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Ending an HIV epidemic among persons who inject drugs (PWID) in a middle-income country: Extremely low HIV incidence among PWID in Hai Phong, Viet Nam

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Abstract

Objective: To determine whether it is possible to “end an HIV epidemic” among PWID in a low/middle income country.

Design: Serial cross-sectional surveys with a cohort of HIV seronegative participants with 6-month follow-up visits recruited from surveys.

Methods: Surveys of PWID using respondent driven and snowball sampling were conducted in 2016, 2017, 2018, and 2019 (Ns = 1383, 1451, 1444 and 1268). HIV recency testing was used to identify possible seroconversions in the window period prior to study entry. Structured interviews covering drug use histories, current drug use, and use of HIV-related services were administered by trained interviewers. Urinalysis was used to confirm current drug use. HIV and HCV testing were conducted. Electronic fingerprint readers were used to avoid multiple participation in each survey and to link participants across surveys. A cohort of HIV seronegative participants with

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6-month follow-up visits was recruited from the surveys, 480 from 2016, 233 from 2017, and 213 from 2018.

Results: Participants were predominantly male (95%), mean age approximately 40, all reported injecting heroin, HIV prevalence ranged between 26% - 30%. We had 3 seroconversions in 1483-person years at risk (PYAR) in the cohort study, and 0 in 696 PYAR among repeat survey participants, and 0 seroconversions in 1344 PYAR in the recency testing. Overall HIV incidence was 0.085/100 PYAR, 95% CI 0.02 - 0.25/100 PYAR.

Conclusion: The data from Hai Phong clearly demonstrate that it is possible to achieve very low HIV incidence—"end an HIV epidemic"--among PWID in a middle-income country.

Keywords

HIV; Persons who Inject Drugs; PWID; incidence; low/middle income countries

Introduction

Rapid transmission of HIV through multi-person use of needles and syringes for injecting psychoactive drugs has occurred in many parts Central and Southeast Asia, Europe, and North America. HIV prevalence among persons who inject drugs (PWID) has exceeded 30% in many of these areas [1-3]. Since 2009, the global HIV community has seen the development of "combined prevention and care for HIV among PWID," including needle and syringe programs (NSP), opioid substitution treatment (OST), and antiretroviral treatment (ART) for HIV seropositive persons [4, 5]. The effectiveness of combined prevention and care relies on implementation of the interventions at a public health scale. For example, UNAIDS technical guideline recommend a standard of 300 syringes/PWID/year [6]. Application of the technical guidelines has led to ending HIV epidemics among PWID in many high-income settings, with HIV incidence reduced to 1/100 person-years at risk (PYAR) or less [7, 8]. Whether similar success in reducing HIV transmission in resource constrained settings is a major issue for the control of HIV transmission among PWID.

Viet Nam experienced a heroin injecting epidemic beginning in the 1970s,[9, 10] followed by an HIV epidemic among PWID in the early 2000s. HIV prevalence reached very high levels in some provinces—over 60% in Hai Phong in 2006 [11]. Methadone maintenance treatment began in 2008 and stabilized around 2017 with approximately 4000 persons in treatment at any one time in Hai Phong. Access to sterile syringes has primarily been through pharmacy purchase. Community-based syringe exchange is available in Hai Phong, but with relatively few sites compared to many local pharmacies. ART for all HIV seropositive persons was implemented beginning in 2016, and full implementation of the UNAIDS technical guidelines for combined prevention and care for PWID was achieved by 2018 in Hai Phong [12, 13]. A dual capture-recapture study gave an estimate of PWID in the community who are currently injecting drugs as 5000 (+/−1000 individuals), plus another 1000 in detention centers (not in the community) and 4000 in methadone maintenance treatment and not currently injecting drugs for a total of approximately 10,000 PWID. (This capture/recapture study defined current injecting status through urinalysis and presence of

recent injecting marks, the same criteria used for the eligibility criteria for current injecting in the surveys presented in this report.) [14].

To our knowledge, we do not have compelling evidence that combined prevention and care can greatly reduce HIV incidence in PWID populations in low/middle income countries (LMIC) to very low levels. Provision of services to PWID is generally extremely low in LMIC; between 2007 and 2016, there was a 25% reduction in international funding for harm reduction activities in LMIC. [15]. Viet Nam, however, did not reduce HIV prevention and care services, with the national and provincial governments contributing increasing shares of the costs, and some patient fees for methadone treatment [16].

A recent randomized control trial found that combined prevention and care with "navigators" could reduce HIV incidence among PWID to a very low level in both the experimental and control groups, but with no significant difference in HIV incidence (0.0/100 person-years; 95% CI: 0, 1.7 vs. 1.0/100 person-years, 95% CI: 0.4, 2.1)[17]. This study did suggest that scaling up services to the population level should be quite effective in controlling HIV transmission among PWID.

In this report we present data from the DRIVE (DRug use Infections in ViEt Nam) study on "ending the HIV epidemic among PWID" in Hai Phong, Viet Nam. The study included epidemiologic monitoring and interventions to reduce HIV transmission. We previously specified achieving an HIV incidence of 0.5/100 person-years among persons living in the community and actively injecting drugs as a defining characteristic of "ending an HIV epidemic in PWID population"[5, 18, 19]. (Note that this population would not include persons with histories of injecting but not currently injecting, or persons residing in detention centers, prisons or inpatient facilities.) The objective of this study is to assess whether Hai Phong has achieved an HIV incidence of 0.5/100 person-years or less among PWID, thus signifying the "end of the HIV epidemic" among PWID in the city.

Methods

Respondent Driven and Snowball Sampling (RDSS) Surveys:

We conducted four large community-based surveys among PWID using respondent driven and snowball sampling methods in 2016, 2017, 2018 and 2019. The target number of participants for each survey was 1500. The eligibility criteria for participation in the surveys were: age 18 or greater, recent injection drug use, validated through urine testing for an injectable drug (heroin/morphine or methamphetamine) and presence of recent injection marks, residence in Hai Phong, and ability to provide informed consent. Participants were permitted to participate in multiple surveys but only once in each survey. For each of the surveys, there were modest numbers (100-150) of persons who presented at the research sites but did not meet eligibility requirements, primary due to lack of recent injection marks.

We began each of these surveys using standard RDS methods [20, 21]. Each survey began with the approximately 20 "seeds," selected by community-based organization (CBO) staff for diversity (age, gender, HIV status) and having large social networks of PWID. Each seed first participated in all study procedures, and then was given 3 numbered coupons for

recruiting new participants. As new persons participated in the study, they were then given numbered coupons for recruiting additional new participants. Participants were paid modest honoraria for both their own time and effort in the study and for recruiting new participants. An electronic fingerprint reader was used to protect against multiple participation in each survey and to link persons who participated in more than one survey.

After five weeks and approximately 1000 participants into each of the surveys, recruitment of new participants slowed considerably, to the point where it became clear that continuing standard RDS methods would not permit us to reach our desired sample sizes of 1500 participants. We continued the RDS methods, including using coupons to track recruiting, and added a “snowball” sampling [22] component in which participants were permitted to recruit more than 3 (up to 20) new participants. This did permit us to come very close to our target numbers of participants in each survey.

As the change to snowball recruiting violated RDS assumptions, we did not use RDS weighting in our analyses but treated the surveys as independent convenience samples with replacement. We did examine reaching equilibria and homophilies for major study variables. Rapidly reaching equilibria and low homophilies were also observed for all major variables. We also compared demographic characteristics, drug use behaviors and HIV and HCV seroprevalence among participants recruited under RDS procedures and snowball sampling procedures. There were no significant differences in any of these comparisons (Data not shown, available on request).

Data Collection:

After informed consent was obtained, study eligibility was determined using urinalysis for injectable drugs and visual inspection for recent marks of injecting, then face-to-face structured interviews were administered including information on demographic characteristics, drug use and sexual behavior, and use of drug-related and HIV-related services. The questions on drug use referred to frequency of use in the previous 6 months and the number of days on which each drug was used in the previous 30 days. Despite assuring respondents that the data would be kept confidential, social desirability bias was a concern for many risk behavior questions. Counseling for HIV and HCV testing was provided, and blood samples collected.

Urine samples were tested for heroin/morphine, methamphetamine, and methadone using Drug-screen Multi 7A carte (Nal von Minden, Germany). The provincial HIV reference laboratory was in charge of blood collection, on site blood testing, and giving results to participants. HIV serology followed national guidelines including an initial rapid test using SD BIOLINE HIV 1/2 3.0 (Standard Diagnostic Inc., South Korea), with confirmation using two other rapid tests (Alere Determine HIV 1/2 (Abbott Alere Medical Co., Japan, and VIKIA®HIV1/2 (Biomerieux, France). CD4 counts were done using the BD FACS Count system (BD Biosciences, San José, USA). HCV serology relied on a rapid test SD BIOLINE HCV (SD Standard Diagnostic Inc, South Korea). We used the Asante HIV-1 rapid recency®, developed by the Sedia Biosciences, Portland USA. We complied with the manufacturer’s algorithm which requires that several conditions are met to confirm a recent infection (less than 6 months): 1) no participant report of HIV-infection diagnosis within the

last 12 months or longer, 2) plasma viral load greater than 1000 copies/ml, 3) CD4 counts greater than 200, 4) not on ART, and 5) positive recency testing [23].

Cohort intervention studies:

During each of the first three RDSS surveys, we invited participants to participate in an open cohort study with follow-up every six months. The objective of the intervention study was to assist participants in initiating methadone treatment, entering and being adherent to ART and education on practicing safer injection and sexual behaviors. (A separate manuscript is in preparation that will give full details on the intervention study). Eligibility criteria included having contact information confirmed by CBO staff and not currently receiving methadone maintenance treatment. Consecutive eligible participants were enrolled in the seronegative cohort until the sample size from each RDSS was completed (480 for the 2016 survey, 233 for the 2017, and 213 for the 2018 surveys). Data collection at each 6-month cohort study visit included HIV testing. Participants in the cohort study received Social Health Insurance cards, peer support for safer injection and safer sex, and CBO staff navigation to access methadone treatment. The CBO staff attempted to maintain monthly contact with cohort participants and encouraged cohort members to participate in follow-up visits. Cohort members also received telephone calls or home visits to encourage them to participate in follow-up.

Statistical analyses:

Means with standard deviations and proportions with 95% confidence intervals were used to describe the participants in the RDSS surveys. Subjects with missing data for specific variables were excluded from the descriptive data for that variable and the statistical tests. Chi-square, Fisher's exact, and t-tests were used to compare participant characteristics across the surveys.

We calculated HIV incidence using three techniques:

1. HIV recency testing [23] was used to identify seroconversions that would have occurred in the 6 month "window period" prior to the first HIV test we conducted among participants.
2. Time from first seronegative HIV test to last HIV seronegative test for persons who participated in multiple surveys but did not participate in the cohort study and remained seronegative.
3. Time from first seronegative test to last seronegative test for persons who participated in the cohort study and remained seronegative.

For persons who did seroconvert, we estimated the time of seroconversion as halfway between the last seronegative test and the first seropositive test. The total incidence rate was then calculated using the total number of seroconversions divided by the total time-at-risk (i.e., totals of recency testing, survey repeater and cohort time-at-risk plus time at risk among seroconverters using exact confidence intervals).

STATA 15 [24] was used for data analysis. The study was reviewed and approved by the Institutional Review Boards of Hai Phong University of Medicine and Pharmacy, Icahn School of Medicine at Mount Sinai and the New York University School of Medicine.

Results

Participant characteristics.

Demographic characteristics, drug use, HIV and HCV prevalence, and HIV transmission and acquisition injecting risk behaviors are presented for the four RDSS surveys in Table 1. Participants were predominantly male, and a majority were married or living as married. The mean age was near 40 years and increased over the surveys ($t=-7.9$; $p<0.0001$). All reported injecting heroin—verified by urinalysis—with a decline over time in the percentages reporting daily or more frequent heroin injection. Methamphetamine was used by a substantial minority, over 40%, in each of the surveys. Methamphetamine was used primarily by "smoking," heating the drug and inhaling the vapor. Less than 2% of those reporting methamphetamine use reporting injecting methamphetamine in each of the surveys, and all of these participants reported smoking.

Methadone—detected in urinalysis—was also used by more than half of the participants, and with a significant increase over time (chi square (3) = 159.9; $p<0.001$).

Most participants reported obtaining an average of one or more new syringes/day, with pharmacies being the primary source of syringes in each of the surveys. Overall, 97% of the participants reported pharmacies as their primary source of syringes. The percentages reporting any syringe sharing in the 6 months prior to each survey were quite low, under 5% in each survey.

HIV prevalence declined modestly over time and HCV prevalence remained stable. The percentage of HIV seropositive participants who reported receiving ART increased over time ($z=11.2$; $p < 0.001$ by trend test). The percentage of PWID most likely to transmit HIV through syringe sharing—who were HIV seropositive, not on ART, and reported syringe sharing—was very low, and also declined over time.

HIV incidence.

(See Table 2.) There was a total of 926 seronegative PWID enrolled in the cohort study, of whom we had at least one follow-up HIV test for 807 (87%) who accounted for 1483 person-years for calculating time at risk (average of 1.8 person-years per participant). Follow-up rates for individual study visits ranged from 63% to 81%. There were multiple reasons for loss to follow-up: not able to be contacted, not desiring to participate in a visit, sent to detention centers, moving out of Hai Phong, and death. Participants who were no longer living in the community were considered as outside of the target population. Persons who remained in the community and did not participate in follow-up were considered to be receiving "treatment as usual" in the community.

HIV incidence rates for PWID during the recency test period, for PWID who participated multiple times in RDSS surveys but did not participate in the cohort study, and for PWID

who participated in the HIV seronegative cohort study are presented in Table 2. As indicated by the overlapping confidence intervals, there were no significant differences in the HIV incidence rates as measured by the three methods.

Only three HIV seroconversions were observed. This small number of seroconversions precluded statistical testing for risk factors, or for trends over time, or for time participating in the cohort study prior to seroconversion, or for RDS versus snowball recruitment. One seroconversion occurred when the participant entered into a new drug use/sexual relationship, and the partner did not inform the participant of their HIV seropositive status. A second seroconversion occurred shortly after the participant had been released from a detention center (the period after leaving detention or incarceration is a high-risk period for both HIV infection and overdose) [25, 26]. Presumably, this seroconverter had relapsed to drug injection, may not have obtained sufficient supplies of sterile syringes, and may have joined a new injecting network. We were not able to obtain a case history interview for the third seroconverter. One seroconverter was identified in 2018 and 2 were identified in 2019.

Discussion

Prevention and care for PWID in Vietnam reflects the national policy, with Hai Phong being one of the locations where the implementation of these policies occurred early and on a public health scale [16].

The very low HIV incidence among participants requires some consideration of whether our sampling procedures might have missed substantial numbers of HIV seroconversions. Our CBO staff did report that there were PWID who did not participate in the study because of concerns over confidentiality, travel costs, and having other demands on their time such as employment. We see no reason to believe, however, that these under-represented groups would have substantially higher HIV incidence than the PWID who participated in our study. These groups would have been receiving “treatment as usual” in the community and that we had no seroconversions among PWID receiving treatment as usual in the community (recency testing window period and repeat RDSS survey participants).

There were 199 participants enrolled in the cohort study but were lost to contact before their first follow-up visit (and second HIV test). Some of these were lost to follow up for reasons that would have removed them from the target population of the study, e.g. moving out of Hai Phong, being in a detention center, or death. Others were lost to follow-up but were likely to have remained in the community and continued injecting. These latter persons were assumed to be receiving “treatment as usual” in the community. As there were no seroconversions among our participants receiving only treatment as usual, we would assume that HIV incidence would be very low among persons who left the cohort.

In this study, we reached approximately two thirds of the estimated 5000 active PWID in Hai Phong [14] and our observed HIV incidence (< 0.1/100 PYAR) was well below the target rate of 0.5/100 PYAR specified as a component for “ending the HIV epidemic among PWID” in Hai Phong [19]. Even if HIV incidence had been 13 times higher among the

PWID who did not participate in the study, we would still have matched our target rate for ending the epidemic.

Research logic for studying very low HIV incidence among PWID:

Studies of reducing HIV incidence among PWID typically compare incidence in two or more groups of PWID who receive different levels of HIV prevention services, with the expectation that the groups receiving more services will show lower incidence.

We do not believe that this design logic is appropriate for interpreting the results of the present study. Incidence was not lower in the cohort group, which received more services than participants who received “treatment as usual” in the community. HIV incidence did not decline over time, despite declines in self-reported injecting risk behavior and an increase in the percentage of HIV seropositive subjects on ART.

We believe that the more appropriate logic for analyzing our results is to consider the populations level factors that protect against HIV transmission within the group regardless of variation in the services received by individual PWID. There are several population-level factors present in Hai Phong that could lead to the very low HIV incidence that we observed.

First, PWID in Hai Phong are obtaining very large numbers of sterile syringes—an average of approximately 450 syringes per PWID per year. This is 50% higher that the “high” level recommended in the UNAIDS technical guidelines [27].

Second, there is a considerable amount of methadone use in Hai Phong, including among persons who are currently injecting. Methadone use, either through receiving methadone maintenance treatment or through the use of diverted methadone would decrease the frequency of injecting and thus reduce the chances for syringe sharing [28, 29].

Third, there are very few HIV seropositive PWID likely to transmit HIV through sharing syringes. A high percentage of HIV seropositive PWID in Hai Phong were on ART (from 52% to 83%) across the four surveys. The percentage of PWID who were HIV seropositive, not on ART and reported syringe sharing was < 1% of the PWID population in RDSS1 and declined to almost zero in RDSS4. This factor is a combination of low population viral load, which has been associated with reduced HIV transmission [30, 31] and the low percentage of HIV seropositive PWID who share syringes.

Note on the effectiveness of the interventional cohort studies.

As descried above the cohort intervention studies were intended to provide increased access to and support for PWID to use various services such as methadone and ART. Participation in the cohort studies was not associated with lower HIV incidence, but was associated with increased use of methadone treatment, of ART, with a higher likelihood of achieving viral suppression, and with a decrease in HCV incidence over time. The dynamics of these effects were clearly different from those of the HIV incidence and will be described in a separate analysis that will include a full description of the intervention activities.

Limitations

The primary limitation of this study is the likelihood of social desirability in the self-report data, particularly in the very low rate of syringe sharing. We do take these data as an indication of strong social norms against sharing in the PWID population. That the HIV incidence is very low, however, does indicate that syringe sharing is also likely to be very low.

A second, very desirable limitation, is that we did not have enough seroconversions in the study to clearly identify factors for seroconversion or test for trends over time. Two of our three seroconversions involved possible transitions to new injecting networks, which would be consistent with the literature on partner change and release from detention as occasions of relatively high risk for HIV transmission [32, 33].

Conclusions

HIV incidence has been reduced to very low rates (less than 1/100 PY) in many high-income settings. Implementation of “combined prevention and care for HIV among PWID” has been limited in low/middle income countries and funding for HIV prevention in low/middle income countries has been declining. The data from Hai Phong, however, clearly demonstrate that it is possible to achieve very low HIV incidence—and to “end an HIV epidemic”—in a PWID population in a middle-income country. The Hai Phong data can serve as an example for other low/middle income countries.

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Table 1

Demographics, drug use characteristics, and HIV and HCV risk behaviors and prevalence among PWID in Hai Phong, Viet Nam, 2016 – 2019

	RDSS1[a]		RDSS2[a]		RDSS3[a]		RDSS4[a]	
Average age (SD)	39(9)		39 (9)		41 (9)		42 (9)	
	N	%	N	%	N	%	N	%
Total	1383	100	1451	100	1445	100	1268	100
Gender								
Female	83	6	66	5	77	5	72	6
Male	1294	94	1381	95	1362	94	1193	94
Daily injection *	1107	80	1127	78	1015	70	788	62
Sharing syringes *	68	5	50	4	49	3	23	2
Methadone (based on urinalysis) *	582	42	822	57	923	64	778	61
Unsafe sex (primary partner)	489	35	504	35	566	39	420	33
Unsafe sex (casual partner)	40	3	71	5	43	3	40	3
HIV seropositive *	411	30	390	27	395	27	328	26
HIV seropositive PWID on ART among all seropositive PWID *[1]	212/411	52	278/390	71	327/395	83	281/328	86
HIV seropositive PWID not on ART and reporting syringe sharing among all PWID *[2]	10	0.7	4	0.3	3	0.2	1	0.1
HCV seropositive	972	71	1005	69	1016	72	923	73

[a] Totals for variable categories may not equal the total N for the survey due to missing data. Percentages were calculated on subjects with no missing data.

* Significant trend (non-parametric trend test; $p < 0.05$) across RDSS surveys.

Note: Non-parametric trend test was not conducted for age.

[1] This reflects coverage of ART for HIV seropositive PWID.

[2] This reflects the percentage of PWID in the population who are most likely to transmit HIV to others through syringe sharing.

Table 2

HIV incidence rate by sample grouping among persons who inject drugs, Hai Phong, Viet Nam, 2016 - 2019

Sample group	N	Years-at-risk	Incident cases	Incidence rate (95% CI)[a]
Recency window testing [b]	2569	1285	0	0 (0 - 0.29)
RDSS repeat participants [c]	418	696	0	0 (0 - 0.53)
Cohort participants [c]	807	1483	3	0.20 (0.04, 0.59)
Total	2569	3464	3	0.085 (0.02, 0.25)

[a] per one-hundred person-years at risk

[b] Includes 6 months prior to first seronegative test for all participants including 1344 participants who did not repeat in RDSS surveys and did not participate in the cohort study

[c] RDS repeat participants and cohort participants are also part of the recency window testing group, but their years at risk in the table is based on time from first seronegative test to last seronegative test plus one half of the time from first seronegative test to first seropositive test for 3 seroconverters