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HIV incidence among people who inject drugs (PWIDs) in Ukraine: results from a clustered randomised trial

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Summary

Background HIV prevalence among people who inject drugs (PWID) in Ukraine is among the highest in the world. In this study, we aimed to assess whether a social network intervention was superior to HIV testing and counselling in affecting HIV incidence among PWID. Although this was not the primary aim of the study, it is associated with reducing drug and sex risk behaviours, which were primary aims.

Methods In this clustered randomised trial, PWID who were 16 years of age or older, had used self-reported drug injection in the past 30 days, were willing to be interviewed for about 1 hour and tested for HIV, were not too impaired to comprehend and provide informed consent, and, for this paper, who tested HIV negative at baseline were recruited from the streets by project outreach workers in three cities in southern and eastern Ukraine: Odessa, Donetsk, and Nikolayev. Index or peer leaders, along with two of their network members, were randomly assigned (1:1) by the study statistician to the testing and counselling block (control group) or the testing and counselling plus a social network intervention block (intervention group). No stratification or minimisation was done. Participants in the network intervention received five sessions to train their network members in risk reduction. Those participants assigned to the control group received no further intervention after counselling. The main outcome of this study was HIV seroconversion in the intent to treat population as estimated with Cox regression and incorporating a γ frailty term to account for clustering. This trial is registered with ClinicalTrial.gov, number NCT01159704.

Findings Between July 12, 2010, and Nov 23, 2012, 2304 PWIDs were recruited, 1200 of whom were HIV negative and are included in the present study. 589 index or peer leaders were randomly assigned to the control group and 611 were assigned to the intervention group. Of the 1200 HIV-negative participants, 1085 (90%) were retained at 12 months. In 553·0 person-years in the intervention group, 102 participants had seroconversion (incidence density 18·45 per 100 person-years; 95% CI 14·87–22·03); in 497·1 person-years in the control group 158 participants seroconverted (31·78 per 100 person-years; 26·83–36·74). This corresponded to a reduced hazard in the intervention group (hazard ratio 0·53, 95% CI 0·38–0·76, p=0·0003). No study-related adverse events were reported.

Interpretation These data provide strong support for integrating peer education into comprehensive HIV prevention programmes for PWID and suggest the value in developing and testing peer-led interventions to improve access and adherence to pre-exposure prophylaxis and antiretroviral therapy.

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Introduction

Although worldwide the HIV epidemic is declining, in eastern Europe and central Asia prevalence and incidence continue to increase. UNAIDS indicates that new HIV infections have fallen 38% since 2001, from 3·4 million (95% CI 3·3–3·6) in 2001 to 2·1 million (1·9–2·4) in 2013.[1] However, in eastern Europe and central Asia, new infections rose by 5% between 2005 and 2013 to 110 000 (95% CI 86 000–130 000) in 2013.

In 1995, WHO characterised Ukraine as a country of low HIV prevalence,[2] yet within 2 years all 27 regional capitals reported cases of HIV.[3] In 2011, WHO and UNAIDS estimated that 230 000 (95% CI 180 000–310 000) people were living with HIV in Ukraine.[4] At the end of 2014, Ukrainian officials reported a total of 264 489 HIV cases.[5] Similar to the USA and elsewhere, the HIV epidemic is unevenly distributed across Ukraine. Southern and eastern oblasts have roughly three times the HIV prevalence than the rest of Ukraine.[6] By 1997, people who inject drugs (PWID) accounted for nearly 85% of all infections.[7] Since 2008, sexual transmission of HIV has accounted for most new infections;[8,9] however, most are probably linked to PWID.[10]

In 2010, we initiated an experimental randomised controlled trial comparing a social network intervention, combined with HIV testing and counselling, with testing and counselling alone targeting PWID in three southern and eastern cities in Ukraine: Odessa, Donetsk, and Nikolayev. In a national survey, HIV prevalence among PWID in Ukraine was estimated to be 19·1%, including 30·2% in Odessa, 26·5% in Donetsk, and 31·8% in Nikolayev.[11] We selected a social network intervention approach because our previous experience suggested that PWIDs in Ukraine tended to have small, stable networks, and typically prepared drug solutions and injected together.[12–14] Network characteristics, including size and the length of time members have known one another, have been associated with drug-related and sex-

Research in context

Evidence before this study

We searched the International Social Network Analysis website, MEDLINE, PubMed, PsycINFO, Social Science Citation Index, and Web of Science, from Jan 3, 1980, to Jan 15, 2016, with the terms "substance use", "drug use", "injecting drug use", "people who inject drugs", "HIV", and "AIDS" combined with the terms "social network" and similar terms ("sociometric", "sociograms", and "respondent driven sampling"). We identified 15 HIV prevention interventions targeting people who inject drugs (PWIDs); 11 studies included control groups, and six were randomised clinical trials. Evidence from these studies suggests that social network interventions could change HIV risk behaviours among PWID. However, there was a dearth of evidence as to whether this approach could lead to a significant reduction in HIV incidence, because reductions in risk behaviours have not always translated into reductions in HIV incidence.

Added value of this study

This study suggests that social network interventions are a viable method to reduce new HIV infections among PWIDs and that active drug users can serve as effective change agents within their social networks to promote behaviour changes that lead to reductions in HIV incidence.

Implications of all the available evidence

These results, in combination with findings from other social network interventions, suggest that in addition to syringe exchange and opioid substitution programmes, practitioners and policy makers should involve drug users in HIV prevention activities and train them to promote risk reduction and health promotion behaviors with their sex and injection partners. Future research should examine the feasibility and use of involving active drug users and other key populations in HIV care and medication adherence programmes as well.

related risk behaviours, as well as HIV serostatus.[15,16] Empowering active users to influence network members' risk behaviours is a potentially low cost approach to promote behaviour change within difficult to reach populations. The intervention was based on theories of social norms, cognitive dissonance, social diffusion, social identity, and role theory.[17–19] This study was designed to assess whether peer educators could influence the injection and sex risk behaviours of members of their social network leading to reduced HIV incidence relative to those receiving the standard of care in Ukraine.

Methods

Study design and participants

In this clustered randomised clinical trial, outreach workers in Odessa, Donetsk, and Nikolayev, employed by non-government organisations (NGOs) recruited peer educators or "index" participants. In addition to being 16 years of age or older, having used self-reported drug injection (verified through inspection for recent venipuncture) in the past 30 days, willing to be interviewed for about 1 h and tested for HIV, not too impaired to provide informed consent, and HIV negative, indexes were required to bring in two members of their injecting network to be eligible.

There were 16 phases of recruitment, each lasting 8 weeks, with 4 weeks dedicated to recruitment of indexes and their two network members, 1 week of randomisation and informing indexes in the experimental condition of the training schedule, 2 weeks of intervention training, and 1 week planning for the next phase. Overall, recruitment took 64 weeks, beginning July 12, 2010, and extending to Nov 23, 2012. Participants were interviewed again and tested for HIV at 6 months and 12 months.

The study, including procedures for informed consent, was approved by the Colorado Multiple Institutional Review Board (IRB) at the University of Colorado Denver and by the Ukrainian Institute on Public Health Policy.

Randomisation and masking

When 16 eligible indexes were recruited, they were randomly assigned, with their network members, to one of the two study groups (1:1) with a blocked randomisation scheme to ensure that balance between the two study conditions was maintained over the course of the entire trial and that the assignment sequence was not predictable. No stratification or minimisation techniques were used. Randomisation was done by the study statistician, a member of the US team, who e-mailed participant numbers to the Ukraine data coordinator allocating participants to the two conditions. Randomisation occurred after participants received their baseline interview and after HIV testing and counselling, hence masking was not necessary.

Procedures

For those randomly assigned to the control group, no further intervention was planned for indexes or their network members. Network members in the intervention group also received no further intervention, because the model was based on indexes in this group providing interventions to members of their network after they were trained.

NGOs in each of the three cities, Odessa, Donetsk, and Nikolayev, were located in areas with high concentrations of drug injectors, with staff familiar recruiting, interviewing, and intervening with PWID. Although recruitment was extended throughout all districts in each city, specific areas were targeted based on the NGO staff's knowledge of where PWID congregated. Recovering drug users served as outreach workers to recruit index

participants, an approach effective in recruiting PWID.[20,21] Potential index participants were initially screened for eligibility on the street by outreach workers and referred to NGO offices where eligibility was finalised by interviewers. Eligibility requirements were 16 years of age or older, having used self-reported drug injection in the past 30 days, willingness to be interviewed for about 1 hour and tested for HIV, being not too impaired to comprehend and provide informed consent, and, for this paper, testing HIV negative at baseline. Comprehension of informed consent was assessed with an eight-item questionnaire covering key items from the consent form. Index participants were also required to bring two members of their injecting network, who also met eligibility criteria, for study participation. Drug injection was verified through visual signs of recent injection. Although urinalysis was done, a positive sample was not required because of the frequent low quality of drugs in Ukraine, particularly opiates.[12] Participants were compensated the equivalent of US$6·00 for their baseline interview, $7·00 for the 6 month interview, and $8·00 for the 12 month interview. Additionally, index participants received the equivalent of $5·00 for each eligible network member they brought to the project, $2·00 for completing the network inventory, $4·00 for each of the five training sessions attended, and a $7·00 bonus if they attended all sessions.

Interviews were done with an audio computer-administered self-interview to minimise social desirability. The interview schedule was adapted from the Risk Behavior Assessment (RBA) developed during the Cooperative Agreement sponsored by the National Institute on Drug Abuse (NIDA). It assessed demographics, health history, criminal justice involvement, drug use, and injection-related and sex-related risk behaviours. Reliability and validity assessments of the RBA support its use with PWIDs for this purpose.[22,23] We modified the instrument based on information from focus groups with drug users and dealers and a review by NGO staff. For example, a common method to obtain drugs in Ukraine is by purchasing preloaded syringes. Russian translation was done for both the questionnaire and consent form by an IRB-certified translator and verified. After the interview, participants were provided HIV testing, using the HIV I + II One-Step Test finger-stick rapid test (Orgenics Ltd, Yavne, Israel) registered by the Ukranian Ministry of Health.

At the beginning of the project, a 1 week centralised training was held in Yalta for all staff from the three NGOs, including outreach workers, interviewers, HIV testers or counsellors, and directors. The training was done by the US team and included a detailed presentation of the research protocol and of Good Research Practices for all staff. After this, separate trainings were held for interviewers, outreach workers, and HIV counsellors.

The testing and counselling intervention, Ukraine's standard of care, was an updated version of the Counselling and Education (C&E) model developed during NIDA's Cooperative Agreement.[24] The manual was updated based on the HIV rapid test, which was not available when the model was first created. In the pretest counselling session, a series of cue cards describing basic information about HIV/AIDS and how to reduce HIV transmission were discussed with participants. The content of the cue cards was modified from the original C&E model based on the injection practices of drug users in Ukraine. Participants rehearsed how to clean injection equipment and how to use condoms with anatomical models. HIV test results were then provided and additional cue cards were presented on the basis of test results. Participants who tested positive were provided a list of HIV service agencies and referred to the AIDS Centre in their city for confirmation of results and treatment, if HIV positive.

The C&E intervention was selected for the comparison condition primarily because in an earlier study we did in Ukraine, participants in the C&E only group reduced their HIV-related drug and sex risk behaviours as much as those receiving an intensive individually focused intervention plus the C&E model.[25] This absence of significant differences between more intensive and sophisticated interventions and the C&E alone was similar to that found during NIDA's Cooperative Agreement across multiple sites.[26,27]

This intervention was developed by Latkin and colleagues.[17,19] Intervention training consisted of five sessions delivered in small groups over a 2 week period designed to motivate peer leaders to become educators within their injection network and provide them with skills training in how to teach HIV risk reduction behaviours to network members effectively. Peer leaders were encouraged to model safe behaviours with their network members. Training sessions consisted of role playing and other interactive learning techniques. The initial sessions included discussions of how HIV was affecting their community and the part they could play in reducing transmission. The sessions included exercises on how and when to talk with network members about HIV risk reduction. Role plays focused on problem solving scenarios, especially overcoming barriers to risk reduction At the end of each session (lasting about 90 min), peer leaders were provided outreach assignments to do with their network members. In the subsequent session they were asked to discuss their experiences, with the group helping to address issues that might have arisen. The final session included a graduation ceremony. Outreach workers from the NGOs were expected to hold similar five session trainings with peer leaders once the recruitment began. No intervention sessions were to occur with leaders after the final training session and none with network members.

Outcomes

Using an intent-to-treat design, the mainoutcome

measure, in this study, was differences in HIV incidence between the control group and the intervention group. HIV incidence was not a primary outcome in the original study design that sought to examine changes in HIV risk behaviours resulting from the intervention. However, in view of the high prevalence of HIV among PWID in this region, and a large population of HIV-negative individuals recruited at baseline, we were able to use an opportunistic approach to track HIV incidence and how it might be associated with the intervention and HIV risks.

	Intervention group (n=611)	Control group (n=589)
City		
Odessa	216 (35%)	205 (35%)
Dontesk	176 (30%)	187 (32%)
Nikolayev	219 (36%)	197 (33%)
Sex		
Men	446 (73%)	453 (77%)
Women	165 (27%)	136 (23%)
Age (years)	31·66 (7·96)	31·96 (8·77)
Daily injector		
Yes	274 (45%)	246 (42%)
No	337 (55%)	343 (58%)
Always inject with others		
Yes	294 (48%)	290 (49%)
No	317 (52%)	299 (51%)
Years of injecting	11·35 (8·79)	11·96 (9·14)
Log_{10} 30 day injection frequency	3·05 (0·90)	3·03 (0·89)
Common container*		
Yes	228 (37%)	236 (40%)
No	382 (63%)	353 (60%
Front and back loading with others†		
Yes	433 (71%)	430 (73%)
No	178 (29%)	159 (27%)
Shared works‡		
Yes	170 (28%)	170 (29%)
No	441 (72%)	417 (71%)
Overall drug risk score	1·56 (0·91)	1·62 (0·88)
More than one sexual partner		
Yes	122 (20%)	117 (20%)
No	487 (80%)	468 (89%)
Unprotected sex		
Yes	241 (39%)	240 (41%)
No	359 (59%)	340 (58%)
Sex with an injection drug user		
Yes	255 (42%)	238 (40%)
No	350 (57%)	342 (58%)
Sex with HIV positive partner		
Yes	15 (2%)	16 (3%)
No	595 (97%)	574 (97%)

Data are n (%) or mean (SD), unless otherwise shown. *Common container refers to groups of people who inject drugs who draw the drug solution from the same jar or cup. †Front or back loading occurs when the needle or plunger, respectively, is removed from the syringe and the drug solution squirted in. ‡Shared works refers to sharing drug paraphernalia, such as cotton, cooker, or water.

Table 1: **Baseline unadjusted comparisons between treatment groups**

Statistical analysis

Sample size estimates were based on an earlier Ukraine study we did between 2003 and 2008 (RO1 DA01762), as well as a pilot study between 2005 and 2007 (RO1 DA01762-S1), targeting the same HIV-related risk behaviours. Allowing for an estimated 10% loss to follow-up at 6 months and 15% at 12 months, 125 index participants in each group at each location provided adequate power (80–90%) to detect differences of 20% or more in rates of endorsing key behaviours between interventions. To assess possible differences due to loss to follow-up between the groups, we developed a generalised estimating equation logistic regression model. This model used an exchangeable error structure to account for correlations within peer networks. Baseline predictors of attrition were explored and tested for differences between the two groups. Interactions by intervention group were also explored to examine behaviours related to attrition that might have been unique to each intervention. Participation at 12 months was the binomial outcome of interest, with a saturated model of covariates used along with backwards selection to arrive at a parsimonious model. Additionally, the success of randomisation was assessed with *t* tests or χ^2 as appropriate.

The date of HIV seroconversion was estimated as the midpoint between an individual's last negative and first positive test. Overall incidence density and incidence density stratified by intervention group are reported and 95% CIs calculated with normal approximation given the frequent events. Kaplan-Meier survival curves were calculated for groups and a log-rank test was done to test differences between groups. At baseline, 1200 participants were at risk and, at the 6 month interview, 1034 were at risk. Intraclass correlation of networks was estimated with a linear random effects model for peer networks model with person-time as the offset and HIV event as the outcome.

A Cox proportional hazards model with a γ frailty term was used to identify predictors of HIV seroconversion and to test HIV hazard differences between groups. The γ frailty term was used to fit a random intercept for peer networks. The proportional hazard assumption was assessed by visual inspection, χ^2 analysis of Schoenfeld residual trends, and interactions with time. Time varying exposures, such as injection frequency, were lagged; for example, behaviours reported at baseline were assumed to be the exposure for an HIV seroconversion event occurring between the baseline and 6 month visit.

The primary test of interest in the multivariate Cox regression was HIV hazard ratio differences between intervention groups. Covariates were explored manually with forward selection, including age and sex, as well as drug-use and sexual HIV risk behaviours. Variables

examined at both baseline and follow-up, which assessed the 30 day period before the interview, included always injecting with others, frequency of injecting, years injecting, sharing injection paraphernalia, use of needles or syringes known to have been used by another injector, more than one sex partner, unprotected sex, sex with another PWID, sex with someone known to have been HIV positive or whose HIV status was unknown, and sex for trade. Sex between men was reported too infrequently to be included. All covariates met the proportional hazard assumption and were significant at an α of less than 0·05. No corrections for multiple comparisons were made.

Data were analysed with the survival package and the geepack package of R (version 3.0.1).[28]

This study is registered with ClinicalTrials.gov, number NCT01159704.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of this report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 12, 2010 and Nov 23, 2012, 2304 PWID were recruited into the study, 1200 of whom were HIV negative and included in these analyses. 589 HIV-negative individuals were included in the control group and 611 HIV-negative individuals in the intervention group. 256 indexes at each site were assigned to one of the two study groups, half of whom, or 128, were trained to be peer leaders. Of the 1200 negative participants, 1085 (90%) were retained at 12 months. Overall, 931 (40%) of 2304 interviewed at baseline were HIV positive. 173 who were HIV negative at baseline were missing follow-up data and not included. At baseline, 899 (75%) participants of the cohort were men, with a mean age of 31·8 years (SD 8·4), mean age at first injection was 20·2 years (SD 4·8) at first injection. Baseline characteristics were well balanced between intervention groups (table 1). The intraclass correlation coefficient of peer networks was estimated to be 0·22, suggesting a level of correlation of HIV events within individuals in shared peer networks.

At the 12 month follow-up, 260 HIV seroconversions occurred among 1050·1 person-years (figure). Overall, HIV incidence density during the study was 24·8 events per 100 person-years (95% CI 21·8–27·8). 158 participants seroconverted in 497·1 person-years of observation in the control group (HIV incidence density 31·9 per 100 person-years; 95% CI 26·8–36·7,) compared with 102 events in 553·0 person-years in the intervention group (18·4 per 100 person-years; 14·8–22·0). The intervention group had a marked 47% reduced HR compared with the control group (table 2). After adjustment for significant HIV drug and sex risk factors, a significant 47% reduction in HIV hazard was retained in the intervention group (table 3). Increased injection frequency and increased age were associated with increased hazard of HIV. Important differences in HIV hazard were found among the cities where, relative to Donetsk, both Odessa and Nikolayev had reduced HIV hazard.

Overall, including those with incident HIV during the study, attrition was similar between groups: 62 (10%) of 611 in the intervention group and 53 (9%) of 589 in the control group (p=0·63). Similarly 53 (9%) HIV-negative individuals dropped out from the intervention group and 46 (8%) from the control group before the final HIV assay was done at the 12 month interview. Direct causes for individual dropouts are unknown; however, baseline predictors were identified. Two significant covariates were noted to be related to attrition: city, for which participants from Nikolayev (OR 0·51, 95% CI 0·30–0·88, p=0·02) and Odessa (0·39, 0·21–0·70, p=0·002) had lower odds of attrition than did those from Donetsk, and those who always injected with others had lower attrition (0·72, 0·52–0·995, p=0·047) than did those that did not. No other predictors, including interaction terms by intervention group, were significant (p>0·15).

Discussion

We found that the peer leader network intervention condition (C&E plus) was associated with substantially reduced HIV incidence relative to the control condition, which was associated with a 47% reduced HIV hazard in the intervention group. PWIDs are a stigmatised and marginalised population engaging in high drug and sex risk behaviours.[29–31] These results replicate and expand on a similar intervention applied in St Petersburg, Russia, where HIV incidence density was lowered from 19·6 per 100 person-years to 7·8 per 100 person-years,[32] and further supports the use of peer-led interventions as a viable and economical mechanism to reduce HIV incidence among exceptionally risky and difficult to reach populations. Several previous studies have supported this approach through observed changes in behaviour. Specifically, the SHIELD and STEP studies in

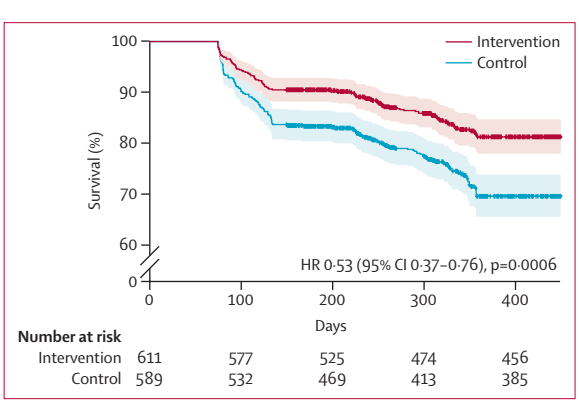

Figure: **Kaplan-Meier seroconversion free survival curve**

	Overall (baseline)	HIV+	Remained HIV-	Unadjusted HR (95%CI)
Time invariant characteristics				
Control group	589 (49%)	150	385	1
Intervention group	611 (51%)	94	456	0·53 (0·37–0·76); p=0·0006
City				
Odessa	421 (35%)	98	299	0·96 (0·62–1·51); p=0·87
Donetsk	363 (30%)	93	214	1
Nikolayev	416 (35%)	53	328	0·36 (0·23–0·58); p<0·0001
Sex				
Male	899 (75%)	179	630	1
Female	301 (25%)	65	211	1·28 (0·92–1·80); p=0·15
Time varying exposures				
Mean age (years, SD)	31·81 (8·36)	35·02 (7·72)	31·73 (8·48)	1·05 (1·03–1·07); p<0·0001
Daily injector				
Yes	520 (43%)	120	310	1·50 (1·11–2·02); p=0·008
No	680 (57%)	128	523	1
Always inject with others				
Yes	584 (49%)	99	326	1·00 (0·75–1·30); p=0·92
No	616 (51%)	149	507	1
Mean years of injecting (SD)	11·65 (8·97)	14·88 (8·34)	11·54 (9·16)	1·05 (1·03–1·07); p<0·0001
Mean log injection frequency (SD)	3·04 (0·89)	3·11 (1·20)	2·92 (1·01)	1·10 (1·04–1·16); p=0·0004*
Common container (N=1199)				
Yes	464 (39%)	94	332	1·06 (0·77–1·45); p=0·74
No	735 (61%)	154	500	1
Front and back loading with others				
Yes	863 (72%)	198	605	1·59 (1·11–2·28); p=0·012
No	337 (28%)	50	227	1
Front back loading with dealer, others, or both				
Yes	1162 (97%)	242	799	6·20 (1·45–26·51); p=0·014
No	38 (3%)	6	34	1
Shared works (N=1199)				
Yes	341 (28%)	88	274	1·42 (1·02–2·00); p=0·04
No	858 (72%)	160	559	1
Mean overall drug risk score (SD)	1·59 (0·90)	1·57 (0·94)	1·52 (0·89)	1·13 (0·95–1·33); p=0·18
More than one sexual partner (N=1194)				
Yes	267 (22%)	157	673	0·61 (0·45–0·84); p=0·003
No	927 (78%)	91	160	1
Unprotected sex (N=1180)				
Yes	481 (41%)	87	292	1·07 (0·80–1·43); p=0·63
No	699 (59%)	161	536	1
Sex with an injection drug user (N=1185)				
Yes	493 (42%)	105	399	0·92 (0·67–1·25); p=0·59
No	692 (58%)	141	424	1
Sex with HIV positive				
Yes	31 (3%)	11	22	1·05 (0·43–2·54); p=0·92
No	1169 (97%)	237	811	1
Sex for trade (N=1197)				
Yes	25 (2%)	3	20	0·88 (0·32–2·43); p=0·81
No	1172 (98%)	245	813	1

Totals will not sum to total baseline numbers because of loss to follow-up. Total denominator is 1200 unless otherwise reported. Injection frequency is right tailed and log transformed. HR=hazard ratio. *Per ten injections.

Table 2: **Time invariant characteristics for final visit and time varying exposures or 6 month visit to parallel the lagged cox regression analysis**

Baltimore[33–35] and the HIV Prevention Trials Network 037 study in Philadelphia,[36] as well as studies in other areas of Ukraine[13,14] showed the effectiveness of peer-led interventions to reduce HIV risk behaviours among PWID. Unlike these previous investigations, which focused on self-reported risk behaviours, this study showed a significant reduction in HIV incidence associated with assignment to intervention.

We also noted several risk factors associated with HIV incidence. Increased injection frequency and increased age were associated with increased HIV risk in the multivariate analysis. However, the extent to which peer educators influenced injection and sex risks leading to reduced HIV incidence is unclear. Further planned analyses will address this topic and, hopefully, elucidate the effect of peer-led interventions on risk behaviours. The lower hazard of HIV in Odessa and Nikolayev than in Donetsk warrants investigation. Reports of behavioural differences between other cities in Ukraine, however, suggest that HIV risk behaviours among PWID, including the types of drugs injected as well as injection and sex behaviours, might differ.[37–39]

There are several limitations to consider when drawing inferences from this study. Primarily, other than HIV testing data, findings were based on self-report. Although extensive research in populations of PWID have shown the use of self-report,[40,41] errors in self-report could have contributed to the absence of findings of specific behavioural changes regarding injection practices, such as injection frequency, that could help to explain the HIV incidence reduction. Recall error should have been minimised, however, by the brief 30 day period that participants were asked to remember. Importantly, no evidence suggests recall of behaviours was differential between groups, and the differences detected are likely valid. Social desirability could also have influenced participants' self-report, although this was the same in both conditions. Additionally, the recruitment strategy called for recruiting leaders in each city based on outreach workers' knowledge or recommendations by members of the network. How representative the samples were of PWID leaders or their standing within their network is not possible to know. Because of the street-recruitment approach used, the sample probably over-represents people willing to spend the time required to participate and who were motivated by the modest stipend. Another possible limitation is the difference we noted in HIV incidence and prevalence and that reported by other investigators who, generally, rely on official figures from government agencies in Ukraine for their HIV estimates.[42] Our samples were recruited on the street by NGO outreach workers who were former drug injectors. They had knowledge of where PWIDs congregated and the rapport necessary to establish trust and recruit index participants who were active drug injectors. They, in turn, recruited other active drug injectors. We verified drug use through inspection for recent venipuncture and urinalysis. Our experience in the past 15 years working in Ukraine is that most street users will not go to the AIDS centers or military recruitment facilities (for example), to be tested, because there is little benefit to be gained and much to lose (eg, stigma, discrimination, etc). Moreover, a recent study by Cakalo and colleagues[43] reported that misclassification of PWID is common: as many as 34·5% of men who reported as heterosexual from 2005 to 2011 could have actually been PWID. Moreover, our samples were recruited from Odessa, Donetsk, and Nikolayev, located in the southern and eastern regions of Ukraine where, historically and today, rates of HIV are the highest in the country. Conversely, this study has notable strengths, including the outcome measure of HIV seroconversion and the randomised longitudinal clinical trial design with a large sample size. Finally, there were no study-related adverse events.

	HR (95% CI)	p value
Intervention	0·53 (0·38–0·75)	0·0003
Injection frequency	1·06 (1·007–1·12)	0·026
Age	1·06 (1·03–1·06)	<0·0001
Odessa*	0·62 (0·41–0·94)	0·030
Nikolayev*	0·30 (0·20–0·48)	<0·0001

HR=hazard ratio. *Versus Donetsk.

Table 3: **Reduced multivariate cox proportional hazard model**

Despite the strong intervention effect noted in the peer network group, HIV incidence was still unacceptably high, indicating that the intervention should be implemented alongside other HIV prevention effective interventions. Further work leveraging the ability of the peer-led intervention to reach marginalised populations, combined with expanded access to needle-exchange programmes and opioid agonist therapies (eg, methadone and buprenorphine), HIV antiretroviral treatment, and pre-exposure prophylaxis, could lead to further reductions in HIV incidence and improve access and retention in HIV medical care. In view of the conflict in eastern Ukraine, especially in Donetsk, WHO and other international health organisations must continue to assess the health of drug users and implement feasible and effective interventions.

Contributors

REB, CAL, SD, and JTB were responsible for the study design, securing funding, and drafting the protocol. REB, the principal investigator, supervised all aspects of the study. JMD was responsible for data cleaning, writing the statistical analysis plan, and doing the statistical analyses. CAL conceptualised the social network intervention and provided support for intervention development and implementation. SAS assisted with the analyses and data interpretation. SD and JTB did the intervention training and monitoring. OL oversaw data collection at each non-governmental organisation through quarterly site visits and monitored the trial during the course of intervention delivery. REB, CAL, JMD, SAS, and JTB wrote the initial draft of the report. All authors contributed to, and approved, the final report.

Declaration of interests
We declare no competing interests.

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