A Cohort Approach to Real-Time Detection of Acute HIV Infections Among People Who Inject Drugs in St. Petersburg, Russia

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Abstract

To detect acute HIV infections (AHIs) in real time among people who inject drugs (PWID) in St. Petersburg, Russia and to test the feasibility of this approach. Prospective cohort study. One hundred seronegative or acutely HIV-infected at screening PWID were enrolled and followed until the end of the 12-month pilot period. Each participant was evaluated, tested, and counseled for HIV monthly. Two HIV tests were used: HIV antibody and HIV RNA PCR. If diagnosed with AHI, participants were followed weekly for a month; then, monthly for 3 months; and then, quarterly for the duration of the follow-up period. HIV risk behavior was assessed at each study visit. Most enrolled PWID were 30–39 years old, male, completed high school or more, not employed full-time, heroin users, and frequently shared injection paraphernalia. AHI prevalence at screening was 1.8% [95% confidence interval (CI): 0.4, 5.5]. Three participants with AHI at enrollment represented 3% (95% CI: 0.6, 8.5) of the 100 participants who consented to enroll. Among the HIV-uninfected participants ($n=97$), the AHI incidence over time was 9.3 per 100 person-years. Persons with AHI were more likely to report alcohol intoxication within the prior 30 days. This was the first study to detect AHI using a cohort approach. The approach proved to be feasible: recruitment, retention, AHI detection, and virological endpoints were successfully reached. A cost analysis in a real-world setting would be required to determine if this strategy could be brought to scale. The study revealed continued high HIV incidence rate among PWID in St. Petersburg, Russia and the importance of prevention and treatment programs for this group.

Keywords: acute HIV incidence, PWID cohort, Russia

Introduction

THE DEVASTATING HIV EPIDEMIC among people who inject drugs (PWID) in Russia has not improved in the past decade and more than 50% of all cases are still attributed to injection drug use.^{1,2} During this period, the HIV prevalence among PWID in St. Petersburg ranged from 30% to 50%,^{3–5} with the HIV incidence ranging from 4.5 to 19.6 per 100 person-years.^{6–8} Generalized stigma, governmental repression, and the lack of appropriate HIV and drug abuse prevention and treatment services contribute to this public health catastrophe.^{9–11} To reduce ongoing transmission, a timely HIV diagnosis when the likelihood of HIV transmission is at its highest is necessary for PWID.

The earliest stage of HIV infection is acute HIV infection (AHI), when a person is still HIV seronegative or their Western Blot is negative or indeterminate. AHI is usually associated with very high plasma HIV RNA concentration. The risk of HIV transmission during this period is extreme.^{12,13} Identifying persons with AHI is important to reduce this transmission¹⁴ and is also relevant with regard to the global policy of treatment as prevention.^{15,16} In addition, identifying AHI will guide the determination of correlates of protection to assist with HIV vaccine development.^{17,18} However, accurately identifying people with AHI remains challenging as most routine settings rely on rapid tests to detect anti-HIV antibodies rather than the virus. In certain resource limited settings, fourth and fifth generation antibody tests have reduced

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the number of persons with AHI who go undetected during standard HIV testing services.¹⁹ However, until a globally relevant, inexpensive, and highly sensitive and specific point of care HIV antigen test is available, the problem of incorporating acute HIV detection and prevention programs into standard HIV testing and counseling services will remain.

Within research settings, the challenge is often to discover and follow persons with AHI in real time. Most routine care settings (i.e., HIV testing and counseling centers, STI clinics, out-patient departments, and emergency rooms) involve cross-sectional testing of large clinical populations. Developing a cohort of HIV-uninfected people to follow longitudinally is used less frequently.^{6,7,20–24} This alternative approach is generally reserved for key populations with very high probabilities of acquiring HIV, such as PWID. The primary challenge for this longitudinal approach is to recruit and enroll the highest risk persons and retain them in care while conducting frequent HIV testing. Furthermore, sophisticated laboratory systems are necessary to conduct efficient RNA testing with the results immediately available to the clinical staff who can notify the AHI patient as early as possible.²⁵

Identifying AHI among PWID is critical to understand and prevent transmission, especially in the era of treatment as prevention. The goal of this study was to determine the feasibility to recruit, enroll, and follow a cohort of high-risk PWID with the objectives to ascertain persons with AHI in real time and to determine their AHI prevalence/HIV incidence.

Methods

Study design

We conducted a prospective cohort study in St. Petersburg, Russia in 2010–2011 to determine the feasibility of enrolling and retaining HIV-seronegative PWID in monthly follow-up visits; identifying, notifying, counseling, and evaluating PWID with AHI; and retaining acutely infected PWID in follow-up after diagnosis. Inclusion criteria included the following: (1) being an active PWID defined as injecting at least 4 times within the past 30 days; (2) reporting one of the following for the prior 3 months: shared injection paraphernalia at least three times per month, shared paraphernalia with an HIV-infected person, or used psychostimulants; (3) being HIV-seronegative or acutely infected with HIV at screening; (4) willing to return for visits every 4 weeks and discuss sexual and injection-related behavior; and (5) being ≥ 18 years of age.

The primary feasibility endpoints for the study included a recruitment endpoint: the proportion of the cohort enrolled by 3 months; a retention endpoint: the proportion of persons completing at least 80% of scheduled appointments within 1 week of appointment date; AHI detection endpoints: proportion of participants diagnosed with AHI, proportion of cases of AHI determined within five working days of the study visit, and the proportion of cases of AHI evaluated within three working days of diagnosis; and a virologic endpoint: the viral load at initial diagnosis and each subsequent visit thereafter.

Study procedures and assessments

Participants were recruited for screening procedures from preexisting PWID cohorts^{6,7} at the Biomedical Center and from PWID social networks in St. Petersburg. At screening,

participants read, discussed, and signed the screening consent to determine study eligibility. After screening, participants were asked to return approximately a week later to receive their screening results and to enroll in the study if they were eligible.

All seronegative or acutely HIV-infected participants were eligible to enroll, including people found to be acutely infected at screening or at enzyme-linked immunosorbent assay (ELISA), and RNA negative at screening, but ELISA and RNA positive at enrollment. At the enrollment visit, informed consents for study participation and specimen storage were obtained, as well as detailed locator information. All participants were followed until the end of the 12-month pilot period, with a minimum follow-up period of 8 months, depending on their enrollment date. Each participant was evaluated monthly. If a participant was diagnosed with AHI, he/she was followed weekly for a month, then monthly for 3 months, and then quarterly for the rest of the study.

Participants were followed using a case management system.²⁶ Upon enrollment, each participant was introduced to a social worker who was their primary liaison throughout the study. The case manager worked to establish a trustful relationship; participants knew that they could call or visit their case manager to discuss problems at any time. The case management system was used to maximize retention. Participants identified with AHI continued to be followed by their case manager and referred to the St. Petersburg City AIDS Center for their HIV care.

During each visit, participants underwent testing for HIV using two tests: an HIV antibody and HIV RNA PCR. Antibody testing was performed using ELISA (DS-EIA-ANTI-HIV-UNIF; PRC Diagnostic Systems, Nizhny Novgorod, Russian Federation) and western blot (NEW LAW BLOT 1; Bio-Rad, France). HIV RNA PCR testing was performed using two kits (AmpliSens HIV-Monitor-FRT; InterLab-Service, Russia) and (Amplicor Monitor HIV 1; Roche Molecular Systems). Persons with newly diagnosed HIV infection also underwent testing by western blot. CD4 lymphocyte concentration was assessed at the first and last visit for all persons with AHI.

HIV risk behavior was assessed at each study visit, including screening, using an abbreviated questionnaire to assess sexual and injection behaviors over the previous month. An in-depth questionnaire was completed at enrollment and AHI diagnosis. This interview included assessments of both injection and sexual behavior, with an emphasis on specific potential transmission events. To facilitate recall, the interview was conducted with reverse chronology for the previous 6 weeks before the last visit, focusing on more recent events first.

HIV testing was conducted with pre- and posttest counseling based on the UNAIDS HIV pre- and posttest counseling model.²⁷ This model was also used to develop the methods for counseling participants when AHI was detected, as there are no standard guidelines for counseling people with AHI in Russia. Following AHI detection, counseling sessions took place once a week until HIV antibodies were detected, then once a month for 3 months, then once every 3 months. The counseling goal in the first month was AHI understanding and raising awareness to decrease the possibility of HIV transmission to sex and injection partners. After HIV antibodies were detected, the goal was to help people accept

their HIV status, find support in their social environment, and establish connection with their healthcare provider. Counseling was carried out by trained psychologists.

Sample size and study population

The sample size was based on the needs of the feasibility assessment. Our goal was to enroll 100 high-risk active PWID. Based on an incidence rate of 7.2/100 person-years as observed in a previous cohort,²⁸ we expected to identify ~7–9 participants with AHI within the pilot year. From previous work, we expected the population to be ~70% male with a median age of ~24, primarily single, with a high school or vocational education, underemployed, and living with parents or relatives.^{5,6}

Statistical analyses

All analyses were performed using SAS (version 9.3). We evaluated differences between all those screened for participation by enrollment status using the Mantel–Haenszel test ($\alpha=0.05$). To explore the associations between risk behaviors and AHI, we matched risk behaviors for each acutely infected person with risk behaviors of those HIV negative based on the visit when AHI was identified. Differences between acutely infected persons and HIV-negative persons were examined using Fisher exact tests ($\alpha=0.05$). We calculated prevalence differences (PDs) and 95% confidence intervals (CIs). We also used simple binomial regression to estimate prevalence ratios (PRs) and 95% CIs as frequency distributions permitted.

Ethical approvals

This study was conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), applicable regulatory requirements,

and the ethical considerations stated in the Declaration of Helsinki. The Institutional Review Boards at the Biomedical Center and at the University of North Carolina carefully reviewed and approved the study. Participants with AHI were referred to the local HIV care system and treated according to the guidelines of the Russian Health Ministry. (Note: When this study was conducted between 2010 and 2011, neither the Russian Health Ministry nor the WHO recommended treating Acute HIV with antiretroviral therapy [ART].)

Results

Study population characteristics

A total of 163 active PWID were recruited and screened in St. Petersburg, Russia to participate in the acute HIV cohort study. Of the 163 screened, 40 (25%) tested seropositive, and 123 (75%) were considered eligible (Fig. 1). Among the 123 eligible, 23 (19%) refused to enroll, and 100 (81%) provided consent and enrolled in the cohort. Of those enrolled, three had AHI (3.0%). Also, 3 (3%) were lost to follow-up immediately after the enrollment visit and had no follow-up visits.

Demographic and risk behavioral characteristics at baseline were similar comparing groups who had established infection, refused enrollment, and enrolled (Table 1). The enrolled cohort was mostly male (79%), between the ages of 30–39 years (59%), completed at least high school (91%), and not employed full-time (86%). Over 80% of those in the enrolled cohort had injected drugs by the age of 25 years with a third injecting before 18 years of age. Within the prior 30 days, 84% ($n=84$) injected heroin at least once to twice weekly, 66% ($n=68$) used the same water, dishes, or filter at least once to twice weekly, and 41% ($n=41$) used substances from another syringe at least once to twice weekly.

FIG. 1. Participant eligibility, follow up, and AHI testing. AHI, acute HIV infection.

TABLE 1. BASELINE DEMOGRAPHIC AND RISK BEHAVIORS BY HIV AND ENROLLMENT STATUS FOR ALL SCREENED (N=163)

	<i>Ineligible: HIV positive, N=40</i>		<i>Refused: HIV negative, N=23</i>		<i>Consented: HIV negative or AHI at baseline, N=100</i>	
	n	%	n	%	n	%
Age						
18–24	4	10	2	9	3	3
25–29	8	20	54	22	16	16
30–34	18	45	8	35	45	35
35–39	4	10	7	30	24	24
≥40	6	15	1	4	12	12
Sex						
Male	34	85	18	78	79	79
Female	6	15	5	22	21	21
Education ^a						
Did not complete high school	9	23	6	26	8	8
Completed high school or more	31	77	17	74	91	91
Employed full-time ^a						
Yes	3	8	6	26	13	13
No	37	92	17	74	86	86
Age at first injection ^a						
≤17	19	48	7	30	35	35
18–24	15	38	14	61	49	49
25–29	5	12	2	9	11	11
≥30	1	2	0	0	5	5
Alcohol intoxication at least one to two times weekly (past 30 days)						
Yes	21	53	14	61	46	46
No	19	47	9	39	54	54
Injected heroin at least one to two times weekly (past 30 days)						
Yes	35	88	16	70	84	84
No	5	12	7	30	16	16
Injected psychotropic stimulants at least once (past 30 days)						
Yes	12	30	9	39	18	18
No	28	70	14	61	82	82
Used a syringe or a needle after someone else at least one to two times weekly (past 30 days)						
Yes	3	8	4	17	9	9
No	37	92	19	83	91	91
Used same water, dishes, or filter at least one to two times weekly (past 30 days)						
Yes	30	75	12	52	68	68
No	10	25	11	49	32	32
Used substances from another syringe: front and back loading at least one to two times weekly (past 30 days) ^b						
Yes	24	60	8	35	41	41
No	16	40	15	65	59	66
Washed someone's used syringe with water before use at least one to two times weekly (past 30 days)						
Yes	2	5	4	17	5	5
No	38	95	19	83	95	95
Sexual partners (past 30 days)						
>1 partner	10	25	6	26	28	28
≤1 partner	30	75	17	74	72	72

^aMissing data: education: *n* = 1; employed full-time: *n* = 1; age at first injection: *n* = 1.

^b*p*-value < .05.

AHI, acute HIV infection.

Feasibility

Among the 100 enrolled, the proportion of the cohort enrolled by 3 months was 77% (*n* = 77), with full enrollment by 4 months. The proportion of participants who completed at least 80% of schedule appointments within 1 week of appointment date was

67% (*n* = 67). Among the 100 enrolled, the mean follow-up period was 6.9 (standard deviation: 2.3) months and the median follow-up time was 6.9 [interquartile range (IQR): 5.7–8.7]. Overall, there were 7 (7%) deaths and 4 (4%) incarcerations.

The proportion of participants diagnosed with AHI determined within five work days was 100%. Similarly, the

TABLE 2. PREVALENCE OF ACUTE HIV AND HIV INCIDENCE

	Enrollment, N = 100	Postenrollment, N = 94
AHI persons	3	5
Prevalence (95% CI)	3.0 (0.6, 8.5)	—
Total person/years		53.74
Incidence Rate per 100 pys (95% CI)		9.3 (3.9, 22.4)

CI, confidence interval; pys, person/years.

proportion of participants with AHI evaluated within three working days of a diagnosis was 100%.

Acute HIV incidence and viral load progression

At baseline, 3 of the 163 participants screened were acutely infected for a baseline AHI prevalence of 1.8% (95% CI: 0.4, 5.5). These three participants represented 3% (95% CI: 0.6, 8.5) of the 100 participants who consented to enrollment. Among the HIV-uninfected participants ($n=97$), the AHI incidence was 9.3 per 100 person-years (Table 2).

Among the five persons with AHI detected after enrollment, two were detected at the 2-month visit, two at the 7-month visit, and one at the 8-month visit.

Half (4/8) of AHI persons were ELISA negative at the time of AHI diagnosis and were categorized as Fiebig stage I–II.²⁹ All four seroconverted within 1–2 weeks (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/aid).

The median viral load at detection was 325,000 copies/ml (IQR: 206,000–395,000) (Fig. 2). After the first 4 weeks of follow-up post-AHI detection, the median viral load dropped to a median of 15,000 copies/ml (IQR: 2,000–287,500). None of the participants with AHI initiated ART during their follow-up period.

Exploratory comparison of HIV risk behaviors of acutely infected persons and HIV-negative persons matched on AHI identification dates

When compared with HIV-negative persons in follow-up, persons with AHI were significantly more likely to report alcohol intoxication within the prior 30 days (Table 3). Three-

quarters of persons with AHI injected heroin at least one to two times weekly in the prior 30 days compared with 58% of those noninfected persons. The PD of injecting psychostimulants at least once in the prior 30 days between persons with AHI and noninfected persons was 8.3 (95% CI: –16.2, 17.0). The prevalence of persons who injected psychostimulants were 2.1 (95% CI: 0.4, 9.8) times as likely to be acutely infected compared with persons who did not inject psychostimulants. The PD of those reporting a history of front/back loading in the prior 30 days between persons with AHI and noninfected persons was 12.2 (95% CI: –4.1, 28.5). Comparing AHI to noninfected persons, the PR of front/back loading was 3.3 (0.9, 12.0).

Discussion

In a setting of high HIV prevalence and incidence among this key population, a cohort approach was preliminarily feasible to identify persons with AHI. Controlling the epidemic among populations of high transmitters has become increasingly important.^{30–32} Aggressive test and treat strategies among these populations will be one of the primary platforms to achieve reductions in incidence.³³ However, because up to 40% of all transmission occur during the acute phase,³⁴ strategies must be considered to address this gap in AHI case ascertainment.

In this pre-cost analysis feasibility study, we were able to recruit and enroll an appropriate cohort in a reasonable period of time, retain most participants in care with monthly visits, provide laboratory results, and notify persons with AHI, while their risk of infection was still very high. Attainment of these goals was facilitated by the strong clinical, laboratory, case management, and community outreach infrastructure at the Biomedical Center in St. Petersburg. However, this activity was conducted in a research environment without a cost analysis, and it is yet to be determined if such a strategy would be affordable and implementable in a real-world setting. In addition, despite intense recruitment efforts, about 20% of this HIV uninfected, high-risk PWID population refused participation and had no further contact with prevention activities. preexposure prophylaxis (PrEP) programs, providing ART to the uninfected, is not available in Russia. However, considering the high incidence and high risk of this PWID population, there is an urgent need for PrEP availability in Russia.

FIG. 2. Median (IQR) viral load progression for first 4 weeks among person with AHI. IQR, interquartile range.

TABLE 3. ASSOCIATIONS BETWEEN MATCHED HIV RISK BEHAVIORS AND ACUTE HIV INFECTION (N=100)

	AHI (n=8)		HIV negative (n=92)		PD per 100 persons (95% CI)	Unadjusted PR (95% CI)
	n	%	n	%		
Alcohol intoxication at least one to two times weekly (past 30 days) ^a						
Yes	8	100	51	55	13.6 (4.8, 22.3)	—
No	0	0	41	45		—
Injected heroin at least one to two times weekly (past 30 days)						
Yes	6	75	53	58	5.3 (−4.9, 15.4)	2.1 (0.4, 9.8)
No	2	25	39	42		1.0
Injected psychotropic stimulants at least once (past 30 days)						
Yes	1	12	11	12	8.3 (−16.2, 17.0)	1.0 (0.1, 7.8)
No	7	88	81	88		
Used a syringe or a needle after someone else at least one to two times weekly (past 30 days)						
Yes	1	12	4	4	12.6 (−22.8, 48.1)	2.7 (0.4, 18.0)
No	7	88	88	96		1.0
Used same water, dishes, or filter at least one to two times weekly (past 30 days)						
Yes	5	63	49	53	2.7 (−7.8, 13.3)	1.4 (0.4, 5.6)
No	3	37	43	47		1.0
Used substances from another syringe: front and back loading at least one to two times weekly (past 30 days)						
Yes	4	50	19	20	12.2 (−4.1, 28.5)	3.3 (0.9, 12.0)
No	4	50	73	80		1.0
Washed someone's used syringe with water before use at least one to two times weekly (past 30 days)						
Yes	0	0	0	0	—	—
No	8	100	92	100		—
Sexual partners (past 30 days)						
>1 partner	3	37	17	18	8.8 (−7.8, 25.3)	2.2 (0.58, 8.6)
≤1 partner	5	63	75	82		1.0

PD, prevalence difference; PR, prevalence ratio.

^aDifference between groups, $p < .05$ using Fisher's Exact test.

In recent years, HIV treatment guidelines have shifted to incorporate AHI treatment.³⁵ In preliminary studies, behavioral and biological interventions appear feasible to reduce sexual transmission associated with AHI. But interventions during AHI for PWID have not been evaluated. In this study, we have shown that PWID with AHI can be identified in real-time, suggesting that rapid intervention is possible.

In many settings, the PWID population continues to experience extraordinary high HIV prevalence and incidence. A quarter of the population screened for our study had HIV infection and the incidence was remarkably high—nearly 10 cases per 100 person-years. The incident cases occurred throughout the follow-up period, despite monthly counseling support. This incidence is comparable to what we observed in a previous cohort study about 2 years before the current study.²⁸ The persistently high incidence among PWID in Russia is probably due to social factors related to substance use, although we cannot say with certainty that incident infections were acquired parenterally rather than sexually. The high incidence undoubtedly reflects an environment with lack of HIV prevention programs among PWID, where PWID are stigmatized by local police, and the real scope of HIV is ignored by the government. Indeed, over 10% of the participants in this HIV-uninfected cohort died or were incarcerated during this relatively short follow-up period, proving the extremely high vulnerability of this group in Russian society.

In this cohort, the use of psychostimulants appears to not be a contributor to HIV acquisition among PWID in St. Pe-

tersburg. The proportion of PWID who acquired AHI during follow-up reported using stimulants similarly to the cohort who remained uninfected. This is contrary to our previous findings, in which we observed an association between seroconversion and recent psychostimulant injection.⁶

Alcohol use among PWID, including those in this cohort, is common. Among PWID, alcohol use leads to both high-risk sexual and injection behaviors, which could mediate the relationship with HIV acquisition.³⁶ In Canada, PWID who reported daily alcohol use had an increased likelihood of HIV seroconversion compared to less than daily alcohol use.³⁷ Targeted interventions that focus on alcohol reduction among PWID with AHI can potentially reduce ongoing sexual and injection transmission.

Our feasibility study had a small sample size, which limited the precision of estimates and the power to assess associations with risk behaviors. In addition, many of the common risk behaviors associated with HIV acquisition were reported with relatively low frequency, suggesting some social desirability bias in reporting behaviors. These issues would need to be addressed in any larger future cohort study.

PWID continue to experience high HIV incidence in many areas worldwide. In this study in Russia, the vulnerability of PWID was shown in their high HIV incidence, mortality, and incarceration rates. As treatment as prevention becomes the norm worldwide, efforts to ensure that all PWID have access to HIV prevention services will be essential.

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Author Disclosure Statement

No competing financial interests exist.

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