Research Paper

Reducing opioid overdose in Kazakhstan: A randomized controlled trial of a couple-based integrated HIV/HCV and overdose prevention intervention "Renaissance"

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A B S T R A C T

Objectives: To evaluate the efficacy of a couple-based integrated HIV/HCV and overdose prevention intervention on non-fatal and fatal overdose and overdose prevention behaviors among people who use heroin or other opioids in Almaty, Kazakhstan.
Methods: We selected 479 participants who reported lifetime heroin or opioid use from a sample of 600 participants (300 couples) enrolled in a randomized controlled trial (RCT) conducted between May 2009 and February 2013. Participants were randomized to either (1) a 5-session couple-based HIV/HCV and overdose prevention intervention condition or (2) a 5-session Wellness Promotion and overdose prevention comparison condition. We used multilevel mixed-effects model with modified Poisson regression to estimate effects of the intervention as risk ratios (RR) and the corresponding 95% CIs.
Results: About one-fifth (21.9%) of the sample reported that they had experienced an opioid overdose in the past 6 months at baseline. At the 12-month follow-up, both the intervention and comparison conditions reported significant reductions in non-fatal overdose and injection heroin/opioid use and significant increases in drug treatment attendance and naloxone use to prevent death from overdose. However, we found no differences between the study arms on any of these outcomes. There were three intervention condition participants (1.3%), compared to seven comparison condition participants (2.9%) who died from opioid overdose during the 12-month follow up period although this difference was not significant.
Discussion: There were no significant conditions on any outcomes: both conditions showed promising effects of reducing non-fatal overdose and overdose risks. Integrating overdose prevention into a couple-based HIV/HCV intervention may be an efficient strategy to target the syndemic of opioid overdose, HIV and HCV in Kazakhstan.

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Introduction

Burgeoning heroin use in Central Asia is fueling the intertwined epidemics of opioid overdose, HIV and HCV, which represent the leading causes of mortality among people who people who inject or use heroin or other opioids in the region and worldwide (Mathers et al., 2013). A meta-analysis found that people who inject drugs (PWID) who are HIV positive are twice as likely to experience opioid overdose as those who are HIV negative (Green,

McGowan, Yokell, Pouget, & Rich, 2012). Recent research has also found a strong association between HCV and overdose (Arasteh, Des Jarlais, & Perlis, 2008; Mateu-Gelabert et al., 2017). The overlapping structural, behavioral and biological factors driving overdose, HIV and HCV have prompted researchers to call for integrated overdose and HIV/HCV prevention interventions (Arasteh et al., 2008; Coffin, Rowe, & Santos, 2015; Mathers et al., 2013; Mueller, Walley, Clacaterra, Glanz, & Binswanger, 2015).

The syndemic of opioid overdose, HIV and HCV is particularly acute in Kazakhstan and other countries in Central Asia. Some of the highest rates of injection heroin use in the world are found in towns along major drug trafficking routes in Central Asia (Aceijas

et al., 2006). Although there remains a dearth of surveillance data on overdose, data suggests between 21 and 24% of people who use heroin or other opioids in Central Asia experienced a non-fatal overdose in the past year (Kazakhstan RAC, 2016; Tajikistan RAC, 2011). Central Asia also has some of the fastest growing HIV and HCV epidemics in the world (Mohd Hanafiah, Groeger, Flaxman, & Wiersma, 2013; UNAIDS, 2017). There is an urgent need for integrated overdose and HIV/HCV interventions that can stem the tide of deaths and morbidity from overdose, HIV and HCV among PWID in this region.

Over the past two decades, emerging evidence has documented the safety and effectiveness of brief overdose prevention interventions that include lay administration of naloxone, an opioid antagonist to reverse potentially fatal respiratory suppression of heroin and other opioids (Beletsky et al., 2006; Bird, Parmar, Perry, & Hunter, 2016; Clark, Wilder, & Winstanley, 2014; Giglio, Li, & DiMaggio, 2015; Mann, 2003). A meta-analysis of pooled data found that naloxone (Narcan) administration by bystanders was associated with significantly increased odds of recovery compared to no naloxone administration (Giglio et al., 2015). This meta-analysis and other systematic reviews, however, noted several methodological limitations of these overdose prevention studies and highlighted several gaps in existing evidence-based overdose prevention strategies (Clark et al., 2014; Giglio et al., 2015; Mueller et al., 2015). To date, only two recent overdose prevention interventions have been evaluated using more rigorous randomized controlled trial (RCT) designs (Dunn et al., 2017; Parmar, Strang, Choo, Meade, & Bird, 2016) and very few have been evaluated outside of North America or Europe, or in low or middle income countries. To our knowledge, none of the existing evidence-based overdose prevention and naloxone administration interventions have combined HIV or HCV intervention strategies although non-fatal overdose has been associated with HIV, HCV and drug-related and sexual risk behaviors (Gilbert et al., 2013; Green et al., 2012). By addressing the primary life-threatening concern of overdose, HIV services are more likely to build trust with people who use heroin or other opioids and link and retain them in a continuum of HIV and HCV services, including HIV and HCV testing, treatment and care services as well as drug treatment and harm reduction services (Curtis & Dasgupta, 2010; El-Bassel et al., 2011; Gilbert et al., 2013).

Couple-based interventions have been shown to be efficacious in reducing HIV risk behaviors, completing HIV testing, increasing ART adherence as well as reducing drug and alcohol misuse (El-Bassel et al., 2010, 2011, 2014; Winters, Fals-Stewart, O'Farrell, Birchler, & Kelley, 2002). Recent research indicates that romantic injection partnerships may be at increased risk of both overdose and HIV/HCV infection as a result of frequent injecting and syringe sharing within the relationship, which suggests that a couple-based modality may be optimal in addressing overdose and HIV/HCV infection (Rowe, Santos, Raymond, & Coffin, 2017). A couple-based modality may also be particularly effective in preventing overdose as both partners can work together to reinforce overdose prevention behaviors and administer naloxone to each other in the event of an overdose. To date, however, no known couple-based naloxone overdose prevention interventions have been evaluated using randomized or non-randomized designs.

This study aimed to address several gaps in overdose prevention research by evaluating the efficacy of a 5-session couple-based integrated HIV/HCV and overdose prevention education, which included lay naloxone administration (HIV/HCV + OD), compared to an attentional comparison condition (WP + OD) in reducing overdose risk behaviors among people who inject or use heroin, opium, or prescription opioids over the 12-month follow-up period. The attentional comparison condition delivered the same overdose prevention and naloxone administration intervention in a single gender group session to opioid users and their heterosexual partners in a 5-session wellness promotion intervention (El-Bassel et al., 2014). The primary outcome paper from this RCT found that this couple-based integrated intervention, entitled "Renaissance", was efficacious in reducing the number and proportion of unprotected sex acts and significantly lowering the HCV incidence by 69%, compared to the wellness promotion comparison condition (El-Bassel et al., 2014). The overdose prevention outcomes for this study include: reducing non-fatal and fatal opioid overdose, injection heroin use and any opioid use and increasing access to naloxone, naloxone use and linkage to drug treatment.

Methods

This RCT was conducted in Almaty, Kazakhstan between May 2009–February 2013 among 300 couples (N = 600 participants) where one or both partners reported injecting heroin. This paper includes a subset of this sample, 479 participants who reported any lifetime use of heroin, opium or any opioid prescription drug at baseline, and therefore may be at risk of opioid overdose. The large majority of these participants (91%, N = 436) reported injecting heroin in the past 90 days at baseline. We have described detailed methods, sample characteristics, and sample power calculations elsewhere (El-Bassel et al., 2014) and included a CONSORT diagram in Fig. 1.

Recruitment and eligibility

Research assistants conducted recruitment primarily using word-of-mouth from participants to their injecting network members as well as from street-based venues where PWID congregate and needle syringe programs (NSPs). Eligibility criteria included: (1) age 18 or older; (2) having had an intimate relationship with a partner of the opposite sex that lasted for at least six months, who would be willing to participate in the study for the following 12 months; (3) at least one partner reporting injecting drugs in the past year and (4) having had unprotected sex with study partner in the past 90 days. Couples were excluded if either partner: (1) showed evidence of significant impairment as determined during informed consent; (2) reported severe violence perpetrated by the study partner in the past year; or (3) was not fluent in Russian.

After providing informed written consent, participants completed a pre-intervention baseline assessment with repeated follow-up assessments at 3, 6, and 12 months post-intervention using an Audio Computer-Assisted Self-Interview (ACASI), which was administered in a private room, as well as biological testing for HIV and HCV. The Institutional Review Boards at Columbia University and the Kazakhstan School of Public Health approved all study protocols. Participants received $10 USD (1500 tenge) for completing the ACASI interview and biological testing for each assessment visit to cover their time, as well as $5 USD (750 tenge) for travel at each intervention session.

Randomization and masking

We used a computer-generated randomization algorithm to randomly assigned couples in a one-to-one ratio to receive the five-session HIV/HCV + OD intervention or a five-session WP + OD intervention, which served as a comparison condition. The algorithm was designed to balance the number of couples per study arm via an adaptive, biased-coin procedure (Wei, Smythe, & Smith, 1986). The investigator who designed the randomization program was not involved in the conduct of the trial, but consulted on the statistical analysis. Investigators were masked to treatment
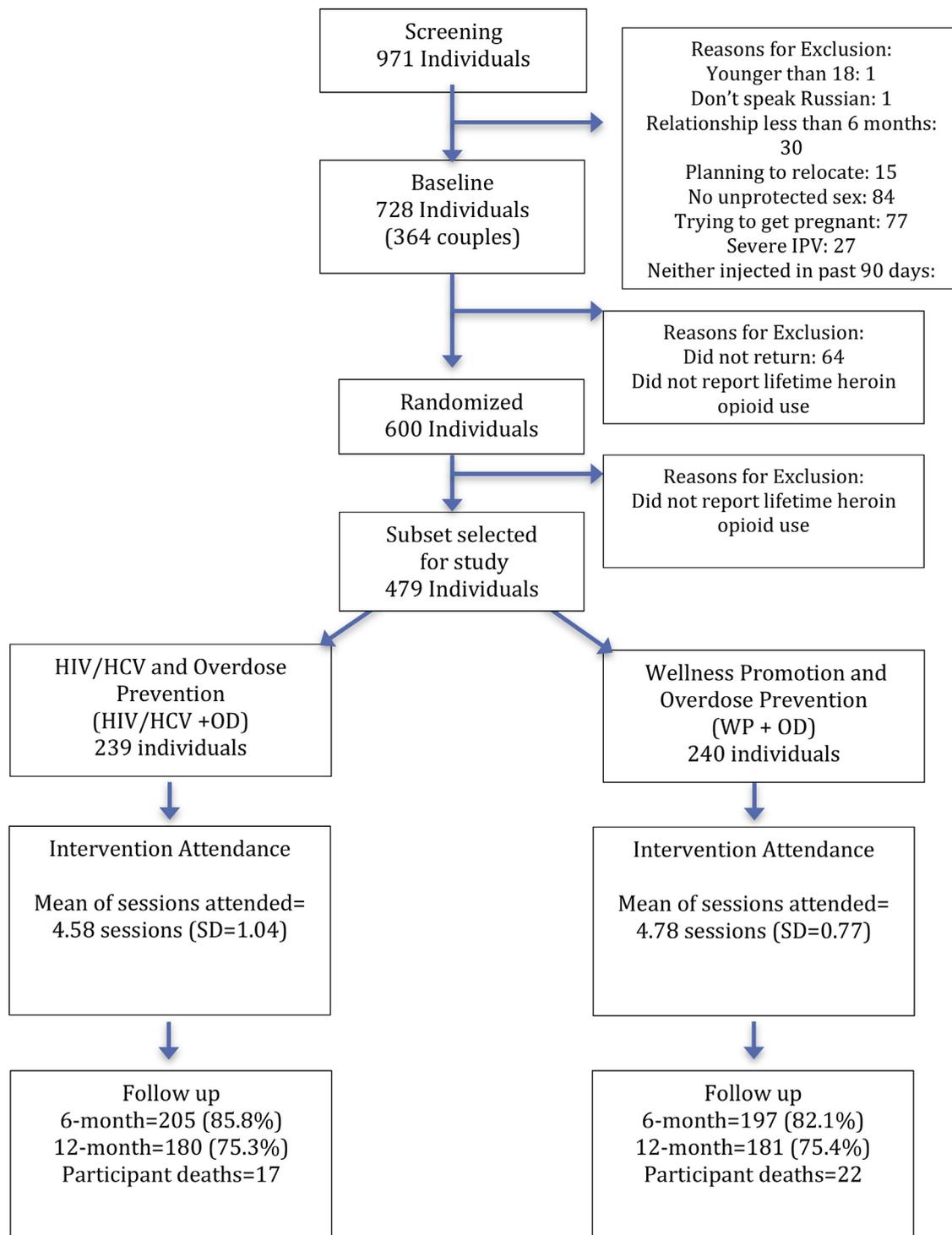
Fig. 1. CONSORT flow diagram.

assignment until the final 12-month follow-up assessment was completed. Data were locked on February 1, 2013 at which point the study arms were unmasked.

Intervention and comparison conditions

Both study arms were matched by modality and dosage and consisted of five two-hour sessions spaced at least five days apart: the first three sessions were single gender groups for male partners and female partners, led by same-gender facilitators. These single gender groups were conducted simultaneously in separate rooms. These group sessions were followed by two individual couple sessions.

The couple-based HIV/HCV and overdose prevention intervention was guided by social cognitive theory and a relationship-oriented ecological framework (Bandura, 1977). The couple-based integrated HIV/HCV and overdose prevention intervention was adapted from Project Connect II, an evidence-based HIV prevention

intervention that was tested with substance-using couples in New York City (El-Bassel et al., 2011) and the Skills and Knowledge on Overdose Prevention (SKOOP), an evidence-based opioid overdose prevention intervention with lay naloxone administration (Piper et al., 2008) (see Fig. 2). The core components focused on strategies to reduce risk behaviors for HIV, HCV, and overdose (Gilbert, El-Bassel, Terlikbayeva, & Rozental, 2010).

We adapted the SKOOP naloxone overdose prevention education model to enhance its contextual relevance for PWID in Kazakhstan by conducting formative interviews with emergency care medical directors, ambulance drivers, paramedics and PWID and their families to elicit common risk environments in which overdose occurs among PWID in Kazakhstan. Several key themes emerged from these interviews that guided the adaptation of the overdose prevention content. Most PWID tend to inject with their partners and others in hidden social settings (e.g., cars, stairwells, abandoned buildings, etc.) rather than inject alone, highlighting the importance of training members of injecting networks to carry and administer naloxone as an overdose prevention strategy. The adapted intervention addressed several common myths of frequently used ineffective responses to overdose among PWID, such as injecting saline solution and rolling people overdosing in snow. We also adapted the intervention to be consistent with Ministry of Health protocols which require medical staff to distribute naloxone and thus formed a service agreement to refer participants with a voucher to a HIV care clinic for the distribution of naloxone kit.

The core components of the adapted intervention included: (1) encouraging both partners to disclose and identify personal risks for overdose delivered; (2) modeling, role-playing, and practicing communication and problem-solving skills to reduce risk of overdose; (3) reviewing the six-step SKOOP overdose prevention education approach using naloxone, which included identifying and addressing risks for overdose and recognizing early symptoms of overdose; and (4) reviewing appropriate responses to overdose. The steps in the appropriate response to an overdose were i) to rub the sternum; ii) if person doesn't respond, call emergency services; iii) clear the airway and perform rescue breathing; iv) administer naloxone, wait and see if the person responds, and administer second vial if necessary; and v) to stay with the person until emergency services arrive. In this session, participants also received a voucher to get a naloxone kit and brief training review from the local HIV care clinic. HIV/HCV risk reduction activities in other sessions also included overdose prevention content

Intervention Core Components of Treatment and Comparison Conditions

HIV/HCV and Overdose Prevention Treatment	Wellness Promotion and Overdose Prevention Comparison
Couple's perceived risk of HIV other STIs (including HIV/AIDS/STI, HCV knowledge) [initial session for both single gender group (SGG) and couple sessions (CS)]	Develop individualized health risk assessment (SGG and CS)
Review information on the levels of infectivity and HIV transmission (viral load, acute infection, ART adherence and impact on transmission risk) (SGG and CS)	Introduce the concept of body mass index and healthy weight assessment
Build couple communication skills to enhance understanding and commitment to healthier choices as a dyad (speaker listener technique) (SGG and CS)	Building knowledge of Tobacco and alcohol health risk and review other common diseases (SGG and CS)
Review options for HIV testing and care, including the rationale for testing over time and potentially, testing together (SGG and CS)	Build knowledge of healthy nutrition and associated foods (SGG and CS)
Practice condom technical skills and address barriers to use (SGG and CS)	Identify and practice strategies to improve and maintain health, including nutrition, exercise, Yoga, relaxation techniques (SGG and CS)
Using a problem-solving model to identify risks and to develop an action plan with goals for sexual risk reduction. This includes examining biomedical options including treatment available for serodiscordant couples, in addition to condom use and harm reduction strategies such as sterile syringe usage and overdose (OD) prevention (SGG and CS)	Increase help seeking skills to address health problems, by identifying and addressing service barriers to health care and drug treatment (SGG)
Examine gender roles and expectations related to sexuality, reproductive health and safer sex practices (SGG and CS)	Practice stress-reduction exercises, and setting personal health goals (SGG and CS)
Define SMART goals to enhance safer sex and drug use related behaviors including overdose prevention and response planning	Define SMART goals to enhance health including overdose prevention and response planning
Evaluate social support and risk networks and set improvement goals to increase sustainability of healthier behaviors (SGG and CS)	Enhance effective overdose (OD) response and prevention including knowledge and skills to utilize naloxone and safer injection kits (SGG and CS)
Enhance knowledge of risk associated with drug use including HIV risk of sharing syringes/needles and OD (SGG and CS)	
Apply the problem-solving model to address triggers for unsafe sex, drug use and drug-related risks, including OD (SGG and CS)	
Enhance effective overdose (OD) response and prevention including knowledge and skills to utilize naloxone and safer injection kits (CS)	

Fig. 2. Intervention core components of treatment and comparison conditions.

including: using problem solving skills to avoid or navigate drug risk situations, expanding social support for drug risk reduction, drug risk reduction goal setting, and linkage to drug treatment. These specific core components addressing overdose were delivered in the fourth couple-based session.

The Wellness Promotion comparison condition included core components focused on maintaining a healthy diet, promoting physical fitness in daily routines, improving access to health care services and drug treatment by identifying and addressing service barriers, learning stress-reduction exercises, and setting and following up on personal health goals and included the same SKOOP naloxone-based overdose education content described above that was delivered in the third single-gender group session for both male and female participants.

Measures

Primary overdose risk outcomes

We adapted questions from the SKOOP program evaluation questionnaire on self-reported opioid overdose risk and prevention behaviors which asked participants: (1) whether they had experienced an overdose both ever and in the past 6 months; (2) whether saline solution or naloxone was injected in response to an overdose in the past 6 months; and (3) whether they injected someone else with naloxone in the past 6 months. Data on fatal overdose was collected from participant case reports, which recorded reasons for participant deaths, collected by research assistants from personal contacts that participants provided at baseline. Data on exchanging study vouchers for naloxone was collected using returned study vouchers from the HIV care clinic.

Current and past substance use and drug risk behaviors

The Risk Behavior Assessment (RBA) (Dowling-Guyer et al., 1994) asked participants whether or not they injected heroin ever and in the past 90 days and whether or not they used non-injected heroin, opium or prescription opioids ever and in the past 90 days.

Socio-demographic variables

Participants self-reported sociodemographic characteristics including gender, age, ethnicity, marital status, education, currently employment status, prior incarceration history, homelessness and food insecurity in the past 90 days.

HIV and HCV testing

We conducted a serial two-test strategy of a standard enzyme-linked immunosorbent assay (ELISA) drawn from a dried blood spot sample using a U.S.-manufactured Abbott Murex Biotech tests.

The Murex anti HIV ABBOTT and anti HCV ABBOTT has a sensitivity of 99.9% and specificity of 99%.

Analysis plan

A power analysis was based on our primary HIV/HCV outcomes for the study. (El-Bassel et al., 2014). Power for primary non-fatal overdose outcome was not estimated.

We estimated intervention effects by analyzing participants based on their experimental assignment (i.e., intent to treat). We used all available data on randomized participants at any follow-up visit in the statistical models (see Fig. 1 for attrition by visit and study arm). Mortality was high over the course of the follow-up period for the 479 participants included in this study, with 39 deaths, including 10 due to drug overdose. These 39 participants did not significantly differ from the other participants on socio-demographic characteristics. Of the participants who died during the follow-up period, 29 completed the 6-month follow-up assessment and these data were included in the statistical analyses. The overall retention rate over the entire follow-up period up was 88%. Attrition analyses revealed that no baseline measures were significantly different between those who attended vs. those who missed assessments for all follow-up time points.

Multivariate analyses employed multilevel mixed-effects models to handle non-independence in observations. Repeated measurements were also nested within couples. The analytical approach we used included couple as a random effect in the multilevel mixed effects models. The models to estimate intervention effects at each follow-up visit also included follow-up time, the interaction between treatment condition and follow-up time and covariate adjustments for gender. We used multilevel mixed-effects model with modified Poisson regression to estimate effects of the intervention as risk ratios (RR) and the corresponding 95% CIs. We used Stata (version 12.0) for statistical analyses.

Results

Background characteristics

Of the 479 participants considered in this paper, 240 of them were randomized to the HIV/HCV + OD condition, and 239 to the WP + OD condition. Socio-demographic, substance use and HIV/HCV rates are reported in Table 1. We did not find significant differences in any of these characteristics by study condition.

Table 1
Baseline Characteristics by study condition (n = 479).

	WP + OD Comparison (*n* = 239)	HIV/HCV + OD Treatment (*n* = 240)	Total (*N* = 479)
Age: Mean (SD)	35.3 (7.1)	35.7 (7.8)	35.5 (7.5)
Male	143 (59.8%)	147 (61.3%)	290 (60.5%)
Russian	156 (65.3%)	168 (70.0%)	324 (67.6%)
Kazakh	26 (10.9%)	24 (10.0%)	50 (10.4%)
Married (including common-law marriage)	208 (87.0%)	212 (88.3%)	420 (87.7%)
High School	176 (73.6%)	186 (77.5%)	362 (75.6%)
Currently employed	60 (25.1%)	58 (24.2%)	118 (24.6%)
Homeless: past 90 days	31 (13.0%)	37 (15.4%)	68 (14.2%)
No enough money for food: past 90 days	121 (50.6%)	118 (49.2%)	239 (59.9%)
In jail or prison: ever	178 (74.5%)	178 (74.2%)	356 (74.3%)
In drug treatment: ever	89 (37.2%)	87 (36.3%)	176 (36.7%)
HIV positive	75 (31.4%)	67 (27.9%)	142 (29.7%)
HCV positive	220 (92.1%)	217 (90.4%)	437 (91.2%)

*p < 0.05 **p < 0.01 for the comparison of non-overdose vs. overdose.

Overdose-related risk and prevention behaviors over time

Rates of self-reported non-fatal overdose and heroin use substantially decreased from baseline to the 12-month follow up for both conditions. Use of naloxone and drug treatment similarly increased over the 12-month follow-up period for both conditions. However, only approximately one-third of participants in the HIV/HCV + OD intervention (n = 69, 33.8%) and the WP + OD comparison condition (n = 79, 37.6%) exchanged their study vouchers for naloxone from the HIV care clinic (Table 2). Over the 12-month follow up period, there were 105 participants who reported using naloxone to reverse an opioid overdose or that someone else administered naloxone to them. There were no participant deaths due to overdose reported during administration of naloxone and no adverse events related to naloxone administration reported during the study. However, there was one participant who indicated that they administered naloxone to someone who was unconscious due to intoxication from alcohol and heroin who then subsequently died.

Intervention outcomes

In Table 3, we present the results from random-effects modified Poisson regression models of overdose and overdose risk and prevention behaviors. There were no significant differences between the HIV/HCV + OD intervention and WP + OD comparison conditions with respect to self-reported non-fatal overdose, any opioid use and any injection heroin use and overdose prevention behaviors of obtaining naloxone, using naloxone and attending drug treatment over the 12-months follow-up period. Participants in both conditions reported significantly less non-fatal overdose and significantly less heroin injection use and any opioid use as well as significantly less use of injecting saline to reverse an overdose over the 12-month follow-up period. Participants in both conditions also reported a significant increase in use of naloxone to prevent overdose for themselves or others over the 12-month follow-up period and a significant increase in the use of drug treatment over the 12-month follow-up period (Table 3). There were three participants assigned to the HIV/HCV + OD intervention who died from overdose over the 12-month period, compared to seven participants in WP + OD comparison condition. However,

this difference was not significant (RR = 0.44, CI = 0.12, 1.64, p = 0.220).

Discussion

To our knowledge, this is the first RCT to evaluate the efficacy of a couple-based integrated HIV/HCV and overdose prevention model with lay naloxone administration among PWID on overdose outcomes. Study findings indicate that there were no differences between the HIV/HCV + OD intervention and WP + OD comparison conditions on any overdose outcomes over the 12-month follow-up period. Participants in both conditions reported significant reductions in non-fatal overdose, overdose risk behaviors and increases in overdose prevention behaviors. Taken together, the consistency of results across a range of overdose outcomes suggest the promising effects of both conditions in reducing risk of overdose among people who use heroin and other opioids in a relatively low resource setting in Central Asia.

There were fewer participant deaths attributed to overdose in the integrated HIV/HCV+ OD condition (3 participant deaths, 1.3%) compared to the comparison WP + OD condition (7 deaths, 2.9%), however this difference was not statistically significant. Over the 12-month follow up period, there were 105 participants who reported using naloxone to reversing an opioid overdose or that naloxone was administered on them. In all but one reported case where a person died from mixture of alcohol and heroin intoxication, peer administration of naloxone was reported to be successful in preventing a fatal overdose. Participants in both conditions also reported significant decreases in the common but ineffective practice of injecting saline to reverse overdoses over the follow-up period. These findings and lack of adverse events reported related to naloxone administration suggest the overall safety of having family members and peers administer naloxone, consistent with other research indicating the safety of lay administration of naloxone (Clark et al., 2014; Giglio et al., 2015; Mueller et al., 2015).

Both conditions also observed significant decreases in injection heroin use and any opioid use and significant increases in drug treatment attendance over the 12-month follow-up period. Consistent with accumulating research (Clark et al., 2014; Giglio et al., 2015; Mueller et al., 2015) study findings suggest that having

Table 2
Overdose Risk and Prevention Behaviors in the past 6 months by Study Condition at the baseline and each follow-up.

	Arm	Frequency (percentage)			
		Baseline (n = 479)	6-month follow-up (n = 402)	12-month follow-up (n = 361)	Entire follow-up (n = 414)
Used any opioid	WP + OD	217 (90.8%)	101 (49.3%)	79 (43.9%)	121 (57.6%)
	HIV/ HCV + OD	225 (93.8%)	111 (56.4%)	92 (50.8%)	137 (67.2%)
Injected heroin	WP + OD	213 (89.1%)	94 (45.9%)	72 (40.0%)	112 (53.3%)
	HIV/ HCV + OD	223 (92.9%)	104 (52.8%)	82 (45.3%)	127 (62.3%)
Overdosed	WP + OD	55 (23.0%)	19 (9.3%)	15 (8.3%)	30 (14.3%)
	HIV/ HCV + OD	50 (20.8%)	19 (9.6%)	15 (8.3%)	29 (14.2%)
Cash voucher for naloxone	WP + OD	–	–	–	79 (37.6%)
	HIV/ HCV + OD	–	–	–	69 (33.8%)
Administered naloxone for self or others	WP + OD	12 (5%)	44 (21%)	35 (19%)	59 (28%)
	HIV/ HCV + OD	5 (2%)	35 (18%)	23 (13%)	46 (23%)
Injected saline when overdosed	WP + OD	26 (10.9%)	0 (0%)	2 (1.1%)	2 (1.0%)
	HIV/ HCV + OD	17 (7.1%)	2 (1.0%)	0 (0%)	2 (1.0%)
In drug treatment program	WP + OD	20 (8.4%)	18 (8.8%)	14 (7.8%)	29 (13.8%)
	HIV/ HCV + OD	18 (7.5%)	22 (11.2%)	18 (9.9%)	36 (17.7%)

Note: WP + OD COMPARISON = Wellness Promotion + Overdose Prevention. HIV/HCV + OD TREATMENT = HIV/HCV + Overdose Prevention Intervention.

Table 3
Multilevel Models of Intervention (HIV/HCV + OD intervention vs. WP + OD comparison) on overdose risk and prevention behaviors.

	Arm	Risk ratios [95% confidence intervals] (p-value)		
		6-month vs. baseline	12-month vs. baseline	Follow-up vs. baseline
Used any opioid	WP + OD	**0.54 [0.46, 0.63]**[**] **(p < 0.001)**	**0.48 [0.41, 0.58]**[**] **(p < 0.001)**	**0.63 [0.56, 0.72]**[**] **(p < 0.001)**
	HIV/HCV + OD	**0.60 [0.52, 0.69]**[**] **(p < 0.001)**	**0.54 [0.46, 0.63]**[**] **(p < 0.001)**	**0.72 [0.64, 0.80]**[**] **(p < 0.001)**
	HIV/HCV + OD vs. WP + OD	1.11 [090,1.36] (p = 0.336)	1.12 [0.89, 1.42] (p = 0.341)	1.13 [0.96, 1.33] (p = 0.154)
Injected heroin	WP + OD	**0.51 [0.44, 0.61]**[**] **(p < 0.001)**	**0.45 [0.37, 0.55]**[**] **(p < 0.001)**	**0.60 [0.52, 0.69]**[**] **(p < 0.001)**
	HIV/HCV + OD	**0.57 [0.49, 0.66]**[**] **(p < 0.001)**	**0.49 [0.41, 0.59]**[**] **(p < 0.001)**	**0.67 [0.59, 0.76]**[**] **(p < 0.001)**
	HIV/HCV + OD vs. WP + OD	1.10 [0.88, 1.38] (p = 0.385)	1.09 [0.83, 1.42] (p = 0.544)	1.12 [0.93, 1.35] (p = 0.239)
Overdosed	WP + OD	**0.40 [0.25, 0.64]**[**] **(p < 0.001)**	**0.37 [023,0.60]**[**] **(p < 0.001)**	**0.62 [0.43, 0.90]**[*] **(p = 0.013)**
	HIV/HCV + OD	**0.46 [0.29, 0.71]**[**] **(p < 0.001)**	**0.39 [0.24, 0.63]**[**] **(p < 0.001)**	**0.68 [0.48, 0.96]**[*] **(p = 0.029)**
	HIV/HCV + OD vs. WP + OD	1.13 [0.60, 2.15] (p = 0.697)	1.06 [0.54, 2.09] (p = 0.872)	1.09 [0.65, 1.82] (p = 0.746)
Administered naloxone for self or others	WP + OD	**4.34 [2.21, 8.54]**[**] **(p < 0.001)**	**3.96 [2.10, 7.48]**[**] **(p < 0.001)**	**5.60 [2.99, 10.50]**[**] **(p < 0.001)**
	HIV/HCV + OD	**8.44 [3.58, 19.89]**[**] **(p < 0.001)**	**6.04 [2.50, 14.61]**[**] **(p < 0.001)**	**10.85 [4.59, 25.63]**[**] **(p < 0.001)**
Cashed a voucher for naloxone	WP + OD	–	–	–
	HIV/HCV + OD	–	–	–
	HIV/HCV + OD vs. WP + OD	–	–	0.90 [0.65, 1.25] (p = 0.530)
Injected saline solution when overdosed	WP + OD COMPARISON	–	–	**0.09 [0.02, 0.34]**[**] **(p < 0.001)**
	HIV/HCV + OD	–	–	**0.14 [0.03, 0.55]**[**] **(p = 0.005)**
	HIV/HCV + OD vs. WP + OD	–	–	1.57 [0.23, 10.96] (p = 0.646)
Attended a drug treatment program in past 6 months	WP + OD	1.06 [0.56, 2.01] (p = 0.860)	0.93 [0.53, 1.63] (p = 0.800)	**1.68 [1.00, 2.82]**[*] **(p = 0.050)**
	HIV/HCV + OD	1.53 [0.86, 2.72] (p = 0.152)	1.30 [0.72, 2.34] (p = 0.391)	**2.31 [1.41, 3.80]**[**] **(p = 0.001)**
	HIV/HCV + OD vs. WP + OD COMPARISON	1.44 [0.61, 3.42] (p = 0.408)	1.39 [0.62, 3.15] (p = 0.426)	1.38 [0.67, 2.83] (p = 0.383)

Note: 1. Risk ratios were estimated via modified Poisson regression model with couple and repeated measure as random effects and with covariate adjustment for gender.
2. WP + OD = Wellness Promotion and Overdose Prevention Comparison Condition; HIV/HCV + OD = HIV/HCV and Overdose Prevention Treatment Condition.
[*] $p < 0.05$.
[**] $p < 0.01$.

access to naloxone does not result in risk compensation of increased use of heroin as some critics of naloxone have asserted.

In spite of the promising outcomes observed for both conditions in preventing overdose, several factors impeded the potential impact of the interventions. First is a government regulation of having a medical doctor to write a prescription for naloxone, which required providing vouchers for naloxone kits to participants that they could exchange at the HIV care clinic for naloxone. The stigma, time and travel barriers to exchanging vouchers at the HIV clinic were substantial; only about one-third of participants in both conditions obtained naloxone using their study vouchers. Secondly, several participants expressed concern that carrying naloxone would increase their risk of arrest by the police. Third was the absence of any opioid substitution therapy (OST) in Almaty at the time we were conducting the study, which is critical to the recovery and long-term risk reduction of overdose as well as decreasing risk of HIV/HCV transmission and promoting adherence to HIV treatment (Volkow & Collins, 2017; Volkow, Frieden, Hyde, & Cha, 2014; Woody, 2017).

Limitations and strengths

This study was limited by several factors that continue to challenge overdose prevention research in general. First is the lack of statistical power to observe statistically significant effect sizes on overdose outcomes given that overdose is a relatively rare event. This study was powered on the primary HIV/HCV risk outcome, not on

overdose outcomes. Second, because we did not include a control condition without overdose prevention content for ethical reasons, we cannot rule out the possibility that the significant reductions in overdose risk behaviors and non-fatal overdose observed for both conditions may be due to non-intervention related effects. Third is the use of self-reported outcome of non-fatal overdose without confirmation by a biological outcome or administrative report. Finally, the overdose prevention component of the WP + OD comparison group was delivered in separate single-gender group sessions, but to both members of the couple together in the HIV/HCV + OD arm. However, in the WP + OD comparison group, both male and female partners were simultaneously exposed to overdose prevention content. This concurrent presentation of the overdose prevention activities could have reinforced overdose prevention strategies in couples and reduced the likelihood of observing significant differences on outcomes for the couple-based integrated intervention.

Despite these limitations, this study has several strengths, including use of a randomized design, high rates of participation and retention over the 12-month follow up, a relatively long follow-up period, and blind assessment of outcomes.

Conclusions and recommendations

The extremely high rate of non-fatal opioid overdose (20%) in the past 6 months at baseline and high rate of fatal opioid overdose reported over the 12-month follow-up period (10 deaths – 2.3% of

the sample), underscore the urgent need to redress overdose among PWID in Kazakhstan as a public health priority. Although both conditions demonstrated promising effects in reducing risks for overdose over the 12-month follow-up and there was no significant difference between conditions, the overdose and HIV/ HCV prevention condition has the added benefit of significantly reducing overdose and HIV risk behaviors and HCV incidence to maximize the public health benefit. Integrating a low-threshold overdose prevention intervention into the continuum of HIV services may further build the trust and increase the engagement of people who use heroin and other opioids in HIV services to achieve the UNAIDS 90-90-90 goals by 2020, while preventing the substantial loss of lives to overdose. Evaluations of progress towards these 90-90-90 goals among PWID should consider the number of overdose deaths and progress in reducing overdose fatalities.

Accumulating research has documented multiple behavioral, structural and biological mechanisms linking overdose to HIV and HCV infection (Gilbert et al., 2013; Green et al., 2012; Walley, 2015). Identifying key mediators associated with both overdose prevention and HIV/HCV risk outcomes may guide the design of interventions that most efficiently target the syndemic biological, behavioral and structural mechanisms linking overdose to HIV and HCV.

There remains a critical need for implementation research to evaluate the effectiveness and cost-effectiveness of integrated interventions on reducing HIV, HCV and overdose among people who inject or use heroin or other opioids in a range of settings worldwide. Implementation research that employs adaptive designs or time series designs (e.g. stepped wedge) would allow for more rigorous, but ethical research designs comparing intervention conditions with and without overdose prevention components. Mixed-methods implementation research is also needed to examine the multi-level structural, community and organizational factors that influence the effectiveness of delivering integrated interventions in a range of settings. Such implementation research may inform future efforts to scale up integrated interventions to redress the deadly syndemic of overdose, HIV and HCV in Central Asia and worldwide.

Conflict of interest

The authors declare that they have no conflicts of interest.

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