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Novel Interventions to Prevent HIV and HCV Among Persons Who Inject Drugs

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Abstract Persons who inject drugs (PWID) are at high risk for infection with and poor outcomes from HIV and hepatitis C virus (HCV). Well-established interventions for HIV/HCV prevention among PWID include syringe access, opioid agonist maintenance treatment, and supervised injection facilities, yet these interventions remain unavailable or inadequately resourced in much of the world. We review recent literature on biomedical and behavioral interventions to reduce the burden of HIV/HCV among PWID, with an emphasis on randomized controlled trials and quasi-experimental studies. Since 2013, there have been significant advancements in utilizing antiviral therapy and behavioral interventions for prevention among PWID, including approaches that address the unique needs of couples and sex workers. In addition, there have been significant developments in pharmacotherapies for substance use and the implementation of naloxone for opioid overdose prevention. Notwithstanding multiple ongoing structural challenges in delivering HIV/HCV prevention interventions to PWID, these emerging and rigorously evaluated interventions expand possibilities for prevention among PWID.

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Introduction

The estimated 16 million (CI 11–21 million) people who inject drugs (PWID) worldwide [1] carry a disproportionate burden of HIV and hepatitis C (HCV). Around 3 million PWID (range 1–6 million) are infected with HIV [1] and seroprevalence estimates range from 12 to 37 % in the three countries with the largest number of PWID—China, the USA, and Russia—with even higher prevalence in other countries across Eastern Europe and Asia [1]. United Nations Programme on HIV/AIDS (UNAIDS) estimates that PWID are 28 times more likely to be infected with HIV than the general adult population [2]. The risk of acquiring HIV for each act of injection drug use is estimated to range from 0.63 to 2.4 % [3]. Furthermore, injection drug use as a risk factor for HIV accounts for 2.1 million (range 1.1–3.6) disability adjusted life years (DALYs) worldwide [4].

PWID have the highest burden of HCV globally. In the USA, an estimated 43 % of PWID have chronic HCV [5]. The US Centers for Disease Control and Prevention (CDC) estimates at least 18,000 new HCV infections per year, almost exclusively among PWID, with a 50 % increase in the number of acute cases from 2010 to 2012 [6, 7]. This is of particular importance because while approximately 20–30 % of those living with HIV are co-infected with HCV, co-infection rates among PWID are closer to 90 % [8]. HIV/HCV co-infection is associated with increased risk for HIV disease progression, AIDS-related mortality, and more rapid progression of HCV-related liver disease [8].

Despite the high prevalence of HIV and HCV among PWID, the global coverage of HIV/HCV prevention and treatment services for PWID remains poor, with few countries

intervening at a level sufficient to slow the HIV epidemic [9]. For example, needle-syringe programs (NSP) and opioid substitution therapy (OST) are effective, evidence-based HIV and HCV prevention strategies for PWID [10], yet they are only available in 82 and 71 out of 192 member states in the United Nations, respectively [11]. UNAIDS estimates that for each PWID, about 200 clean syringes are needed per year [12], yet on average, only 90 syringes are available [12] and 22 are distributed [11] annually per PWID. However, there is extreme variability in the level of NSP coverage between regions and countries, ranging from 0.1 to 0.3 syringes distributed annually per PWID in Sub-Saharan Africa and Latin America, respectively, to 202 syringes annually per PWID in Australasia [9]. Similarly, OST coverage ranges from less than or equal to one OST recipient per 100 PWID in central Asia, Sub-Saharan Africa, and Latin America to 61 recipients per 100 PWID in Western Europe, contributing to similar gaps in coverage [9]. In addition, the criminalization of injection drug use and the stigmatization of people who use substances persist as major barriers for PWID to access and benefit from services. In particular, harsh punishments and punitive laws for drug use impede the ability of PWID to utilize critical HIV/HCV prevention services [13, 12, 14].

Notwithstanding these longstanding challenges, novel strategies have emerged since 2013 that present promising new options to prevent HIV/HCV by addressing the needs of PWID. In addition to highlighting these new findings, we will discuss how these strategies can be utilized in concert with existing evidence-based strategies to more effectively address HIV and HCV among PWID. In this review, we have emphasized effective HIV/HCV interventions for PWID that were rigorously evaluated through randomized controlled trials or quasi-experimental studies published since 2013. The interventions fall broadly into the following three domains: 1) antiviral-based interventions, 2) risk behavior reduction interventions, and 3) substance use treatment and overdose management interventions (see Fig. 1). The characteristics and the key findings of the randomized and quasi-experimental studies are briefly summarized in Table 1. When randomized or quasi-experimental studies specific to PWID were lacking or sparse in these domains (e.g., pharmacotherapy intervention trials for stimulant users), we provided additional relevant literature from observational studies and mathematical modeling, as well as from experimental studies among substance-using populations, inclusive of PWID.

Antiviral-based HIV/HCV Interventions

Antiviral-based interventions present a promising new arena for HIV/HCV prevention. Broadly, these interventions use antiviral medications to prevent new HIV or HCV infections among uninfected individuals by reducing the level of infectiousness of infected persons [15]. These approaches include pre-exposure prophylaxis (PrEP) and treatment as prevention (TasP), which have increasingly compelling data and acceptance among high-risk groups. However, there is a paucity of studies exclusively among PWID. Many intervention trials in fact have exclusionary criteria that make PWID ineligible to participate in the studies [16]. Seminal studies are highlighted below that are of particular relevance for PWID.

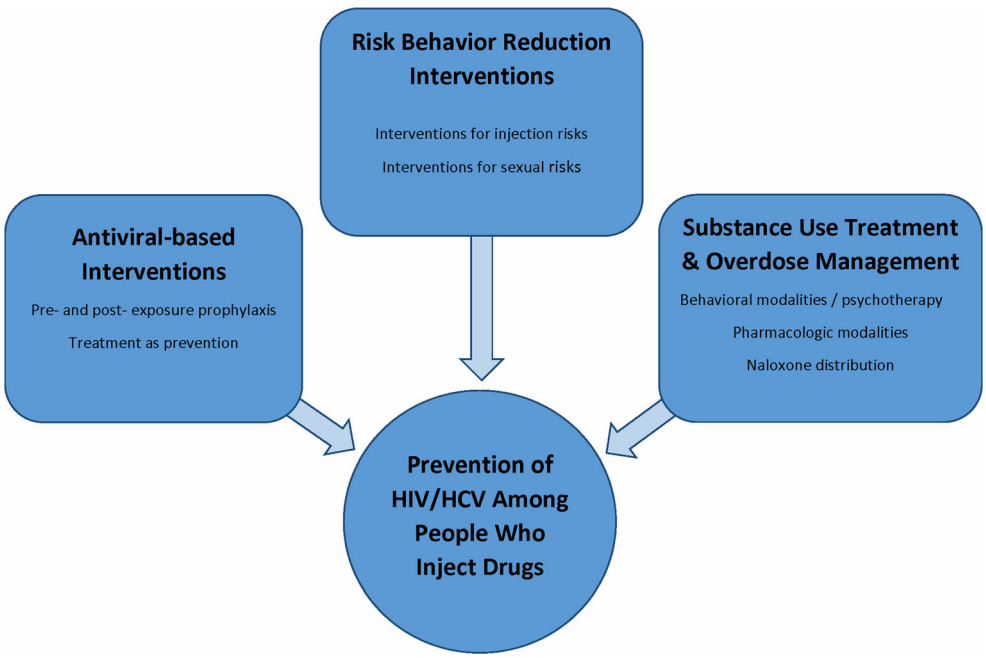

Fig. 1 Domains of interventions for HIV/HCV prevention among PWID

Table 1 Published intervention trials for HIV/HCV prevention among PWID since 2013

Category	Title	Year	Author(s)	Population/setting	Study design*	Intervention	Control	Primary outcomes	Significant findings
Antiviral-based HIV/HCV interventions	Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial	2013	Choopanya et al.	HIV-negative injection drug users in Bangkok, Thailand (n=2413)	RCT	Daily use of tenofovir disoproxil fumarate (tenofovir), monthly HIV testing, and individualized risk reduction and adherence counseling (n=1204)	Placebo, monthly HIV testing, and individualized risk reduction and adherence counseling (n=1209)	HIV infection	•There was a significant reduction (treatment efficacy=48.9 %; 95 % confidence interval [CI] 9.6–72.2; P=0.01) in HIV incidence among the tenofovir group compared to the placebo group, using a Cox regression and Kaplan-Meier hazard ratio to estimate the cumulative probability of HIV
Antiviral-based HIV/HCV interventions	Directly observed pegylated interferon plus self-administered ribavirin for the treatment of hepatitis C virus infection in people actively using drugs: a randomized controlled trial	2013	Hilsden et al.	Crack cocaine or injection drug users with chronic hepatitis C virus (HCV) (n=66)	RCT	Immediate treatment with directly observed pegylated interferon (pegylated interferon (peg-IFN)) alfa-2a and self-administered ribavirin (n=48)	Delayed treatment with directly observed peg-IFN alfa-2a and self-administered ribavirin (n=18)	Sustained virologic response (SVR) defined by undetectable HCV RNA 24 weeks after treatment completion	•The intent-to-treat SVR was 65 % (95 % CI=49–78 %) among participants receiving immediate treatment and 39 % (95 % CI=17–64 %) among participants receiving delayed treatment (P=0.060) •The SVR of treatment among people using crack cocaine or injection drugs within 30 days of start of treatment was comparable to non-drug users (63 vs. 67 %; P=0.60) •For those with an SVR and available follow-up data, HCV reinfection rates were low (reinfection rate=2.7 cases per 100 person-years; 95 % CI=0.0–14.5)
HIV/HCV risk behavioral interventions	Effects of a couple-based intervention to reduce risks for HIV, HCV, and STIs among drug-involved heterosexual couples in Kazakhstan: a randomized controlled trial	2014	El-Bassel et al.	Couples in Almaty, Kazakhstan where one or both partners reported injecting drugs in the past 90 days (n=300 couples, 600 participants)	RCT	A 5-session HIV, HCV, STI (sexually transmitted infection) prevention intervention (risk reduction) (n=302)	A five-session wellness promotion intervention (n=298)	•Incidence of HIV, HCV, and STIs •Rates of unprotected sex •Rates of unsafe injection	•Participants who received the risk reduction intervention had significantly lower incidence of HCV infection (incident rate ratio [IRR]=0.41; 95 % CI=0.10–0.90; P=0.031), fewer numbers of unprotected vaginal sex acts with their study partners (IRR=0.58; 95 % CI=0.36–0.93; P=0.024), and more consistent condom use (odds ratio [OR]=2.30;

Table 1 (continued)

Category	Title	Year	Author(s)	Population/setting	Study design*	Intervention	Control	Primary outcomes	Significant findings
									95 % CI=1.33–4.00; P=0.003) compared to those who received the wellness promotion intervention
HIV/HCV risk behavioral interventions	Do community-based strategies reduce HIV risk among people who inject drugs in China? A quasi-experimental study in Yunnan and Guangxi provinces	2014	Wang et al.	People who inject drugs in four cities in Yunnan and Guangxi provinces in China (n=1035)	Quasi	Harm reduction intervention through community-based drop-in centers only (24.2 %), peer-led outreach only (8.9 %), and a combination of both (22.8 %)[a]	No harm reduction intervention through community-based drop-in centers or peer-led outreach (44.1 %)[a]	•Rates of sharing needles or syringes •Rates of always keeping a clean needle on hand •Rates of HIV testing and counseling •Rates of consistent condom use	•Those who participated in both peer-led drop-in center activities and were exposed to peer-led outreach were more likely to have new needles on hand (OR=1.53; 95 % CI=1.07–2.19; P<0.05) and to consistently use condoms (OR=3.31; 95 % CI=1.52–3.50; P<0.001) •Participants in Kunming who participated in both peer-led drop-in center activities and were exposed to peer-led outreach were more likely to undergo HIV testing (OR=2.79; 95 % CI=1.42–5.47; P<0.01) •Participants in Gejiu, Nanning, and Luzhai who were exposed to peer-led outreach only were more likely to undergo HIV testing (OR=3.63; 95 % CI=1.17–11.28; P<0.05)
HIV/HCV risk behavioral interventions	The staying safe intervention: training people who inject drugs in strategies to avoid injection-related HCV and HIV infection	2014	Mateu-Gelabert et al.	Injection drug users 18 years or older recruited in New York City (n=51)	Pre-post	Five 2-h small-group social/behavioral intervention sessions aiming to reduce injection risk (n=51)	N/A	•Drug intake and perceived control over drug use •Injection risk behavior (needle sharing, back-loading, cooker sharing, cotton sharing, etc.)	•Participants had significant reductions in self-reported drug intake (effect size=0.83; P<0.001), syringe sharing (effect size=0.65; P<0.001), "backloading" (effect size=0.66; P<0.01), sharing of drug cookers (effect size 0.74; P<0.001), sharing of cotton filters (effect size=0.72; P<0.001), sharing water to dilute drugs (effect size=0.70; P<0.001), and sharing of water containers (effect size=0.66; P<0.001)

Table 1 (continued)

Category	Title	Year	Author(s)	Population/setting	Study design*	Intervention	Control	Primary outcomes	Significant findings
HIV/HCV risk behavioral interventions	Transitions in latent classes of sexual risk behavior among young injection drug users following HIV prevention intervention	2014	Mackesy-Amiti et al.	HIV- and HCV-negative injection drug users aged 15–30 years old in Baltimore MD, Chicago IL, Los Angeles CA, New York City NY, and Seattle WA (n=854)	RCT	Six peer education training intervention sessions related to injection-related and sexual risk behaviors (n=365)	Six video discussion sessions addressing social and health issues of interest to the target population (n=343)	Transition across four distinct classes of sex-related HIV/HCV risk using latent transition analysis	•Male participants who were in a high-risk class at baseline and received the treatment intervention were significantly more likely to transition to a low-risk class compared to the control group (OR=1.86; 95 % CI=1.08–3.21; P=0.025) •Male participants in the second highest risk group and received the treatment intervention were significantly more likely to transition to the second lowest risk group compared to the control group (OR=2.16; 95 % CI 1.01–4.61; P=0.048)
HIV/HCV risk behavioral interventions	Hepatitis C multimedia prevention program in poor Hispanic HIV-infected injecting drug users: 6 months after intervention	2013	Mayor et al.	Low-income Hispanic HIV-infected injection drug users (n=88)	Pre-post	Multimedia educational intervention program (n=88)	N/A	Awareness regarding HCV clinical manifestations and treatments, HCV risky behaviors, and HIV/HCV co-infection synergisms 8 weeks and 6 months post-intervention (determined via questionnaire)	•Eight weeks post-intervention, participants showed a significant increase in awareness in three items pertaining to HCV clinical manifestations and treatments, three items pertaining to HCV risky behaviors, and two items pertaining to HIV/HCV co-infection synergisms (P<0.5) •Six months post-intervention, participants showed a significant increase in awareness in three items pertaining to HCV clinical manifestations and treatments, four items pertaining to HCV risky behaviors, and one item pertaining to HIV/HCV co-infection synergisms (P<0.5)
HIV/HCV risk behavioral interventions	Characterizing and improving HIV and hepatitis knowledge among primary prescription opioid abusers	2013	Dunn et al.	Primary prescription opioid abusers participating in a larger randomized, double-blind clinical trial evaluating efficacy of buprenorphine tapers and	Pre-post	Brief HIV/HCV educational intervention (n=54)	N/A	HIV and HCV knowledge (determined via questionnaire)	•Participants showed 31 % increase in accuracy on the Marsch HIV knowledge questionnaire (t(53)=−9.2; P<0.001), a 78 % increase in accuracy

Table 1 (continued)

Category	Title	Year	Author(s)	Population/setting	Study design*	Intervention	Control	Primary outcomes	Significant findings
				subsequent oral naltrexone maintenance (n=54)					on the HCV knowledge test ($t(53)=-11.1$; $P<0.001$), and a 14 % increase in self-reported likelihood of using a condom before having sex ($t(53)=-2.01$; $P=0.05$)
HIV/HCV risk behavioral interventions	Effects of an HIV peer prevention intervention on sexual and injecting risk behaviors among injecting drug users and their risk partners in Thai Nguyen, Vietnam: a randomized controlled trial	2013	Go et al.	HIV-negative index injection drug users aged 18 years or older (n=419) and injecting and sexual network members (n=516) in Thai Nguyen, Vietnam	RCT	Six small-group peer educator-training sessions and three booster sessions in addition to HIV testing and counseling (n=210 index participants)	HIV testing and counseling only (n=209 index participants)	Self-reported rates of unprotected sex and needle sharing	•At 12-months, intervention participants had a greater decline in unprotected sex compared to control participants (Wald test [W]=10.8, df=4, P=0.03)
HIV/HCV risk behavioral interventions	Reductions in HIV/STI incidence and sharing of injection equipment among female sex workers who inject drugs: results from a randomized controlled trial	2013	Strathdee et al.	Female sex workers aged 18 years or older who inject drugs and reported sharing injection equipment and unprotected sex with clients within the last month in Tijuana and Ciudad Juarez, Mexico (n=584)	RCT	Four brief, single-session interventions combining an interactive version of a sexual risk intervention and an interactive version of an injection risk intervention (n=144)	Four brief, single-session interventions combining the following: •Interactive sexual risk intervention and didactic injection risk intervention (n=146) •Didactic sexual risk intervention and interactive injection risk intervention (n=148) •Didactic sexual risk intervention and didactic injection risk intervention (n=146)	HIV/STI incidence and receptive needle sharing frequency	•The interactive sexual risk intervention significantly reduced HIV/STI incidence compared to the didactic sexual risk intervention in both Tijuana (adjusted rate ratio [ARR]=0.38; 95 % CI=0.16–0.89) and Juarez (ARR=0.44; 95 % CI=0.19–0.99) •In Juarez, women receiving the interactive injection risk intervention showed declines in receptive needle sharing (P=0.04)
HIV/HCV risk behavioral interventions	Effects of a 1-hour intervention on condom implementation intentions among drug users in Southern California	2013	Nydegger et al.	Convicted non-violent drug offenders participating in drug diversion programs in Southern California (n=143)	RCT	HIV survey after a 1-h intervention on condom implementation intentions (n=72)	HIV survey before a 1-h intervention on condom implementation intentions (n=71)	Implementation intentions to use condoms	•The group that was assessed after the 1-h intervention reported stronger intentions to use condoms (experimental median total score=35 vs. control median total score=25; Mann-Whitney U test [Z]=4.48; $P<0.001$) compared to those who were assessed before the intervention
HIV/HCV risk behavioral interventions	The dynamic relationship between social norms and behaviors: the results of an HIV prevention network intervention for injection drug users	2013	Latkin et al.	Index injection drug users (n=232) and their social network members who were drug or sex partners (n=420) in Philadelphia, PA	RCT	Six 2-h peer educator sessions and two booster sessions for index participants and a two-session voluntary HIV counseling and testing for all index and network member participants (n=314)	A two-session voluntary HIV counseling and testing for all index and network member participants (n=338)	Injection-related HIV risk behaviors (sharing needles, sharing cookers, sharing cotton, front-/back-loading) and social norms of these four risk	•Participants who received the peer educator intervention reported less risky social norms associated with sharing needles (change in mean score=−0.24; P=0.007), sharing cookers (change

Table 1 (continued)

Category	Title	Year	Author(s)	Population/setting	Study design*	Intervention	Control	Primary outcomes	Significant findings
								behaviors measured longitudinally	in mean score=−0.33; P=0.004), sharing cotton (change in mean score=−0.28; P=0.0165), and front-/back-loading (change in mean score=−0.23; P=0.002)
HIV/HCV risk behavioral interventions	Peer-education intervention to reduce injection risk behaviors benefits high-risk young injection drug users: a latent transition analysis of the CIDUS 3/DUIT study	2013	Mackesy-Amiti et al.	HIV- and HCV-negative injection drug users aged 15–30 years old in Baltimore MD, Chicago IL, Los Angeles CA, New York City NY, and Seattle WA (n=854)	RCT	Six peer education training intervention sessions related to injection-related and sexual risk behaviors (n=365)	Six video discussion sessions addressing social and health issues of interest to the target population (n=343)	Transition across four distinct classes of injection-related HIV/HCV risk using latent transition analysis	•Participants in the highest risk behavior class at baseline who received the peer education intervention were 90 % more likely to be in the lowest risk class compared to the control group
HIV/HCV risk behavioral interventions	Psychoeducation improves hepatitis C virus treatment during opioid substitution therapy: a controlled, prospective multicenter trial	2013	Reimer et al.	Patients with chronic HCV in opiate substitution therapy (n=198)	RCT	Twelve regular and 5–10 update 60-min psychoeducation sessions tailored to injection drug users in HCV treatment and standard HCV treatment (n=82)	Standard HCV treatment (n=107)	Completion of HCV treatment and sustained virologic response (SVR)	•Individuals with specific HCV genotypes (1 or 4) who received psychoeducation in conjunction with treatment were significantly more likely to complete HCV treatment (odds ratio [OR]=2.60; 95 % CI=1.04–6.49; P=0.038) compared to individuals who did not receive psychoeducation •Individuals with specific HCV genotypes (1 or 4) who received at least five psychoeducation sessions in conjunction with treatment showed an increased SVR (OR=2.57; 95 % CI=1.05–6.28; P=0.037) compared to individuals who did not receive psychoeducation
HIV/HCV risk behavioral interventions	A randomized controlled trial of the community-friendly health recovery program (CHRP) among high-risk drug users in treatment	2013	Copenhaver et al.	HIV-negative opioid-dependent methadone patients who reported HIV risk behaviors (n=304)	RCT	Community-Friendly Health Recovery Program (CHRP); 4 50-min group sessions that address HIV risk behaviors tailored to opioid-dependent adults in treatment (n=149)	Four 50-min group sessions that address methadone maintenance and general health care information (n=155)	•Self-reported sex- and drug-related HIV risk behaviors •Demonstrated sex- and drug-related HIV risk reduction skills •Sex- and drug-related HIV risk reduction knowledge	•Participants who participated in the intervention group showed improvements in both drug-related HIV risk reduction knowledge (F(4724)=3.02; P=0.017) and drug-related HIV risk reduction skills (F(1185)=25.99; P<0.001)

Table 1 (continued)

Category	Title	Year	Author(s)	Population/setting	Study design*	Intervention	Control	Primary outcomes	Significant findings
								•Motivation to reduce HIV risk behavior	•Participants in the intervention group improved to a greater extent than did those in the control group in both female ($F(4740)=6.87$; $P<0.001$) and male ($F(4740)=3.34$; $P=0.01$) condom demonstration skills
Substance use treatment and overdose management	Naloxone therapy in opioid overdose patients: intranasal or intravenous? A randomized clinical trial	2014	Sabzghabaee et al.	Opioid overdose patients at Department of Poisoning Emergencies at Noor and Ali Asghar (PBUH) University Hospital in Iran ($n=100$)	RCT	Receipt of intranasal (IN) naloxone ($n=50$)	Receipt of intravenous (IV) naloxone ($n=50$)	•Level of consciousness (descriptive and Glasgow Coma Scales) •Vital signs •Time interval to response •Arterial blood O2 saturation •Side effects •Duration of hospital stay	•IN group had significantly higher levels of consciousness after administration (IN 14.3±0.73 Glasgow Coma Scale vs. IV 13.2±1.5 Glasgow Coma Scale; $P<0.001$), significantly lower heart rate after administration (IN 90±8.3 bpm vs. IV 97±12.9 bpm; $P=0.003$), and significantly longer response time after administration (IN 2.56±0.64 min vs. IV 1.48±0.58 min; $P<0.001$)
Substance use treatment and overdose management	Training family members to manage heroin overdose and administer naloxone: randomized trial of effects on knowledge and attitudes	2014	Williams et al.	Family members and carers at training events delivered in community addiction treatment services in England ($n=187$)	RCT	Take-home naloxone training ($n=95$)	Basic information on overdose management ($n=92$)	Opioid Overdose Knowledge Scale and an Opioid Overdose Attitudes Scale (determine via self-completed survey)	•Participants who received take-home naloxone training reported both greater overdose-related knowledge (mean difference=4.08; 95 % CI=2.10–6.06; $P<0.001$) and attitudes relative to those receiving basic information only (mean difference=7.47; 95 % CI=3.13–11.82; $P=0.001$)
Substance use treatment and overdose management	Brief overdose education can significantly increase accurate recognition of opioid overdose among heroin users	2014	Jones et al.	Current heroin users aged 21–65 in New York City ($n=84$)	Pre-post	Standard overdose prevention training ($n=44$)	No standard overdose prevention training ($n=40$)	Overdose knowledge (determined via questionnaire of 16 putative overdose scenarios)	•Participants who received overdose training had increased ability to identify opioid overdose ($t(43)=18.57$; $P<0.05$) as well as scenarios where naloxone administration should be administered ($t(43)=10.72$; $P<0.05$)

Table 1 (continued)

Category	Title	Year	Author(s)	Population/setting	Study design*	Intervention	Control	Primary outcomes	Significant findings
Substance use treatment and overdose management	Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis	2013	Walley et al.	Massachusetts communities with at least five fatal overdoses in each of the years 2004 to 2006 (n=19)	Natural	High or low rates of overdose education and naloxone distribution (OEND) implementation[b]	No OEND implementation[b]	Adjusted rate ratios for annual deaths related to opioid overdose and utilization of acute care hospitals	•Community-year strata with low (ARR=0.73; 95 % CI=0.57–0.91; P<0.01) and high (ARR=0.54; 95 % CI=0.39–0.76; P<0.01) rates of OEND implementation had significantly lower rate ratios of annual deaths related to opioid overdose
Substance use treatment and overdose management	Randomized controlled trial of contingency management for stimulant use in community mental health patients with serious mental illness	2013	McDonell et al.	Outpatients with serious mental illness and stimulant dependence (n=176)	RCT	Three months of contingency management for stimulant abstinence plus treatment as usual (mental health, chemical dependency, housing, and vocational services) (n=85)	Treatment as usual with reinforcement for study participation only (n=91)	Urine drug tests and self-report, clinician report, and service utilization outcomes	•Participants in the contingency management group were 2.4 times more likely (95 % CI=1.9–3.0; P<0.05) to submit a stimulant-negative urine test compared with control participants •Contingency management participants also had significantly lower levels of alcohol use during treatment (β=2.44; 95 % CI=0.60–4.29; P<0.05) and reported fewer days of stimulant use (β=2.70; 95 % CI=0.91–4.31; P<0.05) •Control participants were more likely to report injection drug use (OR=3.3; 95 % CI=1.8–5.9; P<0.05), stimulant use (OR=1.4; 95 % CI=1.0–1.9; P<0.05), and psychiatric symptoms (β=0.25; 95 % CI=0.08–0.43; P<0.05)
Substance use treatment and overdose management	The therapeutic workplace to promote treatment engagement and drug abstinence in out-of-treatment injection drug users: a randomized controlled trial	2014	Holtyn et al.	Out-of-treatment injection drug users in Baltimore, Maryland (n=98)	RCT	Twenty six-week participation in a therapeutic workplace where participants had to enroll in methadone treatment and provide opiate- and cocaine-negative urine samples to work and maximize pay (abstinence, methadone, and work reinforcement) (n=33)	•Twenty six-week participation in a therapeutic workplace where participants had to enroll in methadone treatment to work and maximize pay (methadone and work reinforcement) (n=35) •Twenty six-week participation in a therapeutic workplace where participants only had to work to earn pay	•Enrollment in methadone treatment •Urinalysis for opiates and cocaine	•Participants in the work reinforcement only group were significantly less likely to abstain from cocaine (OR=0.37; 95 % CI=0.36–0.38; P=0.02) and opiates (OR=0.39; 95 % CI=0.38–0.41; P=0.02) compared to participants in the abstinence, methadone, and work reinforcement group

Table 1 (continued)

Category	Title	Year	Author(s)	Population/setting	Study design*	Intervention	Control	Primary outcomes	Significant findings
							(work reinforcement) (n=30)		•Participants in the work reinforcement only group were significantly less likely to abstain from cocaine (OR=0.39; 95 % CI=0.38–0.41; P=0.02) compared to participants in the methadone and work reinforcement group
Substance use treatment and overdose management	Methadone and buprenorphine-naloxone are effective in reducing illicit buprenorphine and other opioid use, and reducing HIV risk behavior—outcomes of a randomized trial	2013	Otiashvili et al.	Opioid-dependent injection drug users in Tbilisi, Georgia (n=80)	RCT	Twelve-week trial of daily observed methadone treatment (n=40)	Twelve-week trial of daily observed buprenorphine-naloxone treatment (n=40)	•Drug use by urine screen •Addiction Severity Index •Visual analog scale for current opioid craving •Self-reported measure of drug and sexual HIV risk behaviors	•At the 20-week follow-up, participants in both treatment arms (methadone and buprenorphine-naloxone) had significantly lower use of illicit buprenorphine (2.7 vs. 13.8 %; P=0.005) and illicit opioids (5.6 vs. 27.6 %; P<0.001) compared to those who were not in treatment •Participants in both treatment arms showed significant reductions in reported HIV risk injection behaviors over the treatment period
Substance use treatment and overdose management	Methadone maintenance for HIV positive and HIV negative patients in Kyiv: acceptability and treatment response	2014	Dvoriak et al.	HIV+ (n=25) and HIV− (n=25) opioid addicted individuals in Kyiv, Ukraine	Pre-post	Twelve-week course of methadone treatment	N/A	•Drug use by urine screen •HIV risk behaviors by self-reported Risk Assessment Battery	•Both HIV+ and HIV− participants had significant reductions in use of heroin (P value for time effects for heroin use <0.001) and other opiates (P value for time effects for other opiate use <0.001) as well as HIV risk behaviors (drug risk, sex risk, and total risk) (P value for time effects for HIV risk behaviors <0.001)
Substance use treatment and overdose management	Randomized clinical trial examining duration of voucher-based reinforcement therapy for cocaine abstinence	2013	Kirby et al.	Cocaine dependent adults enrolled in a methadone treatment program at time of the study (n=130)	RCT	Extended (36 weeks) voucher-based reinforcement therapy (VBRT) with escalating voucher amounts contingent on cocaine abstinence	Standard (12 weeks) VBRT with escalating voucher amounts contingent on cocaine abstinence	•Cocaine use by urine screen	•Participants receiving the extended VBRT had significantly longer durations of cocaine abstinence during weeks 1–24 (5.7 vs. 2.7 weeks; F(1127)=9.19; P=0.003) as well as proportionally more abstinence during weeks 24–36 (odds ratio

Table 1 (continued)

Category	Title	Year	Author(s)	Population/setting	Study design*	Intervention	Control	Primary outcomes	Significant findings
									[OR]=2.18; 95 % CI=1.07–10.22; χ^2=4.57; *P*=0.03) •Longer continuous abstinence during VBRT was significantly associated with abstinence both during aftercare (OR=1.23; 95 % CI=1.13–1.34; χ^2=14.8; *P*=0.001) and during the last 12 weeks of the study (OR=1.12; 95 % CI=1.06–1.19; χ^2=12.23; *P*<0.001) •Average cost per week of abstinence attained was significantly higher in the Standard VBRT group ($96 vs. $43; *P*<0.001)

RCT randomized control trial, *Quasi* quasi-experimental trial, *Pre-post* pre-post-intervention trial, *Natural* natural experiment, *CI* confidence interval, *ARR* adjusted relative risk, *IRR* incident rate ratio, *OR* odds ratio, *HCV* hepatitis C virus, *IFN* interferon, *SVR* sustained viral response, *STI* sexually transmitted infection, *IN* intranasal, *IV* intravenous, *OEND* overdose education and naloxone distribution, *VBRT* voucher-based reinforcement therapy

[a] Sample sizes for each intervention arm were not provided, only the percentage of the total sample size

[b] Sample sizes for each intervention arm were made up of community-year strata and were not explicitly defined

HIV

In 2013, the *Bangkok Tenofovir Study* (BTS) became the first study with efficacy data on the use of antiretroviral therapy (ART) for PrEP to reduce HIV incidence among PWID [17••]. Although PrEP has efficaciously reduced HIV among other key populations at risk for HIV, including men who have sex with men and transgender women [18], and serodiscordant heterosexual couples, [19] BTS was the first study exclusively among PWID. Investigators randomized 1204 HIV-negative PWID from 17 drug treatment clinics in Bangkok, Thailand to either daily tenofovir or placebo and followed participants for 84 months. In modified intent-to-treat analyses, tenofovir was significantly associated with a 48.9 % reduction in HIV incidence [17••]. Furthermore, tenofovir was associated with a 74 % reduction in HIV infection among those who had detectable study drug in their plasma [17••]. There were no significant differences in the occurrence of serious adverse events between study arms, suggesting that PrEP is tolerable for PWID [17••].

Some concerns about the study may limit its external generalizability, however. First, only a small proportion of participants reported frequent (at least weekly) injection drug use, as well as needle sharing. It is unclear whether the findings from BTS would be generalizable to other PWID with higher risk profiles. Furthermore, the use of directly observed therapy (DOT) raises concerns as to whether the use of PrEP for PWID will show a similar benefit in the absence of DOT, as would be expected in most clinical practices. In addition, attrition was higher in the third year of the study, which is the period when a significant intervention effect was noted. Hence, although the findings of BTS are significant, further research may be needed to establish the effectiveness of providing PrEP for PWID and establishing the best way to implement this strategy on a broad scale. Thus, PrEP is not yet recommended as part of the combination package for HIV prevention intervention in this population by the World Health Organization [20].

Since the transmission of HIV is reduced by ART due to reductions in HIV RNA, TasP is likely also to be effective among PWID. Indeed, observational data among cohorts of PWID (e.g., Amsterdam, ALIVE, BART, and VIDUS cohorts) suggest that declines in HIV incidence are associated with reductions in community plasma HIV viral load as a result of widespread scale-up of the ART among PWID [21–23]. To date, no trials have been conducted exclusively among PWID to demonstrate that early treatment compared to delayed treatment is associated with significant reductions in HIV transmission, as was done in HIV Prevention Trials Network (HPTN) 052 [15]. However, TasP trials evaluating implementation strategies to increase virologic suppression among HIV-positive substance users are underway. For example, Clinical Trials Network (CTN) 0049, the Hospital visit as Opportunity for Prevention and Engagement for HIV-infected drug users (HOPE), randomized 800 substance users living with HIV to one of the following treatment conditions: 1) patient navigation, 2) patient navigation with contingency management, or 3) treatment as usual [24]. Follow-up is expected to end in early 2015. Highly anticipated data from this study will inform TasP implementation strategies to achieve virologic suppression among HIV-positive substance users. Ultimately, the broad expansion of ART is essential to fully realize the potential benefits of TasP in reducing new HIV infections among PWID [11]. Unfortunately, the ART coverage remains particularly low among PWID living with HIV; based on available data, it is estimated that for every 100 PWID worldwide living with HIV, only 4 are currently receiving ART [11].

HCV

Rapid advancements in the treatment of HCV have raised the prospect of TasP for HCV among PWID. Because HCV treatment is curative, with apparently lifelong absence of viremia, treating those at risk of secondary transmission should reduce incident disease. At most, 6 % of PWID historically were eligible for and willing to accept interferon-based therapy [25–31]. Providers and patient concerns included adherence, reinfection, the absence of advanced disease to justify a toxic therapy, the duration and complexity of treatment, the risk of toxicities, and the low likelihood of cure [32–34]. In contrast, the simplicity, high cure rate, and minimal toxicities of interferon-free regimens obviate most medical reasons to consider withholding or refusing treatment. The recently FDA-approved combination of ledipasvir and sofosbuvir, for instance, consists of one pill daily for 8 to 12 weeks for most genotype 1 patients with a 94–100 % sustained viral response rate, including in HIV/HCV co-infected patients, negligible adverse effects [35–39], and no apparent archiving of resistance mutations [40]. Mathematical models predict that utilizing these treatments could result in substantial reductions in incidence of HCV: treating 8 % of PWID annually for HCV could reduce HCV prevalence by 90 % over 15 years according to one conservative model that assumed reinfection rates post-treatment were the same as initial infection rates [41•]. Cohort studies, however, estimate reinfection rates to be from 2.8 to 6.0 % [42–44], about half the rate for initial infections [45], suggesting that the impact of HCV TasP for PWID could be greater than existing models predict. Data are needed to establish if, in fact, treating active injectors is feasible and can effectively reduce incident infection; hopefully, therapies will be more affordable once such data exist.

HIV/HCV Behavioral Risk Reduction Interventions

Behavioral risk reduction interventions for HIV/HCV prevention, the mainstay of research efforts in the 1990s, lost favor in recent years due to several prominent studies producing largely negative results [46, 47]. Although some recent studies continue to produce modest results [48], others have noted positive results in a variety of behavioral outcomes and a few have also reported significant results on biologic endpoints related to HIV/HCV prevention. These include Project Renaissance, a trial that randomized 600 participants in Almaty Kazakhstan to a five-session HIV/HCV and sexually transmitted infection risk reduction intervention or a wellness promotion control condition [49••]. The key feature of this study was the involvement of 300 heterosexual couples where at least one partner reported recent injection drug use. In the 12-month follow-up, investigators found that those who received the behavioral intervention had a 69 % lower incidence of HCV, compared to those in the control group. Moreover, intervention recipients had significantly higher rates of consistent condom use and lower rates of unprotected sexual risk behaviors. The *Mujer Mas Segura* (Safer Woman) study is another promising intervention with a significant intervention effect on a biologic endpoint [50••]. This study was geared toward a uniquely vulnerable population: female sex workers who inject drugs (FSW-IDU). Women recruited in this randomized factorial study were at heightened risk for HIV due to sexual transmission from their clients and sexual partners but also from their injection drug use. A total of 584 HIV-negative FSW-IDU from Tijuana and Ciudad Juarez, Mexico were randomized to either an interactive injection risk intervention, an interactive sexual risk intervention, a combination of these two interventions, or an educational control group and followed for 12 months. Compared to the control group, the interactive sexual risk intervention was associated with a 62 and 56 % decrease in HIV/STI incidence among FSW-IDU from Tijuana and Ciudad Juarez, respectively.

Several recently published interventions have demonstrated promising reductions in self-reported risk behaviors, knowledge, or social norms. “Staying Safe” is a strength-based intervention for HIV/HCV risk reduction among PWID involving five 2-h sessions over 1 week [51•]. A pilot study of Staying Safe among 68 PWID using a pre- vs. 3-month post-test design demonstrated significant reductions in drug use and injection-related risk behaviors. Other investigators found that a multimedia intervention on HCV led to long-lasting changes in HCV risk behaviors and knowledge in a pre-post design among 88 low-income, Latino, HIV-positive PWID [52]. An educational activity for prescription opioid injectors led to significant improvements in knowledge and self-reported condom use but no change in injection-related behaviors [53]. Efforts to develop effective interventions for this population are urgently needed in the USA given the dramatic expansion in the use of prescription opioids and multiple studies documenting that those transitioning from the oral use of prescription opioids to injecting have very poor knowledge of injection-related HIV and HCV risks [53].

Additionally, peer-led and community-based interventions have noted positive findings. Wang et al. conducted a quasi-experimental study that compared the presence to the absence of peer-led harm reduction programs involving 1035 PWID from the Yunnan and Guangxi provinces of China [54]. Participants in peer-led programs were more likely to have clean needles, use condoms, and undergo HIV testing. Latkin et al. reported results from a randomized trial of a six-session, peer-driven intervention in which the index participant was trained to deliver the intervention, focused on safer sex and injection practices, to their network [55]. The study reported on 652 PWID who were recruited and followed for up to 30 months as part of HPTN 037; only Philadelphia participants were included because the Chiang Mai participants were facing a mass incarceration and execution campaign during the study. Intervention participants reported significantly improved social norms compared to control participants around all four measures: needle sharing, sharing cookers, sharing cottons, and front/back-loading. The Community-friendly Health Recovery Program (CHRP) was designed to deliver an HIV prevention curriculum under the Information-Motivation-Behavior theory within the confines of an active methadone maintenance program. A total of 304 HIV-negative patients were randomized to CHRP or active control, with the CHRP participants showing superior improvements in drug risk reduction knowledge and both sex and drug risk reduction skills [56].

Finally, some recent secondary analyses of prior studies have suggested hidden benefits. For example, a latent class analysis of the Third Collaborative Injection Drug Users Study (CIDUS 3/DUIT) found that participants reporting the highest level of HIV/HCV risk at baseline were 90 % more likely to be in the lowest risk class at follow-up if they had been randomized to the intervention compared to control [47].

Substance Use and Overdose Management Interventions

Behavioral Modalities to Address Substance Use

Recent behavioral interventions for managing substance use have emphasized incentive-driven and employment focused strategies, with mixed results. A randomized study of escalating payments for urine samples negative for cocaine among methadone-maintained patients was efficacious, although extending the duration of incentives did not influence resumption of cocaine use after the incentives were terminated [57]. A small randomized trial among opioid-dependent, minimally employed to unemployed persons leaving 3-day

detoxification compared incentivized working only if abstinent, incentivized working regardless of drug use, and working without incentive. The target sample size was 156, but the study was terminated early, after 46 participants were randomized, due to failure of the test condition to produce drug abstinence. One potential explanation for this failure noted by the authors is the very limited benefit of opioid detoxification without follow-up pharmacotherapy [58]. In contrast, another trial included 98 opioid injectors in work for pay, work plus methadone maintenance for pay, or work plus methadone maintenance and abstinence from cocaine and other opioids for pay. The latter two groups both provided significantly more cocaine-negative urines and the third group also had more opioid-free urines compared to the work for pay group [59]. The most notable difference between these two studies is the utilization of a proven treatment for opioid dependence, agonist maintenance treatment, in the latter study.

Pharmacologic Modalities to Address Substance Use

The most well-established pharmacotherapies for opioid use disorders are methadone and buprenorphine maintenance, which have been repeatedly associated with reduced HIV, HCV, and overdose risk [9]. Nonetheless, in many of the regions of the world hardest hit by injection-related HIV and HCV transmission, these therapies are unavailable or severely restricted. Among recent literature, a randomized trial of daily observed methadone compared to buprenorphine-naloxone dosing among 80 illicit buprenorphine injectors in the Republic of Georgia found that both groups similarly reduced illicit opioid use and HIV injection risks, again suggesting that the selection of one of these agents over the other should be made on a case-by-case basis [60•]. In addition, an observational study of 50 opioid-dependent persons, both HIV+ and HIV −, started on methadone in Hyiv, Ukraine observed dramatic reductions in the use of heroin and other opioids as well as both drug and sex-related HIV risk behaviors; 96 % of participants elected to continue methadone after the study concluded [61]. The use of depot naltrexone, an opioid antagonist that remains active for 30 days when injected and has been used successfully for alcohol dependence, has recently emerged as a potentially viable therapy for opioid dependence. A 1-year open-label extension of 114 subjects from a randomized, double-blind trial of depot naltrexone for preventing heroin relapse in Russia [62•] found that, among those who continued in the extension, 50 % remained abstinent from heroin after 1 year. The absence of reported overdose events or deaths in this study is consistent with the original paper [63] yet notably inconsistent with the epidemiology of high opioid overdose rates in Russia [64, 65].

Pharmacotherapies for stimulant use disorders have encountered much less success, with limited exceptions such as a small study of mirtazapine for methamphetamine dependence [66] and a modest study of topiramate for cocaine dependence [67•]. A randomized controlled trial of methylphenidate among 79 amphetamine/methamphetamine-dependent persons failed to demonstrate superiority to placebo [68], as did a randomized trial of aripiprazole for methamphetamine-dependent men who have sex with men [69] and methylphenidate among heroin prescription recipients using cocaine [70]. Modafinil [71] and bupropion [72] also continued to produce underwhelming results for methamphetamine dependence, as did buspirone [73], n-acetylcysteine [74], atomoxetine [75], and vigabatrin [76] for cocaine dependence. Early-stage studies have explored therapies such as varenicline [77], disulfiram [78], doxazosin [79], and stimulant vaccines [80]. Most investigators now believe that pharmacotherapies for stimulant use disorders will require agents that target multiple neurotransmitter systems.

Opioid Overdose Prevention and Naloxone

Opioid overdose and resultant mortality have been linked to HIV risk behaviors and HIV-seropositivity [81–85]. The most compelling intervention for addressing opioid overdose mortality is naloxone, which has rapidly gained favor in recent years and whose use has been associated with the reduced likelihood of syringe sharing among PWID [85]. Naloxone is the short-acting, high-affinity opioid antagonist used as an opioid reversal agent by paramedics and anesthesiologists since the 1960s. Since 1993, naloxone has been provided directly to drug users to ensure its presence at the site of overdose events [86]. For many years, only program evaluation data existed, reporting the number of naloxone "kits" dispensed and the number of passively reported reversal events [87, 88]. Since 2013, more compelling data has emerged, such as an interrupted time series analysis of naloxone distribution in Massachusetts that demonstrated an adjusted rate ratio of 0.73 (95 % CI 0.57–0.91) and 0.54 (95 % CI 0.39–0.76) in communities that enrolled 1–100 and over 100 naloxone recipients per capita, respectively [89••]. In addition, Scotland initiated naloxone provision upon release from prison for all inmates with a history of heroin injection beginning in 2010. Prisoners have an extremely elevated risk of death from opioid overdose following release, as high as 1706 per 100,000 person-years in the first week [90•]. Scottish authorities recently reported a persistent decline in all opioid overdose deaths and a decline in the proportion that occurred among former inmates in the 4 weeks after release from prison since naloxone provision was initiated (from 9.8 % of all opioid deaths for 2006–2010 to 4.7 % in 2013) [91•].

Additional studies have addressed other elements of naloxone provision. As naloxone is expanding to clinical settings, Walley et al. evaluated naloxone distribution from methadone maintenance and drug detoxification programs and found successful implementation of the program and numerous

reversals [92]. Many programs now distribute naloxone for intranasal administration rather than injection. Thus, Sabzghabaee et al. compared intranasal to intravenous naloxone in a randomized design and found superior, although slightly delayed, return to consciousness among intranasal recipients [93]. To evaluate the ability of lay responders to properly utilize naloxone, two teams demonstrated that drug users and family members can be readily trained to recognize an overdose and properly administer naloxone [94, 95]. Finally, mathematical modeling suggests that providing naloxone to heroin users is likely to be robustly cost-effective, with a conservative estimate of $400 per quality-adjusted life year gained [96].

Discussion

Multiple interventions have been developed or enhanced since 2013 to address HIV and HCV among PWID. In particular, PrEP among PWID now has compelling data for HIV, and TasP for HCV and HIV among PWID is supported by mathematical modeling, although clinical trial data are needed. Research into behavioral interventions to address HIV/HCV risk directly and through substance use treatment among PWID has once again begun to produce exciting results and novel promising interventions. Research into pharmacotherapies for substance use has reconfirmed the value of opioid agonist maintenance treatment and added an additional option in the form of long-acting naltrexone. However, promising prospects for treatment of stimulant drug use disorders remain largely elusive. Research into opioid overdose has demonstrated the apparent effectiveness of lay naloxone distribution, leading to a recommendation from the World Health Organization HIV guidelines that all PWID and their associates have access to naloxone for lay overdose reversal [20].

Notwithstanding these exciting developments, stigma remains a formidable barrier to managing HIV and HCV risks among PWID. Distinct from sexual behavior, injecting drugs remains an illegal practice around the world, limiting the ability of peers and other providers to reach those at risk and engender improvements in their risks for and management of blood-borne viral infections. This stigma extends to healthcare providers, as evidenced by the reluctance of many providers to adhere to treatment guidelines and provide indicated ART for PWID living with HIV [14]. Innovative strategies to address these risks, such as the supervised injection facility in Vancouver [97, 98], have also gone a long way toward overcoming the stigma toward PWID facing the greatest hazards. Nonetheless, significant legal reforms are clearly needed to ensure appropriate service provision.

The scope of this review was limited primarily to experimental and quasi-experimental studies. We did not address the numerous epidemiologic and observational studies among PWID, nor did we emphasize literature on community- and structural-level interventions, which have been previously highlighted elsewhere [99, 11, 100].

Conclusion

We identified 23 experimental and quasi-experimental studies reporting positive findings on behavioral and biologic outcomes to reduce HIV and HCV for PWID published since 2013. These novel interventions provide additional tools in our armamentarium against HIV for PWID. Scaling up of these strategies needs to be done in combination, as comprehensive, multilevel interventions will likely maximize their impact. Structural and legislative reforms will be needed to successfully implement many of these interventions.

Compliance with Ethics Guidelines

Conflict of Interest Phillip O. Coffin, Christopher Rowe, and Glenn-Milo Santos declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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