), non-traffic accident (1, 2%), and unknown causes (8, 18%). The all-cause mortality rate was 6.3% (95% CI = 4.6–8.5) per 100 person-years. The standardized mortality ratio was 13.4. The HIV incidence rate was 5.2 (95% CI = 3.5–7.6) per 100 person-years. In multifactorial analysis, hiv infection (hazard ratio [HR] = 3.5, 95% CI = 1.9–6.3) and previous diagnosis of tuberculosis (HR = 10.0, 95% CI = 4.1–24.3) were significantly associated with increased hazard of death.

**Conclusions**—The all cause, age and sex standardized mortality among Vietnamese IDUs is 13fold higher than the general population and substantially higher than IDUs studied in developed countries. Effective prevention and control of HIV infection and tuberculosis are urgently needed.

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#### Introduction

Substance abuse has been a growing public health problem in Vietnam since the mid-1990s. The number of drug users in the country known to the government increased 70%, from 101,000 to 170,000, between 2000 and 2004.[1] The drug use epidemic was followed by multiple outbreaks of HIV transmission among injection drug users (IDUs) in many provinces throughout the country. By 2006, most (93%) of the provinces and cities where the national HIV sero-surveillance was conducted had an HIV prevalence rate among IDUs greater than 20%, reaching rates as high as 70–85% in some areas, compared to the prevalence of less than 1% in the general population.[2]

Deaths among Vietnamese IDUs are anecdotally reported as common, especially among those who are HIV-infected, but little is known about the extent of the mortality among drug users and associated characteristics that may help to identify drug users who are at higher risk of mortality to better target public health interventions. This study aims to quantify the mortality and assess predictors of all-cause mortality among IDUs, specifically among male opioid injectors, who were enrolled and followed prospectively in Thai Nguyen province in the northern region of Vietnam between 2005 and 2007.

# Methods

We analyzed data from a randomized, controlled trial examining the efficacy of a behavioral intervention in reducing HIV risks among IDUs and their network members in northern Vietnam. The trial enrolled and followed networks of IDUs. Each network was comprised of an index participant and at least 1 network member. Eligibility criteria for index participants were (a) being 18 years or older; (b) having injected drugs in the past 3 months; (c) having HIV-negative antibody test results; and (d) being able to recruit at least 1 eligible network member. Eligibility criteria for network members were (a) being 18 years or older; and (b) having injected drugs with or had sexual intercourse with their index participant in the past 3 months. Network members were not required to be HIV-negative. Eligible networks were randomized to either intervention arm or control arm (1:1 ratio) in blocks of consecutively accrued networks (block size range, 12–24). Index participants, whose networks were assigned to the intervention arm, attended a series of 6 intervention sessions over a 6-week period, where participants were instructed in methods of harm reduction, communication skill building, role-playing, and problem-solving activities. All participants were followed up at 3-month intervals for 1 year, or exceptionally (if lost to follow-up within the first year) to the end of study (up to 2 years). In each of the baseline and follow-up visits, participants were tested for HIV antibody, counseled, and administered a face-to-face interview using a structured questionnaire. The questionnaire included questions on demographics, alcohol use, drug use, sharing and disinfecting injection equipment, number of sex partners, and condom use. Information on health service utilization was not collected. Blood specimens were tested for HIV antibody. All participants were provided with pre-test and post-test HIV and sexually transmitted diseases counseling and appropriate referrals.

In this report, we focus on all-cause mortality among 894 male drug injectors, who accounted for 97.7% of the IDU sample and for all deaths. Drug injector was defined as

having injected drugs in the 3 months before baseline visit. In Vietnam, deaths are significantly under-registered and quality of death registration data is poor, with the completeness of death registration for ages older than 5 years ranging from 32% to 51%.[3] In this study, deaths were recorded based on notifications made by the deceased's family members or based on home visits after missed study visits. All 45 deaths (100%) were confirmed by family members, of them 27 (60%) were also identified in government's recorded based on the deceased's family members' reports. As commonly seen in developing countries, International Classification of Diseases (ICD) codes for underlying causes of death were not available.[3,4]

Mortality rates were calculated based on person-years of follow-up. The follow-up time was calculated as the number of days between baseline visit and the date of death or the last day each participant was seen during follow-up. Poisson regression was used to calculate confidence intervals (CIs) for mortality rates. To compare the observed mortality rate among the male IDUs with one among males in the general population, we used indirect standardization method, in which age-specific death rates among male population as of 2006,[5] are applied to the age groups of the IDU sample. The standardized mortality ratio (SMR) was calculated from the 'expected' deaths and the actual number of deaths observed. We also calculated SMR by HIV serostatus at baseline. IDUs who did not return for any non-baseline visits were not included in analysis of predictors of death. The follow-up time for HIV incidence analysis among HIV-negative IDUs was calculated from baseline to the mid-point between the last HIV-negative visit and the first HIV-positive visit. Marginal Cox proportional hazards models for clustered data, with networks as clusters, were constructed to determine the independent predictors of death, using both fixed baseline measurements and time-dependent repeated measurements.[6] The model estimated the parameters by maximizing partial likelihood under the independent working assumption and used a robust sandwich covariance estimate to account for intracluster dependence. The fixed variables included age, ethnicity, self-report of a previous tuberculosis diagnosis, and number of years injecting drugs, measured at baseline. The time-dependent variables included drugs of use (e.g. benzodiazepines, amphetamine), the Center for Epidemiologic Studies Depression Scale score (CES-D), and prevalent and incident HIV infections. Variables that were statistically significant at the 0.10 level were considered for entry into a multifactorial model. The assumption of a constant risk ratio over time for the proportional hazards analysis was tested and found to be valid for all variables modeled. There were no significant interactions among any variables included in the final multifactorial model. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC).

## Results

Among 1434 participants who were screened, 935 (65.2%) were eligible for trial enrollment. Among the enrollees, 915 (97.9%) were drug injectors, of whom 894 (97.7%) were men (413 index participants and 481 injecting partners). The sex distribution is consistent with existing statistics of drug users in Thai Nguyen (99% male). This study investigates mortality in this group of 894 male drug injectors.

Among the male drug injectors, during the mean follow-up of 9.5 months (median = 12.1 months), the retention rates were 83% at month 3, 80% at month 6, 77% at month 9, and 69% at month 12. Among 151 participants (17%) who did not return to any follow-up visit, 49 (32%) moved out of town, 47 (31%) were incarcerated, and 32 (21%) provided incorrect addresses and thus could not be located. Baseline characteristics of these 151 participants did not differ significantly from those who returned with respect to ethnicity, drug injection frequency, or HIV sero-status (all with p > 0.05), although they were slightly younger (median age of 30 vs. 32, p < 0.001).

The baseline characteristics of 894 male drug injectors are presented in Table 1. The injectors (median age of 32 years, range = 18-59) reported having injected drugs for a median of 5.3 years (range = 0.1-17.4). The drugs which have been used by the injectors included heroin (894, 100.0%), opium (649, 72.6%), benzodiazepine (284, 31.8%), amphetamines (165, 18.5%), promethazine (137, 15.3%), morphine (99, 11.1%), cannabis (50, 5.6%), and cocaine (12, 1.3%). At baseline, 204 (22.8%) drug injectors were HIV - positive.

#### Mortality

During 710.1 person-years of follow-up, 45 of 894 (5.0%) drug injectors died. The causes of deaths were aids-related death (14 cases [13 HIV-positive cases at baseline, 1 HIV incident case], 31%), drug overdose (12, 27%), suicide (3, 7%), traffic accident (3, 7%), violence (2, 4%), pneumonia (2, 4%), non-traffic accident (1, 2%), and unknown causes (8, 18%). The all-cause mortality rate was 6.3% (95% CI = 4.6–8.5) per 100 person-years. The standardized mortality ratio (SMR) was 13.4 (95% CI = 11.4–15.3). The SMR calculated by baseline HIV status was 34.6 (95% CI = 27.2–42.0) for HIV-positive IDUs and was 8.4 (95% CI = 6.7–10.2) for HIV-negative IDUs. The mortality rates by selected baseline characteristics are presented in Table 1.

#### **HIV Incidence**

Among 690 drug injectors who were HIV-negative at baseline, during 535.7 person-years of follow-up, 28 (4.1%) injectors HIV-seroconverted. The HIV incidence density was 5.2 (95% CI = 3.5-7.6) per 100 person-years.

#### Predictors of All-Cause Mortality

Table 2 presents data from univariate and multifactorial analyses of factors potentially associated with all-cause mortality among the male drug injectors. In univariate analyses (Table 2), there was a tendency for younger age being associated with increased hazard of death, but the association did not reach significant level (p = 0.11). Being married was associated with lower mortality, but because participants who were married were significantly older than the others (median age of 35 years vs. 31 years, p < 0.001), this variable was not included in the multifactorial model. Higher frequency of heroin injection and a recent history of drug overdose were associated with higher hazard of death (20-percent and 10-percent increase, respectively) but the associations did not attain statistical significance. Every 5-point increase in the CES-D score was associated with an 10-percent increase in the hazard of death, but with a p-value of 0.09. In multifactorial analysis (Table

2), factors that remained significantly associated with increased hazard of death were hiv infection (hazard ratio [HR] = 3.5, 95% CI = 1.9-6.3), a previous tuberculosis diagnosis (HR = 10.0, 95% CI = 4.1-24.3).

#### Discussion

This cohort study provides the most in-depth empirical data on mortality and its determinants among Vietnamese community-dwelling injection drug users to date and adds valuable data to the currently scarce research on IDU mortality in developing countries.[7] The data show that the Vietnamese IDUs have a high all-cause mortality rate (6.3% per year), 13-fold higher than the rate in the general population after standardization for age and sex. The rate is somewhat higher than rates reported in studies of IDUs in India (4.3% per year) or Thailand (3.8% per year) and is substantially higher than rates in developed countries (USA, 0.7% per year; Australia, 0.8% per year).[8–11] We found that HIV infection and a tuberculosis diagnosis significantly increase the total mortality among these IDUs. The mortality rate, though high, may still be underestimated because the proportion of HIV-infected individuals enrolled in this study (22.8%), by design, is lower than the HIV prevalence (33.2–40.7%) among IDUs estimated from HIV sero-surveillance in Thai Nguyen province in the same period.[2]

Injection drug users, by far, have been the population group most affected by the rapidly evolving HIV epidemic in Vietnam. Up to 69% of the country's HIV cases are among IDUs and the HIV prevalence in this group is high, reaching 70-85% in some provinces (Khanh Hoa, 85.0% in 1998; Ho Chi Minh City, 83.7% in 2001; Quang Ninh, 75.2% in 2002).[2] Monitoring the HIV epidemic among the IDUs has primarily relied on HIV sero-prevalence data collected through the national HIV sero-surveillance system, [2] which is useful in providing estimates of the treatment burden to the AIDS program, but is insufficient to evaluate the trends of HIV transmission in order to direct prevention efforts without data on new HIV infections and AIDS-related deaths. Data from this cohort of IDUs indicate a rapid HIV transmission (5.2% per year, compared to 3.0% per year in Thailand in 2003 [12], 3.1% per year in China in 2006 [13]) and high mortality (6.3% per year) among IDUs while HIV sero-surveillance data suggest a slow increase in HIV sero-prevalence between 2003 and 2005, a 7-percent increase of in 2006, and a 5-percent decline in 2007 (29.2% in 2003, 32.0% in 2004, 33.2% in 2005, 40.7% in 2006, 35.5% in 2007). Monitoring HIV transmission is not the only area that may benefit from improvement, the HIV incidence and mortality data also underscore the need for major efforts to reduce HIV transmission and deaths among IDUs. In many parts of the developed world, HIV infection is no longer a death sentence after the introduction of highly active antiretroviral therapy (HAART), whose efficacy in reducing deaths has been established.[14] The 3.5-fold increase in the hazard of death associated with HIV infection among the IDUs is likely to be explained by a limited access to HAART in the study area.

Tuberculosis (TB) is a common infectious disease and a major cause of death in Vietnam. Though estimates of the magnitude of latent TB infection in Vietnam are not available, studies of Vietnamese immigrants to the United States and Australia suggest that nearly half (44–48%) of Vietnamese are infected,[15,16] and approximately 150,000 individuals

develop active TB every year.[17] Studies in recent years also documented a high proportion of death or treatment failure among TB patients, regardless of their completion of treatment regimens (15%) or not (33%),[18] for which the emergence of Beijing genotype associated with drug resistance may be an important cause.[19,20] Injection drug users, particularly those with HIV infection, are reported to be more susceptible to developing active TB,[21] have less access to healthcare services, less likely to adhere to the long course of TB treatment, and may be at increased risk of tuberculosis-related death.[22] Nevertheless, neither the magnitude of the TB problem, the access to TB prophylaxis and treatment, nor the effectiveness of treatment regimens has been specifically assessed among the IDU population in Vietnam. The finding of a significant increase in hazard of death associated with a TB diagnosis among IDUs should be of public health concern and re-emphasize the need for programs to prevent, detect and treat TB among IDUs.

Drug overdose is among the leading cause of deaths among opioid injectors worldwide. This study found a high proportion of deaths (27%) among Vietnamese opioid injectors was reportedly due to drug overdose. In a survey of 299 out-of-treatment opioid injectors in northern Vietnam, 43% reported experiencing one or multiple episodes of drug overdose. [23] These data suggest that measures to prevent drug overdose among the IDUs are of public health importance.

Several limitations of this study should be noted. First, participants who were enrolled in this study met the trial's eligibility criteria but were not randomly selected. Therefore, the estimated mortality rates do not necessarily represent rates among drug users elsewhere in Vietnam. Second, because of the socially undesirable nature of drug use, certain drug use behaviors may be underreported, which may result in lower prevalence of drug use behaviors, and subsequently, certain risks for mortality may not have been detected or were biased toward the null. Similarly, causes of death were recorded based on the deceased family's reports and given the strong stigma associated with HIV infection and drug use in Vietnam, these reports may not be accurate, and thus, causes of death should be interpreted with caution. Forth, because of short follow-up time in this study (710.1 person-years for 894 participants), some risk estimates have wide confidence intervals and certain chronic disease-associated deaths may be underrepresented. Fifth, data on access to healthcare and antiretroviral therapy, which could be useful to explain mortality among HIV-infected individuals, were not collected. Finally, the poor quality of registration of causes of death did not allow for conducting cause-specific mortality analyses, including risks for drug overdosed deaths.

In summary, the study results are provocative and are an important contribution to mortality research among IDUs in developing countries. The estimated 6% of Vietnamese drug injectors dying each year indicates a need for immediate intervention. Effective prevention and control of HIV infection and tuberculosis are likely to be important strategies for reducing the risk of death in this context.

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# Table 1

Baseline characteristics and mortality rates in a cohort of 894 male injection drug users, Vietnam, 2005–2007.

Characteristic	No. participants	Percent	Person-years	No. deaths	Mortality rate (per 100 person-years)	(95% CI)
All	894	100.0	710.1	45	6.3	(4.6–8.5)
Age (median, range)	32 (18–59)					
30 yrs	583	65.2	483.5	28	5.8	(3.8 - 8.4)
< 30 yrs	311	34.8	226.6	17	7.5	(4.4–12)
Currently married/living with a partner						
No	604	67.6	458.8	38	8.3	(5.9 - 11.4)
Yes	290	32.4	251.3	7	2.8	(1.1 - 5.7)
Ethnicity						
Kinh (ethnic Vietnamese)	821	91.8	651.6	39	6.0	(4.3 - 8.2)
Ethnic minority	73	8.2	58.5	9	10.3	(3.8–22.3)
Being arrested by police, past 3 mo						
No	474	53.0	373.6	24	6.4	(4.1 - 9.6)
Yes	420	47.0	336.5	21	6.2	(3.9 - 9.5)
Being incarcerated, past 3 mo						
No	567	63.4	446.4	29	6.5	(4.4 - 9.3)
Yes	327	36.6	263.8	16	6.1	(3.5 - 9.8)
Years of drug injection (median, range)	5.3 (0.1–17.4)					
5 yrs	484	54.1	389.8	23	5.9	(3.7 - 8.9)
< 5 yrs	410	45.9	320.4	22	6.9	(4.3 - 10.4)
Injection frequency						
Less than daily	227	25.4	180.9	10	5.5	(2.7 - 10.2)
Daily	667	74.6	529.2	35	6.6	(4.6–9.2)
Amphetamine use, past 3 mo						
No	882	98.7	701.9	44	6.3	(4.6 - 8.4)
Yes	12	1.3	8.3	1	12.0	(0.3-67.1)
Cannabis use, past 3 mo						
No	889	99.4	707.3	43	6.1	(4.4 - 8.2)
Yes	ŝ	0.6	2.9	2	69.0	(8.4–249.1)

Benzodiazepine use, past 3 mo No Y es Overdosed any drug, past 3 mo					,	
No Yes Overdosed any drug, past 3 mo						
Yes Overdosed any drug, past 3 mo	793	88.7	639.6	40	6.3	(4.5 - 8.5)
Overdosed any drug, past 3 mo	101	11.3	70.5	5	7.1	(2.3 - 16.6)
No	874	97.8	695.9	44	6.3	(4.6–8.5)
Yes	20	2.2	14.2	1	7.0	(0.2 - 39.2)
In drug treatment, past 3 mo						
No	866	96.9	689.9	44	6.4	(4.6 - 8.6)
Yes	28	3.1	20.2	1	5.0	(0.1 - 27.6)
Excess alcohol use						
No	869	97.2	689.5	44	6.4	(4.6 - 8.6)
Yes	25	2.8	20.6	1	4.9	(0.1 - 27)
Having 2 sex partners, past 12 mo						
No	666	74.5	531.6	31	5.8	(4-8.3)
Yes	228	25.5	178.5	14	7.8	(4.3 - 13.2)
Having unprotected sex, past 3 mo						
No	607	67.9	475.7	34	7.1	(4.9 - 10.0)
Yes	287	32.1	234.5	11	4.7	(2.3 - 8.4)
CES-D score (median, range)	23 (0–51)					
23	471	52.7	389.8	23	5.9	(3.7 - 8.9)
> 23	423	47.3	320.3	22	6.9	(4.3 - 10.4)
Tuberculosis diagnosis, self-report						
No	876	98.0	701.3	41	5.8	(4.2 - 7.9)
Yes	18	2.0	8.8	4	45.5	(12.4–116.4)
HIV sero-status at enrollment						
HIV-negative	069	77.2	559.7	23	4.1	(2.6–6.2)
HIV-positive	204	22.8	150.4	22	14.6	(9.2 - 22.1)
Study arm assignment						
Control	442	49.4	352.8	23	6.5	(4.1 - 9.8)
Behavioral intervention	452	50.6	357.3	22	6.2	(3.9 - 9.3)

#### Table 2

Predictors of all-cause mortality among 894 male injection drug users, Thai Nguyen province, Vietnam, 2005–2007

Characteristic	Univariate model	n voluo	Multifactorial model*,***	
Characteristic	р- НR (95% CI)	p-value	HR (95% CI)	p-value
Age (10-year incremental)	0.7 (0.4–1.1)	0.11	0.7 (0.4–1.2)	0.21
Being married	0.3 (0.2–0.7)	0.006		
Ethnic minority	1.7 (0.7–4.1)	0.23	1.7 (0.7–4.1)	0.21
Drug detoxification treatment, past 3 mo	0.8 (0.1–5.0)	0.78		
Arrest by police, past 3 mo	1.0 (0.5–1.8)	0.91		
No. years injecting drugs (incremental)	1.0 (0.9–1.1)	0.77		
Frequency of drug injection (daily vs. less frequent)	1.2 (0.6–2.5)	0.57		
Overdosed any drugs, past 3 mo	1.1 (0.2-8.0)	0.90		
Benzodiazepine use, past 3 mo**	0.8 (0.3–2.6)	0.71		
Amphetamine use, past 3 mo <sup>**</sup>	0.9 (0.1–6.1)	0.88		
No. days drinking alcohol, past 30 days (incremental)	1.0 (0.9–1.0)	0.60		
Having >= 2 female sexual partners, past 12 mo	1.3 (0.7–2.6)	0.40		
Having unprotected sex, past 3 mo	0.6 (0.3–1.3)	0.22		
CES-D score (5-point incremental)**	1.1 (1.0–1.3)	0.09	1.1 (1.0–1.2)	0.25
Tuberculosis diagnosis	8.2 (2.8–24.2)	< 0.001	10.0 (4.1–24.3)	< 0.001
HIV infection (prevalent and incident cases)**	3.7 (2.1–6.7)	< 0.001	3.5 (1.9–6.3)	< 0.001
Study arm assignment (intervention vs. control)	0.9 (0.5–1.7)	0.81		

\*Marginal Cox proportional hazards model for clustered data; yes versus no unless noted otherwise

\*\* Time-dependent repeated measurement; CI, confidence interval; HR, hazard ratio; CES-D score, Center for Epidemiologic Studies Depression Scale score.

\*\*\* The final multifactorial model includes five variables whose data are presented in the last two columns.